Neurobiological Correlates of Violent Behavior Among Persons With Schizophrenia

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Men and women who develop schizophrenia are at increased risk, compared with the general population, to engage in violence toward others. The reasons for this robust finding remain obscure. We undertook a review of studies comparing neuropsychological test performance, neurological soft signs, and structural brain images of persons with schizophrenia with and without a history of violence. Our search identified 17 studies. The results are inconsistent and contradictory, mainly due to varying definitions of violence, differences in sample characteristics, and the use of diverse measures to tap the neurobiological correlates of violent behavior. The results suggest, however, that among men with schizophrenia, those who have displayed a stable pattern of antisocial and aggressive behavior since childhood, as compared with those with no such history, perform better on neuropsychological tests tapping specific executive functions and more poorly on assessments of orbitofrontal functions, show fewer neurological soft signs, and display larger reductions in volume of the amygdalae, more structural abnormalities of the orbitofrontal system, more abnormalities of white matter in the amygdala-orbitofrontal system, and smaller reductions in volumes of the hippocampus.

Key words: Schizophrenia/violence/neuropsychology/neurological soft signs/structural brain imaging

Introduction

Evidence has accumulated showing that persons who have, or who will develop, schizophrenia are at increased risk for violent offending and at even higher risk to commit homicide as compared with the general population. This evidence comes from investigations of birth and population cohorts that compare the criminality of persons with and without schizophrenia,\textsuperscript{1-5} from diagnostic studies of representative samples of incarcerated offenders,\textsuperscript{8-11} and from investigations of complete cohorts of homicide offenders.\textsuperscript{12,13} Given that these findings derive from investigations that have used different designs, examined different samples from countries with distinctly different cultures, health, and criminal justice systems, and were conducted by different teams of researchers, they may be considered as robust.

Persons with schizophrenia who engage in violent behavior constitute a very heterogeneous population. Some display a history of antisocial behavior from a very early age; others begin engaging in antisocial behavior around the time schizophrenia onsets; others commit only 1 violent attack in their lives, while others behave aggressively only when acutely psychotic.\textsuperscript{14} While in this last group there are approximately equal numbers of males and females,\textsuperscript{15,16} in all the other groups males far outnumber females.\textsuperscript{1,2,12}

Studies examining the neurobiological correlates of violent behavior among persons with schizophrenia have generally presumed that the correlates are the same regardless of the age of onset, the persistence of violent behavior, and the phase of illness when the violence occurred. This could explain, at least in part, the contradictory and inconsistent results of studies that have examined the links between neuropsychological test performance, neurological soft signs, structural and functional brain imaging, and violence among persons with schizophrenia. We undertook a review of studies that addressed this topic in an effort to clarify the available evidence and develop hypotheses for future studies.

Method

Medline, PsycInfo, and Embase were searched to identify studies of neuropsychological test performance, neurological soft signs, and structural and functional brain imaging of persons with schizophrenia or schizoaffective disorder who engaged in aggressive behavior, defined as a physical assault on another person. The term “violence” was used in many of the articles reviewed, and
throughout we use the authors’ terminology when describing each study but report how each study operation- alized this key variable. In conducting the review, we made an effort to distinguish participants by age of onset and persistence of antisocial behavior. In most cases where this was possible, the diagnosis of Antisocial Personality Disorder (APD) was used to index early-onset persistent antisocial behavior.17,18 An effort was also made to distinguish study samples by phase of illness (stabilized or acute), location (inpatient ward or community), history of substance misuse, and intoxication at the time of the aggressive incident. We also took account of the time period covered by the measure of aggressive behavior, for example, reports of incidents during the past 10 weeks versus information extracted from lifetime criminal records. Each of the studies is briefly presented in Table 1.

Results

Neuropsychological Test Performance

Nine studies were found that examined persons with schizophrenic disorders and compared neuropsychological test performance between the aggressive and nonaggressive. Results are inconsistent, with 3 studies reporting that aggressive persons with schizophrenia displayed better performance, 3 showing that they performed more poorly, and 3 reporting no group differences.

