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Neural substrates of child irritability in typically developing and psychiatric populations

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ABSTRACT

Irritability is an aspect of the negative affectivity domain of temperament, but in severe and dysregulated forms is a symptom of a range of psychopathologies. Better understanding of the neural underpinnings of irritability, outside the context of specific disorders, can help to understand normative variation but also characterize its clinical salience in psychopathology diagnosis. This study assessed brain activation during reward and frustration, domains of behavioral deficits in childhood irritability. Children (age 6–9) presenting in mental health clinics for extreme and impairing irritability ($n = 26$) were compared to healthy children ($n = 28$). Using developmentally sensitive methods, neural activation was measured via a negative mood induction paradigm during fMRI scanning. The clinical group displayed more activation of the anterior cingulate and middle frontal gyrus during reward, but less activation during frustration, than healthy comparison children. The opposite pattern was found in the posterior cingulate. Further, in clinical subjects, parent report of irritability was dimensionally related to decreased activation of the anterior cingulate and striatum during frustration. The results of this study indicate neural dysfunction within brain regions related to reward processing, error monitoring, and emotion regulation underlying clinically impairing irritability. Results are discussed in the context of a growing field of neuroimaging research investigating irritable children.

1. Introduction

Irritability is an aspect of the negative affectivity domain of temperament, which captures variation in the intensity, duration and regulation of children's angry mood and behavior (Rothbart et al., 2000; Snaith and Taylor, 1985). While anger is a normative response to frustration, intense, pervasive and/or dysregulated irritability is maladaptive. In particular, it is a hindrance to early school success and peer relationships (Blair, 2002; Blair et al., 2004; Denham et al., 2011) and is noted as a marker for psychiatric illness, bridging the gap between internalizing and externalizing child psychopathology (Stringaris, 2011). Thus, irritability is a prime construct for investigation within the National Institute of Health's Research Domain Criteria Project (RDoC) which emphasizes symptoms rather than categorical disorders and highlights the strong, mostly unexplored, neurodevelopmental origins of psychiatric illness (Morris and Cuthbert, 2012; Sanislow et al., 2010).

Although irritability is a growing focus for psychiatric research and therapeutic interest (Leibenluft et al., 2003; Stringaris, 2011), we know little about its neural mechanisms. Critical questions concern the neural deficits associated with excessive irritability and the nature of those defects that might underlie the poor mental health outcomes associated with high irritability. Detecting neural markers could be helpful in differentiating when high irritability in children is an indicator of abnormality (e.g. marking a prodromal phase of psychopathology) from when children are displaying high levels of normative irritable temperament. In already clinically diagnosed children, the nature of ongoing variation and/or deterioration in this circuitry might be linked to increasing impairment and could possibly aid clinicians in therapeutic decisions or predict treatment response.

Several adult neuroimaging studies have investigated the neural correlates of negative mood by inducing it through

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autobiographical scripts (Cerqueira et al., 2010), emotional images or music (Dyck et al., 2011), or direct instruction (Habel et al., 2005). The literature investigating the neurodevelopment of irritability has specifically focused on the negative mood of frustration, defined as the affective response to the prevention of goal attainment or absence of expected reward. Frustration is widely noted in the individual differences literature (Abler et al., 2005; Campbell, 1995; Rich et al., 2011) and clinical community (Fergus et al., 2003; Leibenluft et al., 2003) as the most commonly observed precipitant for temper outbursts in highly irritable children. Frustration is often induced while collecting neural data though paradigms that increase in difficulty (Lewis et al., 2006; Moadab et al., 2010; Perlman and Pelphrey, 2010) or involve an unsolvable task (Pawliczek et al., 2013), which blocks a desired goal, or deceives participants into believing that failing performance will decrease the likelihood of an expected reward (Deveney et al., 2013; Rich et al., 2007).

