ORIGINAL ARTICLE

Reduced Prefrontal Gray Matter Volume and Reduced Autonomic Activity in Antisocial Personality Disorder

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Background: Major damage to gray and white matter in the prefrontal cortex and autonomic deficits have been found to result in pseudopsychopathic personality in patients with neurological disorders, but it is not known whether people with antisocial personality disorder (APD) in the community who do not have discernable brain trauma also have subtle prefrontal deficits.

Methods: Prefrontal gray and white matter volumes were assessed using structural magnetic resonance imaging in 21 community volunteers with APD (APD group) and in 2 control groups, comprising 34 healthy subjects (control group), 26 subjects with substance dependence (substance-dependent group), and 21 psychiatric controls. Autonomic activity (skin conductance and heart rate) was also assessed during a social stressor in which participants gave a videotaped speech on their faults.

Results: TheAPD group showed an 11.0% reduction in prefrontal gray matter volume in the absence of ostensible brain lesions and reduced autonomic activity during the stressor. These deficits predicted group membership independent of psychosocial risk factors.

Conclusions: To our knowledge, these findings provide the first evidence for a structural brain deficit in APD. This prefrontal structural deficit may underlie the low arousal, poor fear conditioning, lack of conscience, and decision-making deficits that have been found to characterize antisocial, psychopathic behavior.

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BRAIN IMAGING research on antisocial, violent offenders is beginning to reveal potentially important functional abnormalities in these subjects. Ranging from small pilot studies of 4 cases[1] to group studies of more than 40 cases,[2] there is increasing evidence that poor prefrontal functioning is a characteristic of violent, antisocial persons as indicated by both positron emission tomography[3-5] and single-photon emission computed tomography.[6,7] Nevertheless, few if any of these studies control for comorbidity of substance abuse, schizophrenia-spectrum disorders, and other psychiatric comorbidity, and all have been conducted on selected samples derived from psychiatric hospitals, prisons, or forensic settings. Unlike these functional imaging findings, there have been no prior magnetic resonance imaging (MRI) studies of structural brain deficits in antisocial groups, and nothing is known about brain abnormalities in noninstitutionalized violent offenders.

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In contrast, studies of patients with neurological disorders have provided provocative insights into which structural brain mechanisms, when damaged, may predispose some persons to irresponsible, antisocial, and psychopathic behavior. Ranging from single case studies[8] to series of neurological patients,[9,10] those who have suffered demonstrable damage to both gray and white matter within the prefrontal region of the brain acquire an antisocial, psychopathic-like personality. These patients also show autonomic arousal and attention deficits to socially meaningful events,[9,11] a finding consistent with the role played by the prefrontal cortex in modulating emotion, arousal, and attention[10,12,13] and with the somatic marker hypothesis that appropriate autonomic functioning is critical to experiencing emotional states that guide prosocial behavior and good decision making.[11] On the other hand, not all persons with prefrontal lesions show antisocial, psychopathic behavior.

While these "acquired sociopaths"[11] provide intriguing links between ostensible brain damage and the onset of antisocial personality disorder (APD), it could be argued

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SUBJECTS AND METHODS

SUBJECTS

All subjects were drawn from 5 temporary employment agencies in Los Angeles, Calif. This recruitment strategy was used because pilot data had shown that this community group had relatively high rates of violence perpetration.[15] Subject groups were as follows: 21 men with a diagnosis of APD (APD group), 34 men who had neither APD nor alcohol or other drug dependence (control group), and 27 men with substance dependence (substance-dependent group), who had a lifetime diagnosis of drug or alcohol dependence but not APD. Full demographic, cognitive, physical, and criminal measures for the 3 groups are presented in **Table 1**. All subjects who read a description of the study and who wished to participate were included. Subjects were otherwise unselected, with the exception of the following exclusion criteria: age younger than 21 years or older than 45 years, nonfluency in English, history of epilepsy or claustrophobia, use of a pacemaker, and metal implants. In addition, one subject was excluded a priori because brain scanning revealed major atrophy of the right superior temporal gyrus. Full informed, written consent was obtained from all subjects in accordance with institutional review board procedures at the University of Southern California, Los Angeles. Subjects were paid $5.50/h for participation and were informed that the study concerned the biological basis to personality and behavior problems, including criminal behavior.

Because the APD group had comorbid clinical conditions other than alcohol and substance abuse, a psychiatric control group was formed (n = 21) by matching the 21 subjects in the APD group with 21 subjects from the control and substance-dependent groups to assess whether brain and psychophysiological differences were an artifact of psychiatric comorbidity. Twenty-one subjects in the psychiatric control group were matched with the 21 subjects in the APD group on schizophrenia-spectrum disorders, affective disorders, anxiety disorders, and other personality disorders that do not fall under the category of APD; results of this matching are presented in **Table 2**. There were no significant differences between groups using the χ^2 test ($P>.35$ in all cases), with the psychiatric control group having slightly higher rates than the APD group for all diagnoses.

DIAGNOSTIC, COGNITIVE, PHYSICAL, AND PSYCHOSOCIAL ASSESSMENT

All diagnoses were made using *DSM-IV* criteria[16] and ascertained using the Structured Clinical Interview for Axis I *DSM-IV* Disorders[17] and the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders.[18] Diagnoses were made by research assistants who had participated in a standardized training and quality assurance program for diagnostic assessment.[19] Subjects also completed an alcohol use questionnaire.