Aggressive Behavior Is Associated With Better Performance. Three studies reported that among men with schizophrenia, those with a history of aggressive behavior, as compared with those without, performed better on neuropsychological tests. Roy et al.,19 in the United States, examined 20 male inpatients with chronic schizophrenia described as treatment resistant. Violence included physical and/or verbal assaults against people, property, or self. Based on observations and file review, 11 of the patients were classified as violent and 9 as low violent.20,21 The mean length of current hospitalization was 83.9 weeks. The violent, as compared with the nonviolent, patients performed significantly better on the performance subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R),22 suggesting better visuomotor and visuo-perceptual organization, psychomotor coordination, and external manipulation.

Lapierre et al.,23 in Canada, examined 31 male outpatients with schizophrenia, 13 with a comorbid diagnosis of APD, and 30 healthy men screened for neurological and mental disorders. Information on lifelong history of aggressive behavior was obtained through in-depth interviews with the participants and from medical and criminal files. Significant positive correlations were observed between performance on both the Wisconsin Card Sorting Test (WCST)24 (categories achieved) and the Controlled Oral Word Association Test (COWAT)25 (number of correct words) and the number of assaults that caused injury to the victim. Nonsignificant positive associations were reported between aggressive behavior and results on the Porteus Maze,26 the Trail Making,27 and the WAIS-R.22

A study28 from Norway compared 2 groups of men with schizophrenia and a group of healthy men: (1) 13 inpatients on a ward for aggressive patients within a maximum-security hospital; (2) 13 nonaggressive patients—8 inpatients and 5 outpatients—recruited from general psychiatric services; and (3) 13 healthy nurses. No details are provided as to the nature and severity of aggressive behavior that was required to have been admitted to the maximum-security ward. In general, both groups of patients with schizophrenia performed more poorly than the healthy participants on the neuropsychological tests. The nonaggressive patients showed poorer performance than the aggressive patients on the Trail Making Test,27 slower reaction times on the Trigram Tests (ie, a lexicon decision task),29 similar performance on the Perceptual Maze Test29 and the Necker Cube Test (ie, passively perceived perspective reversals of a cube),29 and better performance on the Finger Tapping Test.29 The nonaggressive patients performed more slowly, on average, than the other 2 groups on all reaction time tests (visual, auditory, Go-NoGo).29 On the Go-NoGo test, the aggressive group had significantly more failed inhibitions than the nonaggressive patients.

Aggressive Behavior Is Not Associated With Performance on Neuropsychological Tests. Krakowski et al.,30 in the United States, examined aggressive behavior on an inpatient ward. Physical assaults were recorded and rated by ward staff using the Modified Overt Aggression Scale31 during a 4-week period. Thirty-two patients were classified as transiently violent, as their frequency of assaults decreased during the study period, and 27 patients were classified as persistently violent. At the end of 4 weeks, all patients completed the WAIS-R.22 No significant differences were observed in the average Performance and Verbal IQ scores obtained by the 2 groups of patients. The results of this study may not generalize, however, as the average global IQ scores of both groups were well below the means usually reported for patients with schizophrenia (transiently violent patients $M = 79.15$ [SD = 15.9]; persistently violent patients $M = 75.54$ [SD = 8.8]).32

Wong et al.33 studied 39 male offenders with schizophrenic disorders, 20 of whom had committed several violent offenses and 19 who had committed only 1 violent offense, in a forensic hospital in the United Kingdom. Global IQ scores on the WAIS32 did not differ for the 2 groups (several violent offenses $M = 89$ [SD = 12]; only 1 violent offense $M = 95$ [SD = 19]).

