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Reward processing, functional connectivity, psychopathy and RDoC

R. James and **R. Blair**

Section of Affective and Cognitive Neuroscience, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD, 20892

Psychopathy is a disorder characterized by pronounced emotional deficits (including reduced guilt and empathy) and an increased risk for displaying antisocial behavior. The disorder was initially described by Cleckley before being more formally characterized via a behavioral checklist and then interview by Robert Hare (1). The importance of Hare's characterization was that it provided the description of a behavioral presentation associated with specific causal factors. In contrast, a wide variety of causal factors are associated with the more general antisocial behavior descriptions provided by the DSM or ICD.

Progress in psychopathy research has been rapid since 1980. In particular, there has been enormous growth in the understanding of the pathophysiology of this disorder. Indeed, DSM5 has recognized this progress alluding to the constructs of psychopathy in the revisions of both Conduct Disorder and Antisocial Personality Disorder. The two papers in this issue represent both the consolidation and potential expansion of this understanding. One concerns the structural integrity and functional connectivity of adults with psychopathy (2). The other concerns sensitivity to reinforcement information in adolescents with persistent disruptive behavior and psychopathic traits (3).

Understanding the pathophysiology of psychopathy requires determining both the systems that are dysfunctional, and the functional processes that are impaired, in patients with the disorder. A series of studies have investigated neural structural MRI integrity in psychopathy. The findings of Contreras-Rodriguez et al. (2015) usefully consolidate this literature confirming previous reports (e.g., 4) of gray matter reduction within ventromedial frontal cortex, orbital frontal cortex and the amygdala in adults with psychopathy relative to comparison adults.

With respect to functional processes, there has also been a long running assumption that psychopathy and conduct problems more generally are associated with heightened sensitivity to reward and reduced sensitivity to punishment. Yet up until recently the data has been inconclusive. In particular, behavioral studies failed to provide definitive evidence in support, or refutation, of this assumption. However, fMRI studies, including the study by

Correspondence: Dr. James Blair, National Institutes of Health, National Institute of Mental Health, Section of Affective and Cognitive Neuroscience, 9000 Rockville Pike, Building 15k, Room 300-E, MSC 2670, Bethesda, MD, 20814, USA, 301-435-6059 (Tel.), 301-594-9959 (Fax), jamesblair@mail.nih.gov.

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Cohn et al. (2015), have been more informative. These studies have shown that patients with conduct problems show reduced, *not* increased, responsiveness to reward information (e.g., 5). Most previous work has examined responsiveness to reward outcomes in instrumental contexts; i.e., when the participant has to make the correct response to engender reward and the outcome information leads to response-outcome association formation (5). Cohn et al. (2015) extends this literature by showing reduced ventral striatal reward responses to outcome information regarding cues; i.e., when the participant is learning about the reward value of objects and has to form stimulus-outcome associations. Moreover, they show that this impairment is marked in patients with *persistent* disruptive, antisocial behavior; participants engaging in criminal offending before the age of 12 but stopping by late adolescence did not show this impairment.

Of course, it is an interesting time to be engaged in mental health research. The emergence of the Research Domain Criteria (RDoC) project (6) has lead to an increased focus on the clinical implications of dysfunction in particular neuro-cognitive systems rather than on identifying dysfunctional neuro-cognitive systems in particular clinical conditions. It is perhaps useful to consider these two papers in terms of RDoC.

Appropriate reward signaling by the striatum is clearly critical for successful behavior. Signaling the reinforcement associated with an object or action allows the individual to learn the value of that object or action and thus whether it should be approached (undertaken) or avoided in the future. But what forms of behavior are compromised when this function is disrupted?

Cohn et al. (2015) relate a deficient ventral striatal reward response to persistent disruptive behavior. Yet similar impairments on this task have been related to level of impulsivity in patients with Attention Deficit Hyperactivity Disorder (ADHD) (7) and severity of anhedonia in patients with major depressive disorder (MDD) (8). Cohn et al. (2015) report that ADHD diagnostic status was not a significant predictor of ventral striatal response in their supplemental material. Moreover, is unlikely that MDD status is the feature that distinguishes those whose antisocial behavior persists versus those whose does not. There are many reasons why deficient reward sensitivity should result in persistent antisocial behavior. Some of these were outlined by Cohn et al. (2015) and include increased frustration due to poor decision-making and impulsiveness due to inadequate representation of the consequences of actions. But, of course, there are reasons why deficient reward sensitivity should result in anhedonia too. It will be critical to determine what the behavioral sequelae of a compromised striatal response to reward are. Perhaps the specific behavioral sequelae of this impairment are determined by environmental factors? But alternatively they might be determined by other neuro-cognitive impairments that the child faces.

Notably, deficient reward sensitivity is *not* associated with psychopathic traits. Both Cohn et al. (2015) and previous work (e.g., 5) report no relationship between reward sensitivity and callous-unemotional traits (the emotional - reduced guilt and empathy – component of psychopathic traits). Instead, callous-unemotional traits appear to be behavioral sequelae of deficient amygdala responsiveness. Cohn et al. (2015) report a relationship between callous-unemotional traits and a reduced amygdala response to punishment information. Previous

work has reported a relationship between amygdala hypo-responsiveness and callous-unemotional traits to other cues (e.g., 9).

It is important to note that future work determining the behavioral sequelae of a compromised striatal response to reward will require work with patients. While reduced sensitivity to reward is associated with increased impulsiveness in patients with ADHD, an *increased* sensitivity to reward is associated with increased impulsiveness in healthy participants (for a review of the literature, see 7). The RDoC project encourages a dimensional approach but it is important to remember that the relationship between a behavioral dimension and neural responding may be curvilinear. Relationships identified in work with healthy participants may not be (and, in the face of striatal reward responsiveness, are not) the same as those identified with patients.

The findings of Contreras-Rodriguez et al. (2015) are also worth considering from an RDoC perspective. In particular, this paper reported that a relatively large region of dorsomedial frontal cortex showed greater functional connectivity in adults with psychopathy relative to comparison adults. They also conducted a seed based functional connectivity analysis with a seed focused on the region of dorsomedial frontal cortex where adults with psychopathy showed both greater functional connectivity and reduced gray matter relative to comparison adults. The results of this analysis were particularly interesting. The region appeared to serve as a nexus showing positive correlations with lateral frontal cortical activity and negative correlations with amygdala activity in *both* patients with psychopathy and healthy adults. Strikingly, the patients with psychopathy showed an *enhancement* in both positive and negative correlations relative to the healthy adults. Given previous studies have reported reduced connectivity in individuals with psychopathy relative to comparison adults (e.g., 10), it would be useful to determine the functional roles of this circuitry. Of course, such a question is difficult to answer from connectivity data obtained during resting state. There are no manipulations of task variables to aid interpretation of system function. However, future functional studies might be highly informative.

In summary, these papers further reinforce the importance of the psychopathy construct. It is readily possible to point to a body of work identifying consistent impairments in this population. This body of work identifies treatment targets for future intervention studies. The question remains though for work with this disorder and many others – what are the specific behavioral sequelae associated with identified neural system dysfunction and to what extent are these behavioral sequelae determined by environmental features or other uninvestigated forms of dysfunction.

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