Disentangling Structural Brain Alterations Associated With Violent Behavior From Those Associated With Substance Use Disorders

Boris Schiffer, PhD; Bernhard W. Müller, PhD; Norbert Scherbaum, MD; Sheilagh Hodgins, PhD; Michael Forsting, MD; Jens Wiltfang, MD; Elke R. Gizewski, MD; Norbert Leygraf, MD

Context: Studies aimed at identifying structural brain alterations associated with persistent violent behavior or psychopathy have not adequately accounted for a lifetime history of substance misuse. Thus, alterations in gray matter (GM) volume that have been reported to be correlates of violent behavior and/or psychopathy may instead be related to lifelong substance use disorders (SUDs).

Objective: To identify alterations in GM volume associated with violent behavior and those associated with lifelong SUDs.

Design: Cross-sectional study.

Setting: Participants were recruited from penitentiaries, forensic hospitals, psychiatric outpatient services, and communities in Germany. Structural magnetic resonance imaging was performed at a university hospital.

Participants: Four groups of men were compared: 12 men with SUDs who exhibited violent behavior (hereafter referred to as violent offenders), 12 violent offenders without SUDs, 13 men with SUDs who did not exhibit violent behavior (hereafter referred to as nonoffenders), and 14 nonoffenders without SUDs.

Main Outcome Measures: Voxel-based morphometry was used to analyze high-resolution magnetic resonance imaging scans. Assessments of mental disorders, psychopathy (using the Psychopathy Checklist–Screening Version), aggressive behavior, and impulsivity were conducted by trained clinicians.

Results: Compared with nonoffenders, violent offenders presented with a larger GM volume in the amygdala bilaterally, the left nucleus accumbens, and the right caudate head and with less GM volume in the left insula. Men with SUDs exhibited a smaller GM volume in the orbitofrontal cortex, ventromedial prefrontal cortex, and premotor cortex than did men without SUDs. Regression analyses indicated that the alterations in GM volume that distinguished the violent offenders from nonoffenders were associated with psychopathy scores and scores for lifelong aggressive behavior. The GM volumes of the orbitofrontal cortex and prefrontal cortex that distinguished the men with SUDs from the men without SUDs were correlated with scores for response inhibition.

Conclusions: These findings suggest that a greater GM volume in the mesolimbic reward system may be associated with violent behavior and that reduced GM volumes in the prefrontal cortex, orbitofrontal cortex, and premotor area characterize men with SUDs.

the etiological mechanisms driving their persistent violence. Studies of the brain morphology of violent offenders can provide clues to causal mechanisms (hypotheses to be tested in prospective investigations of children) and can provide information about mechanisms that contribute to maintaining the violent behavior and its associated features. Such information may be useful for increasing the effectiveness of learning-based programs aimed at reducing violent behavior.12,13

Synthesizing knowledge relevant to the brain morphology of violent offenders is complicated because the small number of structural magnetic resonance imaging (MRI) studies have included participants defined by different criteria.11 Although almost all of the studies have included only men, some describe participants as having high scores on the Psychopathy Checklist—Revised (PCL-R)14-18 or the Psychopathy Checklist—Screening Version (PCL-SV)19 or as presenting with the syndrome of psychopathy20 (a score of 30 or higher among North American men and 25 or higher among European men21,22). Other studies describe participants as having ASPD, without reporting PCL scores or noting the proportion of participants with high PCL scores.22,23 Furthermore, although some of the participants with the syndrome of psychopathy or with high scores on the PCL have a history of violent behavior,15,27 others have only a few convictions,15,27 and still others have no record of violent behavior.23

The interpretation of studies of the brain morphology of violent offenders is further limited by the fact that most of these men present with a substance use disorder (SUD).20,26 During childhood, these individuals were exposed to alcohol and drugs20 much earlier than other children, and most go on to abuse multiple types of drugs.31 A common genetic factor confers a vulnerability for antisocial behavior that begins during childhood and persists through adulthood and that includes substance misuse.4 Thus, teasing apart alterations in brain structure associated with persistent violent behavior and those associated with SUDs presents an ongoing challenge.

Not surprisingly, studies of brain structures of violent offenders and participants labeled as “psychopathic” have yielded mixed results (for reviews, see Wahlund and Kristiansson22 or Dolan33). Most studies,14,16,19,23,26,27 but not all,22,25 have reported associations between violent behavior and/or high PCL scores and smaller gray matter (GM) volume in the prefrontal cortex (PFC) and in temporolimbic structures.14,16,17,19,24,25 However, smaller GM volumes, particularly in the PFC, have been reported to distinguish people with SUDs.34,35

All but 2 of the studies24,26 that compared violent offenders and men who did not exhibit violent behavior (hereafter referred to as nonoffenders) reported that the offenders currently presented with SUDs, whereas the nonoffenders did not have substance abuse problems.14,22,24,26,27 This was also true of all14,16-21 but 2 of the studies10,23 that defined participants by use of PCL scores.14,18 All of the studies of violent offenders, except one,25 reported smaller GM volumes in the PFC (including the orbital frontal and frontopolar cortices)14,18,22,26,27 and the temporal lobe.14,24,25 However, one study that excluded offenders with current SUDs did not observe smaller PFC volumes in the offenders.24 Among the studies of psychopathic criminals,16,17,19,23 only 2 controlled for substance misuse.16,23 and both reported that psychopathy was associated with larger GM volumes in the striatum16 and smaller GM volumes in the PFC.23 Thus, studies of structural brain alterations associated with persistent violence have not adequately accounted for lifetime SUDs, thereby leaving open the possibility that the observed brain volume alterations were not associated with violent behavior but rather with substance abuse.32,33