Lafayette et al.34 examined the relationship between cognitive functioning and history of violent offending among 96 outpatients (70 males, 26 females) with schizophrenia in the United States. The participants were
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Sample Size</th>
<th>Sex</th>
<th>Inpatients</th>
<th>Outpatients</th>
<th>Period Violence Assessed</th>
<th>Source of Information</th>
<th>Subjects</th>
<th>Recent Substance Abuse</th>
<th>Current Antipsychotics</th>
<th>Results (violent group compared to nonviolent)</th>
</tr>
</thead>
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<tr>
<td>Roy et al.(^{19})</td>
<td>1987</td>
<td>20</td>
<td>M</td>
<td>Stable</td>
<td>n/a</td>
<td>6 months</td>
<td>Medical file review; Observation</td>
<td>Outpatients (n = 31);</td>
<td>High violent (n = 11); Low violent (n = 9)</td>
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<tr>
<td>Lapierre et al.(^{23})</td>
<td>1995</td>
<td>61</td>
<td>M</td>
<td>n/a</td>
<td>Stable</td>
<td>Lifelong</td>
<td>Medical and criminal file review; Interview</td>
<td>Healthy volunteers (n = 30)</td>
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<td>Yes</td>
<td>Better</td>
</tr>
<tr>
<td>Rasmussen et al.(^{28})</td>
<td>1995</td>
<td>39</td>
<td>M</td>
<td>Stable</td>
<td>n/a</td>
<td>Unclear</td>
<td>Medical file review</td>
<td>Violent (n = 13); Nonviolent (n = 13); Healthy controls (n = 13)</td>
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<td>Unclear</td>
<td>Better</td>
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<td>1997</td>
<td>94</td>
<td>M</td>
<td>Acute</td>
<td>n/a</td>
<td>4 weeks</td>
<td>MOAS</td>
<td>Persistently violent (n = 27); Transiently violent (n = 32); Nonviolent (n = 45)</td>
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<td>No difference</td>
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<td>1997</td>
<td>39</td>
<td>M</td>
<td>Stable</td>
<td>n/a</td>
<td>Lifelong</td>
<td>Medical file review</td>
<td>Several violent offenses (n = 20); 1 violent offense (n = 19)</td>
<td>No</td>
<td>Yes</td>
<td>No difference</td>
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<tr>
<td>Lafayette et al.(^{34})</td>
<td>2003</td>
<td>96</td>
<td>M (n = 70); F (n = 26)</td>
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<td>Stable</td>
<td>Lifelong</td>
<td>Criminal files</td>
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<td>Unclear</td>
<td>No difference</td>
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<td>1989</td>
<td>89</td>
<td>M (n = 71); F (n = 18)</td>
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<td>n/a</td>
<td>1–6 months</td>
<td>Medical file review; Observation</td>
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<td>Worse</td>
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<td>1990</td>
<td>37</td>
<td>M</td>
<td>Acute</td>
<td>n/a</td>
<td>Lifelong</td>
<td>Criminal and police files</td>
<td>NIMP (n = 12); IMP (n = 25)</td>
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<td>Barkataki et al.(^{42})</td>
<td>2005</td>
<td>28</td>
<td>M</td>
<td>Stable</td>
<td>n/a</td>
<td>Lifelong</td>
<td>Medical file review; Interview</td>
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<tr>
<td>Krakowski et al.(^{38})</td>
<td>1989</td>
<td>89</td>
<td>M (n = 71); F (n = 18)</td>
<td>Acute</td>
<td>n/a</td>
<td>1–6 months</td>
<td>Medical file review; Observation; QNS</td>
<td>High violent (n = 28); Low violent (n = 27)</td>
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<td>More</td>
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<tr>
<td>Krakowski et al.(^{30})</td>
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<td>94</td>
<td>M</td>
<td>Acute</td>
<td>n/a</td>
<td>4 weeks</td>
<td>MOAS; QNS</td>
<td>High violent (n = 28); Low violent (n = 27)</td>
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<td>More</td>
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<tr>
<td>Arango et al.(^{49})</td>
<td>1999</td>
<td>63</td>
<td>M (n = 46); F (n = 17)</td>
<td>Acute</td>
<td>n/a</td>
<td>4–5 weeks</td>
<td>OAS; NES</td>
<td>Violent (n = 16); Nonviolent (n = 47)</td>
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<td>Braun and Lapierre(^{22})</td>
<td>1995</td>
<td>61</td>
<td>M</td>
<td>n/a</td>
<td>Stable</td>
<td>Lifelong</td>
<td>Medical and criminal file review; Interview; QNS</td>
<td>Outpatients (n = 31); Healthy volunteers (n = 30)</td>
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<td>Convit et al.(^{24})</td>
<td>1996</td>
<td>18</td>
<td>M</td>
<td>Acute</td>
<td>n/a</td>
<td>Unclear</td>
<td>CT scan</td>
<td>Repetitively violent (n = 9); No history of violence (n = 9)</td>
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<td>Sylvian fissure</td>
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<td>Wong et al.(^{33})</td>
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<td>39</td>
<td>M</td>
<td>Stable</td>
<td>n/a</td>
<td>Lifelong</td>
<td>MRI scan</td>
<td>Several violent offenses (n = 20); 1 violent offense (n = 19)</td>
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</tr>
</tbody>
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Table 1. Continued

