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Prefrontal Structural and Functional Brain Imaging findings in Antisocial, Violent, and Psychopathic Individuals: A Meta-Analysis

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Abstract

Brain imaging studies suggest that antisocial and violent behavior is associated with structural and functional deficits in the prefrontal cortex, but there is heterogeneity in findings and it is unclear whether findings apply to psychopaths, non-violent offenders, community-based samples, and studies employing psychiatric controls. A meta-analysis was conducted on 43 structural and functional imaging studies and results show significantly reduced prefrontal structure and function in antisocial individuals. Effect sizes were significant for both structural and functional studies. With minor exceptions, no statistically significant moderating effects of sample characteristics and methodological variables were observed. Findings were localized to the right orbitofrontal cortex, right anterior cingulate cortex, and left dorsolateral prefrontal cortex. Findings confirm the replicability of prefrontal structural and functional impairments in antisocial populations and highlight the involvement of orbitofrontal, dorsolateral frontal, and anterior cingulate cortex in antisocial behavior.

Keywords

antisocial; violent; psychopathy; prefrontal

1. Introduction

In the past decade, research on antisocial behavior (aggression, psychopathy, and conduct problems) has been able to identify several environmental, psychological, and social pathways that potentially lead to these behaviors (Holmes, Slaughter, and Kashani, 2001; Raine, 2002; Vermeiren et al., 2002). In addition, mounting evidence has shown structural and functional abnormalities in antisocial individuals and hypotheses have been presented linking antisocial behavior to deficits in the prefrontal cortex, temporal cortex, insula, amygdala, hippocampus/parahippocampus, and anterior/posterior cingulate gyrus (Blair, 2001; Kiehl, 2006; Raine and

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Yang, 2006). Among these brain regions, the prefrontal cortex has been most commonly recognized as the most crucial (although not only) brain structure to be compromised in violent and antisocial populations (Davidson, Putnam, and Larson, 2000; Henry and Moffitt, 1997; Raine, 1993; Raine and Buchsbaum, 1996). However, clear interpretation of the literature has proved elusive due to some failures to replicate and some complex findings (e.g. significantly increased rather than decreased activation).

One problem in drawing conclusions from these disparate studies is that most studies treat the prefrontal cortex as one unitary structure based on the fact that it is rich in inter-cortical connectivity, and many areas overlapped in their functions (Dum and Strick, 1991; Ongur, Ferry, and Price, 2003; Petrides and Pandya, 1999, 2001). However, based on anatomical landmarks, studies have suggested that the prefrontal cortex can be broadly subdivided into the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and the medial prefrontal cortex (MPFC) (Ongur, Ferry, and Price, 2003; Petrides and Pandya, 1999, 2001). Functional studies have also supported such delineation by showing functional specificity of these prefrontal sub-regions (Bechara, 2004; Campbell, 2007; Volz, Schubotz, and von Cramon, 2006; Duncan & Own, 2000; Stuss et al., 2001). Therefore, it is of value to investigate the specificity of any abnormality to prefrontal sub-regions (Raine & Yang, 2006).

Another important issue concerns whether there are both structural and functional abnormalities in antisocial populations. Despite the fact that studies have shown a correlation between volumetric reduction and decreased brain activation (Johnson et al., 2000; Thomsen et al., 2004), very few if any imaging studies examine both structure and function in the same population. Additional issues that might contribute to variability in findings include heterogeneity in antisocial samples and variation in imaging methodology. Violence, psychopathy, and comorbid psychiatric disorders may moderate study outcomes (Mena et al., 2005; Raine and Yang, 2004; Spampinato et al., 2005; Yang and Raine, 2006). Several imaging methodology variables have been shown to influence quality, including the magnet strength, repetition time (TR), full-width-at-half-maximum (FHWM), and uptake time (Levin and Hoffman, 1999; McCarley et al., 1999), and differences in findings on antisocial behavior could be attributable to these factors.

In order to address these problems, the present meta-analytic review was undertaken to: (a) aggregate the outcomes of all imaging studies on the prefrontal cortex in antisocial individuals, (b) examine the association between antisocial behavior and sub-regions of the prefrontal cortex, (c) evaluate whether such an association is more prominent in functional or structural imaging studies, and (d) delineate reasons for variability in previous findings.

2. Method

2.1. Study Selection

The search for candidate studies to be included in the meta-analysis was conducted using 35 keywords relevant to antisocial behavior and brain imaging (i.e. Antisocial personality disorder / APD, antisocial behavior, conduct disorder / CD, oppositional defiant disorder / ODD, disruptive behavior disorder / DBD, psychopath, psychopathy, psychopathic, violent, violence, aggressive, aggression, offender, criminal, anatomical magnetic resonance imaging / aMRI, volumetric magnetic resonance imaging / vMRI, diffusion tensor imaging / DTI, structural imaging, functional magnetic resonance imaging / fMRI, magnetic resonance spectroscopy / MRS, perfusion emission tomography / PET, single photon emission computerized tomography / SPECT, functional imaging, prefrontal cortex / PFC) in three electronic indices (PubMed, PsycINFO, ISI Web of Science) for English language studies published between January 1965 and September 2007. In addition, all of the reference lists of

the studies included for analysis, as well as several review articles on the relation of brain imaging with aggression and antisocial behavior were reviewed (e.g. Anckarsater, 2006; Brower and Price, 2001; Raine, 2002; Raine and Yang, 2004, 2006; Yang, Glenn, and Raine, 2008; Yang and Raine, 2008).

