ORIGINAL ARTICLE

ONLINE FIRST

The Antisocial Brain: Psychopathy Matters

A Structural MRI Investigation of Antisocial Male Violent Offenders

Sarah Gregory, PhD; Dominic ffytche, MD, MRCPsych; Andrew Simmons, PhD; Veena Kumari, PhD; Matthew Howard, PhD; Sheilagh Hodgins, PhD; Nigel Blackwood, MA, MD, MRCPsych

Context: The population of men who display persistent antisocial and violent behavior is heterogeneous. Callous-unemotional traits in childhood and psychopathic traits in adulthood characterize a distinct subgroup.

Objective: To identify structural gray matter (GM) differences between persistent violent offenders who meet criteria for antisocial personality disorder and the syndrome of psychopathy (ASPD+P) and those meeting criteria only for ASPD (ASPD–P).

Design: Cross-sectional case-control structural magnetic resonance imaging study.

Setting: Inner-city probation services and neuroimaging research unit in London, England.

Participants: Sixty-six men, including 17 violent offenders with ASPD+P, 27 violent offenders with ASPD–P, and 22 healthy nonoffenders participated in the study. Forensic clinicians assessed participants using the Structured Clinical Interview for *DSM-IV* and the Psychopathy Checklist–Revised.

Main Outcome Measures: Gray matter volumes as assessed by structural magnetic resonance imaging and volumetric voxel-based morphometry analyses.

Results: Offenders with ASPD+P displayed significantly reduced GM volumes bilaterally in the anterior rostral prefrontal cortex (Brodmann area 10) and temporal poles (Brodmann area 20/38) relative to offenders with ASPD–P and nonoffenders. These reductions were not attributable to substance use disorders. Offenders with ASPD–P exhibited GM volumes similar to the nonoffenders.

Conclusions: Reduced GM volume within areas implicated in empathic processing, moral reasoning, and processing of prosocial emotions such as guilt and embarrassment may contribute to the profound abnormalities of social behavior observed in psychopathy. Evidence of robust structural brain differences between persistently violent men with and without psychopathy adds to the evidence that psychopathy represents a distinct phenotype. This knowledge may facilitate research into the etiology of persistent violent behavior.

Arch Gen Psychiatry. 2012;69(9):962-972.
Published online May 7, 2012.
doi:10.1001/archgenpsychiatry.2012.222

Author Affiliations: Departments of Forensic and Neurodevelopmental Sciences (Drs Gregory, Hodgins, and Blackwood), Clinical Neuroscience (Dr ffytche), Neuroimaging (Drs Simmons and Howard), and Psychology (Dr Kumari), Institute of Psychiatry, King's College London, and The North London Forensic Service (Dr Blackwood), London, England; and Département de Psychiatrie, Université de Montréal, Montréal, Canada (Dr Hodgins).

VIOLENCE IS A GLOBAL PUBlic health problem.[1] Most violent crimes are committed by a small group of life-course-persistent male offenders, who meet diagnostic criteria for conduct disorder as children and antisocial personality disorder (ASPD) as adults.[2-4] Behavioral genetic research suggests that such stable antisocial behavior is moderately heritable.[5,6]

Significant clinical heterogeneity exists within this life-course-persistent offending group. Most are characterized by emotional lability, impulsivity, high levels of mood and anxiety disorders, and reactive aggression.[2,7-10] However, a minority are characterized by deficient affective experience, typified by a lack of empathy and remorse, as well as persistent reactive and instrumental aggression.[11] This subgroup meets diagnostic criteria for conduct disorder with callous-unemotional traits in childhood[12] and for the syndrome of psychopathy as defined by the Psychopathy Checklist–Revised (PCL-R)[13] in adulthood (ASPD+P).[11,14] Men with ASPD+P begin offending earlier,[15] engage in a broader range and greater density of offending behaviors,[16] and respond less well to treatment programs in childhood[17,18] and adulthood[19] compared with those with ASPD without psychopathy (ASPD–P). Behavioral genetic research suggests that conduct problems coupled with callous-unemotional traits

©2012 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/02/2015

are highly heritable,[20,21] while developmental studies support the stability of childhood psychopathic traits into adolescence[22,23] and early adulthood.[24]

Given the differences in patterns of antisocial and aggressive behavior, emotion processing, personality traits, and criminal offending between men with ASPD–P and men with ASPD+P, it is reasonable to hypothesize that the neurobiological mechanisms that initiate and maintain their aggressive behaviors differ. Reactive violence is purportedly underscored by dysfunction within the ventromedial prefrontal cortex (vmPFC). This region regulates emotional reactivity to perceived environmental threats or frustration in the absence of an expected reward and modulates behavior accordingly.[11,25-27] By contrast, instrumental violence is hypothesized to be associated with abnormalities within both the vmPFC and amygdala. Deficits in aversive conditioning, reinforcement learning, and recognition of fearful facial expressions, which characterize children with conduct problems and callous-unemotional traits[28-31] and adult psychopaths,[32-36] are associated with dysfunction in both regions.

Evidence of differences in brain structure between offenders with ASPD–P and ASPD+P is limited.[37,38] Structural magnetic resonance imaging (sMRI) studies have typically contrasted participants with ASPD+P[39-45] or offenders with ASPD who have not been assessed for psychopathy[46-49] with nonoffenders. Among men with ASPD+P, those studies using whole-brain analyses have identified localized gray matter (GM) volume reductions in the frontopolar and orbitofrontal regions,[42,43] the anterior temporal cortex,[43] the superior temporal sulcus,[42,43] and the insula.[43] Studies using region-of-interest analyses have established localized GM volume reductions in the prefrontal cortex, particularly the frontopolar and orbitofrontal regions,[41,50-53] the anterior temporal cortex,[52] the superior temporal sulcus,[53] the posterior cingulate, the corpus callosum,[40] the striatum,[45] and the hippocampus.[39,54] Despite the hypothesized importance of amygdalar dysfunction among offenders with ASPD+P, only 2 studies have demonstrated reduced amygdala volumes.[44,53] Both employed targeted manual tracing techniques, while automated whole-brain methods have failed to replicate these differences. A validation study of the PCL-R demonstrated that cutoff scores for the syndrome of psychopathy varied in North America (30 out of 40) and Europe (25 out of 40).[55] In several of the structural imaging studies conducted in the United States, the criteria used to diagnose the syndrome of psychopathy were modified by lowering the cutoff score from 30 to 23.[41,44,45,51-53,55] The use of this lower cutoff score led to the inclusion of participants with ASPD who did not present with the syndrome of psychopathy as usually defined, making the findings difficult to interpret. Other structural imaging studies of antisocial men have either failed to report psychopathy ratings[56] or have used mixed groups of offenders with ASPD and psychopathy.[46,48,49,57]

Furthermore, some studies of men with ASPD+P failed to exclude Axis I pathology such as schizophrenia spectrum diagnoses,[45,51,52,56] which are independently associated with GM volume decrements in the areas of interest.[45,51,52,56,58] Most studies have included offenders with comorbid substance use disorders (SUDs)[39-45,49-53,56,57,59] that are also independently associated with GM volume decrements in regions of interest such as the orbitofrontal cortex.[48,60] These studies have attempted to control for the presence of SUDs either by including a group of control participants with similar histories of substance misuse (although significant differences between the groups have remained)[39-41,43-45,51-53,56] or by entering a measure of SUDs as a nuisance covariate in the analysis of brain structure.[42,49,50,57,59]

Thus, the extant evidence describes a series of brain regions that may be structurally abnormal in ASPD and psychopathy, but it fails to clarify the abnormalities that characterize men with ASPD–P and those with ASPD+P. Only 2 studies have attempted a categorical distinction between small numbers of men with ASPD–P and ASPD+P to date and neither reported volumetric differences in GM.[49,57] One study used whole-brain analysis[49] and the other employed manual tracing of the hippocampus.[57] These results may represent a type 2 error owing to small sample sizes. Furthermore, the notionally ASPD–P group in these studies included participants who exceeded the PCL-R cutoff score for a diagnosis of psychopathy among Europeans,[55] which may have further minimized group differences.

