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Impact Assessment of Neuroimaging

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Final Report

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Brain imaging methods, applications and scientific background, conclusions, recommendations

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ACG	Anterior cingulated gyrus
AChEI	Acetylcholine esterase inhibitors
AD	Alzheimer's disease
ADC	Apparent diffusion coefficient
ADP	Adenosine diphosphate
APOE	Apolipoprotein E
ATP	Adenosine triphosphate
AVMs	Arteriovenous malformations
BAG	Federal Office of Public Health, *Bundesamt für Gesundheit*
BOLD	Blood-Oxygen-Level-Dependent
BOLD-fMRI	Blood-Oxygen-Level-Dependent fMRI
BStP	*Bundesgesetz über die Bundesstrafrechtspflege*
BV	Swiss Federal Constitution, *Bundesverfassung*
CAT	Computer-Aided Translation
CNS	Central Nervous System
COMT	Catechol-o-methyltransferase
DBM	Deformation-based morphometry
CEN	Comité Européen de Normalisation
CENELEC	Comité Européen de Normalisation Electrotechnique
CSF	Cerebrospinal fluid
CT	Computed tomography
DC-potential	Direct current potential (slow cortical potential)
DLPFC	Dorsolateral prefrontal cortex
DSC-MRI	Dynamic susceptibility-weighted contrast material-enhanced magnetic resonance imaging
DSM-IIR/ DSM-IV	American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion tensor imaging
DTT	Diffusion tensor tractography
DWI	Diffusion-weighted imaging
EEG	Electroencephalography
ELISA	Enzyme-linked Immunosorbent Assay
EPI	Echoplanar imaging
ERD	Event-related desynchronisation
ERP	Event-related potential

ETSI	European Telecommunications Standards Institute
EUV	Extreme ultraviolet
FDA	Food and Drug Administration
FDG PET	F-fluoro-deoxyglucose positron emission tomography
fMEG	Fetal magnetoencephalography
fMRI	Functional magnetic resonance imaging
FTD	Frontotemporal dementia
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GDP	Gross Domestic Product
GLI	Gray level index
Gy	Gray
H	Equivalent dosage
HB	Deoxygenated blood
HG	Heschl's gyrus
HMG	Swiss Federal Law on Medicinal Products, *Heilmittel-gesetz*
IA-DAS	Intra-arterial digital subtraction
ICER	Incremental cost-effectiveness ratio
ICNIRP	International Commission on Non-Ionizing Radiation Protection
IGNS	Image-guided neurosurgery
iv	Intravenous
LAC	Location Area Code
LDLPFC	Left dorsolateral prefrontal cortex
LED	Light Emitting Diode
LES	Left extrastriate cortex
LFP	local field potential
LPAR	Left parietal cortex
LPRC	Left precentral cortex
LTEMP	Left temporal cortex
LORETA	Low resolution electrical tomography
MCI	Mild cognitive impairment
MEG	Magnetoencephalography
MEP	Motor evoked potential
MMN	Mismatch negativity
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MRS	MRI spectroscopy

MS	Multiple sclerosis
NAA	N-acetylaspartate
NC	Control subjects
NINCDS-ADRDA	National Institute of Neurologic, Communicative Disorders and Stroke-AD and Related Disorders Association
NIR	Near infrared
NIRS	Near infrared spectroscopy
OEM	Original equipment manufacturers
PAC	Primary auditory cortex
PACS	Picture archiving and communication systems
Pi	Inorganic Phosphate
PDE	Phosphodiesters
PET	Positron emission tomography
phospho-tau, P-tau	Tau phosphorylated at various epitopes
PME	Phosphomonoesters
PFC	Prefrontal cortex
PP	Planum parietale
PT	Planum temporale
PU	Parcellation units
p-value	Lowest significance level at which one would still have obtained a significant result for a given data set, a given significance test, and a given test problem
q	Weighting factor
rCBF	Regional cerebral blood flow
rCMRO2	Regional oxygen consumption
RF	Radiofrequency
ROI	Regions of interest
r score	Linear correlation coefficient
rTMS	Repetitive TMS
SAMS	Swiss Academy of Medical Sciences
SAR	Specific absorption rate
Sv	Sievert
SPECT	Single photon emission computed tomography
StGB	Swiss Criminal Code, *Strafgesetzbuch*
sMRI	Structural magnetic resonance imaging
sTMS	Single-pulse TMS
SZ	Schizophrenic subjects
T-tau	Total-tau

TBI	Traumatic brain injury
TBM	Tensor-based morphometry
TEM	Transmission electron microscope
TMS	Transcranial magnetic stimulation
TPG	Federal law on the transplantation of organs, tissue and cells, *Bundesgesetz über die Transplantation von Organen, Geweben und Zellen*
UCLA	University of California, Los Angeles
VBM	Voxel-based morphometry
VMPFC	Ventromedial prefrontal cortex
WBIC	Wolfson Brain Imaging Centre
WHM	White matter hyper intensities
3DAC	3-dimensional anisotropy contrast
5-HTT	5-hydroxytryptamine transporter, serotonin transport protein
z score	Standard scores
z position	Position of a particular z-score ono the z-scale
^{15}O	Oxygen-15
^{11}C	Carbon-11
^{13}N	Nitrogen-13
^{18}F	Fluorine-18

Executive Summary

The human brain plays an important role in what makes humans human: sensations, movements, emotions, language, memory, intelligence, creativity, thought and social interaction are accomplished with the help of this extraordinary organ. Due to the outstanding importance of the brain for human life, it is expected that knowledge arising from brain research will have considerable cultural, social, economic and health impacts. It is the aim of this study to contribute to an internationally largely unexploited field by assessing the impacts of neuroimaging from an interdisciplinary technology assessment perspective.

In recent years, powerful neuroimaging methods have been developed which allow the non-invasive analysis of human brain anatomy as well as *function* in living humans, thus opening up unprecedented ways of exploring the human brain. This toolbox comprises the anatomical techniques computed tomography (CT) and structural magnetic resonance imaging (sMRI), and the functional techniques positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), and near infraread spectroscopy (NIRS). Electroencephalography (EEG), magnetoencephalography (MEG), and variants of transcranial magnetic stimulation (TMS) techniques are used as supplementary tools. Moreover, molecular imaging, employing different modalities such as PET, SPECT, MRI/MRS and MR microscopy, is rapidly gaining importance in biomedical and pharmaceutical research. Each of these imaging modalities has its specific strengths and weaknesses. All in all, the different neuroimaging methods in their combination allow brain imaging on different spatial levels from gross anatomy down to genes and molecules.

The scope of actual and potential future applications of neuroimaging is broad: In addition to its invaluable contributions to basic biological and biomedical research, neuroimaging is firmly established and still expanding in clinical diagnostics, monitoring of disease progression, neurosurgery, and pharmaceutical research. Neuroimaging has had, and continues to have, a significant impact on the study of cognition, leading to the new discipline of cognitive neurosciences which altered our understanding of the brain significantly: it is now seen as a complex organ of extraordinary individuality and plasticity, which shows dynamic self-organisation in response to stimu-

li, and which significantly matures and changes during individual development.

Moreover, there is a growing interest to extend the application of brain imaging into new fields, ranging from screening and prediction of cognitive abilities and performance, of personality traits or aberrant behaviour to lie-detection and "mind-reading". To illustrate these trends, neuroimaging as a tool to improve educational practice and learning, to support forensic psychology, and its use in market research were analysed as examples in this report. They showed that brain imaging is often – and mistakenly – presented and perceived as direct, intrinsically objective and accurate "hard science". The expensive high-tech instrumentation and the representation of results as aesthetic visual maps of the brain in action may have contributed to this notion, leading to a misconception of the power, sensitivity and limits of brain imaging both on the supply and demand side of such information. This may lead to unjustified expectations, undue concerns, but also bears the risk of a premature broad use of not sufficiently substantiated findings, accompanied by an over-reliance on or misapplication of neuro-imaging information.

However, the report clearly shows that the concerns of "mind-reading" and far-reaching inference on one's personality by neuroimaging alone are clearly not supported by the present state of the art in cognitive neurosciences. In general, brain imaging methods used in the realm of cognitive psychology have not yet advanced to a stage in which their diagnostic specificity and sensitivity goes beyond established psychological and psychiatric diagnostic tests. Presently, the state of the art in cognitive neurosciences does not support the application of neuroimaging beyond well-controlled research studies. It also does not support to make far-reaching assessments about cognitive abilities, personality, future behaviour, or ability to lead a fulfilled life.

In order to exploit the potentials of neuroimaging further and to provide effective safeguards against misuse and over-reliance on the methods, it is recommended

- to closely monitor the developments in neuroimaging, as well as neurosciences in general, and take actions, if appropriate,

- to actively stimulate and engage in public debates about the goals, potentials, research endeavours, limits, frame conditions and possible impacts of brain imaging,
- to substitute the presently fragmentary and inconsistent Swiss regulation of research on human beings by a consistent, modern Federal law on research on human beings,
- to further improve the conditions for interdisciplinary neurocognitive research and for the transfer of research findings into routine clinical practice,
- to strive for high levels of quality control and professional standards in neurocognitive and biomedical neuroimaging research as well as in clinical use,
- to specifically address the issues of informed consent, incidental findings and data protection, and to
- support further research into possible health risks associated with certain forms of MRI and to adapt safety regulations accordingly.

Résumé

Le cerveau contribue largement à l'essence même de l'homme : la percep-
tion des sens, les mouvements, les sentiments, la langue, la mémoire, l'in-
telligence, la créativité, la pensée et l'interaction sociale sont des perfor-
mances qui ne peuvent être fournies qu'à l'aide du cerveau. Du fait de l'im-
portance prépondérante du cerveau pour la vie humaine, il faut s'attendre à
ce que les découvertes liées à la recherche cérébrale aient de grandes
conséquences culturelles, sociales, économiques et sanitaires. L'objectif de
cette étude est de réaliser dans la perspective interdisciplinaire de l'évalua-
tion des choix technologiques, une analyse des conséquences de la neuro-
imagerie, c'est à dire de l'application de cette technique à la recherche sur
le cerveau, et ainsi de contribuer à un domaine largement inexploré sur le
plan international.

Au cours des dernières années, des techniques d'imagerie ont été déve-
loppées qui permettent l'emploi de méthodes d'examen non-invasives des
structures et fonctions cérébrales, et qui de fait ouvrent de nouvelles possi-
bilités d'étude du cerveau humain. Les méthodes anatomiques telles que la
tomographie computérisée (CT) et l'imagerie structurelle par résonance
magnétique (IRMs) ainsi que les méthodes fonctionnelles comme la tomo-
graphie à émission de positron (TEP), l'imagerie fonctionnelle par réso-
nance magnétique (IRMf), la spectroscopie par résonance magnétique
(SRM), et la spectroscopie proche infrarouge (NIRS) font partie de ces pro-
cédés. Les méthodes comme l'électroencéphalographie (EEG), la magné-
to-encéphalographie (MEG) ainsi que des variantes de stimulation magné-
tique transcrânienne (SMT) sont utilisées de façon complémentaire. En
outre, l'imagerie moléculaire a rapidement gagné de l'importance dans la
recherche biomédicale et pharmaceutique grâce à différents outils tels que
la TEP, le SPECT, l'IRM/SRM et la microscopie par résonance magné-
tique. Chacune de ces techniques d'imagerie a ses points forts et ses fai-
blesses spécifiques. Grâce à leur combinaison, la recherche sur le cerveau
à différentes échelles, de l'anatomie entière jusqu'aux gènes et aux molé-
cules, est devenue possible.

Le domaine actuel d'application et les potentialités futures de la neuro-
imagerie vont au delà de leurs précieuses contributions à la recherche fon-
damentale biologique et biomédicale. La neuro-imagerie gagne de plus en

plus d'importance dans des domaines tels que le diagnostic clinique, la surveillance de la progression d'une pathologie, la neurochirurgie, ainsi que dans la recherche pharmaceutique. La neuro-imagerie revêt une importance particulière pour le développement des sciences cognitives. Dans ce domaine elle a contribué au développement d'une nouvelle discipline scientifique, la neuroscience cognitive, laquelle a modifié et étendu notre compréhension du cerveau. Aujourd'hui, le cerveau est perçu comme une organe complexe faisant preuve d'une individualité et d'une plasticité extraordinaires. Le cerveau se modifie dynamiquement et se réorganise en fonction des stimulis extérieurs, il mûrit au cours du développement de l'individu et se modifie fortement lors de ce processus.

Étendre la neuro-imagerie à de nouveaux domaines d'application éveille un intérêt croissant. Ces domaines vont de la prévision des capacités et performances cognitives ou d'un comportement divergent à l'analyse de la personnalité, la détection de mensonge voire la lecture des pensées. Pour illustrer ces tendances, le rapport examine à titre d'exemple l'emploi de la neuro-imagerie comme outil d'aide à l'apprentissage scolaire, à la psychologie judiciaire ainsi que pour des études de marché. D'où le constat que la neuro-imagerie est fréquemment représentée et perçue faussement – comme une science exacte, objective et précise et donc «dure». Les appareils coûteux de haute technologie ainsi que la représentation des résultats expérimentaux en forme d'images de cerveau agréables à l'oeil pourraient contribuer à ce point de vue et conduisent au final à des perceptions fausses et trompeuses concernant la valeur, la sensibilité et les limitations de la neuro-imagerie, et ce tant au niveau des diffuseurs que des récepteurs des informations en question. De fait, des attentes non justifiées, mais également des craintes non fondées peuvent surgir, de même qu'une surestimation des possibilités offertes par la neuro-imagerie.

Ce rapport montre par exemple clairement que la crainte de pouvoir lire dans les pensées et de tirer des conclusions quant à la personnalité d'un individu à l'aide de la seule neuro-imagerie ne sont pas fondées. D'une façon générale, les méthodes de neuro-imagerie utilisées dans le cadre de la psychologie cognitive n'ont pas suffisamment progressé pour pouvoir supplanter, en termes de spécificité et de sensibilité, les tests reconnus utilisés dans le cadre de diagnostics psychologiques et psychiatriques. À l'heure actuelle, les méthodes de la neuro-imagerie devraient être employées exclusivement dans le cadre de projets de recherche contrôlés. Leur applica-

tion pour faire des prévisions étendues sur les capacités cognitives, la personnalité, un comportement futur, ou l'épanouissement personnel ne sont pas prouvées dans l'état actuel des connaissances.

Les recommandations suivantes concernent tant l'exploitation des potentialités de la neuro-imagerie que la protection contre tout abus et le risque de surestimation des possibilités offertes :

- observer attentivement les développements dans les domaines de la neuro-imagerie et des neurosciences dans leur ensemble pour prendre les mesures nécessaires le cas échéant,
- initier des dialogues publics portant sur les buts, les potentiels, les résultats, les limitations, les conditions générales ainsi que les conséquences possibles de la neuro-imagerie,
- légiférer au niveau fédéral pour mettre fin aux contradictions actuelles portant sur la recherche sur des sujets humains et répondre aux exigences internationales,
- améliorer les conditions dans lesquelles se déroulent les recherches en sciences neurologiques cognitives ainsi que le transfert des résultats vers les milieux cliniques,
- aspirer à des normes de qualité élevées en termes d'assurance-qualité, de standards professionnels dans les domaines des neurosciences cognitives, de la recherche biomédicale et des pratiques médicales,
- prêter attention aux problèmes résultants de techniques d'échantillonnage aléatoire et de la protection de l'anonymat et des données individuelles en rapport avec la neuro-imagerie
- continuer à soutenir l'étude des risques sanitaires potentiellement liés aux applications de l'imagerie par résonance magnétique et adapter les consignes de sécurité en conséquence.

Zusammenfassung

Das Gehirn trägt wesentlich zu dem bei, was den Menschen als Menschen ausmacht: Sinneswahrnehmungen, Bewegungen, Gefühle, Sprache, Gedächtnis, Intelligenz, Kreativität, Denken und soziale Interaktion sind Leistungen, die nur mit Hilfe des Gehirns erbracht werden können. Wegen der herausragenden Bedeutung des Gehirns für das menschliche Leben ist zu erwarten, dass Erkenntnisse, die aus der Erforschung des Gehirns erwachsen, große kulturelle, gesellschaftliche, wirtschaftliche und gesundheitliche Auswirkungen haben werden. Es ist das Ziel dieser Studie, eine Analyse der Folgen des Neuroimaging, d. h. der Anwendung bildgebender Verfahren auf die Untersuchung des Gehirns, aus der interdisziplinären Perspektive der Technologiefolgen-Abschätzung durchzuführen und damit einen Beitrag zu einem international weitgehend unerforschten Gebiet zu leisten.

In den letzten Jahren wurden leistungsfähige bildgebende Verfahren entwickelt, die die nicht-invasive Untersuchung der Gehirnstrukturen und -funktionen am lebenden Menschen ermöglichen. Damit eröffnen sie neuartige Möglichkeiten zur Erforschung des menschlichen Gehirns. Zu diesen Verfahren gehören die anatomischen Methoden Computertomografie (CT) und strukturelle Magnetresonanztomografie (sMRI) sowie die funktionellen Methoden Positronenemissionstomografie (PET), funktionelles Magnetresonanzimaging (fMRI), Magnetresonanzspektroskopie (MRS) und Nahinfrarot-Spektroskopie (NIRS). Elektroenzephalografie (EEG), Magnetenzephalografie (MEG) sowie Varianten der Transkraniellen Magnetstimulation (TMS) werden ergänzend eingesetzt. Zudem hat das Molekulare Imaging unter Verwendung verschiedener Modalitäten wie PET, SPECT, MRI/MRS und Magnetresonanzmikroskopie sowohl in der biomedizinischen als auch der pharmazeutischen Forschung rasch an Bedeutung gewonnen. Jedes der genannten bildgebenden Verfahren hat seine spezifischen Stärken und Schwächen. Ihre Kombination ermöglicht jedoch die Untersuchung des Gehirns auf verschiedenen räumlichen Ebenen, von der Gesamtanatomie bis hin zu Genen und Molekülen.

Der aktuelle und mögliche künftige Anwendungsbereich des Neuroimaging ist groß: Es leistet nicht nur wertvolle Beiträge in der biologischen Grundlagenforschung und der biomedizinischen Forschung. Ihm kommt auch große und noch wachsende Bedeutung in der klinischen Diagnostik, bei der

Überwachung von Krankheitsverläufen und Heilungsprozessen, in der Neurochirurgie sowie in der pharmazeutischen Forschung zu. Von besonderer Bedeutung war und ist das Neuroimaging aber für die Untersuchung kognitiver Leistungen. Hier hat es zur Herausbildung der neuen Wissenschaftsdisziplin der kognitiven Neurowissenschaften geführt, die unser Verständnis des Gehirns deutlich erweitert und verändert haben: Das Gehirn wird heutzutage als ein komplexes Organ aufgefasst, das eine außergewöhnliche Individualität und Plastizität aufweist, sich in Abhängigkeit von äußeren Reizen dynamisch verändert und neu organisiert, und das während der Individualentwicklung heranreift und sich dabei stark verändert.

Darüber hinaus gibt es ein wachsendes Interesse, das Neuroimaging auf neue Anwendungsfelder auszudehnen. Sie reichen vom Screening und der Vorhersage kognitiver Fähigkeiten und Leistungen oder von abweichendem Verhalten über die Analyse der Persönlichkeit bis hin zu Lügendetektion und Gedankenlesen. Zur Illustration dieser Trends wurden im vorliegenden Bericht der Einsatz von Neuroimaging als Werkzeug zur Verbesserung der schulischen Wissensvermittlung und des Lernens, zur Unterstützung der forensischen Psychologie sowie im Rahmen der Marktforschung exemplarisch untersucht. Dabei zeigte sich, dass Neuroimaging häufig – und zwar fälschlicherweise – als direkte, objektive und genaue, "harte Wissenschaft" dargestellt und wahrgenommen wird. Die teuren Hightech-Geräte sowie die Darstellung der experimentellen Ergebnisse in Form ästhetisch ansprechender Gehirnbilder dürften zu dieser Auffassung beitragen und führen insgesamt zu falschen und irreführenden Annahmen über die Aussagekraft, Empfindlichkeit und Grenzen des Neuroimaging – und zwar sowohl auf der Seite der Anbieter als auch der Rezipienten solcher Informationen. Hierdurch kann es zu nicht gerechtfertigten Erwartungen, aber auch unbegründeten Befürchtungen kommen, sowie zu einer Überschätzung und unzulässigen Anwendung der Informationen, die mit Neuroimaging erhoben werden können.

In diesem Bericht wird jedoch auch klar gezeigt, dass die Befürchtungen, allein durch Neuroimaging könne man z. B. Gedanken lesen und weitreichende Rückschlüsse auf die Persönlichkeit eines Menschen ziehen, beim gegenwärtigen Stand der Forschung unbegründet sind. Generell sind Methoden des Neuroimaging, die im Rahmen der kognitiven Psychologie eingesetzt werden, nicht so weit fortgeschritten, dass sie in Bezug auf ihre Spezifität und Sensitivität über etablierte, in der psychologischen und psy-

chiatrischen Diagnostik eingesetzte Testverfahren hinausgingen. Zum gegenwärtigen Zeitpunkt sollten Methoden des Neuroimaging ausschließlich im Rahmen von kontrollierten Studien und Forschungsvorhaben eingesetzt werden. Ihr Einsatz für weitreichende Aussagen über kognitive Fähigkeiten, Persönlichkeit, künftiges Verhalten, oder Lebenschancen ist durch den gegenwärtigen Stand der Forschung *nicht* gedeckt.

Um die Potenziale des Neuroimaging weiter auszuschöpfen, aber auch Sicherungen gegen Missbrauch und Überschätzung der Methoden bereitzustellen, werden folgende Empfehlungen ausgesprochen:

- die Entwicklungen auf dem Gebiet des Neuroimaging, aber auch der Neurowissenschaften insgesamt, aufmerksam zu verfolgen und gegebenenfalls aktiv zu werden,
- gesellschaftliche Dialoge über Ziele, Potenziale, Forschungsergebnisse, Grenzen, Rahmenbedingungen und mögliche Folgen des Neuroimaging zu initiieren und sich aktiv darin einzubringen,
- die Forschung am Menschen, die gegenwärtig in der Schweiz lückenhaft und widersprüchlich geregelt ist, in einem Bundesgesetz einheitlich und internationalen Anforderungen entsprechend zu regeln,
- die Bedingungen, unter denen interdisziplinäre Forschung auf dem Gebiet der kognitiven Neurowissenschaften sowie der Transfer von biomedizinischen Forschungsergebnissen in die klinische Routine erfolgt, weiter zu verbessern,
- hohe Qualitätsstandards sowohl in Bezug auf die Qualitätssicherung als auch in Standards der Berufsstände anzustreben, sowohl in den kognitiven Neurowissenschaften, der biomedizinischen Forschung als auch in der ärztlichen Praxis,
- sich speziell der Probleme der informierten Zustimmung, der Zufallsbefunde sowie des Datenschutzes anzunehmen, die durch das Neuroimaging aufgeworfen werden, und
- die Erforschung möglicher Gesundheitsrisiken, die mit bestimmten MRI-Anwendungen verbunden sein könnten, weiter zu unterstützen und die Sicherheitsbestimmungen entsprechend anzupassen.

1   Introduction

The human brain plays an important role in what makes humans human: sensations, movements, emotions, language, memory, intelligence, creativity, thought and social interaction are accomplished with the help of this extraordinary organ. Brain research aims at elucidating how the brain works, what its capabilities are and how its functions can be understood on all levels, ranging from genes and molecules to human behaviour. Due to the outstanding importance of the brain for human life, it is expected that knowledge arising from brain research will have considerable cultural, social, economic and health impacts.

Brain research makes use of a diverse methodological toolbox, among them psychological tests, pharmacological interventions, neurosurgery, and molecular biology. In recent years, powerful imaging methods such as positron emission spectroscopy (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG) and magnetoencephalography (MEG) as well as molecular imaging and others, have significantly expanded this toolbox: they open up the possibility to non-invasively analyse human brain functions *in vivo*, and thus contribute to understanding human brain functions on a much more detailed level than before.

The applications that could emanate from this knowledge are manifold: e. g. in healthcare for the diagnosis and therapy of neurological diseases, in pharmaceutical research for the development of new drugs, in psychology and pedagogy, for the development of innovative products. Thus, both the individual as well as society could benefit from brain research. On the other hand, neuroimaging bears the potential to reveal sensitive information about the individual's health, personality, leanings and preferences, or cognitive and emotional abilities. It is especially this latter aspect which raises many health, ethical, legal and social issues which bear – with respect to their scope, potential pervasiveness and disruptiveness – resemblances to the health, ethical, legal and social issues inherent to molecular genetics and genetic engineering.

However, while these issues have been rather high on the agenda in the field of molecular genetics since its early days, the exploration of ethical

and social issues raised by the progress in neurosciences on a broader scope has begun only recently (see e. g. Moreno 2003; Farah, Wolpe 2004, p. 35-36, EGE 2005). To our knowledge, only few technology assessment studies have been carried out internationally on developments in the neurosciences (e. g. International Bioethics Committee (IBC) 1995; Nuffield Council on Bioethics 1998; Steering Committee on Bioethics (CDBI) 2000; Nuffield Council on Bioethics 2002; Pieters et al. 2002; Raeymaekers et al. 2004[1]). They often focus on psychopharmaceuticals and mental disorders or molecular genetics whereas the impacts of neuroimaging have not yet been assessed from an interdisciplinary technology assessment perspective.

Against this background, it is the aim of this study to contribute to an internationally largely unexploited field by assessing the impacts of neuroimaging from an interdisciplinary technology assessment perspective. The following guiding questions will be addressed:

- What are the aims of the application of neuroimaging methods? Which solutions to social aims and challenges are expected?
- What are the present and future uses and applications? What is the respective state of the art? What are the future perspectives?
- What kind of information can be obtained with these methods, what is their validity?
- What are possible risks and unintended impacts of the application of neuroimaging?
- Which drivers and restraints significantly influence the future development? What is their likely impact on possible intended and unintended future developments?
- Which are the options for shaping future developments?
- What are the implications for the planned Federal Law on Research on Human Beings that is presently under preparation in Switzerland?
- Which recommendations can be derived for Switzerland in order to exploit the potentials of neuroimaging, to limit risks and to avoid unintended impacts?

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1   Related are the citizens' panels "Meeting of Minds – European Citizens' Deliberation on Brain Science" in nine European countries 2005, see http://www.meetingmindseurope.org

2   What is brain imaging?

In the 1970s, researchers have been starting to use computers and sophisticated computer software to process information from x-rays passed through the brain to reconstruct images of the brain. This technique commercially introduced as Computed Tomography (CT or CAT scanning), has turned out an extremely important medical tool for structural imaging of the human brain in living people. These first attempts have given birth to the new research field of brain imaging. Although, to our best knowledge, no one has explicitly defined what brain imaging really is, the CT technique implicitly demonstrates the basic principle of brain imaging which is the digital construction of brain tissue from images using computers and sophisticated software. Thus, simply making photography of a cadaver brain or a brain slice is not brain imaging. In addition mapping the electrical or magnetic fields on the surface of the skull is also not brain imaging. Brain imaging (sometimes also called neuroimaging) can be described as the (mathematical) construction of brain tissue (on different spatial levels from gross anatomy down to the genes) on the basis of physical measures.

Brain imaging methods include both anatomical techniques – which create "constructed" images of brain structure – and functional techniques, which create a series of dynamic brain images reflecting ongoing brain activity. Thus, brain imaging cannot simply be equated with measuring neurophysiological activity (e. g. measuring evoked potentials or recording neural firing rates of a single neuron). It is rather necessary to relate the dynamic neurophysiological measurements to precisely defined and reconstructed parts of the brain. Thus, it is *recording* and *reconstruction* which is the essence of brain imaging.

The advent of brain imaging techniques for use in humans has led to an explosion of research on the neural basis of cognitive processes in humans throughout the past decade. In the early 1990s, the term cognitive neuroscience was coined to describe a renaissance in the study of cognition. Cognitive psychology which was a major scientific direction in the late 60s and the entire 70s received refreshed interest by the imaging methods (for a summary see Raichle 1998; Raichle 2000; Beaulieu 2003).

3 Overview of brain imaging methods

In cognitive neurosciences different brain imaging methods are used:

1. Anatomical methods. These are the classical methods to image the brain. They comprise:

- Computed tomography (CT)
- Structural magnetic resonance imaging (sMRI)
  - in vivo morphometry of regions of interest (ROI)
  - diffusion tensor imaging (DTI)
    - voxel-based morphometry (VBM)
    - deformation-based morphometry (DBM)
    - tensor-based morphometry (TBM)

2. Functional methods. Functional methods comprise both direct and indirect measures of neural activity. These techniques are only labelled as brain imaging methods as long as data obtained by these techniques are modelled in relation to brain structures. Typical examples are modelling intracerebral activations using distributed source localisation methods or dipole localisation models. They comprise:

a) Direct measures of neural activity

- Electroencephalography (EEG)
- Magnetoencephalography (MEG)
- Fetal magnetoencephalography (fMEG)

b) Indirect measures of neural activity. These methods basically measure haemodynamic responses or differences in metabolic concentrations to cognitive stimulation.

- Positron-emission-tomography (PET)
- Single photon emission computed tomography (SPECT)

- Functional magnetic resonance imaging (fMRI)
  - BOLD-fMRI
  - Perfusion fMRI
  - Diffusion weighted fMRI
  - MRI spectroscopy (MRS)
- Near infrared spectroscopy (NIRS)

In the following chapters 4 and 5 we will give a short overview of the brain imaging methods which are usually used in the context of cognitive neuro-scientific research. For a summary see also Jäncke 2005.

4   Overview of anatomical brain imaging methods

Different anatomical techniques are used to study cognition, emotion, or motor functions in the healthy brain. These techniques are also used to understand neurological or psychiatric diseases. A typical approach is to localise anatomical abnormalities in patients with cognitive disabilities or to compare the size of specific brain structures between groups of subjects by means of volumetric analysis. Another approach receiving much attraction is to compare the brains of normal and healthy subjects with exceptional capabilities (e. g. absolute pitch, exceptional intelligence) in terms of anatomical differences in distinct parts of the brain. Recently, it has been shown that these methods can be used to track the normal and abnormal development of neural pathways in childhood up to the adolescents. The major advantage of these anatomical brain imaging methods is that one now can examine the living brain in the context of various neuropsychological questions. In 1992 the famous neuroscientist Sandra Witelson has coined this new scientific approach "*cognitive neuroanatomy*" to indicate that human cognition can now be studied with modern anatomical methods (Witelson 1992).

Beside the advantage to precisely measure anatomical peculiarities of the living human brain, modern brain imaging methods are also used to enhance the precision in analysing human post mortem brains. For example, on the basis of brain slices obtained from human cadaver brains it is now possible to delineate cytoarchitectonic properties of various brain structures. Before we will describe the main approaches of these anatomical techniques we will give a short introduction into the main brain imaging methods. We will focus our description on those methods mainly used in the context of cognitive neuroscience research (Jancke 2002; for a summary see also Jancke, Steinmetz 2002).

4.1   Computed tomography (CT)

The earliest brain imaging technique was commercially introduced in 1973 and is called computed tomography (CT). During CT scanning, the patient or volunteer is placed in a CT scanner in supine position. The basic principle is to project x-radiation through the brain and to measure the non-absorbed x-ray passing the brain. For this, an x-ray source and a concomitant x-ray detector are located on opposite sites of the scanner with the brain of the volunteer positioned in between. The source and the detector are mounted on specific devices (a so called ring) rotating around the brain, hence, the x-beams can be projected from all possible directions. By using different positions of the source and the detector, x-ray beams pass through the head. Some radiation in the x-beam is absorbed by the intervening tissue. This process (sending x-ray beams through the brain tissue and measure the remainder passed through by detectors) is repeated for many positions. The number of sources and detectors determines the spatial resolution and, thus, accuracy of anatomical measurement. These recordings are fed into a computer that reconstructs 2D or 3D images of the brain. Depending on the density of the brain tissue through which the x-ray beams were sent the constructed CT images vary in terms of grey-white shading. For example, high-density material such as bone absorbs a lot of radiation while low-density material such as air or blood absorbs little radiation. Thus, on CT images high-density regions (like bone) are shown as lightly coloured and low-density (like water or cerebrospinal fluid) regions as darkly coloured. The typical spatial resolution of modern CT scans is approximately 0.5 to 1 cm^3. Since the cortex is only up to 4 mm thick, it is, thus, very difficult to see the boundary between grey and white matter. However, large brain structures like major sulci or gyri can easily be identified. CT measures have been very important in diagnosing neurological disease and they are still used in many hospitals because CT scans are cheap and relatively easy to handle. The impact of CT measures on cognition has been very limited. Only a few studies have used anatomical CT measures to study brain lateralisation in the context of functional hemispheric specialisation.
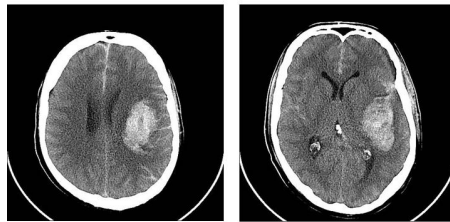
The dark regions along the midline are the ventricles, the reservoirs of cerebrospinal fluid. The marked white boundary is the skull while the white clusters on the right show a strong haemorrhage.

Figure 4.1:   *Two transverse computed tomography (CT) scans (source: Jäncke 2005)*

4.2   Magnetic resonance imaging (MRI)

The more recent non-invasive magnetic resonance imaging (MRI) technique was developed in the 1980s. This technique was firstly used to study brain anatomy. In the 90s functional imaging based on MRI was invented opening a new era in neuroscience. The basic principle of MRI is to place the subject in an MRI machine which creates a powerful magnetic field (measured in Tesla units). While the early MRI scanners made use of magnetic fields ranging from 0.05 to 0.1 Tesla, current human MRI scanners use 1.5-3 or even to 7 and 9 Tesla. Thus, the magnetic field strengths are more than 10,000 to 100,000 stronger than the magnetic field strength on earth. When a person is exposed to such a magnetic field, the protons (e. g. as part of the hydrogen nuclei) change their orientation preferably parallel to the magnetic field. High-frequency radio waves (in the megahertz domain) are then passed through the brain, and as the protons absorb the energy in these waves, their orientation changes. After turning off these radio waves, the protons precess in a plane perpendicular to the magnetic field and then rebound towards the original orientation. This precession produces signals that are measured by specific detectors surrounding the bore and thus the head of the subjects. By measuring these signals and conducting comprehensive mathematical operations, the MRI system can

then construct brain images, reflecting the distribution of the protons and their magnetic properties (e. g. relaxation properties). The result of these processes is a high-resolution image of the human brain with spatial resolutions ranging from 0.5 mm^3 to 3 mm^3. Thus, MRI images give a more detailed picture of the brain than it is possible with CT scans. This improvement reflects the fact that the density and the relaxation properties of protons are considerably different in grey compared to white matter. This high spatial resolution and the excellent separation of grey from white matter make it easy to distinguish single gyri and sulci. The spatial resolution also allows detecting small brain structures like the superior colliculi or even the basal ganglia including the amygdale. This technique has stimulated the new research field of "*cognitive neuroanatomy*" and also stimulated a new research line which is called "*computational neuroanatomy*".
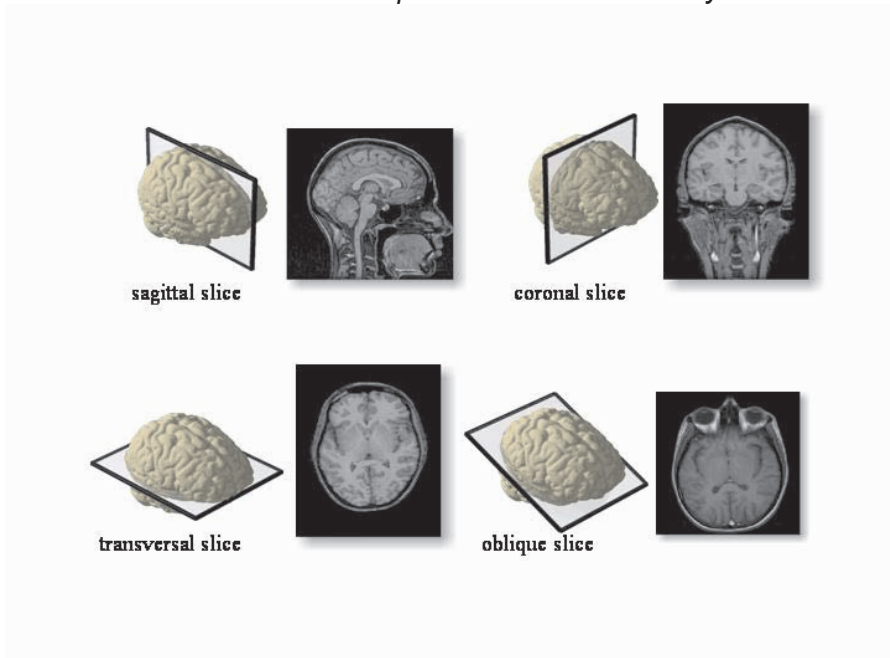
In addition four typical slices are cut through the 3D image representing sagittal, coronal, transversal, or oblique slices through the brain.

Figure 4.2:   A reconstructed 3D image of the human brain shown from different positions (source: Jäncke 2005)

4.3   Cognitive neuroanatomy

With the advent of MRI techniques, morphometry of human brain structures has been revolutionised. This revolution has brought up several advantages:

- Now it is possible to measure brain structure applying different segmentation protocols for different structures.
- Thus, repeated morphometric analysis of human brains is possible therefore making the problem of the dissection of post mortem brains irrelevant.
- In addition, three-dimensional image acquisition protocols have become the standard method for image acquisition and have replaced the two-dimensional image sets. This has led to improvements in image precision, resolution and contrast, and reductions in slice thickness. As a consequence the perception of anatomical features has substantially been improved.
- Different research groups have employed different methods for quantification of specific brain volumes. One widely used method is to manually trace the boundaries of the specific structure of interest in subsequent slices and calculate the volume within the traced structure. An alternative method is to include tracing and calculating the volumes from dimensional brain mapping or surface tessellation.
- New software tools have been developed employing a three-dimensional visualisation of the brain images, without the possibility of adjusting resolution or image contrast. Meanwhile fully-scalable three-dimensional imaging is also available, allowing for precise display and enlargement of regions of interests in coronal, sagittal and horizontal orientations.

However, the basic principle underlying these in vivo morphometry methods is to identify the anatomical structure of interest, trace the boundaries (either manually or automatically), and to calculate the volume within the traced structure (region of interest analysis: ROI). Despite the many degrees of freedom when performing the tracing, the main problem is to define appropriate anatomical landmarks which are easily and reliably identified. A first approach to divide the cortical surface of MRI brain images into a set of parcellation units (PU) has been developed by Rademacher and colleagues (1992).

A relatively new but nevertheless very promising method has been intro-
duced by Thompson and colleagues (1999) (*Three-dimensional sulcal ana-
lysis)*. The basic principle is to develop surface models of the brain and to
manually trace on magnified cortical surface models major cortical sulci
(central sulcus, pre-central sulcus, post-central sulcus, inferior frontal sul-
cus, superior frontal sulcus, sylvian fissure, intraparietal sulcus, olfactory
sulcus, collateral sulcus, and the occipitotemporal sulcus). Because these
sulci are traced three-dimensionally they can be transformed into standard
space allowing the calculation of mean maps across different brains. A fur-
ther very promising approach is to compare these sulcal maps between
different groups or between both hemispheres for the same subjects.
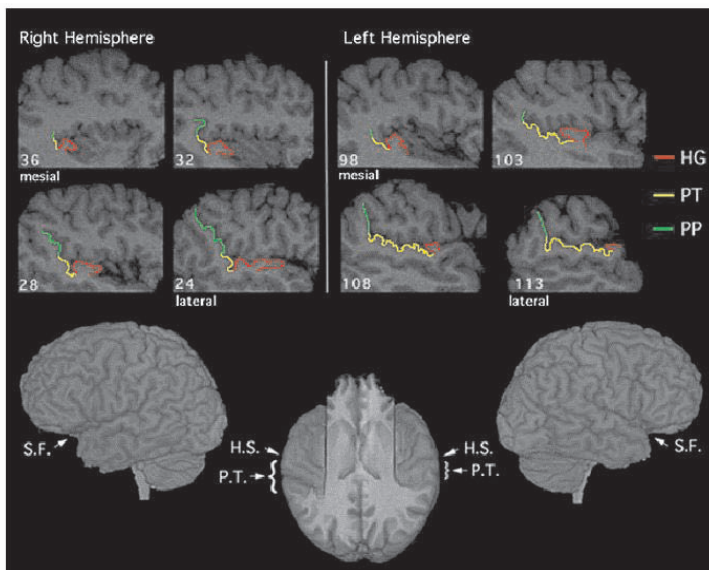
Tracing line in red indicates Heschl's gyrus (HG), in yellow the planum temporale
(PT), and in green the planum parietale (PP). Reconstructed brain in the lower row
indicates the position of Heschl's sulcus (H.S.) and the PT. (courtesy of Gottfried
Schlaug).

*Figure 4.3:   Example of delineated anatomical regions on the superior
              temporal plane on a representative brain (source: Jäncke
              2005)*
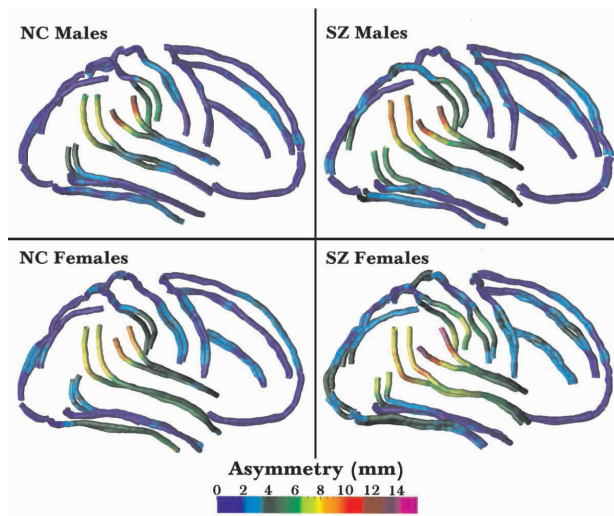
The maps were obtained for male and female control subjects (NC) and for male and female schizophrenic subjects (SZ). Differences in sulcal shape profile and between hemisphere differences are indicated in different colours (courtesy to Katherine Narr).

Figure 4.4:   *Between hemisphere difference maps for the three-dimensional sulcal maps*

The new approaches which have been developed within the last eight years are mainly motivated to detect structural differences in larger populations more or less automatically. The classical region of interest (ROI) or anatomical "landmark" approach as outlined above has the disadvantage that many regions are not appropriately defined. Furthermore, in the majority of studies ROIs are segmented in consecutive slices either manually by hand or semi-automatically. This interactive approach introduces not only user bias, but is also highly time-consuming. This leads to the analysis of a limited number of a priori defined ROIs and to a restricted number of subjects. Beside these drawbacks, there is a lack of sensitivity to detect and assess diffuse spatially distributed alterations in regional brain structure. The recently developed approaches which are also called *computational neuroanatomy* are in principle based on stereotaxic normalisation, thus transforming individual brains in a standard space for later morphometry. The particular methods with which morphometry is performed are ranging from simple mapping of anatomical landmarks within the standard space, to the automatic detection of cortical surface differences which

may be related to gender, hemispheric asymmetries, age, or pathological processes. In the following we will shortly review some of the most prominent developments in this field. For a more sophisticated review the interested reader should refer to Thompson and Toga (1999).

4.3.1   Voxel-based morphometry

In the context of the new stereotaxic normalisation tools, additional techniques have been developed to detect group differences in the stereotaxic distribution of tissue types in the brain. In these approaches, grey matter, white matter, and cerebrospinal fluid volumes are analysed separately after linear alignment of individual MRI scans to an image template in "Talairach space". These volumes are produced using appropriate tissue classifiers. Differences in incidence of tissue, at each stereotaxic voxel, are revealed by computing a statistical parametric map in which each voxel is assessed by statistically quantifying the difference between groups at that particular stereotaxic position. For each voxel, the value is compared with a reference distribution. This gives a p-value indicating the probability that such difference could occur by chance. Because a vast number of voxels are assessed, p-values have to be corrected for multiple comparisons before the significance of the results is assessed, unless there was an a priori hypothesis of an effect at a specific stereotaxic voxel. The methods for adjusting the p-values are not simple Bonferroni adjustments (adjusting p-values based on the total number of independent tests) because the neighbouring voxels are highly correlated. Approaches to obtain corrected p-values include the theory of Gaussian random fields, statistical flattening (spatial smoothing), and permutation.

4.3.2   Deformation-based morphometry

The deformation-based morphometry (DBM) approach is a development which has its origin in the methods developed to transform individual brains into the "Talairach space". While the conventional methods used linear functions for this transformation more recent methods have been applying non-linear functions, deforming the brain in order to optimally fit to a reference brain. These non-linear transformations result in deformation fields. Deformations are obtained by a non-linear registration routine transforming a reference brain (template) onto another brain (object) or vice versa. The deformation field is defined by a displacement vector in each voxel.
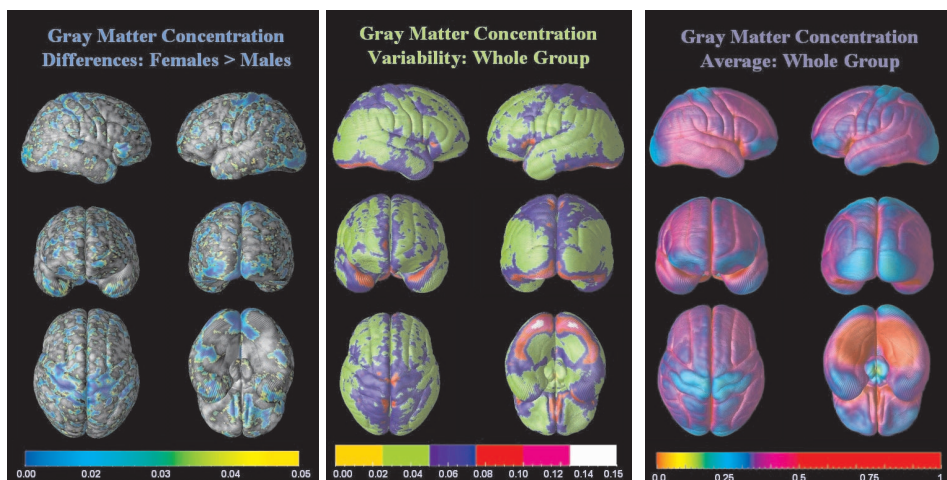
Left: Increased cortical grey matter concentration in women compared to men in standard 305 stereotaxic space. Middle: Grey matter variability for both sexes. Right: Grey matter concentration for both sexes (courtesy to Eileen Luders, UCLA LONI laboratories).

Figure 4.5:   A typical example for the potential of voxel-based morpho-metry (VBM)

These displacement vectors constitute the transformations required for the anatomical correspondence between the template and an object brain. After estimation of this field for each subject, one can characterise differences between groups by comparing the associated deformation fields. The application of this method has been presented in a paper by Gaser et al. (1999) who investigated the brains of schizophrenic patients and appropriate control subjects. They observed significant changes caused by volume reduction in brains of these patients bilaterally in the thalamus and in the superior temporal gyrus. There was also distorted grey matter in the left superior frontal gyrus, the precentral gyrus, the right middle frontal gyrus, bilaterally within the occipital lobe, and within the cerebellum. This technique can be performed automatically, thus allowing for examination of large samples with no user bias or a priori-defined ROIs.

In order to localise structures which have different shapes between groups, some form of tensor-based morphometry (TBM) is required to produce statistical parametric maps of regional shape differences. A deformation field that maps one image to another can be considered as a discrete vector

field. By taking the gradients at each element of the field, a Jacobian matrix field is obtained, where each element is a tensor describing the relative positions of the neighbouring elements. Morphometric measures derived from this tensor field can be used to locate regions with different shapes. The field obtained by taking the determinants at each point gives a map of the structure volumes relative to those of a reference image. Statistical parametric maps of these determinant fields (or possibly their logs) can then be used to compare the anatomy of groups of subjects. Other measures derived from the tensor fields have also been used by other researchers, and these are described by Thompson and Toga (1999).
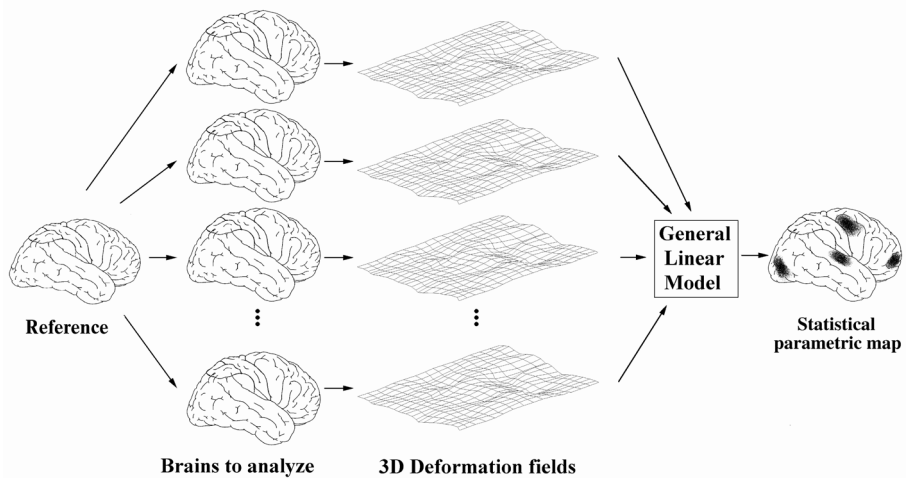
Figure 4.6:   *Schematic description of the deformation-based-morphometry method (source: Gaser et al. (1999) (courtesy to Christian Gaser))*

4.3.3   Brain atlases

As has been demonstrated there is considerable interindividual variability with respect to anatomical landmarks. There is also no perfect overlap between anatomical landmarks and cytoarchitectonic fields. Thus, one may reason as to whether stereotaxically normalised brain atlases are useful at all, i. e. when cortical activation originating from various brain imaging methods are presented within this normalised space. A promising solution for this problem is the development of so called probabilistic atlases. The basic principle underlying these atlases is to calculate the mean and the

variability of shape, extent, and location of a particular anatomical structure across a set of different brains (as many as possible). Based on these data it is now possible to calculate the probability of the occurrence of a specific anatomical landmark within the standard space. Meanwhile not only anatomical landmarks have been mapped in this way, but also cytoarchitectonic fields. Its usefulness has been demonstrated recently for the motor, somatosensory, visual, auditory cortex as well as for Broca's area. These maps can be used as an atlas to localise a specific area. For example, Rademacher et al. (2001) mapped the cytoarchitectonic area of the primary auditory cortex (PAC) into the "Talairach space". The area with an 80-100 % probability range for obtaining the PAC is a small area extending from the medial retroinsular region on Heschl's gyrus laterally. As expected the right PAC is located more superior and extends more anteriorly than the left PAC. Another interesting finding was, that the 80-100 % probability range for PAC extends for 10 to 8 mm from superior to the inferior position (z position right PAC: 14-4 mm, left PAC: 12-8 mm).
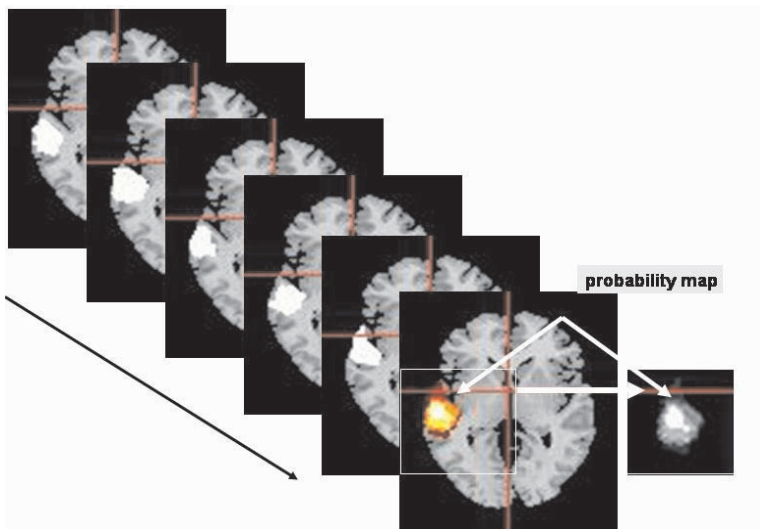
Five brain slices of different subjects on which the left primary auditory cortex is delineated are shown. The sixth slice shows the average location and distribution of the auditory cortex coded in hot colours. White indicates that all subjects have an auditory cortex while deep red indicates that only one subject has an auditory cortex at this position.

Figure 4.7:   An example of a probability map of the auditory cortex
                (source: Jäncke 2005)

A further new application is the 3D-visualisation of the brain for educational purposes. The aim is to develop a software tool allowing automatic identification, categorisation, and visualisation of specific brain areas of different brains. Thus, these tools need stereotaxic normalisation algorithms to transform brains precisely to a standard brain for which anatomical landmarks have been identified. After this normalisation students can navigate through individual brains in order to identify and visualise specific brain structures. A very powerful tool has been developed by Höhne et al. (2001), but simpler versions are also available either at the internet (e. g. the Harvard brain atlas; http://www.med.harvard.edu/AANLIB/home.html), or from various other authors (e. g. Nowinski et al. 2001).

4.3.4   Computational quantitative cytoarchitectony

A relatively new but nevertheless promising brain imaging approach has been introduced by the anatomist Karl Zilles and his co-workers. They analyse post mortem brains by generating histological sections of these brains which are then analysed by sophisticated computer software. In short, this method involves staining of the relevant slices allowing better contrast between cell bodies and neuropil[2]. These stained slices are then digitised, analysed by morphometry and multivariate statistical analysis. From these images grey value differences are obtained (grey level index: GLI) which allow the discrimination, delineation, and quantification of cytoarchitectonic boarders. This new technique allows the precise mapping of cytoarchitectonic uniqueness of individual brains. Thus, behavioural differences (like extraordinary language competence but also strong sociopathy) can now be related to cytoarchitectonics.

4.4   Future developments

The tremendous pace in the development of new approaches and tools to assess human neuroanatomy has opened new research fields. We now have the opportunity for in vivo morphometry in large samples thus offering

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2   Neuropil is the brain tissue that lies between the cell bodies. It is a fibrous network consisting of axons, dendrites and glial processes.

the power to detect significant between-group differences with enhanced objectivity, reliability, and spatial precision. First representative findings of these new approaches are the discovery of different brain forms in European and Japanese brains, gender differences in the relation between grey and white matter, differences in the spatial distribution of major sulci in schizophrenic patients, and the marked differences between dementia patients and normal controls. A very promising and current development is the so-called dynamic (4D) brain mapping approach allowing the mapping of dynamic changes in brain structure over a period of time. For this purpose, the brain of one subject is imaged repeatedly and analysed applying combined voxel-based, deformation-based, or tensor-based morphometry methods. A first application of this approach revealed an anterior-to-posterior wave of peak growth rates at the corpus callosum during the first 15 years of life. This approach offers the opportunity to track effects of therapeutic interventions in patients with tumour growth, active lesions, and traumatic brain injury. Beside this 4D brain mapping the development of anatomical probabilistic atlases will also be a main focus of future work. Probabilistic atlases will be developed for various anatomical structures and cytoarchitectonic fields in order to assist the anatomical localisation of haemodynamic responses obtained in fMRI and PET studies. Nevertheless, beside these new routes in the assessment of human neuroanatomy new tools have substantially improved classical morphometry during which specific brain areas of interest are traced and measured. In summary, cognitive neuroanatomy now has an exciting arsenal of tools helping to shed light on the complex structural and functional organisation of the human brain.

5   Overview of functional brain imaging methods

In the past decade functional techniques have been the dominant force in cognitive neuroscience, because they enable us to determine when and where neural activity in the brain is associated with the ability to perform a particular cognitive task. In addition, these techniques allow measuring how the brain is activated during emotional states. A further interesting topic to address by means of these techniques is to study how the brain of neuro-logical or psychiatric patients operate during cognitive or emotional tasks. In this context, it is standard procedure to design several task variants that differ only slightly in terms of task requirements. On the basis of this approach, differences in brain activation between the task variants enable us to isolate brain structures that are involved in hypothesised cognitive processes.

Basically, three different experimental approaches are used to study brain activation in the context of cognitive processes (chapter 5.1):

- subtraction designs,
- parametric designs, and
- functional coupling.

A variety of non-invasive functional brain imaging techniques is available for use in humans. These techniques fall into two main classes. The first ensemble consists of methods which directly measure electrical activity associated with neuronal firing, such as electroencephalography (EEG) and magnetoencephalography (MEG) (chapter 5.2). The second group consists of methods which indirectly measure neuronal activity (chapters 5.3 and 5.4). This approach is based on the principle that neural activity is accompanied by increased local blood flow and metabolic activity. These methods include positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and near-infrared spectroscopy (NIRS). More information on each of these methods is provided below.

5.1   Basic principles of functional imaging designs

5.1.1   Subtraction designs

The study of human cognition using modern brain imaging methods was aided greatly by the involvement of cognitive psychologists in the 1980s whose experimental designs for dissecting human behaviours and cognition fitted well with the demands placed on functional brain imaging. As a result of this collaboration among neuroscientists, imaging scientists, and cognitive psychologists, the subtraction logic for the functional mapping of neuronal activity had been established. This strategy was based on a concept introduced by the Dutch physiologist Donders (1868) who studied human cognition using clever reaction time experiments. The basic idea based on the understanding that subtracting the reaction time obtained for the more complex task (comprising the additional psychological function) with the reaction time of the less complicated psychological function would yield the extra processing time needed for the additional function. For example, Donders subtracted the time required to respond to a light (say, by pressing a key) from the time needed to respond to a particular colour of light. He found that discriminating colour required about 50 milliseconds. For the first time, Donders isolated and measured a mental process by subtracting a control state (i. e. responding to a light) from a task state (i. e. discriminating the colour of the light). Exactly this procedure is successfully applied in the context of functional imaging studies where functional brain images obtained during a task are subtracted by functional brain images obtained by a rest condition. The difference image is supposed to uncover only the measured neural activation which is due to the additional psychological processes compared to the control task. This kind of research has first been used in the context of PET studies. Meanwhile most brain imaging studies have used this approach so far.

However, some problems are associated with this strategy. Firstly, by calculating subtraction images one mostly obtains images with relatively small additional activations. Let us imagine that a particular psychological process involved functions A and B while an additional psychological process would require A, B and C. Furthermore, let us hypothesise that each psychological function is controlled by different neural assemblies. Thus, the difference image would show only one activation spot for the neural assembly that is involved in processing psychological function C. Typically,

one might argue that the identified brain area is specialised for this particular function. However, this might be misleading because it is not brain area C which is important for the second psychological function but rather the network or connection between areas A, B and C. Another problem for subtraction designs is to decide how to threshold a statistical parametric map to consider a difference significant.
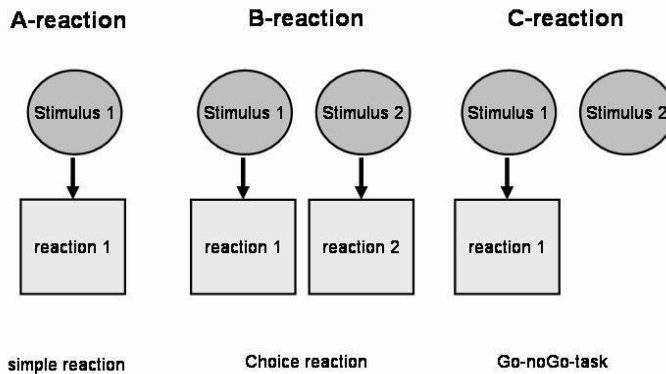
Demonstrated are three different types of reactions evoked by three different stimulus settings. A-reactions are reactions in the context of one stimulus according to which the subject has to react. B-reactions are defined by two different stimuli requiring two different reactions. Thus, a kind of choice is necessary and selection of motor programs is necessary while A-reactions did not make use of choices. The so-called C-reaction is defined by one stimulus requiring a particular reaction while stimulus 2 does not require any action. Thus, inhibition and selection are the operating psychological functions. By appropriate subtraction of reaction times obtained in reaction time experiments employing these types of reactions, it is possible to disentangle the duration of different psychological processes (initiation of motor responses, selection of motor responses and inhibition of motor responses). The subtraction logic is used for the analysis of many brain imaging experiments.

Figure 5.1:   *Principle of the Donder's subtraction logic used for cognitive experiments (source: Jäncke 2005)*

5.1.2   Parametric designs

For example, if one wanted to identify brain regions involved in controlling finger movements of different speed (referred to as tapping rate), one might

parametrically vary the number of finger taps that subjects needed to per-
form within a specific time period and then identify brain regions in which
the level of activation varied according to the tapping rate (rate effects). A
classical finding is that the activation in the primary motor cortex is strongly
correlated with tapping rate indicating that the imperative neurophysiologi-
cal adjustments to control faster finger movements are realised in the pri-
mary motor cortex. Similarly, rate effects are found in the visual and audi-
tory cortex in the context of different presentation rates of visual and audi-
tory stimuli. An example is given in figure 5.2. Although parametric variation
is supposedly the most powerful functional brain imaging manipulation, only
a fraction of brain imaging studies have used this powerful design.
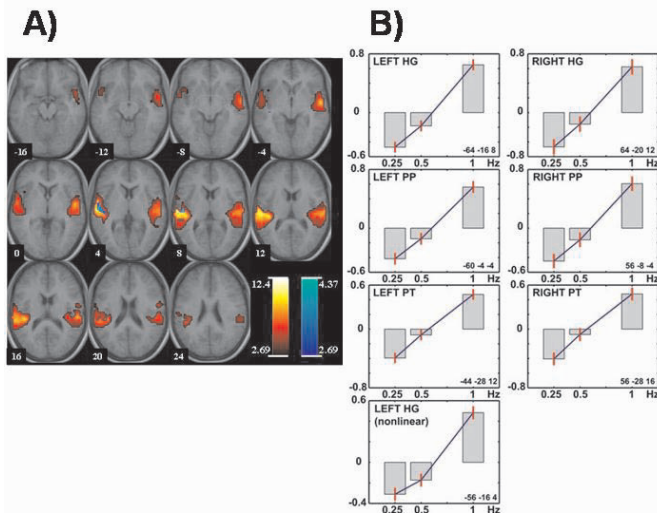
The different presentation rates (0.25, 0.5, and 1 Hz) with which the auditory stimuli
are presented are correlated with the BOLD response in the auditory cortex. A)
Demonstrates the correlation in colour coded values (r scores transformed into z
scores). B) Shows the BOLD response (ordinate) in relation to the presentation
rate (abscissa).

Figure 5.2:   An auditory rate effect analysed in the context of a parame-
               tric analysis (source: Noesselt et al. 2003)

5.1.3   Functional connectivity
A relatively new approach is to study whether distributed brain regions
show correlated activity. Thus, the researchers are seeking correlated acti-
vations on the basis of individual data or on the basis of group analysis,

respectively. This relatively new approach has attracted much interest be-
cause many eminent researchers hypothesise that the human brain
operates like a coupled oscillator and many higher cognitions should be
due to a kind of "binding" (synchronised coupling) between different neural
modules. A combination between the aforementioned parametric design
and the functional connectivity approach is to use individual performance
data and to calculate the correlation between these performance measures
and the functional activation of distributed brain areas. This approach re-
veals the distributed activation within the brain which is correlated with the
performance variance.
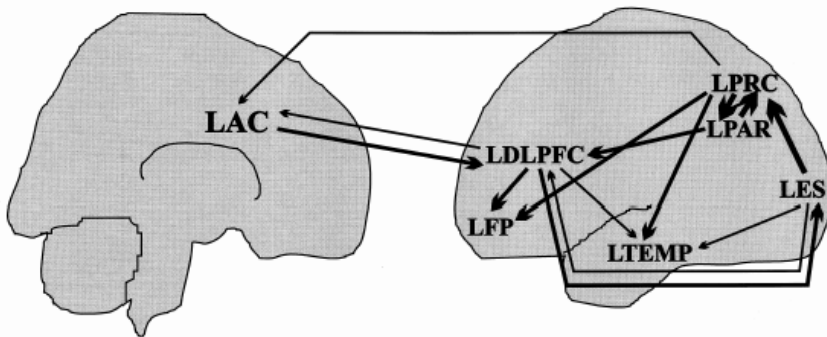
The arrows indicate functional coupling between different brain areas during work-
ing memory tasks (adapted from Krause et al. 2000).

Figure 5.3:   *Schematic description of a functional connectivity model ob-*
                 tained from PET data in the context of a series of working
                 memory studies

5.1.4   Genetic brain imaging

Traditionally, the impact of genetic polymorphisms on human behaviour has
been examined using indirect methods such as psychological question-
naires and neuropsychological test batteries. Some of these studies have
reported significant associations between specific genetic polymorphisms
and behaviours. However, the collective results have been weak and in-
consistent. This is not surprising given the fact that most behavioural
probes and neuropsychological tests allow for the use of alternative task
strategies by different individuals that may obscure potential gene effects
on the underlying neural substrates meant to be engaged by the tests.

To overcome the obstacles of relating behavioural or psychological measures with genetic polymorphisms several researchers propose to relate genetic polymorphisms to specific brain functions (for a recent review see Hariri, Weinberger 2003). The brain functions typically are those which are known to be essentially involved in controlling cognitive or emotional processes. The idea is that functional genetic polymorphisms may have a more robust impact on the level of the brain than on the level of behaviour. Thus, functional polymorphisms in genes weakly related to behaviours and, in an extended fashion, psychiatric syndromes may be strongly related to the function of neural systems involved in processing cognitive and emotional information in brain. This is the underlying assumption of imaging genomics. The potential for marked differences at the neurobiological level in the absence of significant differences in behavioural measures underscores the need for a direct assay of brain function. Accordingly, imaging genomics provides a unique opportunity to explore and evaluate the functional impact of brain-relevant genetic polymorphisms potentially more incisively and with greater sensitivity than existing behavioural assays. Typical examples of imaging genomics are given below:

1) Apolipoprotein E and memory systems,
2) Catechol-o-methyltransferase and the prefrontal cortex,
3) 5-HTT and the amygdale.

A common allelic variant of the apolipoprotein E (APOE) gene has been associated with late-onset familial Alzheimer's disease. Specifically, the APOE Epsilon 4 allele has a dose-dependent effect on risk and age of onset for this disease. A typical approach in this context is to identify subjects carrying this allele without exhibiting classical Alzheimer symptoms and to require them to conduct various memory experiments while PET- or fMRI-measurements of the brain are performed. By relating the memory performance and the group membership to the pattern of cortical activations one can asses the influence of genetic predisposition on the neural networks involved in memory processes. Several studies of this type have been conducted so far showing that subjects carrying this allele indeed expose different cortical networks during different memory processes. Most interesting are those results showing different cortical activations for the same task in subjects carrying the allele or not but who show similar behavioural measures. Thus, at the time of testing their memory performance is similar although the brain activations are strikingly different.

It is known that the prefrontal cortex which houses many important executive functions (e. g. working memory) is strongly regulated by dopaminergic pathways. However, dopamine itself is strongly influenced by catechol-o-methyltransferase (COMT) enzymatic activity. Therefore, it has been reasoned that genetically driven alterations in COMT enzymatic activity and subsequent synaptic prefrontal dopamine concentrations may lead to diminished prefrontal functions. In fact it has been shown that the load of the high-activity val allele consistently predicted a relatively exaggerated prefrontal response during the working memory task either in correlational or group studies. Since Schizophrenia is strongly related to deficiencies in executive functions as well as to deficiencies within the dopaminergic system, it is assumed that the above mentioned approach will be helpful in elucidating the origins of Schizophrenia.

Abnormal levels of anxiety, fear, or social phobias have been related to a dysfunctional amygdale. It has been reasoned that the dysfunctional amygdale might be related to genetically driven alterations of both 5-HTT (serotonin) transcription and 5-HTT uptake. In fact recent functional imaging studies support the idea that subjects carrying the less efficient "s allele" of the 5-HTT promoter gene had an increased amygdala response to fearful stimuli in comparison to subjects homozygous for the "l allele". This finding made researchers to suggest that the increased anxiety and fear associated with individuals possessing the "s allele" may reflect the hyperresponsiveness of their amygdale to relevant environmental stimuli.

The examples given above clearly demonstrate that genetic polymorphisms have substantial influence on brain activation patterns during different cognitive tasks. Thus, the new research branch of *functional genomics* (or *genetic brain imaging*) is a promising approach not only to study brain-behaviour relationships but also to study the genetic influences on brain functions.

5.2   Magnetoencephalography (MEG) and electroencephalography (EEG)

Electroencephalography is the oldest functional brain imaging technique, dating back to Berger's discovery in 1929 that brain electrical activity could

be recorded from electrodes placed on the scalp. This technique is still widely used today, because of its potential to provide real-time measurements of brain activity. EEG records transient electrical dipoles generated by the net flow of electrical current across the cellular membrane during neuronal depolarisation associated with postsynaptic potentials. Global EEG is used to measure neural activity during different brain states, such as sleeping and waking. A more powerful tool for cognitive neuroscience than global EEG measurements consists of event-related potentials (ERPs), which are derived from spontaneous EEG activity averaged over a series of instances (or trials) triggered by the same event (such as the presentation of a visual stimulus). In addition, event-related desynchronisation (ERD) is widely used which means the recording of alpha-power decrease during a particular cognitive task compared to a rest condition. Whereas EEG records the electrical activity associated with neuronal depolarisation, the more recent technique of MEG records the magnetic field produced by this electrical activity.

Although EEG and MEG rely on the same primary (or intracellular source) currents flowing simultaneously in the same direction (dipoles), they differ with respect to the secondary signals (volume currents and magnetic flux). The source currents give rise to a secondary extracellular current (*volume current*) propagating outside the nerve cell throughout the brain volume. This secondary volume is irregular because it follows lines of least electrical resistance as they spread away from the source. Thus, as the volume current spreads it encounters various tissues with different resistances resulting in distortions of the volume current. When this current arrives at the head surface it is distorted and modified to a more or less unknown extent. Thus, the shape and voltage distribution of these secondary currents recorded by EEG electrodes only imperfectly mirrors the primary (dipole) source from which it arises. There are many researchers who believe that functional images constructed from such EEG signals may not be of high anatomical fidelity. With MEG, however, one records the surface distribution of the second type of signals arising from the primary dipole source which is the *magnetic flux* or the *magnetic field*. The major disadvantage of MEG is that the magnetic field measured at the head is only due to one of the three components that constitute the source activity, namely the dendritic current. Synaptic and axon terminal current do not contribute to the magnetic fields.

On the left a 78 electrode EEG montage is shown. On the right the montage is shown in the context of studying children. The electrodes are placed on the skull.

Figure 5.4:   Electroencephalography (EEG) (source: Jäncke 2005)

On the left is a typical head MEG while on the right a newly designed fetal MEG (fMEG) is shown. The fetal MEG is used to non-invasively measure magnetic signals from the fetus after auditory stimulation.

Figure 5.5:   Schematic description of current MEG machines (source: Jäncke 2005)

A further difference between EEG and MEG is that EEG records electrical activity oriented perpendicular to the surface of the brain, whereas MEG

records activity oriented parallel to the surface of the brain. Thus, EEG measures the activity of pyramidal cells in cortical gyri and the depths of the sulci, whereas MEG is sensitive primarily to the activity of pyramidal cells in the superficial parts of the sulci, and is therefore more limited in its scope. A most recent development is the fetal MEG (fMEG) allowing to measure MEG responses of the fetus to auditory stimuli. Although this technique is a demanding endeavour, recent publications have evidenced that this approach does work. Thus, this technique will stimulate many new research questions in the context of developmental neuroscience and prenatal medicine.

The major achilles-heel of both EEG and MEG is known as the "inverse problem," which is the challenge of identifying the source of the underlying signal. This source can be a great distance from the point on the scalp at which it is measured, and is affected by factors such as head shape and dipole location and orientation. Thus, it is necessary to develop source localisation algorithms to determine the likely source of a signal.

However, tremendous advances have been made to solve the "inverse problem" using sophisticated mathematical methods. The main principle to solve this problem is to simplify assumptions about the physics of the brain and head tissue, as well as the electrical nature of the active neurons. A critical issue is the assumption that the intracerebral sources of activation can be modelled as electrical dipoles conducting with one positive end and one negative end. Calculation and estimation of the location of these dipoles is principally straightforward. In a first step one estimates the location of a particular dipole and then calculates the estimated scalp distribution from this particular dipole. The estimated and actually measured scalp distribution is statistically compared. If both distributions are similar, one may take the estimated dipole as a good estimator for the measured electrical scalp distribution. In many cases it is necessary to use more than one dipole to obtain a good match.

Currently, several researchers are trying to improve the match between estimated and actual electrical scalp distribution by using individual brain images taken from MRI scans in order to calculate the electrical scalp distribution more precisely. Many variants of this dipole localisation method are used revealing fairly good anatomical localisations (Michel et al. 2001; Michel et al. 2004; Pascual-Marqui et al. 2002).

The advantage of EEG and MEG is the unprecedented time resolution (in the range of 1 millisecond). However, the spatial resolution is not as good as for MRI although the most recent methods to solve the "inverse problem" have revealed extremely good localisations especially in the context of cognitive experiments. Thus, EEG is very cheap, relatively easy to use and, thus, is an attractive alternative to fMRI or PET for cognitive neuroscientists. MEG is more or less of marginal relevance because an MEG machine is roughly as expensive as an fMRI scanner and similarly expensive to keep it maintained. Thus, many current neurophysiologists believe that the MEG-technique is not advantageous compared to EEG. These and more content-related arguments have proceeded the distribution of EEG in cognitive neuroscience. The EEG is one of the most influential neuroscience methods available.
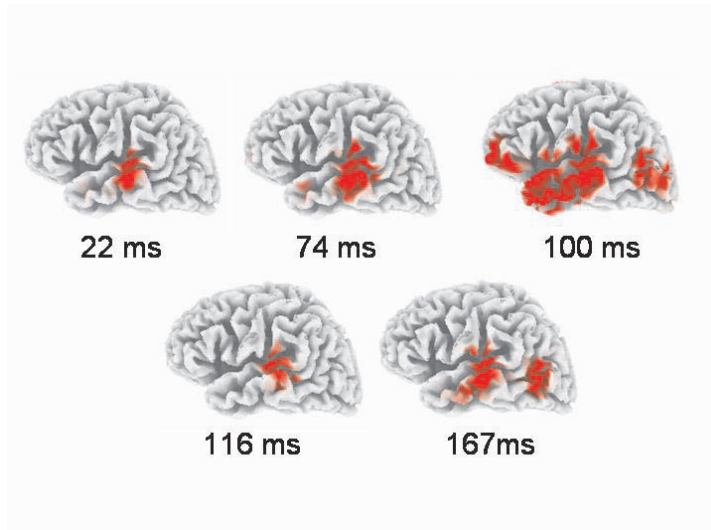
As apparent from the figures cortical activations start approximately at 22 milliseconds after stimulus onset and spreads from the primary auditory cortex to frontal, parietal and occipital regions. This figure demonstrates the superiority of EEG in the context of LORETA in showing the dynamics of cortical activation on a millisecond range (data are taken from an unpublished experiment of the Zurich neuropsychology lab).

Figure 5.6:   Time course of intracerebral electrical activations after presenting an emotionally laden auditory stimulus

5.3   Positron emission tomography (PET) and single photon emission computed tomography (SPECT)

Neurons utilise a variety of organic molecules and compounds in order to receive and transmit messages. These molecules and compounds are either brought to the cells by the blood or are manufactured by the cells from raw material supplied by the blood. PET images capture the distribution of particular organic molecules and compounds throughout the brain reflecting local variations in either metabolic or blood flow rates. To tag these molecules and compounds specific *probes* or *tracers* are necessary. These probes are positron emitting *isotopes* which are manufactured in specific machines called *cyclotrons* by bombarding atoms of stable chemical elements with protons. As a result of this bombardment, atoms emerge with more positive charge in their nuclei that can be balanced by the negative charge of their orbiting electrons. These new atoms – called *isotopes* – are unstable and, over a period of time, shed their excess positive charge in the form of discrete positron emissions. The PET signal is generated when a positron breaks off from its unstable isotope and collides with electrons. A by-product of this collision is the generation of two gamma rays or photons moving into opposite directions. This process is called *annihilation.* On the basis of these photons moving into opposite directions the PET scanner measures this gamma ray and calculates their source.

The most commonly used isotopes are Oxygen-15 (^{15}O), Carbon-11 (^{11}C), Nitrogen-13 (^{13}N), or Fluorine-18 (^{18}F). These isotopes are combined with other chemical elements like water, 2-Fluoro-2-deoxy-8-glucose, or 6-Fluoro-DOPA and many others. For PET scanning these probes are injected into a vein. The tracer enters the brain after about 30 seconds and in the following 30 seconds radiation in the brain rises to its maximal value. A picture of the regional cerebral blood flow (rCBF) is taken during this time frame.

Using PET and ^{15}O labelled water, scientists can locate the regions that become active while a person speaks, listens to music, or performs other activities. By comparing these images to those taken before or after a task, they are gaining many new insights about brain organisation (see above: subtraction designs). PET also helps reveal how drugs and certain disor-

ders, such as depression and Parkinson's disease affect the brain. The results are usually reported in terms of a change in regional cerebral blood flow between different experimental conditions. Currently, PET scanners are capable of resolving metabolic activity to regions that are approximately 4-6 mm^3 in volume. While this size includes thousands of neurons, it is sufficient to identify cortical and subcortical areas and even show variation within a given cortical area.

PET can also be used to map receptors (receptor imaging and receptor mapping). The human brain is highly complex and for normal function relies on the interaction of over 100 neurotransmitters with 300 receptors. When used with appropriate radioligands, PET can reveal the distribution of neuroreceptors in living human brain, and their interactions with neurotransmitters or administered drugs. For example, using radiopharmaceutical compounds that bind to dopamine or serotonin receptors (C-11 or F-18 N-methylspiperone), opiate receptors (C-11 carfentanil), PET is likely to continue to be important for understanding the role of various neurotransmitters in cognition and emotion.

A variety of other imaging techniques are now available. One of the most popular is single photon emission computed tomography (SPECT), which is similar to PET but detects a different type of photon. SPECT provides lower resolution but is much less expensive than PET.

Meanwhile, fMRI is used for most cognitive studies because to our best knowledge fMRI does not cause any harms to the subjects and it is cheaper than PET. In addition more and more ethics committees do not permit cognitive PET studies in female subjects because of potential negative influences on fertility. Another problematic aspect of PET is that one is confined to conduct group studies because one can only acquire a few PET images per subject. Thus, one has to concatenate PET images of several subjects in order to calculate meaningful summary statistics.