We used high-resolution structural MRI in combination with voxel-based morphometry to compare the structural brain integrity of persistent violent offenders and nonoffenders with and without SUDs. We hypothesized that persistent violent offenders, compared with nonoffenders, would be characterized by abnormalities of the mesolimbic reward system (amygdala, nucleus accumbens, and striatum) and that men with SUDs, compared with men without SUDs, would be characterized by alterations in medial PFC and orbitofrontal cortex (OFC). We also explored the associations between the structural alterations that distinguished the violent offenders from the nonoffenders and a history of aggressive behavior and psychopathic traits. Finally, we hypothesized that features of brain morphology distinguishing the participants with and without SUDs would be associated with self-reported impulsivity and response inhibition.

METHODS

PARTICIPANTS

The sample included 51 men between 23 and 54 years of age living in Germany. Twenty-four violent offenders were recruited from penitentiaries and forensic facilities specializing in the treatment of offenders with SUDs. Each offender had been convicted of 3 or more crimes (range, 3-14) with a mean (SD) of 3.3 (1.2) violent offenses. The violent offenders were divided into 2 groups: 12 without a current or lifetime diagnosis of alcohol and/or drug abuse and/or dependence, except for nicotine (without SUDs), and 12 who met diagnostic criteria for an alcohol and/or drug abuse and/or dependence diagnosis (with SUDs). The nonoffender group included 13 men with SUDs who were recruited from community substance misuse treatment programs and 14 healthy men with no Axis I disorders or criminal histories who were recruited by use of advertisements and from local employment agencies (nonoffenders without SUDs).

Diagnoses were confirmed by interviews using the Structured Clinical Interview for DSM-IV10-12 disorders. As presented in Table 1, the 4 groups were matched on age and level of education. The duration of SUDs was similar for the 2 groups of participants with these diagnoses. No participant had a current or past severe mental illness, history of significant medical or neurologic illness, or head injury resulting in loss of consciousness for more than 30 minutes. All participants were right-handed with IQ scores of 90 or higher on the multiple choice vocabulary test.30 Urine analysis indicated that no participant had consumed any substance in the year prior to study entry.

Our study was approved by the local committee on medical ethics of the medical faculty of the University of Duisburg-Essen, Germany, and was conducted in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki). After a detailed description of the study, written informed consent was obtained from all participants.
Measurement of Impulsivity

Impulsivity was assessed in 2 ways: (1) by self-report using the Barratt Impulsiveness Scale, which provides scores for attentional, motor, and nonplanning impulsivity, and (2) by the number of perseverative errors on the Wisconsin Card Sorting Test.