Improved categorization within the broad ASPD phenotype has important implications for establishing the neurobiological underpinnings of the disorders and for developing optimal treatment approaches tailored to the distinct underlying emotional dysfunctions. Our study aimed to identify GM volume differences between violent offenders with ASPD+P and ASPD–P and a matched sample of nonoffenders using structural MRI together with fully-automated voxel-based morphometry (VBM) analyses. Voxel-based morphometry enables statistically principled between-group comparisons of GM volume, unconstrained by anatomical landmarks.[61] Use of the VBM5 toolbox additionally enables robust cluster-based inferences to be made. Such automated techniques are not prone to the biases inherent in manual tracing methods, which may account, at least in part, for the excess significance bias reported in the structural imaging literature on brain volume abnormalities.[62] The syndrome of psychopathy was assessed using the PCL-R and defined using the empirically derived European cutoff score of 25 to distinguish between violent offenders with ASPD–P and ASPD+P.[55] Participants with comorbid Axis I disorders other than SUDs were excluded. The proportions of offenders with ASPD+P and ASPD–P with past and current SUDs were similar. We studied only men because men commit most violent crimes, and most life-course-persistent offenders are male as are persons with ASPD with or without psychopathy.[3,11] Furthermore, some of the brain regions associated with ASPD and offending differ morphologically between men and women.[56] We hypothesized that the ASPD+P group would display reductions in GM volume in key frontal (vmPFC and frontal poles) and temporal (amygdala, anterior temporal cortex, and superior temporal sulcus) cortical areas relative to both the ASPD–P and healthy nonoffenders. We also hypothesized that the ASPD–P group would display GM volume decrements in the vmPFC compared with the nonoffenders. If established, such morpho-

©2012 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/02/2015

Table 1. Comparisons of Sociodemographic, Clinical, and Behavioral Characteristics of Violent Offenders With ASPD+P, Violent Offenders With ASPD–P, and Nonoffenders[a]

	Group			Group Comparison		Post Hoc Test, *P* Value		
	NO (n = 22)	ASPD–P (n = 27)	ASPD+P (n = 17)	Statistic	*P* Value	NO vs ASPD–P	NO vs ASPD+P	ASPD–P vs ASPD+P
Age, mean (SD), y	32.4 (7.7)	36.1 (8.2)	38.9 (9.4)	$F_{2, 63} = 3.02$	.06	.32	.05	.63
FSIQ, mean (SD)	99.4 (12.9)	90.9 (11.4)	89.9 (11.7)	$F_{2, 63} = 4.05$	.02	.05	.05	.99
Education, mean (SD), y	11.8 (1.3)	10.5 (0.8)	10.1 (1.1)	$F_{2, 63} = 15.99$	<.001	<.001	<.001	.54
Personality disorder, in addition to ASPD, %								
Cluster A	0	11.1	11.8	2.84	.25			
Cluster B	0	14.8	17.6	4.36	.10			
Cluster C	0	3.7	5.9	1.43	.72			
Total PCL-R score, 0-40, mean (range)	3.8 (0-10)	16.4 (10-24)	28.1 (26-32)	$F_{2, 62} = 294.70$	<.001	<.001	<.001	<.001
Four-facet model, mean (range)								
Facet 1, interpersonal, 0-8	0.4 (0-4)	1.7 (0-4)	3.7 (2-6)	$F_{2, 62} = 31.66$	<.001	<.001	<.001	<.001
Facet 2, deficient affect, 0-8	0.5 (0-2)	2.9 (0-6)	6.2 (2-8)	$F_{2, 62} = 69.13$	<.001	<.001	<.001	<.001
Facet 3, lifestyle, 0-10	2 (0-5)	5.2 (1-9)	6.7 (3-9)	$F_{2, 62} = 34.48$	<.001	<.001	<.001	.02
Facet 4, antisocial, 0-10	0.3 (0-2)	5.5 (1-9)	8.6 (6-10)	$F_{2, 62} = 158.90$	<.001	<.001	<.001	<.001
Age at first violent conviction, mean (SD), y	NA	23.2 (8.38)	17.24 (3.63)	$t = 3.15$, $df = 37$	.003			
Violent convictions, mean (SD), No.	NA	4.44 (3.41)	6.76 (5.21)	$t = -1.79$, $df = 42$	.08			
Total aggression scores, mean (SD)	7.32 (3.15)	16.04 (8.22)	23.71 (12.91)	$F_{2, 62} = 17.76$	<.001	<.001	<.001	.11
Proactive aggression scores	2.59 (3.08)	8.00 (5.11)	13.59 (6.87)	$F_{2, 62} = 22.45$	<.001	<.001	<.001	.02
Reactive aggression scores	4.72 (3.10)	8.04 (5.57)	11.88 (7.10)	$F_{2, 62} = 8.54$	<.001	.04	.003	.20

Abbreviations: ASPD–P, antisocial personality disorder without psychopathy; ASPD+P, antisocial personality disorder with psychopathy; FSIQ, full-scale IQ; NA, not applicable; NO, nonoffenders; PCL-R, Psychopathy Checklist–Revised.

[a]Two-tailed probabilities used for comparison of age, full-scale IQ, and education. One-tailed probabilities used for comparison of psychopathy scores, violent convictions, and aggression scores.

logic differences among offenders with ASPD would add to the mounting evidence of distinct phenotypes within this population.

METHODS

PARTICIPANTS

The final sample included 66 men aged between 20 and 50 years, with English as a first language and a reading age of greater than 10 years. Participants had no history of neurological problems or head injury resulting in loss of consciousness for 1 hour or longer, no significant visual or hearing impairment, and no self-reported history of claustrophobia or contraindications to an MRI scan.

Violent offenders were recruited from the National Probation Service. A preliminary screening of potential participants was conducted by forensic psychologists to assess criminal, medical, and psychiatric history based on self-report and probation officer reports and files as well as to assess reading level. Offenders with a history of convictions for violent crimes (murder, rape, attempted murder, and grievous bodily harm), English as a first language, and a reading level of at least age 10 years were invited to participate in a diagnostic interview. If the interview indicated that they met *DSM-IV* criteria for ASPD, with no lifetime history of major mental disorders (bipolar 1, bipolar 2, major depressive disorder, and psychotic symptomatology) or SUDs in the past month, they were invited to complete further tests. Following a PCL-R interview and a file review, offenders who obtained PCL-R scores of 25 or higher were assigned to the ASPD+P group, while those with scores of less than 25 were assigned to the ASPD–P group.

Healthy nonoffender participants were recruited using community websites and bulletin boards in local unemployment offices. None had been convicted of a criminal offense, met criteria for ASPD, or had a PCL-R score of 25 or higher.

Comparisons of the 3 groups of participants are presented in **Table 1**. There was a trend toward significant age differences between the 3 groups, with nonoffenders being significantly younger than the violent offenders with ASPD+P. There were significant differences in IQ and years of schooling, with nonoffenders differing from each of the offender groups but with no differences between the 2 offender groups. As intended, there were significant differences between all 3 groups on total and 4-facet PCL-R scores. None of the nonoffenders and small, but similar, proportions of the offenders with ASPD+P and ASPD–P met criteria for other personality disorders. The ASPD+P group had a significantly younger average age at first conviction for a violent offense than the offenders with ASPD–P and there was a trend suggesting that they had accumulated more convictions for violent crimes. The 3 groups differed in both total aggression scores and scores for reactive and proactive aggression. The offenders with ASPD+P obtained significantly higher scores for proactive (instrumental) aggression than the offenders with ASPD–P.

As presented in **Table 2**, significant differences emerged between the offenders and the nonoffenders with respect to lifetime diagnoses of abuse and/or dependence for alcohol, cannabis, and cocaine. Importantly, however, there were no significant differences between the ASPD–P and ASPD+P groups in the proportions with lifetime SUDs.

MEASURES

Forensic psychiatrists conducted diagnostic interviews with all the participants using the Structured Clinical Interview for *DSM-IV* I and II.[63] Both trained psychiatrists and forensic psychologists administered the PCL-R.[64] Psychopathy Checklist–Revised interviews were videotaped and a random 25% sample was rerated by a second trained psychologist. Intraclass correlation coeffi-

©2012 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/02/2015

Table 2. Comparisons of Substance Use Disorder Diagnoses of Violent Offenders With ASPD+P, Violent Offenders With ASPD–P, and Nonoffenders[a]

	Group			Statistic		Post Hoc Test					
	NO	ASPD–P	ASPD+P	FET	*P* Value	NO vs ASPD–P	*P* Value	NO vs ASPD+P	*P* Value	ASPD–P vs ASPD+P	*P* Value
Alcohol, %											
Abuse	11.1	20.0	25.0	11.33	.02	10.35	.005	5.79	.05	0.53,	.81
Dependency	5.6	44.0	33.3								
Cannabis, %											
Abuse	5.6	20.0	25.0	11.99	.01	10.38	.004	7.26	.02	0.34	.99
Dependency	5.6	40.0	33.3								
Cocaine, %											
Abuse	0	0	0	7.60	.02		.03		.02		.99
Dependency	0	29.2	33.3								
Stimulants, %											
Abuse	0	4.2	8.3	3.79	.38	NA		NA		NA	
Dependency	0	12.5	8.3								
Sedatives, %											
Abuse	0	8.0	0	2.99	.77	NA		NA		NA	
Dependency	0	4.0	0								
Opioid, %											
Abuse	0	4.0	8.3	4.61	.24	NA		NA		NA	
Dependency	0	12.0	16.7								
Hallucinogenics, %											
Abuse	0	16.7	0	5.33	.15	NA		NA		NA	
Dependency	0	4.2	0								
Polysubstance, %											
Abuse	0	0	0	3.76	.14	NA		NA		NA	
Dependency	0	16.7	0								

Abbreviations: ASPD–P, antisocial personality disorder without psychopathy; ASPD+P, antisocial personality disorder with psychopathy; FET, Fisher exact test; NA, not applicable; NO, Nonoffenders.
[a]Two-tailed probabilities.

cient values for PCL-R total scores were acceptable (0.81). Total and scores for 4 facets were calculated.[65] All participants completed the Wechsler Adult Intelligence Scale[66] and the Reactive-Proactive Aggression Questionnaire[67] to assess levels of violent and aggressive behaviors. Criminal records for all participants were obtained from the Police National database.