To be included in this meta-analysis, the study had to meet all criteria listed below. First, if a group comparison was used, a study had to include at least one antisocial group (defined as a group that contains individuals with APD, antisocial behavior, conduct disorder, oppositional defiant disorder or disruptive behavior disorder, psychopaths, criminals, violent offenders, or aggressive individuals), and one control group of either appropriate psychiatric controls or healthy normal subjects. If correlational analysis was used, a study must have had at least one assessment of antisocial behavior (defined as above). Second, studies needed to include one or more of the following imaging methods: aMRI, DTI, fMRI, MRS, PET, or SPECT. Third, the imaging method the study used had to include assessment of either the structure (e.g. volume, neural connectivity) or function (e.g. hemodynamic response, regional cerebral blood flow) of the prefrontal cortex. The prefrontal cortex was defined as the frontal region anterior to the precentral sulcus (primary and association motor areas were excluded). Results found in the following prefrontal sub-regions were also included for region of interest (ROI) analyses: OFC (Brodmann area (BA) 11, 12, 47), DLPFC (BA 8, 9, 10, 46), VLPFC (BA 44, 45), MPFC (medial section of BA 8, 9, 10, 11, 12), and ACC (BA 24, 32) (see Figure 1). For papers that used a different nomenclature for anatomical regions (e.g. inferior frontal cortex instead of VLPFC), their findings were classified into the four ROIs examined in this review using the information provided by the authors (i.e. BA location, anatomical landmarks). For studies reporting findings in the MPFC, further examination of the Talairach coordinates or delineation methods was conducted to determine whether they actually localized in the ACC to minimize overlapping between these two ROIs. For aMRI studies, if prefrontal tissue classification was applied, only findings on gray matter were included to maintain comparability with other imaging methodologies on cortical blood flow and glucose metabolism. Lastly, studies had to report sufficient statistical details to permit the calculation of effect size. Prefrontal abnormalities reported from interaction effects that were specific to a particular study design (e.g. 3 phase × 2 conditioned-stimulus type × 3 group interaction in Veit et al., 2002) were also excluded from this review due to the difficulty in evaluating the compatibility of these indirect results to the results from other studies and/or the lack of sufficient statistical results in follow-up pairwise group comparisons for calculating effect sizes.

Studies of animals, articles written in languages other than English, studies in which antisocial behavior was manipulated experimentally (e.g. showing images that provoke anger), pharmacological studies, and case reports or observations on patients with antisocial symptoms were excluded. In addition, only studies published in peer-reviewed journals were included to assure the quality of the study and that sufficient information would be provided to allow the calculation of the effect sizes as well as the conduction of moderator analyses. When a sample was used in more than one publication, the one with the largest sample size was selected to be included in the analysis.

As a result of the systematic search of the databases, a total of 54 publications were initially found and among them 11 studies were excluded due to insufficient statistical results for calculating effect sizes. The demographic information and antisocial sample characteristics of the remaining 43 studies included in this meta-analysis are presented in Table 1. There were a total of 789 antisocial individuals and 473 control subjects. Close to half of the studies used only male participants and the percentage of males in the antisocial sample was 83.9 % across studies (see Table 1). Diagnostic criteria were broadly comparable, with studies using DSM-III-R or DSM-IV criteria for APD diagnosis and Psychopathy Checklist - Revised (PCL-R) or

Psychopathic Personality Inventory (PPI) for psychopathy (Hare, 2003;Lilienfeld and Andrews, 1996).

2.2. Meta-Analysis Procedure

Meta-analyses were performed using Comprehensive Meta-Analysis, Version 2, Biostat, Englewood NJ (Borenstein et al., 2005). For each study included in the meta-analyses, the effect size was calculated using Cohen's method as the difference between means divided by the pooled standard deviation and expressed as Cohen's d (Hedges and Olkin, 1985; Cohen, 1988). If more than one probability (P) was presented for a sub-region, results were combined following the method proposed by Rosenthal (Rosenthal, 1978). If multiple independent samples were reported separately in one study (e.g. violent schizophrenia and violent APD, men and women), these samples were treated as separate. According to the classification adopted by Cohen, small, medium and large effect sizes were defined by Cohen's d values of 0.2, 0.5, and 0.8, respectively (Cohen, 1988). Negative effect sizes in the present meta-analysis reflect reduced / smaller prefrontal activation/volume associated with increased antisocial behavior. The 95% confidence interval around the composite effect size was also calculated (Hedges and Olkin, 1985).