Table 1. Demographic, Forensic, and Clinical Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Measure</th>
<th>Nonoffenders Without SUDs (n=14)</th>
<th>Nonoffenders With SUDs (n=13)</th>
<th>Violent Offenders Without SUDs (n=12)</th>
<th>Violent Offenders With SUDs (n=10)</th>
<th>P Value for Violence</th>
<th>P Value for Addiction</th>
<th>P Value for Violence × Addiction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36.7 (11.4)</td>
<td>37.3 (7.9)</td>
<td>37.4 (10.6)</td>
<td>36.4 (5.5)</td>
<td>.96</td>
<td>.95</td>
<td>.78</td>
</tr>
<tr>
<td>Education, y</td>
<td>9.93 (0.99)</td>
<td>9.69 (1.44)</td>
<td>9.55 (1.21)</td>
<td>9.50 (0.97)</td>
<td>.41</td>
<td>.68</td>
<td>.78</td>
</tr>
<tr>
<td>Criminal history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first conviction for violent offense, y</td>
<td>NA</td>
<td>NA</td>
<td>20.2 (4.6)</td>
<td>19.8 (5.0)</td>
<td>NA</td>
<td>.85</td>
<td>NA</td>
</tr>
<tr>
<td>Convictions, No.</td>
<td>0</td>
<td>0</td>
<td>4.9 (3.8)</td>
<td>5.1 (3.4)</td>
<td>&lt;.01</td>
<td>.89</td>
<td>NA</td>
</tr>
<tr>
<td>Prison sentences, No.</td>
<td>0</td>
<td>0</td>
<td>1.6 (0.9)</td>
<td>2.3 (1.4)</td>
<td>&lt;.01</td>
<td>.06</td>
<td>.06</td>
</tr>
<tr>
<td>Duration of current incarceration, y</td>
<td>NA</td>
<td>NA</td>
<td>5.9 (3.3)</td>
<td>4.8 (1.4)</td>
<td>NA</td>
<td>.34</td>
<td>NA</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASPD, No. of participants</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>10</td>
<td>&lt;.01</td>
<td>.44</td>
<td>.96</td>
</tr>
<tr>
<td>PCL-SV total score</td>
<td>4.4 (2.6)</td>
<td>6.5 (2.6)</td>
<td>9.3 (2.9)</td>
<td>12.8 (2.8)</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
<td>.61</td>
</tr>
<tr>
<td>Interpersonal facet</td>
<td>1.5 (1.3)</td>
<td>1.1 (1.1)</td>
<td>2.0 (1.5)</td>
<td>3.2 (1.6)</td>
<td>.01</td>
<td>.32</td>
<td>.03</td>
</tr>
<tr>
<td>Affective facet</td>
<td>1.2 (0.9)</td>
<td>2.0 (1.0)</td>
<td>2.4 (1.2)</td>
<td>3.3 (0.8)</td>
<td>&lt;.01</td>
<td>.01</td>
<td>.50</td>
</tr>
<tr>
<td>Lifestyle facet</td>
<td>1.1 (0.7)</td>
<td>2.1 (1.2)</td>
<td>2.1 (1.3)</td>
<td>3.0 (1.8)</td>
<td>.01</td>
<td>.02</td>
<td>.68</td>
</tr>
<tr>
<td>Antisocial facet</td>
<td>0.6 (0.7)</td>
<td>1.4 (1.0)</td>
<td>2.8 (1.3)</td>
<td>3.2 (1.3)</td>
<td>&lt;.01</td>
<td>&lt;.05</td>
<td>.62</td>
</tr>
<tr>
<td>LHA score (range, 0-55)</td>
<td>11.1 (5.5)</td>
<td>18.7 (5.9)</td>
<td>20.0 (8.1)</td>
<td>28.1 (7.0)</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
<td>.89</td>
</tr>
<tr>
<td>BIS total score</td>
<td>63.9 (9.1)</td>
<td>67.2 (9.0)</td>
<td>58.9 (9.7)</td>
<td>66.3 (7.4)</td>
<td>.24</td>
<td>.04</td>
<td>.43</td>
</tr>
<tr>
<td>Attentional impulsivity</td>
<td>15.3 (3.0)</td>
<td>17.7 (3.8)</td>
<td>15.1 (2.4)</td>
<td>16.9 (2.4)</td>
<td>.57</td>
<td>.02</td>
<td>.74</td>
</tr>
<tr>
<td>Motor impulsivity</td>
<td>23.3 (3.9)</td>
<td>23.1 (2.9)</td>
<td>20.5 (4.5)</td>
<td>22.3 (3.7)</td>
<td>.10</td>
<td>.45</td>
<td>.34</td>
</tr>
<tr>
<td>Nonplanning impulsivity</td>
<td>25.3 (5.0)</td>
<td>26.5 (4.5)</td>
<td>23.3 (4.7)</td>
<td>27.0 (3.4)</td>
<td>.58</td>
<td>.06</td>
<td>.33</td>
</tr>
<tr>
<td>Behavioral measure of impulsivity, z score</td>
<td>0.22 (0.25)</td>
<td>−0.59 (1.10)</td>
<td>0.15 (0.37)</td>
<td>−0.36 (0.69)</td>
<td>.70</td>
<td>&lt;.01</td>
<td>.44</td>
</tr>
<tr>
<td>SUDs, No. of participants</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>10</td>
<td>&lt;.01</td>
<td>.44</td>
<td>.96</td>
</tr>
<tr>
<td>Alcohol dependence (code 303.90)</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>12</td>
<td>.92</td>
<td>&lt;.01</td>
<td>.91</td>
</tr>
<tr>
<td>Cannabis abuse (code 305.20)</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>8</td>
<td>.75</td>
<td>&lt;.01</td>
<td>.80</td>
</tr>
<tr>
<td>Opiate abuse (code 305.50)</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>6</td>
<td>.58</td>
<td>&lt;.01</td>
<td>.76</td>
</tr>
<tr>
<td>Cocaine abuse (code 305.60)</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>6</td>
<td>.58</td>
<td>&lt;.01</td>
<td>.76</td>
</tr>
<tr>
<td>Stimulants abuse (code 305.70)</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>.69</td>
<td>&lt;.01</td>
<td>.88</td>
</tr>
<tr>
<td>MAST score (range, 0-25)</td>
<td>1.6 (2.3)</td>
<td>14.2 (6.9)</td>
<td>3.2 (4.4)</td>
<td>8.4 (7.1)</td>
<td>.47</td>
<td>&lt;.01</td>
<td>.09</td>
</tr>
<tr>
<td>DAST score (range, 0-20)</td>
<td>0.9 (0.9)</td>
<td>12.8 (6.3)</td>
<td>3.5 (3.3)</td>
<td>9.8 (8.1)</td>
<td>.88</td>
<td>&lt;.01</td>
<td>.08</td>
</tr>
<tr>
<td>Duration of substance misuse, y</td>
<td>NA</td>
<td>11.2 (5.3)</td>
<td>NA</td>
<td>11.0 (4.1)</td>
<td>.93</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of recent abstinence, y</td>
<td>NA</td>
<td>1.6 (0.5)</td>
<td>NA</td>
<td>3.3 (1.3)</td>
<td>&lt;.01</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>109.9 (11.7)</td>
<td>106.4 (6.0)</td>
<td>104.4 (7.9)</td>
<td>107.7 (11.3)</td>
<td>.46</td>
<td>.98</td>
<td>.23</td>
</tr>
</tbody>
</table>

Abbreviations: ANOVA, analysis of variance; ASPD, antisocial personality disorder; BIS, Barratt Impulsiveness Scale; DAST, Drug Abuse Screening Test; LHA, Life History of Aggression; MAST, Michigan Alcohol Screening Test; NA, not applicable; PCL-SV, Psychopathy Checklist—Screening Version; SUDs, substance use disorders.

Men who exhibited violent behavior are hereafter referred to as violent offenders, and men who did not exhibit violent behavior are hereafter referred to as nonoffenders.

Self-report measure.

The higher the value, the better the performance.

Using codes from the DSM-IV.

Using the multiple choice vocabulary test.