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<th>Authors</th>
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<th>Outpatients</th>
<th>Period Violence Assessed</th>
<th>Source of Information</th>
<th>Subjects</th>
<th>Recent Substance Abuse</th>
<th>Current Antipsychotics</th>
<th>Results (violent group compared to nonviolent)</th>
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<tr>
<td>Hoptman et al.</td>
<td>2002</td>
<td>14</td>
<td>M</td>
<td>Acute and stable</td>
<td>n/a</td>
<td>Lifelong</td>
<td>Medical file review; Interview; LHA scale; BIS-II; DTI scan</td>
<td>All violent (n = 14)</td>
<td>No information</td>
<td>Yes</td>
<td>Amygdala-OFC</td>
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<tr>
<td>Barkataki et al.</td>
<td>2004</td>
<td>28</td>
<td>M</td>
<td>Stable</td>
<td>n/a</td>
<td>Lifelong</td>
<td>Medical file review; Interview; MRI scan</td>
<td>History of severe violence (n = 13); No history of severe violence (n = 15)</td>
<td>No</td>
<td>Yes</td>
<td>Whole brain volume hippocampus PUTMEN</td>
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<td>Functional Brain Imaging</td>
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<tr>
<td>Wong et al.</td>
<td>1997</td>
<td>39</td>
<td>M</td>
<td>Stable</td>
<td>n/a</td>
<td>Lifelong</td>
<td>PET scan</td>
<td>Several violent offenses (n = 20); 1 violent offense (n = 19)</td>
<td>Yes</td>
<td>Unclear</td>
<td>Reduced FDG uptake at anterior inferior temporal cortex</td>
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<tr>
<td>Spalletta et al.</td>
<td>2001</td>
<td>15</td>
<td>No information</td>
<td>Acute</td>
<td>n/a</td>
<td>No week of hospitalization</td>
<td>Medical file review; SPECT scan</td>
<td>Violent (n = 3); Nonviolent (n = 12)</td>
<td>No information</td>
<td>No information</td>
<td>Reduced prefrontal rCBF at anterior inferior temporal cortex</td>
</tr>
</tbody>
</table>

Note: MOAS: Modified Overt Aggression Scale; OAS: Overt Aggression Scale; QNS: Quantified Neurological Scale; NES: Neurological Evaluation Scale; LHA scale: Lifetime History of Aggression scale; BIS-II: Barratt Impulsiveness Scale; DTI: Diffusion Tensor Imaging; FDG: Fluorodeoxyglucose; rCBF: Regional Cerebral Blood Flow; IMP: Neuropsychologically impaired; NIMP: Not neuropsychologically impaired.
Violence was defined as fatal or near fatal acts of aggression against another person. Compared to a group of healthy controls, both violent and nonviolent schizophrenia groups had global, but marginal, deficits involving measures of general intellectual functioning (WAIS-III\textsuperscript{35}), memory (Wechsler Memory Scale-III\textsuperscript{43}), executive functioning (Executive Golf Task,\textsuperscript{44} WCST,\textsuperscript{24} Tower of London Test,\textsuperscript{45} Stroop Color-Word Test\textsuperscript{36}), attention (Continuous Performance Task\textsuperscript{46}), and cognitive processing speed (Adult Memory and Information Processing Battery\textsuperscript{37}). On all of these tests, only performance on the WCST distinguished the violent and nonviolent patients, with the violent patients making significantly more perseverative errors.

**Neurological Soft Signs**

Four studies were found that examined neurological soft signs among men with schizophrenia comparing those with and without a history of violence. Two studies reported no differences between the aggressive and nonaggressive patients. Krakowski et al.\textsuperscript{38} used a quantified neurological scale (QNS) consisting of 56 items that assessed hard and soft neurological signs.\textsuperscript{48} The high violence group was most impaired and the nonviolent patients the least impaired. The groups differed most markedly on measures of integrative sensory function and complex coordination of motor activity. In a later study the same group\textsuperscript{30} reported that the persistently violent group obtained a higher total score, reflecting more severe neurological impairment, particularly frontal lobe impairment, as reflected in the score on the frontal lobe subscale. The differences between violent and nonviolent patients in both studies were not attributable to demographic variables, drug or alcohol abuse, or dosage of antipsychotic medications. Again, the results of these 2 studies may not generalize because of the patients’ low global IQ scores.

