Roskilde University

International Basic Studies in Natural Sciences

3rd semester project report

Could an antisocial behaviour be influenced by our genes?

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Abstract

Since the early '90, some hypothesis have been developed in order to understand if an antisocial behaviour could be generated by a low level of a particular enzyme called Monoamine Oxidase A (MAOA). Recently, such correlation influenced the discussion of three important murder cases in which the involved persons were affected by this MAOA-L genotype (where L states for low level). Nowadays, the progress in the genetic technologies, permits to map an entire genome and its known polymorphism in an easy and secure way, which could be used as proof during the trial. Such possibility lead to some important questions: How the court should take into consideration a MAOA deficiency? Should a genetic test help to prevent further crimes? There is the possibility that a person affected by MAOA-L genotype will be discriminated? Moreover, once tested that a subject possesses MAOA-L, should we get this information freely or there must to be some restrictions concerning the safeguard of the individual?

Here we take into consideration some of the more famous cases of MAOA-L genotype and their relation to the behaviour. We also discuss the ethical and moral aspects concerning the genes importance in relation with the person's attitude an how they can affect the judges during the sentences.

Acknowledgement

I would like to thank my supervisor Ole Andersen for his advise and helpful comment regarding this study, I also appreciate the constructive critics and comment from mine opponent groups and supervisors.

1. Introduction

The first case of appearance of genetic link to crime has been observed in the writings of Plato, where there was a Greek man that was justified from his crime because it was state that he was the third generation of his family to be found to commit crimes such as murder. The court hypothesised that certain characteristics such as an antisocial behaviour could be inherited, continuing therefore in subsequent generations (Plato 856d.).

Regarding the actuality, two important murder cases have been reported in scientific papers. One occurred in 1993 when Han Brunner published a study of a Dutch family (Brunner et al. 1993), whereas the most recent fact took place in Italy in 2009, where a man accused of murder was given a reduction of sentence on the basis that "*his genetic makeup made him more likely to commit violent acts*" (Baum 2011). In both cases there was a common precursor called MAOA (Monoamine Oxidase A) gene located on the X chromosome that if present in low amount (or even absent as the Dutch family), can be associated with an impulsive aggression, without forgive the environment interaction (such as childhood maltreatment) (Caspi et al. 2002).

One of the central goals of the society has always been to make it safe by preventing violent behaviour. This purpose is more likely to be accomplished if law makers and security force can denote violent individuals and predict their future behaviour (Nadelhoffer et al. 2010). New genetic techniques and knowledge development make possible to map the genome of any individual for the presence of known polymorphisms (such as MAOA), with a wish for diagnosis and the discover of a cure. On the other hand, the genetic prediction of an antisocial behaviour leads to ethical concerns about how this information will be collected and, if it is right to do so, who will have access to it. Another important questionable concerns regards the response of the court in sentencing murders cases linked to MAOA-L (Monoamine Oxidase A enzyme present in low level) (Glick et al. 2003).

1.1 Problem formulation

The purpose of this report is to shed more light on behavioural genetics, especially if an antisocial behaviour is conditioned by its genetic makeup and to what extend. Since it has been scientifically proven that genes can influence our behaviour and that MAOA is the major candidate gene to be more likely to express an antisocial behaviour, the main question of this project is:

Main question:
What has to be made with an antisocial individual who possesses a low MAOA enzyme level?

Sub-questions:
How shall society react?
What role does the environment play in the development on an antisocial behaviour?
What could be an ethical and moral implication of antisocial behavioural genetics?

1.2 Semester theme

3rd semester theme is *Reflection on natural science and the dissemination of knowledge in the field of natural science.* This project fits the third semester theme since there are disagreements between the scientific community and the society in terms of importance of antisocial behavioural genetics. Additionally, ethical considerations include how responsibility and punishment could be determined in an antisocial individual which is compromised by its genes. In this project I am going to analyse scientific and ethical/moral aspects of antisocial behaviour determined by genes.

2 The history of behavioural genetics

Francis Galton (1822-1911), Charles Darwin's half-cousin, is considered one of the initiators of a discipline called behaviour genetics, which examines the role of genetics in animal (including human) behaviour and studies the inheritance of behavioural traits. Behaviour is defined as "*the reactions and the interactions of an organism to its environment and with other organisms*" (Bloom et al. 2000). This discipline is a mixture of biology, genetics, ethology, psychology and statistics. In the 1860s Galton intended to study the extent to which genius is hereditary. This research led to the publication of *Hereditary Genius* in 1869, with the aim to show "*that a man's natural abilities are derived by inheritance, under exactly the same limitations as are the form and physical features of the whole organic world*" (Bloom et al. 2000; Galton 1869).

2.1 Research in behavioural genetics

Research in behavioural genetics cover the effects of genotype and environment on a range of phenotypic traits such as anxiety, intelligence, sexual orientation and antisocial behaviour. It can be classified in two main categories: one is called quantitative genetics, the other is called molecular genetics. The aim of quantitative genetics is to examine the extent to which variation in a trait is influenced by genetic factors in a population. It uses statistical methods to examine and compare groups of people such as twins or siblings and adopted children, without focusing on particular genes. On the other hand molecular genetic search differences in genes that can contribute to trait variation in characteristics or between individuals (Kennedy et al. 2002).

2.2 The relationship between genes and the environment

Genes and environment (including experience) are considered to play an essential role for what concern our behaviour. The genetic importance is explicit because all behaviour is controlled by the brain and the nervous system. Genes direct the development of the brain through transcription and translation of DNA into proteins. Therefore, genes affect the molecular structure of the brain at every level, including brain anatomy, neurotransmitter levels and receptors, and the processes that control the development of interconnection among neurons. Behaviour also, is influenced by experience and other

aspects of the environment including a person's culture and interactions with family and friends (Bloom et al. 2000). As example of genes and environment correlation, a child inherits genes from his parents but he is also exposed to environments that influence his well being. In fact sociable parents supply an environment to their children that support the improvement of sociability in their children (Kennedy et al. 2002).

Another interesting factor that can influence behaviour is the development. Development is graduated in nature: "*what an organism is today depends on what it was yesterday and is a substrate for what it will be tomorrow*". Certain genes are active or act differently depending on a specific developmental stages. Hence, the influence of development in behaviour depends on historical events and the timing of which certain circumstances occur, resulting in different behaviour outcome (Bloom et al. 2000).

2.3 Antisocial behaviour

In this current project, it has been decided to incorporate many antisocial aspects in one. The reason of doing so is that, if all of them came from a common precursor (such as MAOA) it is much easier to report a big problem instead of focusing more in a single antisocial comportment (such as impulsivity for instance). If relevant, it will denote the particular antisocial behaviour giving more emphasis at that specific disorder/antisocial behaviour. Antisocial personality and behaviour (APB) include aggression, violence, impulsivity, stealing, antisocial personality disorder and psychopathy (Ferguson 2010). Without any doubt each aspect is singular and should be considered apart. However, what is of peculiar importance here is to try to estimate how much interconnection there is between genes and behaviour, and what can be made to reduce the risk of criminality in cases where it is possible to prove this relationship.

Antisocial aggression is a widespread and expensive social problem. Studies conducted in USA reveal that "*adult antisocial behaviour is estimated to range as high as 12.3% of the population, each costing society up to ten times more than their healthy counterparts in aggregate health care and social service expenditure*" (Buckholtz et al. 2008). Such high criminality suggests heritable factors in a such antisocial environment. Thus, the heritability of antisocial behaviour has been confirmed by performing

twin and adoption study, with the result that "*genetic factor account for between 40% and 50% of population variance in risk"*. However, antisocial behaviour is genetically complex, in fact there are multiple variants that are more likely to influence the effect of one gene in interaction with one another (epistasis) and the environment. On the other hand there is a candidate gene for human aggression, the MAOA gene (Buckholtz et al. 2008).

3 Monoamine oxidase gene (MAO)

Monoamine oxidase genes (MAO) code for enzymes called monoamine oxidases. MAOs is present in two major forms called A and B. The two isoenzymes are involved in the breakdown of neurotransmitters such as serotonin and dopamine, rendering them inactive. The level of MAOs in brain and other tissues are important because they influence the metabolism of these neurotransmitters. It seems that the levels of these MAO enzymes in brain tissue can have significant effects on behaviours varying from anxiety and panic disorder to aggression and violence (Hook 2009).
The table below illustrates a list of behavioural disorder implicating mutations on the MAO gene with low level of MAOA.

Disorder	Reference
Anxiety	Chen et al. (2004)
Personality disorders	Samochowieca et al. (2004)
Antisocial behaviour	Caspi et al. (2002); Samochowiec et al. (2004)
Violence and risk taking	Lea and Chambers (2007); Widom and Brzustowicz (2006)
Risk taking	Lea and Chambers (2007)
Antisocial behaviour	Widom and Brzustowicz (2006)
Aggressive behaviour	Newman et al. (2005); Buckholtz & Meyer-Lindenberg (2008); Cases et al. (1995); Rosenberg (2006)
Impulsive aggression	Buckholtz & Meyer-Lindenberg (2008)
Mental disorders	Pinsonneault et al. (2006)
Obesity	Need et al. (2006)
Impulsivity	Manuck et al. (2000)
Depression and suicidality	Bernet al. (2007)
Impaired impulse control	Rosenberg et al. (2006)
Mental retardation (Brunner syndrome)	Rosenberg et al. (2006)
Mental retardation, autism, seizures, sleep disturbances (Norrie disease)	de la Chapelle et al. (1985); Levy et al. (1989)
Panic disorder	Deckert et al. (1999)

Table 1: List of disorders possibly caused by low level of MAOA (Hook 2009).

MAOA and MAOB have different substrates and inhibitor specificities and are encoded by two genes on the short arm of the X chromosome at location Xp11.23-11.4 (Hook 2009; Lenders et al. 1996; Beaver et al. 2009).