5.4   Functional magnetic resonance imaging (fMRI)

Magnetic Resonance Imaging (MRI) of the brain is well-recognised for its excellent spatial resolution, allowing neuroanatomic structures to be viewed

and analysed in detail. In the early 90s, it has become possible to modify a conventional MRI scanner to study the brain's function as well. This new technology, called functional Magnetic Resonance Imaging (fMRI), has attracted much attention by brain researchers and is definitively the most important driving force of current cognitive neurosciences. The most commonly used fMRI technique called BOLD-fMRI (Blood-Oxygen-Level-Dependent fMRI) potentially offers imaging with a temporal resolution on the order of 100 milliseconds and a spatial resolution of 1-2 milli-metres, which is much better than that of PET and SPECT scanning. This new brain imaging technique offers several main advantages compared to other brain imaging methods. For a summary of these points see Turner, Jones 2003:

- Transient cognitive events can potentially be imaged and small struc-tures like the amygdale and other basal ganglia structures can be more precisely resolved.
- Unlike PET and SPECT, most fMRI techniques are non-invasive and do not involve the injection of radioactive materials so that a person can be imaged repeatedly. This may allow imaging of a volunteer repeatedly during different states (e. g. imaging a bipolar patient through manic, de-pressive, and euthymic states), developmental changes (cognitive stages of development), or during learning.
- It also allows for investigations in healthy children due to the low risk of fMRI.
- With fMRI, one can easily make statistical statements in comparing dif-ferent mental and cognitive states within an individual in a single session whereas PET and SPECT scans usually rely on making statistical statements about group differences between cognitive and mental states.

Thus, fMRI may be of important use in understanding how an individual's brain functions. It is, in fact, already starting to being used in presurgical planning to map functions like language, motor function, and memory. The basic principles underlying all types of MRI have been discussed in a previ-ous section on structural imaging. In this chapter we will discuss the four main types of functional MRI:

- BOLD-fMRI which measures regional differences in oxygenated blood
- Perfusion fMRI which measures regional cerebral blood flow

- Diffusion-weighted fMRI which measures random movement of water molecules
- MRI spectroscopy which can measure certain cerebral metabolites non-invasively

5.4.1   Blood-Oxygen-Level-Dependent fMRI (BOLD-fMRI)

BOLD-fMRI is currently the most common fMRI technique. Here, the MRI scanner is tuned to resonate and image hydrogen atoms as in conventional MRI. However, T2*-weighted images are collected which take advantage of the fact that deoxygenated haemoglobin is magnetic whereas oxygenated haemoglobin is not. Due to the magnetic properties of the magnetic deoxy-haemoglobin molecule which causes rapid dephasing, T2* signal is retained longer in a region when it has more oxygenated blood compared to when there is less oxygenated blood. Thus, an area with more oxygenated blood will light up more intensely on T2*-weighted images compared to when there is a weaker local concentration of oxygenated blood.

By means of this technique, it is assumed that an area is relatively more active when it has more oxygenated blood compared to another point in time. This is based on the principle that when a particular brain region is being used, arterial oxygenated blood will redistribute and flow to this area. This principle has one caveat: there is a time lag of 3-8 seconds from the onset of regional activation to the inflow of fresh oxygen supply. During this time lag of 3-8 seconds, in fact, the activated areas experience a relative decrease in oxygenated blood as oxygen is extracted by the active regional neurons. Afterwards, the amount of blood flowing to the area far outweighs the amount of oxygen that is extracted so that the amount of oxygenated blood is now super proportional. Although images can be acquired every 100 milliseconds with echoplanar imaging (EPI; a rapid acquisition technique), the delayed onset of the BOLD response limits the immediate temporal resolution to several seconds instead of the 100 milliseconds potential. In the future, researchers may be able to improve the temporal resolution of fMRI by measuring the initial decrease in oxygenated blood with activation (the "initial dip"). However, as long as MR scanners with relatively low magnetic strength are being used, this "initial dip" is difficult to detect.
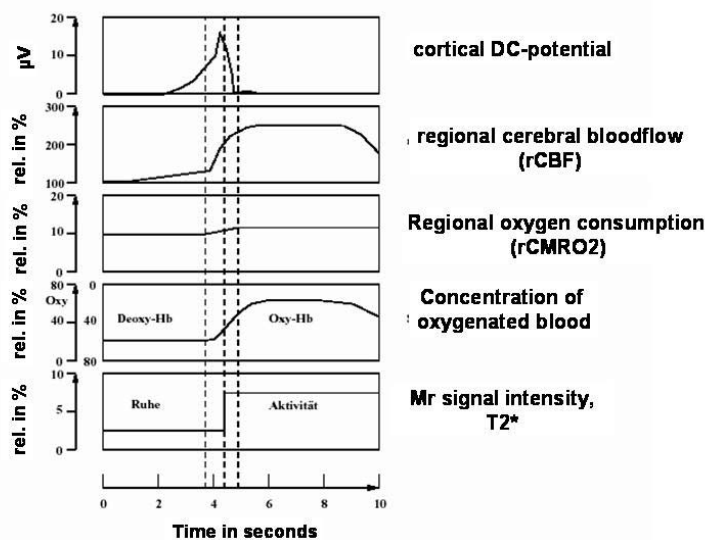
Figure 5.7:   *Schematic description of the different neurophysiological processes in the context of fMRI measurement (source: Jäncke 2005)*
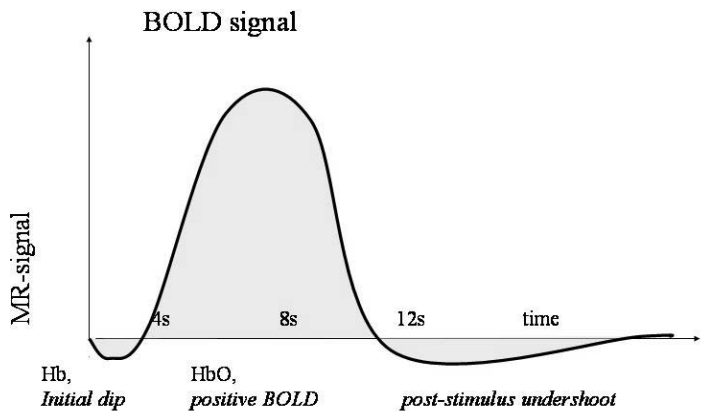
The "initial dip" reflects the increase of deoxygenated blood (HB). HB is paramagnetic and causes signal loss. During the following phase more oxygenated blood is available (oxygen overshoot) decreasing the relative concentration of HB and, thus, increases the MR signal.

Figure 5.8:   *Schematic description of the time course of the BOLD signal (source: Jäncke 2005)*

BOLD-fMRI is a relative complex technique in that it must compare images taken during one cognitive state to another to create a meaningful picture. As images are acquired very rapidly (e. g. a set of 15 coronal brain slices every 3 seconds is common standard in most labs), one can acquire sufficient images to measure the relative differences between two states to perform a statistical analysis within a single individual. Ideally, these states differ in only one aspect so that everything is controlled except the behaviour under investigation.

Traditional BOLD-fMRI paradigms generally include several periods of rest alternating with several periods of activation (so called box-car designs). Images could then be compared throughout the entire activation to the rest periods. Images obtained throughout the first 3 to 6 seconds of each period are generally discarded due to the delay in haemodynamic response. Alternating paradigms are used because the signal intensity generated by the MRI scanner drifts with time.

BOLD-fMRI is an optimal technology to study processes that can be rapidly turned on and off like language, vision, movement, hearing, and memory. The study of emotion is hampered by its slow and variable onset and its inability to be quickly reversed. Some have, however, succeeded in using this technique to study emotional processes.

Problems with BOLD-fMRI

BOLD-fMRI is very sensitive to movement so that tasks are limited to those which do not go along with strong head movements. Thus, speaking is difficult to examine in the context of fMRI. BOLD-fMRI is also limited in that artefacts are often present in brain regions that are close to air (i. e. sinuses, around the eye holes or at the ventricles). Thus, there are some problems in observing important emotional regions at the base of the brain like the orbitofrontal and medial temporal cortices. Another problem is that sometimes observed areas of activation may be located adjacent to large draining veins rather than directly at a capillary bed near the site of neuronal activation.

The main problem however is that it is not entirely clear what kind of neurophysiological process is really reflected by the BOLD response. As men-

tioned above there is a relation between the fMRI-BOLD signal and the amount of haemoglobin supplied to a sample tissue. However, though this relation holds, its precise underpinnings are not known yet. Recently, it has been argued on the basis of fMRI measurements combined with simultaneously collected single-cell recordings in the visual cortex of monkeys that the BOLD-signal most strongly correlates with the local field potential (LFP) (Logothetis 2002). This was the only electrophysiological signal with which the BOLD-signal correlated (although not strongly). Interestingly, there was no correlation between the BOLD signal single-unit as well as multi-unit spiking. This observations in alliance with similar studies let us assume that the BOLD signal reflects intracortical processing like synaptic activity and processing of input signals possibly in layer IV of the visual cortex. Recently, it has also been shown that the BOLD signal in the visual cortex depends on the number of activated neurons or processing columns. With increasing number of processing modules (neural assemblies or columns) the BOLD-signal decreases (Marcar, Lonneker 2004). Thus, there is more opaque relationship between the strength and spatial extent of the BOLD-signal with the neurophysiological underpinnings as anticipated in the beginnings of fMRI.

5.4.2   Perfusion fMRI

Two fMRI methods have been developed for measuring cerebral blood flow. The first method, called intravenous bolus tracking, relies on the intravenous (iv) injection of a magnetic compound such as a gadolinium-containing contrast agent and measuring its T2*-weighted signal as it perfuses through the brain for a short period of time. Areas perfused with the magnetic compound show less signal intensity as the compound creates a magnetic inhomogeneity that decreases the T2* signal. The magnetic compound may be injected once during the control and once during the activation task and relative differences in blood flow between the two states may be used to develop a perfusion image; alternatively, one can measure changes in blood flow over time after a single injection to generate a perfusion map. Belliveau et al. (1991) used the technique to create the first functional magnetic resonance maps of human task activation using a visual stimulation paradigm. They imaged the occipital lobe after injecting gadolinium-DTPA once during darkness and again during presentation of a flashing light to map the visual response.

Although gadolinium-based contrasts are not radioactive, the number of boluses that can be given to an individual is limited by the potential for kidney toxicity with repeated tracer administration. This technique also only generates a map of relative cerebral blood flow, not absolute flow as in the next technique. Arterial spin labelling is a T1-weighted non-invasive technique where intrinsic hydrogen atoms in arterial water outside of the slice of interest are magnetically tagged ("flipped") as they diffuse through the blood and are then imaged as they enter the slice of interest.

Arterial spin-labelling is non-invasive, does not involve an intravenous bolus injection, and can, thus, be repeatedly performed in individual subjects. Also, absolute regional blood flow can be quantified which cannot be easily measured with SPECT or BOLD-fMRI and requires an arterial line with PET. Absolute blood flow information may be important in imaging such processes as anxiety which may be hard to turn on and off. For instance, in social phobics, a relaxation task may be imaged on one day and anticipating making a speech may be imaged on the next day. Comparing these separate tasks in different imaging sessions is not possible with BOLD-fMRI. While there is currently no clinical indication for this technique, it may soon be used clinically to help characterise the different stages of acute ischemic stroke. However, this technique might be an interesting alternative to BOLD-fMRI to study emotional processes.

It should be mentioned that arterial spin-labelling also has some limitations in that it takes several minutes to acquire information on a single slice of interest. Therefore, one must have a specific brain region that one is interested in. Also, as it currently takes several minutes to acquire a single slice, it would be tedious obtaining enough images on this slice within a single session to make a statistical statement on a given subject. Thus, this approach does not appear to be a useful mapping technique within individuals unless scanner acquisition time is shortened.

5.4.3   Diffusion-Weighted Imaging

Diffusion-weighted imaging (DWI) is very sensitive to the random movement of ^{1}H in water molecules (*brownian movement*) (for a summary see DaSilva et al. 2003; Sundgren et al. 2004). The amount of water diffusion for a given pixel can be calculated and is called the apparent diffusion coef-

ficient (ADC). Areas with low ADC values (e. g. low diffusion) appear more intense. ADC values are direction sensitive. For instance, if images are taken perpendicular to myelin fibre tracts like the optic chiasm, arcuate fasciculus, or corpus callosum, ADC values will be lower than if the images are taken along the length of these fibres as there is probably little diffusion across myelin sheaths. Thus, ADC direction sensitivity permits detection of myelination and may allow researchers to understand in greater detail myelin development in infants. On the other hand, this direction sensitivity hampers the study of diffusion in other processes as ADC values differ, depending on the imaging plane (axial, coronal, or sagittal). There are now ways to calculate average ADC values incorporating all planes for each pixel, removing "artefacts" due to the direction of acquisition. Removing the directional diffusion sensitivity has been helpful in studying stroke.

Diffusion tensor imaging (DTI) is the more sophisticated form of DWI, which allows for the determination of directionality as well as the magnitude of water diffusion. This kind of imaging can estimate damage to nerve fibres that connect the area of the brain affected by the stroke to brain regions that are distant from it, and can be used to determine the effectiveness of stroke prevention medications. DTI can map subtle changes in the brain's white matter associated with diseases such as multiple sclerosis and epilepsy, as well as assessing diseases where the brain's wiring is abnormal, such as schizophrenia. The development of new imaging methods and some useful analysis techniques, such as 3-dimensional anisotropy contrast (3DAC) and spatial tracking of the diffusion tensor tractography (DTT), are currently under study.

While it is currently unclear to what extent diffusion-weighted imaging will be useful in studying psychiatric disorders, it holds great promise for changing the clinical treatment of acute ischemic stroke by potentially refining the criteria for patients most likely to benefit from thrombolytic therapy. A further important application of this method is to study the development of fibre tracts due to learning and functional plasticity.

In the early post-stroke period, ADC values are heterogeneous in the ischemic region and the presence of areas that have only mildly diminished ADC values may indicate salvageable tissue. In this way, diffusion-weighted imaging may help reveal the likelihood of whether thrombolytic

therapy may be useful. In addition, while ADC values continue to decrease over the first week post stroke; old strokes have ADC values that are normal or high. This allows distinction of old from new strokes which is often difficult to characterise with structural imaging and clinical tests exclusively when old and new strokes appear in the same brain region.

5.4.4   MRI Spectroscopy (MRS)

MRI spectroscopy (MRS) offers the capability of using MRI to non-invasively study tissue biochemistry. In the conventional and functional MRI techniques listed above, the hydrogen atom in water is the main one that is flipped (resonated). In MRS, either ^{1}H atoms in other molecules or other atoms such as ^{31}P, ^{23}Na, K, ^{19}F, or Li are flipped.

Within a given brain region called a voxel, information on these molecules is usually presented as a spectrograph with precession frequency on the x-axis revealing the identity of a compound and intensity on the y-axis which helps quantify the amount of a substance. The quantity of a substance is related to the area under its spectrographic peak; the larger the area, the more of a substance is present.

The reason why several molecules can be identified and quantified within a single scan is that the resonant magnetic pulse has a bandwidth over a narrow precession frequency range so that it can flip several molecules at once. The signal intensity at each of these precession frequencies can then be identified using a mathematical procedure called a Fourier-transform. For a given precession frequency (or spectrographic peak of a given molecule), information can also be presented spatially as metabolic maps which are created with similar principles to the 1H atom in water spatial maps in conventional MRI. The spatial resolution of these maps is generally less than that of conventional MRI as the substance concentration is much less than that of water. Consequently, the minimum area needed to obtain a detectable signal is larger.
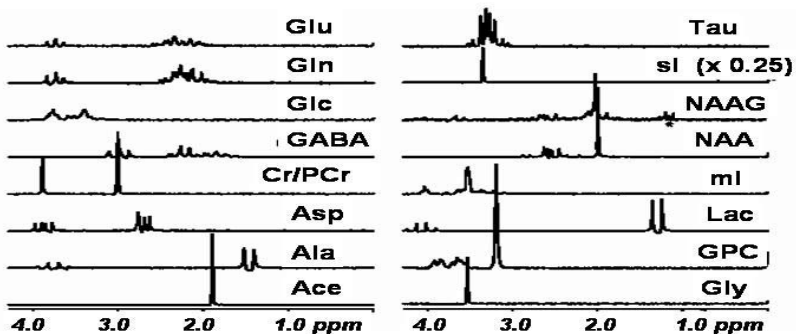
*Figure 5.9:   Typical spectral information of a particular brain area
(source: Jäncke 2005)*

The two most widely used MRS techniques involve either viewing ^{1}H atoms in molecules other than water or ^{31}P-containing molecules. In ^{1}H MRS, the water signal must first be suppressed as it is much greater than the signal from other [1]H-containing compounds and has overlapping spectroscopic peaks with these compounds. Compounds that can be resolved with ^{1}H-MRS include:

- N-acetylaspartate (NAA) which is assumed to be a neuronal marker that decreases in processes where neurons die;
- Lactate which is a product of anaerobic metabolism and may indicate hypoxia;
- Excitatory neurotransmitters glutamate and aspartate;
- Inhibitory neurotransmitter gamma-aminobutyric acid (GABA);
- Cytosolic choline which includes primarily mobile molecules involved in phospholipid membrane metabolism but also small amounts of the neurotransmitter acetylcholine and its precursor choline;
- Myoinositol which is important in phospholipid metabolism and intracellular second messenger systems; and
- Creatine molecules such as creatine and phosphocreatine which usually have relatively constant concentrations throughout the brain and are often used as relative reference molecules (i. e. one may see NAA concentration reported as the ratio NAA/creatine in the literature).

Phosphorus (^{31}P) MRS allows the quantification of ATP metabolism, intra-cellular pH, and phospholipid metabolism. ATP metabolism quantification is possible because ATP is involved in the following reactions:
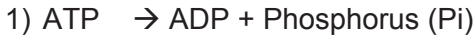
1) ATP $\rightarrow$ ADP + Phosphorus (Pi)
   where the relative concentrations of ATP and Pi can be determined with P MRS and
2) ADP + phosphocreatine $\rightarrow$ ATP + Creatine
   where the relative concentrations of phosphocreatine and ATP can also be determined with ^{31}P MRS.

pH can be measured because $H_2PO_4 \rightarrow H^+ + HPO_4^{-2}$, and the resonance frequency for H_2PO_4 is different from HPO_4^{-2}. As the shift between these two molecules is so rapid, they present as one spectrographic peak. However, when one of these compounds is present at its equilibrium, the peak is shifted closer to that compound's true precession frequency, allowing changes in pH to be measured by its position. Mobile phospholipids, including phosphomonoesters (PME – putative cell membrane building blocks) and phosphodiesters (PDE – putative cell membrane breakdown products) can also be measured, supplying information on phospholipid membrane metabolism.

MRS can be used to identify regional biochemical abnormalities. For example, ^{31}P-MRS studies of euthymic bipolar patients have revealed decreased frontal lobe PMEs (cell membrane building blocks) compared with healthy controls. However, when bipolar patients become either manic or depressed, their PMEs increase. These findings appear to be unrelated to medication treatment. The finding of decreased frontal PMEs in euthymic bipolars has also been demonstrated in schizophrenia and speculatively accounts for the finding of decreased frontal lobe metabolism in both of these disorders. The schizophrenia finding also appears to be medication-independent.

MRS may also be of future help in the differential diagnosis of certain psychiatric diseases such as dementia. In normal aging, there is a decrease in PMEs and increase in PDEs. In early Alzheimer's Dementia, there appears to be increased PMEs which may be help distinguish it from normal aging. Researchers have also found increased myoinositol and decreased NAA

levels in Alzheimer's Dementia compared with healthy controls. Some believe that a decrease in NAA coupled with an increased myoinositol level helps in differentiating probable Alzheimer's Dementia from healthy age-matched controls as well as other dementias (usually decreased NAA but normal myoinositol levels).

With MRS, changes in metabolic activity can be measured over time within an individual scanning session. MRS can also be used to measure changes in metabolic activity between sessions, such as before and after medication treatment. For psychiatry, MRS is presently a research tool. In neurology and neurosurgery, however, MRS is going to be used in the characterisation of tumour, stroke, and epileptogenic tissue and in presurgical planning.

Although MRS can be considered a promising tool and has the potential to partially replace PET, it is restricted to studying mobile magnetic compounds. As neurochemical receptors are not usually mobile, they cannot be measured by MRS. Thus, receptor-ligand studies are still the domain of SPECT and PET. Another problem associated with MRS is that due to the low concentrations of many of the imaged substances, larger areas penetrated with water are needed to obtain detectable signals. Larger volume units imaged over longer periods are thus used with this technique, limiting both temporal and spatial resolution compared with conventional MRI, and BOLD-fMRI. However, stronger magnetic fields which can spread out precession frequencies over a wider range may improve this resolution (e. g. a magnetic field twice as strong will double the difference between two substances' precession frequencies, thus increasing resolution). Stronger magnetic fields may also allow detection of compounds that are currently not detectable.

While there are currently no clinical indications for ordering any of these fMRI techniques, they hold considerable promise for unravelling the neurocircuitry and metabolic pathways of psychiatric disorders in the immediate future. Furthermore, they are assumed to be invaluable in psychiatric diagnosis and treatment planning. Their initial widespread clinical use will likely be in neurosurgical planning and perhaps, the treatment of acute stroke. As these techniques are generally non-invasive, can be performed on upgraded conventional MRI scanners, and are less expensive than acquiring a cyclotron to perform PET, they have a greater chance of becoming avail-

able in most hospitals over the next several years. Once fMRI techniques are optimised, they will likely offer considerable advantage towards PET and SPECT scanning in all aspects except receptor-ligand studies which cannot currently be performed by means of fMRI.

5.4.5   Near infrared spectroscopy (NIRS)

A relatively new technical development is the near infrared spectroscopy (NIRS) technique. This is a non-invasive technique that uses the differential absorption properties of haemoglobin and myoglobin to evaluate tissue oxygenation and can indirectly measure regional haemodynamics and blood flow (Gratton et al. 2003; for an overview see Gratton, Fabiani 2003). Near infrared light can penetrate through tissues and is differentially absorbed by oxygenated vs. deoxygenated forms of haemoglobin and myoglobin at particular wavelengths. Illumination of intact tissue with near infrared light allows qualitative assessment of changes in the tissue concentration of these molecules. However, this technique has some limitations.

First, the near infrared light penetrates only several centimetres into the living tissue (appr. 5 cm). Thus, deeper brain structures can not be measured by this technique. Another problem is related to the fact the tissue is not only absorbing near infrared light but also highly scattering the reflected or penetrating light. Scattering properties vary quite substantially between different types of tissue: At one extreme are blood and cerebrospinal fluid (which scatter light very little), and at the other extreme is white matter (which is very highly scattering). However, the currently commercially available devices can handle these problems with fairly good precision. Thus, this technique offers another non-invasive alternative to map cortical structures during different tasks. This technique is especially reliable and promising in the context of measuring brain activation in babies because it only takes a few minutes to setup the sensors and LEDs, but also because the baby's skull is thin and excellently penetrable by near infrared light.
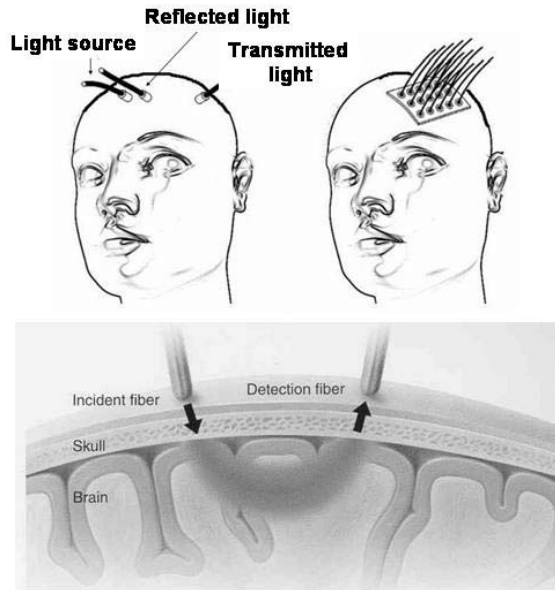
Near-infrared light is projected through the brain and the emitted light is measured at specific detector sites. This emitted signal can be used to measure the time course of haemoglobin and deoxyhaemoglobin.

Figure 5.10:   *Schematic description of the near-infrared technique used in the context of studies with humans*

5.5   Transcranial magnetic stimulation (TMS)

Whether transcranial magnetic stimulation (TMS) is a brain imaging method is not entirely clear. In principle TMS is a method used to stimulate brain tissue by applying strong magnetic fields to particular brain areas. By doing this the researcher is in the position to selectively inhibit or excite specific brain regions. Thus, TMS is a classical neurophysiological method. However, many brain imaging papers describe the combined use of TMS and a classical brain imaging method. The reason is that the brain activation maps obtained by means of fMRI do not reveal what these activation blobs really mean. Are they due to neurophysiological activation or deactivation? In order to answer this question one can simply influence the brain areas identified by means of fMRI by selectively inhibiting or exciting those using

standard TMS paradigms. Thus, TMS is becoming a necessary tool in the context of brain imaging.
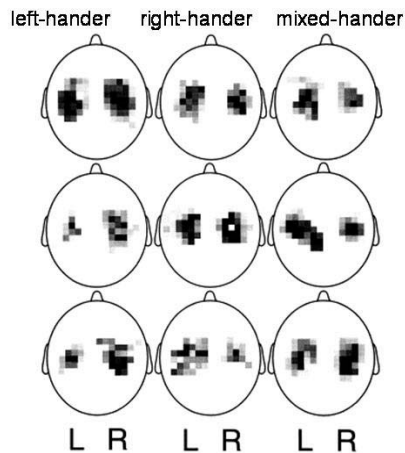
The grey-shaded areas demonstrate the cortical sites where TMS pulses evoked motor evoked potentials (MEPs) in a particular finger muscle. The darker the shading, the stronger the MEP amplitude. The figure is taken in a modified form from Triggs et al. 1999.

Figure 5.11:   Cranial mapping of sensitive areas at which Transcranial Magnetic Stimulation evoked MEPs at a particular finger muscle

However, what is also interesting in the context of brain imaging is the fact that TMS itself can be used as brain imaging method. Currently, at least two approaches describe this new application of TMS. First, TMS can be used to cortically map the hand motor area. By identifying the skull positions at which motor evoked potentials can be evoked, it is possible to "construct" the shape and size of the hand motor areas. In addition, one can map the visual cortex in order to map the precise positions where phosphenes (illusiory visual perceptions evoked by TMS pulses) can be evoked.

5.6   Other imaging methods

While the above mentioned brain imaging techniques are classically used to construct structural or functional images of the human brain, several new

methods have been designed for specific scientific purposes. For example brain imaging methods have been developed to image small animals, receptors, cells, molecules, or genes. In the following we will give a short description of some of these technical developments.

A relatively new development in this field is the micro-PET technology. This comprises a special PET scanner designed for high resolution imaging of small laboratory animals. It has been developed and built by a team of researchers at the Crump Institute for Biological Imaging, UCLA but another machine is located at the Research Centre Juelich in Germany. The aim was to build a compact and relatively low cost PET scanner with unprecedented spatial resolution that would be useful to researchers in a wide range of biomedical research applications.

A novel approach is the so-called biophotonic imaging technique. It uses a bioluminescent reporter gene to tag a target of interest – which can be a gene, a cell, or a microorganism – in a whole mouse. Because light passes through tissue, the labelled mouse can be anesthetised and photographed with a camera capable of detecting the bioluminescence. This method can be used to label bacteria, infect an organism, and study the effect of antibiotics on the infection, or the effects of various physiological conditions or drugs that can modify response to infection. In oncology, this approach can be used to label tumour cells and follow the effects of chemotherapeutic treatments on the cancer. One can do assays both in cell culture and in whole animals with a gene tagged with the same reporter, and one can follow changes in gene expression in real time both in cell culture and in whole animals.

With the a better understanding of biological processes at a molecular level coupled with the development of new biological reagents and probes, and recent developments and improvements in imaging technology, it is appropriate to focus attention on fusing these advances. More importantly, it is recognised that molecular and cell-based imaging can impact directly on cancer treatment and diagnosis, and that the development and testing of new molecular based therapies would benefit substantially from advances in our ability to image specific molecular and cell processes.

A very new technique for cell imaging is cryoelectron tomography. This is a technology for taking three-dimensional pictures of a cell. In 2002 it mas-

tered key technical obstacles, now providing insights into how the cell's machinery carries out some of the basic processes of life. "Cryoelectron tomography" works essentially like a doctor's CT scan; a computer constructs a 3-D image of a flash-frozen cell from a series of image "slices" created by penetrating electron beams. This technique has been ranked as one of the top 10 developments in 2002 by the internationally renowned Science journal. Related to that technique is electron tomography. Presently, it is possible to determine the 3-D structure of proteins in a biological specimen, e. g. a protein solution or a tissue section, using low-dose electron beam intensity and recordings from a large number of view angles in a transmission electron microscope (TEM). Refinement of modern software allows the 3-D reconstruction at around 2 nm resolution for proteins in buffer solutions and between 2-3 nm resolution for proteins in situ, e. g. in their membrane setting. Thus, individual protein molecules can be scrutinised in a specific buffer for their conformational flexibility or their tendency to deviate from a perhaps known x-ray crystallographic structure. The stoichiometry and flexibility of multicomponent structures can be analysed in buffer as well as in situ.

New imaging technologies like molecular imaging promise invaluable insight into the biological mechanisms underlying many disease processes, particularly challenging diseases characterised by slow progression. Key elements necessary for molecular imaging are: 1) highly specific imaging probes with high affinity for their targets and acceptable biological delivery, 2) identification of suitable targets, 3) appropriate amplification strategies, and 4) sensitive and fast imaging systems with high resolution. Molecular imaging scientists are challenged with "learning the language" of the basic molecular sciences. In addition, they must keep up with the vast amount of information generated in the maturing fields of molecular imaging and molecular biology. Molecular Imaging fuses the disciplines of molecular biology, genetic engineering, immunology, cytology, and biochemistry with imaging. Advances in MRI/MRS, MR microscopy, cellular tags, PET and SPECT are used to evaluate normal and abnormal tissue metabolism and perfusion in response to genetic, physiological, or therapeutic challenges.

Imaging molecules makes use of more sophisticated methods to increase spatial resolution down to the nanometer domain. Imaging of this spatial dimension is called nanoimaging. This is a sub cellular imaging of structure, function, properties and metabolism. Many researchers believe that this

technique has the potential to make enormous contributions to solving bio-medical problems. One of the technical features to do nanoimaging is the nanodetector. The nanodetector is an extreme ultraviolet (EUV) conversion microscope designed to use short wavelength light to obtain high resolution images. It is well known that one must use light with a wavelength at least as small as the imaged feature. The nanodetector uses EUV radiation with wavelengths between about 3 nm and 20 nm (60 eV and 400 eV) to probe structures with features as small as tens of nm. Typically, the microscope is configured to do transmission microscopy.

5.7   Future developments

While in the beginning of brain imaging the particular brain imaging method exclusively was used, currently more and more papers describe studies in which different brain imaging methods are combined. A popular approach is to combine the relatively slow but spatially precise methods fMRI and PET with EEG to exploit the excellent time resolution of EEG. While in former times (e. g. Heinze et al. 1994) these combinations required separate data collection inside and outside the scanner (to conduct the EEG measure-ment) it is now possible to simultaneously record EEG and fMRI signals. For this specific purpose EEG equipments have been developed allowing the combined measurements. The first experiments conducted so far have revealed very promising results with respect to both methodological and content-related reasons (for example Laufs et al. 2003). Similarly, TMS measurements are combined with PET and fMRI measurements to eluci-date the functional implications of the haemodynamic responses obtained by means of fMRI or PET.

However, the most evident trend in brain imaging is a transformation from the so-called low magnetic field strength of about 1 Tesla to high-field scanning. Meanwhile 3 and 4 Tesla machines are widely distributed. Some brain imaging centres even use 7 or 9 Tesla machines. The reason for this change is that high-field strengths promise enhanced spatial resolution and sensitivity for the MR signal.

6   Safety of brain imaging methods

6.1   Safety issues in MR imaging

Since the introduction of MRI as a clinical and research tool in the early 1980s, more than 100,000,000 diagnostic procedures (estimated) have been completed worldwide, with relatively few major incidents. Interestingly, safety concerns and discussions about potential hazards associated with magnetic resonance imaging systems and procedures have been very controversial over the past decade. The reasons for this controversy are manifold. Basically, there is a kind of polarisation of stakeholders ranging from those who emphasise the role of electromagnetic fields in carcino-genesis or the promotion of abnormalities in growth and development to those who argue that MRI is an inherently safe procedure. It might be that the latter argument has reduced the importance of the publication of nega-tive results. Moreover, epidemiological studies on possible health effects are still patchy, and the definition of safety thresholds, levels of exposure to magnetic fields during MR examinations as well as dosimetric concepts and personal protective equipment are still under development.

In fact, the highest acute risk associated with MRI are severe accidents which may even lead to death (Kulynych 2002). These accidents are mainly due to the ignorance of certain basic safety requirements with respect to metallic objects, implants, and biomedical devices. In order to avoid injuries due to movement or dislodgement of objects consisting of ferromagnetic materials, it is required to carefully remove all metallic objects, especially with sharp edges, from the vicinity of the magnet. In addition, the MR en-vironment is unsafe for patients with certain implants (e. g. electrically, magnetically or mechanically activated life-support systems or implants (e. g. cardiac pacemakers) or certain metallic implants), primarily due to but also because of heating and induction of electrical currents, which may lead to the failure of these devices. To date, more than one thousand implants and devices have been tested for safety or compatibility with MR systems[3], and the range is still being expanded by the medical device industry. To

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[3]   This information is available at http://www.MRIsafety.com

prevent these accidents, patients must be thoroughly screened for MR imaging eligibility in order to identify patients with contra-indications to MRI. Moreover, continued education of responsible staff and their strict compliance with existing safety rules is required.

During MR examinations, both patients and staff are exposed to acoustic noise which in some scanning procedures may cause hearing loss without the use of ear protection. Additional risks for the patient or volunteer include potentially acute discomfort and psychological distress from lying in the confined gantry of the MRI scanner (experience of claustrophobia). Often, restraints or sedation have to be used in order to fix the subjects during analysis, especially when scanning children (Hinton 2002; Hardy, Armitage 2002).

Although the above mentioned issues are the main safety hazards associated with MR scanning, there is currently an ongoing discussion of so called bio-effects produced by MRI systems acting directly on the human body or brain. In this chapter we will give a short review of the possible effects of MR scanning on the human body and brain. Three main sources of electromagnetic fields utilised in MRI procedures are thought to exert influences on body tissue (Formica, Silvestri 2004; Shulman 2001). These are:

- Biological effects of the static magnetic field
- Biological effects the gradient magnetic field
- Biological effects of radiofrequency (RF) fields

6.1.1   Biological effects of the static magnetic field

The discussion of safety issues associated with exposure to static magnetic fields has a long history lasting now more than a century. The early studies basically did not provide comprehensive data supporting the idea that static magnetic fields have substantial influences on the human brain or body. The interest in studying the influence of static magnetic fields has gained further interest in the beginnings of the 1980s when MR scanning became popular. The majority of these studies did not report any significant influence of static magnetic fields on human health. Two main published reviews concluded that there is no substantial influence on cell growth, and morphology, cell reproduction and teratogenicity, DNA structure and gene expression, pre- and postnatal reproduction and development, blood-brain

barrier permeability, nerve activity, cognitive functions, cardiovascular dynamics, hematologic indexes, temperature regulation, circadian rhythms, immune responsiveness, and a variety of other biological processes (Shellock 1992; Shellock 2000; Shellock 2002; Shellock 2003; Shellock, Crues 2002). The majority of the studies, thus, conclude that there is no substantial harmful biological effect of static magnetic fields on the organism. However, the most recent one also mentioned that, "because of the difficulty in establishing a negative conclusion, it should not be concluded that it has been proven that there are no significant biological effects of static magnetic fields" (Shellock 2003).

On a theoretical basis one might anticipate interactions between tissues and static magnetic fields that could lead to pathological changes in humans. Currently, most theoretical analyses indicate that the static magnetic field strengths used today are below the threshold for inducing potential health hazards. However, one should keep in mind that currently more and more laboratories install magnets with high field strengths which are considerably stronger than those field strengths used in the earlier safety studies. Thus, some authorities argue that carefully controlled studies are needed demonstrating the "absolute safety" of exposure to high magnetic fields. In addition, it should also be studied to what extent repeated exposure to static magnetic fields might have detrimental effects on the human organism. This issue will become increasingly important because of the widespread use of "interventional MRI" scanners and the growing number of MRI studies conducted by scientists especially in the context of learning studies.

6.1.2   Biological effects of gradient magnetic fields

It is well known and described that the gradient magnetic fields may stimulate nerves or muscles by inducing electric fields in the neural tissue. In case of sufficient exposure levels these stimulations are perceived as "tingling" or twitches. With increasing magnetic field, volunteers and patients may become uncomfortable and partly experience pain sensations. It has been noted that extremely high stimulation levels are potentially dangerous for the cardiac system. However, cardiac stimulation with gradient magnetic fields requires exceedingly strong or rapid gradient magnetic fields which are more than an order of magnitude greater than those used in commercially available MR systems (Schaefer et al. 2000).

6.1.3   Biological effects of radiofrequency fields

The majority of radiofrequency (RF) power transmitted for MR imaging is transformed into heat when the RF waves pass the subject`s tissue. Prior to 1985 there was basically no study systematically testing and describing thermal responses of human subjects exposed to RF radiations. Meanwhile, several reports have been published carefully examining these thermal effects (Shellock 2000). Induced heating in body tissues may provoke various physiological and thermoregulatory responses, including a decreased ability to perform mental or physical tasks as body temperature increases. Similar effects have been reported in people subject to heat stress: for example, those working in hot environments or suffering a prolonged fever. Induced heating may affect the development of a fetus. Birth defects would occur only if the temperature of the fetus is raised by 2-3 °C for hours. Induced heating can also affect male fertility and lead to the induction of eye opacities (cataracts)[4].

An important parameter in this context is the specific absorption rate (SAR). The SAR is the mass normalised rate at which RF power is coupled to biological tissue and is typically expressed in watts per kilogram (W/kg). Using standard clinical MR scanners (with SARs of approximately 4 W/kg) it has been shown that the change in body temperature was relatively minor (<0.6°C). Even if higher SARs were used (6 W/kg) there was no stronger heating of the tissue in individuals with normal thermoregulatory function. However, one has to keep in mind that more and more scanners are installed with increasing field strengths. With the doubling of field strength (e. g. 1.5 to 3 T), the RF power deposition increases four times for a given MR pulse sequence. Thus, additional studies are urgently needed characterising thermal responses in humans measured with high-field MR systems.

In addition, there is a scientific controversy whether there are additional biological effects of radiofrequency fields with implications for human health beyond the thermal effects. Especially, concerns about an increased risk of cancer have been raised. Current scientific evidence indicates that exposure to RF fields is unlikely to induce or promote cancers, but this is being monitored and evaluated by further research in order to provide enough

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4   http://www.who.int/docstore/peh-emf/publications/facts_press/efact/efs183.html

information to allow a proper evaluation of human cancer risk from RF exposure[4].

6.1.4   Preventive and protective measures against possible health effects due to exposure to magnetic fields

During MR examinations, both patients and staff are exposed to acoustic noise and different types of magnetic fields, i. e. static magnetic field; time-varying magnetic field gradients and radiofrequency magnetic fields which exert different biological effects. On the one hand, the mechanisms of interaction of these fields with the living matter are today sufficiently understood to identify the main categories of potentially associated health hazards. In order to minimise these health hazards, the International Commission on Non-Ionizing Radiation Protection (ICNIRP), among others, has set upper limits for exposure of patients (see e. g. ICNIRP 2004) as well as for occupational exposure of staff. These limits have also been incorporated into national standards and guidances, but may differ from one country to another in certain details.

It is recommended to divide exposure limits for patients into three tiers (ICNIRP 2004):

1) Normal operating mode: Routine examinations for all patients. Internationally, the recommended upper limit for clinical routine wholebody exposure to static magnetic fields is 4 T, due to the limited information concerning possible effects above these static field strengths, in some countries below 2.5 T for head and trunk examinations. The rise of the body core temperature should not exceed 0.5 °C.
2) Controlled operating mode: MR examinations outside the normal operating range where discomfort and/or adverse effects for some patients may occur. A clinical decision must be made to balance such effects against foreseen benefits, and exposure must be carried out under medical supervision. According to international recommendations, this is the case for wholebody exposure to static magnetic fields above 4 T. The rise of the body core temperature should not exceed 1° C, and 0.5 °C for infants, pregnant women and persons with cardiocirculatory impairment. Real-time temperature monitoring in the patient may be performed during MR procedures, as well as monitoring of blood pressure and heart rate.

3) Experimental operating mode: Experimental MR procedures, at levels outside the controlled operating range, for which special ethical approval is required in view of the potential risks. According the FDA recommendations, this is the case for static magnetic fields greater than 8 T for adults, children and infants aged > 1 month, and greater than 4 T for neonates (children under 1 month). Real-time temperature monitoring in the patient should be performed during MR procedures, as well as monitoring of physiological parameters such as blood pressure and heart rate.

While these recommendations and limits are based on acute effects of MR procedures, the knowledge base is still insufficient regarding possible long-term health effects in patients, volunteers and staff with occupational exposure, especially in those with high-levels of cumulative exposure. Moreover, there is presently insufficient knowledge regarding pregnant patients so that unequivocal guidance for use of MRI procedures for this patient (and staff) group has not yet been established. As a consequence, more research into these issues and the subsequent implementation of the results in guidelines is required (ICNIRP 2004).

Besides patients and volunteers, workers (i. e. medical doctors, medical staff working with MR equipment as well as employees in development, manufacturing and technical service) are also occupationally exposed to noise and electromagnetic fields. Internationally, guidelines for occupational exposure have been developed (ICNIRP 1994; ICNIRP 1998a; ICNIRP 1998b). Because the ICNIRP guidelines were written many years ago and do not take into account recent developments in medical MR procedures (e. g. trend towards higher field strengths, MR examinations of pregnant women, infants etc, occupational exposure during interventional MR procedures), current guidance and recommendations for prevention of health hazards during MRI do not adequately cover the risks (Strahlen-schutzkommission 2003). As a consequence, the ICNIRP is currently reviewing its guidelines on occupational exposure to static magnetic fields (ICNIRP 2004).

Limits for occupational exposure to static magnetic fields have been and continue to be a controversial issue in the European Union. ICNIRP guidelines currently state that staff should not be exposed to a whole body exposure greater than 2 T, or an time averaged exposure of 200 mT in any

24 hour period (ICNIRP 1994). In 2004, a new directive on restricting occu-
pational electromagnetic field exposure[5] has been adopted by the Euro-
pean Parliament and the Council of Ministers which has to be implemented
into national law in the EU member states by 2008. This directive, however,
does not include a static field exposure limit value[6]. Consequently, there is
presently no restriction on the static magnetic field, but this may be subject
to change in the future, depending on the future recommendations of the
ICNIRP. However, the limit set in the ICNIRP guideline is likely to be ex-
ceeded already today even in the normal operation of very high field mag-
netic resonance units (e. g. 3-8 T). This means that the working practices
that have been developed for the lower field systems (e. g. 2 T) need to be
revised, especially because suitable personal protective equipment against
static magnetic fields generated by medical MR devices is lacking. More-
over, the limits in the ICNIRP guideline and the EU directive 2004/20/EC
set for gradient and radiofrequency fields may also be well exceeded in
certain situations, such as during trouble shooting during maintenance and
repair, and during interventional MR procedures (Hill et al. 2005). For safe
operation, interventional MR departments require policies and procedures
beyond those required for diagnostic MR departments (Hushek et al. 2005).

Against this background, the limits will have to be taken into account by MR
equipment manufacturers as well as by centres operating such MR sys-
tems in order to comply with the Directive. In addition, research into the
biological effects of strong static magnetic fields need to be performed,
especially on the effects of chronic exposure on reproduction and develop-
ment (Feychting et al. 2005), and the results need to be incorporated into
the ICNIRP guidelines which are currently under review, and subsequently
also into the EU Directive 2004/40/EC. Moreover, there is a need for inter-
national harmonisation of standards for the assessment, measurement and
calculation of worker's exposure to electromagnetic fields. A mandate to
develop such harmonised standards has been given to CEN, CENELEC
and ETSI by the European Commission.

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[5]   Directive 2004/40/EC of the European Parliament and of the Council of 29 April 2004 on the
      minimum health and safety requirements regarding the exposure of workers to the risks arising
      from physical agents (electromagnetic fields) (18th individual Directive within the meaning of
      Article 16(1) of Directive 89/391/EEC) (Official Journal of the European Union L 159 of 30 April
      2004)
[6]   The directive only gives an action value of 200 mT.

Although the EU Directive does not directly apply to Switzerland, according to BAG officials, the Swiss national regulations usually comply with international recommendations, guidelines and standards.

Many European ethics committees do not allow MRI experiments with children younger than 18 years. This decision is not based on known substantial harmful effects on the brain of children; it is rather guided by the precautionary principle.

6.2   Safety issues in PET and SPECT imaging

PET and SPECT are working with ionising radiation. If a human body is exposed to this radiation it is absorbed and, thus, interacts with the tissue. This interaction results in disturbances or destructions of cell functions. The extent of these disturbances depends on several constraints. For example, evoking a chemical change in the DNA will cause stronger effects than a change in the cell membrane. The number of affected cells and the extent of the disturbance depend on the energy which is absorbed by the cells. The energy dosage of a given radiation delivered per weight unit to a tissue is measured in "Gray" (Gy; 1 Gray = 1 J/kg). Beside the energy dosage it is also important to know the specific radiation. For example, α-radiation with a given energy dosage has a 20times larger effect on the cell than γ-radiation. Thus, in order to compare different radiations the term equivalent dosage (H) is used which is the product of the energy dosage and a weighting factor (q) for each particular radiation. The dimension for the equivalent dosage is "Sievert" (Sv). High equivalent dosages result in extended radiation effects in many cells with increasing likelihood of harmful effects. In PET and SPECT studies one distinguishes between external or internal exposition to radiation.

External exposition describes the irradiation of the body tissue (or parts of it) by radionuclides which are located outside the body. A typical example for external exposition is when staff members of the PET department are preparing a syringe containing radionuclides. In this situation α-radiation and β-radiation do not have an effect because their radius of affect is limited. The only exception is when α-radiation and β-radiation is in direct contact with the skin. However, γ-radiation mostly contributes to the exter-

nal radiation effects. The term internal exposition describes the situation when radiation enters the body either via the respiratory tract, digestive tract, skin, or via blood circulation (e. g. iv-injection). In contrast to the external exposition α-radiation and β-radiation are more important in determining the radiation exposure.

In order to classify the toxicity of the radiation the radionuclides generating radiation are classified in four toxicity classes.

- Class 1: Radionuclides with the highest toxicity. This class contains radionuclides which are stored in the bones. These radionuclides are generally not used in nuclear medicine.
- Class 2: Radionuclides with high toxicity (e. g. ^{45}Ca, ^{39}Fe, ^{131}I). These radionuclides are used only in very rare medical indications. They are not used in the context of cognitive neuroscience methods so far.
- Class 3: Radionuclides with moderate toxicity.
- Class 4: Radionuclides with low toxicity (e. g. ^{3}H, ^{14}C, ^{51}Cr). These are the mostly used radionuclides for PET.

The lawmaker (also in Switzerland) provides specific radiation limits for PET centre staff members, patients, and volunteers. For example, the limit radiation is 15 mSv for PET centre staff as well as for patients and volunteers. In addition, women who are younger than 45 years of age should not be exposed to 1/10 of 15 mSv within one month. These limits substantially differ between countries.

Because of the invasive nature of PET and SPECT these methods are not used in children for regular cognitive experiments. Thus, PET and SPECT are only used for studying children if specific medical implications can be answered by these methods. Currently, PET and SPECT experiments are not allowed to be conducted with female subjects in Switzerland[7] and in some other European countries. These limits have been introduced in order to minimise possible gene defects or other health hazards like cancer (Bergstrom et al. 2003; Roberts et al. 2004; Roberts, Shulkin 2004).

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[7]   In the county of Zurich there is a general ban for scanning young women.

6.3   Safety issues in EEG and MEG

There are currently not any known safety problems associated with EEG/MEG measurements. The only restriction is to use EEG and MEG amplifiers and dewars which are designed and built on a high standard quality basis. For example, they should meet all imperative requirements for medicals tools and devices in order to avoid harmful effects caused by electrical short circuits, voltage variations, or other forms of machine break-down.

EEG and MEG are established as being non-obtrusive, non-harmful, and non-invasive. Thus, there are no substantial medical or ethical constraints associated with these methods. Therefore, these methods can easily be used to study brain processes of normal and healthy subjects.

6.4   Safety issues of TMS

Basically single-pulse (sTMS) is considered a safe procedure if the applied intensity of the pulse is not more than 130-150 % of the motor threshold. If TMS is repetitively delivered at rates lower or equal than 1 Hz it is called low-frequency repetitive TMS (low-frequency rTMS). For repetitive TMS with higher frequencies, the term higher-frequency rTMS is used. This distinction is based on the different physiological effects and degrees of hazards associated with low- and high-frequency stimulation. According to the U.S. Food and Drug Administration (FDA), stimulation frequencies of more than 1 Hz *always* bear significant danger, whereas certain studies using lower frequencies may not carry significant risk.

Some high-frequency rTMS studies have reported that some subjects mentioned to transiently suffer from headaches after stimulation. However, these patients responded well to mild analgesics. A further problem is the experience of local pain especially in ventral frontal brain areas mainly due to the collateral stimulation of eye muscles. The most problematic risk of TMS is the potential to evoke epileptic seizures in some patients. Based on a workshop hold in 1996, Wassermann and colleagues (1998) have published guidelines for conducting rTMS experiments in order to prevent or

minimise potential harmful effects which are associated with high-frequency rTMS studies. According to these guidelines low-frequency rTMS protocols are safe for more than 1800 repetitions if they use an intensity of not more than 110 % of the motor threshold. In case of 1 Hz stimulation rate this means that 30 minutes rTMS can be delivered without any harmful effect. With increasing frequency the safety substantially decreases. For example, 5Hz rTMS stimulation with 110 % of the motor threshold can be delivered approximately for 10 secs; 10Hz rTMS can be delivered for 5 secs with any known harmful effect. Thus, it is recommendable to design the TMS protocols strictly according to these guidelines in order to avoid any harmful effects on the subjects. Currently, these guidelines explicitly recommend not to investigate children using TMS methods.

Maximum safe duration (s) of single trains of rTMS based on the NINDS experience

Frequency (Hz)	Intensity (% of MEP threshold)												
	100	110	120	130	140	150	160	170	180	190	200	210	220
1	>1800	>1800	360	>50	>50	>50	>50	27	11	11	8	7	6
5	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2
10	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4	0.3	0.3
20	2.05	1.6	1.0	0.55	0.35	0.25	0.25	0.15	0.2	0.25	0.2	0.1	0.1
25	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12	0.08	0.08

Numbers preceded by > are the longest durations tested. No after discharge or spread of excitation has been encountered with single trains of rTMS at these combinations of stimulus frequency and intensity.

Figure 6.1:   Maximum safe duration(s) of single trains of rTMS (source: Jäncke 2005)

Similar as for each brain imaging study, informed consent must be obtained from the participating subject. The informed consent demands that the subject's decision to participate must be voluntary and is based on the provision of all relevant information.

All TMS studies in normal subjects and patients for whom there is no potential benefit (in terms of healing a disorder or to improve a handicap) should proceed only with maximally stringent safety measures and limits on stimulation parameters. Exhaustive disclosure of known and potential risks, including the psychological and social risks of having a seizure, is mandatory in all rTMS studies.

6.5   Safety issues of NIRS

There are currently not any known safety problems associated with NIRS measurements. The only minor problem is a potential heating of the LEDs attached to the skull. Thus, careful monitoring of the temperature and timely termination of the study will prevent any harmful effect. As there are no substantial medical or ethical constraints associated with NIRS, it can easily be used to study brain processes of normal and healthy subjects.

6.6   Summary

As outlined in the previous chapters (chapters 6.1 to 6.5), relevant health risks are known for PET and SPECT as well as MRI and TMS, whereas EEG, MEG and NIRS do not pose any major safety problems at the present state of knowledge.

Health risks of PET and SPECT are mainly due to toxicity and ionizing radiation emanating from the radionuclides used in these techniques. The definition and adoption of protection standards in the field of ionizing radiation is well advanced (chapter 6.2), and according to experts' assessment, no major amendments of the standards and their enforcement are presently required. Health risks for high-frequency repetitive TMS comprise headaches and the risk to evoke epileptic seizures.

For MRI, the highest acute risks are severe accidents due to interference of the scanner's magnet with metallic objects or patient's implants. To prevent these accidents, continued education of responsible staff and their strict compliance with existing safety guidelines is required. On the other hand, there is considerable controversy about possible biological effects of the different types of magnetic fields, i. e. static magnetic fields; time-varying gradient magnetic fields and radiofrequency magnetic fields to which patients, volunteers and MRI staff are exposed. Despite some knowledge gaps, the mechanisms of interaction of these fields with the living matter are today sufficiently understood to identify the main categories of poten-

tially associated health hazards. Preventive and protective measures[8] have been developed and implemented, which allow, in the large majority of routine clinical neuroimaging procedures, a safe operation of the devices with minimal acute health risks for both patients and staff.

However, the currently valid guidelines for occupational exposure to electromagnetic fields do not adequately take recent developments in medical MR procedures into account, among them

- the trend towards higher field strengths of the MR scanners (3-8 Tesla),
- the trend towards high throughput scanning of patients, leading to a high level of cumulative exposure of staff,
- the trend to 4D imaging and monitoring of disease progression by MRI, leading to repeated exposure of patients and volunteers,
- interventional MR procedures during which staff is exposed to various electromagnetic fields to a much higher level than in diagnostic MR procedures.

Moreover, current occupational exposure limits are often exceeded during non-routine procedures such as trouble-shooting and repair, and there is a general lack of knowledge regarding the long-term effects of electromagnetic fields, especially their effect on pregnant women, which comprise both exposed staff as well as patients, and the biological effects of strong static magnetic fields, with special emphasis on chronic exposure and their effects on reproduction and development.

Against this background that current guidance and recommendations for the prevention of health hazards during MRI do not adequately cover all potential risks, it is recommended to

- support and conduct research into possible long-term health effects of exposure to electromagnetic fields, especially carefully controlled studies

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8   e. g. by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) (ICNIRP 2004 for patient protection). For protection of workers during occupational exposure, see ICNIRP 1994; ICNIRP 1998a; ICNIRP 1998b and Directive 2004/40/EC of the European Parliament and of the Council of 29 April 2004 on the minimum health and safety requirements regarding the exposure of workers to the risks arising from physical agents (electromagnetic fields) (18th individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) (Official Journal of the European Union L 159 of 30 April 2004)

in those with high levels of cumulative exposure (e. g. staff with occupational exposure), in order to broaden the knowledge base,

- support and conduct research into the biological effects of strong static magnetic fields, especially carefully controlled studies on the effects of chronic exposure on reproduction and development,
- to subsequently incorporate the results of the above-recommended research into the ICNIRP guidelines, the EU Directive 2004/40/EC as well as the corresponding Swiss regulations,
- to closely monitor the broadening of the knowledge-base for possible health effects of MRI procedures on pregnant women and on the development of their children, in order to establish unequivocal guidance for use of MRI procedures for this patient and staff group,
- to support the international harmonisation of standards for the assessment, measurement and calculation of worker's exposure to electromagnetic fields, presently underway on the European level at CEN, CENELEC and ETSI,
- to initiate and support the development and implementation of adequate policies and procedures for safe operation in interventional MR departments which go beyond those required for diagnostic MR departments,
- to call upon MR equipment manufacturers as well as MRI centres to develop devices and operating procedures which comply with currently valid exposure limits to electromagnetic fields also during trouble-shooting, repair, and interventional MRI.

7   Equipment requirements and costs of brain imaging

Most brain imaging methods require sophisticated and expensive hard- and software tools. For example a typical 1.5 Tesla MRI scanner will cost approximately about 1.5 to 3 million CHF. In addition, there are some specific requirements needed for installing and emplacement of the MRI scanner. Specific rooms (e. g. equipped with specific power supply and specific statics) are needed for emplacement (including a separate room shielding for the RF field), installing and storing all necessary technical equipment, as well as rooms for subject preparation. In addition, specific MRI compatible tools are necessary allowing the presentation of visual or auditory stimuli, registering of the subject's responses, monitoring eye movements during scanning, and monitoring further psychophysiological signals (like EEG, heart rate, electro dermal responses). For data acquisition, storage and data analysis high-end workstations are also needed. Finally, helium (for cooling the magnet) has to be replaced at least once a year. Thus, expenses per year are approximately in the range of 150.000 to 200.000 CHF not including commitments for specialised MR physicists. Most MR centres employ two MR physicists for maintaining the scanners. Thus, expenses for scanning one subject per hour are estimated to be in the range of approximately 400-600 CHF.

Similar expenses are estimated for MEG. The basic price for purchasing an MEG machine is roughly similar to an MRI scanner of 1.5 Tesla, maybe slightly less expensive (1.5-2.5 million CHF). Similarly to MRI, the MEG needs specifically designed and shielded rooms. In addition, because the MEG captures very weak magnetic signals (in the range of pico Tesla), it is necessary to avoid different sources of interfering signals (e. g. electrical currents, magnetic fields, or even slightest vibrations of the building where the MEG is located). For MEG, liquid helium (for cooling the dewar containing the squids) has to be replaced each year although the average costs are slightly lower than for the MRI because the MEG machine needs less helium than regular MRI machines. However, the additional requirements are approximately the same as for MRI machines. Similar to MRI, high-end workstations are needed for data acquisition, storage and data

analysis. The estimated expenses per subject per hour are slightly less compared to MRI (300-500 CHF).

PET (and to some extent SPECT) is much more expensive and technically demanding. The main reason for the higher costs is that a cyclotron is needed which mostly is only available in specifically equipped labs also used for nuclear medical therapies. Sometimes these machines are located in specific research centres also working in the area of nuclear research (e. g. research centre Jülich, Germany). In terms of investment and main-tenance the costs are approximately similar to MRI machines. Similar to MRI machines, specifically trained staff is necessary maintaining and hand-ling the machine and cyclotron which also increases the expenses for PET scanning. Thus, the average costs for scanning one subject per hour are approximately the same as they are for MRI experiments (500-1.000 CHF).

NIRS, TMS, and EEG are much cheaper. For example, modern NIRS equipment with 16 sensors and LEDs costs approximately 150.000-400.000 CHF. There are no follow-up costs unless the machines need re-pair. In addition, there are no specific academic personnel needed to run this machine. After a short training, medical or academic staff can easily operate these systems. Another important argument in favour of this device is that these systems could be used in regular offices without specific tech-nical adjustments (apart from the possibility to darken the room to avoid the registration of scattered light). The costs for high-end TMS devices with anatomical navigation equipment are in the range of 60.000-150.000 CHF. There is no need for specific additional equipment to run TMS and there are also no additional costs.

The cheapest brain imaging method is EEG. A 64 high-end channel system costs about 60.000 to 100.000 CHF including electrodes, amplifiers, cables, electrode caps, and software for recording and analysing. EEG systems with more electrodes (128-256) are slightly more expensive (120.000-180.000 CHF). Meanwhile several (freeware, shareware, commercial) soft-ware tools are also available for EEG data analysis allowing to partly solve the inverse problem and to cortically map the intracerebral sources of acti-vation during various cognitive tasks. While in former times it was obligatory to use faraday shielded rooms for registering EEG signals, nowadays it is not necessary to conduct EEG measurements in such specifically designed labs. The modern EEG preamplifiers are excellent in suppressing different

electric interference signals. However, it is recommendable to use a sound-shielded chamber to avoid disturbing acoustic sounds. A modern sound-shielded chamber costs approximately 40.000 CHF. Similar to NIRS and TMS there is no specific academic expertise necessary for maintaining and handling the machines. The follow-up costs are also relatively low and only contain costs for electrode gel, new electrodes, or costs for repairs. Thus, the costs for conducting an EEG measurement per subject per hour is very low (approximately 60 CHF). Based on the estimated costs per subject and hour, the following ranking of the different brain imaging methods can be given:

1) PET, SPECT, MRI (10-15 times more expensive than EEG),
2) MEG (up to 10 times more expensive than EEG),
3) EEG, TMS, NIRS (approximately 60 CHF per subject per hour).

8   Qualification and training requirements of the operating personnel and scientists

Brain imaging methods differ in terms of the required manpower to operate these techniques. For example, MRI, PET, SPECT, and to some extent MEG need specifically trained staff who have received formal academic training with respect to the physics of these machines. PET and SPECT also require operators who have received formal training in generating and handling the isotopes. Thus, besides the scientists who are interested in collecting their data for content-related reasons, academically trained specialists are necessary supporting these scientists in working with MRI, PET, and SPECT. While PET and SPECT require academic training mostly in the field of nuclear medicine, operating MRI machines requires formal training in MR physics. Many labs have employed two physicists for operating and maintenance of the MR machines. NIRS, EEG, and to some extent TMS do not need specifically trained personnel. Neuroscientists may learn to handle these machines appropriately after an intensive training lasting several weeks. The only restriction is that the operating personnel has to be trained in basic medical treatment (first aid) to handle unlikely cases of epileptic seizures which may be evoked by TMS. However, medical and neuropsychological academic personnel could be trained within several days to operate TMS machines appropriately.

With PET, SPECT and MRI being expensive equipment this will be a certain restraint against an immediate, quick and broad diffusion of these modalities into clinical practice beyond specialised centres and into non-clinical, non-research uses. Nevertheless, due to increasing complexity of the devices, their broadening range of applications and their continued diffusion into clinical and non-clinical practice, attention should be paid to qualification and quality assurance aspects. In analogy to the experience made during the broad introduction of ultrasound into the clinic it is not unlikely that sub-standard application of these imaging techniques may occur outside specialised centres. On the one hand, radiologists trained in the use of CT and x-ray may not be familiar enough with MRI, and neuroimaging may also be performed by radiologists who may not have the specific expertise

of neuroradiologists. In addition, specific expertise is required in designing meaningful test settings and data acquisition protocols, and in processing and interpreting the raw data. Given the sensitivity of personal information that can be gleaned through brain imaging, high professional standards are required.

In Switzerland, no specific formal qualification (*"Fähigkeitsausweis"*, proof of special knowledge) is required for conducting brain imaging experiments and diagnoses, for data processing and interpretation, and for informing the patient of the results of the examination. Nevertheless, regulations against a substandard application of medical imaging exist which are outlined in detail in chapter 20.

9   Persons subjected to brain imaging

9.1   Person groups and purposes of brain imaging

The basic motivation to use brain imaging methods is to visualise the anatomy and function of the human brain. Thus, all kinds of subject groups are meanwhile interesting study subjects in the context of brain imaging. While in the beginning of fMRI and MRI mostly normal and healthy adults in the age range of 20-40 years were scanned, nowadays brain imaging is applied for nearly all possible subject groups. Even foetuses or very young children (at the age of several months) are meanwhile scanned not only for medical purposes (Krageloh-Mann 2004; Krageloh-Mann 2005; Sury et al. 2000) but also for purely scientific reasons (Deutsch et al. 2005; Jancke et al. 1999; Preis et al. 1999; Schapiro et al. 2004; Schlaggar et al. 2002; Sowell et al. 2003). All kinds of neurologically and psychiatrically ill patients are meanwhile scanned as a matter of routine. In addition, even cadaver brains are subject of structural brain imaging (Peters et al. 1998).

A relatively new approach is to scan subjects in the context of questions derived from marketing, politics, theology, economy, and forensic (Azari et al. 2001; de Quervain et al. 2004; Farah 2004; Fehr, Rockenbach 2004; Fugelsang, Dunbar 2004; Ganis et al. 2003; Grezes et al. 2004; Kozel et al. 2004b; Kozel et al. 2004a; Langleben et al. 2002; Newberg et al. 2003; Phan et al. 2005; Spence et al. 2004; Wuerfel et al. 2004; see also chapters 15 and 16).

9.2   Informed consent

9.2.1   Critical issues in obtaining informed consent

Following the important ethical principle of respect for human beings, their autonomy and dignity, it is required to seek informed consent prior to any neuroimaging analysis. Informed consent is the agreement of an individual to participate in the procedure after having been made fully aware of what

the procedure entails and any potential benefits and/or risks that are associated with it. Two preconditions must be fulfilled: the clinician/researcher must provide all relevant information, and the participant must understand the rationale, risks and benefits associated with it (see also chapter 20.4). In addition to the general aspects that must be addressed in the informed consent, there are some critical aspects which are specific to neuroimaging:

- the safety of the procedure (chapter 6),
- the possibility of incidental findings (chapter 9.3),
- limits to the validity of findings (Rosen, Gur 2002; Davatzikos 2004; chapter 10),
- options for treatment and intervention in case of positive results[9], and
- the scope of consent (is it allowed to use the brain scans only for the purposes that were included in the informed consent? Are other uses allowed? Under which conditions?).

In chapter 9.2.2, an example is given how informed consent is usually obtained from volunteers for neuroimaging in neurocognitive research projects.

From the short overview presented in chapter 9.1, it can be concluded that additionally, specific challenges for balancing benefits and risks, for obtaining valid informed consent, and for data protection and privacy arise from neuroimaging:

- *Balancing benefits and risks.* Volunteers who are subjected to neuroimaging in the course of cognitive neuroscience studies often do not have a direct benefit from neuroimaging – which is in contrast to neuroimaging in the medical context. This imposes the obligation to carefully balance possible risks for the volunteers (e. g. health risks of neuroimaging for specific target groups (chapter 6), privacy risks (chapters 20.6.1 and 20.6.4) or risk of incidental findings (chapter 9.3) against the benefits for third parties, and this even more so, if persons with impaired ability to give informed consent are affected.

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9   This aspect is discussed in more detail for the diagnosis of Alzheimer's disease in chapter 13.

- *Impaired ability to give informed consent.* Many neuroimaging studies are performed with subjects who are unable to give informed consent on their own because their decision-making ability is (temporarily) impaired, for various reasons. For example, they may suffer from brain disorders or mental illnesses which affect their decision-making ability (e. g. dementia, Alzheimer's disease (Rosen et al. 2002), addiction, depression), they are fetuses, neonates or children; or the subject is in coma vigil (Laureys 2005), or neuroimaging is to be carried out with the dead body, or even with the digitised scan of the subject's brain. Nevertheless, the obligation remains to obtain valid informed consent, which in these cases would have to be given by given by the subject's legally authorised representative (for details, see chapters 20.4 and 20.7).
- *Data protection and privacy.* Because neuroimaging data are acquired, processed and stored in digitised form, it becomes possible to do research on "virtual brains", reconstructed from stored imaging data. As a consequence, the analysis can be separated spatially and temporally from the physical neuroimaging investigation and from the direct involvement of the patient or research subject, may be made available to third parties, and may be linked with other data. Moreover, "surplus information" may be generated. This creates challenges for privacy and data protection which are outlined in more detail in chapters 20.6.1 and 20.6.4.

9.2.2   Guidelines for obtaining informed consent from volunteers participating in research of cognitive processes

In this chapter, an overview is given of the procedure that is usually applied to obtain informed consent from volunteers who are subjected to neuroimaging within a research project studying cognitive processes. This example therefore only covers a small section of the entire issue "Informed consent". For a more detailed discussion, which also emphasises the need of clear boundaries to be set by law in Switzerland, see chapter 20.

For brain imaging studies it is mandatory to receive informed consent by the volunteer. This consent is documented and serves as a proof that the subjects have been informed intensively and in depth. Several general guidelines are available according to which many institutions are generating their individual consent forms. However, most consent forms include the following points:

- The subject is informed about the title of the study and a brief introduction into the research topic is given to the volunteer. During the course of this introduction, the participant is informed whether this is a basic research study or a clinical study. Most important is the part where the volunteer is explicitly informed that if he takes part on a voluntary basis. If he/she is a student his/her decision whether or not to participate will not have any affect on his/her academic status. In addition, the volunteer is explicitly encouraged to ask questions at any time if there is anything he/she does not understand.
- Secondly, the volunteer is informed about the purpose of the brain imaging study and why he/she has been asked to participate. It should also be mentioned that his/her data with that from other subjects are part of a scientific study to appear in the peer-reviewed literature.
- Thirdly, after the general information the participant should be informed about the particular study procedure (fMRI, sMRI, TMS, PET, MEG, or EEG). This part also includes technical issues like lying in the bore of the scanner, receiving visual or auditory stimulation via specific devices, that the volunteers will be visible to the experimenter by means of a video camera, and that he/she will be in direct verbal communication with the MRI personnel. At this part it is important to inform the subject that the procedures used in this study are different from clinical brain imaging and that there is no intention to make any medical diagnosis with the brain imaging method as used in this research setting.
- Fourthly, a description of the collected data is necessary. For example, it is necessary to mention that the research will result in imaging data, behavioural, and physiological data and that these data are used for modelling and theoretical purposes. In addition, it is also worth to mention that data concerning sex, handedness, task performance, etc. will also be collected as part of the study. An important part is to mention the expiration date on the viability of the data collected and that the investigator is in charge of saving and protect these data.
- A further point is the explicit description of the possible health benefits and health risks to the volunteer. Special considerations are made for metal in MRI environments, women of child bearing potential, hearing in fMRI environment due to scanner noise, and claustrophobia within the scanner.
- An explicit mentioning is necessary to inform the volunteer that he has the right to withdraw from the study at any time of the experimental

stage which will not involve any penalty or loss of benefits to which he/she is entitled.

- Beside the financial considerations for participating (no cost for the participant, payment for participation) it is necessary to inform the participant that all information he/she is providing will be kept confidential except as required by law. The data may also be shared with other researchers around the world or with a publicly available data archive. In such cases, every reasonable effort will be made to remove identifiers from the data that would indicate any connection to the particular subject (e. g. the removal of the name, address, etc.). His/her name will not be used in any publication that may result from this study. The local ethics committee may request access to the consent form to ensure procedures designed to protect research participants are being properly followed. In addition, the manufacturer of the MRI scanner may request the use of images acquired in the particular study, although they will not have access to the names of any subjects.

- A specific part is also necessary to include in the consent form defining the right to revoke consent to participate in the particular brain imaging study. The participant is informed that at any time now or in the future he/she can indicate that his/her data should no longer be used for research purposes. Thus, he/she has the right to revoke the consent he/she gave in signing the consent form. However, the participant is informed if his/her data are anonymised, or brain image data have been shared with other researchers, or placed in a centralised archive, then it may be impossible to have these copies deleted.

- Finally, study funding (funding organisation) and investigator contact information is necessary to include on the consent form. All the above mentioned information must be clear to the subject and personally signed. A typical formulation is "Informed consent: I have read the above information about this study "insert complete study title", and have been given an opportunity to ask questions. I agree to participate in this study and have been given a signed copy of this consent for my own records". Thus, the consent form should include the participant's signature and date as well as the signature of the investigator.

9.3   Possibility of incidental findings and informing the person affected

Brain imaging for research purposes bears the potential of indicental neuro-radiological findings that appear to be outside expected norms. Meanwhile brain imaging techniques are used worldwide in the context of thousands of cognitive experiments. Preliminary data on the prevalence of incidental findings in neuroimaging research suggested that in 20-40 % of cases incidental neuroradiological findings have been detected, with a small percentage requiring referral (Illes et al. 2002). A recent study has uncovered that 82 % of brain-imaging researchers have dredged-up such findings. 2-8 % even report that they accidentally have found clinically significant findings (Illes et al. 2004b). Moreover, brain scans may show structural characteristics that may appear to be unusual, but without any known functional consequence (Hinton 2002). On the one hand, most research fMRI studies involving volunteers are performed by non-physicians. This bears the risk that unanticipated findings may go unrecognised and thereby leave subjects without appropriate referral or counselling. It also bears the danger that an inappropriate interpretation of the data is done, confronting the subject with a false-positive result. This may cause undue concern that an individual "has something in the brain that should not be there", due to a possible bias towards negative interpretation of unclear and uncertain findings (Hinton 2002). On the other hand, informing the subject about the incidental finding may challenge the subject's right not to know (chapter 20.4.3). These aspects are outlined in more detail in the following paragraphs.

Suppose a cognitive neuroscientist is studying the neural basis of working memory. Thus, he/she hires several volunteers who are scanned during a working memory task. While the researcher (a neuropsychologist, psychologist, physicist, or biologist) is scanning the brain he/she notices that one of the volunteers is missing his entire temporal lobe which is important for object recognition. What should the researcher do with this finding? Many would say that the volunteer should be referred to a medical doctor for further consultation. But it is not as easy as it sounds because this poses risks for both researchers and their subjects. First, it challenges the responsibility of a principal investigator who has no medical (e. g. neurological) training. Is she/he in the position to diagnose a neurological or neu-

roanatomical problem reliably? In situations when the researchers might face a gross anatomical deficit (e. g. missing or deformation of larger brain structures) the problem seems to be less overwhelming but nevertheless it bears a fundamental problem. Should a researcher inform the volunteer? This might cause that the volunteer might be exposed to unnecessary risks from extra medical procedures. It might be that the volunteer did not report or feel any health hazards and after this information he might change his/her attitude to his life. A least one case has been published of a volunteer (a graduate student) who has decided not to go to graduate school because of perceived brain defects uncovered by brain scans. A most problematic aspect in this context is informing the volunteer of suspected brain abnormalities for which no clear association with brain disease or other obstacles are known. A typical example is the so-called white matter hyper intensities (WHM) which are abnormal plaques of white matter often found in brain scans. Although there is a correlation between the number of WHMs and several brain diseases (e. g. multiple sclerosis or brain degeneration) these correlations are far from being perfect. Thus, a brain showing WHM might function without any problems for many years to come. Informing the volunteer about the correlation between WHM and the neurological diseases might induce a detrimental cascade of psychological problems although there is no obvious problem.

Beside the above mentioned problems an incidental finding might affect a subject's ability to buy health insurances and turn out to be medically insignificant, cause tremendous stress for the volunteer and their families (an impressive report of a volunteer who accidentally noticed to have a tumour has been published in Nature, 434, 17, 2005). These arguments have scared researchers (at least in the US) because of impending lawsuits. If researchers accept any responsibility for detecting medical information they will be legally accountable for diagnosing brain problems that are completely unrelated to their studies. This might hinder future studies and increase the costs of basic neuroscience research. A final point which has not been debated intensively so far definitively will be a matter of dispute in the near future. If researchers will increase their knowledge of brain function and use their knowledge for predicting and proving behaviour abnormalities, private insurances might make use of these data. For example, if it will turn out that a brain marker might indicate sociopathy, insurances might prevent to insure these subjects. The problem might become even worse because it is now possible to store brain data (structural and functional

brain data) digitally for a long time. What will happen if a volunteer has taken part in a cognitive experiment during which brain scans have been obtained for scientific reasons and the brain data are available to insurances many years after the initial experiment? Thus, the insurance can argue that brain data have been available indicating that the subject is a sociopath for which a legal insurance might be inappropriate. Possibly the insurance might argue that an insurance contracted many years before is invalid.

Recently, the directors of the Wolfson Brain Imaging Centre (WBIC) have published their guidelines for reducing "the risk of brain-scan shocks" (Nature, 435, 17, 2005). In their communication they argue that they "separate the responsibility for the research itself, which properly lies with the investigator, from the duty of care owed by the WBIC". They introduce a cascade of informed consent including careful information of the volunteer about the potential risks of the study. In addition, they offer insurances (paid by the WBIC) and medical counselling. "All structural MRI studies are reviewed by a consultant neuroradiologist and a confidential report is generated, which is not included within the normal hospital information system". An important part of this policy is that in case of identifying some kind of abnormality, "the principal investigator is informed that it is no longer appropriate to include that individual in their study" and "the researcher is not told why and plays no further part in the progress" (taken from the published policy of the WBIC; Nature, 435, 17, 2005). However, it should be kept in mind that these are first attempts to deal with this upcoming problem. Nevertheless, much has to be done in future a point which has been recognised by specialists in this field (e. g. Dr. Judy Illes who has published several papers about this topic, Illes et al. 2004b; Illes 2004a; Illes 2004b; Illes, Racine 2005a; Illes, Racine 2005b; Illes et al. 2006).

10   Validity of and limitations to functional brain imaging

10.1   Technical constraints affecting the measurements

Each method has its own technical obstacles. For example, for MRI measurements the subjects have to be positioned into the bore of the magnet. First, the head is fixated within the coil. This fixation is very important to avoid head movements during scanning. Thus, the head sometimes is fixated by a cushion or by a set of screws. This may evoke aversive emotions, pain or disturbance throughout the scanning session. Secondly, the diameter of the bore is ranging between 60 cm to 100 cm (depending on the machine). Thus, this constriction often evokes claustrophobic experiences in the subjects (approximately 8-10 %) which may have an impact on emotional and cognitive studies. Thirdly, because of the magnetic environment and constriction only specific devices can be used by the subject during scanning. Thus, one has to use relatively small and flexible devices which can easily be inserted within the bore without detrimental influence on the MR signal and the subject's health. Because of the uncomfortable position within the MR scanner it is basically impossible to conduct MR experiments longer than 90 minutes. Another relevant issue is that this specific environment makes it difficult (or even impossible) to scan people suffering from claustrophobia, strong trait anxiety, autistic subjects, or sociopaths. Finally, during boring and long-lasting MRI measurements subjects may fall asleep and thus, they do not track the experimental procedure any more. Sometimes head movements increase during early phases of sleep during scanning causing distorted MRI images.

PET scanning requires the insertion of radioactive isotopes. Thus, subjects who are fearful and anxious of needles and catheters might experience high levels of anxiety. Sometimes the insertion of the injection needle was painful which might have some influence on the following experimental conditions. Let us assume that the researcher is interested in studying the influence of picture material on positive emotions and the insertion of the needle was painful and the pain continues during the entire experiment.

Thus, one has to anticipate that there might be transfer (in this case *negative transfer*) from emotions experienced during needle insertion to emotions experienced during the cognitive experiment. In addition, even subliminal concerns might influence the cortical and subcortical activation pattern. A final issue which is holds for PET scanning is the fact that operating staff (especially those staff in charge for isotope injection) is sitting or standing close to the subject. Thus, some kind of social influences cannot be ruled out or in other words are very likely (e. g. audience effects which have been documented by social psychology and cognitive psychology).

MEG and EEG are less obtrusive than MRI and PET methods. For MEG measurements the subjects are sitting on a specific chair with the surface of the head placed inside the magnetometer. Thus, there is no placement of the entire body inside the measurement device as for the MRI. Another advantage is that the subject is sitting alone inside the experimental room, thus, minimising social influences. The only problem is that head movements have to be avoided. Therefore, the subject's head is fixated to some degree at the magnetometer and subject has to sit calmly without any movements. EEG is less vulnerable for head movements because the electrodes are fixated on the skull. Therefore, small or even moderate head movements do not substantially influence the EEG signals. However, the main problem of EEG is to set up a larger number of electrodes. Using the conventional electrode caps it takes about 30 minutes to prepare 32 electrodes and up to 60 minutes to prepare 64 electrodes. Modern EEG systems working with specific electrodes are now available allowing fixations of 128 or even 256 electrodes within 15 minutes (e. g. the modern Geodesic and BioSemi systems). Thus, one of the main disadvantages of EEG (the boring and long-lasting electrode fixation) has been eliminated. Another advantage of EEG registration is that one can use many experimental devices which cannot be used in MRI, MEG and even PET environments. For example one can use a piano as device to study motor behaviour or a driving simulator to study sensorimotor coordination. Thus, EEG meanwhile offers many advantages in contrast to traditional brain imaging methods.

