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Impulsive-antisocial psychopathic traits linked to increased volume and functional connectivity within prefrontal cortex

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Abstract

Psychopathy is a personality disorder characterized by callous lack of empathy, impulsive antisocial behavior, and criminal recidivism. Studies of brain structure and function in psychopathy have frequently identified abnormalities in the prefrontal cortex. However, findings have not yet converged to yield a clear relationship between specific subregions of prefrontal cortex and particular psychopathic traits. We performed a multimodal neuroimaging study of prefrontal cortex volume and functional connectivity in psychopathy, using a sample of adult male prison inmates ($N = 124$). We conducted volumetric analyses in prefrontal subregions, and subsequently assessed resting-state functional connectivity in areas where volume was related to psychopathy severity. We found that overall psychopathy severity and Factor 2 scores (which index the impulsive/antisocial traits of psychopathy) were associated with larger prefrontal subregion volumes, particularly in the medial orbitofrontal cortex and dorsolateral prefrontal cortex. Furthermore, Factor 2 scores were also positively correlated with functional connectivity between several areas of the prefrontal cortex. The results were not attributable to age, race, IQ, substance use history, or brain volume. Collectively, these findings provide evidence for co-localized increases in prefrontal cortex volume and intra-prefrontal functional connectivity in relation to impulsive/antisocial psychopathic traits.

Key words: psychopathy; medial orbitofrontal cortex; dorsolateral prefrontal cortex; volume; functional connectivity

Introduction

Psychopathy is a mental health disorder characterized by shallow affect, callous disregard for others, and impulsive antisocial behavior. Present in roughly one-fourth of adult prison inmates, psychopathy is associated with a disproportionately high incidence of violent crime, substance abuse, and recidivism (Smith and Newman, 1990; Hare, 2003). Identifying the psychological

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and neurobiological mechanisms underlying these deficits could thus have profound implications for the clinical and legal management of psychopathic criminals, as well as for the basic understanding of human social behavior.

One area of the brain that is believed to play a central role in the pathophysiology of psychopathy is the prefrontal cortex. Subregions of the prefrontal cortex mediate a variety of functions that contribute to behavioral control, emotion, social cognition, and value-based decision-making. For instance, ventromedial prefrontal cortex (vmPFC) and medial orbitofrontal cortex (mOFC) are thought to represent the values of potential decision outcomes and update these values based on ongoing experiences of reward or punishment (Damasio, 1996; Grabenhorst and Rolls, 2011), as well as subserve aspects of moral judgment (Greene and Haidt, 2002) and emotion states such as guilt, regret, and empathy (Barrash *et al*., 2000; Camille *et al*., 2004; Vollm *et al*., 2006). Dorsolateral prefrontal cortex (dlPFC), which consists of the middle frontal gyrus (MFG) and superior frontal gyrus (SFG), has been implicated in abstract reasoning (Greene *et al*., 2004) and cognitive control (Miller and Cohen, 2001). Also, the anterior cingulate cortex (ACC), a limbic structure surrounded by and densely interconnected with prefrontal cortex, has been linked to error detection, performance monitoring, cognitive control, goal-directed behavior, and emotion processing (Devinsky *et al*., 1995; Shackman *et al*., 2011). Psychopathic individuals, as well as individuals with acquired damage to the prefrontal cortex, display deficits in many of these functions. Indeed, some of the earliest evidence to suggest involvement of prefrontal cortex dysfunction in psychopathy came from studies of patients who began to display psychopathic-like traits—including conspicuously diminished guilt, shame, and empathy; irritability; poor planning; irresponsibility; and failure to learn from punishment—after acquiring damage to the vmPFC/mOFC (Eslinger and Damasio, 1985; Damasio, 1994; Bechara *et al*., 1997; Barrash *et al*., 2000). Subsequent behavioral studies of psychopathic individuals have expanded on these findings, documenting deficits in reversal learning (Budhani *et al*., 2006), response perseveration (Molto *et al*., 2007), moral judgment (Koenigs *et al*., 2012), and economic decision-making (Koenigs *et al*., 2010).

