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Aggressive Behavior Among Persons With Schizophrenia and Those Who Are Developing Schizophrenia: Attempting to Understand the Limited Evidence on Causality

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People with, and those who are developing, schizophrenia are at increased risk to engage in aggressive behavior (AGB). Some incidents lead to criminal prosecution. Most people with schizophrenia who commit crimes engage in delinquency and/or AGB prior to first episode. A large proportion of these individuals have a history of childhood conduct disorder (CD) and brain abnormalities suggestive of abnormal neural development distinctive from that of others with schizophrenia. Factors contributing to schizophrenia that is preceded by CD include failing to learn not-to-behave aggressively in early childhood, impairments in understanding emotions in the faces of others, maltreatment, and subsequent re-victimization. Others with no history of antisocial behavior begin engaging in AGB as positive symptoms increase and illness onsets. They too are at elevated risk to be victimized. Specific genetic variants linked to stress regulation in combination with adversity have been associated both with AGB and psychotic symptoms. Effectively treating conduct problems and preventing victimization would reduce AGB by persons with schizophrenia.

Key words: aggressive behavior/development/gene-by-environment interactions

Schizophrenia is a highly heritable neurodevelopmental disorder.[1] Children carrying the multiple risk alleles show social and behavioral impairments by age 4 that broaden to implicate other domains as they age.[2] Prospectively collected data show that from conception onwards, children who subsequently develop schizophrenia differ from other children, showing internalizing problems,[3] lower than average IQ,[4] deficits in working memory,[3] motor abnormalities,[5] and psychotic-like-experiences.[3] Consequently, a developmental perspective is essential to understanding people with schizophrenia, the causes of schizophrenia, and the elevated rates of aggressive behavior (AGB) among persons with, and those who are developing, schizophrenia.

Throughout the article, the term "developing schizophrenia" is used to designate individuals with schizophrenia during the earlier stages of their lives prior to formal diagnosis. Presently, there is no way to accurately identify such children and adolescents. Ultra-high-risk and clinical high risk criteria do identify some of those developing schizophrenia but relatively soon before onset. However, adopting a developmental perspective to interpret the extant literature and to propose hypotheses for future research involves using data from prospective studies of which there are very few (eg, studies of members of the Dunedin birth cohort who developed schizophreniform disorder), and from follow-back studies. Follow-back studies compare characteristics in childhood/adolescence, before first diagnosis, of adults with schizophrenia and healthy adults. Follow-back studies may include objective data, eg, teacher ratings of participants' behavior, family videos, juvenile criminal records, official records of child maltreatment or subjective data, retrospective, reports, eg, from participants, parents, and siblings, or both.

Persons with schizophrenia, or who are developing schizophrenia are more likely than persons without this disorder to engage in AGB toward others (for a review, see Hodgins et al[6]). Some incidents of AGB lead to prosecution. Robust evidence confirms that persons with schizophrenia are at increased risk for nonviolent crime, at higher risk to engage in violent crime, and at even higher risk to kill as compared to the general population where they live.[6] Importantly, the correlates of violent offending and AGB toward others when patients are living in the community are similar.[6]

Most (72%) people with schizophrenia who will commit a criminal offence, do so prior to first contact with mental health services.[7] Notably, a recent meta-analysis showed that 35% of individuals who contacted services for a first episode of psychosis (FEP) had previously committed at least one assault,[8] and subsequent studies of FEP samples show similarly elevated rates of past AGB.[9] Another meta-analysis showed that the risk of homicide is 15.5 times higher in individuals experiencing a FEP who were not treated as compared to the general population.[10] Consistent with these findings, studies show that among adolescents engaging in delinquency, particularly violent delinquency,[11] and substance misuse,[12] there are a disproportionate number who subsequently develop schizophrenia.

