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The role of prefrontal cortex in psychopathy

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Abstract

Psychopathy is a personality disorder characterized by remorseless and impulsive antisocial behavior. Given the significant societal costs of the recidivistic criminal activity associated with the disorder, there is a pressing need for more effective treatment strategies and, hence, a better understanding of the psychobiological mechanisms underlying the disorder. The prefrontal cortex (PFC) is likely to play an important role in psychopathy. In particular, the ventromedial and anterior cingulate sectors of PFC are theorized to mediate a number of social and affective decision-making functions that appear to be disrupted in psychopathy. This article provides a critical summary of human neuroimaging data implicating prefrontal dysfunction in psychopathy. A growing body of evidence associates psychopathy with structural and functional abnormalities in ventromedial PFC and anterior cingulate cortex. Although this burgeoning field still faces a number of methodological challenges and outstanding questions that will need to be resolved by future studies, the research to date has established a link between psychopathy and PFC.

Keywords: anterior cingulate cortex; antisocial personality disorder; crime; decision-making; emotion; neuroimaging; ventromedial prefrontal cortex.

Introduction

Psychopathy – a personality disorder characterized by callous and impulsive antisocial behavior – has devastating effects on society, particularly through crime. It is estimated that the prevalence of psychopathy is approximately 1% in the general population, but 15–25% in the USA adult prison population. Compared to prisoners without psychopathy, psychopathic prisoners have significantly higher rates of violent crime and recidivism. Given that (1) the societal cost of all criminal behavior in the US is estimated at over a trillion dollars per year, (2) psychopaths constitute up to 25% of the prison population, and (3) psychopaths are known to commit a disproportionate amount of crime, this disorder costs society roughly several hundred billion dollars per year. Despite the dire consequences of the disorder, there are currently no effective treatment strategies. One likely reason for the limited treatment options for psychopathy is that the psychobiological mechanisms of the disorder remain poorly understood. In this regard, neuroscience holds much promise. Identification of reliable neural correlates of psychopathy could serve to refine diagnostic criteria for the disorder, help predict the likelihood of future offense, locate potential biological targets for pharmacological treatment, and identify neuropsychological dysfunction that may be addressed through novel cognitive-behavioral therapies. The aim of this review article is to evaluate the evidence linking psychopathy to a particular area of the brain with diverse roles in cognitive and affective function – the prefrontal cortex (PFC).

Psychopathy and how it is measured

To assess the putative role of PFC in psychopathy, it is first necessary to detail the principal characteristics of the disorder and how they are typically measured for research purposes. The concept of psychopathy, in its modern formulation, is based largely on the personality disorder described at length by Hervey Cleckley in 'The Mask of Sanity' (Cleckley, 1941, 1976). To develop his conception of psychopathy, Cleckley cataloged a series of cases he had observed in his psychiatric practice – individuals with no apparent cognitive defect or traditional mental illness, yet a severe and pervasive disregard for the rights and welfare of others. In summary of these individuals, Cleckley states, 'My concept of the psychopath's functioning postulates a selective defect or elimination which prevents important components of normal experience from being integrated into the whole human reaction, particularly an elimination or attenuation of those strong affective components that ordinarily arise in major personal and social issues' (Cleckley, 1976, p. 374). Distilling the common personality and behavioral traits that he observed in these cases, Cleckley outlined a number of hallmark characteristics (Table 1, left column).

Building on Cleckley's conception, Robert Hare subsequently developed a formal assessment procedure for psychopathy in forensic settings, the Psychopathy Checklist-Revised (PCL-R; Hare, 2003), which has become the most widely used and most extensively validated measure of psychopathy. The PCL-R assessment involves a 60–90 min semi-structured interview and file review to obtain information used to rate 20 psychopathy-related items as 0, 1, or 2, depending on the degree to which the individual exhibits each trait (Table 1, middle column). As will later be shown in the review of neuroimaging studies of psychopathy, total scores on the PCL-R can be treated categorically to classify inmates as non-psychopathic (e.g., PCL-R$\leq$20) or psychopathic (e.g.,

Table 1 Measures of psychopathy.