MEASURES

Diagnosis

The Structured Clinical Interview for DSM-IV was administered by an experienced psychiatrist trained to use the instrument.

Psychopathic Traits

On the basis of interviews and file reviews, psychopathic traits were assessed by an experienced psychiatrist trained to use the 12-item PCL-SV. The PCL-SV has a hierarchical model comprising 2 factors and 4 facets, similar to the PCL-R. Factor 1 includes an interpersonal facet (individual is superficial, grandiose, and/or deceitful) and an affective facet (individual lacks remorse, lacks empathy, and/or does not accept responsibility), and factor 2 includes a behavioral or lifestyle facet (individual is impulsive, lacks goals, and/or is irresponsible) and an antisocial facet (individual has poor behavioral controls, adolescent antisocial behavior, or adult antisocial behavior).

Aggressive Behavior

A semistructured interview, the Life History of Aggression Assessment, was used to assess history of temper tantrums, verbal assaults, property assaults, physical fights, and assaults against persons. The total score (range, 0-55) was calculated by summing 3 subscale scores: aggression (5 items), consequences/antisocial behavior (4 items), and self-directed aggression (2 items).

Impulsivity

Impulsivity was assessed in 2 ways: (1) by self-report using the Barratt Impulsiveness Scale, which provides scores for attention, motor, and nonplanning impulsivity, and (2) by the number of perseverative errors on the Wisconsin Card Sorting Test.
and the number of commission errors on a Go/NoGo task. The scores for the 2 behavioral tasks were z-transformed and averaged to provide an index of response inhibition, such that low scores indicated poor response inhibition.

Substance Misuse

The Michigan Alcohol Screening Test and the Drug Abuse Screening Test were completed by participants to provide scores for lifetime use of alcohol and illicit drugs.

Image Acquisition

Brain images were acquired on a 1.5-T MRI system (Siemens Sonata, Erlangen, Germany) using a 3-dimensional T1-weighted magnetization-prepared rapid acquisition gradient-echo sequence with a repetition time of 1900 milliseconds, an echo time of 3.93 milliseconds, a flip angle of 5°, 160 contiguous 10-mm sagittal slices, a field of view of 240 mm x 240 mm, a matrix size of 240 x 240, and a voxel size of 1.0 x 0.9 x 1.0 mm.

Image Processing

Data were processed using Matlab 7.4 (MathWorks, Natick, Massachusetts) and statistical parametric mapping software (SPM5; Welcome Department of Imaging Neuroscience, London, England). We applied voxel-based morphometry (VBM) standard routines and default parameters implemented in the VBM5 toolbox (http://dbm.neuro.uni-jena.de/vbm.html). Images were bias field-corrected, tissue-classified, and registered using linear (12-parameter affine) and nonlinear transformations (warping) within the same generative model. Subsequently, analyses were performed on GM segments that were multiplied by the nonlinear components, which were derived from the normalization matrix in order to preserve actual GM values locally (modulated GM volumes) because we are interested in analyzing regionally specific between-group differences in GM volume rather than GM concentration. The segmentation procedure was further refined by applying a hidden Markov random field with a weighting of 0.3. Gray matter segments were not multiplied by the linear components of the registration in order to account for individual differences in brain orientation, alignment, and size globally. All images were written out to 1 x 1 x 1 mm isotropic voxel in standard anatomical space (Montreal Neurological Institute, http://www.bic.mni.mcgill.ca/brainweb). Finally, the modulated GM volumes were smoothed with a Gaussian kernel of 12 mm (full-width at half-maximum) because smoothing kernels of 8 mm or smaller increase the risk of false positives.

Using the tissue-classified partitions from the VBM analysis (ie, GM, white matter [WM], and cerebrospinal fluid [CSF]), we determined the overall volumes in units of cubic centimeters as the sum of voxels representing GM, WM, and CSF (total brain volume), total GM volume, total WM volume, and total CSF volume.

STATISTICAL ANALYSIS

Demographic, forensic, clinical, and total brain volume measures of the 4 groups of participants were compared using a 2 (violence: nonoffenders vs violent offenders) by 2 (SUDs: participants with SUDs vs participants without SUDs) analysis of variance with SPSS version 16.0 for Windows (SPSS Inc, Chicago, Illinois).

Employing general linear models, we performed statistical group analyses on GM volumes on a voxel-by-voxel basis. Regionally specific between-group differences in GM volume were then assessed using a 2 (violence: violent offenders vs nonoffenders) by 2 (SUDs: participants with SUDs vs participants without SUDs) analysis of covariance with global GM volume, age, and IQ as covariates of no interest (see De Brito et al for the advantages and disadvantages of this strategy). For each contrast, statistical parametric maps were computed on a voxel-by-voxel basis to test for differences associated with violent behavior or SUDs. In comparisons of GM volumes of violent offenders and nonoffenders, lifetime measures of alcohol and drug misuse were included as covariates. In comparisons of GM volumes of men with SUDs and men without SUDs, PCL-SV scores were entered as covariates. To avoid possible edge effects between different tissue types, we excluded all voxels with GM values of less than 0.1 (absolute threshold masking). Consistent with previous VBM analyses, results of the whole-brain analysis were considered significant at the threshold of P < .05, corrected for multiple comparisons after determining the false discovery rate. All significant outcomes were also restricted to clusters exceeding different numbers of voxels (spatial extent threshold) to protect against type 1 error. The spatial extent threshold corresponds to the expected number of voxels per cluster, calculated according to the theory of Gaussian random fields.

