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# Paralimbic structural abnormalities in psychopathy : a voxel-based morphometry study

Lora Cope

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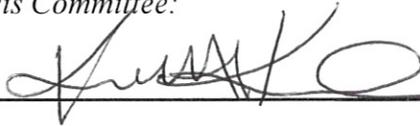
Psychology

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**PARALIMBIC STRUCTURAL ABNORMALITIES IN  
PSYCHOPATHY: A VOXEL-BASED  
MORPHOMETRY STUDY**

**BY**

**LORA M. COPE**

**BACHELOR OF SCIENCE**

**THESIS**

Submitted in Partial Fulfillment of the  
Requirements for the Degree of

**Master of Science  
Psychology**

The University of New Mexico  
Albuquerque, New Mexico

**August, 2009**

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**ABSTRACT**

Previous functional neuroimaging studies of psychopathy have demonstrated abnormal functioning in several brain regions associated with emotion and decision-making, including amygdala, orbital frontal cortex, insula, cingulate, anterior superior temporal gyrus, and parahippocampal gyrus. However, investigations of structural differences in these regions are sparse. The relation between structural abnormalities and psychopathy was investigated using Voxel-Based Morphometry (VBM) and the Psychopathy Checklist-Revised (PCL-R). Factor analysis of the PCL-R has revealed a two factor model that was utilized here. Seventy-seven participants from a community sample of substance users were scanned using high-resolution structural magnetic resonance imaging and assessed for psychopathy using the PCL-R. VBM was used to investigate morphometric differences correlated with PCL-R total score, factor one (interpersonal/affective), and factor two (behavioral/antisocial). Results showed a negative correlation between gray matter concentration and total PCL-R score in middle and superior temporal areas, inferior parietal cortex, middle occipital gyrus, caudate, and posterior cingulate. A similar result was found for factor two. There was a negative correlation between gray matter concentration and factor one score in several regions, including bilateral insula, bilateral middle temporal gyri, bilateral superior temporal gyri, right temporal pole, bilateral amygdala/parahippocampal gyri, right orbital frontal cortex, bilateral anterior and posterior cingulate, and thalamus. These results are consistent with functional studies showing abnormal functioning in paralimbic regions.

## TABLE OF CONTENTS

<b>Introduction.....</b>	<b>1</b>
History and Assessment.....	2
Factor Analysis.....	4
Paralimbic Hypothesis.....	4
Clinical Examples.....	5
Neuroimaging Studies of Affective Processing.....	7
Voxel-Based Morphometry.....	8
Structural Studies.....	10
<b>Methods.....</b>	<b>16</b>
Participants.....	16
Psychopathy Assessment.....	16
Substance Use Assessment.....	17
Clinical Assessment.....	17
MRI Acquisition and Image Analysis.....	17
Choice of Covariates.....	18
<b>Results.....</b>	<b>20</b>
Total, Factor One, and Factor Two.....	20
Facets One and Two.....	20
Facets Three and Four.....	21
Substance and Alcohol Use.....	21
<b>Discussion.....</b>	<b>23</b>
Testing the Two Factor-Four Facet Model.....	25

Substance and Alcohol Use .....	25
Future Directions .....	27
<b>References.....</b>	<b>45</b>

## Introduction

Stephen Stanko was an intelligent, seemingly polite, 39-year-old – described in his high school yearbook as the “all-American boy.” In the fall of 2004, he met divorced librarian and single mother Laura Ling in a small South Carolina town. Moved by his kindness, intelligence, and quiet confidence, Laura allowed Stanko to move in with her and her teenage daughter after just two months. Life seemed to be quite normal for the new couple, and everyone got along just fine. Things changed, however, when during the early morning hours of April 8, 2005, Stanko viciously murdered Laura and raped and attempted to murder her daughter. Stanko then stole Laura’s car and used an ATM to empty her bank account. He drove to a nearby town where Henry Turner, his friend and business associate, lived. Stanko found Turner at his home and told him that Stanko’s father had died. After talking the rest of the night and having breakfast the next morning, Stanko shot Turner in the back and then in the chest. Stanko then ditched Laura’s car, jumped into Turner’s, drove to Columbia, and went to happy hour.

During the trial, experts presented positron emission tomography (PET) scans of Stanko’s brain allegedly showing abnormalities in the medial orbital frontal lobes. One expert witness explained that “People with damage to that area of the brain become anti-social. They’re more likely to be impulsive. They’re more likely to be aggressive and violent.” In short, the witness said, “My diagnosis is Mr. Stanko is a psychopath” (Schorn, 2007).

The story of Stephen Stanko, though perhaps less well-known than those of infamous killers such as Ted Bundy, Kenneth Bianchi, and John Wayne Gacy, nevertheless illustrates the type of characteristics common to approximately 25% of

incarcerated criminals – in short, Stanko was a manipulative, impulsive, lying psychopath. Psychopathy is a complex personality disorder that is characterized by traits such as superficial charm, pathological lying, impulsivity, need for stimulation, and lack of guilt or remorse. Psychopaths are also parasitic, callous, and versatile criminals. In general, psychopathy affects approximately 1% of the general population (Hare, 2003), the same as schizophrenia and obsessive-compulsive disorder (Nesse, 2005). Compared to non-psychopaths, psychopaths are responsible for a disproportionate amount of both violent and repetitive crime (Hare, 1998). The average incarcerated psychopath has been convicted of five serious crimes by the time he turns forty (Hemphill, Hare, and Wong, 1998) and costs society tens of millions of dollars in insurance, policing, prosecution, and incarceration. Despite this significant negative impact on society, very little is known about the etiology or neurobiological correlates of this serious disorder.

### *History and Assessment*

The body of knowledge about psychopathy is far from complete, but nonetheless it has progressed a great deal since the early nineteenth century. At that time French psychiatrist Philippe Pinel used the phrase, “*manie sans delire*” (“insanity without delirium”; Kinner, 2003) to describe individuals who exhibited antisocial behavior without any signs of hallucinations or delusions. The term that is used today, “psychopath,” was first coined in the late nineteenth century, when German psychiatrist Emil Kraepelin used it in his influential psychiatry textbook (Kinner, 2003).

Great strides were made during the middle of the twentieth century, contributed mainly by American psychiatrist Hervey Cleckley. Cleckley collected years of clinical experience in psychiatric hospitals, and published *The Mask of Sanity* in 1941 based on

his countless interviews with the adult male “psychopaths” who were institutionalized there. In the 1982 revised edition, Cleckley detailed the stories of thirteen of these individuals, and concluded with a clinical profile as well as a section on “some questions still without adequate answers,” including issues of legal competency and criminal responsibility. The sixteen characteristics outlined in Table 1 emerged from his studies of these individuals who are able to “know the words but not the music.” Despite there being over 60 years since the first edition was published, Cleckley’s books remain as some of the most influential and definitive writings on the topic, and have served as the basis for Hare’s scales, to be discussed shortly.

During the next half century, psychopathy was associated with terms such as “sociopathic personality” and “antisocial personality” (ASPD) in various editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM; American Psychiatric Association, 1952; 1968; 1994), but these conceptualizations are not synonymous with psychopathy. The diagnostic criteria for ASPD were originally intended to assess psychopathy, but have been criticized for relying too heavily on antisocial behaviors that are easier to identify than interpersonal and affective traits. Additionally, ASPD seems not to be a good predictor in forensic samples, as 80-90% of inmates in a maximum-security prison will meet criteria for ASPD. In contrast, just 15-25% of inmates will meet criteria for psychopathy. Moreover, Tranel (1994) and others (Anderson et al., 1999) have used the term “acquired sociopathy” to describe individuals who exhibit psychopathic-like behaviors after sustaining damage to prefrontal areas. An inconsistency of terms has hampered research in this area.

The current gold standard in psychopathy assessment has become Robert Hare's Psychopathy Checklist-Revised (PCL-R; Hare 1991; 2003), first introduced in 1991 as the Psychopathy Checklist. Hare expanded and operationalized Cleckley's criteria into a 20-item model that measures both the affective and behavioral characteristics of psychopathy. The 20-item scale is scored based on institutional, psychiatric, and/or medical files, as well as an in-depth semi-structured interview, in which school, family, relationship, employment, substance use, and criminal histories are acquired. The individual is then given a score of 0-2 on each item, where 0 = doesn't apply, 1 = applies somewhat, and 2 = definitely applies. The maximum score is 40, and the standard range needed in order to be considered a psychopath is at least one standard deviation above the mean, which is 30 and above (Hare, 1991).

#### *Factor Analysis*

The PCL-R has been subjected to multiple factor analysis studies (Harpur et al., 1988, 1989; Cooke and Michie, 1997; Hare, 2003), from which there has emerged multiple models. The current study focuses on the most recent model (Hare, 2003), which yielded two factors and four facets. This model is outlined in Table 2.

#### *Paralimbic Hypothesis*

The psychopathy literature is a diverse collection of studies from multiple areas, including behavioral studies of patients with focal brain damage, cognitive and affective studies of psychopaths, and recent neuroimaging studies. Psychopathy is a relatively new area of research, however, and the etiology remains unknown. Some studies have suggested ventromedial/orbital frontal dysfunction (Blair, 2007), whereas others have

suggested amygdala dysfunction (Blair, 2007; Kiehl et al., 2001; Birbaumer et al., 2005; Veit et al., 2002). Others still have found hippocampal and callosal abnormalities (Laakso et al., 2001; Raine et al., 2003; Raine et al., 2004). One common feature among most of these studies is that the specific regions reside within the paralimbic system – the network of structures that neuroanatomists and cytoarchitectologists have identified as: anterior superior temporal gyrus (temporal pole), anterior cingulate, orbital frontal cortex (OFC), insula, parahippocampal region, and amygdala (Brodmann, 1909; Mesulam, 2000). These regions are important for linking evolutionarily newer cortical regions responsible for cognition with older structures responsible for emotion (Mesulam, 2000). Noting this commonality, Kiehl (2006) has suggested that psychopathy may be characterized by abnormalities across major components of the paralimbic system. Additional work will be required to determine whether this explanation is the most accurate and parsimonious.

### *Clinical Examples*

There is utility in studying patients with focal brain lesions who display psychopathic-like traits. One might reason that areas in which these lesions occur are related in some (likely complex) way to the manifestation of psychopathy. Perhaps the most famous example of focal brain damage that led to psychopathic-like behavior is Phineas Gage, the railroad worker who sustained a penetrating injury to the ventromedial prefrontal cortex, including parts of the rostral anterior cingulate and anterior medial and lateral temporal lobe. Because of the injury, Gage was transformed from a responsible and hard-working individual to an impulsive, irresponsible, and sexually promiscuous vagrant (Damasio et al., 1994). These behavioral characteristics are consistent with those associated with psychopathy.

In another example, Anderson et al. (1999) studied two frontal lobe-damaged patients. The first patient, who was 20 years old at the time of examination, had been hit by a car at 15 months of age and sustained damage to her bilateral polar and ventromedial prefrontal cortices. She appeared to recover within a few days, but behavioral problems began to appear when she was about 3 years old. She became unresponsive to medication and verbal or physical punishment, and was placed in a treatment facility at age 14. Additionally, she was arrested multiple times, lied chronically, had few friends, and did poorly in school, despite being described as intelligent and academically capable by her teachers. This patient became pregnant at age 18 but was completely insensitive to her baby's needs. She lacked remorse and guilt and blamed her problems on others.