Estimated intelligence was based on 5 subtests (vocabulary, arithmetic, digit span, digit symbol, and block design) of the Wechsler Adult Intelligence Scale (Table 1).[20] Degree of right vs left hand preference was assessed using the abbreviated Oldfield Inventory (Table 1),[21] with high scores indicating a stronger preference for right-handedness. History of head injury was defined as head trauma resulting in hospitalization (Table 1). The 10 demographic and psychosocial measures were derived from a structured psychosocial interview with the participant,[15] with social class measured using the Hollingshead classification system.[22] A physical examination was conducted after psychophysiological testing to derive measures of height, weight, and head circumference (Table 1). Body mass index (a measure of obesity) was calculated as weight in kilograms divided by the square of height in meters (Table 1).

VIOLENCE AND ASSESSMENT OF PSYCHOPATHY

Perpetration of serious violence was measured using an adult extension of the self-report delinquency measure used in the National Youth Survey (Table 1),[15,23] and was defined as acts that caused bodily injury or trauma or were life-threatening. Eight items fit this definition: history of an attack on a spouse or girlfriend causing bruises or bleeding, attack on relative or friend causing bruises or bleeding, attack on a stranger causing bruises or bleeding, rape, using a weapon in a fight, using force or a weapon to rob, firing a gun at someone, and attempted murder or murder.

To help minimize false negatives (denial of violence by truly violent offenders), a certificate of confidentiality was obtained from the Secretary of Health, Education, and Welfare, Washington, DC, that protected the research investigators under section 303(a) of Public Health Act 42 from being subpoenaed by any federal, state, or local court in the United States to release the self-reported crime data.

that these findings have little relevance to "life-course persistent"[14] offenders in the community who have consistent antisocial behavior throughout their lives, yet have not suffered gross brain damage. It has been speculated that these developmental sociopaths possess much more subtle prefrontal dysfunction than the blunt macroscopic damage in the acquired sociopath,[11] but there have been no tests of this hypothesis. Specifically, it is not known whether (1) antisocial persons in the community have subtle structural deficits to the prefrontal cortex in the absence of discernable lesions; (2) these prefrontal deficits are restricted to gray matter as opposed to white matter; (3) prefrontal structural and autonomic functional deficits are specific to APD as opposed to other forms of psychopathology; (4) autonomic deficits are independent of, or conversely linked to, prefrontal deficits; and (5) prefrontal and autonomic deficits account for variance in antisocial personality over and above that explained by psychosocial risk factors.

This study attempts to address these 5 questions by conducting structural MRI on volunteers from the community with APD and by making volumetric assessments of prefrontal gray and white matter. Skin conductance and heart rate activity during a social stressor were also measured to assess whether persons with APD show reduced autonomic activity in a socially meaningful context, and also to assess whether antisocial persons with prefrontal structural deficits are especially characterized by reduced electrodermal activity.[11] In addition, psychosocial

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Consequently, subjects were protected from the possible legal action that could be taken against them for crimes they committed and admitted in the interview, but which were not detected and punished by the criminal justice system.

Psychopathic personality was assessed using the Hare Psychopathy Checklist[24] with collateral interview information from the Interpersonal Measure of Psychopathy[25] and from criminal history transcripts obtained from the Department of Justice. The scale ranges from 0 (low psychopathy) to 40 (high psychopathy).

PSYCHOPHYSIOLOGICAL ASSESSMENT

Heart rate and skin conductance was recorded during a social stressor using a Grass model 7 polygraph with a constant 0.5 V potential across electrodes. Skin conductance was recorded from the distal phalanges of the first and second fingers of the left hand using silver/silver chloride electrodes (1 cm in diameter) (Sensor Medics Corp, Yorba Linda, Calif) and physiological saline (0.9% sodium chloride) in Unibase (Warner Chilcott Laboratories, Morris Plains, NJ) as the electrolyte, with the skin contact area delineated using double-sided adhesive masking tape with a hole 1 cm in diameter. Heart rate was monitored using silver/silver chloride electrodes and a standard lead-I configuration, with conductivity gel (Medi-Trace; Graphic Control Corp, Buffalo, NY) serving as the electrolyte. During the social stressor, subjects were told to spend 2 minutes preparing a speech about their faults,[26] followed by a 2-minute period in which they gave their speech to the experimenter while being videotaped. Heart rate and skin conductance levels were sampled each minute and averaged across the 4-minute stress paradigm (see below) to create indices of electrodermal and cardiovascular activity.

MAGNETIC RESONANACE IMAGING

Structural MRIs were conducted on a scanner (S15/ACS; Phillips, Selton, Conn) with a magnet of 1.5-T field strength. After an initial alignment sequence of 1 midsagittal and 4 parasagittal scans (spin echo T1-weighted image acquisition, TR = 600 milliseconds, TE = 20 milliseconds) to identify the anterior commissure–posterior commissure plane, 128 three-dimensional T1-weighted gradient-echo coronal images (TR = 34 milliseconds; TE = 12.4 milliseconds; flip angle, 35°; overcontiguous slices, 1.7 mm; matrix, 256 × 256; field of view, = 23 cm) were obtained in the plane directly orthogonal to the anterior commissure–posterior commissure line.