Arango et al.\textsuperscript{49} examined inpatients with a diagnosis of schizophrenia. Violence was described as physical aggression against others but included threatening behaviors (a score of 2 or higher on the Overt Aggression Scale).\textsuperscript{50} Neurological soft signs were assessed with the Neurological Evaluation Scale.\textsuperscript{51} Of the 63 patients studied, 16 (25.4%) were physically violent toward others, and 47 (74.6%) were not, during hospital stays of 1 month on average. The groups did not differ on the numbers or types of neurological soft signs (sensory integration, motor coordination, and sequencing of complex motor acts).

Braun and Lapierre\textsuperscript{52} assessed neurological soft signs in the sample previously described\textsuperscript{23} of 31 male outpatients with schizophrenia, 13 with a comorbid diagnosis of APD, and 30 healthy men. A 108-item version of the scale used in the 2 studies described above\textsuperscript{48,52} was administered. While both groups of patients obtained significantly higher scores than the healthy men, a nonsignificant positive relationship was observed between the frequency of aggressive behavior and neurological soft signs. Neuropsychological tasks measuring impulsivity (Porteus Maze, Go-NoGo) that are thought to tap orbitofrontal activity related very robustly to the soft signs, in particular to right-body signs.

**Structural Brain Imaging Studies**

Four studies were identified that examined structural brain scans among men with schizophrenia comparing those with and without a history of violence. Violent patients were distinguished by volume reductions of the amygdala, altered frontal white matter microstructure in the orbitofrontal cortex-amygdala, reductions in whole brain volume and hippocampus, and increased volume of the putamen.

Convit et al.\textsuperscript{54} in the United States, conducted Computed Tomography (CT) scans to examine 18 male inpatients with schizophrenia. Of these, 9 patients were selected from consecutive admissions to an intensive psychiatric service and had a history of repetitive violence, and 9 other patients had no history of violence. Ratings of cortical atrophy were higher for the violent than the nonviolent group, but none of the comparisons came close to reaching statistical significance. Neither the ratings of hippocampal atrophy nor white matter lesions differentiated the 2 groups. Subjective ratings of the Sylvian Fissure were, on average, significantly larger, bilaterally, for the violent than the nonviolent patients. The authors suggested that this enlargement in the violent group was most likely related to the chronicity of the illness.

As previously described, Wong et al.\textsuperscript{33} in the United Kingdom, examined 31 offenders with schizophrenia or schizoaffective disorder, 17 with a history of repetitive violence, 14 who had committed 1 violent offense, and 8 healthy participants with no history of violent behavior. Amygdala volumes varied by group, with the largest volumes observed among the healthy comparison group participants, intermediate volumes observed among the persistently violent patients, and the smallest observed among the patients with a history of 1 violent offense. The differences between the once-violent patients and healthy comparison group, and between the repeatedly violent patients and the healthy comparison group, were statistically significant while difference between the 2 patient groups did not reach statistical significance. However, post-hoc t-tests indicated that the amygdala volume reduction in the repetitive offenders was limited to the right side, while the one-time violent offenders displayed bilateral reductions.
Hoptman et al.,\textsuperscript{55} in the United States, examined 14 male inpatients with schizophrenia. File review indicated great variance in the frequency of violent behavior, ranging from none or very low levels to persistent aggression. Aggressive behavior was evaluated by means of a self-report questionnaire, the Life History of Aggression Scale.\textsuperscript{56} Impulsivity was assessed using the Barratt Impulsiveness Scale–Version 11.\textsuperscript{57} Axial Diffusion Tensor Images (DTI) were acquired using a pulsed gradient, double spin echo, echo planar imaging method. White matter microstructural measures were calculated from these data. Regions of interest were placed in frontal white matter. The results suggested that right inferior frontal white matter microstructure of the orbitofrontal cortex-amygdala was associated with impulsivity and aggression in men with schizophrenia.