NIRS is also a very unobtrusive method. The subjects wear a cap on which LEDs and sensors are fixated. Thus, the advantages are similar to EEG. A slight disadvantage is the heating of the LEDs during longer lasting experiments. However, this side effect has not been shown to influence the subject's comfort so far.

The magnetic pulses applied by TMS on the skull mostly evoke tickling sensation on the skull and, thus, are not painful. However, depending on the stimulation location the tickling can change to painful sensations. For example, stimulations over parietal and dorsal occipital regions are only accompanied by a kind of tickling sensations. However, stimulation of more ventral parts of the lateral prefrontal cortex often also evoke twitches of the eye muscles which are perceived as annoying and painful by some sub-jects. Similarly, stimulations of the temporal cortex evoke annoying twitches of the masseter muscle while stimulation of ventral parts of the occipital cortex evokes twitches of neck muscles. Therefore, it is an open question whether TMS can be used as a reliable tool in studying emotional processes. Another issue which is important in this context is the fact that many subjects experience some kind of initial concern with this method, a fact which might also have an influence on the studied cognitive functions. This concern is enhanced by the initial briefing during which the subjects are informed about potential harmful effects on brain activation.

10.2 Content-related constraints of brain imaging results

The different brain imaging methods are suited for different tasks. MRI-based methods (like sMRI and DTI) achieve high spatial resolution of the measured anatomical structures ($0.5mm^3$-$4 mm^3$). High-field magnets will substantially improve spatial resolution allowing the fine-graded measure-ment and imaging of brain structures down to the level of cortical columns.

fMRI methods combine good spatial resolution with moderate temporal resolution. The reason for this is the fact that the fMRI signal originates from vascular responses that are correlated with neuronal activity. This im-poses physiological constraints on temporal and spatial resolution. The haemodynamic response occurs throughout several seconds, and it slightly varies across brain tissue. Thus, a temporal resolution of at best 250 milliseconds can be obtained (using specific methods). Normally, a parsimonious resolution in the range of a few seconds (e. g. 4-8 seconds) can be expected, much coarser than the temporal response of neurons, in the millisecond range. The spatial resolution is limited by three factors: (i) the imprecision of the vascular control of blood flow; (ii) the resolution of

the MR images (in turn limited by available signal-to-noise ratio); and (iii) the contaminating effect of blood withdrawing from activated neuronal tissue with changed oxygenation, which progresses down the venules and draining pial veins to give apparent activation outside of the neurally activated area. For well-designed experiments, in which the differential areas of brain activation are expected to be small, this does not constitute a major problem. A typical value for the spatial resolution of fMRI is about 3 mm^3.

A final limitation, previously mentioned, is due to the high sensitivity of the images to slight variations in the magnetic field used for scanning, required to observe BOLD contrast. Because the magnetic susceptibility of tissue is slightly different from that of air, air-filled cavities in the head close to the brain, such as the nasal sinuses and the ear canal, may cause distortion and loss of signal in some brain regions, typically orbitofrontal cortex and inferior temporal cortex.

PET on the other hand is similar or slightly worse in terms of spatial resolution compared to fMRI. However, the time resolution is very poor ranging from 1-2 minutes. The reason for the poor temporal resolution is based on the fact that it takes that time for the isotopes to distribute within the brain. Spatial resolution is limited by similar aspects as for fMRI. Thus, the maximum spatial resolution to achieve with PET is slightly worse than for fMRI and is in the range of 4-6 mm^3.

EEG/MEG methods can measure neurophysiological activations on a millisecond basis (on the speed of thoughts). While in former times the spatial resolution for inferring the intracerebral sources of the EEG/MEG waves from scalp electrodes was poor, recent mathematical solutions to solve the inverse problem have substantially improved the spatial precision in localising the electrical sources. Using these measures the localisation error is not larger than 15 mm even if only 32 electrodes are used (Michel et al. 2001; Mulert et al. 2004). Thus, EEG/MEG provides an attractive and cheap alternative for scanning neurophysiological activations with excellent and unrivalled temporal resolution combined with meanwhile good spatial resolution. However, EEG/MEG are disadvantageous in detecting intracerebral electrical sources inside the *basal ganglia* or *mesial brain structures* although some studies exist which report activations in these areas. Due to the nature of the EEG/MEG signal, cerebellar activations

cannot be measured. This might be a major obstacle since the cerebellum has repeatedly been shown as a kind of computational hub involved in many cognitive and emotional processes.

NIRS is another method providing excellent temporal resolution compa-rable to the temporal resolution provided by EEG/MEG. However, the spa-tial resolution is not as good as for EEG/MEG. Most of the currently avail-able NIRS scanners provide limited spatial resolution because of the rela-tively large size of the sensors and LEDs placed over the skull. Thus, only a limited number of LEDs are currently placed over the skull ranging from 6 to maximally 32 LEDs. NIRS is currently most relevant in supplementing fMRI studies. The reason for this is that NIRS provide excellent measures about the time course of deoxygenated and oxygenated haemoglobin, molecules which are also important in determining the BOLD response.
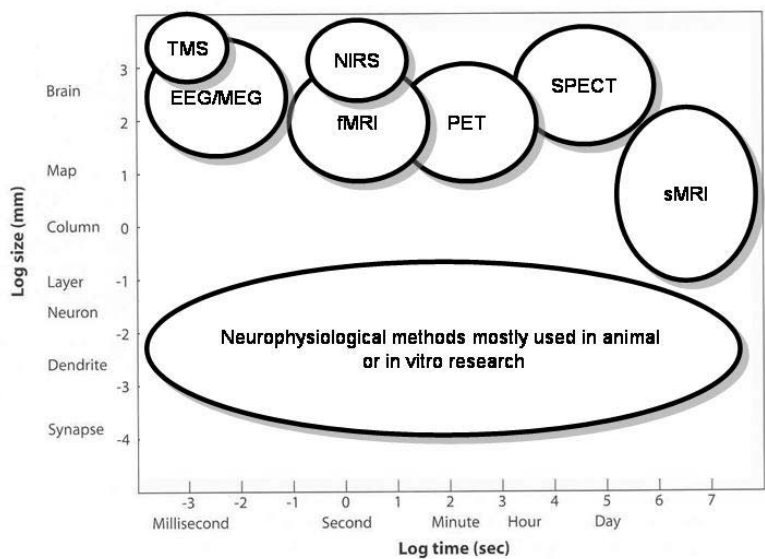
Figure 10.1:   Schematic classification of different brain imaging methods used in the realm of cognitive neurosciences (source: Jäncke 2005)

TMS can be used to deliver temporally precise (within a millisecond range) electrical stimuli to specific brain areas. These stimuli can be used to inter-fere with ongoing neural activation associated with psychological functions. The spatial resolution of the TMS pulses is limited by the focus of the mag-

netic field generated by the used coil. Mostly, figure-of-eight coils are used in cognitive studies allowing the application of magnetic fields with a diameter of 2 cm. Thus, the spatial resolution is limited by this factor. In addition, one has to keep in mind that the induced electrical activation spreads from the stimulated area to adjacently located brain regions also reducing the spatial precision. It is important to mention that TMS does not allow stimulation of deep brain structures like *basal ganglia* or the *hippocampus*. Even stimulation of the *cingulum* is considered a problem. Many experts suggest that TMS pulses can stimulate brain areas 2 cm vertically apart from the skull. The different brain imaging methods are classified in terms of spatial and temporal resolution (figure 10.1).

10.3   Interpretation of brain imaging results

In this chapter we will shortly compare the different methods in terms of their interpretational strength.

Structural MRI provides excellent images of the brain allowing very good delineation of brain structures down to the level of neural columns. Distinction of grey and white matter is also excellent. Studies comparing anatomical measures obtained from MRI measurements with measurements obtained from analyses of post mortem brains have provided very good correspondence between both modalities (Peters et al. 2000). The scientific community currently acknowledges the problem to adequately interpret the BOLD response. What the BOLD response really indicates is a matter of dispute. Most researchers accept the interpretation that the BOLD signal to some degree reflects synaptic activity or the local field potential. However, it is known that the correlation between the BOLD signal and the corresponding neurophysiological effects is not too strong. Thus, the BOLD signal is possibly affected by several additional factors. The PET signal used in cognitive and emotional studies strongly depends on the cerebral blood flow. However, the coupling between neuronal activation and the haemodynamic response is not perfect and in many situations non-linear. Thus, it is not evident what increased or decreased blood flow really means.

The most important and thus most substantial problem with fMRI and PET is the fact that they measure very slow physiological processes ranging

from 4 secs to several minutes. Thus, they do not capture and reflect the very fast psychological processes associated with thinking, perception, attention, and emotional experiences. Thus, these haemodynamic measures only measure some kind of average activations obtained during a period from 4 secs to 2 minutes. For many questions coming from cognitive and affective neurosciences, this time scale is definitively too crude. For example, a recent EEG experiment (Sinai, Pratt 2003) using a modern method to solve the inverse problem shows that the intracerebral activation within the secondary auditory cortex (including the planum temporale) shifts between both hemispheres within the first 250 milliseconds after stimulus presentation (figure 10.2). These kinds of rapid alterations in cortical activations cannot be captured by PET or by fMRI.
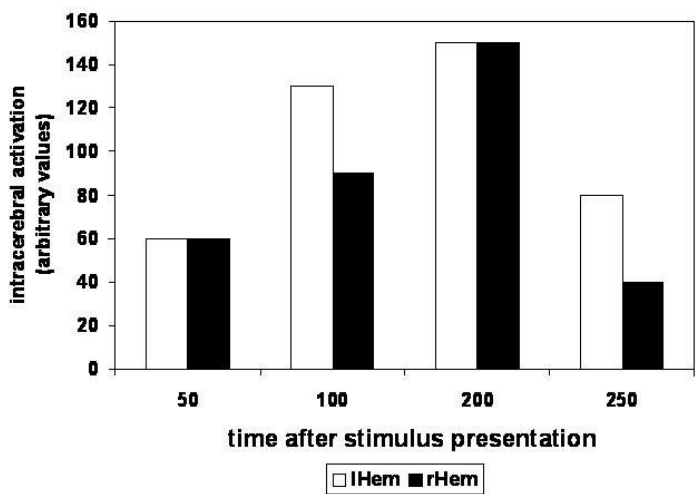
Shown are the intracerebral electrical activations 50, 100, 200, and 250 milliseconds after auditory presentation of single syllable words.150 and 250 milliseconds after stimulus presentation there is a left-sided preponderance of cortical activation while 50 and 200 milliseconds after stimulus presentation no functional asymmetry can be found. Data are calculated from Sinai and Pratt (2003).

Figure 10.2:   *Intracerebral activation as calculated with low resolution electrical tomography (LORETA) from evoked potentials (source: Jäncke 2005)*

Since more and more neurophysiological data point to the fact that the basic code of the human nervous system is coupled oscillated activation be-

tween different brain areas, EEG and MEG are basically measuring more directly the most interesting and important signals. PET and fMRI measure signals which are in some part only loosely related to these relatively fast oscillations.

Although EEG or MEG are much better in terms of temporal resolution fMRI is superior in spatial resolution although the difference between both methods is continuously diminishing. However, EEG and MEG cannot pick up reliable signal from the cerebellum, basal ganglia or the hippocampus. On the other hand fMRI is relatively poor in measuring reliable activations from orbitofrontal and mesio-temporal structures.

However, more fundamental is the question what the signals from functional brain imaging methods (either from fMRI, PET, or EEG/MEG) really mean. Do they indicate the neurophysiological basis or an epiphenomenon of psychological functions? Currently, we cannot give a plausible answer to this question without losing the firm grounds of sciences.

10.4   Advantages and limitations of brain imaging techniques

To date, much of what we know about the functions of different brain regions comes from neuropsychological studies in humans and lesion studies in animals. A distinct drawback of brain imaging techniques is that, unlike neuropsychological and lesion techniques, they cannot demonstrate the *necessity* of a brain region for a specific cognitive process. However, neuroimaging techniques can demonstrate that humans not suffering from neurologic damage routinely recruit this region to perform the task. Moreover, it is possible to compare levels of activation across individuals and to state that greater activation of this region is associated with better performance on a task. In other words, it is possible to compare activation between trials within an individual, and to state that for trials in which the subject made an error, activation was lower in this region than for trials that the subject performed correctly. Thus, functional brain imaging techniques can be used to characterise a region's contribution to specific cognitive processes. Moreover, brain imaging techniques can be combined with

techniques for temporarily disrupting neural activity in a temporally and spatially precise manner (TMS). There are several important advantages of brain imaging techniques over classical neuropsychological studies.

- Classical neuropsychological studies necessarily focus on the output of behaviour as the critical dependent variable, whereas neuroimaging studies can target cognitive processes that take place prior to a behavioural response. For example, it is impossible to determine to what extent lesions that result in a long-term memory impairment are associated with a deficit at encoding and/or retrieval. By means of brain imaging, however, one can identify brain regions associated with the effective encoding of memories separately from brain regions associated with effective retrieval. In addition, by using brain imaging methods one now can measure brain activity during processes which are not inevitably linked to overt behaviours. Typical examples are imagery processes.
- Second, brain imaging techniques enable us to identify the *entire* neural circuit underlying a cognitive process. Lesion studies in animals can accomplish this only piecemeal, by lesioning each area in turn. Clinical neuropsychological studies in humans would be difficult to accomplish this at all, given the limited availability of patients with specific brain lesions. This issue is an important one, because lesion studies bear the potential risk to completely ignoring the contributions of a specific region to a particular cognitive function. For example, the hippocampus has long been thought to be the primary structure contributing to the encoding and retrieval of memories. However, brain imaging has demonstrated that, in the healthy brain, the prefrontal cortex routinely contributes to memory encoding and retrieval.
- The third issue relates to the limited availability of neuropsychological patients: brain imaging techniques enable the neuroscientific community to examine the role of a particular human brain region in cognition even if one does not have access to specific patient groups. Moreover, it could be very difficult (or next to impossible, depending on the brain region) to find a patient with a lesion confined to this region one is interested in, because most brain lesions are rather coarse. Furthermore, cortical reorganisation can lead to recovery of function over time, which could lead one to assume mistakenly that a lesioned brain region is not normally involved in a specific cognitive process.
- Finally, brain imaging techniques with high temporal resolution, such as EEG and MEG, provide us with important clues about brain mecha-

nisms. It is beneficial to say that brain regions X and Y are involved in memory retrieval, but if we can say that brain region X is active a short time after region Y, we can begin to gain insight into the cascade of events leading to memory retrieval. In addition, brain imaging methods with high temporal resolution can provide additional important clues in understanding the dynamics of interhemispheric communication.

A common criticism of neuroimaging studies is that they can be highly unconstrained and atheoretical (Kosslyn 1999). Like any scientific tool, however, brain imaging can be used wisely or foolishly. Certainly, many exploratory brain imaging studies have been conducted, particularly in the initial phase of brain imaging, when it was important to validate the new techniques. However, the second generation of imaging studies, starting in the late 1990s, has been much more focused. Generally, cognitive neuroscientists carefully devise experimental manipulations designed to test psychological theories or specific predictions about brain function. Brain imaging techniques are likely to be an indispensable tool in cognitive neuroscience for the foreseeable future.

10.5   Summary

With respect to the methodological limits of neuroimaging for the study of cognitive processes, it has to be kept in mind that the psychological phenomenon of interest usually is a complex cognitive or emotional one which requires operationalisation, i. e. dissection into sub-processes and reduction of influencing factors in order to become amenable to a neuroimaging experiment. Additional restraints come from the required imaging equipment, which, for example in the case of fMRI, require the research subject to lie in the bore of the magnet and to avoid head movements. All in all, this may lead to a highly artificial and abstract test situation which requires careful assessment to which extent it really represents the cognitive process and behaviour which was intended to be studied. It also requires a critical discussion to which extent inference can be made from artificial test situations to human behaviour in "normal life" outside experimental settings.

Additional limits lie in the incomplete knowledge about the mechanism by which the measured signal is correlated with cognitive brain processes –

what does for example the BOLD response tell us about the underlying physiological processes? Moreover, it is currently intensively debated whether the first person perspective (e. g. subjective feelings) can be explored at all from the third person perspective (like brain imaging) because of insurmountable differences between both perspectives.

Many neuroimaging methods require the comparison of one cognitive state (e. g. active, or impaired function) to another (e. g. passive, base-line, or normal function). Due to a substantial intraindividual as well as interindividual and temporal variability of most brain processes, the integration of many repeated measurements in one individual over time, or the averaging of data from many subjects is required. This implies that many cognitive abnormalities that characterise particular deficits or deviations can only be demonstrated by brain imaging when small groups of subjects are compared to control subjects. Brain imaging is not diagnostic at the level of an individual with certainty, unless other psychological and psychiatric tests are additionally applied. To improve neuroimaging for these purposes, a higher sensitivity and specificity, and a much more refined normalisation of data and comparison against better standards would be required.

A very important point is that functional brain imaging methods probe the neural basis, the *mechanisms* of brain functions. This must be strictly distinguished from *contents* of cognitive processes which are not inferable from brain imaging. Therefore, "mind reading" is definitively beyond the scope of brain imaging, and it can only be speculated whether this might become possible in the future.

Because the results of complex brain imaging experiments are often presented as colourful visual maps, this conveys the impression of neuroimaging being a direct probe of brain functions, and that the essence of a complex experiment could be understood even by the lay-man. However, this bears the risk to forget that these visual maps are the result of extensive raw data processing, and that the results strongly depend on the chosen data processing procedures and subsequent data interpretation. All in all, this bears the risk of simplification and over-reliance on the method without taking its limits into account ("it is believed what is being seen"). It also bears the risk of reductionism, in the sense of that "one understands the brain by seeing it".

11   Applications of brain imaging: overview

The diverse set of neuroimaging methods, as described in the chapters 4 and 5 has provided the neurosciences with a new toolbox. Exploiting the unique properties of these methods in neuroscientific research has made it possible to investigate the brain from a new and different perspective: now brain functions, its dynamic processes, plasticity and self-organisation became the focus of research in an unprecedented way. As a consequence, the research focus of the neurosciences expanded to new areas, e. g. to cognition, behaviour and emotions. This led to the development of a new field within the neurosciences – the cognitive neurosciences. On the other hand, other disciplines such as psychology which had, in their study of cognition, behaviour etc., considered the brain predominantly as a "black box", by adopting the new toolbox, gained an understanding of the brain which was of a new quality and which triggered a broad range of new research questions and new research directions (Beaulieu 2003).

In addition to the stimulation of research, described above, neuroimaging methods themselves as well as the knowledge generated from their use in research lead to new applications. In the following chapters, we will outline the contribution of neuroimaging, the present state of the art and future perspectives in some selected fields. These are:

- *Clinical medicine.* In chapters 12 and 13, the actual and potential contributions of neuroimaging to the diagnosis and treatment of brain diseases and disorders will be presented. Special reference is given to neurosurgery (chapter 12.2), and to the early diagnosis and management of neurodegenerative diseases such as Alzheimer's disease, a major public health and social challenge in the coming years (chapter 13).
- *Pharmaceutical R&D*. Imaging, and especially molecular imaging methods play an increasing role in the research and development of new drugs (chapter 14).
- *Cognitive neurosciences*. Within the neurosciences, cognitive neurosciences have received a major stimulation by neuroimaging methods.

Using a bibliometric approach, we present data based on publication frequency to which extent and how the adoption of neuroimaging methods has impacted research in the cognitive neurosciences (chapter 15.2). Important topics within the cognitive neurosciences are investigations of brain processes involved in decision-making, learning, emotions and social interaction. To which extent these research findings can stimulate and be exploited in other fields, is analysed for the following examples:

− *Education (pedagogy).* In chapter 15.3, it is analysed to which extent findings from neuroimaging studies of learning could be used to improve individual learning behaviour or formal education, e. g. school lessons,
− *Economics and marketing.* Neuroimaging could, on the one hand, contribute to a better understanding of decision-making, but could also be used for manipulation of decision-making, e. g. in purchase or voting behaviour (neuromarketing) (chapter 15.3),
− *Forensic psychology*, e. g. for assessment of the credibility of a witness or suspect (lie detection), for the assessment of an offender's criminal liability, for the prognosis of offensive or criminal behaviour etc. (chapter 15.5).

The more neuroimaging is used to empirically investigate mental issues which have, for centuries, been the exclusive domain of the humanities, especially philosophy and theology, the more it touches upon deeply philosophical questions regarding the *conditio humana*. Possible mutual resonances between neuroimaging and the philosophy of mind are discussed in chapter 16. The possible impacts of neuropsychological findings regarding the free will has become a prominent issue in the present debate. Its possible impacts on the responsibility of man, and thus on the fundamentals of our criminal law are discussed in chapter 21. Some neuroimaging methods, especially TMS and EEG, do not only allow the analysis of brain processes, but also intervention into brain processes. This could, for example, be used for the purpose of cognitive enhancement. This issue is discussed in chapter 17.

12 Clinical applications of brain imaging

Apart from neuroimaging uses in research, most applications can be found in clinical settings, both in hospitals as well as in physician's surgeries. This is the main market where MRI, PET, and CT scanners are sold and the manufacturing companies design the scanners exactly for this purpose (chapter 18).

12.1 Clinical diagnosis

Currently various MRI techniques are used for diagnosing pathological processes of the central nervous system. For some of these diseases, brain imaging techniques have emerged as standard tools while for other diseases these techniques are either used as supplementary information or in the context of scientific questions. The diseases for which brain imaging techniques are currently used are:

- Degenerative dementia,
- Vascular disorders,
- Traumatic head injuries,
- Tumours,
- White matter diseases,
- Infections,
- Cortical dysplasias.

12.1.1 Degenerative Dementia

Dementia refers to an acquired and persistent syndrome of intellectual impairment. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines the two essential diagnostic features of dementia as

(1) memory and other cognitive deficits, and
(2) impairment in social and occupational functioning.

Some researchers distinguish degenerative and non-degenerative dementias. The degenerative dementias are pathological processes that are primarily intrinsic to the nervous system and tend to affect certain neural systems selectively. Many degenerative dementias are presumed to have a degree of genetic transmission. Non-degenerative dementias are a heterogeneous group of disorders with diverse aetiologies, including vascular, endocrine, inflammatory, nutritional deficiencies, and toxic conditions. The degenerative dementias comprise Alzheimer's disease (the most common form), frontotemporal dementias, prion-related dementias (e. g. Creutzfeld-Jacob disease), leukodystrophies (e. g. adrenoleukodystrophy), and dementias primarily affecting the extrapyramidal system (Wilson's disease, Huntington's disease, Parkinson's disease).

Although modern brain imaging techniques are useful in identifying gross degenerative processes like increased ventricles, loss of grey or white matter in particular structures, and hypometabolism in particular brain structures, it is currently basically impossible to use brain imaging techniques for the purpose of differential diagnosis. However, intensive research efforts are under way to design appropriate brain imaging techniques and statistical analysis for identifying subtle brain abnormalities which are typically associated with specific dementias.

A good example where significant progress has been made is the case of frontotemporal dementia where the more frontal type is associated with decreased grey matter volume and significant reduction of frontal metabolism. On the other hand the temporal variant of this type of dementia is associated with anatomical and metabolic deficiencies in the temporal pole. A similar progress has been made for the primary progressive aphasia (PPA) which is a specific variant of a degenerative process associated with strong grey matter reductions in the language areas located in perisylvian brain areas.

Although current brain imaging efforts are unsatisfactory in differentiating between different dementia types, recent publications offer more optimistic views (see also chapter 13). A typical example is the paper published by Thompson et al. (2004) who demonstrate that on the basis of time course anatomical analysis of brain structures in AD patients similar anatomical abnormalities are found as in post mortem brains of AD patients. Thus, with

the advent of new methods to analyse MRI images of the brain it might be possible to develop the differential diagnosis of dementias further.

12.1.2   Vascular disorders

A frequently occurring disease in this context is stroke, which is a sudden appearance of neurological symptoms as a result of interruption of blood flow. Stroke can result from a wide variety of vascular disorders, but not all vascular disorders produce stroke. The onset can be insidious, spanning months or even years. Strokes can produce infarcts, an area of dead or dying tissue resulting from an obstruction of blood vessels normally supplying the area. Of the numerous vascular disorders that affect the central nervous system, the most common are ischemia, migraine stroke, cerebral haemorrhage, angiomas, and arteriovenous aneurysms.

In particular the diagnosis and description of strokes have benefited from the advent of brain imaging (Chalela, Gomes 2004). For example, the exact location and extent of the infarcts can now be delineated by MRI techniques. A particular interesting approach is to localise the so-called *penumbra*. In focal strokes, the *core* territory refers to the region with the most severe reduction in blood flow and within which brain cells rapidly die. Adjacent to the core is the *penumbra*, a peripheral zone of moderate to mild ischemia where residual blood flow might transiently sustain tissue viability. Imaging studies have validated the concept that tissue viability is heterogeneous distal to an occluded brain blood vessel. In humans, positron-emission tomography (PET) and magnetic resonance imaging (MRI) can be used to visualise the ischemic penumbra. PET can detect oxygen-utilising tissue within regions of low blood flow. With MRI, there is often a volume mismatch between tissue showing reduced water molecule diffusion (a signature for cell swelling and ischemic tissue) and a larger area of compromised tissue perfusion early after stroke onset. The difference reflects potentially salvageable tissue. Imaging methods such as these can optimise the selection of candidates for specific therapies or for adjunctive therapy many hours after stroke onset.

12.1.3   Tumours

MR imaging is an important standard tool in the evaluation of intracranial tumours. Its effectiveness is due to its inherent high sensitivity to pathologic

alterations of normal parenchymal water content, as demonstrated by ab-
normal high or low signal intensity on T2- or T1-weighted images, respec-
tively. The goals of diagnostic imaging in the evaluation of patients with
suspected intracranial neoplasia are fourfold:

1) lesion detection,
2) lesion localisation,
3) lesion characterisation, and
4) determination of tumour extension.

Compared to CT, MR imaging allows more accurate determination of lesion
location and extent and better demonstrates subtle mass effects or atrophy,
particularly along the cerebral convexities. MRI better depicts the presence
of sub acute or chronic haemorrhage and permits more accurate distinction
between a vascular structure and adjacent parenchyma. CT is superior in
depicting the presence of calcification and bone abnormalities. MRI is supe-
rior to CT for differentiating between tumour and perifocal oedema, for de-
fining extent of tumour, and for showing the relationship of the tumour to
critical adjacent structures. Heavily T2-weighted sequences are the most
sensitive for the detection of tumour and oedema extent, but the tumour
focus is not well separated from surrounding oedema. T1-weighted images
following contrast enhancement generally provide better localisation of the
tumour nidus and improved diagnostic information relating to tumour grade,
blood-brain barrier breakdown, haemorrhage, oedema and necrosis. Con-
trast-enhanced T1-weighted images also better show small focal lesions
such as metastases, small areas of tumour recurrence, and ependymal or
leptomengeal tumour spread because of improved signal contrast. Proton
density images are useful for distinguishing tumour and edema from adja-
cent cerebrospinal fluid, which may have a similar appearance as high-sig-
nal areas on heavily T2-weighted images. In summary MRI allows a rela-
tively precise differential diagnosis of various kinds of intracranial and ex-
tracranial tumours. All this information is essential for surgical planning and
planning neuropsychological rehabilitation.

12.1.4   Traumatic Brain Injury

Traumatic brain injury (TBI) is an insult to the brain caused by an external
physical force that may produce a diminished or altered state of conscious-
ness. The direct effects of trauma may be skull fractures, and/or bleeding

into or around the brain. Injury to the brain can occur at several different levels, and depends upon the nature of the trauma. Penetrating injuries can be fairly well circumscribed, such as from a knife or bullet. In injuries such as from motor vehicle accidents or blunt trauma, common sites of contusions are the front part of the brain (frontal lobes) and the temporal lobes. This is because these parts of the brain sit next to bony prominences within the skull. MRI can be helpful in identifying brain damage due to the trauma. However, the application MRI is limited because any obvious neurological sign does not accompany even chronic effects of many closed-head injuries although substantial neuropsychological symptoms exist (attention and memory deficits). Thus, modern MRI techniques using higher field strength or MR spectroscopy might help to overcome this problem in the future.

12.1.5 White matter diseases

Diseases of the white matter are pathological changes of the white matter including the association and projection fibres as well as the commissures. Because of the excellent grey and white matter contrast offered by MRI images these diseases can easily be delineated and located. A disease where MRI has become an important diagnostic tool is Multiple sclerosis (MS). MS is a disease characterised by the loss of myelin, largely in motor tracts but also in sensory tracts. The loss of myelin is not uniform; rather it is lost in patches – small, hard circumscribed scars, called sclerotic plaques in which the myelin sheath and sometimes the axons are destroyed (Filippi, 2001). MS produces strange symptoms that usually first appear in adulthood. The initial symptoms may be a loss of sensation and control in one or several limbs. Electrophysiological methods are used to measure the conduction velocity of nervous system tracts in order to diagnose MS, because the speed of conduction is reduced in damaged nerve fibres. Today, MRI provides additional diagnostic tools that allow areas of sclerosis to be identified in the spinal cord and brain. Moreover, advanced MR imaging techniques have made it possible to better monitor a patient's response to MS therapies that may reduce relapse rate and may delay onset of disability (Minagar et al. 2005).

In spite of its value in diagnosing MS, however, MRI is poor in revealing the extent of the damage to myelin and axons. Fortunately, new imaging techniques are allowing describing and diagnosing mild from severe damage. Another shortcoming of MRI, is that is has not helped neurologists correlate

the brain lesion of MS with specific behavioural impairments (Ciccarelli, Brex, Thompson, & Miller, 2002). This lack of correlation is due in part to the fact that the sclerotic lesions are scattered throughout the white matter. It is also due in part to the brain damage but also have a propensity and ability to adjust their behaviour to compensate for brain injury. Thus, even though MRI is useful in neurological diagnosis; it is unlikely to ever fully replace behavioural assessment.

12.1.6   Brain infections

Brain infections are diseases caused by pathogenic microorganisms invading brain tissue. Because the central nervous system can be invaded by a wide variety of infectious agents (including viruses, bacteria, fungi, and metozoa parasites) the diagnosis and treatment of brain infection are important components of clinical neurology. Although infections of the nervous system usually spread from infection elsewhere in the body they finally affect the brain by causing head trauma, skull fractures, and killing nerve cells. CT and MRI are used to diagnose locate some infectious disorders. For example most viral infections produce non-specific widespread lesions of the brain. Bacterial infections of the brain result from an infestation of these organisms, usually through the bloodstream. The common neurological disorder resulting from bacterial infection is meningitis and brain abscess. In meningitis the meninges are infected by any of a variety of bacteria. Brain abscess also are produced by a variety of bacteria, secondary to infection elsewhere in the body. An abscess begins as a small focus of prudent bacteria that cause necrosis of cells in the affected region. As the bacteria multiply and destroy more brain cells, the abscess behaves like an expanding mass (one that is often hollow in the centre). These damages can be delineated by MRI methods. A problem is however, that currently available tests such as CT scans and MRI cannot clearly distinguish between different brain infections and other brain disorders such as tumours. This means patients often have to undergo invasive and dangerous brain surgery to diagnose their illness before treatment with antibiotics can begin. Recently, Magnetic Resonance Spectrometry (MRS) has been suggested to provide diagnostic tools to overcome this obstacle and to accurately and quickly differentiate between tumour and infection.

12.1.7   Cortical Dysplasia

Focal cortical dysplasia (FCD) is a malformation of cortical development corresponding to a localised disruption of the normal cortical lamination. This distinctive anatomical feature is associated with an excess of large, aberrant neurons, an increase in cortical thickness, and abnormal neuro-glial elements in the underlying white matter (WM). Because the dysplastic tissue retains sufficient connectivity FCD often is the reason for seizures. FCD is the most common form of developmental disorder in patients with intractable partial epilepsy referred for presurgical evaluation.

On T1-weighted MRI images, FCD is mainly characterised by variable degrees of cortical thickening, a poorly defined transition between grey matter (GM) and WM, and hyperintense signal within the dysplastic lesion relative to normal cortex. With the advent of high-resolution MRI of the brain it is now possible to identify FCD in an increasing number of patients. However, in many patients, lesions of FCD are characterised by minor structural abnormalities which are not recognised yet because the lesions are too subtle to be detected by standard radiological analysis. Previous attempts in assisting lesion detection included different contrast imaging, multiplanar curvilinear reformatting of 3D MRI, and statistical parametric mapping.

12.2   Neurosurgery

One of the disciplines which has strongly benefited from the advent of brain imaging definitively is neurosurgery. Using modern brain imaging methods neurosurgery has gained unprecedented anatomical and spatial precision.

On the one hand, neuroimaging is used before neurosurgery in order to precisely plan the operation. A major advantage of this approach is that the surgeon is now in the position to simulate his intervention and to adjust his intervention according to the individual anatomy of the patient's brain. This new method can help to eliminate detrimental tumours suppressing or inhibiting various psychological functions. A further advantageous aspect of MRI is that neurosurgical interventions can be optimised by identifying the size and location of anatomical regions responsible for the control of important psychological functions. A typical example is the identification of the

language centres in the brain which are localised on one hemisphere in most subjects. However, by precisely identifying the size and location of these language centres the surgeon can plan his intervention more precisely (e. g. conservative vs. anticonservative ablation).

In addition, neuroimaging is not only used before a neurosurgical intervention, but also during an operation. Within this approach of interventional MRI, low-field MRI scanners scan the patient's brain while the neurosurgeon is operating it. These simultaneously acquired MRI images support and guide the surgeon during the intervention with high spatial precision. In this context a new discipline has evolved which is called image-guided neurosurgery (IGNS). The central hypothesis of IGNS is that neurosurgical procedures can be made more effective and less invasive if the neurosurgeon can be provided with anatomically precise image-based information describing the underlying anatomy, function, and vascularity. In addition, the new tools will also allow him to interpret and use this information effectively. These image-guided tools provide a virtual, non-invasive "window" into the brain, allowing the neurosurgeon visual access to anatomical details of the brain area and the associated physiological functions that are not available using other means. The ultimate objective of this form of neurosurgery is to re sect the smallest possible volume of brain tissue, causing the least trauma to the patient, to achieve the desired therapeutic result. To achieve this objective, the goal of an ideal IGNS system is to report the position of an intra-operative guidance device within the brain with perfect accuracy. Thus, this goal is exactly the same as for structural and functional brain imaging which also tries to achieve perfect accuracy in transforming the digitised brain data to a 3D brain model.

Within IGNS there are mainly seven approaches which are currently of strong interest:

1) Developing of digital brain atlases,
2) Modelling of surgical tools,
3) Integration of endoscopic tools and MRI images,
4) Stereoscopic visualisation of IGNS tools,
5) Modelling of tissue movement during surgery,
6) Tactile interfaces for navigation in 3-D images,
7) Integration of diagnosis and treatment.

In the following chapters 12.2.1 to 12.2.7 we will present a brief overview of these different approaches. Additional information is also available in chapter 18.2.3. Applying these interventional MRI scanners exposes not only the patient, but also the surgical staff to the electromagnetic fields generated by these devices. The present discussion on possible occupational health risks is covered in chapters 6.1 and 6.6.

12.2.1   Brain atlases

In order to achieve accurate navigation within the entire cortex but also within the basal ganglia, thalamus, and cerebellum detailed anatomical and functional atlases are currently used or under development (for applications coming from basic research see also chapter 4.3.3). Precise atlases (anatomical and functional) allow accurate targeting of functional lesion sites, thus substantially improving non-invasive or minimally invasive surgery. Many structures within the brain are not visualised well by standard MR images, because either, a) the grey/white matter borders defining anatomical landmarks are too small for the resolution of the scanner, or, b) that the regions of different functionality do not appear as differences in white/grey matter contrast. In addition, cortical structures are highly variable across several subjects, thus it will be necessary to either use probability atlases (see also chapter 4.3.3). A further problem in identifying anatomical substructures arises for the much smaller structures in the basal ganglia, thalamus, and cerebellum. Structures such as the thalamus and basal ganglia are made up of groups of cells that control different functions, but can only be differentiated histologically or physiologically. Brain atlases, based on histological or cytoarchitectonic divisions have to be developed allowing the integration with the anatomical images to properly identify these regions. Functional data must supplement this information to distinguish those areas that are histologically identical but functionally distinct. This is of particular importance during functional neurosurgery using thalamotomy and/or pallidotomy for the treatment of Parkinson's disease.

12.2.2   Modelling of surgical tools

The main advantage of the incorporation of brain atlases into IGNS is to improve planning and guidance of surgical procedures for various brain diseases which require neurosurgery. The advantage is that surgical interventions can be done virtually and the surgeon can test the route he has to

take through the brain tissue and he can model the extent of resection he is causing. Thus, he can simulate several strategies before he operates on real brain tissue.

In addition, these tools are now increasingly used for training purposes, so that surgeons can improve their skills in a virtual system before using them on patients.

12.2.3   Integration of endoscopic and MR images

Endoscopy has been employed for decades as a surgical tool, mostly in orthopaedics and abdominal surgery, and more recently within the brain, where it has the advantage that the imaging lens may be introduced into the brain close to the surgical site. However, to use endoscopy effectively in the IGNS environment requires accurate tracking during a procedure. A technical endeavour is to integrate the simultaneous visualisation of endo-scopic tools placed at the target site in the brain and to integrate these images with pre-operative MRI images. Also, the resulting images must be registered with the pre-operative MRI volume. These techniques take a standard 3-D MRI scan and compute the image that the endoscope would "see" from a chosen viewpoint. The tracked endoscope images will then be matched to, and displayed alongside the MRI image computed from the same viewpoint as the 3-D pre-operative MRI. This merging process allows the endoscope image to be visualised in its proper context relative to its surroundings.

12.2.4   Stereoscopic visualisation in IGNS

Because the brain is a relatively small organ with tiny structures, neurosur-gery demands high accuracy in terms of visual-motor integration to guide the surgeon through the brain. Therefore, many neurosurgeons currently examine whether stereoscopic visualisation in surgical planning and guid-ance is an effective means of conveying three-dimensional information. Stereoscopic information enhances visual spatial perception and might im-prove the effectiveness of neurosurgery as a routine part of IGNS systems.

12.2.5   Tissue movement during surgery

Standard IGNS techniques yield superb visualisation of the anatomy of the lesions and target, both in 2-D planes and 3-D reconstructed images. How-

ever, during procedures that require craniotomy, brain shift of 10-20 mm can occur which are difficult to track, and render pre-operative images inaccurate. Therefore, several technical constructions are currently under development allowing tracking and visualising tissue movements during surgery. To solve this problem several approaches are currently used, two of them are 1) tracking the cortical surface and 2) integration of MRI with 3D ultrasound.

12.2.6   Tactile interfaces for navigation in 3-D images

Finally, new applications are under development allowing augmenting tactile feedback to enhance the interpretation and manipulation of 3D medical images during surgical planning and guidance. Thus, the surgeon will receive more information about the IGNS tools while he/she is navigating through the patient's brain.

12.2.7   Integration of diagnosis and treatment

One of the modern techniques which are used in the context of IGNS is the Gamma Knife method and the treatment of acoustic neuromas. An acoustic neuroma is a benign tumour that grows from Schwann cells of the vestibular nerve leading to progressive hearing loss, ringing in the ear (tinnitus) and balance problems. An acoustic neuroma often grows first in the auditory canal and then expands to compress the brain. Treatment options for acoustic neuroma include surgical re section, stereotactic radio surgery or fractionated radiation therapy. The Gamma Knife can destroy deep-seated vascular malformations and brain tumours once considered inoperable. The treatment is unique because, with the Gamma Knife, no surgical incision is performed to 'expose' the tumour. The Gamma Knife technology represents one of the most advanced means currently available to treat brain tumours, arteriovenous malformations (AVMs), collections of abnormal brain arteries and veins.

12.3   Summary

Apart from neuroimaging uses in research, most applications can be found in clinical settings, both in hospitals as well as in physician's surgeries. This

is the main market where MRI, PET, and CT scanners are sold and the manufacturing companies design the scanners exactly for this purpose (chapter 18).

One of the main clinical applications for brain imaging is to precisely measure brain anatomy. This can support diagnosis of neurodegenerative disorders, of anatomical brain abnormalities (e. g. atrophies, lesions) and the determination which brain regions are affected by e. g. stroke or vascular dementia. Another application is the detection and staging of brain tumours. Moreover, information about precise brain anatomy is used for planning and conducting brain surgeries.

Up to now, *functional* neuroimaging is still mainly restricted to research settings, while only few applications are on the verge of being used in the clinic. Among them is the functional mapping of brain regions (e. g. language centres) adjacent to a brain tumour or to foci in epileptic patients in order to precisely plan brain surgery. Moreover, functional imaging may be used to support neurological or psychiatric therapies.

Several restrictions for a quick adoption of functional neuroimaging in clinical medicine exist, e. g.

- further development of functional neuroimaging procedures which were developed in research settings for the routine clinical use, e. g. by improving the normative databases[10], by standardisation of clinical test protocols, data processing and data interpretation,
- lack of diagnostic added-value compared to established examinations, need for improvement of sensitivity and specificity,
- lack of appropriate qualification in medical staff,
- lack of reimbursement of functional neuroimaging procedures by health insurances.

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10   Brains show a remarkable interindividual variability of neuroanatomical structures (in terms of shape, size, and relative grey-white matter composition). In order to properly interpret patient data, individual neuroanatomical features must be compared to a "standard", a normative database. Thus, several international brain anatomy centres are collaborating in order to build up huge databases in order to provide brain atlases with normative databases. These databases will help the clinician, but also the researcher in improving the quality of neuroradiological diagnosis (see also chapter 4.3.3).

13   Applications of brain imaging: Alzheimer's Disease

13.1   Alzheimer's disease as a major health, socio-economic and research challenge

Dementias are a group of age-related neurodegenerative diseases which result in a global decline of cognitive functions so severe that they interfere with the affected person's daily functioning. Today, the most widely used definition of the dementia syndrome is that of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IIR and DSM-IV). The core symptom is severe memory loss accompanied by at least one or two of the following symptoms: apraxia, aphasia, problems in spatial cognition, attention deficits or problems in action control.

However, this definition has two important limitations. First, in requiring that all demented persons have memory impairment, it excludes disorders that spare memory or that present with predominantly behavioural and language disorders. Second, the requirement of social or occupational disability renders the definition imprecise and unquantifiable. As a consequence, patients in minimally demanding environments are not considered demented whereas the same disability would warrant the diagnosis of dementia in a more demanding situation.

A more updated definition describes dementia as a syndrome of acquired, persistent intellectual impairment produced by brain dysfunction. This impairment compromises at least three of the following spheres of mental activity: language, memory, visuospatial skills, emotion and cognition (abstraction, calculation, judgment and executive function).

Exact determination of the frequency of different types of dementia also varies according to diagnostic criteria and cohort. The diagnostic formulations of dementia that are most widely used are the clinical definitions contained in the DSM-IIIR or the DSM-IV and the clinical criteria contained in the National Institute of Neurologic, Communicative Disorders and Stroke-AD and Related Disorders Association (NINCDS-ADRDA) Work Group.

According to recent publications and consortium meetings Alzheimer's disease is the considered to be the most frequent dementia with a prevalence of about 60 % of all dementias. Lewy-body dementia clearly overlaps with Alzheimer's disease. Dementia with Lewy bodies is present in about 15 and 30 % of cases diagnosed by the pathologist as also having Alzheimer's disease. Conversely, of cases showing Lewy-body dementia, 60 to 90 % also have Alzheimer's pathology. A further type of dementia is frontotemporal dementia (FTD) which represents 5 to 10 % of cases. FTD does occur in a significant number of people with dementia, often in those with earlier onset, in their 40s or 50s. Thus, FTD may be more troubling to affected individuals and their families because patients may still be employed while suffering early symptoms. The fourth variant of dementia is the so called vascular dementia which overlaps with Alzheimer's disease. The majority of elderly people may have a lesion that would qualify as a stroke, stroke-like micro-vascular disease, or cerebrovascular disease. Depending on the series and the criteria, vascular dementia represents somewhere between 5 and 20 % of cases. A large number of cases have mixed Alzheimer's pathology and vascular pathology. It is important to note that on the basis of current knowledge precise diagnosis of the type of dementia can only be done using autopsy data.

Dementias lead to a global decline of cognitive functions (e. g. memory, deliberation and language, to behavioural changes) and brain volume (loss of grey matter volume in several brain areas). Thus, as a consequence these subjects need intensive custodial care including therapeutic approaches include general medical management, psychosocial interventions as well as pharmacotherapy of cognitive and non-cognitive deficits. Depending on the type of dementia, death occurs, on average, 9 years after diagnosis or onset of evident symptoms, respectively. The symptomatic treatments that have been developed offer, at best, incomplete and transient benefit to patients, but do not significantly modify the course of the disease. At the present state of knowledge, the progression of the disease can at best be slowed down for some time, but it cannot be reversed or cured. Moreover, stigma and discrimination against people suffering from dementia are widespread, with far-reaching consequences. Among them are poor quality treatment and care, because of the general notion that these conditions are untreatable, poor quality of life and marginalisation (e. g. within the care system, in defining research priorities, in social distancing and exclusion) (Graham et al. 2003).

In the next few decades dementia will affect a considerably increasing number of the elderly. In the year 2000, 7.1 million people suffered from dementia in Europe. It is expected that this number will rise to about 16.2 million dementia sufferers in 2050. The number of new dementia cases per year will increase from about 1.9 million in the year 2000 to about 4.1 million in the year 2050. Contrarily, the working-age population will considerably decrease during the next 50 years. In the year 2000, 7.1 million dementia cases faced 493 million persons in working-age. This equals a ratio of 69.4 persons in working-age per one demented person. Until the year 2050, this ratio will decrease to only 21.1. (Wancata et al. 2003). In Switzerland, the number of persons suffering from age-related dementia is estimated at 89,000. Per year, 18,000 dementia patients die, while the number of newly diseased persons is estimated at 21,000. As a consequence, the number of demented patients is expected to rise to 113,000 in 2020 (Schweizerische Alzheimervereinigung 2004).

Alzheimer's disease (AD) is the most common cause of dementia in aging. It is a progressive, neurodegenerative disease characterised by a loss of function and death of neurons in several brain areas, leading to decline of mental functions, especially memory. More than 15 million individuals worldwide suffer from Alzheimer's disease. In Switzerland, approximately 70,000 persons suffer from AD. As with other dementias, the number will rise significantly in the coming decades. This is due to the general increase in life expectancy, the demographic development and the fact that the risk of AD dramatically increases in individuals beyond the age of 70[11].

Because dementia in old age is a source of massive burdens and massive costs for individuals as well as society, major challenges have to be mastered by policy, health care systems, social security systems and society. Quality of life of the demented persons has to be improved without overexerting social security systems and the working population, e. g. by

- developing effective preventive interventions in order to lower the incidence of dementia,
- developing improved treatment and care for demented persons,

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[11]   From the age of 65 onwards, the number of affected persons doubles with every five years: In the group of the 65-year-olds, the prevalence is 1 to 5 %, in the 75-year-olds, it is 10-12 %, and in the age group above 85, it is in the range of 25-35 % (Walsh, Selkoe 2004).

- providing good care for demented persons. According to principles stated in the United Nations resolution on the Rights of the mentally ill to protection and care, adopted in 1991, every patient shall have the right to be treated and cared for in his or her own community, and in the least restrictive environment, with the least restrictive or intrusive treatment,
- ensuring access of demented persons to good care, major obstacles being stigma and financial burdens for the social system.

Neurodegenerative disease research has increased considerably. In the last ten years, more than 65,000 publications were entered into a major database of medical literature, PubMed, under the keyword "neurodegenerative disease", including over 20,000 publications on Alzheimer's disease (Forman et al. 2004). Alzheimer's disease research addresses, among others, the following issues:

- characterisation and diagnosis of Alzheimer's Disease, course of progression, differentiation from other forms of dementia,
- identification of risk factors and predispositions for AD,
- elucidation of the mechanism of disease,
- identification and validation of targets for therapeutic interventions,
- development of drugs,
- testing the safety and efficacy of the drug candidates.

Neuroimaging methods have a role in all these issues. This will be outlined in more detail in the following chapters 13.2 and 14.

13.2   Neuroimaging biomarkers in clinical diagnosis and management of Alzheimer's Disease

Most neurodegenerative disorders, and this also hold true for AD and other forms of dementia, are heterogeneous, genetically complex and difficult to diagnose. It has been estimated that more than 15 % of AD are misdiagnosed in the clinic (Lansbury 2004). Because dementias differ greatly in their underlying pathophysiology and the extent to which they are treatable, a correct diagnosis is of great clinical importance in order to choose a therapeutic strategy to which the patient is likely to respond. Moreover, in

AD, neurodegenerative changes in the brain begin well before cognitive deficits become evident. Presently, only drug treatments are available which can delay, but not reverse the progression of the disease. They seem to be of larger benefit in patients in an early stage of the disease before severe pathology is established and massive neuronal loss has taken place.

Against this background, there is an increasing need not only for an accurate diagnosis of AD in the clinical practice, but also for diagnosis in early, presymptomatic stages of the disease, often termed "mild cognitive impairment". In this stage, the cognitive deficits are limited to memory alone and the everyday abilities are still preserved, but the affected persons are at high risk of developing full AD in the next few years. From the point of view of the affected individual, an early diagnosis and predictions of future development of cognitive abilities may allow time to plan for caretaking, legal and financial arrangements. Moreover, it is hoped that it could become possible to significantly delay the onset of severe dementia symptoms by early intervention, so that the symptom-free period is prolonged and the period of severe impairment until death is shortened. Model calculations show that delaying the onset of dementia by five years could translate into a 50 % decrease in AD prevalence (DeKosky, Marek 2003). This could compensate for the additional cases that are due to the demographic development, thus keeping the number of patients suffering from dementia on today's level.

Therefore, diagnostic tools or biological markers, respectively, are highly desirable which can be used in the clinic to

- diagnose AD, and reliably differentiate AD from other diseases with similar symptoms,
- diagnose AD even in the early stage of mild cognitive impairment, which is difficult to differentiate from "normal ageing",
- follow the conversion from normal cognitive function via mild cognitive impairment to fully developed AD over time,
- monitor the effects of therapeutic interventions on the time course and progression of the disease.

Related analytical tools and biomarkers could also be of great importance in AD research and in the development of new AD drugs. It is likely that

several biomarkers will be necessary to address all relevant stages and forms of AD. In addition to genetic, clinical and biochemical biomarkers, major contributions are expected from structural as well as functional neuroimaging which is increasingly used to aid diagnosis in dementia (Scheltens et al. 2002). In addition, approaches for imaging biochemical markers with the help of PET and SPECT, especially for receptor-ligand studies, as well as MRI spectroscopy are considered highly promising (Villemagne et al. 2005). The present state of the art will be outlined in the following paragraphs.

Suitable markers for the early detection of AD should fulfil the following requirements (Nestor et al. 2004):

- high sensitivity in detecting earliest cognitive or biological changes due to AD,
- high specificity, thus allowing differentiation among early AD, normal aging, other organic brain disorders that cause memory loss, and depression,
- robust test-retest reliability,
- close correlation with the pathophysiological mechanism of AD,
- non-invasive,
- ready applicability,
- low cost, easy to perform,
- suitable for widespread application.

Potential markers must be thoroughly tested and validated in order to avoid their failure due to the following reasons (Pien et al. 2005):

- The biomarker does not represent the pathophysiological pathway.
- There are several pathophysiological pathways, and the biomarker is only in one of them.
- The biomarker is not in the pathophysiological pathway affected by the therapeutic intervention.
- The therapeutic intervention acts through different and potentially unknown pathways.
- The biomarker does not correlate well with traditional clinical endpoints or other diagnostic criteria because it is more (or less) sensitive than the traditional endpoints.

Three lines of research are being followed in order to identify and validate such markers:

- neuropsychological markers,
- analysis of biomarkers in cerebrospinal fluid (CSF),
- neuroimaging markers.

They will be described in more detail in the following paragraphs. However, direct comparisons of different markers regarding specificity, sensitivity or the other requirements listed above, are largely unavailable (Nestor et al. 2004).

Neuropsychological markers

Dementias are not exclusively but most prominently described and diagnosed by means of neuropsychological test profiles. Before discussing the main findings in this area it is necessary to emphasise the fact that both international diagnostic manuals describing the core symptoms of dementia (ICD and DSM IV) rely on purely psychological symptoms. Thus, neuropsychological test profiles are presently the most sensitive, reliable and valid measures to diagnose dementia. Other measures (including brain imaging, EEG, MEG, or other biological markers) are only recommended as supplementary tools. This view is fully supported by current literature on that topic. For example the most comprehensive and exhaustive review using meta-analytic techniques examined the sensitivity of neuropsychological, structural, and physiological measures to diagnose dementia of the Alzheimer's type (Zakzanis 1998). Effect sizes (representing normalised differences between AD patients and normal controls) are reported for the California Verbal Learning Test, the Wechsler Memory Scale-Revised, structural (i. e. magnetic resonance imaging [MRI]), and functional (i. e. positron emission tomography [PET], single photon emission computed tomography [SPECT]) neuroimaging methods. Overall, effect sizes from MRI studies are larger than those obtained from SPECT and PET, respectively, but not as large as those obtained from the neuropsychological measures! On the basis of this finding, the neuropsychological and gross pathologic similarities between Alzheimer's disease, other dementing conditions, and mixed dementias, warrants the coupling of neuropsychological evaluation for its

sensitivity with neuroimaging visualisation for its specificity in improving diagnostic and differential accuracy.

Currently, several neuropsychological test batteries are used for dementia diagnosis. The most widely used battery is the CERAD (Chandler et al. 2005; Whyte et al. 2005), or test batteries combining several sub tests from other test batteries (mostly verbal and nonverbal memory tests, tests for examining various attentional and spatial functions, as well as tests measuring social and emotional competencies) (Jahn et al. 2004; Linde-boom, Weinstein 2004). It is strongly recommended from many authorities not to use quick screening tests (mini mental scale: MMSE, DEMTEC etc.) for dementia diagnosis because of their poor objectivity, reliability, and va-lidity. Recently. Jahn et al. (2004) have elegantly shown that using the CERAD battery 90 % of demented and non-demented depressive patients (pseudo-dementia) were correctly classified. Increasing the CERAD test battery from 11 to 18 tests with some additional more refined motor and memory tests even increased the discrimination of both groups up to 95 %.

Even for the purpose to differentiate between different types of dementias (AD, Lewy body, frontotemporal or vascular) the exact quantification and conscientious use of measures taken from standardised neuropsychologi-cal tests is recommended (Vicioso 2002). Medical measures (e. g. neuro-leptic sensitivity, hachinski score etc.) are only supplementary measures for differential diagnosis. At the current state brain imaging measures are useful in helping to differentiate between frontal dementias and other types of dementia.

Currently, it is debated whether one might distinguish mild cognitive im-pairment (MCI) which is considered as being the precursor state of demen-tia from the fully developed dementia form on the basis of neuropsychologi-cal test results (Petersen 2004; Winblad et al. 2004). The findings are mixed mainly because MCI as detected by neuropsychological tests can be due to different underlying reasons including emerging degenerative rea-sons to psychological problems and diseases (e. g. depression, alcohol intoxication). A major problem in using neuropsychological tests is that neuropsychological measures can be strongly influenced by the partici-pant's motivation which may be affected by different reasons (Nestor et al. 2004).

However, as mentioned above the major advantage of neuropsychological testing is that the tests are standardised and the test results are compared to precisely designed norms covering different subgroups (e. g. gender, age, education etc.). None of the brain imaging methods used so far are standardised and refer to norms like the neuropsychological tests. Thus, this is a major advantage of neuropsychological testing and a major disadvantage of using brain imaging methods in this context.

Analysis of biomarkers in cerebrospinal fluid (CSF)

The rationale that biomarkers should reflect the pathophysiological mechanisms of AD led to the analysis of proteins in cerebrospinal fluid which are involved in mismetabolism of beta-amyloid and neurofibrillary degeneration. Three cerebrospinal fluid (CSF) biomarkers have been most extensively evaluated as markers of sporadic AD:

- total-tau (T-tau),
- tau phosphorylated at various epitopes (phospho-tau, P-tau), and
- the 42 amino acid form of β-amyloid (Aβ42).

The cerebrospinal fluid levels of these proteins reflect the metabolism of these proteins in the central nervous system. Usually, they are quantified by ELISA methods. Evidence suggests that no single CSF biomarker can be used to diagnose Alzheimer's disease definitively. Rather, the combination of all three markers must be employed to obtain sufficient diagnostic accuracy: Measurement of total tau and Aβ42 in the cerebrospinal fluid seems useful to discriminate early and incipient AD from age-associated memory-impairment, depression, and some secondary dementias, but early and differential diagnosis is significantly improved by measurement of various phosphorylated tau proteins. If combined with magnetic resonance imaging, monitoring the time course of AD becomes possible (de Leon et al. 2004).

While the neuropsychological tests and structural neuroimaging are already part of established clinical diagnostic work-up for suspected AD, but need further refinement, measurement of CSF biomarkers is still confined to research settings. It will need to demonstrate a considerable increase in predictive value over existing diagnostic schemes, if it is to be incorporated

into routine diagnostic practice (Nestor et al. 2004). At present, it is strongly recommended to use CSF biomarkers in the clinical evaluation of MCI cases only if it is combined with the cumulative information from the clinical examination, standard laboratory tests and brain-imaging techniques SPECT and MRT (Blennow 2004).

EEG and MEG

The electroencephalogram (EEG) has been used as a tool for diagnosing AD and other dementias for several decades. The hallmark of EEG abnormalities in AD patients is a shift of the power spectrum to lower frequencies and a decrease in coherence of fast rhythms (Adler et al. 2003; Jeong 2004; Mattia et al. 2003). These abnormalities are interpreted as reflecting functional disconnections among cortical areas resulting from death of cortical neurons, axonal pathology, cholinergic deficits, etc. In addition, new approaches have been developed improving the accuracy of differential diagnosis and early detection of AD based on multimodal approaches, longitudinal studies on nonlinear dynamics of the EEG, drug effects on the EEG dynamics, and linear and nonlinear functional connectivity among cortical regions. EEG abnormalities of AD patients are characterised by slowed mean frequency, less complex activity, and reduced coherences among cortical regions. These abnormalities suggest that the EEG has utility as a valuable tool for differential and early diagnosis of AD. Beside these EEG measures ERPs have also been examined in the context of Alzheimer diagnosis. Several reviews and experimental studies have shown that the P300, the N400 or other ERP components are very good measures to differentiate between Alzheimer patients, other dementias, pseudodementias and control subjects. Thus, these measures should be used as routine tools in near future as a means of objectively and reliably diagnosing Alzheimer dementia and other dementias (Katada et al. 2004; Olichney, Hillert 2004; Polich, Herbst 2000). The advantage of these methods is that they are relatively cheap and can be used on a routine basis in a clinical setting.

Neuroimaging markers

Both structural as well as functional imaging studies may be useful (Laven, Bednarczyk 2001). Structural studies (magnetic resonance imaging and computerised tomography) are especially suitable to detect the presence of

stroke lesions and vascular dementia, whereas functional studies (magnetic resonance spectroscopy, positron emission tomography and single-photon emission computed tomography) can disclose metabolic and blood flow alterations that may be characteristic for different types of dementia. The following trends can be observed in neuroimaging in dementia diagnostics:

- *Focus*. The focus in neuroimaging research, especially magnetic resonance imaging, has shifted to early diagnosis and monitoring of the disease course, with a special interest in predicting dementia in patients with mild cognitive impairment.
- *Refinement and routine use of structural neuroimaging.* In the past, structural brain imaging using CT or MRI was mainly used to exclude surgically treatable causes of cognitive impairment which, however, account for only about 1 % of all causes of dementia. In recent years, however, the focus has shifted from its use to rule out certain diseases towards a supporting role for the clinical diagnosis. For the diagnosis of vascular dementia and vascular cognitive impairment, MRI is the method of choice. It appears to be desirable to obtain a structural brain scan at least once during the work-up of patients with cognitive decline (Scheltens et al. 2002; van Straaten et al. 2004). The emphasis is on improving diagnostic accuracy in the further development of structural neuroimaging. With respect to early diagnosis of AD and risk of converting from MCI to AD, structural MRI can be employed. Highly predictive MRI biomarkers for AD are the atrophy and/or volume loss of certain brain regions (medial temporal lobe, entorhinal cortex). Serial registration of MRI scans to identify cerebral volume changes over time, using the patient as his own control, seem to be highly accurate for predicting the transition from MCI to AD in individuals. However, to achieve diagnostic certainty, this would require repeated imaging possibly for more than two years. Moreover, additional research is required to make data interpretation simpler, thus rendering it clinically applicable (Nestor et al. 2004).
- *Increasing importance of functional neuroimaging.* While in the past, functional studies were mainly used for understanding pathophysiological mechanisms of AD, PET and SPECT brain imaging now also become important in the early and differential diagnosis of dementia. (18)F-fluoro-deoxyglucose positron emission tomography (FDG PET) can aid to predict AD in an early stage (Mirzaei et al. 2005). Following a decision of the Centers for Medicare and Medicaid in autumn 2004, FDG PET

examinations have become reimbursable in the USA for patients that have been diagnosed with some sort of dementia.

In addition, specific radioligands have been developed which make possible to image beta-amyloid plaques in vivo in the aging human brain with the help of PET and SPECT (Villemagne et al. 2005). Because plaque formation precedes AD onset by many years the non-invasive detection of such plaques could be very useful for presymptomatic AD diagnosis. It could also be used in clinical trials to monitor the patients' response to treatment with candidate medications (Higuchi et al. 2005; Francis et al. 2005). Recently, a proof of concept study was published which shows that the imaging of amyloid plaques in human subjects in vivo with PET is feasible (Klunk et al. 2004). Imaging neurofibrillary tangles, separately or in concert with A beta plaques, remains to be demonstrated (Mathis et al. 2004; Mathis et al. 2005). Because PET and SPECT require the use of radiotracers and the vicinity of a cyclotron for their preparation, whereas MRI is cheaper and has a better spatial resolution, research is underway to establish molecular imaging MRS procedures for the early detection of AD (Valenzuela, Sachdev 2001; Jessen et al. 2005; Marjanska et al. 2005) and also to visualise amyloid plaques with the help of MRI (Higuchi et al. 2005). However, the latter approach has up to now only been realised in mice and still has to be translated into humans.

Moreover, several studies have addressed the question from a health-economic perspective what the economic impacts of incorporating of FDG PET into the clinical diagnostic work up of patients with early symptoms of cognitive decline would be. The following results have been reported:

Two studies relate to the inclusion of functional imaging in the early-stage diagnosis of AD: In a study with relevance for Europe, the conventional diagnostic procedure was compared to a similar procedure which additionally included (18)F-fluoro-deoxyglucose positron emission tomography (FDG PET), and the overall cost per patient in either strategy; diagnostic accuracy and cost per accurate diagnosis were analysed. Cost-savings per accurate diagnosis ranged from 623-6,110 € in favour of the strategy with PET. For the same cost, more accurate diagnoses were made, resulting in benefit for patients and society. The positive results were maintained over a wide range of values for the critical variables cost of PET, sensitivity and

specificity of PET and delay in cognitive decline because of appropriate medication. Therefore, they seem to be transferable from Belgium to other European countries with a similar health system. On the basis of these results, the authors advocated the incorporation of FDG PET into the clinical diagnostic work up of patients with early symptoms of cognitive decline (Moulin-Romsee et al. 2005). A similar study, carried out for the USA, came to the conclusion that appropriate use of PET for evaluating early dementia in geriatric patients could add valuable information to the clinical work-up, without adding to the overall costs of evaluation and management, resulting in a greater number of patients being accurately diagnosed for the same level of financial expenditure (Silverman et al. 2002).

Two other studies address the question to which extent functional imaging is useful for the diagnosis of mild to moderate AD:

The objective of a US study was to evaluate the cost-effectiveness of PET, SPECT and dynamic susceptibility-weighted contrast material-enhanced magnetic resonance imaging (DSC-MRI) as additional strategies to the standard clinical examination, for the diagnosis of AD in community-dwelling patients with mild or moderate dementia who presented to specialised AD centres. The rationale for the study was the high cost of diagnosis, especially with PET, and also of medical care, for patients with AD. The analysis adopted a societal perspective and included both direct and indirect costs[12]. The authors conclude that both DSC-MRI and PET may have high diagnostic accuracy. Dynamic susceptibility-weighted contrast material-enhanced magnetic resonance imaging (DSC-MRI), added to the standard examination, may even be preferable to PET for the diagnosis of AD. However, adding these functional imaging strategies to the standard diagnostic regimen at AD clinics would yield limited, if any, benefits at very high costs, expressed as high incremental cost-effectiveness ratio (ICER) in comparison with the standard examination alone. Improvements in therapies and non-pharmacologic strategies for AD treatment would result in a more favourable ICER for functional imaging strategies (McMahon et al.

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12   The direct costs included the costs of the methods examined (PET, SPECT, DSC-MRI, standard examination, donepezil treatment) and follow-up visits, annual costs of AD care for combinations of different stages (mild, moderate, severe AD, non-AD dementia) and health care settings (community, nursing home), and travel costs. The standard examination costs were further analysed in terms of the consultation costs, laboratory costs, and non-enhanced CT costs. Indirect costs included were patient and caretaker opportunity costs.

2003; Centre for Reviews and Dissemination 2005b). This study confirms at large findings of a previous study by the same authors which concluded that addition of functional neuroimaging to the usual diagnostic regimen of mild to moderate AD at Alzheimer disease clinics is not cost-effective given the effectiveness of currently available therapies (McMahon et al. 2000; Centre for Reviews and Dissemination 2005a).

However, although the above mentioned studies suggest the importance of brain imaging methods for the diagnosis and evaluation of Alzheimer's disease recent comprehensive reviews comparing different methods are more reluctant. For example, two recent comprehensive reviews of the imaging literature used meta-analytic techniques to characterise the magnitude of hippocampal deficit in probable Alzheimer's disease (AD) and examines whether other neuroanatomic structures in AD can discriminate the disease from normal aging (Poulin, Zakzanis 2002; Zakzanis et al. 2003). In addition, these studies quantified the influence of duration of disease as well the age of the examined subjects to determine those structures most sensitive to AD in its early and late stages. One hundred twenty-one studies published between 1984 and 2000 were included in these meta-analyses. In total, structural (i. e. CT and MRI) and functional (i. e. SPECT and PET) neuroimaging results from 3,511 patients with AD, and 1,632 normal healthy controls were evaluated across meta-analyses. The results include neuroimaging profiles for both early onset and longer duration patients with AD. In sum, these profiles yield a signature of diagnostic markers in both cortical and subcortical neuroanatomic areas that corresponds to the clinical phenomenology of Alzheimer's dementia. Early stages of AD are best distinguished from normal aging by hippocampal deterioration, whereas patients of longer duration were best distinguished by pathology within the medial temporal lobes and the anterior cingulate gyrus. It has been shown that this signature is consistent with the progressive clinical characteristics of Alzheimer's dementia. Such a signature image feature should aid in the positive identification of AD and could significantly contribute to improvements in the application of therapy as well as early differential diagnosis.

However, the main disadvantage of current approaches to use brain imaging measures for diagnosing our evaluating Alzheimer's disease and other dementias is the fact that the brain imaging measures are not referred to a normative database. Thus, neuroradiologists mostly (or exclusively) judge

for example hippocampal volume decrease or ventricle enlargement more or less by eye-balling. In order to strengthen the judgement it would be necessary to compare the anatomical measures with standard data bases (either on the basis of brain atlases, or in the context of voxel-based approaches) containing mean volume measures (for grey and white matter, as well as the ratio between them) as well as the standard deviations across several subject groups, similar as it is standard for neuropsychological testing. First steps towards this approach have been published recently (Thompson et al. 2004; Toga, Thompson 2003).

13.3   Implications for the introduction of AD neuroimaging biomarkers into clinical practice

It has been suggested that neuroimaging of AD-related biomarkers can make possible the diagnosis of AD at a stage where cognitive impairment is so mild that it is hardly distinguishable from memory changes due to healthy ageing, and that therapeutic intervention, if provided already at these early stages, could considerably delay the onset of severe AD pathology. In this way, the imminent burden of a substantially growing share of the population, suffering from severe AD could be reduced to manageable numbers (DeKosky, Marek 2003). In the following paragraphs, it will be discussed

- what the prerequisites and requirements are that must be met if the final goal is to be attained,
- how likely it is that the requirements are met and goals achieved,
- which options should be considered in order to shape the future development.

Prerequisites and requirements

The following prerequisites and requirements must be met if the final goal should be achieved – provision of appropriate care for people suffering from AD without without overexerting available resources:

- methods for AD diagnosis in the presymptomatic stage are established and validated,
- effective treatments are available which significantly delay the onset of severe AD,
- patients in need of the available diagnostic tools and treatments have good and equal access,
- additional costs for diagnosis and treatment are at least compensated for by savings due to later onset of severe AD.

AD diagnosis in the presymptomatic stage

In recent years, significant progress has been made in research to identify biomarkers and establish diagnostic tests which allow an AD diagnosis already in the presymptomatic stage of mild cognitive impairment.

Both structural MRI as well as functional PET and other imaging methods allow the early diagnosis of AD, and, if used in combination, improve the performance of existing diagnostic tools. However, comparisons of different diagnostic tools in terms of accuracy, specificity and sensitivity, as well as cost-effectiveness is largely missing, but would be needed to draft appropriate diagnostic work-up algorithms. At present, the neuroimaging diagnosis is mainly confined to the research setting or highly specialised centres whereas for the time being, neuropsychological test profiles are presently the most sensitive, reliable and valid measures to diagnose dementia. For its adoption on a wider scale, further validation and adaptation to routine clinical practice is necessary (chapter 13.2).

Some patients may find an early AD diagnosis helpful. It could be perceived as a welcome reduction of uncertainty, and it could be appreciated that the remaining time span until fully developed AD can be used for caretaking, legal and financial arrangements. Other patients, however, may choose not to know at all or to know only if effective treatments are available.

Due to the predictive character of the early AD diagnosis and the lack of effective, disease-modifying therapeutic interventions, it would be detrimental if not sufficiently validated biomarkers would be used in early AD diagnostics without appropriate quality control and without embedding the diagnostic procedure into appropriate counselling provided by specifically

qualified staff. This is not unlikely that these tests will be offered to patients in the foreseeable future because the technical equipment of performing such tests is already widely available at hospitals and radiologists' surgeries. Against this background, it should be considered whether these tests should – until sufficient validation – be restricted to special centres where these requirements can be met. Similar models have, for example, been implemented for genetic testing of inherited breast cancer susceptibility.

Disease-modifying therapeutic interventions

Only few drugs for symptomatic treatment of AD have been approved, especially cholinesterase inhibitors for the treatment of mild to moderate AD and memantine for the treatment of moderate to severe AD. The clinical improvements these drugs can offer are rather modest and only of transient nature. Although new drugs with different and/or combined modes of action are in various stages of development, there is considerable uncertainty in the prognosis whether and when drugs with improved efficacy will become available. From a health system's perspective, the cost-effectiveness of these drugs is currently questioned with the preliminary recommendation (e. g. in the UK) that the gain in quality of life is too limited to justify the allocation of limited resources in the health care system to cover the additional costs for this medication.

The limited efficacy of the presently available AD drugs also affects the introduction of neuroimaging methods for (standard) AD diagnosis into standard diagnostic routine. Although these methods add additional accuracy, the standard procedure is sensitive and specific enough for AD diagnosis. Only if the early MCI stages are to be accurately diagnosed, neuroimaging methods – in addition to clinical and neuropsychological tests will become more important. Several studies have pointed out that in this case, more accurate diagnoses can be made for the same costs with the additional use of PET. Several variables influence this result: They are likely to change within the coming years, among them the diagnostic quality of the standard diagnostic procedure, the costs and diagnostic quality of the neuroimaging tests, and the costs and efficacy of available therapeutic interventions. Therefore, the timely adaptation of these health economic assessments to the changing state of the art is recommended.

Accessibility of available diagnostic tools and treatments for patients

Should improved diagnostic tools and therapeutic interventions become available in the future, the goal of improving quality of life of AD patients can only be achieved if the diagnostic and interventional options are really made available to the patients who could benefit from them. From an ethical perspective, equal access for all patients would be desirable. As outlined above, this is on the one hand a decision how resources should be allocated in the health system, e. g. mediated through the coverage by health insurances. On the other hand, evidence from present AD clinical practice and from the analysis of mental disorders in general suggests that certain additional barriers would have to be overcome in order to make equal access to treatments possible:

Primary care physicians have a key role in evaluating older patients for early signs of dementia, in referring them to specialists for accurate diagnosis and in initiating appropriate treatment and care. However, there is evidence that AD is underrecognised or undercoded in primary care settings in many countries, and also in Switzerland: according to e. g. estimations of the Schweizerische Alzheimervereinigung, two thirds of patients suffering from dementia have not been diagnosed at all. 60 % of persons (53,400) affected by AD live at home and receive primary care, but only 38 % of them have been properly diagnosed, either by general practioners or by neurologists (Schweizerische Alzheimervereinigung 2004). In order to reduce the problem of underrecognition, physicians' awareness of the need for diagnosis and possible intervention needs to be addressed.

The problem of underrecognition does not only relate to diagnosis, but also to prescribing behaviour after diagnosis. A survey carried out in Germany suggests that a certain reluctance prevails among general practitioners, but also neurologists to prescribe acetylcholin esterase inhibitors (AChEI) for AD patients. While positive attitudes were prevailing regarding the safety and efficacy of AChEI, prescription of these drugs was hampered by perceived negative impacts on the drug budget (Ruof et al. 2002). The survey was conducted before the cost-effectiveness of AChEIs was controversially discussed.

The reasons for these biases are manyfold, among them also stigma and discrimination (Graham et al. 2003):

- dementia is often seen as a natural part of ageing, and is therefore not recognised or managed appropriately,
- the actual or perceived absence or inadequacy of preventive strategies and treatments for AD,
- the lack of information systems (or their use) to educate both professionals and the general public,
- lack of incentives to provide appropriate AD management and care,
- negative professional attitudes towards older people with mental disorders,
- negative attitudes towards professionals and services that care for older people with mental disorders,
- specific symptoms of dementia which are powerfully stigmatising (e. g. disturbed behaviour, poor self care, incontinence), both in the community and the care settings,
- the perception of older people with dementia as having no quality of life or capacity for pleasure, with the possible consequence that appropriate management is denied ("would be a waste").

These issues point at the need to embed diagnostic and therapeutic interventions into supportive environments and flank them by strategies which aim at reducing stigma and discrimination and at providing incentives for appropriate care for AD patients (Graham et al. 2003).

Health economic assessments

Several health economic assessments have been carried out, of which few have been reviewed in this chapter. In these studies, the chosen perspective (costs to society or to specific payers) is important. Moreover, different results and conclusions may be due to methodological issues and differences in the underlying assumptions. Two results, however, can be generalised:

- At present, it is clear that diagnostic and drug costs are low compared to the major cost of institutionalisation. Therefore, any measures which effectively reduce the need for custody care will significantly improve cost-effectiveness over today's levels.
- The presently available therapeutic interventions, such as cholinesterase inhibitors, result in small improvements regarding cognition and func-

tionality over the first 2 years in patients with mild to moderate AD, but no significant benefits were seen in behavioural and psychological symptoms, dependency, disability, risk of entering institutional care, duration of institutionalisation, adverse events or deaths, formal care costs, unpaid caregiver time or carers' psychological wellbeing (AD 2000 Collaborative Group 2004). Although it may be disputed whether the (limited) benefits justify the medication, major improvements over this situation can only be expected if more effective treatments than cholinesterase inhibitors become available for Alzheimer's disease.

14   Applications of brain imaging: drug development and pharmaceutical industry

With the technical advances in medical imaging, especially in non-invasive in vivo imaging modalities such as CT, MRI and PET, there is considerable interest in their use in pharmacological research and drug development. Using in vivo imaging biomarkers in drug development bears the potential to considerably accelerate the drug discovery process, mainly due to the ability to quantify drug properties in vivo, both in animal and man, with the same experimental paradigm (Eckelman 2002). This is of great importance in the pharmaceuticals market where time to market is crucial for economic success (Pien et al. 2005). The major pharmaceutical companies therefore have invested in their own preclinical and/or clinical imaging facilities (Lammertsma 2004).

Imaging plays an important role in all stages of the drug development process (Beckmann et al. 2004):

- Epidemiological research
  - Describing the phenotype of diseased subjects with the aim to obtain clues for risk factors and potential drug targets.
- Preclinical research
  - Investigation of the disease mechanism.
  - Identification and validation of potential drug targets.
  - Determining the phenotype of model organisms for the disease.
  - Compound profiling: In vivo imaging allows quantitative determination of pharmacokinetic properties, efficacy and safety profiles of drug candidates in animal models of human disease. The results obtained in vivo are often superior to results from in vitro studies in terms of their translation into the situation in humans. A second specific feature of in vivo imaging experiments is that repetitive measurements are possible and inter-individual variances can be reduced by using each test subject as its own control, thereby enhancing statistical power of the experiments and reducing the number of required test animals.

- Clinical trials
  - In vivo imaging of biomarkers can be used to analyse the pharmaco-kinetic behaviour of the drug, the appropriate dosing regime, and the efficacy of the therapeutic intervention in humans. A specific advantage of imaging is that the same technology for drug testing can be employed both in preclinical testing of animal models as well as in clinical testing of human subjects. It is anticipated that this will facilitate the translation from animal models to human subjects because the changes in experimental design are minimised, and preclinical findings can be directly linked to clinical findings through relevant imaging biomarkers.
  - Preselection of study populations. In the research phase, inconsistent findings or blurred results in epidemiological research, clinical research or drug development may be due to the inclusion of patients with different forms or stages of the disease, or different aetiologies (e. g. inherited vs. sporadic forms). If this variability could be reduced by clear inclusion/exclusion criteria which make possible a better pre-selection of the population under study, clinical research might give better results and development of new drugs could be speeded up.
- Regulatory approval of the drug
  - Imaging of biomarkers can provide data which are required for regulatory approval of the drug.

In order to be used on an even wider basis than today, pharmaco-imaging needs to evolve from the research stage to a routine tool in drug development. This requires the integration of different imaging technologies, and their application in preclinical as well as clinical stages. Moreover, efforts have to be devoted to the systematic and rigorous validation of new imaging biomarkers (Pien et al. 2005).

15 Applications of brain imaging: cognitive neuroscience

15.1 Contributions of brain imaging to the study of cognition

Brain imaging research has been used to enrich our understanding of the neural basis of a wide variety of cognitive abilities including attention, language, memory, and a variety of emotional processes. In addition, brain imaging techniques have been used to gain insight into the aetiology of neurobehavioral disorders, for surgical planning, and to assess functional recovery after brain damage. One area in which brain imaging studies contribute essentially is that of memory and learning. For example, studies of long-term semantic memory have begun to uncover the ways in which stored information is organised in the brain. These studies show that different attributes of an object are stored in a distributed manner across several brain regions, with visual form information stored in a region that processes form, and functional information stored near a region that processes motion. Further, studies of memory encoding have been able to pinpoint the precise regions for which level of activation during stimulus processing predicts subsequent memory for that stimulus. Additionally, studies of memory retrieval are being used to adjudicate between models of episodic memory positing that recollection (i. e. distinct remembrance of an item and the context in which it was previously encountered) and familiarity (a vague sense that the item has previously been encountered) are either distinct processes or merely on a continuum of memory retrieval. These examples show how brain-imaging studies can be used to test or adjudicate between psychological models. The most important contribution of neuroimaging to the field of cognition is the capability to study higher cognitive functions, including the ability to manipulate and integrate representations in working memory – which is critical for reasoning and problem-solving – as well as the ability to control our behaviour on the basis of short-term and long-term goals. These cognitive abilities are not highly developed in nonhuman species and are therefore best studied in humans. Well-designed brain imaging experiments have begun to subtly fractionate

the cognitive processes that underlie reasoning, problem-solving, and goal maintenance, but further investigation is necessary.

