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Neuroimaging of Psychopathy and Antisocial Behavior: A Targeted Review

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Abstract

The goal of this article is to provide a selective and targeted review of the neuroimaging literature on psychopathic tendencies and antisocial behavior and to explore the extent to which this literature supports recent cognitive neuroscientific models of psychopathy and antisocial behavior. The literature reveals that individuals who present with an increased risk for reactive, but not instrumental, aggression show increased amygdala responses to emotionally evocative stimuli. This is consistent with suggestions that such individuals are primed to respond strongly to an inappropriate extent to threatening or frustrating events. In contrast, individuals with psychopathic tendencies show decreased amygdala and orbitofrontal cortex responses to emotionally provocative stimuli or during emotional learning paradigms. This is consistent with suggestions that such individuals face difficulties with basic forms of emotional learning and decision making.

Keywords

Amygdala; Orbital frontal cortex; Psychopathy; Instrumental aggression; Reactive aggression

Introduction

The disorder of psychopathy characterizes an individual who shows pronounced problems in emotional processing (reduced guilt, empathy, and attachment to significant others; callous and unemotional [CU] traits) and who is at increased risk for displaying antisocial behavior [1, 2]. It is a developmental disorder. Recent work has confirmed the stability of CU traits in particular and the disorder more generally from childhood into adulthood [3].

The goal of this article is to provide a selective and targeted review of the neuroimaging literature on psychopathy and antisocial behavior. My goal is to explore the extent to which the current literature supports the cognitive neuroscientific models of psychopathy and antisocial behavior that I have been developing during the past 10 years [4, 5••].

It should be noted, however, that functional MRI (fMRI) studies of psychopathic traits have used a variety of assessment tools and populations. There have been studies of healthy undergraduates and unemployed individuals distinguished by their scores on self-report measures [6-8] as well as studies on clinical/forensic populations and youth with disruptive behavior disorders distinguished by their scores on the Psychopathy Checklist-Revised and

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Psychopathy Checklist-Youth Version, respectively [9-11]. The current review concentrates on these studies. However, it also considers fMRI studies of conduct disorder (CD) [12, 13] and recent work on reactively aggressive populations [14••, 15, 16]. This review does not, however, consider the early imaging studies on antisocial populations that, although critical in laying the foundation of this literature, lacked contemporary techniques for anatomic precision and thus are difficult to interpret.

The Models to Be Evaluated

The models described subsequently have been presented in considerably greater detail elsewhere [5••]. They make a fundamental distinction between instrumental and reactive aggression. Reactive aggression is triggered by a frustrating or threatening event and involves unplanned, enraged attacks on the object perceived to be the source of the threat/frustration. In contrast, instrumental aggression is purposeful and goal directed (eg, to obtain the victim's possessions). This distinction between instrumental and reactive aggression has been made for some time [17]. Moreover, considerable data suggest the existence of two relatively separable populations of aggressive individuals: individuals who present with mostly reactive aggression and those who present with high levels of proactive and reactive aggression [17]. Patients with intermittent explosive disorder and anxiety disorders such as post-traumatic stress disorder are at increased risk for reactive aggression. In contrast, individuals with psychopathy show increased levels of proactive and reactive aggression [18].

With respect to reactive aggression, animal work indicates a gradated response to threat: distant threats induce freezing, then, as they draw closer, flight and finally reactive aggression when they are very close and escape is impossible [19]. Animal work further indicates that this progressive response to threat is mediated by a basic threat system that runs from medial amygdaloidal areas downward, largely via the stria terminalis to the medial hypothalamus, and from there to the dorsal half of the periaqueductal gray (PAG) [20]. This neural system—amygdala-hypothalamus-PAG—is thought to mediate reactive aggression, including frustration-induced reactive aggression, in humans as well [5••, 20]. It is proposed that this system is regulated by medial, orbital, and inferior frontal cortices. Frontal regulatory activity can involve 1) attentional priming of nonemotional stimuli (and consequent reduced representation of emotional stimuli) either automatically [21] or in a controlled fashion [22] or 2) the suppression of amygdala activity by medial orbitofrontal cortex (OFC) [23] and/or more anterior and slightly lateral regions of the OFC [21].