Barkataki et al.,\textsuperscript{58} in the United Kingdom, as previously described, examined 28 male inpatients with schizophrenia, 13 with a history of violence and 15 without. When compared with healthy men, both violent and nonviolent schizophrenia groups exhibited increased lateral ventricles. Among the men with schizophrenia, the violent group displayed reduced whole brain volumes, reduced hippocampal volumes, and increased putamen size as compared with the nonviolent group. While these structures have been reported to be involved in schizophrenia,\textsuperscript{59} the authors suggest that hippocampal deficits may reflect impaired memory and emotion processing known to play a role in violence.\textsuperscript{60} The putamen abnormality observed among the violent patients might be associated with altered motor inhibition and control.

Functional Brain Imaging Studies

Wong et al.\textsuperscript{61} used fluorodeoxyglucose (FDG) positron emission tomography brain scans to examine 31 offenders with schizophrenia and schizoaffective disorder recruited from a maximum security psychiatric hospital. In the sample previously described, 17 patients had a history of repetitive violent offending, and 14 had committed only 1 violent offense. These patients were compared with 6 healthy controls with no history of violence. Non-repetitive violent offenders had significantly reduced FDG uptake in the inferior anterior temporal cortex of both hemispheres, while the repetitively violent offenders had abnormally reduced FDG uptake in the anterior inferior temporal cortex of the left hemisphere only. Selective reduction in the prefrontal cortex was not evident in this study. Spalletta et al.\textsuperscript{62} assessed the relationship between prefrontal function and aggression in 15 inpatients with schizophrenia using single photon emission tomography (SPECT). Three patients were classified as violent and 12 as nonviolent. There was no difference between violent and nonviolent patients in prefrontal regional Cerebral Blood Flow (rCBF) at rest. However, there was a difference between the 2 groups in prefrontal rCBF scores during completion of the WCST, with significantly reduced prefrontal rCBF among the violent subjects. It was suggested that reduced prefrontal rCBF could result in a loss of inhibition and may lead to aggression.

Discussion

Methodological Issues

Our search identified 17 studies, reported in 14 articles, comparing neuropsychological test performance, neurological soft signs, and structural brain imaging of violent and nonviolent persons with schizophrenia or schizoaffective disorder. The results are inconsistent and contradictory. This situation is primarily due to varying definitions of violence, characteristics of the samples, and the use of different measures to tap neurobiological correlates of violent behavior.

Definitions of Violence. In most of the studies, violence was defined as the number of violent incidents that had occurred over a specific period of time, ranging from 1 week\textsuperscript{39} to the entire life span.\textsuperscript{55,58} While some studies included only aggressive behavior that led to criminal prosecution,\textsuperscript{34,42} others examined aggressive behavior reported by ward staff,\textsuperscript{30} while still others used both patients’ self-reports and psychiatric files to assess aggressive behavior over the life span.\textsuperscript{23} Some studies added a qualitative component, assessing the severity or nature of the assault(s). For example, Lapierre et al.\textsuperscript{23} included only violent incidents that caused physical injury to the victim. A minority of studies included incidents of verbal aggression with physical aggression.\textsuperscript{19} The failure of studies to discriminate between a pattern of aggressive behavior that emerged in early childhood and remained stable through adulthood, aggressive behavior that first occurred when schizophrenia onset, and aggressive behavior that only occurred during acute psychotic episodes is likely the primary reason for the inconsistent findings regarding the neurobiological correlates of violence. Behavioral genetic studies have consistently demonstrated that early-onset stable aggressive behavior is at least partially hereditary,\textsuperscript{63} and other evidence indicates that environmental factors operating in the prenatal period and in early life play a role.\textsuperscript{64,65} It is hypothesized that both the genetic and nongenetic factors influence aggressive behavior via effects on the brain,\textsuperscript{66} consistent with findings on impairments in cognitive performance from an early age.\textsuperscript{67} Further, none of the studies reviewed distinguished between instrumental and reactive or emotionally charged aggression,\textsuperscript{68} which, evidence suggests, are associated with different neural mechanisms.\textsuperscript{69,70}

Sample Characteristics. The samples in the studies reviewed were generally small, for instance, 13 aggressive
patients, 13 nonaggressive, and 13 healthy controls \(^{28}\) or 14 participants. \(^{35}\) Some studies did not include a comparison group of healthy participants. \(^{39,55}\) Apart from 2 studies, \(^{34,38}\) all participants were men. Among persons with schizophrenia, evidence suggests, more men than women engage in aggressive behavior toward others in the community \(^{2,5}\); however, on inpatient wards, where patients are in an acute psychotic state, violence is as common among women as it is among men. \(^{16}\) These findings indicate the necessity of taking account not only of the onset and persistence of the aggressive behavior but also phase of illness, location, and gender of the protagonist.