Cleckley characteristics	Hare PCL-R items (Factors 1 or 2)	PPI subscales
Superficial charm and good intelligence	Glibness/Superficial Charm (F1)	Social Potency
Pathologic egocentricity and incapacity for love	Grandiose Sense of Self-Worth (F1) Need for Stimulation/Proneness to Boredom (F2)	Machiavellian Egocentricity Fearlessness
Untruthfulness and insincerity	Pathological Lying (F1) Conning/Manipulative (F1)	
Lack of remorse or shame	Lack of Remorse or Guilt (F1)	
General poverty in major affective reactions	Shallow Affect (F1)	
Unresponsiveness in general interpersonal relations	Callous/Lack of Empathy (F1) Parasitic Lifestyle (F2)	Coldheartedness
Poor judgment and failure to learn by experience	Poor Behavioral Controls (F2)	
Sex life impersonal, trivial, and poorly integrated	Promiscuous Sexual Behavior (F2) Early Behavior Problems (F2)	
Failure to follow any life plan	Lack of Realistic, Long-Term Goals (F2)	Carefree Non-planfulness
Inadequately motivated antisocial behavior Unreliability	Impulsivity (F2) Irresponsibility (F2) Failure to Accept Responsibility for Own Actions (F1) Many Short-term Marital Relationships (neither) Juvenile Delinquency (F2) Revocation of Conditional Release (F2) Criminal Versatility (neither)	Impulsive Non-conformity Blame Externalization
Absence of delusions and irrational thinking		
Absence of 'nervousness'		Stress Immunity
Specific loss of insight		
Fantastic and uninviting behavior with drink or sometimes without		
Suicide rarely carried out		

Similar items between measures are placed in the same row.

PCL-R≥30) for between-group analyses, or continuously, to provide a quantity for correlation or regression analyses. Furthermore, the PCL-R has been shown to consist of interrelated clusters of items, or factors. The conventional two-factor model consists of an interpersonal/affective cluster (Factor 1) and an antisocial/lifestyle cluster (Factor 2) (Harpur et al., 1989; Hare, 2003). Each factor score can be entered separately in regression analyses.

Although forensic studies of psychopathy have almost uniformly employed the PCL-R, studies of non-criminal samples have commonly used self-report scales to measure psychopathy-related traits. The most widely used such instrument, the Psychopathic Personality Inventory (PPI) (Lilienfeld and Andrews, 1996), includes 187 first-person statements (e.g., 'I am easily flustered in pressured situations'), which are rated on a 4-point scale (1=false, 2=mostly false, 3=mostly true, 4=true). Total scores are obtained by summing across items after reversing specified items. The test consists of eight factors or subscales (Table 1, right column).

With the cardinal features of psychopathy (and their measurement) in mind, we will now turn to a discussion of how this disorder may relate to dysfunction in the PFC.

Functional anatomy of PFC relevant to psychopathy

Ventromedial PFC and pseudopsychopathy

Perhaps the earliest evidence for a critical role of PFC in psychopathic personality is the famous case of Phineas Gage, the 19th century railroad construction foreman who had an iron rod shot through his face and out the top of his head in a freak excavation accident (Harlow, 1868). Remarkably, Gage survived the blast, but his personality was permanently altered. Whereas before the accident Gage had been dependable and trustworthy, afterwards he became disrespectful, profane, impulsive, and unreliable – traits reminiscent of psychopathy. Based on posthumous measures of his skull, Gage's brain injury was projected to primarily involve the medial PFC (Damasio et al., 1994). Throughout the 20th century, a number of similar cases of personality change following brain injury were reported. In 1975, Blumer and Benson coined the term 'pseudopsychopathy' to encapsulate the personality changes ('the lack of adult tact and restraints') observed in a subset of neurological patients with brain damage involving ventral PFC (Blumer and Benson, 1975). The connection between PFC injury and pseudopsychopathic changes was

