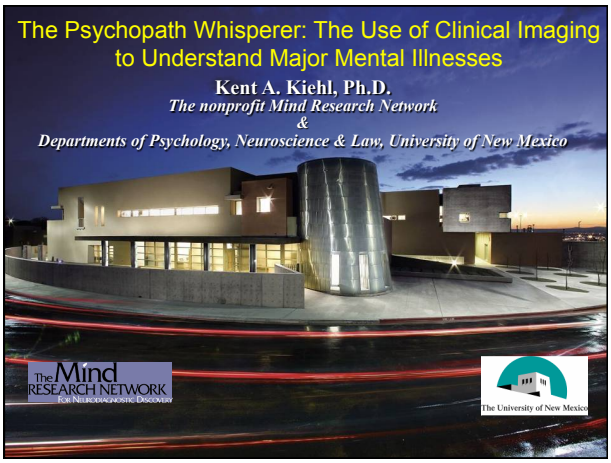


Summary of your client "Justin"

History:

- 16 year old male
- Above average IQ
- Normal high school performance
- No head injuries, no drug use
- Involved in sports and other social activities
- Out with friends, drinking a little alcohol
- Fight ensues with youth at a rival high school over football game
- Justin hits another teen with a bottle; coma, serious head injury result

- Justin in charged with attempted murder, use of a weapon
- Mugshot of Justin

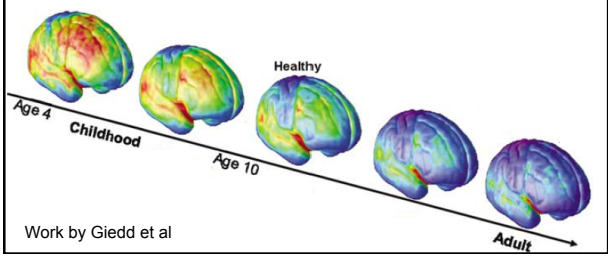
Summary of your client "Justin"

History:

- Prosecution raises Justin to adult court and seeks sentence of life without the possibility of parole for attempted murder
- Wait……
- I remember the U.S. Supreme Court had a case about something like this……..
- **2009** – **Graham v Florida**; U.S. Supreme Court eliminates the sentence of life without the possibility of parole for non-homicide cases
- Why?
- For the first time in a criminal case the court says:

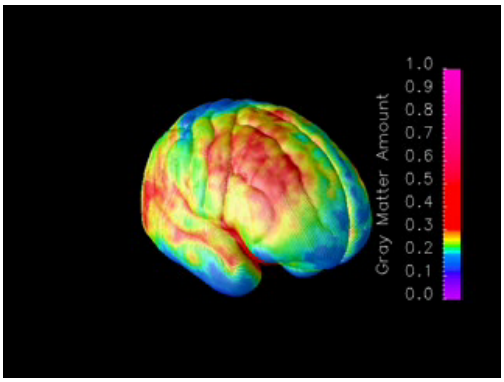
Graham v Florida

U.S. Supreme Court:
"…. **developments in psychology and brain science continue to show fundamental differences between juvenile and adult minds. For example, parts of the brain involved in behavior control continue to mature through late adolescence."**



Work by Giedd et al

Neuroscience of Brain Maturation (age)



Summary of your client "George"

History:

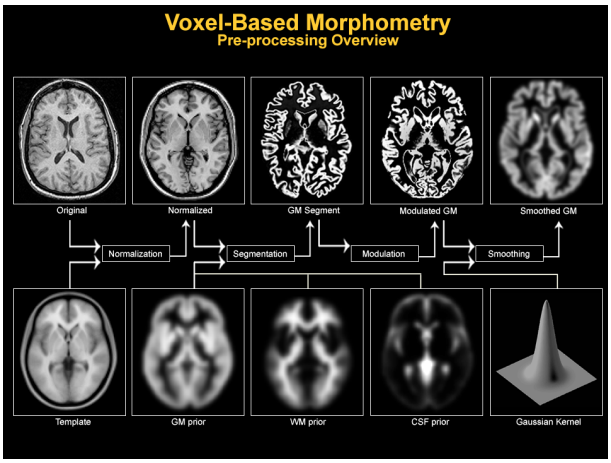
- 55 year old white male
- Lifetime history of nonviolent crimes, in and out of jail
- IQ estimates since childhood have been low, around 65
- George arrested for **murder**
- Prosecution seeks **death penalty**
- **Atkins v Virginia**: Individuals with low IQ ineligible for death penalty
- Prosecution expert finds George's IQ to be **72**
- Defense expert says **60**

Can Neuroscience Inform Case of "George"?

Prosecutors are using it!

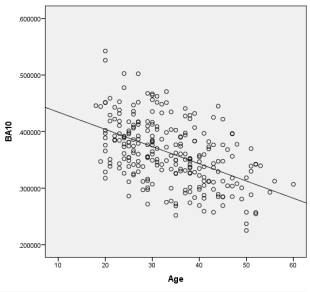
- Defense introduced evidence of 'borderline intellectual functioning' to mitigate intent (first degree)
- Gov argued that testing was incomplete because defense expert failed to get functional brain imaging scans to support argument
- Defense refused to get functional MRI scans and case was lost

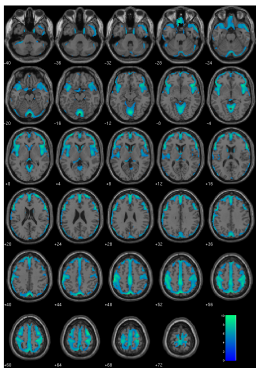
United States v. Williams, 2008 U.S. Dist. LEXIS 81577 (D. Haw., Oct. 15, 2008)



What do Neuroscientist's know about "Gray Matter"

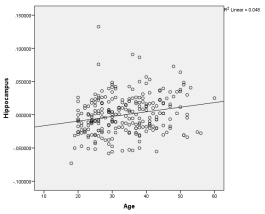
The Bad News:
As age goes up, gray matter goes down

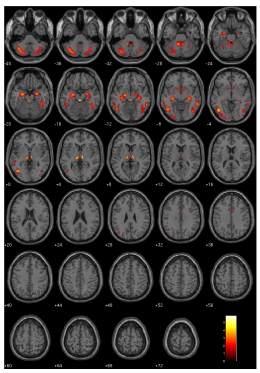




What do Neuroscientist's know about "Gray Matter"

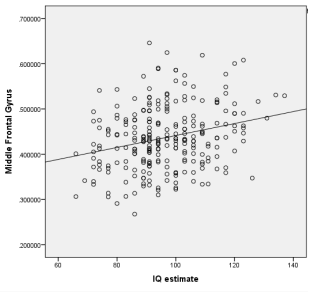
The Good News:
As age goes up, some gray matter goes up too!!!

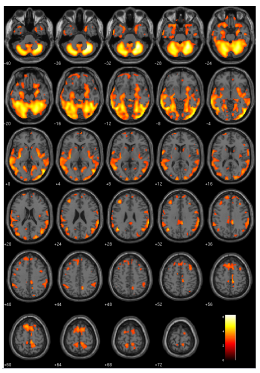




What do Neuroscientist's know about "Gray Matter"

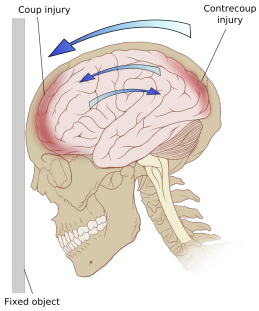
IQ highly correlated with Gray Matter



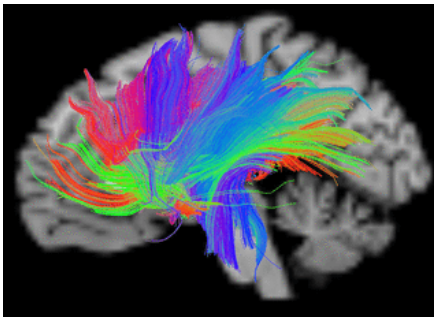


Can Neuroscience Inform These Cases?

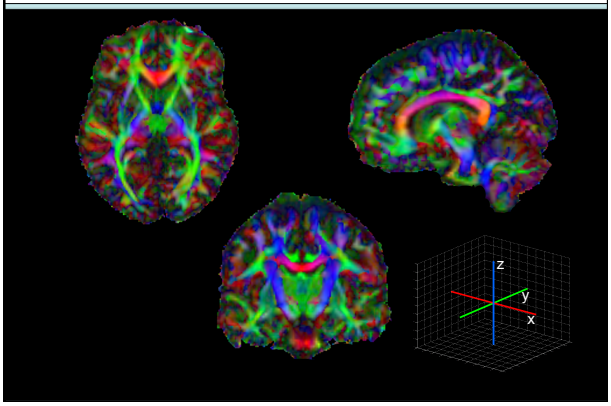
Traumatic Brain Injury



Diffusion-Weighted MRI

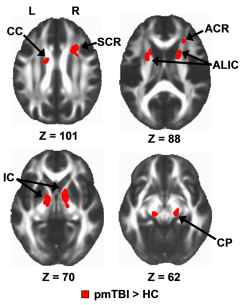


Diffusion-Weighted MRI



DTI Results: Youth (10-17 y.o.) Cohort

- FA and RD Results (pmTBI = 15; HC = 15)



- Increased FA & decreased RD in ROI analyses
- ROI data classify 13/15 pmTBI patients and 14/15 HC
- Increased FA also present in voxel-wise analyses

Mayer et al., 2012; *Journal of Neuroscience*

Can Neuroscience Inform This Case?

Can Neuroscience Inform This Case?

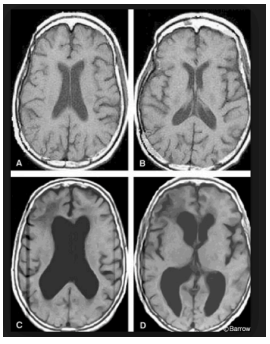
Summary of John Hinckley

- 26 year old male
- Tried to assassinate President Ronald Reagan in 1981
- Hinckley said he did crime to gain the attention (which he did) and affection (which he did not) of actress Jodie Foster
- Hinckley pleads insanity
- Brain images, for the first time, were used to support diagnosis of "psychosis"
- Hinckley found insane sentenced to mental hospital

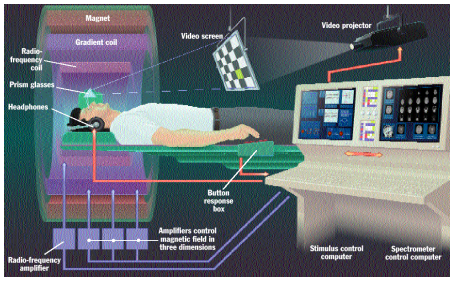
Can Neuroscience Inform This Case?

Summary of John Hinckley

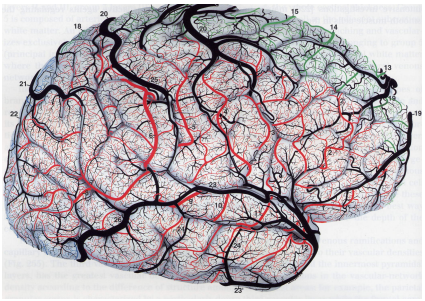
- Hinckley's brain images depicted enlarged ventricles (fluid filled spaces in the brain)
- We know now that enlarged ventricles are risk factor for psychosis, not diagnostic
- Any developments since 1981 in the neuroscience of psychosis?

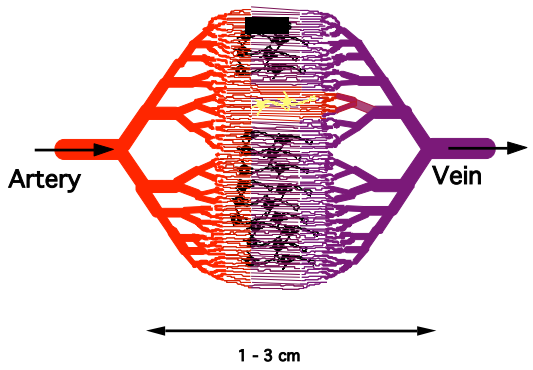


Modifications to MRI



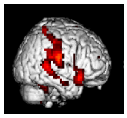
Basic Principles of Functional Brain MRI





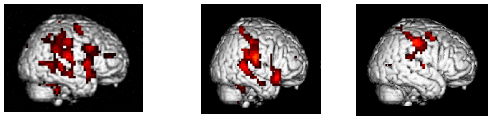
PSYCHIATRIC DIAGNOSIS

First episode patient

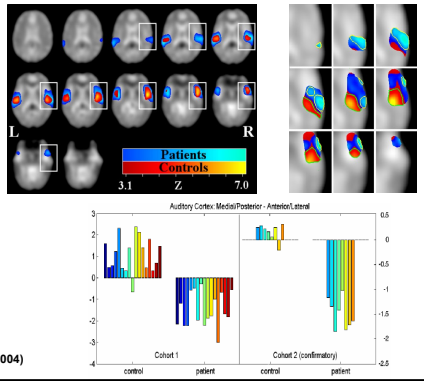


Database of other first episode patients

Bipolar | Schizophrenia | Affective

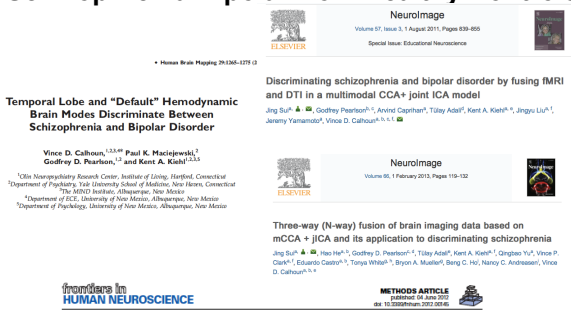


Brain Scans Discriminate Patients with Schizophrenia from Healthy Controls



Calhoun et al (2004)

Brain Scans Discriminate Patients with Schizophrenia/Bipolar from Healthy Controls



Temporal Lobe and "Default" Hemodynamic Brain Modes Discriminate Between Schizophrenia and Bipolar Disorder

Vince D. Calhoun, Paul K. Maciejewski, Godfrey D. Pearlson and Kent A. Kiehl

Human Brain Mapping 29:1265–1275 (2

NeuroImage

Volume 57, Issue 3, 1 August 2011, Pages 839–855

Special Issue: Educational Neuroscience

Discriminating schizophrenia and bipolar disorder by fusing fMRI and DTI in a multimodal CCA+ joint ICA model

Jing Sui, Godfrey Pearlson, Arvind Caprihan, Tülay Adalı, Kent A. Kiehl, Jingyu Liu, Jeremy Yamamoto, Vince D. Calhoun

NeuroImage

Volume 66, 1 February 2013, Pages 119–132

Three-way (N-way) fusion of brain imaging data based on mCCA + jICA and its application to discriminating schizophrenia

Jing Sui, Hao He, Godfrey D. Pearlson, Tülay Adalı, Kent A. Kiehl, Qingbao Yu, Vince P. Clark, Eduardo Castro, Tonya White, Bryon A. Mueller, Beng C. Ho, Nancy C. Andreasen, Vince D. Calhoun

frontiers in HUMAN NEUROSCIENCE

METHODS ARTICLE

High classification accuracy for schizophrenia with rest and task fMRI data

Wei Du, Vince D. Calhoun, Hualiang Li, Sai Ma, Tom Eichele, Kent A. Kiehl, Godfrey D. Pearlson and Tülay Adalı

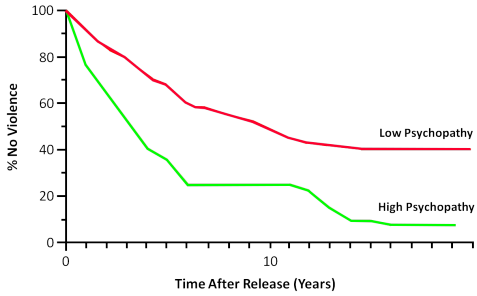
Can Neuroscience Inform This Case?