All but 2 \(^{23,34}\) of the studies reviewed included inpatients. Results of the review suggest that men with schizophrenia who engage in violence toward others in the community have less frontal impairment, as indexed by performance on the WAIS, WCST, and the COWAT, and fewer frontal soft signs than those who do not. The inconsistencies in the literature regarding the neurobiological correlates of violence among persons with schizophrenia may result, at least in part, from a difference between persons who engage in aggressive behavior only when acutely psychotic and those who show persistent aggressive behavior when not acutely psychotic. For example, the samples studied vary as to phase of illness, ranging from recently admitted, acutely ill patients, \(^{30,38}\) to treatment-resistant, long-term inpatients, \(^{19,28}\) to patients who had recently been arrested for a serious violent offense. \(^{39}\)

**History of Substance Abuse.** Information on history of substance abuse is lacking in some of the studies. \(^{19,28,55}\) Surprisingly, evidence suggests that among men with schizophrenia better cognitive and psychosocial functioning is associated with substance misuse and with antisocial behavior. \(^{71-75}\)

Planning and organizational skills reflected by fewer frontal abnormalities and few negative symptoms may be necessary to initiate and maintain illegal drug abuse. Further, there may be important differences among men with schizophrenia who abuse illicit drugs and those who abuse only alcohol. Pencer and Addington \(^{76}\) carried out a prospective study of 226 patients admitted to an early psychosis service and reassessed 159 of them twice, at yearly intervals. Most were outpatients. At the initial assessment and at follow-up assessments, no significant associations were found between performance on neuro-psychological tests and the use of illicit drugs. Stirling et al. \(^{75}\) followed up 112 participants from a first-episode clinic for 10 to 12 years. Individuals who had not used cannabis before the first episode of illness were generally indistinguishable from cannabis users at follow-up, except that the latter group showed markedly spared neurocognition. Taken together, these results suggest that individuals with schizophrenia who abuse substances, in particular alcohol and cannabis, do not exhibit more cognitive impairment than those who do not. In light of evidence suggesting that alcohol has more damaging effects on the brains of men with schizophrenia than without, \(^{77}\) the above findings may be interpreted to suggest that men with schizophrenia who engage in persistent misuse of alcohol and drugs are characterized by fewer structural brain abnormalities before the onset of schizophrenia than those with no history of substance misuse. \(^{72}\)

**Medication.** Information on current medication was not always reported. \(^{30,38}\) In those studies where medications were noted, there is great variance in both type, conventional and atypical, and dosage of antipsychotics. Since antipsychotic medications differ in their effects on neurocognitive performance, \(^{78}\) the failure to take account of type and dosage may have limited the detection of group differences. By contrast, soft signs have been shown to be independent of antipsychotic exposure. \(^{79,80}\) Recent evidence suggests that persistently aggressive inpatients, similar to those in several of the studies reviewed, show more marked reductions in positive and negative symptoms when treated with clozapine, while risperidone and olanzapine achieved the highest levels of symptom reduction among nonaggressive patients. \(^{81}\) These findings suggest that the neurobiology of schizophrenia may differ between those who persistently engage in aggressive behavior and those who do not. In addition, clozapine has been shown to have superior anti-aggressive effects in this inpatient sample, and atypicals have been shown to reduce violent behavior in the community. \(^{82,83}\) In summary, by not taking account of medication type and dosage, the studies reviewed may have failed to detect differences between aggressive and nonaggressive patients and may have misclassified patients into aggressive and nonaggressive groups.