subsequently elaborated by Antonio Damasio and colleagues. Reports from the Damasio group associated damage to a specific sector of the PFC – the ventromedial prefrontal cortex (vmPFC) (Figure 1) – with an array of emotion and decision-making deficits, including conspicuously diminished guilt, shame, and empathy; irritability; poor planning; irresponsibility; and failure to learn from punishment (Eslinger and Damasio, 1985; Damasio, 1994; Bechara et al., 1997; Barrash et al., 2000). Experimentally, both psychopaths and vmPFC lesion patients have demonstrated reduced autonomic arousal to emotionally charged stimuli (Hare et al., 1978; Damasio et al., 1990; Patrick et al., 1993, 1994) and deficits in reversal learning (Hornak et al., 2004; Budhani et al., 2006). More recent studies have linked vmPFC damage to changes in moral judgment (Ciaramelli et al., 2007; Koenigs et al., 2007; Young et al., 2010), economic decision-making (Koenigs and Tranel, 2007; Krajbich et al., 2009; Moretti et al., 2009), and reductions in negative affect (Koenigs et al., 2008a,b). In some cases, comparable moral and economic decision-making profiles have been observed in primary (low anxious) psychopaths (Koenigs et al., 2010, 2011). Overall, this collection of findings hints strongly that vmPFC dysfunction may underlie certain aspects of psychopathy (Blair, 2007, 2008). Accordingly, the review of neuroimaging results for psychopathy below will specifically address the extent to which this neuroanatomical hypothesis has been supported.

Before evaluating neuroimaging studies of vmPFC dysfunction in psychopathy, it is perhaps first worthwhile to consider the normal function of vmPFC, as it is pertains to emotion, social/moral behavior, and decision-making. Although there is no clear consensus on the essential function of vmPFC, there are several proposals with significant empirical support. The seminal theory of vmPFC function is Damasio's 'somatic marker hypothesis' (Damasio, 1994, 1996), which was initially developed to explain the personality and behavioral changes and decision-making deficits associated with vmPFC damage. This theory, supported by neuropsychological and electrodermal data (Bechara et al., 1997), posits that vmPFC links potential decision outcomes with an associated emotion, or somatic state, based on previous experiences of reward or punishment, which effectively marks the outcome as something to pursue or avoid. A second, related proposal supported by more recent functional neuroimaging data is that vmPFC plays a key role in representing the value of goal-directed outcomes and options (Grabenhorst and Rolls, 2011; O'Doherty, 2011). A third proposal is that vmPFC serves to regulate negative affect by exerting top-down inhibition of amygdala, which is noted for its role in processing emotionally and socially relevant information, particularly fear and anxiety (Phelps et al., 2004; Milad et al., 2006; Rauch et al., 2006). This model is supported by human and animal data from fear conditioning paradigms, as well as human imaging data of anxiety disorders (but see also Myers-Schulz and Koenigs, 2012). However, this amygdala-based model appears to conflict with the longstanding theory that psychopathy arises from an underlying deficit in processing fear – the 'low fear hypothesis' (Lykken, 1957, 1995). If vmPFC serves to regulate negative affect through top-down inhibition of the amygdala, then vmPFC dysfunction would be associated with disinhibition of the amygdala, and consequently higher levels of fear and anxiety. According to this model, vmPFC dysfunction would seemingly not be expected to yield psychopathic personality traits. Finally, a fourth model suggests that vmPFC may underlie aspects of self-processing, such as self-reflection and rumination, which facilitate social emotions such as empathy, guilt, and embarrassment (Mitchell et al., 2005; Beer et al., 2006; Qin and Northoff, 2011). Regardless of the precise function (or functions) of vmPFC, it is a brain area that warrants particular attention in the neuroscientific study of psychopathy.

