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Neurobiology of Aggression and Violence in Schizophrenia

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There is much evidence that schizophrenia patients have an increased risk for aggression and violent behavior, including homicide. The neurobiological basis and correlates of this risk have not been much studied. While genome-wide association studies are lacking, a number of candidate genes have been investigated. By far, the most intensively studied is the catechol-*O*-methyltransferase (COMT) gene on chromosome 22. COMT is involved in the metabolism of dopamine, a key neurotransmitter in schizophrenia pathophysiology. Several studies suggest that the Val158Met polymorphism of this gene affects COMT activity. Methionine (Met)/Met homozygote schizophrenia patients show 4- to 5-fold lower COMT activity than valine (Val)/Val homozygotes, and some but not all studies have found an association with aggression and violence. Recently, a new functional single-nucleotide polymorphism in the COMT gene, Ala72Ser, was found to be associated with homicidal behavior in schizophrenia, but this finding warrants further replication. Studies published so far indicate that an association with the monoamine oxidase A, B, or tryptophan hydroxylase 1 genes is unlikely. Data for the brain-derived neurotrophic factor gene are conflicting and limited. Data from the limited number of neuroimaging studies performed to date are interesting. Frontal and temporal lobe abnormalities are found consistently in aggressive schizophrenia patients. Positron emission tomography and single photon-emission computed tomography (SPECT) data indicate deficits also in the orbitofrontal and temporal cortex. Some functional magnetic resonance imaging studies found a negative association of violent behavior with frontal and right-sided inferior parietal activity. Neuroimaging studies may well help further elucidate the interrelationship between neurocognitive functioning, personality traits, and antisocial and violent behavior.

Key words: aggression/genetics/violence/neurobiology/neuroimaging/schizophrenia

Introduction

Numerous studies have indicated that aggression and homicide are more frequent in schizophrenia than in the general population.[1–3] The most robust data on this interrelationship come from Fazel and Grann,[4] whose study indicated that 5.2% of severe acts of violence are committed by individuals with a major psychiatric disorder, most commonly schizophrenia. A 7- to 12-year follow-up study of 1662 former schizophrenic inpatients in Germany indicated that 169 patients (10.7%) were later convicted of a crime, in 94 cases violent crimes.[3]

Aggression and violence in schizophrenia can be explained by psychopathological symptoms such as delusions or hallucinations, comorbid substance use, social deterioration, or other clinical symptoms,[1–3] but distinct neurobiological mechanisms also may play a role. Few studies have addressed the neurobiology of aggression and violence in schizophrenia. This is not surprising because the neurobiological pathology of schizophrenia is poorly understood.[5] Many findings indicate that a more or less pronounced brain function disorder and above all (neuronal) developmental disorder underlies schizophrenia. For example, the cognitive deficits, such as disorders of attention, executive functions, or working memory, provide a clinical indication that this is the case. Newer neuroimaging techniques have found structural abnormalities in schizophrenia, in particular an enlargement—although often only discrete—of the third and fourth ventricles, a disturbance mainly in the area of the temporal lobe (hippocampus and parahippocampal gyrus), and a volume reduction primarily on the left side of the superior temporal gyrus and frontal brain, in particular in the prefrontal and orbitofrontal regions and parietal lobe. Other abnormalities, eg, disturbances in the area of the basal ganglia and thalamus,[5] also have been found. However, it remains unclear whether or not these structural changes are progressive.[6]

Neuropathological studies have not found clear indications that schizophrenia is a degenerative disorder, although they have found discrete abnormalities in cytoarchitecture, eg, in the area of the entorhinal gray matter and other corticolimbic regions. The question whether schizophrenia can be seen as a progressive brain disorder is a matter of heated debate. Overall, the findings in this area are complex, and the evaluation approaches mentioned above have not yet contributed to the "clinical" diagnostics of schizophrenia.