Reactive aggression need not be maladaptive—it may be an appropriate response to the level of threat/frustration. However, it can become maladaptive because of prior priming of the basic amygdala-hypothalamus-PAG threat system (due to prior threat exposure of an endogenous condition) and/or impaired frontal regulation. Under these circumstances, the response of the basic threat system to a threatening/frustrating provocation will be disproportionately strong (ie, much more likely to involve extreme reactive aggression). This predicts that patients at heightened risk of showing reactive (although not instrumental) aggression should show heightened amygdala responses to emotionally provocative stimuli and reduced frontal emotional regulatory activity.

With respect to instrumental aggression/antisocial behavior, it is argued that this form of goal-directed motor response is no different than any other form of motor response [5••]. As such, it is mediated by motor cortex and caudate. However, the interesting thing about instrumental aggression/antisocial behavior is that this type of behavior was chosen to achieve the goal rather than a more prosocial alternative. Motor response selection is a function of available choices, and the costs and benefits are represented as being associated

with these choices. For most individuals, the benefits of antisocial goal solutions are not sufficiently great (relative to prosocial alternatives) and/or the costs of these antisocial goal solutions are too great (eg, the harm to the victim, the risk of loss of liberty) to make these solutions desirable. However, for individuals with psychopathy, the instrumental antisocial behavior can be maladaptive (ie, it is initiated because of dysfunctional representation of the costs of the behavior). It is argued that this relates to amygdala and OFC dysfunction [5••]. The amygdala is critical for stimulus reinforcement learning and feeding reinforcement expectancy information forward to the OFC to allow good decision making to occur. It is argued that both these critical processes are disrupted in individuals such that they have difficulty socializing (due to dysfunction in stimulus reinforcement learning) and make poor decisions (relating to the OFC dysfunction) [5••]. In short, this predicts that individuals with psychopathic traits will show reduced amygdala and OFC responses to emotional provocation and during emotion-based decision-making tasks.

Testing the Models

Maladaptive Reactive Aggression

Relatively few studies have considered populations that show a marked increase for reactive, but not instrumental, aggression. Two recent studies investigated a population of spouse abusers who, they demonstrated, show an increased risk for reactive, but not instrumental, aggression [14••, 24]. Work also has been done to investigate patients with intermittent explosive disorder [15]. Such patients are characterized by recurrent acts of impulsive, affectively driven aggression that are disproportionate to any actual provocation. Paradigms used included viewing of emotional images [24], viewing of emotional expressions [15], and an emotional Stroop test [14••]. The greatest amount of work has been done with patients with borderline personality disorder (BPD), another patient group characterized by impulsive, affectively driven aggression [16].

The model briefly outlined above hypothesizes that patients with a selectively increased risk for reactive aggression will show increased responsiveness of the basic amygdala-hypothalamus-PAG threat system and/or reduced frontal regulatory activity. In line with this hypothesis, all three patient groups showed increased amygdala responsiveness to threatening stimuli relative to comparison individuals [14••, 15, 16, 25-28]. It should be noted that one of these studies did not note increased amygdala responsiveness to emotional images in the spouse abusers [24]. However, the investigators did observe increased fusiform and occipital cortex activity. The amygdala is intimately connected with the fusiform and occipital cortex and serves to prime emotional representations within these regions. Thus, it is possible that this increased cortical activity reflects increased amygdala activity that was obscured by the difficulty of scanning the amygdala due to susceptibility artifacts. None of the three studies reported increased responsiveness of the hypothalamus and PAG. However, neither region is typically investigated in current fMRI work.

With respect to reduced frontal regulatory activity, there has been one report of reduced activations in the spouse abusers proximal to the right anterior cingulate cortex (ACC) and left middle frontal gyrus during the emotional Stroop test [14••]. Strikingly, reduced middle frontal cortex activation across facial expressions has been reported in the patients with intermittent explosive disorder, as has been a notably reduced OFC response in these patients selectively to angry expressions [15]. However, it should be noted that these indications of hypofrontality were not seen in the second study on spouse abusers [24]. The other study on spouse abusers did report reduced activity in the middle frontal cortex, but the region involved white rather than gray matter; thus, these data must be considered with caution [14••]. Data on patients with BPD have been mixed. Two studies reported reduced cingulate cortex activity during aggression provocation [16] and expression processing [27].