PROCEDURE

This study was approved by the South London and Maudsley National Health Service and the Institute of Psychiatry research and ethics committees (reference 06/Q0706/87). Potential participants who met the inclusion and exclusion criteria were invited to take part in the study that included diagnostic interviews, an interview assessing maltreatment in childhood, completion of neuropsychological tests, and a structural and functional brain scan during a period of 4 days. After being fully informed about the study requirements and risks and having all of their questions answered, participants signed consent forms that included authorization for the research team to access their official criminal records. Participants were paid minimum hourly wage for their time, and they were strongly encouraged to desist from using substances 2 weeks prior to participation and during the period of testing. Each day on arrival at the laboratory, participants provided samples of urine and saliva, which showed that despite the request to refrain from substance use, some offenders' test results were positive for substances on the day of scanning. These individuals were assessed by the forensic psychologist and one of the authors (S.G.) to ensure that they were in a suitable state to enter the scanning environment and adhere to all safety requirements.

IMAGE ACQUISITION AND PROCESSING

All participants were scanned in a 1.5T GE Signa Excite MRI scanner (General Electric Healthcare) using an 8-channel head coil for radio frequency detection at the Centre of Neuroimaging Sciences, Institute of Psychiatry. Participants were supine on the scanner bed, wearing headphones to reduce interference from scanner noise. Each participant underwent a 14-minute spoiled gradient-recalled echo scan, which is a structural scan that maximizes differences between tissue types. One hundred twenty-four slices of 1.6-mm thickness were collected with repetition time of 34 ms, echo time of 9 ms, a flip angle of 30°, and field of view of 20 cm. The acquisition matrix measured 256 × 192. Image preprocessing and analysis were carried out using Statistical Parametric Mapping software (SPM version 5.0, www.fil.ion.ucl.ac.uk/spm), running under Matlab 7.0.1 on a UNIX platform. All spoiled gradient-recalled echo images were initially checked for motion and hardware artifacts and reoriented to the intercommissural line to improve registration across the groups. Images were then analyzed using VBM for whole-brain comparisons.[61] The data were processed using an iterative algorithm that incorporates tissue classification, bias correction, and normalization to achieve the model of best-fit.[68] Using the VBM5 toolbox (http://dbm.neuro.uni-jena.de/vbm/), a Markovian spatial prior was added to prior templates during segmentation. This incorporates spatial information (tissue class belonging) from neighboring voxels and enhances the accuracy of tissue classification to enable more sensitive cluster-based statistical inference. Accordingly, the VBM5 toolbox adjusts cluster size to correct for the nonstationary smoothness of the VBM data. The VBM5 toolbox also

©2012 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/02/2015

corrects for individual differences in total GM volume during the preprocessing stages. A modulation step is also inherent within the iterative process, which compensates for the effect of nonlinear spatial normalization and preserves the volume of GM within a voxel. Finally, all images were spatially smoothed using a Gaussian kernel of 8-mm full-width at half maximum to improve the signal to noise ratio and allow for inherent gyral variability across participants. This size of smoothing kernel was chosen to ensure that both the amygdala and the vmPFC could be identified.[69,70] Data for 2 offenders with ASPD–P and 3 healthy nonoffenders were excluded owing to poor image quality.

STATISTICAL ANALYSES

Comparisons of the 3 groups of participants on demographic and clinical variables were conducted using either 2-sample *t* tests or univariate analysis of variance with corresponding post hoc tests, or χ^2 and Fisher exact tests. One-tailed probabilities were employed to infer group differences predicted by a prior hypothesis. All analyses were carried out using the Statistical Package for Social Sciences version 15.

Group comparisons of GM volumes were performed using both voxel- and cluster-level inference within the framework of the general linear model using an absolute threshold of 0.2. Two covariates of no interest were included in the models: age, because of a difference at the trend level between the nonoffenders and offenders, and IQ, because it is associated with GM volume.[71] Results from *t* tests modeled within an analysis of covariance design in SPM were corrected for nonstationary cluster extent using the VBM5 toolbox and assessed for significance using an initial cluster-defining threshold of $z > 2.7$ and a corrected cluster-significance threshold of $P = .05$ according to random field theory. Using the MarsBaR toolbox (http://marsbar.sourceforge.net//), volumetric values were extracted from significant regions for graphic presentation. In addition to the whole-brain analysis, we applied small volume correction in the a priori regions of interest using a threshold of $P < .05$ after false discovery rate[72] correction for multiple comparisons. Based on previous findings, the WFU Pickatlas (Wake Forest University) was used to create multiple masks for small volume correction in the vmPFCs, the frontopolar cortex, the amygdala, the temporal poles, and the superior temporal gyri. Following previous examples in the literature,[73,74] sphere volumes with radii of 8 mm and 7 mm were also applied to the ventral striatum and the anterior insula, respectively.

RESULTS

COMPARISONS OF GM VOLUME OF OFFENDERS WITH ASPD+P AND NONOFFENDERS

As presented in **Table 3**, the offenders with ASPD+P demonstrated reduced GM volume in the bilateral anterior rostral medial prefrontal cortex, bilateral anterior temporal areas, and bilateral anterior insula when compared with the healthy nonoffenders. Frontal clusters were located medially with a peak in the anterior rostral area, extending posteriorly along the superior frontal gyrus (Brodmann are [BA] 9/10) and anteriorly toward the frontal poles. Within the temporal lobe, 2 similarly sized clusters extended from lateral temporal pole regions (BA 38) into the inferior temporal gyrus (BA 20). Bilateral clusters were also identified in the anterior insula, extending into the primary motor (BA 4) and premotor (BA 6) cortices. There were no areas where GM volumes were significantly increased in the ASPD+P group compared with nonoffenders. Region-of-interest analyses revealed no significant between-group differences in GM volume bilaterally in the vmPFC, the amygdala, the superior temporal gyrus, or the ventral striatum.

COMPARISONS OF GM VOLUME OF OFFENDERS WITH ASPD-P AND NONOFFENDERS

Neither VBM nor region-of-interest analyses detected areas in which GM volumes differed between the violent offenders with ASPD–P and the nonoffenders.

COMPARISONS OF GM VOLUME OF OFFENDERS WITH ASPD+P AND ASPD–P

Among the violent offenders, those with ASPD+P compared with those with ASPD–P displayed significantly reduced GM volume bilaterally in the anterior rostral medial prefrontal and temporal pole regions. As presented in **Figure 1** and **Figure 2**, prefrontal peak clusters were located medially, extending caudally from the superior to the medial frontal gyri (BA 9/10). As presented in **Figure 3** and **Figure 4**, in the temporal region, both clusters extended from the temporal pole area into the inferior/medial temporal gyri. There were no areas where GM volumes were significantly increased in the ASPD+P group compared with the ASPD–P group. Region-of-interest analyses revealed no significant between-group differences in the vmPFC, the amygdala, the superior temporal gyrus, the anterior insula, or the ventral striatum.

Group comparisons were rerun after excluding participants who tested positive for drug misuse (mainly for tetrahydrocannabinol) on the scanning day, leaving 9 with ASPD+P and 19 with ASPD–P. The highly significant differences between the ASPD+P and ASPD–P groups in the bilateral anterior temporal cortex remained at the corrected level, while those in the bilateral anterior rostral medial prefrontal cortex remained significant at the uncorrected level.

The analyses were also rerun excluding participants with a comorbid personality disorder, leaving 12 with ASPD+P and 21 with ASPD–P. Again, the highly significant differences between the ASPD+P and ASPD–P groups in the bilateral anterior temporal cortex remained at the corrected level, while those in the bilateral anterior rostral medial prefrontal cortex remained significant at the uncorrected level.