More recently, brain imaging studies have attempted to elucidate the structural and functional neural correlates of psychopathy. While a host of studies have demonstrated abnormal structure and function of the prefrontal cortex in psychopathy, the findings have not yet converged to yield a clear relationship between abnormalities in specific subregions of prefrontal cortex and particular psychopathic traits. In forensic studies, psychopathic traits are typically measured using the Psychopathy Checklist-Revised (PCL-R), from which levels of overall psychopathy severity (PCL-R Total score), interpersonal-affective psychopathic traits (Factor 1 score), and impulsive-antisocial traits (Factor 2 score) can be assessed. Studies reporting group differences between psychopathic and non-psychopathic groups have almost exclusively found prefrontal gray matter reductions in psychopathic individuals (Yang *et al*., 2005; de Oliveira-Souza *et al*., 2008; Muller *et al*., 2008; Ly *et al*., 2012; Contreras-Rodriguez *et al*., 2015), but correlational findings between PCL-R Total, Factor 1, and Factor 2 scores and prefrontal gray matter have been mixed. For example, medial PFC volume has inversely been correlated with Factor 1 scores (de Oliveira-Souza *et al*., 2008; Ermer *et al*., 2013; Contreras-Rodriguez *et al*., 2015), Factor 2 scores (Cope *et al*., 2014), and PCL-R Total scores (de Oliveira-Souza *et al*., 2008; Ermer *et al*., 2013; Cope *et al*., 2014) in a variety of subject populations [adult male and female community psychiatric patients (de Oliveira-Souza *et al*., 2008), incarcerated adult male offenders (Ermer *et al*., 2012a; Contreras-Rodriguez *et al*., 2015), incarcerated male youth offenders (Ermer *et al*., 2013), and incarcerated female youth offenders (Cope *et al*., 2014)], whereas positive correlations between medial PFC volumes and Factor 1 scores (Cope *et al*., 2012) and Factor 2 scores (Cope *et al*., 2012; Ermer *et al*., 2013; Contreras-Rodriguez *et al*., 2015) have also been observed in these and other samples [a community sample of adult male and female substance abusers (Cope *et al*., 2012)]. It is notable that two of these studies (Ermer *et al*., 2013; Contreras-Rodriguez *et al*., 2015) found that medial PFC volume related negatively to Factor 1 scores and positively to Factor 2 scores within the same sample. The mixed findings may be attributable to differences in analysis methodologies (e.g. voxel-based morphometry *vs* surface-based morphometry; manual *vs* automated tracing methods; measurement of either gray matter volume, density, or thickness; peak height *vs* cluster-based statistical thresholds), inclusion/exclusion of moderating variables (e.g. total brain volume, IQ, substance abuse severity), subject populations (e.g. prison inmates *vs* community samples; adult *vs* youth samples; male *vs* female samples), psychopathy severity, and sample sizes.

In addition to structural measures such as volume, another important metric of prefrontal cortex integrity is resting-state functional connectivity (RSFC). RSFC measures the degree of spontaneously correlated blood–oxygen–level dependent (BOLD) activity between brain regions while a subject is at rest. The degree of spontaneously correlated activity at rest is thought to reflect the extent to which macroscopic brain areas are functionally interconnected. As such, RSFC provides valuable information about the integrity of communication between different areas of the brain. Studies have found decreased RSFC between the prefrontal cortex and amygdala (Motzkin *et al*., 2011), posterior cingulate cortex (Pujol *et al*., 2012), insula (Ly *et al*., 2012), and limbic and paralimbic regions (Contreras-Rodriguez *et al*., 2015) in psychopathic individuals (but see Shannon *et al*., 2011; Juarez *et al*., 2013). On the other hand, two studies provide evidence for increased RSFC within prefrontal cortex in psychopathic individuals (Contreras-Rodriguez *et al*., 2015; Philippi *et al*., 2015), particularly in relation to increasing Factor 2 scores (Philippi *et al*., 2015). With regard to the relationship between the structural and functional abnormalities in the prefrontal cortex in psychopathy, only two studies have reported evidence of co-localization of these deficits within the same sample (Ly *et al*., 2012; Contreras-Rodriguez *et al*., 2015).

To help resolve some of the inconsistencies and gaps in knowledge reviewed here, we conducted a multimodal neuroimaging investigation of prefrontal cortex structure and function in psychopathy. Using a mobile scanner, we collected magnetic resonance imaging (MRI) from a sample of adult male prison inmates ($N = 124$) with a broad range of psychopathy severity. First, we assessed whether the volumes of frontal lobe subregions were correlated with psychopathy severity, in terms of PCL-R Total, Factor 1, and Factor 2 scores. We performed region of interest (ROI)-based analyses in two separate image processing software programs (FreeSurfer and SPM), as well as a voxel-wise analysis in SPM. Next, we analyzed RSFC data from the same participants to determine whether the observed prefrontal structural abnormalities were accompanied by alterations in prefrontal RSFC. This set of analyses comprises the largest study to date to examine both structural and functional features of the prefrontal cortex in psychopathy.

Table 1. Participant characteristics

	All ($n = 124$)		Non-psychopathic ($n = 35$)		Intermediate ($n = 48$)		Psychopathic (n=41)		P[a]
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age	31.6	7.3	31.3	7.9	31.8	6.7	31.5	7.7	0.93
IQ	98.1	11.5	97.3	12.0	95.3	11.6	101.5	10.3	0.19
Total PCL-R score	24.8	7.1	15.3	3.4	25.6	2.3	32.1	1.6	<.001
Factor 1 score	9.2	3.3	5.5	2.1	9.3	2.3	12.3	1.8	<.001
Factor 2 score	13.6	3.9	8.6	2.8	14.3	1.9	17	1.5	<.001
ASI (transformed)	0.59	0.37	0.56	0.29	0.54	0.40	0.66	0.38	.203
	%	***n***	%	***n***	%	***n***	%	***n***	
Race									
Caucasian	56.6	70	60	21	45.8	22	65.6	27	0.52
African-American	41.1	51	34.3	12	52.1	25	34.1	14	0.52
Hispanic	1.6	2	2.9	1	2.1	1	0	0	N/A
Native American	0.8	1	2.9	1	0	0	0	0	N/A

Participant demographic and neuropsychological information is presented by group for non-psychopathic (PCL-R ≤20), intermediate (PCL-R >20 and <30) and psychopathic (PCL-R ≥30) inmates.

[a]P-values are reported for two-sample *t*-tests (for age, IQ, ASI, and psychopathy scores) and Fisher's Exact test (for race) comparing psychopathic and non-psychopathic inmates.