Symptoms of Psychopathy from Hare PCL-R

Interpersonal/Affective Factor 1	Impulsive/Behavioral Factor 2
1) Glib/ superficial	11) Need for stimulation
2) Grandiose	12) Parasitic lifestyle
3) Pathological liar	13) Impulsivity
4) Conning/Manipulative	14) Sexual promiscuity
5) Lack of Remorse/ Guilt	15) Many marital relationships
6) Shallow affect	16) Poor behavioral controls
7) Callous/ Lacks empathy	17) Early behavioral problems
8) Lack of realistic long term plans	18) Juvenile Delinquency
9) Failure to accept consequences of actions	19) Recidivist
10) Irresponsibility	20) Criminal versatility

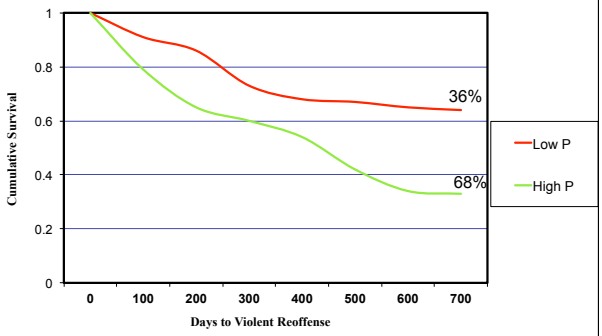
(Hare, 1993; 2003)

Decision-making in Psychopathy



(Rice & Harris,1997)

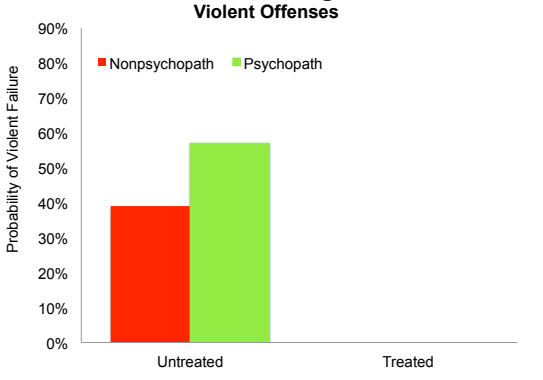
Decision-making in Youth with CU/CD



(Vincent et al., 2003)

Recidivism Following Treatment

Violent Offenses



(Rice, Harris & Cormier, 1992)

Mind Research Network Mobile Imaging System

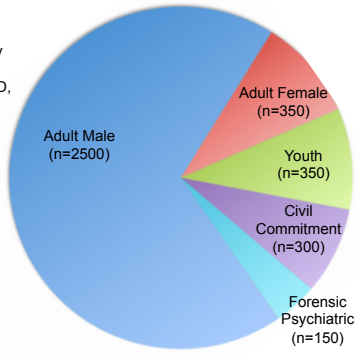
Sample Characteristics (n>3500)

Adults – psychopathy, substance abuse, trauma, decision-making, impulsivity

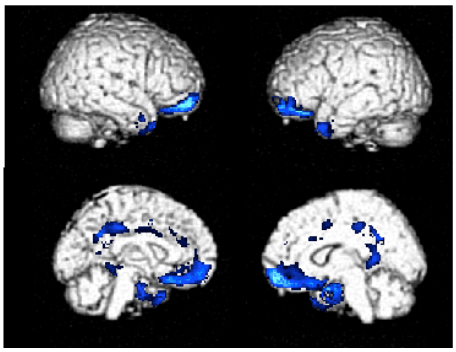
Youth – development, ADHD, CU/CD Traits, empathy

Forensic Psychiatric – psychosis, depression, impulsivity

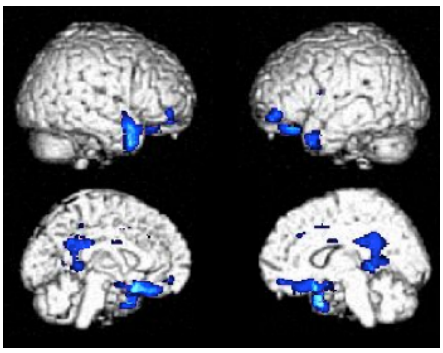
Civil Commitment – IQ, paraphilia



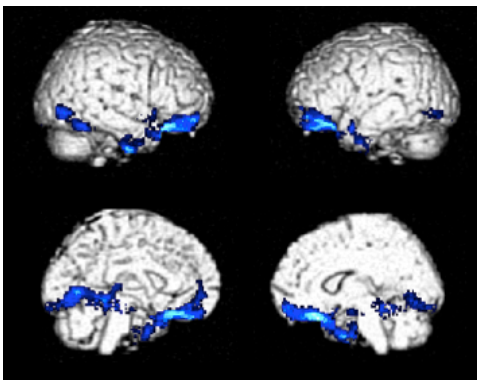
Brain gray matter abnormalities in adult males with psychopathy (n=298; Ermer et al., 2012)

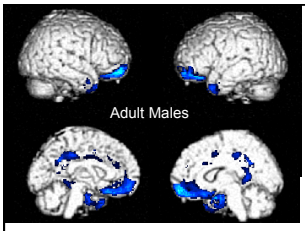


Brain gray matter abnormalities in boys with Callous/ Unemotional Traits (n=199; Ermer et al., 2013)



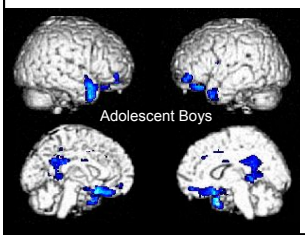
Brain gray matter abnormalities in girls with Callous/ Unemotional Traits (n=39; Cope et al., in press)

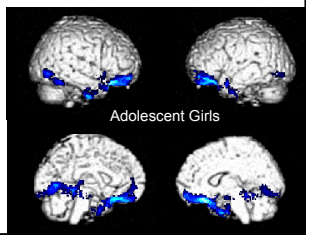




Brain Gray Matter Abnormalities associated with Psychopathic Traits

Samples are from Ermer et al 2012 (left top), 2013 (bottom left); Cope et al., 2014 (bottom right).





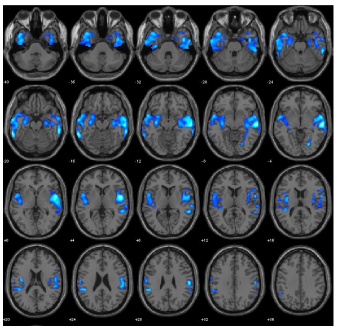
The Avielle Foundation
Research & Community

"Preventing Violence Through Research and Community Education"

Jeremy and Jennifer Richman created the foundation following the loss of the 26 child/educators at Sandy Hook elementary school.

Foundation Mission is to raise awareness and funding to study violence with ultimate goal to improve outcomes.

Is there anything 'special' about youth who commit homicide?



Youth Incarcerated Sample
Homicide (n=20) vs not (n=135)

VBM results, controlling for brain volume, PCL-YV, substance abuse.

Overall: 85.16%
Sensitivity: 90%
Specificity: 84%

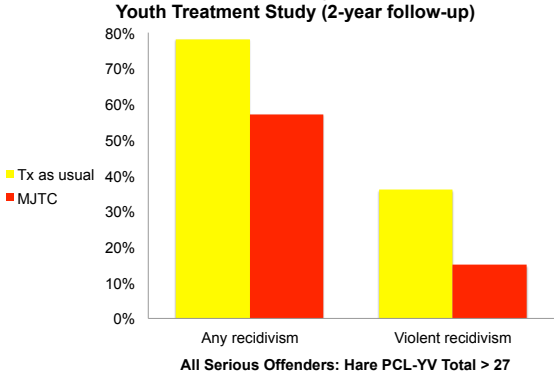
Cope et al., 2014

Burden of Crime in Wisconsin

- Wisconsin budget is $1.1 billion for the 180,000 students in the University of Wisconsin system ($6000/per)
- State of Wisconsin spends $1.0 billion on 22,000 inmates; over 45,000 per inmate
- 7.5x the cost per inmate as UW student!

Importance of Early Intervention

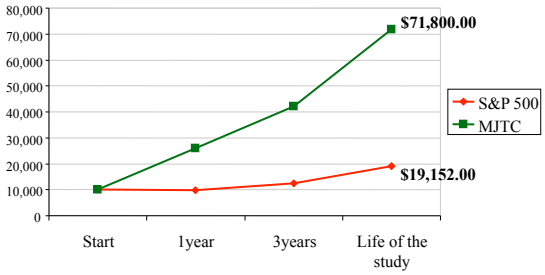
Youth Treatment Study (2-year follow-up)



All Serious Offenders: Hare PCL-YV Total > 27

(Caldwell et al., 2006)

Return on $10,000 investment in treatment



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- **Washington Univ**– Ben Shannon, Marc Raichle
- **UCSB** – Scott Grafton, Mike Miller, Mike Gazzaniga
- **UW Madison –** Joe Newman, Mike Koenigs
- **UMass** – Gina Vincent
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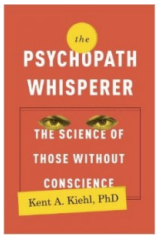
- MacArthur Law and Neuroscience Project (Phase 1)



More details: email Kent Kiehl: kkiehl@unm.edu

www.kentkiehl.com

Aberrant Paralimbic Gray Matter in Incarcerated Male Adolescents With Psychopathic Traits

Elsa Ermer, Ph.D., Lora M. Cope, M.S., Prashanth K. Nyalakanti, M.S., Vince D. Calhoun, Ph.D., Kent A. Kiehl, Ph.D.

Objective: To investigate the relationship between brain structure and psychopathic traits in maximum-security incarcerated male adolescents, and to examine whether the associations between brain volumes in paralimbic and limbic regions and psychopathic traits observed in incarcerated adult men extend to an independent sample of incarcerated male adolescents. **Method:** A structural magnetic resonance imaging (MRI) study of regional gray matter volumes by using voxel-based morphometry in maximum-security incarcerated male adolescents (N = 218) assessed for psychopathic traits using the Hare Psychopathy Checklist–Youth Version (PCL-YV). All analyses controlled for effects of age, substance use, and brain size. **Results:** Consistent with hypotheses and the adult literature, psychopathic traits were associated with decreased regional gray matter volumes in diffuse paralimbic regions, including orbitofrontal cortex, bilateral temporal poles, and posterior cingulate cortex. **Conclusions:** These results strengthen the interpretation that paralimbic regions are central for understanding neural dysfunction associated with psychopathic traits and that psychopathy is best conceptualized as a neurodevelopmental disorder. J. Am. Acad. Child Adolesc. Psychiatry; 2012;52(1):94–103. **Key Words:** paralimbic dysfunction, juvenile delinquency, voxel-based morphometry, psychopathy, antisocial.

For most antisocial male adolescents, problematic behavior peaks in late adolescence or early adulthood and drops off rapidly thereafter; however, some individuals remain on a life-course–persistent trajectory of antisocial behavior throughout adulthood.[1] Some adults on the life-course–persistent trajectory meet diagnostic criteria for psychopathy, a predictor of persistence in criminal activity and violent behavior.[2–4]

Psychopathy is a serious and enduring personality disorder marked by interpersonal, affective, and behavioral traits such as glibness, lack of moral emotions (e.g., remorse, empathy), irresponsibility, and impulsivity.[5] Clinical psychopathy is commonly assessed with the Hare Psychopathy Checklist–Revised (PCL-R),[6] the most widely accepted diagnostic instrument for psychopathy in adults. The assessment of psychopathic traits in youth raises a number of important issues. In the *DSM*,[7] antisocial personality disorder (in adults) and conduct disorder (in youth) are most closely related to the construct of psychopathy; however, these diagnoses focus on more readily observable behavioral traits rather than affective and interpersonal traits conceptualized to be at the core of the disorder.[5] Thus, others have emphasized the particular importance of callous and unemotional traits in conceptualizing psychopathy in adolescents.[8,9] Hare *et al.* constructed a modified version of the PCL-R, the Psychopathy Checklist–Youth Version (PCL-YV),[10] designed for use with adolescents, identifying both interpersonal and affective traits (factor 1) and lifestyle and antisocial traits (factor 2). Although distinguishing psychopathic traits from normative adolescent development can be challenging,[11] and although it is critical to avoid the assumption that adolescents with psychopathic traits are on a predetermined path of adult psychopathy[12,13] or are untreatable,[14] the assessment of psychopathic traits in youth evidences reliability and construct validity.[11,15] Furthermore, male adolescents, like

This article is discussed in an editorial by Dr. Tonya J.H. White on page 9.

Supplemental content cited in this article is available online.

adults,[16] who score high on these traits are quicker to reoffend, including violent offenses.[17,18]

The pervasive nature of emotional and behavioral symptoms of psychopathy suggests that a number of associated brain regions may contribute to the disorder. Among adults, converging evidence from electrophysiology,[19,20] functional neuroimaging,[21,22] and lesion studies[23] implicates paralimbic cortex and limbic structures as dysfunctional in psychopathy.[24] These regions are linked based on cytoarchitectural similarities,[25] which suggests a partially shared neurodevelopmental trajectory. These regions include the temporal poles, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), orbitofrontal cortex (OFC), parahippocampal regions, amygdala, and hippocampus.[24]

The existing structural imaging literature supports the hypothesis that dysfunction in paralimbic and limbic regions is associated with psychopathy. Structural differences in the form of reduced regional gray matter volumes (GMV) are observed in adult men with psychopathic traits.[26–28] However, it is not known when these differences begin to appear and whether they are apparent in adolescence, a time when the brain is still undergoing significant development[29] and psychopathic traits may begin to be observed.[11]

To date, no research has examined brain structure in incarcerated adolescents with psychopathic traits assessed by the PCL-YV. Some previous work has looked at structural differences in (primarily) male adolescents with psychopathic traits, using diverse assessment methods. Youths (mean = 16 years) with early-onset conduct disorder (CD) had reduced temporal lobe volumes; prefrontal volumes were also reduced in these youths, but the difference did not reach statistical significance.[30] Reduced GMV in bilateral insula and left amygdala was reported in male adolescents (mean = 13 years) with CD compared to controls, but there were no significant differences in the ACC or OFC.[31] However, reduced GMV was reported in the temporal lobes bilaterally, left amygdala, left hippocampus, OFC, and ventromedial PFC, and greater GMV in the cerebellum, in male adolescents (mean = 14 years) with early onset CD compared to controls.[32] In contrast, one study of boys from the community (mean = 11 years) with callous and unemotional traits found increased GMV compared to controls in several regions, including the OFC, ACC, superior temporal gyrus, left hippocampus, insula, and PCC.[33]

These studies suggest that adolescents with early CD symptoms have aberrant paralimbic and limbic structure; however no studies have examined psychopathic traits assessed with the expert-rater–based PCL-YV and thus may not be directly comparable to adult samples. In addition, prior studies[30-33] have relied on relatively small samples (N = 20–48) drawn largely from community and outpatient populations; thus, these samples were likely associated only with low to moderate levels of psychopathic traits and had limited ability to control for potential confounds (e.g., substance abuse).