For each meta-analysis, a homogeneity (Q) test was performed to determine whether the studies can reasonably be described as sharing a common effect size (Hedges and Olkin, 1985). Publication bias was assessed using both Egger's regression (Egger et al., 1997) and Orwin's fail-safe N (Orwin, 1983) to evaluate whether the available literature was biased toward excluding non-significant studies. Egger's method regresses the effect size against the precision of the d, and bias is likely when the P value is significant (less than 0.05). Orwin's fail-safe N addresses the “file drawer problem” (Rosenthal, 1979, 1991) by computing the number of studies (with an effect size of 0) required to reduce the mean effect size to non-significance ($P > 0.05$).

The meta-analyses were based on the more conservative random effects model (Hedges and Olkin, 1985). Under this model, both the within-study variances (e.g. sample size of each group) and the between-study variances (e.g. the number of studies, the Q tests and the weight for each study) are considered. Studies were weighted by the precision of their d estimate, which is proportional to the study sample size. For the overall effect size of the prefrontal impairment, a meta-analysis was performed combining all sub-regions in all of the studies. In addition, for each of the sub-regions, a meta-analysis was conducted for all studies combined and also for each hemisphere separately.

2.3. Potential Moderators

Coding of antisocial sample moderators—Several potential moderators were coded in order to address the issue of heterogeneity among antisocial populations. Studies were coded for each of the five moderators: violent vs. non-violent, institutional-based vs. community-based, with comorbidity vs. without comorbidity, psychiatric control vs. healthy control, and psychopathy vs. non-psychopathy. The violent code was assigned to studies which the majority of the antisocial individuals (i.e. more than half) have a history of aggressive behavior, have displayed clinically significant aggressive behavior, have been convicted or charged with violent crimes, or have displayed physical aggression toward family members (e.g. spouse abuse). Studies that did not specify their antisocial samples as violent were coded as non-violent. Studies were coded as institutional-based if their antisocial individuals were recruited from controlled environments such as hospitals and prisons. Studies that recruited antisocial samples from non-confined environmental settings such as outpatient clinics and temporary employment agencies were coded as community-based. Studies that had participants from both sources were excluded for the analysis. The comorbidity code was assigned to studies reporting

that antisocial patients had comorbid psychiatric disorders (e.g. alcohol/substance abuse), while the others were coded as without comorbidity. The code for psychiatric control was assigned to studies that either a psychiatric comparison group was used to match any comorbid psychiatric disorder in the antisocial group (e.g. alcoholics with APD compared with alcoholics without APD) or a correlational analysis was used (e.g. correlation between psychopathy score and aggression). The code for healthy control was assigned to studies that used a healthy comparison group that was clear of any neurological and psychological illness. The studies were coded as psychopathy if their antisocial samples also fulfilled criteria for psychopathy. The mean age (or median age if mean age was not available), the male proportion, and the total PCL-R score of the antisocial sample were also recorded as potential moderators.

Coding of imaging methodology moderators—First, aMRI and DTI studies were coded as structural while fMRI, PET, SPECT, and MRS studies were coded as functional. For MRI studies (aMRI/DTI/MRS/fMRI), four imaging methodology moderators were coded: magnet strength (Tesla), slice thickness (mm), TR (ms), and field-of-view (FOV; cm^2). In addition, task type (i.e. emotional, cognitive) was also coded for fMRI studies. As for PET and SPECT studies, two imaging methodology moderators were coded including FWHM (mm), and uptake period (min). In addition, PET studies were also coded on whether the subject was cognitively engaged in a task versus resting.

Statistical analyses for moderators—Moderators reported in each study are listed in Table 1. The influence of each moderator effect was individually tested using analysis of variance for categorical moderators and fixed effect regression for continuous moderators. For analysis of the moderator effect significance, the minimum level of significance was set at $p < 0.05$.

3. Results

3.1. Meta-Analyses

Results of the meta-analyses across all 43 structural and functional studies are detailed in Table 2. A meta-analysis including all prefrontal and prefrontal sub-regional findings indicated antisocial individuals showed reduced structure / function in the prefrontal cortex, Cohen's d = - 0.60, P < 0.001. The association between antisocial behavior and prefrontal reduction was somewhat stronger in the 31 functional imaging studies (d = - 0.72, P < 0.001) than the 12 structural imaging studies (d = - 0.37, P = 0.038), however the difference was non-significant (P = 0.15). Analyses on the region of interests showed the prefrontal abnormality to be localized in the right OFC (d = - 0.48, P < 0.001), left DLPFC (d = - 0.83, P = 0.009), and right ACC (d = - 1.12, P = 0.006). The assessments of publication bias confirmed that there was no publication bias for the right OFC (Egger's t = 0.98, P = 0.36; Fail-safe N = 25), left DLPFC (Egger's t = 2.36, P = 0.05; Fail-safe N = 63), and right ACC (Egger's t = .72, P = 0.51; Fail-safe N = 35) (see Table 2). In contrast, no significant abnormality was found in the left OFC, right DLPFC, left ACC, VLPFC, or MPFC.