Materials and methods

Participants

Participants ($N = 124$) from a medium-security Wisconsin correctional facility were selected based on the following inclusion criteria: (1) <55 years old; (2) IQ >70; (3) no history of psychosis or bipolar disorder; (4) no history of significant head injury or post-concussion symptoms; (5) no current use of psychotropic medications; and (6) completed interview assessments for psychopathy and substance use disorder (SUD) (see below). Of these 124 subjects, RSFC data were obtained for 115 subjects; 8 of these were excluded due to excessive motion in the scanner, leaving a total of 107 subjects for RSFC analysis (see Supplementary Methods for motion exclusion criteria). Informed consent was obtained both orally and in writing. The present participant sample was included in two prior neuroimaging studies (Philippi *et al.*, 2015; Korponay et al., 2017).

Psychopathy was assessed with the Psychopathy Checklist Revised (PCL-R) (Hare, 2003) by trained research assistants. The PCL-R is a 20-item scale completed based on a semi-structured interview and file review. Each item is scored as 0, 1, or 2 based on the severity of each trait. Total scores ≥30 indicate psychopathy ($n = 41$); scores >20 and <30 are considered intermediate ($n = 48$), and scores ≤20 are non-psychopathic ($n = 35$) (Hare, 2003). Inter-rater reliability (intraclass correlation) for PCL-R Total score was 0.98 based on 10 dual ratings. PCL-R Total, Factor 1, and Factor 2 scores were used for separate regression analyses (Harpur *et al.*, 1989). Cronbach's alpha for the factor scores in this sample was 0.75, and the correlation between factor scores was 0.61 ($P < 0.001$).

Substance use severity was assessed with the Addiction Severity Index (ASI) (McLellan *et al.*, 1992). Following the method used previously in adult male inmates (Ermer *et al.*, 2012b), years of regular use were summed for each substance (alcohol and drug) that the participant reported using regularly (three or more times per week for a minimum period of 1 month); total scores were then divided by age (to control for opportunity to use) and a square root transformation was applied. Participant characteristics are summarized in Table 1.

MRI acquisition

MRI data were acquired using the Mind Research Network's Siemens 1.5T Avanto Mobile MRI System equipped with a 12-element head coil. All participants underwent scanning on correctional facility grounds. A high-resolution T1-weighted structural image was acquired for each subject using a four-echo magnetization-prepared rapid gradient-echo sequence (TR = 2530 ms; TE = 1.64, 3.5, 5.36, and 7.22 ms; flip angle = 7°; FOV = 256 × 256 mm^2; matrix = 128 × 128; slice thickness = 1.33 mm; no gap; voxel size = 1 × 1 × 1.33 mm^3; 128 interleaved sagittal slices). All four echoes were averaged into a single high-resolution image (Ly *et al.*, 2012). Resting-state functional images (T2*-weighted gradient-echo functional echo planar images) were collected while subjects lay still and awake, passively viewing a fixation cross for 5.5 min (158 volumes) (Philippi *et al.*, 2015) and were acquired with the following parameters: TR = 2000 ms; TE = 39 ms; flip angle = 75°; FOV = 24 × 24 cm^2; matrix = 64 × 64; slice thickness = 4 mm; gap = 1 mm; voxel size = 3.75 × 3.75 × 5 mm^3; 27 sequential axial oblique slices.

Preprocessing and analyses of structural MRI data were conducted in both FreeSurfer 5.1 (Fischl, 2012) in Linux and Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm). RSFC data analysis was performed using AFNI (Cox, 1996) and FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Refer to Supplemental Methods for structural and RSFC preprocessing details.

Analytic strategy

Because processing pipelines and ROI parcellations differ between image processing software programs, and because studies have reported that results may vary as a function of program (Rajagopalan and Pioro, 2015), we computed volumes of the prefrontal cortex ROIs (mOFC, lateral orbitofrontal cortex, inferior frontal gyrus, MFG, SFG, and ACC) from two separate programs (FreeSurfer and SPM) and performed separate analyses with both sets of values (see Supplementary Table S1 for correlations between FreeSurfer and SPM for the average volume of each prefrontal cortex subregion). Statistical significance for the ROI analyses was evaluated at a Bonferroni-corrected $P < 0.004$ that accounted for the 12 analyses conducted in each program (left and right hemisphere of six ROIs). In addition, SPM was used to perform small volume-corrected voxel-wise analyses within the prefrontal cortex. This type of analysis can detect smaller, focal aberrations in volume that may not be

detected in the subregion volume analysis, and allows for more specific localization of the areas where volume is most strongly linked to psychopathy severity. These analyses were restricted to a mask encompassing the union of the six bilateral ROIs listed above. Peak height with correction for multiple comparisons using a family-wise error (FWE) rate of $P < 0.05$ was used to assess statistical significance for these voxel-wise analyses.

After performing the volumetric analyses, we then examined whether the identified volume abnormalities were associated with abnormalities in RSFC. We chose seeds centered at the peak coordinates of the focal volume clusters identified in the voxel-wise analyses in order to directly assess whether areas where volume correlated with psychopathy severity also had functional connectivity relationships that correlated with psychopathy severity, as the co-localization of these abnormalities may point to a common underlying pathophysiology (Korponay *et al.*, 2017). We created a 6mm-radius spherical seed around these peak coordinates, and subsequently assessed RSFC between these seeds and other areas of the brain in relation to psychopathy ratings. While creating seeds based on the exact voxel sizes and shapes of each volume cluster would have provided the greatest degree of precision in assessing the overlap between volume and RSFC metrics, 6-mm radius spheres are the standard seed size and shape for cortical resting-state analyses based on the literature. Seeds were visually inspected to ensure that they did not include volume outside of the whole-brain mask; seeds that did expand beyond the brain mask were excluded from analysis.