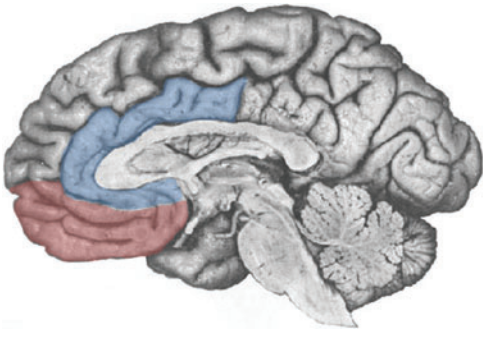

Figure 1 Mid-sagittal view of the brain illustrating vmPFC (red) and ACC (blue).
The vmPFC also includes the medial sector of the orbital surface.

Despite the intriguing degree of similarity between psychopathic personality characteristics and personality changes accompanying vmPFC damage, it is important to note that vmPFC lesion patients do not typically exhibit the full-blown disorder, particularly with respect to antisocial and criminal behavior. Moreover, there are additional regions of PFC whose functions are also likely germane to psychopathy.

Anterior cingulate cortex and behavioral control

A second area of PFC that may play an especially important role in psychopathy is the anterior cingulate cortex (ACC) (Figure 1). The ACC is widely regarded to be a key brain area for motivating and regulating behavior through cognitive and affective mechanisms. Activity in the ACC has been related to a number of functions potentially relevant to psychopathy, including reward, punishment, pain, negative affect, empathy, error detection, performance monitoring, and cognitive control (for reviews see Devinsky et al., 1995; Bush et al., 2000; Ridderinkhof et al., 2004; Rushworth and Behrens, 2008; Etkin et al., 2011; Shackman et al., 2011). Moreover, like the vmPFC, lesion studies of the ACC confirm its importance for emotion and social behavior; cingulotomy patients typically exhibit blunted affect and reduced motivation but greater irritability and social disinhibition (Tow and Whitty, 1953). The functional relationship between ACC and vmPFC is reflected in brain structure, as the two regions are anatomically adjacent with dense reciprocal connections (Carmichael and Price, 1996; Ongur and Price, 2000).

Although this section has highlighted two particular subregions of PFC – the vmPFC and ACC – that figure to play a role in psychopathic behavior, it is important to keep in mind that these regions interact and interconnect with more dorsal and lateral sectors of PFC as well. The following section will summarize neuroimaging data associating psychopathy with structural and functional deficits in PFC.

Neuroimaging evidence for PFC dysfunction in psychopathy

Scope of review

Before summarizing the neuroimaging results, this section will first outline the scope of the studies that were evaluated for this article. This review covers original published reports of human neuroimaging data wherein the authors associate abnormalities in PFC structure or function with psychopathy in adults (in particular, neuroimaging reports with 'psychopathy', 'psychopaths', or 'psychopathic' in the title; see Table 2). This approach omits two important related lines of research, which are briefly mentioned here. One is the study of the neural correlates of antisocial traits commonly associated with, but not limited to, psychopathy. Examples include violence (Volkow et al., 1995; Raine et al., 1997), antisocial personality disorder (Raine et al., 2000; Barkataki et al., 2006), aggressive/impulsive behavior (Dolan et al., 2002), and pathological lying (Yang et al., 2005a). Although these traits may commonly overlap with psychopathy, none are unique to psychopathy. Accordingly, neuroimaging findings associated with these traits may not specifically inform the neural basis of psychopathy, and thus such studies are omitted in this review. (For a recent review on neuroimaging of antisocial behavior see Yang and Raine, 2009.) The other line of research omitted here is the neuroimaging of children and adolescents with psychopathic tendencies (e.g., Marsh et al., 2008; De Brito et al., 2009; Jones et al., 2009). Research in children and adolescents is of course critical for understanding the development of antisocial behavior. However, the comparison of imaging data from adult and child/adolescent studies can be challenging for a number of reasons. One reason is that the diagnostic criteria for antisocial behavior in children/adolescents (such as conduct disorder) are necessarily somewhat different than the criteria for adult psychopathy, reflecting the considerable differences in life circumstances for children, adolescents, and adults. A second reason is that the brain undergoes substantial structural and functional development throughout childhood and adolescence, such that neuroimaging findings vary significantly across pre-adult age groups, even among neurologically and psychologically healthy individuals (Giedd et al., 2009). Given these important differences, the child/adolescent literature warrants its own separate review and evaluation. (For a recent review on neuroimaging findings related to antisocial behavior in children, see Crowe and Blair, 2008.)