However, this has not been observed in other studies examining expression processing [25, 28] or emotionally provocative images [26]. Moreover, there have been reports of increased activity in patients with BPD within the lateral OFC during aggression provocation [16] and inferior frontal cortex in response to expressions [25]. In short, no definitive support currently exists for the hypothesis of reduced regulatory activity, at least not using affective provocative paradigms in reactively aggressive individuals. There have been consistent findings examining the impact of serotonergic challenges (d,l fenfluramine and meta-chloropiperazine) on patients with BPD reporting reduced serotonergic uptake within the medial OFC [29, 30]. However, although this does indicate serotonergic abnormalities in BPD, particularly within the OFC, it cannot be taken as direct evidence of reduced emotional regulation by the OFC. Importantly, though, the affective provocation paradigms used up to now would not necessarily have revealed frontal regulatory activity (which has proven difficult to replicably demonstrate in paradigms that do not implicate the lateral frontal cortex in emotional reappraisal). As such, the hypothesis remains relatively untested.

Maladaptive Instrumental Aggression

A growing body of literature has examined a population at marked increased risk for instrumental aggression: youth and adults with psychopathic traits. This work has involved structural and functional imaging. The model briefly outlined above hypothesizes that individuals with psychopathic traits should show impairment in the role of the amygdala in stimulus reinforcement learning and in the role of the OFC in reinforcement expectancy-based decision making [5••].

With respect to the structural imaging studies, most findings have been isolated and not yet replicated. There have been reports of reduced amygdala volume [31], asymmetric [32] and reduced hippocampus volume [33], increased colossal white matter volume and length, and reduction in callosal thickness [34] in adults with psychopathic traits. There has also been a report of increased striatum size in adults with psychopathic traits [35], a region of interest because of its role in emotional learning [36]. It should be noted, however, that these structural imaging studies used manual tracing or semiautomated region-of-interest-guided measurement of brain structures, thereby potentially introducing an observer bias [37••]. However, four recent studies used voxel-based morphometry, a fully automated and unbiased technique for characterizing regional brain volume and tissue concentration [38]. The results of these studies have been more consistent [37••, 39-41]. All four studies reported structural abnormalities within the superior temporal cortex, and three of the four reported structural abnormalities within the OFC and insula [39, 40]. However, it should be noted that whereas the studies with adult samples reported reduced gray matter volume within these regions, the study with youth with psychopathic tendencies reported increased gray matter volume [37••]. De Brito et al. [37••] interestingly proposed that this inconsistency may reflect a potential delay in cortical maturation, but clearly more work is needed.

With respect to the functional imaging studies, the findings have been relatively consistent. The paradigms investigated have all involved stimulus reinforcement-based decision making (emotional expressions, particularly of fear, sadness, and happiness, serve to initiate reinforcement-based decision making) [5••] or other amygdala-dependent forms of emotional learning. These paradigms include expression processing [6, 11, 42-44], blocked presentation of emotional and neutral images [45], aversive conditioning [46], emotional memory [9], moral reasoning [47], prisoner's dilemma [7], and reversal learning [10]. In line with the model outlined previously, in almost all of these studies, the individuals with psychopathic traits showed reduced amygdala and OFC responses.

There are four exceptions to this generalization. First, in line with findings that the OFC is only infrequently seen responding to emotional expressions [48], studies of expression processing only identified reduced amygdala, and not OFC, responding in individuals with psychopathy [6, 11, 42, 43], although one study [42] observed reduced amygdala-OFC functional connectivity during expression processing. Second, in line with findings that the amygdala is not necessary for reversal learning [49], no reduced amygdala responding was seen in the youth with psychopathic tendencies during reversal learning [10]. Thus, the first two of these exceptions would be expected on the basis of our understanding of the functional roles of the amygdala and OFC. Indeed, these exceptions are theoretically critical. They demonstrate that the amygdala and OFC dysfunction cannot be attributed to dysfunction in only one of these systems that is propagated, because of their intimate connections [50] to the other system. This is because atypical activity is seen in both regions on tasks in which the other region has no or limited involvement.