Regression analyses were calculated to estimate linear and quadratic associations between the nonadjusted relative GM volumes of each cluster (distinguishing violent offenders from nonoffenders) and the PCL-SV and lifetime aggressive behavior scores. Pearson correlation coefficients were calculated to estimate the associations between the nonadjusted relative GM volumes of each cluster (distinguishing men with SUDs from men without SUDs) and the impulsivity scores.

RESULTS

DEMOGRAPHIC, FORENSIC, AND CLINICAL CHARACTERISTICS OF THE PARTICIPANTS

As presented in Table 1, the 2 (violence: nonoffenders vs violent offenders) by 2 (SUDs: participants without SUDs vs participants with SUDs) analysis of variance revealed that, compared with nonoffenders, violent offenders were similar in age, level of education, IQ, lifetime alcohol and drug use, and total and subscale scores on the Barratt Impulsiveness Scale and on the measure of response inhibition. The violent offenders also obtained higher scores than did the nonoffenders for aggressive behavior, and three-quarters of them, as opposed to none of the nonoffenders, met criteria for ASPD. The violent offenders obtained higher PCL-SV scores than did the nonoffenders, and these scores were comparable to those reported for prison inmates and forensic patients with ASPD.20,55

The participants with SUDs and those without were similar in age, level of education, IQ, and total psychopathy scores. Those with SUDs obtained higher scores for lifetime alcohol and drug misuse, the interpersonal and antisocial facets of psychopathy, self-reported impulsivity, and response inhibition.

GLOBAL VOLUME MEASURES

As presented in Table 2, violent offenders, as compared with nonoffenders, did not differ with respect to total brain volume, total GM volume adjusted for total brain volume, total WM volume, and total CSF volume. Participants with SUDs, compared with participants with-
out SUDs, displayed similar total brain volumes, total WM volumes, and total CSF volumes and smaller total GM volumes. This latter difference was reduced after adjusting for total brain volume. There was a significant violent behavior × SUDs interaction on adjusted GM volumes. Among the nonoffenders, those with SUDs presented with a smaller GM volume than those without SUDs; among the violent offenders, those with SUDs showed greater GM volume than those without SUDs.

WHOLE-BRAIN ANALYSES

Violent offenders, as compared with nonoffenders, exhibited greater GM volumes in mesolimbic areas, including the left nucleus accumbens, the bilateral amygdala, and the right caudate head, and smaller GM volumes in the left anterior insula (Figure 1A and B). No differences were detected in GM volumes of the PFC or OFC between the violent offenders and the nonoffenders.

As shown in Figure 2A and B, the men with SUDs, compared with those without SUDs, showed significantly reduced GM volumes in the medial orbitofrontal cortex (Brodmann area 11), the ventromedial prefrontal cortex (Brodmann areas 9 and 10), and the premotor area (Brodmann area 6). None of the interaction terms were significant.

ASSOCIATION ANALYSES

Psychopathy Scores

Scatterplots depicting the association between PCL-SV total scores and relative GM volumes in the left nucleus accumbens, the left and right amygdala, the right caudate, and the left anterior insula that had distinguished the violent offenders from the nonoffenders are presented in Figure 1C. As can be seen, the associations appear to be quadratic (U shaped), and as presented in Table 3, the quadratic coefficients were stronger than the linear ones for all these regions. Pearson correlation coefficients between GM volumes and facets of psychopathy are presented in Table 3.

The volumes of the left amygdala and the left nucleus accumbens were positively correlated with both factor 1 and factor 2 PCL-SV scores. However, only the volumes of the left nucleus accumbens were positively correlated with both facets (interpersonal and affective) of factor 1. As would be expected, the volumes of the right and left amygdala and the right caudate were positively correlated with scores for the affective facet and also with the score for the antisocial facet. By contrast, the volume of the left insula was negatively correlated with both factor 1 and factor 2 PCL-SV scores.

Aggressive Behavior

As presented in Table 3, scores for aggressive behavior were positively correlated with the volumes of the right and left amygdala and the right caudate head.

Impulsivity

As hypothesized, one of the primary characteristics distinguishing the participants with SUDs from those without SUDs was impulsivity, in particular, self-reported attentional impulsivity but also response inhibition. To test our hypothesis of an association between impulsivity and prefrontal volume deficits shown in participants with SUDs compared with those without SUDs, correlational analyses were calculated. No associations between the volumes of the medial OFC, ventromedial PFC, and premotor area and the self-report measures of impulsivity were detected. However, as shown in Figure 2C, significant positive correlations between scores for response inhibition and GM volumes of the medial OFC (r = 0.441, P = .002) and the ventromedial PFC (r = 0.410, P = .004) were observed, indicating that the smaller the volume, the more impaired the ability to withhold responses. The correlation of the volume of the premotor cortex and the score for response inhibition (r = 0.222, P = .09) was not significant.