Across the 31 functional imaging studies, antisocial individuals showed a significant decrease in prefrontal functioning, again in the right OFC (d = - 0.57, P < 0.001), left DLPFC (d = - 0.89, P = 0.031), and right ACC (d = -1.35, P = 0.002) (see Table 3). The assessments of publication bias again confirmed that there was no publication bias for the right OFC (Egger's t = 1.51, P = 0.19; Fail-safe N = 26), left DLPFC (Egger's t = 2.28, P = 0.07; Fail-safe N = 33), and right ACC (Egger's t = 0.31, P = 0.78; Fail-safe N = 34) (see Table 3). However, the number of structural imaging studies (12 in total) was insufficient to conduct meaningful region of interest analyses.

3.2. Moderator Analysis

Results of the meta-analyses on the moderators are detailed in Table 4. For the antisocial sample characteristic moderators, the ANOVAs showed that effect sizes did not differ significantly between studies using samples that were violent or non-violent (d = - 0.62, - 0.57, respectively; P = 0.87), institutional-based or community-based (d = - 0.47, - 0.82, respectively; P = 0.12), compared to healthy or psychiatric controls (d = - 0.76, - 0.42, respectively; P = 0.14), with or without comorbidity (d = - 0.49, - 0.77, respectively; P = 0.24), and psychopathic or non-psychopathic (d = - 0.56, - 0.62, respectively; P = 0.87). The analyses of fixed-effect regression also showed that the effect size was not moderated by male proportion (b = - 0.1, P = 0.79), mean age (b = 0.01, P = 0.08) or the mean PCL-R score (b = - 0.03, P = 0.21) of the antisocial samples.

For the imaging methodology moderators, the effect size was strongest for fMRI studies (d = - 0.89, P = 0.001), followed by PET studies (d = - 0.76, P < 0.001), aMRI studies (d = - 0.36, P = 0.085), and SPECT studies (d = - 0.23, P = 0.36). However, group comparison was non-significant (P = 0.13). Studies using DTI (2 studies) and MRS (1 study) were excluded due to insufficient numbers of studies for conducting meaningful comparisons. Moderator analyses were also conducted separately for each of the four imaging methods. For fMRI studies, larger effect sizes were associated with increased TR (b = 0.0003, P < 0.001), decreased slice thickness (b = - 0.28, P = 0.01), and decreased FOV (b = - 0.008, P < .001). However, no significant association was found for scanner strength (b = - 0.27, P = 0.35). Comparable effect sizes were obtained for emotional tasks (d = - 0.87, P = 0.026) and cognitive tasks (d = - 0.90, P = 0.01) used in fMRI studies. For PET studies, no moderator effect was found for FHWM (b = - 0.022, P = 0.79), uptake time (b = - 0.059, P = 0.14), or the use of a challenge task (P = 0.10). For SPECT studies, a significant positive correlation was found between smaller FHWM and larger effect size (b = 0.34, P < 0.001). However, no moderator effect was found for the uptake time across SPECT studies (b = 0.003, P = 0.53). For aMRI studies, a significant positive correlation was found between FOV and the effect size (b = 0.003, P = 0.048). However, no such moderator effect was found for the scanner strength (b = - 0.305, P = 0.38), TR (b = 0.00003, P = 0.76), or slice thickness (b = 0.014, P = 0.87) across the aMRI studies.

4. Discussion

This is the first brain imaging meta-analysis of antisocial behavior, evaluating the relationship between prefrontal impairment and antisocial / violent / psychopathic behavior across 43 independent studies. Results demonstrated that antisocial behavior was significantly associated with reduced prefrontal structure and function. Specifically, increased antisocial behavior was particularly associated with structural and functional reductions in the right OFC, left DLPFC, and right ACC. Results were not moderated by the antisocial characteristics such as age, gender, psychiatric control, comorbid psychiatric disorder, or psychopathy. Imaging methodology moderated results, depending upon the type of imaging methods. Overall, findings establish fairly robust and significant prefrontal structural and functional impairments in antisocial populations as assessed by brain imaging.

4.1. Localization and Lateralization of the Prefrontal Reductions

The findings of this meta-analysis review are consistent with the prefrontal sub-regions hypothesized to be impaired in antisocial individuals in several previous reviews, which include the OFC, DLPFC and ACC (Blair, 2001; Kiehl, 2006; Raine and Yang, 2006; Yang, Glenn, and Raine, 2008). When study findings were analyzed separately for each hemisphere, the association between DLPFC reduction and antisocial behavior was found to be limited to the left hemisphere, while reductions in the ACC and OFC was more prominent in the right hemisphere. These findings echo evidence that antisocial behavior is more associated with

right-sided prefrontal pathology, particularly in the OFC and ACC. For example, Tranel, Bechara and Denburg (2002) showed patients with unilateral lesion to the right OFC to be impaired in social conduct, decision-making, emotional processing, and personality, whereas the left OFC patients had normal social and interpersonal behavior. This notion is supported by several other studies on patients with antisocial / psychopathic features showing damage predominantly limited to their right OFC (e.g. Angrilli et al., 1999; Erlinger and Damasio, 1985).