The second patient, who was 23 at the time of examination, underwent a resection of a right frontal tumor at 3 months of age and sustained right medial and dorsal prefrontal damage as a result of the surgery. Like the first patient, the second patient appeared to have a normal recovery, and demonstrated only mild behavioral problems in school. At age 9, however, he began to display a general lack of motivation, neutral affect, limited social interaction, and anger outbursts. After graduation from high school, he became obese, with terrible eating habits and filthy living quarters. He could not hold a job, engaged in petty thievery and physical assault, and lied constantly and accrued large debts. He, too, had no remorse or empathy.

Interestingly, both patients grew up in middle-class, otherwise normal families, and had normal IQs. However, both patients' moral reasoning was said to be equivalent to that of a child. Researchers attributed the patients' marked behavioral problems to frontal lobe damage sustained when they were children. These individuals demonstrate

many of the same behavioral characteristics as psychopaths, but their conditions are not identical. The term “acquired sociopathy” has been used to describe such cases, and further research should investigate the relationship between seemingly acquired and developmental etiologies.

### *Neuroimaging Studies of Affective Processing*

Abnormalities in affective processing in psychopaths is well-documented. For example, Kiehl et al. (2001) showed that compared to criminal non-psychopaths and non-criminal controls, criminal psychopaths demonstrate less affect-related activity in the amygdala, parahippocampal gyrus, ventral striatum, and anterior and posterior cingulate during an affective verbal memory task. Additionally, they found that criminal psychopaths show increased activity in bilateral fronto-temporal cortex when processing affective stimuli. The authors interpreted these results as evidence for abnormal limbic structure input in psychopaths.

Birbaumer et al. (2005) investigated the hypothesis that psychopaths are deficient in fear conditioning, a process that has been shown to utilize amygdala, anterior cingulate, insula, and sometimes prefrontal and cerebellar circuits (Buchel and Dolan, 2000; Buchel et al., 1998; Knight et al., 2004; Fischer et al., 2002). They tested 10 individuals scoring high on psychopathy (mean PCL-R = 24.89, SD = 5.23) and 10 healthy controls on an aversive differential delay conditioning task in which neutral faces served as the conditioned stimulus and painful pressure served as the unconditioned stimulus. Compared with healthy controls, psychopaths exhibited significantly less engagement of left amygdala, left middle and right anterior insula, anterior cingulate, OFC, and right secondary somatosensory cortex when the faces were followed by painful

pressure compared with when the faces were not followed by painful pressure. In spite of this reduced engagement, psychopaths responded normally to the painful pressure, indicating that sensation of the pain was intact. These results were interpreted as support for a deficient amygdala-anterior cingulate-orbital frontal-parietal network in psychopaths that is critical for assigning emotional significance to social stimuli. Veit et al. (2002) also used a differential delay conditioning task in which neutral faces were paired with painful pressure. Compared with healthy controls and individuals with social phobia, psychopaths displayed hypoactive frontolimbic circuitry during the aversive conditioning.

Müller et al. (2003) also found dysfunction in emotion-related regions in psychopathy. Using positive, negative, and neutral pictures, they found that psychopaths had increased engagement of orbital frontal and dorsolateral prefrontal regions, right amygdala, and right insula in response to negative pictures, indicating an abnormal emotional response by the psychopaths.

### *Voxel-Based Morphometry*

Before reviewing the structural findings in psychopathy, it might first be helpful to understand the method that underlies these studies: voxel-based morphometry. Voxel-based morphometry (VBM) is a whole-brain unbiased technique for identifying differences in the local composition of brain tissue after large differences in shape have been discounted (Ashburner and Friston, 2000). It has been used in a variety of clinical populations, including schizophrenia (Barkataki et al., 2006), alcoholism (Taki et al., 2006), post-traumatic stress disorder (Jatzko et al., 2006), and antisocial personality disorder and psychopathy (Raine et al., 2000; Laakso et al., 2001; Raine et al., 2003;

Yang et al., 2005; Müller et al., 2008; Oliveira-Souza et al., 2008). VBM is preferred over other morphometric methods because it is capable of interrogating the whole brain and is not confined to any one or two structures. Additionally, other methods require that the brain regions be easily identified and defined (e.g. hippocampus or ventricles), whereas VBM is a whole-brain technique.

The procedure for VBM is relatively simple. First, the images are spatially normalized to the same stereotactic space (e.g. Montreal Neurological Institute template) and segmented into gray matter, white matter, and cerebrospinal fluid. In practice, it must first be determined manually that the non-normalized images are reasonably well aligned to the template before proceeding with spatial normalization. In the statistical software toolkit Statistical Parametric Mapping (SPM5; Wellcome Department of Imaging Neuroscience, London, UK), normalization and segmentation are performed together in an integrated step (Ashburner and Friston, 2005). (It is important to note that spatial normalization does not match every cortical feature exactly, otherwise there would be no differences to compare.) After the images have been normalized and segmented, the segments are smoothed by convolving them with an isotropic Gaussian kernel (Ashburner and Friston, 2000). Smoothing makes the subsequent voxel by voxel comparison comparable to a region of interest approach, because each voxel in the smoothed images contains the average local concentration of tissue from around the voxel, the size of which is defined by the size of the smoothing kernel (Ashburner and Friston, 2000). Smoothing also makes the data more normal (by the central limit theorem), thereby increasing the validity of the parametric statistical tests. Additionally, it makes the residuals more normally distributed and helps to compensate for inexact

normalization. After preprocessing has been completed, the General Linear Model is used to identify regions of gray matter, white matter, or CSF that are related to the variables of interest.

### *Structural Studies*

Neuroimaging studies on psychopathy have thus far focused mainly on functional abnormalities associated with the behavioral deficits that individuals with psychopathy demonstrate. Research suggests that this disorder might also be associated with structural abnormalities as well, though the literature here is sparse. Another limitation of previous structural studies is that inconsistent samples have been used – habitually violent offenders with ASPD and alcoholism who also score high on psychopathy (Laakso et al., 2001), community psychiatric samples with high PCL Screening Version (PCL:SV) scores (Oliveira-Souza et al., 2008), healthy controls who score high on impulsivity measures (Matsuo et al., 2008), and “unsuccessful” and “successful” psychopaths (Raine et al., 2004; Yang et al., 2005). In general, these studies have focused on brain areas previously shown to have abnormal functioning in various antisocial and psychopathic samples, including the ventromedial prefrontal cortex (vmPFC), amygdala, medial temporal cortex, hippocampus, and corpus callosum. Because of the aforementioned limitations of previous studies, the current study is valuable in that it will help fill a void in this line of research and utilize a sample of individuals who have been assessed using the PCL-R.

One of the earliest studies to assess structural abnormalities in psychopathy was conducted by Laakso and colleagues (2001), and investigated the correlation between regional volumes of the hippocampus along the anteroposterior axis and degree of

psychopathy, as assessed using the PCL-R. Participants were 18 habitually violent offenders with a diagnosis of ASPD and type two alcoholism. Laakso et al. found that posterior bilateral hippocampal volume was negatively correlated with PCL-R score. The authors concluded that these results support previous studies showing that dorsal hippocampus lesions are associated with impairment of conditioned fear acquisition, and noted that this impairment is thought to be present in individuals with psychopathy. In another study by Laakso et al. (2002), total prefrontal, prefrontal white, and cortical prefrontal volumes were measured in a sample of 24 males with ASPD and alcoholism who were also assessed for psychopathy, and 33 age-matched healthy controls. Prefrontal differences were found in the ASPD group, but were attributed to duration of alcoholism, and no significant correlations between prefrontal volume and psychopathy were found.

Raine and colleagues (2003) investigated corpus callosum abnormalities in a sample of 15 men with both ASPD and high psychopathy (PCL-R) scores and 25 matched controls. Using MRI and VBM, they measured callosal volume, thickness, and length. Compared to healthy controls, subjects with high psychopathy scores showed a 22.6% increase in callosal volume, a 6.9% increase in callosal length, a 15.3% decrease in callosal thickness, and an increase in overall functional connectivity. Additionally, Raine et al. assessed whether callosal abnormalities correlated with affective/interpersonal (PCL-R factor one) or social deviance (PCL-R factor two) scores. They found that factor one was associated with larger callosal volume, low autonomic stress reactivity, and low spatial ability. Factor two was independent of any callosal abnormalities. Raine et al. concluded that these results support a neurodevelopmental

etiology of psychopathy, which could include an arrest of early axonal pruning and/or increased white matter myelination.

Raine et al. (2004) also investigated hippocampal structure, this time in a sample of incarcerated (“unsuccessful”) psychopaths, community (“successful”) psychopaths, and healthy controls. In this first study comparing successful and unsuccessful psychopaths, Raine et al. tested whether a prior finding of functional hippocampal asymmetry in caught violent offenders would generalize both to the structural domain and to unsuccessful psychopaths. They found that unsuccessful psychopaths, relative to successful psychopaths and healthy controls, showed exaggerated hippocampal asymmetry (right > left) in the anterior region. They concluded that these results suggest that psychopathy is associated with a neurodevelopmental abnormality that disrupts hippocampal-prefrontal networks, which results in poor affect regulation, abnormal contextual fear conditioning, and insensitivity to cues predicting capture.

Yang et al. (2005) used the same sample of unsuccessful and successful psychopaths and tested the hypothesis that psychopathy (as manifested in unsuccessful psychopaths only) is associated with a reduction in prefrontal gray matter volume. Using structural MRI, they measured prefrontal gray matter and white matter volume. The authors found that higher psychopathy scores were related to lower prefrontal gray matter volume, and that unsuccessful psychopaths had a 22.3% reduction in prefrontal gray matter compared to healthy controls. They concluded that these results support a prefrontal theory of psychopathy, and highlight important differences between successful and unsuccessful psychopaths.

Oliveira-Souza et al. (2008) investigated gray matter abnormalities in brain regions associated with moral conduct using optimized VBM and the PCL:SV. Participants were 15 community psychiatric patients with high PCL:SV scores and 15 healthy controls. They found gray matter reductions in frontopolar, orbital frontal, and anterior temporal cortices, superior temporal sulcus, and insula. Additionally, they found that the degree of abnormality was related to PCL factor one (interpersonal/affective) but not factor two (lifestyle/antisocial). The authors concluded that the regions of interest where reductions were found are part of a fronto-temporal network that is important for moral sensibility and moral-guided behavior, which are two characteristics found to be deficient in psychopaths.

Matsuo et al. (2008) used VBM to investigate frontal gray matter correlates of impulsivity in a sample of healthy subjects. They used the Barratt Impulsiveness Scale (BIS) and optimized VBM to investigate the relationship between gray and white matter volumes in the amygdala and vmPFC (including orbital frontal, anterior cingulate, and medial prefrontal cortices) and impulsivity. They found a negative correlation between gray matter volumes of bilateral OFC and BIS score and a negative correlation between left ACC gray matter volume and BIS score. Additionally, they found that right OFC gray matter volume is inversely correlated with BIS *nonplanning* impulsivity, and left OFC gray matter volume is inversely correlated with BIS *motor* impulsivity. No significant white matter correlations were found. The authors concluded therefore that smaller OFC gray matter volume is related to high impulsivity. Additionally, these results extend the prior finding that the vmPFC is involved in modulating impulsivity, which is an important (deficient) feature of psychopathy.

Tiihonen et al. (2008) examined both white and gray matter in a sample of 26 persistently violent offenders and 25 healthy controls. Violent offenders showed increased white matter in bilateral occipital and parietal lobes, but after adding several different covariates to the model, these differences were not found to be associated with psychopathy score, substance abuse, psychotropic medication, or IQ. Offenders also showed decreased gray matter in frontopolar and orbital frontal areas compared with the healthy controls, and these differences were greatest in those offenders with high psychopathy scores.