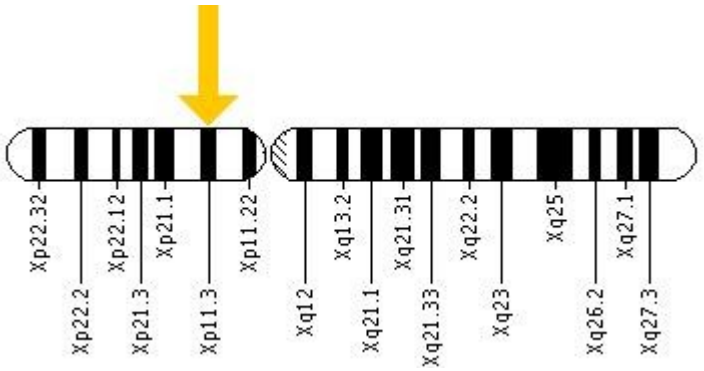

Fig. 1: location of the MAOs genes on the short arm of the X chromosome (http://ghr.nlm.nih.gov/gene/MAOA)

The A form is of peculiar scientific interest because its gene contain a 30 base pair repeat polymorphism (MAO-A30bp-rpt) that encoded the MAOA enzyme, which metabolises serotonin and norepinephrine (NE). In the MAOA gene's promoter, a region that controls transcription and expression, there are variable number of nucleotide tandem repeats (VNTR). If the VNTRs is repeated four times, the individual is referred to posses high MAOA (normal allele). If the sequence is repeated three times, the individual has low MAOA (variation in allele of the MAOA gene also called polymorphism). The consequence of the gene only repeating three times is that it will give rise to 10 times less MAOA than the four repeat gene. A less production of MAOA causes a less serotonin and dopamine metabolism, such that higher levels of these remain in the system. (Baker et al. 2006). High levels of serotonin and dopamine are known to lead to various behavioural disorders, particularly aggressive behaviour (Merriman and Cameron 2007). *Figure 2* show that approximately 65% of males in the human population *(big circle)* possess the MAOA High gene variant (MAOA-H) while approximately 30% of males in the human population *(small circle)* possess the MAOA Low variant (MAOA-L). The remaining 5% of males is refers to a rare case of absence of MAOA (also called Brunner syndrome). When equal portions of these 2 groups are exposed to an adverse environment during childhood *(the oval)* only the MAOA-L shows a significantly increased probability of aggression (Baum 2011). Of particular Interest, in vitro studies indicate that the variant with three repeats is expressed less efficiently than the variant with four repeats (Baum 2011).

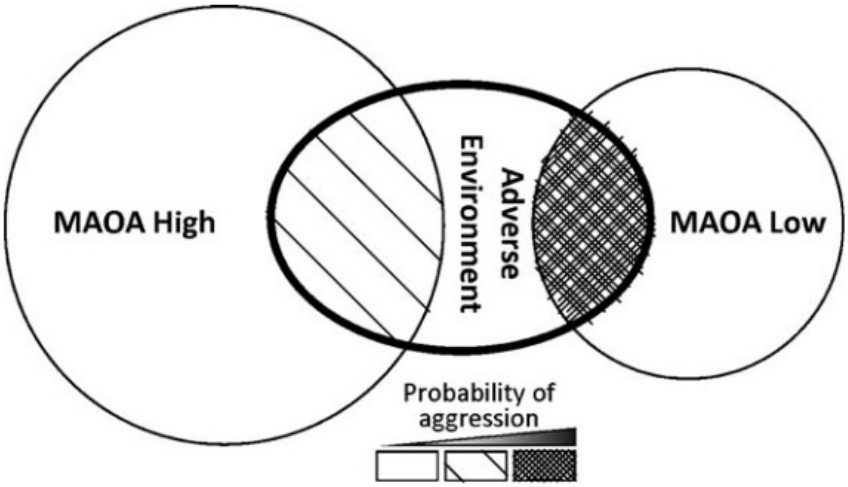

Fig. 2: Diagramatic representation of the MAOA gene x environment interaction (Baum 2011).

Caspi and colleagues (Caspi et al. 2002) tested the hypothesis that the low- expressing variant (MAOA-L) would be related with antisocial behaviour (Baum 2011). Moreover, while the MAOA-L allele does not confer an increased risk for violent behaviour, the results suggest that it still incline males with an history of childhood maltreatment (Nadelhoffer et al. 2010).

The fact that the gene is located on the X chromosome explains why violent crimes and antisocial personality disorder are observed in enormous amount in men rather than females. Men inherit a single X chromosome while females inherit two, which puts men at greater risk for inheriting a mutated polymorphism of the MAOA gene simply because is less probable that in both XX chromosomes there is a MAOA-L activity. (If for instance one X chromosome possesses a MAOA-L activity it can be compensate with the other X chromosome, still resulting at the end a MAOA-H activity in females) (Baum 2011).

3.1 MAOA and MAOB metabolism

Since the MAOA and MAOB enzymes have been found in the outer membrane of mitochondria in neurons, astroglia and outside the central nervous system (CNS) in peripheral tissues such as liver,

kidney and intestine, in order to understand their crucial role with the metabolism of neurotransmitters, a general overview of neurons, brain noradrenergic system and nature of some neurotransmitters (biogenic amines) will be given.

Neurons (nerve cells that transfer information through all the body) communicate via two different types of signals: long-distance electrical signals (consisting of sensory neurons) and short distance chemical signals (being interneurons). Sensory neurons use electric discharge to receive, transmit, and regulate the information flow over long distances within the body. In transferring information over short distance, meaning from one cell to another, neurons use chemical signals. Interneurons are organised in CNS, including the brain and a longitudinal nerve cord. The neurons that carry information into and out of the CNS represent the peripheral nervous system (PNS). As the *Figure 3* illustrate, neurons possesses a ramified axon that permit to transfer the information flow to another cell via a junction called synapse. At most synapses, chemical messengers called neurotransmitters pass information from the transmitting neuron (the presynaptic cell) to the receiving cell (postsynaptic cell) (Campbell and Reece 2008).

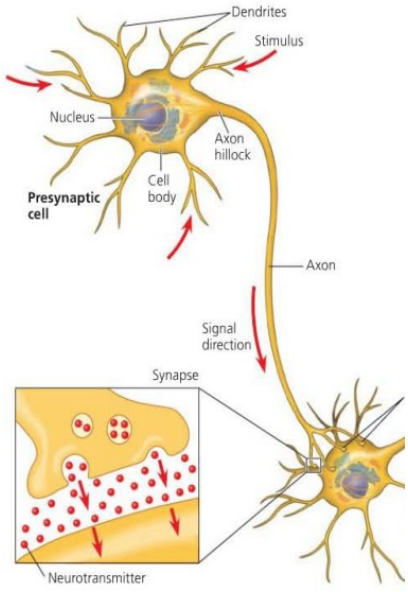

Fig. 3: Neuron structure and organization (Campbell and Reece 2008).

The brain noradrenergic system is a system of neurons located in the brain that is responsible for the synthesis, storage and release of the neurotransmitter such as adrenaline (also called

epinephrine), dopamine and norepinephrine (NE) (also called noradrenaline). (Meloni 2008). These substances are catecholamines, a class of biogenic amines (derived from amino acids as shown in *Figure 4*), characterised by a catechol (benzene-1,2-diol) and an amino group (tyrosine). The biogenic amine serotonin is synthesised from tryptophan. Dopamine and serotonin acts only as a neurotransmitter whereas norepinephrine and adrenaline act both as neurotransmitters and as hormone.

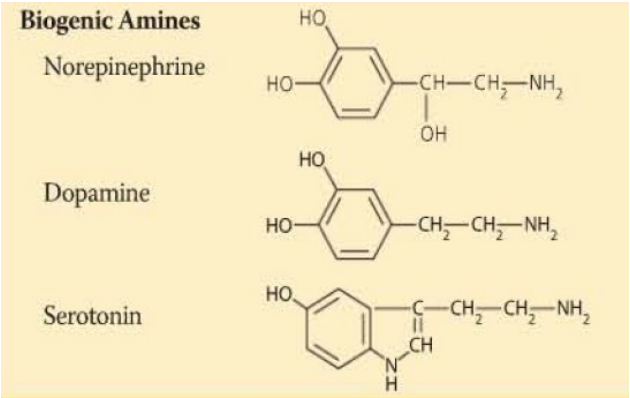

Fig. 4: Structure of three major neurotransmitters metabolized by MAOA and MAOB (Campbell and Reece 2008).

Dopamine and serotonin are released at many sites in the brain and affect sleep, mood, attention, and learning. In the brain the cell bodies that contain NE are found in the brainstem, extending from the forebrain to the spinal cord. These neurons are associated with the stress response and with the control of drive and motivation, alertness and sleep patterns, along with stress related manifestations such as anxiety and fear (Meloni 2008; Campbell and Reece 2008).

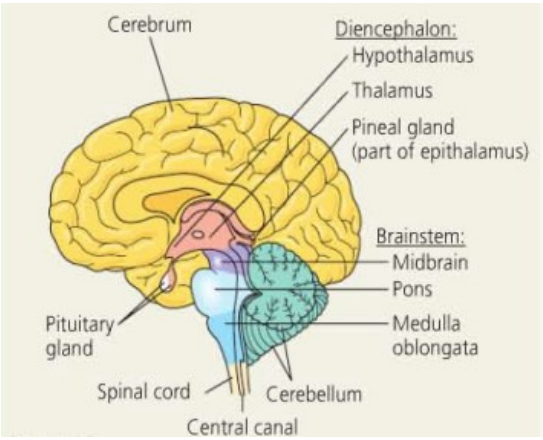

Fig. 5: Brain structure present in humans (Campbell and Reece 2008).

Monoamine oxidase (MAO) was discovered in the 1930s by Balschko and is a mitochondrial enzyme that helps in controlling the concentration of monoamines in the CNS. It is one of the most important enzymes in neurotransmitter metabolism. The inhibition of MAO on dopamine (DA), NE and serotonin (5-HT) have played an important role in understanding the functions of these neurotransmitters in the CNS (Youdim and Riederer 2004). The MAOA and MAOB enzymes oxidises the neurotransmitters by taking off the nitrogen containing amine groups by a process called deamination.

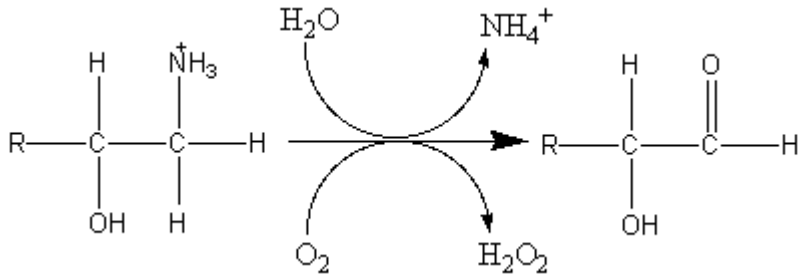

Fig. 6: Deamination process in the metabolism of monoamines by MAOA and MAOB

The MAOA enzyme is responsible for the deamination of NE and 5-HT (as *Figure 7* illustrate), whereas the MAOB enzyme metabolises phenylethylamine (PEA).