Similarly, unilateral lesions to the right ACC, but not the left ACC, were found to cause impairments in inhibitory control as well as emotional processing (e.g. Danckert et al., 2000; Hornak et al., 2003). On the other hand, damage to the DLPFC, particularly the left DLPFC, has been associated with impairments in higher cognitive and self-regulatory processes such as attention, cognitive flexibility, and impulse control as revealed by the Stroop task and Iowa Gambling task (e.g. Grattan and Eslinger, 1992; Hornak et al., 2004; Stuss et al., 2001). The failure in patients with left DLPFC deficits in performing these tasks has been attributed to attention deficits and poor goal-directed behavior (e.g. Colvin, Dunbar and Grafman, 2001; Hornak et al., 2004; Stuss et al., 2001). Overall, as suggested by the lesion studies, it may be hypothesized that the reduction in right prefrontal cortex, including the OFC and ACC, is associated with emotional deficits and poor decision-making in antisocial individuals, while reduction in the left DLPFC is more linked to antisocial features of impulsivity and poor behavioral control.

Findings of this meta-analysis review are in line with several biological theories on antisocial behavior and psychopathy. For example, the results support the Frontal Lobe Dysfunction Theory (Gorenstein & Newman, 1980) and Somatic Marker Hypothesis (Damasio, 1994) in suggesting that antisocial behavior in humans might be a consequence of inherited or acquired deficits in the frontal brain areas, especially the OFC. However, the implication of the findings may be less direct for theories such as the Left Hemisphere Activation Hypothesis of psychopathy (Kosson, 1998). Based on the findings that psychopaths made more errors following cues presented in the right visual field (processed initially by left hemisphere), Kosson (1998) proposed that difficulty in processing information in the left hemisphere and shifting attention from left to right hemisphere may contribute to attentional abnormalities observed in psychopathic individuals (Kosson, 1998). Findings in this meta-analysis support the hypothesis and suggest that structural and functional deficits in the left DLPFC impair the allocation and sustaining of attention in antisocial, psychopathic individuals. The additional deficits in the right OFC and ACC may also indirectly support the hypothesis because these regions are key in processing secondary cues such as emotional contents, thus if damaged may fail to effectively direct attention to important information in the right hemisphere when needed. Nevertheless, future development of neurobiological theory on antisocial behavior incorporating neuroimaging, neuropsychological and behavioral data is needed to understand the complex mechanism underlying antisocial personality disorder and psychopathy.

Although the VLPFC and MPFC have generated a great deal of interest in antisocial research, non-significant results were found for both regions in this meta-analysis. However, there were trend associations between antisocial behavior and prefrontal reduction in the left MPFC ($p = 0.061$). It is notable that, for both regions, some studies included in the meta-analysis demonstrate effects in opposing directions. We caution however against firm conclusions on null results because effects sizes were quite substantial for some subregions, and small sample sizes reduce statistical power. For example a d of - 1.0 was obtained from the four studies assessing left MPFC, an effect which may be significant with more studies. Similarly, the overall non-significant effect size for right DLPFC from 8 studies was non-trivial (- 0.49). Confirmation or refutation of these null results and the possible lateralization and localization of the prefrontal deficits in antisocial individuals constitutes important issues for future studies.

Although no significant moderator effect for sample characteristics was found, the null findings may be contributed in part by the method of study classification for moderator analyses, specifically for the violent and comorbidity nature of the samples, which depends solely on information reported by the investigators. This approach did not allow us to draw conclusions with full confidence that the results are truly reflective of the confounding effect that violent behavior and comorbid psychiatric disorders has on the frontal structure and function. Another limitation of this meta-analysis is that, although we were able to assess the frontal structural and functional correlates of global psychopathy scores, the small number of studies providing separate results for sub-factors of psychopathy (one sMRI and one fMRI) prevents us from conducting meaningful subsidiary analyses to further assess the effect of sub-features of psychopathy. Therefore, despite that the mean PCL-R score was found to show no moderator effect on the results, it remains a possibility that the prefrontal findings may be moderated by sub-factors of PCL-R, particularly the antisocial-lifestyle sub-factor, which is associated more closely with frontal deficits such as impulsivity and poor behavioral control.

Effect of Imaging Methodology—Several imaging methodology variables were found to moderate the association between antisocial behavior and the prefrontal cortex. For example, larger effect sizes were associated with an increase in TR, but a decrease in both FOV and slice thickness in fMRI studies. These findings are somewhat surprising due to the fact that studies have found shorter TR to be associated with better BOLD contrast sensitivity (e.g. Menon, Thomas, Gati, 1997). However, the higher signal-to-noise ratio permitted by the use of longer TR improves the quality of the fMRI scans which are known to be sensitive to motion and image-to-image fluctuation. On the other hand, smaller FOV and thinner slice improve the spatial resolution of the images, thus increased the chance of localizing activation differences between groups (Creasy, Partain, and Price, 1995). However, when the matrix size is fixed, a decrease in FOV results in a drop in the signal-to-noise ratio. These factors may contribute to the ability of an fMRI study to better detect brain activity changes associated with antisocial behavior.