Here we begin to address these limitations by presenting results from a voxel-based morphometry analyses on the relationship between brain structure and psychopathic traits in large sample of maximum-security incarcerated male adolescents. The aberrant structure and dysfunction observed in paralimbic cortex and limbic structures in adult psychopathy predicts that higher scores on psychopathic traits will be associated with reduced GMV in the parahippocampus, amygdala, hippocampus, temporal pole, ACC, PCC, and OFC.

METHOD

Participants

The data analyzed were drawn from the National Institute of Mental Health (NIMH)–funded SouthWest Advanced Neuroimaging Cohort, Youth sample (SWANC-Y), collected between June 2007 and March 2011, from ongoing research studies at a maximum-security youth detention facility in New Mexico. This research was approved by the University of New Mexico Health Sciences Center Human Research Review Committee, and individuals volunteered to participate after providing written informed consent (if ≥18 years of age) or after providing written informed assent and parent/guardian written informed consent (if <18 years of age). Participants were excluded from participation if they had a history of seizures, psychosis, traumatic brain injury, other major medical problems, or failed to show fluency in English at or above a grade four reading level. High-resolution structural magnetic resonance imaging (MRI) scans and PCL-YV scores were available from 218 male adolescents. Our final sample included 191 individuals, after excluding 18 individuals for excessive motion or radiological findings and nine who were determined to meet the above exclusion criteria after scanning.

Participants were incarcerated for crimes that included murder, assault, rape, arson, weapons possession, burglary, fraud, drug possession/distribution, and criminal mischief (Table 1). Participants were predominantly Hispanic/Latino (56.6%), white (14.8%), or Native American (11.7%). From self-report, 89.0% of

TABLE 1 Descriptive Statistics for Analyzed Sample (n = 191)

Variable	Mean	SD	n
Age	17.3	1.18	191
IQ	92.8	12.06	178
Substance dependence	2.2	1.63	191
Regular substance use	5.5	2.70	184
Criminal Convictions[a]			
Total	7.7	7.84	153
Violent	1.6	1.96	153
Nonviolent	6.6	7.54	153
Psychopathic Traits			
Total scores	23.6	6.19	191
Factor 1 (interpersonal/affective)	6.6	3.14	191
Factor 2 (impulsive/antisocial)	11.3	2.69	191
KSADS Diagnoses, n (%)	**Current**	**Past**	**Total**
Anxiety disorders	8 (4.2)	8 (4.2)	16 (8.4)
Depressive disorders	6 (3.1)	25 (13.1)	31 (16.2)
Attention-deficit/hyperactivity disorder	5 (2.6)	17 (8.9)	22 (11.5)
Oppositional defiant disorder	11 (5.7)	46 (24.1)	57 (29.8)
Conduct disorder			180 (94.3)
Childhood onset	96 (50.3)		
Adolescent onset	84 (44.0)		

Note: From state records. KSADS = Kiddie Schedule for Affective Disorders and Schizophrenia.

participants were right-handed, 9.4% left-handed, and 1.6% ambidextrous. Participants were paid a flat rate, yoked to the standard institutional hourly pay scale, for participation in the study.

Psychopathy

The PCL-YV[10] assessment includes a review of institutional records and a semi-structured interview that reviews individuals' school, family, work, and criminal histories, and their interpersonal and emotional skills. Individuals are scored on 20 items that measure personality traits and behaviors characteristic of psychopathy. Scores range from 0 to 40. For adults, the accepted diagnostic cutoff for psychopathy is 30 and above.[34] For comparison to adult samples, in addition to total PCL-YV scores, we examined a two-factor model of psychopathic traits,[6,35] with factor 1 composed of interpersonal and affective traits and factor 2 composed of lifestyle and antisocial traits.

This sample covered a wide range of PCL-YV scores, including a sufficient number of high scorers (PCL-YV $\geq$ 30, n = 35; Figure S1, available online) indicating a high level of psychopathic traits. The mean scores are comparable to those observed in adult male incarcerated populations.[6] Interviews were conducted by trained researchers and videotaped for reliability assessment (intraclass correlation coefficient (ICC 1,1) = 0.90 for PCL-YV total scores; 12% of interviews (randomly selected) were double rated).

Control Measures

Full-scale IQ (IQ) was estimated from the Vocabulary and Matrix Reasoning sub-tests of the Wechsler Adult Intelligence Scale[36,37] for participants older than 16 years and from the Wechsler Intelligence Scale for Children–Fourth Edition[38,39] for participants younger than 16 years (Table 1). The mean IQ estimate in this sample is consistent with other studies of juvenile offenders suggesting a negative relationship between delinquency and IQ.[40]

Trained researchers administered a post–head injury symptoms questionnaire[41] to evaluate history of traumatic brain injury (TBI) and the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS).[42] From the KSADS, we counted the total number of substances (alcohol and drug) for which an individual met the lifetime dependence diagnostic criteria ("substance dependence"). A modified version of the Addiction Severity Index[43] was also administered. Following the method that we used previously in adults,[28] years of regular use were summed for each substance (alcohol and drug) that the participant reported using regularly (three or more times per week for a minimum period of 1 month). Total scores were then divided by age

(to control for opportunity to use), multiplied by 100, and a square root transformation was applied to correct for any skew (''regular substance use''; Table 1).

MRI Acquisition

High-resolution T1-weighted structural MRI scans were acquired using the Mind Research Network Mobile Siemens 1.5T Avanto MRI scanner, stationed at the detention facility. A multi-echo MPRAGE pulse sequence (repetition time = 2530 ms, echo times = 1.64 ms, 3.50 ms, 5.36 ms, 7.22 ms, inversion time = 1100 ms, flip angle = 7°, slice thickness = 1.3 mm, matrix size = 256×256) was used, yielding 128 sagittal slices with an in-plane resolution of 1.0 mm×1.0 mm. Data were pre-processed and analyzed using Statistical Parametric Mapping software (SPM5). T1 images were manually inspected by an operator blinded to subject identity and realigned to ensure proper spatial normalization. Images were spatially normalized to the SPM5 T1 Montreal Neurological Institute (MNI) template using nonlinear registration, segmented into gray matter, white matter, and cerebrospinal fluid, and modulated to preserve total volume.[44,45] These segments were then averaged to create a study-specific template. Next, the original gray matter segments were normalized to the customized template. Finally, the images were resampled to 2×2×2 mm and smoothed with a 10-mm full-width at half-maximum (FWHM) Gaussian kernel. Voxels with a gray matter value of <0.15 were excluded to remove possible edge effects between gray matter and white matter. Only gray matter segments were used in this analysis.

Analytic Strategy

As expected, total PCL-YV scores were not significantly correlated with IQ, TBI, handedness, or total brain volumes, and the typical negative correlations between PCL-YV scores and age[46] and substance use[28] were observed (Table S1, available online). Psychopathy is frequently comorbid with substance use in adults[47] and adolescents[48]; substance use has been linked with GMV differences, although the direction and duration of effects, and the role of related third variables (e.g., psychopathy), is not currently settled.[49,50] Thus, all analyses included the measure of substance dependence as a covariate. Age at scan was included as a covariate in all analyses, because of the developmental changes in brain structure over adolescence.[29] PCL-YV scores were used continuously. We also included brain volume (BV; white matter + gray matter) as an additional covariate in all analyses to account for individual variation in brain size[51] and to focus on regionally specific changes.

Whole-Brain Analysis

Multiple regression analyses were performed on a voxel-by-voxel basis over the whole brain using the general linear model to evaluate the relationship between PCL-YV and regional GMV, including BV, age at scan, and substance dependence in the model as covariates. In multiple regression analyses evaluating the relationship between the psychopathy factors and regional GMV, both factors were included in the model simultaneously, in addition to the BV, age at scan, and substance dependence covariates.

Results from an independent adult sample[28] indicated that GMV abnormalities are extensively distributed in paralimbic and limbic regions, but the effect size at each voxel is small. We used the two common methods in whole-brain analyses to assess for effects across voxels: peak height, using a false discovery rate (FDR) correction for multiple comparisons (to test for focal peak effects); and cluster size, estimating the cluster size necessary to correspond to a desired statistical threshold (to test for small, distributed effects).

Monte Carlo simulation conducted using AlphaSim[52] determined that a 1,643-voxel extent at height threshold of $p < .05$ uncorrected yielded a familywise error rate (FWE) corrected threshold of $p < .05$, accounting for spatial correlations between GMVs in neighboring voxels. Peak height-based whole-brain analyses were thresholded at a FDR of $p < .05$.

Region-of-Interest Analysis

In addition to the whole-brain analyses, we also tested our hypotheses in a priori regions of interest. Anatomical image masks based on regions of interest (ROIs; ACC, PCC, left and right parahippocampal gyrus, left and right amygdala, left and right hippocampus, left and right temporal pole, left, right, and medial OFC) identified in the adult literature were created using the Wake Forest University (WFU) Pick Atlas Toolbox in SPM5. For each region in each hemisphere, a small volume correction (SVC) was applied to the area within each mask; we report the FWE correction.

As an additional a priori analysis, we also examined the association between PCL-YV scores and brain structure at the anatomical ROI peak coordinates identified in an independent adult sample[28] (N = 254). We averaged the coordinates from these analyses (Table 1 in Ermer *et al.*[28]). Because the peaks associated with the amygdala, hippocampal, and parahippocampal anatomical masks were very close spatially, we averaged these peak coordinates to produce one set of coordinates for the right and for the left parahippocampal region. We then used these coordinates to conduct an SVC analysis, using 10-mm-diameter spheres, in our adolescent sample. All tables and figures are presented in MNI space.

RESULTS

Association of Psychopathic Traits With Brain Structure

As found in adults,[28] cluster-extent analyses (1,643-voxel threshold) across the whole brain

showed that GMV in paralimbic regions was negatively associated with PCL-YV scores. Two clusters, in PCC and OFC (extending into the parahippocampal cortex and the temporal poles), were found. In addition, a significant cluster in prefrontal cortex was positively associated with PCL-YV total scores (Figure 1). These results suggest a potentially large extent of structural abnormalities in psychopathy. In contrast, peak-height whole-brain analysis corrected for multiple comparisons (FDR, $p < .05$) revealed no regions with GMV significantly negatively or positively associated with total PCL-YV scores.

Anatomical ROI analyses with SVC identified several paralimbic regions with GMVs significantly negatively associated with PCL-YV total scores: the FWE $p < .05$ threshold was met (Table 2) within the left OFC and medial OFC. This threshold was approached in the right and left amygdala, left temporal pole, and PCC.

A priori SVC analyses on 10-mm-diameter spheres around peak coordinates from an independent adult sample[28] showed that PCL-YV scores were significantly (FWE, $p < .05$) negatively associated with GMV (Table 3[28]) in the left temporal pole, left parahippocampal cortex, and PCC, and this threshold was approached for the right temporal pole, right parahippocampal cortex, and left and right lateral OFC.

Variance in PCL-YV Scores Accounted for by Brain Structure

For each of the a priori anatomical ROIs, we identified the cluster peak negatively associated with total PCL-YV scores, controlling for BV, substance dependence, and age, and extracted the regional GMV for each subject at these peaks. To reduce multicollinearity, we scaled each regional volume by the subject's total GMV and summed values for neighboring regions (right amygdala, right hippocampus and right parahippocampal gyrus; left amygdala, left hippocampus and left parahippocampal gyrus; right, left, and medial OFC). These regions showed acceptable independence (all tolerance values > 0.42) and were entered as predictors in a multiple regression. As a group, these seven a priori regions (OFC, ACC, PCC, right parahippocampal cortex, left parahippocampal cortex, right temporal pole, and left temporal pole) accounted for 19.5% of the variance in total PCL-YV scores ($F_{7,183} = 6.32$, $p < .001$, adjusted $R^2 = 16.4\%$).

As a more stringent analysis, we extracted the regional GMV at each of the peaks (Table 3) identified in the independent adult sample,[28] and conducted multiple regression to predict PCL-YV scores from these volumes. As above, to reduce multicollinearity, we scaled each regional volume by the subject's total GMV and summed values for neighboring regions (right, left, and medial OFC). These regions showed acceptable independence (all tolerance values >0.46) and were entered as predictors in a multiple regression. As a group, these seven regions (OFC, ACC, PCC, right parahippocampal cortex, left parahippocampal cortex, right temporal pole, and left temporal pole) accounted for

FIGURE 1 Regional gray matter volumes (GMV) significantly associated with Total Psychopathy Checklist–Youth Version (PCL-YV) scores, controlling for brain volume (BV), age at scan, and substance dependence. Note: These regions are significant in the whole brain at $p < .05$, uncorrected for multiple comparisons, with an extent threshold of 1,643 voxels, yielding a corrected threshold of $p < .05$, accounting for spatial correlations between GMVs in neighboring voxels. Coordinates are in Montreal Neurological Institute (MNI) space. Color bar represents *t* values. GMV increases are in yellow/orange/red, and decreases are in green/blue. Negatively associated clusters can be found in the orbitofrontal cortex (OFC), extending into parahippocampal cortex and the temporal poles, and in the posterior cingulated cortex (PCC). There is a positively associated cluster in the prefrontal cortex.

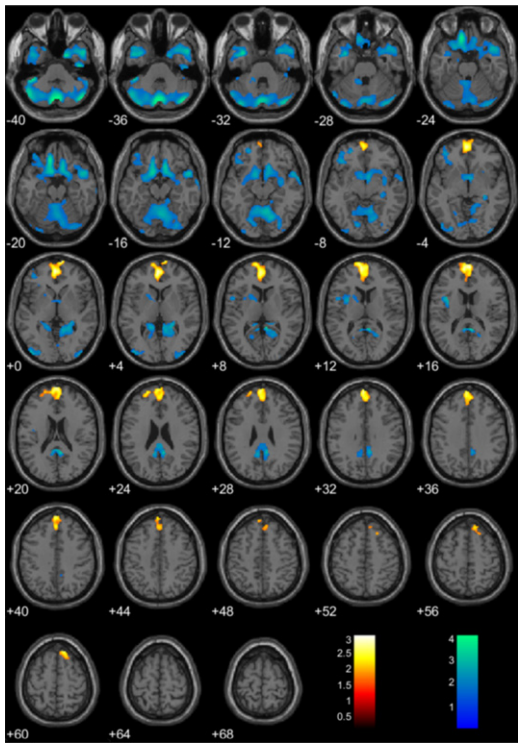


TABLE 2 Negative Associations Between Total Psychopathy Checklist–Youth Version (PCL-YV) Scores and Gray Matter Volumes (GMV) in Anatomical Regions of Interest (ROI) Using Small Volume Correction (SVC)

		Gray Matter Volumes				
		MNI Coordinates				
Paralimbic Region	H	x	y	z	t Value	FWE
Lateral OFC	L	−10	32	−24	3.81	**0.025**
	R	12	18	−18	3.11	0.175
Medial OFC	—	−10	34	−22	3.84	**0.011**
ACC	—	16	18	14	1.28	0.944
Temporal pole	L	−32	6	−34	3.28	*0.072*
	R	52	10	−16	3.08	0.140
Parahippocampal gyrus	L	24	2	−16	2.47	*0.084*
	R	−22	6	−18	2.50	*0.084*
Amygdala	L	−12	−40	8	2.46	0.256
	R	24	−38	2	2.62	0.194
Hippocampus	L	−16	2	−18	1.83	0.593
	R	30	10	−32	2.67	0.204
PCC	—	4	−46	12	3.05	*0.066*

Note: Brain volume (BV), age at scan, and substance dependence were included in the model as covariates. Montreal Neurological Institute (MNI) x, y, and z coordinates, t values, and familywise error (FWE) rate p values are for the peak voxel in each region. Significant regions (p < .05) are indicated in boldface type, and marginal regions (p < .10) are indicated in italic type. ACC = anterior cingulate cortex; H = hemisphere; L = left; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; R = right.