COMMENT

To our knowledge, this study is the first to identify structural differences between violent offenders with ASPD+P and ASPD–P matched on age, IQ, and histories of SUDs, and who did not have comorbid major mental disorders. Using whole-brain analyses, our study demonstrated discrete areas of reduced GM volume in the bilateral anterior rostral medial prefrontal cortex (arMPFC) and the bilateral temporal poles among the violent offenders with ASPD+P compared with those with ASPD–P. The ASPD+P

©2012 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/02/2015

Table 3. Comparisons of Gray Matter Volumes of Violent Offenders With ASPD+P, Violent Offenders With ASPD–P, and Nonoffenders

Group Comparison	Brain Region	Location	BA	MNI Coordinates X	Y	Z	Cluster Size	*Z* Score	*P* Value[a]
Violent offenders with ASPD+*P* < nonoffenders	Anterior rostral PFC								
	Medial frontal gyrus	L	10	–10	59	21	8951	5.03	.001
	Medial frontal gyrus			–11	62	10			
	Superior frontal gyrus			–17	47	32			
	Superior frontal gyrus	R	9	13	50	33	9869	4.69	.001
	Superior frontal gyrus			14	38	42			
	Medial frontal gyrus			14	61	14			
	Temporal poles								
	Inferior temporal gyrus	L	21/38	–31	–10	–38	6670	3.93	.001
	Inferior temporal gyrus			–38	3	–42			
	Uncus			–26	5	–41			
	Inferior temporal gyrus	R	20/38	42	0	–42	4638	4.16	.003
	Inferior temporal gyrus			34	8	–40			
	Temporal pole			33	15	–35			
	Anterior insula								
	Insula	L	13	–44	–8	17	4408	4.51	.004
	Postcentral gyrus			–60	–19	24			
	Insula			–44	6	12			
	Insula	R	6	53	–3	12	3514	3.78	.014
	Postcentral gyrus			61	–14	25			
	Precentral gyrus			47	–9	21			
Violent offenders with ASPD+*P* < violent offenders with ASPD–P	Anterior rostral PFC								
	Superior frontal gyrus	L	10	–14	62	15	3560	4.05	.013
	Medial frontal gyrus			–11	47	26			
	Superior frontal gyrus			–14	58	24			
	Superior frontal gyrus	R	10	12	49	35	2945	4.9	.03
	Medial frontal gyrus			12	38	42			
	Temporal poles								
	Inferior temporal gyrus	L	20/38	–39	–1	–43	2784	3.81	.04
	Inferior temporal gyrus			–30	–10	–37			
	Middle temporal gyrus			–45	–5	–41			
	Middle temporal gyrus	R	21/38	42	3	–41	3734	4.46	.01
	Middle temporal gyrus			24	1	–34			
	Temporal pole			29	–7	–35			

Abbreviations: ASPD–P, antisocial personality disorder without psychopathy; ASPD+P, antisocial personality disorder with psychopathy; BA, Brodmann area; L, left; MNI, Montreal Neurological Institute; PFC, prefrontal cortex; R, right.
[a] False discovery rate cluster-corrected.

group also demonstrated GM volume reductions in the bilateral insulae as compared with nonoffenders.

Both the arMPFC and anterior temporal cortex independently feature in the assessment of current social stimuli using stored information. The medial prefrontal cortex monitors and coordinates action on complex social goals.[75] The arMPFC engages in self-reflective processing,[75-77] which not only facilitates other-person perception but also enables an emotional understanding of others' intentional acts.[78-81] Recent computational modeling studies have demonstrated cognitive branching within the arMPFC, which enables 2 sets of competing information to be concurrently maintained, thus facilitating the simultaneous consideration of self and other perspectives.[82,83] The arMPFC is additionally engaged during fear appraisal through functionally dissociable cingulate pathways.[84-87] The temporal poles use stored social conceptual knowledge and contextual framing to facilitate understanding of social stimuli within a wider semantic and emotional context by way of multimodal sensory inputs.[88-91] Temporal pole atrophy in such disorders as Kluver-Bucy syndrome and frontotemporal dementia[92,93] is associated with emotional blunting,[94] socially inappropriate behavior,[95] and diminished empathy.[96,97]

The arMPFC and temporal poles work together to use stored knowledge representations to facilitate the understanding of emotional experience in others, while self-referential thinking and the use of conceptual knowledge extend the awareness of how we are perceived by others (our social reputation). These brain regions are thus central to the development of self-conscious emotions, such as guilt or embarrassment, which promote prosocial behavior and form the basis of moral learning.[98-100] Both regions are routinely activated in moral reasoning tasks and in the recognition of moral violations.[101-105] Based on this evidence, the structural volume decrements observed in these regions among the offenders with ASPD+P may contribute to the profound social impairments that characterize psychopathy. While the basic cognitive aspects of empathic processing (as assessed by first- and second-order mentalizing tasks)[106,107] appear to be intact in ASPD+P, the emotional aspects are clearly impaired, with diminished responsivity to both fear and distress in others.[31,32,35,108] Men with the syn-

©2012 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/02/2015

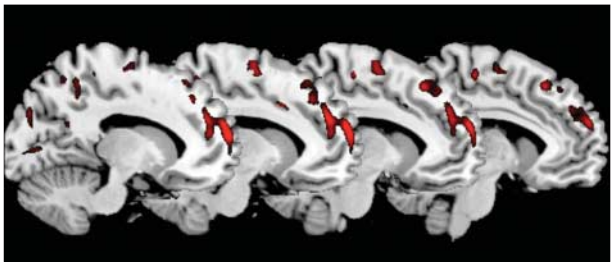

Figure 1. Sagittal view of the bilateral anterior rostral prefrontal cortex. Areas of significantly reduced gray matter volume among the violent offenders with antisocial personality disorder with psychopathy compared with those with antisocial personality disorder without psychopathy (*z* score threshold = 2.3).

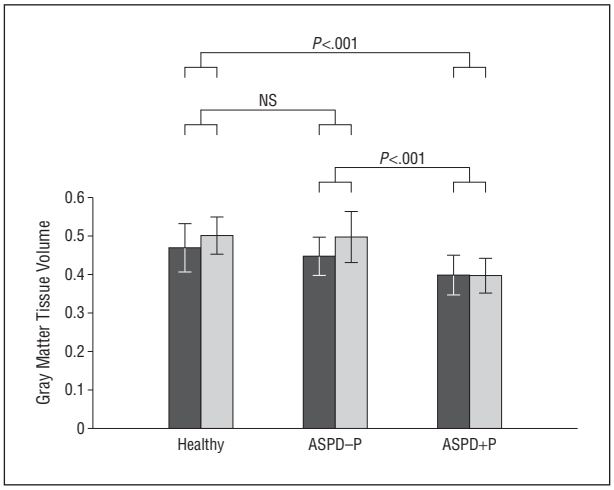

Figure 2. Gray matter tissue volume values extracted from the bilateral anterior rostral prefrontal cortex (left hemisphere = blue; right hemisphere = orange). Error bars represent standard deviations. ASPD-P indicates antisocial personality disorder without psychopathy; ASPD+P, antisocial personality disorder with psychopathy; NS, not significant.

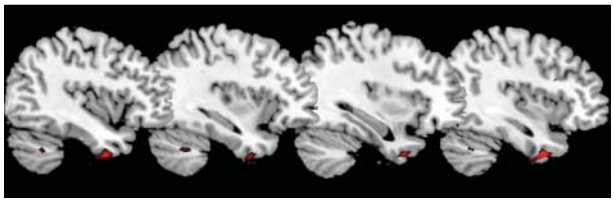

Figure 3. Sagittal view of bilateral temporal poles. Areas of significantly reduced gray matter volume among the violent offenders with antisocial personality disorder with psychopathy compared with those with antisocial personality disorder without psychopathy (*z* score threshold = 2.3).

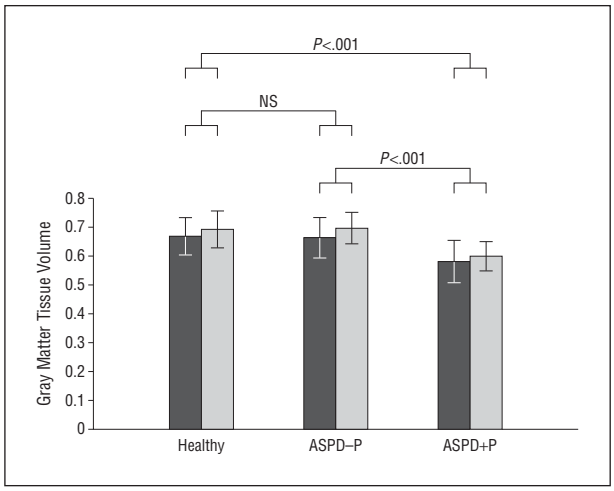

Figure 4. Gray matter tissue volume values extracted from the bilateral anterior temporal cortex (left hemisphere = blue; right hemisphere = orange). Error bars represent standard deviations; NS, not significant.

drome of psychopathy fail to learn from their experience of punishment[29,109] and to experience self-conscious emotions such as guilt, remorse, or embarrassment,[32,51] which facilitate desistance from the use of inappropriate behaviors, most significantly aggression and violence.[11]