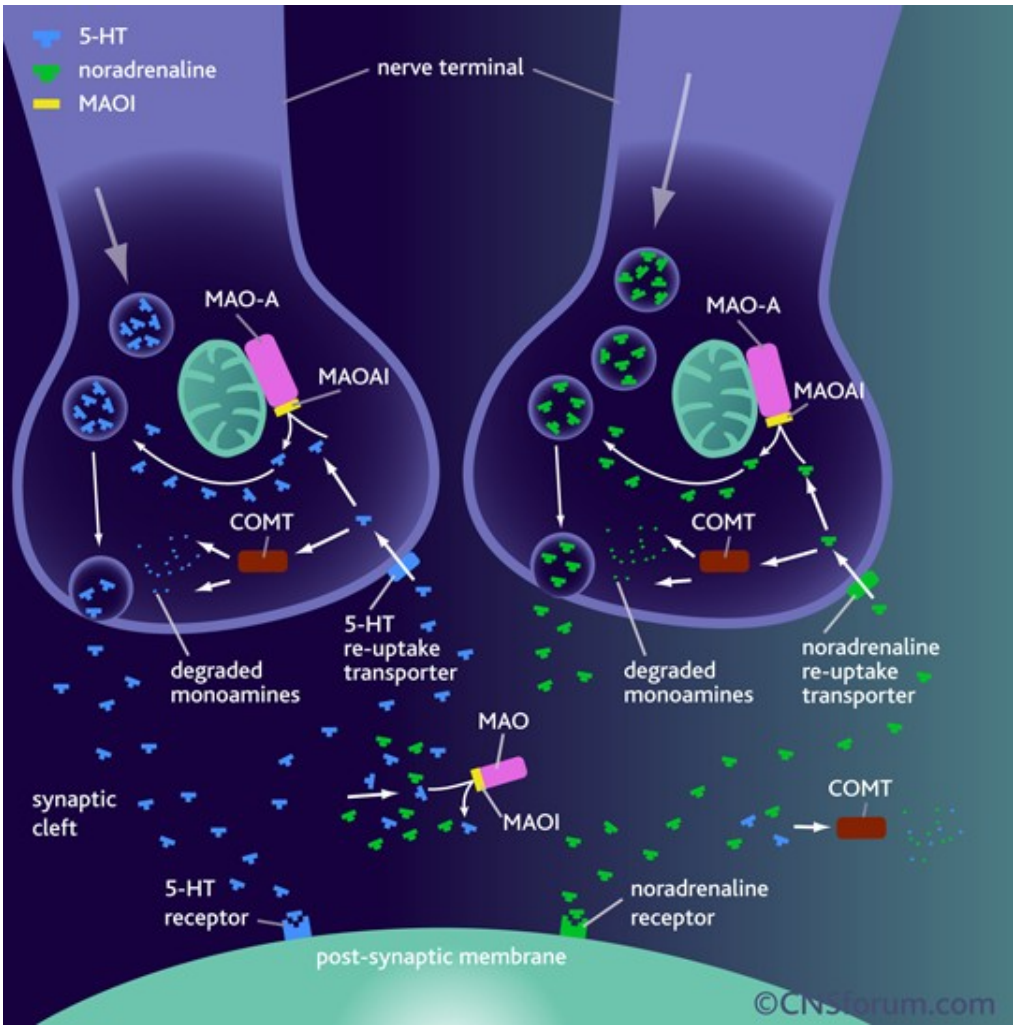

Fig. 7: the role of MAOA in the catabolism of NE and 5-HT. Note that MAOI correspond to MAOA inhibitor.
http://www.cnsforum.com/imagebank/item/Drug_MOAI_2/default.aspx

MAOA inhibitors bind to and inhibit MAOA, preventing the degradation of monoamine neurotransmitters. MAOA inhibitors are used in the treatment of depression where subjects suffering of depression possesses lower than normal levels of the monoamines and MAOA inhibitors restore this levels. Both MAOA and MAOB metabolises tyramine and dopamine as the table below illustrates (Youdim and Riederer 2004). The two MAO isoforms can be distinguished by using synthetic compounds that function as inhibitors. MAO-A is selectively inhibited by clorgyline whereas MAOB is selectively inhibited by L-deprenyl (selegiline). MAOs are involved in many behavioural processes and their inhibition has a marked effect on brain function and blood pressure regulation (Mihalik et al. 2011).

	MAO type		
	A + B	A	B
Neurotransmitters and metabolites			
Epinephrine			
Norepinephrine		+	
Dopamine	+		
Serotonin (5-HT)		+	
Metanephrine		+	
Normetanephrine		+	
Tele-N-methylhistamine			+
MPTP			+
Trace amines, dietary amines, drugs			
Tyramine	+		
Octopamine		+	
Phenylethylamine			+
Tryptamine		+	
Phenylethanolamine			+
Synephrine	+		
Phenylephrine	+		

Table 2: Natural and synthetic substrates metabolized by MAOA, MAOB and both MAOA and MAOB enzymes. Note that MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) (Youdim, Riederer 2004).

Both MAOA and catechol-O-methyltransferase (COMT) coordinate the degradation of NE. They generate aldehyde intermediates, which are reduced to 3,4-dihydroxyphenyl-glycol (DHPG) and 3-methoxy-4-hydrophenylglycol (MHPG) by cytosolic aldehyde reductase or oxidised to vanyl-mandelic acid (VMA) by mitochondrial aldehyde dehydrogenase (Meloni 2008). *Figure 8* shows the pathways of biosynthesis of catecholamines and serotonin (Haavik et al. 2008). (see abbreviation for enzymes).

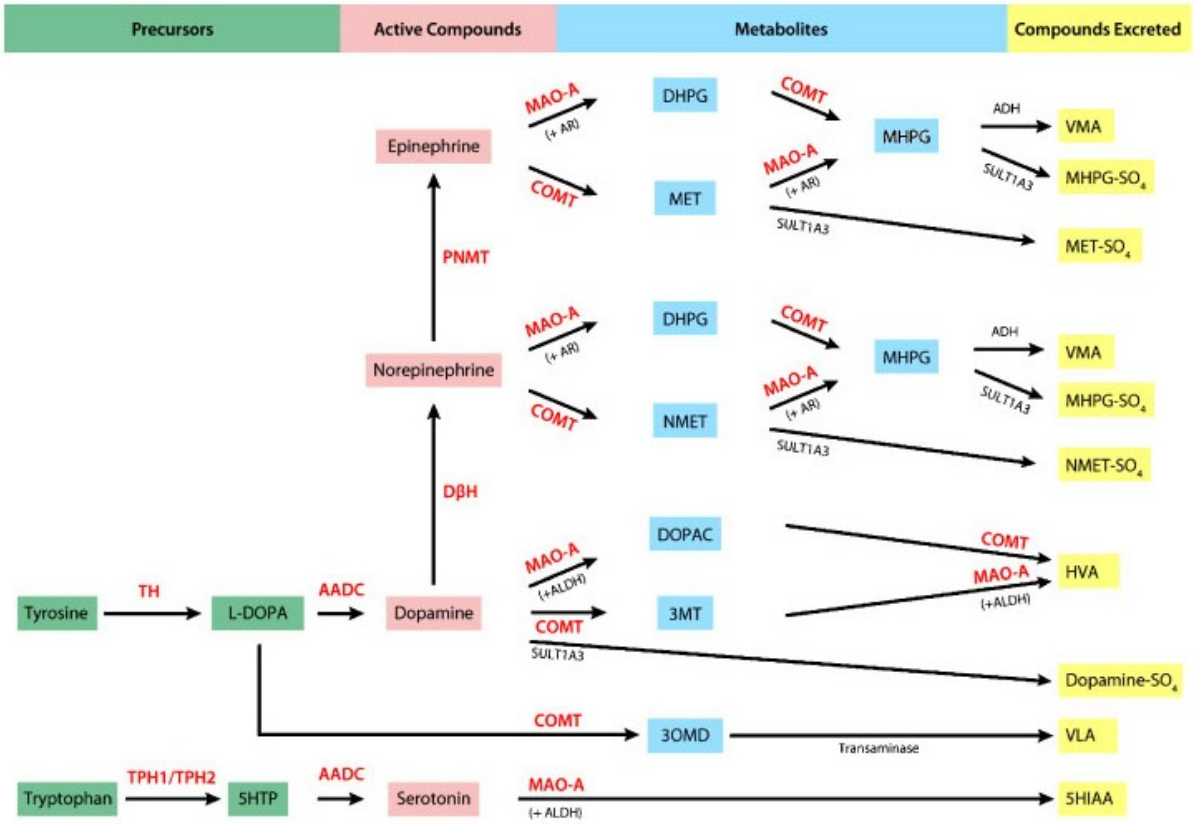

Fig. 8: Metabolism of catecholamines and serotonin (Haavik et al. 2008).

The degradation of serotonin involves an oxidative deamination caused by MAOA, leading to 5-hydroxy-indol- acetaldehyde which in turn is oxidised into 5-hydroxy-indol-acetic acid (5-HIAA) (Haavik et al. 2008).

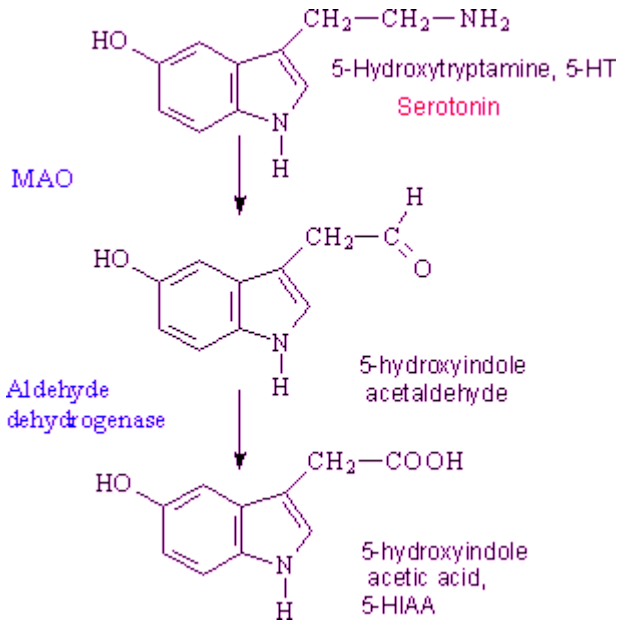

Fig. 9: Degradation of serotonin
http://www.pharmacorama.com/en/Sections/images/Serotonin_2_clip_image006_0000.gif

In 1988 an important improvement has been made, it was mapped the MAOA and MAOB genes sequence. This work had an important effect in the scientific community since it demonstrate that MAOA and MAOB were made of different proteins. Moreover from that genome was possible to make comparison and estimate how much of MAOA and MAOB every organism possesses. *Figure 10* shows the deduced amino acid sequences of MAOA and MAOB genes in humans liver (Chen Shih 2004).