Another major contribution of brain imaging is that unconscious processing of emotional stimuli produces specific brain activations in the amygdale. Studies like this have evidenced the existence of an implicit pathway for processing emotional stimuli and have emphasised theories reasoning about implicit preparation, modulation, reasoning, and memory processes. Thus, brain imaging has opened new doors and thus new realms for cognitive psychology.

15.2 Bibliometric analysis of the contribution of brain imaging methods to the study of cognition

15.2.1 Impact of brain imaging methods in the neuroscientific community

Cognitive neuroscience is a relatively recent branch of neurosciences which studies the neuroscientific basis of cognition and emotion. Typical psychological processes subsumed under the topic "cognitive" are attention, perception, action, motor behaviour, language, reasoning, intelligence, memory, learning, reading and writing. The term "emotion" covers several research topics which have not been directly related to cognition in former times. But recently, emotion and cognition are viewed as closely interrelated parts of the human and animal cognitive apparatus. The term "emotion" considers processes like feeling, affect, reward, motivation, drives, social behaviour and altruism. These topics (subsumed under the term "cognitive" and "emotion") are fundamental psychological functions necessary for all kinds of human behaviour. Disturbances or deficiencies in some of these psychological functions can result in a variety of psychological disorders. For example, deficiencies within the reading and writing module might cause reading and writing problems. Deficiencies in the emotion module can result in anxiety, depression or anhedonia. Thus, the study of the fundamentals of cognitive processes is important not only for basic researchers but also for psychiatrists and neurologists. In order to analyse how the impact of cognitive research is reflected in current scientific literature we conducted a bibliometric analysis of publications, listed in the data-

base MEDLINE which is the standard database for medical and neuro-scientific research and the major database for neuroscientific papers.

In 1990, approximately 51,000 papers dealing with cognition, emotion or motor-related issues were published in international journals covered by MEDLINE. In 2003, 110,000 papers are listed for these categories indicating that the number of publications has doubled within this period of 13 years. Many reasons account for this blast of publications, amongst them increased interest in the brain and its function ("Decade of the Brain") but also increased research funding for these topics.
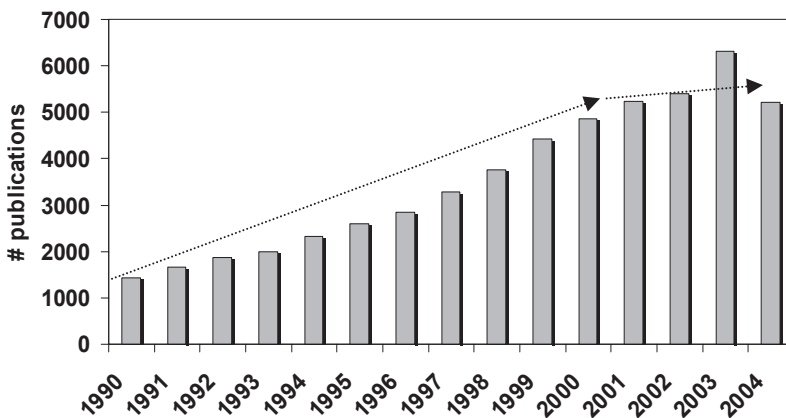
Database used: MEDLINE. Please note that the numbers for 2004 are slightly lower because the database search was conducted in the middle of November (15.11.2004). Thus one can anticipate that the numbers for 2004 will slightly increase.

Figure 15.1:   Absolute number of brain imaging papers dealing with cognitive, emotional, or motor-related issues

In order to analyse the relevance of brain imaging within studies on cognition, emotion, or motor-related issues, we analysed the use of fMRI, PET, MEG, EEG, TMS, NIRS, CT, or SPECT in the context of cognitive studies. We found an approximate doubling of brain imaging studies when comparing the records for 1990 to 2003 (figure 15.1). There is a constant increase of publications each year. However, the records for 2004 are relatively low, thus one can anticipate that they will not extremely outnumber the records found for 2003. Based on the data for 1998 to 2003 one would predict approximately the same number for 2004 as for 2003.
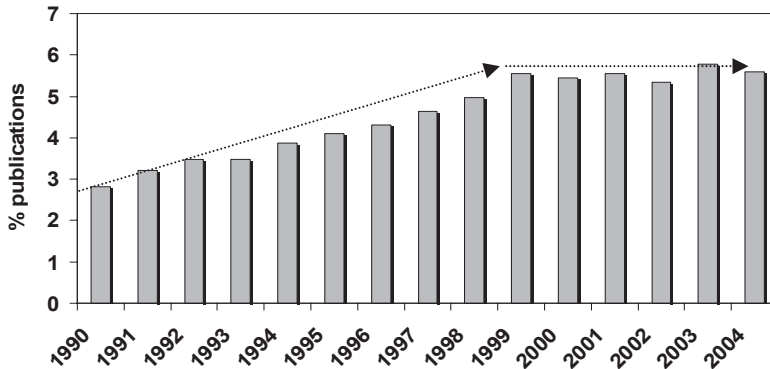
Database used: MEDLINE. Please note that the numbers for 2004 are slightly lower because the database search was conducted in the middle of November (15.11.2004). Thus one can anticipate that the numbers for 2004 will slightly increase or at least will be in the same range as 2003. The arrows indicate the different slopes for the relative number of publications. From 1990 to 1998 there is a steep linear increase of relative number of publications while from then on there is no increase.

Figure 15.2:   Share of brain imaging papers dealing with cognitive, emotional, or motor-related issues (%) related to the total amount of publications dealing with these issues

The share of brain imaging methods in all publications dealing with cognitive, emotional or motor-related issues is approximately 3 % in 1990 and increases to approximately 6 % in 2003 (the average contribution to the cognitive literature as listed in MEDLINE is 4.7 %) (figure 15.2). This shows the increasing importance of brain imaging, but also indicates that other methods and techniques also increased their impact, among them genetic or pharmacological studies. In addition, traditional approaches – for example using behavioural experimentation techniques or carefully analysing brain lesions or psychiatric symptoms – are still major tools in studies of cognition. Figure 15.2 also shows a steep increase in percentage of brain imaging publications from 1990 to 1998. This increase is perfectly linear and highly significant (r^2 = 0.98). However, there is no significant increase of the relative amount of brain imaging publications until 2003 (r^2 = 0.14). Even if one predicts the number of publications for 2004 there is no indication for a substantial increase of publications for this year. Thus, there is a kind of stagnation in terms of the relative amount of brain imaging publications in cognitive neuroscience.

15.2.2   Use of different brain imaging methods

As demonstrated in chapters 3, 4 and 5, several brain imaging methods are currently available. Looking at the records of publications based on the different methods a clear picture emerges (figure 15.3): In the realm of cognitive studies, the MRI methods (fMRI, sMRI, DTI sMRI) have gained significantly in importance: The share of published papers using MRI methods has increased from 30 % in the 1990s (at that time mostly sMRI has been used) to more than 50 % in 2003. On the other hand, the relative importance of EEG methods has decreased: In 1990 approximately 40 % of all brain imaging studies used EEG methods while in 2003 only 18 % of publications reported the use of EEG. The use of PET and CT has remained relatively stable over time, ranging from 7-12 % of the papers. MEG and SPECT have been used only rarely (figure 15.4). NIRS is the less frequently used method although it has been used quite early. However, new techniques and devices have been developed recently which now offer the opportunity to conduct NIRS experiments elegantly. It could well be that NIRS may turn out to be an interesting non-invasive brain imaging technique within the years to come. Interestingly, TMS has attracted the interest of more and more scientists. The relative amount of publications substantially increased from 1 % in 1990 to approximately 8 % in 2004.

The analysis is based on the data presented in figure 15.1. Please note that the numbers for 2004 are slightly lower because the database search was conducted in the middle of November (15.11.2004). Thus one can anticipate that the numbers for 2004 will slightly increase.

Figure 15.3:   Relative amount of papers using different brain imaging methods for the most frequently used methods
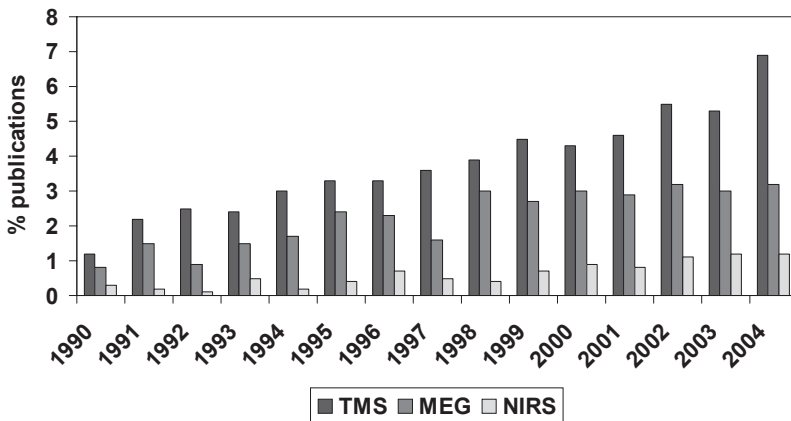
The analysis is based on the data presented in figure 15.1. Please note that the numbers for 2004 are slightly lower because the database search was conducted in the middle of November (15.11.2004). Thus one can anticipate that the numbers for 2004 will slightly increase.

Figure 15.4:   Relative amount of papers using different brain imaging methods for the less frequently used methods

15.2.3   Topics studied with modern brain imaging methods

Traditional areas of cognitive psychology and thus, cognitive neuroscience, are "attention", "memory", "comprehension", "language", "perception", "action", and "reasoning". Meanwhile, emotion, motor behaviour and even social issues are thought to be closely related to cognition. In addition, meanwhile many researchers not directly involved in traditional cognitive psychology even assign issues regarding "personality" and "personality disorders" to the broad umbrella of cognitive psychology. In order to provide a more detailed view of the topics studied by means of brain imaging methods, we separately listed publications more specifically focussing on the traditional cognitive issues like "attention", "memory", "perception", "language", "action", "reasoning", or "mental representation". This research area will hereafter be denoted as "*cognition*". In addition, we searched for publications studying emotion-related issues like "emotions", "mood", "reward", "social behaviour", or "affect". These studies are subsumed under the topic "emotion": A third category was introduced to subsume studies focussing on movement or motor behaviour-related questions. This topic is entitled "motor" and typical keywords are "motor control", "motor cortex",

"motor cortices", or "motor learning". Because many spectacular findings have found their way into the tabloid press related to functional plasticity of the human nervous system we have included the search topic "learning" and "functional plasticity". All papers related to these keywords were labelled as "learning" papers. In addition, a category entitled "personality" was defined because we had the impression that more and more studies are focussing on this topic. Typical keywords used for this search are "personality", "personality disorders", "traits" or "habits".

Looking at the percentages of publications, "cognition" is the most frequently found keyword in the context of brain imaging studies (figure 15.5). During the course of the last 13 years the relative amount of published papers associated with this keyword increased from 21 % to approximately 50 % in 2003. The topic "motor" also showed increased numbers with starting with 6 % in 1990 to 13 % in 2003. "Emotion" and "Learning" also have doubled their percentage of publications during 1990 to 2003, however, on a much lower level than the aforementioned categories. "Personality" shows no evident linear trend of relatively increasing publication numbers and remains a more or less marginal topic.
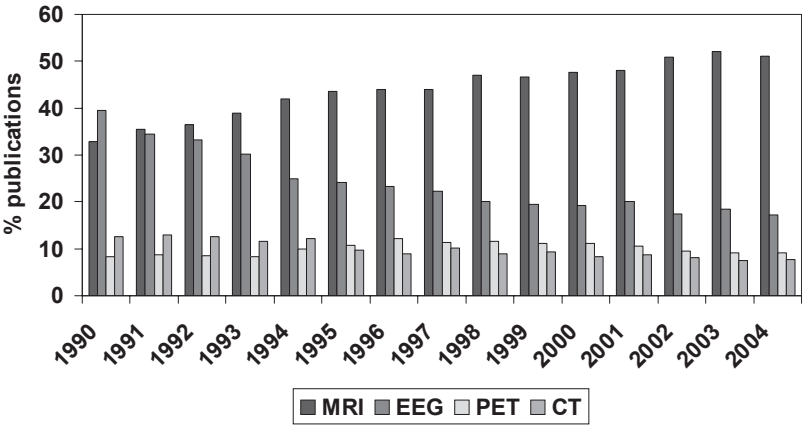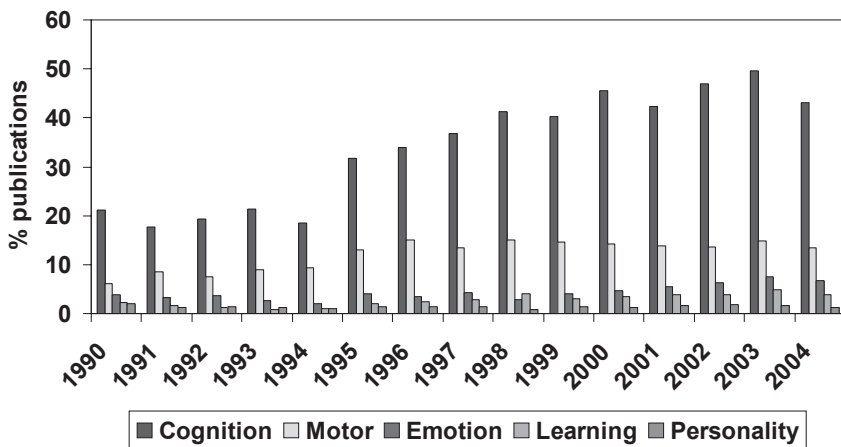

100 % is the total number of brain imaging studies. Please note that the numbers for 2004 are slightly lower because the database search was conducted in the middle of November (15.11.2004).

Figure 15.5:   Share of brain imaging papers studying the topics cognition, motor, emotion, learning, and personality in all brain imaging papers

Another bibliometric analysis with a different scope than the one described above has been carried out by Illes et al. 2003. They show that "over time, the terrain of fMRI studies has expanded from examination of basic sensorimotor and cognitive processes to topics that more directly relate to human motivation, reasoning and social attitudes", so that there has been "a steady expansion of studies with evident social and policy implications" (Illes et al. 2003).

15.3   Learning and "neuropedagogy"

15.3.1   Introduction

Both educational scientists as well as cognitive neuroscientists are interested in learning processes, their prerequisites and influencing factors, and how to optimise learning. In recent years, findings in cognitive neuroscience related to learning processes, especially those resulting from neuroimaging studies, have attracted much interest – not to say a hype – among those concerned with education – e. g. researchers active in the learning and instruction research, teachers, parents, providers of special education, as well as politicians in educational policy (Stern et al. 2005). They wonder whether findings in cognitive neuroscience might have implications for their practice. A rather controversial scientific[13] as well as social debate has arisen on what the significance of both cognitive neuroscience as well as learning and instruction research for the future shaping of the educational system and the educational practices is, could be and should be. Several "camps" can be distinguished with respect to their orientation towards cognitive neuroscience with implication for education (Byrnes, Fox 1998b):

1) Ready acceptance of a leading role of neuroscience within educational research, advocating "brain-based" curricula and learning strategies.
2) Rejection of the neuroscientific approach and considering the findings from neuroimaging as meaningless for educational research and practice.

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13   For a representation of the scientific debate, refer e. g. to the papers published in the Educational Psychology Review 10 (4), 1998

3) A middle position, which acknowledges the merits, but also limitations of both scientific approaches to human learning and tries to actively exploit synergies between the two approaches.

Several factors contribute to the observable controversial debate: A good education is, in our knowledge-based society, one of the key factors for personal success and quality of life, and it is in the interest of parents as well as the educational system to provide the best possible education. However, in the highly politicised field of education, there is a considerable controversy about the adequate pedagogic ways how to achieve internationally competitive outcomes, as measured e. g. in the OECD PISA[14] study. Traditionally, both cognitive neuroscience as well as learning and instruction research have been rather separated scientific communities which look at the common issue of learning processes from different perspectives with different methodologies and different underlying theories. They use different professional vocabulary, pursue different goals and explore different questions (OECD 2002). In this context, pedagogy as well as research on education and instruction are often – mistakenly – perceived as "soft sciences" which seem to base their findings more on opinions than on empirical data whereas neurosciences and especially neuroimaging are often – again mistakenly – presented and perceived as direct, intrinsically objective and accurate (Farah 2002). The expensive cutting edge high-tech instrumentation and the representation of results as visual maps of the brain in action may have contributed to this notion and the perceived attractiveness of the approach (Beaulieu 2002; Beaulieu 2003; Dumit 2004; Racine et al. 2005).

However, it is not always clear what the neuroscience has actually found and how, specifically, it relates to ways in which individuals and society could support development and learning (Hannon 2003; Stern et al. 2005): Some popular beliefs about what brain science can actually deliver to education are quite unrealistic. Moreover, "neuromyths" abound. This term was coined in an OECD report (OECD 2002) to demonstrate the ease and rapidity with which scientific findings have also translated into misinformation regarding education: Ill-informed "experts" spread pseudoscientific

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14   Programme for International Student Assessment (PISA); ttp://www.pisa.oecd.org/pages/
      0,2987,en_32252351_32235731_1_1_1_1_1,00.html

educational advice and tools for "brain-based" education which are mainly oversimplified and too general to address the crucial issues[15] how to improve education and learning effectively. At best, these pseudoscientific advice and tools are only ineffective and do not do any direct harm. However, they imply a misallocation and waste of resources for ineffective instead of effective measures.

Brain imaging methods are currently one of the most intensively used methods to study the consequences and antecedents of human learning. Therefore, in the following chapters, we will first give an overview of cognitive neuroscience findings with relevance for learning (chapters 15.3.2 to 15.3.7). Then, we will discuss the potential implications of neuroimaging research for education by focussing on the third position presented above which acknowledges the merits, but also limitations of both scientific approaches to human learning and which tries to actively exploit synergies between the two approaches (chapter 15.3.8).

15.3.2   Plasticity of the human brain, regarding anatomy and activation patterns

The most important finding uncovered in this context is that the human brain is plastic throughout the entire life span. A very important aspect is that learning induces plastic changes not only in terms of changed neurophysiological functions but also in terms of changed anatomical structure. The importance of this finding can only be acknowledged by emphasising that in the early 1990s no one has seriously thought about the possibility that the human brain can change its anatomical structure due to experience, learning or practise.

One root of research was to use professional musicians as a model for neuroplasticity because these subjects mostly start very early in life with their musical training and continue to practise throughout their entire life many hours a day (Munte et al. 2002; Schlaug 2001). In fact it was shown that professional musicians revealed substantial changes (changed volumes, grey matter densities) in those brain areas housing neural net-

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15   These issues comprise adequate pedagogical content knowledge as well as its use to optimise learning opportunities (Stern 2005).

works involved in controlling psychological functions involved in musical processing (motor and auditory areas). Besides the principle finding that musical training triggers anatomical changes in the brain, the size and extent of these anatomical changes are due to the intensity and amount of musical training. Some of these changes are also due to the age of commencement of musical training. Beside these findings, several other research lines have shown structural changes in the human brain due to training of skills other than musical skills (e. g. motor training, juggling, spatial orientation in taxi drivers, etc.)(Draganski et al. 2004; Jancke et al. 2001; Maguire et al. 2000; Menning et al. 2000; Menning et al. 2002).

Nowadays the research focus is directed onto short-term and medium-term changes in the function of neural networks. Using brain imaging methods it was shown that training of various psychological functions leads to changed activation patterns both in terms of haemodynamic responses or electrophysiological activation (Pascual-Leone et al. 2005). Interestingly, even psychological interventions such as those used during psychotherapy lead to changed activation patterns to visual or auditory stimuli normally evoking neurotic responses (Straube et al. 2004; Straube et al. 2005). Thus, brain imaging is thought to be used as a method to additionally prove the feasibility and appropriateness of psychological interventions.

Besides the fact that brain imaging methods have shown that learning and practise change the brain in terms of anatomy and functions, more and more data are now available suggesting that life long experiences shaping attitudes or cognitive strategies also influence brain functions. For example several brain imaging studies have shown that using different cognitive strategies to solve problems or to cope with emotional situations are associated with typical patterns of brain activations (Jordan et al. 2002; Jordan et al. 2004; Lorist et al. 2005; Ridderinkhof, van den Wildenberg 2005). Thus, individual differences with respect to psychological functions are also related to individual differences with respect to brain activation patterns.

Besides these differences modern brain imaging methods have tracked time courses of learning psychological functions and the activation of the involved brain areas. For example, training hand movement skills it was shown that there is an initial activation increase (indexed as increased haemodynamic response or electrical activation) with the motor areas contralateral to the trained hand which is followed by a decrease of activation

of continuing practise (Ungerleider et al. 2002). This pattern of activation is accompanied by a sharp increase of activation in the ipsilateral motor cortex followed by a quick and steep decrease of activation which is interpreted in the context of models arguing for interhemispheric communication during motor learning. Similar dynamics of learning-related activation changes have been shown for the auditory cortex challenging current models of functional plasticity.

Recent brain imaging studies also have demonstrated that successfully learning words or figures is associated with a typical pattern of activation with particular brain areas (the hippocampus, parahippocampal gyrus, and frontal cortex). Thus, these findings might be used to guide future drug or electrical stimulation studies examining the possibility to enhance memory and learning functions. In addition, it was shown that successful learning is related to particular electrical brain oscillations. If one will be able to induce these oscillations one might be able to enhance memory and learning functions. First approaches are currently under study (see chapter 17 for first results).

15.3.3   Developmental changes (maturation) of brain architecture

Modern methods to analyse and visualise anatomical peculiarities of the human brain have changed our view about brains in different stages of development (Luders et al. 2005; Sowell et al. 2004; Sowell et al. 2003; Thompson et al. 2004; Thompson et al. 2000; Toga, Thompson 2003; Jancke 2002; Steinberg 2005; Paus 2005; Casey et al. 2005). First, we have learned from these modern methods that the human brain and especially the frontal cortex matures and thus changes it architecture up into the late teens. This long maturation supports the view that the executive functions which are controlled by this brain area do not function optimally. Thus, many of the behavioural inconsistencies in children and adolescents possibly are based on this anatomical background. Secondly, anatomical studies have demonstrated that the human brain is changing its anatomy even in late adulthood possibly due to detrimental or positive experiences. These data support the view that the human brain is constantly adapting and changing its anatomy in reaction to experience. In addition, these data also support the view that anatomical foundations of cognition (e. g. maturation of the frontal cortex) might influence ongoing cognition or executive functions (e. g. motivation, empathy, emotion, attention etc.). Thus, a closer link

between anatomy of the human brain and psychological functions has been woven and the speculation of Sandra Witelson of a new era with a new discipline coined "cognitive neuroanatomy" made in the early 1990s turns out to become reality (Witelson 1992).

15.3.4   "Critical periods" for optimal learning

Whether critical periods exist in human life for optimally learning specific psychological functions is still a matter of dispute. A major problem in this discussion is that the term "critical period" has semantically different meanings depending on the scientific faculty. For example, more biologically influenced researchers are strongly influenced by the imprinting research in ducks, chickens or other animals. Cognitive neuroscientists and more strongly psychologists are reluctant to use the imprinting concept for explaining human learning in early childhood. Thus, the proposal of critical periods for various brain functions is largely limited to anecdotes. For language it seems to be a little bit different because of Lenneberg's (1967) conclusion (on the basis of an extensive literature overview) who proposed that a critical period for language ends around puberty. Since this first influential publication an intense debate has since centred on whether native languages are truly crystallised or merely interfere with second-language learning later in life. Although detailed cellular and structural substrates are difficult to identify in humans, developmental psychology and in especially advanced brain-imaging techniques are revealing developmental milestones that may underlie a critical period. However, the brain imaging studies reveal that the critical periods are not as strict as in the animal kingdom, they rather suggest that an initial period-bond can be followed by an increase of learning capacities.

15.3.5   Language learning

In the following we will give a short overview for language learning and the specific contribution brain imaging methods have provided to the data corpus (Hensch 2004; for a summary see Kuhl 2004).

Full-term neonates already exhibit left-hemisphere dominance (by optical topography) for normal speech and segregate concurrent streams of sound (as detected by electrical mismatch negativity, MMN) like adults. Functional MRI confirms the precursors of adult cortical language areas at three

months of age. A baby's speech then emerges through a series of stages. The auditory perceptual map is refined by six months of age (exploiting statistical properties of language input) to eliminate non-native phoneme distinctions (like "r" from "l" in Japanese). Thus, more often heard sounds are strongly implemented in the phonetic system while rarely occurring sounds are erased. At the age of ten months, vision has been matured sufficiently, and information about the speaker's face is combined with the concurrent acoustic signal, leading to perceptual illusions such as the McGurk effect. Ultimately the cumulative critical period for language ends with the ability to properly discriminate subtle grammatical errors by the age of 12 years. Other linguistic features, such as semantics, can be learned throughout the entire life.

Bilingual subjects reveal a sequential neural commitment to competing stimuli. Originally sensitive to all speech sounds, the MMN is observed only for native language contrasts after 12 months of age, reflecting the great difficulty to hear, as well as to produce, non-native phonetic distinctions later in life. Interference effects are minimal before adolescence and several different languages can be acquired, perhaps by switching inhibition of unused maps. Functional MRI reveals, when both languages are learned before age 11, that overlapping regions of Broca's area are activated, whereas second languages acquired later must employ two distinct areas. Age of acquisition also affects the cortical representation of grammatical (but not semantic) processes.

Social context is instrumental. In the rare cases when children have been raised in isolation, or in children with autism, language skills and social deficits are tightly coupled. Conversely, in normal nine-months-old American infants, limited (5 h) exposure to Chinese speakers spaced over one month prevents the loss of Mandarin speech sound distinctions. The reward of a live tutor is essential, since similar exposure to taped instructors has no rescuing effect. From personal anecdote, learning is further facilitated if each tutor speaks exclusively one of the two languages rather than both.

Training paradigms based on exaggerated acoustic cues characteristic of motherese, multiple instances by many talkers, and mass listening experience may succeed to incrementally rewire the brain of adults as it already has for learning disabled children. By paradoxically overcoming our

"mature" cognition, we may one day learn new skills more naturally and efficiently, as our children do so effortlessly during their critical periods. Such phenomenon has been recently been shown for Korean subjects who left Korea at the age of 8-9 and completely lost their proficiency to understand and speak their mother tongue. However, they have learned French perfectly and were even not able to distinguish Korean (their mother tongue) from unknown languages like Polish (Pallier et al. 2003). An interesting aspect of this study was that the Korean subjects used the same brain areas as their French speaking control subjects to perceive and process French. However, different brain areas were activated when the Korean subjects heard their mother tongue or another unknown language like Polish. Thus, the Korean subjects have unlearned their mother language and established a new language using a neural network similar to native French speaking subjects. This finding suggests that even the language system is maximally plastic although it might be very difficult and effortful to acquire the new language.

15.3.6   Procedural and explicit learning processes

A further important finding of brain imaging studies is that they provide substantial information that procedural and explicit learning are not only different in terms of behavioural consequences, they are also different in terms of the involved brain structures. Thus, brain imaging has provided subsequent and confirming data for the distinction between these two learning processes. A new finding coming from brain imaging is that there is a negative correlation between the activation of frontal brain areas mostly controlling the explicit learning processes and the basal ganglia controlling the procedural learning mechanisms (Fletcher et al. 2002; Fletcher et al. 2005). Thus, brain imaging offers new insights into these two learning processes which might help to guide pedagogic strategies.

15.3.7   Role of emotions in learning processes

A further set of findings coming from brain imaging is that emotional information is very important for learning process. This knowledge is not new because we know from lesion data and from cognitive psychology relying on the analysis of behavioural that emotion either has an enhancing or inhibiting effect on memory processes. With the brain imaging data we know

the involved brain regions and, most importantly, that emotional information is unconsciously transferred to the brain (Whalen et al. 1998).

15.3.8   Potentials of neuroimaging for learning and instruction research and pedagogy

Both educational scientists as well as cognitive neuroscientists are interested in learning processes, their prerequisites and influencing factors, and how to optimise learning. They look at the common issue of learning processes from different perspectives with different methodologies and different underlying theories. They use different professional vocabulary, pursue different goals and explore different questions (OECD 2002). They investigate learning processes on different levels of explanation. The decision which of these levels is chosen primarily depends on the goal what is to be explained (Schumacher 2005). It is the goals where there are fundamental differences between the neuroscientific approach and the pedagogic approach: Learning-related neuroscience research aims at elucidating how the brain works during learning processes whereas learning and instruction research and pedagogy aim at devising the best way to help humans learn (Mayer 1998; Stern et al. 2005).

Within these goals, neuroscientific approaches of learning processes are especially strong in revealing the neurophysiological frameconditions and prerequisites which are essential for successful learning. Moreover, they provide insight into the mechanisms and physiological changes which underlie learning behaviour. If these findings relate to learning forms such as classical conditioning, the implications for education are likely to be limited. But especially findings which relate to typically human learning processes which make use of systems of symbols (e. g. language, letters, mathematics and writing, reading, mathematics and pictorial presentations) can be expected to have both theoretical as well as practical relevance for educational research (Stern 2005): On the one hand, the gained insight into the nature of cognitive processes helps to

- support, build and refine existing models of learning processes,
- suggest mechanisms how the known psychological phenomena arise,
- discriminate between alternative mechanisms and theories, and
- identify differences in cognitive processes, which are not observable on the level of behaviour,

- suggest new hypotheses that would not be imagined without knowing something about the underlying brain processes.

It must be stressed, however, that it is a mandatory requirement that the phenomenon under investigation must be well-studied and well-described at the psychological level before the neurological basis of that phenomenon can be investigated. In this way, neuroscientific approaches heavily rely on findings from educational psychology (Schumacher 2005; Byrnes, Fox 1998a, p. 434; Berninger, Corina 1998).

In this sense, neurophysiological studies have significantly broadened our understanding of several learning deficits, such as dyslexia, dyscalculia and impaired language acquisition (Schumacher 2005; Goswami 2004a; Goswami 2004b; Dehaene et al. 1999; Dehaene et al. 2004) and are therefore considered valuable in contributing to special education[16] in the following ways:

For example, neuroimaging studies of children or adults with specific reading disability (dyslexia) emphasise the importance of the ability to recognise and manipulate component sounds in words (phonological awareness), thus contributing to the understanding of prerequisites for successful reading learning. Moreover, targeted special education programmes tailored to remedy these deficits were shown to affect very specific areas of the brain. Because it is also argued that dyslexia may also have a visual basis, or could be due to a deficit in the cerebellum, neuroimaging could be used to distinguish between different cognitive theories regarding the underlying causes of dyslexia. If there were different causes for cognitive deficits such as dyslexia, diagnostic neuroimaging could help to distinguish between dyslexia of different aetiology which is indistinguishable on the behavioural level. Neuroimaging also offers the potential to distinguish between deviance and delay when studying developmental disorders. This means that it could be investigated whether affected children develop along the same

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16   Specially designed instruction to meet the unique needs of students with disabilities; Direct instructional activities or special learning experiences designed primarily for students identified as having certain disabling exceptionalities in one or more aspects of the cognitive process or as being underachievers in relation to general level or model of their overall abilities. Such services are provided to qualifying children with the following conditions: learning disabled, speech pathology, visually impaired, intellectually disabled, behaviour disorders, mild or moderately disabled, severely disabled, hearing impaired, and physically impaired.

trajectory as unaffected children, but more slowly, or whether they take a different trajectory. A better knowledge of the neural basis of the cognitive deficit would have important practical implications for the requirement, timing and type of intervention and remediation (Goswami 2004b). Despite these potentials, it must be pointed out that to date, neuroimaging studies have largely confirmed what was already known about reading and its acquisition from behavioural studies, so that the current practice of dyslexia diagnosis (and related disorders) through specific psychological tests is (not yet) challenged.

Findings from neuroimaging studies which study maturation of the brain and the development of cognitive abilities could provide some information with relevance to curricula. They could support decisions what should be learnt when and which issues need special instruction, and which ones not (privileged learning).

While neuroimaging can support decisions regarding the requirement, timing and type of intervention in case of a learning disability, it has to be stressed that it cannot answer the question *how* a suitable intervention should be designed in detail. This is the core competency of learning and instruction research and pedagogy.

Learning and instruction research and pedagogy study cognitive processes to devise effective instructional practices. For higher-order learning processes, it is known from psychological research that it is the key for higher-order learning processes that already available knowledge is applied for the accomplishment of new tasks and solving of new problems, thereby reorganising and expanding the knowledge base (Stern 2005). To devise effective instructional practices the following information is required (Schumacher 2005):

- Which knowledge must already be established, which concepts must be known to the learner, and how must this knowledge base be organised so that learners can solve certain problems associated with certain learning objectives?
- What is the actual state of the learners' knowledge base? Which concepts and explanations do they use intuitively? Which misconceptions and mistakes can be expected if learners try to accomplish the given task with this knowledge?

- What is the learning objective? How should the learners' knowledge base be structured after the learning objective has been achieved?

In order to transform this information into successful lessons, pedagogical content knowledge is required. This means the knowledge possessed by expert teachers. It comprises the synthesis of three knowledge bases: subject matter knowledge, pedagogical knowledge, and knowledge of context in order to know how certain subjects, problems or questions should be structured, presented, adapted to the interests and abilities of the learners and be prepared for lessons. It included the "most useful forms of representation of these ideas, the most powerful analogies, illustrations, examples, explanations, and demonstrations – in a word, the ways of representing and formulating the subject that make it comprehensible to others" (Shulman 1987). It is this crucial aspect which is the specific domain of learning and instruction research and pedagogy whereas it cannot be covered by neuroscientific approaches alone (Stern et al. 2005).

15.3.9   Summary

The short overview of findings from neuroimaging studies of learning processes provided in the chapters 15.3.2 to 15.3.7 demonstrates that brain imaging methods have substantially contributed to the understanding of the neural basis of human learning processes and the associated brain plasticity. Brain imaging results have substantially complemented electrophysiological and behaviour studies mostly coming from the psychological literature.

Thus, this research area is an ideal candidate for demonstrating that multidisciplinary perspectives on current educational challenges are welcome and fruitful. Although many publications suggest a uni-directional relationship in the sense of "What can educational psychology learn from cognitive neuroscience?", an increasing number of experts propose a bidirectional collaboration in which synergies to the benefit of both scientific disciplines are exploited (see e. g. Byrnes, Fox 1998a; Berninger, Corina 1998; Geake, Cooper 2003). Thus, there is now a close link between traditional research lines like learning psychology and cognitive neurosciences. Both are rather complementing than competing or mutually exclusive approaches with their specific strengths and limits. Specific research pro-

grammes have for example been launched in the USA (Gura 2005), Japan (Koizumi 2004; Ito 2004) and Germany[17] (Stern et al. 2005).

Thus, it is not only a speculation to anticipate a stronger impact of brain imaging on education. Currently, especially the laymen and politicians are excited by the coloured pictures generated by brain imaging studies. Thus, many of these people believe that brain imaging has revolutionised our understanding about learning and memory. They are somehow correct if they relate to the characterisation of the neural basis of learning processes. However, it would be misleading to expect a direct influence on pedagogic or educational questions. Only some of the findings are currently useful for direct transformation from basic research to recommendation for application in educational fields (e. g. the neuroanatomical maturation of the frontal cortex which may have implications for curriculum design in the sense of "what to learn when", and the negative correlation between explicit and procedural learning).

Up to now, findings from neuroimaging studies of learning have mainly supported existing models, helped to refine them, have suggested mechanisms how the known phenomena arise, and also help to discriminate between alternative explanations. Although there are also several new findings which are supporting our understanding how the human brain operates to learn, store and retrieve new and old information, brain imaging in the context of learning and memory mostly have substantiated our knowledge coming from behavioural studies. Most of these findings do not have major immediate implications for existing educational practice and educational policy in that they challenge what is currently done (or not done) (Hannon 2003). They rather support specific theories of cognitive processes and the instructional programs that are implied by these. This is also true for the study of learning disabilities such as dyslexia or acalculia where a synergistic approach, comprising both neuroimaging as well as learning psychology, has been pursued.

If the specific strengths and limits of both cognitive neuroscience, educational psychology and pedagogy are taken into account, their synergistic exploitation would comprise

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17   http://www.mpib-berlin.mpg.de/de/forschung/eub/projekte/nil/de/index.htm

- psychologically well-characterised learning phenomena as objects of research,
- neuroimaging findings and behavioural studies for the elucidation of pre-requisites, temporal courses and trajectories, and mechanisms of both successful learning processes and learning disorders,
- approaches of learning and instruction research for devising effective educational interventions, with direct implications for teaching practices.

In order to make more value-added discoveries, it is necessary to create more bridges between the two research communities (OECD 2002). Then, it could be expected that important contributions to e. g. the following issues could arise:

- refinement of learning theories and models, discrimination between competing theories and models,
- explanations for cognitive deficits,
- early diagnosis of special educational needs,
- differentiation between different forms of cognitive deficits which are indistinguishable on the behaviour level (e. g. dyslexia with different aetiologies, differentiation between deviance and delay in cognitive deficits),
- discovery and validation of neural markers for the assessment of learning processes beyond the behaviour level (e. g. very early diagnosis of special educational needs; deviations from usual trajectories; accomplishment of interim stages in learning processes which are not detectable with psychological tests),
- choice of the most appropriate interventional strategy to compensate diagnosed deficits,
- monitoring the effects of interventional strategies,
- comparison of the effects of different kinds of educational input on learning, tools for the comparative assessment of different types of educational input,
- increased understanding of individual differences in learning.

15.4   Decision-making and neuroeconomics/ neuromarketing

A research issue common to different scientific disciplines is decision-making. In psychology, the aim is to uncover the psychological mechanisms and influencing factors (e. g. information and knowledge, trust, uncertainty, emotions) underlying human decisions which are not seldomly strange and barely not understandable. In economics, most economic theories and models are based on the well-known 'homo economicus'-principle which implies that economic-related behaviour is always ruled by controlled, deliberative processes. It is assumed that individuals try to maximise their profit or rather 'utility' at all times. Although these models work well in many cases they are not able to explain certain anomalies within human economic behaviour. These anomalies gave rise to the branch called behavioural economics. This branch aims at developing extended economic models which take into account that humans do not act rationally at all times and hence tries to explain the economic decisions that people make in 'real life'. Moreover, a subfield of economics, namely marketing, aims at understanding and influencing decision-making processes with relevance for purchase behaviour.

Neuroimaging methods have stimulated research in the above-mentioned disciplines by providing additional tools to study human decision-making behaviour. A transdisciplinary field, often called "Neuroeconomics", is developing from a convergence of economics, psychology, and neuroimaging. Generally speaking, it is based on the investigation of decision-making behaviour in the context of economic or marketing research with the help of neuroimaging techniques (interestingly not with findings from the greater and more fruitful realm of cognitive neurosciences). While the scientific branch (chapter 15.4.2) is trying to better understand the decision-making processes of individuals in order to build more precise economic models the "neuromarketing" branch (chapter 15.4.1) aims at revealing consumer preferences.

15.4.1   Neuromarketing

The interesting and somewhat worrying aspect of neuroeconomic research is that the layman press is so excited by the simple idea to scan a subject

for the purpose of uncovering needs and motivations in the context of marketing questions that nearly every breath is published. These publications (in newspapers, business journals or internet publications) mostly are written in terms of presenting sensational new findings and discussing spectacular views for the future. The negative part of this kind of publications is mostly focussing on scenarios similar to what George Orwell has described in his seminal novel "Nineteen Eighty-Four (1984)" and describes the fear of people to lose their control of their personal thought and ideas.

This boom of neuroeconomics started in Germany as a consequence of the 2001 German Decade of the Brain initiative in Bonn[18] where first fMRI results of a marketing study conducted at the Otto-von-Guericke-University Magdeburg were presented. This presentation (lasting no longer than 5 minutes) evoked a storm of press releases with spectacular titles[19]. Interesting enough the researchers responsible for this finding (Profs. Jäncke and Heinze) were very reluctant and they never made the too far reaching interpretations made by the laymen press. However, market research companies and scientists have been stimulated by this press announcement and conduct "neuromarketing" studies. In these studies, the reaction of test subjects to certain stimuli is recorded with the help of brain imaging methods, with the aim of revealing consumer preferences. The results of these experiments build the basis for targeted advertising campaigns. Furthermore, the different findings are applied in designing products and shops (Lindner et al. 2005). Recent objects of research have been certain brands (e. g. Coke/Pepsi), different types of consumer products (e. g. cars, underwear, travelling) and, more general, the effect of certain visual stimuli e. g. different schemes like "nature", "family" etc.[20] In addition the combination of certain visual and olfactory stimuli was analysed[21].

There are several market research companies in the USA and Europe which have specialised in neuromarketing, among them for example

- Brighthouse Neurostrategies Group, Atlanta, GA, USA,
- Market Psychology Consulting (Finance), San Francisco, CA, USA,

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18   http://www.meb.uni-bonn.de/epileptologie/aktion/dekade/dekade.htm
19   http://www.meb.uni-bonn.de/epileptologie/aktion/dekade/presse/presse.htm
20   http://www.shopconsult.at/pages/pdf/Neuronen.pdf
21   http://www.shopconsult.at/pages/pdf/NM_OLF-ZF_D.pdf

- Neurosense Ltd., Oxford, UK,
- NeuroniX[2], UK,
- SalesBrain LLC, San Francisco, CA, USA and Paris, France,
- ShopConsult by Umdasch, Amstetten, Austria.

Moreover, neuromarketing experiments are carried out by academic neuroimaging centres on an occasional contract research basis for commercial customers. In the USA, there are 88 for-profit imaging centres (The Lancet Neurology 2004) which, however, are not necessarily conducting neuromarketing experiments.

Currently, fears exist that neuroimaging in marketing could lead to violations of the informational self-determination and that information about individual preferences could be collected even without the individual's knowing or consent. In the USA the non-profit organisation Commercial Alert has started a campaign against the use of neuromarketing for corporate or political advertising[22]. Commercial Alert points out that the experiments were unethical because they would make possible more effective promotion of degraded values (materialism, violence, gambling etc.) or even more effective political propaganda. Moreover, study inferences could possibly be used to tailor products, services and advertising campaigns in a way that a "buy button" could be pushed or unwilled behaviour induced.

According to Kenning et al. "worldwide, barely more than fifty research groups deal explicitly with the subject of "Neuroeconomics". Similarly, several commercial suppliers have already been able to establish themselves in the market. However, their work is both ethically and methodologically controversial".[23] This statement clearly describes the enormous boom of this research area which by the hand also evokes critical voices (Blakeslee 2004; The Lancet Neurology 2004).

Interesting enough there is not one single scientific paper published until now even tentatively supporting the hypotheses that the motivation and need to buy a specific good can be uncovered by brain imaging methods. Nearly all publications published so far describe the hypothesised potential

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22   http://www.commercialalert.org/issues-landing.php?subcategory_id=82&category=1
23   (http://www.wiwi.uni-muenster.de/~02/neuroeconomics/publikation/publikation_informationen.htm)

of brain imaging in the context of marketing research (see e. g. the position paper of Kenning et al.[23]).

Only three papers have been published in peer reviewed journals (listed in Medline) which are partly examining marketing-related questions:

- The first paper used MEG measurements to track the temporal dynamics of neural responses in 16 subjects (8 men and 8 women) choosing among different day-to-day consumer items (Braeutigam et al. 2004). The authors demonstrated that a distributed neural network is activated during the decision process. However, this distributed network (including parietal, temporal and frontal brain areas) strongly depends on gender differences, whether the presented items have previously been bought or not, the used cognitive strategy and the category-specific knowledge about the test items. The authors relate their findings to current theories of memory and decision-making however the authors strongly emphasize the substantial gender differences.
- The second experiment of this type examined the neural underpinnings of choosing between Coca-Cola (Coke) and Pepsi which are famous beverages nearly identical in chemical composition but different in terms of cognitive associations (McClure et al. 2004a). The authors report that there are two separate brain systems which correlate with their preferences. When judgements are based solely on sensory information (for example when tasting Coke or Pepsi), relative activity in the ventromedial prefrontal cortex (VMPFC) is strongly activated and predicts people's preferences. However, if brand knowledge is introduced (choosing between Coke and Pepsi on the basis of brand names) preference decisions are biased and recruits the hippocampus, dorsolateral prefrontal cortex (DLPFC), and midbrain. Thus, this finding demonstrates that memory systems as well as brain areas housing executive functions are strongly involved in choosing the preferred brand. In addition, this study shows that explicit information is obviously necessary to control brand guided decisions.
- A further study partly using the same approach (Deppe et al. 2005) found that the favourite brand evokes reduced activation in a network comprising the dorsolateral prefrontal, posterior parietal areas, occipital cortices and the left premotor area. Simultaneously, activity was increased in the inferior precuneus and posterior cingulate, right superior frontal gyrus, right supramarginal gyrus, and, most pronounced, in the

ventromedial prefrontal cortex. The authors conclude a kind of *winner-take-all effect* for a participant's favourite brand which is associated with reduced activation in brain areas related to working memory and reasoning processes. However, brain areas involved in emotion processing and self-reflections revealed increased activation. In some way this finding is contradictory to the findings of McClure et al. who showed increased activation in memory structures for the favourite brand.

These first three papers clearly uncover the need for further thorough examination whether brain imaging is indeed useful for this research line.

15.4.2   Neuroeconomics

In contrast to the "neuromarketing" research line, the "neuroeconomics" research line is more strongly based on theoretical foundations and appropriately derived hypotheses and is associated with the study of the neural underpinnings of the control of social behaviour including moral judgement, altruism, revenge, empathy, and the so called theory of mind (making predictions of the intentions of a social partner). This is a very fruitful research line going back into the early 1960s when biological ideas were first introduced to explain human social behaviour and culminated on the one hand in the publication of the seminal socio-biology book of Wilson 1975. On the other hand, the ideas were also taken up by behavioural economics.

Against this background, neuroimaging methods are exploited by neurobiologists, cognitive neuroscientists, psychologists, and economists in order to investigate decision-making (see e. g. Camerer et al. 2003; Camerer et al. 2005; Glimcher 2003; McCabe 2003; Glimcher, Rustichini 2004; Zak 2004; Paulus 2005; Sugrue et al. 2005; Hsu et al. 2005; Camerer, Fehr 2006), and worldwide, about fifty research groups are active in this field[23].

A substantial number of peer-reviewed publications have been published in recent years, dealing with topics such as

- cooperation, trust and deception (McCabe et al. 2001),
- altruistic behaviour (de Quervain et al. 2004; Fehr, Rockenbach 2004),
- choices under risk and uncertainty (Smith et al. 2002; Sanfey et al. 2003; Hsu et al. 2005),

- empathy for pain (Singer et al. 2004a; Singer et al. 2004b; Singer, Frith 2005),
- intertemporal choice (valuation of immediate and delayed rewards) (McClure et al. 2004b; McClure et al. 2004c),
- reputation and trust in social interaction (King-Casas et al. 2005; Kosfeld et al. 2005).

These studies are exclusively conducted to scientifically increase the knowledge about the human decision-making behaviour without the ultimate motive to uncover concealed and private motivations or to manipulate motivation or need. Rather, they aim at developing extended economic models of human behaviour which take into account that humans do not act rational at all times, e. g. a neuroeconomic theory of decision (Glimcher et al. 2005).

These new findings now complemented by brain imaging findings showing the brain areas involved in social behaviour, direct attention onto the human brain and emphasises that the human brain is strongly involved (or even responsible) in generating social behaviour. Thus, questions related to social behaviour are meanwhile not only a domain for social psychologists or philosophers, they are rather subject of a discussion integrating a greater scientific community.

15.5   Forensic psychology

Psychological expertise in criminal investigations and forensic psychology deal with the following issues (Kröber, Steller 2005):

- development of, contribution to and refinement of models of human criminal behaviour,
- assessment of the credibility of a witness or suspect, "lie detection",
- assessment of the suggestivity of criminal investigations and of suggestibility of witnesses (mainly children),
- assessment of an offender's criminal liability and responsibility,
- prognosis of the dangerousness of an offender and the risk of reoffense,

- assessment of an offender's ability to respond to therapeutic interventions, choice of suitable therapeutic interventions, evaluating the effects of a therapeutic intervention.

Neuroimaging methods could be applied in each of these issues in order to complement and support established methods in forensic psychology. In the following chapters 15.5.1 and 15.5.2, selected present and future contributions of neuroimaging in forensic psychology are presented and discussed.

Moreover, some proponents have fueled the debate of possible impacts of neuroscience by their interpretation of certain neuroimaging experiments that the free will were only an illusion (see chapter 16). In their view, this also challenges the fundamentals of our criminal law which is based on the individual's responsibility for his behaviour. If the behaviour cannot be subjected to a free will (because the latter is only an illusion), then, so their conclusion, there cannot be responsibility (see e. g. Roth in Präsident der Berlin-Brandenburgischen Akademie der Wissenschaften 2004). This aspect of the public discourse and its possible impacts on the fundamentals of the criminal law is analysed in detail in chapter 21.

15.5.1   Contribution of brain imaging to the assessment of a witness's or suspect's credibility

Classically, psychologists are trying to uncover deceptions or lies using a variety of methods. One is the so called polygraphic test which is based upon autonomic responses: A polygraph machine records the body's involuntary responses to an examiner's questions in order to ascertain deceptive behaviour. The test measures physiological data from three or more systems of the human body – generally the respiratory, cardiovascular, and sweat gland systems. The validity and reliability of this test has been challenged for decades, the most recent review being carried out by the US National Research Council (Committee to Review the Scientific Evaluation on the Polygraph 2003). A similar reluctant review has been given by the German Psychological Association. In addition the German Federal Supreme Court has decided not to admit polygraph lie detector tests (BGH 1 StR 156/98 – Urteil v. 17. Dezember 1998, LG Mannheim).

A major drawback of the polygraph test (among various methodological aspects) mentioned in these reviews is its potential susceptibility to countermeasures. Countermeasures are those strategies (overt or covert) which are used by the tested individual in an effort to defeat or distort a polygraph test. Polygraph tests have been shown that they can be altered by conscious efforts through cognitive or physical means.

Thus, researchers have tried to circumvent these problems by using cortical indices of deception. One promising method is thought to record the P300 event-related potential (ERP) which is obtained with a parietal maximum in the context of an odd-ball paradigm and electroencephalographic measurements. This ERP has been measured in the context of concealed information tests or the guilty knowledge test utilising the P300 amplitude as an index of recognition of critical details of the crime or other concealed information. Even the American National Research Council reported that this novel method offers new insights into the cognitions and emotions underlying deceptive behaviour (Committee to Review the Scientific Evaluation on the Polygraph 2003).

Thus, several private institutes (e. g. http./www.brainwavescience.com/) and even the CIA is obviously using this method for uncovering deception or lying in various contexts. The basic idea of this test is to present rare probe stimuli which represent guilty knowledge elements and more frequent crime-irrelevant stimuli. Because guilty subjects are expected to recognise guilty knowledge items as meaningful, these rare and meaningful items are expected to elicit P300 responses to the probe stimuli. On the other hand meaningless stimuli will not evoke a P300. Using this rationale, several studies have shown that this logic obviously holds true (Allen et al. 1992; Farwell, Donchin 1991; Johnson, Rosenfeld 1992; Rosenfeld et al. 1991). A major problem of these studies is that they did not introduce and thoroughly study countermeasures and their influence on the P300. In fact several most recent studies have shown that simple overt and covert countermeasures can change the occurrence and size of the P300 in such a way that test-beaters cannot be caught. Thus, these studies have shown that deception detection based on P300 amplitude as a recognition index may be readily defeated with simple countermeasures (covert acts during presentation of the probes) that can easily be learned and used (Rosenfeld et al. 2004; Rosenfeld et al. 2005).

Because of this and other problems with this method, fMRI has been used to study brain activations in the context of deception. The few studies which have been published so far report increased activity in executive brain regions, specifically in areas of the prefrontal cortex (PFC) and the anterior cingulated gyrus (ACG) (Ganis et al. 2003; Langleben et al. 2002; Lee et al. 2002; Spence et al. 2001; Spence et al. 2004; Spence 2004). In a recent publication, discrimination between true and false responses with the help of fMRI was achieved with high accuracy even in individuals (Davatzikos et al. 2005; Wild 2005). A further finding of these studies is that there is no report of increased activation in any brain region during truthful cognitions compared to deception. This pattern of activation is thought to be consistent with the notion that lying and deception is a conscious and voluntary process which is constrained by cognitive and neurobiological resources. Typical executive functions are planning, problem solving, initiating and inhibition of behaviour, as well as manipulation of memory data within the working memory. These functions engage specific regions within the PFC. These regions are essential for adaptive behaviour in novel situations and circumstances. On the other hand "lower" regions, often entitled as "slave systems" are thought to be sufficient for the control of routine or automated tasks (Gilbert, Shallice 2002; Shallice 2001). Based on theories of deception, suppressed or deceiving information is voluntarily managed by controlling emotions and the remembered cognitions. Thus, suppressing or controlling this information should make use of executive functions. Therefore, if the executive is overloaded during deception (e. g. while performing a dual task) deceiving or lying subjects will exhibit decrements in performance while attempting to perform dual or multiple tasks concurrently. A liar might therefore "slip up" and mistakenly utter the truth. Thus, lying and deception is thought as being a cognitive process requiring a lot of cognitive resources. Although this theory is quite plausible and the fMRI data support this idea one has to keep in mind that none of the conducted fMRI experiments have used an explicit countermeasure experiment similar to the one that has been done in the context of the above mentioned P300 studies. Using voluntary countermeasures would even increase the activation in the PFC and would make it more likely that the subject were classified as a liar.

On the other hand even innocent and emotionally labile subjects may contemplate about the testing situation and will make predictions and hypotheses about what is currently going on. Thus, these subjects will have strong activations during the entire fMRI session. If this activation is similar during

the "deception" and "truth" trials the extra activation caused by the voluntary deception and lying process will be detected on the basis of simple sub-traction methods. However, this model only holds if there is a linear rela-tionship between the increase of cognitive effort and the activation in the frontal cortex, an assumption which is challenged by recent methodological studies exploring the neurophysiological underpinnings of fMRI (Marcar, Lonneker 2004).

A further problem is that it might be possible to learn strategies to control brain activity in order to direct the pattern of activation into the desired di-rection. Recent papers describing relatively simple neurofeedback approaches where the subjects have learned to control their brain activa-tion have shown that after a training of 2-4 weeks the pattern of brain acti-vation substantially has been changed (Hinterberger et al. 2003; Hinterber-ger et al. 2005). Not to mention the unusual different brain activation of Buddhist monks who showed increased theta activity (measured with EEG) due to their life-long practise in meditation (Lutz et al. 2004).

In conclusion, the brain imaging methods are currently explored whether they can be used to objectively detect deception and lying. A major problem is to design the appropriate task to evoke brain signals which can be used to disentangle cognition due to processing of the truth and deception. In addition, the role and influence of countermeasures has been pinpointed at least in the context of EEG measurements and P300 recordings. However, it remains to be shown whether countermeasures can influence the fMRI signal and mask typical brain responses due to deceptive behaviour.

15.5.2 Assessment of an offender's criminal liability, dangerousness and risk of reoffense

A further major finding from brain imaging research is the maturing frontal brain which changes its architecture during the first 20 years (Sowell et al. 2004). As mentioned above the frontal cortex houses the executive func-tions (attention, motivation, action control etc.) which are responsible for many functions typical for humans. In addition, we do know from be-havioural studies that children, adolescents, and patients with lesions in the frontal cortex are outperformed by adults in typical executive tasks. Thus, there is a kind of correlation between the anatomical integrity of the frontal cortex and the efficiently operating executive functions. Recently, it has

been demonstrated that sociopaths revealed anatomical deficits in the ventral part of the frontal cortex supporting the view that these subjects might show detrimental social behaviour because of the anatomical deficiencies in the frontal cortex (Raine et al. 2004; Yang et al. 2005). Although it is currently unclear whether the deficiencies in the frontal cortex are the cause or the consequence of antisocial behaviour some researchers strongly suggest that the anatomical deficiencies are the anatomical foundation for antisocial behaviour.

If this were true then these anatomical deficiencies in the frontal cortex might be used to predict and diagnose antisocial behaviour. Whether these ideas represent scientific progress supporting law issues is not substantiated today. However, this issue is currently under intense discussion. Although there is currently no consensus in this issue there are nevertheless court trials especially in the US during which anatomical deficiencies in the frontal cortex are used as an argument for excusing a murderer in that sense that he has no control over his actions. If the court follows this argumentation the offense will not be classified as murder (driven by conscious intentions) rather than as kill without the participation of voluntary cognitive control. If this case will turn out this way, this will be a typical example how brain imaging results will have an impact on everyday behaviour.

A most problematic aspect with this interpretation is the fact that there is currently no knowledge available according to which frontal anatomical deficiencies can be diagnosed. For a valid and reliable diagnosis it will be necessary to refer the anatomical data to normative data bases and to calculate appropriate statistics (e. g. the relative deviation of an anatomical score from a norm expressed as z-value) an endeavour which has not even been started so far. Thus, from the present point of view this approach is scientifically interesting but far away from being usable in the context of law-related issues.

15.6   Concerns regarding the application of brain imaging beyond the classical biomedical fields

As outlined in the chapter 15, neuroimaging techniques increasingly diffuse into new fields of application. Drivers for these trends are technological developments which deliver cheaper, easier-to-use brain scanners which will increasingly become affordable and can be operated also outside specialised imaging centres. Other drivers are scientific developments which address increasingly turn to higher cognitive functions, personality traits and psychological states and healthy individuals instead of focussing on mental illnesses and impaired cognitive functions (see e. g. Illes et al. 2003). Moreover, it is assumed that there is a (latent) demand from various stakeholders to improve the present capabilities of inferring higher cognitive functions, personality traits and psychological states of an individual, even without the individual's knowledge, cooperation or consent. Among these stakeholders are secret services, military forces, police and criminal justice, employers, insurances, market research and others (Farah 2002; Farah, Wolpe 2004; Illes, Kirschen 2003). Neuroimaging has been well received of being capable of doing so because it is often presented and/or perceived as direct, intrinsically objective, and accurate (Farah 2002). The high-tech instrumentation and the representation of results as visual maps of the brain in action may have contributed to this notion and the perceived attractiveness of the approach (Beaulieu 2002; Beaulieu 2003; Dumit 2004; Racine et al. 2005).

Despite the undisputed strengths of neuroimaging techniques, it is a misconception of the method to be "intrinsically objective" and accurate. Together with the above-mentioned drivers this bears the potential that there is a premature broad use of neuroimaging techniques, accompanied by an over-reliance on or misapplication of neuroimaging information both on the supply and demand side of such information. Moreover, there may be misconceptions of the power and sensitivity of these methods, leading to undue concerns and fears (e. g. "mind-reading", prediction and manipulation of behaviour).

16   Brain imaging and philosophy of mind

In recent years, a lively and often controversial debate has arisen about whether and, if yes, to which extent and in which respect, findings from neuroimaging studies are of relevance for the philosophy of mind. A key issue in the debate is the question in which respect neuroscientific findings can contribute to our understanding of human conciousness. One line in the debate deals especially with the epistemological aspects. It analyses the fundamental question whether neuroscientific research paradigms and theories are in principle adequate and comprehensive for the explanation of consciousness, mental phenomena and selfconsciousness (chapter 16.2.3). Another line of the debate deals with the freedom of will which is closely related with the philosophical concept of consciousness. In the following chapters, we will focus on the "free will debate" for the following reason: it could have far-reaching implications in many areas of society if the concept of humans as beings capable of a free will were challenged.

16.1   Philosophical positions on freedom of will

One of the oldest questions in philosophy is the body-mind problem with its main topics "mind" and "consciousness". Closely related with the different philosophical concepts of consciousness is the freedom of will. According to Walter, freedom of will is characterised by three components: to be able to do otherwise, intelligibility (i. e. reflected, purposeful action, due to reasons), and authorship (that the decisions originate from the self, a person) (Walter 1999). On the one hand, our everyday experience is that man is author of his actions, and is able to decide, after thorough deliberation, in an autonomous, self-determined, "free" way, which means, one could also have decided otherwise. On the other hand, and contradicting to the first intuition, is the experience that each effect has a cause, which, in turn, may be an effect of another cause, so that the natural world is causally closed. Against this background, it is argued that man is part of the natural world. As a logical consequence, his decisions and actions would also have to

follow the causal natural laws and would therefore be determined. However, this would not be compatible with the existence of a free will. Because our understanding of moral action and responsibility, personhood, theory of criminal law, as well as questions of education, social control and addiction are closely connected with freedom of will, challenging this concept could have far-reaching implications, not only within the philosophical discourse, but in many areas of society.

Within the philosophical discourse, four major families of theories or concepts of freedom of will have developed, dealing with the paradoxon outlined above. They can be differentiated from one another in their answers to the following central questions:

- Is determinism true?
- Is freedom of will compatible with determinism?
- If yes, in which way are freedom of will and determinism compatible?
- What does freedom of will mean?
- How can, if determinism is true, the moral practice be justified, which reasons could be given for it, and how could it change?

The four major families of theories are

- *Libertarianism*. Determinism and freedom of will are incompatible. Determinism is not true, and freedom of will exists (see e. g. Chisholm 2005).
- *Determinism*. All natural processes are subject to the causal principle: a cause gives rise to a certain effect to which there is no alternative. Because human decisions are also natural processes, there is no freedom of will (see e. g. Honderich 1993).
- *Compatibilism*. Although determinism is true, freedom of will is nevertheless compatible with it (see e. g. Pauen 2004; Walter 1999).
- *So what*. Irrespective of whether determinism is true or not, it has no relevance for the attribution of actions to a person, on establishing responsibility, and current moral practice (see e. g. Dennett 1984).

Libertarianism and determinism have in common that freedom of will is seen as incompatible with determinism, and can therefore be contrasted as "incompatibilism" with compatibilism. In the contemporary philosophical discussion, the debate between determinism and compatibilism takes the largest space.

16.2   Implications of neuroscientific findings for the philosophical debate

Neuroscience, especially with the advent of neuroimaging techniques, increasingly addresses phenomena, among them also consciousness and wilful decisions, which have been, for centuries, the exclusive domain of humanities. This bears the potential to complement "armchair philosophy" by empirical studies, and to enrich neuroimaging approaches with knowledge arising from philosophy, to the benefit of both faculties. A new transdisciplinary field, neurophilosophy, has arisen, which explores the intersection of neuroscientific and philosophical questions (Churchland 1986, Northoff 2000; Walter 1999).

Moreover, a lively, controversial and rather complicated debate has arisen (see e. g. Präsident der Berlin-Brandenburgischen Akademie der Wissenschaften 2004; Nida-Rümelin 2005; Herrmann et al. 2005; Köchy, Stederoth 2006) which can be understood as a continuation of the differentiated philosophical debate on freedom of will, as depicted in chapter 16.1. In this report, we focus on four selected aspects of the contemporary debate:

- Which are the empirical neuroscientific findings which contribute especially to the free will debate?
- How are these findings discussed, in view of the different philosophical positions on freedom of will?
- Which epistemological problems arise?
- What could be "practical" impacts of the debate, to which extent would present practices have to be altered, and why?

16.2.1   Neuroscientific experiments with relevance for the freedom of will debate

Neuroscientific studies of consciousness have found that all mental processes are correlated with brain activity, but that the majority of mental processes are unconscious ones. Different types of consciousness can be distinguished, and both memory and emotions are closely interconnected with consciousness. These findings are very much in line with contemporary philosophers. The brain as "basis of thinking" is only in severe conflict with dualistic theories in the tradition of Descartes, but which are hardly

represented by contemporary philosophical positions. However, neuro-science and philosophy differ in the importance assigned to both conscious and unconscious processes – while philosophy primarily focuses on con-scious, deliberative processes, neuroscience stresses the importance of unconscious processes. Moreover, assignment of decisions to a "self" from a philosophical point of view could suggest a specific brain region function-ing as carrier of freedom of will and of decision (often also termed "homun-culus") but no such region could be discovered by neuroscience.

Two experiments have provided substantial input to the freedom-of-will de-bate: The oldest and most influential discovery is the time course of the so called readiness-potenial (*Bereitschaftspotenzial)* which poses problems to those claiming that human beings operate on the basis of a free will. The *Bereitschaftspotenzial* is an event-related potential which emerges 1-2 seconds before simple self-initiated movements. Experiments conducted by Libet (1983; 2002; 2003) and Haggard and Eimer (1999) have shown that the time point when subjects first consciously noticed the will to move their finger occurs approximately 200-400 milliseconds later than the first deflection of the *Bereitschaftspotenzial* over the human skull. Thus, it is thought that the brain does initiate the movement far before we become aware of our intention to move. This paradoxon is the basis of an ongoing discussion between psychologists, neuroscientists, and philosophers. Some believe that this paradigm indicates a general operating principle of the human brain which is also true for other cognitive functions. This idea culminates in the suggestion that the human being does not possess something like a free will and the brain is operating on itself based on stored and information which have been processed beforehand (Roth 2001).

However, whether it is justified to apply this paradigm and the associated finding to all cognitive processes has to be proved by additional experi-ments. The validity of the Libet experiments for such far-reaching claims is being questioned with the following arguments: firstly, the experimental design does not represent a free decision to act, because only the timing of the finger movement could be freely chosen in the experiment, but it was not allowed to decide whether the finger should be moved at all. What was measured was the timing of becoming aware of the decision, but not of the wilful decision itself. A free decision is not necessarily also a conscious de-cision. Moreover, the finger movement is an ethically and emotionally ir-

relevant act which may not be transferable to other, e. g. more complex types of decisions to act. It is also possible that other brain mechanisms may have been activated in the Libet experiment than in an emotionally and ethically relevant decision.

Besides this discussion, brain imaging studies have provided evidence that the brain is processing information although the subjects are not aware of this stimulation. For example, presentation of masked emotional stimuli evoked strong haemodynamic responses in the amygdalae although the subjects were not aware of this stimulation. In addition, implicit memory processes have shown to activate the amygdale and the hippocampus (Henke et al. 2003b; Henke et al. 2003a; Whalen et al. 1998). Thus, these studies have shown that implicit information not only influences our behaviour (e. g. memory and emotion) but also brain activation. If one follows the thesis of limbic control, the will could not be free because it would depend on the unconscious functions of the limbic system. Therefore, in this line of argumentation, the existence of a will is undisputed, but its experience as "free" is seen as an illusion. The function of this illusion is seen in e. g. evolutionary advantages of forming social systems (Singer 2004).

With respect to the philosophical positions regarding free will, these neuroscientific findings derived from the Libet experiments have sometimes been interpreted in a way as if they showed that determinism were true, whereas the thesis of limbic control challenges the view of a will being truly free. However, it is heavily disputed whether determinism could be strictly proven at all, and it is widely agreed that an experimental setting like the one chosen by Libet does not meet the required criteria (see e. g. Hartmann 2004).

As outlined above, three lines can be distinguished in the debate of these neuroscientific findings:

- an assessment of the neuroscientific findings in the light of the different philosophical positions on freedom of will,
- epistemological questions, and
- practical implications beyond the philosophical discourse,

which will shortly be discussed in the following chapters.

16.2.2 Assessment of the neuroscientific findings in the light of the different philosophical positions on freedom of will

That the brain is the physical basis for the mind, and that all mental processes have neural correlates is hardly compatible with philosophical dualistic theories in the tradition of Descartes. Also libertarian positions of the free will do not conform with neuroscientific findings. However, these positions are usually not pursued by contemporary philosophers.

Although philosophical determinism and neuroscience have in common that they see the world as causally closed, and that man and mental processes are also subjected to natural laws, they differ in their argumentation with respect to the postulated non-existence of a free will. While philosophical determinism rejects freedom of will mainly for logical reasons, neuroscientific positions mainly refer to the argument that the relevant brain mechanisms for decisions are unconscious and not accessible by consciousness, whereas a freedom of will would be linked to conscious deliberations.

The compatibilistic view is also consistent with many empirical neuroscientific findings: according to compatibilistic positions, wilful acts would be due to reasons, and a different action would have resulted from different reasons. This is considered to be free will because the person could have decided otherwise, even in the same situation.

16.2.3 Epistemological aspects

In recent years, the debate between philosophy and neuroscience increasingly addresses epistemological aspects. In short, the neuroscientific research paradigm is the analysis of brain processes from a third-person-perspective, whereas phenomena such as mind, consciousness and free will are mainly accessible from the first-person perspective by introspection. Against this background, it is discussed to which extent these mental phenomena can be amenable to studies within neuroscientific paradigms at all, to which extent philosophical and neuroscientific theories can be (made) compatible with one another, or whether they are so distinct that they must remain separated discourses.

16.2.4   Practical implications

The concept that human beings are capable of autonomous, free decisions forms an integral part of our understanding of moral action and responsibility, personhood, theory of criminal law, as well as questions of education, social control and addiction. Against this background, far-reaching implications could be assumed if this concept were challenged. It could, for example, question the basis of our criminal law and justice because our intuitions about a person's responsibility for his actions depends on a free will. If there were no free will, then our ways of thinking about responsibility and blame would be challenged, with possible, yet disputed impacts on the criminal law and justice. This aspect is discussed in depth in chapter 21.

17   Enhancement of cognitive functions

17.1   Introduction

In recent years, substantial progress has been made regarding the intervention in brain functions. Most prominent among these techniques are drugs with psychoactive substances targeted at the CNS, but neurosurgery with unprecedented precision, neural prostheses and implants, genetic modification of neural systems, stem cell transplantation and nanotechnology can also be employed (Wolpe 2002; McGuire, McGee 1999). Although also transcranial magnetic stimulation (TMS) and neurofeedback with fMRI and EEG can also be used in an interventional way, neuroimaging methods rather play a supportive than a direct role, e. g. by supporting the implantation of neural prostheses, implants or brain-machine interfaces, by supporting the development of psychopharmaceutical drugs, or by monitoring the effects of genetic modification or stem cell transplantation.

Nevertheless, the above mentioned techniques, in their combination, bear the potential of not only being used to cure impaired brain functions, but also for enhancing normal brain functions. In this context, enhancement is understood as interventions which aim at an improvement of human abilities and performance beyond "normal" levels – also in an excessive and undesired manner (Friele, Fulford 2004). Against this background, it must be discussed what the difference is between helping someone whose capacities are below average to reach the average, and helping someone already above average to reach a still higher level of functioning (Helmchen 2005; Friele, Fulford 2004). The question of enhancement is not at all new or specific to the neuroscience field; examples can be found e. g. in the use of growth hormones in paediatrics, in plastic and cosmetic surgery, in doping in sports, or in genetic engineering (Fuchs et al. 2002). In the neuroscience field, enhancement is predominantly discussed in the context of mood and memory enhancing drugs and implantable brain chips (e. g. for deep brain stimulation) (Lynch 2004; Kennedy 2004; Marshall 2004; McGuire, McGee 1999; Wolpe 2002; Farah et al. 2004; Chatterjee 2004; Helmchen 2005; EGE 2005).

In the following chapters, we focus on the direct use of neuroimaging methods for the the enhancement of brain functions. The present state of the art regarding transcranial magnetic stimulation (TMS) (chapter 17.2) and neurofeedback (chapter 17.3) will be presented, and possible impacts and ethical aspects will be discussed (chapter 17.4).

17.2   Enhancement of brain functions by TMS

A currently intensively disputed application of transcranial magnetic stimulation (TMS) is the stimulation of the frontal cortex in the context of approaches trying to modify depressive behaviour. Several studies have demonstrated that the application of high-frequency TMS pulses over the left frontal cortex enhances mood and counteracts depressive symptoms. On the other hand, inhibiting the right frontal cortex by applying low-frequency TMS pulses has the same effect. Thus, positive emotions are obviously associated with a particular neural activation pattern in both frontal cortices (Loo, Mitchell 2005).

Besides using brain imaging methods in the context of improving psychological functions in neurologically ill subjects, it has recently been shown that brain imaging methods can be used to enhance cognitive functions in healthy subjects or in psychiatrically ill subjects without any obvious brain lesion. For example, it has been shown that spatial processing performance (mental rotation of numbers and figures) can be enhanced in normal subjects by using TMS for the application of short pulses over the parietal cortex (Klimesch et al. 2003). Although this enhancing effect disappears after several minutes, this study demonstrates that the (external) manipulation of neural activity of specific brain areas changes psychological performance.

The opposite effect, i. e. attenuation of a psychological function, has also been shown. For example, low frequency TMS pulses (<= 1 Hz, 10-20 minutes) inhibit neural activation of the stimulated brain area and, thus, attenuate the performance of the controlled psychological function. This effect has been demonstrated for several motor functions, visual object performance tasks, for working memory processes, and for emotion functions (Pascual-Leone, Walsh 2003).

17.3   Neurofeedback approaches employing fMRI or EEG

With the advent of modern brain imaging methods a new approach is on the way to be used in the context of cognitive neuroscience. This approach makes use of brain signals (either measured with fMRI or EEG) which are fed back to the subject. The subject is instructed to monitor the brain signals which are transformed to visible or audible signals. By monitoring these signals the subject can learn to manipulate the activity of the brain and in turn change her/his behaviour. This approach is qualitatively different from the conventional biofeedback approach which makes use of peripheral physiological signals (heart rate, electrodermal activation, etc.) because the brain controls itself by monitoring its own brain signal. Currently, so called real-time fMRI approaches are under construction allowing to measure haemodynamic responses and activations which are transformed into easy-to-identify auditory or visual signals. The most intriguing aspect of this approach is that haemodynamic responses of a particular and small brain can be monitored and manipulated by the subject. Although several papers have been published so far demonstrating that this approach is possible in principle, this approach lacks fine-graded time resolution because of the slow haemodynamic response (Posse et al. 1997; Weiskopf et al. 2004; Yoo et al. 2004; Yoo, Jolesz 2002). Thus, the subjects monitor brain signals with a delay of up to 1s.

A relatively new and faster method is the so-called electric tomography feedback approach which makes use of EEG signals measured from the subject's skull (Congedo et al. 2004). With a slight delay of approximately 50-100 milliseconds the scalp electrical distribution can be used to infer the intracerebral sources. This estimation is possible because of the advantages made in solving (better estimating) the inverse problem. The first and only paper so far has demonstrated the feasibility of this method by training the subjects to change their activation within the anterior cingulum. Because this approach is fast and less expensive than the neurofeedback approach based on fMRI signals it is very promising and offers wide applications including psychotherapy, education, neurology, or psychiatry.

17.4   Possible impacts and ethical aspects

As outlined in the chapters 17.2 and 17.3, the – few – uses of neuroimaging techniques for direct interventions in brain functions are still in an early stage of research and an infant stage of development. They are presently developed within a medical context, with the aim of treating diseases and disorders and compensate for severe handicaps and disablements. Presuming considerable progress, it could become possible in the future to use these interventions for the treatment of deficits and disorders of sensory functions (e. g. impaired vision, hearing, taste, smelling), of motor functions, of cognitive functions (e. g. memory, learning, apprehension, alertness), and of emotions, e. g. mood.

An open or latent demand can be assumed to use such interventions not only in a curative and restorative, but also in an enhancing way: For example, human enhancement is prominently and openly advocated by the transhumanists and extropiers. This is a sociocultural group which advocates "the moral right for those who so wish to use technology to extend their mental and physical (including reproductive) capacities and to improve their control over their own lives. [They] seek personal growth beyond [their] current biological limitations" and aim at "redesigning the human condition, including such parameters as the inevitability of aging, limitations on human and artificial intellects, unchosen psychology, suffering, and our confinement to the planet earth"[24]. Apart from these utopian and far-reaching visions, enhanced sensory, motor, and cognitive functions could be of interest e. g. for military forces or secret services to gain a decisive competitive advantage in warfare or espionage (see e. g. National Science Foundation 2002). But also in other fields of society, there could be an at least latent demand to enhance brain functions in order to gain an advantage in all sorts of competitions or to better cope with challenges (e. g. sport, exams in education, job performance through enhanced endurance, alertness, motor and cognitive performance), to compensate for existing socio-economic inequalities, or to achieve non-competitive, intrinsic benefits for personal satisfaction (e. g. enjoying extraordinary motor skills, enjoying being in good spirits due to mood-enhancement).

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[24]   quoted from "The Transhumanists Declaration", see http://transhumanism.org/index.php/WTA/declaration/; accessed Oct 23, 2005

Because possible interventions into brain functions using neuroimaging techniques are presently developed in the medical context with a therapeutic aim, it is most likely that the medical profession will be the first who has to deal with the problem of enhancement. An argument often brought forward in the debate is that interventions into brain functions are considered to be ethically legitimate if they relate to diseases or significant deviations from what is perceived as "normal" brain function, e. g. for the treatment of severe depressions. However, to choose health and disease conditions as a distinction whether interventions into brain functions should be considered ethically legitimate or not is problematic because there is no fixed and clear definition of what can be considered as "healthy" or "normal". As a consequence, the borderline between "health/enhancement/illegitimate" and "disease/treatment/legitimate" is blurred. This is due to several factors:

- Broad biological variation of brain functions, cognitive abilities and performance.
- Social, cultural and subjective elements play an important role in the perception of what is "normal", and are also subject to change.
- It is inherent to the interventional procedure that it can be both used for treatment as well as enhancement. One cannot have the treatment options without having the risk of using it also with the aim of enhancement.

It also challenges the medical ethos according to which physicians have (only) the obligation to heal (but not to enhance). On the other hand, some authors challenge this view: They argue that patient autonomy is increasing, and physician's duties also aim at improving patients' quality of life, so that physicians' roles could well also encompass enhancement if it contributed to the (subjective) improvement of an individual's quality of life.

Brain interventions with an enhancement purpose also raise health economic questions: Should health care systems be obliged to provide and pay for such interventions, and if yes, under which conditions? If a health care system is understood as a system which only has the duty to compensate impaired equality of opportunity if it is due to disease, and to restore it to a level which is the normal function within the species or relevant reference group of the population, the provision of such interventions could be rejected. It would be an unjust allocation of scarce resources to provide interventions beyond this level. On the other hand, it could also be argued that

subjects could already subjectively suffer from their abilities if the latter are still within the reference group range. If the perceived level of suffering were equivalent to suffering from disease, it could be considered unfair not to provide the intervention.

If enhancement of brain functions is used to gain a competitive advantage, be it in sport, exams, occupational settings etc., a central concern is equality and fairness. It is likely that access to brain-function-enhancing interventions will not be equal, so that certain segments of the population will be favoured over others, thus leading to a further widening of the socio-economic divide. This does not rule out the possibility that enhancement of brain functions could also be used to compensate for existing inequalities, and to narrow the socioeconomic gap. In the latter case, however, it should be considered whether other means (e. g. changing the social conditions) would be more effective and ethically more acceptable than enhancement on the individual level. In this context, also the issue of accomplice arises: it is a controversial issue to which extent the interests of the affected individual should be followed by provision of enhancement – even if this perpetuates unfair and discriminating tendencies, or whether the individual's wishes should be denied due to these reasons.