In the present study, additional volume reductions were observed in the anterior insula when comparing the offenders with ASPD+P and nonoffenders. The insula acts as an interface between body-state representations and social/contextual information, facilitating the conscious experience of emotions[110] and contributing to basic emotion processing,[111,112] decision making[113] and empathic processing.[114,115] Among men with psychopathy, aversive conditioning impairments correlate with functional reductions in anterior insula activity.[32] The structural differences observed in our study remained statistically significant after controlling for both IQ and histories of SUD and are consistent with findings from previous studies.[43] Moreover, the evidence that substance misuse can lead to GM atrophy in the insula is inconsistent.[116,117]

No structural differences were observed between the offenders with ASPD+P and those with ASPD–P and the healthy nonoffenders in either the amygdala or the vmPFC. Abnormalities of amygdalar function have been observed in functional imaging investigations of affective processing among men with the syndrome of psychopathy.[32,33] However, only 2 manual tracing–based studies have demonstrated reductions in amygdalar volumes in offenders with ASPD+P.[44,53] Voxel-based morphometry is capable of detecting structural change in the amygdala, as evidenced in studies of people with schizophrenia and depression.[58,118] However, the results of our study cannot be interpreted to suggest that the amygdala is structurally intact in violent offenders with ASPD. Cortical volume within a given region is a product of 2 lower-order spatial properties—cortical thickness and surface area. Thus, an absence of differences in volume may result from marked alterations in opposing directions in these 2 dimensions (such that their product—cortical volume—does not indicate a group difference). Consequently, further investigations of cortical thickness and surface area are required. Similarly, there is limited evidence of structural abnormalities within the vmPFC among violent offenders with ASPD.[47,56] As discussed previously, these studies included participants with comorbid major mental disorders,[51,52,56] and 2 of the studies used manual tracing methods,[44,53] which may have introduced user bias. Either or both of these factors may have resulted in the observed differences in the vmPFC. Equally, multiple other factors impact vmPFC volume beyond categorical diagnosis, including, for example, the interaction between monoamine oxidase A genotype and drug misuse.[119] Our strict exclusion of comorbid Axis I lifetime diagnoses (including significant mood disorders) may have significantly reduced the chances of observing dif-

©2012 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/02/2015

ferences in GM volume in the amygdala or vmPFC.[120] Nevertheless, abnormal function and connectivity of these areas may still occur in the context of intact structure.[36,121] Consistent with this latter proposal, reduced fractional anisotropy in the right uncinate fasciculus (the primary white matter connection between vmPFC and the anterior temporal lobe) has recently been documented using diffusion tensor MRI in both psychopathic[122-124] and nonpsychopathic[123] men with ASPD.

Surprisingly, no significant differences in GM volume were observed in the comparisons between the offenders with ASPD-P and the nonoffenders despite differences in lifelong histories of antisocial and violent behavior, SUDs, and personality traits. Findings from our study suggest that violent offenders with ASPD–P do not present abnormalities of GM volume. Previous studies that reported such abnormalities among violent offenders[49] or men with ASPD[46,51,56] may have included participants with the syndrome of psychopathy. Our study was limited to structural MRI measures of GM volumes. It is possible that alternate techniques for examining brain structure, such as cortical surface area and thickness measures and diffusion tensor MRI, will detect abnormalities in this subgroup of persistently violent men.

Several limitations of our study should be considered when interpreting the results. The study included only men. The violent offenders with ASPD who participated in the study, like most men with this disorder, had additional personality disorders and histories of SUDs.[125,126] However, the ASPD+P and ASPD–P groups were closely matched on age, IQ, and the proportions of comorbid personality disorders and SUDs. Consequently, the observed volumetric differences cannot be simply attributed to any of these factors. The strengths of the study include diagnoses made by trained clinicians, the inclusion of official criminal records, and daily objective checks during the testing period of alcohol and drug use. Furthermore, the MRI images were optimized for discerning morphological anomalies and analyzed using a fully automated, whole-brain technique.

The broader implications of our study relate to diagnostic classification systems and treatment approaches. There is currently robust evidence to suggest that life-course-persistent offending incorporates at least 2 distinct subgroups.[127] Our study has demonstrated that, in addition to divergence in the nature of aggressive behaviors, emotion processing, and personality traits, offenders with the syndrome of psychopathy display abnormalities of GM in key social brain structures. However, in contrast to the empirical literature, the *DSM-5* proposes 1 antisocial personality disorder diagnosis that would merge these subgroups. For example, the criterion for pathological personality traits refers to antagonism as characterized by manipulativeness, callousness, deceitfulness, and hostility. While the 2 former traits are core characteristics of psychopathy, hostility, defined as persistent or frequent angry feelings, or irritability in response to minor slights or insults is characteristic of the larger group of persistently violent men who repeatedly engage in reactive aggression and show heightened threat responses. Failing to distinguish between these 2 subgroups may have an adverse impact on etiological research and efforts to develop intervention programs tailored to the differing behavioral and temperamental characteristics.[128] Among adult offenders, those with ASPD-P benefit from cognitive and behavioral rehabilitation programs showing reductions in criminal recidivism, while those with the syndrome of psychopathy do not.[128]

In conclusion, to our knowledge, this is the first structural imaging study to compare 2 subtypes of violent offenders. All the offenders were characterized by lifelong histories of antisocial behavior, but they differed as to the personality traits of psychopathy. Furthermore, the 2 groups of violent offenders were matched on age, IQ, and lifelong SUDs. The violent offenders with ASPD+P were characterized by reduced GM volumes bilaterally in both the arMPFC and the temporal poles. These structural abnormalities may subserve the emotional dysfunctions that characterize psychopathy, underpinning deficits of empathic processing, moral reasoning, and the generation of prosocial behaviors. Taken together, the results of our study and those of previous studies of men with the syndrome of psychopathy,[43,53] as well as studies of boys with high levels of both conduct problems and callous-unemotional traits that identified abnormalities of GM concentration[129] and white matter volumes,[130] suggest that psychopathy is a neurodevelopmental disorder characterized by structural abnormalities from a young age. Prospective, longitudinal investigations with repeated brain scans are required to test this hypothesis. Advancing understanding of the etiology of persistent violence and how to prevent and treat it will be facilitated by recognizing the accumulating evidence of distinct phenotypes.

Submitted for Publication: October 10, 2011; final revision received January 6, 2012; accepted February 17, 2012.
Published Online: May 7, 2012. doi:10.1001/archgenpsychiatry.2012.222
Correspondence: Nigel Blackwood, MA, MD, MRCPsych, Forensic and Neurodevelopmental Sciences Department, Institute of Psychiatry, King's College London, PO Box 23, De Crespigny Park, Camberwell, SE5 8AF England (nigel.blackwood@kcl.ac.uk).
Author Contributions: Drs Gregory and Blackwood take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had full access to all the data in the study.
Financial Disclosure: None reported.
Funding/Support: This research was funded by research grants from the Department of Health (the National Forensic Mental Health Research and Development Program); the Ministry of Justice (The Dangerous People with Severe Personality Disorder Program grant); the Psychiatry Research Trust; and the National Institute for Health Research Biomedical Research Centre, South London and Maudsley National Health Service Foundation Trust and Institute of Psychiatry (King's College London).
Additional Contributions: We gratefully acknowledge the work of Sam Russell, MSc; Clare Goodwin, MSc; William Wainwright, MA; Ruben Azevedo, BSc; Francis

©2012 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/02/2015

Vergunst, MSc; Lucy Butler, MSc; Leila Niknejad, BSc; Anna Plodowski, PhD; Philip Baker, MRCPsych; Timothy Rogers, MRCPsych; Preethi Chabbra, MRCPsych; Stephen Attard, MRCPsych; Seema Sukhwal, MRCPsych; Nathan Kolla, MSc; Paul Wallang, MRCPsych; and Clare Conway, DClinPsy, in participant recruitment and assessment.