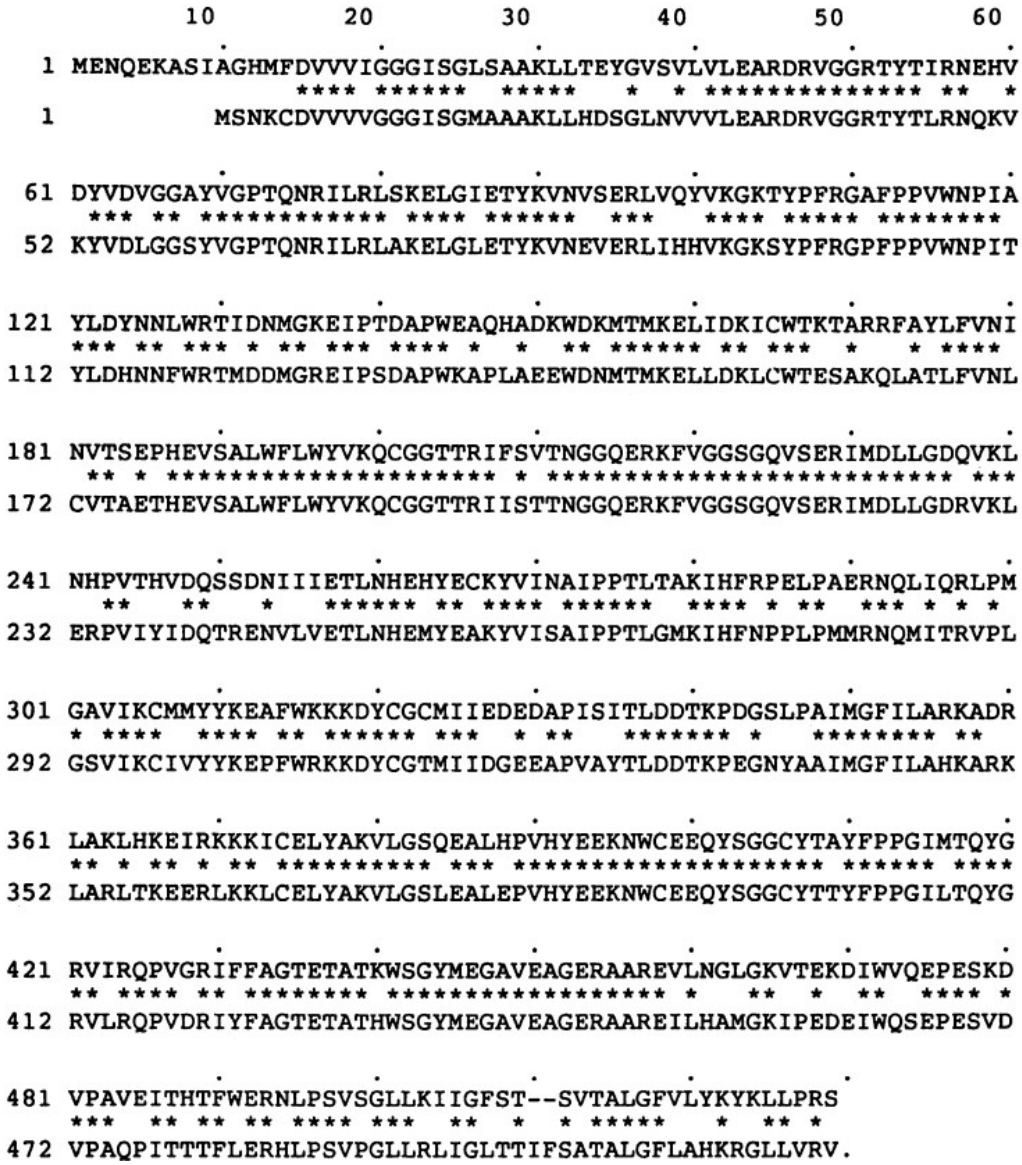

Fig. 10: Amino acid sequences of human liver MAOA and MAOB respectively. Note that the asterisks indicate positions occupied by identical amino acids (Chen Shih 2004).

3.2 Consequences in deficiency of MAOA, MAOB and MAOA/MAOB

In humans both MAOA and MAOB genes are absent in subjects with Norrie's disease, a rare X-linked recessive neurological disorder defined by blindness, hearing loss and mental retardation (Lan et al. 1989). A particular mutation called deletion was diagnosed in the males of a Dutch family (Brunner et al. 1993) resulting in a complete MAOA deactivation that causes an abnormal aggressive behaviour which is related to an increased levels of NE and setoronin (Meloni 2008).

A functional polymorphism located in the MAO-A gene promoter 1.2 kb upstream of the encoding sequence lie in a 30 bp repeated sequence present in 3, 3.5, 4, or 5 copies (Meloni 2008). This polymorphism is able to affect the transcriptional activity of the MAO-A gene promoter (Sabol et al. 1998). Genetic studies have found that MAOA-H were associated with panic disorder (Deckert et al. 1999) and depressive disorder in females (Schulze et al. 2000), where the MAOA-L alleles were associated with schizophrenia and aggressive behaviour in males (Jonsson et al. 2003). Other studies reached negative results for panic disorders (Hamilton et al. 2000), schizophrenia (Syagailo et al. 2001; Fan et al. 2004) and mood disorders (Huang et al. 2004). Nevertheless, more consistent results have been found taking into account also an environment factor (Caspi et al. 2002).

An interesting study (Lenders et al. 1996), shows that the MAO-B deficient subjects does not manifest abnormal behaviour nor mental retardation (such as respectively MAOA mutation and MAOA/MAOB deficiency). In MAOA deficient subject, there is a decrease in deaminated catecholamine metabolites and at the same time an elevation of O-methylated amine metabolites. These neurochemical changes are only magnified in patients with lack of MAOA and MAOB together. Contrarily, the only biochemical abnormalities detected in subjects with the MAOB gene deletion are an absence of MAOB activity and an increased urinary excretion of phenyethylamine, showing however a normal behaviour (Lenders et al. 1996). Despite the majority of MAOB in relation to MAOA in the human brain, the salient abnormal aggression in behaviour in MAOA deficient subject and the normal behaviour in MAOB deficient subjects indicate that MAOA plays a more critical role in the metabolism of catecholamines and serotonin (5-HT) than MAOB. A relationship in the observed behavioural abnormalities in MAOA deficient subjects is supported by a recent study in transgenic mice with a deletion in the MAOA gene. The aggressive behaviour in these animals were related with

an elevated brain 5-HT concentrations (Lenders et al. 1996).

In conclusion, deficiency of MAOB does not lead to a specific clinical phenotype and is not associated with apparent disturbances in behaviour such as are observed in deficiencies of MAOA. The absence in neurochemical alterations in MAOB deficiency indicates that MAOA is substantially more important than MAO-B for metabolism of most biogenic amines (Lenders et al. 1996).

3.3 Murder cases linked to MAOA

The first request to the MAOA genotyping in the court occurred in 1995 for the rare mutation found in the Dutch family in the Brunner et al. study on Stephen Mobley, a 29 year old man accused of murder (Baum 2011). His lawyers demanded finding to investigate if there was the possibility that his behavioural history was the result of a genetic status. There were proves of familial history over several generations of violent behaviour, alcoholism and abuse to support a possible genetic link to Mobley's behaviour (Baum 2011). In the Dutch family, MAO-A deficiency was tested based on urinary samples which reveals only in male members an elevated concentration of Normetanephine (NMET) and tyramine, low 5-Hydroxyindoleacetic acid (5HIAA), vanyl-mandelic acid (VMA) and Homovanillic acid (HVA), and the MAOA-mutant allele p.Q296X, a premature termination codon in exon 8 that give rise to nonfunctional proteins (Haavik et al. 2008).

Brunner concluded that "*isolated complete MAOA deficiency in this family is associated with a recognizable behaviourable phenotype that includes disturbed regulation of impulsive aggression*" (Brunner et al. 1993). The judge determined that genotyping was not guaranteed on the basis that "*the theory of genetic connection is not a level of scientific acceptance that would justify its admission*" and Mobley was then condemned to death (Baum 2011). In 2008 Pieri et al. conducted an investigation collecting various opinion of law professionals in which "*almost all participants were skeptical about the possibility that research into the genetics of aggressiveness and violence might benefit, or even enter, their fields of practice, in the foreseeable future or even*". However, by 2007, genotyping evidence on MAOA variants (of the gene-environment type) had been presented in the court for few criminal cases. *Table 3* summarised the cases and the final sentence (Baum 2011).

Case	Brief description	Genotype	Adverse environment?	Result
Mobley (1995)	Charged with murder. During trial, asked for genotyping according to rare Brunner et al. study	Genotyping refused	n/a	Executed
Waldroup (2009)	Charged with murder (capital offense) of estranged wife's friend, attempted murder of wife, and two counts of kidnapping after escalating argument	MAOA L	Childhood Abuse	Voluntary manslaughter (instead of murder); two counts of aggravated kidnapping; attempted 2nd degree murder. 32 year sentence
Bayout (2009)	Defendant assaulted by group of youths, after which he buys a knife and follows victim down street. Kills victim, mistakenly thinking victim was one of the assailants. Possibly delusional at time	MAOA L	Unclear. Culture shock/social isolation? Schizophrenia?	Sentence reduced by 1 year for genetic evidence

Table 3: MAOA genotyping in court (Baum 2011).

In the Bayout case occurred in Italy, the defendant had a history of mental disorder, however no childhood abuse or maltreatment were mentioned in the case. Could schizophrenia itself count as an adverse environment? Schizophrenia does not generally attack until 17–21 years not exactly childhood. On the other hand the prefrontal cortex does not finish maturing until the early-mid twenties (he was 24 year old) and the brain remains plastic throughout life. It is questionable that Bayout reported an adverse environment that could combine with his MAOA-L gene (Baum 2011). The judge found MAOA-L gene evidence "*particularly compelling*" and accepted that this " *would make him particularly aggressive in stressful situations*". Bayout's sentence was reduced by one year (Baum 2011).

In the Waldroup case that took place in Tennessee, the defendant was both abused as a child and suffered of the MAOA-L variant. No behavioural tests on impulse control or emotional sensitivity were performed. Waldroup's lawyers, however, did argue that "*he suffered from both intermittent explosive disorder and acted in passion*", both conditions that could be connected with the MAOA-L alleles polymorphism. The court made the decision in considering the MAOA evidence (Baum 2011).