10.6% of the variance in total PCL-YV scores ($F_{7,183} = 3.11$, $p = .004$, adjusted $R^2 = 7.2\%$).

Association of PCL-YV Factors With Brain Structure in Paralimbic Regions

In multiple regression analyses evaluating the relationship between the PCL-YV factors and regional GMV, both factors were included in the model simultaneously, in addition to BV, substance dependence, and age covariates. Cluster extent threshold whole-brain analysis (1,643 voxels) showed that factor 1 scores were negatively associated with GMV in one cluster centered in the OFC (Figure 2A). Factor 2 scores were negatively associated with GMV in clusters in the left and right inferior parietal lobule and the PCC, and positively associated with GMV in the mOFC and ACC (Figure 2B). In contrast, peak height whole-brain analysis corrected for multiple comparisons (FDR, $p < .05$) revealed no regions with GMV significantly negatively or positively associated with factor 1 or factor 2 scores.

Robustness of Results to Model Variation

The models above used substance dependence as the measure of substance use. When regular use was the covariate, results for cluster extent analyses were substantively the same for negative associations with psychopathy scores (Figure S2; Tables S2 and S3, available online). However, there was no evidence of a positive association between GMV in the medial prefrontal cortex (mPFC) and total PCL-YV scores.

DISCUSSION

Among adults, evidence from multiple methodologies has converged on a set of brain regions, in paralimbic cortex and limbic structures, as dysfunctional in adults with psychopathic traits. The present study adds to this literature by investigating structural abnormalities using voxel-based morphometry in a large sample of incarcerated male adolescents assessed for psychopathic traits using the PCL-YV. Cluster extent analysis showed that PCL-YV total scores were associated with decreased GMV in the PCC and in the OFC, extending into the parahippocampal cortex, and the temporal poles. PCL-YV total scores were associated with increased GMV in the medial PFC. In contrast, whole brain analyses focusing on peak height and correcting for multiple comparisons using an FDR $p < .05$ threshold revealed that there were no regions with GMV significantly associated with psychopathic traits

TABLE 3 Negative Associations Between Total Psychopathy Checklist–Youth Version (PCL-YV) Scores and Gray Matter Volumes (GMV) in Regions of Interest (ROI) Using Small Volume Correction (10-mm-Diameter Spheres)

		Peak for Search (from adults)			Peak within Volume					
Region	**H**	**x**	**y**	**z**	**x**	**y**	**z**	**t Value**	***p* Value (uncorr)**	**FWE**
Lateral OFC	L	−26	32	−20	−28	28	−22	2.22	.014	*0.086*
	R	28	48	−18	24	46	−16	2.21	.014	*0.088*
Medial OFC	—	4	52	−20	6	50	−24	1.07	.132	0.374
ACC	—	−2	48	2	0	46	−2	−1.63	.612	0.631
Temporal pole	L	−38	12	−40	−42	14	−38	2.68	.004	**0.033**
	R	34	20	−38	36	16	−36	2.45	.008	*0.056*
Parahippocampal	L	−32	−2	−28	−34	2	−30	276	.003	**0.027**
	R	34	−8	−24	32	−6	−20	0.99	.150	*0.069*
PCC	—	−6	−54	32	−8	−52	28	2.60	.005	**0.040**

Note: Brain volume (BV), age at scan, and substance dependence were included in the model as covariates. Search coordinates based on an independent adult sample[28] (N = 254). Montreal Neurological Institute (MNI) x, y, and z coordinates, t values, and p values are for the peak voxel in each region. Significant regions (p < .05) are indicated in boldface type, and marginal regions (p < .10) are indicated in italic type. ACC = anterior cingulate cortex; FWE = familywise error rate; H = hemisphere; L = left; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; R = right; uncorr = uncorrected.

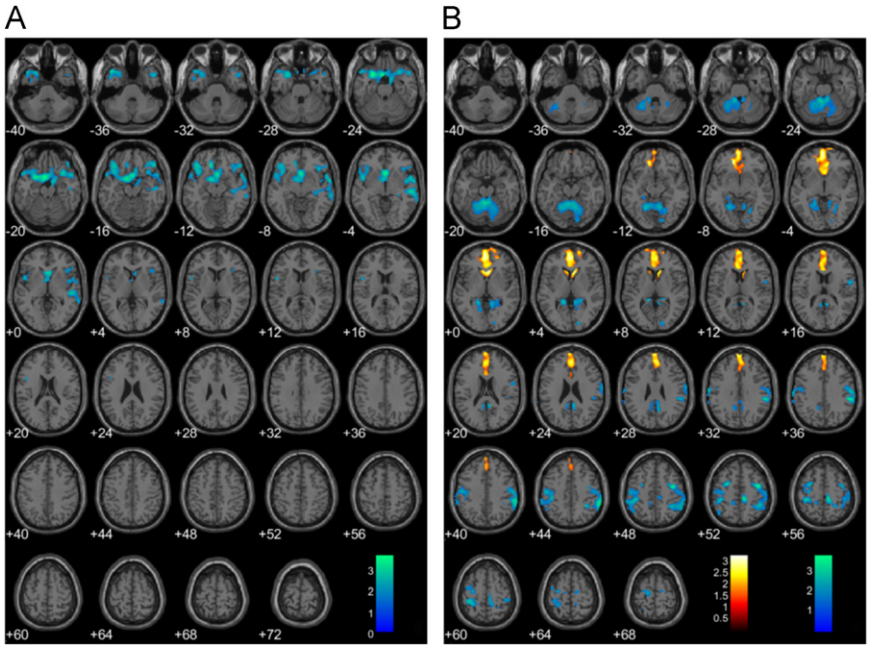
in adolescence, either negatively or positively. Given our sample size, population sampled, and methodology, this null result is unlikely to be due to lack of power. These findings suggest that structural abnormalities associated with psychopathic traits reflect distributed network(s) of subtle impairment, rather than focal lesions.

To our knowledge, this is the first structural MRI study of adolescents assessed using the PCL-YV. As such, the findings in the extant adolescent literature are not directly comparable.[53] However, recent research on structural MRI in incarcerated male adults, assessed using the PCL-R, demonstrates several commonalities. GMV decreases were found in the temporal poles, parahippocampal cortex, posterior cingulate, and lateral OFC in both adults and adolescents, when the same covariates were used.[28] In contrast to the present study in juveniles, however, no positive associations between psychopathic traits and GMVs were identified in adults. This difference may reflect the variable trajectory of brain development: male adolescents with psychopathic traits showed increased GMV in medial PFC, one of the last regions to reach developmental maturity. Notably, evidence from functional MRI suggests that medial PFC activity is abnormal in adolescents with psychopathic traits.[54] The differential associations of factor 1 and factor 2 traits on GMV in the OFC may account for this disparity between adolescents and adults. Analyses of the unique contributions of the factors (Figure 2) support the hypothesis that the positive association between GMV and PCL-YV total scores is driven by factor 2 traits. Some factor 2 traits, such as impulsivity and need for stimulation, are elevated in adolescence generally and tend to decrease over the lifespan. Plausibly, this pattern may be related to the maturation of the prefrontal cortex. The pattern of increased GMV in this region in adolescents with psychopathic traits may reflect a delayed trajectory of brain development.[55]

Unlike adults, adolescents with psychopathic traits also showed decreased GMV throughout much of the cerebellum. At present, there is limited knowledge about the precise role of the cerebellum in cognitive and emotional processes, although evidence increasingly suggests that the cerebellum may have a significant role in these areas.[56] Notably, the cerebellum has been implicated in other child-onset disorders such as ADHD[57]; however, psychopathic traits were unrelated to ADHD diagnosis in this sample ($r[191] = 0.10$, $p = .17$). In healthy adolescents, cerebellar volume was found to follow an inverted-U–shaped trajectory, peaking around age 15.5 years in males.[55] The observed decreased GMV in the cerebellum in male adolescents with psychopathic traits is consistent with a delayed developmental trajectory, although other explanations remain possible.

Despite the fact that observed brain abnormalities were relatively subtle, these differences accounted for a substantial amount of variance

FIGURE 2 Regional gray matter volumes (GMV) negatively associated with the Hare Psychopathy Checklist–Youth Version (PCL-YV) factor 1 scores (A) and negatively (blue) and positively (red) associated with PCL-YV factor 2 scores (B), controlling for brain volume (BV), age at scan, and substance dependence. Note: These regions are significant in the whole brain at $p < .05$ and 1,643-voxel extent. Numeric values indicate the Montreal Neurological Institute (MNI) z-coordinate of the slice. Color bar represents *t* values.



in psychopathic traits in our sample. Together, volumes from anatomically defined a priori paralimbic regions accounted for nearly 20% of the variance in total PCL-YV scores. Volumes from the peak coordinates in an independent adult sample[28] accounted for more than 10% of the variance in total PCL-YV scores.

Incarcerated populations in general show high comorbidities with substance problems, early life stress, and mental health problems. Thus, our results may be subject to other interpretations and it is difficult to tease out all possible moderating variables. We chose to pursue a broad sampling strategy to ensure that our sample was representative of incarcerated populations in general and individuals with psychopathic traits in particular. The negative associations between PCL-YV scores and GMV in paralimbic regions were robust to different specifications of substance use (Figure S2). Importantly, existing comorbidities may be risk factors for developing psychopathic traits and thus may reflect true group differences rather than introducing confounds. Nevertheless, future research comparing brain structure in typically developing youth and youth with other disorders would help to clarify the specificity of these results.

Voxel-based morphometry can be sensitive to methodological parameters (e.g., covariates), affected by atypical brains, and produce less precise localization compared to other methods.[44] We followed the same methodological choices in the present study as we did in our study of incarcerated adults[28] (including use of the same MRI scanner), used a study-specific template, compared brain structure across a large number of individuals, and found relatively widespread deficits across paralimbic regions. Future studies with alternative analytical techniques may identify additional abnormalities associated with psychopathic traits.

The finding that adolescents with psychopathic traits exhibit many of the same structural abnormalities as adults with psychopathy supports the hypothesis that this disorder is neurodevelopmental in nature. These results suggest that the brain abnormalities observed in adults with psychopathy are present as early as age 14 years. Furthermore, these results provide further support for the construct validity of psychopathic traits assessed in adolescence[11] and the concept of psychopathy as a developmental disorder.

The details of the developmental process(es) of psychopathic traits are questions for future research, but one possibility is that genetic and/or environmental events perturb the normal developmental process, leading to decreased GMV in some areas and increased GMV in others. These structural abnormalities may then be directly or indirectly related to the functional deficits exhibited by both adults with psychopathic traits and adolescents with psychopathic traits.

Finally, it is unknown when the neurodevelopmental trajectory to psychopathy begins. Individuals in this study were in late adolescence, but one study with younger children also demonstrated brain abnormalities[33]; it is noteworthy, however, that the investigators reported *increased* GMVs among children with callous and unemotional traits in paralimbic and limbic regions. At this point, it is unclear whether differences between these results and the present study are to be accounted for by sample age (mean = 11.6 years versus mean = 17.6 years), sample size (N = 46 versus N = 191), population source (community versus incarcerated), psychopathy assessment (other report versus expert rater), or other factors. Future studies of younger adolescents and children that use the PCL-YV (or downward extension) would allow more direct comparison with the findings from adults and older adolescents. Overall, our results strengthen the interpretation that paralimbic regions are central for understanding neural dysfunction associated with psychopathic traits and that psychopathy may best be conceptualized as a neurodevelopmental disorder. &

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Dr. Ermer is with Adelphi University. Ms. Cope, Mr. Nyalakanti, and Drs. Calhoun and Kiehl are with the Mind Research Network. Ms. Cope and Drs. Calhoun, and Kiehl are also with the University of New Mexico.

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REFERENCES

1. Moffitt TE. Adolescence-limited and life-course-persistent antisocial behavior. Psychol Rev. 1993;100:674-701.
2. Hemphill JF, Hare RD, Wong S. Psychopathy and recidivism. Legal Criminol Psychol. 1998;3:139-170.
3. Singh JP, Grann M, Fazel S. A comparative study of violence risk assessment tools. Clin Psychol Rev. 2011;31:499-513.
4. Yang M, Wong SCP, Coid J. The efficacy of violence prediction. Psychol Bull. 2010;136:740-767.
5. Cleckley H. The Mask of Sanity, 5th ed. St. Louis: MO: Mosby; 1976.
6. Hare RD. Manual for the Hare Psychopathy Checklist—Revised. 2nd ed. Toronto, ON, Canada: Multi-Health Systems; 2003.
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Health Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
8. Barry CT, Frick PJ, DeShazo TM, McCoy M, Ellis M, Loney BR. The importance of callous–unemotional traits for extending the concept of psychopathy to children. J Abnorm Psychol. 2000;109:335-340.
9. Frick PJ, Cornell AH, Barry CT, Bodin SD, Dane HE. Callous-unemotional traits and conduct problems in the prediction of conduct problem severity, aggression, and self-report of delinquency. J Abnorm Child Psychol. 2003;31:457-470.
10. Forth AE, Kosson DS, Hare RD. The Psychopathy Checklist: Youth Version. Toronto, ON, Canada: Multi-Health Systems; 2003.
11. Salekin RT, Rosenbaum J, Lee Z, Lester WS. Child and adolescent psychopathy. Youth Viol Juvenile Just. 2009;7:239-255.
12. Salekin RT. Psychopathy and therapeutic pessimism. Clin Psychol Rev. 2002;22:79-112.
13. Seagrave D, Grisso T. Adolescent development and the measurement of juvenile psychopathy. Law Hum Behav. 2002;26:219-239.
14. Caldwell M, Skeem J, Salekin R, van Rybroek G. Treatment response of adolescent offenders with psychopathy features. Crim Justice Behav. 2006;33:571-596.
15. Lynam DR, Miller DJ, Vachon D, Loeber R, Stouthamer-Loeber M. Psychopathy in adolescence predicts official reports of offending in adulthood. Youth Viol Juvenile Just. 2009;7:189-207.
16. Rice ME, Harris GT, Cormier CA. An evaluation of a maximum security therapeutic community for psychopaths and other mentally disordered offenders. Law Hum Behav. 1992;16:399-412.
17. Edens JF, Campbell JS, Weir JM. Youth psychopathy and criminal recidivism. Law Hum Behav. 2006;31:53-75.
18. Gretton HM, Hare RD, Catchpole REH. Psychopathy and offending from adolescence to adulthood. J Counsel Clin Psychol. 2004;72:636-645.
19. Kiehl KA, Hare RD, Liddle PF, McDonald JJ. Reduced P300 responses in criminal psychopaths during a visual oddball task. Biol Psychiatry. 1999;45:1498-1507.
20. Kiehl KA, Hare RD, McDonald JJ, Brink J. Semantic and affective processing in psychopaths. Psychophysiology. 1999;36:765-774.
21. Birbaumer N, Viet R, Lotze M, Erb M, Hermann C, Grodd W, Flor H. Deficient fear conditioning in psychopathy. Arch Gen Psychiatry. 2005;62:799-805.