Seeds were evaluated in RSFC regressions only in relation to the specific psychopathy score-type (PCL-R Total, Factor 1, and/or Factor 2) for which the focal area (on which the seed was based) had demonstrated a relationship with in the volumetric analysis. To correct for multiple comparisons, we used FWE-correction at the cluster level using a whole-brain mask (3dClustSim in AFNI, using the version updated December 2015) (Forman *et al.*, 1995; Carp, 2012) and applied cluster extent thresholding. We used the autocorrelation function to calculate the full width at half maximum in order to address the non-Gaussian nature of functional MRI data (Eklund *et al.*, 2016). The cluster extent threshold corresponded to the statistical probability ($\alpha = 0.05$, or 5% chance) of identifying a random noise cluster at a predefined voxel-wise (i.e. whole-brain) threshold of $P < 0.001$ (uncorrected). Using this whole-brain FWE cluster correction, a cluster-corrected size of $\geq$47 voxels was significant at $P_{FWE} < 0.05$.

Covariates

We found the expected (Walhovd *et al.*, 2005) negative correlations between age and the gray matter volume of all ROIs (significant at $P < 0.05$ in 10 out of 12 FreeSurfer ROIs and in 3 out of 12 SPM ROIs). Thus, age was included as a covariate in all models. Also, Factor 2 scores had a trending positive relationship with substance use severity as measured by the ASI ($P = 0.055$). Because gray matter volume has been shown to relate to substance use (Franklin *et al.*, 2002; Fein *et al.*, 2006; Makris *et al.*, 2008; Tanabe *et al.*, 2009; Yuan *et al.*, 2009), we included substance use severity using the transformed ASI variable as a covariate in all regression models. Furthermore, we observed a significant group effect ($P < 0.05$) of race (between Caucasian and non-Caucasian subjects) on volume of 11 out of 12 ROIs in FreeSurfer and ten out of 12 ROIs in SPM, and thus race was also included as a covariate in all regression models. IQ was not related to psychopathy severity (PCL-R Total: $P = 0.405$; Factor 1: $P = 0.726$; Factor 2: $P = 0.730$) but was significantly positively correlated ($P < 0.05$) with the volumes of three ROIs in FreeSurfer and ten ROIs in SPM. However, when race was added to the model testing the main effect of IQ on volume, the relationship between IQ and volume did not remain significant in any ROI in either program. On the other hand, when IQ was added to the model testing the main effect of race on volume, race maintained a significant relationship with the volume of 11 of the 12 ROIs in FreeSurfer and 9 of the 12 ROIs in SPM. These data suggest that race accounts for much of the variance in IQ in this model. Coupled with the observation that race was highly correlated with IQ ($P < 0.001$), we excluded IQ from our main analysis models in order to reduce multicollinearity. In addition, in order to account for variation in overall brain size, we included brain volume (gray matter + white matter) as a covariate in all structural analyses. There was no significant relationship between PCL-R Total score and brain volume as measured by either SPM ($P = 0.65$) or FreeSurfer ($P = 0.43$). We also ensured that problematic levels of multicollinearity were not present between brain volume and age; the variance inflation factor was <1.4 for both brain volume and age in regression models for all of the ROIs, indicating unproblematic levels of multicollinearity (Hair *et al.*, 1995). In regressions where the main variable of interest was a Factor score, the other Factor score was also included as a covariate. In addition to regression analyses, we calculated zero-order (bivariate) correlations between PCL-R scores and structural volumes.

Results

ROI volume analysis

PCL-R Total scores and Factor 2 scores were positively related to specific subregion volumes throughout the prefrontal cortex (covariates: age, race, substance abuse severity, and brain volume; Factor 1 score was also included as a covariate for Factor 2 analyses). The most robust relationships (surviving a $P < 0.004$ Bonferroni correction for multiple comparisons) were observed between Factor 2 scores and volume of the right mOFC, left MFG, and left SFG (Figure 1). Zero-order correlations between Factor 2 scores and each of these three subregions were significant ($P < 0.05$) in SPM but were not always significant in FreeSurfer. The directions of findings were consistent for the volume values extracted from both SPM and FreeSurfer, though significance levels differed. See Tables 2–4 for regression data. There were no significant relationships between Factor 1 scores and ROI volumes.

In addition to these main analyses, we performed the following Supplementary analyses with different models to assess the sensitivity of the findings to covariates: factor score analyses without covarying for the other factor; replacing the continuous ASI substance use severity covariate with the categorical SUD covariate (None, Abuse, or Dependence) from the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-IV) (First, 2002); and the original model but analyzed separately by race. Findings remained essentially the same with the alternate factor score and substance abuse models. The analyses split by race showed that findings only reached significance at the Bonferroni-corrected threshold in non-Caucasian subjects, though the direction of findings was the same for both race groups (see Supplementary Tables S2–S9 for full results).