Lastly, Müller et al. (2008) attempted to resolve the discrepant findings in prefrontal and temporal areas by investigating regional gray matter abnormalities in psychopathy using the PCL-R. They compared 17 male forensic patients with PCL-R scores of 29 and above (mean = 33.3) with 17 male controls with PCL-R scores of less than 10 (mean = 0.5), and found reduced gray matter in bilateral superior temporal gyri, bilateral prefrontal cortex, and right cingulate in the high psychopathy group. The authors concluded that abnormalities in cortical and subcortical frontotemporal brain regions that are part of the paralimbic network are structurally altered in individuals with psychopathy.

Indeed, the psychopathy morphometric literature is inconsistent and is fraught with methodological heterogeneity. The current study was undertaken in an attempt to clarify some of these discrepancies. In order to investigate gray matter structural abnormalities in psychopathy, voxel-based morphometry was performed on a sample of community substance users assessed for psychopathy using the PCL-R. A regression analysis with psychopathy score (coded as a continuous variable) as the main predictor

was carried out. It was hypothesized that compared with those scoring low on the PCL-R, those classified as psychopaths would demonstrate reduced gray matter concentration in paralimbic regions (anterior superior temporal gyrus, anterior and posterior cingulate, orbital frontal cortex, insula, parahippocampal region, and amygdala) based on previous functional and structural findings.

## Methods

### *Participants*

Seventy-seven right-handed adults (32 female) were recruited from a community sample of substance users (mean age = 36.7 years; SD = 8.1). Four subjects were excluded for excessive head motion in the scanner, leaving 73 participants. Consistent with standard MRI research, subjects were excluded if they were over 55 years of age, were pregnant, had a history of seizures, epilepsy, or psychosis, had experienced a loss of consciousness exceeding 30 minutes, or had a pacemaker or metal implants. In addition, all participants were required to show fluency in English at or above a grade four reading level. Ethnic groups and their distributions are presented in Table 3. Full scale IQ was estimated using the Hopkins Adult Reading Test (HART; mean = 97.7, SD = 10.0). All subjects gave written, informed consent, according to the standards of the Institutional Review Board. Participants were compensated for their time.

### *Psychopathy Assessment*

Participants were assessed for psychopathy using the Psychopathy Checklist-Revised (PCL-R; Hare, 1991, 2003). Trained research personnel conducted each interview and scored individuals based on information obtained from the interview as well as collateral file information. Official criminal background files were obtained for those recruited from local probation or parole offices. These files contained detailed information about criminal history, including number of arrests, explanation of crimes and sentences received, as well as information related to school, work, social, emotional, and substance use history. For those recruited through drug and alcohol treatment

facilities, participants agreed to have credit and background checks completed (performed by SSC Inc., Hartford, Connecticut), which provided relevant information including chronological history of all criminal charges, driving record, and credit history. Psychopathy scores in this sample ranged from 2.1 to 36 (mean = 18.7; SD = 8.0).

### *Substance Use Assessment*

The comorbidity between psychopathy and substance use has been consistently high (Alterman, Cacciola, and Rutherford, 1993; Hemphill, Hart, and Hare, 1994). In order to address this issue, substance use information was obtained using a customized substance use questionnaire. Years of regular use (3 or more times per week) of the major drugs classes – stimulants (i.e. cocaine, crack, and methamphetamine), cannabis, opioids (mainly heroin), and hallucinogens – were summed to obtain a measure of drug use severity (mean = 27.86; SD = 19.24). Years of regular alcohol use was summed separately (mean = 14.14; SD = 9.52).

### *Clinical Assessment*

Participants were administered the Structured Clinical Interview (SCID) for Axis I and Axis II disorders (First, Spitzer, Gibbon, and Williams, 2002) in order to identify any mental or personality disorders (including substance use disorders). Rates of diagnosis are presented in Tables 4 (Axis I) and 5 (Axis II).

### *MRI Acquisition and Image Analysis*

High-resolution T1-weighted structural MRI scans were acquired on a Siemens 3T Allegra scanner, using an MPRAGE pulse sequence (TR = 2500 ms, TE = 2.74 ms, TI

= 900 ms, flip angle = 8°, slice thickness = 1 mm, matrix size = 176 × 256) yielding 256 sagittal slices with an in-plane resolution of 1 mm × 1 mm.

Data were pre-processed and analyzed using SPM5. T1 images were inspected manually by an operator blind to subject identity and reoriented if improper spatial normalization was likely due to gross misalignment. Images were then spatially normalized to the SPM5 T1 (MNI) template and segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). No modulation of the normalized segmented images was performed, due to the potential for atrophy associated with severe and chronic substance use (Eckert et al., 2006). Lastly, segmented images were smoothed with a 10 mm full-width at half-maximum (FWHM) Gaussian kernel.

Group analyses were performed on a voxel-by-voxel basis using the General Linear Model, controlling for total intracranial volume (TIV). A whole-brain multiple regression analysis was performed in order to determine which regions were correlated with PCL-R total, factor one, factor two, facet one, facet two, facet three, and facet four scores.

#### *Choice of Covariates*

For any VBM study, there is a long list of potential covariates that could be included in the correlational analysis. This list includes age, gender, TIV, IQ, and substance use severity, to name a few. In VBM studies of gray matter, it has been shown that of the three most common covariates (age, gender, and TIV), the optimal strategy is to use TIV only (Pell et al., 2008). TIV is preferable over gender because of the high degree of multi-collinearity between the two variables, and the continuous nature of TIV is preferable over the categorical nature of gender. Age and IQ should also not be

included because they account for very little variance over and above the TIV-dependent structural variance, and statistical over-control should be avoided. Substance use severity was included in this study in a secondary analysis.

## Results

Using voxel-based morphometry, scores on the PCL-R (total, factor one, and factor two, and facet one, facet two, facet three, and facet four) were used to correlate psychopathy with gray matter (GM) concentration in a sample of community substance users. GM concentration was negatively correlated with all seven scores. Positive correlations were far less numerous, and can be found in Table 6.

### *Total, Factor One, and Factor Two*

All regions were significant at the uncorrected level of  $p < .01$ . PCL-R factor one score was negatively correlated with GM concentration in the following paralimbic regions: bilateral insula, right amygdala, bilateral parahippocampal gyri, right orbital frontal areas, bilateral anterior and posterior cingulate/precuneus, and right temporal pole (see Figure 1). Factor two PCL-R score was negatively correlated with GM concentration in left posterior cingulate (see Figure 2). Total PCL-R score was also negatively correlated with GM concentration in left posterior cingulate (see Figure 3). Whole-brain results can be found in Tables 7-9, respectively.

### *Facets One and Two*

All regions were significant at the uncorrected level of  $p < .01$ . PCL-R facet one score was negatively correlated with GM concentration in the following paralimbic regions: bilateral insula, right amygdala, bilateral parahippocampal gyri, right orbital frontal areas, right anterior and left posterior cingulate/precuneus, and bilateral temporal pole (see Figure 4). PCL-R facet two score was negatively correlated with GM concentration in right temporal pole, bilateral insula, bilateral parahippocampal gyri, right

orbital frontal cortex, bilateral anterior and posterior cingulate/precuneus, and right amygdala (see Figure 5). Whole-brain results can be found in Tables 10 and 11, respectively.

#### *Facets Three and Four*

All regions were significant at the uncorrected level of  $p < .01$ . PCL-R facet three score was negatively correlated with GM concentration in left superior and middle temporal gyrus, bilateral supramarginal gyrus, right lingual gyrus, left middle occipital gyrus, and left posterior cingulate (see Figure 6, Table 12). PCL-R facet four score was negatively correlated with GM concentration in left inferior parietal cortex, left middle temporal gyrus, and right cuneus (see Table 13).

#### *Substance and Alcohol Use*

Previous studies have found high correlations between drug and alcohol use and psychopathy (Alterman, Cacciola, and Rutherford, 1993; Hemphill, Hart, and Hare, 1994), and it was therefore necessary to assess this relationship in the current study. Here, PCL-R total score was significantly positively correlated with a measure of regular substance use ( $r = .365$ ;  $p = .003$ ), but not regular alcohol use ( $r = .177$ ;  $p = .156$ ). PCL-R factor one score was not significantly correlated with either substance use ( $r = .226$ ;  $p = .069$ ) or alcohol use ( $r = .191$ ;  $p = .124$ ), but PCL-R factor two score was significantly positively correlated with substance use ( $r = .394$ ;  $p = .001$ ) but not alcohol use ( $r = .148$ ;  $p = .237$ ). Total gray matter volume was significantly negatively correlated with both substance use ( $r = -.285$ ;  $p = .02$ ) and alcohol use ( $r = -.319$ ;  $p = .009$ ). In order to control

for this high degree of correlation, substance and alcohol use information was used in a secondary analysis for PCL-R total, factor one, and factor two scores.

PCL-R score was the main predictor variable, and TIV, substance use, and alcohol use were entered as covariates. For PCL-R total score, there was a significant negative correlation with gray matter concentration in middle temporal gyrus, middle occipital gyrus, and cuneus. For PCL-R factor one score, only one region remained significantly negatively correlated with gray matter concentration: middle temporal gyrus. Lastly, for PCL-R factor two score, there remained a significant negative correlation with gray matter concentration in middle temporal gyrus, cuneus, and supramarginal gyrus. Removing outliers in substance use severity from the analysis did not change the results.

## Discussion

Despite the growing interest in the neurobiological correlates of psychopathy, no definitive answer has emerged from the functional and structural imaging literature. This discrepancy may be due to a number of inconsistencies among studies, such as methods or participant characteristics. The current study was performed in order to better characterize the structural differences related to psychopathy.

PCL-R total, factor one, factor two, facet one, facet two, facet three, and facet four were analyzed separately in order to identify the relationship between specific gray matter regions and distinct aspects of psychopathy.

Factor one scores were shown to be negatively related to a number of regions, including several previously identified as being functionally abnormal in psychopaths. These regions include insula, amygdala, parahippocampal gyri, orbital frontal cortex, and cingulate. Factor one consists of interpersonal and affective items, including conning/manipulative, lack of remorse or guilt, shallow affect, and callous/lack of empathy. Indeed, the finding that these regions are related to factor one but not factor two scores is consistent with other studies in which significant regions associated with emotion and morality were negatively related to factor one but not factor two (Oliveira-Souza et al., 2008). This makes sense, given the affective characteristic of factor one and the affective functions of amygdala, parahippocampal gyri, and cingulate (Mesulam, 2000).

The results for total score and factor two were similar to each other. Both total score and factor two were found to be negatively correlated with GM concentration in mainly posterior regions, including posterior cingulate, posterior temporal areas, middle

occipital, and inferior parietal regions. Why might this be the case? One possibility is that factor two was more highly correlated with total score ( $r = .917$ ) than was factor one ( $r = .833$ ). Additionally, mean factor two score was significantly higher than mean factor one score ( $t_{72} = -14.59$ ,  $p = .000$ ) indicating that in this sample, factor two contributed more to total score than did factor one.

Factor two consists of behavioral and lifestyle items such as impulsivity, irresponsibility, juvenile delinquency, and criminal versatility. These aspects of psychopathy are closely related to ASPD, a DSM construct that is present in approximately 80-90% of incarcerated individuals. Previous studies have suggested that the vmPFC, including OFC, anterior cingulate, and medial prefrontal cortex, as well as the amygdala, are important for modulating impulsivity and aggression (Bechara et al., 1999; Berlin et al., 2004). Studies of ASPD have also found prefrontal (dorsolateral, orbital frontal, and medial frontal) gray matter differences in violent individuals with ASPD and alcoholism, but these differences did not remain when education and duration of alcoholism were added to the model (Laakso et al., 2002). Tiihonen et al. (2008) found smaller gray matter volumes in postcentral gyri, frontopolar cortex, and orbital frontal cortex in violent offenders with ASPD. In contrast, previous psychopathy studies have found no differences in brain structure related to PCL-R factor two (Raine et al., 2003; Oliveira-Souza et al., 2008) and the results of the present study are more consistent with these latter findings. However, a larger sample size and the inclusion of individuals scoring over 30 in the present study could explain the discrepancies between the present study and other studies in which no factor two differences were found.