Biomedical enhancement also challenges the authenticity of an accomplishment. In e. g. contests or exams, not the achieved result or level of performance alone is important, but also whether it can be attributed to a person as his/her personal accomplishment. If the result were, however, achieved with the help of cognitive enhancement, this would undermine the accomplishment. Moreover, there is the risk that enhancement of brain functions may also alter the authenticity of a personality, a person's identity and autonomy.

And finally, cognitive enhancement can also be seen as a means to override the human contingency, in the sense of fragility, imperfection and finitude. If a high moral status is assigned to these integral elements of the conditio humana, enhancement would have to be rejected.

To sum up, the discussion whether enhancement can be seen as an ethically legitimate goal focuses on the arguments of fairness and justice, accomplishment, authenticity, and the moral status of human contingency (Fuchs et al. 2002; Helmchen 2005).

18   Markets and market developments for brain imaging devices

18.1   Introduction

The access to and the use of sophisticated imaging devices (chapters 4 and 5) is the prerequisite for neuroimaging, which – in turn – will be substantially influenced by the market for these devices.

In order to better understand how the application of neuroimaging is likely to develop in the coming years, we analyse the market, market development and main drivers and restraints for both the total medical imaging market (chapter 18.2) as well as for the key modalities for neuroimaging, i. e. PET, MRI and EEG (chapters 18.3 to 18.5), according to the following guiding questions:

- What are the market size and major market segments?
- What are the major trends, drivers and restraints for future market development?
- Which are the leading companies as technology providers in these markets, which strategies do they pursue?
- What are the impacts on the use and the demand side?

18.2   Market for medical imaging

18.2.1   Market size and segmentation

The medical imaging market is a segment of the medical device market. The medical imaging market comprises the following segments:

- Imaging equipment. This segment includes the hardware equipment for the different medical imaging modalities. The most important modalities are

- x-ray (including conventional x-ray, analogue radiography, digital radiography, and fluoroscopy),
- magnetic resonance imaging (MRI),
- computed tomography (CT),
- ultrasound, and
- nuclear medicine (e. g. PET, gamma cameras, SPECT).

In addition to modalities for human use, devices for small animal imaging which are presently mainly used in research and drug development fall into this category.
- Imaging information technology. This segment includes soft- and hardware for picture archiving and communication systems (PACS), 3 D imaging, and computer aided detection.
- Contrast agents and radiopharmaceuticals.

Information on the size of these market segments is available for the USA, which is the world's largest single market for medical imaging. In the USA, the imaging equipment segment is the largest segment of the medical imaging market which accounts for nearly two thirds (63 %), followed by the contrast agents and radiopharmaceuticals segment (22 %) and the imaging IT segment (15 %) (figure 18.1). It is assumed that the US imaging equipment market is appr. 40-45 % of the world imaging equipment market (Frost & Sullivan 2004c).

This corresponds well with data from a Medtech Insight report cited in Landesbank Baden-Württemberg Equity Research/Strategy 2005, which states that the *world* market for medical imaging equipment was 15.5 billion US$ in 2002. Table 18.1 gives an overview of its segmentation. While the prices for the individual device differ substantially depending on the technical specifications of the device, MRI tomographs are the most expensive modality, followed by PET and CT. For MRI tomographs, costs amount to appr. 1 million €/Tesla, and scanners presently in clinical use usually have magnetic field strengths of 0.5 to 1.5 Tesla, with some devices up to 3 Tesla (figure 18.2). MRI scanners with even higher magnetic field strenghts (e. g. 7 Tesla) and higher corresponding costs are used for research purposes only (see also chapter 18.4).
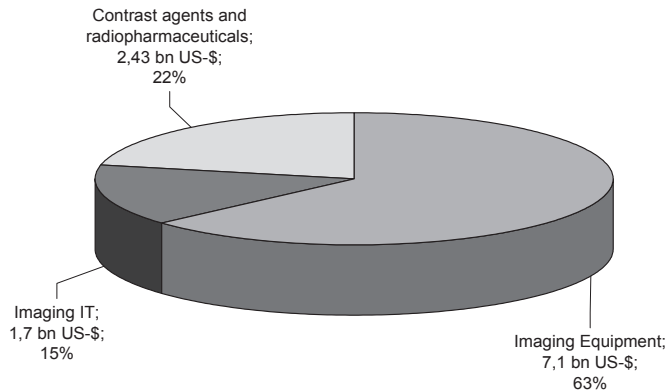
Figure 18.1:   *Segmentation of the total medical imaging market in the USA, 2003 (source: Frost & Sullivan 2004c)*

Table 18.1:   *World market for medical imaging equipment in 2002 (source: Landesbank Baden-Württemberg Equity Research/ Strategy 2005)*

Market segment	World market 2002 (bn. US$)	Share (%)
x-ray	4.5	30
Ultrasound	3.4	22
MRI	3.2	21
CT	3.0	19
Nuclear medicine	1.3	8
Medical imaging total	15.5	100
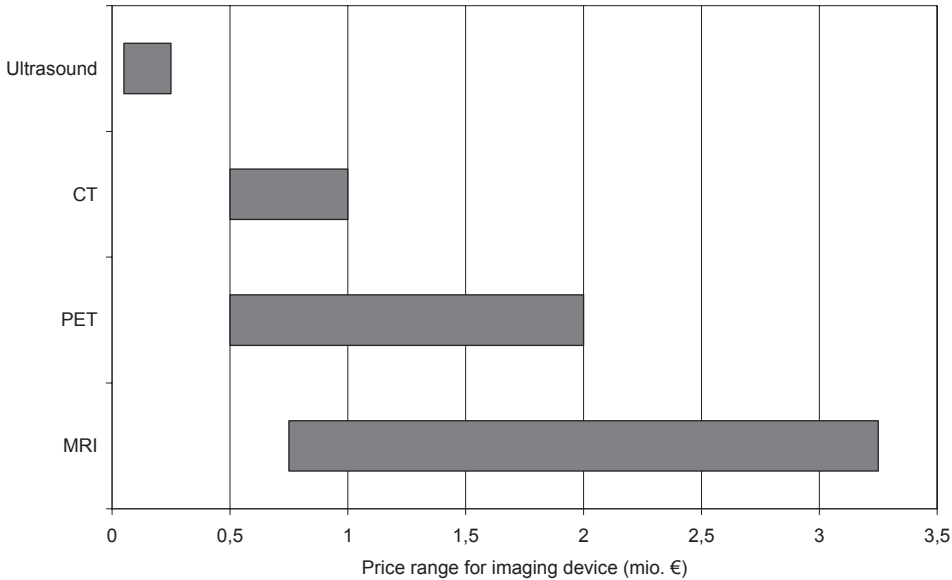
*Figure 18.2:   Price ranges for medical imaging devices, presently em-
              ployed in clinical settings (source: Landesbank Baden-
              Württemberg Equity Research/Strategy 2005, p. 14)*

There are large differences between countries to which extent these mo-
dalities are used (see table 18.2). In general, there is a correlation with the
Gross Domestic Product (GDP) and health-related expenditure in general,
but other factors such as government policies, structure of healthcare de-
livery, reimbursement decisions etc. also play a role.

Switzerland is generally considered as a small market for medical imaging
devices due to its relatively small population, but as an attractive one due to
its high health expenditures per capita. This is reflected in a high rate of
advanced medical technology per million of population (table 18.2) where
Switzerland is among the best-equipped countries.

Table 18.2:   *Adoption of advanced medical technology (CT, MRI) in different countries, 2002 (source: OECD Health Data, cited by ECHI (European Community Health Indicators) project, http://europa.eu.int/comm/health/ph_information/ dissemination/echi/echi_21_en.pdf)*

Country	Number of scanners/mio. population	
	Computerised Tomograph Scanners (CT)	Magnetic Resonance Imaging Units (MRI)
Austria	27.3	13.4
Canada	9.7*	4.2*
Czech Republic	12.1	2.2
Denmark	13.8	8.6
Finland	13.3	12.5
France	9.0*	2.4*
Germany	13.3*	5.5*
Greece	17.7	2.4
Hungary	6.8	2.5
Iceland	20.9	17.4
Italy	23.0	10.4
Japan	92.6	35.3
Luxembourg	24.7	4.5
Slovak Republic	10.6	2.0
Spain	12.8	6.2
Switzerland	18.0	14.1
Turkey	7.5	3.0
United Kingdom	5.8	4.0
USA	12.8*	8.2*
* Data from year 2001		

18.2.2   Market structure on the suppliers' side

In the medical imaging market, there are three categories of providers of medical imaging equipment, IT and radiopharmaceuticals (Frost & Sullivan 2004c):

1) Large original equipment manufacturers (OEM) with revenues in imaging equipment, imaging IT and contrast agents exceeding 1 billion US$ per year.
2) Multi-modality companies with revenues between 100 million US$ and < 1 billion US$.
3) Niche manufacturers with revenues below 100 million US$.

Table 18.3:   Company market share in the US medical imaging market 2002/2003 (source: Frost & Sullivan 2004c, p. 2-26)

Company	Share of the total US medical imaging market (%)	Share of the medical imaging market without imaging agents (%)
GE Healthcare	28.0	34.9
Siemens Medical	17.7	22.0
Philips Medical	16.8	20.9
Sum Category (1) companies	62.5	77.8
Toshiba America Medical Systems	4.1	5.0
Companies with 1-3 % market share (Hitachi, Kodak, Agfa, Fuji, Hologic, BMS)	8.4	6.7
Others	25.0	10.5
Total	100	100

Only three companies belong to category (1). These are GE Healthcare, Philips Medical and Siemens Medical. Together, they had a market share of 63 % of the US medical imaging market and of 78 % of the medical imaging equipment and radiopharmaceuticals market in 2002/2003 (table 18.3). These market leaders provide all key imaging modalities. In recent years, they have shifted their strategic focus from providing (only) imaging solutions to delivery of healthcare (imaging as an integral part of diagnostic, treatment and aftercare procedures). Indicators for this strategic shift is a broadening of the product portfolio, alliances or acquisitions of companies which provide imaging agents, pharmaceuticals, and IT solutions. Competitive factors are range of product portfolio, innovation, brand

loyality, pricing, customer service, and financing options. The "Big Three" nearly exclusively sell to large hospitals and integrated delivery networks whereas category (2) and (3) companies are at a competitive disadvantage for these customers.

Companies belonging to categories (2) and (3) play a significant role in certain modalities (e. g. EEG, MEG), or specialised products (e. g. small animals imaging, imaging software). Moreover, they often sell their products to smaller hospitals or physicians, and may be attractive partners in alliances, or mergers and acquisitions with the leading companies.

18.2.3   Market characteristics, drivers and trends
Although the market for medical imaging comprises very different devices ranging from low to high tech, several trends characterise this market which are valid irrespective of modality. These are (Farkas, Becks 2005, p. 304f; Frost & Sullivan 2005a):

Scientific-technological developments on the device side

- *4D imaging and functional imaging.* Whereas "classical" biomedical imaging focuses on morphological features and static images which represent a "snapshot", technological advances aim at providing functional information in addition to morphological information, and to provide alterations over time (4th dimension, "movies"). Functional imaging is at the core of cognitive neurosciences, but has also many applications beyond brain imaging. fMRI and PET are the presently most important modalities for functional imaging.
- *Biomolecular imaging.* It is the aim to image cell-biological parameters in vivo and non-invasively. This would be a major advantage compared to the present situation, where many tests can only be performed after a sample has been retrieved from the body and prepared and analysed in the laboratory. Presently, these techniques are of major importance in biological and biomedical research and in pharmaceutical drug development (see chapter 14) whereas clinical applications in diagnosis, therapeutic interventions and evaluation of therapeutic interventions (see e. g. chapter 13) are still in an infant stage. Biomolecular imaging is seen as a major development within the strategy of major imaging companies

of integrating medical imaging into all stages of health care delivery (i. e. prevention, diagnosis, therapeutic intervention, following the course of disease, evaluation of treatment success; also see below). As a consequence, larger medical imaging equipment companies are already active in the (rather small) small animal imaging market because it is seen as integral part of the molecular imaging toolset.

- *Multimodal systems.* Because each of the medical imaging modalities has its specific strengths and weaknesses, full information can often only be obtained by combination of different modalities. This requires, on the one hand, that new methods for digital image processing and registration are implemented to merge data from sequential analysis by different modalities. On the other hand, devices which combine different modalities in one device are also required. Combined PET-CT-scanners are already on the market (chapter 18.3). PET-MRI-systems are in development, and other combinations may also be useful.

Broadening the range of (clinical) applications

- *Screening and early diagnosis.* It is the aim to use medical imaging in rapid whole-body or organ screening procedures in order to identify diseases in very early stages even before clinical symptoms become evident. The underlying assumption is that the progression or onset of disease could be more effectively prevented in presymptomatic stages. In this way, medical imaging could substitute or complement many biochemical test and screening or diagnostic surgical procedures. Examples are screening of blood vessels or coronary arteries for stenoses, screening for tumours, diagnosis of Alzheimer's disease before the onset of mild cognitive impairment (see chapter 13). Challenges lie in developing imaging devices with high throughput of patients which allow the screening of large patient numbers in acceptable time and at acceptable costs. Moreover, selectivity and specificity of the diagnostic imaging procedures must be substantially improved in order to avoid false positive or negative results. If this strategy were successful, it would expand the market for medical imaging considerably by opening new markets. This trend is described in more detail in chapter 13 with the example of Alzheimer's disease.

- *Evaluation of therapeutic interventions.* It is the aim to monitor the effect of therapeutic interventions (e. g. medications) on the progression (or

rather regression) of disease. While this is already implemented in clinical practice for the staging in tumour therapies, analogous procedures still have to be developed and implemented in the clinic for other diseases, therapies and modalities. If this strategy were successful, it would expand the market for medical imaging considerably by opening new markets.

- *Integration of diagnosis and therapy.* It is the aim to integrate diagnosis and therapeutic intervention into one procedure. If, e. g. a tumour or stenosis is detected by medical imaging, it should become possible to remove or treat it immediately. In this way, the number of subsequent interventions performed on one patient should be minimised. An example is the Gamma Knife for the localisation and destruction of acoustic neuromas (chapter 12.2.7).

- *Image-guided interventions.* Many surgical procedures, especially minimally-invasive ones, require some sort of imaging during the intervention. Although considerable progress has been made in recent years, existing solutions need to be further improved, e. g. with respect to integration of single solutions into the overall surgical procedure, or the ability to take movements into account (see also chapter 12.2).

- *Integration of medical imaging into all stages of health care delivery.* The above-mentioned trends contribute to the strategy of major medical imaging companies to integrate medical imaging into all stages of health care delivery (i. e. prevention, diagnosis, therapeutic intervention, following the course of disease, evaluation of treatment success). This is also a contribution to a general trend towards individualised medicine.

Product-accompanying services

An important competitive factor in the medical imaging market is the range and quality of services which are offered by the equipment companies beyond the sale and maintenance of the imaging devices themselves. In addition to the factors mentioned here, financing of device purchase, leasing, offering refurbished and used devices, as well as education and training play an important role. They will be described in more detail in the section "demand side" below.

- *One-stop-shop for medical imaging.* Many companies try to achieve competitive advantages by offering the full range of products and ser-

vices related to medical imaging with a given modality. This means that they do not only provide the imaging device itself, but also the required consumables such as radiopharmaceuticals or contrast agents, IT systems, financing, and training and qualification of staff. This is done by cooperations, licensing agreements, and mergers and acquisitions.

- *Improved workflow.* In synergy with the trend towards multimodal systems is the requirement by customers (e. g. hospitals, radiologists) that the imaging modalities are fully integrated into the clinical workflow. This requires the manufacturer not only to offer the imaging device, but rather to offer comprehensive solutions with the necessary peripherals, software and connectivity. Improved workflow also generates a demand in the imaging information technology market segment of the medical imaging market, because there is a growing demand for computer-assisted data analysis (e. g. filtering the most valid images for diagnosis out of the vast amount of data generated during a scan). Improved workflow also means that the medical imaging service must fully comply with hospital quality assurance systems etc.

- *Application-specific sequences ("Push-button").* Advanced medical imaging devices are rather complex devices which require specific knowledge for data acquisition and interpretation. The technological capabilities of the sophisticated devices can, however, be fully exploited only if the relevant measurement parameters are tailored to the specific application. This requires specific knowledge for data acquisition and interpretation, and time to tune the device according to the desired application, and bears the risk of errors which invalidate the diagnostic quality. For reasons of qualification, quality assurance, high-throughput of patients, and versatile use of expensive imaging devices, equipment manufacturers develop application-specific sequences which allow a "push-button" use of the imaging devices for different diagnostic procedures.

Strategic positioning of major imaging device companies in the market

The few very large medical imaging companies focus on the two strategies described above:

- From imaging equipment provider to supporter of healthcare delivery.
- One-stop-shop for medical imaging.

In addition, there are many smaller companies which serve highly special-
ised needs and niche markets.

Important influencing factors on the demand side

- *Reimbursement.* The application of medical imaging and thus also the
  purchase of imaging devices depends to a large extent on the reim-
  bursement conditions set by the relevant health insurances. The reim-
  bursement conditions are country- and insurance-specific.
- *Financing of device purchase, leasing.* Advanced medical imaging de-
  vices are expensive equipment which require a high fixed asset invest-
  ment in which a large proportion of the costs must be committed prior to
  any revenue generation. An important competitive factor for equipment
  companies is the offer of attractive and flexible financing options for the
  device purchase, among them attractive credit conditions, discounts and
  incentives (e. g. in the form of free additional features of the equipment,
  additional services such as training), leasing options and the sale of re-
  furbished or used systems.
- *Profitability of advanced medical imaging*. MRI as well as PET have
  rather high fixed costs, whereas are variable costs are relatively low.
  Fixed costs must be shared over the volume of examinations conducted
  annually, whereas variable costs are incurred only when an examination
  is conducted. As a consequence, users of MRI and PET will aim at in-
  creasing the patient throughput in order to improve profitability which, on
  the one hand, requires the scanners to support high-throughput, and on
  the other hand may negatively impact the quality of the data acquisition
  and interpretation for economic reasons.
- *Education and training, quality assurance.* Scientific-technological pro-
  gress in medical imaging devices, together with the trend towards multi-
  modality, higher performance and improved workflow lead to a shorten-
  ing of product cycles: new device generations with improved perform-
  ance and higher functionality enter the market. This creates, on the one
  hand, the challenge for radiologists, physicians and researchers to keep
  up to date with the increasing complexity and points to the need of ap-
  propriate education and training. On the other hand, the validity of the
  imaging results depends to a large extent on the expertise with which
  the data acquisition and interpretation is performed. As a consequence,
  education and training are also of great importance for quality assurance

of medical imaging. Medical imaging suppliers respond to this by offering device-specific training courses for staff, and by developing application-specific sequences ("push button") in order to support quality assurance.

Table 18.4:   Typical fixed and variable components of MRI expenses (source: Bell 2001)

Expense Category	Type of Expense	Typical Cost/Year (US$)	Cost per 1,000 examinations	Cost per 3,000 examinations
MRI Equipment	Fixed	300,000	300	100
Maintenance	Fixed	100,000	100	33
Space	Fixed	50,000	50	17
Personnel	Fixed	125,000	125	63
Overhead	Fixed	50,000	50	17
Office Expenses	Fixed	15,000	15	5
Marketing	Fixed	10,000	10	3
Utilities	Fixed	50,000	50	17
Medical Supplies	Variable	25	25	25
Film	Variable	30	30	30
Billing and Collect	Variable	35	35	35
Total			790	344

18.3   Market for Positron Emission Tomography (PET)

The PET market comprises stand-alone PET scanners and PET-CT scanners which combine both PET and CT modalities in one device. Moreover, in order to operate these modalities, cyclotrons for the production of radio-

chemicals, radiochemicals and software to fuse images generated by distinct PET and CT modalities are required, but are not included in the market figures presented below.

In 2003, the US market for PET and PET-CT was 505 million US$, corresponding to a total of 270 sold units (table 18.5). The European market is estimated at 130 million €, which corresponds to appr. 80-85 sold scanners per year[25]. Manufacturers are GE Healthcare, Philips Medical and Siemens Medical.

Table 18.5:   Key characteristics of the US PET and PET-CT market 2003 (source: Frost & Sullivan 2004d)

Characteristic		Share
Market size total	506 mio. US$	100 %
Market size PET	110 mio. US$	22 %
Market size PET-CT	396 mio. US$	78 %
Sold units 2003 total	270	100 %
PET	85	31 %
PET-CT	185	69 %
Installed base	1,077 sites	
PET	781 sites	
PET-CT	296 sites	
Average price PET	1.3 mio. US$	
Average price PET-CT	2.1 mio. US$	

Although the majority of installed PET devices are stand-alone PET scanners, they face increasing competition from PET-CT scanners which were introduced into the market not before 2001. In 2003, hybrid PET-CT scanners accounted for 78 % of the US market size in terms of turnover, and for 69 % in terms of sold units (table 18.5).

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25   The average price in Europe is about 1.2 million € for a stand-alone PET and 2 million € for PET-CT devices.

It is not yet fully clear how the competition between PET and PET-CT will proceed in the future. According to experts' estimations, the sales for PET-CT will continue to grow moderately, but mainly at the expense of new stand-alone PET scanners. However, the market for used and refurbished[26] stand-alone PET equipment is expected to grow considerably in the coming years.

PET and PET-CT are predominantly used in clinical settings (hospitals, radiologists) which account for appr. 90 % of the market, whereas research uses are in the order of magnitude of 10 %.

In the clinic, the vast majority of PET procedures are performed for oncology purposes (appr. 90 %), e. g. pulmonary nodule characterisation, and staging and restaging of lung cancers and lymphoma. The remaining 10 % of procedures are split between cardiology applications (e. g. examination of myocardial perfusion) and neurology. In neurology, PET or PET-CT are mainly used for pre-surgery examinations in epilepsy, and for early stage Alzheimer diagnostics (see chapter 13). The extent to which certain procedures are performed is significantly influenced by national reimbursement decisions.

18.4   Market for Magnetic Resonance Imaging (MRI)

The MRI market can be segmented according to the openness of the magnet (open or closed MRI systems) and the field strength. The MRI market comprises the following segments (Frost & Sullivan 2004c):

- Closed MRI systems. Closed MRI systems are the "classical" MRI systems in which the patient is located in the bore of the magnet.

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26   In the EU, a medical device is fully refurbished when the process involves stripping into component parts or subassemblies, checking their suitability for reuse, replacement of those parts not suitable for reuse, assembly of the reclaimed or replaced components, and testing the assembled device against original or revised release criteria. In addition to "refurbished" medical devices, equipment is often also sold in "as is" form which means that the scanners are deinstalled from one site and sold to another site in the same condition.

- Open MRI systems. Open MRI systems are, compared to closed MRI systems, a newer development which employ an open magnet. These systems are useful for interventional MRI (chapter 12.2) as well as for claustrophobic or obese patients.
- Low-Field MRI systems with field strengths of less than 0.5 Tesla.
- Mid-field MRI systems with field strengths of 0.5 to 1 Tesla.
- High-field MRI systems with field strengths of 1.5 Tesla.
- Very-high field MRI systems with field strengths of 3 Tesla.
- Experimental MRI and small animal MRI systems with field strengths of 7 Tesla and higher.

Moreover, in order to operate these modalities, contrast agents and IT so-lutions for image management and analysis are required. They are not in-cluded in the market figures presented below, although they are substan-tial: The European[27] MRI contrast media market in 2003 was estimated at 212 million US$ (Frost & Sullivan 2004b). MRI contrast media increase the contrast for a specific tissue, thus making MRI tissue specific. The major applications of MRI contrasting agents are found in MRI procedures for brain and the central nervous system, liver and the detection of breast can-cer (Gillies, Morse 2005).

Table 18.6:   MRI market size worldwide, in the USA and Europe (source: Landesbank Baden-Württemberg Equity Research/Strategy 2005; Frost & Sullivan 2004c; Frost & Sullivan 2005a)

Region	Year	Market size (mio. US$)	Installed base
World	2002	3,200	n. a.
USA	2002	1,456	6,284
Europe	2004	605	2,927 (2002) 3,820 (2004)

The world market for MRI equipment was estimated at 3.2 billion US$ in 2002 (Landesbank Baden-Württemberg Equity Research/Strategy 2005), with the USA market at 1.4 billion US$ (2002) and Europe at 0.605 billion US$ in 2004 (table 18.6). The vast majority of the MRI scan-

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27   The following European countries are included in this figure: UK, France, Germany, Benelux, Scandinavia, Italy, Spain.

ners are used predominantly for clinical diagnostics (appr. 90 % of the devices), approximately 10 % of the scanners are shared between research and clinical facilities, whereas research-only MRI scanners are sold in quantities of appr. 20 units/year.

In Switzerland, appr. 110 MRI scanners for human use are installed of which appr. 5 are used in research-only institutions.

Comprehensive data for market segmentation according to field strength and type of magnet are only available for the USA (table 18.7). It shows that the "standard" MRI is now in the high field with 1.5 T which accounts for appr. three quarters of the market. However, very high field MRI scanners with 3.0 T are increasingly installed, mainly due to their use in orthopaedic imaging, cardiovascular imaging and mammography. The number of 3 T-MRI scanners installed in Europe[27] is estimated at approximately 55 (2004). MRI scanners with even higher field strengths of up to 7-8 T are research-only scanners, with only few scanners produced and installed per year worldwide. It is planned to install two such MRI scanners in Switzerland in the coming years. Small animal MRI scanners operate with even higher field strengths of 7 to 16 Tesla, but are mainly used in basic research and pharmaceutical R&D, especially for molecular imaging. They have a small share of the small animal imaging market which is estimated at appr. 60 million US$ worldwide (Frost & Sullivan 2004a).

Scanners with field strengths of 1 T and above in principle support structural as well as functional imaging. However, clinical MRI applications which dominate the device market, are still predominantly structural. As a consequence, only 20-25 % of all MRI scanners with field strengths above 1 T are equipped with fMRI options.

MRI is the most expensive of all the medical imaging modalities (figure 18.2, table 18.7). As a rule of thumb, costs for MRI equipment are in the order of magnitude of 1 million US$/Tesla. Additional substantial investment is required for appropriate construction of the facility (e. g. electricity installations, climate conditioning, shielding of electromagnetic fields). With the entrance of high to very high field MRI onto the market, prices have decreased for mid- to low field MRI. On the other hand, a significant price decrease for high to very high field MRI scanners is not to be expected in the short to medium term. Manufacturers aim at replacing low-

field MRI scanners by high- to very high field scanners thus keeping price levels constant but to sell devices with improved performance and more value-for-money.

Table 18.7:   Market segmentation for MRI systems according to field strength and magnet, USA 2002 (source: Frost & Sullivan 2004c)

MRI system	US market 2002, mio. US$	Share (%)	Units sold	Average price per unit mio. US$
Very high field MRI, 3 T	55	4	25	2.2
High field MRI, 1,5 T	1,052	72	722	1.5
Mid-field MRI, 0.5-1 T	296	20	217	1.4
Low-field MRI, < 0.5 T	54	4	91	0.6
Total	1,457	100	1,055	1.4
Closed MRI systems	1107	76	747	1.5
Open MRI systems	350	24	308	1.1
Total	1,457	100	1,055	1.4

Pancreas, liver, kidney; 10 %

Cardiovascular; 20 %

Neurology; 50 %

Orthopedics; 30 %

100 % corresponds to 21 mio. MRI scans/year (US data)
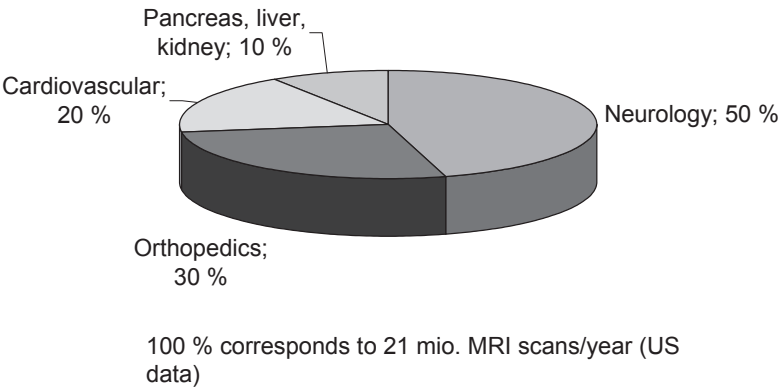
Figure 18.3:   MRI procedures in the USA (2004)

With clinics and specialised imaging centres gradually upgrading their MRI equipment, low end systems with less than 0.5 T have found buyers among smaller private imaging centres and radiology practitioners who cannot afford high strength scanners. This group prefers refurbished[26] MRI scanners, or buy the even cheaper "as is" equipment. It is estimated that in the coming years, the MRI refurbished market will see a trend towards 1.5 T scanners. The European[27] market for refurbished MRI was estimated at 42 million US$ in 2004, with strong growth expectations. However, Europe is mainly considered to be a good market to buy refurbished equipment, whereas the refurbished devices are resold primarily in Eastern Europe, parts of Asia and Africa, as well as in the USA (Frost & Sullivan 2005b).

In the USA, approximately 21 million MRI procedures are performed annually (2004). Approximately 50 % of these procedures can be attributed to neurology: MRI is the most important tool in brain diagnostics (figure 18.3).

18.5   Market for Electroencephalography (EEG)

In addition to research uses (see chapter 5.2), electroencephalography (EEG) has clinical applications in the following areas (Frost & Sullivan 2003):

- epilepsy diagnosis and long-term epilepsy monitoring,
- sleep monitoring,
- monitoring of post-surgery and head-injury patients in intensive care units, confirmation of brain death.

According to these clinical applications, the EEG market can be divided into the three segments "sleep monitoring", "long-term epilepsy monitoring", and "EEG for clinical diagnostic and monitoring procedures". The US market for EEG equipment amounted to 177 million US$ in 2002, with sleep monitoring accounting for 49 %, clinical EEG for 31 % and long-term epilepsy monitoring for 20 % of the total market. This corresponded to more than 7,000 sold EEG units. The price range for EEG units is 18,000-60,000 US$, and the average cost of a routine EEG procedure is between 350-450 US$.

In contrast to the PET and MRI markets, a larger number of manufacturers are active in this market. In the USA, at least 15 companies provide EEG equipment, with the larger companies being Nicolet Biomedical, BioLogic Systems, Nihon Kohden, Grass-Telefactor, Nellcor Puritan Bennett and Medcare.

Competitive factors are product features, functionality and ease-of-use, brand reputation and longevity in the marketplace, price, after sales service, alliances and partnerships with the research community, and marketing and distribution network (Frost & Sullivan 2003).

18.6   Summary

At present, manufacturer's strategies regarding medical imaging in general and neuroimaging in particular primarily aim at clinical applications whereas research applications are of subordinate importance in terms of sales. Because functional neuroimaging has, up to now, only found few applications in the clinic, structural imaging is a much larger market segment than functional imaging. In addition to scientific-technological progress regarding new clinical applications of neuroimaging, reimbursement decisions by the national health insurances play a major role in the question to which extent these procedures are really applied in clinical practice.

Against this background, non-medical uses represent no significant market segment and are not in the focus of the few top medical imaging companies. However, a large number of smaller, highly specialised companies are also active in this market which could serve these niche markets. To which extent this is the case has, however, not been investigated in this study.

At present, a trend of replacing PET by PET-CT and low-field MRI by high- to very high-field MRI scanners can be observed. Although this has led to a certain price drop for the "low-end" devices and to the emergence of a market for refurbished and used scanners, no general erosion for device prices is expected in the coming years. PET and MRI remaining rather expensive equipment this will be a certain restraint against an immediate, quick and

broad diffusion of these modalities into clinical practice beyond specialised centres and non-clinical uses.

Nevertheless, due to increasing complexity of the devices, their broadening range of applications and their continued diffusion into clinical practice, attention should be paid to qualification and quality assurance aspects. In analogy to the experience made during the broad introduction of ultrasound into the clinic it is not unlikely that sub-standard application of these imaging techniques occurs. On the one hand, radiologists trained in the use of CT and x-ray may not be familiar enough with MRI, and neuroimaging may also be performed by radiologists who may not have the specific expertise of neuroradiologists. In Switzerland, there is presently no requirement for a specific qualification of staff for using MRI (*"Fähigkeitsausweis"*, proof of special knowledge). Nevertheless, regulations against a substandard application of medical imaging exist which are outlined in detail in chapter 20.

19   Legal relevance of neuroimaging in brain research – overview

Knowledge of how the human brain is structured and how it works is growing at a rapid rate. The hope is that the mass of information generated by neuroimaging may be converted into realistic or analogous models, correctly assessed, and combined for a quality of understanding – more than that of the sum of each individual piece of knowledge – of the brain and how it functions, and possibly also of human consciousness. Neuroimaging makes a valuable contribution towards understanding cerebral performance and yet is only in its infancy.[28] Against this background, and given the dynamic and complex structure of modern societies, the potential of neuroimaging in brain research procedures must be evaluated from a legal point of view. For both the information already gleaned and the new scope for manoeuvre expected lead simultaneously to new contexts for decision-making, influence role expectations and the focus of stigma, and may possibly change the perception of man in society.

This task is made more complex by the fact that findings from brain research are made both nationally and internationally[29], are analysed and – sometimes in isolation, sometimes as bundled information – incorporated into in an overall context and evaluated. That this leads to a confluence of various moral concepts and ideals entails both opportunities and risks. In addition to new insights and the significant synergy effects of linking the data, a high potential for conflict and the fear of known and unknown dangers must not be disregarded. Any comprehensive effort to weigh the opportunities and threats of neuroimaging in brain research would have to engage with completely different parts of society and adhere to very distinct criteria. The following is an attempt to highlight a selection of these topics. This paper is concerned with identifying the central legal issues related to the development, application and consequences of neuroimaging in brain research and fleshing out, in particular, the legal gaps, the areas where

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[28]   SPITZER, MANFRED, Die funktionelle Bildgebung des Gehirns, Magazin 2/2003, Bildgebende Verfahren in der Hirnforschung.

[29]   For information on the Brain Elsa Project of the European Commission, see VOLLMANN, JOCHEN, Ethik in der Medizin (1999) 11, p. 35 et seqq.

legislation is required and the possible solutions, thus enhancing public discourse on the matter.

In this, the intention is not to create the impression that the law is independent of the technical, physical, medical and sociological principles of neuroimaging in brain research and the associated ethical issues this entails. It must always be observed that, in a pluralistic, democratic society, different values and perceptions exist with regard to how humans are to be both physically and mentally treated and what research, medical therapy and interventions are permitted.[30] This is particularly true insofar as the human brain is the focus of our attentions and evaluation. A democracy founded on the rule of law is obliged to respect and protect the various positions – to the extent that they conform to the fundamental values of the Confederation. The guaranteed fundamental rights of human dignity (Article 7 of the Swiss Federal Constitution – *Bundesverfassung*)[31], the general protection of personal data and respect for physical and mental integrity (Article 10 of the Swiss Federal Constitution, corresponding to Article 8 of the ECHR) are there to ensure that new developments must be seen in light both of the shared values of the community and of the guarantees of individuality, and that conflicts are resolved in a manner commensurate with the harmony of values sought in the constitution. However, where uncertainty exists with respect to moral concepts, it cannot be the purpose of law to declare one of the valid positions generally binding to the ultimate and final exclusion of the others. For the understanding of what laws are and should be is subject to sets of values in constant flux. Moreover, only when laws serve the common purpose, when they are recognised by society as correct and thus legally justifiable from an ethical point of view, can they hope to be accepted by the community and be confident of meeting with a positive response.

The number of people directly and indirectly affected by neuroimaging is considerable. Neuroimaging includes first those who use it to treat patients and/or to perform medical research. Also directly affected are the patients

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30   For more, see SPRUMONT, D., BÉGUIN, M.-L., La nouvelle réglementation des essai cliniques des médicaments, Schweizerische Ärztezeitung 2002, S. 894 ff.; KNOPPERS, B. M., SPRUMONT, D., Human Subjects Research, Ethics, and international Codes on genetic research, in: Encyclopaedia of Ethical, Legal, and Policy Issues in Biotechnology, 2000, S. 566 ff.

31   For more, see MASTRONARDI, PHILIPPE, in: EHRENZELER U. A. (Publisher), Die schweizerische Bundesverfassung, 2002, Art. 7 apostille 15 et seqq., with further references.

who are to be examined, the human research subjects and, indirectly, those from their close family and social environs. Those who bear the costs of this research and treatment, cooperating partners from industry and business who develop and market the relevant equipment and medicaments, are also involved. Moreover, neuroimaging is also of interest to those who see the promise of neuroimaging in brain research in terms of producing important findings,[32] be they in the field of education, marketing or administrative intervention and public welfare.

Distinctions may be made between several important issues related to the application of neuroimaging. On the one hand, the examination itself, and thus the effects on the brain, and, on the other hand, the use of the data thus generated. A distinction must be made here between examinations of living persons and examinations of the deceased. The right of the person involved to know or not to know the information pertaining to himself or herself requires a separate examination of the rights of access and information of third parties. Moreover, the use of neuroimaging may be divided into three groups: the individual observation of patients (diagnosis, observation of reactions to a treatment, etc.), biomedical research (on the condition or with a view to developing new treatments, and also on normal brain functions), and behavioural research (on the normal brain functions). Moreover, the different settings in which neuroimaging may be performed (e. g. in clinical settings with in-patients, or in research settings with volunteers) has to be taken into account.

Neuroimaging gives rise to a special set of problems with regard to the data collected from patients or research subjects, respectively. They are collected for different purposes and in different contexts: to impart medical knowledge in general and with respect to the individual patient, to understand how the brain works, and to explain human behaviour – the latter being especially of criminal law relevance, if this behaviour is under the influence of emotions and affects. The data collected may indicate the examined persons' state of health, quite probably also their psychic health, their emotional world, their decision-making processes and their personality profile. In general, these data are stored in data bases and may also be

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32   Reflections on how the brain and methods of legal finding function may be found in BRUCKMANN, ERNST-OTTO, Deutsche Richterzeitung (DRiZ) 1989, 81 et seqq.

linked with each other. Only once they have been interpreted can the data thus gleaned be considered as information and knowledge. However, this entails a certain susceptibility to error, which can have severe consequences when it involves making statements on how the brain functions or on the respective person. This brief overview illustrates the fact that the data gleaned through neuroimaging are clearly personal data and, even more, sensitive data which are recognised by the Swiss Constitution, by federal and cantonal legislatures as in particular need of protection. It therefore has to be examined in this report whether the data protection risks inherent in neuroimaging call for new instruments with respect to the protection of the fundamental right to self-determination and the protection against abuse of personal data.

Given this broad spectrum, it is hardly surprising that, as in the field of neuroethics[33], there is little or no solid consensus on the substance and boundaries of "neurolaw". For socially (in)adequate patterns of behaviour in relation to research and examinations of and on the brain are just as varied as the brain itself and its functions. Correspondingly large is the range of permissible treatment and impermissible intervention and interpretation possibilities. The brain's complexity, the current standard of neuroimaging in brain research and the ways in which this can be interpreted make the creation and establishment of an effective early-warning system to detect possible incidences of abuse and misuse all the more difficult. If this leads to the detection of conditional hazards or injuries caused to the person, it is probable that they will be recognised as the mere results of physical or mental defects or as a chain of unfortunate circumstances without the true (co-)causes or causal chains becoming known. However, the calculation models should be accorded the highest importance with respect to all the areas mentioned – regardless of whether the conclusions thereby arrived at can be verified or whether they later turn out to be misinterpretations.[34]

Even the judicature is being drawn in by the wake of these developments. This is shown exemplarily in the field of criminal law: whether performing neuroimaging constitutes an offence of bodily harm caused wilfully or negli-

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33 Specified in chapter 16 et seqq.
34 See argument on brain research between the neurobiologist Scheich, Henning and the philosopher Beckermann, Ansgar on the topic "Jeder muss sein Gehirn selbst in die Hand nehmen", GEHIRN&GEIST 3/2005, p. 59.

gently, whether the accused committed a crime while capable of acting and sane, what effects emotions may have had on the crime committed, whether the prisoner or the detainee should be freed at all, all of these cases require a solid knowledge of neuroimaging and its significance.

In the field of politics, neuroimaging bestows upon those responsible the obligation to anticipate the relevant opportunities and risks, to recognise at an early stage any modifications needed to the methods of examination and interpretation, and to implement these modifications by way of explicitly or implicitly related provisions[35]. These dynamics do not make it easy for the legislature to anticipate the degree of regulation needed and to provide for the appropriate legislation in the form of abstract, general provisions, as appears necessary from an ex-post observation in terms of the necessity and worthiness of punishment.

The net is thus widely cast. Nevertheless, the hugely different issues can be reduced to one common denominator. The following shows that the traditional legal norms do not always do justice to modern developments, and for a variety of reasons are unlikely to meet the need for rapid and simple means of adapting. Nevertheless, it should be remembered that, in particular, the provisions of criminal law and those governing medicine, despite all efforts to make them exhaustive[36], are of a fragmentary and subsidiary nature. Criminal law as an ethical minimum and simultaneously the most potent means of intervention for the state should not become the primary means of guiding the development of neuroimaging in brain research. Otherwise progress, and, thus, also society's legitimate interest in how the brain functions, would be disproportionately stunted. Moreover, criminalising medical practice and the regular modes of research would result in criminal law being turned into a "minor work" or a so-called *kleine Münze*. Wide-ranging but unenforceable criminal law provisions and the associated preliminary investigations and investigations on suspicion are regularly attended by the loss of general and special preventative effect. The intended objective of legal certainty is thus rendered less attainable.

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[35]   Specified in chapter 16.
[36]   For inflation of criminal laws and associated effects see KILLIAS, MARTIN, Grundriss der Kriminologie, Berne 2002, N. 807 et seqq.

20   Criminal relevance of neuroimaging as bodily harm or assault

20.1   Neuroimaging as a diagnostic procedure

The criminal relevance of neuroimaging in brain research is determined pursuant to the provisions of the Criminal Code (*Strafgesetzbuch*) as the so-called core of criminal law, and the provisions of secondary criminal law.

Just as there are no special provisions in Swiss federal law governing contracts for medical treatment, so too are there no special criminal provisions in force governing the permissibility and boundaries of neuroimaging.

The 26 Swiss cantons currently have different rules concerning medical treatment. And they also address some questions regarding research on human beings.

Cantonal health or hospital laws contain principles of biomedical research.[37] In addition, cantonal provisions on the legal status of the patients as well as on the establishment of ethics committees are also important. These provisions, despite being many-facetted in individual cases, are nevertheless incomplete. They even contradict each other in parts – a fact clearly demonstrated in the area of research for benefit of third parties.

For this reason the Swiss Federal Office of Public Health is in the process of drafting the so called Federal Law on Research Involving Human Subjects (*Humanforschungsgesetz*). At all, we have to recognise: Neuroimaging research is not necessarily biomedical research. What regulation applies in the case of behavioural research, this question remains open. In this case non-standardised regulations apply. Concerning the regulation of

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[37]   For a good overview, see SCHWEIZER, R.J, in: POLEDNA T., KIESER, U. [Publisher.], Schweizerisches Bundesverwaltungsrecht, Band VIII, Gesundheitsrecht, Basel, Genf, München 2005, G. Recht der Forschung im Gesundheitsbereich, section 6 et seq.. Also: AYER, A., CLÉMENT, T., HÄNNI, C., La relation patient-médecin: état des lieux. Rapport IDS No. 1, Neuchâtel 2003, 134 p.

biomedical research, the cantonal laws play an important role together with the Federal Law on Medicinal Products (*Heilmittelgesetz*).[38] However, medical data and behavioural data relating to individuals which may be indicative for future developments, require specific protection.

Examinations are carried out on living persons, for example in the case of multiple sclerosis and Alzheimer[39], to better determine where the diseased areas are located, and to better plot the progression of disease. In cases of schizophrenia, the existence of changes to the asymmetry, which is the normal state between the right and left hemispheres of the brain, have been confirmed. By examining these conditions, it is expected that indications can be found to highlight the mechanisms that causes them.[40] Current discussions also involve the application of neuroimaging in the areas of Parkinson's disease, chronic pain, brain tumours, aneurysms and compulsion neurosis.[41]

The use of neuroimaging helps not only to recognise medical conditions but may also mean violating the physical integrity of a patient. Within this context, the offences against life and limb, in particular those of bodily harm and violence, constitute the focus[42] of criminal liability.

Under Article 123 (1) of the Swiss Criminal Code (StGB), anyone who wilfully causes damage in any other way to the physical integrity or health of another shall, on a complaint, be liable to prosecution. Under Article 125, anyone who negligently causes damage to the physical integrity or health of another shall, on a complaint, be liable to imprisonment or a fine (paragraph 1). If the injury is serious, the offender shall be prosecuted even in the absence of a complaint (paragraph 2). According to Article 126, an act of violence committed by someone against another without this act resulting in damage to the physical integrity or health of the other shall constitute an offence, on complaint, punishable with imprisonment or fines (paragraph 1). Where the act is repeatedly carried out against a person who is in

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38   For more see SPRUMONT, D., La répartition des compétences entre la Confédération et les cantons dans le domaine des recherches sur l`homme, AJP/PJA 1994, p. 1007 ff.
39   Specified in chapter 13.
40   RTD Info 22/99 (Magazine for European research), Medical Imaging. When the brain reveals its secrets.
41   SCHEICH, GEHIRN&GEIST 3/2005, p. 62.
42   The criminal offences of duress and false imprisonment should be excluded in the following.

the custody of the offender, it shall be prosecuted even in the absence of a complaint (paragraph 2).

20.2   Extent of protection by constituent elements of offence in order to protect physical integrity

Not only healthy persons, but also those who are ill are protected by the provisions described above.[43] Physical and mental integrity must be understood in a relative sense, especially as a person can have a physical or mental handicap from birth on or he or she can acquire such during the course of his or her life. In contrast to that which constitutes an offence of bodily harm in Germany, the protection provided for by the Swiss definition also explicitly includes mental health.[44] In this, it is immaterial whether the psychological impairment has a physical cause or whether it results in health impairments. This can be gleaned from the wording of Article 122(3) of the StGB, where grievous bodily harm is committed by "anyone who wilfully causes serious damage to the body or the physical or mental health of another".[45]

Case law decides on medical diagnostic investigation and medical treatment, and therefore also the neuroimaging methods used in this context, using the benchmarks which apply with respect to every other form of bodily harm or violence.[46] Under the premise that the examination is to be judged based on the one act compromising the physical integrity, and not in relation to an improvement or maintenance of the overall physical condition thus brought about, diagnostic investigations, insofar as they have an impact on the physical integrity, can in isolated cases constitute acts of bodily harm or violence. As such, it is essentially irrelevant if the intervention was performed out of medical necessity, lege artis and successfully. The patient

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[43]   BGE (Federal Court Decision) 83 IV 140; 103 IV 70; RS (Case) 1946 N0. 230 (on mental health).

[44]   BGE 103 IV 65, 70; TRECHSEL, STEFAN, Schweizerisches Strafgesetzbuch, Kurzkommentar, Zurich 1997, vor Art. 122 N. 5; CORBOZ, BERNARD, Les infractions en droit suisse, volume I, 2002, Art. 122 N. 10; Art. 123 N. 14.

[45]   ROTH, ANREAS, in: NIGGLI, MARCEL ALEXANDER/WIPRÄCHTIGER, HANS (Publisher), StGB, Volume II, Basel 2002, vor Art. 122 N. 13; STRATENWERTH, GÜNTER/JENNY, GUIDO, Schweizerisches Strafrecht, Besonderer Teil I: Straftaten gegen Individualinteressen, 6th edition, Berne 2003, § 3 N. 6.

[46]   BGE 99 IV 209 et seq.; 117 Ib 197; 124 IV 258 et seqq.

nevertheless has the right by reason of his autonomy in decision-making to release by way of consent[47] the doctor's leeway from the narrow confines placed on it by criminal law.

This doctrine is rooted in the fundamental right to protection of physical integrity, Article 10(2) of the Swiss Federal Constitution, and the right to self-determination. For to detach the physical-biological organism from the self-determined person replete with human dignity would lead to an un-acceptable objectification of man.

Alternatively, where the actual consent of the patient cannot be secured in individual cases, for example, as a result of the physical or mental disposi-tion of the patient or if, where any delay is dangerous, it cannot be obtained in time or at all, hypothetical or supposed consent, or in exceptional cases the existence of a conflict of duties or necessity, Article 34 of the StGB, can be invoked as justification.

If the doctor erroneously presumes that effective consent has been given or acts under the false belief that the patient has given his effective consent to an indicated examination of the brain using neuroimaging a distinction must be made. Where he erroneously assumes the existence of the conditions for consent or supposed consent, this does not constitute an act of wilful bodily harm. This is provided for by Article 19 of the StGB, which states: "Whoever acts under the influence of an erroneous impression of the facts shall be judged according to this impression of the facts where this is in his favour. Where the defendant could have avoided the error by taking the

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47   The classification of consent as a defence or as a reason to exclude an offence is controversial. Case law and some literature, e. g. TRECHSEL, StGB, vor Art. 122 N. 6; BUSSMANN, DANIEL, Die strafrechtliche Beurteilung von ärztlichen Heileingriffen, Diss. Zurich, 1984, p. 28, assume a justifying effect. The literature also makes a case for the so-called corpus delicti solution, where consent to remedial treatment in itself excludes the presence of the elements of an offence of bodily harm, see for example B. GERMANN, OSKAR ADOLF, Das Verbrechen im neuen Strafrecht, Zurich 1942, p. 239; in detail HURTADO POZO, JOSÉ, Droit pénal, Partie spéciale I, 3rd edition, Zu-rich 1997, N 394 et seqq.; LEHMANN, SUZANNE, Zur Frage der rechtlichen Beurteilung von Doppel-blindversuchen an Patienten, ZStrR 99 (1982), p. 175; PFENNINGER, HANS FELIX, Ist freiwillige Ste-rilisation strafbar? ZStrR 82 (1966), pp 136, 152; SCHUBARTH, MARTIN, Kommentar zum schwei-zerischen Strafrecht, Besonderer Teil, volume I: Delikte gegen Leib und Leben, Art. 111-136 StGB, 1982, Art. 123 N 49; SCHULTZ, HANS, Die eigenmächtige Heilbehandlung eine kantonal-rechtliche Lösung? ZStrR 107 (1990), pp 281, 287 et seqq.; STRATENWERTH/ JENNY, Strafrecht BT I, § 3 N 16 et seqq.; TAG, BRIGITTE, Der Körperverletzungstatbestand im Spannungsfeld zwischen Patientenautonomie und Lex artis, Heidelberg, 2000, p. 18 et seqq., with further references.

necessary precautions, he shall be liable to prosecution for negligence where the negligent execution of the act is punishable by law."

In contrast, where the examining doctor has sufficient grounds to overstep the limits of a defence, a further differentiation must be made: Those of the opinion that actual consent is to be qualified as a justification in addition to supposed consent, the existence of a justifying conflict of duties and necessity, must examine the legal error diminishing or eliminating guilt. To this extent, Article 20 of the StGB applies: "Where the defendant had sufficient reason to assume that he was entitled to carry out the act, the judge may at his own discretion decide to reduce the punishment (Article 66) or refrain from imposing a punishment". This is not the view of those who are of the opinion that the consent of the patient excludes criminal offence. They say that an error with regard to actual consent, qualified as excluding the constitution of a crime, is also to be qualified in relation to an erroneous overstepping of the boundaries under Article 19 of the StGB.

Where these legal principles are applied to neuroimaging, the related procedures – even in the absence of symptoms – can assume relevance in several aspects as bodily harm.

20.3   Detailed issues

20.3.1   Detrimental changes
Currently, neuroimaging can have criminal relevance as an act of bodily harm where it causes damage to the mental or psychic health of the patient. Concerned here are those cases in which the performance or results of the examination have long-term negative effects on memory, consciousness or other psychic or mental capacities.

Further, it cannot be ruled out to the best knowledge available at present that the radiation accompanying the various methods of examination leads to somatically-subsumable detrimental changes to the physical condition or substance of the brain, even if clinically recognisable damage cannot or cannot immediately be determined. Whether inducing this condition affects the health in a manner that is more than just negligible is subject to normative evaluation. The case law of the Federal Court relating to infection with

a not wholly trivial disease or virus (e. g. HIV) can provide guidance in how this matter should be interpreted. Very often here, the question of whether damage was caused to the health is answered in the affirmative, without it being necessary for the disease to have appeared.[48] For the infection entails serious and irreversible consequences for the physical and mental state of health of the person concerned. The direct effects of ionising rays on the human body are to be judged in a similar fashion.[49] Although the one-off, limited or only occasionally repeated correct use of neuroimaging generally cannot yet be deemed bodily harm, a distinction should be made from the case where the destruction of cell structures by radiation – in particular with regard to persons who have already at an earlier stage been exposed regularly to ionising rays – more than insignificantly increases the risk of long-term damage. The legislature has long recognised the potential risk of damage from radiation and has already passed provisions for the protection of both those who must deal with radiation as a result of their profession and those who as patients are consciously exposed to these rays.[50] These norms are based on the awareness that unnecessary exposure to radiation should be avoided. Expert help is called upon to decide exactly when in individual cases the permissible boundary has been overstepped and damage to health has been caused.

20.3.2   Medical indication and medical or technical standard

The medical indication and the medical and technical standard of neuroimaging are important in this context. Medical indication conveys the circumstances which, in addition to patient autonomy, form the basis for medical, psychiatric or psychotherapeutic action. It regularly influences the decision for or against using certain diagnostic or therapeutic procedures. For a procedure to be indicated, it is not sufficient to determine a possible condition. Rather, the patient's personal data such as age, seriousness and duration of condition, mental and psychic state, personal resilience, acceptance of condition and personal circumstances must also be taken into account.

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48   BGE 125 IV 242.
49   BGH NJW (Neue Juristische Woche) 1998, 833.
50   See, for example, Radiation protection law (*Strahlenschutzgesetz-StSG*) of 22 March 1991; Radiation protection regulation (*Strahlenschutzverordnung-StSV*) of 22 June 1994; Regulation on the sources of medical radiation (*Medizinische Strahlenquellen-Verordnung-MeSV*) of 15 November 2001.

Linking medical diagnosis and therapy to an indication is part of the ethical-legal norms of the medical profession. In general, neuroimaging indication can be justified in medical terms as a method of diagnosis if the diagnosis is followed by a specific preventative or therapeutic treatment. Whether neuroimaging is an appropriate means of recognising sicknesses or pathological deviations from the normal functions of the brain, and can thus provide the basis to redress the situation, must be essentially assessed according to the experience and findings of the researchers and doctors working in this special field.[51] To the extent that there exists core knowledge which is considered firm and which provides reliable information on the necessity of performing neuroimaging for diagnostic and therapeutic purposes, this knowledge acts concurrently as a guideline for the legal evaluation of diagnosis and treatment.

The inter-disciplinary standard thus outlined, which legitimises and restricts neuroimaging to an equal degree, is not set in stone. For that which according to the principles of conscientious neurologists, psychologists and specialist medical companies is deemed lex artis is subject to constant change. Moreover, a wide corridor exists between examinations with a view to providing maximum medical care and those providing so-called basic care. Although the general tying of neuroimaging to an indication is part of the ethical-legal norms of the medical profession, its scope of effect is ambivalent from a legal point of view. In order to differentiate between neuroimaging, both in its practice and its intention, as a diagnostic method as part of medical treatment and the traditional, stigmatised view of bodily harm or violence, it is important but not imperative to place it within a context of healing. Besides, not everything which in medical terms or in keeping with the practice of a conscientious doctor is appropriate, expedient, measured or necessary, reflects to the wishes of the patient. The professional benchmark of neuroimaging indication and the values of the patient do not necessarily lead to congruent decisions, but can instead conflict.[52] Thus it can arrive that a patient refuses an examination although it is medically indicated. It is also conceivable that the person concerned or a

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[51]   For more on so-called neurofeedback in treating conditions, e. g. epilepsy, see Birbaumer, Niels, Neurofeedback: Gezielte Kontrolle des Gehirns, in: Das Magazin 2/2003, Bildgebende Verfahren in der Hirnforschung.

[52]   For more in general on medical treatment Bucher, Eugen, Die Ausübung der Persönlichkeitsrechte, insbesondere die Persönlichkeitsrechte des Patienten als Schranken der ärztlichen Tätigkeit, Zürcher Dissertation 1956, p. 25 et seq.

third party on their own responsibility calls for neuroimaging which is not medically indicated, for example, where further exploration of the brain, human behaviour and consciousness, and behavioural predictions are concerned.

Within this context, it must be pointed out that in neuroimaging used purely for research activities, those to be examined are seen above all as human research subjects and not as patients. In addition, there are ever more examples to be found of offers to perform neuroimaging which are more appropriately regarded as part of the "services" sector and in which the person to be examined often assumes the role of "customer". Included here, for example, is the field of education if neuroimaging is to be used to try to optimise mental performance.[53] But the advertising sector, too, is beginning to use neuroimaging in its quest to determine the stimuli and messages to which potential customers are particularly sensitive. Medical ethics, in which the coupling of medical treatment to an indication is accorded a not unimportant role, cannot be applied fully to these areas. This excuses these forms of research or service, however, neither from observing the principle of "primum non nocere" nor from performing the examination in the correct manner.

Irrespective of this, "state of the art" in a medical context is important in terms of criminal law. The doctor, psychologist and even the researcher have an obligation to the person to be examined to use those methods which satisfy the current state of the art[54]. No more can subsequently be asked of him than was available at the time of the examination. In determining the diagnostic measures based on an objective state of knowledge, there is very often a certain decision-making leeway which permits selection from several possible measures.[55] The examiner breaches his duty only where he makes a diagnosis or selects a therapy or other course of action which no longer appears justifiable under the current general level of expert knowledge and which therefore does not satisfy the objective requirements of lex artis.[56] The requirements relating to the due diligence to

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53 SPITZER, MARTIN, Die funktionelle Bildgebung des Gehirns, Magazin 2/2003, Bildgebende Verfahren in der Hirnforschung; specified in chapter 17.
54 The safety of brain imaging methods is specified in chapter 6.
55 LARGIER, ANDRÉ, Schädigende medizinische Behandlung als Unfall, Zurich 2002, p. 127.
56 BGE 120 Ib 411 E. 4a with further references; 130 IV p. 12; HAUSHEER, HEINZ, Unsorgfältige ärztliche Behandlung, in: MÜNCH, PETER/GEISER, THOMAS (publisher), Schaden-Haftung-Versiche-

be applied and the duty to explain the risks involved, however, are especially high if neuroimaging is performed in the absence of a healing context and of medical indication.[57] Where neuroimaging is the subject of criminal proceedings, the court must adopt an ex-ante view based on the time of performance of the diagnostic procedure.[58] Later findings are not admitted in principle.

A method is deemed outmoded and no longer capable of satisfying the standard to be maintained where updated methods recognised by experts exist which entail less risk and/or place less of a burden on the person being examined. In this case, the method hitherto used no longer meets the requirements of appropriate treatment, so that yesterday's standard constitutes today's error. If neuroimaging performed using an outmoded method leads to somatic changes of the sort already described, the objective elements of a crime of simple bodily harm or also those of an offence of violence may be fulfilled, depending on how serious the effects thus caused. Bodily harm through negligence, Article 125 of the StGB, may be decided where the examiner as a result of insufficient diligence assumed that the specific methods were not harmful.[59]

20.4   Self-determination

20.4.1   Significance

Where neuroimaging is performed in breach of the self-determination[60] of the person to be examined, an act of bodily harm or violence must be considered, depending on the degree of damage caused. Moreover, the re-

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rung, Handbücher für die Anwaltspraxis, volume V, N. 15.14; KUHN MORITZ, Die rechtliche Beziehung zwischen Arzt und Patient, in: HONSELL, HEINRICH (Publisher), Handbuch des Arztrechts, Zurich 1994, p. 27.

[57] Fore more on the parallel problem of cosmetic operations, see Bezirksgericht Zurich SGW 1987 N. 51; BGE 108 II 59; for the practice in Germany, see BGH NJW 1994, 801; 1998, 1784.

[58] BVR 2004 p. 296; BGE 120 Ib 411 E. 4c/aa; 115 Ib 175 E. 3b at the end.

[59] Punishability for a negligent act cannot be considered as no punishability is ordered by statute, Art. 18 und 19 StGB in conjunction with Art. 126 StGB.

[60] HONSELL, HEINRICH, Schweizerisches Haftpflichtrecht, 3rd edition, Zurich 2000, § 5 N 23; ROBERTO, VITO /HRUBESCH-MILLAUER, STEPHANIE, Offene und neue Fragestellungen im Bereich des Persönlichkeitsschutzes, in: Festschrift für JEAN NICOLAS DRUEY, Allgemeines Zivilrecht, Obligationenrecht und Internationales Privatrecht, 2002, p. 229 et seqq., 235 et seq.; case law to this end focuses on personal integrity, see BGE 117 IB 197 et seqq.; 108 II 59 et seqq.

cognition of the decision-making autonomy is an incontrovertible basis of brain diagnosis with the aid of neuroimaging. For decisions relating to diagnosis and therapy are – especially where they relate to the brain – a part of the most sensitive and important responsibilities of the neurologist or psychologist. However, they are not exclusively the preserve of medicine or psychology. Rather they are the result of consultation between the doctor or psychologist performing the examination and the patient. The patient depends on the expert counsel of specialists in order to familiarise himself with neuroimaging and its associated complexities, which, at the same time, are solely based on prognosis. This is particularly true with respect to the question of whether therapy can be applied to a hazardous disposition, quite possibly discovered as a result of neuroimaging, and what the actual and legal consequences of this are. Of importance here is whether the person affected and the public at large, being aware of the disposition in question, must be aware that the ultimate fate is thus irrevocably determined. As the person to be examined himself or herself must face the consequences of the possibly serious diagnosis and as a rule is the only one who knows his personal priorities and values, he fundamentally has the final say on whether neuroimaging should be performed.

The legal basis for this is the constitutional guarantee of the power to decide what is done with one's body, a right accorded every person by virtue of their existence and in the interests of a self-determined life. The related right of self-determination renders more specific, on the one hand, the individual set of values and, thus, precisely the interest in autonomy with regard to one's own body and health. Consent by the bearer of the legal interests (*Rechtsgutsträger*) permits on the other hand the examination to be performed and his legal rights to be encroached upon.[61] However, consent to the performance of neuroimaging is not a declaration of will in the legal sense. It represents rather whether and to what degree the person to be examined permits at the present time intervention into the functions of the body and brain. Thus, consent may be withdrawn in principle at any time without having to give particular reasons or adhere to time limits.[62]

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[61]   NEYEN, WERNER, Die Einwilligungsfähigkeit im Strafrecht, Diss. Trier 1991, p. 6 et seqq.

[62]   GÖBEL, ALFRED A., Die Einwilligung im Strafrecht als Ausprägung des Selbstbestimmungsrechts, Frankfurt among others 1992, p. 137; LAUFS, ADOLF, in: JUNG/SCHREIBER HANS LUDWIG (Publisher), Arzt und Patient zwischen Therapie und Recht, p.71, 81.

Consent must both based on the internal awareness of the authorised person and be explicitly or conclusively declared before the examination. In order for something to prove an act of true self-determination, the person to be examined must be consciously aware, capable of understanding, and prepared to bear the consequences of his decision.[63] What is of interest here is the conflict between autonomy and care.[64] Due to a lack of sufficient legal provisions, the literature and the case law surrounding the subject have developed their own basic principles.[65] Irrespective of legal capacity under civil law and criminal responsibility under criminal law[66], the capacity to consent is determined subject to the existence of the actual capacity to understand and to judge the significance and consequences of the intervention and the permission to perform it.[67] The facts of each individual case are decisive in evaluating the capacity to understand and to express a will.[68]

In principle, persons of legal age have the capacity to consent insofar as no specific reasons exist to suspect the presence of psychic defects, consciousness deficiencies, etc. The rejection of medically-indicated neuroimaging alone does not constitute sufficient reason to conclude a lack of the capacity to consent. For even decisions which contradict objectively, reasonable considerations can certainly be in the best self-determined self-interests.

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[63]   In more detail, RIPPE, KLAUS PETER/SCHWARZENEGGER, CHRISTIAN/BOSSHARD, GEORG / KIESEWETTER, MARTIN, Urteilsfähigkeit von Menschen mit psychischen Störungen und Suizidbeihilfe, Schweizerische Juristenzeitung (SJZ) 101 (2005) 81, 86; REHBERG, JÖRG/DONATSCH, ANDREAS, Strafrecht I, Verbrechenslehre, 6th edition, Zurich 2001, p. 209 with reference to Art. 18 Civil Code (ZGB), RIKLIN, FRANZ, Schweizerisches Strafrecht, Allgemeiner Teil 1. Verbrechenslehre, 2nd edition, Zurich 2002, § 14 N 59; STRATENWERTH, GÜNTER, Schweizerisches Strafrecht. Allgemeiner Teil. Bd.1: Die Straftat, Berne 2nd edition, 1996, § 10 N 19 et seqq.; WEISSENBERGER, PHILIPPE: Die Einwilligung des Verletzten bei den Delikten gegen Leib und Leben, Berne 1996, p. 73 et seqq., differentiation between agreement and consent with a lot of evidence.

[64]   TAUPITZ, JOCHEN, Empfehlen sich zivilrechtliche Regelungen zur Absicherung der Patientenautonomie am Ende des Lebens?, Report A for the 63rd Deutsche Juristentag, Leipzig 2000, A 52.

[65]   For more, see AMELUNG, KNUT, Über die Einwilligungsfähigkeit, Zeitschrift für die gesamte Strafrechtwissenschaft (ZStW) 104 (1992), 522, 541 et seqq., with more references.

[66]   A.A. WEISSENBERGER, Einwilligung, p. 75.

[67]   An insightful approach is given in AMELUNG, KNUT, Vetorechte beschränkt Einwilligungsfähiger in Grenzbereichen medizinischer Interventionen, Berlin, New York 1995; ders., Probleme der Einwilligungsfähigkeit, Recht und Psychiatrie 1995, p. 20 et seqq.

[68]   AMELUNG, KNUT, ZStW 104 (1992), 525, 557 f.; NEYEN, Die Einwilligungsfähigkeit im Strafrecht, p. 44 et seqq.

A meaningful, informative consultation and, thus, effective consent cannot occur if the patient – whether temporarily or absolutely – is unable to grasp and weigh the main elements which are important for a decision. Within this context, those who are psychologically ill and mentally disabled need special attention. They are entitled to the full protection of criminal law as persons of legal capacity and capable of acting and entering into commitments. However, another question is whether the specific person is capable of expressing his or her wishes and of understanding, and therefore has the capacity to make decisions in his or her own affairs. This question must be answered in general by the expert. Where such a deficit is present and where the patient cannot (any longer) manage his or her own affairs, the decision whether to perform neuroimaging becomes a matter for the law or the appointment of an authority.[69] Its consent cannot, however, be given freely, rather it must reflect the well being and, in principle, the wishes of the person in care.

20.4.2   Informative consultation

Consent to the performance of neuroimaging is an act of true self-determination only where it is preceded by a comprehensive informative consultation.[70] The person charged with making the decision should be informed of all known significant factors, within the confines of reason. The decision to be taken is determined by a multitude of factors with the result that the neurologist's or psychologist's sphere of responsibility – in relation to consultation – consists of correctly conveying and assessing the relevant factors, explaining appropriate opportunities offered by other diagnostic measures, and providing expert support to the person seeking counsel in his or her decision for which he or she is individually responsible. The consultation must also extend to cover the known successes and risks associated with neuroimaging. Given the different diagnostic methods often available, it is necessary to explain the specific approaches to be considered and, together with the patient, choose a specific option.

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[69] For more, see RIEMER, HANS MICHAEL, Die Vertretung bei Ausübung von Rechten, die unmündigen oder unter einer vormundschaftlichen Massnahme stehenden Personen um ihrer Persönlichkeit willen zusteht, Zeitschrift für Vormundschaftswesen (ZVW) 1998, 217.

[70] In general on the duty to explain medical remedial treatments, see OTT, WERNER E., Medizinische und rechtliche Abklärung von Ärztehaftpflichtfällen, HAVE 2003, 275, 282.

The consultation must also take place in a timely manner. The patient must be given sufficient time before the intended diagnostic examination to adequately consider the pros and cons before reaching a decision on neuroimaging.

As a general rule, the consultation should take the form of a personal discussion. The wording must be so chosen as to allow a medical layman to understand the situation. Bulletins and data sheets containing information on both how the examination is likely to proceed and the associated risks are expedient as a complement to the personal discussion.

To the extent that it is expected that the neuroimaging examination will produce information, the correct conveyance of which to the patient would require a special informative session, consultation should occur on this matter before the examination. Where the intention exists to put the information gleaned from neuroimaging to further use while retaining anonymity or using pseudonyms, the person to be examined must be informed of such during consultation, as well as of the fact that possible findings as a result of this further use cannot be made known to him or her.[71] Where the person to be examined has declared his or her approval to have the results of the neuroimaging performed on him or her put to further use for the purposes of research and where an individual agreement has been reached to make the research results known to him or her, it must be indicated in the consultation that he or she may have to declare this knowledge to third parties under certain circumstances, e. g. when entering new work or insurance contracts. In addition, a previously agreed individual act of publicising the research results to the donor must be performed by a person who is equipped with the requisite consulting skills. This is particularly the case when advising of discoveries of genetically-induced changes to the brain.

The existence and extent of a "therapeutic privilege" empowering the doctor or psychologist to restrict the conveyance of information is disputed[72]. To the extent that the interpretation of findings of neuroimaging is limited only

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[71]   For more, see the comments of the Central Ethics Commission of the German Medical Association on the (further) use of human bodily material for the purposes of medical research (2003).

[72]   See e. g. GUILLOD, O., Le consentement éclairé du patient: paternalisme ou autodétermination? Neuchâtel: Ides et Calandes, 1986

to that which may be verified by the natural sciences, it is precisely in the field of psychiatry that therapeutic misgivings against explaining everything in full to the patient could be accorded importance. In addition, the personal participation of the doctor or psychologist or a third party plays a special role here, to the effect that within this context the scope of the informative consultations are not oriented exclusively around the personal rights of the person to be examined.[73] Nevertheless, the limits of such restrictions must be drawn tightly. They come into consideration if the comprehensive informative consultation can lead to very serious adverse effects to the mental state or the health of the patient.

20.4.3   The right not to know

The right to self-determination does not automatically imply a corresponding obligation. The reverse of the right to information on the state of one's own physical, mental and general health is the right to decide whether all findings should be requested. Because publicising the brain-specific diagnosis and the associated, possibly confidential, course of therapy represents a more or less certain prognosis of the lifestyle of the person to be examined, each individual must be allowed to decide for himself or herself the extent to which he or she wishes to be burdened by knowledge.[74] Should he or she choose to refuse consultation and instead place the fate of his or her health in the hands of the expert, this decision must be generally respected. The right not to know is not unconditional, however. Rather it is subject to the same requirements as those of consent following consultation. Moreover, the abnegation of the right to consultation is at the limit of constitutional law where through this lack of information the person to be examined makes himself an object of third parties. Although the consequences and scope of the relinquishment must be judged on an individual basis, a basic informative consultation with the person capable of understanding appears, in principle, to be indispensable.[75]

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[73] In a similar vein, PETERMANN, FRANK TH., Der Psychotherapeuten-Vertrag – im Spannungsfeld von Übertragung, Gegenübertragung und Realität, Aktuelle Juristische Praxis (AJP/PJA) 2003, 1291, 1298.

[74] In general on this, JONAS, HANS, Technik, Medizin und Ethik, Frankfurt 1987, p. 194.

[75] EISNER, BEAT, Die Aufklärungspflicht des Arztes. Die Rechtslage in Deutschland, der Schweiz und den USA, Diss. Basel 1992, p. 180 et seq.; ROßNER, HANS-JÜRGEN, Verzicht des Patienten auf eine Aufklärung durch den Arzt, NJW 1990, 2291, 2294; VOLL, DORIS, Die Einwilligung im Arztrecht, Frankfurt among others, 1996, p. 129 et seq. The decision by the Federal Court 105 II

20.4.4   Deficiency of will

The autonomy of the person to be examined does not embody an absolute value, but rather moves on a scale between self-determination and freedom, on the one hand, and dependence, on the other. A self-determined decision in favour of neuroimaging can only exist if this decision was made earnestly, voluntarily and in accord with personal values.[76] Therefore, an autonomous decision does not exist, or exists to a qualified extent only, where it is influenced by incorrect assessments, false conclusions or other instances of absent intention. In contrast to civil law[77] there are no provisions in Swiss criminal law relating to the preconditions and legal consequences of an absence of intention. The overriding factor and prerequisite for valid consent in neuroimaging is that the person to be examined is aware of the associated consequences and that existing taboo limits are observed.

Such a taboo limit is the guarantee of human dignity provided for in Article 7 of the Swiss Federal Constitution. It accentuates the force of effect of other rights while simultaneously specifying them. The result of this interdependency is that the substance and scope of human dignity is influenced by the situation to be judged specifically and that a breach of human dignity can only be determined upon consideration of the specific case. An examination method can be inhumane if ordered by the state and at the same time humane if it occurs voluntarily. Within a certain context, dignity also includes not having dignity enforced. Deliberations on whether neuroimaging and human dignity are reconcilable must address the question of whether the person to be examined is treated "merely" as an object.

The decision on the "ifs" and "hows" of such neuroimaging lies squarely in the sphere of responsibility of the individual person. On the other hand, it would represent an encroachment on human dignity and constitute disregard for the value which as a person he or she is accorded if, in the course of enforced examinations, the rights of the person concerned were to be

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289 = Pra 69 Nr. 135 E. 6c assumes that such a relinquishment (also silent) must be possible, for a patient can conduct himself in a very passive manner during treatment and expressly desire the doctor to make decisions regarding treatment. See also PAYLLIER, PASCAL, Rechtsprobleme der ärztlichen Aufklärung, unter besonderer Berücksichtigung der spitalärztlichen Aufklärung, Diss. Zurich 1999, p. 77 et seqq.

76   AMELUNG, KNUT, Irrtum und Täuschung als Grundlage von Willensmängeln, Berlin 1997, p. 41.
77   See Articles 23 – 30 law of obligations in Civil Code (OR).

disregarded. This would even apply if, for example, the detainee were to declare his or her agreement to the performance of neuroimaging in return for the promise of freedom. To this end, the examination must be reviewed more closely on a regular basis to determine whether it is *contra bonos mores*.

The term "*contra bonos mores*" is taken from civil law.[78] An act which runs contrary to the mores of all fair and just thinking people, is deemed to be against good morals. Thus the assessment of whether something contradicts good morals is derived from average sensibilities, not from the subjective perception of one individual. For want of legal specification of the recognised moral and ethical concepts of society, that which constitutes the ethical minimum protected by good morals must be derived from the fundamental principles of the legal system in place, based on the material principle of the rule of law. Here, that fact that a dominant set of social mores can only be determined within a narrow framework, and that punishment as a subsidiary state reaction to an act must not be allowed to be made dependent on contingencies, must be taken into account from the point of view of criminal law. As far as neuroimaging is concerned, the limits of good morals are reached only where the legal censure as an ethical minimum is derived clearly from the legal system. As is the case, for example, if lack of will with regard to performing neuroimaging arises as a result of threats or force and the degree of influence exerted on will constitutes coercion as set out in Article 181 of the Criminal Code.[79]

20.4.5   Summary

The practice of performing neuroimaging on living persons is guided in the first instance by general fundamental principles of law. To be cited in particular is the protection of the living human body and the mind, as they are specified in the elements of an offence constituting an act of bodily harm. For neuroimaging to be performed legally, informed consent must be given. Because the brain as we understand it today represents man's social organ, programmed for connection, relations and dialogue, and is at the

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[78]   See Art. 41(2) OR: "Anyone who causes intentional damage to another in a manner which contravenes good morals shall be equally liable for compensation". Also: Art. 27 al. 2 ZGB

[79]   More detailed, TAG, Der Körperverletzungstatbestand im Spannungsfeld zwischen Patienten-autonomie und Lex artis, p. 366 et seqq.

same time his centre of consciousness, the content, scope and consequences of the examination must be explained to the person to be examined in comprehensible terms. False representations in this regard can lead to the consent being deemed invalid. In performing neuroimaging and evaluating the results so gleaned, the person concerned must as a matter of principle be offered the opportunity to decide on his or her own whether and to what extent he or she wishes to be informed of the examination results relating to himself or herself personally. In terms of both legal and ethical considerations, the person concerned should or must be asked whether, and, if so, to what degree, he or she wishes to be informed of treatable and non-treatable conditions.

20.5   Neuroimaging on recently deceased

20.5.1   Introduction

The question of the permissibility of performing research on dead but artificially respired bodies or on recently dead is becoming ever more relevant and is seen as an urgent problem.[80] "Although research on brain-dead individuals has occurred in the last 25 years, new technologies promise to increase its scope and relevance"[81] , and this could also hold true for neuroimaging. Although it might be assumed that bodies are not of interest of neuroimaging because of the lack of electrical activity of the brain and the irreversibility of the cessation of the functions of the brain, it should be considered that neuroimaging of the brain could generate new findings especially with respect to brain death diagnostics.

Neuroimaging is particularly important when it is used to tie life and the right to life to the characteristics of this psyche-endowed organism. Although it has hitherto been seen mostly as unacceptable to link life (and the right thereto) with characteristics almost impossible to objectify and in need of more research such as consciousness, interests and thus the capacity to

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80   For more see PENTZ, REBECCA ET AL. Ethics guidelines for research with the recently dead, NATURE MEDICINE 11, 2005 p. 1145 ff.; WADIH ARAP ET AL., Steps towards mapping the human vasculature by phage display, NATURE MEDICINE 8, 2002, p. 121, 124 ff.

81   See Pentz (aaO), Page 1145 mwN.

be a person,[82] should the expectations surrounding brain research be ful-filled, namely that neuroimaging can help provide substantiated information, this could have an effect on determining time of death in relation to the cri-teria of brain death.

Today's medical and research standard will be improved tomorrow. Neuroimaging on recently deceased will make a contribution to a better understanding of the interaction between the defunct brain and the corpse. And neuroimaging on deceased persons can help to improve the identifica-tion of the relevant criteria for the diagnosis of brain death. In addition to this, untested hardware and targeted agents can be evaluated in recently dead, for instance if dead bodies being mechanically perfused or ventilated.

Given the uncertain ethical and legal evaluation of the treatment of dead bodies, the following seeks to provide arguments in the interest of clarifica-tion. The intention is to try to find an appropriate balance between the le-gitimate concerns of the research community and (the continuing effects of) the personal rights of those whose "dead" brains are to be better re-searched and those rights of their family members.