PFC structure in psychopathy: gray matter

First we consider studies of PFC gray matter (GM) structure. These studies are largely based on T1 magnetic resonance imaging (MRI) data, from which one can compute measures of GM volume, thickness, and density/concentration. Study designs include between-group analyses (i.e., comparison of psychopathic and non-psychopathic groups) as well as correlation/regression analyses that relate GM measures to psychopathy severity. Together, the studies described in this section converge to associate psychopathy with reductions in PFC GM.

A series of studies by Yang, Raine and colleagues advanced this area of research by recruiting subjects with varying degrees of psychopathy from temporary employment agencies. The first such study (Yang et al., 2005b) compared GM volume across the entire PFC in three subject types: 'unsuccessful' psychopaths (those with one or more criminal convictions; n=16), 'successful' psychopaths (no criminal convictions; n=13), and a non-psychopathic comparison group (n=23). Overall, PFC GM volume correlated negatively with total PCL-R score, as well as with each factor/subscale of psychopathy. Unsuccessful psychopaths had lower PFC volumes than both successful psychopaths and non-psychopaths, although successful psychopaths and non-psychopaths did not significantly differ with respect to PFC volume. In a follow-up study, Yang et al. found reduced GM volume specifically in lateral PFC and ventral PFC/orbitofrontal cortex (OFC) in unsuccessful psychopaths, but not in successful psychopaths, as compared to non-psychopaths (Yang et al., 2010). In a separate study, Yang et al. used cortical pattern matching to examine regional cortical thickness in a group of 27 psychopathic adult males to a group of 32 non-psychopathic males, matched for age, gender, and substance abuse (Yang et al., 2009a). The psychopathic group had reduced cortical thickness in right lateral PFC and, to a lesser extent, in right vmPFC and rostral ACC. In these areas, cortical thickness was negatively correlated with the affective facet of psychopathy (a subset of Factor 1).

Focusing on brain areas involved in moral cognition, de Oliveira-Souza et al. used voxel-based morphometry (VBM) to evaluate GM volume (GMV) and concentration (GMC) in a group of 15 adult neuropsychiatric patients diagnosed with Antisocial Personality Disorder (ASPD) and a group of 15 neuropsychiatric healthy adults matched for age, gender, education, and cognitive ability (de Oliveira-Souza et al., 2008). The ASPD group had significant GMV reductions in OFC and frontopolar cortex, including parts of vmPFC. In addition, GMC in an area of posterior OFC/vmPFC significantly correlated with Factor 1 scores in the patient group.

Whereas the aforementioned studies were performed in non-forensic settings, a number of structural imaging studies of psychopathy have involved incarcerated subject samples. One advantage to studying incarcerated samples is that it is typically easier to recruit individuals with especially high psychopathy scores (see section on 'Methodological caveats' below). In one of the first such studies, Muller et al. used VBM to compare GM in a group of 17 adult male forensic

Table 2 Neuroimaging studies associating psychopathy with abnormal PFC structure or function.