The fMRI studies cited above have found neural activation changes in the context of frustration induction within three main regions: the anterior cingulate cortex (ACC), amygdala, and striatum, all of which are relevant to cognitive and emotional dysfunction in irritability. The ACC has been linked to error monitoring (Carter et al., 1998), deviation from a potential reward (Amiez et al., 2005), and emotion regulation (Bush et al., 2000). The amygdala is involved in the evaluation of the salience of a potential negative stimulus and the coordination of cortical networks during that evaluation (Pessoa and Adolphs, 2010). Finally, the dorsal and ventral striatum has been linked to general reward response in both humans (Delgado, 2007) and animals (Apicella et al., 1991). Studies focused on mood induction in children have noted the modulation of these regions during frustration. In typically developing children (ages 5–11), Perlman and Pelphrey (2010) induced negative mood through fluctuating difficulty levels of a game, leading children to believe that they would lose a desired prize. Activation related to frustration was noted in the dorsal and ventral ACC with increased connectivity between the ACC and amygdala as difficulty increased (Perlman and Pelphrey, 2011). Deveney and colleagues (2013) investigated children with high levels of irritability who were presenting for clinical care. They found that when negative mood was induced by providing participants with rigged feedback on a cued attention task, leading them to believe that they would lose money, subjects demonstrated amygdala and striatum deactivation relative to healthy subjects. The authors reasoned that their findings might imply overall neural dysregulation occurring when an outcome is worse than expected, which might underlie the exaggerated and inappropriate reaction to frustration exhibited in clinically impaired children. Taken together, these findings provide early evidence for brain circuitry underlying varying aspects of irritability (i.e. evaluation of negative stimuli, reward, emotion regulation).

We conducted an fMRI investigation in children who were undergoing clinical treatment for severe irritability and a comparison group of healthy children. We took an RDoC approach to our questions of irritability by recruiting a sample of clinical children who were high in the symptom of irritability, but allowed disorder diagnosis to vary. Based upon previous research, we expected to find (1) decreased anterior cingulate activation in clinically irritable subjects due to difficulties in effective error monitoring and/or emotion regulation during frustration, (2) amygdala deactivation in irritable subjects due to their likely deficits in evaluation of the emotional salience of stimuli during frustration, and (3) potential striatum deactivation during rewarding and punishing episodes due to dysfunctional reward processing in irritable subjects. We further expected greater deficits in our regions of interest in clinical subjects who had greater parent report of irritability.

2. Materials and methods

This study was approved by the Institutional Review Board (IRB) of the University of Pittsburgh.

2.1. Participants

Thirty-five children (ages 6–9) were recruited from local child psychiatric clinics (Clinical). Parents of potential participants were asked by a clinic receptionist if they were interested in talking to a member of the research team about participation when arriving for a scheduled clinic visit. Parents who expressed interest were introduced to a member of the research staff who explained procedures of the study, but did not specify that irritability was the primary research topic. Parents completed a short screening interview in which they were questioned on primary inclusion criteria: (1) irritability present for at least half the day on most days, (2) irritability is noticeable in more than one setting (e.g. home, peers, school), (3) at least three anger/frustration outbursts per week, (4) these symptoms have negatively and severely affected the child's academics and/or family/social life, (5) irritability has been present for a minimum of 6 months, and (6) their initial reason for seeking care was their child's high irritability.[1] Children were not invited to participate in the study if all of these criteria were not met.

Exclusion criteria included severe systemic medical illnesses, neurological disorders, history of head trauma with loss of consciousness, use of non-psychotropic medications that may produce CNS effects (e.g. steroids), IQ < 70 (Wechsler Abbreviated Scale of Intelligence; Weschler, 1999), being unable to complete tasks in English, and autism spectrum disorders or developmental delays. Additional exclusion criteria for scanning purposes included claustrophobia or metal objects in the body. Clinical subjects were permitted to use prescribed medication(s) before scanning, given ethical problems with stopping medication for research purposes.

Thirty-seven physically healthy participants with no personal history of psychiatric diagnosis were recruited from the community (Comparison). There was no history of schizophrenia, autism spectrum disorders, mental retardation or bipolar disorder in first degree relatives or depression, anxiety disorders, ADHD, disruptive behavior disorders, or eating disorders during the lifetime of the child. Recruited participants were matched as closely as possible on age, race, sex, family income, parent education, and IQ (Table 1). Parents/guardians provided written informed consent, and youth provided assent prior to study participation. Participants received monetary compensation, a small prize, and a framed picture of their structural neuroimaging scan (Perlman, 2012).

2.2. Symptom assessment[2]

During an initial study visit, taking place in the laboratory, diagnostic assessments of all participants were performed by interviewing the caregiver and child using the Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS-PL-W; Birmaher et al., 2009), including the Severe Mood Dysregulation Module (SMD; Leibenluft, 2011). K-SADS interviews were completed by a single research assistant who was trained by the

[1] Although recruitment for this study predated the addition of Disruptive Mood Dysregulation Disorder (DMDD) to DSM-5, all subjects in this study would have met DMDD/SMD. We note that, although high levels of irritability might be present, DMDD/SMD is not, currently, dually diagnosed with bipolar disorder. Because this study predated regulations for DMDD diagnosis, and those regulations are still a topic of controversy, all potential subjects who met our high irritability criteria were included in the study regardless of bipolar disorder diagnosis.

[2] Exploratory analyses related to diagnostic category are presented in the supplemental materials.