Three-dimensional brain images were reconstructed using a SPARC workstation and semiautomated software (CAMRA S200 ALLEGRO) used for segmentation of gray matter, white matter, and cerebrospinal fluid. Segmentation of gray and white matter was performed using a thresholding algorithm, with the operator blind to group membership applying a cutoff value to the signal intensity histogram to optimally differentiate white matter from gray matter, areas of which were defined using an automated seeding algorithm on each slice. The left hemisphere (right side) in **Figure 1** shows the seed volume of interest circumscribing the entire cortex (in yellow), illustrating segmentation of gray matter and cerebrospinal fluid. The right hemisphere (left side) shows the seed volume of interest for the white matter (red border), illustrating segmentation of gray and white matter.

The prefrontal region was defined as all of the cortex anterior to the genu of the corpus callosum, and was divided into left and right hemispheres along the longitudinal fissure (Figure 1). Interrater reliability (intraclass correlation coefficient) based on 23 scans (raters blind to each other's ratings and group membership) were as follows: left prefrontal gray matter (0.99), right prefrontal gray matter (0.99), left prefrontal white matter (0.93), right prefrontal white matter (0.94), and total brain volume (0.99).

STATISTICAL ANALYSES

One-way analysis of variance, χ^2, repeated-measures multivariate analysis of variance, and follow-up *t* tests were used to assess group differences on antisocial, demographic, MRI, and psychophysiological variables. All tests of significance are 2-tailed with an α level of .05. The procedure used by Rom[27] a sequentially rejective method, was used to correct for type 1 errors in *t* test comparisons. The repeated-measures analyses of variance used the multivariate approach and were conducted on left and right hemisphere volume measures in a 3 (groups) × 2 (left and right hemisphere) design for gray and white matter separately. The ability of measures to predict group membership was assessed using logistic regression and the Wald χ^2 statistic by using a classification cutoff of 0.5, and with the Nagelkerke statistic used for variance estimation. Brain and autonomic variables were entered using a stepwise forward procedure (Wald χ^2) with an entry probability of .05 and a removal probability of .10, while all psychosocial risk factors were entered simultaneously in one block, and brain and autonomic variables were entered in a stepwise forward procedure. Effect sizes were calculated using Cohen's d.[28]

and demographic risk factors for violence were measured to assess whether brain and autonomic deficits predict group membership after controlling for these factors.

RESULTS

ANTISOCIAL, DEMOGRAPHIC, AND SUBSTANCE ABUSE MEASURES

The APD group reported having committed a greater number of serious violent crimes than both the control group (χ^2_1 = 9.3, *P* = .002) and the substance-dependent group (χ^2_1 = 6.4, *P* = .01) (Table 1). Specifically, 52.4% of the persons with APD reported having attacked a stranger and having caused bruises or bleeding, with rates of 42.9% for rape, 38.1% for firing a gun at someone, and 28.6% for attempted or completed homicide. Persons in the APD group were more likely than both those in the control group (χ^2 = 18.1, *P* = .0001) and those in the substance-dependent group (χ^2 = 4.5, *P* = .03) to have been arrested by the police (see Table 1). Persons in the APD group also scored 1.4 SDs above the mean of persons in the substance-dependent group on psychopathy (t_{52} = 8.9, *P* = .0001), who in turn scored 1.0 SDs higher than the control group (t_{44} = 4.7, *P* = .0001) (Table 1).

Groups were closely comparable in age, social class, ethnicity, intelligence, handedness, history of head injury, weight, and head circumference (*P*>.56 in all cases;

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Table 1. Characteristics of the Study Groups*

Characteristic	Group: Control (n = 34)	Substance-Dependent (n = 26)	APD (n = 21)	Statistic
Demographic				
Age, y	30.4 (6.7)	30.2 (6.2)	31.9 (6.8)	$F_{2,78} = 0.5$, $P = .63$
Social class	35.6 (9.9)	34.2 (11.7)	34.7 (8.9)	$F_{2,78} = 0.1$, $P = .87$
White race, %	47.1	53.8	38.1	$\chi^2_2 = 1.2$, $P = .57$
Cognitive and physical				
Full-scale intelligence	100.9 (15.2)	100.0 (19.1)	98.4 (12.8)	$F_{2,78} = 0.2$, $P = .86$
Handedness†	34.1 (10.0)	32.6 (11.4)	35.4 (9.4)	$F_{2,78} = 0.4$, $P = .66$
Height, cm	176.4 (7.3)	180.3 (7.8)	181.2 (7.0)	$F_{2,78} = 4.0$, $P = .02$
Weight, kg	80.1 (13.7)	82.2 (15.5)	83.9 (8.5)	$F_{2,78} = 0.46$, $P = .64$
Body mass index, kg/m^2	25.7 (4.0)	25.2 (4.0)	25.6 (2.6)	$F_{2,78} = 0.15$, $P = .86$
Head circumference, cm	146.0 (4.4)	145.9 (4.3)	146.8 (4.1)	$F_{2,78} = 0.2$, $P = .82$
History of head injury, %	23.5	34.6	23.8	$\chi^2_2 = 4.8$, $P = .58$
Criminal				
Psychopathy	14.2 (5.5)	20.1 (6.0)	28.5 (5.7)	$F_{2,78} = 38.4$, $P = .0001$
Serious violent crimes	1.2 (2.2)	1.1 (1.3)	3.9 (3.8)	$\chi^2_2 = 10.8$, $P = .004$‡
Arrests, %	14.7	40.7	71.4	$\chi^2_2 = 17.9$, $P = .0001$

*All data are given as mean (SD) unless otherwise indicated. APD indicates antisocial personality disorder.
†High scores indicate greater degree of right-handedness.
‡Kruskal-Wallis χ^2.