REFERENCES

1. World Health Organization. *World Report on Violence and Health.* Geneva, Switzerland: World Health Organization; 2008.
2. Moffitt TE. Adolescence-limited and life-course-persistent antisocial behavior: a developmental taxonomy. *Psychol Rev.* 1993;100(4):674-701.
3. Kratzer L, Hodgins S. Adult outcomes of child conduct problems: a cohort study. *J Abnorm Child Psychol.* 1997;25(1):65-81.
4. Loeber R, Stouthamer-Loeber M. Development of juvenile aggression and violence: some common misconceptions and controversies. *Am Psychol.* 1998; 53(2):242-259.
5. Moffitt TE. Genetic and environmental influences on antisocial behaviors: evidence from behavioral-genetic research. *Adv Genet.* 2005;55:41-104.
6. Rhee SH, Waldman ID. Genetic and environmental influences on antisocial behavior: a meta-analysis of twin and adoption studies. *Psychol Bull.* 2002; 128(3):490-529.
7. Moffitt TE, Caspi A, Harrington H, Milne BJ. Males on the life-course-persistent and adolescence-limited antisocial pathways: follow-up at age 26 years. *Dev Psychopathol.* 2002;14(1):179-207.
8. Robins LN. *Deviant Children Grown Up.* Baltimore, MD: Williams & Wilkins; 1966.
9. Kosson DS, Lorenz AR, Newman JP. Effects of comorbid psychopathy on criminal offending and emotion processing in male offenders with antisocial personality disorder. *J Abnorm Psychol.* 2006;115(4):798-806.
10. Hodgins S, De Brito SA, Chhabra P, Côté G. Anxiety disorders among offenders with antisocial personality disorders: a distinct subtype? *Can J Psychiatry.* 2010;55(12):784-791.
11. Blair RJ, Mitchell DG, Blair K. *The Psychopath: Emotion and the Brain.* Oxford, England: Blackwell Publishing Ltd; 2005.
12. Frick PJ, Cornell AH, Bodin SD, Dane HE, Barry CT, Loney BR. Callous-unemotional traits and developmental pathways to severe conduct problems. *Dev Psychol.* 2003;39(2):246-260.
13. Hare RD. *The Hare Psychopathy Checklist-Revised.* New York, NY: Multi-Health Systems; 1991.
14. Hare RD. Psychopathy: a clinical construct whose time has come. *Crim Justice Behav.* 1996;(23):25-54.
15. Wong S. *Criminal and Institutional Behaviours of Psychopaths.* Ottawa, Ontario: Ministry of the Solicitor General of Canada; 1985.
16. Frick PJ, White SF. Research review: the importance of callous-unemotional traits for developmental models of aggressive and antisocial behavior. *J Child Psychol Psychiatry.* 2008;49(4):359-375.
17. Hawes DJ, Dadds MR. The treatment of conduct problems in children with callous-unemotional traits. *J Consult Clin Psychol.* 2005;73(4):737-741.
18. Wootton JM, Frick PJ, Shelton KK, Silverthorn P. Ineffective parenting and childhood conduct problems: the moderating role of callous-unemotional traits. *J Consult Clin Psychol.* 1997;65(2):301-308.
19. Guy LS, Edens JF, Anthony C, Douglas KS. Does psychopathy predict institutional misconduct among adults? a meta-analytic investigation. *J Consult Clin Psychol.* 2005;73(6):1056-1064.
20. Viding E, Blair RJ, Moffitt TE, Plomin R. Evidence for substantial genetic risk for psychopathy in 7-year-olds. *J Child Psychol Psychiatry.* 2005;46(6):592-597.
21. Viding E, Jones AP, Frick PJ, Moffitt TE, Plomin R. Heritability of antisocial behaviour at 9: do callous-unemotional traits matter? *Dev Sci.* 2008;11(1): 17-22.
22. Frick PJ, Kimonis ER, Dandreaux DM, Farell JM. The 4 year stability of psychopathic traits in non-referred youth. *Behav Sci Law.* 2003;21(6):713-736.
23. Obradović J, Pardini DA, Long JD, Loeber R. Measuring interpersonal callousness in boys from childhood to adolescence: an examination of longitudinal invariance and temporal stability. *J Clin Child Adolesc Psychol.* 2007;36(3): 276-292.
24. Lynam DR, Caspi A, Moffitt TE, Loeber R, Stouthamer-Loeber M. Longitudinal evidence that psychopathy scores in early adolescence predict adult psychopathy. *J Abnorm Psychol.* 2007;116(1):155-165.
25. Anderson SW, Bechara A, Damasio H, Tranel D, Damasio AR. Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nat Neurosci.* 1999;2(11):1032-1037.
26. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition.* 1994; 50(1-3):7-15.
27. Blair RJ, Cipolotti L. Impaired social response reversal: a case of 'acquired sociopathy'. *Brain.* 2000;123(pt 6):1122-1141.
28. Finger EC, Marsh AA, Mitchell DG, Reid ME, Sims C, Budhani S, Kosson DS, Chen G, Towbin KE, Leibenluft E, Pine DS, Blair JR. Abnormal ventromedial prefrontal cortex function in children with psychopathic traits during reversal learning. *Arch Gen Psychiatry.* 2008;65(5):586-594.
29. Budhani S, Blair RJ. Response reversal and children with psychopathic tendencies: success is a function of salience of contingency change. *J Child Psychol Psychiatry.* 2005;46(9):972-981.
30. Marsh AA, Finger EC, Mitchell DG, Reid ME, Sims C, Kosson DS, Towbin KE, Leibenluft E, Pine DS, Blair RJ. Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. *Am J Psychiatry.* 2008;165(6):712-720.
31. Blair RJ, Colledge E, Murray L, Mitchell DG. A selective impairment in the processing of sad and fearful expressions in children with psychopathic tendencies. *J Abnorm Child Psychol.* 2001;29(6):491-498.
32. Birbaumer N, Veit R, Lotze M, Erb M, Hermann C, Grodd W, Flor H. Deficient fear conditioning in psychopathy: a functional magnetic resonance imaging study. *Arch Gen Psychiatry.* 2005;62(7):799-805.
33. Flor H, Birbaumer N, Hermann C, Ziegler S, Patrick CJ. Aversive Pavlovian conditioning in psychopaths: peripheral and central correlates. *Psychophysiology.* 2002;39(4):505-518.
34. Kiehl KA, Smith AM, Hare RD, Mendrek A, Forster BB, Brink J, Liddle PF. Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. *Biol Psychiatry.* 2001;50(9):677-684.
35. Patrick CJ. Emotion and psychopathy: startling new insights. *Psychophysiology.* 1994;31(4):319-330.
36. Herpertz SC, Werth U, Lukas G, Qunaibi M, Schuerkens A, Kunert HJ, Freese R, Flesch M, Mueller-Isberner R, Osterheider M, Sass H. Emotion in criminal offenders with psychopathy and borderline personality disorder. *Arch Gen Psychiatry.* 2001;58(8):737-745.
37. Plodowski A, Gregory SL, Blackwood NJ. Persistent violent offending among adult men: a critical review of neuroimaging studies. In: Hodgins S, Viding E, Plodowski A, eds. *The Neurobiological Basis of Violence: Science and Rehabilitation.* Oxford, England: Oxford University Press; 2009.
38. Koenigs M, Baskin-Sommers A, Zeier J, Newman JP. Investigating the neural correlates of psychopathy: a critical review. *Mol Psychiatry.* 2011;16(8): 792-799.
39. Raine A, Ishikawa SS, Arce E, Lencz T, Knuth KH, Bihrle S, LaCasse L, Colletti P. Hippocampal structural asymmetry in unsuccessful psychopaths. *Biol Psychiatry.* 2004;55(2):185-191.
40. Raine A, Lencz T, Taylor K, Hellige JB, Bihrle S, Lacasse L, Lee M, Ishikawa S, Colletti P. Corpus callosum abnormalities in psychopathic antisocial individuals. *Arch Gen Psychiatry.* 2003;60(11):1134-1142.
41. Yang Y, Raine A, Lencz T, Bihrle S, LaCasse L, Colletti P. Volume reduction in prefrontal gray matter in unsuccessful criminal psychopaths. *Biol Psychiatry.* 2005;57(10):1103-1108.
42. Müller JL, Gänssbauer S, Sommer M, Döhnel K, Weber T, Schmidt-Wilcke T, Hajak G. Gray matter changes in right superior temporal gyrus in criminal psychopaths: evidence from voxel-based morphometry. *Psychiatry Res.* 2008; 163(3):213-222.
43. de Oliveira-Souza R, Hare RD, Bramati IE, Garrido GJ, Azevedo Ignácio F, Tovar-Moll F, Moll J. Psychopathy as a disorder of the moral brain: fronto-temporo-limbic grey matter reductions demonstrated by voxel-based morphometry. *Neuroimage.* 2008;40(3):1202-1213.
44. Yang Y, Raine A, Narr KL, Colletti P, Toga AW. Localization of deformations within the amygdala in individuals with psychopathy. *Arch Gen Psychiatry.* 2009; 66(9):986-994.
45. Glenn AL, Raine A, Yaralian PS, Yang Y. Increased volume of the striatum in psychopathic individuals. *Biol Psychiatry.* 2010;67(1):52-58.
46. Barkataki I, Kumari V, Das M, Taylor P, Sharma T. Volumetric structural brain abnormalities in men with schizophrenia or antisocial personality disorder. *Behav Brain Res.* 2006;169(2):239-247.
47. Narayan VM, Narr KL, Kumari V, Woods RP, Thompson PM, Toga AW, Sharma T. Regional cortical thinning in subjects with violent antisocial personality disorder or schizophrenia. *Am J Psychiatry.* 2007;164(9):1418-1427.
48. Schiffer B, Müller BW, Scherbaum N, Hodgins S, Forsting M, Wiltfang J, Gizewski ER, Leygraf N. Disentangling structural brain alterations associated with violent behavior from those associated with substance use disorders. *Arch Gen Psychiatry.* 2011;68(10):1039-1049.
49. Tiihonen J, Rossi R, Laakso MP, Hodgins S, Testa C, Perez J, Repo-Tiihonen E, Vaurio O, Soininen H, Aronen HJ, Könönen M, Thompson PM, Frisoni GB.