On the neuropharmacological level, the so-called dopamine hypothesis of schizophrenia continues to be of paramount importance,[7] although a range of neurotransmitters (glutamate, gamma amino butyric acid, serotonin, etc.) may contribute to the genesis of schizophrenia.

There is considerable evidence that schizophrenia involves a dysbalance between subcortical and cortical dopaminergic systems. Subcortical mesolimbic dopaminergic projections appear to be hyperactive, while the mesocortical dopamine system, which connects to the prefrontal cortex, is hypoactive. The former could be associated with positive symptoms and the latter with disturbances of cognitive function. Although a range of findings also support a deficiency in the glutamate system in particular (the so-called glutamate hypothesis), treatment research has not yet delivered sufficient proof for this hypothesis. Substances that modulate *N*-methyl-D-aspartate (NMDA) receptors, such as glycine or D-serine, have proven to be effective at the most as add-on treatment and not as monotherapy.[5] Still the glutamate hypothesis is most of the attractive ones in schizophrenia research.

Genetics

Numerous genetic studies have investigated the question of possible candidate genes for schizophrenia. Such candidate genes include neuregulin 1 (localized on chromosome 8p), dysbindin (chromosome 6p), D-amino acid oxidase activator (chromosome 13), Disrupted-in-Schizophrenia 1 (DISC1) (chromosome 1), neurogranin, genes in the major histocompatibility complex, and some others.[5,8] None of these findings is undisputed. Schizophrenia can be viewed as a dynamic process caused by dysregulation in many pathways. The catechol-*O*-methyltransferase (COMT) gene on chromosome 22 has been discussed as a susceptibility gene for schizophrenia[9] and may well be relevant in the search for the neurobiological basis of aggression in schizophrenia. COMT is an enzyme responsible for the breakdown of dopamine. It has a functional polymorphism (valine [Val] or methionine [Met]) on codon 108 that determines the enzyme activity (Val158Met polymorphism): the Met allele is less stable and has a 3- to 4-fold lower biological activity than the Val allele. Individuals with two phenocopies of the Met allele or a deletion are hypothesized to have correspondingly higher dopamine levels in certain brain regions, in particular in the prefrontal cortex. The association of COMT activity with cognitive functions appears to be of particular interest.[5]

Neurobiology

Molecular Biological and Genetic Findings

A range of findings indicates that aggression and criminal behavior are to some extent genetically inherited.[10] To date, no genome-wide association studies have been published on aggression and violence in schizophrenia. The candidate genes being studied in this context include those associated with the personality trait "novelty seeking," substance abuse, related phenotypes such as impulsivity or hostility, and also attention deficit hyperactivity syndrome (ADHS).[11] COMT is one of the key enzymes in this area and involved in the degradation of dopamine, especially in the prefrontal cortex. In contrast to enzymes coded for by other candidate genes (eg, monoamine oxidase [MAO]), COMT metabolizes dopamine, noradrenalin, and adrenalin, but not serotonin. As mentioned above, COMT has a functional polymorphism resulting from a single amino acid exchange in which Val is replaced by Met. The polymorphism is relatively common and was first reported at the beginning of the 1980s. Val/Met and Met/Met carriers have 4- to 5-fold lower COMT activity than Val/Val homozygotes.[12]

A number of studies have addressed the COMT genotype,[13–23] with mixed results (see table 1). This may be explained by differences of the treatment settings in which patients were recruited and different clinical definitions of violence/aggression. Only a minority of studies were performed in homicidal patients or those coming from forensic settings. An association of the COMT polymorphism with aggressive behavior in schizophrenia was first reported by Lachman et al[13] and Strous et al.[14] Kotler et al[11] studied a small sample of schizophrenia patients with homicidal behavior; in contrast to other studies, Kotler et al[11] evaluated a sample with clinical or forensic abnormalities. The rate of Met/Met homozygotes was higher among the 30, mostly male homicidal schizophrenia patients than among the controls (46.7% vs 21.0%), whereas no differences in genotype were found between the nonviolent schizophrenia patients and the controls. Also, more homicidal schizophrenia patients than nonviolent schizophrenia patients were "low-activity" COMT allele carriers. On the other hand, no association was found between homicidal behavior and the dopamine D4 gene or serotonin transporter polymorphism (5-HTTPR).