20.5.2   Diagnosis of death

Whereas dying – as we understand it from a medical and technical point of view – describes an irreversible biological process from a certain point on, the speed of whose progression varies depending on the individual tissue type,[83] death represents a more or less swiftly occurring event, depending on the circumstances of the specific case, within this entire process.[84]

However, the point at which a person can be deemed to be (still) alive is an issue which jurisprudence and philosophy[85] have yet to clarify conclu-

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82   For a critical view, HÖFLING, Juristen Zeitung 1995, 26, 32.
83   Fuchs, Thomas, Außerkörperliche Erfahrungen und Nahtodeserlebnisse bei Wiederbelebten, Berliner Medizinethische Schriften, 19.
84   Communication of 12 September 2001 on Federal law on the transplantation of organs, tissue and cells (Bundesgesetz über die Transplantation von Organen, Geweben und Zellen (Transplan-tationsgesetz)) (Federal Gazette (Bundesblatt – BBl) 2002 29) point 1.3.3.3 p. 88.
85   In place of many HANS JONAS, Technik, Medizin und Ethik, Frankfurt 1987.

sively[86] although the criterion for death has been defined by Article 9(1) of the Federal law on the transplantation of organs, tissue and cells (*Bundesgesetz über die Transplantation von Organen, Geweben und Zellen – TPG*) of 8 October 2004.[87] Paragraph 1 states: "A person shall be deemed dead if the functions of his brain including the brain stem have ceased irreversibly". Paragraph 2 obliges the Swiss Federal Council to enact provisions on the determination of death. The particular concern is to determine the clinical indications which must be present to allow an irreversible failure of the functions of the brain, including the brain stem, to be concluded.

Although the Federal Court has in several judgments confirmed the constitutionality of the concept of death based on the cessation of the brain function,[88] the discussion on the decisive criterion of death has not really been ended.[89] For the various positions continue to be pitted against each other. They are concerned with the questions of whether the normative assessment of brain death is concordant with the actual death, which criteria and indications of death should be used to determine brain death, and whether the provision of the TPG can be transposed to other areas of the law.

It became patently clear during the discussions on the TPG in the course of the legislative process that the normative assessment is needed in determining complete brain death as the time of death.[90] To conclude deductively and with certainty that the fact that functions of his brain including the brain stem have ceased irreversibly means the occurrence of the person's biological death is normative.[91] This means that the determination of the

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[86]   For the development of the definition of death, see LÜTTGER, HANS, Der Tod und das Strafrecht, JR 1971, 309.

[87]   The law is based on the report commissioned by the Swiss Federal Office of Public Health (Bundesamt für Gesundheit) from GUILLOD, OLIVIER/DUMOULIN, JEAN-FRANÇOIS, Définition de la mort et prétèvement d`organes. For more on the criterion of brain death, see p. 14 et seqq.

[88]   BGE 98 Ia 507; 123 I 112.

[89]   A view still maintained is that the brain dead are to be understood as dying, therefore as living people, see HÖFLING, WOLFRAM, Verfassungsrechtliche Grundfragen des Transplantationswesens, in: HÖGLINGER/KLEINERT (Publisher), Hirntod und Organtransplantation, 1998, p. 87; WAGNER, EDGAR/BROCKER, LARS, Hirntodkriterium und Lebensgrundrecht, Zeitschrift für Rechtspolitik (ZRP) 1996, 226; SPITTLER, JOHANN FRIEDRICH, Der menschliche Körper im Hirntod, ein dritter Zustand zwischen lebendem Menschen und Leichnam?, JZ 1997, 747.

[90]   Nationalrat – winter session 2003 – 11th meeting - 17.12.03 *AB 2003 N 2064 / BO 2003 N 2064.*

[91]   LITZ, RAIMUND, Der Hirntod in der pluralistischen Gesellschaft, in: BONDOLFI ALBERTO et al. (Publisher), Hirntod und Organspende, NFPNR 46, Basel 2003, p. 71, 78; STOECKER, RALF, Die Hirntod-Debatte aus philosophischer Sicht, in: BONDOLFI et al. (ibid), p. 49 et seqq.; SCHMIDT-RECLA, ADRAIN, Tote leben länger, MedR 2004, 672, 674 et seqq.; for comments on "naturalistic

time of death is a judgement with whose help the irreversible cessation of the activities of the entire brain is interpreted as the time of death. These deliberations are just as pertinent in resolving the issue surrounding the use of neuroimaging on those who are already or not yet brain dead.

In connection with this, the signs of death play a central role. The official communication on the TPG states that the detailed description of the methods of determining death, e. g. the tests to be applied, are delegated to the Federal Council. For what are concerned here are technical, detailed norms which often require revision and which have no place in the law.[92] These clinical signs of death ultimately decide under the transplantation legislation whether the removal of vital organs is permissible and causes the donor's cardio-vascular system to shut down. Were this situation transferred to neuroimaging, once brain death has occurred, examinations which would lead to serious, fatal injuries in the living person could be performed. The greater the time span between irreversible cardiac arrest and irreversible failure of the functions of the brain, the greater the window of opportunity for further brain research. This shows just how important the signs of death are, also for neuroimaging.

While the diagnosis of death based on the complete cessation of the functions of the brain including the brain stem has been long recognised as the scientific standard, it must be noted that there is no international consensus on the detailed criteria for determining (brain) death.[93] The Swiss Academy of Medical Sciences (SAMS) prescribes various observation periods in its guidelines on determining brain death, which are currently being revised. The minimum time is six hours with regard to adults and children over five.[94] In order to clinically determine the cessation of functions (including both pupils dilated and not responding to light, no gag or cough reflexes, no spontaneous respiration), and because they are subject to particular un-

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fallacy or even Humsches Principle", see HÖFFE, OTFRIED, Lexikon der Ethik (Publisher), 6th edition 2002; CRONIN, HELENA, Die Natur des Menschen – richtig verstanden, in: BROCKMAN, JOHN (Publisher), Die neuen Humanisten. Wissenschaft an der Grenze, 2004, p. 61.

92   Communication of 12 September 2001 on TPG, p. 96.

93   For more, see SCHMIEDEK, PETER/POHLMANN-EDEN, BERND, Zur Problematik des Hirntodes, in: BAUER, AXEL W. (Publisher), Medizinische Ethik am Beginn des 21. Jahrhunderts, Theoretische Konzepte, Klinische Probleme, Ärztliches Handeln, Heidelberg 1998, p. 148, 151.

94   Medizinisch-ethische Richtlinien zur Definition und Feststellung des Todes im Hinblick auf Organtransplantationen, 1996, point 3.2 Beobachtungszeit bis zur Diagnosestellung, with further details.

certainties by nature, it is deemed necessary today to repeat the clinical examinations after six hours (in some countries, after 12 hours). The SAMS (revised) guidelines on the "Determination of death with regard to organ transplantation" (*Feststellung des Todes mit Bezug auf Organtransplantationen*), however, already state: "Besides clinical indications, the irreversibility of the cessation of the functions of the brain may also be concluded by way of technical additional examinations". The latter permit the cessation of brain activity to be determined and thus confirm the irreversibility of the cessation of the functions of the brain, thereby also confirming death. Transcranial Doppler or colour-coded duplex sonography, spiral computer tomography, 99 mTc-HMPAO scintigraphy and intra-arterial digital subtraction (IA-DAS) are all appropriate methods used to provide this confirmation. This means that uncertainty in large clinics (where such equipment is available) regarding the determination of brain death is very low. There may be short-term delays in determining brain death in smaller clinics which still rely on clinical examinations.[95]

The German Medical Association (*Deutsche Bundesärztekammer*) assumes in its guidelines a period of observation of 12 hours for adults and children aged three or more with primary brain damage; for those with secondary brain damage, a period of observation of at least three days is recommended.[96] In addition, there are supplementary examinations which differ greatly within the international context. The criteria being discussed to determine death include proof of electrical inactivity of the brain (electroencephalography, or EEG); evoked potentials, i. e. stimulating the senses to evoke changes in the brain's potential which can be read from the surface of the brain, proof of cessation of intra-cerebral circulation using Doppler or ultrasonic assessment, cerebral perfusion scintigraphy or the depiction of vessels (angiography). Because of these varying criteria, it is certainly possible that in other countries time of death can be determined to have occurred at a point at which the person would have been regarded in Switzerland as still alive[97].

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95   Thanks to Dr. AMSTAD for these clarifying pointers from a medical point of view.
96   Richtlinien zur Feststellung des Hirntodes, 3. Fortschreibung 1997 mit Ergänzungen gemäß Transplantationsgesetz (TPG) [24.07.1998] (Deutsches Ärzteblatt (DÄBI) 95, volume 30 (24.07.1998), page A-1861-1868); for more on determining brain death, see BEIN, THOMAS ET AL., Hirntodbestimmung und Betreuung des Organspenders, DÄBI 102 (2005), A 278 et seqq.
97   Thanks to Prof. Dr. Kretzschmer for proof-reading this submission from a medical view.

Moreover, a further aspect in the field of neuroimaging must be considered, namely that of so-called partial brain death or cortical death. The associated statements being discussed in this regard such as "there are obviously parts of the brain which have no substantial association with the functions that we regard as essential for personality"[98] and consequently "it is not necessary for these parts of the brain to be dead if the patient is dead as a person"[99], are rendered especially relevant by the possibilities of neuroimaging. Whereas cortical death[100] met with vehement rejection during the Swiss legislative procedure with regard to the TPG, there remain those for whom the definition of the criteria of entire brain death does not go far enough, as this declares deceased persons for living.

Neuroimaging can be expected to produce new findings in this area. The well-founded and most widely held position up to now that the right to life cannot be tied to the attributes of the psyche-endowed organism[101] was adopted on the basis of information to date. Given the current body of knowledge in neurology and other sciences, the danger of linking the right to life with characteristics such as consciousness, interests and thus the capacity to be a person,[102] does not speak in favour of the cortical death aspect. Those in apallic state, i. e. patients who retain quantitative consciousness (alertness) but whose qualitative consciousness, in contrast, cannot generally be recovered using current knowledge,[103] or those who are anencephalous,[104] i. e. newborn whose head is marked by characteristic defects (no cranium, cerebrum and meninges, possibly even cerebel-

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[98]   For more, see ANGSTWURM, HEINZ, in: HOFF, JOHANNES / IN DER SCHMITTEN, JÜRGEN (Publisher), Wann ist der Mensch tot? Organverpflanzung und Hirntodkriterium, 2nd edition 1995, p. 41, 44 et seq.; BIRNBACHER, DIETER, in: HOFF/ IN DER SCHMITTEN (Publisher), ibid, p. 25 et seq.; DENCKER, FRIEDRICH, Zum Erfolg der Tötungsdelikte, Neue Zeitschrift für Strafrecht (NStZ) 1992, 311; FUNCK, JAN-ROBERT, Der Todeszeitpunkt als Rechtsbegriff, Medizinrecht (MedR) 1992, 182.

[99]   For more, see KURTHEN, MARTIN/LINKE, DETLEF B., in: HOFF/IN DER SCHMITTEN (Publisher), ibid; p. 82 et seqq.; instructive comments on partial brain death in GEILEN, GERD, Medizinischer Fortschritt und juristischer Todesbegriff, in: Festschrift für Ernst Heinitz, Berlin 1972, 373 et seqq .

[100] Or also neocortical death, see MERKEL, REINHARD, Hirntod und kein Ende, Jura 1999, 113, 116.

[101] ANGSTWURM, in: HOFF/IN DER SCHMITTEN (Publisher), p. 41, 44 f.; BIRNBACHER, in: HOFF/ IN DER SCHMITTEN (Publisher), p. 25.

[102] For a critical view, see HÖFLING, WOLFRAM, Um Leben und Tod: Transplantationsgesetzgebung und Grundrecht auf Leben, JZ 1995, 26, 32.

[103] For information on the recent case of Terri Schiavo, see www.FAZ.net/Sterbehilfe; for more information about "coma vigil" see HÖFLING, WOLFGANG [Hrsg.], Das sog. Wachkoma, Münster 2005.

[104] In detail, ZIEGER, ANDRE AS, Wieviel Gehirn braucht ein Mensch? Interdisziplinäres Fachgespräch "Kinder mit Anencephalie und ihre Angehörigen", Erfurt 2004.

lum, midbrain and diencephalons), are, as living persons, fully protected by the legal system. Despite the tremendous demand to use neuroimaging to examine these persons and thus to generate new findings for brain re-search, it must be taken into account at all times that they enjoy the same fundamental legal and ethical principles to be applied to living persons.

20.5.3   Neuroimaging on deceased in detail

Current legal provisions

Where death has occurred, the rules on the treatment of the corpse also apply with respect to the question of the extent to which neuroimaging may be performed on a deceased artificially respiring and lying in bed, warm and sweating.

A search of the law currently in force for reference to the conditions or limits for of performing neuroimaging, and so implicitly the legal status of the hu-man corpse, would yield scant results. Not only have the Swiss Civil Code and the cantonal burial and cemetery laws nothing to say on the legal status of the corpse, the TPG is equally silent.

A browse through the European laws produces similarly sparse returns. The conventions, additional protocols, regulations and recommendations address the topic of the corpse in fragments only. The proposal for a Direc-tive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells[105] is currently being discussed on a national level.[106] Yet, even the related preparation of future human research legislation and biobanks has so far exhibited no more than tendencies on how the law should treat corpses.

The level of legal uncertainty produced by such heterogeneous legislation is large. For, on the one hand, neuroimaging can help to review and im-prove the limits of hitherto normatively defined total brain death, of the dia-

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105   OJ C 227 E / 505 et seqq. (2002/C 227 E/28) COM(2002) 319 Final — 2002/0128(COD).
106   Expert comment of 3.11.2003 by the ENQUETE-KOMMISSION ETHIK UND RECHT DER MODERNEN MEDIZIN of the German Bundestag (8th session).

gnoses and the therapies applied, to promote the further development of medical knowledge, and thus to aid other patients. On the other hand, performing neuroimaging on the brain dead is not only done in the interests of science.

It also often reflects the individual wishes of the brain dead person who, for reasons of solidarity, offers his or her body post-mortal for research purposes. Nevertheless, it must also be expected that neuroimaging will be met by mistrust and reservations on the part of many people. The fear is that the brain of the deceased and the personal information stored therein could be used in an uncontrolled manner, that principles of data protection could not be adhered to and that the family members are not protected from discrimination and stigmatisation.

Status of the corpse

Considerations on the permissibility of neuroimaging on the dead are materially rooted in the legal status of the corpses. The duties of society and individuals in this respect and the question of the level of protection to be adhered to must be clarified.

Neither legislation nor literature to date can point to a unanimous opinion on whether the corpse is covered by the terms of the Swiss Civil Code, whether it is marketable and, thus, whether it may be owned. It would, therefore, appear prudent to place the starting point of normative judgement within the setting of real circumstances. Death entails the end of the status as legal person; the corpse is no longer the bearer but rather the reference object of rights and obligations. The matter-of-fact treatment of corpses, seen over and over again, speaks for their qualification under property law. However, the associated legal consequences of this, in particular the fact that there are no restrictions on its marketability and ownership, are not appropriate for the "remains" of a former person. With good reason, scores of provisions derived from human dignity maintaining its validity beyond death and thus to be understood analogously speak against applying the full scope of property law. Thus, the TPG, in recognition of the continued validity beyond death of the human dignity guaranteed by the constitution, decided against the objection solution (*Widerspruchslösung*), i. e. removal of organs if the deceased has not stated his objection while

still alive, and for the extended consent solution (*erweiterte Zustimmungs-lösung*), Article 8 of the TPG. Given the special legal position of the corpse, although once the functions of brain and brain stem have ceased irreversibly it becomes an object,[107] the usual legal consequences of this are modified by personal rights provisions. This position is in line with the consensus being sought on both a European and international stage of the Convention on Human Rights and Biomedicine[108] and the corresponding Additional Protocol on transplantation[109].

Protection of the corpse under criminal law

Substantive criminal law provides for the protection of the body from disruption of the right to peace of the deceased, Article 262 StGB, as well as from malicious gossip and defamation, Article 176 StGB. However, the fragmentary nature of both offences does not provide any real protection from unauthorised treatment of the corpse, and consequently from impermissible neuroimaging. For they leave little room for drawing conclusions on the criteria under which neuroimaging is to be permitted in cases where it has not been legitimised through express agreement. The existing provisions do, however, mirror the increasing urgency for legislative action to provide more legal clarity and legal certainty. Nevertheless, for the time being, rules on the permissibility of performing neuroimaging on the dead must be deduced from the general fundamental principles.

Models under discussion

In keeping with the constitutional provisions, it should be generally agreed that the permissibility of performing brain diagnostics on the "fresh", intact corpse is dependent upon the will of the deceased that has been expressed during his lifetime, or, in absence of such a statement, upon the views of those authorised to care for the deceased who must decide on the basis of

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107   With regard to corpses for anatomical instruction, see FIOLKA, GERHARD, in: NIGGLI/WIPRÄCHTIGER (Publisher), StGB, Band II, Art. 262 N. 21; STRATENWERTH, GÜNTER, Strafrecht Besonderer Teil II, 5th edition, Berne 2000, § 39 N. 50.
108   Adopted by European Council on 19.11.1996, CDBI (96) 26.
109   Additional Protocol to the Convention on Human Rights and Biomedicine, on Transplantation of Organs and Tissues of Human Origin, Strasbourg, 24.1.2002.

the assumed will of the deceased.[110] In general, the models for consideration are the solutions discussed during the preparation of the Federal Law on Transplantation (TPG) of objection (*Widerspruchslösung*), declaration (*Erklärungslösung*), information (*Informationslösung*) and the models of narrow consent and extended consent (*enge und erweiterte Zustimmungsmodelle*).[111] A closer look at the various models shows that they differ above all in the significance they accord the self-determination right of the person concerned and the subsidiary right to decide of those authorised to care for the corpse.

Specifically, the following must be considered: the narrow or even modified objection solutions, often favoured in medical practice as the answer to the high demand for research on the corpse, is subject to constitutional concerns. Together with inappropriately low levels of information of the general public, it is likely that because of the lack of knowledge of the option or necessity of objecting, hardly anyone will avail themselves of this right or duty. The later deceased is thus already while still alive degraded somewhat to just an object of society or the interested branches[112], a fact which is especially important in the sensitive area of brain research. Furthermore, the objection solution encroaches upon the right not to have to deal with certain personal questions. In addition, the positive and negative freedoms of religion and philosophy are also important.[113] Not all religions and philosophical creeds are open to research on corpses and thus the possibility of neuroimaging being performed on persons who are brain dead. Moreover, conflicts with the Federal Law on Transplantation must be avoided. Organ transplantation serves to save the lives of strangers. If, however, even such an important act requires the will of the donor in order to be constitutional under the current law and the extended consent solution merely represents a compromise to counter in a manner which is still reasonable the missing organ causing death, this is not the case with respect to research on the corpse. This serves a life-saving purpose as an indirect long-term objective

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110 See PENTZ U. A., Nature Medicine 11, 2005, p. 1145-1148; WADIH ARAP ET AL., NATURE MEDICINE 8, 2002, p. 121, 124 ff.

111 For more details on the individual models, see Communication on TPG, 1.3.1, p. 76 et seqq.

112 On TPG, see KLOTH, KARSTEN, Rechtsprobleme der Todesbestimmung und der Organentnahme von Verstorbenen: eine vergleichende Untersuchung unter besonderer Berücksichtigung ausgewählter Jurisdiktionen des kontinentaleuropäischen und des angloamerikanischen Rechtskreises, Berlin 1994, p. 156 et seq.

113 Decision of the Federal Constitutional Court (BVerfGE), 46, 266, 267; 65, 1, 39.

at best. More often, however, the focus next to the progress of medical research is on other goals.

The information and declaration solutions hardly differ in terms of the breach of the post-mortal self-determination right and the right of the family members to care for the deceased from the extended objection solution and are thus subject to criticism for the same reasons.[114] There are also aspects of data protection which do not speak in favour of the declaration solution. Concerns remain that the declared objection will only be observed if the researcher is obliged to conduct further enquiry. However, it will often prove impossible, or unreasonable given the amount of research it entails, to uncover the objection. This will lead inevitably to the danger of damaging the (post-mortal) interests of the person to be examined. Assuming further that the data generated by neuroimaging were to be saved and transferred in and between databases and could thus lead to conclusions being drawn with regard to the surviving family members, there can be no reasonable doubt that this in general would have to be positively legitimised by the persons concerned.[115]

The model which takes these concerns best into account would be the first-person consent solution, as self-determination beyond death reinforces an individual's set of values and thereby his interest in disposal over his own body. The fact that the legislature nevertheless decided in favour of the extended consent solution reflects a weighing of interests. Experience to date indicates that the narrow consent solution would not produce sufficient numbers of donors. This compromise, which seeks to balance the differing rights and interests, can be transferred with good reason to the field of brain research on bodies. For this research helps to uncover new findings on the process of death in the brain and thus to provide a basis on which the central criterion of brain death, repeatedly open to question both nationally and internationally, can be subjected to a thorough review. There remains, nonetheless, a grey area where no relatives or persons of comparable status can be found and the deceased has not explicitly rejected re-

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114   KÜHN, HERMANN, Die Motivationslösung, Berlin 1998, p. 130; VOLL, DORIS, Die Einwilligung im Arztrecht. Eine Untersuchung zu den straf-, zivil- und verfassungsrechtlichen Grundlagen, insbesondere bei der Sterilisation und der Transplantation unter Berücksichtigung des Betreuungsgesetzes, Frankfurt am Main 1996, p. 297.

115   Also reflected by the National Ethics Committee (Nationaler Ethikrat) in its comments on biobanks, points D 9.2 (p. 54) und D 1 (p. 34).

search. It is possible to conceive of cases in which under strict conditions the interest in performing neuroimaging is so substantial that other possibly conflicting interests are suppressed in the process of finding a comprehensive and conscientious balance: Following the general emergency regulations, situations would have to be assumed in which the ban to conduct neuroimaging on artificially respirated dead bodies without consent may be suspended if the consequences of its enforcement do not seem acceptable in the individual case. This solidarity can, however, only be claimed if the intervention into the post mortem legal position is absolutely required in order to protect a significantly more important interest, and if the related intervention complies with the general principles of proportionality. These deliberations are based on the supposition that an absolute ban would denote the enforcement of the legal order at any price, which, however cannot be the normative guiding principle. This does not mean, however, the automatic preponderance of scientific interests where consent of the family members is lacking. There is also no defence under customary law for performing independent research on the corpse.[116] However, the appropriateness of these instances, which reflect instances of necessity, must be decided on an individual case basis. To avoid the abuse of neuroimaging research on recently deceased a positive votum of an ethics commission should be mandatory. In order to protect the involved interests the law should be precise and should provide clear boundaries.

20.5.4   Summary

The permissibility of performing neuroimaging on dead but artificially respirated bodies is relevant in generating new findings especially to improve the identification of the relevant criteria for the diagnosis of brain death. Today's medical and research standard will be improved tomorrow. Neuroimaging on dead bodies may contribute to a better understanding of the interaction between the defunct brain and the corpse. Unlike persons, the corpse is no longer the bearer but rather the reference object of rights and obligations. The matter-of-fact treatment of corpses speaks for their qualification under property law. However, the associated legal consequences of this are not appropriate for the "remains" of a former person.

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116   UHLENBRUCK, WILHELM/ULSENHEIMER, KLAUS, in: LAUFS, ADOLF/UHLENBRUCK, WILHELM (Publisher), Handbuch des Arztrechts, 3rd edition, Munich 2002, § 133 apostille 24.

Thus scores of provisions derived from human dignity maintain their validity beyond death. In keeping with the constitutional provisions, it should be generally agreed that the permissibility of performing brain imaging on the corpse is dependent upon the (assumed) will of the deceased and the views of those authorised to care for the deceased. There is only very little scope left for exceptional cases to perform neuroimaging without consent. To avoid the abuse of neuroimaging research on bodies a positive votum of an ethics commission should be mandatory. In order to protect the involved interests the law should be precise and should provide clear boundaries.

20.6   Special issues

20.6.1   Neuroimaging and data protection

Neuroimaging gives rise to a special set of problems with regard to the data collected from patients or research subjects, respectively. In general, these data are stored and linked with each other. They are used, on the one hand, to impart medical knowledge. On the other hand, however, they are also used as an aid to understanding how the human brain works. Neuro-imaging is employed to uncover and characterise the performance of the brain. This, at least, is the hope of many scientists. In addition, the aim is to discover how the brain is wired, how consciousness is formed, whether traces of memory can be found in the brain.

Of tremendous interest here is to explain human behaviour, e. g. whether a response to the external stimuli is based on a conscious decision, whether humans are able to identify and critically challenge their own internal processes. If this were indeed the case, this would have implications: the human being could refrain from carrying out an action with negative conse-quences and could instead wait until the conditions become more favour-able. So, he does nothing, even when stimuli would actually require action. If the human being is in a position to decide, he can thus suppress excita-tion or emotions. Thus far, we have assumed that an action which has an unconscious cause is to be evaluated in a different light than an action

carried out deliberately or, for example, under affect.[117] These are externally created conditions of extraordinary psychic arousal which reduce or totally deactivate the critical faculty, the facility of judgement or the ability to restrain oneself. The sudden emotions are felt as a rule intensely, they subside relatively quickly and they are often accompanied by physical-vegetative changes. Rage, anger and hate are so-called sthenic emotions, fright, fear, sadness asthenic.[118]

Current wisdom regards affects as congenital psychobiological forms of reaction. The suspicion that action under affect is determined and cannot thus be allowed as an accusation is being looked at by brain researchers. Of particular importance here is to examine whether the system of affect is the result of reflex and instinct programmes and whether, due to a decoupling of signal and action components, actions are steered by evaluation processes and can be carried out in numerous manners through learning from experience.[119] Such tests are enormously important, for the conscious causing of an outcome is somewhat different to changes to the external world caused by impulsive drives or even simple laws of nature.

At the same time, the various methods of neuroimaging differ from one another with respect to their significance. Only once they have been interpreted can the data thus gleaned be considered as information and knowledge. However, this entails a certain susceptibility to error, which can have severe consequences when it involves making statements on how the brain functions.

The consequences can be seen in all forms of law, but in none more so than criminal law. For its roots are to be found in the socio-ethical set of values of the constitutional community.[120] Reference is often made in crimi-

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117 For more, see TAG, B., Emotionen und Affekte, Ethisch-rechtliche Perspektiven und ihre praktisch-rechtliche Relevanz, in: KICK/TAUPITZ, [Publisher.], Emotionen und Affekte, Mannheim 2005, p. 37 et seqq.

118 For terminology, see BEHRENDT, H.-J., Affekt und Vorverschulden, Baden-Baden 1983, p. 13 et seqq.; DIESINGER, I., Der Affekttäter, Berlin, New York 1977, p. 4 et seqq.; THEUNE, W., Auswirkungen des normalpsychologischen (psychogenen) Affektes auf die Schuldfähigkeit sowie den Schuld- und Rechtsfolgenausspruch, NStZ 1999, p. 273.

119 RESCH F. /PARZER P./BRUNNER, R., Zur Entwicklungspsychologie der Affekte, in: Festschrift KRAUS, Paderborn, Zürich 2002, p. 67 et seqq., with further references.

120 WESSELS/BEULKE, Strafrecht Allg. Teil, 35. Aufl. 2005, N. 9; ARTHUR KAUFMANN, Strafrechtspraxis und sittliche Normen, JuS 1978, 361.

nal law provisions to canons and principles beyond the scope of these provisions. These frequently include socio-ethical views, the state of consciousness, emotions and affects. This is only logical, as modern criminal law acknowledges the act in question in its entirety and recognises both perpetrator and victim.[121] Nevertheless, the forensic and dogmatic possibilities of understanding ways of behaviour which, under the influence of emotions and affects, are of criminal law relevance have hardly been exploited. Thus, here again, the hope is that neuroimaging can lead to new insights, whether with regard to the tendency to commit crimes or to the evaluation of the personality of perpetrator and victim.

This brief overview illustrates the fact that the data gleaned through neuroimaging are highly sensitive. Their relevance is not limited to the field of medical treatment, it also applies within a research context.[122] This can be of a biomedical nature, or can even cover the behaviour of a person as a whole, and can thus be of relevance for the social behaviour of the person examined.

It should be pointed out in this overall context that research with data gleaned through neuroimaging which does not serve merely statistical purposes includes research on the examined person. Thus, not only the medically examined patients are test subjects. The data gleaned from the examined person may indicate their state of health, and quite probably also their psychic health, their emotional world, their decision-making processes and their personality profile. Changes in these areas are therefore generally reflected in changes in the personal data. This thus allows the data of an examined person to be used to carry out research on this person himself, to steer him and control him. The research with respect to the data rather than to the person himself only reduces his capacity to feel himself directly affected. The examined person is important above all as a bearer of characteristics or as part of a subgroup. And very often the individual bearer of characteristics can be found with little effort.

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121   See the aspects of determining punishment in Articles 63 and 64 of the StGB.
122   Fundamentally, SPRUMONT, D., Les principaux modèles de réglementation de la recherche impliquant des êtres humains, Revue suisse de droit de la santé, no. 4, 2003, p. 39 ff.; DERS., La protection des sujets de recherche, notamment dans le domaine biomédical, Berne 1993, p. 205 ff.

There already exist some cases in which the relation between research on patients and research with the data of patients becomes obviously sub-sumable. For example, when findings gathered through the performing of neuroimaging are used, as is the case in the USA, to try to conclude the criminal tendency of the person examined. The vision of the "glass person" in neuroimaging has just crossed the threshold between virtuality and real-ity. In collecting data gleaned from neuroimaging, a further step on the road to significantly increased transparency is being taken. This represents a cause of ill-ease for many of those concerned, some of whom feel even threatened.

At the same time, it must be remembered that the concept of the constitu-tionally-anchored guarantee of the right to self-determination and the pro-tection against abuse of personal data, Article 13, paragraphs 1 and 2 of the Swiss Constitution, leads to the individual right to fundamentally decide oneself on the disclosures and use of one's own personal data. The Swiss Federal Court[123], as early as 1987, already pointed out, citing the "census judgement" (*Volkszählungsurteil*) of the German Constitutional Court[124], that there is such thing as a right to informational self-determination. In addition to the legal position relating to the individual, this guarantee also has a supra-individual component. For it is obvious that the fear of compre-hensive personal data being stored can lead to an individual being pre-vented from exercising his basic rights. The result is that not only are the individual development opportunities of the particular person impaired, but also the common good. Self-determination is an elementary functional con-dition of any free, democratic state founded on the capacity of its people to act and participate.

The data protection guaranteed in Article 13(2) concerns the treatment of so-called personal data. Pursuant to Article 3 of the Swiss Federal Data Protection Act (*Datenschutzgesetz* – DSG), personal data is all information relating to an identified or identifiable person. Article 2(a) of directive 95/46 provides a similar definition, namely "personal data shall mean any infor-mation relating to an identified or identifiable natural person". This data

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123   BGE 113 Ia 1; 113 Ia 257; BGE 120 II 118; 122 I 153; 127 III 481.
124   BVerfG 65, 1 ff.

protection directive imposes obligations on all entities processing personal data.

In addition, the federal and cantonal legislatures also recognise so-called personal data in particular need of protection.[125] Article 3(c) of the DSG lists as personal data in particular need of protection data relating to the religious, philosophical, political or trade unionist views or activities, health,[126] the intimate sphere[127] or race, social aid measures, administrative or criminal prosecutions or sanctions.[128] Under Article 35 of the Swiss Federal Data Protection Act (*DSG*), anyone who in a wilful and unauthorised manner publicises personal data or personality profiles which are secret and especially worthy of protection, and of which he learned in exercising a profession which requires knowledge of such data, shall, on a complaint, be liable to imprisonment or a fine.[129] The same punishment applies with respect to anyone who in a wilful and unauthorised manner publicises personal data or personality profiles which are secret and especially worthy of protection, and of which he learned during work or while serving an apprenticeship or training for the person bound by professional confidentiality. Under Article 36 of the Swiss Constitution, any limitations on the informational right to self-determination in the area of data and personality profiles[130] requiring special protection need a particular justification. Limitations to the right to informational self-determination in this context are permitted only when they follow from a formal law. The restrictions must be proportionate to the goals pursued and must be reasonable.

From a legal perspective, thus, the following must be considered in adequate time: the findings gleaned from neuroimaging and their collection in databases create new data protection risks. They must consequently also lead to new instruments with respect to the protection of fundamental rights.

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125   See PETER, Datenschutz, p. 85 et seqq.; SCHWEIZER, Datenschutzgesetz, p. 22; DERS., in: EHRENZELLER U. A., Kommentar zur Bundesverfassung, Art. 13 N. 41.
126   BGE 119 II 222, 225; VPB 48, [1984] no. 31, p. 183.
127   VPB 44 [1980] No. 131 p. 618.
128   BG in ZBl. 92 (1999), p. 543 et seqq.
129   SR number 235.1.
130   On this term, see decision of the Confederal Data Protection Commission (*Urteil der Eidg. Datenschutzkommission*) [EDSK! of 27.1.2000, VPB 65 [2001] No. 48, p. 544 et seqq.; VPB [1994] No.11, p. 93 et seqq.

Although behaviour-related data which at the same time are not related to health or the intimate sphere or are not collected and saved for the purposes of administrative or criminal prosecution currently are covered by the general term of personal data only, the high sensitivity of data gleaned through neuroimaging and the possibility of creating personality profiles mean that there exists currently a gap in protection which must be examined by the legislature and remedied by means of new legislation. Data protection provisions must thus be modified to reflect the changed conditions. Only by keeping legislation up to date with technical and medical developments can regulations provide instructions on how to perform neuroimaging and save the data thus gleaned in a manner which conforms to the Constitution.

The increased level of sensitivity of data gathered by performing neuroimaging requires the consent of the examined person in order to be permissible. This is a necessary but not sufficient condition. The purposes for which it is permissible to conduct neuroimaging should also be set out. In addition, the position of the persons concerned in terms of their basic rights should be made clear such that, for instance, the person who voluntarily undergoes examination many decide at any given moment on the continuation of the examination and the examined person has a right not to know with regard to the results of the examination. For those incapable of judgement, the legal representative decides. Furthermore the restrictions named in the Convention must be observed.

As these are clearly personal data and, even more, sensitive data, the mere collection of this information is an infringement of the personality rights of the concerned individual. Pursuant to Swiss Civil Law (Article 28) and the Swiss Constitution, the free and informed consent of the person from whom the data are collected must therefore be obtained, not only with regard to the collection but also with regard to the processing and handing to third parties of this data, unless specially authorised by the law. The rule of informed consent is essential even if the way the data are collected does not necessarily imply an infringement of the physical integrity. This is true in constitutional law, civil law, contract law and criminal law in a broad sense, including data protection law (criminal public law). The new version of the Declaration of Helsinki as amended in Edinburgh (2000) includes research with personal data in its scope of application, without however formulating special provisions.

Some further instruments for improved protection of the brain data can be derived from general fundamental principles: first of all, what is involved is the design of so-called brain databases in such as a manner as to make them as data protection-friendly and data-sparing as possible. In order to enable the effective protection of data integrity, i. e. protection against falsified data and the ability to recognise the person from whom the data come, measures must be taken in this very area of data from neuroimaging to guarantee the authenticity of the data. Self-governing concepts (including codes of conduct) may provide for stronger obligations for doctors, psychologists and research institutes for as long as the state cannot completely meet its functions of maintaining order.

The transfer of personal data beyond national borders[131] is today already nothing new in the area of brain banks and is set to become even more commonplace in the future. The reasons for such a transfer abroad are many: central data processing and collection by research institutes abroad, outsourcing of data processing, involvement of external experts, etc. Where the question of the global accessibility of brain banks and the data held therein is concerned, national legal provisions have diminished influence. Even on a European comparison, and despite European legislation in this area, data protection law rarely reflects the level in Switzerland. There are tremendous differences to other countries, such as the USA. In order to be effective here, the law must adopt a more international character.

20.6.2   Confidentiality

The StGB provides for medical professional confidentiality in Article 321 and research confidentiality in 321[bis]. The right of refusal to give evidence of the medical profession, contained in both cantonal civil and cantonal criminal procedure ordinances[132], complements the protection provided by substantive criminal law. Article 321 of the StGB provides for punishment with imprisonment or fine of every wilful[133] breach of medical professional confidentiality, in principle particularly when the persons to whom the secret is

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[131] In order to compare the level of protection between the European and the European Union, see C(2000) 2304, OJ EC No. L 215 of 25.8.2000, pp 1-3.

[132] See, for example, § 130 Code of criminal procedure (StPO) of Zurich Canton.

[133] Negligence remains without criminal punishment, can however be punished by disciplinary measures.

disclosed on their part – for example as doctors or a body representing the medical profession – are bound to secrecy.[134]

Both the fact that neuroimaging has been performed and the information thus produced constitute medical findings which, as a rule, are protected under Article 321 of the StGB. However, not every instance of the doctor or his assistant passing on this confidential information is punishable under criminal law. For example, it does not constitute a punishable act of disclosure when a doctor discusses the neuroimaging results with a patient and explains a possible course of treatment to him.[135] Moreover, the law recognises four restrictions on professional confidentiality – the consent of the person concerned, the approval of the legally-competent authority, the duty to inform an authority, and the duty to give evidence.[136]

The objects of protection of Article 321[bis] of the StGB are the instances subject to confidentiality set out in Article 321. The use of this information for research purposes in the fields of medicine or health care may be punished with the penalties provided for in Article 321[bis] of the StGB. Paragraph 2 provides for a special defence for the use and disclosure of the information. Whereas the anonymous use of data on the basis of which no conclusions may be drawn as to the identity of the patient is already not deemed to constitute an offence, the non-anonymous use of data is also permitted if the person concerned has not objected after having been informed of his rights and an expert commission for professional confidentiality in medical research has also granted its approval with regard to the use of the data.[137] In order to conform to the personal rights guaranteed by the constitution and with the interests in authorising the use of the data, the embedment of a modified consent solution should be considered *de lege ferenda*.

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134   BGE 114 IV 48; Bezirksgericht Uster ZR 96-129290.

135   REHBERG, JÖRG, in: HONSELL, HEINRICH (Publisher), Handbuch des Arztrechts, Zurich 1994, p. 345.

136   For more, see TAG, BRIGITTE, Die Verschwiegenheit des Arztes im Spiegel des Strafgesetzbuches und der Strafprozessordnung des Kantons Zurich, Schweizerische Zeitschrift für Strafrecht 2004, volume 122, issue 1, p. 1 et seqq.; legal opinion SCHMID, NIKLAUS, HAVE 2004, 52 et seqq.; legal opinion ALBRECHT, PETER, HAVE 2004, 60 et seqq.

137   For more, see OBERHOLZER, NIKLAUS, in: NIGGLI/WIPRÄCHTIGER (Publisher), StGB, Band II, Art. 321bis N. 7 et seqq.

20.6.3   Non-discrimination

Equality before the law is based on the concept of affording equal consideration to the subjective fundamental rights of all people – irrespective of sex, skin colour, cultural origin, age, health and individual capabilities, Article 8(2) of the Swiss Federal Constitution (BV). This makes it necessary to counter direct and indirect discrimination against social groups and indicates the need for the complete social and collective integration of people, regardless of their physical or mental condition, including the functions of their brains. The exclusion of persons with physical, mental or psychic disabilities from social life is fundamentally impermissible.

The duty of the legislature to create institutional framework conditions to counter the disadvantages affecting disabled people is anchored in the BV, Article 8 (4). It should be pointed out that, with respect to neuroimaging, the unrestricted development of methods to measure and evaluate the brain activity of people carries the risk of negative consequences for people with disabilities. The availability of neuroimaging can lead to a change in social climate to the extent that people displaying certain brain activity are treated differently on a regular basis. Measures must be taken to prevent this, in particular those which aim to counter social discrimination and promote integration with respect to disabled persons. The danger of neuroimaging results being used to discriminate against people on the basis of their cerebral attributes must be counteracted by clear legal provisions; for example, by limiting the use of such information in the areas of employment and insurance. The possible stigmatisation of people, for whom neuroimaging has determined brain functions which deviate from the norm, must be countered by way of well-balanced information.

20.6.4   Brain databases

Also being discussed at present are the permissibility and modalities of brain databases.[138] These are databases in which, among other things, the information and personal data produced by performing neuroimaging are stored. Such databases are an important resource to shed light on the

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[138]   For general information on biobanks, see Swiss Academy of Medical Sciences (SAMS), "Biobanken: Gewinnung, Aufbewahrung und Nutzung von menschlichem biologischen Material für Ausbildung und Forschung, Medizin-ethische Richtlinien und Empfehlungen", 1st publication for consultation April 2005

causes and mechanism of different illnesses, especially those which are widespread among the general population, such as Alzheimer, Parkinson, chronic pain and brain tumours. However, brain data bases can be established and used for different purposes. The data are sometimes collected especially for biomedical research purposes, sometimes they arise in medical, diagnostic or behavioural contexts or they are used to create personality profiles. The information may be of value for biomedical research, in particular for epidemiology, and lead to progress in terms of the public good. Moreover, brain databases are important sources of information for establishing the cause of diseases and at the same time represent a central pillar for controlling and assuring quality in medicine. This is demonstrated, for example, in how a condition evolves, such as the progression associated with BSE. To this end, the object of the examination is not always only the data of the individual, but also that of the larger collective. However, at the same time this poses questions of self-determination, solidarity, altruism and justice.[139]

In order to ensure equal consideration is given to the interests of those involved, special rules should be drawn up on the preconditions and limits of recycling and collecting information gleaned from performing brain imaging. The central point of reference here is the right to self-determination of the person concerning whom the information was generated. The effective consent of the person involved is needed not only to perform the brain imaging in itself, but also with regard to the related intention to save the information thus generated in order to make it available at a later point in a "brainbank" for research purposes. This also applies to the so-called "multi-use" of data originally collected for medical purposes. Such use of brain data is highly valued in medical and behaviour research. The concession of

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[139] In more detail, the Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells (2004/23/EC); Expert comments of 03.11.2003 by German Enquete-Kommission Ethik und Recht der modernen Medizin of the German Bundestag (8th session) to adopt a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells (Interinstitutionelles Dossier 2002/0128); Nationaler Ethikrat, Stellungnahme, Biobanken für die Forschung, 2004; Zentraler Ethikrat bei der Bundesärztekammer Stellungnahme vom 17. März 2004   First amendments from 19 May 2003 on the Stellungnahme der Zentralen Ethikkommission: Die (Weiter-)Verwendung von menschlichen Körpermaterialien für Zwecke medizinischer Forschung (20.02.2003).

a right to object [140] alone does not meet the requirements of effective protection of the personal and highly sensitive data.

There remains, nonetheless, a grey area. However, in the past, the multifunctional use of brain data was often done without informed consent. And often no close relatives or persons of comparable status can be found who could give consent. In order to guarantee that brain data remain available in the future the process of obtaining informed consent must not be unnecessarily complicated. Situations similar to emergencies may arise in which not only the interest in performing neuroimaging, but also in storing the brain data is so substantial that other, possibly conflicting, interests are suppressed in the process of finding a comprehensive and conscientious balance. Such situations should be regulated by law. However, care must be taken to render the data, where possible, anonymous and to secure the consent of an independent commission comprising experts and representatives of the patient or family members before the data are stored.

When there is no longer a viable connection between brain data and person the protected interests of a person are not serious affected. The same applies when the brain data are known only to a selected group of people who are supplied with the code to remove such data with prevents researchers from having access to the relevant information. The researchers are therefore excluded from the retrieval of the brain data. In order to protect the patient's privacy, his or her personal details must be encrypted as far as possible. The code itself and the encoded brain data must both be stored and administered separately.

The surveillance of the data protection is charged with the task of ensuring that all comply with the legal requirements of data protection. When this exception rises it is necessary to value the ethic-commissions. The same applies for the permission for the long-term storage and use of brain data. Patients should permit the use of brain data for an undefined length of time. Setting time limits dramatically reduces the scientific value of brain databases. Neuroimaging also strongly depends on national and international cooperation and networks. Therefore, the permission of the use of brain data for purposes of brain research should be made available to third par-

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140   As currently in Art. 321[bis] StGB.

ties. However, the passing on can be allowed when the patient remains anonymous or when the brain data is encoded in such a way that the recipient remains without knowledge of the code. Finally, every passing on of brain data has to be documented.

The collection and use of brain data are part of standard medical research. Therefore a general authorisation for brain databases is not mandatory. But, the duty to license brain databases has to be taken into consideration in the case next to the individual data protection. Therefore, a register of all brain databases should be created which is generally available not only to experts but also to lay persons.

Due to the data protection rights brain databases are required to be supervised by an independent data protection official who is obliged to ensure that data protection rights are not abused. Normally, no further supervisor is necessary but possible. However, the falsification or manipulation of results must be cut off by the imposition of sanctions. At all, before the implementation of neuroimaging research projects using brain data from brain databases the approvals of an ethics commission should be obtained.

20.6.5   Summary

The findings generated through neuroimaging and the use of brain databases touch upon data protection. There exits a high degree of sensitivity due to the data's predictive element and character as statements of probability. Due to this, the following application areas require specific attention: the informed consent of the person concerned, protection of privacy; confidentiality; non-discrimination; data-protection; documentation; judicial protection to prevent or to put a stop to an infringement of these rights and to provide for appropriate sanctions to be applied in the event of infringement. Especially behavioural and sociological research requires stricter provisions of national law.

20.7   Research-related neuroimaging on persons able to consent and persons unable to consent

Research in the field of neuroimaging is of central importance. It is necessary in order to produce basic findings which can be used to develop new methods of diagnosis, therapy and prevention. In addition, it is also needed to provide safety and quality in performing neuroimaging. Nevertheless, research carried out on humans needs special justification, both legally and ethically.[141] Where neuroimaging is not used as a medical method of diagnosis, and thus one benefiting the individual, but rather as a means of producing findings of benefit to third parties, it can be used to create generalisations. Where the research is performed as a human experiment[142] without benefit to the research subject, basic principles other than those relating to an attempted treatment which benefits the individual are relevant. For the further neuroimaging advances in its development, the more often its research-oriented application will at the same time represent the pursuit of objectives of medical treatment and research.

Research-oriented neuroimaging entails the more or less serious exploitation of the person to be examined and is associated with a danger of particular risks and damages. As a result, it can only be regarded as legally and ethically justifiable under special conditions. Thus persons able to consent must have effectively done so and must have been effectively informed.[143] In addition to the provisions to be adhered to in performing a medical diagnosis, research must observe the guidelines of Good Clinical Practice (GCP)[144] and the Council of Europe's Convention on Human Rights and Biomedicine (Biomedicine Convention, Oviedo Convention).[145]

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[141] In general on this, SPRUMONT DOMINIQUE, Les principaux modèles de réglementation de la recherche impliquant des êtres humains. Revue suisse de droit de la santé 1/2003, pp. 39 et seqq. DERS., La protection des sujets de recherche, notamment dans le domaine biomédical (thèse de doctorat), Stämpfli, Berne 1993.

[142] For terminology, see the World Medical Association Declaration of Helsinki as amended in Edinburgh 2000, Article 28 g et seqq. Interpretation TAUPITZ, JOCHEN, Die Neufassung der Deklaration von Helsinki, MedR 2001, 277 et seqq.

[143] For the area covered by the HMG, see Art. 54 (1)(a)

[144] For general information, see SPRUMONT DOMINIQUE, HIRTLE MARIE, LEMMENS TRUDO, A Comparative Analysis of Research Ethics Review Mechanisms and the ICH Good Clinical Practice Guideline. European Journal of Health Law 7 (2000), pp. 265 et seqq.

[145] Article 15 f.; http://conventions.coe.int/treaty/en/treaties/html/164.htm.

This includes the documented consent, after having been informed, of the person to be examined. It is also necessary to weigh against each other the lack of alternatives to neuroimaging and the extent of the predictable risks,[146] on the one hand, with the expected benefits for the individual subject and society, on the other hand. A clinical test should be commenced and continued only where the expected benefits outweigh the risks. This is legally grounded in the need for consent by the Ethics Commission, as standardised in the area of application of the Swiss federal law on medicaments and medicinal products (*Heilmittelgesetz* – HMG) in Article 54 (1)(C), Article 57(1) of the HMG. A further requirement is that the subject of neuroimaging must be able to discontinue the procedure at any time without any detrimental consequences for his or her health or the treatment of his condition. Insurance protection is also required for participation in the research. Overall, the rights, safety and well-being of the research subject must be accorded high priority – also in view of the significant interest of academia and society.

There are special problems associated with the use of neuroimaging to conduct research on people who are unable to give their informed consent to the research.[147] At the same time, there is manifestly an irrefutable need to conduct examinations of those unable to consent. Such cases include advanced senility, Alzheimer's disease, BSE. The corner stones of the basic principles to be observed are as follows: Where the possibility exists that neuroimaging is of benefit to the subject himself and it is apparent after weighing the opportunities and risks that the benefits to the subject are greater, it is, as a rule, legally and ethically justifiable to have the informed consent given by his legally authorised representative.

Whether research which does not have the potential to produce direct benefits for the subject may be carried out on persons unable to consent is not agreed. Article 17 (2) (II) of the Biomedicine Convention allows such

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146   In general on this, SPRUMONT D., BOILLAT, S., AMSTAD H., Klinische Versuche, Haftpflicht und Versicherungsverträge, Schweizerische Ärztezeitung 2002, 2097 et seqq.; GUILLOD OLIVIER, SPRUMONT DOMINIQUE, The liability for and insurability of biomedical research involving human subjects under Swiss law, in: DUTE, J./FAURE, M., KOZIOL, H. (Eds), Liability for and Insurability of Biomedical Research with Human Subjects in a Comparative Perspective, Vienna/New York 2004, p. 315 et seqq.

147   For more, see SEELMANN, KURT, Drittnützige Forschung an Einwilligungsunfähigen, in: Festschrift für STEFAN TRECHSEL, Zurich 2002, p. 569 et seqq.

research on condition that it entails only minimal risk and minimal burden.[148] Furthermore it is required that there is neither an alternative method of comparable effectiveness to research on human beings, nor research of comparable effectiveness on individuals capable of giving informed consent, see Art. 16. Additionally the brain imaging must have the aim of contributing to the ultimate attainment of results capable of conferring a benefit to the person concerned or to other persons in the same age category, or afflicted with the same disease or disorder or having the same condition through significant improvements in the scientific understanding of individual's conditions, disease or disorder (so-called *Gruppennützigkeit*) and that there is no alternative treatment for the groups concerned. Additionally, the principle of subsidiary has to be preserved. Over and above, the consent of the responsible ethics commission and the legal representative must have been given and the person concerned must not have signalled an objection. A similar provision can be found in the Declaration of Helsinki as amended in Edinburgh 2000 (No. 24 et seqq.).[149]

Neuroimaging pertains to an especially innovative and sensitive area in which it is hardly possible to predict threats and risks. For this reason, provisions for additional (quality) assurances must be made in the field of research, e. g. including additional expertise, performing the research only in designated centres thus limiting it to institutions and persons who meet certain quality and qualification requirements, and registering research projects.

20.7.1   Summary

Research-related neuroimaging on persons unable to give consent requires new regulations as they are expected in the draft of the Federal Law on Research Involving Human Subjects (*Humanforschungsgesetz*) in Switzerland. The principal legal stipulations should make grade on the provisions of the Council of Europe's Convention of Human Rights and the draft additional Protocol. Due to this, the following application areas require specific intentness: principle of subsidiary, especially in the field of researching

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148   For information on the so-called *Bagatellprinzip* see SEELMANN, KURT in: Festschrift TRECHSEL, p. 569, 582 et seqq.

149   The German version may be located at http://www.gesundheitspolitik.net/04_medikamente/-zulassung/helsinki/Deklaration-Weltaerztebund.pdf

persons without the capacity to consent; neuroimaging has to assess risks and benefits which have to be proportional; in principle, neuroimaging has to be in accord with the advantage of the researched person; if the person has suffered undue damage resulting from neuroimaging he or she is entitled to fair compensation; according to the conditions and procedures prescribed by law.

21   Free will in (criminal) law

21.1   Introduction

As a complex source of information on the brain and how it functions and as a means of improving understanding of illnesses or deviations from the norm, or of performing more comprehensive research on the brain, neuro-imaging is a diagnostic method which must be examined in more than just a criminal law context. It is also the focus of much public attention as scores of scientists use it as an instrument to demonstrate that free will and consciousness are no more than a fortress built on sand, rendered un-steady by the force of new findings.[150]

For those not versed in the law, it is not easy to see the connection be-tween neuroimaging, objective law and the legal system as such. The latter represents the entirety of laws, legal rules and legal provisions governing the basic principles of society and allowing communities to live together in a regulated fashion. The legal norms are of a more objective, generalising nature, they govern a variety of issues in a basic manner and are regularly built around the average observer, the reasonable representative of the respective groups to whom they are addressed.[151] Thus it would appear that they allow little space for both the concept of free will,[152] which be-cause of neuroimaging is being newly discussed and sometimes even radi-cally questioned, and subjective sensibilities.

Yet, this impression deceives. Despite the objectivity of the law, free will and subjective views are constantly assuming more importance in the fields of law and legal ethics. Article 6 of the Federal Constitution speaks clearly of the responsibility of all persons for themselves and their duty to make use of their abilities to contribute to achieving the goals of state and society. This provision is based on the premise of free will. For as we currently un-

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150   SINGER, WOLF, Ein neues Menschenbild, Baden-Baden 2003; forensic psychology as an application of brain imaging is specified in chapter 15.5.
151   TAG, BRIGITTE, in MAY, HERBERT (Publisher), Lexikon der ökonomischen Bildung, 4th edition, Munich 2004, Topic: legal system.
152   PRINZ called freedom of will an illusion, a social construct, see PRINZ, WOLFGANG, Der Mensch ist nicht frei, Magazin 2/2003, Bildgebende Verfahren in der Hirnforschung.

derstand it, there can be no responsibility for an act not originating in freedom. Without the freedom to form one's own will and to choose from a variety of options, legal responsibility as we understand it today, just as ethics, would become mere illusions.

"In a time in which man no longer knows anything elementary"[153], however, the door is wide open for conflicting positions even in the fundamental questions of life. The discussion of free will in particular highlights that the band holding together the divergences as they exist today in the philosophical, legal and ethical evaluation of fundamental questions, is quickly dissolving.

Criminal law has a prominent role to play within this overall context. Its roots are to be found in the socio-ethical set of values of the constitutional community,[154] and there are numerous terms associated with the conditions for an offence and the legal consequences which need to be interpreted. Very often here, reference is made to rules and principles not covered by criminal law norms and, additionally, which can be of an extra-judicial nature. It is not only the objective characteristics of an act which determines the rights and wrongs of it, but also further factors found in the subject or perpetrator. These include state of awareness, socio-ethical views, feelings and emotional states. Under the proviso that the principle of certainty is taken into account in the manner required[155], this accessoriness is logically consistent. For modern criminal law recognises the act to be judged in its entirety. It calls for offender and victim and their relation to the act, often not free of emotion, to be taken into consideration.[156] Nevertheless, the forensic and dogmatic means of covering the sources and influencing factors of subjective behaviour have yet to be fully plumbed.

The following is intended first to give a brief overview of how free will and criminal law dovetail and subsequently to discuss the interplay between the results of modern, neuroimaging-assisted brain research and criminal law.

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153   KÜCHENHOFF, GÜNTER, Der Begriff des "Minimums" in der Rechtswissenschaft, NJW 1959, 1254, 1257.
154   ARTHUR KAUFMANN, JuS 1978, 361.
155   Article 1 StGB: "Only a person who commits an act which is explicitly punishable under the law shall be liable to prosecution".
156   See the principles for determining punishment set out in Article 63 of the StGB.

21.2   The link between free will and criminal law

21.2.1   Free will and the wrongfulness of the act

As we understand them today, the elements that constitute an offence are based on the assumption that these do not standardise just any objective, neutral acts. The rules and prohibitions of substantive criminal law instead govern typical types of behaviour, which stand out from an immeasurable number of human acts because they are notably condemned and thus threatened with punishment by the legislature for demonstrating a qualified lack of values and being damaging to society.[157] However, what constitutes in detail the wrongfulness of an act and the degree to which the free will of the offender must be considered is not carved in stone. In fact, the discussion has rather produced differing standpoints on the matter.

The older, classical dogma[158] predominant around the beginning of the 20th century derived the wrongfulness from the victim based on the doctrine of causal action (*kausale Handlungslehre*). It understood wrongfulness as a negative assessment of an objective situation caused by an act. Consequently, the judgment of wrongfulness was limited to the violation of the legal interest (*Rechtsgut*) as such. The focus of consideration was, for example, the fact that someone had been killed or had an item taken away from them. The criminal law norms underlying the examples given, i. e. homicide, Article 111 of the StGB, and theft, Article 139 of the StGB, were understood as evaluation standards. Their binding character was not supposed to depend on whether the individual was capable of using free will to live them out.[159] For wrongfulness was committed through external behaviour alone, not through thoughts and intentions, through the attitude of the offender. Related to this were the doctrines of causal actions. These held that an act was relevant in criminal law if a physical movement caused arbitrarily, i. e. with intent, had consequences on the external environment.[160] The division thus created between objective wrongfulness and subjective

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[157]   TAG, BRIGITTE, Der Körperverletzungstatbestand im Spannungsfeld zwischen Patientenautonomie und Lex artis, § 9, with further references.

[158]   v. LISZT, FRANZ, Lehrbuch des Deutschen Strafrechts, 16th/17th edition, Berlin 1908, p. 115; BELING, ERNST, Die Lehre vom Verbrechen, Tübingen 1906, p. 43 et seqq., 178 et seqq.

[159]   GOLDSCHMIDT, JAMES, Normativer Schuldbegriff, in: Festgabe für REINHARD VON FRANK, volume 1, Tübingen 1930, Nachdruck Aalen 1969, p. 458 et seqq.

[160]   For more, see TRECHSEL, STEFAN/NOLL, PETER, Schweizerisches Strafrecht, Allgemeiner Teil I, 6th edition, Zurich 2004, § 21 A.

guilt seemed plausible and easily administered. Legal reality and criminal law dogma soon showed, however, that the restriction of the moral value-judgement of reproach purely to the unworthiness of the result (*Er-folgsunwert*) was not in itself suitable to determine generally the judgement of unworthiness (*Unwertsurteil*) of an act. The result otherwise would be to refute the difference between wrongfulness and accident, insofar as a person influenced the occurrence of the act.[161]

The view that the descriptions of offences contained in the Criminal Code are not exhausted in terms of objective elements rightly prevailed. Circumstances belonging in the offender's psychic sphere and conceptual world,[162] which characterise the unworthiness of the action (*Handlungsunwert*) and the particular manner in which the act was committed, must already be considered in the wrongfulness of the act. Such subjective elements of an offence are found in particular in so-called "crimes of intent", see Article 139 of the StGB "appropriation intent, enrichment intent". Intent, loosely described in many papers as "knowledge and will", Article 18(2) of the StGB,[163] and negligence as failing to take the necessary care "which the offender was obliged to take according to the circumstances and his personal situation", Article 18(3) of the StGB, characterise the wrongfulness of the act. Subjectively-tainted constituent elements, such as deceitful misleading in fraud, Article 146 of the StGB, or unscrupulousness in murder, Article 112 of the StGB, show that very often it is only by examining the subjective intent of the offender that it can be determined whether an act constitutes the elements of an offence. In order to account correctly for the manifold forms ambiguous acts can assume, it is imperative that the character of an act and its relevance to criminal law are determined not only by the external result, but also in accordance with the standard underlying the wrongfulness. To this end, the decisive elements here are the mental and psychological attitude on which the act rests and the manner in which the act was carried out. The goals behind the offender performing the objective act, his mental disposition in carrying it out, the duties to which he was bound while doing so, all this influences decisively the wrongfulness,

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161   MAYER, MAX ERNST, Der allgemeine Teil des deutschen Strafrechts, 2nd edition, Heidelberg 1923, p. 62 et seqq.

162   Grundlegend MEZGER, EDMUND, Die subjektiven Unrechtselemente, GS 89 (1924), 207 et seqq.

163   Art. 18(2) states: "Anyone who performs an offence or misdemeanour with knowledge and will shall be deemed to have wilfully performed such act".

next to the possible violation of the legal interests. For wrongfulness also has an offender-related aspect, is personal wrongfulness.[164]

Even this small excursion into criminal law dogma shows that jurisprudence and case law wrestled long and hard with the question of the extent to which subjective factors in the wrongfulness of an act should be taken into account. Under the dominant view today of man as an autonomous person endowed with free will, the unworthiness of the act of committing an offence can be defined in neither a purely objective manner nor a purely subjective manner. The latter would amount to impermissible wrongfulness inherent in the mental attitude of the offender (*Gesinnungsunrecht*),[165] which is not consistent with the understanding of criminal law as covering the legal interests (*Rechtsgüter*) as well. A criminal offence is a social act to which the offender, often a victim[166], and/or the public in general belong.[167] Criminal behaviour is neither exclusively an internal matter for the offender nor purely an external matter for society.[168] A criminal action by a person as an autonomous being may only be understood as a synthesis of objective and subjective factors.[169] It is not limited to the conscious exercise of purposive activity.[170] It is not the finality of an act which forms the criterion for criminal evaluation, rather the fact that it deviates from a certain norm. As a synthesis of ontological and normative elements, action within the meaning of criminal law describes socially-relevant behaviour controlled or capable of being controlled by will.[171]

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164 As already given by WELZEL, HANS, Deutsches Strafrecht, 11th edition, Berlin 1969, p. 62.
165 STRATENWERTH, GÜNTER, Strafrecht Allgemeiner Teil I, 3rd edition, Berne 2005, § 3 N. 19.
166 For more on the "rediscovery" of the victim in criminal law, see HILLENKAMP, THOMAS, Zur Einführung: "Viktimologie", Juristische Schulung (JuS) 1987, 940.
167 DENCKER, FRIEDRICH, Erfolg und Schuldidee, in: Gedächtnisschrift für ARMIN KAUFMANN, Cologne, Berlin, Bonn, Munich 1990, p. 441, 451.
168 GALLAS, WILHELM, Zur Struktur des strafrechtlichen Unrechtsbegriffs, in: Festschrift für PAUL BOCKELMANN, Munich 1979, p. 155, 164; HIRSCH, HANS JOACHIM, Die Entwicklung der Strafrechtsdogmatik nach Welzel, in: Festschrift der Rechtswissenschaftlichen Fakultät zur 600-Jahr-Feier der Universität zu Köln, Cologne 1988, p. 409.
169 GALLAS, in: Festschrift BOCKELMANN, p. 155, 161 et seqq.; STRATENWERTH, GÜNTER, Zur Relevanz des Erfolgsunwertes im Strafrecht, in: Festschrift für FRIEDRICH SCHAFFSTEIN, Göttingen 1975, p. 177, 178 footnote 9.
170 WELZEL, HANS, Deutsches Strafrecht, p. 34: "Der das Kausalgeschehen lenkende Wille ist das Rückgrat der finalen Handlung.", i. e. the will guiding the causal occurence is the backbone of final action.
171 So-called *sozialer Handlungsbegriff (*concept of social action), see TRECHSEL/NOLL, Strafrecht AT, § 21 C.

21.2.2   Free will of the bearer of the legal interest (*Rechtsgutsträger*)

However, criminal law is by no means limited to according free will to the offender only. Even the person whose legal position is criminally threatened or violated is deemed fundamentally to be an autonomous person. Where an act constituting an offence by the offender serves to protect individual interests, such as health, property, wealth, sexual self-determination, the power of disposal over the legal interest (*Rechtsgut*) assigned to the bearer is also a constituting factor of the protected legal position. Without discussing in detail the concept of legal interest,[172] it should be pointed out briefly that the constitutional imperative to respect all others as autonomous and equal persons forms the fundamental basis under criminal law for the protection of the legal interests of individual persons. For the criminal law concept of legal interest is derived not from criminal law, but from the constitution. Without loosening the connection between objective good and autonomy, the object protected by criminal law must be seen as dynamic. Because of the prerequisite free will self-evident under the legal system, the legal interests of an individual form the basis for action of a permanently functioning[173], free evolution of the person.

This personal freedom and self-determination at the same time guarantee the bearer of the legal interest the opportunity to dispose of this interest within the confines of the legal system. Should one, or should one wish to, use the results of neuroimaging to deny the free will of the bearer, this would entail serious consequences even for how the concept of a bearer of legal interest is understood.

21.2.3   Free will and guilt

Whereas in the field of wrongfulness a criminal act is examined with regard to its conformity to a prescriptive order, the offender is made responsible for his behaviour violating legal prohibitions or rules by being sentenced to a

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[172] For an instructive view, AMELUNG, KNUT, Rechtsgüterschutz und Schutz der Gesellschaft, Frankfurt 1972; ROXIN, CLAUS, Strafrecht Allg. Teil/1, 3rd Edition, Munich 1997, § 2 apostille 9 et seqq.; RUDOLPHI, HANS JOACHIM, Besprechung von ARZT, GUNTHER, Willensmängel bei der Einwilligung, ZStW 86 (1974), p. 69, 94 et seqq.

[173] WELZEL, HANS, Studien zum System des Strafrechts, ZStW 58 (1939), 490, 515; RUDOLPHI, HANS JOACHIM, Die verschiedenen Aspekte des Rechtsgutsbegriffs, in: Festschrift für RICHARD M. HONIG, Göttingen 1970, p. 151, 163.

punishment. This is only permitted if he can be charged personally with the act.[174] For punishment requires guilt, *nulla poena sine culpa*.[175] Until a final judgement has been passed, everyone is deemed innocent, see Article 32(1) of the Swiss Constitution. The offender's guilt is the basis for determining punishment, Article 63 of the StGB,[176] and pertains to the offender's relation to his act. Hence the formulation frequently read: "the court 'finds him guilty' of murder".[177]

The older doctrine understood guilt as the subjective-psychological relation of the offender to his act.[178] Intent and negligence were consistently understood as forms of guilt.[179] Such a purely psychological understanding of guilt cannot possibly be persuasive, however, as even those lacking the capacity to be adjudged guilty can be commit an offence in a wilful and unlawful manner.[180] This becomes immediately apparent if one considers the case of a mentally ill offender threatening children with a flamethrower. This constitutes, despite the mental incapacity of the offender, a wilful, unlawful attack justifying in principle self-defence and emergency assistance, Article 33 of the StGB. The "natural" intent necessary to constitute an offence relates primarily to whether the will to act is directed towards the realisation of the objective elements of the offence. As a result, it can be present even with regard to the mentally ill. For good reason, the normative

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174 STRATENWERTH, Strafrecht AT I, § 22 N. 5; BOMMER, FELIX, in: NIGGLI, MARCEL ALEXANDER/ WIPRÄCHTIGER, HANS (Publisher), Basler Kommentar, StGB, Band I, Basel 2002, vor Art. 10 N. 5; HUTARDO PUZO, JOSÉ, Droit pénal, Partie générale I, 2nd edition Zurich 1997, N. 489; REHBERG/DONATSCH, Verbrechenslehre, p. 219; RIKLIN, Strafrecht AT I, § 15 N. 3; SCHULZ, HANS, Einführung in den Allgemeinen Teil des Strafrechts, Band I, 4th edition, Berne 1982, p. 176; SCHWANDER, VITAL, Das Schweizerische Strafgesetzbuch, 2nd edition, Zurich 1964, N. 167; SEELMANN, KURT, Strafrecht Allgemeiner Teil, Basel 1999, p. 61.

175 TRECHSEL/NOLL, Strafrecht AT, § 28 A. p. 146; Decisions of the Federal Criminal Court (BGHSt) 2, 200 et seq.

176 Art. 63: "The judge shall administer punishment according to the degree of guilt of the offender; he shall take into account the motive, the life before the act and the personal circumstances of the accused."

177 REHBERG/DONATSCH, Verbrechenslehre, § 23.

178 TEMME, JODOCUS DEODATUS HUBERTUS, Lehrbuch des Schweizerischen Strafrechts, 1855, p. 91 et seqq.; MEZGER, EDMUND, Lehrbuch des Strafrechts, Allgemeiner Teil, 6th edition, Munich 1955, § 33.

179 Allusion is still made to this today in the title of Art. 18 StGB where intent and negligence are classified under guilt. This description has rightly been removed in the revised part of the StGB AT which has not yet come into effect, see Art. 12.

180 STRATENWERTH, Strafrecht AT I, § 11 apostille 3.

understanding of guilt[181] dominant today thus includes in deliberations in addition to the psychological circumstances also the extent to which the offender can be charged with them.

Under this understanding, guilt can be divided into two parts: guilt in its normative sense means the capability of charging the offender with criminal and unlawful conduct – when legal behaviour should have been demanded from him. With a judgment of reproach of guilt, the offender is accused of choosing wrong when he could have chosen right. This potential to decide differently is part of free will and equally important for the existence of a criminally-relevant act as it is for that of guilt.[182]

However, whether the view existing in the literature dealing with the question of freedom with respect to guilt is so perplexing that the only constant is disaccord[183] seems doubtful to this degree of rigour. Guilt is at any rate an indispensable evaluation grade in according personal responsibility to an offender, in judging the commensurability of an act in light of the emotional or mental condition of the offender.[184]

The predominate view of Swiss jurisprudence is that criminal guilt incorporates sanity, Article 11 of the StGB,[185] possibly prerequisite special elements of guilt, the form of guilt in the sense of wilful or negligent guilt, Article 18 of the StGB, the possibility of understanding that a wrong has been committed, so-called awareness of wrongfulness (*Unrechtsbewusstsein*), Article 20 of the StGB, and the lack of excusing reasons, see for example Article 34(2) of the StGB.

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[181] Substantiated by FRANK, REINHARD, Über den Aufbau des Schuldbegriffs, in: Festschrift für die JURISTISCHE FAKULTÄT GIESSEN, 1907; see also TRECHSEL/NOLL, Strafrecht AT, § 28 A. p. 147 et seq.

[182] For the individual positions in the determinism-indeterminism debate, see SPILGIES, GUNNAR, Die Bedeutung des Determinismus-Indeterminismus-Streits für das Strafrecht, Hamburg 2004, p. 17 et seqq. with critical review KUDLICH, HANS, HRRS 6/2004, p. 219 et seqq. and reply by SPILGIES in HRRS 2/2005 p. 43, rejoinder KUDLICH, p. 51 et seqq.

[183] Thus states SCHIEMANN, ANJA, Kann es einen freien Willen geben? - Risiken und Nebenwirkungen der Hirnforschung für das deutsche Strafrecht, NJW 2004, 2056; GEISLER, CLAUDIUS, Zur Vermeidbarkeit objektiver Bedingungen der Strafbarkeit mit dem Schuldprinzip: zugleich ein Beitrag zum Freiheitsbegriff des modernen Schuldstrafrechts, Berlin 1998, p. 33, 38 et seqq.

[184] Federal Constitutional Court Judge HOHMANN-DENNHARDT, Ärzte Zeitung of 08.03.2005, at a discussion round by the Max-Planck-Forum in Berlin.

[185] Indicated as the capacity to be adjudged guilty in the revised part of the StGB AT, see Art. 19, 20 StGB, as amended.

The consequences of the offence are also based on the assumption of the ideal concept of man as an autonomous person. For only those forms of behaviours which threaten or damage a society based on the freedom and social responsibility of the individual can be punished.[186] The function of a constitutional state is not wholly exhausted through the mere presence of a formal country of legality in the sense of the existence of formal institutions for the separation of powers and of associated guarantees such as legal certainty. The internal determination and legitimising of the constitutional state is rooted in its being bound by material justice. The authority to impose and enforce punishment is a reflection of this principle.

Punishment requires free will.[187] While the Criminal Code does not state this explicitly, it does assume that the adult person has the capacity to be adjudged guilty and is responsible for his actions. Where in an individual case this cannot be assumed because the offender was not capable due to a mental illness, mental defect, or profound consciousness disorder of appreciating the wrongfulness of the act or acting in accordance with such appreciation at the time of execution of the act, the offender shall not be punishable, Article 10 of the StGB. Where diminished responsibility exists, the court may mitigate the punishment at its own discretion, Articles 11 and 66 of the StGB. In the cases of Articles 10 and 11 of the StGB, the court must also decide whether and to what extent measures of correction and prevention appear prudent, Article 42 et seqq. of the StGB.

In contrast to adults, the determination of guilt with respect to children or juveniles is subject to its own rules. Children who have yet to complete their seventh year are not covered by the StGB,[188] Article 82 of the StGB. For children up to 15, juveniles between 15 and 18, and young adults between 18 and 25, special punishments are provided for which focus on instructive aspects. The capacity to be adjudged guilty must be examined particularly with respect to the degree of maturity.

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186   See RUDOLPHI, in: Festschrift HONIG, p. 151, 161.
187   In detail, HILLENKAMP, THOMAS, Strafrecht ohne Willensfreiheit? Eine Antwort auf die Hirnforschung, JZ 2005, 313, 316 et seqq.
188   Under future law, the age of criminal accountability will be raised to 10 years, Art. 3(1) of the Criminal Code for Juveniles (JStG). With respect to crimes by children under 10 years of age, only custodial and correctional measures will be available, see STRATENWERTH, Strafrecht AT I, § 11 apostille 10.

These exceptions confirm the general rule, under which the legal system and the Criminal Code are based on the assumption of the ideal concept[189] of man as an autonomous adult. That his actions are based on free, responsible self-determination. That this capacity allows man the power of disposal over the legal interests accorded to him, to choose right before wrong, to conduct himself or herself according to legal requirements and to avoid that which is legal prohibited.

The question of which conditions must be met in order to pass a fair sentence is closely tied to the (potential) free will of the offender. To ensure that punishment is not meted out arbitrarily, the so-called absolute theories choose the offence as the starting point for the punishment, which thus assumes a fixed dimension.[190] The roots of these theories are to be found in Kant[191] and Hegel.[192] For Kant, autonomy is the epitomised basis of morality. Kant posits the independence of moral will from all instances and objects external to it. Moral will creates its own laws according to which it acts and it is this self-legislation, i. e. autonomy, which makes it moral will in the first place.[193] The theories of retribution based on this are oriented regressively on the *ius talionis* considerations[194] of the deserved punishment and describe an equivalent to the offence. Punishment serves to settle or compensate for a moral debt or guilt.[195] Kant focuses on the famous island example,[196] while Hegel[197] sees punishment as "negation of negation".

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189 On relative indeterminism, see HÖFFE, Universitas 2004, 193 et seqq ; TRECHSEL/NOLL, Strafrecht AT, sprechen von "Fiktion", § 28 A. p. 148.

190 For an instructive view, see ZACZYK, RAINER, Zur Begründung der Gerechtigkeit menschlichen Strafens, in: Festschrift für ALBIN ESER, Munich 2005, p. 207 et seqq., 217.

191 The main source for this is KANT'S script: Grundlegung zur Metaphysik der Sitten, Riga 1785.

192 HEGEL, G.W.F., Grundlinien der Philosophie des Rechts oder Naturrechts und Staatswissenschaft im Grundriss (a work in 20 volumes, published by MOLDENHAUER and MICHEL, 1971, volume 7).

193 KANT, IMMANUEL, Metaphysische Anfangsgründe der Rechtslehre, 1797, Akademie-Ausgabe der Gesammelten Schriften, volume 6 (1907), p. 227.

194 With respect to HEGEL, G.W.F., in Form des Äquivalents, compare Grundlinien der Philosophie des Rechts oder Naturrechts und Staatswissenschaft.

195 For more, see WOLF, JEAN CLAUDE, Verhütung oder Vergeltung? Einführung in ethische Straftheorien, Munich/Freiburg 1992, p. 56 et seqq.

196 KANT, IMMANUEL Die Methaphysik der Sitten, Rechtslehre, Werke, volume 7, A 199/B 299. For more on the island example, see ZACZYK, RAINER, Zur Begründung der Gerechtigkeit menschlichen Strafens, in: Festschrift für ALBIN ESER, Munich 2005, p. 207 et seqq., 209; DERS., Staat und Strafe – Bemerkungen zum sog. Inselbeispiel in Kants Methaphysik der Sitten, in: LANDWEHR (Publisher), Freiheit, Gleichheit, Selbstständigkeit, 1999, p. 73 et seqq.

197 HEGEL, G.W.F., Grundlinien der Philosophie des Rechts oder Naturrechts und Staatswissenschaft im Grundriss (a work in 20 volumes, published by MOLDENHAUER and MICHEL, 1971, volume 7).

These neoclassical, absolutist theories are opposed by the relative views which like to see themselves as modern.[198] They derive the reason for the punishment from the intended purposes of the punishment, whereupon the focus is on stabilising awareness of the law in general and with respect to the offender, as well as on determent.[199] Both aspects become more relevant with regard to the free will of the offender. For the relative arguments contradict the absolute theories in assuming that retributive guilt cannot have a punishment imposed. Individual guilt is dependent on the existence of free will. Free will, though, cannot be proven and is thus not suitable as the sole basis of punishment.[200] However, were purely preventative criminal law to be applied and were one to derive from the benefit of many a right against the individual, this would mean that man is no longer treated as a subject, but as a minor, an object.[201]

Moreover, it must be remembered that, although purely preventative criminal law is supported by the well-being of the public at large, it is nevertheless created by people. However, should it be possible to prove the theory of determinism (what is heavily being disputed), for example with the help of neuroimaging, natural evolution would seem to indicate that it is valid for all people, and thus for society as a whole. Where no-one is in possession of self-determined free will, every yardstick of reasonable punishment is lacking. Furthermore, were one to assume that from the "is" a "should be" can be completely derived, the rationale for the "should be" is allowed its own quality.[202] This would mean that the "should be" and thus the legal system would have to be substantiated in a self-contained manner. If however neither the populace nor the individual possess free will, the question arises of which authority is responsible for drawing up the rules of that which should be. The fact that the presumed or proven "lack of freedom" of man results in a responsibility vacuum and creates opportunities for this vacuum to be filled by newly enforced claims to power represents a not

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[198] SCHÜNEMANN, BERND, Kritische Anmerkungen zur geistigen Situation der deutschen Strafrechtswissenschaft, GA 1995, 201 et seqq.

[199] The general and special preventive purposes of punishment are linked in the so-called unification theories (*Vereinigungstheorien*), see WIPRÄCHTIGER, HANS, in: NIGGLI/WIPRÄCHTIGER (Publisher), StGB Band I, Art. 63 N. 27 et seqq. According to the Federal Court, criminal law does not primarily serve retribution, BGE 120 IV 1, 4.

[200] ROXIN, Strafrecht AT, § 3 N. 8.

[201] As impressively demonstrated in SINGER, Ein neues Menschenbild, p. 10.

[202] ZACZYK, in: Festschrift für ESER, p. 209, 213, with further refrences.

insignificant consequence of the whole non-determinism-determinism de-
bate.

Aside from the areas already mentioned, neuroimaging can be of impor-
tance in criminal proceedings.[203] It can be used as an investigative method
to access evidence. The main area of application could be in proving
changes which affect soundness of mind or lack thereof of the person
concerned, the degree to which he can be treated with therapy, and his
capacity for resocialisation. From a criminological point of view, it remains
to be seen whether certain brain structures or changes correlate to person-
ality traits which could be relevant for criminality in general and criminologi-
cal tendencies in individual cases in particular and the danger of a relapse.
Although the so-called biological theories of criminality meet with criticism
because of unresolved methodological questions, they have not yet been
fully refuted. The possibility cannot be excluded that neuroimaging in brain
research can also provide answers to questions hitherto unsolved and can
lead to new findings in criminology.

Hopes are growing in the USA that neuroimaging in brain research can play
a decisive role in prosecuting crimes. In the future, neuroimaging of the
brain is to also be used instead of biometric features as evidence.
LAWRENCE FARWELL, an American neuroscientist, claims to have made a
discovery with which not only terrorists and criminals who have already
committed an offence can be convicted, but also those who belong to such
groups, i. e. are potential criminals. His technique, called "brain fingerprint-
ing", can supposedly be used to prove both without error and objectively
the existence of information in the brain, even when the subject tries to hide
this knowledge.[204] This test is said to show the presence of certain know-
ledge, for example information only the offender can know, in the brain of a
person.