4 Investigations done in relation to antisocial behaviour

In this session I will present some of the most relevant experiences conducted in the laboratory concerning the Monoamine oxidase A genotype in relation to antisocial behaviour. I decided to cite "*Monoamine oxidase A genotype is associated with gang membership and weapon use*" (Beaver et al. 2010), because it examine the association between MAOA and gang membership, a serious violent offenders."*Role of genotype in the cycle of violence and maltreated children*"(Caspi et al. 2002), studies the gene-environment connection between childhood maltreatment and adult antisocial behavior, and "*Neural mechanisms of genetic risk for impulsivity and violence in humans*"(Meyer-Lindenberg et al. 2006) analyse the effects of MAOA-L in relation to the regulation of emotions in the limbic system (Beaver et al. 2010). It will be briefly described the method of analysis with a focus on their results and discussion.

4.1 *"Monoamine oxidase A genotype is associated with gang membership and weapon use".*

The participants (1155 females and 1041 males) were genotyped on the X chromosome (at location Xp11.24-11.4) from a 30 base pair VNTR upstream in the 5' regulatory region of the gene. As primer sequences were used: 5' ACAGCCTGACCG-TGGAGAAG-3' and its complementary strand. A polymerase chain reaction (PCR) assay produces 291bp (2-repeat allele consisting of MAOA-L activity), 321bp (3-repeat allele consisting of MAOA-L activity), 336bp (3.5-repeat allele consisting of MAOA-H activity), 351bp (4-repeat allele consisting of MAOA-H activity) and 381bp (5-repeat allele consisting of MAOA-H activity). Results showed that 42.3% of males had MAOA-L and 57% of males had MAOA-H. For females, 17.4% were homozygous for the MAOA-L, 44.7% were heterozygous, and 37.9% were homozygous for the MAOA-H. The table below summarised the results obtained (Beaver et al. 2010).

MAOA (males), no. (%)	
Low MAOA	440 (42.3)
High MAOA	601 (57.7)
MAOA (females), no. (%)	
Low MAOA/Low MAOA	201 (17.4)
Low MAOA/High MAOA	516 (44.7)
High MAOA/High MAOA	438 (37.9)
Gang member, no. (%)	
Yes	77 (3.5)
No	2119 (96.5)
Weapon use, no. (%)	
Yes	58 (2.6)
No	2138 (97.4)
Sex, no. (%)	
Male	1041 (47.4)
Female	1155 (52.6)
Race, no. (%)	
White	1484 (67.6)
African American	383 (17.4)
Other	329 (15.0)
Age, mean (SD)	16.47 (1.69)

Table 4: Results collected. Note that () indicate the percentage of the total (Beaver et al. 2010).

A logistic regression models has been calculated to determine whether MAOA is related with gang membership and with weapon use in a fight. Note that P values (that explains how well the results fits) are not mentioned but expressed as significantly relevant (when P= 0.05 or lower) when occur * as symbol. Moreover odds ratio (OR= ratio of the probability that an event will occur, such as being gang members and using weapon in fight, versus the probability that the event will not occur, such as not being gang members and not using weapon in fight) are mentioned without calculations of it (Beaver et al. 2010).

	Gang member			Weapon use		
	b	SE	Odds ratio	*b*	SE	Odds ratio
MAOA	−0.05	0.32	0.950	−0.24	0.43	0.787
White	−0.39	0.64	0.677	−0.83	1.17	0.469
African American	0.03	0.71	1.04	1.24	1.10	3.47
Age	−0.59*	0.13	0.375	−0.47*	0.16	0.627

Huber/White standard errors presented.
* $P < .05$ level, 2-tailed.

Table 5: Logistic regression models predicting gang membership and weapon use among females (1155), where b= slope of the sample regression line, and SE= standard error of the slope (Beaver et al. 2010).

Table 5 shows that MAOA and race were not related to gang membership and weapon use, whereas age maintained an inverse relationship with gang membership and weapon use (Beaver et al. 2010).

	Gang member			Weapon use		
	b	SE	Odds ratio	*b*	SE	Odds ratio
MAOA	0.66*	0.30	1.94	0.60*	0.30	1.82
White	−1.07*	0.35	0.342	−0.22	0.40	0.802
African American	−0.14	0.38	0.872	−0.34	0.50	0.715
Age	−0.08	0.07	0.927	−0.10	0.09	0.902

Huber/White standard errors presented.
* $P < .05$ level, 2-tailed.

Table 6: Logistic regression models predicting gang membership and weapon use amongmales (1041) where b= slope of the sample regression line, and SE= standard error of the slope (Beaver et al. 2010).

Table 6 shows a statistically significant and positive effect on gang membership and weapon use (because males with MAOA-L were 1.94 and 1.82 times more likely to be gang members and to have used a weapon respectively) (Beaver et al. 2010).

A logistic regression models has been calculated to determine the relationship between MAOA and weapon use among gang membership in both female and males (Beaver et al. 2010).

	Females (n = 23)			Males (n = 54)		
	b	SE	Odds ratio	*b*	SE	Odds ratio
MAOA	−2.22	1.21	0.108	1.47*	0.71	4.37
White	−4.51*	2.26	0.011	1.19	0.78	3.28
African American	−1.35	2.54	0.257	−0.35	0.89	0.706
Age	0.61	0.51	1.85	0.47*	0.22	1.61

Huber/White standard errors presented.
* $P < .05$ level, 2-tailed.

Table 7: A logistic regression models predicting the relationship between MAOA and weapon use among gang membership, where b= slope of the sample regression line, and SE= standard error of the slope (Beaver et al. 2010).

Table 7 shows that MAOA was not related to weapon use for females, whereas it shows a statistically significant and positive effect weapon use among males gang members (because males gang members with MAOA-L were 4.37 times more likely to use a weapon than males gang members with MAOA-H) (Beaver et al. 2010).

As conclusion from the results, it is possible to denote that males with MAOA-L can risk of joining a gang and using a weapon in a fight. Once a gang member, there are more possibilities to use a weapon for males with MAOA-L (Beaver et al. 2010).

4.2 "Role of genotype in the cycle of violence and maltreated children".

The participants (1037 children where 52% of males) were genotyped on the X chromosome (at location Xp11.24-11.4) from a 30 base pair VNTR upstream in the 5' regulatory region of the gene. The ages of the children were 3, 5, 7, 9, 13, 15, 18, 21 and 26 years. Between the ages of 3 and 11 years, 8% of the study children experienced "severe" maltreatment, 28% experienced "probable" maltreatment and 64% experienced "no maltreatment". The association between childhood maltreatment (with subsequent antisocial behaviour) and MAOA activity has been measured. Four measures are taken into account: *adolescent conduct disorder*, assessed according to the Diagnostic and Statistical Manual of

Mental Disorders (DSM-IV), *personality disposition toward violence* (assessed by psychologists once the subject was at age 26), and *symptoms of antisocial personality disorder* (assessed at people of 26 years by collecting information about them) (Caspi et al. 2002).

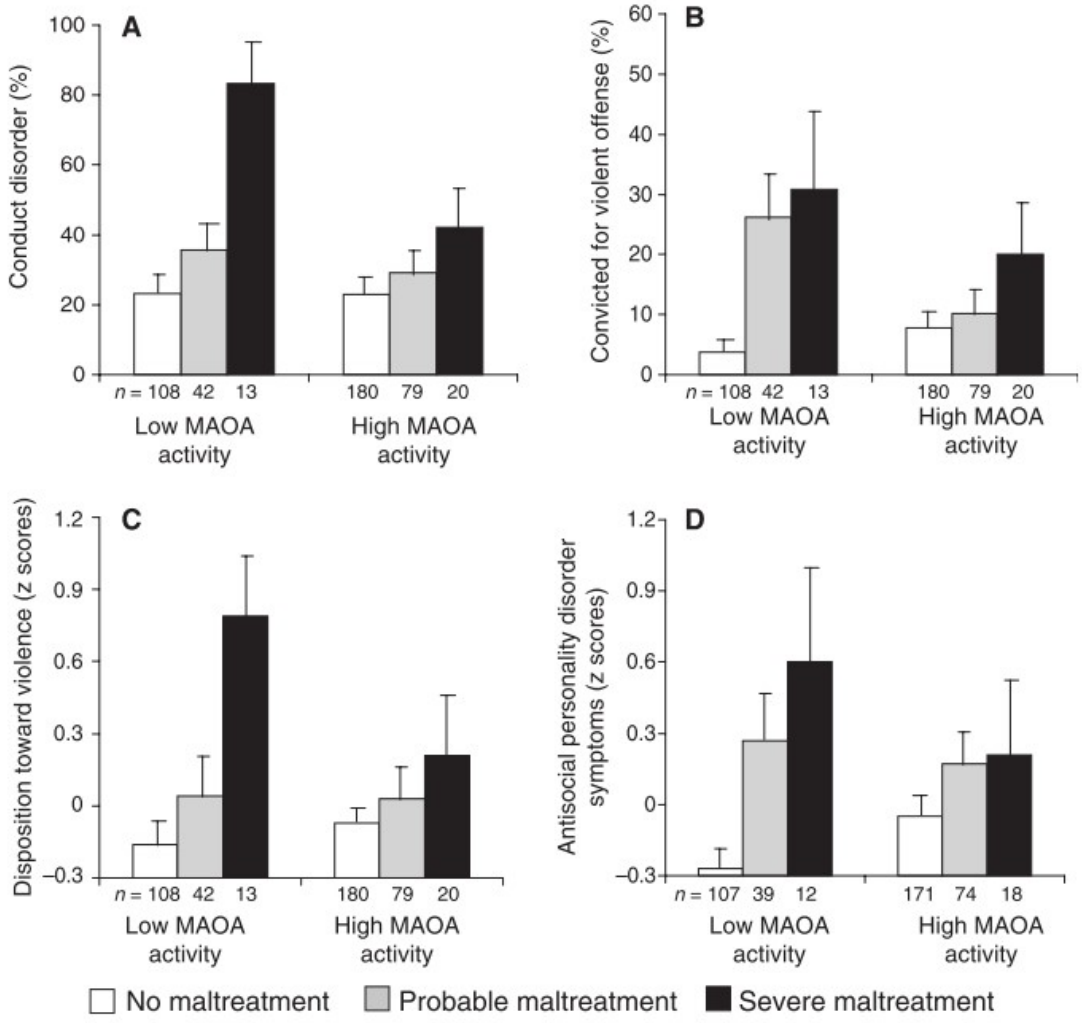

Fig. 11: The association between childhood maltreatment as a function of MAOA activity (Caspi et al. 2002).