©2012 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/02/2015

Brain anatomy of persistent violent offenders: more rather than less. *Psychiatry Res*. 2008;163(3):201-212.
50. Laakso MP, Gunning-Dixon F, Vaurio O, Repo-Tiihonen E, Soininen H, Tiihonen J. Prefrontal volumes in habitually violent subjects with antisocial personality disorder and type 2 alcoholism. *Psychiatry Res*. 2002;114(2):95-102.
51. Raine A, Lencz T, Bihrle S, LaCasse L, Colletti P. Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Arch Gen Psychiatry*. 2000;57(2):119-127, discussion 128-129.
52. Yang Y, Raine A, Colletti P, Toga AW, Narr KL. Abnormal temporal and prefrontal cortical gray matter thinning in psychopaths. *Mol Psychiatry*. 2009; 14(6):561-562, 555.
53. Yang Y, Raine A, Colletti P, Toga AW, Narr KL. Morphological alterations in the prefrontal cortex and the amygdala in unsuccessful psychopaths. *J Abnorm Psychol*. 2010;119(3):546-554.
54. Laakso MP, Vaurio O, Savolainen L, Repo E, Soininen H, Aronen HJ, Tiihonen J. A volumetric MRI study of the hippocampus in type 1 and 2 alcoholism. *Behav Brain Res*. 2000;109(2):177-186.
55. Cooke DJ, Michie C. Psychopathy across cultures: North America and Scotland compared. *J Abnorm Psychol*. 1999;108(1):58-68.
56. Raine A, Yang Y, Narr KL, Toga AW. Sex differences in orbitofrontal gray as a partial explanation for sex differences in antisocial personality. *Mol Psychiatry*. 2011;16(2):227-236.
57. Boccardi M, Ganzola R, Rossi R, Sabattoli F, Laakso MP, Repo-Tiihonen E, Vaurio O, Könönen M, Aronen HJ, Thompson PM, Frisoni GB, Tiihonen J. Abnormal hippocampal shape in offenders with psychopathy. *Hum Brain Mapp*. 2010;31(3):438-447.
58. Ellison-Wright I, Bullmore E. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. *Schizophr Res*. 2010;117(1):1-12.
59. Laakso MP, Vaurio O, Koivisto E, Savolainen L, Eronen M, Aronen HJ, Hakola P, Repo E, Soininen H, Tiihonen J. Psychopathy and the posterior hippocampus. *Behav Brain Res*. 2001;118(2):187-193.
60. Franklin TR, Acton PD, Maldjian JA, Gray JD, Croft JR, Dackis CA, O'Brien CP, Childress AR. Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biol Psychiatry*. 2002; 51(2):134-142.
61. Ashburner J, Friston KJ. Voxel-based morphometry: the methods. *Neuroimage*. 2000;11(6, pt 1):805-821.
62. Ioannidis JP. Excess significance bias in the literature on brain volume abnormalities. *Arch Gen Psychiatry*. 2011;68(8):773-780.
63. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for *DSM-III-R* (SCID), I: history, rationale, and description. *Arch Gen Psychiatry*. 1992;49(8):624-629.
64. Hare RD, Harpur TJ, Hakstian AR, Forth AE, Hart SD. The Revised Psychopathy Checklist: reliability and factor structure. *Psychol Assess*. 1990;2(3):338-341. doi:10.1037//1040-3590.2.3.338.
65. Hare RD, Neumann CS. Structural models of psychopathy. *Curr Psychiatry Rep*. 2005;7(1):57-64.
66. Weschler D. *WAIS-III: Administration and Scoring Manual*. San Antonio, TX: Harcourt Brace and Co; 1997.
67. Raine A, Dodge K, Loeber R, Gatzke-Kopp L, Lynam D, Reynolds C, Stouthamer-Loeber M, Liu J. The Reactive-Proactive Aggression Questionnaire: differential correlates of reactive and proactive aggression in adolescent boys. *Aggress Behav*. 2006;32(2):159-171.
68. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage*. 2005;26(3):839-851.
69. Santana MT, Jackowski AP, da Silva HH, Caboclo LO, Centeno RS, Bressan RA, Carrete H Jr, Yacubian EM. Auras and clinical features in temporal lobe epilepsy: a new approach on the basis of voxel-based morphometry. *Epilepsy Res*. 2010;89(2-3):327-338.
70. Schiltz K, Witzel J, Northoff G, Zierhut K, Gubka U, Fellmann H, Kaufmann J, Tempelmann C, Wiebking C, Bogerts B. Brain pathology in pedophilic offenders: evidence of volume reduction in the right amygdala and related diencephalic structures. *Arch Gen Psychiatry*. 2007;64(6):737-746.
71. Colom R, Jung RE, Haier RJ. General intelligence and memory span: evidence for a common neuroanatomic framework. *Cogn Neuropsychol*. 2007;24 (8):867-878.
72. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage*. 2002;15 (4):870-878.
73. Elliott R, Newman JL, Longe OA, Deakin JF. Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. *J Neurosci*. 2003;23(1): 303-307.
74. Paulus MP, Feinstein JS, Leland D, Simmons AN. Superior temporal gyrus and insula provide response and outcome-dependent information during assessment and action selection in a decision-making situation. *Neuroimage*. 2005; 25(2):607-615.
75. Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. *Nat Rev Neurosci*. 2006;7(4):268-277.
76. Kelley WM, Macrae CN, Wyland CL, Caglar S, Inati S, Heatherton TF. Finding the self? an event-related fMRI study. *J Cogn Neurosci*. 2002;14(5):785-794.
77. Ochsner KN, Beer JS, Robertson ER, Cooper JC, Gabrieli JD, Kihsltrom JF, D'Esposito M. The neural correlates of direct and reflected self-knowledge. *Neuroimage*. 2005;28(4):797-814.
78. Benoit RG, Gilbert SJ, Volle E, Burgess PW. When I think about me and simulate you: medial rostral prefrontal cortex and self-referential processes. *Neuroimage*. 2010;50(3):1340-1349.
79. Mitchell JP, Banaji MR, Macrae CN. General and specific contributions of the medial prefrontal cortex to knowledge about mental states. *Neuroimage*. 2005; 28(4):757-762.
80. Mitchell JP, Banaji MR, Macrae CN. The link between social cognition and self-referential thought in the medial prefrontal cortex. *J Cogn Neurosci*. 2005; 17(8):1306-1315.
81. Ruby P, Decety J. How would you feel versus how do you think she would feel? a neuroimaging study of perspective-taking with social emotions. *J Cogn Neurosci*. 2004;16(6):988-999.
82. Koechlin E, Hyafil A. Anterior prefrontal function and the limits of human decision-making. *Science*. 2007;318(5850):594-598.
83. Behrens TE, Hunt LT, Rushworth MF. The computation of social behavior. *Science*. 2009;324(5931):1160-1164.
84. Delgado MR, Nearing KI, Ledoux JE, Phelps EA. Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. *Neuron*. 2008; 59(5):829-838.
85. Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn Sci*. 2011;15(2):85-93.
86. Schiller D, Levy I, Niv Y, LeDoux JE, Phelps EA. From fear to safety and back: reversal of fear in the human brain. *J Neurosci*. 2008;28(45):11517-11525.
87. Mechias ML, Etkin A, Kalisch R. A meta-analysis of instructed fear studies: implications for conscious appraisal of threat. *Neuroimage*. 2010;49(2):1760-1768.
88. Fink GR, Markowitsch HJ, Reinkemeier M, Bruckbauer T, Kessler J, Heiss WD. Cerebral representation of one's own past: neural networks involved in autobiographical memory. *J Neurosci*. 1996;16(13):4275-4282.
89. Lambon Ralph MA, Sage K, Jones RW, Mayberry EJ. Coherent concepts are computed in the anterior temporal lobes. *Proc Natl Acad Sci U S A*. 2010; 107(6):2717-2722.
90. Rogers TT, Lambon Ralph MA, Garrard P, Bozeat S, McClelland JL, Hodges JR, Patterson K. Structure and deterioration of semantic memory: a neuropsychological and computational investigation. *Psychol Rev*. 2004;111(1):205-235.
91. Zahn R, Moll J, Krueger F, Huey ED, Garrido G, Grafman J. Social concepts are represented in the superior anterior temporal cortex. *Proc Natl Acad Sci U S A*. 2007;104(15):6430-6435.
92. Kluver HB, Bucy BC. Preliminary analysis of functions of the temporal lobe in monkeys. *Arch Neurol Psychiatry*. 1939;42.
93. Lilly R, Cummings JL, Benson DF, Frankel M. The human Klüver-Bucy syndrome. *Neurology*. 1983;33(9):1141-1145.
94. Hoefer M, Allison SC, Schauer GF, Neuhaus JM, Hall J, Dang JN, Weiner MW, Miller BL, Rosen HJ. Fear conditioning in frontotemporal lobar degeneration and Alzheimer's disease. *Brain*. 2008;131(pt 6):1646-1657.
95. Gorno-Tempini ML, Rankin KP, Woolley JD, Rosen HJ, Phengrasamy L, Miller BL. Cognitive and behavioral profile in a case of right anterior temporal lobe neurodegeneration. *Cortex*. 2004;40(4-5):631-644.
96. Lough S, Kipps CM, Treise C, Watson P, Blair JR, Hodges JR. Social reasoning, emotion and empathy in frontotemporal dementia. *Neuropsychologia*. 2006; 44(6):950-958.
97. Rankin KP, Gorno-Tempini ML, Allison SC, Stanley CM, Glenn S, Weiner MW, Miller BL. Structural anatomy of empathy in neurodegenerative disease. *Brain*. 2006;129(pt 11):2945-2956.
98. Berthoz S, Armony JL, Blair RJ, Dolan RJ. An fMRI study of intentional and unintentional (embarrassing) violations of social norms. *Brain*. 2002;125 (pt 8):1696-1708.
99. Moll J, De Oliveira-Souza R, Zahn R. The neural basis of moral cognition: sentiments, concepts, and values. *Ann N Y Acad Sci*. 2008;1124:161-180.
100. Takahashi H, Yahata N, Koeda M, Matsuda T, Asai K, Okubo Y. Brain activation associated with evaluative processes of guilt and embarrassment: an fMRI study. *Neuroimage*. 2004;23(3):967-974.
101. Greene JD, Sommerville RB, Nystrom LE, Darley JM, Cohen JD. An fMRI investigation of emotional engagement in moral judgment. *Science*. 2001;293(5537): 2105-2108.