Table 2. Rates of Psychiatric Disorder in the APD Group and the Psychiatric Control Group, Together With χ^2 Analyses*

Disorder	Group: Psychiatric Control (n = 21)	APD (n = 21)	χ^2, P
Schizophrenia spectrum†	38.1	33.3	$\chi^2_1 = 0.10$, $P = .74$
Affective‡	52.4	38.1	$\chi^2_1 = 0.87$, $P = .35$
Anxiety§	23.8	19.0	$\chi^2_1 = 0.14$, $P = .71$
Other personality disorders‖	33.3	23.8	$\chi^2_1 = 0.46$, $P = .73$

*APD indicates antisocial personality disorder.
†Includes schizotypal personality, paranoia, schizoid personality, psychosis, and schizophrenia.
‡Includes major depression, bipolar depression, and other depressive disorders.
§Includes phobia, panic, and generalized anxiety.
‖Includes borderline, histrionic, narcissistic, avoidant, dependent, and obsessive-compulsive disorders.

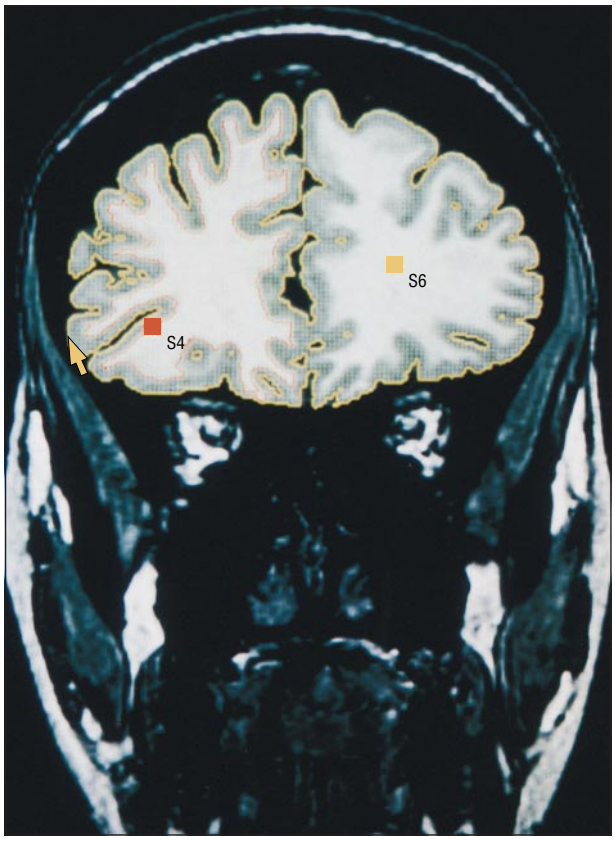

Figure 1. *Coronal slice of the prefrontal cortex illustrating the seeding program for calculation of gray and white volumes.*

see Table 1). As predicted by recent findings on aggressive children,[29] persons in the APD group were significantly taller than those in the control group ($t_{53} = 2.4$, $P = .02$).

Antisocial personality disorder and substance-dependent groups were compared in terms of alcohol and other substance use disorders (sedatives, hypnotics, anxiolytics, cannabis, stimulants, opioids, cocaine, hallucinogens, phencyclidine, polysubstances, and other substances) both in severity (abuse vs dependence) and current usage (**Table 3**). Of 18 χ^2 analyses, one was marginally significant, with persons in the APD group having rates of cocaine dependence higher than those in the substance-dependent group ($\chi^2_4 = 6.1$, $P = .05$). Groups did not differ in age of onset of drug use (APD group, mean [SD], 16.4 [4.8]; substance-dependent group, 16.6 [3.6]; $t_{45} = 0.2$, $P = .87$).

Antisocial personality disorder and substance-dependent groups were also compared on frequency of alcohol usage, the results of which are given in **Table 4**.