Other studies also indicate that low COMT activity may be linked to aggression in schizophrenia. Han et al[15] studied 132 first-episode schizophrenia patients and 80 healthy controls and found not only higher aggression levels in carriers of $COMT^{L}$ (the low-activity allele) than in $COMT^{H}$ (the high-activity allele) homozygotes but also more delusions and cognitive deficits.

Table 1. Studies on COMT Val158Met Polymorphism and Aggression in Schizophrenic Patients

	Patients	Clinical Assessment	Results
Lious et al[22]	N = 198 schizophrenics (72 history of violence); N = 188 controls	Chart review	No effect on aggression
Kotler et al[11]	N = 30 schizophrenics "maximum-security psychiatric facility"; N = 415 controls; N = 62 nonviolent schizophrenics	Homicidal schizophrenics	Met/Met allele genotype more often in homicidal schizophrenics (46% vs 26%)
Lachman et al[13]	N = 55 schizophrenics/ schizoaffective	History of aggressive behavior	Significant association of COMT and history of violent behavior
Jones et al[17]	N = 180 schizophrenics (136 males and 44 females)	OAS	Association of high-activity COMT homozygote and aggression (not shown in females)
Zammit et al[18]	N = 346 schizophrenics	OAS	No association of COMT genotype and OAS score
Kim et al[20]	N = 61 aggressive schizophrenics; N = 104 nonaggressive; N = 415 controls	Modified OAS	No association of COMT genotype and aggression but dose-dependent relation between Met allele and verbal aggression
Strous et al[14]	N = 37 schizophrenics	History of violent behavior	Met/Met genotype with higher risk for aggressive behavior
Han et al[15]	N = 132 first-onset schizophrenics; N = 80 healthy controls	Cognitive testing psychopathological scales OAS	$COMT^{L}$ carriers had higher delusion attention scores and aggression score than $COMT^{H}$ carriers
Han et al[16]	N = 168 male schizophrenics; N = 158 healthy controls	OAS	Association of $COMT^{L}$ genotype and aggression
Gu et al[19]	N = 252 violent schizophrenics; N = 332 nonviolent schizophrenics	Modified OAS	No association between individual single-nucleotide polymorphisms and violent behavior haplotype A-A-G in the case group, G-G-A in the control group. A-A-G scored higher on physical aggression against objects than G-G-A
Tosato et al[23]	N = 141 baseline; N = 115 follow-up; N = 80 genotyped	6-year follow-up study scan interview, OAS	Met/Met genotype: effect on aggression

Note: COMT, catechol-*O*-methyltransferase; OAS, Overt Aggression Scale; Met, methionine; Val, valine.

The results were interpreted such that the respective symptoms were associated with higher tonic dopaminergic activity and cognitive stability. Previously, the research group of Han et al[16] had investigated the relevance of COMT and the serotonin transporter 5-HTTPR (genotypes) for aggression in schizophrenia. A total of 168 patients were included in the study. Like most other studies, these were not schizophrenia patients who had committed crimes but patients in whom aggressiveness was measured clinically, with the Overt Aggression Scale (OAS). The serotonin transporter genotype was found to have a significant effect on the total score. The COMT gene was associated with the degree of aggression and also with physical aggression toward people.