Age of Onset of Antisocial and Aggressive Behavior

Among persons with schizophrenia who engage in AGB prior to treatment, there are 2 distinct types, those who presented conduct disorder (CD) since childhood and those who begin engaging in AGB as illness onsets.[6,13,14] Between 20% and 40% of males and females with schizophrenia present CD prior to age 15.[6,13] Individuals who present CD in childhood/adolescence and schizophrenia in adulthood are responsible for most crimes committed by persons with schizophrenia. The severity of childhood conduct problems is positively, and linearly, associated with the number of convictions for violent and nonviolent crimes, and AGB, even after taking account of substance misuse.[15–17] Among persons with schizophrenia, those with prior CD show similar symptom profiles,[18] less reduction of positive symptoms with antipsychotic medications,[19] and distinct alterations of brain structures[20] and functioning.[21] These findings together with the distinct pattern of behavior from childhood onwards suggests a distinct abnormality of neural development among individuals with schizophrenia and prior CD. Thus, one pathway to AGB among adults with schizophrenia includes antisocial behavior that onsets in childhood and remains stable over the life span.

Factors Contributing to the Development of CD Followed by Schizophrenia

The prevalence of CD is 4 times higher among men and 15 times higher among women who develop schizophrenia than in the general population. Both genetic and environmental factors associated with schizophrenia promote CD. From toddlerhood onwards, all children have to learn not to behave aggressively.[22] Given that by age 2, children who are developing schizophrenia show motor abnormalities such as delays in walking and talking and specific neurological soft signs,[3–5] and in the subsequent years further motor deficiencies, neurological signs, receptive language deficits[3] and lower than average IQ,[4] it may be that for some of them the challenge of learning not-to-be-aggressive is too great.

Children developing schizophrenia may also show abnormalities in the recognition of emotions in the faces of others as do adults with schizophrenia[23] even at the prodrome,[24] their healthy siblings,[25] and children with CD.[26] Inaccurate reading of the facial expressions of others have profound consequences for the child's understanding of his/her environment and also for his/her behavior as adults communicate much information to children via facial expressions, including information regarding inappropriate behavior. Among adults with schizophrenia, poor recognition of emotions in faces, especially fear and anger,[27] has been associated with past violent behavior.[28,29]

One, if not the key factor, known to promote CD is nonoptimal parenting.[30] There are no studies of parenting practices among parents of people with schizophrenia. Parents of people with schizophrenia show elevated rates of antisocial behavior[13] that is known to be associated with poor parenting practices.[31] Additionally, some of them abuse their children.[32] Further, as many as 40% present a spectrum disorder[33] which may limit their ability to establish secure attachments with their children that in turn lead to long-term dysregulation of the stress system.[34]

In summary, CD in childhood characterizes a large minority of persons with schizophrenia. Multiple motor and cognitive deficits, including difficulty understanding information communicated by emotions in the faces of others may hinder learning not to engage in AGB and other inappropriate behaviors. Parents' limited abilities to form secure attachments, adequately and appropriately reward and sanction their children`s behavior, and in some cases to engage in maltreatment add to the child's deficits and promote CD and the developing illness. As one study of men with schizophrenia showed, however, it was CD, not maltreatment, that was associated with subsequent violent behavior.[35] This finding concurs with a wealth of evidence showing that one pathway to AGB among adults with schizophrenia includes CD. It also adds support to the hypothesis that maltreatment early in childhood promotes CD.[36]

Another Pathway to AGB Among People With Schizophrenia

Some individuals with no childhood/adolescent history of antisocial behavior engage in physical aggression toward others as illness onsets. One hypothesis is that AGB is a response to increased positive symptoms[6] reflecting an increase in dopamine production that leads to stress dysregulation.[37] When positive psychotic symptoms are elevated, large proportions of patients engage in AGB.[38] Within days of taking antipsychotic medications, AGB decreases. A study of a population cohort showed

that persons with schizophrenia presented a lower risk of violent crime when taking antipsychotic medication than during periods when they did not receive medication,[39] as did male prisoners with schizophrenia.[40] During an acute phase, only positive symptoms[41] and disorganization are associated with AGB.[42] Among male patients, 3 specific delusions—being spied on, persecution, and conspiracy—when accompanied by anger have been associated with an increased risk of AGB,[43] and among untreated offenders with schizophrenia, persecutory delusions were associated with an increased risk of violence.[44] However, when psychotic symptoms are lower, they are not associated with AGB, nor with other aspects of psychosocial functioning.[44] When accompanied by positive symptoms and/or distress and/or impulsivity,[38] depression may promote AGB, even after taking account of past AGB and substance misuse.[45,46]