Voxel-wise volume analysis

Voxel-wise regressions identified focal areas within the prefrontal cortex where volume was positively correlated with

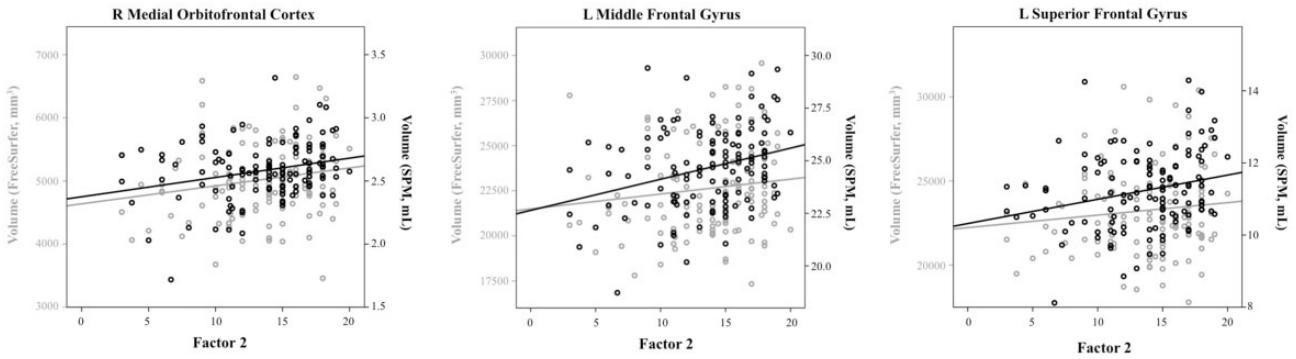

Fig. 1. Zero-order correlation plots for significant relationships ($P < 0.004$) between Factor 2 scores and volume of prefrontal cortex subregions.

Table 2. Total PCL-R regional volume regression results from FreeSurfer and SPM

Region	Standardized beta	*t*-value	*P*-value	Zero-order correlation *R*-value (*P*-value)
FreeSurfer				
MFG (L)	0.127	1.815	0.072	0.165 (0.067)
SPM				
Lateral orbitofrontal cortex (L)	0.141	2.025	0.045	0.162 (0.074)
MFG (L)	0.186	2.629	0.010	0.219 (0.015)
Inferior frontal gyrus (L)	0.173	2.108	0.037	0.206 (0.022)
Lateral orbitofrontal cortex (R)	0.166	2.358	0.020	0.181 (0.045)
mOFC (R)	0.184	3.382	**0.001**	0.224 (0.013)
MFG (R)	0.161	2.550	0.012	0.196 (0.029)

Displaying relationships with $P < 0.10$. Relationships with $P < 0.004$ (surviving Bonferroni correction) are bolded.

Table 3. Factor 1 (covarying for Factor 2) regional volume regression results from FreeSurfer and SPM

Region	Standardized beta	*t*-value	*P*-value	Zero-order correlation *R*-value (*P*-value)
SPM				
SFG (L)	−0.215	−2.293	0.024	−0.011 (0.901)

Displaying relationships with $P < 0.10$. Relationships with $P < 0.004$ (surviving Bonferroni correction) are bolded.

Factor 2 scores (covariates: age, race, substance abuse severity, brain volume, and Factor 1 score) (Figure 2). Mirroring the ROI results, these relationships were found in the right mOFC, left MFG, and left SFG, as well as in the right MFG, left mOFC, right SFG, and right ACC. There were no significant relationships between PCL-R Total scores or Factor 1 scores and prefrontal cortex focal volumes. There were also no negative relationships between any psychopathy score-type and prefrontal focal volumes. See Table 5 for complete results.

In addition to the voxel-wise regressions restricted to the prefrontal cortex mask, we also performed whole-brain voxel-wise regressions to assess the specificity of psychopathy severity relations to volumes in the prefrontal cortex. These results show that while relationships between psychopathy severity and volume are not isolated to the prefrontal cortex, consistent with both the main analyses of this study and of a previous study of this sample (Korponay *et al.*, 2017), the prefrontal cortex and striatum are brain regions where volume is strongly positively correlated with Factor 2 severity. See Supplementary Results and Figure S1 for full results of these analyses.

Table 4. Factor 2 (covarying for Factor 1) regional volume regression results from FreeSurfer and SPM

Region	Standardized beta	*t*-value	*P*-value	Zero-order correlation *R*-value (*p*-value)
FreeSurfer				
mOFC (R)	0.175	1.952	0.053	0.202 (0.025)
SPM				
SFG (L)	0.329	3.499	**0.001**	0.244 (0.007)
MFG (L)	0.293	3.238	**0.002**	0.298 **(0.001)**
SFG (R)	0.179	2.156	0.033	0.153 (0.092)
MFG (R)	0.200	2.459	0.015	0.245 (0.006)
mOFC (R)	0.216	3.068	**0.003**	0.263 **(0.003)**

Displaying relationships with $P < 0.10$. Relationships with $P < 0.004$ (surviving Bonferroni correction) are bolded.

Resting-state functional connectivity analysis

Increased functional connectivity was observed between multiple regions of the prefrontal cortex in relation to Factor 2 scores (covariates: age, race, substance abuse severity, and Factor 1 scores) (Figure 3). In particular, Factor 2 scores were positively correlated with functional connectivity between left MFG and right anterolateral prefrontal cortex and between right MFG and right frontal polar cortex. See Table 6 for complete results. RSFC was not evaluated for PCL-R Total scores or Factor 1 scores because there were no focal volumes significantly related to these score-types.