Jones et al[17] studied the relevance of the COMT genotype for aggression in 180 schizophrenia patients. The homozygotes for the highly active allele showed a higher rate of aggression (OAS score), while the heterozygotes had lower rates. In the study sample, the results were significant only for men. The results of this study are not consistent with the earlier findings of Lachman et al[13] and of other research groups. Negative findings were reported also by Zammit et al[18] in a sample of 346 schizophrenia patients, which included the patients of the study of Jones et al.[17] More recently, Gu et al[19] did not find an association between individual single-nucleotide polymorphisms (SNPs) and violent behavior in 252 Chinese schizophrenia patients with violent behavior and 332 without. However, an association was found between haplotypes and violent behavior (A-A-G in the case group and G-G-A in the control group). In a smaller, Korean sample, Kim et al[20] did not find a significant

association between aggression in the schizophrenia patients and the COMT Val158Met polymorphism but a dose-dependent relationship between the Met allele and verbal aggression, supporting the hypothesis of a moderating role of the COMT gene in some schizophrenia patients. Finally, an interesting association between another new functional SNP in the COMT gene, Ala72Ser, and homicidal behavior was reported from a comparison of schizophrenia patients with and without homicidal behavior. In haplotype analysis, the frequency of the combination of the high-high activity allele (Ala-Val) was lower in the homicidal group than in the control group.[21]

Finally, while a previous study in schizophrenics with a history of violence did not show an association of COMT genotype with aggression,[22] an interesting and recent study of Tosato et al[23] presenting 6-year follow-up data of a patient group showed an effect of Met/Met genotype on aggression.

Despite these inconsistent findings, the COMT genotype is currently the best biological hypothesis for explaining aggressive behavior in schizophrenia, particularly because a pathophysiological explanation is provided via the dopamine system and the findings also are clinically plausible, eg, in view of the increased productive psychotic symptoms in aggressive schizophrenia patients. More studies in homicidal patients or those with severe aggression, not just measured by scales such as the OAS, are necessary to further elucidate the interrelationship between COMT genotype with an aggression/violence.

Other Genetic Studies

Other relevant candidate genes studied in this context are MAO-A, which is involved in the metabolization of both dopamine and serotonin, and the dopamine receptor D4 gene, which is presumed to be associated with novelty seeking. Only a few studies have been performed on either gene. Fresán et al[24] reported preliminary findings from a study in 71 patients, which found that both the MAO-A gene and the DRD4 48-bp repeat axon III polymorphism may be of relevance in schizophrenia patients. MAO-A has been shown repeatedly to be relevant for aggressive behavior,[25,26] and MAO-A promoter polymorphism in particular appears to be involved. A higher frequency of the allele with 3.5 and 4 repeats (''high-activity'' variants) of the promoter polymorphism was found in schizophrenia patients with aggression.[27] Two further studies also found no association of MAO-A and MAO-B with aggressiveness in schizophrenia patients.[18,28] In addition, Strous et al[29] found negative results for the MAO-A gene.

No association was found between aggression in schizophrenia and the A218C polymorphism of the tryptophan hydroxylase 1 gene,[30] serotonin 1B receptor (A-161T) genetic polymorphism,[31] or the Val66Met polymorphism of the brain-derived neurotrophic factor (BNDF) gene.[32] An association of BNDF Met alleles with increased aggressive behavior was reported by Spaletta et al,[33] however.

Other Hypotheses

The relevance of neuroactive steroids also has been discussed. In a pilot study in 8 patients, Spalletta et al[34] found a higher rate of aggressiveness in schizophrenia patients with increased 3alpha,5alpha-tetrahydroprogesterone (THP) plasma levels. However, so far, the relevance of neuroactive steroids is not at all clear.

A study by Ritsner et al[35] that found a decreased number of benzodiazepine receptors on platelets in consistently violent schizophrenia patients is also of interest in the context of this article. However, the relevance of these findings has yet to be fully clarified. The same is true for a study in 75 schizophrenia patients that found a negative correlation between *n*-3 polyunsaturated fatty acids in red blood cells and the hostility score of the Positive and Negative Syndrome Scale (PANSS).[36]

Cognitive Deficits

Another question that requires urgent investigation is whether patients with certain cognitive impairments have a particular risk for violence and aggression. Neurobiological cross-connections to the hypotheses on the genesis of schizophrenia (developmental disorder and neurodegenerative process), as described above, are conceivable.