Such methods, should they actually function,[205] entail major problems. For,
first of all, the possibility of training the brain to respond to stimuli cannot be

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203   For more, see ROMANUCCI, L./TRANCREDI, L., Criminal Behaviour and Brain Imaging Techno
      Science. In: ROMANUCCI-ROSS/TANCREDI L. (Publisher), When Law and Medicine meet: A cultural
      view. Dordrecht, Boston et al., (2004), p. 61 et seqq.
204   For more, http://www.brainwavescience.com/, page last visited on 01.06.05.
205   For an impression of the unsuitability of this method, see Kriminalistik 1999, p. 11.

excluded. Secondly, the term "brain fingerprinting" chosen by FARWELL is misleading. Everyone who has witnessed an event or at least seen pictures of the event may call up these memories. Such uncertainties have led to lie-detector tests, particularly in Germany[206] and Switzerland, currently not being permitted for criminal proceedings. A general tenet can be found in the cantonal criminal procedures and the Swiss BStP: in principle,[207] no one is allowed to use evidence-gathering methods which are capable of reducing or even neutralising consciousness and free will. For such methods cannot be reconciled with human dignity and the statutory ban in Article 3 of the ECHR on degrading treatment.[208] Such methods are not allowed even when the accused agrees to them. Any statements produced in contravention of this prohibition are regularly ruled impermissible. These rules also apply for the time being to the process of using neuroimaging to produce evidence.

21.3   Results of neuroimaging

Summarising the comments on free will in criminal law, the central issue remains the question of whether and how the fundamental commitment of the legal system to free will can be reconciled with the findings of modern brain research. The fact is that numerous, and in part spectacular, results of examinations have moved the natural sciences to consider questions of free will and consciousness, traditionally the preserve of humanities.[209] The quote from CREUTZFELDT that "the answer of neurophysiology is the beginning of philosophy"[210] has lost its validity in that some brain scientists draw fundamental consequences for how we see man from the interpretation of technical calculation models.[211] A reluctance to interfere in highly-complex, well-reasoned matters of humanities using controversial statistical

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206   BGHSt 44, 308 et seqq.; BGH NStZ 2000, 35 et seqq.; Europäische Grundrechte Zeitschrift (EuGRZ) 25 (1998) 351
207   Limited by Federal Court 23.9.1998 if the lie detectors are used to exonerate accused and not against his will; see TA No. 23 of 29.1.1999, p. 2.
208   SCHMID, NIKLAUS, Strafprozessrecht, 3rd edition 2004, RN. 626, 686 with further references
209   SINGER, Menschenbild, p.10.
210   CREUZFELDT, in: Reproduktion des Menschen. Beiträge zu einer interdisziplinären Anthropologie, Frankfurt/ Berlin, 1981, p. 29 et seqq.
211   SINGER, Menschenbild, p. 20, 34, 66; ROTH, GERHARD, Homo es Machina – Geformt nach welchem Bilde?, Das Magazin 3/2001, p. 3 et seqq.

evidence cannot always[212] be observed. There is no reticence even with respect to criminal law and the hardest sanctions that society has against the individual, the legal consequences of an offence. Theses in which "there has to be a move away from the crime and punishment principle", "society simply has to protect itself from its outlaws – regardless of the question of guilt, however hard to answer"[213] reflect the changed manner in which the natural sciences see themselves and the subsequent related claims to hitherto non-existent competences.[214] At the same time, the research results arrived at to date make clear that the relevance of the findings of neuroimaging can be judged neither in isolation of the social context of the examinations performed nor decoupled from humanity.

In interpreting terms such as autonomy, consciousness, self-determination, one must venture far into the philosophical, theological and legal disciplines. Neurobiology, philosophy and jurisprudence can learn much from each other. In addition, there is an interaction between findings from the natural sciences and their philosophical and legal evaluation. Whether or not this results in the vehemently-discussed naturalistic fallacy depends decisively on whether or not the respective inter-disciplinary expertise required exists. Even if it is possible with the help of experts to overcome knowledge barriers, a solid body of knowledge and a deep well of experience on the formation of consciousness and free will are needed. To date, there is certainly no guarantee as to whether a correct view of the matter exists. On the contrary, the discussion of free will and brain research demonstrates that highly differing views and a decisive lack of understanding in parts already come to the fore without a solid body of knowledge, especially as human mental activity, which heretofore could not be fully grasped using the natural sciences alone, present problems even for the

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212   Conservative positions may also be found, e. g. DRESSLING, "a simple reductionistic-biological explanation of complex bio-psychosocial defects, which may be the root of sex crimes, is thus also neither to be expected with the new research approaches, nor intended", see DRESSLING, HARALD, Was passiert im Kopf eines Sexualstraftäters, Magazin 2/2003, Bildgebende Verfahren in der Hirnforschung.

213   SINGER, Menschenbild, p. 51, 65; DERS., Der Beobachter im Gehirn, 2002, p. 32 et seq.; DERS., in: GEYER CHRISTIAN (Publisher), Hirnforschung und Willensfreiheit, Frankfurt 2004, p. 30 et seqq.; see further PRINZ, in: von Cranach/Foppa (Publisher), Freiheit des Entscheidens und Handelns, 1996, p. 86 et seqq.; DERS., Das Magazin 2/2003, http://www.wz.nrw.de/magazin/magazine.asp; ROTH, GERHARD, Fühlen, Denken, Handeln, 2001, p. 427 et seqq.; DERS., Aus Sicht des Gehirns, 2003, p. 166 et seqq.; DERS., in: Festschrift für LAMPE, 2003, p. 43 et seqq.

214   KRÖGER, HANS-LUDWIG, Der Begriff strafrechtlicher Verantwortlichkeit, in: GEYER, (Publisher), Hirnforschung und Willensfreiheit, p. 103, 107.

expert and in spite of all the progress made. The obstacle of meeting reality with an appropriate legal response and according it corresponding recognition is highly set. In addition, neuroimaging is entangled in conflicting fields of budget reductions and rationalisation measures. At the same time, it is supposed to help plumb the depths of the mind or break through mental barriers and thus raise questions as to man's capabilities and to underline his capacity to be manipulated. These many factors all contributed to the prominence in the debate of the not always objective discussion on the relevance and reliability of neuroimaging.

In addition to these rather general problems, direct concept-related aspects of neuroimaging must also be considered. Thus, it is unclear whether or to what extent given his expertise the doctor or brain researcher is given leeway for interpretation, without it being subject to legal evaluation. Related to this is the question of whether a canon of findings exists which allows for reliable legal assessment or whether brain research reveals itself to be the most changeable of all sciences, not capable of being made subject to any categorisation.

It would appear that, despite the modern findings of brain research, the law, and in particular criminal law, persist with the traditional paradigms of free will and autonomy. In the argument with regard to free will, determinism and non-determinism, the different points of view have been reconciled and model solutions have been established at the levels of wrongfulness, guilt and the consequences of the offence which function satisfactorily as the basis for according criminal responsibility.[215] However, this consensus is vehemently criticised by some brain researchers. SINGER repeats his view: "From the point of view of the natural sciences, it must be concluded that 'will' cannot be free".[216] ROTH concludes: "A society must never punish someone only because he has been guilty in some moral sense – this would make sense only if this thinking subject had had the option of acting in a manner different to that which has actually occurred". Some legal experts assume this position[217], however the majority reject it for different reasons.

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215   TRECHSEL/NOLL, Strafrecht AT, § 28 A.
216   SINGER, Menschenbild, p. 59.
217   See, for example, somewhat uncritically, SCHIEMANN, NJW 2004, 2056 et seqq.

LÜDERSSEN objects to the determinism theory popular with brain research-ers in saying that even if there can be no doubt as to the natural scientific basis, observations to date of brain research do not support the conclu-sions thus made.[218] HELMRICH sees the "readiness-potential" in the brain as subconscious preactivation which can nevertheless be preceded by the planning of and decision on an act. The last, measurable "jolt of will" (*Wil-lensruck*) only occurs after the readiness-potential.[219] GUSS does not see any argument against free will in the findings of modern brain research. The problem is how to reconcile free will with our mental model concepts.[220] On the other hand, a group of criminal law experts believe in general awareness of freedom. The constant experience of one's own freedom and the corresponding recognition of alien behaviour should be justification enough for freedom relevant to personal blame. Looked at in this manner, an action carried out freely is an action performed in awareness of the ca-pacity to do otherwise. This awareness of the capacity to do otherwise is the freedom to decide.[221]

The future will show whether there are winners and losers in the discussion on determinism and non-determinism, or whether those involved can find a way to jointly explore the options and models of thinking generated by new findings. At present, SINGER, ROTH and PRINZ among others, are attempting to avoid a legal order of the way things should be which only makes sense if that which should be hasn't already been determined by causal law[222]. In doing so, they are reviving the causal, meaningless doctrine of action and that of pure wrongfulness inherent in the results of the act (*Erfolgsunrecht*). Even the born criminal portrayed by CESARE LOMBROSO as part of first indications of empirical research seems to be gaining in importance in its

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218   LÜDERSSEN, KLAUS, Wir können nicht anders. Ändert die Hirnforschung das Strafrecht? FAZ 4.11.2003, also in: GEYER, CHRISTIAN, (Publisher), Hirnforschung und Willensfreiheit, 2004, p.98.

219   HELMRICH, HERBERT, Das verbiete ich mir im Hirn: Bereitsein ist noch kein Wollen, FAZ 30.12.2003; ders. Wir können auch anders. Kritik der Libet-Experimente, in: GEYER (Publisher), Hirnforschung und Willensfreiheit, p. 92 et seqq.

220   GUSS, KURT, Willensfreiheit oder Beruht das deutsche Strafrecht auf einer Illusion? Borgenteich 2002, p. 91 et seq.

221   BURKHARDT, BJÖRN, Das Magazin 2/2003, Bildgebende Verfahren der Hirnforschung, p. 22 et seqq.; SCHÜNEMANN, BERND, Die Funktion des Schuldprinzips im Präventionsstrafrecht, in: SCHÜNEMANN, BERND (Publisher) Grundfragen des modernen Strafrechtssystems, 1984, p. 153, 163 et seqq.; ROXIN, Strafrecht AT I, § 19 apostille 41. Critical view, HILLENKAMP with a reference that when the first-person perspective turns out to be a fallacy, the illusion of freedom of will is no longer maintainable, JZ 2005, 313, 320.

222   As already given in ZIPPELIUS, REINHOLD, Das Wesen des Rechts, 4th edition, Munich 1978, p. 1.

modern guise.[223] The far-reaching modern findings of brain research accepted by experts cannot and should not in any way be compared with the meagre, error-ridden beginnings of criminological empiricism. Nevertheless, the merits ascribed to early research that not only were there approaches to crime drawn up based on theoretical considerations, but attempts at empirical research were also made[224], that the offender became an object of unbiased research of the facts, are also become more valid in terms of modern methods of examination. It can only be hoped, however, that research today can replace the serious errors of interpretation made in earlier times with persuasive concepts. At present, there is no answer to what the result will be in relation to man's free will. Nonetheless, it does appear doubtful with the level of current knowledge whether, as is being suggested, neuroimaging can ever be used to detect brain defects which indicate a criminal tendency.[225]

This does not, however, mean stagnation. For the question of whether the assertions of the natural sciences with regard to neuroimaging are infallible is less urgent if the interpretations to date do not support the argument of determinism. To this end, some cornerstones of the discussion should be mentioned: the "autonomy" recognised to date in man is not an invention of modern times. The term "autonomy" derives from Greek and can mean both "legality" and "legislation". Its etymological meaning describes the ability and authority to set out laws oneself which are valid for one's own existence.[226] While the existence of this capability is just as impossible to prove as that of determinism, it is a precondition of the legal system, by which it is simultaneously restricted.[227] This can be seen clearly in the catalogue of fundamental rights in the Swiss Constitution. Rights such as the right to live and personal freedom, Article 10, the freedom of religion and philosophy, Article 15, the freedom of opinion and information, Article 16, the freedom of language, Article 18, the freedom of art, Article 21 and economic freedom, Article 27, only make sense if the person bearing these rights is capable of taking decisions freely.

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223   LOMBROSO CESARE, L`uomo delinquente, 2nd edition 1878.
224   According to GÖPPINGER, HANS, Kriminologie, 4th edition, Munich 1980, p. 24.
225   GREENLY, HENRY in an interview, see New Focus of 11.3.2005, p. 1548.
226   HÄRLE, WILFRIED, Autonomie – ein vielversprechender Begriff, in: DERS. (Publisher), Menschsein in Beziehungen, Tübingen 2005 (in print).
227   BURKHARDT, BJÖRN, Und sie bewegt uns doch – die Willensfreiheit, Magazin 2/2003. Bildgebende Verfahren in der Hirnforschung.

But even the less complex laws assume man's freedom to make decisions deliberately. This assumption is very clear in the field of obligation law where it relates to concluding contracts. In criminal law, behavioural norms describing the wrongfulness of the criminal act are only reasonable where they can be followed thus allowing the person acting in breach of the norms to be made responsible for his or her act or omission. The statutory elements of a crime as we understand them today aim to induce their addressee to behave in a manner which conforms to the norms (inductive norms – *Bestimmungsnormen*) and to subject the breaches of the norm to legal evaluation (evaluation norms – *Bewertungsnormen*).

For all that, the legal system does not assume a radical autonomy by which man derives from himself all the laws which are valid and binding for him and exclude others.[228] The constitution of man as a person to whom the norms are addressed is rather based on heteronymous considerations. Thus he or she remains in his or her autonomous approaches dependent on conditions which he himself or she herself has not set but can only make use of.

In order to understand what "free will" as a synonym for "autonomy" means, it is necessary to differentiate between the capacity to execute a self-chosen or self-planned action and that to control and change self will. Härle calls the former "freedom of action" (*Handlungsfreiheit*) and the latter "freedom of will in a narrow sense" (*Willensfreiheit im engeren Sinne*). A free act must – without the need for a more far-reaching reason – be separated from causal processes outside human control, such as volcanic eruptions, lightning strikes, or seaquakes. But even within the course of occurrences which can be influenced by people, not everyone can be deemed to have free will, e. g. an unconscious person falling to the ground, reflex action as triggered by medical examinations. It can hardly be questioned here that even the capacity to control self will is not present. The fact that a person is forced through *vis absoluta* (irresistible force) to act or fail to act, on the other hand, does not lead to a loss of ability to act[229], but to a loss of the

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228   For more on this self-legislation, see FICHTE, J.G., Grundlage der gesamten Wissenschaftslehre (1794), 2nd improved edition 1802 (FW I, Berlin 1971, p. 83-328).

229   Different view BECKERMANN, ANSGAR, Neuronale Determiniertheit und Freiheit, in: KÖCHY, KRISTIAN & STEDEROTH, DIRK (Publisher), Willensfreiheit als interdisziplinäres Problem. Freiburg i.Br. 2006, p. 20 et seq. (according to which, to this end, the freedom to act is removed).

capacity of will in a narrow sense. Even the heroin addict who cannot escape his urge for the next needle although he would gladly do so in principle is not acting freely.[230] And when a person is made through threats to carry out an act against his or her will, this act, although the result of balanced consideration, is by no means autonomous.

These few examples illustrate that people cannot always choose freely, even when they effect a change in the external world.[231] And it corresponds to our understanding of everyday life that if they consciously choose and perform an action, in no way do people act in a random,[232] or arbitrary manner. For purposeful action generally means the decision between several options. The capacity to follow the understanding of the rightness of an act[233] is central to freedom.[234] Nevertheless, in realistic terms free will can only be understood as being influenced not only by external conditions for realisation but also by affective, given conditions, over which people have no influence.[235] Neuroimaging provides important findings in this context in that it traces and interprets how the brain works. The far-reaching consequences arrived at as a result of neuroimaging, however, are controversial and confusing. This is demonstrated by the renowned LIBET experiments, now criticised even by their creator.[236]

The test subjects were asked in this experiment to raise their right or left arm according to no fixed pattern. In doing so, they were required to note

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[230] See BIERI, PETER, Unser Wille ist frei, Der Spiegel, Issue 2, 2005: "Our will is not free when judgement and will diverge [...] it is the case with internal compulsion, where we are subject to an addicted will, against our better judgement. To overcome the lack of freedom and to find our way back to freedom means in each case reuniting judgement and will..."

[231] For a detailed and instructive view, see PAUEN, MICHAEL, Illusion Freiheit? Mögliche und unmögliche Konsequenzen der Hirnforschung, Frankfurt a. M., 2004.

[232] BECKERMANN, in: KÖCHY (Publisher), Willensfreiheit als interdisziplinäres Problem. p. 20 et seq. http://www.uni-bielefeld.de/philosophie/personen/beckermann/neuronale %20determiniertheit.pdf.

[233] This is precisely what an addict cannot do.

[234] BECKMANN, ibid., with reference to JOHN LOCKE'S theory of free will.

[235] HÄRLE, WILFRIED, Autonomie – ein vielversprechender Begriff, in: DERS. (Publisher), Menschsein in Beziehungen; BIERI, PETER, Das Handwerk der Freiheit. Über die Entdeckung des menschlichen Willens, Munich 2001, p. 243: "It is a fundamental error to associate the difference between the freedom and lack of freedom of the will with the contrast between indetermination and determination". Uncritical, SCHIEMANN, NJW 2004, 2056, 2057.

[236] See LIBET, BENJAMIN/ GLEASON, C.A./ WRIGHT E.W. /PEARL, D.K. Time of conscious intension to act in relation to onset of cerebral activity (readiness-potential), in: Brain 106/1983, p. 623-642 and LIBET, BENJAMIN, Unconscious cerebral initiative and the role of conscious will in voluntary action, in: Behav. Brain Sciences 8/1985, p. 529 et seqq.

the time at which they made this decision. Because the motoric activation potential could be identified in the brain earlier than the subjective feeling to decide, human determinism was concluded. LIBET wanted to use these experiments to discover the temporal – and causal – relationship between the conscious, deliberate decision of the subject and the formation of readiness-potential. The result was that readiness-potential was created roughly 0.5 to 0.8 seconds before the consciously-performed movement and 0.35 seconds before the conscious decision. LIBET also showed that the subjects were able to stop the impulse to act before executing the corresponding movement, i. e. that they could "veto" the impulse.[237] The resulting discussion on whether man's behaviour, apparently based on free will, is determined[238] by higher sources and independent brain activity, the so-called readiness potential[239] is a long way from being concluded.[240] LIBET himself has recently said that he is not inclined to abide by his earlier interpretations in this form. He contradicts neurological determinism in his book published in March 2005, "Mind Time. The Temporal Factor in Consciousness (Perspectives in Cognitive Neuroscience)". He claims that the debate between determinism and indeterminism cannot be solved by experiments. The physical events observable from the outside and the mental attributes observable internally are two phenomenologically independent categories. As a result, the brain scientist categorically rejects the reductionist position. Knowledge of neuronal structures and functions (or of their molecular bases) should be sufficient for the definition and explanation of consciousness and mental activity. It is foolish, summarises LIBET with regard to the current debate, on the basis of an unproved theory of determinism to abandon our belief that we have a certain freedom of action and are not pre-

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237 On this, see LIBET, BENJAMIN, Timing of Conscious Experience. Reply to the 2002 Commentaries on Libet's Findings, in: Consciousness and Cognition 12/2003, p. 321 et seqq.

238 ROTH, GERHARD, Das Gehirn und seine Wirklichkeit. Kognitive Neurobiologie und ihre philosophischen Konsequenzen, Frankfurt/Main 1997; HERMANNI F./ KOSLOWSKI, P., Der freie und der unfreie Wille. Philosophische und theologische Perspektiven, Munich 2004.

239 On the discovery of the so-called readiness-potential, which is measurable in the brain directly before an arbitrary movement, see KORNHUBER H.H./DEEKE, L., Hirnpotentialänderungen bei Willkürbewegungen und passiven Bewegungen des Menschen. Bereitschaftspotential und reafferente Potentiale, in: Pflügers Archiv für die gesamte Physiologie 284/1965, pp 1-17. In this, comments on how to stop the movement, i. e. as LIBET said – to impose a veto. The design and interpretation of the LIBET experiments is today the object of lively debate in which their significance is being controversially discussed.

240 From the field of criminal law, see critical view in REINELT, EKKEHART, Entscheidungsfreiheit und Recht – Determinismus contra Indeterminismus, NJW 2004, 2792 et seqq.; affirmative view SCHIEMANN, ANJA, NJW 2004, 2056 et seqq.

programmed robots. There is an unexplained gap between the category of physical phenomena and that of subjective phenomena.

These self-critical remarks by LIBET, while not going to end the discussion on free will, make an important statement. In addition, ROTH und SINGER themselves admit that brain research has "just begun to examine the world of feelings" and that, in spite of neuroimaging, by no means are "all the tools available in order to analyse the complex functions of the brain".[241] ROTH writes in his book "Fühlen, Denken, Handeln": "Whether this all works exactly as I have described remains to be determined through further research". Related to this, the misconception claimed by SCHOCKENHOFF, KEMPERMANN and KRÖBER[242] must be observed in which they vehemently argue against the competence of the neurosciences with regard to their conclusions in the field of ethics and philosophy.

Consolidating these findings and imponderables together into an overall view, it appears at present as if the new insights on the brain and how it functions produced by neuroimaging has not significantly changed our previous knowledge of free will.[243] The fact that man makes decisions on a materially-subsumable basis does not allow for any compelling conclusion on the lack of free will and responsibility under (criminal) law.[244] The view of man held by the legal system largely reflects the specific cognitive and emotional capacities which separate man from other beings. Were neurobiology to deliver a neuronal explanation for these capacities, this would not necessarily mean that these capacities do not exist.[245] Were one to place human behaviour in an overall context in which a distinction was made between positive action and non-action, purposeful behaviour and randomness, this would mean in addition that deliberations can precede human

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241 ROTH, GERHARD, Das Ich ist nicht Herr im Hause, Das Magazin 3/2001, p. 32 et seq.; SINGER, Menschenbild, p. 23.

242 SCHOCKENHOFF, EBERHARD, Wir Phantomwesen, Frankfurter Allgemeine Zeitung of 17 November 2003, p. 31 (Feuilleton), KEMPERMANN, GERD, Infektion des Geistes, Frankfurter Allgemeine Zeitung of 2 March 2004, p. 37 (Feuilleton); KRÖBER, HANS-LUDWIG, Das limbische System – ein moralischer Limbus, Frankfurter Allgemeine Zeitung of 13 November 2003, p. 37.

243 See HILLENKAMP, JZ 2005, 313, 319 et seqq.

244 KRÖBER, HANS LUDWIG, Der Begriff der strafrechtlichen Verantwortlichkeit, in. GEYER, CHRISTIAN (Publisher) Hirnforschung und Willensfreiheit, pp 103, 109; LÜDERSSEN, KLAUS, Ändert die Hirnforschung das Strafrecht, in: GEYER (ibid), pp 98, 101; BIERI, PETER, Der Spiegel, Issue 2 2005.

245 BECKERMANN, ANSGAR, GEHIRN&GEIST 3/2005, pp 59, 61.

behaviour, with whose help alternatives can be evaluated, considered and ultimately reflected in a decision. Consequently, man is often in a position to offer reasons for his actions. This experience belongs to the category "freedom of action".[246] To the extent that brain research can provide no clear arguments for action which is not free, and given the current level of knowledge, much speaks for the fact that the freedom to make decisions remains the freedom to make decisions even on the basis of neuronal processes.[247]

21.4   Conclusion

The merits of neuroimaging are extensive and undisputed. That this is accompanied by a decoding of consciousness in the sense of determinism, of *l'homme machine*, cannot be concluded according to the current stand of knowledge. Nonetheless, an increased use of neuroimaging in biological methods of research will be able to make an important contribution to a greater understanding of biologically-damaged brain processes, also with respect to criminal offenders, and will probably inform future prognosis and therapy decisions. The current findings of modern brain research, however, do not refute freedom of action and will in the form in which they are idealised as the basis for the Swiss legal system. A paradigm shift in the legal system is at present neither necessary nor required. The conclusions for criminal law that in future there will be no more punishment, only people in custody, that delinquency is reduced to – genetically-influenced – fate and the possibility of resocialisation rejected is a scenario with much resonance with the public at large. There are currently no sufficient indications that this corresponds to reality.

The rudimentary and inconsistent legal situation with regard to the permissibility of neuroimaging as part of human research is in need of legally clear, modern rules standardised across the Federation. At present, the

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246   Reference is correctly made to the importance of deliberation and reasoning for man's freedom in BIERI, PETER, Das Handwerk der Freiheit. Über die Entdeckung des eigenen Willens, Frankfurt/Main 2003.

247   BECKERMANN, ANSGAR, Willensfreiheit – nichts als eine Illusion? Pressedienst Forschung 24/2005, University of Bielefeld, p. 12.

provisions are oriented around fragmented federal law and patchy cantonal law. In addition, the fundamental rights, particularly those provided for in the Swiss constitution, must be observed. Given the high importance accorded to the (continuing) protection of the person, neuroimaging and the storage of information produced requires consent. Where neuroimaging on the brain dead in the broadest sense serves the interest of the deceased or his close family, the extended consent solution is appropriate.

The use of the personal data thus gleaned is restricted in principle to solving the problem in respect of which the person concerned or his family members consented. Nevertheless, consent or an order, however wide-ranging, justifies neither measures which were unlawful at the time of its declaration nor measures which at the time of their execution were unlawful. Special basic principles apply with respect to the further use of anonymous data.

Much yet remains to be done. The high complexity of the brain as an object of research not only requires intensive medical-scientific research, but is of concern also for the social sciences and humanities. A strengthened public discussion will help remove unreasonable fear of neuroimaging. At the same time, any risks should be uncovered before they reach a potential to cause damage.

22   Summary and conclusions

22.1   What is brain imaging? What is it used for?

In recent years, powerful neuroimaging methods have been developed which open up unprecedented ways of exploring the human brain. This toolbox comprises computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), and near infraread spectroscopy (NIRS) to name only the currently most important methods. In addition, electroencephalography (EEG), magnetoencephalography (MEG), and variants of transcranial magnetic stimulation (TMS) techniques are used in the context of brain imaging studies as supplementary tools.

The basic principle of neuroimaging is the mathematical construction of brain tissue on the basis of physical measures using computers and sophisticated software for processing the vast amount of quantitative raw data. The measurements are related to precisely defined and reconstructed parts of the brain. Thus, it is recording *and* reconstruction which is the essence of neuroimaging. The results of such experiments are often presented as colourful visual maps or "brain pictures". Brain imaging methods include both anatomical techniques and functional techniques.

Anatomical techniques comprise computed tomography (CT) and structural magnetic resonance imaging (sMRI)(chapter 4). With the help of these techniques, "constructed" images of brain structure can be created. Anatomical neuroimaging is widely applied today in clinical neuroradiology and neurosurgery (chapter 12).

Functional techniques either record direct measures of neural activity, e. g. electrical activity or magnetic fields associated with neuronal activity, as with EEG and MEG, or are based on indirect measures by recording changes in local metabolic activity or local blood flow due to neuronal activity, e. g. with the help of PET, SPECT, fMRI and NIRS (chapter 5). These techniques create a series of dynamic brain images reflecting ongoing brain activity. Presently, the functional techniques are of major importance in

cognitive neuroscience (chapter 15), but also in biomedical and pharmaceutical research (chapter 14) whereas only few procedures are already applied in clinical settings.

Moreover, molecular imaging, employing different modalities such as PET, SPECT, MRI/MRS and MR microscopy, is rapidly gaining importance in biomedical and pharmaceutical research (chapter 5.6). Molecular imaging fuses the disciplines of molecular biology, genetic engineering, immunology, cytology, and biochemistry with imaging: by using highly specific imaging probes with high affinity for biological targets, subcellular structures, functions, properties and metabolism become amenable to imaging. In this way, it is expected to gain invaluable insights into the biological mechanisms underlying many disease processes, to speed up the development of new drugs and to improve the sensitivity and specificity of diagnostic procedures.

The above-mentioned neuroimaging modalities differ from one another in the

- underlying measuring principle,
- spatial and time resolution as well as the specificity and sensitivity of the measurements, and the signal-to-noise ratio,
- ease of use, and
- the requirements, sophistication and costs of the required equipment, devices and auxiliaries, ranging from several ten thousand € for EEG up to several million € for state-of-the-art MRI scanners (chapters 7 and 18),

thus requiring a careful choice of the appropriate technique for the question that is to be answered. Because each of the imaging modalities has its specific strengths and weaknesses, full information can often only be obtained by combination of different modalities. This requires, on the one hand, that new methods for digital image processing and registration are implemented to merge data from sequential analysis by different modalities. On the other hand, devices which combine different modalities in one device are also required. Combined PET-CT-scanners are already on the market, PET-MRI-systems are in development, and often, the relatively slow but spatially precise methods fMRI and PET are combined with EEG to exploit the latter's excellent time resolution.

All in all, the different neuroimaging methods in their combination allow brain imaging on different spatial levels from gross anatomy down to genes and molecules. What distinguishes neuroimaging from other methods usually applied in neuroscience is that they open up the possibility to analyse human brain anatomy as well as *function*, and that this can be done non-invasively and in vivo, i. e. in living humans. As will be outlined in more detail below, the unique combination of properties of these methods leads to

- a new quality of our understanding of the brain,
- new avenues of brain research within neuroscience, especially in cognitive neuroscience,
- a stimulation of other scientific disciplines than neuroscience, e. g. psychology and related disciplines,
- method-driven bridges between formerly distinct scientific disciplines, leading to new synergistic research questions and directions,
- improved or novel clinical diagnostic procedures and therapies.

22.2 Attractiveness and public perception of brain imaging

Brain imaging enjoys a high attention not only in clinical and research settings, but also e. g. in the media, among politicians, and in the general public. Several factors contribute to this attractiveness for non-experts:

- *Brain as research object*. Because the brain plays an important role in what makes humans human, knowledge arising from brain research is expected to have considerable cultural, social, economic and health impacts and is therefore also of interest for non-experts.
- *Cognitive functions as research topic.* As brain imaging increasingly addresses neural mechanisms underlying typically human higher cognitive functions, personality traits and psychological states, practical applications outside research settings emerge, and social and policy implications become evident.
- *Brain images.* Brain imaging has become highly visible – also literally. Within cognitive neuroscience, the visual maps reflect the experimental strategy that measures and explores brain functions quantitatively, and

the visualisation is a means to present the vast amount of quantitative data, that have to be specifically processed and interpreted, in a form that can be grasped by the researcher. Beyond the neuroimaging community itself, the images are often seen as aesthetic[248] pictures showing "the mind at work". On the one hand, there is some evidence that the visual element plays a role in the attractiveness of this research to the media (Dumit 2004). In this sense, the brain images clearly fulfil a popularising role for cognitive neuroscience, and even have attained iconic status for "the mind in the brain". On the other hand, the impression that by seeing brain images, the essence of a complex experiment can be understood even by the lay-man bears the risk of simplification and over-reliance on the method without taking its limits into account ("it is believed what is being seen"). It also bears the risk of reductionism, in the sense of that "one understands the brain by seeing it" (Beaulieu 2002; Racine et al. 2005).

- *Brain imaging as "hard cutting-edge science".* Brain imaging is often – and mistakenly – presented and perceived as direct, intrinsically objective and accurate "hard science". The expensive high-tech instrumentation and the representation of results as visual maps of the brain in action may have contributed to this notion, especially if brain imaging is contrasted with disciplines such as psychology, pedagogy, marketing research, philosophy etc. which investigate, among others, related research topics. The latter are often – again mistakenly – perceived as "soft science" which seem to base their findings more on opinions than on empirical data and usually do not employ highly sophisticated instrumentation. This contrasting is, however, undue and hinders the exploitation of synergies between the different disciplines.

The attractiveness of neuroimaging even to non-experts has positive as well as negative aspects: It helps to mobilise resources for brain imaging research (albeit possibly to the detriment of other research fields), and a certain alertness to this research field can be considered a good starting point for embedding this research field into a public debate about its goals, applications and frame conditions for its use (see also Illes et al. 2005). On the other hand, "neuromyths" and misconceptions of potentials and limits of these methods abound, both on the supply and demand side of neuro-

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248   or, with a negative connotation, "pretty pictures"

imaging findings. Moreover, the presentation of this research field and its possible applications and impacts in the public is strongly biased towards the extremes of both potentials and benefits on the one hand, and on potential unintended or disruptive impacts on the other. This is in part inevitable and can be attributed to the logic of the mass media and to how some exposed proponents of the debate present their provocative positions. However, the majority of correcting and mediating voices may be overheard, and the exploitation of synergies between neuroscience and other scientific disciplines may be delayed by an – unnecessarily – polarised debate.

22.3   Actual and future applications of brain imaging – overview

The scope of actual and potential future applications of neuroimaging is broad: In addition to its invaluable contributions to basic biological and biomedical research, neuroimaging is firmly established and still expanding in clinical diagnosis, monitoring of disease progression, neurosurgery, and pharmaceutical research. Neuroimaging has had, and continues to have, a significant impact for the study of cognition, leading to the new discipline of cognitive neuroscience. It is this field which is of special relevance for a technology assessment study of neuroimaging: Because sensations and movements, but especially higher cognitive functions such as emotions, language, memory, intelligence, creativity, thought, behaviour and social interaction have become a focus of this research field, brain research increasingly touches upon topics with evident social and policy implications. As outlined in this report one can identify a growing interest to extend the application of brain imaging into new fields, ranging from screening and prediction of cognitive abilities and performance or aberrant behaviour to lie-detection and "mind-reading" or tailoring marketing activities. This, on the one hand, underlines the power of the methods, but on the other hand raises many questions, such as

- What is the validity and explanatory power of brain imaging for possibly far-reaching judgements about a person's cognitive abilities and behaviour?

- For which purposes will or should these techniques be applied?
- What could be the possible impacts, both desired and unintended?
- How could frame conditions be shaped in order to influence the development?

These actual and potential uses and applications as well as the relevant frame conditions and related possible impacts will be outlined in more detail below.

22.4   Actual and future clinical applications of brain imaging

22.4.1   Present state

At present, the majority of brain imaging devices are installed in clinical settings, both in hospitals as well as in radiologists' practices. This is the main market where MRI, PET, and CT scanners are sold and the manufacturing companies design their products exactly for this purpose. In international comparison, Switzerland is among the best-equipped countries (e. g. according to OECD health data, 18 CT scanners and 14 MRI units per million population; a total of appr. 110 MRIs for human use installed). In clinical settings, the majority of neuroimaging procedures are anatomical techniques whereas only few functional methods have already been developed to clinical applicability. In addition to scientific-technological progress, reimbursement decisions by the national health insurances play a major role in the question to which extent new clinical applications of neuroimaging are really applied in clinical practice.

MRI is the most important diagnostic tool in neuroradiology, and approximately 50 % of all clinical MRI procedures can be attributed to neurology. MRI has become an important standard tool in, e. g. the differential diagnosis of various brain tumours, in planning brain tumour surgery and neuropsychological rehabilitation, and in investigations of brain vasculature, such as aneurysms, pathological changes of vasculature, and in assessing potentially salvageable tissue after stroke damage. In multiple sclerosis, MRI is routinely applied to detect areas of sclerosis in brain and spinal cord, and to monitor an MS patient's response to MS therapies. Brain imaging is also

applied for detecting acute inflammation in the spinal chord, to support diagnosis of CNS infections and for diagnosing cortical dysplasia. Brain imaging methods have also made it possible that neurosurgery has gained unprecedented anatomical and spatial precision. They do not only provide detailed information for neurosurgical planning. With the help of specific interventional MRI scanners, MRI images are acquired during the surgical intervention and support and guide the neurosurgeon with high spatial precision.

For other neurological diseases, brain imaging methods are either used as supplementary diagnostic information or in the context of biomedical research, but have not (yet) attained the status of a standard tool. An example is Alzheimer's Disease (AD), a major public health and social challenge in the coming years (chapter 13). Currently, only few therapies are available which, at best, may transiently slow down the progression of the disease, but do not significantly modify the course of the disease. Against this background, it has been suggested that neuroimaging could help to diagnose AD in very early stages of the disease of only very mild cognitive impairment and minimal damage to brain tissue and function. The hope is that therapeutic interventions, provided already at these early stages, could considerably delay the onset of severe symptoms, thus prolonging the symptom-free period and shortening the period of severe impairment until death. Despite significant progress in AD research in recent years and the development of diagnostic protocols for different modalities, such as EEG, MEG, MRI, FDG PET and SPECT and molecular imaging (for details, see chapter 13), their use in early AD diagnosis is mainly confined to research settings or highly specialised centres. For the time being, neuropsychological test profiles are presently the most sensitive, reliable and valid means to diagnose dementia in routine clinical practice. Whether neuroimaging diagnostic procedures for age-related dementias will reach clinical maturity in the coming years remains to be seen: not only are further standardisation, validation and improvements in terms of accuracy, specificity, sensitivity and cost-effectiveness and their adaptation to routine clinical practice required, but also more effective therapeutic interventions are needed that could be offered to those patients for which a high risk of developing AD could be detected.

22.4.2   Trends

At present, there is a trend of replacing standard imaging equipment by multi-modality devices (e. g. replacement of PET by PET-CT) or by high-performance scanners (e. g. upgrading MRI to high field MRI scanners with magnetic field strengths of 1.5 Tesla or even very high field MRI scanners with 3 Tesla[249]). These high-tech devices offer, on the one hand, improved performance and functionality, but, on the other hand, also significantly contribute to enhancing the reputation of the respective institution. Purchase decisions may, therefore, not be solely driven by medical needs.

In order to broaden the range of clinical applications of medical imaging in general, and neuroimaging in particular, there is a trend to integrate medical imaging into all stages of health care delivery: As exemplified for Alzheimer's Disease (chapter 13), there is a trend to screening and disease diagnosis in very early stages. In this way, medical imaging could substitute or complement many biochemical or psychological tests or diagnostic surgical procedures. Challenges lie in developing imaging devices with high throughput of patients which allow the screening of large patient numbers in acceptable time and at acceptable costs. Moreover, selectivity and specificity of the diagnostic imaging procedures must be substantially improved in order to avoid false positive or negative results. Neuroimaging will increasingly be applied for the choice of appropriate therapeutic interventions (e. g. stroke) and for monitoring their effects on the progression or regression of disease (e. g. multiple sclerosis). There is also a trend towards integration of diagnosis and therapy into one procedure. An example is the gamma knife which is used for the localisation and destruction of acoustic neuromas, i. e. tumours of hearing nerves adjacent to the brain. Moreover, image-guided interventions, e. g. in neurosurgery, are developed further (chapter 12.2).

22.4.3   Challenges and needs for action

Despite the undisputed merits of neuroimaging for clinical practice, advanced medical imaging devices are costly and rather complex devices. In order to fully exploit the technological capabilities of the sophisticated devices and to obtain valid results, specific expertise in data acquisition,

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249   and even 7 Tesla for some MRI scanners used for research purposes.

analysis and interpretation is required. Moreover, the device must be specifically tuned for the respective diagnostic question. Device manufacturers develop such "application-specific sequences" which allow a "push-button use" of the imaging devices for different routine diagnostic procedures. As outlined in chapters 12 and 13, a broad range of brain imaging procedures have been and are being developed in biomedical research which bear the potential of being used beneficially in clinical practice. While these procedures may work well in highly specialised and specifically qualified institutions, significant additional efforts have to be taken to make these procedures applicable in routine clinical practice. In view of the severity of many brain-related diseases and disorders, the sensitivity of the information obtained with these methods, the often predictive character of the diagnosis, and, for certain diseases and disorders, the lack of effective, disease-modifying therapies, it is most important that there is no premature application of not sufficiently substantiated findings or of not sufficiently validated procedures in the clinic. However, existing structures and incentives in both biomedical and clinical research may not be fully supportive of making research procedures applicable to routine clinical practice.

On the other hand, the ready availability of the required technical equipment in Switzerland in hospitals and radiologists' surgeries, the economic need to work these devices to capacity in order to return the high investment costs, the reputation-building effect of the high-tech equipment, and demand from patients (see e. g. Illes et al. 2004a) may act as incentives to apply neuroimaging even beyond the medically necessary and reasonable level.

Against this background, there is a need to actively strive for this transfer from research to clinic, e. g. by providing specific incentives and institutional settings for both biomedical research as well as clinical research in order to make imaging procedures, that work in research settings, applicable in routine clinical practice. In view of the high direct costs associated with neuroimaging, but also its innovative and cost-saving potential if the full course of a disease and its management is taken into account, health technology assessments as well as health economic analyses are required as an integral part of this effort, in order to make possible the clinical application of those neuroimaging procedures which offer a well-balanced cost-benefit ratio. It could also be considered on a case-by-case basis whether these procedures should – until sufficient standardisation and validation –

be restricted to special centres where the requirements outlined above can be met. Similar models, have, for example, been implemented for genetic testing of inherited breast cancer susceptibility.

Moreover, the complexity of neuroimaging devices is increasing, the range of neuroimaging clinical applications broadening, while radiologists trained in the use of CT and x-ray may not be familiar enough with MRI, and neuroimaging may also be performed by radiologists who may not have the specific expertise of neuroradiologists. In view of the fact that presently no specific formal qualification (*"Fähigkeitsausweis"*, proof of special knowledge) is required in Switzerland for conducting brain imaging, and in analogy to the experience made during the broad introduction of ultrasound into the clinic, it is not unlikely that sub-standard application of neuroimaging techniques may occur outside specialised centres. However, the responsible doctor, psychologist and even the researcher have a legal obligation to the person to be examined to use those methods which satisfy the current state of the art. In case of severe negligence of the state of the art in neuroimaging and non-compliance with existing regulations, substandard neuroimaging could be regarded and prosecuted as bodily harm or assault (see chapter 20). This implies, on the one hand, the need to regularly adjust the present regulations for the safe operation of the devices to scientific-technical progress, as outlined in chapter 22.6.4 below. On the other hand, in Switzerland the doctor-patient-relationship which is relevant in this context is presently regulated mainly by cantonal laws which differ from one another in several aspects. In view of the aim of legal certainty, a federal act might be taken into consideration which establishes uniform regulations across the Federation. On the other hand, both the Federal Constitution with its guarantees of personal rights and human dignity as well as standards elaborated by the medical professions with respect to the patient-physician-relationship seem suitable to solve the problem of "neuroimaging as bodily harm" appropriately, so that a federal law might be desirable, but is not urgently needed.

Given the complexity of the methods and the sensitivity of personal information that can be gleaned through brain imaging, specifically qualified staff in well-organised institutions is mandatory. Therefore there is a need to pay specific attention to high professional standards in qualification and to quality assurance aspects. It should be explored in further studies to which extent quality assurance in neuroimaging should be improved, e. g.

by taking the following options into account: a restriction of brain imaging to staff and institutions which comply with certain quality and qualification requirements as well as a restriction of brain imaging to certain purposes which are to be defined by law.

22.5   Actual and future applications of brain imaging in cognitive neuroscience research

22.5.1   Present state

Before the development of non-invasive brain imaging methods, examinations of the brain were mainly restricted to post-mortem brains which only allow structural and anatomical analysis whereas brain functions were explorable mainly through psychological experiments or through electroencephalographic measurements from the human scalp. With modern brain imaging methods, the brain of living persons became accessible in a new way. Thus, the biological basis of brain functions and dynamic brain processes became a focus of research in neuroscience in the 1990s, first the neural basis of motor and sensory functions, followed by cognitive and emotional processes. In turn, also cognitive psychology, a major scientific discipline in the 1960s and 1970s, experienced a significant stimulation by brain imaging methods. The term "cognitive neuroscience" was coined to describe this new research trajectory. Experimental paradigms and knowledge from cognitive psychology form the indispensable basis for conducting meaningful and well-designed neuroimaging experiments, illustrating the synergies and convergence between formerly separated scientific disciplines.

Viewing the brain from this new perspective revealed a new quality for the study of the brain and brain functions and altered our understanding of this organ significantly: the brain is now seen as a complex organ of extraordinary individuality and plasticity, which shows dynamic self-organisation in response to stimuli, and which significantly matures and changes during individual development (chapter 15.3).

Cognitive neuroscience studies the biological basis of cognition and emotion. Psychological processes usually subsumed under the topic "cognition"

are attention, perception, action, motor behaviour, and typically human higher cognitive functions such as language, intelligence, reasoning and problem-solving, memory, learning, reading, writing and calculating. "Emotion" covers processes such as feeling, affect, reward, motivation, leanings and preferences, social behaviour, and altruism. All these are fundamental psychological functions necessary for all kinds of behaviour, and well-designed brain imaging experiments significantly contributed to subtly fractionate the brain processes that underlie cognitive functions and human behaviour. This approach has proven to be especially fruitful in order to

- gain insight into the biological basis of these psychological phenomena (e. g. involvement and interplay of specific brain areas),
- suggest mechanisms how the psychological phenomena arise, and to better understand the prerequisites for normal cognitive processes (e. g. the ability to recognise and manipulate component sounds in words for successful reading learning),
- support, build and refine existing models of cognitive functions, emotions and resulting human behaviour,
- identify and discriminate between alternative mechanisms, causes and etiologies,
- suggest new hypotheses that would not be imagined without knowing something about the underlying processes,
- support decisions about the requirement, timing and type of appropriate interventions to develop normal or remedy impaired cognitive functions, and
- monitor the effects of interventions if they are not observable at the level of behaviour.

These studies are not only of interest for basic neuroscientific research, but also in psychological and neurological research. It is a mandatory requirement that the phenomenon under investigation must be well-studied and well-described at the psychological level before the neurological basis of that phenomenon can be investigated by neuroimaging. In this way, neuroscientific approaches heavily rely on findings from cognitive psychology. However, neuroimaging cannot answer the question *how* a suitable and effective intervention should be designed in detail. This is the core competency of other disciplines, e. g. of learning and instruction research and pedagogy in the case of devising effective instructional practices in learning

and education. This again underlines the importance of interdisciplinary approaches in cognitive neuroscience.

22.5.2   Trends

Broadening the scope of persons subjected to neuroimaging, changes in purpose and context

The non-invasive nature of brain imaging methods in synergy with the study of cognition has led to a significant expansion of the range of humans who are subjected to an analysis of their brain: Brain imaging is no longer restricted to the medical context in which persons with impaired brain functions are examined for diagnostic or therapeutic purposes. It is also applied to the brains of healthy adults, of children, of unborn, of persons in coma vigil or in the vegetative state (Laureys 2005), of dying persons or of dead bodies for research purposes. Volunteers who are subjected to neuroimaging in the course of cognitive neuroscience studies often do not have a direct benefit from neuroimaging – which is in contrast to neuroimaging in the medical context. This results in the need to specifically assess the safety and applicability of neuroimaging procedures to the target group (e. g. the presently insufficient knowledge of long-term exposure or exposure to very strong static magnetic fields during MRI on pregnant women, on fertility and development, see chapter 6; the possibility of incidental findings, see chapter 9.3) in order to carefully balance risks and benefits, and this even more so, if persons with impaired ability to give informed consent are affected (for details see chapter 22.6.1 below).

A characteristic property of neuroimaging data is that they are acquired, processed and stored in digitised form. This makes it possible that data processing, data analysis and data interpretation can be done on "virtual brains", reconstructed from stored imaging data. As a consequence, the analysis can be separated spatially and temporally from the physical neuroimaging investigation and from the direct involvement of the patient or research subject. This creates challenges for privacy and data protection which are outlined in more detail in chapter 22.6.3.

The challenges for obtaining valid informed consent, for data protection and privacy, for balancing benefits and risks which arise from neuroimaging are analysed in more detail in chapter 22.6.

Emerging applications for neuroimaging beyond research contexts

The stimulation of both neuroscience and cognitive psychology by neuro-imaging in the 1990s has already been outlined above. Although the impact on other disciplines is difficult to predict, current research lines suggest that neuroimaging continues to stimulate a large number of diverse scientific disciplines, formerly separated from neuroscience. In this report, we have highlighted as examples pedagogy, economics, forensic psychology and philosophy (see chapters 15 and 16), but the list may, without effort, be continued. A typical example is the discussion within philosophy and psychology about the human self and consciousness which, in recent years, has been strongly influenced by brain imaging. Some influential cognitive neuroscientists even notice a change in the concept of man (*"Menschenbild"*). Although this view is heavily disputed, the discussion demonstrates the vividness and importance of these ideas.

By critically evaluating the relevance of brain imaging techniques and findings, and by adopting, adapting or complementing these methods for and by their discipline, method-driven synergies begin to be exploited. This even leads to "hyphenated disciplines", such as neuro-economics or neuro-pedagogics. It bears the potential that *new* research questions can be addressed along the lines presented above for cognitive neuroscience which are beyond the scope of each "mother discipline". However, there seems to be a fine borderline between an exploration of the useful applicability of brain imaging in these related disciplines with the aim to strive for true interdisciplinarity and new research questions, and a "mere" adoption because brain imaging is "fashionable", is often – and mistakenly – presented and perceived as direct, intrinsically objective and accurate "hard, cutting-edge science" and therefore may help to acquire research resources and improve one's reputation.

Because of the tremendous pace with which cognitive neuroscience investigates human behaviour and neuroimaging is taken up by application-oriented scientific disciplines, there is a need to clarify to which extent

neuroimaging and the knowledge achieved with these techniques can be applied outside research contexts, in "everyday life". Emerging research lines which spontaneously evoke objections in the public comprise the assessment of brain-behaviour relationships in the context of personality research, predictions of future behaviour and of intellectual capabilities. Although these research lines have been followed for decades with "conventional" methods, they will most likely attain a new quality in public opinion if brain imaging methods are applied. This is due to the laymen's perception that the more or less "fungous" and vague concepts from psychology are now related to allegedly "precise" information about brain functions. Although many scientists having a reputation in cognitive neuroscience are reluctant whether brain imaging will ever be able to provide a deep and unbiased insight into human personality and subjective processes (e. g. due to the unsolved first vs. third person problem, see below) it is necessary to constantly inform the public about ongoing research endeavours in this field and to implement appropriate legal provisions and procedures to prevent misuse and over-rating of these methods.

In this report, several examples were analysed to illustrate this trend: How could neurocognitive studies of human learning be used to facilitate learning and to improve formal education in schools, with the overall goal to fully unfold the cognitive abilities of children, pupils and students? The analysis in chapter 15.3 showed that some popular beliefs about what brain science can actually deliver to education are quite unrealistic. The term "neuromyths", coined by the OECD, demonstrates the ease and rapidity with which findings from cognitive neuroscience have translated into misinformation regarding education, and pseudoscientific educational advice and tools for "brain-based" education are offered which are mainly oversimplified and too general to address the crucial issues how to improve education and learning effectively. At best, these pseudoscientific advice and tools are only ineffective and do not do any direct harm. However, they imply a misallocation and waste of resources for ineffective instead of effective measures.

Neurocognitive research into human decision-making has not only been taken up by behavioural economics, but is currently also exploited for product marketing and marketing campaigns. Several market research companies in the USA and Europe have specialised in neuromarketing, and neuromarketing experiments are also carried out by academic neuroimaging

centres on an occasional contract research basis for commercial customers. Although up to now, the neuroimaging studies carried out in the context of marketing research have not yielded any findings which go beyond what is already well-known from classical psychological tests and cannot provide detailed information of how effective marketing instruments should be designed, much of the hype currently associated with neuromarketing can be attributed to the concern – or hope, respectively – that very private thoughts and preferences could be revealed, even without the subject's knowledge or cooperation, and that this could be used to tailor products or campaigns in a way that a new quality of manipulation and induction of unwilled behaviour could be achieved.

Research is also underway which aims at elucidating whether neuroimaging could be an appropriate tool to support established methods in forensic psychology. Presuming a certain demand by several stakeholders such as secret services, military forces, police and criminal justice, especially in the USA in the frame of "homeland security", associated fears and concerns are that brain imaging may be used for "mind-reading" or reading people's private thoughts and feelings, e. g. in the sense of a polygraph, even without their consent and cooperation, or that it could be inferred from brain imaging to deviant or even criminal behaviour, addiction, a person's preferences, e. g. with respect to sexuality, or race, or to establish responsibility and guilt of criminal suspects. Because undue application, misinterpretation and overrating of neuroimaging may have far-reaching and detrimental consequences for the affected persons, extreme caution must be paid to quality assurance and the methodological limits of neuroimaging here.

On the one hand, the above-mentioned concerns seem to be justified in view of the following trends: It can be presumed that a certain demand exists to use neuroimaging methods in diagnostic and predictive ways outlined above, at least latently and for some stakeholders. Moreover, the use of neuroimaging methods in diagnostic procedures for a large variety of normal and impaired cognitive functions is the goal of many research groups in order to refine and complement existing psychological and psychiatric diagnostic tests. And finally, several – albeit still few – applications, ranging from pseudo-scientific brain-based learning tools to neuromarketing studies have reached the marketplace.

On the other hand, the concerns of "mind-reading" and far-reaching infer-ence on one's personality by neuroimaging alone are clearly not supported by the present state of the art in cognitive neuroscience: With respect to the methodological limits of neuroimaging for the study of cognitive processes, it has to be kept in mind that the psychological phenomenon of interest usually is a complex cognitive or emotional one which requires operation-alisation, i. e. dissection into sub-processes and reduction of influencing factors in order to become amenable to a neuroimaging experiment. On the one hand, this requires input from cognitive psychology how to design meaningful experimental settings, on the other hand additional restraints on the experimental setting come from the required imaging equipment, which, for example in the case of fMRI, require the research subject to lie in the bore of the magnet and to avoid head movements (see chapter 10). All in all, this may lead to a highly artificial and abstract test situation which re-quires careful assessment to which extent it really represents the cognitive process and behaviour which was intended to be studied. It also requires a critical discussion to which extent inference can be made from artificial test situations to human behaviour in "normal life" outside experimental settings. Additional limits lie in the incomplete knowledge about the mechanism by which the measured signal is correlated with cognitive brain processes – what does for example the BOLD response tell us about the underlying physiological processes? In addition, it is difficult or even impossible to infer from brain images underlying processes like subjective feelings or covered thoughts. This problem is currently intensively debated and many philosophers and psychologists believe that the first person perspective cannot be explored from the third person perspective (like brain imaging) because of insurmountable differences between both perspectives.

Moreover, many neuroimaging methods require the comparison of one cognitive state (e. g. active, or impaired function) to another (e. g. passive, base-line, or normal function). Because most brain processes show a sub-stantial intraindividual as well as interindividual and temporal variability, an acceptable signal-to-noise-ration requires the integration of many repeated measurements in one individual over time, or the averaging of data from many subjects. This implies that many cognitive abnormalities that charac-terise particular deficits or deviations can only be demonstrated by brain imaging when small groups of subjects are compared to control subjects. Brain imaging is not diagnostic at the level of an individual with certainty, unless other psychological and psychiatric tests are additionally applied. To

improve neuroimaging for these purposes, a higher sensitivity and specificity, and a much more refined normalisation of data and comparison against better standards would be required. As the results of complex brain imaging experiments are often presented as colourful visual maps, this conveys the impression of neuroimaging being a direct probe of brain functions, and that the essence of a complex experiment could be understood even by the layman. However, this bears the risk to forget that these visual maps are the result of extensive raw data processing, and that the results strongly depend on the chosen data processing procedures and subsequent data interpretation. All in all, this bears the risk of simplification and over-reliance on the method without taking its limits into account ("it is believed what is being seen"). It also bears the risk of reductionism, in the sense of that "one understands the brain by seeing it".

A very important point is that functional brain imaging methods probe the neural basis, the *mechanisms* of brain functions. This must be strictly distinguished from *contents* of cognitive processes which are not inferable from brain imaging. Therefore, "mind reading" is definitively beyond the scope of brain imaging, and it can only be speculated whether this might become possible in the future.

In general, brain imaging methods used in the realm of cognitive psychology have not yet advanced to a stage in which their diagnostic specificity and sensitivity goes beyond established psychological and psychiatric diagnostic tests, and their application in psychological research has mainly confirmed from a different analytical perspective what was already known before, albeit they may provide additional and complementary tools. Presently, the state of the art in cognitive neuroscience does not support the application of neuroimaging beyond well-controlled research studies. It also does not support to make far-reaching assessments about cognitive abilities, personality, future behaviour, or ability to lead a fulfilled life. Because of the possibly far-reaching consequences for the individual's self-image, perception by others, future behaviour, and future way of living there is a need for safeguards against the premature application of not sufficiently substantiated findings.

22.5.3   Challenges and needs for action

Structures and governance

In order to exploit the potentials of brain imaging for the study of cognition and emotions further, one must look at the structures in which brain imaging is conducted: most brain imaging methods require major investments into the sophisticated, expensive equipment, into buildings, installations and supplies, as well as into qualified staff to operate the devices. In addition, supportive infrastructure such as brain image databases and brain atlases are required. At present, the majority of devices are installed in clinical settings, whereas there are only relatively few research-only brain imaging centres worldwide, some of them located in Switzerland. As a consequence, the majority of cognitive neuroscience research is carried out with scanners in clinics in peripheral hours when patients' examinations have been completed. Against this background, the extent, ease and conditions of access to brain imaging equipment for researchers has an important gatekeeper function for brain imaging research, giving the "owner" of this equipment significant influence over *what* is being researched by *whom*. This issue of governance in brain imaging research has, to our knowledge, not yet been investigated in depth nor has it been the issue of a broader debate. Given the importance of brain research for society due to its possible impacts, this would, however, be desirable.

Interdisciplinarity

Traditionally, cognitive neuroscience and other disciplines such as pedagogy, psychology, economics, or philosophy, have been separated scientific communities which look at the common issue of cognition, human behaviour and the mind from different perspectives with different methodologies and different underlying theories. They use different professional vocabulary, pursue different goals and explore different questions. In the competition for resources and reputation, brain imaging is presently often perceived and/or presented as "superior" discipline due to its alleged objectivity and accuracy, and the aesthetic attractiveness of colourful brain pictures and the expensive high-tech instrumentation may have contributed to this notion. However, this does not only lead to a (often fruitless) controversial debate of the merits of each discipline, but also is a bad starting

point for developing the research field for the mutual benefit of all concerned disciplines. Against this background, there is a need to actively build bridges between the research communities and to support a bidirectional collaboration in order to exploit synergies at the inter section of formerly distinct disciplines to the benefit of all involved parties. Against this background, there is a need for establishing joint fora (e. g. conferences, workshops), interdisciplinary research teams and interdisciplinary research projects and programmes which help to build these bridges. In addition, the problem must be tackled that – despite efforts to alleviate the effects – the research system in general still poses significant hurdles to establishing true interdisciplinarity: Structural difficulties are usually encountered when trying to mobilise resources for interdisciplinary research (e. g. access to brain imaging equipment and patients, formation of interdisciplinary research teams), and when building a scientific reputation (e. g. publications in high-ranking journals) and a scientific career, pointing to the need to take additional measures beyond funding of these interdisciplinary research fields.

Safeguards against "unscientific" application of cognitive neuroimaging, quality assurance

There is a clear need for safeguards against "unscientific" applications of cognitive neuroimaging. Due to its attractiveness, brain imaging bears the risk that research is conducted by non-specialists not overseeing the field of cognitive neuroscience, neurology, or psychiatry. Therefore it is strongly recommended to maintain peer-review by specialists in the particular research field, and to implement research committees which review the planned research within research institutions. Review processes also enhance the rethinking and improvement of scientific processes. Replication of findings by independent laboratories, together with peer-review, are necessary prerequisites for reliable research in brain imaging.

An integral part of this is a high level of awareness and transparency for the limitations of the neuroimaging methods and experimental approaches, and a critical discussion of the inferability from experimental or diagnostic procedures to far-reaching assessments about cognitive abilities and behaviour of the affected persons. Special attention should be paid to these aspects in education and training of students and scientists, in good scientific

practice, in professional ethics, and in peer-review. Moreover, it should be a topic of both expert and public debates.

Depending on the extent and time-course of diffusion of neuroimaging beyond research settings, it should be analysed whether legal provisions for additional quality assurance measures should be taken into consideration, e. g. a restriction of brain imaging to staff and institutions which comply with certain quality and qualification requirements as well as a restriction of brain imaging to certain purposes which are to be defined by law.

22.6   Special issues

22.6.1   Informed consent

For neuroimaging to be performed legally, informed consent must be given. A valid informed consent is mandatory irrespective of whether the brain imaging procedure is conducted in the context of medical diagnostics and therapeutic interventions, or as part of biomedical or neurocognitive research. The content, scope and consequences of the examination must be explained to the person to be examined in comprehensible terms. It must also provide for the right not to know and the right to withdraw, i. e. the subject of neuroimaging has the right to discontinue the procedure at any time without sanctions. From the constitutionally-anchored guarantee of the right to self-determination of personal data, it also follows that the informed consent by the person subjected to neuroimaging does not only comprise the consent to the procedure itself, but must also cover the collection of the data, their storage and processing, and their handing to third parties, and the purposes of their use (see also chapter 20.6.3).

Many brain imaging institutes have established procedures for obtaining informed consent including the following points: (1) information about the title of the study and the research topic; (2) information about the purpose of the study and whether the study is going to be published, (3) information about the study procedure and which technical features are used, (4) information about the kind of data which are collected and how long these data will be stored; (5) information about the explicit description of the possible health benefits and health risks to the subject, (6) explicit information that the volunteer has the right to withdraw from the study at any time

of the experimental stage, (7) information that the data will be kept confidential except as required by law, (8) information that the volunteer has at any time the right now or in the future to indicate that his/her data should no longer be used for research purposes, and finally information about study funding (funding organisation) and investigator contact information. These information should be included in the signed consent form in order to document that the subjects have been informed comprehensively. In terms of both legal and ethical considerations, the person concerned must as a matter of principle be offered the opportunity to decide on his or her own whether and to what extent he or she wishes to be informed of the examination results relating to himself or herself personally ("right not to know").

Both in clinical practice as well as in research, there is often an irrefutable need to subject persons to brain imaging who, for various reasons, are impaired in their ability or incapable to give informed consent on their own: This may be the case for patients suffering from cognitive impairments and psychological disorders or due to age, for unborn and under-age children, for persons in the state of coma vigil or for dead bodies. This poses specific challenges and requirements to obtaining informed consent. Where the possibility exists that neuroimaging is of benefit to the subject himself and it is apparent after weighing the opportunities and risks that the benefits to the subject are greater, it is, as a rule, legally and ethically justifiable to have the informed consent given by his legally authorised representative. Whether research which does not have the potential to produce direct benefits for the subject may be carried out on persons unable to consent is not agreed. The Biomedicine Convention allows such research on condition that it entails only minimal risk and minimal burden. Furthermore it is required that there are no comparable alternatives, and the brain imaging must have the aim of providing benefit to persons with the same condition as the person under study (so-called *Gruppennützigkeit*). Over and above, the consent of the responsible ethics commission and the legal representative must have been given and the person concerned must not have signalled an objection.

However, the present regulatory situation with regard to the permissibility of neuroimaging as part of human research in Switzerland is rudimentary and inconsistent as relevant provisions are oriented around fragmented federal law and patchy cantonal law. Therefore, there is an urgent need for a federal law which consistently guarantees a high level of protection for research

on humans, be they able or unable to give informed consent, specifying the indispensable legal and ethical requirements for research involving living humans as well as dead bodies. The principal legal stipulations should make grade on the provisions of the Council of Europe's Convention of Human Rights and the draft additional Protocol.

Although no systematic or quantitative data were collected during this impact assessment study, evidence from expert interviews and the literature indicates that established procedures in institutions conducting neuroimaging to obtain informed consent do not always fully comply with all of the above-mentioned principles.

Especially, problems may lie in comprehensively informing the subjects about the possibility and consequences of incidental findings (see chapters 9.3 and 22.6.2), in data use and data protection issues (see chapters 20.6 and 22.6.3), and with respect to consent for performing research on dead bodies. This, on the one hand, again points to the urgent need of a federal law on research on human beings in which the legal provisions and requirements should be clearly specified. Its scope should also encompass behavioural research. On the other hand, it is recommended to all persons and institutions involved in brain imaging that they

- support the consistent implementation of legal and ethical principles regarding informed consent in their area of responsibility and enforce the compliance with these standards,
- provide adequate qualification of the responsible staff in these matters,
- make the compliance with these standards mandatory for funding of research projects, publications, clinical studies etc.

22.6.2   Incidental findings

The number of healthy volunteers who are subjected to neuroimaging examinations for research purposes and without immediate benefit to the research subjects is increasing. This is, on the one hand, due to the development of cognitive neuroscience which, among others, studies "normal" cognitive functions. On the other hand, the study of e. g. age-related cognitive impairment or cognitive deficits due to developmental disorders also requires the comparison of the affected population with a group of healthy, unaffected subjects. Due to the increasing number of healthy persons sub-

jected to neuroimaging, also the problem of incidental findings, i. e. the incidental discovery of unexpected brain anomalies increases. According to recent estimations, this is the case in 2 to 8 % of all brain imaging studies conducted in the context of cognitive (non-medical) experiments (chapter 9.3), and therefore not in a negligible order of magnitude.

Volunteers being informed about the unanticipated finding of anomalies in their brain will find themselves and their partners and relatives exposed to significant psychic stress due to the possibly far-reaching consequences for the subject, but perhaps also to third parties such as relatives. This situation requires careful counselling und support by specifically qualified staff. Moreover, referral to specialists and additional diagnostic procedures and therapeutic interventions are often required which may cause additional costs and may pose health hazards to the person affected. It is obvious that high professional standards and well-established procedures to manage such cases are required.

The deliberations on informed consent (see chapter 20) showed that the informed consent which has to be obtained for such studies must also comprise the possibility of incidental findings and their possible consequences, as outlined above. In terms of both legal and ethical considerations, the study participant also has the right not to know (chapter 20.4.3). As a consequence, management procedures must be designed in a way that the person concerned must be offered the opportunity to decide on his or her own whether, and, if so, to what degree, he or she wishes to be informed of possible incidental findings and treatable and non-treatable conditions.

On the other hand, brain imaging studies in cognitive neuroscience are often performed by psychologists or other scientists who have not received formal training in interpreting brain scans with respect to abnormalities of clinical significance, and with respect to disclosing sensitive personal information to patients and counselling them appropriately. This raises the question whether the investigator is in the position to diagnose and interpret an abnormality reliably, and this even more, if one takes into account that often brain abnormalities do not show any clear associations with diseases or disorders, and the interpretation of brain scans are often of prognostic character with considerable uncertainty for the individual case about the probability, timing and severity of the disease or disorder. This bears the

risk that unanticipated findings may go unrecognised and thereby leave subjects without appropriate referral or counselling. It also bears the danger that an inappropriate interpretation of the data is done, confronting the subject with a false-positive result. This may cause additional diagnostic procedures and related costs as well as undue concern that an individual "has something in the brain that should not be there". It also raises the question under which conditions an investigator or an institution can be held liable if a pathological condition goes undetected (see chapter 20). On the other hand, if scans of all study participants were subjected to routine clinical assessment by specifically qualified medical staff, this would sub-stantially increase the workload, manpower requirements and costs for such studies.

Although no systematic or quantitative data were collected during this im-pact assessment study, evidence from expert interviews and the literature indicates that established procedures in institutions conducting neuroimag-ing of healthy volunteers often do not take the above-mentioned aspects into account appropriately: informed consent and management procedures for dealing with incidental findings are established on an institution-by-in-stitution basis and differ widely with respect to the awareness of the prob-lem, the scope of the relevant issues taken into account, the compliance with mandatory ethical principles and legal provisions (e. g. inclusion of incidental findings in the scope of the informed consent, inclusion of the option to exert one's right not to know), and the procedural and organisa-tional provisions taken.

Although there is no general consensus on how to deal with this problem effectively, some brain imaging centres have established specifically de-signed procedures. In this report, we presented as an example the proce-dure established by the Wolfson Brain Imaging Centre (WBIC) (chap-ter 9.3). The basic principle of this procedure is that conducting the brain imaging study is strictly separated from the diagnosis of brain abnormalities and dealing with them, both organisationally and with respect to the staff involved. All structural MRI studies are reviewed by a consultant neurora-diologist and a confidential report is generated, which is not included within the normal hospital information system. They also introduce a cascade of informed consent including careful information of the volunteer about the potential risks of the study. In addition, they offer insurances (paid by the WBIC) and medical counselling.

As this is only a first attempt to deal with this upcoming problem there is a need to

- further analyse the status-quo situation and make available current best practices,
- raise awareness to the problem,
- encourage institutions active in neuroimaging
  - to develop adequate procedures to manage incidental findings,
  - to initiate and engage in debates among investigators, physicians, study participant representatives, ethics committees, ethicists and lawyers about the requirements of such procedures,
  - to implement these procedures in their institutions and educate and encourage their staff to comply with them
- strive for harmonisation of such procedures, standards and rules on an ethically high level nationally and internationally, since these problems are encountered by all brain imaging centres worldwide,
- support the implementation of such high-standard procedures in neuro-imaging institutions by making compliance mandatory for eligibility for public funding and for publication in high-ranking scientific journals.

22.6.3   Data protection

Neuroimaging implies the acquisition, collection, processing and interpreta-tion of large amounts of data. Following the broad scope of actual and po-tential applications of neuroimaging, the respective data are also collected for different purposes and different contexts: the range covers the exami-nation of a patient during individual medical diagnosis or therapy, the screening of larger populations for medical reasons or epidemiological pur-poses, neuroimaging in the context of both biomedical and non-medical (e. g. studies of cognition and behaviour) research, and analysis of cogni-tion and behaviour in different non-research application contexts.

Often, these data are collected and stored in databases from which they can be retrieved and reanalysed, and where they can be interlinked with other data. These databases are often maintained and used in international cooperation, which is of vital importance for neuroscience, and therefore imply a transfer of data across national borders, diminishing the influence of national legal provisions regarding data protection. A characteristic property of neuroimaging data is that they are acquired, processed and stored in

digitised form. This makes it possible that data processing, data analysis and data interpretation can be separated both spatially and temporally from the physical neuroimaging investigation and direct involvement of the patient or research subject. Depending on the type and amount of data acquired and stored and the extent of measures taken to anonymise or encrypt the data, a reidentification of an individual from the stored data may, under certain circumstances, be possible.

Because brain functions are closely related with personality and individuality, with quality of life, the ability to lead an autonomous and fulfilled life (*Lebenschancen*), and with social interaction, neuroimaging and brain data derived from neuroimaging bear the potential to yield very sensitive information about the individual. Having knowledge of this personal information may have profound consequences for the individual's self-image, his perception by others, his future behaviour and his future way of living. Because social stigma is attributed to the impairment of brain functions, a deviation of a subject's brain scan from "normal" findings might lead to inferring to the person's personality and his behaviour with subsequent discrimination of the respective person. Moreover, in many cases, it will not be known or only with considerable prognostic uncertainty what the possible impacts of a "positive" finding might be for the individual.

From this, it is obvious that neuroimaging data are personal data, and even more are likely to be highly sensitive data which, by current law, require special protection. This poses the question whether data protection risks inherent to neuroimaging are adequately covered by existing legislation and established practice, or whether an amendment of the existing legislation and instruments is required. In view of the importance of access to neuroimaging data for the advancement of science, it must also be ensured that equal consideration is given to the interests of all concerned parties and a fair balancing is achieved.

In Switzerland, existing legislation guarantees a high level of protection of personal data, compared to international standards: the Swiss Constitution guarantees the right to self-determination and the protection against abuse of personal data which leads to the individual right to fundamentally decide oneself on the disclosures and use of one's own personal data. "Personal data" is all information relating to an identified or identifiable person, and obligations are imposed on all entities processing personal data – among

them also institutions active in neuroimaging. In addition, the federal and cantonal legislatures also recognise so-called "personal data in particular need of protection". The Swiss Federal Data Protection Act (Daten-schutzgesetz, DSG) lists as personal data in particular need of protection data relating to the religious, philosophical, political or trade unionist views or activities, health, the intimate sphere or race, social aid measures, ad-ministrative or criminal prosecutions or sanctions. Anyone who in a wilful and unauthorised manner publicises personal data especially worthy of protection is liable to imprisonment or a fine.

For the advancement of science, it is of importance that e. g. researchers have – under specific preconditions – access to data gleaned from neuro-imaging. The Swiss Constitutions allows limitations to the informational right to self-determination, which, however, need a particular justification if personal data and personality profiles requiring special protection are con-cerned. These limitations must follow from a formal law, and the restrictions must be reasonable and in proportion to the goals pursued.

As outlined above, neuroimaging data are likely to qualify as data requiring special protection. However, only medical neuroimaging data acquired in the context of medical diagnosis or therapy or in the context of biomedical research are covered by existing law. In contrast, behaviour-related neuroimaging data which at the same time are not related to health or the intimate sphere or are not collected and saved for the purposes of adminis-trative or criminal prosecution currently are covered by the general term of personal data only, but are not classified as data requiring special protec-tion. This means that there exists currently a gap in protection which must be examined by the legislature and remedied by means of new legislation in order to conform with the Constitution.

From the constitutionally-anchored guarantee of the right to self-determina-tion of personal data, it also follows that the informed consent by the person subjected to neuroimaging does not only comprise the consent to the pro-cedure itself, but must also cover the collection of the data, their storage and processing, and their handing to third parties, and the purposes of their use. The concession of a right to object alone is not sufficient. In the past, a so-called "multifunctional use" of brain imaging data, i. e. data originally collected for medical purposes were later used for research purposes, was often done without appropriate comprehensive informed consent. This often

had practical reasons, e. g. that, due to a time lapse, no person could be found who could have given the consent, but this is a practice no longer acceptable. On the other hand, in order to guarantee that neuroimaging data remain available also in the future, the process of obtaining informed consent must not be unnecessarily complicated. This requires the careful balancing of questions of self-determination, solidarity, altruism, and justice. Against this background, it should be regulated by law, e. g. the planned federal legislation on research on human beings, under which preconditions, limits and for which purposes the collection, storage, retrieval and use of neuroimaging data in databases should be possible. Because international cooperation is of vital importance for neuroscience, the law must also adopt a more international character. Moreover, self-governing concepts (including codes of conduct) may provide for stronger obligations of doctors, psychologists and research institutes. The following instruments and options could be taken into consideration in order to strike an appropriate balance between the right to informational self-determination and protection of personal data against abuse on the one hand, and legitimate interests of research in using these data without undue restrictions on the other, among them e. g.

- a design of the databases in a way as to make them as data-protection-friendly and data-sparing as possible, e. g. by anonymisation or encryption of personal data as far as possible, by keeping code and encoded data separately, by implementing measures to guarantee the authenticity of the data,
- mandatory informed consent regarding the storage, processing, purpose of use, and passing on of data to third parties for an undefined length of time,
- a public register of all brain databases,
- a license for brain data bases, if their scope is beyond standard medical research,
- a mandatory approval by an ethics committee for research projects which make use of data from brain databases.

22.6.4   Safety of neuroimaging

At the present state of knowledge, the neuroimaging techniques EEG, MEG and NIRS do not pose any major safety or health problem. In contrast, health risks are known for both patients and occupationally exposed staff

due to PET, SPECT, MRI and TMS. These health risks are mainly due to toxicity and ionizing radiation emanating from the radionuclides used in PET and SPECT, and comprise headaches and the risk to evoke epileptic seizures in high-frequency repetitive TMS. For MRI, the highest acute risk are injuries from metallic objects which are moved like a missile by the strong magnets and failure of medical devices and implants due to electro-magnetic interference and heating. Moreover, both patients and staff are exposed to acoustic noise and different types of magnetic fields, i. e. static magnetic field; time-varying magnetic field gradients and radiofrequency magnetic fields which exert different biological effects. However, preventive and protective measures have been developed and implemented which allow, in the large majority of routine clinical neuroimaging procedures, a safe operation of the devices with minimal acute health risks for both pa-tients and staff. Thus, MRI can be considered as a safe technique causing no known health hazards if the safety guidelines are used for the MRI measurements.

However, the currently valid guidelines for occupational exposure to elec-tromagnetic fields do not adequately take recent developments in MR pro-cedures into account, among them

- the trend towards higher field strengths (3-8 Tesla),
- the trend towards high throughput scanning of patients, leading to a high level of cumulative exposure of staff,
- the trend to 4D imaging and monitoring of disease progression by MRI, leading to repeated exposure of patients and volunteers,
- interventional MR procedures during which staff is exposed to various electromagnetic fields to a much higher level than in diagnostic MR pro-cedures.

Moreover, current occupational exposure limits are often exceeded during non-routine procedures such as trouble-shooting and repair, and there is a general lack of knowledge regarding the long-term effects of electromag-netic fields, especially their effect on pregnant women, which comprise both exposed staff as well as patients, and the biological effects of strong static magnetic fields, with special emphasis on chronic exposure and their effects on reproduction and development. Because current guidance and recommendations for prevention of possible health hazards have not kept pace with the rapid change in device development and MRI use, there is a

need to broaden the knowledge base through well-controlled studies with respect to long-term effects of exposure to magnetic fields, with respect to possible biological effects of strong static magnetic fields, and with respect to pregnant women, to subsequently incorporate the knowledge thus gleaned into the corresponding regulations and guidelines, and to support the development and implementation of adequate policies and procedures for safe operation in interventional MR departments.

23   Recommendations

Need for further monitoring of neuroscience and the application of its findings

The neurosciences are an area with a dynamic development. Knowledge arising from the neurosciences is expected to bear considerable health, cultural, social, and economic potentials. At the same time, they raise many health, ethical, legal and social issues which are – with respect to their scope and potential pervasiveness and disruptiveness – comparable to the respective issues inherent to molecular genetics and genetic engineering. However, compared to genetic engineering, the social and political debate of neurosciences and their possible impacts as well as their coverage by technology assessment studies is still in its infancy.

Neurosciences and their possible impacts touch upon the areas of responsibilities of a broad range of institutions, organisations, and individuals who are active in the field of neuroscience, who analyse and shape the relevant frame conditions and impacts, or who may be affected. Among them are, for example, researchers and clinicians active in neuroscience, politicians, administration, research policy and research funding bodies, TA SWISS, the Swiss National Advisory Commission on Biomedical Ethic NEK-CNE, and NGOs, such as professionals or patients associations. We encourage these institutions, organisations, and individuals, to closely monitor the developments in the neurosciences, to actively engage in expert and public debates, to initiate, if necessary, further studies for the analysis of selected topics, and to take appropriate actions. We here give recommendations for such actions which are derived from the analysis of neuroimaging. However, we recommend to also extend the activities of monitoring, analysis and action to the neurosciences in their entirety.

Need for a more intensive and balanced public debate

Brain imaging enjoys a high attention not only by experts, but also by laymen. However, "neuromyths" and misconceptions of potentials and limits of these methods are wide-spread. Moreover, the presentation of this research field and its possible applications and impacts in the public sphere is

strongly biased, focussing on the extremes of both potentials and benefits as well as possible unintended or disruptive impacts. This may lead to unjustified expectations as well as undue concerns. The public debate is still in an infant stage in Switzerland.

It is recommended to actively stimulate the public debate about the goals, potentials, research endeavours, limits, frame conditions and possible impacts of brain imaging. Measures should be tailored to different target groups, such as the general public, decision-makers in policy and administration, patients, volunteers participating in brain imaging research, as well as neuroimaging experts.