Figure 11A shows the percentage of males that meets conduct disorder between 10 and 18 years versus the genotyped polymorphism MAOA-L and MAOA-H both in relation to severe, probable and no maltreatment, (as example from a total of 108 males with MAOA-L activity and with no maltreatment, 25% of them experienced conduct disorder). The moderated regression analysis has been used to predict the interaction between maltreatment and MAOA activity. It is important to remind that significant results are obtained if the p value is less than the significance level that is 0.05. Moreover t/z

indicate the test statistic and is calculated as it follows: z = b/SE where b= slope of the sample regression line, and SE= standard error of the slope. Results showed that the effect of maltreatment was highly significant in the MAOA-L activity group (b = 0.96, SE = 0.27, z = 3.55, p = <0.001) compared to the MAOA-H activity group (b = 0.34, SE = 0.20, z = 1.72, p = 0.09).

Figure 11B shows the percentage of males convicted of violent crime at 26 years versus the genotyped polymorphism MAOA-L and MAOA-H both in relation to severe, probable and no maltreatment. The gene-environment interaction was significant in the MAOA-L activity group (b = 1.20, SE = 0.33, z = 3.65, p = <0.001) but was not significant in the MAOA-H activity group (b = 0.37, SE = 0.27, z = 1.38, p = 0.17) (Caspi et al. 2002).

Figure 11C shows the mean z scores (M = 0, SD= 1) on the disposition toward violence at age 26. Results showed that the effect of maltreatment was highly significant in the MAOA-L activity group (b = 0.35, SE = 0.11, z = 3.09, p =0.002) but was not significant in the MAOA-H activity group (b = 0.12, SE = 0.07, z = 1.34, p =0.17) (Caspi et al. 2002).

Figure 11D shows the mean z scores (with Mean = 0, Standard Deviation = 1) on the antisocial personality disorder symptoms at age 26. Results showed that the effect of maltreatment was highly significant in the MAOA-L activity group (b = 0.45, SE = 0.13, z = 3.83, p =<0.001) but was not significant in the MAOA-H activity group (b = 0.14, SE = 0.09, z = 1.57, p =0.12) (Caspi et al. 2002). The table below summarises all the data collected presenting the main effects of MAOA, maltreatment (MAOA-L activity) and MAOA x maltreatment (gene environment interaction) in relation to the four antisocial outcomes (Caspi et al. 2002).

Antisocial outcomes	Predictor variables											
	MAOA				Maltreatment				*MAOA* × Maltreatment			
	b	SE	*t/z*	*p*	*b*	SE	*t/z*	*p*	*b*	SE	*t/z*	*p*
Composite Antisocial Index	.16	.11	1.45	.15	.54	.11	4.73	.001	-.36	.14	2.53	.01
Conduct Disorder (%)	.06	.28	.20	.84	.96	.27	3.55	.001	-.63	.33	1.87	.06
Violence Conviction (%)	.32	.46	.70	.48	1.2	.33	3.65	.001	-.83	.42	1.95	.05
Disposition Toward Violence Scale	.11	.11	.95	.35	.35	.12	3.04	.003	-.24	.15	1.62	.10
Antisocial Personality Symptoms Scale	.22	.12	1.90	.06	.45	.12	3.74	.001	-.31	.15	2.02	.04

Fig. 12: Results of the final regression analysis testing G × E interaction effects on antisocial outcomes (http://www.sciencemag.org/content/suppl/2002/08/01/297.5582.851.DC1.html)

As conclusion, it is possible to denote that there is an evidence in the MAOA-L contribute to the development of antisocial behaviour with previous childhood maltreatment in males.

4.3 *"Neural mechanisms of genetic risk for impulsivity and violence in humans"*

It has been studied the impact of a polymorphism in MAOA on brain structure and function in a large sample of healthy human volunteers. To investigate circuits of *emotional arousal*, it has been used stimuli such as angry and fearful faces that demonstrated to activate amygdala (Meyer-Lindenberg et al. 2006). All the images have been performed with fMRI (Functional magnetic resonance imaging), an imaging technique used to visualise detailed internal structures that measures the change in blood flow related to neural activity in the brain (for more details see (Meyer-Lindenberg et al. 2006).

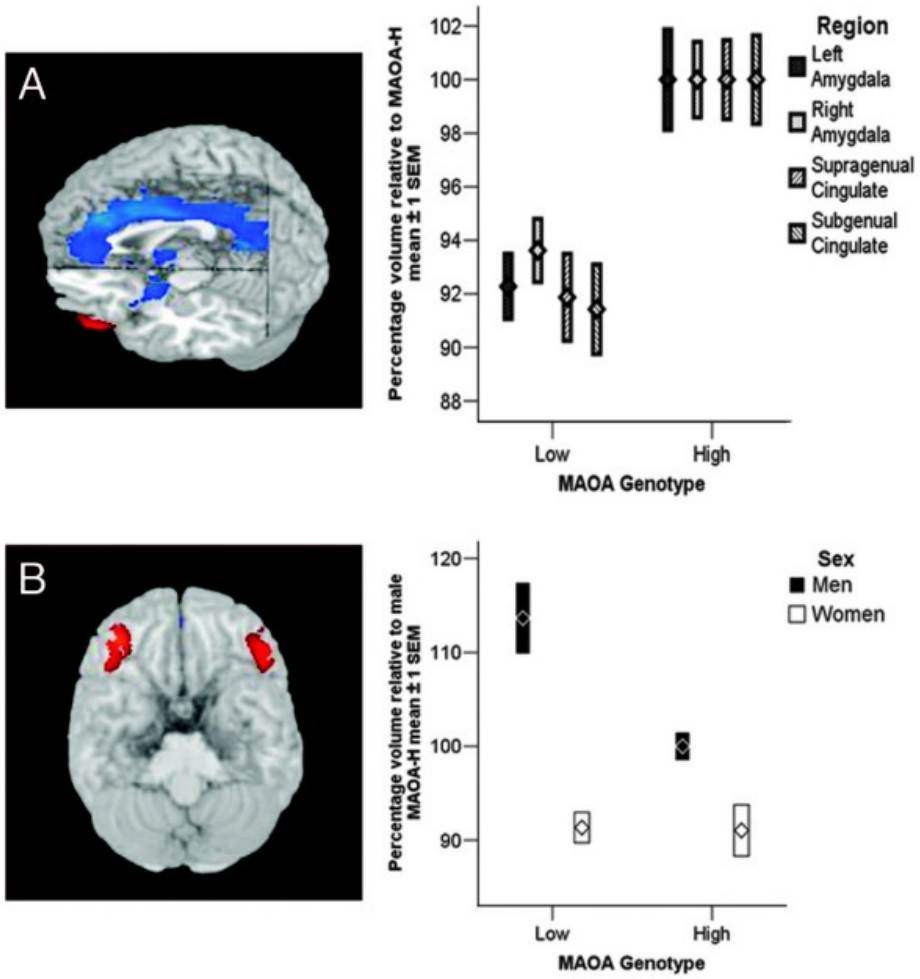

Fig. 13: Genotype Effects on Brain Structure.(A) MAOA-L individuals exhibit volume reductions in bilateral amygdala, supragenual anterior cingulate, and subgenual anterior cingulate cortex.(B) Compared with MAOA-H subjects, male MAOA-L individuals show increased lateral orbitofrontal volume, whereas females show no differences between MAOA-L and MAOA-H (Meyer-Lindenberg et al. 2006).

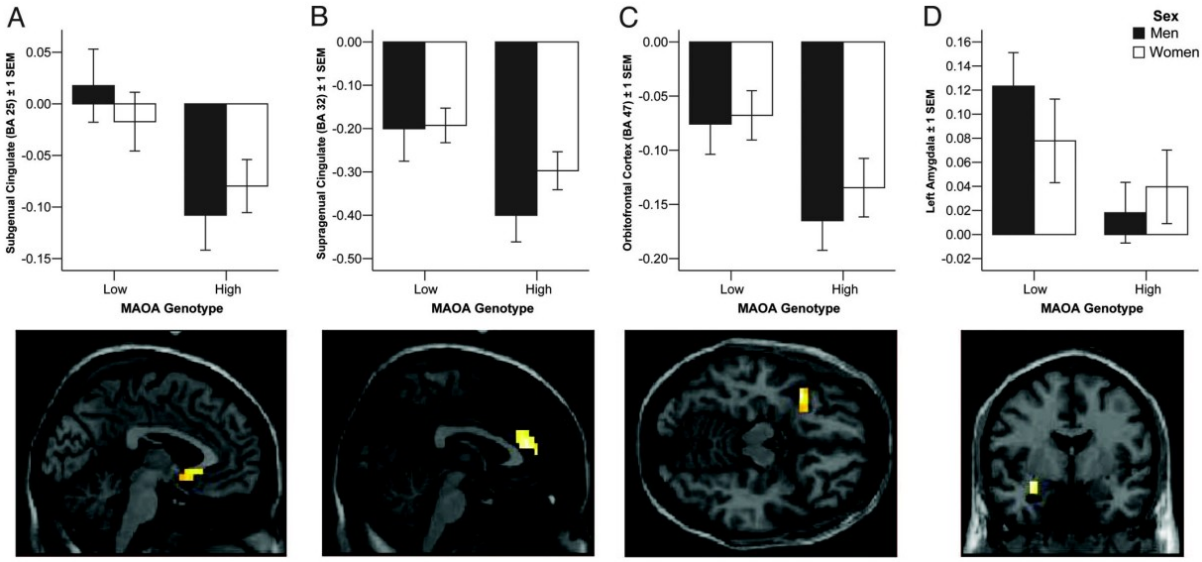

Fig. 14: Genotype Effects on Brain Function. Emotional arousal. fMRI data analysis reported during the matching of angry and fearful faces in MAOA-L individuals in several limbic and paralimbic regions: (A) subgenual anterior cingulate (B) supragenual anterior cingulate, (C) left lateral OFC, (D) left amygdala (Meyer-Lindenberg et al. 2006).

Figure 14 show that MAOA-L individuals (both males and females) reported an increased in activity in left amygdala and decreased response of subgenual anterior cingulate, supragenual anterior cingulate and left lateral OFC, relative to MAOA-H subjects. Because OFC function is implicated in amygdala regulation, it has been studied the effects of MAOA-L and MAOA-H activity in both males and females on amygdala orbitofrontal connectivity. *Figure 15* shows a significant decreased reactivity of OFC in MAOA-L individuals in both sexes. Additionally, when compared, it is possible to see clearly a decreased reactivity of OGC in males rather than females (Meyer-Lindenberg et al. 2006).