### *Testing the Two Factor-Four Facet Model*

In the current study, the two factor-four facet model of psychopathy was tested. Facets one and two (which comprise factor one) were similar to factor one and to each other, but not identical, and facets three and four (which comprise factor two) were likewise similar to each other and to factor two, but not identical. These findings, though very preliminary, support the presence of two factors and four facets of psychopathy. However, it is likely that a psychometric approach is not the proper tool for the job in this particular case. One potential future approach is to utilize a brain-coupled factor analysis (e.g. independent components analysis fusion), which would provide a more direct link between PCL-R factor structure and brain structure and function.

### *Substance and Alcohol Use*

In addition to investigating the relationship between gray matter concentration and PCL-R score, substance and alcohol use were included in a secondary analysis. This was done for three main reasons. The first is that substance and alcohol use have traditionally been highly correlated with psychopathy (Alterman, Cacciola, and Rutherford, 1993; Hemphill, Hart, and Hare, 1994).

The second reason is that previous neuroimaging work has demonstrated a significant impact of heavy substance and alcohol use on brain structure. For example, Fein et al. (2006) demonstrated that long-term abstinent alcoholics (individuals who met a lifetime criteria for alcohol dependence, had a lifetime average of at least 100 drinks per month for men and 80 drinks per month for women, and had been abstinent for at least 6 months) show a bilateral reduction of gray matter in the amygdala. Tanabe et al. (2009) found reduced gray matter in bilateral medial OFC in substance dependent individuals

(indicated by DSM-IV dependence on one or more illicit substances) compared to healthy controls. Franklin et al. (2002) reported decreased gray matter in cocaine dependent subjects in ventromedial, orbital frontal, and superior temporal cortices, as well as anterior cingulate and insula. Several of these areas overlap with regions implicated in psychopathy, again underscoring the importance of assessing psychopathy and substance and alcohol use separately.

Lastly, given the present sample of community substance users, it seemed necessary to include this variable in an analysis of brain structure. Alcohol and substance use severity were measured by summing years of regular use of alcohol and the major classes of drugs, respectively. These variables were entered into the regression analysis with PCL-R score and TIV. Including substance and alcohol use in the model had a significant impact on all three analyses (total, factor one, and factor two), raising the possibility that substance and alcohol use, not PCL-R score, drove the obtained results. This effect has been documented previously, as Müller et al. (2008) found no significant gray matter differences between the psychopathy group and healthy control group when drug intake was entered as a nuisance variable into an ANCOVA.

It is important to note that the correlation between total score and substance use ( $r = .365$ ) and between factor two and substance use ( $r = .394$ ) were significant, and there was a trend for factor one and substance use ( $r = .226$ ). This indicates that there was overlap between the substance and alcohol use measures and PCL-R scores. Thus, one cannot assume a causal effect, and it is not possible to know whether these results are related to psychopathy, a chronic, antisocial way of life, or some other factor. Individuals in this sample had extremely high measures of substance use, and it might be necessary to

utilize a sample with less extreme histories of abuse in the future. Another possibility might be to exclude individuals with extremely high severity scores in order to see if the present effects remain. This issue will continue to be difficult to handle given the high comorbidity between psychopathy and substance use. Furthermore, it will be difficult to find an independent measure of substance use in psychopathic samples.

### *Future Directions*

This study remains as one of the few investigations of brain structure and psychopathy, and avenues for future investigations are plentiful. For example, others have proposed a PCL-R factor structure (Cooke and Michie, 1997) that is different from the one used in this study (Hare, 2003). It could be fruitful to analyze the present data using a three factor model as opposed to the two factor-four facet model that was utilized here. On a similar note, there is an ongoing debate in the field about whether psychopathy is truly a continuous or categorical construct. Future studies could address this question by doing both a regression analysis as well as a group comparison, where those scoring low ( $\leq 20$ ) are compared with high scorers ( $\geq 30$ ) on the PCL-R.

Future studies could also investigate white matter differences in psychopathy using diffusion tensor imaging (DTI), based on evidence that psychopaths exhibit abnormal functional interhemispheric connectivity (Kosson, 1996, 1998; Raine et al., 2003; Hiatt and Newman, 2007). Another potential avenue for future studies is to dig deeper into the relationships among psychopathy, substance and alcohol use, and brain structure. It is well known that chronic substance and alcohol use affects both gray and white matter integrity (Mechtcheriakov et al., 2007), but how this effect interacts with psychopathy is unknown. One possibility would be to use substance and/or alcohol use

severity as the main predictor in a VBM analysis. Additionally, animal work in substance use could be informative about the causal effects of chronic substance and alcohol use without the confound of psychopathy.

In conclusion, the preponderance of the evidence suggests that the etiology of psychopathy is at least partly neurodevelopmental. Dysfunctional axonal pruning potentially could be to blame for any increases in regional size, whereas deficient growth could be to blame for regional decreases in size. This theory would be consistent with what is currently known about psychopathy, including its early behavioral manifestation, its resistance to traditional therapies and treatments, and its genetic component. A recent comment by Oliveira-Souza et al. (2008) perhaps best summarizes a complicated process:

Although we might suppose that regions showing anatomical changes are dysfunctional and that such impairment is causally related to at least some core symptoms of psychopathy, it is not yet possible to tell if that impairment interferes with all functions of these areas more or less equally, or if some degree of selectivity is in order.

Indeed, additional research will be needed in order to better characterize the causal link between the demonstrated anatomical abnormalities and functional deficits in psychopaths.

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***Cleckley's 16 Diagnostic Criteria (1982)***

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Superficial charm and good "intelligence"  
Absence of delusions and other signs of irrational thinking  
Absence of "nervousness" or psychoneurotic manifestations  
Unreliability  
Untruthfulness and insincerity  
Lack of remorse or shame  
Inadequately motivated antisocial behavior  
Poor judgment and failure to learn by experience  
Pathologic egocentricity and incapacity for love  
General poverty in major affective reactions  
Specific loss of insight  
Unresponsiveness in general interpersonal relations  
Fantastic and uninviting behavior  
Suicide rarely carried out  
Sex life impersonal, trivial, and poorly integrated  
Failure to follow any life plan

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Table 1. Diagnostic criteria of psychopathy from *The Mask of Sanity* (Cleckley, 1982).

<i>Psychopathy Checklist-Revised Item</i>	<i>Factor</i>	<i>Facet</i>
1. Glibness/Superficial Charm	1	1
2. Grandiose Sense of Self Worth	1	1
3. Need for Stimulation/Proneness to Boredom	2	3
4. Pathological Lying	1	1
5. Conning/Manipulative	1	1
6. Lack of Remorse or Guilt	1	2
7. Shallow Affect	1	2
8. Callous/Lack of Empathy	1	2
9. Parasitic Lifestyle	2	3
10. Poor Behavioral Controls	2	4
11. Promiscuous Sexual Behavior	*	*
12. Early Behavioral Problems	2	4
13. Lack of Realistic, Long-Term Goals	2	3
14. Impulsivity	2	3
15. Irresponsibility	2	3
16. Failure to Accept Responsibility for Own Actions	1	2
17. Many Marital Relationships	*	*
18. Juvenile Delinquency	2	4
19. Revocation of Conditional Release	2	4
20. Criminal Versatility	2	4

Table 2. Factor structure of the Hare Psychopathy Checklist-Revised (Hare, 1991; 2003). Factor one is comprised of the interpersonal (facet one) and affective (facet two) characteristics. Factor two is comprised of the lifestyle (facet 3) and antisocial (facet 4) characteristics that are more closely related to antisocial personality disorder criteria. Items 11 and 17 (Promiscuous Sexual Behavioral and Many Marital Relationships, respectively) did not load on any factor. One goal of the current study was to investigate the neurobiological correlates of each factor and facet separately.

<i><b>Ethnicity</b></i>	<i><b>Number</b></i>
White	34
Black or African American	23
Hispanic or Latino	11
Asian/Pacific Islander	1
Other/Unknown	4

Table 3. Distribution of ethnicity.

<i><b>Axis I DSM Diagnosis</b></i>	<i><b>Number</b></i>
Alcohol Use Disorder	56
Cannabis Use Disorder	47
Sedative, Hypnotic, or Anxiolytic Use Disorder	4
Cocaine Use Disorder	61
Opioid Use Disorder	23
Amphetamine Use Disorder	1
Hallucinogen Use Disorder	12
Other/Unknown Substance Use Disorder	2
Anxiety Disorder	15
Mood Disorder	20

Table 4. Number and distribution of individuals with an Axis I DSM diagnosis. Alcohol and drug “use” disorders include both abuse and dependence. Anxiety Disorder includes Anxiety Disorder Not Otherwise Specified (3), Social Phobia (3), Post-Traumatic Stress Disorder (5), Obsessive-Compulsive Disorder (1), Other/Unknown Substance-Induced Anxiety (1), Panic Disorder (1), and Anxiety Disorder Due to General Medical Condition (1). Mood Disorder includes Major Depressive Disorder (12) and Substance-Induced Mood Disorder (6), Dysthymic Disorder (1), Mood Disorder Not Otherwise Specified (1).

<i><b>Axis II DSM Diagnosis</b></i>	<i><b>Number</b></i>
Antisocial Personality Disorder	39
Borderline Personality Disorder	3
Obsessive-Compulsive Personality Disorder	1
Narcissistic Personality Disorder	1
Personality Disorder Not Otherwise Specified	1

Table 5. Number and distribution of individuals with an Axis II DSM diagnosis.

<b>Factor/Region</b>	<b>MNI Coordinates</b>	<b>t-value</b>
<i>Factor One</i>		
Lentiform nucleus	12 -2 -2	3.29
<i>Facet two</i>		
Lentiform nucleus	10 -2 -2	3.34
Thalamus	-14 -8 0	2.84
<i>Facet three</i>		
Postcentral gyrus	-28 -36 44	2.59
<i>Facet four</i>		
Postcentral gyrus	30 -40 72	2.58

Table 6. Brain regions where gray matter concentration is **positively** correlated (uncorrected,  $p < .01$ ) with PCL-R score, controlling for TIV. No positive correlations were found for factor two, total, or facet one.