Conclusions

This meta-analytic review highlights the significance of prefrontal structural and functional impairments in antisocial individuals. More specifically, reductions in the prefrontal cortex were particularly marked in the right OFC, right ACC, and left DLPFC. This meta-analysis underscores the critical need for longitudinal imaging studies as well as studies that include female antisocial individuals and which assess potential mediating variables (e.g.. impulsivity, emotional regulation). We emphasize that multiple regions other than the prefrontal cortex are likely to be significantly implicated in antisocial and violent behavior (Raine and Yang, 2006). Consequently, although additional research on the prefrontal cortex is warranted, future brain imaging research on antisocial populations could usefully focus on other regions of interest (amygdala, hippocampus, insula, angular gyrus) which have been much less studied to date.

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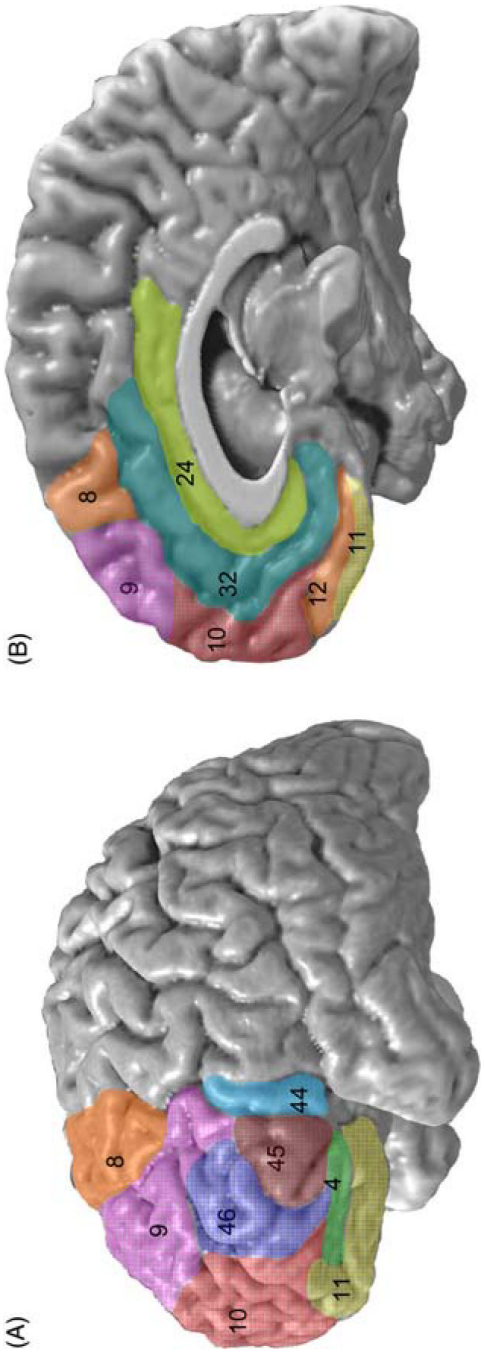

Figure 1.
Lateral (A) and medial (B) illustration of the Brodmann Areas (BA) in the orbitofrontal, dorsolateral prefrontal, ventrolateral prefrontal, medial prefrontal, and anterior cingulate cortices. The orbitofrontal cortex included BA 11, 12, and 47. The dorsolateral prefrontal cortex included BA 8, 9, 10, and 46. The ventrolateral prefrontal cortex included BA 44 and 45. The medial prefrontal cortex included BA 8, 9, 10, 11, and 12. The anterior cingulate cortex included BA 24 and 32.

Table 1

Demographics information and sample characteristics of the 43 studies.