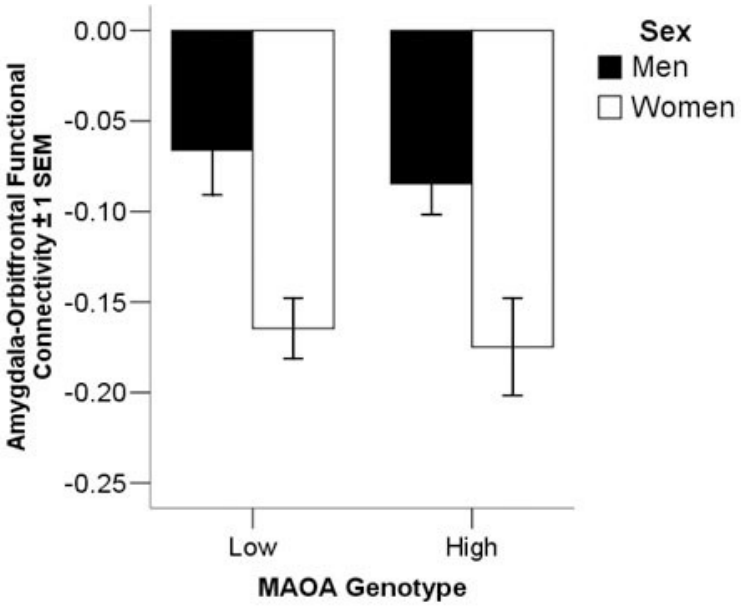

Fig. 15: Functional connectivity between amygdala and orbitofrontal cortex is lower in male subjects (http://www.pnas.org/content/103/16/6269/suppl/DC1)

As conclusion it is possible to denote that MAOA-L activity predicted a reduction in limbic system (the hippocampus, amygdala, anterior thalamic nuclei and limbic cortex) which is involved in emotion, behaviour and long term memory. Additionally, the results showed an increased amygdala volume during emotional arousal, with lower reactivity of regulatory prefrontal regions, compared with the MAOA-H activity that means that the MAOA-L group was less able to inhibit strong emotional impulses (Hunter 2010). Moreover a reduction of OFC is correlated with an antisocial behaviour (Meyer-Lindenberg et al. 2006).

5 Ethical and moral implications

Without any doubt the antisocial behavioural genetics arise some ethical and moral questionable concerns that are listed below:

- **Is the MAOA-L relevant to criminal trials?** From a biological point of view we can state that the MAOA-L gene-environment interaction is related to a metabolism of neurotransmitters and it is consequentially involved in anger production and predisposition to impulsive violence (Baum 2011). Such consideration let think that the MAOA-L genotype has to be taken into consideration during the trial. However, a precise regulation for these cases is not yet decided since different opinions in the scientific and juridic community are still present.
- **How the court has to take into account a MAOA deficiency?** Such unclear method of judgment lead to some incongruences. Those were already seen in two similar murder cases which have been sentenced in two different ways. By now it has been proven that the MAOA polymorphism does exist and that it can affect the social behaviour of a person. On this basis we can consider such disorder as a fact to take into consideration but automatically rises another question like: **Must there be a reduction of the sentence because of the MAOA-L and how can we quantify this reduction?** (Raine 2008)
- **Is it possible to test the level of MAOA?** There exists a technique called DNA Microarray (also called DNA chip) that is especially used to investigate differences in gene expression by making a comparison between two samples (in specific the normal allele and its probable MAOA polymorphism), identifying tens of thousands of DNA sequences and its known polymorphisms from blood or saliva samples. A microarray can be prepared from a known DNA sequence that can be amplified by PCR (Polymerase chain reaction). This DNA sequence usually consist of a single strand of 20 nucleotides long (called probe). Each probe consist of an unique region of the gene in the genome being attached to the solid surface on the microarray. The two samples of interest are mRNA samples that are converted to cDNAs by reverse transcriptase. To distinguish each of them, they are made with nucleotides that fluorescence in different colours, often green and red. The cDNA samples are added to the microarray and if the strands are complementary the cDNA will bind to the probes otherwise they are washed away. The result will show differences in spots and colours that will identify which mRNA sample is

more abundant:green indicates expression in one sample, red in the other, yellow in both, and black in neither. It results indicative for testing the differences in gene expression, having an high accuracy. (Glick et al. 2003, Campbell and Reece 2008, Lehninger et al.2008)

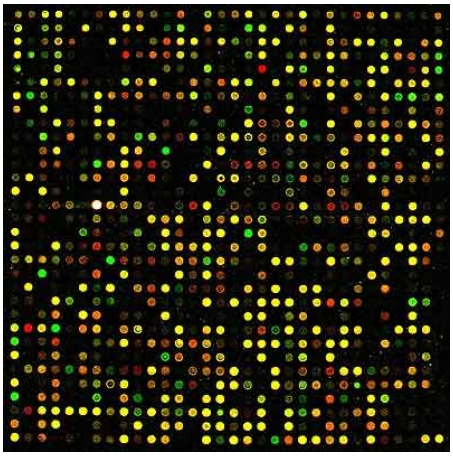

Fig. 16: DNA microarray (http://www.microarray.ntnu.no/html/micrarray_scanning_services.html)

- **Is it right to test an individual that may have inherit the MAOA-L gene, having also an environment interaction favourable to manifest antisocial behaviour (such as childhood maltreatment) without having commit any crimes yet?** Regarding a general safety an accurate prediction of the level of MAOA will prevent any further crimes (Farahany et al. 2006); on the other hand doing so the individual has to suffer of a judgment just because of its genetic makeup.
- **If the subject possesses the MAOA-L genotype who should have the authority to collect or access this data?What has to be made?** This is the most tricky task that our society should seriously consider. If this information is of public domain the subject can be discriminated as possible criminal, even if he has not commit any crimes. The subsequent complications could rise up the limit in finding jobs etc. that makes impossible to pursue a normal life because the person is excluded from the society itself. There must be a safeguard of the subject in order to prevent possible discriminations. (Nadelhoffer et al. 2010). Moreover, there must be a distinguish between who inherit low MAOA with and without an environment such childhood maltreatments. It has been tested that this combination enhance possible aggressive traits.

6 Conclusion

The main question of the current project has given a possibility to analyse in scientific way a specific gene-environment polymorphism that make an individual more likely to express an antisocial behaviour. Once individuated the gene polymorphism of interest (the MAOA-L) and researched its function (metabolising some neurotransmitters), it has been discussed some results regarding the correlation between MAOA-L and respectively the possibility to join a gang membership and weapon use, the gene-environment connection, and its relation to emotions in the limbic system. It has been described some murder cases involving the MAOA-L gene to show how was the response of the court in front of an antisocial behaviour. Finally, It has been enumerated a series of ethical concerns involving the MAOA-L gene-environment interaction to present the difficulty of some moral implications. This project gave a detailed information regarding the correlation between genes and our behaviour, trying to touch only scientific arguments excluding psychology.

7 Perspectives for the future

As perspective for the future I wish that genetic testing will play an increasing role in criminal trials. Future research could be used to support or disprove that some individuals are more likely to commit some crimes. A more accurate analysis must be performed in order to delineate how much freedom of will should an antisocial individual with MAOA-L gene-environment have. Moreover a discussion regarding the reduction of the sentence has to be taken into account. Finally this project gave me the opportunity to understand that until now there is no treatment available for subjects suffering of an antisocial behaviour, a problem that I wish will be solve soon.

8 Personal comments

Personally I think that the introduction of detailed analysis of a particular gene and its known polymorphism in sentencing some crimes could help in understanding partly a reason of the attack, that for my point of view should be taken into account when determining a sentence. At the same point a prediction of the level of MAOA activity in an individual having a history of severe child maltreatment

could preserve further violent and aggressive behaviour, helping the subject with an appropriate cure.

9 Abbreviation

5-HT: serotonin.

APB: Antisocial Personality and Behavior.

CNS: Central Nervous System.

COMT: catechol-O-methyltransferase.

DA: Dopamine.

DHPG: 3,4-dihydroxyphenyl-glycol.

MAO: Monoamine oxidase genes.

MAOA-H: MAOA High gene variant.

MAOAI: MAOA inhibitor.

MAOA-L: MAOA Low gene variant.

MHPG: 3-methoxy-4-hydrophenylglycol.

NE: norepinephrine.

PEA: phenylethylamine.

PNS: peripheral nervous system.

VMA: vanyl-mandelic acid.

VNTR: variable number of nucleotide tandem repeats.

Abbreviation for enzymes on Figure 8:

AADC: Aromatic l-amino acid decarboxylase.

ADH: Alcohol dehydrogenases.

ALDH: aldehyde or aldose dehydrogenase/oxidoreductase.

AR: aldehyde or aldose reductase.

DßH: dopamine beta-hydroxylase.

PNMT: Phenylethanolamine N-methyltransferase.

SULT1A3: Sulfotransferase 1A3.

TH: Tyrosine 3-hydroxylase or tyrosine 3-monooxygenase.

TPH1: Tryptophan hydroxylase 1 or tryptophan 5-monooxygenase.

TPH2: Tryptophan hydroxylase 2.

Abbreviation for metabolites on Figure 8:

3-MT: 3-methoxytryptamine.

3OMD: 3-O-methyldopa.

5-HIAA: 5-Hydroxyindoleacetic acid.

5-HTP: 5-Hydroxytryptophan.

DOPAC: Dihydroxy-Phenylacetic Acid.

HVA: Homovanillic acid.

L-DOPA: L-3,4-dihydroxyphenylalanine.

MET: Metanephrine.

MHPG: 3-Methoxy-4-hydroxyphenylglycol.

NMET: Normetanephine.

SO_4 :sulfate.

VLA: vanillactic acid.

References

Baker L., Bezdjian S., Raine A, (2006): Behavioural Genetics: The Science Of AntiSocial Behaviour. Law and Contemporary Problems 7.

Baum M.L. (2011): The monoamine oxidase A (MAOA) genetic predisposition to impulsive violence: is it relevant to criminal trials? Neuroethics 1-20. (and Fig.1, Table 3).

Beaver K.M., DeLisi M., Vaughn M.G., Barnes J.C. (2009): Monoamine oxidase A genotype is associated with gang membership and weapon use. Compr Psychiatry 51:130-134.

Bernet W., Vnencak-Jones C.L., Farahany N., Mongomery S.A. (2007): Bad nature, bad nurture, and testimony regarding MAOA and SLC6A4 genotyping at murder trials. Juornal of forensic Sciences 52 (6): 1362-1371.

Bloom M., Cutter M.A., Davidson R., Dougherty M.J., Drexler E., Gelernter J., McCullough L.B., et al. " Genes, environment, and human behavior", p.13-14, 19-22. Biological Sciences Curriculum Study (BSCS), Colorado, 2000.

Brunner H.G., Nelen M., Breakfield X.O., Ropers H.H., Van Oost B. (1993): Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. Science 262: 578-580.

Buckholtz J.W, Meyer-Lindenberg A. (2008): MAOA and the neurogenetic architecture of human aggression. Trends in Neurosciences 31(3): 120-129.