In their literature review, Naudts and Hodgins[37] determined that 17 published studies had compared neuropsychological findings or results of structural or functional brain imaging in violent and nonviolent schizophrenia patients. However, most of the included studies had methodological shortcomings.

Naudts and Hodgins[37] formulated the hypothesis that schizophrenia patients with early onset of antisocial behavior problems show rather fewer structural abnormalities than other schizophrenia patients and that patients with aggressiveness tend to perform better in neuropsychological test evaluations than other schizophrenia patients. Furthermore, Naudts and Hodgins[37] indicated that violent schizophrenia patients show rather more neurological soft signs than other schizophrenia patients.

Studies are inconsistent in this area. Serper et al[38] discussed that patients with neurocognitive and especially executive dysfunction may not possess the behavioral inhibition skills needed to cope with the presence of symptoms and other stressful life events, which may result in aggressive behavior.

The Val158Met polymorphism of the COMT gene has been discussed to be of relevance for neurocognitive functioning in schizophrenia, although results of Golimbet

et al were negative,[39] which possibly could be important also for aggressive behavior.[15]

Neuroimaging Studies

The amount of data from neuroimaging studies is particularly limited. A previous review identified 48 articles indicating a connection between dysfunctional parts of the frontal and temporal lobes and violent antisocial behavior and psychopathy.[40] A very recent update on this issue is provided by Hoptman and Antonius,[41] who concluded that frontal and temporal abnormalities appear to be a consistent feature of aggression in schizophrenia.

Magnetic Resonance Imaging Studies

Structural abnormalities repeatedly have been shown in violent and aggressive schizophrenia patients. Barkataki et al[42] reported that men with a history of violence showed reduced whole-brain and hippocampus volumes. Hoptman et al[43] found indications of disturbed connectivity between the orbitofrontal cortex and the amygdala, and Wong et al[44] also reported structural abnormalities in the amygdala. Kumari et al[45] found that impulsiveness correlated negatively with reduced orbitofrontal gray matter volume and discussed whether dysfunctional, but not functional, impulsivity is elevated in patients with schizophrenia with a propensity for repetitive violence. Furthermore, the propensity for repetitive violence appeared to be associated with reduced volumes of both the orbitofrontal gray matter and the hippocampus. There is also some evidence for white matter abnormalities in this patient group. Hoptman et al[43] reported an association between measured aggression and increased diffusivity in inferior frontal white matter.

Hoptman et al[46] published a quantitative magnetic resonance imaging (MRI) study of the orbitofrontal cortex in patients with chronic schizophrenia or schizoaffective disorder. Psychopathology was assessed with the PANSS and OAS. In this study, larger volumes of the right orbitofrontal cortex were associated with worse neuropsychological performance. Larger gray matter volumes in the left orbitofrontal cortex and larger white matter volumes in the orbitofrontal cortex were found to be associated with a higher degree of aggression. Hoptman et al[46] discussed these somewhat surprising findings as indicating that larger volumes also may represent a reduced neuronal density or other pathophysiological processes.

Puri et al[47] reported results of an MRI study that compared structural changes in schizophrenia patients with and without violence. Schizophrenia patients with violence were found to have reduced gray matter volumes. Significant disturbances were found in the cerebellum, among other areas, which may be of relevance for input from ventrolateral prefrontal cortex and parietal regions. The findings were interpreted as showing that there may be disturbances in neuronal processes and, in particular, in parietotemporal connections, which may be particularly relevant for nonverbal working memory.

One of the most relevant confounding factor possibly explaining some of the variance is the effect of medication, especially in the elder studies. First, generation neuroleptics may have a profound effect on neurons and volumetric measures.

