Archival Report

Biological Psychiatry: CNNI

Negative Valence in Autism Spectrum Disorder: The Relationship Between Amygdala Activity, Selective Attention, and Co-occurring Anxiety

John D. Herrington, Brenna B. Maddox, Alana J. McVey, Martin E. Franklin, Benjamin E. Yerys, Judith S. Miller, and Robert T. Schultz

ABSTRACT

BACKGROUND: A critical agenda of the National Institutes of Health Research Domain Criteria (RDoC) initiative is establishing whether domains within the RDoC matrix are truly transdiagnostic. Rates of anxiety disorders are elevated in autism spectrum disorder (ASD), but it is unclear whether the same mechanisms contribute to anxiety in individuals with and without ASD. As changes in selective attention are a hallmark of anxiety disorders in non-ASD samples, the identification of these changes in ASD would support the transdiagnostic nature of anxiety.

METHODS: This functional magnetic resonance imaging study focused on the negative valence domain from RDoC (manifest as anxiety symptoms) in youth with ASD (n = 38) and typically developing control participants (n = 25). The task required selective attention toward and away from social information (faces) with negative and neutral affect. Participants underwent in-depth characterization for both anxiety and ASD symptoms.

RESULTS: Dimensional and categorical measures of anxiety were significantly related to increased amygdala activation—evidence of enhanced attentional capture by social information.

CONCLUSIONS: This pattern fits with decades of research among non-ASD samples using selective attention and attentional bias paradigms, suggesting that anxiety in ASD shares mechanisms with anxiety alone. Overall, results from this study support the transdiagnostic nature of the negative valence domain from RDoC and increase the likelihood that anxiety in ASD should be responsive to interventions targeting maladaptive responses to negative information.

Keywords: Amygdala, Anxiety disorders, Autism spectrum disorder, Negative valence, Research Domain Criteria, Selective attention

http://dx.doi.org/10.1016/j.bpsc.2017.03.009

Although anxiety disorders constitute their own diagnostic grouping within DSM (1), anxiety symptoms occur in varying levels across normal and abnormal psychology, as reflected by the negative valence domain of the National Institutes of Health Research Domain Criteria (RDoC) (2). The Fear (Acute Threat) construct within the RDoC negative valence domain, defined as a "defensive motivational system to promote behaviors that protect the organism from perceived danger" (https://www.nimh.nih.gov/research-priorities/rdoc/negative-valence-systems-workshop-proceedings.shtml), manifests clinically as symptoms of anxiety.[1] Robust dimensional models of anxiety and negative valence (or affect) actually precede RDoC by decades [in particular, see the tripartite model of anxiety and depression by Clark and Watson *et al.* (3–5)]. Yet, the recent emergence of RDoC brings renewed focus on the strengths and weaknesses of categorical and dimensional approaches to psychopathology (6,7).

The case of anxiety among individuals with autism spectrum disorder (ASD) illustrates the problems that can arise when dimensional models intersect with categorical ones. Estimated rates of co-occurring anxiety disorders in ASD exceed 40% (well above population norms) (8–11). Many individuals with ASD present with symptoms of anxiety that fall clearly within DSM diagnostic criteria. However, individuals with ASD also present with symptoms that are best described as anxiety but focus on themes that are rare in non-ASD populations. For example, individuals with ASD frequently present with highly unusual specific phobias (e.g., the sound of a toilet flushing, specific songs on the radio), generalized anxiety surrounding unusual themes (in particular, minor changes in the order of daily events and activities), and social anxiety without fear of negative evaluation [for review see (8,12)]. These symptoms do fit within many prevailing models of anxiety [e.g., the negative affect and hyperarousal dimension of Clark and Watson's

[1] Although the RDoC matrix defines "anxiety" as an analogue to a construct it calls "Potential Threat," in this study, we follow the tradition of referring to anxiety as a superordinate construct that subsumes fear as well as other related constructs (worry, anxious arousal, etc.).

tripartite model (3–5)], but their absence outside of ASD complicates the premise that they fall on the same continuum as anxiety symptoms generally.

The present study tests whether individuals with ASD share cognitive profiles that are known to relate to anxiety in the typically developing population—specifically, abnormal selective attention for social and emotional information. Selective attention refers to the capacity to focus on specific information in the environment, while diminishing attention paid to irrelevant information. Selective attention is closely associated with fear and is therefore integral to the negative valence domain of RDoC.