Campbell N.A., Reece J.B. "Biology" (8th edition), p.410, 1047-1049, 1059, 1070. Pearson Benjamin Cummings, San Francisco, 2008.

Cases O., Seif I., Grimsby J., Gaspar P., Chen K., Pournin S., et al. (1995): Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA. Comment in Science 270 (5235) 362-364.

Caspi A., McClay J., Moffitt T.E., Mill J., Martin J., et al. (2002): Role of genotype in the cycle of violence in maltreated children. Science 297: 851-854.
Supplement http://www.sciencemag.org/content/suppl/2002/08/01/297.5582.851.DC1.html

Chen K., Holschneider D.P., Wu W., Rebrin I., Shih J.C. (2004): A spontaneous point mutation produces monoamine oxidase A/B knock-out mice with greatly elevated monoamines and anxiety-like behavior. Journal Biological Chemistry 279: 39645-39652.

Chen Shih J., (2004): Cloning, After Cloning, Knock-out Mice, and Physiological Functions of MAO A and B. NeuroToxicology 25: 21–30. (and Fig.3).

Comparative animal physiology (2010) "Pathophysiology: Focus on serotonin"
http://www.pharmacorama.com/en/Sections/images/Serotonin_2_clip_image006_0000.gif (Fig. 9).

de la Chapelle A., Sankila E. M., Lindlöf M., Aula P., Norio R. (1985): Norrie disease caused by a gene deletion allowing carrier detection and prenatal diagnosis. Clin Genet, 28(4): 317-20.

Deckert J., Catalano M., Syagailo Y., Bosi M., Okladnova O., et al. (1999): Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder. Hum Mol Genet 8: 621-624.

Fan J.B., Yang M.S., Tang J.X., He L., Xing Y.L., et al. (2004): Family-based association study of the functional monoamine oxidase a gene promoter polymorphism and schizophrenia. Schizophr Res 67: 107-109.

Farahany N., Bernet W. (2006): Behavioural genetics in criminal cases: past, present, and future. Genomics, Society and Policy 2 (1):72-79.

Ferguson C.J., (2010): Genetic contributions to antisocial personality and behavior: a meta-analytic review from an evolutionary perspective. The journal of social psychology 150(2): 160-180.

Galton, F. "Hereditary Genius: An Inquiry into Its Laws and Consequences", p.1.Macmillan, London, 1869.

Genetics home reference (2011) http://ghr.nlm.nih.gov/gene/MAOA (on the web 04.07.2011) (Fig.1).

Glick D., Soreq H. (2003): Ethics, Public Policy and Behavioral Genetics IMAJ 5 :83–86.

Haavik J., Blau N., Thony B. (2008): Mutations in human Monoamine-related neurotransmitter pathway genes. Human mutation 29(7): 891-902. (and Fig.2).

Hamilton S., Slager S., Heiman G., Haghighi F., Klein D., et al. (2000): No genetic linkage or association between a functional promoter polymorphism in the monoamine oxidase-A gene and panic disorder. Mol Psychiatry 5: 465-466.

Hook G.R., (2009): Warrior Genes And The Disease Of Being Maori MAI Review 2. (and Table 1).

Huang Y., Cate S., Battistuzzi C., Oquendo M., Brent D., et al. (2004): An association between a functional polymorphism in the monoamine oxidase a gene promoter, impulsive traits and early abuse experiences. Neuropsychopharmacology 29: 1498-1505.

Hunter P. (2010): The psycho gene. EMBO reports 11 (9):667-669.

Jonsson E.G., Norton N., Forslund K., Mattila-Evenden M., Rylander G., et al. (2003): Association between a promoter variant in the monoamine oxidase A gene and schizophrenia. Schizophr Res 61: 31-37.

Kennedy I., Bobrow M., Baldwin T., Burke R., Calman K., et al. " Genetics and human behaviour: the ethical context", p. 27-34. Nuffield Council on Bioethics, London, 2002.

Lan N.C., Heinzmann C., Gal A., Klisak I., Orth U., et al. (1989): Human monoamine oxidase A and B genes map to Xp 11.23 and are deleted in a patient with norrie disease. Genomics 4: 552-559.

Lea R., Chambers, G. (2007): Monoamine oxidase, addiction, and the "warrior" gene hypothesis. Journal of the New Zealand Medical Association, 120(1250).
Lenders J.W.M., Eisenhofer G., Abeling N.G.G.M., ,Berger W., Murphy D.L.,Konings C.H.,et al. (1996): Specific genetic deficiencies of the A and B isoenzymes of monoamine oxidase are characterized by distinct neurochemical and clinical phenotypes. J. Clin. Invest. 97: 1010-1019.

Lehninger, A., Nelson, D.L., Cox, M:"Principles of biochemistry" (5th edition),p.325-327. W.H.Freeman and Company, New York, 2008.

Levy E.R., Powell J.F., Buckle V.J., Hsu Y.P., Breakefield X.O., Craig I.W. (1989): Localization of human monoamine oxidase-A gene to Xp11.23-11.4 by in situ hybridization: implications for Norrie disease. Genomics, 2: 368-370.

Lundbeck Institute CNS forum (2005) "The mechanism of action of monoamine oxidase A inhibitors" http://www.cnsforum.com/imagebank/item/Drug_MOAI_2/default.aspx (on the web 14.02.2005) (Fig.7).

Manuck S.B., Flory J.D., Ferrell R.E., Mann J.J., Muldoon, M.F. (2000): A regulatory polymorphism of the monoamine oxidase-A gene may be associated with variability in aggression, impulsivity, and central nervous system serotonergic responsivity. Psychiatry Research, 95(1): 9-23.

Meloni, R."Handbook of Neurochemistry and Molecular Neurobiology: Molecular Genetics of Brain Noradrenergic Neurotransmission"(3rd edition), p.130-140. Vizi, Sylvester E. ,2008.

Merriman T., Cameron V., (2007): Risk Taking: Behind The Warrior Gene Story. New Zealand Medical Journal 120(1250).

Meyer-Lindenberg, A., Buckholtz J. W., Kolachana B., R. Hariri, A., Pezawas, L., Blasi, G., Wabnitz, A., et al. (2006): Neural mechanisms of genetic risk for impulsivity and violence in humans. Proceedings of the National Academy of Sciences, 103(16): 6269 -6274.
supporting material: http://www.pnas.org/content/103/16/6269/suppl/DC1

Mihalik, J., Toth, S., Hodorova, I., Vecanova, J.,Rybarova, S. (2011): Histochemical detection of monoamine oxidases in rat female genital organs during preimplantation period of pregnancy. Bratislavské Lekárske Listy, 112(5): 244-248.

Nadelhoffer T., Bibas S., Grafton S., Kiehl K.A., Mansfield A., et al. (2010): Neuroprediction, violence, and the law: setting the stage. Neuroethics 1-33.

Need A.C., Ahmadi K.R., Spector T.D., Goldstein D.B. (2006): Obesity is associated with genetic variants that alter dopamine availability. Annals of Human Genetics 70(3): 293-303.

Newman T.K., Syagailo Y.V., Barr C.S., Wendland J.R., Champoux M., Graessle M., et al. (2005):

Monoamine oxidase A gene promoter variation and rearing experience influences aggressive behavior in rhesus monkeys. Biological Psychiatry 57(2): 167-172.

NTNU Genomics Resource Center:
http://www.microarray.ntnu.no/html/micrarray_scanning_services.html (Fig.16)

Pinsonneault J.K., Papp A.C., Sadée W. (2006): Allelic mRNA expression of X-linked monoamine oxidase a (MAOA) in human brain: dissection of epigenetic and genetic factors. Human Molecular Genetics 15(17): 2636-2649.

Plato, Laws Book IX, 856d. English version:http://classics.mit.edu/Plato/laws.9.ix.html

Raine A. (2008): From genes to brain to antisocial behavior. Current Directions in Psychological Science 17 (5): 323-328.

Rosenberg S., Templeton A., Feigin P., Lancet D., Beckmann J., Selig S., et al. (2006): Human genetics 120(4): 447-459.

Sabol S., Hu S., Hamer D. (1998): A functional polymorphism in the monoamine oxidase A gene promoter. Hum Genet 103: 273-279.

Samochowieca J., Syreka S., Michaa P., Ryewska-Wódeckaa A., Samochowieca A., Horodnickia J., et al. (2004): Polymorphisms in the Serotonin Transporter and Monoamine Oxidase A Genes and their relationship to personality traits measured by the temperament and character inventory and NEO Five-Factor inventory in healthy volunteers. Neuropsychobiology 50: 174-181.

Schulze T., Muller D., Krauss H., Scherk H., Ohlraun S., et al. (2000): Association between a functional polymorphism in the monoamine oxidase A gene promoter and major depressive disorder. Am J Med Genet 96: 801-803.

Syagailo Y., Stober G., Grassle M., Reimer E., Knapp M., et al. (2001): Association analysis of the functional monoamine oxidase a gene promoter polymorphism in psychiatric disorders. Am J Med Genet 105: 168-171.

Widom C.S., Brzustowicz L.M. (2006): MAOA and the "cycle of violence:" childhood abuse and neglect, MAOA genotype, and risk for violent and antisocial behavior. Biological Psychiatry 60(7): 684-689.

Youdim M.B.H., Riederer P.F. (2004): A review of the mechanisms and role of monoamine oxidase inhibitors in Parkinson’s disease. Neurology 63(Suppl 2): s32-s35 (and Table 2).

Milestone plan

Week nr.	*Phases/Milestones*	*Activities*
36	Problem formulation	Finding the main research question, narrowing ideas down to the necessary/relevant.
37	Theoretical phase. Literature Research	Finding scientific material on the chosen areas, taking notes and writing the main ideas down including references
38	Theoretical phase. Literature Research	Finding scientific material on the chosen areas, taking notes and writing the main ideas down including references
39	Literature search for the experiments performed by others	Finding scientific material on the chosen area
40	Theoretical phase	Putting together the mid-term report.
41	Theoretical phase	Putting together the mid-term report including references.
42	Midterm evaluation	Preparation for the mid- term evaluation.
43	Theoretical phase. Literature Research	Finding scientific material on the chosen area
44	Theoretical phase. Literature Research 1st project intensive period	Finding scientific material on the chosen area, writing the results (from others) and discussion part of the report
45	Writing phase	Putting together the report, writing the abstract, the introduction, middle section of the report and the conclusion.
46	Writing phase	Putting together the report: organizing the list of reference, the appendices and the outline of the project
47	Writing phase	Additional time as a precaution. Handing in the first version of the project report
48	Project presentation seminar.	Additional time for anything that needs to be added.
49	2nd project intensive period	Time for final changes in the report
50	Deadline for handing in the report to the printing office	