Discussion

This study used a multimodal neuroimaging approach to examine the relationship between psychopathic traits and structural and functional features of the prefrontal cortex. First, we

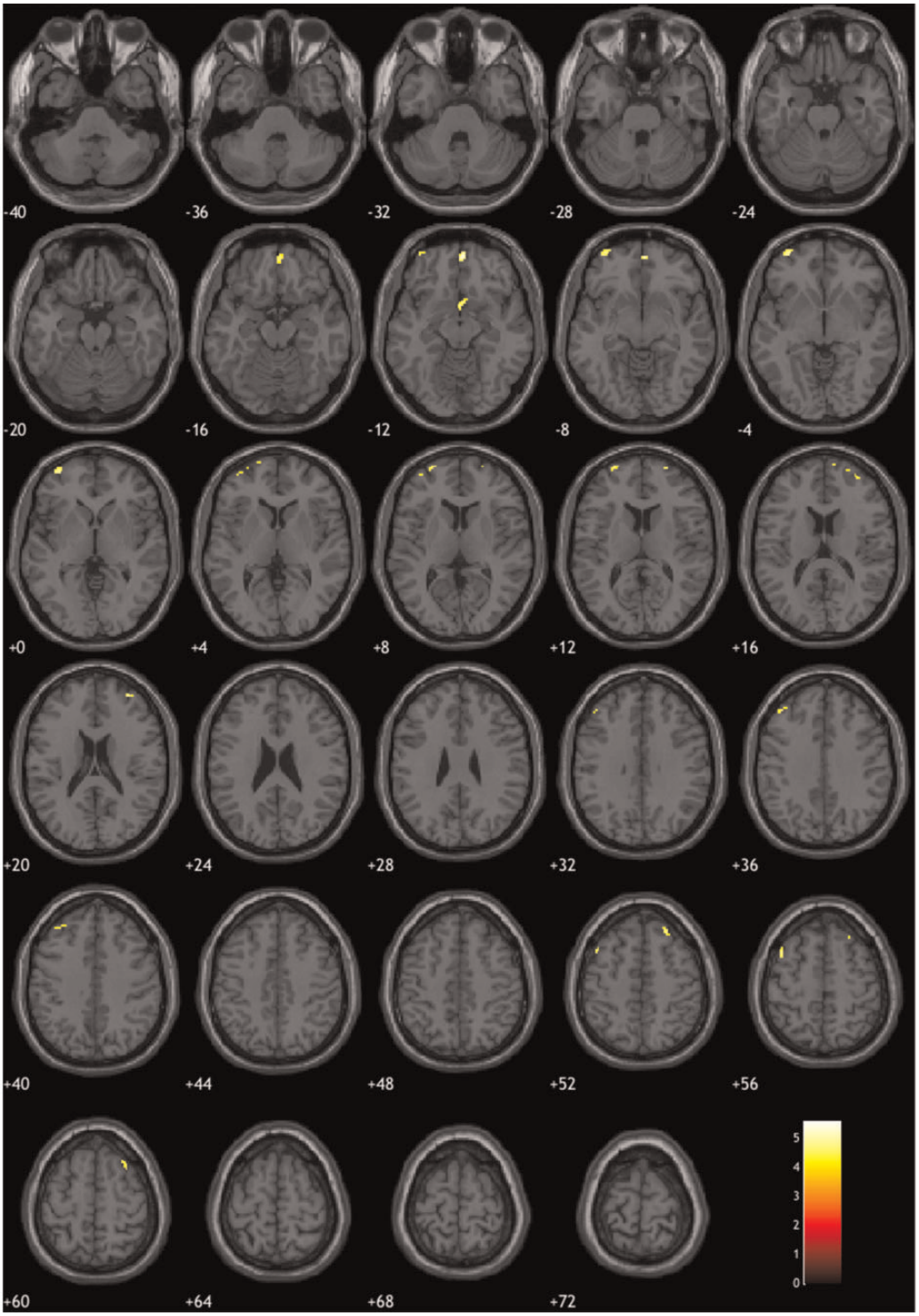

Fig. 2. Results of voxel-wise analysis for the relationship between Factor 2 scores and volume in the prefrontal cortex. Positive relationships are shown in yellow.

investigated how volumes of frontal lobe subregions relate to psychopathy severity as measured by PCL-R Total, Factor 1, and Factor 2 scores. We found that across both FreeSurfer and SPM, PCL-R Total scores and Factor 2 scores were exclusively linked to larger prefrontal cortex subregion volumes. The most robust relationships were observed between Factor 2 scores and the volume of right mOFC and left dlPFC (middle and superior frontal gyri). Next, we performed complementary voxel-wise analyses within the prefrontal cortex, which had the potential to reveal volumetric relationships within or across ROIs. This analysis also revealed exclusively positive relationships between Factor 2 severity and volume in specific regions of prefrontal cortex, including mOFC and dlPFC. Finally, we assessed RSFC in areas where volume was related to psychopathy severity. We found that Factor 2 scores were positively correlated with functional connectivity between prefrontal subregions,

including between left MFG and right inferior frontal gyrus and between right MFG and right lateral orbitofrontal cortex.