Deficits in selective attention are considered to be part of the etiology of anxiety disorders and to predispose anxious individuals to threats in the environment that would otherwise be disregarded—both initiating and perpetuating anxiety symptoms (13–17). However, almost all the data we have on the selective attention/anxiety relationship come from typically developing samples. The present study focuses on visual selective attention in ASD—specifically, responses to irrelevant social and emotional information occurring outside of one's attentional focus. Amygdala is widely considered to be a major brain structure in attentional orienting toward emotional information and may have privileged access to input from very early in the sensory information processing stream (18–20) [see (21) for alternative accounts]. Until fairly recently, the prevailing view has been that ASD is associated with decreased amgydala activation, which has been related to diminished social and emotional information processing [for reviews see (22–24)]. However, this view has generally failed to explain why anxiety—associated with increased amygdala function—occurs so frequently in ASD. The present results add to a growing number of studies suggesting that prior perspectives on diminished amygdala function and social deficits in ASD that fail to consider the role of anxiety are at best incomplete.

Among typically developing individuals, anxiety disorders have been consistently associated with increased attentional capture by emotional stimuli (15–17,25), which have been associated with increased amygdala activity (26–30). One widely used paradigm in this area, developed by Vuilleumier *et al.* (31–33), involves the simultaneous presentation of pairs of faces and nonface objects (e.g., houses) (Figure 1). Participants are asked to make a same/different identity judgment on either the faces or the houses (varying from trial to trial), while ignoring the other stimuli on the screen. The presented faces have either a neutral or a negative expression (also varying from trial to trial)—either fear or anger [see (34) for a discussion of similarities and differences between these two facial emotions in selective attention tasks]. The seminal finding from this paradigm was that amygdala activity was increased for negative faces regardless of whether participants were carrying out the same/different judgment for the faces or the houses on the screen. This has been considered evidence that amygdala responsiveness to emotional information is at least partially obligatory—i.e., independent of visual selective attention (19).

The present study used functional magnetic resonance imaging (fMRI) to test the hypothesis that anxiety in the context of ASD is associated with the enhanced processing of peripherally presented social information, as would be predicted by the negative valence domain of RDoC. Although evidence in favor of this hypothesis could come from several different brain areas, we focus specifically on the amygdala, owing to the centrality of this structure in the etiology of both anxiety and ASD [for review see (35)]. The analytic approach follows RDoC in taking a dimensional approach to anxiety symptoms, while also using a categorical (diagnostic) approach to examine whether anxiety disorders in the context of ASD are related to similar mechanisms as in non-ASD anxiety samples (6).

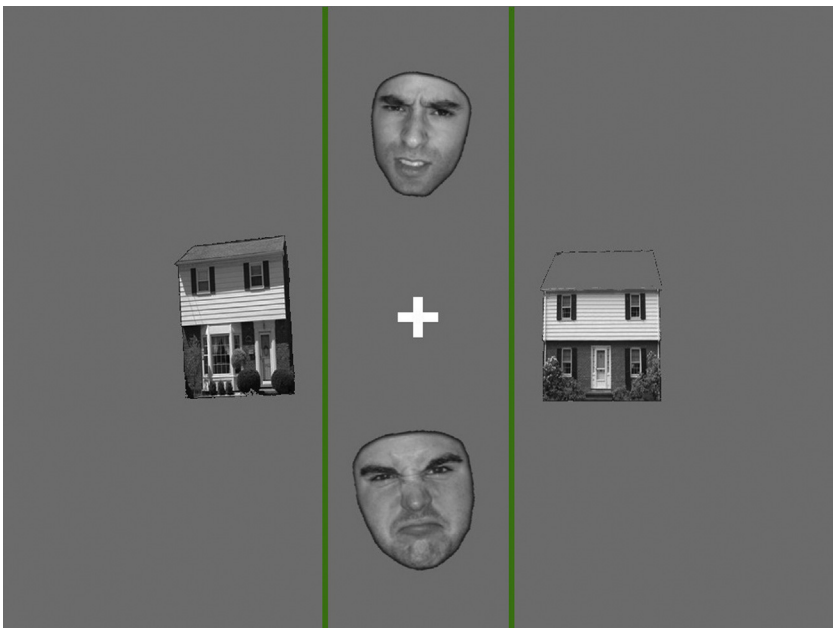

Figure 1. Selective attention task stimuli. Participants were asked to indicate, via button press, whether the two pictures in between the green lines represented the same person (or house) or not. Stimuli alternated between faces and houses as the to-be-attended picture type (following a block design).