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Table 3. Lifetime Rates of Substance Abuse and Other Psychiatric Disorders in the Substance-Dependent and APD Groups*

Disorder	Group: Substance-Dependent (n = 26)	Group: APD (n = 21)	χ^2,† *P*
Alcohol use			0.2_4, .90
Abuse	23.1	28.6	
Dependence	65.4	61.9	0.05_2, .82
Yes in past month	11.5	9.5	
Use of sedatives, hypnotics, and anxiolytics			1.7_4, .42
Abuse	7.7	4.8	
Dependence	3.8	14.3	1.3_2, .26
Yes in past month	0.0	4.8	
Cannabis use			1.8_4, .41
Abuse	23.1	38.1	
Dependence	50.0	47.6	0.11_2, .74
Yes in past month	23.1	19.0	
Stimulant use			2.1_4, .35
Abuse	11.5	23.8	
Dependence	7.7	14.3	NA
Yes in past month	0.0	0.0	
Opioids			1.7_4, .43
Abuse	3.8	4.8	
Dependence	3.8	14.3	2.6_2, .11
Yes in past month	0.0	9.5	
Cocaine			6.1_4, .05
Abuse	7.7	4.8	
Dependence	30.8	66.7	0.02_2, .89
Yes in past month	3.8	4.8	
Hallucinogens/PCP			2.71_4, .26
Abuse	23.1	33.3	
Dependence	3.8	14.3	1.3_2, .26
Yes in past month	0.0	4.8	
Polysubstance use			2.6_4, .27
Abuse	0.0	4.8	
Dependence	0.0	4.8	NA
Yes in past month	0.0	0.0	
Other			2.0_4, .38
Abuse	3.8	9.5	
Dependence	0.0	4.8	NA
Yes in past month	0.0	0.0	

*APD indicates antisocial personality disorder group; NA, not applicable.
†χ^2 Analyses are conducted on psychiatric disorder categorization and substance use in the past month. Subscript numbers indicate degrees of freedom.

Table 4. Comparisons of Alcohol Use in Substance-Dependent and APD Groups*

Alcohol Use	Group: Substance-Dependent (n = 26)	Group: APD (n = 21)	*t*,† *P*
Times used in past week	1.73 (1.61)	1.76 (2.02)	0.1_{45}, .95
Times used in past month	6.62 (5.55)	7.75 (8.53)	0.5_{45}, .59
No. of drinks when drinking	4.08 (4.11)	3.00 (2.85)	1.0_{45}, .31
Largest No. of drinks on 1 occasion	10.96 (9.94)	6.85 (7.52)	1.5_{45}, .13

*All data are given as mean (SD) unless otherwise indicated. APD indicates antisocial personality disorder.
†Subscript numbers indicates degrees of freedom.

Groups did not differ significantly on number of times alcohol was used in the past week and past month, number of drinks taken when drinking, and largest number of drinks taken on one occasion.

MRI PREFRONTAL VOLUMES

Persons with APD showed a significant reduction in the volume of prefrontal gray matter, but not white matter (**Figure 2**). A repeated-measures multivariate analysis of variance on gray matter showed a main effect for group ($F_{2,78}$ = 3.7, *P* = .02). The APD group had lower prefrontal gray volumes than both the control group (t_{53} = 2.2, *P* = .03) and the substance-dependent group (t_{45} = 2.5, *P* = .009). In contrast, groups did not differ on white matter prefrontal volume ($F_{2,78}$ = 1.4, *P* = .25). There was a main effect of hemisphere on prefrontal gray matter volume ($F_{1,78}$ = 119.5, *P* = .0001), indicating increased right relative to left prefrontal gray matter volume, but no group × hemisphere interaction for gray ($F_{2,78}$ = 1.9, *P* = .16) or white matter volumes ($F_{2,78}$ = 1.4, *P* = .26). The APD group had an 11.0% reduction (9.01 cc) in prefrontal gray matter volume compared with the control group, and a 13.9% reduction (11.9 cc) compared with the substance-dependent group.

When prefrontal gray matter was expressed as a function of whole-brain volume, groups were again found to differ significantly ($F_{2,28}$ = 4.5, *P* = .01). Persons with APD had lower mean (SD) prefrontal gray matter to whole-brain ratios (0.075 [.015]) compared with both the control group (0.086 [.012]; *t* = 2.6, *P* = .01) and the substance-dependent group (0.086 [.014]; *t* = 2.6, *P* = .01). Conversely, groups did not differ on prefrontal white matter whole-brain volume ($F_{2,78}$ = 1.3, *P* = .28).

AUTONOMIC ACTIVITY

Persons with APD also showed reduced autonomic activity during the social stressor (**Figure 3**). An analysis of variance on skin conductance showed a main effect for group ($F_{2,78}$ = 4.6, *P* = .01), with persons with APD showing lower mean (SD) skin conductance (5.4 [2.5]) compared with both the control group (7.9 [3.4]; t_{53} = 2.8, *P* = .007) and the substance-dependent group (7.4 [0.5]; t_{45} = 2.6, *P* = .01). Similarly, there was a main effect of group on heart rate levels ($F_{2,78}$ = 6.8, *P* = .002). Persons with APD had lower heart rates (69.0 [8.0] beats/min) compared with both the control group (77.6 [8.1] beats/min; t_{53} = 3.8, *P* = .001) and with the substance-dependent group (76.8 [9.8] beats/min; t_{45} = 3.6, *P* = .004).