Victimization and Adverse Events

Victimization is more common among children developing schizophrenia and adults with schizophrenia than in the general population.[47] Evidence from prospective studies of general population samples shows that individuals who experienced maltreatment in childhood were more likely than others to continue to experience various forms of victimization through adolescence.[48] Trauma in childhood, including inadequate bonding with a parent, has enduring effects on stress regulatory systems and brain structure and functioning, leading to increased vulnerability to stress[37] throughout life. A recent study indicates that among persons with schizophrenia, victimization and adverse events are likely to lead to AGB. The study focused on a large sample of adult Swedes. Diagnoses were extracted from the health register and prosecutions for violence from the criminal register. Six potential triggers of violence were investigated: exposure to violence, parental bereavement, self-harm, traumatic brain injury, unintended injuries, and substance intoxication. Results showed that in a week following any trigger, as compared to a week following no exposure to triggers, all individuals showed an increased likelihood of committing a violent crime, but those with schizophrenia showed a much greater increase in violent crime than did individuals with bipolar disorder or no disorder. Exposure to violence had the strongest association with subsequent violence. A similar difference in the response to parental bereavement was detected among those with schizophrenia.[49]

Interactions of Multiple Genes With Each Other and With Negative and Positive Environmental Factors

Individuals developing schizophrenia carry a distinct set of genetic variants that act from conception onwards to alter brain structure and function. These genetic variants interact with each other genes (epistasis) and with both negative and positive environmental events to alter brain that in turn determines behavior, cognition, and emotion processing. Genome-Wide Association Studies (GWAS)[50] have detected associations of a set of alleles with schizophrenia. These associations, however, may in fact reflect combinations of alleles with negative environmental factors that were not measured. Similarly, GWAS may have failed to detect associations of other alleles with schizophrenia that were minimized by a positive environmental factor. Complicating the picture even further, is evidence that positive environmental factors can overcome the effects of a negative environmental factor among persons carrying a risk allele.[51] Additionally, the time during the course of development when these genes affect brain and when environmental factors occur modifies the consequences.[52]

Some genes, eg, mono-amine oxidase A (MAOA) and the serotonin transporter (5-HTTLPR functional polymorphism in the promoter region of the 5-HTT/SLC6A4) regulate brain serotonergic activity early in life such that specific alleles within these polymorphisms become highly sensitive to the effects of both negative and positive environmental factors and thereby modify behavior.[51,52] Meta-analyses of the mono-amine oxidase gene show that among male carriers of the low activity variant and female carriers of the high activity variant those who are exposed to childhood adversity showed elevated levels of CD and AGB through adulthood.[53] These variants are carried by 25%–30% of males and females. Thus, it is reasonable to speculate that some individuals developing schizophrenia carry these genetic variants and are exposed to childhood maltreatment thereby putting in place one neural mechanism for promoting CD in childhood and AGB in adulthood. Other variants that also combine with childhood adversity to increase the risk of antisocial behavior, have been identified in the serotonin transporter (5-HTTLPR functional polymorphism in the promoter region of the 5-HTT/SLC6A4),[51] the brain-derived neurotropic factor val66 met gene (BDNF)[51] and FKBP5.[54] The risk of antisocial behavior is not only determined by interactions of such genes each interacting with maltreatment but also by these genes interacting with positive environmental factors such as positive parenting, and with each other.[51]

Both MAOA and 5HTT act in the brain very early in life to regulate serotonin and other amines such that specific alleles increase sensitivity to both negative and to positive environmental factors and thereby promote or protect against CD.[51,52] If for example, young children carrying risk genes for schizophrenia also carry MAOA and/or 5HTT sensitivity alleles and they are maltreated in childhood, they are likely to react with a pattern of antisocial and aggressive behavior that is labeled CD. CD then adds to deficits in motor, cognitive, and social functioning, and internalizing problems reflecting the developing schizophrenia. But the CD may also promote the development of schizophrenia. For example, CD increases the

likelihood of repeated victimization[55] that in turn is associated with dysregulation of the stress system, increases in dopamine production, and the development of psychosis and psychotic-like-experiences.[37] Additionally, CD increases the risk of heavy cannabis use in early adolescence that in the presence of specific genetic alleles acts as a trigger for the onset of schizophrenia.[56]