Study	Imaging Type	Antisocial Sample No. of Subject patient	control	Male (%)	Mean age (years)	violent	institutional -based	psychiatric control	Characteristics comorbidity	psychopathy	effect size (d)
Amen et al, 1996	SPECT	40	40	75	30	Yes		Yes	Others		.36
Antonucci et al, 2006	aMRI	15		73.3	39	Yes		Yes	Others		-.94
Barkataki et al, 2006	aMRI	13	15	100	31.6	Yes	Yes		Others		-.06
Barkataki et al, 2006	aMRI	13	15	100	34.5	Yes	Yes	Yes	Schizophrenia		-.77
Birbaumer et al, 2005	fMRI	10	10	100	35.3					Yes	-.98
Coccaro et al, 2007	fMRI	10	10	50	34.3	Yes			Others		-1.77
Critchley et al, 2000	MRS	10	8	90	23	Yes	Yes	Yes	Others		-1.57
Dolan et al, 2002	aMRI	18	19	100	30.3	Yes	Yes		Others	Yes	-.15
Frankle et al, 2005	aMRI	10	10	50	35	Yes			Others		-.25
Frankle et al, 2005	PET	10	10	50	35	Yes			Others		-1.06
George et al, 2004	PET	8	11	100	32.9	Yes		Yes	Alcoholism		-.37
Gordon et al, 2004	fMRI	10	10	100	23.5						-.98
Goyer et al, 1994	PET	17		70.6	24.6		Yes	Yes	Others		-1.17
Hirono et al, 2000	SPECT	10	10	40	75.3	Yes		Yes	Dementia		-2.22
Hoptman et al, 2005	aMRI	49		87.8	41.5	Yes	Yes	Yes	SA		.82
Hoptman et al, 2002	DTI	14		100	40.5	Yes		Yes	Schizophrenia		.26
Intrator et al, 1997	SPECT	8	9	100	36.8		Yes	Yes	SA	Yes	.37
Joyal et al, 2007	fMRI	12	12	100	42	Yes	Yes	Yes	Schizophrenia/SA		-.33
Juhasz et al, 2001	PET	6	7	50	9.9	Yes		Yes	Epilepsy		-1.90
Kiehl et al, 2001	fMRI	8	8	n/a	33.9		Yes	Yes		Yes	-2.59
Kiehl et al, 2004	fMRI	8	8	100	33.9		Yes			Yes	-2.68
Kruesi et al, 2004	aMRI	10	10	90	16.1				ADHD		-.61
Kumari et al, 2006	fMRI	10	13	100	31.3	Yes	Yes				-1.67
Kumari et al, 2006	fMRI	12	13	100	34	Yes	Yes	Yes	Schizophrenia		-.77
Kuruoglu et al, 1996	SPECT	50		100	37.5		Yes	Yes	Alcoholism		-.77
Laakso et al, 2002	aMRI	24	33	100	31	Yes	Yes		Alcoholism	Yes	-.11
Li et al, 2005	DTI	36	40	60.5	14	Yes					-.78
Li et al, 2006	fMRI	27		63	36.2		Yes	Yes	SA		.44
Mathews et al, 2005	fMRI	19	19	74	14.1	Yes					-.22
Müller et al, 2003	fMRI	6	6	100	33		Yes			Yes	-.01
Nakano et al, 2006	SPECT	22		63.6	62.9			Yes	FTD		.51
Oder et al, 1992	SPECT	36		86.1	30.2	Yes	Yes	Yes	CHI		-.02
Parsey et al, 2002	PET	25		52	40.3	Yes		Yes			-1.04
Raine et al, 1997	PET	41	41	95.1	34.3	Yes	Yes	Yes	Others		-.56
Raine et al, 2000	aMRI	21	26	100	31.9			Yes	SA	Yes	-.79
Rilling et al, 2006	fMRI	30		50	21.2			Yes			-.20
Schneider et al, 2000	fMRI	12	12	100	31.5		Yes			Yes	.95
Soderstrom et al, 2000	SPECT	21	11	95.2	27	Yes	Yes		SA		-.41
Soderstrom et al, 2002	SPECT	32		90.6	31.5	Yes	Yes	Yes	Others		-.11
Stadler et al, 2007	fMRI	27		100	12.9	Yes		Yes	ADHD		-.70
Sterzer et al, 2005	fMRI	13	14	100	12.9	Yes			ADHD		-2.08
Volkow et al, 1995	PET	8	8	100	34	Yes	Yes				-1.09
Woermann et al, 2000	aMRI	25	25	68	27	Yes		Yes	Temporal lobe epilepsy		-1.16

(a) APD vs. control. BPD: borderline personality disorder, (b) Violent schizophrenia vs. non-violent schizophrenia, ADHD: Attention deficit hyperactivity disorder, SA: substance abuse, FTD: frontotemporal dementia, CHI: closed head injury, Others: a mix of psychiatric disorders other than APD.

Table 2

Mean effect sizes for the 5 regions of interest across all 43 structural and functional imaging studies.

Region of Interest	No. of studies	Random Effect Model			Heterogeneity		Publication Bias		
		Cohen's d	95% Confidence Interval	P	Q	P	Egger's Regression t	P	Fail-safe N
OFC (combined)	16	-0.43	[-0.79, -0.07]	0.019	40.3	< 0.001	.94	.36	44
Left	8	-0.20	[-0.66, 0.26]	0.38	15.8	0.027			
Right	9	-0.48	[-0.74, -0.22]	< 0.001	8.1	0.42	.98	.36	25
DLPFC (combined)	15	-0.29	[-0.78, 0.20]	0.24	96.5	< 0.001			
Left	9	-0.83	[-1.46, -0.21]	0.009	53.4	< 0.001	2.36	0.05	63
Right	8	-0.49	[-1.17, 0.19]	0.16	40.2	< 0.001			
VLPFC (combined)	8	-0.30	[-1.09, 0.49]	0.46	33.2	< 0.001			
Left	5	-0.25	[-1.11, 0.62]	0.58	37.6	< 0.001			
Right	6	0.31	[-0.70, 1.32]	0.55	24.3	< 0.001			
MPFC (combined)	13	-0.24	[-0.93, 0.46]	0.51	81.3	< 0.001			
Left	4	-1.0	[-2.11, 0.05]	0.061	14.6	0.002			
Right	7	-0.28	[-1.30, 0.74]	0.59	40.4	< 0.001			
ACC (combined)	17	-0.82	[-1.28, -0.35]	0.001	61.8	< 0.001	1.0	0.33	170
Left	6	-0.60	[-1.80, 0.61]	0.34	41.23	< 0.001			
Right	6	-1.12	[-1.93, -0.32]	0.006	17.5	0.004	0.72	0.51	35