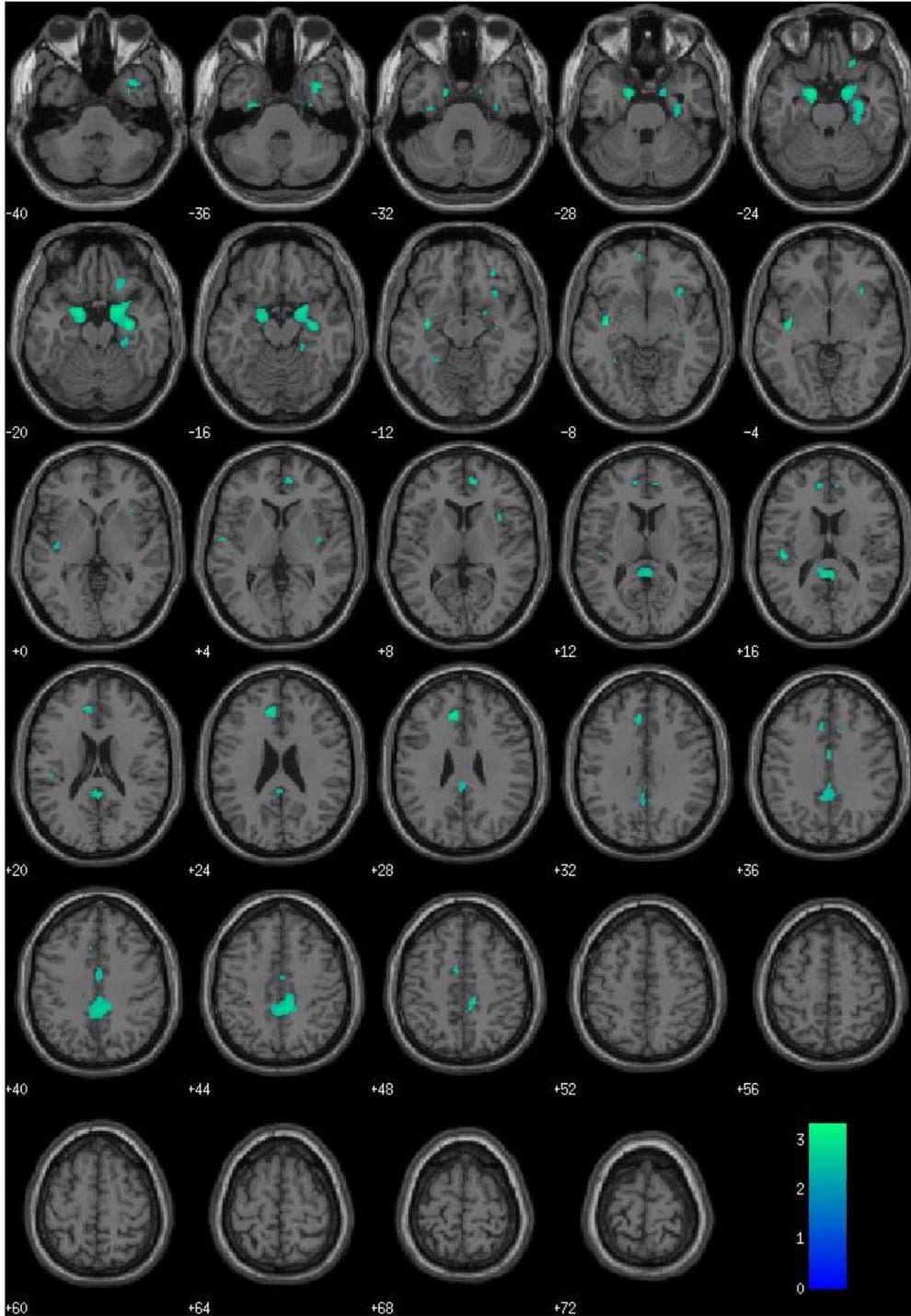


Figure 1. Depicted here are paralimbic areas where gray matter concentration is negatively correlated (uncorrected,  $p < .01$ ) with PCL-R **factor one** score, controlling for TIV. Results are overlaid on an SPM5 canonical T1 image. A mask of the paralimbic regions has been applied to facilitate visualization of regions where a priori hypotheses were made.

Region	MNI Coordinates	t-value	Region	MNI Coordinates	t-value
<i>Temporal Regions</i>			<i>Parietal Regions</i>		
Middle temporal gyrus	-58 -42 -2 *	3.77	Post-central gyrus	-62 -14 24	2.56
	-62 -58 2	2.60	Inferior parietal	-48 -34 38	3.01
	46 -64 22	2.97		40 -46 40	2.78
	68 -24 -14	2.49			
Superior temporal gyrus	56 -48 16	2.89	<i>Occipital Regions</i>		
	50 -34 2	2.86	Cuneus	12 -78 12	3.18
	-56 -12 4	2.96		-22 -86 22	3.17
Inferior temporal gyrus	60 -46 -14	2.53		-40 -86 8	2.57
	68 -46 -10	2.45		-36 -90 14	2.52
	-46 -70 -6	2.66	Inferior occipital	34 -96 -2	2.52
	66 -16 -20	2.86	Lingual gyrus	26 -72 -2	3.32
	-62 -18 -22	2.72		16 -78 -10	3.24
	62 -6 -28	2.63		-28 -80 -12	2.93
Insula	-36 -10 -8 *	3.43			
	-46 -26 16	3.02	<i>Cingulate</i>		
	-56 -38 20	2.68	Mid cingulate	8 -38 42	2.93
	38 12 8	2.49		12 -32 46	2.93
	38 -10 6	2.46		-6 -4 50	2.68
	34 20 6	2.45		2 -8 40	2.53
	32 22 -8	2.65	Anterior cingulate	-8 34 28	3.00
Temporal pole	38 6 -38	2.98		-6 20 38	2.53
Parahippocampal gyrus	-16 0 -24	3.25		12 48 10	2.98
	28 -28 -22	2.58	Posterior cingulate / precuneus	-8 -68 26	2.50
Parahippocampal gyrus / amygdala	20 0 -20	3.15		10 -62 26	2.45
Hippocampus	32 -12 -20	3.18			
Fusiform	20 -50 -14	2.69	<i>Subcortical</i>		
	30 -64 -18	2.58	Thalamus	10 -28 8	2.41
	-42 -44 -20	2.57			
	-26 -12 -40	2.82	<i>Cerebellum</i>		
				28 -86 -28	2.68
				32 -68 -40 *	3.29
				-22 -70 -34	3.06
<i>Frontal Regions</i>					
Orbital frontal	22 26 -20	2.69		-44 -60 -30	2.69
	30 38 -10	2.65		-24 -48 -18	2.60
	50 38 -14	2.56		18 -58 -22	2.49
Superior medial frontal	-10 58 4	2.61		24 -48 -50	3.02
Superior frontal gyrus	28 44 18	2.95		-18 -54 -44	2.73
	22 -10 56	2.76			
Middle frontal gyrus	-26 10 50	2.93			
	-38 10 34	2.61			
Inferior frontal gyrus	42 28 8	2.45			
	-48 18 12	2.86			
	38 10 26	2.75			
Precentral gyrus	-50 -6 30	2.88			
	-6 -26 54	2.84			

Table 7. Brain regions where gray matter concentration is negatively correlated (uncorrected,  $p < .01$ ) with PCL-R **factor one** score, controlling for TIV. Extent threshold = 10 voxels. \* = uncorrected  $p < .001$ .

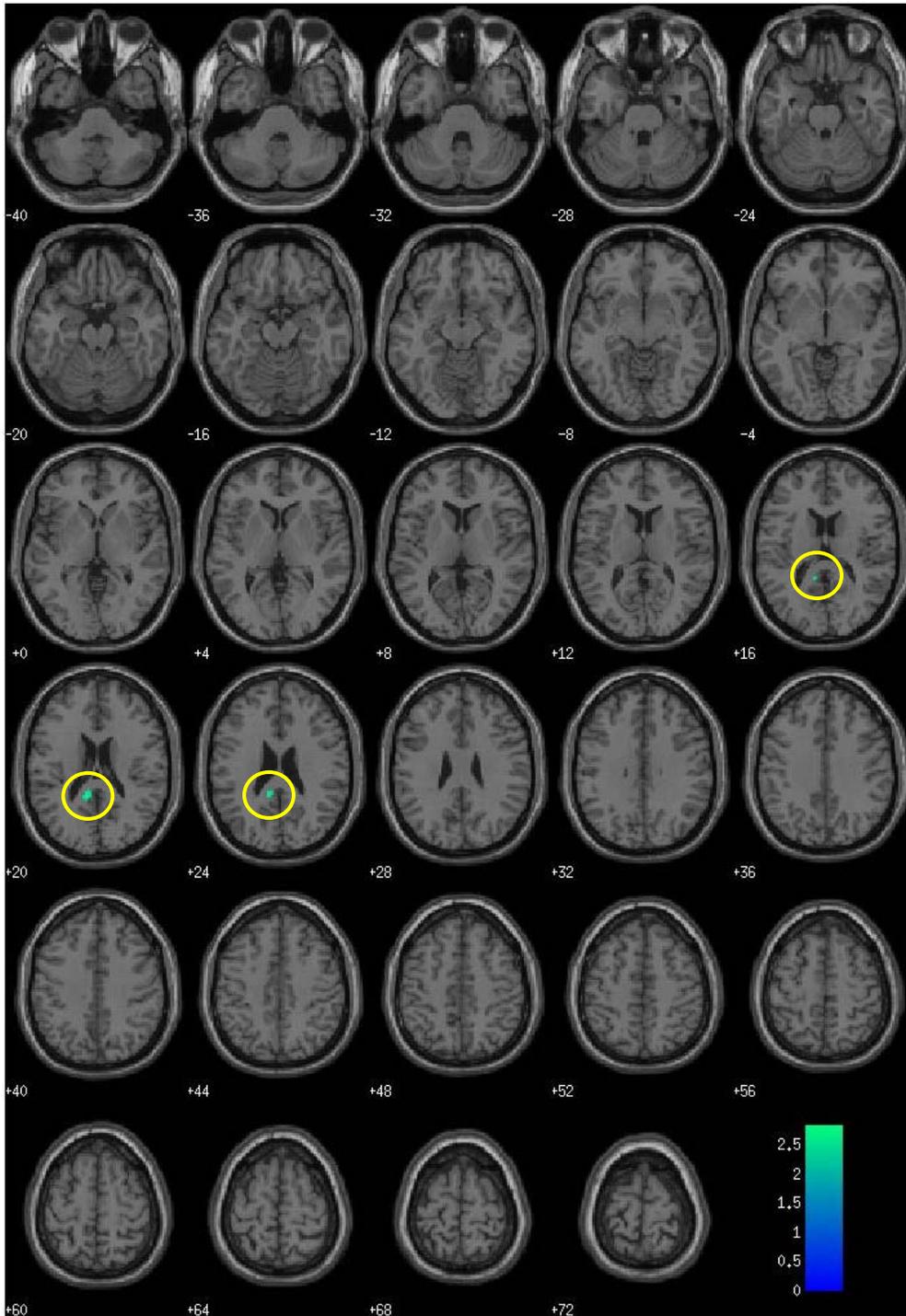


Figure 2. Depicted here are paralimbic areas where gray matter concentration is negatively correlated (uncorrected,  $p < .01$ ) with PCL-R **factor two** score, controlling for TIV. Results are overlaid on an SPM5 canonical T1 image. A mask of the paralimbic regions has been applied to facilitate visualization of regions where a priori hypotheses were made.

<b>Region</b>	<b>MNI Coordinates</b>	<b>t-value</b>
Middle temporal gyrus	-56 -42 -6	3.50
Superior temporal gyrus	-48 -26 2	2.78
Angular/supramarginal gyrus	42 -44 34	3.03
Posterior cingulate	-10 -44 20	2.83
Lingual gyrus	-12 -78 0	2.72
	24 -72 0	2.65
Middle occipital gyrus	-32 -70 14	2.79
Inferior parietal cortex	-48 -38 36	3.15

Table 8. Brain regions where gray matter concentration is negatively correlated (uncorrected,  $p < .01$ ) with PCL-R **factor two** score, controlling for TIV. Extent threshold = 10 voxels.