Although prior studies using group-level designs have almost exclusively found decreased prefrontal gray matter in psychopathic individuals compared with non-psychopathic individuals (Yang *et al.*, 2005; de Oliveira-Souza *et al.*, 2008; Muller *et al.*, 2008; Ly *et al.*, 2012; Contreras-Rodriguez *et al.*, 2015), our results are consistent with a number of prior studies that have shown positive relationships between Factor 2 scores and regions of PFC, including medial dorsal and lateral frontal cortex (Contreras-Rodriguez *et al.*, 2015), mOFC and ACC (Ermer *et al.*, 2013), and medial, middle, and superior frontal gyri (Cope *et al.*, 2012). It is interesting to note that most studies analyzing prefrontal gray matter and Factor 1 scores find a negative relationship (de Oliveira-Souza *et al.*, 2008; Ermer *et al.*, 2013; Contreras-Rodriguez *et al.*, 2015), while most studies analyzing prefrontal gray matter and Factor 2 scores find a positive relationship (Cope *et al.*, 2012; Ermer *et al.*, 2013; Contreras-Rodriguez *et al.*, 2015). These findings suggest that Factor 1 and Factor 2 traits are dissociable at the neural level despite being highly correlated in terms of PCL-R score. Thus, it is possible that measures of prefrontal gray matter structure in a given sample of psychopathic individuals depend on the relative severity of Factor 1 and Factor 2 traits in that sample. It is also worth noting that Factor 1 traits are more uniquely associated with psychopathy, whereas Factor 2 traits are shared more broadly as features of a number of disorders (e.g. antisocial personality disorder, impulse control disorders, etc.). Thus, the present results may speak more broadly to the neural correlates of impulsive-antisocial traits rather than psychopathy, specifically.

A positive association between prefrontal gray matter volume and Factor 2 trait severity could potentially be the result of aberrant neurodevelopment. Gray matter volume decreases throughout adolescence and early adulthood in several distinct clusters of prefrontal cortex, including the medial and dorsolateral prefrontal subregions (Gogtay *et al.*, 2004; Giorgio *et al.*, 2010). One possibility is that the observed positive associations between Factor 2 scores and PFC subregion volumes reflects deficient synaptic and neuronal pruning in these areas, resulting in ineffective and/or dysfunctional processing. Our data do not address this level of analysis directly, but they do suggest an interesting avenue for future research.

Factor 2's relevance to prefrontal cortex neurobiology can be understood conceptually by considering the types of experimental tasks on which psychopathic individuals perform poorly and the consequences that these deficits are likely to yield outside the laboratory. For instance, psychopathic individuals have been shown to perform poorly on tasks that require learning from punishment (Newman, 1987); this function has been shown to involve OFC (O'Doherty *et al.*, 2001), a region found here to be enlarged in psychopathic individuals. A deficit in this function may increase the likelihood that psychopathic individuals engage in poor decision-making that results in impulsive and criminal behavior—traits that are indexed by Factor 2 score. Consistent with this interpretation, in a previous study with this same inmate sample we found that Factor 2 scores were specifically associated with volume of the nucleus accumbens subnucleus of the striatum (Korponay *et al.*, 2017). The medial OFC region identified in this study is known to be densely interconnected with the nucleus accumbens (Sesack *et al.*, 1989; Gabbott *et al.*, 2005), and both regions are central components of the brain circuitry involved in processing value and reward (Pujara and Koenigs, 2014).

Table 5. Factor 2 (covarying for Factor 1) focal volume voxel-wise regressions in SPM

Region	$p_{FWE\text{-}corr}$	Cluster size	MNI peak coordinates	Relationship
MFG (L)	0.003	184	(−34, 60, −3)	Positive
	0.013	92	(−42, 38, 34)	Positive
	0.005	84	(−26, 63, 10)	Positive
	0.008	55	(−42, 15, 54)	Positive
MFG (R)	0.005	43	(34, 52, 20)	Positive
	0.012	27	(26, 62, 12)	Positive
mOFC (R)	<0.001	162	(3, 56, −10)	Positive
SFG (R)	0.006	83	(27, 26, 57)	Positive
	0.036	4	(10, 66, 16)	Positive
SFG (L)	0.015	13	(−26, 15, 63)	Positive
	0.038	4	(−18, 68, 6)	Positive
ACC (R)	0.020	11	(3, 56, 3)	Positive
mOFC (L)	0.004	69	(2, 8, −10)	Positive

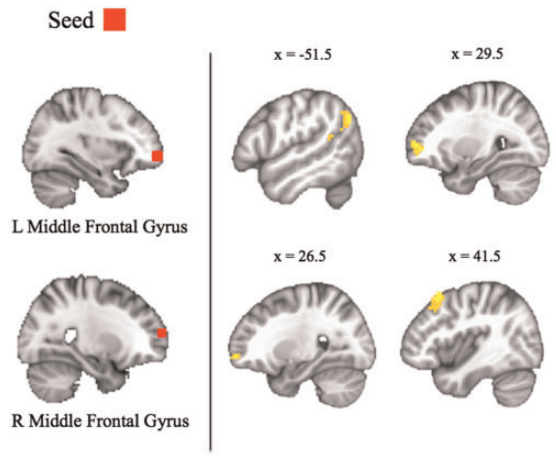

Fig. 3. RSFC results. Positive relationships between RSFC and Factor 2 scores are shown in yellow.