Given our finding that alterations to mesolimbic structures distinguished violent offenders from nonoffenders, we conducted a post hoc analysis based on previous evidence of an association of these structures with impulsivity. We correlated mesolimbic brain volumes and PCL-SV scores, parceling out the scores for impulsivity (the total score on the Barratt Impulsiveness Scale and

<table>
<thead>
<tr>
<th>Measure</th>
<th>Nonoffenders Without SUDs (n=14)</th>
<th>Nonoffenders With SUDs (n=13)</th>
<th>Violent Offenders Without SUDs (n=12)</th>
<th>Violent Offenders With SUDs (n=12)</th>
<th>P Value for Violence</th>
<th>P Value for Addiction</th>
<th>P Value for Violence × Addiction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total brain volume, cm³</td>
<td>1767.4 (181.4)</td>
<td>1753.5 (77.2)</td>
<td>1803.3 (176.6)</td>
<td>1729.0 (138.9)</td>
<td>.25</td>
<td>.03</td>
<td>.48</td>
</tr>
<tr>
<td>Total GM volume, cm³</td>
<td>713.6 (59.7)</td>
<td>649.8 (56.4)</td>
<td>718.8 (101.4)</td>
<td>691.1 (60.5)</td>
<td>.25</td>
<td>.03</td>
<td>.37</td>
</tr>
<tr>
<td>Adjusted GM volume, cm³</td>
<td>714.1 (39.1)</td>
<td>653.9 (55.7)</td>
<td>703.0 (73.9)</td>
<td>705.0 (28.7)</td>
<td>.18</td>
<td>.06</td>
<td>.04</td>
</tr>
<tr>
<td>Total WM volume, cm³</td>
<td>529.4 (80.6)</td>
<td>517.1 (36.9)</td>
<td>549.2 (69.7)</td>
<td>519.6 (50.2)</td>
<td>.53</td>
<td>.24</td>
<td>.63</td>
</tr>
<tr>
<td>Total CSF volume, cm³</td>
<td>524.4 (77.4)</td>
<td>586.7 (78.3)</td>
<td>535.3 (104.5)</td>
<td>518.3 (87.7)</td>
<td>.22</td>
<td>.34</td>
<td>.09</td>
</tr>
</tbody>
</table>
The total score for response inhibition). The correlations between PCL-SV scores and mesolimbic GM volumes remained significant at the α level of .05 (eTable, http://www.archgenpsychiatry).

**COMMENT**

Our study used structural MRI to examine the structural brain integrity of violent offenders and nonoffenders and men with SUDs and men without SUDs. Results confirmed our hypothesis that persistent violent offenders would be characterized by abnormalities of the mesolimbic reward system as evidenced by greater GM volumes in the left nucleus accumbens, the bilateral amygdala, and the right caudate head. Additionally, violent offenders exhibited less GM volume in the left insula. Unlike most previous studies, no differences were detected in the GM volume of the PFC between the violent offenders and the nonoffenders.

Our hypothesis that men with SUDs, compared with those without SUDs, would be characterized by alterations in the PFC was confirmed. Substance use disorders were associated with smaller GM volumes in the ventromedial PFC, the OFC, and the premotor cortex. This finding concurs with a relatively large body of literature on structural deficits associated with SUDs.

The results of our study suggest that previous reports of reduced GM volumes in the OFC, the ventromedial PFC, and the premotor cortex among violent offenders, compared with nonoffenders, may have failed to disentangle the structural brain correlates of persistent violence and SUDs. This conclusion is supported by the results of 2 previous studies. One study that took account of current substance abuse found no difference in GM volumes in the PFC between offenders and nonoffenders. Another study that examined violent offenders with type 2 alcoholism found that smaller GM volumes in the PFC were associated with alcoholism rather
### Table 3. Correlation Coefficients Between Mesolimbic and Insula Gray Matter Volumes and Scores for Life History of Aggressive Behavior and Psychopathy

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Life History of Aggression</th>
<th>PCL-SV Total Score</th>
<th>PCL Factor 1</th>
<th>PCL Factor 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interpersonal Facet</td>
<td>Affective Facet</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>Total</td>
</tr>
<tr>
<td>Left amygdala</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson correlation r</td>
<td>0.340 \textsuperscript{a}</td>
<td>0.515 \textsuperscript{b}</td>
<td>0.074</td>
<td>0.421 \textsuperscript{b}</td>
</tr>
<tr>
<td>Quadratic correlation R\textsuperscript{2}</td>
<td>0.157 \textsuperscript{b}</td>
<td>0.307 \textsuperscript{b}</td>
<td>0.056</td>
<td>0.180 \textsuperscript{b}</td>
</tr>
<tr>
<td>Right amygdala</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson correlation r</td>
<td>0.285 \textsuperscript{a}</td>
<td>0.503 \textsuperscript{b}</td>
<td>0.073</td>
<td>0.340 \textsuperscript{a}</td>
</tr>
<tr>
<td>Quadratic correlation R\textsuperscript{2}</td>
<td>0.100 \textsuperscript{a}</td>
<td>0.297 \textsuperscript{b}</td>
<td>0.060</td>
<td>0.119 \textsuperscript{a}</td>
</tr>
<tr>
<td>Right caudate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson correlation r</td>
<td>0.348 \textsuperscript{a}</td>
<td>0.480 \textsuperscript{b}</td>
<td>0.072</td>
<td>0.377 \textsuperscript{b}</td>
</tr>
<tr>
<td>Quadratic correlation R\textsuperscript{2}</td>
<td>0.127 \textsuperscript{a}</td>
<td>0.327 \textsuperscript{b}</td>
<td>0.115 \textsuperscript{b}</td>
<td>0.144 \textsuperscript{b}</td>
</tr>
<tr>
<td>Left nucleus accumbens</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson correlation r</td>
<td>0.284</td>
<td>0.472 \textsuperscript{b}</td>
<td>0.072</td>
<td>0.377 \textsuperscript{b}</td>
</tr>
<tr>
<td>Quadratic correlation R\textsuperscript{2}</td>
<td>0.093</td>
<td>0.351 \textsuperscript{b}</td>
<td>0.136 \textsuperscript{b}</td>
<td>0.172 \textsuperscript{b}</td>
</tr>
<tr>
<td>Left insula</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson correlation r</td>
<td>−0.260</td>
<td>−0.381 \textsuperscript{b}</td>
<td>−0.341 \textsuperscript{a}</td>
<td>−0.160</td>
</tr>
<tr>
<td>Quadratic correlation R\textsuperscript{2}</td>
<td>0.099</td>
<td>0.158 \textsuperscript{b}</td>
<td>0.121 \textsuperscript{a}</td>
<td>0.082</td>
</tr>
</tbody>
</table>

Abbreviation: PCL-SV, Psychopathy Checklist–Screening Version.