22. Kiehl KA, Smith AM, Hare RD, *et al*. Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. Biol Psychiatry. 2001;50:677-684.
23. Malloy P, Bihrle A, Duffy J, Cimino C. The orbitomedial frontal syndrome. Arch Clin Neuropsychol. 1993;8:185-201.
24. Kiehl KA. A cognitive neuroscience perspective on psychopathy. Psychiatric Res. 2006;142:107-128.
25. Mesulam MM. From sensation to cognition. Brain. 1998; 121:1013-1052.
26. Tiihonen J, Rossi R, Laakso MP, *et al*. Brain anatomy of persistent violent offenders. Psychiatry Res Neuroimaging. 2008;163:201-212.
27. Muller JL, Ganssbauer S, Sommer M, *et al*. Gray matter changes in right superior temporal gyrus in criminal psychopaths. Psychiatry Res Neuroimaging. 2008;163:213-222.
28. Ermer E, Cope LM, Nyalakanti PK, Calhoun VD, Kiehl KA. Aberrant paralimbic gray matter in criminal psychopathy. J Abnorm Psychol. 2012;121:649-658.
29. Giedd JN. Structural magnetic resonance imaging of the adolescent brain. Ann N Y Acad Sci. 2004;1021:77-85.
30. Kruesi MJ, Casanova MF, Mannheim G, Johnson-Bilder A. Reduced temporal lobe volume in early onset conduct disorder. Psychiatry Res Neuroimaging. 2004;132:1-11.
31. Sterzer P, Stadler C, Poustka F, Kleinschmidt A. A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. Neuroimage. 2007;37:335-342.
32. Huebner T, Vloet TD, Marx I, *et al*. Morphometric brain abnormalities in boys with conduct disorder. J Am Acad Child Adolesc Psychiatry. 2008;47:540-547.
33. De Brito SA, Mechelli A, Wilke M, *et al*. Size matters. Brain. 2009; 132:843-852.
34. Hare RD. Manual for the Hare Psychopathy Checklist. Toronto, ON, Canada: Multi-Health Systems; 1991.
35. Harpur TJ, Hare RD, Hakstian AR. Two-factor conceptualization of psychopathy. Psychol Assess. 1989;1:6-17.
36. Wechsler D. Wechsler Adult Intelligence Scale. New York, NY: Psychological Corporation; 1997.
37. Ryan R, Lopez S, Werth T. Development and preliminary validation of a Satz-Mogel short form of the WAIS-III in a sample of persons with substance abuse disorders. Int J Neurosci. 1999; 98:131-140.
38. Wechsler D. Wechlser Intelligence Scale for Children. Fourth Edition San Antonio, TX: Psychological Corporation; 2003.
39. Sattler JM, Dumont R. Assessment of Children: WISC-IV and WPPSIIII Supplement. San Diego: CA: Jerome M. Sattler Publishing; 2004.
40. Lynam D, Moffitt T, Stouthamer-Loeber M. Explaining the relation between IQ and delinquency. J Abnorm Psychol. 1993;102:187-196.
41. King NS, Crawford S, Wenden FJ, Moss NEG, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire. J Neurol. 1995;242:587-592.
42. Kaufman J, Birmaher B, Brent D, *et al*. Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (K-SADS-PL). J Am Acad Child Adolesc Psychiatry. 1995;36:980-988.
43. McLellan AT, Kushner H, Metzger D, *et al*. The fifth edition of the Addiction Severity Index. J Subst Abuse Treat. 1992;9:199-213.
44. Ashburner J, Friston KJ. Voxel-based morphometry. Neuroimage. 2000;11:805-821.
45. Ashburner J, Friston KJ. Unified segmentation. Neuroimage. 2005; 26:839-851.
46. Harpur TJ, Hare RD. Assessment of psychopathy as a function of age. J Abnorm Psychol. 1994;103:604-609.
47. Smith SS, Newman JP. Alcohol and drug abuse-dependence disorders in psychopathic and nonpsychopathic criminal offenders. J Abnorm Psychol. 1990;99:430-439.
48. O'Neill ML, Lidz V, Heilbrun K. Adolescents with psychopathic characteristics in a substance abusing cohort. Law Hum Behav. 2003;27:299-313.
49. Tanabe J, Tregellas JR, Dalwani M, *et al*. Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals. Biol Psychiatry. 2009;65:160-164.
50. 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;51:134-142.
51. Pell GS, Briellmann RS, Chan CH, Pardoe H, Abbott DF, Jackson GD. Selection of the control group for VBM analysis. Neuroimage. 2008;41:1324-1335.
52. Ward DB. Simultaneous Inference for fMRI Data. Milwaukee, WI: Medical College of Wisconsin; 2000.
53. Fink B, Tant A, Tremba K, Kiehl KA. Assessment of psychopathic traits in a youth forensic sample. J Abnorm Child Psychol. 2012; 40:971-986.
54. Finger EC, Marsh AA, Mitchell DG, *et al*. Abnormal ventromedial prefrontal cortex function in children with psychopathic traits during reversal learning. Arch Gen Psychiatry. 2008;65:586-594.
55. Shannon BJ, Raichle ME, Snyder AZ, *et al*. Premotor functional connectivity predicts impulsivity in juvenile offenders. Proc Natl Acad Sci USA. 2011;108:11241-11245.
56. Tiemeier J, Lenroot RK, Greenstein DK, Tran L, Pierson R, Giedd JN. Cerebellum development during childhood and adolescence. NeuroImage.. 2010;49:63-70.
57. Siedman LJ, Valera EM, Markis N. Structural brain imaging of attention deficit/hyperactivity disorder. Biol Psychiatry. 2005; 57:1263-1272.

FIGURE S1 Distribution of Psychopathy Checklist–Youth Version (PCL-YV) total scores (n = 191).

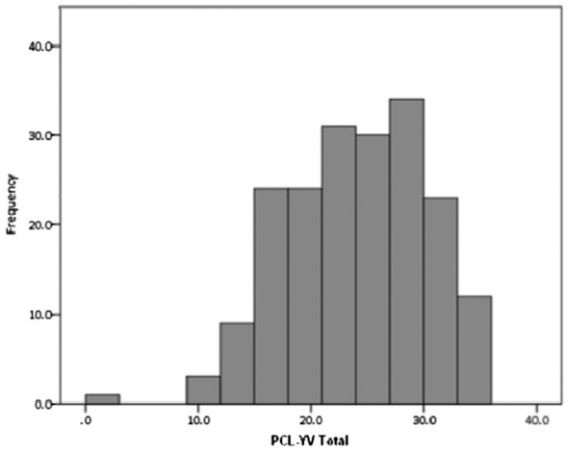

FIGURE S2 Regional gray matter volumes significantly associated with Total Psychopathy Checklist–Youth Version (PCL-YV) scores, controlling for brain volume (BV), age at scan, and regular substance use. Note: These regions are significant in the whole brain at $p < .05$, uncorrected for multiple comparisons, with an extent threshold of 1,643 voxels, yielding a corrected threshold of $p < .05$, accounting for spatial correlations between gray matter volumes (GMVs) in neighboring voxels. Coordinates are in Montreal Neurological Institute (MNI) space. Color bar represents t values.

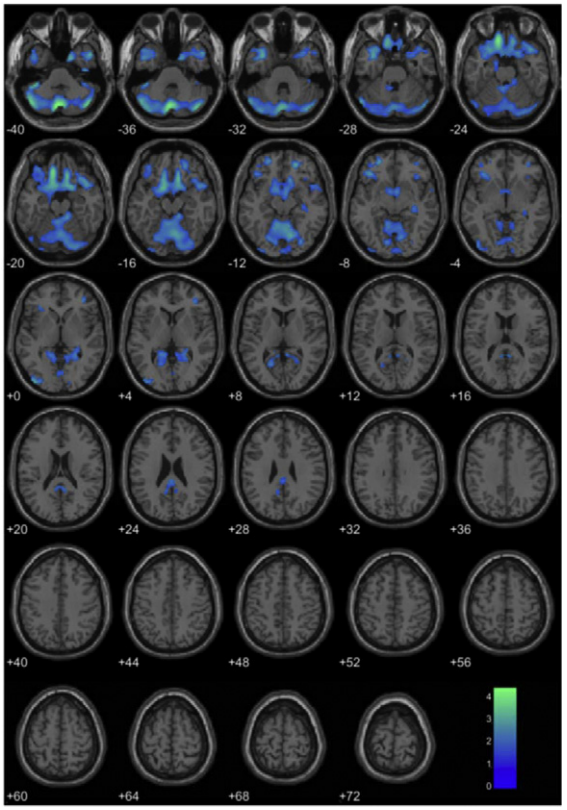

TABLE S1 Zero-Order Correlations (and Two-Tailed *p* Values) Among Psychopathy Checklist–Youth Version (PCL-YV) Total, Factor 1 Scores, Factor 2 Scores, and Control Variables

Variable	n	Total Scores	Factor 1 Scores	Factor 2 Scores
IQ	178	−0.04 (.63)	0.10 (.21)	−0.13 (.08)
TBI history	191	0.08 (.63)	0.02 (.88)	0.09 (.20)
TBI duration	188	0.10 (.16)	0.03 (.68)	0.13 (.09)
Handedness[a]	191	−0.03 (.64)	−0.05 (.49)	−0.001 (.99)
Substance dependence	191	0.24 (.001)	0.17 (.02)	0.24 (.001)
Regular use	184	0.37 (<.001)	0.25 (<.001)	0.37 (<.001)
Age at scan	191	−0.12 (.10)	−0.03 (.70)	−0.17 (.02)
Brain volume	191	−0.01 (.92)	<0.001 (.997)	−0.004 (.95)
Gray matter volume	191	−0.01 (.94)	−0.004 (.95)	−0.003 (.97)
White matter volume	191	−0.01 (.91)	0.005 (.95)	−0.005 (.94)

Note: The two substance use measures, substance dependence and regular use, were significantly positively correlated ($r = 0.48$, $p < .001$. As is typical,[1,2] factor 1 and factor 2 scores were significantly positively correlated ($r = 0.52$, $p < .001$). TBI = traumatic brain injury.
[a]Spearman's rho.

TABLE S2 Negative Associations Between Total Psychopathy Checklist–Youth Version (PCL-YV) Scores and Gray Matter Volumes (GMV) in Anatomical Regions of Interest (ROI) Using Small Volume Correction (SVC)

		Gray Matter Volumes				
		MNI Coordinates				
Paralimbic Region	H	x	y	z	t	FWE
Lateral OFC	L	−12	32	−24	4.23	**.007**
	R	12	18	−18	3.24	.134
Medial OFC	—	−10	32	−22	4.15	**.004**
ACC	—	6	26	18	2.20	.647
Temporal pole	L	−32	8	−30	3.32	*.069*
	R	42	16	−22	3.04	.156
Parahippocampal gyrus	L	−16	6	−20	2.59	.218
	R	20	8	−20	3.12	*.076*
Amygdala	L	−16	2	−16	2.57	*.070*
	R	20	6	−18	2.57	*.076*
Hippocampus	L	−16	−4	−22	1.97	.524
	R	26	−4	−22	2.33	.337
PCC	—	4	−46	12	2.36	.294

Note: Brain volume (BV), age at scan, and regular substance use were included in the model as covariates. Montreal Neurological Institute (MNI) x, y, and z coordinates, t values, and familywise error rate (FWE) p values are for the peak voxel in each region. Significant regions ($p < .05$) are indicated in boldface type, and marginal regions ($p < .10$) are indicated in italic type. ACC = anterior cingulate cortex; H = hemisphere; L = left; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; R = right.

TABLE S3 Negative Associations Between Total Psychopathy Checklist–Youth Version (PCL-YV) Scores and Gray Matter Volumes (GMV) in Regions of Interest (ROI) Using Small Volume Correction (SVC; 10-mm-diameter spheres)

		Peak for Search (from adults)			Peak within Volume					
Region	**H**	**x**	**y**	**z**	**x**	**y**	**z**	**t Value**	***p* Value (uncorr)**	**FWE**
Lateral OFC	L	−26	32	−20	−26	28	−22	2.48	.007	**0.053**
	R	28	48	−18	24	46	−16	2.60	.005	**0.042**
Medial OFC	—	4	52	−20	2	52	−24	1.53	.062	0.247
ACC	—	−2	48	2	2	46	0	−1.06	.575	0.629
Temporal pole	L	−38	12	−40	−40	8	−38	2.51	.006	**0.050**
	R	34	20	−38	36	16	−36	1.88	.030	0.156
Parahippocampal	L	−32	−2	−28	−34	2	−30	2.40	.009	*0.062*
	R	34	−8	−24	32	−10	−20	0.48	.270	0.519
PCC	—	−6	−54	32	−8	−52	28	1.95	.026	0.141

Note: Brain volume (BV), age at scan, and regular substance use were included in the model as covariates. Montreal Neurological Institute (MNI) x, y, and z coordinates, t values, and p values are for the peak voxel in each region. Significant regions ($p < .05$) are indicated in boldface type, and marginal regions ($p < .10$) are indicated in italic type. Search coordinates based on an independent adult sample[3] ($N = 254$). ACC = anterior cingulate cortex; FWE = familywise error rate; H = hemisphere; L = left; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; R = right; uncorr = uncorrected.

SUPPLEMENTAL REFERENCES

1. Hare RD. Manual for the Hare Psychopathy Checklist-Revised. 2nd ed. Toronto: Multi-Health Systems; 2003.
2. Hare RD. Manual for the Hare Psychopathy Checklist: Toronto: Multi-Health Systems; 1991.
3. Ermer E, Cope LM, Nyalakanti PK, Calhoun VD, Kiehl KA. Aberrant paralimbic gray matter in criminal psychopathy. J Abnorm Psychol. 2012;121:649-658.

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Title Page

Abnormal Brain Structure in Youth Who Commit Homicide

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Abstract

Background: Violence that leads to homicide results in an extreme financial and emotional burden on society. Juveniles who commit homicide are often tried in adult court and typically spend the majority of their lives in prison. Despite the enormous costs associated with homicidal behavior, there have been no serious neuroscientific studies examining youth who commit homicide. **Methods:** Here we use neuroimaging and voxel-based morphometry to examine brain gray matter in incarcerated male adolescents who committed homicide (n = 20) compared with incarcerated offenders who did not commit homicide (n = 135). Two additional control groups were used to understand further the nature of gray matter differences: incarcerated offenders who did not commit homicide matched on important demographic and psychometric variables (n = 20) and healthy participants from the community (n = 21). **Results:** Compared with incarcerated adolescents who did not commit homicide (n = 135), incarcerated homicide offenders had reduced gray matter volumes in the medial and lateral temporal lobes, including the hippocampus and posterior insula. Feature selection and support vector machine learning classified offenders into the homicide and non-homicide groups with 81% overall accuracy. **Conclusions:** Our results indicate that brain structural differences may help identify those at the highest risk for committing serious violent offenses.

Keywords: voxel-based morphometry (VBM); magnetic resonance imaging (MRI); incarcerated adolescents; pattern classifier; support vector machine (SVM); gray matter volume

1. Introduction

Estimates of the financial burden of homicide exceed $17 million per offense, including costs associated with policing, prosecution, incarceration, and lost productivity (1). With approximately 15,000 homicides committed each year (2), the fiscal cost of homicide in the U.S. was over $250 billion in 2011 alone. And whereas the financial burden of homicide is staggering, these figures do not capture the emotional toll that the 9.3% of U.S. adults who have been directly affected by homicide experience (3).

Adolescence is a time of significant biological, cognitive, and neural change (4), and is sometimes associated with reckless, irresponsible, delinquent, and at times, violent behavior. Most adolescents age out of this type of behavior, but a small percentage of youth continue this antisociality into adulthood and are referred to as being on the "life-course persistent" trajectory (5). Research that attempts to identify youth at the highest risk of committing serious and violent crimes as adolescents and/or adults could be particularly valuable for prevention and treatment efforts (6,7).