First author	Year	Title	Type of imaging	Type of analysis	PCL-R cut-off for P	Mean PCL-R for P
Birbaumer	2005	Deficient fear conditioning in **psychopathy**: a functional magnetic resonance imaging study	F	BG	15	24.9
Bjork	2012	**Psychopathic** tendencies and mesolimbic recruitment by cues for instrumental and passively obtained rewards	F	C/R	n/a	n/a
Boccardi	2011	Cortex and amygdala morphology in **psychopathy**	S	BG	21	29.9
Craig	2009	Altered connections on the road to **psychopathy**	S	BG, C/R	25	28.4
de Oliveira-Souza	2008	**Psychopathy** as a disorder of the moral brain: fronto-temporo-limbic grey matter reductions demonstrated by voxel-based morphometry	S	BG, C/R	n/a	n/a
Dolan	2009	**Psychopathy** and functional magnetic resonance imaging blood oxygenation level-dependent responses to emotional faces in violent patients with schizophrenia	F	BG, C/R	n/a	n/a
Ermer	2011	Aberrant paralimbic gray matter in criminal **psychopathy**	S	C/R	n/a	n/a
Glenn	2009	The neural correlates of moral decision-making in **psychopathy**	F	C/R	n/a	n/a
Gordon	2004	Functional differences among those high and low on a trait measure of **psychopathy**	F	BG	n/a	n/a
Harenski	2009	Neuroticism and **psychopathy** predict brain activation during moral and nonmoral emotion regulation	F	C/R	n/a	n/a
Harenski	2010	Aberrant neural processing of moral violations in criminal **psychopaths**	F	BG, C/R	30	31.8
Intrator	1997	A brain imaging (single photon emission computerized tomography) study of semantic and affective processing in **psychopaths**	F	BG	25	29.9
Kiehl	2001	Limbic abnormalities in affective processing by criminal **psychopaths** as revealed by functional magnetic resonance imaging	F	BG	24	32.8
Ly	2012	Cortical thinning in **psychopathy**	F, S	BG	30	31.8
Motzkin	2011	Reduced prefrontal connectivity in **psychopathy**	F, S	BG	30	31.9
Muller	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	F	BG	31	36.8
Muller	2008	Gray matter changes in right superior temporal gyrus in criminal **psychopaths**. Evidence from voxel-based morphometry	S	BG	28	33.4
Muller	2008	Disturbed prefrontal and temporal brain function during emotion and cognition interaction in criminal **psychopathy**	F	BG	28	30.5
Rilling	2007	Neural correlates of social cooperation and non-cooperation as a function of **psychopathy**	F	C/R	n/a	n/a
Sadeh	2011	Emotion disrupts neural activity during selective attention in **psychopathy**	F	C/R	n/a	n/a
Sheng	2010	Default network deactivations are correlated with **psychopathic** personality traits	F	C/R	n/a	n/a
Sommer	2010	In **psychopathic** patients emotion attribution modulates activity in outcome-related brain areas	F	BG	28	28.6
Veit	2010	Aberrant social and cerebral responding in a competitive reaction time paradigm in criminal **psychopaths**	F	C/R	n/a	n/a
Yang	2005	Volume reduction in prefrontal gray matter in unsuccessful criminal **psychopaths**	S	BG, C/R	23	28.4
Yang	2009	Abnormal temporal and prefrontal cortical gray matter thinning in **psychopaths**	S	BG, C/R	n/a	n/a
Yang	2010	Morphological alterations in the prefrontal cortex and the amygdala in unsuccessful **psychopaths**	S	BG	23	n/a

Explicit references to psychopathy in the article titles are in bold.
P, psychopathy; S, structural; F, functional; C/R, correlation or regression analysis; BG, between-group analysis; n/a, not applicable.

inpatients diagnosed with psychopathy (based on the PCL-R) to a group of 17 non-incarcerated, healthy age-matched males (Muller et al., 2008). The psychopathic group had significant GM reductions in right dorsal ACC and dorsolateral PFC bilaterally. In a subsequent study, Boccardi et al. used a cortical pattern matching technique to compare GM density in a group of 26 adult male violent offenders to a group of 25 adult male age-matched non-offenders (Boccardi et al., 2011). The greatest group differences in PFC were observed in vmPFC and ACC – in both areas the psychopathic group had lower GM density. Recently, Ly et al. compared cortical thickness in a group of adult male psychopathic prison inmates (n=21) to a group of adult male non-psychopathic prison inmates (n=31) matched for age, IQ, and substance abuse history (Ly et al., 2012). The psychopathic inmates exhibited significantly thinner GM in the left dorsal ACC and adjacent dorsomedial PFC as well as left dorsolateral PFC. In by far the largest study to date, Ermer et al. used VBM and multiple regression analysis in a group of 254 adult incarcerated men to examine the relationship between psychopathy severity and GM structure, while covarying for age, substance use, and overall brain volume (Ermer et al., 2011). They found a significant negative relationship between total PCL-R score and GMV/GMC in OFC and vmPFC. In addition, they found a negative relationship between GMC and Factor 2 score in left OFC/vmPFC.