The third exception is also theoretically important. Previous fMRI work with reversal learning and other paradigms demonstrated that prediction errors (punishments, or the absence of reward when reward is expected) induce reductions in OFC activity [51]. In the study on reversal learning [10], healthy youth and youth with attention-deficit/hyperactivity disorder (ADHD) showed this reduction in OFC activity following an unexpected punishment. In contrast, youth with psychopathic traits did not and in this condition actually showed increased OFC activity. These data are important in that they indicate that OFC activity, at least when engaged by reinforcement expectancy-based information, is neither upregulated by expectations of reinforcement-based information [7, 46, 47] nor downregulated by reinforcement prediction errors [10].

The fourth exception concerns the two specific studies [44, 45]. The first involved a small number of adults with psychopathic traits and comparison adults (n=6 in each group) performing gender judgements on fearful, happy, and neutral expressions [44]. In contrast to other work [6, 11, 42, 43], this study reported no reduced amygdala responses in the individuals with psychopathy. However, it should be noted that this study did observe reduced fusiform activity and, as noted previously, amygdala responses are typically highly correlated with those of fusiform cortex when processing emotional expressions [48]. Thus, it is perhaps likely, particularly given the other literature and the study's small size, that this result reflects a type II error. This cannot be the explanation for the data obtained by the second study [45]. This study involved passive viewing of emotional images, and although the sample size was again very small (n=6 in each group), it reported that adults with psychopathic traits showed increased amygdala responses relative to the comparison individuals. There is no easy explanation for the inconsistency of this finding with the rest of the literature. However, it is possible that there were problems with classification. It is notable that the results of this study were very similar to those obtained with the reactively aggressive spouse abusers and patients with intermittent explosive disorder [14••, 15, 24].

It should be noted that an alternative theory has suggested that the insula, anterior and posterior cingulate cortex, parahippocampal gyrus, and anterior superior temporal gyrus may also be dysfunctional in psychopathy [52]. All—or at least part of all—these regions show structural connectivity with the amygdala [50], and most show considerable connectivity with the OFC [53]. However, the evidence of reduced activity in individuals with psychopathy is currently mixed. It is best for reduced superior temporal cortex. This has been reported in several fMRI studies [9, 10, 42, 43], although it is not always seen [46, 47]. Notably, this region was also consistently implicated in the structural MRI studies described previously. It has also been reported for the posterior cingulate cortex [7, 9, 10, 42, 46, 47]. The evidence is poorer for the parahippocampus, for which two studies have reported reduced activity in individuals with psychopathic traits [9, 42] and five have not [7, 10, 43,

46, 47]. It is also poor for the ACC, for which again two studies have reported reduced activity [9, 46] and five have not [7, 10, 42, 43, 47]. Finally, the evidence is particularly poor for the insula, for which only one study has found reduced activity [46] and most have not [7, 9, 10, 42, 43, 47]. Indeed, it is worth pointing out that both the dorsal ACC and the anterior insula have been found to show appropriate responses to punished reversal errors, indicating intact sensitivity to at least some of their functional triggers in youth with psychopathic traits [10].

Of course, the extent to which the paradigms used are typically associated with neural activity in these additional regions can be debated. However, should stronger data emerge, it will be necessary to determine whether aberrant neural activity indicates functional impairment in the region identified or a secondary effect of the functional impairment within the amygdala and OFC that is propagated via the connections between these regions and the identified region. Certainly, although considerable neuropsychological data support amygdala and OFC dysfunction [5••], no neuropsychological data support dysfunction within the insula, anterior and posterior cingulate cortex, parahippocampal gyrus, or anterior superior temporal gyrus. Indeed, intact performance on episodic memory [54] and Stroop tasks [55] suggests that at least memory functions of the hippocampus and response conflict/competition functions of the dorsal ACC are not dysfunctional in individuals with psychopathy.