Callous and unemotional (CU) traits and poor behavioral control (i.e., conduct disorder) are risk factors for youth who might be on the life course persistent trajectory of antisocial behavior and lifelong personality problems (8). Recent neuroimaging research has shown that youth who demonstrate such problematic behavior have reduced gray matter in critical cognitive control and emotional brain regions. For instance, one study found that male youth with conduct disorder (CD; n = 12) displayed reduced gray matter volumes in the left amygdala and anterior insula bilaterally compared to healthy controls (n = 12), and that these reductions were specifically related to aggressive behavior (9). In another recent study, adolescent males with CD (n = 23) had reduced gray matter volumes in the left orbitofrontal cortex and bilateral temporal

lobes, as well as the left amygdala and hippocampus. Overall, the CD group had 6% less gray matter volume than healthy controls (10). In a large sample of incarcerated adolescent males (*n* = 191), Ermer and colleagues (11) found gray matter reductions related to high CU/CD traits in the orbitofrontal cortex, posterior cingulate, parahippocampal cortex, and temporal poles. Similar research in adults has identified gray matter reductions primarily in orbitofrontal cortex (12-14), temporal cortex (12-13), and limbic areas (13) related to callous and unemotional traits and impulsive behaviors (i.e., psychopathic traits).

Despite these recent advancements, no studies have sought to examine whether youth who commit homicide have any unique gray matter abnormalities relative to comparison youth. To begin to address this issue we analyzed structural magnetic resonance imaging (MRI) data to examine brain gray matter differences in incarcerated adolescent males who committed homicide (*n* = 20) versus incarcerated adolescent males who did not (*n* = 135). We also compared the homicide offenders (*n* = 20) to a subsample of matched non-homicide offenders (*n* = 20) as well as to a group of non-incarcerated healthy adolescent controls. The non-homicide offenders (*n* = 20) were matched with the homicide offenders (*n* = 20) on the following variables: IQ, age at scan, number of traumatic brain injuries with loss of consciousness, Hare Psychopathy Checklist: Youth Version Total, Factor 1, and Factor 2 scores, substance dependence, years of regular substance use, psychiatric diagnoses, and violent, non-violent, drug, and total number of convictions. We hypothesized that youth who commit homicide represent youth with more profound callous and unemotional traits and poor behavioral controls and thus we expected these youth to show gray matter abnormalities in paralimbic regions.

2. Materials and Methods

2.1 Participants

These data were drawn from the National Institute of Mental Health (NIMH)-funded SouthWest Advanced Neuroimaging Cohort, Youth Sample (SWANC-Y), collected between June, 2007, and March, 2011, from ongoing research studies at a maximum-security youth detention facility in New Mexico. The present study reports on a subsample of the participants from reference 11 (all males; n = 155) for whom official criminal records and self-report criminal activity were available (mean age = 17.5 years, SD = 1.14; 78.1% Hispanic, 14.2% white; 89.0% right-handed). Within this sample, individuals whose official state criminal records included a murder conviction (n = 4) or who self-reported killing another person without being convicted during confidential research interviews (n = 16) were classified as homicide offenders (n = 20); all others were classified as non-homicide offenders (n = 135). Non-homicide offenders included those who had committed serious violent crimes such as rape and assault, and non-violent crimes such as burglary, theft, fraud, and drug possession/distribution. In addition, we report data from n = 21 male healthy adolescent non-offender controls drawn from the community (mean age = 16.4 years, SD = 2.07; 38.6% Hispanic, 47.6% white; 90.5% right-handed).

This research was approved by the University of New Mexico Health Sciences Center Human Research Review Committee and all individuals volunteered to participate after providing written informed consent (if >= 18 years or age) or after providing written informed assent and parent/guardian written informed consent (if < 18 years of age). Participation did not affect institutional status (e.g., security level, privileges, parole or release date). Participants were excluded from participation if they had a history of seizures, epilepsy, psychosis, traumatic brain

injury, other major medical problems, or failed to show fluency in English at or above a grade four reading level.

2.2 Assessments

2.2.1 Psychopathy

All offenders were assessed for psychopathy (i.e., callous and unemotional traits and impulsive/antisocial behaviors) using the expert-rater Hare Psychopathy Checklist: Youth Version (15). The PCL:YV assessment includes a review of institutional records and a semi-structured interview that reviews individuals' school, family, work, and criminal histories, and their interpersonal and emotional skills. Individuals are scored on 20 items that measure personality traits and behaviors characteristic of psychopathy. Scores range from 0 to 40. For adults, the accepted diagnostic cutoff for psychopathy is 30 and above (16). Psychopathy includes interpersonal and affective traits, such as glibness, shallow affect, callousness, and lacking guilt and remorse (Factor 1) and lifestyle and antisocial traits, such as impulsivity, irresponsibility, and poor behavioral controls (Factor 2). The PCL:YV was not administered in the healthy sample.

2.2.2 Substance Use

We calculated the total number of substances (alcohol and drug) for which an individual met the lifetime dependence diagnostic criteria from the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) (17) ("substance dependence"). A modified version of the Addiction Severity Index (18) was also administered. Years of regular use were summed for each substance (alcohol and drug) that the participant reported using regularly (i.e., three or more times per week for a minimum period of 1 month) ("regular substance use"). Healthy control participants from the community were excluded if they self-reported any substance use.

2.2.3 Other Measures

Median household income for each participant's home zip code was used as a proxy for socioeconomic status (SES). Full-scale IQ was estimated from the Vocabulary and Matrix Reasoning subtests of the Wechsler Adult Intelligence Scale (19,20) for participants older than 16 years of age and from the Wechsler Intelligence Scale for Children-Fourth Edition (21,22) for participants younger than 16 years of age. Means and standard deviations are given in **Table 1**. IQ estimates were unavailable for $n = 7$ in the non-homicide offender group and $n = 1$ in the healthy group.

Trained researchers administered a post-head injury symptoms questionnaire (23) to evaluate history of traumatic brain injury (TBI). Number of TBIs with loss of consciousness (LOC) is reported. The Inventory of Callous-Unemotional Traits (Youth Self-Report Version; ICU, 24) and Barratt's Impulsiveness Scale (BIS-11, 25) were also administered to the incarcerated samples.

From the KSADS, offenders with a history of psychosis or bipolar disorders were excluded from further participation. Among non-homicide offenders, 3% met KSADS criteria for a past anxiety disorder and 3.7% met for a current anxiety disorder, 11.1% met for a past depressive disorder and 3.7% met for a current depressive disorder, 9.6% met for past attention deficit-hyperactivity disorder (ADHD) and 3.7% met for current ADHD, 88.1% met for past oppositional defiant (ODD) or conduct disorders (CD) and 8.9% met for current ODD/CD, and 1.5% met for past post-traumatic stress disorder (PTSD) and 5.2% met for current PTSD. Among homicide offenders, these percentages were: 10% past and 10% current anxiety disorder; 25% past and 5% current depressive disorder; 15% past and 0% current ADHD; 90% past and 10% current ODD/CD; 5% past and 20% current PTSD. Homicide offenders did not differ from non-homicide offenders on "past," "present," or "none" proportions for anxiety disorders (p = .097), depressive disorders (p = .155), ADHD (p = .611), or ODD/CD (p = 1.000). Homicide offenders did differ from non-homicide offenders on PTSD diagnoses (p = .021). No one in the healthy sample met KSADS criteria for any of these disorders.

2.3 MRI Acquisition

High-resolution T1-weighted structural MRI scans were acquired on the Mind Research Network Siemens 1.5T Avanto mobile scanner, stationed at the detention facility (for offenders) or Mind Research Network headquarters (for healthy controls), using a multi-echo MPRAGE

pulse sequence (repetition time = 2530 ms, echo times = 1.64 ms, 3.50 ms, 5.36 ms, 7.22 ms, inversion time = 1100 ms, flip angle = 7°, slice thickness = 1.3 mm, matrix size = 256 × 256) yielding 128 sagittal slices with an in-plane resolution of 1.0 mm × 1.0 mm. Data were pre-processed and analyzed using Statistical Parametric Mapping software (SPM5; Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm) and voxel-based morphometry. T1 images were manually inspected by an operator blind to subject identity and realigned to ensure proper spatial normalization. Images were spatially normalized to the SPM5 T1 Montreal Neurological Institute (MNI) template, segmented into gray matter, white matter, and cerebrospinal fluid, and modulated to preserve total volume (26,27). The modulated, normalized gray matter segments were then averaged to create a customized, study-specific template. Next, the original gray matter segments were normalized to the customized template. Finally, the images were resampled to 2 × 2 × 2 mm and smoothed with a 10 mm full-width at half-maximum (FWHM) Gaussian kernel. Voxels with a gray matter value of < .15 were excluded in order to remove possible edge effects between gray matter and white matter.

2.4 Whole Brain Analysis

Two-sample *t*-tests were performed on a voxel-by-voxel basis over the whole brain using the general linear model to evaluate differences in regional gray matter volumes between homicide (n = 20) and non-homicide (n = 135) offenders, homicide (n = 20) and matched non-homicide offenders (n = 20; supplemental information), and homicide offenders (n = 20) and healthy non-offenders (n = 21; supplemental information). Following Ermer and colleagues (11,13), we conducted Monte Carlo simulations in AlphaSim (28) to determine that a 1427 voxel extent at a height threshold of $p < .05$ uncorrected yielded a family-wise error rate (FWE)

corrected threshold of $p < .05$, accounting for spatial correlations between gray matter volumes in neighboring voxels.

The homicide ($n = 20$) versus non-homicide ($n = 135$) offender comparison was made using two separate models: the first was conducted without covariates to determine the regional specificity of reduced overall gray matter volumes in the homicide offender group; the second was conducted with brain volume (i.e., gray matter plus white matter), PCL:YV Total scores, and substance dependence as covariates. These variables differed significantly between offender groups (**Table 1**).

The homicide ($n = 20$) versus a matched non-homicide ($n = 20$) offender subsample comparison as well as the homicide offenders ($n = 20$) versus healthy non-offenders used brain volume as a covariate, as this value differed significantly between groups (**Table 1**).

2.5 Support Vector Machine Learning Classification

Each incarcerated participant was classified as either a homicide offender or a non-homicide offender using built-in support vector machine (SVM; 29-31) functions in MATLAB 7.12.0 (The MathWorks, Inc.). SVM is a sophisticated pattern classifier and is advantageous over other methodologies because it allows for non-linear effects (here we used a radial basis function [RBF] non-linear kernel).

Simple sequential backward feature selection (32) was used to select a set of variables from assessment variables and brain regions of interest (ROIs) for classifying individuals into groups (i.e., homicide offenders, $n = 20$ versus non-homicide offenders, $n = 135$). Simple sequential backward feature selection is an iterative method that begins with all variables included and proceeds by dropping one feature at each iteration until the model cannot be further improved. MRI regions of interest from an independent sample of adult males (13) were used in

the present classification analyses. These regions have been identified as being related to psychopathy, which is strongly associated with violent recidivism. ROIs from a fully independent sample were used so as to avoid biasing the classifier and artificially inflating the ability of brain regions to discriminate groups (cf. 33). These regions were chosen for this initial classification analysis to help identify which assessment variables and brain regions are important for distinguishing the youth at the highest risk for committing the most serious offenses.

Of the nine ROIs (left and right lateral orbitofrontal cortex, medial orbitofrontal cortex, anterior and posterior cingulate, left and right temporal pole, and left and right parahippocampal cortex) and nine assessment variables (IQ, age, PCL:YV Factor 1, PCL:YV Factor 2, years of regular substance use, total number of convictions, BIS-11, ICU, and SES) six ROIs and three assessment variables were identified as useful predictors. The selected variables were: left lateral orbital frontal cortex, medial orbital frontal cortex, anterior and posterior cingulate, right and left temporal pole, PCL:YV Factor 1, total number of convictions, and SES. Feature selection was also run including brain volume. The identified variables were: age, PCL:YV Factor 1, PCL:YV Factor 2, years of regular substance use, total number of convictions, ICU, SES, brain volume, left and right lateral orbital frontal cortex, medial orbital frontal cortex, anterior and posterior cingulate, right temporal pole, and right and left parahippocampal cortex. Mean replacement was employed in order to utilize the full sample. These variable sets were subsequently used for two support vector machine classification analyses.

The parameters for each classifier were selected by grid search, based on the average validation error. Then subjects were classified using two nested leave-one-out validations. In each iteration, one subject was selected as the testing sample and set aside; the remaining

subjects served as the training sample (this is the first leave-one-out). To select the best parameter for the SVM classifier, we performed a grid search over the reasonable range of the parameters. The classification rate was measured for each parameter set using another leave-one-out validation inside the training set. After selecting the best parameter, the left out testing sample was classified. This procedure of using two nested leave-one-out steps avoids use of training data in model selection or model training.

Additional SVM models were computed for validation. In these models, we used a fully unbiased approach using all ROIs and assessment variables (i.e., no feature selection) with and without brain volume, classifying homicide offenders and non-homicide offenders (n = 135).

Finally, at the request of a reviewer and to test the ability of ROIs from the present VBM group comparisons to differentiate groups using SVM learning, we extracted average gray matter values from 10 mm spheres around peak coordinates from the comparison of homicide offenders versus all non-homicide offenders. These ROIs were: superior temporal gyrus (peak at x = 52, y = -4, z = 4), superior temporal gyrus (peak at x = 58, y = -42, z = 8), middle temporal gyrus (peak at x = 62, y = -22, z = -14), parahippocampal gyrus (peak at x = -34, y = -22, z = -32), fusiform gyrus (peak at x = -60, y = -8, z = -30), and inferior temporal gyrus (peak at x = -64, y = -48, z = -16). ROI spheres were visualized in WFU PickAtlas (34) to ensure no overlap. Feature selection without brain volume identified IQ, PCL:YV Factor 1, PCL:YV Factor 2, total number of convictions, BIS-11, superior temporal gyrus (peak at x = 52, y = -4, z = 4), parahippocampal gyrus, fusiform gyrus, and inferior temporal gyrus. Feature selection with brain volume identified IQ, PCL:YV Factor 1, PCL:YV Factor 2, ICU, SES, brain volume, superior temporal gyrus (peak at x = 52, y = -4, z = 4), superior temporal gyrus (peak at x = 58, y = -42, z = 8), parahippocampal gyrus, fusiform gyrus, and inferior temporal gyrus. Two SVMs were run using

these two sets of features. An additional two SVMs were run without feature selection (with and without brain volume).

3. Results

The homicide (n = 20) and non-homicide (n = 135) offender groups did not differ in age, $t(153) = 0.28$, $p = .776$, IQ, $t(146) = 0.04$, $p = .965$, or socioeconomic status, $t(137) = 1.02$, $p = .307$; **Table 1**. The homicide offenders did, unsurprisingly, score higher on CU/CD traits than did non-homicide offenders, including both interpersonal and affective traits and lifestyle and antisocial traits (**Table 1**; Psychopathy Checklist: Youth Version (PCL:YV) Total scores: $t(153) = 4.26$, $p < .001$, $r = .32$; Factor 1: $t(153) = 5.39$, $p < .001$, $r = .40$; Factor 2: $t(153) = 2.57$, $p = .011$, $r = .20$). Homicide offenders also had higher substance dependence scores, $t(153) = 3.43$, $p = .001$, $r = .27$, higher years of regular substance use scores, $t(151) = 2.77$, $p = .006$, $r = .22$, and more past/current PTSD diagnoses ($p = .021$) than did non-homicide offenders.