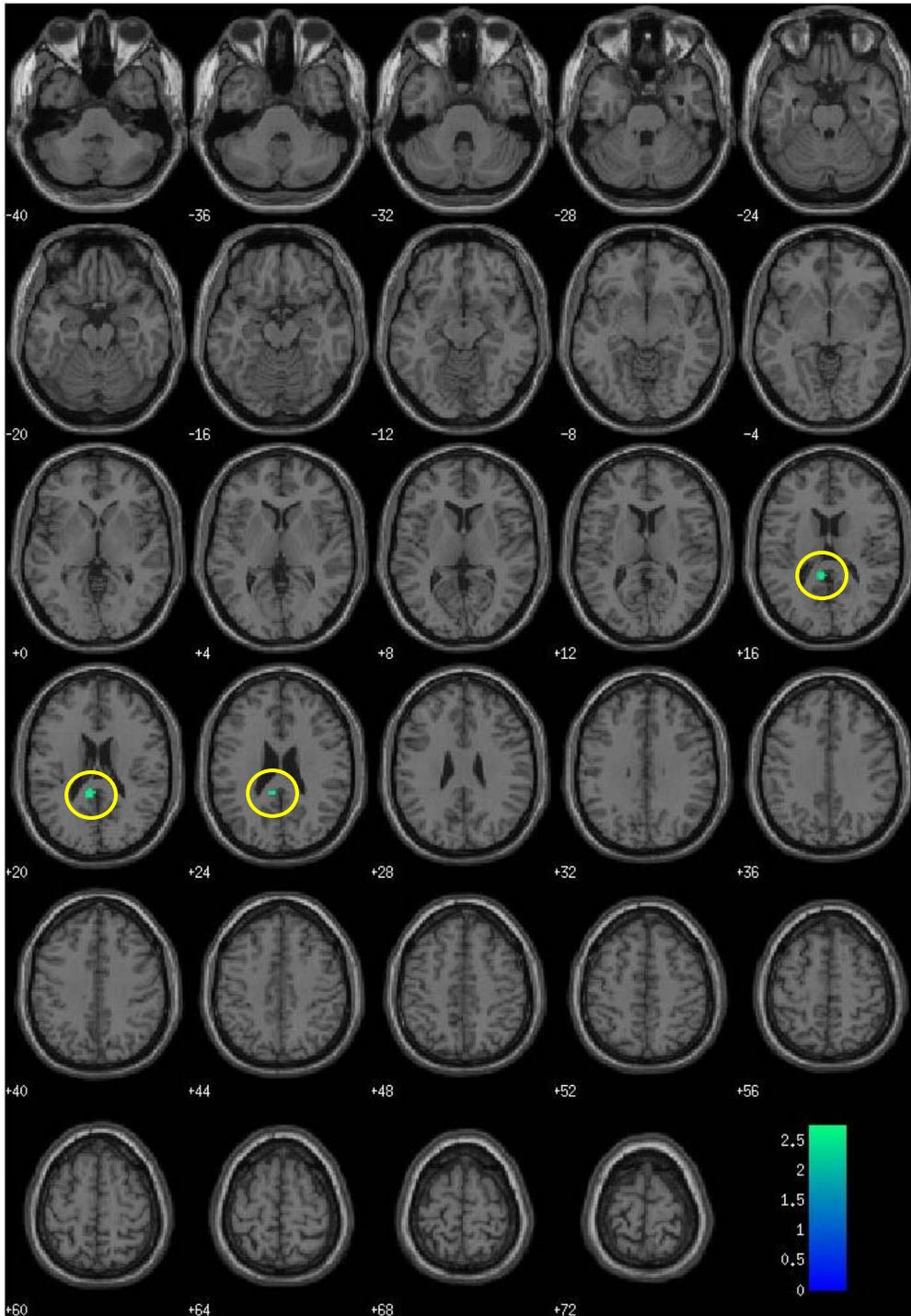


Figure 3. Depicted here are paralimbic areas where gray matter concentration is negatively correlated (uncorrected,  $p < .01$ ) with PCL-R **total** score, controlling for TIV. Results are overlaid on an SPM5 canonical T1 image. A mask of the paralimbic regions has been applied to facilitate visualization of regions where a priori hypotheses were made.

Region	MNI Coordinates	t-value
Middle temporal gyrus	-56 -42 -4 *	3.65
Superior temporal gyrus	-48 -26 2	2.62
Supramarginal gyrus	40 -44 36	3.00
Lingual gyrus	24 -72 0	3.12
	-12 -78 0	2.68
Posterior cingulate	-8 -42 20	2.76
Middle occipital gyrus	-32 -70 14	2.88
Caudate	20 -32 14	2.66
Inferior parietal cortex	-48 -36 36	2.91
Cerebellum	22 -68 -40	2.55
	30 -64 -42	2.43

Table 9. Brain regions where gray matter concentration is negatively correlated (uncorrected,  $p < .01$ ) with PCL-R **total** score, controlling for TIV. Extent threshold = 10 voxels. \* = uncorrected  $p < .001$ .

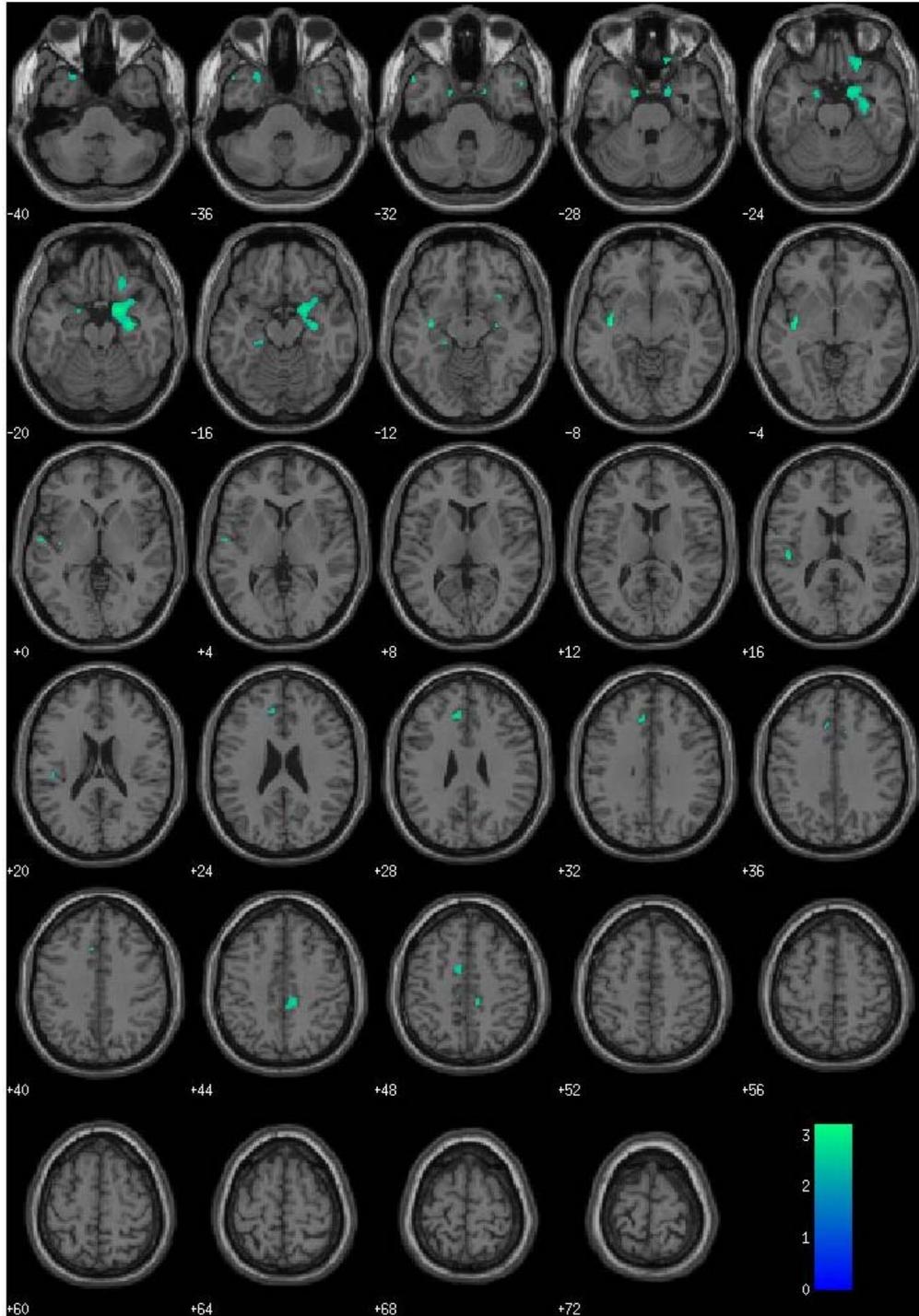


Figure 4. Depicted here are paralimbic areas where gray matter concentration is negatively correlated (uncorrected,  $p < .01$ ) with PCL-R **facet one** score, controlling for TIV. Results are overlaid on an SPM5 canonical T1 image. A mask of the paralimbic regions has been applied to facilitate visualization of regions where a priori hypotheses were made. Facet one items are glibness/superficial charm, grandiose sense of self-worth, pathological lying, and conning/manipulative.

Region	MNI Coordinates	t-value	Region	MNI Coordinates	t-value
<i>Temporal Regions</i>			<i>Parietal Regions</i>		
Middle temporal gyrus	64 -6 -28	3.00	Precuneus	12 -60 26	2.64
	66 -16 -20	2.71	Postcentral gyrus	-64 -8 20	2.46
	68 -24 -14	2.58			
	-62 -60 -2	2.57	<i>Occipital Regions</i>		
Superior temporal gyrus	-58 -44 -2 *	3.57	Lingual gyrus	24 -72 -2 *	3.60
	-56 -12 2	3.22		-24 -84 -8	2.89
	-56 -44 18	2.70		-10 -80 -2	2.65
Inferior temporal gyrus	-64 -16 -26 *	2.88	Cuneus	14 -78 12	2.77
Insula	-36 -10 -8	3.44	Middle occipital	32 -82 20	3.25
	32 10 -18	2.68		46 -66 24	2.74
Supramarginal gyrus	-52 -24 20	3.11			
Parahippocampal gyrus	-20 -30 -14	2.47	<i>Cingulate</i>		
	-14 0 -26	2.63	Anterior cingulate	-8 34 30	2.83
Parahippocampal gyrus / amygdala	20 2 -20	3.14		-8 22 38	2.47
Hippocampus	30 -12 -20	3.02	Mid cingulate	-8 -2 50	2.92
Fusiform	20 -52 -14	2.88		12 -32 46	2.78
	-44 -42 -20	2.64			
Temporal pole	-24 18 -38	2.63	<i>Cerebellum</i>		
	56 8 -34	2.64		-18 -54 -44	3.10
	-52 16 -34	2.73		24 -50 -48	3.28
				34 -66 -42	3.16
				34 -84 -30	2.86
<i>Frontal Regions</i>				-20 -50 -16	2.58
Orbital frontal	26 28 -24	2.87		-20 -72 -34	2.45
	18 34 -26	2.58			
Superior frontal gyrus	28 44 18	3.00			
Middle frontal gyrus	42 2 62	2.81			
Inferior frontal gyrus	38 8 26	2.56			
	50 24 4	2.55			
	-58 24 2	2.51			
	40 2 -36	2.69			
Superior medial frontal	-10 40 24	2.63			
	-8 34 50	2.71			
Precentral gyrus	-8 -26 52	2.85			

Table 10. Brain regions where gray matter concentration is negatively correlated (uncorrected,  $p < .01$ ) with PCL-R **facet one** score, controlling for TIV. Extent threshold = 10 voxels. \* = uncorrected  $p < .001$ .