Table 3

Mean effect sizes for the 5 regions of interest across the 31 functional imaging studies.

Region of Interest	No. of studies	Random Effect Model			Heterogeneity		Publication Bias		
		Cohen's d	95% Confidence Interval	P	Q	P	Egger's Regression t	Egger's Regression P	Fail-safe N
OFC (combined)	12	-0.54	[-0.90, -0.17]	0.004	21.7	0.03	0.58	0.58	41
Left	5	-0.37	[-0.76, 0.02]	0.06	4.3	0.37			
Right	7	-0.57	[-0.84, -0.29]	<0.001	5.4	0.50	1.51	0.19	26
DLPFC (combined)	12	-0.36	[-0.91, 0.20]	0.21	72.5	< 0.001			
Left	7	-0.89	[-1.69, -0.08]	0.031	48.1	< 0.001	2.28	0.07	33
Right	7	-0.56	[-1.35, 0.23]	0.17	39.6	< 0.001			
VLPFC (combined)	7	-0.37	[-1.25, 0.51]	0.41	32.0	< 0.001			
Left	4	-0.28	[-1.25, 0.70]	0.58	37.1	< 0.001			
Right	5	-0.28	[-0.90, 1.46]	0.64	23.7	< 0.001			
MPFC (combined)	11	-0.17	[-1.03, 0.68]	0.69	73.2	< 0.001			
Left	3	-1.45	[-3.11, 0.21]	0.087	12.6	0.002			
Right	6	-0.35	[-1.64, 0.95]	0.60	40.3	< 0.001			
ACC (combined)	16	-0.86	[-1.35, -0.36]	0.001	60.5	< 0.001	0.94	0.36	163
Left	5	-0.65	[-2.18, 0.89]	0.41	41.2	< 0.001			
Right	5	-1.35	[-2.20, -0.51]	0.002	11.8	0.019	0.31	0.78	34

Table 4

Moderator analyses.

	No. of studies	Random Effect Model Cohen's d	95% C.I.	p	Heterogeneity Q	p	Moderator Analysis p
Antisocial Sample Moderators							
Violent	29	-0.62	[-.88, -.35]	< 0.001	87.1	< 0.001	
Non-violent	14	-0.57	[-1.06, -.08]	0.023	44.9	< 0.001	0.87
Institutional-based	22*	-0.47	[-.80, -.14]	0.005	68.7	< 0.001	
Community-based	19*	-0.82	[-1.12, -0.53]	< 0.001	37.8	0.004	0.12
Psychiatric control	21	-0.42	[-0.76, -0.08]	0.015	63.5	< 0.001	
Healthy control	22	-0.76	[-1.07, -0.46]	< 0.001	61.1	< 0.001	0.14
With comorbidity	26	-0.49	[-0.79, -0.20]	0.001	79.8	< 0.001	
Without comorbidity	17	-0.77	[-1.13, -0.41]	< 0.001	44.9	< 0.001	0.24
Psychopathy	9	-0.56	[-1.32, 0.21]	0.16	35.2	< 0.001	
Non-psychopathy	34	-0.62	[-0.86, -0.38]	< 0.001	95.4	< 0.001	0.87
Methodology Moderators							
Functional	31	-0.72	[-1.02, -0.42]	< 0.001	102.3	< 0.001	
Structural	12	-0.37	[-0.73, -0.02]	0.038	29.0	0.002	0.15
aMRI	10	-0.36	[-0.76, 0.05]	0.085	25.1	0.003	
fMRI	15	-0.89	[-1.39, -0.38]	0.001	53.0	< 0.001	
PET	7	-0.76	[-1.08, -0.44]	< 0.001	4.7	0.58	0.13
SPECT	8	-0.23	[-0.73, 0.26]	0.36	26.0	0.001	
Emotional task (fMRI)	9	-0.87	[-1.63, -0.10]	0.026	37.3	< 0.001	
Cognitive task (fMRI)	6	-0.90	[-1.58, -0.21]	0.01	15.6	0.008	0.95
Task (PET)	3	-0.59	[-0.97, -0.21]	0.002	1.2	0.56	
Resting (PET)	4	-1.17	[-1.76, -0.59]	< 0.001	0.88	0.83	0.10

*Two studies (Amen et al, 1996; Antonucci et al., 2006) were excluded due to a mix of in- and out-patients.