Compared to non-homicide offenders, homicide offenders had lower total brain volumes, $t(153) = 2.76$, $p = .007$, $r = .22$, including both lower total gray matter, $t(153) = 2.80$, $p = .006$, $r = .22$, and white matter, $t(153) = 2.10$, $p = .038$, $r = .17$ volumes. For these measures, volumes were about 5% lower in homicide offenders than in non-homicide offenders.

The comparison between homicide offenders (n = 20) and non-homicide offenders (n = 135) showed vast differences in gray matter throughout the majority of the brain, due to significant differences in both overall brain volume and gray matter (**Insert Supplementary Figure S1 here**).

After including brain volumes, PCL:YV scores, and substance dependence in the regression model, offenders who committed homicide still had significantly reduced gray matter

volumes in large bilateral temporal lobe clusters (**Table 2; Fig. 1**). Regions of significant reduction in the homicide group were: hippocampus, posterior insula, superior temporal gyrus, middle temporal gyrus, parahippocampal gyrus, fusiform gyrus, and inferior temporal gyrus[*].

[*] To quantify variability in temporal pole volumes associated with psychopathic traits and homicide offender status, we extracted temporal pole (Brodmann area 38) volumes from each participant and computed multiple regression models with PCL:YV scores and homicide offender status predicting left and right temporal pole volumes (in two separate models). See **Table S1** in supplementary material for results (**Insert Supplementary Table S1 here**).

Compared to a matched subsample of non-homicide offenders (n = 20), offenders who committed homicide (n = 20) had significantly reduced gray matter volumes in bilateral temporal lobe clusters. Specific regions of gray matter reduction were: insula, superior temporal gyrus, and middle temporal gyrus (**Insert Supplementary Table S2, Figure S2 here**). These results are largely similar but less widespread than the comparison with the complete incarcerated sample shown in **Fig. S1**.

The homicide offender and healthy non-offender groups differed on age, $t(39) = 2.04$, $p = .049$, IQ, $t(38) = 4.12$, $p < .001$, number of TBIs with loss of consciousness, $t(39) = 3.96$, $p < .001$, substance dependence, $t(38) = 8.68$, $p < .001$, SES, $t(38) = 3.79$, $p = .001$, and past/current diagnoses of anxiety ($p = .048$) and depressive ($p = .009$) disorders, ODD/CD ($p < .001$), and PTSD ($p = .021$), but not ADHD ($p = .107$) (**Table 1**). The healthy non-offenders were not administered the PCL:YV, ICU, BIS-11, or crime inventory since they were selected on the basis of having no substance use histories, psychiatric symptoms, or contacts with the legal system. Homicide offenders had significantly reduced gray matter volume in bilateral caudate, bilateral amygdala, mid/posterior insula, bilateral hippocampus, medial orbitofrontal cortex, anterior cingulate, bilateral cerebellum, and superior prefrontal cortex relative to healthy controls (**Insert Supplementary Figure S3 here**).

Support vector machine learning, using the six *a priori* ROIs and three assessment variables identified by the feature selection, classified individuals with 81.29% accuracy (overall model), and classified 75.00% of homicide offenders (specificity) and 82.22% of non-homicide offenders (sensitivity) correctly. Including brain volume resulted in 81.29% overall accuracy, 80.00% specificity, and 81.48% sensitivity.

As a validation, two fully unbiased SVM models were calculated. All nine *a priori* ROIs and nine assessment variables (i.e., no feature selection) were used; the overall model classified individuals with 78.06% accuracy and correctly classified 70.00% of homicide offenders (specificity) and 79.26% of non-homicide offenders (sensitivity). When brain volume was included, the model achieved 65.16% overall accuracy, 85.00% specificity, and 62.22% sensitivity.

The SVM models that used ROIs from the present study's VBM group comparison of homicide offenders versus all non-homicide offenders resulted in the following accuracies: 85.16% overall, 90.00% specificity, 84.44% sensitivity (feature selection; without brain volume); 68.39% overall, 100.00% specificity, 63.70% sensitivity (feature selection; with brain volume); 76.77% overall, 80.00% specificity, 76.30% sensitivity (no feature selection; without brain volume); 72.90% overall, 85.00% specificity, 71.11% sensitivity (no feature selection; with brain volume).

4. Discussion

Using high resolution structural magnetic resonance imaging and voxel-based morphometry we identified regional gray matter volume differences in incarcerated adolescent males who committed homicide compared to incarcerated adolescent males who had not committed homicide and healthy controls. Consistent with hypotheses, those who committed homicide showed reduced gray matter volumes relative to comparison youth. In addition to global differences in brain volume and gray matter volume, regional gray matter differences were observed in the medial and lateral temporal cortex, including the hippocampus and

posterior insula, in the offenders who committed homicide compared to incarcerated non-homicide offenders.

The specific regions of gray matter reduction were largely concentrated in the temporal lobes. This is in good accord with findings of violent men with antisocial personality disorder compared to healthy controls (35). It should be noted, though, that the primary findings from the present analyses of adolescent homicide offenders were in comparison with other incarcerated offenders. Thus, the present gray matter deficits may be more specific to the extreme violence and behavioral under-control associated with homicide than with antisocial behavioral more generally.

Bilateral temporal lobe lesions in monkeys and lesions to the bilateral amygdala and inferior temporal cortex in humans can result in Kluver-Bucy syndrome, a disorder that involves emotional blunting and impulsivity (36). Gray matter reductions were also found in the bilateral posterior insula in the homicide offenders relative to comparison youth. Posterior insular cortex has been implicated in agency, interoceptive awareness, and a sense of self (37,38) and evidence has accumulated that interoceptive awareness and emotional experience are strongly linked (e.g., 39). One study of patients with schizophrenia found that cortical surface area and white matter volume of the right posterior insula was negatively related to insight (40). Although in the present study we measured gray matter volumes and not cortical surface area or white matter volumes, it is possible that the observed gray matter deficits in the homicide offenders are related to deficient emotional states involving insight, agency, appreciation of the interpersonal harm and seriousness of one's actions and, in turn, violent homicidal behavior. The posterior insula has also been suggested to represent homeostatic states associated with experiencing risk (41). Thus, it may be that homicide offenders, compared to offenders who do not commit homicide,

experience deficient risk monitoring and are thus more likely to kill. These interpretations should be tested specifically in future work.

Homicide offenders had reduced gray matter volumes in the temporal poles in the present study. Prior work with a similar sample has shown that reduced temporal pole gray matter was related to higher psychopathic traits (11). Here however, PCL:YV scores were included in the VBM group comparison of homicide offenders and non-homicide offenders, and the homicide group did not differ significantly from the *matched* non-homicide offender subsample, suggesting that psychopathic traits cannot explain the observed differences. Additionally, homicide offender status was a significant predictor of temporal pole volumes when PCL:YV scores were also included in the multiple regression model (supplemental information). A growing body of research implicates the temporal poles in social and emotional processing, including theory of mind, detecting deception, moral decision-making, and inferring the emotional states of others (reviewed in 42). For instance, engagement of the temporal poles in an fMRI study was found to be correlated with how much college students felt others' negative emotions (43). Relevant findings also include the role of the temporal poles in supporting group social behaviors (44) and the suggestion that the temporal poles couple emotion with processed sensory stimuli (42). Whether the reductions in temporal pole gray matter observed here are a cause or a consequence of committing homicide is unknown. Nevertheless, the present results support the important role of the temporal poles in appropriate social and emotional behavior, and point to the temporal poles as a target of future research.

To our knowledge this is the first study to examine gray matter volume differences in adolescent homicide offenders. Here we made the comparison with other high-risk (incarcerated) youth, including a well-matched subsample, as well as with healthy controls. The comparison

with matched incarcerated non-homicide offenders is particularly valuable, in that differences in regional gray matter volumes cannot be attributed to differences in age, IQ, SES, PCL:YV scores, callous/unemotional traits, impulsivity, traumatic brain injury, past or current mental disorder diagnoses, number of convictions (including violent, non-violent, drug, and total convictions), or substance use. And whereas we recognize that the commission of a homicide is a behavior and not a disorder, gray matter differences were still found. Thus, there must be something that is different about those adolescents who committed homicide, compared to other maximum-security offenders.

Using feature selection and support vector machine learning (SVM) with fully independent regions of interest, we were able to correctly classify 75% of homicide offenders and 82% of non-homicide offenders. This SVM model utilized non-linear information from six brain regions of interest (left lateral orbital frontal cortex, medial orbital frontal cortex, anterior and posterior cingulate, and right and left temporal pole) and three assessment variables (PCL:YV Factor 1, total number of convictions, and SES) to discriminate homicide offenders from other high-risk offenders.

Identification of the medial orbital frontal cortex as being important for classifying offenders is consistent with the finding that violent men with antisocial personality disorder showed cortical thinning in inferior medial frontal cortex (i.e., medial orbital frontal cortex) compared to healthy controls (45). Additionally, in the present analyses, large differences in medial orbital frontal cortex gray matter were found in the comparison of homicide offenders and healthy controls. This region has been linked to affect dysregulation and impulsivity, as well as impairments in social behavior and decision-making (46), consistent with the gray matter deficits seen here among homicide offenders.

In an additional SVM model, using all nine assessment variables and nine ROIs, the overall model classified individuals with over 78% accuracy. Our pattern classification findings suggest regions and variables that are especially important for identifying those youth at the highest risk for committing serious violent offenses, and provide targets for future research on prevention and treatment.

These results should be interpreted with several limitations in mind. Because these data were collected after the commission of crimes, it is unknown when these gray matter differences developed. If the observed differences were present before the youth committed homicide, one implication is that neuroscience may be able to help identify biomarkers to identify the youth that are at an even higher risk than their high-risk peers. At the present time it is likely fiscally impractical to have every at-risk youth undergo a structural MRI scan. Thus, a future goal should be to develop behavioral measures that index the observed temporal gray matter deficits. Neuroimaging work may be the key to developing such a behavioral measure, or proxy, of this subset of youth with reduced gray matter.

These findings have implications for treatment, remediation, and even prevention of serious violent behavior. Indeed, it is important to note that gray matter is malleable. For instance, one study found that 15 minutes of daily mirror reading for two weeks increased right dorsolateral occipital gray matter (47). This previous finding suggests that cognitive training could be a feasible treatment mechanism to augment gray matter. Additionally, pharmaceutical intervention in conjunction with behavior modification or traditional forms of therapy may result in the most positive treatment outcomes. Certain disorders, such as treatment-resistant depression, are most successfully treated with a combination of drug and cognitive behavior therapy (48). Whereas it would be ideal to provide intervention and treatment for all at-risk

youth, with limited resources it might be necessary to target intervention efforts at the highest-risk youth in an attempt to prevent the most serious harm (49-51).

In summary, we report the first study of gray matter volume deficits in youth who have committed homicide. This work has important implications for the development of biomarkers for youth on a high-risk trajectory of antisocial behavior and it also has important implications for developing novel interventions to help reduce the enormous fiscal and emotional toll homicidal behavior has on society.

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5. References

1. DeLisi M, Kosloski A, Sween M, Hachmeister E, Moore M, Drury A (2010): Murder by numbers: Monetary costs imposed by a sample of homicide offenders. *J Foren Psychi Psych* 21:501-513.

2. Murphy SL, Xu J, Kochanek D (2013): Deaths: Final data for 2010. *National Vital Statistics Report* 61(4):1-118.

3. Armour MP, Umbreit MS (2007): The ultimate penal sanction and "closure" for survivors of homicide victims. *Marquette Law Review* 91:381-424.

4. Sweeten G, Piquero AR, Steinberg L (2013): Age and the explanation of crime, revisited. *J Youth Adolescence* 42:921-938.

5. Moffitt TE (1993): Adolescence-limited and life-course-persistent antisocial behavior: A developmental taxonomy. *Psychol Rev* 100:674-701.

6. Hawkins JD, Herrenkohl TI, Farrington DP, Brewer D, Catalano RF, Harachi TW, Cothern L (2000): *Predictors of Youth Violence*. Washington, DC: U.S. Department of Justice.

7. Davidson RJ, Putnam KM, Larson CL (2000): Dysfunction in the neural circuitry of emotion regulation – A possible prelude to violence. *Science* 289:591-594.

8. Corrado RR, Vincent GM, Hart SD, Cohen IM (2004): Predictive validity of the Psychopathy Checklist: Youth Version for general and violent recidivism. *Behav Sci Law* 22:5-22.

9. Sterzer P, Stadler C, Poustka F, Kleinschmidt A (2007): A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. *Neuroimage* 37:335-342.

10. Huebner T, Vloet TD, Marx I, Konrad K, Fink GR, Herpertz SC, Herpertz-Dahlmann B (2008): Morphometric brain abnormalities in boys with conduct disorder. *J Am Acad Child Psy* 47:540-547.

11. Ermer E, Cope LM, Nyalakanti PK, Calhoun VD, Kiehl KA (2013): Aberrant paralimbic gray matter in incarcerated male adolescents with psychopathic traits. *J Am Acad Child Psy* 52:94-103.

12. de Oliveira-Souza R, Hare RD, Bramati IE, Garrido GJ, Azevedo Ignacio F, Tovar-Moll F, Moll J (2008): Psychopathy as a disorder of the moral brain: Fronto-temporo-limbic grey matter reductions demonstrated by voxel-based morphometry. *Neuroimage* 40:1202-1213.

13. Ermer E, Cope LM, Nyalakanti PK, Calhoun VD, Kiehl KA (2012): Aberrant paralimbic gray matter in criminal psychopathy. *J Abnorm Psychol* 121:649-658.

14. Tiihonen J, Rossi R, Laakso MP, Hodgins S, Testa C, Perez J, *et al.* (2008): Brain anatomy of persistent violent offenders: More rather than less. *Psychiat Res-Neuroim* 163:201-212.

15. Forth AE, Kosson DS, Hare RD (2003): *The Psychopathy Checklist: Youth Version*. Toronto, ON Canada: Multi-Health Systems.

16. Hare RD (2003): *Manual for the Hare Psychopathy Checklist-Revised*, 2nd Ed. Toronto, ON Canada: Multi-Health Systems.

17. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, *et al.* (1997): Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Psy* 36:980-988.

18. McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, *et al.* (1992): The fifth edition of the Addiction Severity Index. *J Subst Abuse Treat* 9:199-213.

19. Wechsler D (1997): *WAIS-III: Wechsler Adult Intelligence Scale*. San Antonio, TX: Psychological Corporation.

20. Ryan JJ, Lopez SJ, Werth TR (1999): Development and preliminary validation of a Satz-Mogel short form of the WAIS-III in a sample of persons with substance abuse disorders. *Int J Neurosci* 98:131-140.

21. Wechsler D (2003): *Wechsler Intelligence Scale for Children – Fourth Edition: Technical and Interpretive Manual*. San Antonio, TX: Psychological Corporation.

22. Sattler JM, Dumont R (2004): *Assessment of Children: WISC-IV and WPPSI-III Supplement*. San Diego: Jerome M. Sattler, Publisher.

23. King NS, Crawford S, Wenden FJ, Moss NE, Wade DT (1995): The Rivermead Post Concussion Symptoms Questionnaire. *J Neurol* 242:587-592.

24. Essau CA, Sasagawa S, Frick PJ (2006): Callous-unemotional traits in a community sample of adolescents. *Assessment* 13:454-469.