Table 6. Factor 2 (covarying for Factor 1) RSFC regressions

Focal seed	Seed origin coordinates	RSFC relationship with:	MNI peak coordinates	Cluster size	*t*-value[a]
MFG (L)	(−34, 60, −3)	Angular gyrus (L)	(−51.5, −65.5, 33.5)	59	4.49
		Anterolateral prefrontal cortex (R)	(29.5, 51.5, 3.5)	57	3.71
MFG (R)	(26, 62, 12)	MFG (R)	(41.5, 18.5, 54.5)	90	5.16
		Frontal polar cortex (R)	(26.5, 60.5, −5.5)	63	4.48

[a]Positive *t*-value indicates positive relationship.

Though the literature on frontal lobe RSFC in psychopathy is more limited, the finding in this sample of a positive association between Factor 2 severity and intra-frontal RSFC is consistent with Contreras-Rodriguez and colleagues' group-level finding that psychopathic individuals had elevated intra-frontal RSFC compared to non-psychopathic individuals. This study found that the RSFC difference was accompanied by decreased prefrontal gray matter concentration in psychopathic individuals compared with non-psychopathic individuals, but also by a positive relationship between prefrontal gray matter concentation and Factor 2 scores. These findings are also consistent with evidence of increased intra-frontal anatomical connectivity in psychopathy (Yang *et al.*, 2012). This converging evidence of heightened intra-frontal structural and functional connectivity in psychopathy is interesting to consider in the context of studies finding increased BOLD activity in prefrontal areas in psychopathic individuals during social decision-making (Rilling *et al.*, 2007), emotion processing (Kiehl *et al.*, 2001; Gordon *et al.*, 2004) and moral judgment tasks (Glenn *et al.*, 2009) (but see also Harenski *et al.*, 2010; Decety *et al.*, 2013, 2014). Psychopathic individuals' heightened recruitment of prefrontal areas that subserve abstract reasoning on these tasks—particularly dlPFC—has been interpreted as a compensatory mechanism used to maintain socially appropriate behavior in the absence of properly functioning limbic structures that subserve emotion processing (Kiehl *et al.*, 2001). It is possible that the enlarged volume of MFG and SFG (parts of the dlPFC) and associated increases in MFG RSFC to other prefrontal areas observed here and in other studies, along with the increased intra-frontal anatomical connectivity observed in relation to psychopathy (Yang *et al.*, 2012), may either facilitate or reflect the enhanced recruitment of dlPFC in psychopathic individuals during these tasks.

One potential issue of this study that warrants consideration is the substantial rate of SUD in this sample. Multiple studies have linked SUD to structural and functional abnormalities in the frontal lobe. We included a continuous substance use severity variable in our regression models to account for this feature of the study population. Hence, the findings we report here do not appear to be due to individual differences in substance abuse histories. Other substance use metrics such as the SUD measure on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-IV) (First, 2002) quantify abuse severity in a categorical manner, though it is not well established which substance abuse measure is best suited for capturing meaningful differences in brain data. In Supplementary analyses, we conducted the regional volume analyses using the SCID-IV's categorical metric for presence of SUD (None, Abuse, or Dependence) instead of the ASI's continuous measure, and findings remained essentially the same. In a future study, we will more fully examine the relationships between substance use characteristics and frontal lobe neurobiology in this sample. A related issue is that this study did not include a non-incarcerated comparison group, which makes it difficult to discern whether the observed findings represent "deficits" or "abnormalities". It is possible that increased prefrontal gray matter and intra-frontal functional connectivity facilitate enhanced function in certain domains and deficits in others. We may only conclude based on the present findings that these neurobiological features are associated with increased impulsive and antisocial traits. Another issue worth addressing in future studies is the relationship between volumetric and RSFC findings. While our approach allowed us to directly assess whether structural and functional abnormalities were co-localized, this method may be considered liable to statistical non-independence (Kriegeskorte *et al.*, 2009), in that the volume and RSFC of frontal lobe regions may be inherently linked. Future studies, in both clinical and non-clinical samples, could establish whether this is indeed consistently the case. Future studies could also examine frontal lobe structure and function with respect to more specific clusters of psychopathic traits (e.g. using the four-facet model of the PCL-R—Cooke and Michie, 2001). Using this four-facet model in the present study, we found no significant ROI volume relationships at the Bonferroni-corrected threshold (Supplementary Tables S10–S13). Another potential methodological issue is that the resting-state scans were collected after subjects had performed a variety of functional tasks, which likely introduced noise into the data. Lastly, it should be noted that another study from our group used subjects from the present sample to examine RSFC in psychopathy within and between the default mode network, frontoparietal network and cingulo-opercular network (Philippi *et al.*, 2015) and some evidence of a positive correlation between Factor 2 scores and intra-frontal RSFC was found. However, as prefrontal RSFC *per se* was not a primary focus of this previous study, only four frontal lobe seeds (mPFC, left and right dlPFC, and dACC) were assessed, seeds were not chosen in relation to volumetric data, and only clusters falling within masks of the specific brain networks of interest to the study were examined. This study thus reports on new and more comprehensive data in relation to prefrontal RSFC in psychopathy.

In sum, we have analyzed a unique set of multimodal neuroimaging data from a large sample of incarcerated criminal offenders to help clarify the structural and functional characteristics of prefrontal cortex in psychopathy. Our findings provide evidence of co-localized prefrontal cortex enlargement and heightened intra-frontal RSFC related predominantly to the impulsive and antisocial traits of psychopathy.

Supplementary data

Supplementary data are available at *SCAN* online.

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