Positron Emission Tomography/Single-Photon Computed Tomography Studies

Interesting data have arisen from functional imaging studies. Wong et al[48] used fluor-deoxyglucose (FDG)-positron emission tomography to study 31 patients with schizophrenia or schizoaffective disorder at a maximum-security psychiatric hospital. Patients with a history of one act of violence showed reduced absorption of radioactively labeled glucose in the inferior, anterior, and temporal cortex of both hemispheres, while patients with a history of multiple acts of violence showed decreased FDG absorption in the anterior, inferior, and temporal cortex of the left hemisphere. This study did not find a selective reduction of glucose utilization in the prefrontal cortex. Spalletta et al[49] used single photon-emission computed tomography (SPECT) to study the association between the function of the prefrontal cortex and aggression in 15 schizophrenia patients. In resting conditions, there were no differences between violent and nonviolent patients. However, under neuropsychological stress (Wisconsin Card Sorting test), prefrontal function was significantly reduced in the violent patients. Finally, Naudts and Hodgins[37] formulated the hypothesis that aggressive patients with schizophrenia show rather better neuropsychological performance than other schizophrenia patients, particularly in executive functions, but more impairments in the area of the orbitofrontal cortex. In addition, structural abnormalities in the amygdala-orbitofrontal system and in the prefrontal cortex and hippocampus may be involved.

Functional MRI

Meanwhile, several additional studies have been published on this topic. Kumari et al[50] compared a small sample of schizophrenia patients with and without violence, patients with antisocial personality disorder, and healthy controls and reported that the group of violent schizophrenia patients showed a bilateral activation deficit in the frontal cortex and precuneus in the functional MRI (fMRI) evaluation when compared with the healthy controls and deficits in the area of the right inferior parietal region when compared with the nonviolent schizophrenia patients. Frontal (bilateral) and right-sided inferior parietal activity was negatively associated with the degree of violent behavior, whereby the right parietal region showed the strongest association. In contrast to the hypothesis of Naudts

and Hodgins,[37] Kumari et al[50] assumed that possible disturbances in executive functions may be part of the explanation for violence in schizophrenia patients. Various studies at the neurobiological level have shown that a dysfunction in the frontal cortex is associated with violence and antisocial behavior.[51]

Another noteworthy study is that by Joyal et al,[52] which used fMRI to compare violent patients with schizophrenia alone, violent patients with schizophrenia and comorbid antisocial personality or substance abuse disorder, and healthy controls. In agreement with their hypothesis, they found that the frontal basal cortices were less well activated in patients with comorbid schizophrenia, substance abuse, and antisocial personality than in both patients with schizophrenia alone and nonviolent people without mental illness. Incidentally, in contrast to these findings, patients with comorbid schizophrenia showed higher activity in the frontal motor and premotor cortex and the anterior cingulum than patients with schizophrenia alone. The authors interpreted their findings as confirmation of the hypothesis formulated by Naudts and Hodgins.[37]

Dolan and Fullham[53] examined a small group of violence-prone schizophrenia patients and measured the responses of patients to emotional faces with high and low psychopathic traits. The former group exhibited compromised amygdala-prefrontal cortex functioning and attenuated amygdala activation when presented with fearful cues. These findings were interpreted such that violent schizophrenia patients with persistent antisocial features are characterized by distinct neural circuit deficits.

Finally, Hoptman et al[54] performed the only functional connectivity study of aggression in schizophrenia that demonstrated significant reductions in functional connectivity between the amygdala and the prefrontal cortex in this group. This reduction tended to predict higher levels of aggression.

Summary

To sum up, no consistent neurobiological theory has been established to explain violent and aggressive behavior in schizophrenia. Most studies have been performed in clinical samples with aggression as measured by psychopathological scales, fewer studies in schizophrenia patients with homicide. A number of candidate genes have been studied, most of which are relevant for dopaminergic or serotonergic neurotransmission. More recently, neuroimaging studies have explored the interrelationship between violence and brain function. Several findings seem to indicate that in schizophrenia patients with aggression or persistent violence, certain brain functions or areas—in particular the prefrontal and frontal cortex—may be more severely impaired than in schizophrenia patients without aggression or violence. However, additional studies, particularly functional imaging studies, are certainly necessary to further evaluate this question.

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