Children at genetic risk for schizophrenia who do not carry risk alleles for CD, are also victims of maltreatment and poor parental bonding, that in turn dysregulates the stress system and dopamine production and increases psychotic symptoms. As maltreatment leads to re-victimization, and alterations to the cortico-limbic-striatum,[37,57] it could be that repeatedly observing AGB leads to engaging in AGB, especially in the absence of social skills to resolve interpersonal conflicts, in the presence of positive psychotic symptoms that reduce judgment and increase fear, and especially if alcohol and/or drugs further reduce judgment, increase positive symptoms, and fear.

Intriguingly, interactions of 3 of the genes (5-HTTLPR, BDNF, FKBP5) that interact with maltreatment to increase the risk of AGB have been implicated in the development of schizophrenia.[37] Variants of these genes in combination with adversity, usually childhood maltreatment or poor parental bonding, lead to dysregulation of the stress system which in turn leads to increased striatal dopamine and psychotic symptoms.[34,37] Both studies of antisocial behavior and studies of psychosis have shown that these gene-by-environment interactions are associated with changes to brain structures and functioning, specifically in the limbic system and cortical areas that down-regulate limbic activity, that are in turn associated with both antisocial behavior and psychosis.[37,57] The recognition that some genetic variants in combination with childhood adversity have been associated both with CD, AGB, and with schizophrenia is consistent with evidence showing that the same additive genetic factors contributed to schizophrenia, violent crime, and substance misuse,[58] and that a schizophrenia polygenic risk score predicts CD.[59]

However, elucidating the multiple gene-by-environment and gene-by-gene interactions that alter neural structures and functioning so as to promote AGB and/or psychosis at different periods during development is beyond the scope of current methodologies. For example, we examined the associations of MAOA, 5HTT, BDNF, family conflict, sexual abuse, and parenting, with delinquency. Teenagers carrying risk alleles showed elevated delinquency when exposed to family adversity, and low levels of delinquency when exposed to positive parenting even if they had been exposed to adversity.[51] Although the study included 1337 teenagers, statistical power was limited even though we measured only 3 genes and 3 environmental factors.[51] Thus, neural and behavioral consequences differ depending on an individual's entire genetic make-up, exposure to negative and positive environmental factors, and importantly, the developmental stage when the gene acts and when the adversity occurs. Additionally, negative environmental factors not only combine with specific alleles to alter the brain, they also modify gene expression through epigenetic mechanisms.[60]

Conclusion

The extant literature provides evidence that could be used to modify current clinical practices so as to reduce AGB among people with schizophrenia. First, validated assessments of the risk of violence should be used in FEP clinics once acute symptoms are reduced. A past history of AGB along with other risks should lead to a program of treatment that includes all the components necessary for effective treatment of schizophrenia[61] and those shown to be effective in reducing AGB.[62,63] Within FEP[64] and prodrome clinics, such programs have been established.[65] Second, patients with schizophrenia need to be encouraged to always report victimization to authorities, and importantly also to clinicians, as evidence indicates that experiencing victimization may increase the risk of AGB in the following days. Third, patients require housing that keeps them safe, and programs that teach them how to resolve interpersonal conflicts without resorting to physical fighting, not to engage in attention-getting behaviors in public, and not to use alcohol and drugs that increase the risk of both AGB and victimization. Additionally, all children must be protected against maltreatment by parents, other adults, and their peers, and all adults from victimization by authorities[66] and peers. Many studies now show the protective effects of positive parenting, especially among children carrying risk alleles suggesting strongly that policies and practices that protect children from harm and that provide them with optimal parenting have the potential to reduce CD but also perhaps, some aspects of schizophrenia.

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