For measures aiming at laymen, specific attention should be paid to providing transparent and well-balanced information and to engaging mediating experts, thus providing a counterbalance to dubious or ill-balanced sources and to polarised debates. Suggested topics are goals, potentials, and impacts of brain imaging; methodological limits of brain imaging; and governance questions in neuroimaging research.

For measures aiming at experts, suggested topics are: appropriate frame conditions for interdisciplinary, high-quality neuroimaging research; methodological limits of neuroimaging approaches; quality assurance; professional ethics and professional codes of conduct as self-governing concepts; governance questions in neuroimaging research; how to strike an appropriate balance between availability of brain imaging data for research and the right of informational self-determination and protection of personal data. Moreover, it is recommended to actively involve stakeholders, e. g. representatives of patients or research volunteers, in these expert debates, and to be transparent about the results of the debates.

Legislation

Neuroimaging comprises a broad scope of actual and possible applications: it is applied in clinical practice to patients for diagnostic and therapeutic medical purposes, it is used on human subjects in the course of biomedical research, and it is applied as research instrument in cognitive neuroscience and behavioural research on healthy volunteers. Depending on the context and purpose of neuroimaging, different needs for legislative action arise:

If neuroimaging is used in the provision of health care, the responsible doctor and psychologist have a legal obligation to the person to be examined to use those methods which satisfy the current state of the art. In Switzerland, the doctor-patient-relationship which is relevant in this context is presently regulated mainly by cantonal laws which differ from one another in several aspects. Together with the Federal Constitution with its guarantees of personal rights and human dignity as well as standards elaborated by the medical professions with respect to the patient-physician-relationship, this seems suitable to solve the possibility of "neuroimaging as bodily harm" appropriately. Although not urgently needed, a federal act would be desirable which establishes uniform regulations across the Federation with the aim of legal certainty, and might therefore be taken into consideration.

The validity of neuroimaging results depends to a large extent on the expertise with which operation of the high-tech equipment and the data acquisition, processing and interpretation is performed. This requires qualified staff, working in well-organised institutions. In view of the fact that presently no specific formal qualification (*Fähigkeitsausweis*) for conducting brain imaging is required, it is recommended to explore the issue of quality assurance in clinical practice of brain imaging further. In this context it should be analysed and assessed whether there is a need to restrict brain imaging to certain purposes defined by law, and possibly to those institutions and staff which comply with certain quality and qualification standards which would have to be specifically defined.

Neuroimaging is also used in human research. The study of brain structures and functions not only encompasses physical examinations of patients, healthy volunteers and dead bodies, but also research with their personal data. It also involves subjects in the research who are not able to give their informed consent. Moreover, the research may not be of benefit to the subjects involved. These research-related issues require specific legal provisions and boundaries. However, the present regulatory situation in Switzerland with regard to the permissibility of human research and therefore also with regard to neuroimaging is rudimentary and inconsistent because relevant provisions are oriented around fragmented federal law and patchy cantonal law. Moreover, they do not always do justice to modern developments both in technology but also to changing social norms and values, and need adapting.

Therefore, there is an urgent need for a federal law on research on human beings which devises legally clear, consistent, modern rules standardised across the Federation, makes grade on the provisions of the Council of Europe's Convention of Human Rights and the draft additional Protocol and which also applies to the permissibility of neuroimaging as part of human research. The planned federal law on research on human beings is therefore an essential step. From the perspective of neuroimaging, this law should especially specify the indispensable legal and ethical requirements for research involving living humans as well as dead bodies, and guarantee a high level of protection for research on humans, be they able or unable to give informed consent and be they involved in research with benefit to themselves or to third parties, by clearly specifying the legal provisions and requirements. Its scope should also encompass behavioural research.

Moreover, it should be specified under which preconditions, limits and for which purposes the collection, storage, retrieval and use of neuroimaging data in databases should be possible. Because international cooperation is of vital importance for neurosciences, the law must also adopt a more international character. In this context, it should also be carefully analysed whether behaviour-related neuroimaging data which at the same time are not related to health or the intimate sphere or are not collected and saved for the purposes of administrative or criminal prosecution currently are covered by the general term of personal data only, although they should be classified as data requiring special protection. If this is the case, this gap in protection must be examined by the legislature and remedied by means of new legislation in order to conform with the Constitution.

Supporting transfer from research to clinical application

Brain imaging bears significant potentials for clinical applications, both in diagnosis and therapy. Promising progress, especially with functional brain imaging, has been made in research. There is a need to actively strive for transferring findings from clinical research to routine clinical application, e. g. by providing specific incentives and institutional settings for both biomedical research as well as clinical research in order to make imaging procedures, that work in research settings, applicable in routine clinical practice.

In view of the high direct costs associated with neuroimaging, but also its innovative and cost-saving potential if the full course of a disease and its management are taken into account, health technology assessments as well as health economic analyses should be conducted as an integral part of this effort, in order to make possible the clinical application of those neuroimaging procedures which offer a well-balanced cost-benefit ratio.

In view of the sensitivity of the information obtained with these methods, it is most important that there is no premature application of not sufficiently substantiated findings and not sufficiently validated procedures in the clinic. It could therefore also be considered on a case-by-case basis whether these procedures should – until sufficient standardisation and validation – be restricted to special centres where the requirements outlined above can be met.

Quality assurance in clinical application

Quality assurance of brain imaging is of prime importance because of their broad application potential and the sensitivity of the obtained personal information. In this sense, quality assurance in brain imaging fits well into the general need to improve quality management in the medical field. Because brain imaging requires specifically qualified staff in well-organised institutions, the quality assurance should comprise the qualification of staff, the institutions where brain imaging is performed, as well as the procedures. Because presently, no specific requirements are mandatory, it is recommended to explore in further studies whether and in which respect quality assurance in neuroimaging should be improved. In these studies, the following options of quality management should be taken into consideration:

- Brain imaging methods and their applications, limits and impacts as part of the curricula in university education in medicine and psychology.
- Specific training in brain imaging as part of regular vocational training in neurology and radiology.
- Requirement for a mandatory specific education or vocational training in order to be permitted to carry out brain imaging investigations ("Fähigkeitsausweis"). Similarly, a restriction of brain imaging to specifically accredited centres could be taken into account. Moreover, it should be discussed whether a legal definition of permissible purposes for which brain

imaging may be carried out, would be appropriate. For these suggested options, it should also be explored how these requirements could be implemented legally, and which requirements are appropriate.

Favourable conditions for high quality brain imaging research

Brain imaging in cognitive neuroscience is highly interdisciplinary. Novel, creative and innovative research can especially be expected for the exploitation of new questions at the inter section of formerly distinct disciplines. There is a need to actively strive for building bridges between the disciplines. It is recommended to establish joint fora (e. g. conferences, workshops) for the initiation and development of mutual understanding, for the development of a common language and new, synergistic research questions, followed by the initiation of interdisciplinary research teams, research projects and programmes and by making available sufficient resources (e. g. in terms of access to equipment, research funding, qualified staff, access to patients) to explore these interdisciplinary research questions. In order to tackle additional hurdles to interdisciplinarity beyond funding, it is recommended

- to analyse the ease, extent and conditions of access to brain imaging equipment and patients for researchers and improve it, where required,
- to investigate the issue of governance in brain imaging research and to make it an issue of a broader debate to which extent "owners" of brain imaging equipment exert significant influence over what is being researched by whom,
- to provide incentives and opportunities to build scientific reputation and scientific careers even in interdisciplinary fields (e. g. publications in high-ranking journals, career paths).

Specific attention should be paid to quality assurance in research, especially if there is the risk that research is conducted by non-specialists not overseeing the field of cognitive neuroscience, neurology, psychology, or psychiatry. Therefore, researchers and institutions active in neuroimaging are encouraged to widely establish peer-review mechanisms by specialists in the particular research field, to encourage the replication of findings by independent laboratories, to establish effective procedures to prevent misuse of the methods or falsification of data, and to critically assess

the methodological limits of neuroimaging methods and experimental approaches. These aspects should be an integral part of the education and training of students and scientists, of good scientific practice, of codes of conduct, and in peer review.

High professional and ethical standards in brain imaging

Specific challenges arise from neuroimaging with respect to obtaining informed consent, to dealing with surplus information and incidental findings, and to privacy and data protection issues. In addition to the need to provide clear legal provisions, as has been outlined above, there is also the need for high professional standards, codes of conduct and institutional procedures.

With respect to obtaining informed consent and its required scope, institutions active in neuroimaging as well as professional organisations are encouraged to

- provide adequate education and qualification of the responsible staff,
- support the consistent implementation in their area of responsibility and enforce the compliance with these standards,
- make the compliance with these standards mandatory for funding of research projects, publications, clinical studies etc.

With respect to the development of appropriate provisions and procedures for the management of incidental findings, institutions as well as professional organisations are encouraged to

- raise awareness to the problem,
- further analyse the status-quo situation and make available current best practices,
- encourage institutions active in neuroimaging
  - to develop adequate procedures to manage incidental findings,
  - to initiate and engage in debates among investigators, physicians, study participant representatives, ethics committees, ethicists and lawyers about the requirements of such procedures,
  - to implement these procedures in their institutions and educate and encourage their staff to comply with them,

- strive for harmonisation of such procedures, standards and rules on an ethically high level nationally and internationally, since these problems are encountered by all brain imaging centres worldwide,
- support the implementation of such high-standard procedures in neuro-imaging institutions by making compliance mandatory for eligibility for public funding and for publication in high-ranking scientific journals.

With respect to data collection, storage, processing, handing to third parties, and the purposes of their use, it is recommended

- to enforce in the institution that valid informed consent is obtained,
- to make an approval by an ethics committee for research projects mandatory which make use of data from brain databases,
- to support debates about an appropriate balance between the right to informational self-determination and protection of personal data against abuse, and legitimate interests of research in using these data without undue restrictions,
- to take into consideration a license for brain data bases, if their scope is beyond standard medical research,
- to design data acquisition protocols and data bases in a way as to make them as data-protection-friendly and data-sparing as possible, e. g. by anonymisation or encryption of personal data as far as possible, by keeping code and encoded data separately, by implementing measures to guarantee the authenticity of the data.

Safety of brain imaging methods

Neuroimaging techniques can be considered as safe procedures in routine clinical application and in the large majority of experimental neuroimaging procedures if the established preventive and protective measures are complied with. However, in the field of MRI, current guidance and recommendations for the prevention of health hazards during MRI have not fully kept pace with recent technological and procedural developments. Against this background, it is recommended to

- support and conduct research into *possible long-term health effects* of exposure to electromagnetic fields, especially carefully controlled studies

in those with high levels of cumulative exposure (e. g. occupationally exposed staff), in order to broaden the knowledge base,

- support and conduct research into the biological effects of *strong static magnetic fields*, especially carefully controlled studies on the effects of chronic exposure on reproduction and development,
- to subsequently incorporate the results of the above-recommended research into the ICNIRP guidelines, the EU Directive 2004/40/EC as well as the corresponding Swiss regulations,
- to closely monitor the broadening of the knowledge-base for possible health effects of MRI procedures on pregnant women and on the development of their children, in order to establish unequivocal guidance for use of MRI procedures for this patient and staff group,
- to support the international harmonisation of standards for the assessment, measurement and calculation of worker's exposure to electromagnetic fields, presently underway on the European level at CEN, CENELEC and ETSI,
- to initiate and support the development and implementation of adequate policies and procedures for safe operation in interventional MR departments which go beyond those required for diagnostic MR departments,
- to call upon MR equipment manufacturers as well as MRI centres to develop devices and operating procedures which comply with currently valid exposure limits to electromagnetic fields also during trouble-shooting, repair, and interventional MRI.

24   Cited literature

AD 2000 Collaborative Group (2004): Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. In: The Lancet, 363 (9427), pp. 2105-2115.

Adler, G.; Brassen, S.; Jajcevic, A. (2003): EEG coherence in Alzheimer's dementia. In: J.Neural Transm., 110 (9), pp. 1051-1058.

Allen, J.J.; Iacono, W.G.; Danielson, K.D. (1992): The identification of concealed memories using the event-related potential and implicit behavioral measures: a methodology for prediction in the face of individual differences. In: Psychophysiology, 29 (5), pp. 504-522.

Azari, N.P.; Nickel, J.; Wunderlich, G.; Niedeggen, M.; Hefter, H.; Tellmann, L.; Herzog, H.; Stoerig, P.; Birnbacher, D.; Seitz, R.J. (2001): Neural correlates of religious experience. In: Eur.J Neurosci., 13 (8), pp. 1649-1652.

Beaulieu, A. (2002): Images are not the (only) truth: brain mapping, visual knowledge, and iconoclasm. In: Science, Technology & Human Values, 27 (1), pp. 53-86.

Beaulieu, A. (2003): Brains, Maps and the New Territory of Psychology. In: Theory Psychology, 13 (4), pp. 561-568.

Beckmann, N.; Laurent, D.; Tigani, B.; Panizzutti, R.; Rudin, M. (2004): Magnetic resonance imaging in drug discovery: lessons from disease areas. In: Drug Discovery Today, 9 (1), pp. 35-42.

Bell, R.A. (2001): MRI Utilisation Mystery. Online: http://www.imagingeconomics.com/library/200105-03.asp.

Belliveau, J.W.; Kennedy, D.N., Jr.; McKinstry, R.C.; Buchbinder, B.R.; Weisskoff, R.M.; Cohen, M.S.; Vevea, J.M.; Brady, T.J.; Rosen, B.R. (1991): Functional mapping of the human visual cortex by magnetic resonance imaging. In: Science, 254 (5032), pp. 716-719.

Bergstrom, M.; Grahnen, A.; Langstrom, B. (2003): Positron emission tomography microdosing: a new concept with application in tracer and early clinical drug development. In: Eur.J Clin.Pharmacol., 59 (5-6), pp. 357-366.

Berninger, V.W.; Corina, D. (1998): Making Cognitive Neuroscience Edu-
    cationally Relevant: Creating Bidirectional Collaborations Between
    Educational Psychology and Cognitive Neuroscience. In: Educa-
    tional Psychology Review, 10 (3), pp. 343-354.

Blakeslee, S. (2004): If you have a 'Buy Button' in your brain, what pushes
    it? In: New York Times, 19.10.2004.

Blennow, K. (2004): CSF biomarkers for mild cognitive impairment. In:
    Journal of Internal Medicine, 256 (3), pp. 224-234.

Braeutigam, S.; Rose, S.P.; Swithenby, S.J.; Ambler, T. (2004): The dis-
    tributed neuronal systems supporting choice-making in real-life
    situations: differences between men and women when choosing
    groceries detected using magnetoencephalography. In: Eur.J Neu-
    rosci., 20 (1), pp. 293-302.

Byrnes, P.J.; Fox, N.A. (1998a): Minds, Brains, and Education: Part II. Re-
    sponding to the Commentaries. In: Educational Psychology Re-
    view, 10 (4), pp. 431-439.

Byrnes, P.J.; Fox, N.A. (1998b): The Educational Relevance of Research in
    Cognitive Neuroscience. In: Educational Psychology Review, 10
    (3), pp. 297-342.

Camerer, C.F.; Loewenstein, G.; Prelec, D. (2003): Neuroeconomics: How
    neuroscience can inform economics. Online: http://sds.hss.cmu.
    edu/faculty/Loewenstein/downloads/neurojep_submitted.pdf
    (Accessed: 25.02.2005).

Camerer, C.F.; Loewenstein, G.; Prelec, D. (2005): Neuroeconomics – why
    economics needs brains. In: Scand J of Economics, 106 (3), pp.
    555-579.

Camerer, C.F.; Fehr, E. (2006): When Does "Economic Man" Dominate
    Social Behavior? In: Science, 311 (5757), pp. 47-52.

Casey, B.J.; Tottenham, N.; Liston, C.; Durston, S. (2005): Imaging the de-
    veloping brain: what have we learned about cognitive develop-
    ment? In: Trends in Cognitive Sciences, 9 (3), pp. 104-110.

Centre for Reviews and Dissemination (2005a): Cost-effectiveness of func-
    tional imaging tests in the diagnosis of Alzheimer disease (Struc-
    tured abstract). In: NHS Economic Evaluation Database
    (NHSEED), 2005 (1), p. CRD database number NHSEED-
    20001532.

Centre for Reviews and Dissemination (2005b): Cost-effectiveness of PET in the diagnosis of Alzheimer disease (Structured abstract). In: NHS Economic Evaluation Database (NHSEED), 2005 (1), p. CRD database number NHSEED-20031045.

Chalela, J.A.; Gomes, J. (2004): Magnetic resonance imaging in the evaluation of intracranial hemorrhage. In: Expert Review of Neurotherapeutics, 4 (2), pp. 267-273.

Chandler, M.J.; Lacritz, L.H.; Hynan, L.S.; Barnard, H.D.; Allen, G.; Deschner, M.; Weiner, M.F.; Cullum, C.M. (2005): A total score for the CERAD neuropsychological battery. In: Neurology, 65 (1), pp. 102-106.

Chatterjee, A. (2004): Cosmetic Neurology, The controversy over enhancing movement, mentation and mood. In: Neurology, 63, pp. 968-974.

Chisholm, R. (2005): Human Freedom and the Self – In: Reason and Responsibility: Readings in Some Basic Problems of Philosophy. 12th edition, Feinberg, J.; Shafer-Landau, R. (eds.): Wadsworth Publishing Company.

Churchland, P.S. (1986): Neurophilosophy: toward a unified science of the mind-brain, Cambridge, Mass.: MIT Press.

Committee to Review the Scientific Evaluation on the Polygraph (2003): The Polygraph and Lie Detection, National Research Council (ed.), Washington D.C.: The National Academies Press.

Congedo, M.; Lubar, J.F.; Joffe, D. (2004): Low-resolution electromagnetic tomography neurofeedback. In: IEEE Trans.Neural Syst.Rehabil Eng, 12 (4), pp. 387-397.

DaSilva, A.F.; Tuch, D.S.; Wiegell, M.R.; Hadjikhani, N. (2003): A primer on diffusion tensor imaging of anatomical substructures. In: Neurosurg.Focus., 15 (1), p. E4.

Davatzikos, C. (2004): Why voxel-based morphometric analysis should be used with great caution when characterizing group differences. In: NeuroImage, 23, pp. 17-20.

Davatzikos, C.; Fan, Y.; Shen, D.G.; Acharyya, M.; Ruparel, K.; Loughead, J.W.; Gur, R.C.; Langleben, D.D. (2005): Classifying spatial patterns of brain activity with machine learning methods: Application to lie detection. In: NeuroImage, 28 (3), pp. 663-668.

de Leon, M.J.; DeSanti, S.; Zinkowski, R.; Mehta, P.D.; Pratico, D.; Segal, S.; Clark, C.; Kerkman, D.; DeBernardis, J.; Li, J.; Lair, L.; Reisberg, B.; Tsui, W.; Rusinek, H. (2004): MRI and CSF studies in the early diagnosis of Alzheimer's disease. In: Journal of Internal Medicine, 256 (3), pp. 205-223.

de Quervain, D.J.; Fischbacher, U.; Treyer, V.; Schellhammer, M.; Schnyder, U.; Buck, A.; Fehr, E. (2004): The neural basis of altruistic punishment. In: Science, 305 (5688), pp. 1254-1258.

Dehaene, S.; Molko, N.; Cohen, L.; Wilson, A.J. (2004): Arithmetic and the brain. In: Current Opinion in Neurobiology, 14 (2), pp. 218-224.

Dehaene, S.; Pinel, P.; Stanescu, R.; Spelke, E.; Tsivkin, S. (1999): Sources of mathematical thinking: Behavioral and brain-imaging evidence. In: Science, 284 (5416), pp. 970-974.

DeKosky, S.T.; Marek, K. (2003): Looking backward to move forward: early detection of neurodegenerative disorders. In: Science, 302 (5646), pp. 830-834.

Deppe, M.; Schwindt, W.; Kugel, H.; Plassmann, H.; Kenning, P. (2005): Nonlinear responses within the medial prefrontal cortex reveal when specific implicit information influences economic decision-making. In: J Neuroimaging, 15 (2), pp. 171-182.

Deutsch, G.K.; Dougherty, R.F.; Bammer, R.; Siok, W.T.; Gabrieli, J.D.; Wandell, B. (2005): Children's reading performance is correlated with white matter structure measured by diffusion tensor imaging. In: Cortex, 41 (3), pp. 354-363.

Donders, F.C. (1868): Die Schnelligkeit psychischer Prozesse. In: Reichert`s & Dubois-Reymond`s Archiv für Anatomie, Physiologie und wissenschaftliche Medizin, pp. 657-681.

Draganski, B.; Gaser, C.; Busch, V.; Schuierer, G.; Bogdahn, U.; May, A. (2004): Neuroplasticity: changes in grey matter induced by training. In: Nature, 427 (6972), pp. 311-312.

Dumit, J. (2004): Picturing Personhood. Brain Scans and Biomedical Identity, Princeton, NJ: Princeton University Press.

Eckelman, W.C. (2002): Accelerating drug discovery and development through in vivo imaging. In: Nuclear Medicine and Biology, 29 (8), pp. 777-782.

EGE (2005): Opinion on Ethical Aspects of ICT Implants in the Human Body: European Commission, European Group on Ethics in Science and New Technologies (EGE). Online: http://europa.eu. int/comm/european_group_ethics/docs/avis20en.pdf (Accessed: 31.10.2005).

Farah, M.J. (2004): Neuroethics: a guide for the perplexed. In: Cerebrum, 6 (4), pp. 29-38.

Farah, M.J. (2002): Emerging ethical issues in neuroscience. In: Nature Neuroscience, 5 (11), pp. 1123-1129.

Farah, M.J.; Illes, J.; Cook-Deegan, R.; Gardner, H.; Kandel, E.; King, P.; Parens, E.; Sahakian, B.; Wolpe, P.R. (2004): Neurocognitive Enhancement: What Can We Do and What Should We Do? In: Nature Reviews Neuroscience, 5 (5), pp. 421-425.

Farah, M.J.; Wolpe, P.R. (2004): Monitoring and Manipulating Brain Function: New Neuroscience Technologies and Their Ethical Implications. In: Hastings Center Report, 34 (3), pp. 35-45.

Farkas, R.; Becks, T. (2005): Zur Situation der Medizintechnik in Deutschland im internationalen Vergleich, Aachen, Frankfurt: Aachener Kompetenzzentrum Medizintechnik; AGIT GmbH; Deutsche Gesellschaft für Biomedizinische Technik im VDE; Konsortialpartner.

Farwell, L.A.; Donchin, E. (1991): The truth will out: interrogative polygraphy ("lie detection") with event-related brain potentials. In: Psychophysiology, 28 (5), pp. 531-547.

Fehr, E.; Rockenbach, B. (2004): Human altruism: economic, neural, and evolutionary perspectives. In: Current Opinion in Neurobiology, 14 (6), pp. 784-790.

Feychting, M.; Ahlbom, A.; Kheifets, L. (2005): EMF and Health. In: Annual Review of Public Health, 26 (1), pp. 165-189.

Fletcher, P.C.; Palomero-Gallagher, N.; Zafiris, O.; Fink, G.R.; Tyler, L.K.; Zilles, K. (2002): The influence of explicit instructions and stimulus material on lateral frontal responses to an encoding task. In: Neuroimage, 17 (2), pp. 780-791.

Fletcher, P.C.; Zafiris, O.; Frith, C.D.; Honey, R.A.; Corlett, P.R.; Zilles, K.; Fink, G.R. (2005): On the benefits of not trying: brain activity and connectivity reflecting the interactions of explicit and implicit sequence learning. In: Cereb.Cortex, 15 (7), pp. 1002-1015.

Forman, M.S.; Trojanowski, J.Q.; Lee, V.M.-Y. (2004): Neurodegenerative diseases: a decade of discoveries paves the way for therapeutic breakthroughs. In: Nature Medicine, 10 (10), pp. 1055-1063.

Formica, D.; Silvestri, S. (2004): Biological effects of exposure to magnetic resonance imaging: an overview. In: Biomed.Eng Online., 3 (1), p. 11.

Francis, P.T.; Nordberg, A.; Arnold, S.E. (2005): A preclinical view of cholinesterase inhibitors in neuroprotection: do they provide more than symptomatic benefits in Alzheimer's disease? In: Trends in Pharmacological Sciences, 26 (2), pp. 104-111.

Friele, M.; Fulford, B. (2004): Introduction-intervening in psychic capacities. In: Poiesis Prax, 2, pp. 259-262.

Frost & Sullivan (2003): U. S. EEG Diagnostic and Monitoring Equipment. Report #A438-56, San José: Frost & Sullivan.

Frost & Sullivan (2004a): Strategic overview of the global small animal imaging markets. Report #A869-50, London: Frost & Sullivan.

Frost & Sullivan (2004b): The European Contrast Media and Radiopharmaceuticals Market. Report #B428-50, London: Frost & Sullivan.

Frost & Sullivan (2004c): U. S. Medical Imaging Industry Outlook. Report #A630-50, Palo Alto: Frost & Sullivan.

Frost & Sullivan (2004d): U. S. PET and PET-CT Markets. Report #F173-50, Palo Alto: Frost & Sullivan.

Frost & Sullivan (2005a): European Markets for Key Medical Imaging Modalities. Report #B544-50, London: Frost & Sullivan.

Frost & Sullivan (2005b): European Markets for Refurbished Medical Imaging Systems. Report #B540-50, London: Frost & Sullivan.

Fuchs, M.; Lanzerath, D.; Hillebrand, I.; Runkel, T.; Balcerak, M.; Schmitz, B. (2002): Enhancement. Die ethische Diskussion über biomedizinische Verbesserungen des Menschen, drze-Sachstandsbericht 1, Bonn: Deutsches Referenzzentrum für Ethik in den Biowissenschaften (drze).

Fugelsang, J.A.; Dunbar, K.N. (2004): A cognitive neuroscience framework for understanding causal reasoning and the law. In: Philos. Trans.R.Soc.Lond B Biol.Sci, 359 (1451), pp. 1749-1754.

Ganis, G.; Kosslyn, S.M.; Stose, S.; Thompson, W.L.; Yurgelun-Todd, D.A. (2003): Neural correlates of different types of deception: an fMRI investigation. In: Cereb.Cortex, 13 (8), pp. 830-836.

Gaser, C.; Volz, H.P.; Kiebel, S.; Riehemann, S.; Sauer, H. (1999): Detecting structural changes in whole brain based on nonlinear deformations-application to schizophrenia research. In: Neuroimage, 10 (2), pp. 107-113.

Geake, J.; Cooper, P. (2003): Cognitive Neuroscience: implications for education? In: Westminster Studies in Education, 26 (1), pp. 7-20.

Gilbert, S.J.; Shallice, T. (2002): Task switching: a PDP model. In: Cognit.Psychol., 44 (3), pp. 297-337.

Gillies, R.J.; Morse, D.L. (2005): In vivo magnetic resonance spectroscopy in cancer. In: Annual Review of Biomedical Engineering, 7 (1), pp. 287-326.

Glimcher, P.W.; Dorris, M.C.; Bayer, H.M. (2005): Physiological utility theory and the neuroeconomics of choice. In: Games and Economic Behavior, 52 (2), pp. 213-256.

Glimcher, P.W. (2003): Decisions, Uncertainty and the Brain: The Science of Neuroeconomics, Cambridge, MA; London, UK: MIT Press.

Glimcher, P.W.; Rustichini, A. (2004): Neuroeconomics: the consilience of brain and decision. In: Science, 306 (5695), pp. 447-452.

Goswami, U. (2004a): Neuroscience and education. In: Br J Educ Psychol, 74, pp. 1-14.

Goswami, U. (2004b): Neuroscience, education and special education. In: British Journal of Special Education, 31 (4), pp. 175-183.

Graham, N.; Lindesay, J.; Katona, C.; Bertolote, J.M.; Camus, V.; Copeland, J.R.; de Mendonca Lima, C.A.; Gaillard, M.; Gely Nargeot, M.C.; Gray, J.; Jacobsson, L.; Kingma, M.; Kuhne, N.; O'Loughlin, A.; Rutz, W.; Saraceno, B.; Taintor, Z.; Wancata, J.; Old Age Psychiatry section – World Psychiatric Association; World Health Organisation (2003): Reducing stigma and discrimination against older people with mental disorders: a technical consensus statement. In: Int J Geriatr Psychiatry, 18 (8), pp. 670-678.

Gratton, G.; Fabiani, M. (2003): The event-related optical signal (EROS) in visual cortex: Replicability, consistency, localisation, and resolution. In: Psychophysiology, 40 (4), pp. 561-571.

Gratton, G.; Fabiani, M.; Elbert, T.; Rockstroh, B. (2003): Seeing right through you: Applications of optical imaging to the study of the human brain. In: Psychophysiology, 40 (4), pp. 487-491.

Grezes, J.; Frith, C.; Passingham, R.E. (2004): Brain mechanisms for inferring deceit in the actions of others. In: J Neurosci., 24 (24), pp. 5500-5505.

Gura, T. (2005): Educational research: Big plans for little brains. In: Nature, 435 (7046), pp. 1156-1158.

Haggard, P.; Eimer, M. (1999): On the relation between brain potentials and the awareness of voluntary movements. In: Exp.Brain Res, 126 (1), pp. 128-133.

Hannon, P. (2003): Developmental neuroscience: implications for early childhood intervention and education. In: Current Paediatrics, 13 (1), pp. 58-63.

Hardy, M.; Armitage, G. (2002): The child's right to consent to x-ray and imaging investigations: issues of restraint and immobilisation from a multidisciplinary perspective. In: Journal of Child Health Care, 6 (2), pp. 107-119.

Hariri, A.R.; Weinberger, D.R. (2003): Imaging genomics. In: British Medical Bulletin, 65, pp. 259-270.

Hartmann, D. (2004): Neurophysiology and freedom of the will. In: Poiesis Prax, 2, pp. 275-284.

Heinze, H.J.; Mangun, G.R.; Burchert, W.; Hinrichs, H.; Scholz, M.; Munte, T.F.; Gos, A.; Scherg, M.; Johannes, S.; Hundeshagen, H.; et al (1994): Combined spatial and temporal imaging of brain activity during visual selective attention in humans. In: Nature, 372 (6506), pp. 543-546.

Helmchen, H. (2005): Forthcoming ethical issues in biological psychiatry. In: World Journal of Biological Psychiatry, 6 (SUPPL. 2), pp. 56-64.

Henke, K.; Mondadori, C.R.; Treyer, V.; Nitsch, R.M.; Buck, A.; Hock, C. (2003a): Nonconscious formation and reactivation of semantic associations by way of the medial temporal lobe. In: Neuropsychologia, 41 (8), pp. 863-876.

Henke, K.; Treyer, V.; Nagy, E.T.; Kneifel, S.; Dursteler, M.; Nitsch, R.M.; Buck, A. (2003b): Active hippocampus during nonconscious memories. In: Conscious.Cogn, 12 (1), pp. 31-48.

Hensch, T.K. (2004): Critical period regulation. In: Annu.Rev.Neurosci., 27, pp. 549-579.

Herrmann, C.; Pauen, M.; Rieger, J.; Schicktanz, S. (2005): Bewusstsein. Philosophie, Neurowissenschaften, Ethik. UTB 2686, Paderborn, Stuttgart: Wilhelm Fink Verlag.

Higuchi, M.; Iwata, N.; Matsuba, Y.; Sato, K.; Sasamoto, K.; Saido, T.C. (2005): 19F and 1H MRI detection of amyloid [beta] plaques in vivo. In: Nat Neurosci, 8 (4), pp. 527-533.

Hill, D.L.G.; Mcleish, K.; Keevil, S.F. (2005): Impact of electromagnetic field exposure limits in Europe: Is the future of interventional MRI safe? In: Academic Radiology, 12 (9), pp. 1135-1142.

Hinterberger, T.; Veit, R.; Strehl, U.; Trevorrow, T.; Erb, M.; Kotchoubey, B.; Flor, H.; Birbaumer, N. (2003): Brain areas activated in fMRI during self-regulation of slow cortical potentials (SCPs). In: Exp.Brain Res, 152 (1), pp. 113-122.

Hinterberger, T.; Veit, R.; Wilhelm, B.; Weiskopf, N.; Vatine, J.J.; Birbaumer, N. (2005): Neuronal mechanisms underlying control of a brain-computer interface. In: Eur.J Neurosci., 21 (11), pp. 3169-3181.

Hinton, V.J. (2002): Ethics of neuroimaging in pediatric development. In: Brain and Cognition, 50 (3), pp. 455-468.

Höhne, K.H.; Petersik, A.; Pflesser, B.; Pommert, A.; Priesmeyer, K.; Riemer, M.; Schubert, M.; Schiemann, T.; Tiede, U.; Urban, M.; Frederking.H; Lowndes, M.; Morris, J. (2001): VOXEL-MAN 3D Navigator: Brain and Skull. Regional, Functional and Radiological Anatomy, Electronic Media: Springer-Verlag Electronic Media: Springer-Verlag.

Honderich, T. (1993): Wie frei sind wir? Das Determinismus-Problem, Stuttgart: Reclam.

Hsu, M.; Bhatt, M.; Adolphs, R.; Tranel, D.; Camerer, C.F. (2005): Neural Systems Responding to Degrees of Uncertainty in Human Decision-Making. In: Science, 310 (5754), pp. 1680-1683.

Hushek, S.G.; Russell, L.; Moser, R.F.; Hoerter, N.M.; Moriarty, T.M.; Shields, C.B. (2005): Safety protocols for interventional MRI. In: Academic Radiology, 12 (9), pp. 1143-1148.

ICNIRP (1994): Guidelines on limits of exposure to static magnetic fields. In: Health Physics, 66 (100), p. 106.

ICNIRP (1998a): Guidelines for limiting exposure to time-varyiing, electric, magnetic and electromagnetic fields up to 300 GHz. In: Health Physics, 74 (494), p. 522.

ICNIRP (1998b): Guidelines for limiting exposure to time-varying, electric, magnetic and electromagnetic fields up to 300 GHz. In: Health Physics, 74 (494), p. 522.

ICNIRP (2004): Statement on Medical Magnetic Resonance (MR) Procedures: Protection of Patients. In: Health Physics, 87 (2), pp. 197-216.

Illes, J. (2004a): Medical imaging: a hub for the new field of neuroethics. In: Acad.Radiol., 11 (7), pp. 721-723.

Illes, J. (2004b): Neuroethics: toward broader discussion. In: Hastings Cent.Rep., 34 (6), pp. 4-5.

Illes, J.; Kann, D.; Karetsky, K.; Letourneau, P.; Koenig, B.A.; Schraedley-Desmond, P.; Atlas, S.W.; Raffin, T.A. (2004a): Advertising, patient decision-making, and self-referral for computed tomographic and magnetic resonance imaging. In: Archives of Internal Medicine, 164 (22), pp. 2415-2419.

Illes, J.; Kirschen, M.P.; Karetsky, K.; Kelly, M.; Saha, A.; Desmond, J.E.; Raffin, T.A.; Glover, G.H.; Atlas, S.W. (2004b): Discovery and disclosure of incidental findings in neuroimaging research. In: J Magn Reson.Imaging, 20 (5), pp. 743-747.

Illes, J.; Racine, E. (2005a): Imaging or imagining? A neuroethics challenge informed by genetics. In: Am.J Bioeth., 5 (2), pp. 5-18.

Illes, J.; Racine, E. (2005b): Neuroethics: dialogue on a continuum from tradition to innovation. In: Am.J Bioeth., 5 (2), p. W3-W4.

Illes, J.; Blakemore, C.; Hansson, M.G.; Hensch, T.K.; Leshner, A.; Maestre, G.; Magistretti, P.; Quirion, R.; Strata, P. (2005): International perspectives on engaging the public in neuroethics. In: Nature Reviews Neuroscience, 6 (12), pp. 977-982.

Illes, J.; Desmond, J.E.; Huang, L.F.; Raffin, T.A.; Atlas, S.W. (2002): Ethical and practical considerations in managing incidental findings in functional magnetic resonance imaging. In: Brain and Cognition, 50 (3), pp. 358-365.

Illes, J.; Kirschen, M.P. (2003): New Prospects and Ethical Challenges for Neuroimaging Within and Outside the Health Care System. In: American Journal of Neuroradiology, 24 (10), pp. 1932-1934.

Illes, J.; Kirschen, M.P.; Gabrieli, J.D.E. (2003): From neuroimaging to neuroethics. In: Nature Neuroscience, 6 (3), p. 205.

Illes, J.; Kirschen, M.P.; Edwards, E.; Stanford, L.R.; Bandettini, P.; Cho, M.K.; Ford, P.J.; Glover, G.H.; Kulynych, J.; Macklin, R.; Michael, D.B.; Wolf, S.M. (2006): ETHICS: Incidental Findings in Brain Imaging Research. In: Science, 311 (5762), pp. 783-784.

International Bioethics Committee (IBC) (1995): Ethics and Neuroscience. Rapporteur: Mr. Jean-Didier Vincent, Series/Report ID CIP/BIO/95/CONF.002/3, Paris: International Bioethics Committee (IBC) of UNESCO.

Ito, M. (2004): Nurturing the brain as an emerging research field involving child neurology. In: Brain & Development, 26, pp. 429-433.

Jahn, T.; Theml, T.; Diehl, J.; Grimmer, T.; Heldmann, B.; Pohl, C.; Lautenschlager, N.; Kurz, A. (2004): CERAD-NP und Flexible Battery Approach in der neuropsychologischen Differentialdiagnostik. Demenz versus Depression. In: Zeitschrift für Gerontopsychologie und -psychiatrie, 17, pp. 77-95.

Jancke, L. (2002): Methods in cognitive neuroanatomy – Modern methods in neuropsychology, Hugdahl, K. (ed.): Kluwer Press.

Jäncke, L. (2005): Methoden der Bildgebung in der Psychologie und den kognitiven Neurowissenschaften, Stuttgart: Kohlhammer.

Jancke, L.; Gaab, N.; Wustenberg, T.; Scheich, H.; Heinze, H.J. (2001): Short-term functional plasticity in the human auditory cortex: an fMRI study. In: Brain Res Cogn Brain Res, 12 (3), pp. 479-485.

Jancke, L.; Preis, S.; Steinmetz, H. (1999): The relation between forebrain volume and midsagittal size of the corpus callosum in children. In: Neuroreport, 10 (14), pp. 2981-2985.

Jancke, L.; Steinmetz, H. (2002): Anatomical brain asymmetries and their relevance for functional asymmetries – Brain asymmetry, Hugdahl, K.; Davidson, R.J. (eds.), Cambridge, MA: MIT Press.

Jeong, J. (2004): EEG dynamics in patients with Alzheimer's disease. In: Clin.Neurophysiol., 115 (7), pp. 1490-1505.

Jessen, F.; Traeber, F.; Freymann, N.; Maier, W.; Schild, H.H.; Heun, R.; Block, W. (2005): A comparative study of the different N-acetylaspartate measures of the medial temporal lobe in Alzheimer's disease. In: Dementia and Geriatric Cognitive Disorders, 20 (2-3), pp. 178-183.

Johnson, M.M.; Rosenfeld, J.P. (1992): Oddball-evoked P300-based method of deception detection in the laboratory II: Utilisation of non-selective activation of relevant knowledge. In: International Journal of Psychophysiology, 12 (3), pp. 289-306.

Jordan, K.; Schadow, J.; Wuestenberg, T.; Heinze, H.J.; Jancke, L. (2004): Different cortical activations for subjects using allocentric or egocentric strategies in a virtual navigation task. In: Neuroreport, 15 (1), pp. 135-140.

Jordan, K.; Wustenberg, T.; Heinze, H.J.; Peters, M.; Jancke, L. (2002): Women and men exhibit different cortical activation patterns during mental rotation tasks. In: Neuropsychologia, 40 (13), pp. 2397-2408.

Katada, E.; Sato, K.; Ojika, K.; Ueda, R. (2004): Cognitive event-related potentials: useful clinical information in Alzheimer's disease. In: Curr.Alzheimer Res, 1 (1), pp. 63-69.

Kennedy, D. (2004): Just Treat, or Enhance? In: Science, 304 (5667), p. 17.

King-Casas, B.; Tomlin, D.; Anen, C.; Camerer, C.F.; Quartz, S.R.; Montague, P.R. (2005): Getting to Know You: Reputation and Trust in a Two-Person Economic Exchange. In: Science, 308 (5718), pp. 78-83.

Klimesch, W.; Sauseng, P.; Gerloff, C. (2003): Enhancing cognitive performance with repetitive transcranial magnetic stimulation at human individual alpha frequency. In: Eur.J Neurosci., 17 (5), pp. 1129-1133.

Klunk, W.E.; Engler, H.; Nordberg, A.; Wang, Y.; Blomqvist, G.; Holt, D.P.; Bergstrom, M.; Savitcheva, I.; Huang, G.F.; Estrada, S.; Ausen, B.; Debnath, M.L.; Barletta, J.; Price, J.C.; Sandell, J.; Lopresti, B.J.; Wall, A.; Koivisto, P.; Antoni, G.; Mathis, C.A.; Langstrom, B. (2004): Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. In: Ann Neurol, 55 (3), pp. 306-319.

Köchy, K.; Stederoth, D. (2006): Willensfreiheit als interdisziplinäres Problem, Freiburg i. Br.: Alber Verlag.

Koizumi, H. (2004): The concept of developing the brain: a new natural science for learning and education. In: Brain & Development, 26, pp. 434-441.

Kosfeld, M.; Fischbacher, U.; Fehr, E.; Heinrichs, M.; Zak, P.J. (2005): Oxytocin increases trust in humans. In: Nature, 435 (7042), pp. 673-676.

Kosslyn, S.M. (1999): If neuroimaging is the answer, what is the question? In: Philos.Trans.R.Soc.Lond B Biol.Sci., 354 (1387), pp. 1283-1294.

Kozel, F.A.; Padgett, T.M.; George, M.S. (2004a): A replication study of the neural correlates of deception. In: Behav Neurosci., 118 (4), pp. 852-856.

Kozel, F.A.; Revell, L.J.; Lorberbaum, J.P.; Shastri, A.; Elhai, J.D.; Horner, M.D.; Smith, A.; Nahas, Z.; Bohning, D.E.; George, M.S. (2004b): A pilot study of functional magnetic resonance imaging brain correlates of deception in healthy young men. In: J Neuropsychiatry Clin.Neurosci., 16 (3), pp. 295-305.

Krageloh-Mann, I. (2004): Imaging of early brain injury and cortical plasticity. In: Exp.Neurol, 190 Suppl 1, p. S84-S90.

Krageloh-Mann, I. (2005): Cerebral palsy: towards developmental neuroscience. In: Dev.Med Child Neurol, 47 (7), p. 435.

Krause, J.B.; Taylor, J.G.; Schmidt, D.; Hautzel, H.; Mottaghy, F.M.; Muller-Gartner, H.W. (2000): Imaging and neural modelling in episodic and working memory processes. In: Neural Netw., 13 (8-9), pp. 847-859.

Kröber, H.-L.; Steller, M. (2005): Psychologische Beurteilung in Strafverfahren. Indikationen, Methoden und Qualitätsstandards, 2. überarbeitete und erweiterte Auflage, Darmstadt: Steinkopff-Verlag.

Kuhl, P.K. (2004): Early language acquisition: cracking the speech code. In: Nat.Rev.Neurosci., 5 (11), pp. 831-843.

Kulynych, J. (2002): Legal and ethical issues in neuroimaging research: human subjects protection, medical privacy, and the public communication of research results. In: Brain and Cognition, 50 (3), pp. 345-357.

Lammertsma, A.A. (2004): Role of human and animal PET studies in drug development. In: International Congress Series: Quantitation in Biomedical Imaging with PET and MRI.Proceedings of the International Workshop on Quantitation in Biomedical Imaging with PET and MRI, 1265, pp. 3-11.

Landesbank Baden-Württemberg Equity Research/Strategy (2005): Branchenanalyse. Medizintechnik 2005, Stuttgart: Landesbank Baden-Württemberg.

Langleben, D.D.; Schroeder, L.; Maldjian, J.A.; Gur, R.C.; McDonald, S.; Ragland, J.D.; O'Brien, C.P.; Childress, A.R. (2002): Brain activity during simulated deception: an event-related functional magnetic resonance study. In: Neuroimage, 15 (3), pp. 727-732.

Lansbury, P.T. (2004): Back to the future: the old-fashioned way to new medications for neurodegeneration. In: Nature Medicine, July, p. S51-S57.

Laufs, H.; Kleinschmidt, A.; Beyerle, A.; Eger, E.; Salek-Haddadi, A.; Preibisch, C. (2003): EEG-correlated fMRI of human alpha activity. In: Neuroimage, 19, pp. 1463-1476.

Laureys, S. (2005): Death, unconsciousness and the brain. In: Nature Reviews Neuroscience, 6 (11), pp. 899-909.

Laven, D.L.; Bednarczyk, E.M. (2001): CNS Assessment Using Functional Neuro-PET Imaging. In: Journal of Pharmacy Practice, 14 (4), pp. 308-331.

Lee, T.M.; Liu, H.L.; Tan, L.H.; Chan, C.C.; Mahankali, S.; Feng, C.M.; Hou, J.; Fox, P.T.; Gao, J.H. (2002): Lie detection by functional magnetic resonance imaging. In: Hum.Brain Mapp., 15 (3), pp. 157-164.

Lenneberg, E. (1967): Biological Foundations of Language, New York: John Wiley & Sons, Inc.

Libet, B. (2002): The timing of mental events: Libet's experimental findings and their implications. In: Conscious.Cogn, 11 (2), pp. 291-299.

Libet, B. (2003): Timing of conscious experience: reply to the 2002 commentaries on Libet's findings. In: Conscious.Cogn, 12 (3), pp. 321-331.

Libet, B.; Wright, E.W., Jr.; Gleason, C.A. (1983): Preparation- or intention-to-act, in relation to pre-event potentials recorded at the vertex. In: Electroencephalogr.Clin.Neurophysiol., 56 (4), pp. 367-372.

Lindeboom, J.; Weinstein, H. (2004): Neuropsychology of cognitive ageing, minimal cognitive impairment, Alzheimer's disease, and vascular cognitive impairment. In: European Journal of Pharmacology, 490 (1-3), pp. 83-86.

Lindner, M.; Hollricher, K.; Rötger, A. (2005): Warum wir kaufen was wir kaufen. In: bild der wissenschaft (9), pp. 16-33.

Logothetis, N.K. (2002): The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. In: Philos.Trans.R.Soc.Lond B Biol.Sci, 357 (1424), pp. 1003-1037.

Loo, C.K.; Mitchell, P.B. (2005): A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. In: J Affect.Disord., 88 (3), pp. 255-267

Lorist, M.M.; Boksem, M.A.; Ridderinkhof, K.R. (2005): Impaired cognitive control and reduced cingulate activity during mental fatigue. In: Brain Res Cogn Brain Res, 24 (2), pp. 199-205.

Luders, E.; Narr, K.L.; Thompson, P.M.; Woods, R.P.; Rex, D.E.; Jancke, L.; Steinmetz, H.; Toga, A.W. (2005): Mapping cortical grey matter in the young adult brain: effects of gender. In: Neuroimage, 26 (2), pp. 493-501.

Lutz, A.; Greischar, L.L.; Rawlings, N.B.; Ricard, M.; Davidson, R.J. (2004): Long-term meditators self-induce high-amplitude gamma synchrony during mental practice. In: Proc.Natl.Acad.Sci U.S.A, 101 (46), pp. 16369-16373.

Lynch, G. (2004): Memory enhancement: the search for mechanism-based drugs. In: Nature Neuroscience Supplement, 5, pp. 1035-1038.

Maguire, E.A.; Gadian, D.G.; Johnsrude, I.S.; Good, C.D.; Ashburner, J.; Frackowiak, R.S.; Frith, C.D. (2000): Navigation-related structural change in the hippocampi of taxi drivers. In: Proc.Natl.Acad.Sci U.S.A, 97 (8), pp. 4398-4403.

Marcar, V.; Lonneker, T. (2004): The BOLD response: a new look at an old riddle. In: Neuroreport, 15, pp. 1997-2000.

Marjanska, M.; Curran, G.L.; Wengenack, T.M.; Henry, P.G.; Bliss, R.L.; Poduslo, J.F.; Clifford, J.; Ugurbil, K.; Garwood, M. (2005): Monitoring disease progression in transgenic mouse models of Alzheimer's disease with proton magnetic resonance spectroscopy. In: Proceedings of the National Academy of Sciences of the United States of America, 102 (33), pp. 11906-11910.

Marshall, E. (2004): A star-studded search for memory-enhancing drugs. In: Science, 304, pp. 36-38.

Mathis, C.A.; Klunk, W.E.; Price, J.C.; DeKosky, S.T. (2005): Imaging technology for neurodegenerative diseases: progress toward detection of specific pathologies. In: Arch Neurol, 62 (2), pp. 196-200.

Mathis, C.A.; Wang, Y.; Klunk, W.E. (2004): Imaging beta-amyloid plaques and neurofibrillary tangles in the aging human brain. In: Curr Pharm Des, 10 (13), pp. 1469-1492.

Mattia, D.; Babiloni, F.; Romigi, A.; Cincotti, F.; Bianchi, L.; Sperli, F.; Placidi, F.; Bozzao, A.; Giacomini, P.; Floris, R.; Grazia, M.M. (2003): Quantitative EEG and dynamic susceptibility contrast MRI in Alzheimer's disease: a correlative study. In: Clin.Neurophysiol., 114 (7), pp. 1210-1216.

Mayer, R.E. (1998): Does the Brain Have a Place in Educational Psychology? In: Educational Psychology Review, 10 (4), pp. 389-396.

McCabe, K. (2003): Neuroeconomics – Encyclopedia of Cognitive Science, Lynn Nadel (ed-in chief) (ed.), New York: Nature Publishing Group; Macmillan Publishing, pp. 294-298.

McCabe, K.; Houser, D.; Ryan, L.; Smith, V.; Trouard, T. (2001): A functional imaging study of cooperation in two-person reciprocal exchange. In: Proceedings of the National Academy of Sciences, 98, pp. 11832-11835.

McClure, S.M.; Li, J.; Tomlin, D.; Cypert, K.S.; Montague, L.M.; Montague, P.R. (2004a): Neural correlates of behavioral preference for culturally familiar drinks. In: Neuron, 44 (2), pp. 379-387.

McClure, S.M.; Laibson, D.I.; Loewenstein, G.; Cohen, J.D. (2004b): Separate Neural Systems Value Immediate and Delayed Monetary Rewards. In: Science, 306, pp. 503-507.

McClure, S.M.; York, M.K.; Montague, P.R. (2004c): The Neural Substrates of Reward Processing in Humans: The Modern Role of fMRI. In: The Neuroscientist, 10 (3), pp. 260-268.

McGuire, G.Q.; McGee, E.M. (1999): Implantable brain chips? Time for debate. In: Hastings Center Report, 29 (1), pp. 7-13.

McMahon, P.M.; Araki, S.S.; Neumann, P.J.; Harris, G.J.; Gazelle, G.S. (2000): Cost-effectiveness of Functional Imaging Tests in the Diagnosis of Alzheimer Disease. In: Radiology, 217 (1), pp. 58-68.

McMahon, P.M.; Araki, S.S.; Sandberg, E.A.; Neumann, P.J.; Gazelle, G.S. (2003): Cost-Effectiveness of PET in the Diagnosis of Alzheimer Disease. In: Radiology, 228 (2), pp. 515-522.

Menning, H.; Imaizumi, S.; Zwitserlood, P.; Pantev, C. (2002): Plasticity of the human auditory cortex induced by discrimination learning of non-native, mora-timed contrasts of the Japanese language. In: Learn Mem, 9 (5), pp. 253-267.

Menning, H.; Roberts, L.E.; Pantev, C. (2000): Plastic changes in the auditory cortex induced by intensive frequency discrimination training. In: Neuroreport, 11 (4), pp. 817-822.

Michel, C.M.; Murray, M.M.; Lantz, G.; Gonzalez, S.; Spinelli, L.; Grave, D.P. (2004): EEG source imaging. In: Clin.Neurophysiol., 115 (10), pp. 2195-2222.

Michel, C.M.; Thut, G.; Morand, S.; Khateb, A.; Pegna, A.J.; Grave, d.P.; Gonzalez, S.; Seeck, M.; Landis, T. (2001): Electric source imaging of human brain functions. In: Brain Res.Rev, 36 (2-3), pp. 108-118.

Minagar, A.; Gonzalez-Toledo, E.; Pinkston, J.; Jaffe, S.L. (2005): Neuroimaging in Multiple Sclerosis – International Review of Neurobiology: Academic Press, pp. 165-201.

Mirzaei, S.; Gelpi, E.; Booij, J.; Rodrigues, M.; Neumann, I.; Zaknun, J.; Koehn, H.; Knoll, P. (2005): New Approaches in Nuclear Medicine for Early Diagnosis of Alzheimer's Disease. In: Current Alzheimer Research, 1 (3), pp. 219-229.

Moreno, J.D. (2003): Neuroethics: An agenda for neuroscience and society. In: Nature Reviews Neuroscience, 4 (2), pp. 149-153.

Moulin-Romsee, G.; Maes, A.; Silverman, D.; Mortelmans, L.; Van Laere, K. (2005): Cost-effectiveness of F-fluorodeoxyglucose positron emission tomography in the assessment of early dementia from a Belgian and European perspective. In: Eur J Neurol, 12 (4), pp. 254-263.

Mulert, C.; Jager, L.; Schmitt, R.; Bussfeld, P.; Pogarell, O.; Moller, H.J.; Juckel, G.; Hegerl, U. (2004): Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localisation and time-course of brain activity in target detection. In: Neuroimage, 22 (1), pp. 83-94.

Munte, T.F.; Altenmuller, E.; Jancke, L. (2002): The musician's brain as a model of neuroplasticity. In: Nat.Rev.Neurosci., 3 (6), pp. 473-478.

National Science Foundation (2002): Converging technologies for improving human performance – Nanotechnology, biotechnology, information technology and cognitive science., Roco, M.C.; Bainbridge, W.S. (eds.), Washington DC: National Science Foundation.

Nestor, P.; Scheltens, P.; Hodges, J. (2004): Advances in the early detection of Alzheimer´s disease. In: Nature Medicine, July, p. S34-S41.

Newberg, A.; Pourdehnad, M.; Alavi, A.; d'Aquili, E. G. (2003): Cerebral blood flow during meditative prayer: preliminary findings and methodological issues. In: Percept.Mot.Skills, 97 (2), pp. 625-630.

Nida-Rümelin, J. (2005): Über menschliche Freiheit. Nachwort. Presented at the Congress Neuro2004: Hirnforschung für die Zukunft. November 17, 2004, Düsseldorf: Reclam-Verlag.

Noesselt, T.; Shah, N.J.; Jancke, L. (2003): Top-down and bottom-up modulation of language related areas – An fMRI Study. In: BMC Neurosci., 4 (1), p. 13.

Northoff, G. (2000): Das Gehirn. Eine neurophilosophische Bestandsaufnahme, Paderborn: Mentis Verlag GmbH.

Nowinski, W.L.; Thirunavuukaresuu, A.; Kennedy, D.N. (2001): Brain atlas for functional imaging. Clinical and Research Applications. CD-ROM, Stuttgart: Georg Thieme Verlag.

Nuffield Council on Bioethics (1998): Mental disorders and genetics: The ethical context, Nuffield Council on Bioethics (ed.), London.

Nuffield Council on Bioethics (2002): Genetics and human behaviour: the ethical context, London: Nuffield Council of Bioethics.

OECD (2002): Understanding the Brain. Towards a new learning science, Paris: Organisation for Economic Cooperation and Development (OECD).

Olichney, J.M.; Hillert, D.G. (2004): Clinical applications of cognitive event-related potentials in Alzheimer's disease. In: Phys Med Rehabil Clin.N.Am., 15 (1), pp. 205-233.

Pallier, C.; Dehaene, S.; Poline, J.B.; LeBihan, D.; Argenti, A.M.; Dupoux, E.; Mehler, J. (2003): Brain imaging of language plasticity in adopted adults: can a second language replace the first? In: Cereb.Cortex, 13 (2), pp. 155-161.

Pascual-Leone, A.; Amedi, A.; Fregni, F.; Merabet, L.B. (2005): The plastic human brain cortex. In: Annu.Rev.Neurosci., 28, pp. 377-401.

Pascual-Leone, A.; Walsh, V. (2003): Transcranial magnetic stimulation studies of asymmetry of cognitive functions in the brain – Brain asymmetry, Cambridge, Massachusetts; London, England: The MIT Press, pp. 231-258.

Pascual-Marqui, R.D.; Esslen, M.; Kochi, K.; Lehmann, D. (2002): Functional imaging with low-resolution brain electromagnetic tomography (LORETA): a review. In: Methods Find.Exp.Clin.Pharmacol., 24 Suppl C:91-5., pp. 91-95.

Pauen, M. (2004): Illusion Freiheit? Mögliche und unmögliche Konsequenzen der Hirnforschung, Frankfurt/M.: S. Fischer.

Paulus, M.P. (2005): Neurobiology of decision-making: quo vadis? In: Cognitive Brain Research, 23 (1), pp. 2-10.

Paus, T. (2005): Mapping brain maturation and cognitive development during adolescence. In: Trends in Cognitive Sciences, 9 (2), pp. 60-68.

Peters, M.; Jancke, L.; Staiger, J.F.; Schlaug, G.; Huang, Y.; Steinmetz, H. (1998): Unsolved problems in comparing brain sizes in Homo sapiens. In: Brain Cogn, 37 (2), pp. 254-285.

Peters, M.; Jancke, L.; Zilles, K. (2000): Comparison of overall brain volume and midsagittal corpus callosum surface area as obtained from NMR scans and direct anatomical measures: a within-subject study on autopsy brains. In: Neuropsychologia, 38 (10), pp. 1375-1381.

Petersen, R.C. (2004): Mild cognitive impairment as a diagnostic entity. In: J Intern Med, 256 (3), pp. 183-194.

Phan, K.L.; Magalhaes, A.; Ziemlewicz, T.J.; Fitzgerald, D.A.; Green, C.; Smith, W. (2005): Neural correlates of telling lies: a functional magnetic resonance imaging study at 4 Tesla. In: Acad.Radiol., 12 (2), pp. 164-172.

Pien, H.H.; Fischman, A.J.; Thrall, J.H.; Sorensen, A.G. (2005): Using imaging biomarkers to accelerate drug development and clinical trials. In: Drug Discovery Today, 10 (4), pp. 259-266.

Pieters, T.; te Hennepe, M.; de Lange, M. (2002): Pills and psyche: cultural swings on medical intervention in the psyche, The Hague: Rathenau Institute.

Polich, J.; Herbst, K.L. (2000): P300 as a clinical assay: rationale, evaluation, and findings. In: Int J Psychophysiol., 38 (1), pp. 3-19.

Posse, S.; Olthoff, U.; Weckesser, M.; Jancke, L.; Muller-Gartner, H.W.; Dager, S.R. (1997): Regional dynamic signal changes during controlled hyperventilation assessed with blood oxygen level-dependent functional MR imaging. In: AJNR Am.J Neuroradiol., 18 (9), pp. 1763-1770.

Poulin, P.; Zakzanis, K.K. (2002): In vivo neuroanatomy of Alzheimer's disease: evidence from structural and functional brain imaging. In: Brain Cogn, 49 (2), pp. 220-225.

Präsident der Berlin-Brandenburgischen Akademie der Wissenschaften (2004): Zur Freiheit des Willens. Streitgespräch in der Wissenschaftlichen Sitzung der Versammlung der Berlin-Brandenburgischen Akademie der Wissenschaften am 27. Juni 2003, Debatte, Berlin: Berlin-Brandenburgische Akademie der Wissenschaften.

Preis, S.; Jancke, L.; Schmitz-Hillebrecht, J.; Steinmetz, H. (1999): Child age and planum temporale asymmetry. In: Brain Cogn, 40 (3), pp. 441-452.

Racine, E.; Bar-Ilan, O.; Illes, J. (2005): fMRI in the public eye. In: Nature Reviews Neuroscience, 6 (2), pp. 159-164.

Rademacher, J.; Galaburda, A.; Kennedy, D.N.; Filipek, P.A.; Caviness, V.S.J. (1992): Human cerebral cortex: localisation, parcellation, and morphometry with magnetic resonance imaging. In: Journal of Cognitive Neuroscience, 4, pp. 352-374.

Rademacher, J.; Morosan, P.; Schormann, T.; Schleicher, A.; Werner, C.; Freund, H.J.; Zilles, K. (2001): Probabilistic mapping and volume measurement of human primary auditory cortex. In: Neuroimage, 13 (4), pp. 669-683.

Raeymaekers, P.; Rondia, K.; Slob, M. (2004): Connecting Brains and Society. The present and future of brain science – what is possible, what is desirable? International Workshop, 22 and 23 April 2004, Amsterdam, the Netherlands. Proceedings and synthesis report, Brussels, The Hague: King Baudouin Foundation, Rathenau Institute.

Raichle, M.E. (1998): Behind the scenes of functional brain imaging: a historical and physiological perspective. In: Proc.Natl.Acad.Sci.U.S.A, 95 (3), pp. 765-772.

Raichle, M.E. (2000): A brief history of human functional brain mapping – Brain Mapping. The systems, Toga, A.; Maziotta, J.C. (eds.), San Diego, San Francisco, New York, Boston, London, Sydney, Tokyo: Academic Press, pp. 33-75.

Raine, A.; Ishikawa, S.S.; Arce, E.; Lencz, T.; Knuth, K.H.; Bihrle, S.; LaCasse, L.; Colletti, P. (2004): Hippocampal structural asymmetry in unsuccessful psychopaths. In: Biol.Psychiatry, 55 (2), pp. 185-191.

Ridderinkhof, K.R.; van den Wildenberg, W.P. (2005): Neuroscience. Adaptive coding. In: Science, 307 (5712), pp. 1059-1060.

Roberts, E. G.; Shulkin, B.L. (2004): Technical issues in performing PET studies in pediatric patients. In: J Nucl.Med Technol, 32 (1), pp. 5-9.

Roberts, E. G.; Vona-Davis, L.; Riggs, D.R.; Jackson, B.J.; Hohseni, H.; Kandzari, S.J.; McFadden, D.W. (2004): COX-2 inhibition and cancer: experimental findings and clinical correlates. In: W.V.Med J, 100 (3), pp. 96-101.

Rosen, A.C.; Bokde, A.L.W.; Pearl, A.; Yesavage, J.A. (2002): Ethical, and practical issues in applying functional imaging to the clinical management of Alzheimer's disease. In: Brain and Cognition, 50 (3), pp. 498-519.

Rosen, A.C.; Gur, R.C. (2002): Ethical considerations for neuropsychologists as functional magnetic imagers. In: Brain and Cognition, 50 (3), pp. 469-481.

Rosenfeld, J.P.; Angell, A.; Johnson, M.; Qian, J.H. (1991): An ERP-based, control-question lie detector analog: algorithms for discriminating effects within individuals' average waveforms. In: Psychophysiology, 28 (3), pp. 319-335.

Rosenfeld, J.P.; Soskins, M.; Bosh, G.; Ryan, A. (2004): Simple, effective countermeasures to P300-based tests of detection of concealed information. In: Psychophysiology, 41 (2), pp. 205-219.

Rosenfeld, J.P.; Biroschak, J.R.; Furedy, J.J. (2005): P300-based detection of concealed autobiographical versus incidentally acquired information in target and non-target paradigms. In: International Journal of Psychophysiology, In Press, Corrected Proof.

Roth, G. (2001): Das Gehirn und seine Wirklichkeit. Kognitive Neurobiologie und ihre philosophischen Konsequenzen, suhrkamp taschenbücher wissenschaft, Frankfurt/Main: Suhrkamp Verlag KG.

Ruof, J.; Mittendorf, T.; Pirk, O.; Graf von der Schulenburg, J.-M. (2002): Diffusion of innovations: treatment of Alzheimer's disease in Germany. In: Health Policy, 60 (1), pp. 59-66.

Sanfey, A.G.; Rilling, J.K.; Aronson, J.A.; Nystrom, L.E.; Cohen, J.D. (2003): The Neural Basis of Economic Decision-Making in the Ultimatum Game. In: Science, 300, pp. 1755-1758.

Schaefer, D.J.; Bourland, J.D.; Nyenhuis, J.A. (2000): Review of patient safety in time-varying gradient fields. In: J.Magn Reson.Imaging, 12 (1), pp. 20-29.

Schapiro, M.B.; Schmithorst, V.J.; Wilke, M.; Byars, A.W.; Strawsburg, R.H.; Holland, S.K. (2004): BOLD fMRI signal increases with age in selected brain regions in children. In: Neuroreport, 15 (17), pp. 2575-2578.

Scheltens, P.; Fox, N.; Barkhof, F.; De Carli, C. (2002): Structural magnetic resonance imaging in the practical assessment of dementia: beyond exclusion. In: The Lancet Neurology, 1 (1), pp. 13-21.

Schlaggar, B.L.; Brown, T.T.; Lugar, H.M.; Visscher, K.M.; Miezin, F.M.; Petersen, S.E. (2002): Functional neuroanatomical differences between adults and school-age children in the processing of single words. In: Science, 296 (5572), pp. 1476-1479.

Schlaug, G. (2001): The brain of musicians. A model for functional and structural adaptation. In: Ann.N.Y.Acad.Sci, 930, pp. 281-299.

Schumacher, R. (2005): Die prinzipielle Unterbestimmtheit der Hirnfor-
        schung im Hinblick auf die Gestaltung schulischen Lernens – Ist
        das psycho-physische Problem gelöst? Bewusstsein, Willensfrei-
        heit und die Neurowissenschaften, Sturma, D. (ed.), Frankfurt am
        Main: Suhrkamp Verlag.

Schweizerische Alzheimervereinigung (2004): Leben mit Demenz in der
        Schweiz. Eckdaten 2: Aktuelle Versorgung, Yverdon-les-Bains:
        Schweizerische Alzheimervereinigung.

Shallice, T. (2001): 'Theory of mind' and the prefrontal cortex. In: Brain, 124
        (Pt 2), pp. 247-248.

Shellock, F.G. (1992): Thermal responses in human subjects exposed to
        magnetic resonance imaging. In: Ann NY Acad Sci, pp. 260-272.

Shellock, F.G. (2000): Radiofrequency energy-induced heating during MR
        procedures: a review. In: J Magn Reson Imaging, 12, pp. 30-36.

Shellock, F.G. (2002): Magnetic Resonance Safety Update 2002: Implants
        and Devices. In: J Magn Reson Imaging, 16, pp. 485-496.

Shellock, F.G. (2003): Reference manual for magnetic resonance safety.
        In: Salt Lake City, Amirsys Inc.

Shellock, F.G.; Crues, J.V. (2002): MR safety and the American College of
        Radiology White Paper. In: AJR Am J Roentgenol, 178 (6),
        pp. 1349-1352.

Shulman, L.S. (1987): Knowledge and Teaching: Foundations of the New
        Reform. In: Harvard Educational Review, 57 (1), pp. 1-22.

Shulman, R.G. (2001): Functional imaging studies: linking mind and basic
        neuroscience. In: Am.J.Psychiatry, 158 (1), pp. 11-20.

Silverman, D.H.S.; Gambhir, S.S.; Huang, H.W.; Schwimmer, J.; Kim, S.;
        Small, G.W.; Chodosh, J.; Czernin, J.; Phelps, M.E. (2002): Evalu-
        ating Early Dementia With and Without Assessment of Regional
        Cerebral Metabolism by PET: A Comparison of Predicted Costs
        and Benefits. In: The Journal of Nuclear Medicine, 43 (2), pp. 253-
        266.

Sinai, A.; Pratt, H. (2003): High-resolution time course of hemispheric
        dominance revealed by low-resolution electromagnetic tomogra-
        phy. In: Clinical Neurophysiology, 114 (7), pp. 1181-1188.

Singer, T.; Frith, C. (2005): The painful side of empathy. In: Nat.Neurosci.,
        8 (7), pp. 845-846.

Singer, T.; Kiebel, S.J.; Winston, J.S.; Dolan, R.J.; Frith, C.D. (2004a):
        Brain responses to the acquired moral status of faces. In: Neuron,
        41 (4), pp. 653-662.

Singer, T.; Seymour, B.; O'Doherty, J.; Kaube, H.; Dolan, R.J.; Frith, C.D. (2004b): Empathy for pain involves the affective but not sensory components of pain. In: Science, 303 (5661), pp. 1157-1162.

Singer, W. (2004): Selbsterfahrung und neurobiologische Fremdbeschreibung. Zwei konfliktträchtige Erkenntnisquellen. In: Deutsche Zeitschrift für Philosophie, 52 (235), p. 255.

Smith, K.; Dickhaut, J.; McCabe, K.; Pardo, J.V. (2002): Neuronal Substrates for Choice Under Ambiguity, Risk, Gains, and Losses. In: Management Science, 48 (6), pp. 711-718.

Sowell, E.R.; Peterson, B.S.; Thompson, P.M.; Welcome, S.E.; Henkenius, A.L.; Toga, A.W. (2003): Mapping cortical change across the human life span. In: Nat.Neurosci., 6 (3), pp. 309-315.

Sowell, E.R.; Thompson, P.M.; Toga, A.W. (2004): Mapping changes in the human cortex throughout the span of life. In: Neuroscientist, 10 (4), pp. 372-392.

Spence, S.A. (2004): The deceptive brain. In: J R.Soc.Med, 97 (1), pp. 6-9.

Spence, S.A.; Farrow, T.F.; Herford, A.E.; Wilkinson, I.D.; Zheng, Y.; Woodruff, P.W. (2001): Behavioural and functional anatomical correlates of deception in humans. In: Neuroreport, 12 (13), pp. 2849-2853.

Spence, S.A.; Hunter, M.D.; Farrow, T.F.; Green, R.D.; Leung, D.H.; Hughes, C.J.; Ganesan, V. (2004): A cognitive neurobiological account of deception: evidence from functional neuroimaging. In: Philos.Trans.R.Soc.Lond B Biol.Sci, 359 (1451), pp. 1755-1762.

Steering Committee on Bioethics (CDBI) (2000): "White Paper" on the protection of the human rights and dignity of people suffering from mental disorder, especially those placed as involuntary patients in a psychiatric establishment. Drawn up by the Working Party on Psychiatry and Human Rights (CDBI-PH), DIR/JUR 2000(2), Strasbourg: Council of Europe.

Steinberg, L. (2005): Cognitive and affective development in adolescence. In: Trends in Cognitive Sciences, 9 (2), pp. 69-74.

Stern, E. (2005): Wieviel Hirn braucht die Schule? Chancen und Grenzen einer neuropsychologischen Lehr-Lern-Forschung. In: Zeitschrift für Pädagogik, 50 (4), pp. 531-538.

Stern, E.; Grabner, R.; Schumacher, R.; Neuper, C.; Saalbach, H. (2005): Lehr-Lern-Forschung und Neurowissenschaften – Erwartungen, Befunde, Forschungsperspektiven, Bundesministerium für Bildung und Forschung (ed.), Bildungsreform, Band 13, Bonn, Berlin: Bundesministerium für Bildung und Forschung.

Strahlenschutzkommission (2003): Elektromagnetische Felder neuer Technologien. Statusbericht der Strahlenschutzkommission, Bonn: Strahlenschutzkommission.

Straube, T.; Glauer, M.; Dilger, S.; Mentzel, H.J.; Miltner, W.H. (2005): Effects of cognitive-behavioral therapy on brain activation in specific phobia. In: Neuroimage.

Straube, T.; Kolassa, I.T.; Glauer, M.; Mentzel, H.J.; Miltner, W.H. (2004): Effect of task conditions on brain responses to threatening faces in social phobics: an event-related functional magnetic resonance imaging study. In: Biol.Psychiatry, 56 (12), pp. 921-930.

Sugrue, L.P.; Corrado, G.S.; Newsome, W.T. (2005): Choosing the greater of two goods: neural currencies for valuation and decision-making. In: Nature Reviews Neuroscience, 6 (5), pp. 363-375.

Sundgren, P.C.; Dong, Q.; Gomez-Hassan, D.; Mukherji, S.K.; Maly, P.; Welsh, R. (2004): Diffusion tensor imaging of the brain: review of clinical applications. In: Neuroradiology, 46 (5), pp. 339-350.

Sury, M.R.; Hatch, D.J.; Millen, W.; Chong, K. (2000): The debate between sedation and anaesthesia for children undergoing MRI. In: Arch Dis.Child, 83 (3), p. 276.

The Lancet Neurology (2004): Neuromarketing: beyond branding. In: The Lancet Neurology, 3, p. 71.

Thompson, P.M.; Giedd, J.N.; Woods, R.P.; MacDonald, D.; Evans, A.C.; Toga, A.W. (2000): Growth patterns in the developing brain detected by using continuum mechanical tensor maps. In: Nature, 404 (6774), pp. 190-193.

Thompson, P.M.; Hayashi, K.M.; Sowell, E.R.; Gogtay, N.; Giedd, J.N.; Rapoport, J.L.; de Zubicaray, G.I.; Janke, A.L.; Rose, S.E.; Semple, J.; Doddrell, D.M.; Wang, Y.; van Erp, T.G.; Cannon, T.D.; Toga, A.W. (2004): Mapping cortical change in Alzheimer's disease, brain development, and schizophrenia. In: Neuroimage, 23 Suppl 1, pp. S2-18.

Thompson, P.M.; Toga, A.W. (1999): Brain warping, San Diego: Academic Press.

Toga, A.W.; Thompson, P.M. (2003): Temporal dynamics of brain anatomy. In: Annu.Rev.Biomed.Eng, 5, pp. 119-145.

Triggs, W.J.; Subramanium, B.; Rossi, F. (1999): Hand preference and transcranial magnetic stimulation asymmetry of cortical motor representation. In: Brain Res, 835 (2), pp. 324-329.

Turner, R.; Jones, T. (2003): Techniques for imaging neuroscience. In: Br.Med.Bull., 65, pp. 3-20.

Ungerleider, L.G.; Doyon, J.; Karni, A. (2002): Imaging brain plasticity during motor skill learning. In: Neurobiol Learn Mem, 78 (3), pp. 553-564.

Valenzuela, M.J.; Sachdev, P. (2001): Magnetic resonance spectroscopy in AD. In: Neurology, 56 (5), pp. 592-598.

van Straaten, E.C.W.; Scheltens, P.; Barkhof, F. (2004): MRI and CT in the diagnosis of vascular dementia. In: Journal of the Neurological Sciences, 226, pp. 9-12.

Vicioso, B.A. (2002): Dementia: when is it not Alzheimer disease? In: Am.J Med Sci, 324 (2), pp. 84-95.

Villemagne, V.L.; Rowe, C.C.; Macfarlane, S.; Novakovic, K.E.; Masters, C.L. (2005): Imaginem oblivionis: the prospects of neuroimaging for early detection of Alzheimer's disease. In: Journal of Clinical Neuroscience, 12 (3), pp. 221-230.

Walsh, D.M.; Selkoe, D.J. (2004): Deciphering the Molecular Basis of Memory Failure in Alzheimer's Disease. In: Neuron, 44 (1), pp. 181-193.

Walter, H. (1999): Neurophilosophie der Willensfreiheit. Von libertarischen Illusionen zum Konzept natürlicher Autonomie, Paderborn: Mentis Verlag GmbH.

Wancata, J.; Musalek, M.; Alexandrowicz, R.; Krautgartner, M. (2003): Number of dementia sufferers in Europe between the years 2000 and 2050. In: European Psychiatry, 18 (6), pp. 306-313.

Wassermann, E.M. (1998): Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. In: Electroencephalogr.Clin.Neurophysiol., 108 (1), pp. 1-16.

Weiskopf, N.; Mathiak, K.; Bock, S.W.; Scharnowski, F.; Veit, R.; Grodd, W.; Goebel, R.; Birbaumer, N. (2004): Principles of a brain-computer interface (BCI) based on real-time functional magnetic resonance imaging (fMRI). In: IEEE Trans.Biomed.Eng, 51 (6), pp. 966-970.

Whalen, P.J.; Rauch, S.L.; Etcoff, N.L.; McInerney, S.C.; Lee, M.B.; Jenike, M.A. (1998): Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. In: J Neurosci., 18 (1), pp. 411-418.

Whyte, S.R.; Cullum, C.M.; Hynan, L.S.; Lacritz, L.H.; Rosenberg, R.N.; Weiner, M.F. (2005): Performance of elderly Native Americans and Caucasians on the CERAD Neuropsychological Battery. In: Alzheimer Dis.Assoc.Disord., 19 (2), pp. 74-78.

Wild, J. (2005): Brain imaging ready to detect terrorists, say neuroscientists. In: Nature, 437 (7058), p. 457.

Wilson, E.O. (1975): Sociobiology, Cambridge: Belknap Press of Harvard University Press.

Winblad, B.; Palmer, K.; Kivipelto, M.; Jelic, V.; Fratiglioni, L.; Wahlund, L.O.; Nordberg, A.; Backman, L.; Albert, M.; Almkvist, O.; Arai, H.; Basun, H.; Blennow, K.; de Leon, M.; DeCarli, C.; Erkinjuntti, T.; Giacobini, E.; Graff, C.; Hardy, J.; Jack, C.; Jorm, A.; Ritchie, K.; van Duijn, C.; Visser, P.; Petersen, R.C. (2004): Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. In: J Intern Med, 256 (3), pp. 240-246.

Witelson, S.F. (1992): Cognitive neuroanatomy: a new era. In: Neurology, 42, pp. 709-713.

Wolpe, P.R. (2002): Treatment, enhancement, and the ethics of neurotherapeutics. In: Brain and Cognition, 50 (3), pp. 387-395.

Wuerfel, J.; Krishnamoorthy, E.S.; Brown, R.J.; Lemieux, L.; Koepp, M.; Tebartz, v.E.; Trimble, M.R. (2004): Religiosity is associated with hippocampal but not amygdala volumes in patients with refractory epilepsy. In: J Neurol Neurosurg Psychiatry, 75 (4), pp. 640-642.

Yang, Y.; Raine, A.; Lencz, T.; Bihrle, S.; LaCasse, L.; Colletti, P. (2005): Volume reduction in prefrontal gray matter in unsuccessful criminal psychopaths. In: Biol.Psychiatry, 57 (10), pp. 1103-1108.

Yoo, S.S.; Fairneny, T.; Chen, N.K.; Choo, S.E.; Panych, L.P.; Park, H.; Lee, S.Y.; Jolesz, F.A. (2004): Brain-computer interface using fMRI: spatial navigation by thoughts. In: Neuroreport, 15 (10), pp. 1591-1595.

Yoo, S.S.; Jolesz, F.A. (2002): Functional MRI for neurofeedback: feasibility study on a hand motor task. In: Neuroreport, 13 (11), pp. 1377-1381.

Zak, P. (2004): Neuroeconomics. In: Philosophical Transactions of the Royal Society B: Biological Sciences, 359, pp. 1737-1748.

Zakzanis, K.K. (1998): Quantitative evidence for neuroanatomic and neuro-psychological markers in dementia of the Alzheimer's type. In: J.Clin.Exp.Neuropsychol., 20 (2), pp. 259-269.

Zakzanis, K.K.; Graham, S.J.; Campbell, Z. (2003): A meta-analysis of structural and functional brain imaging in dementia of the Alzheimer's type: a neuroimaging profile. In: Neuropsychol.Rev., 13 (1), pp. 1-18.

25 Annex

25.1 List of interviewees

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Prof. Dr. Pierre Magistretti, Département de physiologie, Université de Lausanne, Lausanne, Switzerland

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