In summary, across all of the aforementioned studies, psychopathy was associated with significant reductions in prefrontal GM, with the most commonly reported subregions being vmPFC/OFC and ACC.

PFC structure in psychopathy: white matter

There have been comparatively fewer studies examining PFC white matter (WM) structure in psychopathy. Diffusion tensor imaging (DTI) is an MRI technique for assessing microstructural integrity of WM tracts (Pierpaoli and Basser, 1996). To date, only two studies have used DTI to study psychopathy (Craig et al., 2009; Motzkin et al., 2011) and both associate psychopathy with reduced integrity of the uncinate fasciculus, a major WM tract connecting PFC with subcortical structures. Importantly, the uncinate fasciculus includes fibers connecting vmPFC and amygdala. Despite the remarkable convergence of findings between these two studies, there is a need for subsequent studies to confirm the initial findings, which are based on relatively small samples. The first study (Craig et al., 2009) included nine psychopaths and nine non-psychopaths recruited from a forensic psychiatric hospital, whereas the second study (Motzkin et al., 2011) included 14 psychopaths and 13 non-psychopaths recruited from a medium-security prison. Nonetheless, these initial studies of WM integrity are consistent with PFC dysfunction in psychopathy.

PFC function in psychopathy

Functional imaging studies of psychopathy can be divided into two groups based on the type of fMRI analysis: resting-state functional connectivity MRI (rs-fcMRI) or task-related fMRI. rs-fcMRI measures the degree of spontaneously correlated BOLD activity between brain regions while the subject is at rest (e.g., staring at a fixation cross with no task demands). The degree of spontaneously correlated activity at rest is thought to reflect the extent to which macroscopic brain areas are functionally interconnected. Two studies have identified reduced PFC functional connectivity in criminal psychopaths using rs-fcMRI. One study of 20 psychopathic and 20 non-psychopathic adult male prison inmates found reduced functional connectivity between the amygdala and anterior vmPFC in psychopathy (Motzkin et al., 2011), whereas a second study of the same subject sample found reduced functional connectivity between the dorsal ACC and insula (Ly et al., 2012).

Results from task-related fMRI studies are somewhat more difficult to summarize, as they have employed a range of stimulus and response paradigms to test hypotheses regarding particular patterns of brain activation. Despite a variety of task paradigms, a considerable number of studies associate psychopathy with abnormal activity within vmPFC and/or ACC. Such findings have been obtained in studies of fear conditioning (Birbaumer et al., 2005), cognitive control (Sadeh et al., 2011), speech production (Sheng et al., 2010), affective theory of mind (Sommer et al., 2010), anticipation and receipt of reward (Bjork et al., 2012), social competition and aggression (Veit et al., 2010), social cooperation and defection (Rilling et al., 2007), recollection of emotionally salient words (Kiehl et al., 2001), viewing emotionally salient scenes (Muller et al., 2003; Harenski et al., 2009), viewing facial expressions of emotion (Dolan and Fullam, 2009), and viewing pictures of moral violations (Harenski et al., 2010). Psychopathy has also been associated with PFC abnormalities outside vmPFC/ACC, including during tasks involving social-affective processing, such as moral decision-making (Glenn et al., 2009) and recognition of facial expressions of emotion (Gordon et al., 2004).

Overall, the available functional imaging data suggest abnormal PFC function in psychopathy, particularly within vmPFC and ACC.