\( a \) P<.05.

\( b \) P<.01.

---

Figure 2. A, Substance use disorder (SUD)–related gray matter (GM) volume decreases (whole-brain analysis of covariance model accounting for age, IQ, total GM values, and psychopathy scores; P<.05 [all P values corrected for multiple comparisons after determining the false discovery rate]) in the orbitofrontal cortex (Brodmann area [BA] 11; coordinates x, y, z, respectively, in Montreal Neurological Institute [MNI] standard brain: −7, 29, −25; P<.049; z=4.20; k=3911), the ventromedial prefrontal cortex (PFC) (BA 10; MNI coordinates: 7, 58, −2; P=.049; z=4.19; k=5922), and the premotor area (BA 6; MNI coordinates: −7, −27, 74; P=.049; z=3.72; k=1099). Color bars indicate t-statistic values. B, Box plots illustrate these GM volume effects on the single-group level. C, Scatterplots depict the linear correlation of patients with SUDs (green) and participants without SUDs (black) between behavioral inhibition performance and relative GM volume of these areas. Four groups of men were compared: 12 men with SUDs who exhibited violent behavior (hereafter referred to as violent offenders), 12 violent offenders without SUDs, 13 men with SUDs who did not exhibit violent behavior (hereafter referred to as nonoffenders), and 14 nonoffenders without SUDs.

* P<.05. OFC indicates orbitofrontal cortex.
than violent behavior. Also, boys aged 10 to 13 years with conduct problems and callous-unemotional traits and no or little exposure to substances did not exhibit any areas of reduced GM concentration compared with healthy boys of the same age. A recent study observed reduced volumes of the orbital frontal, middle frontal, and right rectal GM in participants with ASPD compared with participants with SUDs. The results are difficult to interpret, however, because the proportions of participants with ASPD who had SUDs and criminal convictions is not reported and because 47% of them presented with a comorbid schizophrenia spectrum disorder. In our study, the results showing larger GM volumes among violent offenders compared with nonoffenders are consistent with the results of previous studies of violent offenders with psychopathy, men with psychopathy, and children with conduct problems and high levels of callous-unemotional traits. All of these studies reported increased GM volumes and concentrations in the medial OFC, rostral and dorsal anterior cingulate cortex, left posterior hippocampus, posterior cingulate cortex, and cerebellum. Thus, the structural alterations associated specifically with persistent violent behavior may be increased GM volume in the mesolimbic region, whereas the structural alterations associated with SUDs are smaller GM volumes in the OFC, ventromedial PFC, and premotor cortex. Future studies are needed to replicate these findings.

Interestingly, in the study of boys with conduct problems and callous-unemotional traits, post hoc analyses suggested that GM concentrations in the medial OFC and the dorsal anterior cingulate were increasing with age, whereas in typically developing boys, GM volumes in these areas were decreasing. Children with conduct problems begin using alcohol and/or drugs earlier than other children. At this young age, use of alcohol and/or specific drugs (eg, cannabis) may have consequences for the brain that differ from the effects observed at later ages. Furthermore, use of alcohol and/or drugs may affect the brains of these boys in distinct ways because of their distinct DNA, which modifies their responses to environmental factors, and because of their distinct pattern of neural development. This hypothesis, which requires testing, is supported by the finding from our study that, among the violent offenders, those with SUDs showed greater GM volumes than those without SUDs and that, among the nonoffenders, those with SUDs presented with smaller GM volumes than those without SUDs.

Offenders with psychopathy exhibit a specific deficit in stimulus-reinforcement learning such that they rely, almost exclusively, on reward and fail to take account of punishment. This impairment may be related to the increased GM volume in the caudate that distinguished the violent offenders in our study. A previous study reported that men with psychopathy were characterized by approximately 9.6% greater GM volume in the striatum than healthy men. Greater GM volume in the caudate head was associated with impulsivity and sensation seeking, whereas greater GM volume in the lenticular nucleus was associated with lifelong antisocial behavior. Furthermore, the increased GM volume in the nucleus accumbens that distinguished the violent offenders from the nonoffenders in our study may also be associated with impaired stimulus-reinforcement learning and could explain the excessive recruitment of the mesolimbic reward circuit by behaviorally relevant reinforcers. Thus, the results from our study add to a growing body of evidence suggesting that structural abnormalities within the mesolimbic limbic reward system are associated with an early onset and stable pattern of antisocial behavior and the traits of psychopathy.

In our study, the violent offenders displayed smaller GM volume in the left insula, similar to previous findings among boys with conduct problems and men with high psychopathy scores. Alterations to the insula may be associated with one of the prime characteristics of psychopathy, reduced reactions in anticipation of punishment. Two functional MRI studies reported reduced activity in the insula in anticipation of punishment among men with high psychopathy scores. Furthermore, patients with lesions in the insular cortex were reported to be unable to adjust their behavior depending on the risk of punishment. The insula, together with the amygdala and the medial PFC, is a key component of the neural circuit involved in the detection of emotional significance and the generation of negative affective states in response to emotional faces, pictures, and recall of personal life events, which have been shown to be disturbed in offenders with psychopathic traits.