Neuroimaging of Conduct Disorder Samples Undifferentiated by Level of Psychopathic Traits

A body of literature has examined youth with CD using both structural and fMRI techniques. Of course, there are complexities involved with interpreting studies of patients with CD. This is because the diagnosis of CD does not consider the presence of psychopathic traits. Thus, patient groups are likely to include individuals who show relatively selectively increased levels of reactive aggression (and heightened amygdala responsiveness) as well as those who show psychopathic traits/reactive and instrumental aggression (and reduced amygdala and OFC responsiveness). Indeed, it is notable that about 40% of patients with CD are comorbid for a mood/anxiety disorder [56], yet the presence of the emotional component of psychopathy protects the individual from depressed mood and anxiety [57].

Three studies have examined structural abnormalities in youth with CD [13, 58, 59]. Two reported reduced amygdala volumes [13, 59], whereas the third reported reduced temporal cortical volume (the amygdala was included within the temporal cortex region of interest examined) [58]. There also have been reports of reduced OFC [59] and insular volumes [13], but these have only been seen in individual studies and have not yet been replicated.

A series of fMRI studies examined patients with CD [12, 60-62••, 63-65]. In two studies by the same group that examined patients with CD during passive viewing, the youth with CD showed a reduced differential response between emotional and neutral images within the dorsal ACC [60, 61]. Both studies took a region-of-interest approach to the data, examining group differences only for the ACC, OFC, amygdala, and hippocampus [61] or only for the ACC [60]. Sterzer et al. [61] found that youth with CD showed a reduced differential response between emotional and neutral images within the amygdala that was moderated by anxiety level; the less anxious youths with CD showed the least amygdala responses. In line with this, anxiety level is usually inversely correlated with the emotion dysfunction component of psychopathy [66].

Rubia and colleagues [12, 62••, 63] conducted a series of fMRI studies examining patients with pure CD (not comorbid for ADHD) and patients with pure ADHD (not comorbid for CD). These studies focused primarily on paradigms such as the Simon [12], continuous performance [62••], and stop tasks [63]. Interestingly, impairment on these tasks is often found in patients with ADHD but not in patients with CD (at least not those without comorbid ADHD) [67]. As such, these studies form an interesting complement to two studies examining youth with psychopathic traits and patients with ADHD [10, 42]. These studies examined reversal learning and the response to fearful expressions, respectively—capacities impaired in individuals with psychopathic traits, but not patients with ADHD. In all three studies by Rubia and colleagues [12, 62••, 63], the patients with ADHD, but not those with CD, showed reduced activity within the inferior frontal cortex, a consistent finding in studies of ADHD. There were findings of reduced activation in the patients with CD in several regions, but none of these replicated across the three tasks. However, interestingly, in the one study that examined responses to rewarded outcomes, patients with CD, but not ADHD, showed reduced responses to these rewarded trials [62••]. This is particularly interesting, as it complements previous findings in which only youth with psychopathic traits, not youth with pure ADHD, failed to demonstrate the reduction in the OFC following the prediction error of unexpected punishment [10].

Two recent fMRI studies of youth with CD examined viewing of emotional stimuli [65] and individuals in pain [64]. In both studies, amygdala responsiveness was increased in the youth with CD relative to control youth. This is notably different from most of the literature on individuals with psychopathic traits. However, such results may be expected if these youth were predominantly reactively aggressive [14••, 15, 24].

Conclusions

In summary, the available data strongly support the suggestion that individuals who are predominantly reactively aggressive (at least spouse abusers and patients with intermittent explosive disorder) show atypically increased amygdala responses to emotional stimuli. This would be consistent with suggestions that the risk for reactive aggression is increased if the basic responsiveness of the threat system is increased; the individual is more likely to show reactive aggression rather than flight/freezing in response to a threatening/frustrating stimulus. Currently, however, the suggestion that reactively aggressive individuals show reduced frontal regulatory activity remains without strong support.

The data also strongly support the suggestion that amygdala and OFC functioning is disrupted in individuals with psychopathic tendencies. Other systems may also be affected, but this has not been clearly demonstrated. Critically, these studies provide us with biomarkers of the disorder. The dysfunctions observed are specific to psychopathic traits and are not seen in other patient populations. As such, they allow us indices of treatment response that are not confounded by a patient's truthfulness or a clinician's skill. It is to be hoped that this work will provide us the information to manage and ideally cure patients with this disorder.

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