Are autonomic deficits in persons with APD related to their prefrontal gray deficits? Those with APD were divided at the median on prefrontal gray volume to create high (n = 10) or low (n = 11) prefrontal gray matter groups. Means (SD) for low and high prefrontal gray matter groups, respectively, were as follows: skin conductance, 4.2 (2.5) vs 6.6 (2.1) microsiemens; and heart rate, 71.6 (8.2) vs 66.5 (7.4) beats per minute. Compared with persons with APD with high prefrontal gray

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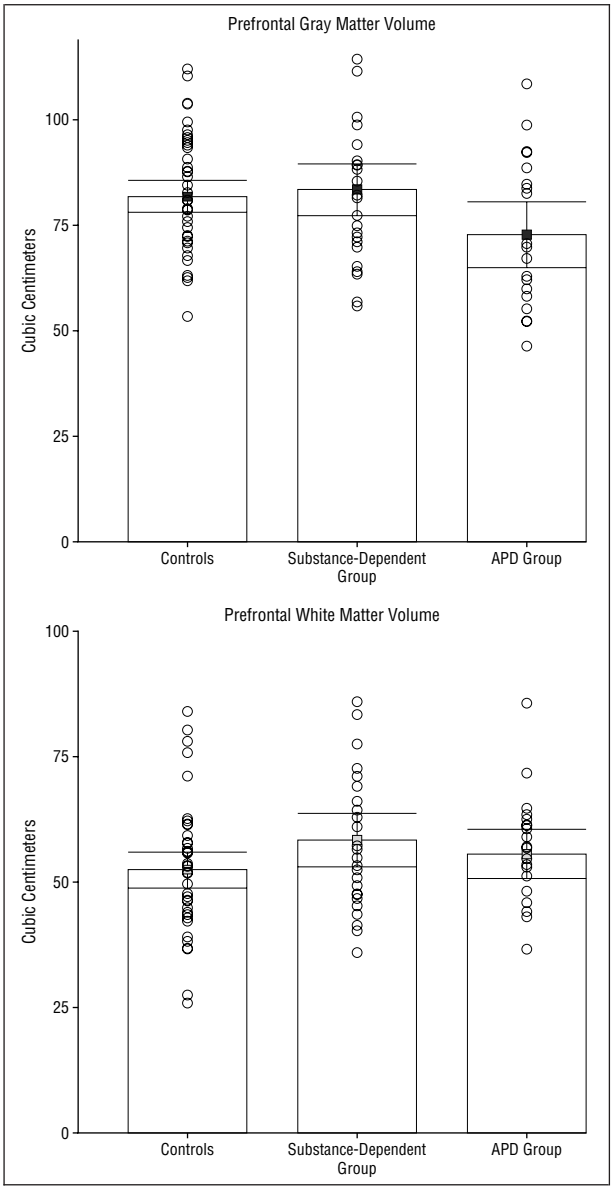

Figure 2. *Scatterplots, means, and SE bars for volumes of prefrontal gray (top) and white (bottom) matter for subjects in the control group (n = 34), substance-dependent group (n = 26), and the antisocial personality disorder (APD) group (n = 21).*

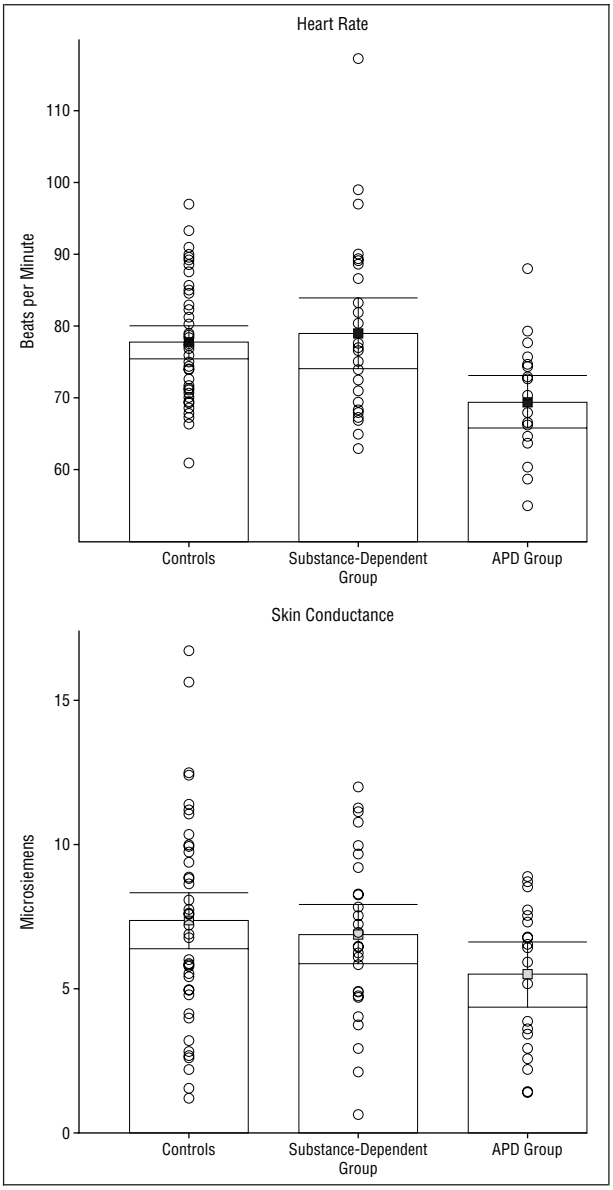

Figure 3. *Scatterplots, means, and SE bars for heart rate levels and skin conductance during the social stressor for the control group (n = 34), the substance-dependent group (n = 26), and the antisocial personality disorder (APD) group (n = 21).*

matter volume, those with APD with low prefrontal gray matter volume had reduced skin conductance activity (t_{18} = 2.3, P = .03), but not reduced heart rates (t_{18} = 1.5, P>.16), indicating that prefrontal gray deficits were linked to electrodermal, but not cardiovascular, deficits within the APD group.