Gray matter volumes in the left nucleus accumbens, the left and right amygdala, the right caudate head, and the left anterior insula that distinguished violent offenders from nonoffenders were associated with psychopathic personality traits and antisocial and aggressive behavior. These associations were best estimated as quadratic correlations, indicating that high scores, and to a lesser extent low scores, were more strongly associated with greater volumes than were medium scores. The associations remained significant even after controlling for both measures of impulsivity. The nucleus accumbens was the only region in which GM volumes were significantly associated with scores for both the interpersonal and the affective facet of psychopathy, whereas the GM volumes in the amygdala and caudate were positively correlated with the affective traits. Although these findings are consistent with much evidence indicating that adults with high psychopathy scores and children with high levels of callous-unemotional traits have difficulty processing visual and auditory displays of fear and sadness and learning in an aversive paradigm, previous studies suggest that the amygdala is hyporesponsive, especially to fearful faces. The men with SUDs were characterized by less GM volume in the PFC. Damage to the PFC is associated with inappropriate social behavior, as indicated by a number of lesion studies. In addition to their long history of substance misuse, the men with SUDs, compared with the men without SUDs, obtained higher scores for psychopathy, lifetime aggressive behavior, and self-reported impulsivity and lower scores for response inhibition. The GM volumes in the medial OFC and the ventromedial PFC that distinguished men with SUDs from men without SUDs were significantly correlated with scores for response inhibition, such that the smaller the volume, the poorer the response inhibition.
The principal strength of our study was the inclusion of 4 groups of men in an effort to disentangle the correlates of violent behavior from the correlates of SUDs. Furthermore, statistical controls for violent behavior (psychopathy scores) and SUDs (Michigan Alcohol Screening Test49 and Drug Abuse Screening Test50 scores) were entered into group comparisons to ensure that violent behavior was not confounded with SUDs and vice versa. Additionally, group comparisons were controlled for age and IQ, each of which is known to affect brain structure.80-82 The groups were relatively large given the populations from which they were recruited and the demands for lengthy interviews and an MRI scan, and they were homogeneous with respect to sex. Furthermore, random urine tests in the year preceding the brain scan confirmed abstinence and thereby ruled out the possibility that structural abnormalities were due to current substance use.

The strengths of our study were also its limitations. Although the inclusion of a group of violent offenders without SUDs may have helped identify morphology specific to violent behavior, this is an unusual group because three-quarters of them met criteria for ASPD and yet they had no history of substance misuse.83 If such participants are to be included in future studies, more information is required to characterize them. Although the sample size was relatively large, it may have been too small to validly detect interaction effects. Another limitation concerns the lack of detailed information on illicit drug use. The differences detected, for example, between the violent offenders with SUDs and the nonoffenders with SUDs could be due to differences in the type, quantities, or combinations of drugs used and to the age of participant. Finally, as previously noted,13,84 homogeneous phenotypes are necessary to elucidate the neurobiological correlates of persistent violent behavior. Our study, like many, failed to take account of comorbid anxiety disorders that characterize approximately half of men with ASPD in both community85 and prison86 samples.

Structural alterations of the mesolimbic reward system were associated with violent behavior, high psychopathy scores, and lifetime aggressive behavior, whereas reductions in GM volume in the medial OFC, lateral PFC, and the premotor area were associated with SUDs. Our study illustrates the use of a strategy for disentangling the correlates of violent behavior from the correlates of SUDs, and if it can be replicated, it may be used in future studies aimed at furthering our understanding of brain mechanisms associated with these 2 conditions. Such knowledge is needed to inform the development of effective interventions and to develop hypotheses about etiology. Future research is needed to link the observed structural abnormalities to specific deficits in functioning assessed by both neuropsychological tests and behavior in the real world and to the interactions of genes and environmental factors.

Submitted for Publication: February 17, 2011; final revision received February 17, 2011; accepted March 31, 2011. Published Online: June 6, 2011. doi:10.1001/archgenpsychiatry.2011.61. This article was corrected on June 14, 2011.

Author Affiliations: Departments of Forensic Psychiatry (Drs Schiffer and Leygraf) and Psychiatry and Psychotherapy (Drs Müller, Scherbaum, and Wiltfang), University of Duisburg-Essen, Department of Psychiatry, Heidelberg University (Dr Hodgins), Department of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen (Drs Forsting and Giezewski), and Department of Neuroradiology, University Hospital Giessen (Dr Giezewski), Germany; Département de Psychiatrie, Université de Montréal, Quebec, Canada (Dr Hodgins); and Institute of Psychiatry, King’s College London, England (Dr Hodgins).

Correspondence: Boris Schiffer, PhD, Department of Forensic Psychiatry, University of Duisburg-Essen, Vichowstr 174, Essen 45147, Germany (boris.schiffer@uni-due.de).

Financial Disclosure: None reported.

Funding/Support: This research was funded by the Landeschaftsverband Rheinland, Germany (Dr Schiffer).

Online-Only Material: The eTable is available at http://www.archgenpsychiatry.com.

Additional Contributions: We thank A. Wormit and C. Pawlitzek, MSc, for assistance in recruiting participants, MRI scanning, and collecting personality data.


44. Schneider M. Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. *Addict Biol*. 2008;13(2):253-263.