©2012 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/02/2015

102. Heekeren HR, Wartenburger I, Schmidt H, Schwintowski HP, Villringer A. An fMRI study of simple ethical decision-making. *Neuroreport*. 2003;14 (9):1215-1219.
103. Harenski CL, Antonenko O, Shane MS, Kiehl KA. A functional imaging investigation of moral deliberation and moral intuition. *Neuroimage*. 2010;49(3): 2707-2716.
104. Moll J, de Oliveira-Souza R, Eslinger PJ, Bramati IE, Mourão-Miranda J, Andreiuolo PA, Pessoa L. The neural correlates of moral sensitivity: a functional magnetic resonance imaging investigation of basic and moral emotions. *J Neurosci*. 2002;22(7):2730-2736.
105. Moll J, Krueger F, Zahn R, Pardini M, de Oliveira-Souza R, Grafman J. Human fronto-mesolimbic networks guide decisions about charitable donation. *Proc Natl Acad Sci U S A*. 2006;103(42):15623-15628.
106. Dolan M, Fullam R. Theory of mind and mentalizing ability in antisocial personality disorders with and without psychopathy. *Psychol Med*. 2004;34 (6):1093-1102.
107. Richell RA, Mitchell DG, Newman C, Leonard A, Baron-Cohen S, Blair RJ. Theory of mind and psychopathy: can psychopathic individuals read the 'language of the eyes'? *Neuropsychologia*. 2003;41(5):523-526.
108. Blair RJ, Jones L, Clark F, Smith M. The psychopathic individual: a lack of responsiveness to distress cues? *Psychophysiology*. 1997;34(2):192-198.
109. Newman JP, Kosson DS. Passive avoidance learning in psychopathic and nonpsychopathic offenders. *J Abnorm Psychol*. 1986;95(3):252-256.
110. Craig AD. How do you feel—now? the anterior insula and human awareness. *Nat Rev Neurosci*. 2009;10(1):59-70.
111. Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, Hichwa RD. Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nat Neurosci*. 2000;3(10):1049-1056.
112. Lane RD, Reiman EM, Ahern GL, Schwartz GE, Davidson RJ. Neuroanatomical correlates of happiness, sadness, and disgust. *Am J Psychiatry*. 1997;154 (7):926-933.
113. Budhani S, Marsh AA, Pine DS, Blair RJ. Neural correlates of response reversal: considering acquisition. *Neuroimage*. 2007;34(4):1754-1765.
114. Lamm C, Batson CD, Decety J. The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *J Cogn Neurosci*. 2007; 19(1):42-58.
115. Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. *Science*. 2004; 303(5661):1157-1162.
116. Makris N, Oscar-Berman M, Jaffin SK, Hodge SM, Kennedy DN, Caviness VS, Marinkovic K, Breiter HC, Gasic GP, Harris GJ. Decreased volume of the brain reward system in alcoholism. *Biol Psychiatry*. 2008;64(3):192-202.
117. Lorenzetti V, Lubman DI, Whittle S, Solowij N, Yücel M. Structural MRI findings in long-term cannabis users: what do we know? *Subst Use Misuse*. 2010; 45(11):1787-1808.
118. Li CT, Lin CP, Chou KH, Chen IY, Hsieh JC, Wu CL, Lin WC, Su TP. Structural and cognitive deficits in remitting and non-remitting recurrent depression: a voxel-based morphometric study. *Neuroimage*. 2010;50(1):347-356.
119. Alia-Klein N, Parvaz MA, Woicik PA, Konova AB, Maloney T, Shumay E, Wang R, Telang F, Biegon A, Wang GJ, Fowler JS, Tomasi D, Volkow ND, Goldstein RZ. Gene x disease interaction on orbitofrontal gray matter in cocaine addiction. *Arch Gen Psychiatry*. 2011;68(3):283-294.
120. Koolschijn PC, van Haren NE, Lensvelt-Mulders GJ, Hulshoff Pol HE, Kahn RS. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Hum Brain Mapp*. 2009;30(11):3719-3735.
121. Blair RJ, Colledge E, Mitchell DG. Somatic markers and response reversal: is there orbitofrontal cortex dysfunction in boys with psychopathic tendencies? *J Abnorm Child Psychol*. 2001;29(6):499-511.
122. Craig MC, Catani M, Deeley Q, Latham R, Daly E, Kanaan R, Picchioni M, McGuire PK, Fahy T, Murphy DG. Altered connections on the road to psychopathy. *Mol Psychiatry*. 2009;14(10):946-953, 907.
123. Sundram F, Deeley Q, Sarkar S, Daly E, Latham R, Craig M, Raczek M, Fahy T, Picchioni M, Barker GJ, Murphy DG; UK AIMS Network. White matter microstructural abnormalities in the frontal lobe of adults with antisocial personality disorder. *Cortex*. 2011;48(2):216-229.
124. Motzkin JC, Newman JP, Kiehl KA, Koenigs M. Reduced prefrontal connectivity in psychopathy. *J Neurosci*. 2011;31(48):17348-17357.
125. Krueger RF, South SC. Externalizing disorders: cluster 5 of the proposed metastructure for *DSM-V* and *ICD-11*. *Psychol Med*. 2009;39(12):2061-2070.
126. Krueger RF, Hicks BM, Patrick CJ, Carlson SR, Iacono WG, McGue M. Etiologic connections among substance dependence, antisocial behavior, and personality: modeling the externalizing spectrum. *J Abnorm Psychol*. 2002; 111(3):411-424.
127. Hodgins S, de Brito S, Simonoff E, Vloet T, Viding E. Getting the phenotypes right: an essential ingredient for understanding aetiological mechanisms underlying persistent violence and developing effective treatments. *Front Behav Neurosci*. 2009;3:44.
128. Antisocial personality disorder: treatment, management and prevention. National Institute for Health and Clinical Excellence website. http://www.nice.org.uk/nicemedia/pdf/CG77NICEGuideline.pdf. Accessed October 5, 2011.
129. De Brito SA, Mechelli A, Wilke M, Laurens KR, Jones AP, Barker GJ, Hodgins S, Viding E. Size matters: increased grey matter in boys with conduct problems and callous-unemotional traits. *Brain*. 2009;132(pt 4):843-852.
130. De Brito SA, McCrory EJ, Mechelli A, Wilke M, Jones AP, Hodgins S, Viding E. Small, but not perfectly formed: decreased white matter concentration in boys with psychopathic tendencies. *Mol Psychiatry*. 2011;16(5):476-477.

©2012 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 09/02/2015