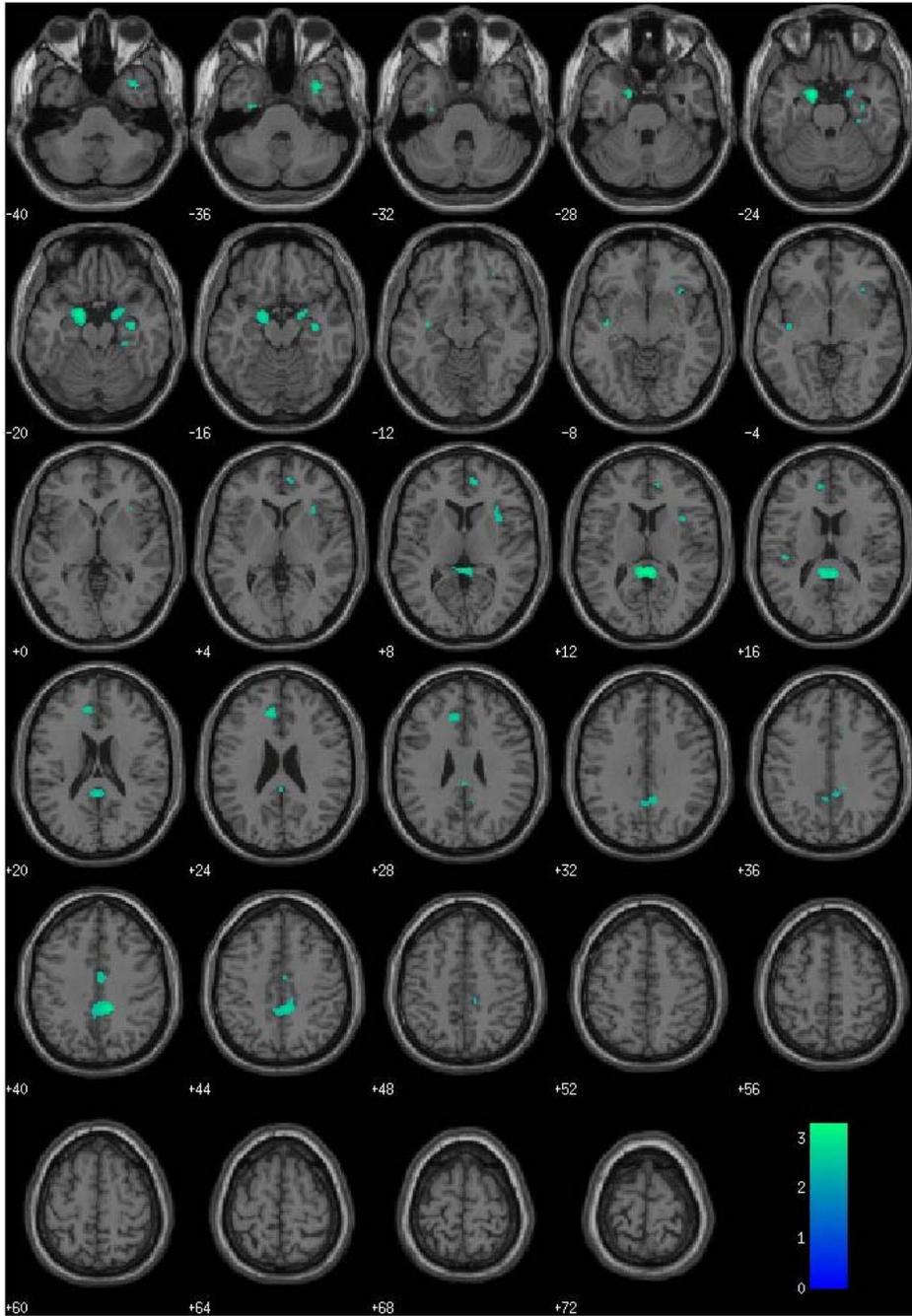


Figure 5. Depicted here are paralimbic areas where gray matter concentration is negatively correlated (uncorrected,  $p < .01$ ) with PCL-R **facet two** score, controlling for TIV. Results are overlaid on an SPM5 canonical T1 image. A mask of the paralimbic regions has been applied to facilitate visualization of regions where a priori hypotheses were made. Facet two items are lack of remorse or guilt, shallow affect, callous/lack of empathy, and failure to accept responsibility for own actions.

Region	MNI Coordinates	t-value	Region	MNI Coordinates	t-value
<i>Temporal Regions</i>			<i>Occipital Regions</i>		
Middle temporal gyrus	-58 -42 -2	3.30	Lingual gyrus	16 -78 -10	2.85
	50 -36 2	3.05		-28 -80 -12	2.65
Superior temporal gyrus	56 -46 14	3.01	Middle occipital	-40 -84 6	2.62
	46 -58 20	2.86		32 -74 30	3.13
Temporal pole	36 6 -38	2.92	Cuneus	-22 -86 22	3.01
Insula	-38 -12 -8			12 -78 12	2.99
	32 24 -8	2.71	Inferior occipital	-46 -70 -6	2.66
	-44 -26 16	2.66			
Parahippocampal gyrus	-16 0 -24	3.21	<i>Cingulate</i>		
	28 -28 -22	2.49	Mid cingulate	6 -10 40	2.58
	24 -34 -18	2.38	Posterior cingulate /precuneus	4 -40 12	3.29
Hippocampus	34 -12 -20	2.88		-4 -42 14	3.17
Fusiform	26 -76 -6	2.66		12 -38 40	3.06
	-28 -14 -36	2.62		8 -50 30	2.63
	30 -66 -16	2.61		-2 -60 34	2.59
			Anterior cingulate	-10 34 26	2.81
<i>Frontal Regions</i>				12 48 10	2.88
Superior frontal gyrus	22 -10 56	2.76		-8 42 20	2.67
Middle frontal gyrus	-24 12 50	3.20			
	38 12 26	2.63	<i>Subcortical</i>		
Inferior frontal gyrus	-48 16 12	2.77	Thalamus	-4 -26 8	2.88
Orbital frontal	28 34 -8	2.48	Amygdala	20 -2 -18	2.71
	50 38 -14	2.56			
Medial frontal	-4 -26 58	2.49	<i>Cerebellum</i>	-22 -70 -34	3.07
				-44 -62 -30	2.62
<i>Parietal Regions</i>				26 -70 -38	2.96
Inferior parietal	-48 -36 38	3.05		-34 -60 -22	2.41
	38 -46 42	2.91			

Table 11. Brain regions where gray matter concentration is negatively correlated (uncorrected,  $p < .01$ ) with PCL-R **facet two** score, controlling for TIV. Extent threshold = 10 voxels.

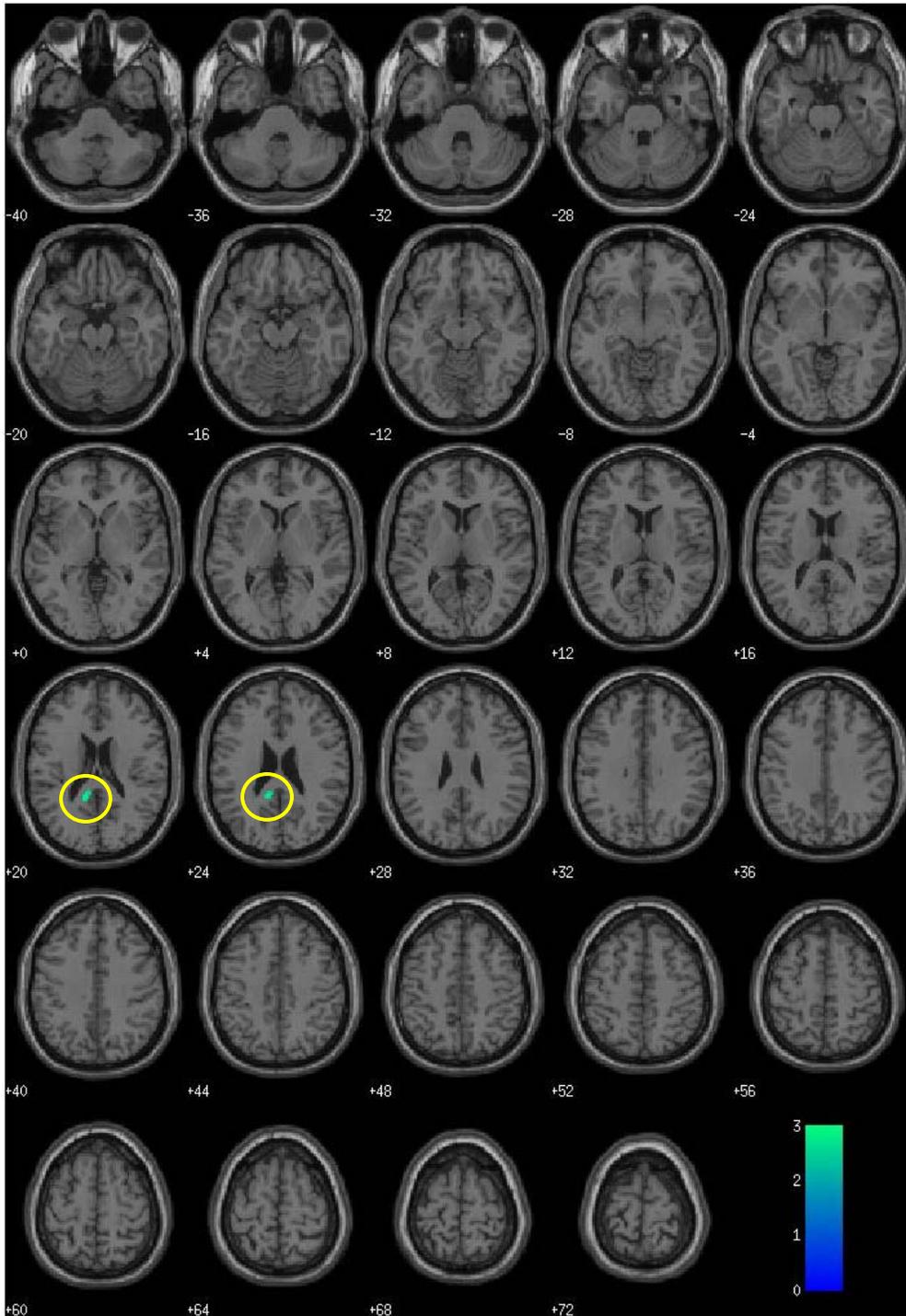


Figure 6. Depicted here are paralimbic areas where gray matter concentration is negatively correlated (uncorrected,  $p < .01$ ) with PCL-R **facet three** score, controlling for TIV. Results are overlaid on an SPM5 canonical T1 image. A mask of the paralimbic regions has been applied to facilitate visualization of regions where a priori hypotheses were made. Facet three items are need for stimulation/proneness to boredom, parasitic lifestyle, lack of realistic long term goals, impulsivity, and irresponsibility.

Region	MNI Coordinates	t-value
Superior temporal gyrus	-50 -28 2	2.71
Middle temporal gyrus	-56 -42 -6	3.20
Posterior cingulate	-10 -44 22	3.00
Supramarginal gyrus	44 -46 34	2.91
	-46 -44 34	2.71
Lingual gyrus	20 -72 0	3.17
Middle occipital gyrus	-32 -70 14	3.22

Table 12. Brain regions where gray matter concentration is negatively correlated (uncorrected,  $p < .01$ ) with PCL-R **facet three** score, controlling for TIV. Extent threshold = 10 voxels.

Region	MNI Coordinates	t-value
Inferior parietal	-48 -38 36	3.04
Middle temporal gyrus	-56 -42 -6	2.99
Cuneus	20 -88 18	2.69

Table 13. Brain regions where gray matter concentration is negatively correlated (uncorrected,  $p < .01$ ) with PCL-R **facet four** score, controlling for TIV. Extent threshold = 10 voxels.