POSSIBLE DIAGNOSTIC CONFOUNDS

Although differences between the APD group and the substance-dependent group indicated that prefrontal and autonomic deficits are not an artifact of comorbidity for alcohol and substance dependence in persons with APD, it is possible that these deficits could be attributed to comorbid affective and schizophrenia-spectrum disorders also present in persons with APD who have been shown to have prefrontal structural deficits.[30-35] This possibility was tested by comparing subjects from the APD group with subjects from the psychiatric control group who were matched for these disorders. Subjects from the APD group had lower mean (SD) prefrontal gray volumes compared with the psychiatric control group (73.51 [17.9] vs 86.19 [12.3] cc, respectively; $F_{1,40}$ = 7.2, P = .01), lower prefrontal gray matter to whole-brain ratios (0.075 [.015] vs 0.089 [0.011] cc, respectively; t_{40} = 3.4, P = .002), lower heart rates (69.0 [8.0] vs 77.2 [9.9] beats per minute, respectively; t = 2.9, P = .007), and lower skin conductance (5.44 [2.5] vs 7.46 [2.7] microsiemens, respectively; t = 2.5, P = .022). Groups did not differ on prefrontal white matter ($F_{1,40}$ = 0.9, P = .34). The APD group showed a 14.7% reduction (12.7 cc) in prefrontal gray matter volume compared with the psychiatric control group.

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PREDICTION OF GROUP MEMBERSHIP

In a logistic regression in which subjects from the APD group were compared with those from the control group, the 3 prefrontal and autonomic variables (prefrontal gray matter/whole-brain volume, heart rate, and skin conductance) predicted 50.8% of the variance in group membership ($\chi^2_{10} = 25.3$, $P = .005$) and predicted group membership with an accuracy of 76.9%. Similarly, in predicting whether a person would belong to the APD or substance-dependent group, these measures accounted for 50.2% of the variance ($\chi^2 = 21.6$, $P<.001$) and correctly classified 76.1% of group members.

INDEPENDENCE OF DEFICITS FROM HEIGHT AND PSYCHOSOCIAL FACTORS

The reduction in prefrontal gray in the APD group was not attributable to the significant group difference between the APD and control groups in height, or a combination of minor group differences in physical and cognitive factors including head circumference, history of head injury, and intelligence. After entry of these variables in a single block in a logistic regression comparing the APD group (n = 21) with the control group (n = 34), effects remained significant for prefrontal gray matter/whole-brain volume ($\chi^2_1 = 4.8$, $P = .03$, d = 0.64), heart rate ($\chi^2_1 = 11.1$, $P<.001$, d = 1.04), and skin conductance ($\chi^2_1 = 7.4$, $P = .007$, d = 0.81). Similarly, after controlling for these variables, APD (n = 21) vs substance-dependent (n = 26) group differences remained significant for prefrontal gray matter/whole-brain volume ($\chi^2 = 7.2$, $P = .008$, d = 0.86), heart rate ($\chi^2 = 7.3$, $P = .007$, d = 0.86), and skin conductance ($\chi^2 = 9.1$, $P = .003$, d = 0.99).

Prefrontal and autonomic deficits were independent of psychosocial risk factors in the APD group. This was demonstrated by first entering all 10 demographic and psychosocial risk factors for APD (parental social class, early parental divorce, parental verbal arguments, parental criminality, parental physical fights, family size, physical abuse, sexual abuse, being raised in an institution, and being raised by foster parents) into a logistic regression in a single block, after which APD vs control group differences remained significant for prefrontal gray matter volume ($\chi^2_1 = 5.7$, $P = .02$, d = 0.70), heart rate ($\chi^2_1 = 8.5$, $P = .004$, d = 0.88), and skin conductance ($\chi^2_1 = 4.6$, $P = .04$, d = 0.62). In a similar analysis comparing the APD with the substance-dependent group, effects remained significant for prefrontal gray matter volume ($\chi^2_1 = 6.3$, $P = .02$, d = 0.79), heart rate ($\chi^2_1 = 7.6$, $P = .006$, d = 0.88), and skin conductance ($\chi^2_1 = 4.1$, $P = .05$, d = 0.62) after controlling for psychosocial measures. These analyses indicate that prefrontal and autonomic deficits in persons with APD cannot be attributed to psychosocial risk factors.

The prefrontal and autonomic deficits added substantially to the prediction of APD vs control group membership over and above psychosocial measures. The 10 psychosocial variables in this logistic regression accounted for 41.3% of the variance. After the additional entry of the 3 prefrontal gray matter, heart rate, and skin conductance measures into the regression equation, the amount of group variance explained increased significantly ($\chi^2_3 = 24.4$, $P<.001$) to 76.7%. Prediction of group membership increased from 73.0% correctly classified to 88.5% after including prefrontal and autonomic measures. Similarly, in a comparison of APD vs substance-dependent groups, the psychosocial variables explained 23.8% of the variance, which increased significantly ($\chi^2_3 = 18.3$, $P<.004$) to 60.0% after entry of the 3 prefrontal and autonomic variables, while accuracy of group prediction increased from 71.4% to 82.6%.