25. Patton JH, Stanford MS, Barratt ES (1995): Factor structure of the Barratt Impulsiveness Scale. *J Clin Psychol* 51:768-774.

26. Ashburner J, Friston KJ (2000): Voxel-based morphometry – The methods. *Neuroimage* 11:805-821.

27. Ashburner J, Friston KJ (2005): Unified segmentation. *Neuroimage* 26:839-851.

28. Ward DB (2000): *Simultaneous Inference for fMRI Data*. Milwaukee, WI: Author.

29. Burges CJC (1998): A tutorial on support vector machines for pattern recognition. *Data Min Knowl Disc* 2:121-167.

30. Cortes C, Vapnik V (1995): Support-vector networks. *Mach Learn* 20:273-297.

31. Melgani F, Bruzzone L (2004): Classification of hyperspectral remote sensing images with support vector machines. *IEEE T Geosci Remote* 42:1778-1790.

32. Jain AK, Duin RPW, Mao JC (2000): Statistical pattern recognition: A review. *IEEE T Pattern Anal* 22:4-37.

33. Vul E, Harris C, Winkielman P, Pashler H (2009): Puzzlingly high correlations in fMRI studies of emotion, personality, and social cognition. *Perspect Psychol Sci* 4:274-290.

34. Maldjian JA, Laurienti PJ, Burdette JB, Kraft RA (2003): An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 19:1233-1239.

35. Barkataki I, Kumari V, Das M, Taylor P, Sharma T (2006): Volumetric structural brain abnormalities in men with schizophrenia or antisocial personality disorder. *Behav Brain Res* 169:239-247.

36. Kluver H, Bucy PC (1937): "Psychic blindness" and other symptoms following bilateral temporal lobectomy in Rhesus monkeys. *Am J Physiol* 119:352-353.

37. Craig AD (2002): How do you feel? Interoception: The sense of the physiological condition of the body. *Nat Rev Neurosci* 3:655-666.

38. Farrer C, Franck N, Georgieff N, Frith CD, Decety J, Jeannerod M (2003): Modulating the experience of agency: A positron emission tomography study. *Neuroimage* 18:324-333.

39. Damasio AR (1996): The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philos Trans R Soc Lond B Biol Sci* 351:1413-1420.

40. Palaniyappan L, Mallikarjun P, Joseph V, Liddle PF (2011): Appreciating symptoms and deficits in schizophrenia: Right posterior insula and poor insight. *Prog Neuro-Psychoph* 35:523-527.

41. Xue G, Lu Z, Levin IP, Bechara A (2010): The impact of prior risk experiences on subsequent risky decision-making: The role of the insula. *Neuroimage* 50:709-716.

42. Olson IR, Plotzker A, Ezzyat Y (2007): The enigmatic temporal pole: A review of findings on social and emotional processing. *Brain* 130:1718-1731.

43. Moriguchi Y, Ohnishi T, Lane RD, Maeda M, Mori T, Nemoto K, Matsuda H, Komaki G (2006): Impaired self-awareness and theory of mind: An fMRI study of mentalizing in alexithymia. *Neuroimage* 32:1472-1482.

44. Myers RE (1969): Discussion of the preceding paper. *Ann NY Acad of Sci* 167:289-292.

45. Narayan VM, Narr KL, Kumari V, Woods RP, Thompson PM, Toga AW, Sharma T (2007): Regional cortical thinning in subjects with violent antisocial personality disorder or schizophrenia. *Am J Psychiatry* 164:1418-1427.

46. Damasio AR, Tranel D, Damasio H (1990): Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. *Behav Brain Res* 41:81-94.

47. Ilg R, Wohlschlager AM, Gaser C, Liebau Y, Dauner R, Woller A, *et al.* (2008): Gray matter increase induced by practice correlates with task-specific activation: A combined functional and morphometric magnetic resonance imaging study. *J Neurosci* 28:4210-4215.

48. Brent D, Emslie G, Clarke G, Wagner KD, Asarnow JR, Keller M, *et al.* (2008): Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents

with SSRI-resistant depression: the TORDIA randomized controlled trial. *JAMA-J Am Med Assoc* 299:901-913.

49. Caldwell M, Skeem J, Salekin R, Van Rybroek G (2006): Treatment response of adolescent offenders with psychopathic features: A 2-year follow-up. *Crim Justice Behav* 33:571-596.

50. Caldwell MF, Van Rybroek GJ (2005): Reducing violence in serious juvenile offenders using intensive treatment. *Int J Law Psychiat* 28:622-636.

51. Caldwell MF, McCormick D, Wolfe J, Umstead D (2012): Treatment-related changes in psychopathy features and behavior in adolescent offenders. *Crim Justice Behav* 39:144-155.

Figure Legends

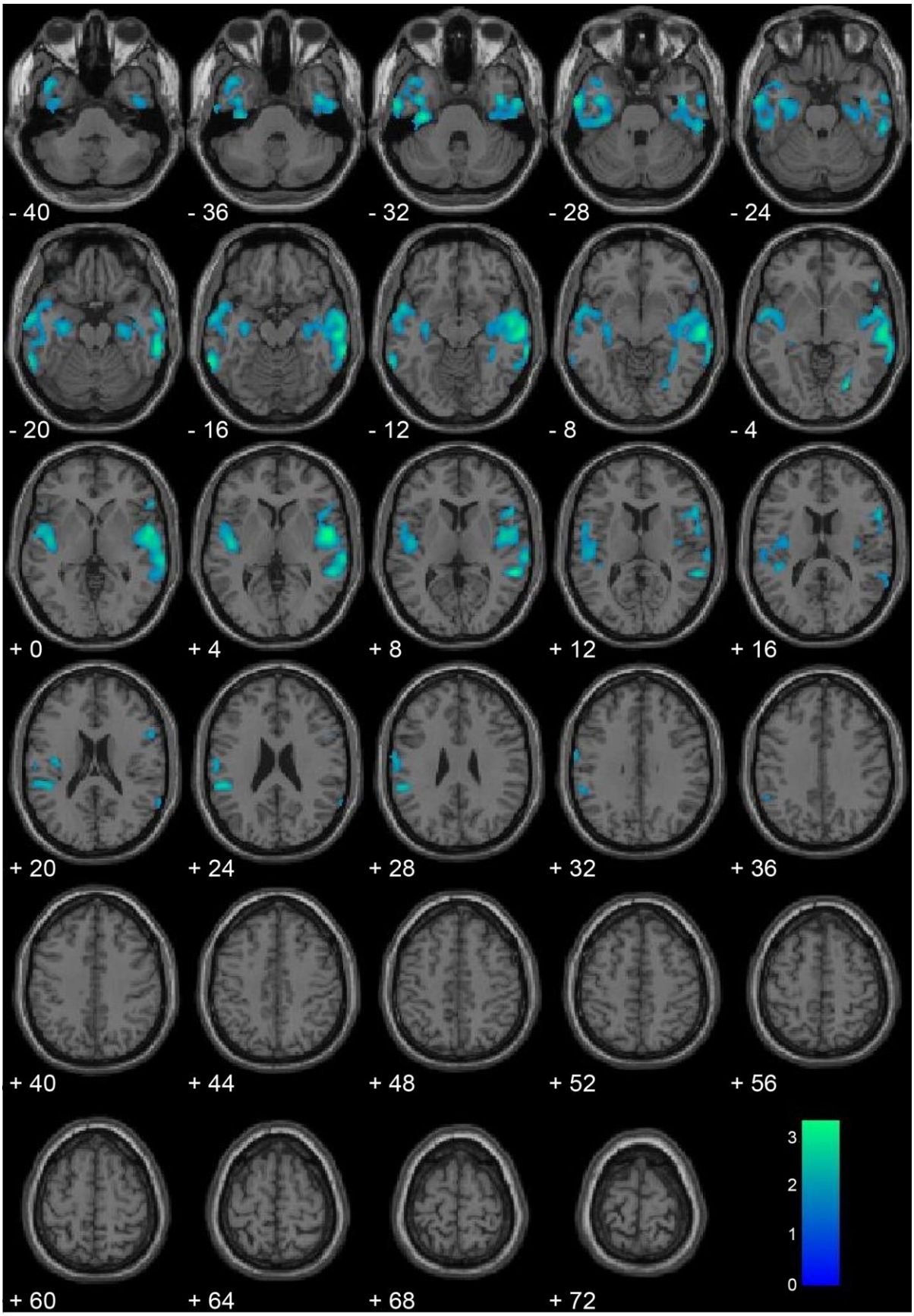
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Figure 1: Homicide Offenders (*n* = 20) versus Non-Homicide Offenders (*n* = 135) with Covariates

Regional gray matter volume decreases in homicide offenders (*n* = 20) compared with non-homicide offenders (*n* = 135), including brain volume, Psychopathy Checklist: Youth Version scores, and substance dependence as covariates. All voxels indicated in blue color map represent regions that are significant after correcting for searching the entire brain using a cluster-corrected threshold of $p < .05$ (i.e., 1427 contiguous voxels at peak height of $p < .05$). Coordinates are in Montreal Neurological Institute (MNI) space. The color bar represents *t*-values. These results suggest that after controlling for important moderating variables, youth homicide offenders show the greatest gray matter deficits in bilateral paralimbic regions including the medial and lateral temporal lobes and posterior insula.

Table 1

Demographic and Assessment Variables

Variable	Subject Group				
	Homicide Offender (A)	Non-Homicide Offender (B)	Non-Homicide Offender (Matched) (C)	Healthy (D)	Significant Group Differences [a]
n	**20**	**135**	**20**	**21**	–
SES	$30,648.75 (6,742.96)	$32,354.08 (6,904.08)	$33,488.26 (6,998.76)	$46,764.75 (17,793.87)	D > A $t(38) = 3.79$ $p = .001$
Age at Scan, in years	17.4 (1.21) range 14.9-19.0	17.5 (1.13) range 13.8-19.2	17.5 (1.32) range 14.9-19.2	16.4 (2.07) range 12.8-19.0	A > D $t(39) = 2.04$ $p = .049$
IQ	93.0 (9.25)	92.8 (12.57)	95.6 (13.84)	110.6 (16.73)	D > A $t(38) = 4.12$ $p < .001$
PCL:YV Total	29.1 (5.24)	23.1 (6.05)	28.8 (2.49)	–	A > B $t(153) = 4.26$ $p < .001$
Factor 1	9.8 (2.69)	6.2 (2.80)	8.6 (1.95)	–	A > B $t(153) = 5.39$ $p < .001$
Factor 2	12.9 (2.01)	11.3 (2.78)	13.4 (0.99)	–	A > B $t(153) = 2.57$ $p = .011$
Substance Dependence	3.4 (1.72)	2.1 (1.50)	3.8 (1.54)	0 (0.0)	A > B $t(153) = 3.43$ $p = .001$ A > D $t(38) = 8.68$ $p < .001$
Regular Substance Use	9.4 (6.99)	6.1 (4.61)	8.7 (5.06)	0 (0.0)	A > B $t(151) = 2.77$ $p = .006$ A > D $t(39) = 6.15$ $p < .001$
Brain Volume	1209.79 (59.41)	1271.96 (98.14)	1279.53 (95.50)	1306.23 (88.61)	B > A $t(153) = 2.76$ $p = .007$ C > A $t(38) = 2.77$ $p = .009$ D > A $t(39) = 4.07$ $p < .001$
Gray Matter	728.59 (39.85)	767.36 (60.00)	763.62 (58.63)	808.66 (46.28)	B > A $t(153) = 2.80$ $p = .006$ C > A $t(38) = 2.21$ $p = .033$ D > A $t(39) = 5.92$ $p < .001$

White Matter	481.20 (29.86)	504.60 (48.49)	515.90 (48.97)	497.57 (52.62)	B > A $t(153) = 2.10$ $p = .038$ C > A $t(38) = 2.71$ $p = .010$
ICU	30.0 (8.12)	27.4 (9.97)	32.0 (9.63)	–	n.s.
BIS-11	72.6 (10.77)	70.0 (10.30)	73.8 (11.35)	–	n.s.
TBIs with LOC	1.1 (0.97)	0.7 (0.99)	1.1 (1.33)	0.2 (0.40)	A > D $t(39) = 3.96$ $p < .001$
Criminal Convictions					
Total	6.2 (4.86)	8.1 (8.23)	7.6 (6.20)	–	n.s.
Violent	2.0 (3.43)	1.4 (1.62)	1.6 (1.54)	–	n.s.
Non-violent	4.6 (3.88)	7.0 (7.95)	6.3 (5.83)	–	n.s.
Drug	0.3 (0.57)	0.3 (0.72)	0.2 (0.37)	–	n.s.
KSADS Diagnoses[b]					
PTSD: Past/Current/None	1/4/15	2/7/126	1/0/19	0/0/21	A vs. B $p = .021$ A vs. D $p = .021$
Anxiety Disorders: Past/Current/None	2/2/16	4/5/126	0/0/20	0/0/21	A vs. D $p = .048$
Depressive Disorders: Past/Current/None	5/1/14	15/5/115	4/1/15	0/0/21	A vs. D $p = .009$
ADHD: Past/Current/None	3/0/17	13/5/117	2/1/17	0/0/21	n.s.
ODD/CD: Past/Current/None	18/2/0	119/12/4	20/0/0	0/0/21	A vs. D $p < .001$

Note. Numbers are means or counts with standard deviations in parentheses and ranges where appropriate. SES = socioeconomic status; PCL:YV = Psychopathy Checklist: Youth Version (15); ICU = Inventory of Callous-Unemotional Traits (24); BIS-11 = Barratt's Impulsiveness Scale (25); TBI = traumatic brain injury; LOC = loss of consciousness; KSADS = Kiddie Schedule for Affective Disorders and Schizophrenia (17); PTSD = post-traumatic stress disorder. ADHD = attention-deficit/hyperactivity disorder. ODD/CD = oppositional defiant disorder/conduct disorder. n.s. = nonsignificant. [a]Independent-samples two-sided *t*-tests were conducted for A vs. B, A vs. C, and A vs. D unless otherwise noted. [b]Group comparisons for

KSADS diagnoses used two-sided Fisher's exact tests. Comparisons that are not reported were nonsignificant.

Table 2

Homicide Offenders (*n* = 20) versus Non-Homicide Offenders (*n* = 135) with Covariates

	BA	Hemi	k	x	y	z	*t*-value	*p*-value (unc.)
Superior Temporal Gyrus	22	R	5597	52	-4	4	3.38	< .001
Superior Temporal Gyrus	22	R		58	-42	8	3.34	.001
Middle Temporal Gyrus	21	R		62	-22	-14	3.32	.001
Parahippocampal Gyrus	36	L	4624	-34	-22	-32	3.22	.001
Fusiform Gyrus	20	L		-60	-8	-30	3.13	.001
Inferior Temporal Gyrus	37	L		-64	-48	-16	3.11	.001

Note. BA = Brodmann area; Hemi = hemisphere; k = number of voxels in cluster. Coordinates are in Montreal Neurological Institute (MNI) space. All regions are areas of reduced gray matter volume in the homicide offenders, significant at a cluster-corrected threshold of $p < .05$ (i.e., 1427 contiguous voxels at peak height of $p < .05$). Brain volume, Psychopathy Checklist: Youth Version scores, and substance dependence were included in the model.

Highlights for "**Abnormal Brain Structure in Youth Who Commit Homicide**":
Cope et al.

- Homicide offenders showed reduced gray matter volumes in medial and lateral temporal lobes.
- Specific areas of reduction included the hippocampus and posterior insula.
- Support vector machine learning classified offenders with 81% overall accuracy.