## References

- Alterman, A. I., Cacciola, J. S., & Rutherford, M. J. (1993). Reliability of the Revised Psychopathy Checklist in substance abuse patients. *Psychological Assessment, 5*, 442-448.
- American Psychiatric Association. (1952). Diagnostic and statistical manual of mental disorders (1<sup>st</sup> ed.). Washington, DC: American Psychiatric Association.
- American Psychiatric Association. (1968). Diagnostic and statistical manual of mental disorders – Second edition. Washington, DC: American Psychiatric Association.
- American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders – Fourth edition. Washington, D.C.: American Psychiatric Association.
- Anderson, S. W., Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1999). Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nature Neuroscience, 2*, 1032-1037.
- Ashburner, J. & Friston, K. J. (2000). Voxel-based morphometry – The methods. *Neuroimage, 11*, 805-21.
- Ashburner, J. & Friston, K. J. (2005). Unified segmentation. *Neuroimage, 26*, 839-851.
- Barkataki, I., Kumari, V., Das, M., Taylor, P., & Sharma, T. (2006). Volumetric structural brain abnormalities in men with schizophrenia or antisocial personality disorder. *Behavioural Brain Research, 169*, 239-247.
- Bechara, A., Damasio, H., Damasio, A. R., & Lee, G. P. (1999). Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *Journal of Neuroscience, 19*, 5473-5481.

- Berlin, H. A., Rolls, E. T., & Kischka, U. (2004). Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. *Brain*, *127*, 1108-1126.
- Birbaumer, N., Veit, R., Lotze, M., Erb, M., Hermann, C., Grodd, W., et al. (2005). Deficient fear conditioning in psychopathy. *Archives of General Psychiatry*, *62*, 799-805.
- Blair, R. J. R. (2007). The amygdala and ventromedial prefrontal cortex in morality and psychopathy. *Trends in Cognitive Sciences*, *11*, 387-392.
- Brodmann, K. (1909). Vergleichende Lokalisationlehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Leipzig, Barth, J.A.
- Büchel, C. & Dolan, R. J. (2000). Classical fear conditioning in functional neuroimaging. *Current Opinion in Neurobiology*, *10*, 219-223.
- Büchel, C., Morris, J., Dolan, R. J., & Friston, K. (1998). Brain systems mediating aversive conditioning: An event-related fMRI study. *Neuron*, *20*, 947-957.
- Cleckley, H. (1982). *The Mask of Sanity*. New York: Mosby.
- Cooke, D. J. & Michie, C. (1997). An item response theory analysis of the Hare Psychopathy Checklist-Revised. *Psychological Assessment*, *9*, 3-14.
- Damasio, H., Grabowski, T., Frank, R., Galaburda, A. M., & Damasio, A. R. (1994). The return of Phineas Gage: Clues about the brain from the skull of a famous patient. *Science*, *264*, 1102-5.
- Eckert, M. A., Tenforde, A., Galaburda, A. M., Bellugi, U., Korenberg, J. R., Mills, D., et al. (2006). To modulate or not to modulate: Differing results in uniquely shaped Williams syndrome brains. *Neuroimage*, *32*, 1001-1007.

- Fein, G., Landman, B., Tran, H., McGillivray, S., Finn, P., Barakos, J., et al. (2006). Brain atrophy in long-term abstinent alcoholics who demonstrate impairment on a simulated gambling task. *Neuroimage*, 32, 1465-1471.
- First, M. B., Spitzer, R. L., Gibbon, M., Williams, J. B. W. (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders – Patient Edition (SCID-I/P)*. Washington, D. C.: American Psychiatric Press.
- Fischer, H., Andersson, J. L., Furmack, T., Wik, G., & Fredrikson, M. (2002). Right-sided human prefrontal brain activation during acquisition of conditioned fear. *Emotion*, 2, 233-241.
- Franklin, T. R., Acton, P. D., Maldjian, J. A., Gray, J. D., Croft, J. R., Dackis, C. A., et al. Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biological Psychiatry*, 51, 134-142.
- Hare, R. D. (1991). *Manual for the Hare Psychopathy Checklist-Revised*. Toronto: Multi Health Systems.
- Hare, R. D. (1998). Psychopaths and their nature: Implications for the mental health and criminal justice systems. In T. Millon, E. Simonsen, et al. (Eds.), *Psychopathy: Antisocial, criminal, and violent behavior* (pp. 188-212). New York: Guilford Press.
- Hare, R. D. (2003). *Manual for the Hare Psychopathy Checklist-Revised, 2nd ed.* Toronto: Multi-Health Systems.
- Harpur, T. J., Hakstian, A. R., & Hare, R. D. (1988). Factor structure of the Psychopathy Checklist. *Journal of Consulting and Clinical Psychology*, 56, 741-747.

- Harpur, T. J., Hare, R. D., & Hakstian, A. R. (1989). Two-factor conceptualization of psychopathy: Construct validity and assessment implications. *Psychological Assessment, 1*, 6-17.
- Hemphill, J. F., Hare, R. D., & Wong, S. (1998). Psychopathy and recidivism: A review. *Legal & Criminological Psychology, 3*, 139-170.
- Hemphill, J. F., Hart, S. D., & Hare, R. D. (1994). Psychopathy and substance use. *Journal of Personality Disorders, 8*, 169-180.
- Hiatt, K. D., & Newman, J. P. (2007). Behavioral evidence of prolonged interhemispheric transfer time among psychopathic offenders. *Neuropsychology, 21*, 313-318.
- Jatzko, A., Rothenhoefer, S., Schmitt, A., Gaser, C., Demirakca, T., Weber-Fahr, W., et al. (2006). Hippocampal volume in chronic posttraumatic stress disorder (PTSD): MRI study using two different evaluation methods. *Journal of Affective Disorders, 94*, 121-126.
- Kiehl, K. A. (2006). A cognitive neuroscience perspective on psychopathy: Evidence for paralimbic system dysfunction. *Psychiatry Research, 142*, 107-128.
- Kiehl, K. A., Smith A. M., Hare R. D., Mendrek A., Forster B. B., Brink J., et al. (2001). Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. *Biological Psychiatry, 50*, 677-84.
- Kinner, S. (2003). Psychopathy as an adaptation: Implications for society and social policy. In R. W. Bloom & N. Dess (Eds.), *Evolutionary psychology and violence: A primer for policymakers and public policy advocates* (pp. 57-81). Westport, CT: Praeger.

- Knight, D. C., Cheng, D. T., Smith, C. N., Stein E. A., Helmstetter, F. J. (2004). Neural substrates mediating human delay and trace fear conditioning. *Journal of Neuroscience*, 24, 218-228.
- Kosson, D. S. (1996). Psychopathy and dual task performance under focusing conditions. *Journal of Abnormal Psychology*, 105, 391-400.
- Kosson, D. S. (1998). Divided visual attention in psychopathic and non-psychopathic offenders. *Personality and Individual Differences*, 24, 373-391.
- Laakso, M. P., Vaurio, O., Koivisto, E., Savolainen, L., Eronen, M., Aronen, H. J., et al. (2001). Psychopathy and the posterior hippocampus. *Behavioural Brain Research*, 118, 187-93.
- Laakso, M. P., Gunning-Dixon, F., Vaurio, O., Repo-Tiihonen, E., Soininen, H., & Tiihonen, J. (2002). Prefrontal volumes in habitually violent subjects with antisocial personality disorder and type 2 alcoholism. *Psychiatry Research: Neuroimaging*, 114, 95-102.
- Matsuo, K., Nicoletti, M., Nemoto, K., Hatch, J. P., Peluso, M. A. M., Nery, F. G., et al. A voxel-based morphometry study of frontal gray matter correlates of impulsivity. *Human Brain Mapping*, 30, 1188-1195.
- Mechtcheriakov, S., Brenneis, C., Egger, K., Koppelstaetter, F., Schocke, M., & Marksteiner, J. (2007). A widespread distinct pattern of cerebral atrophy in patients with alcohol addiction revealed by voxel-based morphometry. *Journal of Neurology, Neurosurgery, and Psychiatry*, 78, 610-614.
- Mesulam, M. M., Ed. (2000). *Principles of behavioral and cognitive neurology*. New York: Oxford University Press.

- Müller J. L., Sommer, M., Wagner, V., Lange, K., Taschler, H., & Roeder, C. H. (2003). Abnormalities in emotion processing within cortical and subcortical regions in criminal psychopaths: Evidence from a functional magnetic resonance imaging study using pictures with emotional content. *Biological Psychiatry, 54*, 152-162.
- Müller, J. L., Gänßbauer, S., Sommer, M., Döhnel, K., Weber, T., Schmidt-Wilcke, T., et al. (2008). Gray matter changes in right superior temporal gyrus in criminal psychopaths. Evidence from voxel-based morphometry. *Psychiatry Research: Neuroimaging, 163*, 213-222.
- Nesse, R. M. (2005). Evolutionary Psychology and Mental Health. In D. M. Buss (Ed.), *The handbook of evolutionary psychology* (pp. 903-27). Hoboken, NJ: Wiley.
- Oliveira-Souza, R., Hare, R. D., Bramati, I. E., Garrido, G. J., Ignacio, F. A., Tovar-Moll, F., et al. (2008). Psychopathy as a disorder of the moral brain: Fronto-temporo- limbic grey matter reductions demonstrated by voxel-based morphometry. *NeuroImage, 40*, 1202-13.
- Pell, G. S., Briellmann, R. S., Chan, C. H., Pardoe, H., Abbott, D. F., & Jackson, G. D. (2008). Selection of the control group for VBM analysis: Influence of covariates, matching and sample size. *Neuroimage, 41*, 1324-1335.
- Raine, A., Ishikawa, S. S., Arce, E., Lencz, T., Knuth, K. H., Bihrlé, S., et al. (2004). Hippocampal structural asymmetry in unsuccessful psychopaths. *Biological Psychiatry, 55*, 185-91.
- Raine, A., Lencz, T., Bihrlé, S., LaCasse, L., & Colletti, P. (2000). Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Archives of General Psychiatry, 57*, 119-127.

- Raine, A., Lencz, T., Taylor, K., Hellige, J. B., Bihrlle, S., LaCasse, L., et al. (2003). Corpus callosum abnormalities in psychopathic antisocial individuals. *Archives of General Psychiatry*, 60, 1134-42.
- Schorn, D. (2007, January 13). Murder on his mind: Can scientific images show what's in the mind of a murderer? Retrieved June 3, 2008, from <http://www.cbsnews.com/stories/2007/01/11/48hours/main2352668.shtml>.
- Taki, Y., Kinomura, S., Sato, K., Goto, R., Inoue, K., Okada, K., et al. (2006). Both global gray matter volume and regional gray matter volume negatively correlate with lifetime alcohol intake in non-alcohol-dependent Japanese men: A volumetric analysis and a voxel-based morphometry. *Alcoholism: Clinical and Experimental Research*, 30, 1045-1050.
- Tanabe, J., Tregellas, J. R., Dalwani, M., Thompson, L., Owens, E., Crowley, T., et al. (2009). Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals. *Biological Psychiatry*, 65, 160-164.
- Tiihonen, J., Rossi, R., Laakso, M. P., Hodgins, S., Testa, C., Perez, J., et al. (2008). Brain anatomy of persistent violent offenders: More rather than less. *Psychiatry Research: Neuroimaging*, 163, 201-212.
- Tranel, D. (1994). 'Acquired sociopathy': The development of sociopathic behavior following focal brain damage. *Progress in Experimental Personality and Psychopathology Research*, 285-311.
- Veit, R., Flor, H., Erb, M., Hermann, C., Lotze, M., Grodd, W., et al. (2002). Brain circuits involved in emotional learning in antisocial behavior and social phobia in humans. *Neuroscience Letters*, 328, 233-236.

Yang, Y., Raine, A., Lencz., T., Bihrlle, S., LaCasse, L., & Colletti, P. (2005). Volume reduction in prefrontal gray matter in unsuccessful criminal psychopaths. *Biological Psychiatry*, 57, 1103-08.