COMMENT

To our knowledge, this study establishes for the first time the existence of a subtle structural deficit in the prefrontal cortex of uninstitutionalized antisocial, violent persons with psychopathic-like behavior who live in community settings, and represents the first MRI findings on APD. It also extends previous neurological research that has observed pseudopsychopathic behavior in patients with neurological disorders with observable lesions affecting both gray and white matter by showing that a much less observable volume reduction specific to prefrontal gray matter is associated with APD in this community sample. The APD group had an 11.0% reduction in prefrontal gray matter compared with the control group, a 13.9% reduction compared with the substance-dependent group, and a 14.0% reduction compared with the psychiatric control group, with effect sizes corresponding to d = 0.76, 0.78, and 0.84, respectively, for absolute gray matter volumes and d = 0.83, 0.76, and 1.1, respectively, for prefrontal gray matter/whole brain volumes. Nevertheless, while these effect sizes are thought to be large,[28] this deficit is visually imperceptible at a clinical radiological level, with group differences translating to less than half a pixel (0.5 mm) in the thickness of gray matter in any coronal prefrontal slice. Reduced autonomic activity during a social stressor was also observed, with large effect sizes in comparison to all 3 control, substance-dependent, and psychiatric control groups for skin conductance of 0.81, 0.80, and 0.79 microsiemens, respectively, and for a heart rate of 1.07, 0.87, and 0.91 beats per minute, respectively. Furthermore, persons with APD who had prefrontal gray matter volume reductions had lower skin conductance activity during the stressor than those without reduced prefrontal gray volume (d = 1.04).

What are the mechanisms and processes through which prefrontal and autonomic deficits could predispose to APD? First, the prefrontal cortex is part of a neural circuit that plays a central role in fear conditioning and stress responsivity.[36,37] Poor conditioning is theorized to be associated with poor development of the conscience,[38] and persons who are less autonomically responsive to aversive stimuli such as social criticism during childhood would be less susceptible to socializing punishments, and hence become predisposed to antisocial behavior. Experiments have repeatedly confirmed that antisocial groups show poor fear conditioning.[38] Second, the prefrontal cortex is involved in the regulation of arousal,[39,40] and deficits in autonomic and central nervous system arousal in antisocial persons have been viewed as facilitating a stimulation-seeking, antisocial be-

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havioral response to compensate for such underarousal.[29] Third, patients with prefrontal damage fail to give anticipatory autonomic responses to choice options that are risky, and make bad choices even when they are aware of the more advantageous response option.[41] This inability to reason and decide advantageously in risky situations is likely to contribute to the impulsivity, rule-breaking, and reckless, irresponsible behavior that make up 4 of the 7 traits of APD.[16]

Relative to the APD group, the substance-dependent group did not show brain or autonomic abnormalities, even though substance abusers and alcoholics previously have been shown to have lower than normal prefrontal gray matter volumes.[42,43] However, these studies did not control for APD, and it is possible that it is only those substance abusers who also have APD who show the prefrontal deficit. Similarly, no study of gray matter volume loss in schizophrenia has controlled for crime and violence, even though there is increasing evidence from several countries that persons with schizophrenia are at increased risk for committing crime and violence.[44-46] One implication of the current findings is that MRI studies of schizophrenic patients and substance abusers need to control for APD and violence, which could be important confounds.

Several caveats need to be made. First, only men were assessed, and findings cannot be generalized at this time to women with APD. Second, areas of the prefrontal cortex extending posterior to the genu of the corpus callosum were not measured and, similarly, gray matter in brain regions other than the prefrontal cortex was not assessed. Third, only an association has been shown between prefrontal deficits and APD—causality has not been demonstrated. Fourth, this study does not delineate which subregion (if any) of the prefrontal cortex is particularly reduced in volume; it is predicted that the orbitofrontal region would be most impaired and the dorsolateral region relatively spared. Nevertheless, this study does provide a basis on which future MRI studies of APD, psychopathy, and violence may build.

Previous neurological research has shown that patients with major damage to the prefrontal cortex show dysregulation of cognition, emotion, and behavior, which predisposes to antisociality.[8-10] Current brain imaging research is now showing the converse, but complementary, perspective, that those who are antisocial have visually imperceptible but meaningful and significant reductions in prefrontal gray matter volume in addition to psychophysiological deficits in emotion reactivity. Different clinical neuroscience paradigms are beginning to converge on the conclusion that there is a significant brain basis to APD over and above contributions from the psychosocial environment, and that these neurobehavioral processes are relevant to understanding violence in everyday society. It is unlikely that only one brain mechanism is compromised in APD, particularly because functional imaging has indicated multiple cortical and subcortical deficits in violent offenders.[2,5] Nevertheless, the current findings of structural deficits in antisocial subjects are consistent with prior research showing prefrontal functional deficits in violent individuals.[1-7] The future challenge lies in placing this specific structural brain deficit within the functional context of more widespread frontolimbic circuits, and in delineating its interplay with the psychosocial contexts in which antisocial personalities in the community are placed.

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