**Primary Diagnosis and Comorbid APD.** Participants’ primary diagnoses vary. In the studies reviewed, most participants had a diagnosis of paranoid schizophrenia, which is associated with higher Verbal IQ scores and better executive functioning on the Wisconsin Card Sorting Test as compared with undifferentiated schizophrenia. \(^{84}\) Another important factor that may account for inconsistencies in findings is comorbid APD, which includes by definition a history of antisocial behavior before age 15. Among men with schizophrenia APD is associated with early onset and persistent violent offending. \(^{16,17}\) Some of the studies did not assess APD, \(^{33}\) and 2 studies included large proportions of patients with APD \(^{23}\) or high scores on the Psychopathy Checklist–Revised. \(^{25}\) Interestingly, the latter 2 studies provide support for the hypothesis that among men with schizophrenia the presence of a stable pattern of antisocial behavior from childhood onward
Conclusions
Three studies reported that violent patients performed more poorly than nonviolent or low violent patients on the WAIS-R, the Luria-Nebraska Battery, and the WCST. Rasmussen et al. also found that aggressive patients showed significantly more failed inhibitions on a Go-NoGo task and more impulsivity on all reaction time tests. By contrast, the results of 6 studies indicate that patients with a history of aggressive behavior, as compared with those with no history of aggressive behavior, performed equally well or even better on the WCST, Trail Making, the WAIS, the Trigram Test, and the COWAT. Taken together, these results suggest that individuals with schizophrenia and a history of violent or antisocial behavior are characterized by fewer abnormalities of the dorsolateral and mesial prefrontal cortex. This is reflected in better executive functioning and verbal skills, particularly in samples of outpatients with a history of violence. The greater impulsivity may relate to an orbitomedial frontal dysfunction.

Arango et al. demonstrated that neurological soft signs are reliably related to measures of neuropsychological performance and that soft signs may be predictive of neurocognitive performance. The better performance on measures of executive functions in the reviewed neuropsychological studies would then reflect fewer neurological soft signs. The results of studies of neurological soft signs also lend support to the notion of orbitofrontal cortex involvement in the neurobiology of repetitive, impulsive violence. Hoptman et al. provided evidence of impaired connectivity between the orbitofrontal cortex and the amygdala, while Wong et al. reported structural abnormalities in the amygdalae of men with schizophrenia and a history of violence and reduced regional blood flow in the anterior inferior temporal cortices. The ventromedial orbitofrontal cortex (OFC) is necessary for inhibiting impulsive decision making and behavior and for physiological anticipation (ie, somatic states) of secondary inducers (ie, punishment or negative events). Studies of patients with lesions acquired at different ages suggest that the amygdalae are necessary in early life for the normal development of this orbitofrontal system. Abnormalities in the amygdala-orbitofrontal system may therefore be the neurobiological basis of persistent impulsive antisocial and violent behavior. Persons with schizophrenia and a history of violence may present abnormalities in the amygdalae from early life that are associated with reduced abilities to experience emotions and to recognize emotions in others. As the individual matures, the connections with the OFC do not develop, and consequently secondary inducers only poorly trigger somatic states. In addition, abnormalities of the OFC may be associated with difficulty in inhibiting impulsive decision making and behavior. The reduced prefrontal regional blood flow observed among violent patients is consistent with this notion, although the sample included only 3 violent patients.

Excessive and chronic stress during adolescence is hypothesized to play a critical role in the development of schizophrenia among genetically vulnerable individuals. Chronic stress is associated with chronic elevations of cortisol that is toxic to the brain. This process may contribute to some of the reductions in the volume of specific brain structures, such as the hippocampus, that have been reported to be present at the onset of a first episode of psychosis. Individuals who display a stable pattern of antisocial behavior since childhood are characterized by lowered stress reactivity and specifically in childhood lower levels of cortisol than other children. This lowered stress reactivity may protect neural structures in such individuals and could be the reason for the finding that men with schizophrenia who have a history of aggressive behavior present less reduction in volumes of critical neural structures, despite abusing alcohol and drugs.

We hypothesize that among a group of men with schizophrenia, those who have displayed a stable pattern of antisocial behavior since childhood, as compared with those with no history of antisocial behavior prior to illness onset, will display larger reductions in volumes of the amygdalae, more abnormalities specific to the orbitofrontal system, abnormalities of white matter in the amygdala-orbitofrontal system, and smaller reductions in volumes of the hippocampus. In testing these hypotheses, it will be necessary to take account of the more severe substance abuse in the antisocial group.

In conclusion, our review highlights evidence that among persons with schizophrenia, those who have displayed a stable pattern of violent or antisocial behavior since childhood, as compared with those with no such history, perform better on neuropsychological tests tapping specific executive functions and more poorly on assessments of orbitofrontal functions, and they are characterized by fewer neurological soft signs, more abnormalities specific to the orbitofrontal system, more abnormalities of white matter in the amygdala-orbitofrontal system, and smaller reductions in volumes of the hippocampus.

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