Caveats

Methodological caveats

When considering the results of neuroimaging studies of psychopathy, it is important to keep in mind some of the methodological challenges associated with studying this disorder. One significant issue is how 'psychopathy' is defined. As described above, most studies of criminal populations rely on the Hare PCL-R to define psychopathy. The PCL-R manual advises standard cut-off scores for grouping subjects: total scores of 30 or greater indicate psychopathy, scores of 20 or less indicate non-psychopathy, and scores of 21–29 are considered intermediate (Hare, 2003). However, because subjects with high PCL-R scores (i.e., ≥30) are typically difficult to recruit for imaging studies, especially outside forensic settings, researchers have employed a variety of minimum PCL-R total scores to define psychopathy. Cut-off scores in

the mid-20s (or even lower) are fairly common (see Table 2). The issue with such lenient classification criteria is that the imaging findings in the 'psychopathic' group may pertain more generally to ASPD or externalizing behavior, rather than specifically to psychopathy, *per se*.

A second methodological challenge for studies of psychopathic criminals is assembling a group of non-psychopathic comparison subjects that are well matched to the psychopathic subjects on important variables that can affect brain structure and function (e.g., age, education, cognitive ability, substance abuse history). In several of the studies described above, the psychopathic group and non-psychopathic comparison group differed dramatically on one or more of these variables (e.g., Muller et al., 2008; Boccardi et al., 2011).

Finally, it is important to make a distinction between studies that involve criminal offenders who meet the diagnostic criteria for psychopathy (e.g., Muller et al., 2003; Harenski et al., 2010; Motzkin et al., 2011; Ly et al., 2012) vs. those studies that involve community samples of relatively normal individuals with varying degrees of 'psychopathic' personality traits (e.g., Rilling et al., 2007; Harenski et al., 2009; Sheng et al., 2010; Sadeh et al., 2011; Bjork et al., 2012). The neurobiological features that correlate with PPI scores in normal functioning individuals (e.g., college undergraduates) may not necessarily correspond to the same features associated with the categorical diagnosis of psychopathy. Future neuroimaging research will be necessary to resolve this question.

Neurobiological caveats

Although this review has focused primarily on subregions of PFC, there are of course regions outside PFC that may also play important roles in psychopathy. In particular, the amygdala has been the focus of considerable attention, with numerous studies associating psychopathy with abnormal size, shape, or activity of this subcortical structure (Birbaumer et al., 2005; Dolan and Fullam, 2009; Glenn et al., 2009; Harenski et al., 2009, 2010; Yang et al., 2009b, 2010; Boccardi et al., 2011). Furthermore, the anterior temporal cortex, which overlies and densely interconnects with the amygdala, has also been repeatedly associated with structural and functional deficits in psychopathy (Kiehl et al., 2004; Yang et al., 2009a; Ermer et al., 2011; Ly et al., 2012). Additional areas that warrant mention are the hippocampus (Laakso et al., 2001; Boccardi et al., 2010), insula (de Oliveira-Souza et al., 2008; Ly et al., 2012), and striatum (Buckholtz et al., 2010; Glenn et al., 2010). The role of PFC in psychopathy probably depends, to a large extent, on its interactions with these areas outside PFC; therefore, future studies of PFC functional and structural connectivity will help elucidate the neurobiological mechanisms of the disorder.

Conclusion

The neuroscientific study of psychopathy has advanced rapidly in recent years, with an increasing appreciation for the potential of the results to impact law, psychiatric medicine, and public policy. Although a growing number of studies are converging to implicate the PFC (and specific subsectors thereof) as key pathophysiological substrates for the disorder, the field continues to face a number of methodological challenges and limitations that will need to be addressed in future studies. Moreover, a comprehensive understanding of prefrontal dysfunction in psychopathy will no doubt depend on further refinement of the basic systems-level understanding of normal prefrontal function. Pending future progress in these areas of research, the sober assessment of Hervey Cleckley from 'The Mask of Sanity' still applies: 'I do not believe that the cause of the psychopath's disorder has yet been discovered and demonstrated. Until we have more and better evidence than is at present available, let us admit the incompleteness of our knowledge and modestly pursue our inquiry'.

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