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Trait-level temporal lobe hypoactivation to social exclusion in unaffected siblings of children and adolescents with autism spectrum disorders

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ABSTRACT

Social exclusion elicits powerful feelings of negative affect associated with rejection. Additionally, experiencing social exclusion reliably recruits neural circuitry associated with emotion processing. Recent work has demonstrated abnormal neural responses to social exclusion in children and adolescents with autism spectrum disorders (ASD). However, it remains unknown to what extent these abnormalities are due to atypical social experiences versus genetic predispositions to atypical neural processing. To address this question, the current study investigated brain responses to social exclusion compared to a baseline condition of fair play in unaffected siblings of youth with ASD using functional magnetic resonance imaging. We identified common deviations between unaffected siblings and ASD probands that might represent trait-level abnormalities in processing Social Exclusion vs. Fair Play, specifically in the right anterior temporoparietal junction extending into posterior superior temporal sulcus. Thus, hypoactivation to Social Exclusion vs. Fair Play in this region may represent a shared genetic vulnerability to developing autism. In addition, we present evidence supporting the idea that one's status as an unaffected sibling moderates the relationship between IQ and neural activation to Social Exclusion vs. Fair Play in anterior cingulate cortex. These results are discussed in the context of previous literature on neural endophenotypes of autism.

1. Introduction

Social deficits are the cornerstone of behavioral symptoms in children with autism spectrum disorder (ASD; Wing and Gould, 1979). Such social deficits include abnormal eye contact or body language and difficulty engaging in normal back-and-forth conversation (APA, 2013). As one can imagine, these atypical social behaviors make children with ASD particularly vulnerable to ostracism by peers (Symes and Humphrey, 2010). However, because of deficits in understanding nonverbal communication, it is difficult to assess whether children with ASD process peer rejection (which is often communicated through actions instead of words) in a manner that it similar to typically developing youth.

The typical experience of being socially excluded has profound effects on basic psychological needs such as feelings of belonging, control, meaningful existence, and self-esteem (Williams et al., 2000; Williams, 2007). The distress of social exclusion has distinct neural correlates that are robust among healthy children, adolescents, and adults (Bolling et al., 2011a,c; Eisenberger et al., 2003; Krill and Platek, 2009; Masten et al., 2009; Moor et al., 2012; Onoda et al., 2009; Sebastian et al., 2011). Abnormal brain responses to social exclusion have been noted in children and adolescents with ASD (Bolling et al., 2011b; Masten et al., 2011). These abnormal brain responses to social exclusion (compared to social inclusion) manifest as hypoactivation in several regions including anterior insula and anterior cingulate cortex (ACC; Bolling et al., 2011b; Masten et al., 2011). However, it is unknown whether these atypical brain responses arise from the neurodevelopmental etiology of ASD or result from the unique social experiences afforded by growing up with ASD. Building on previously established evidence of neural hypoactivation in response to social exclusion in youth with ASD, the current study attempts to identify regions of trait differences, where the hypoactivation found in ASD is also found in a group of unaffected siblings (UAS) of children with ASD who share the genetic risk for developing ASD, but who have not experienced first-hand the social struggles faced by their brother or sister. In this way, we can dissociate biological from environmental influences on the neural response to social rejection in ASD.

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It is likely that a history of atypical social experiences contributes to the abnormal brain activity observed in children with ASD during social interactions. Research examining the nature of social relationships in children and adolescents with ASD has found that compared to typically developing (TD) youth, children with ASD show higher rates of peer victimization (Little, 2001), as well as social rejection and bullying (Symes and Humphrey, 2010). Youth with ASD also report receiving less peer approval (Williamson et al., 2008) and experiencing more loneliness (Bauminger and Kasari, 2000). Children with ASD initiate social interactions less frequently than TD peers (Hauck et al., 1995). High-functioning children with ASD are both cognizant and distressed by social rejection (Ochs et al., 2001). Thus, by adolescence, individuals with ASD have likely endured a very different and profoundly difficult experience of peer relationships relative to their TD counterparts.

One's previous experiences and expectations of social interactions can influence immediate responses to peer rejection. For instance, the expectation of future social exclusion leads to emotional numbing to physical and social pain (DeWall and Baumeister, 2006). While adolescents with ASD exhibit normal anxiety and need threat responses to rejection, they also show decreased modulation of mood following exclusion compared to TD peers (Sebastian et al., 2009). This finding, along with two separate accounts of hypoactivation in brain regions typically responsive to social exclusion including ACC and anterior insula (Bolling et al., 2011b; Masten et al., 2011), led Masten et al. to hypothesize that reduced neural sensitivity to rejection in ASD may be a result of habituation to social exclusion or increased expectancy of being rejected by unfamiliar peers.

In contrast to the idea that experience accounts for abnormal brain responses to exclusion in ASD, other research suggests that endogenous, biological factors influence brain responses to social stimuli in children with ASD. Neuroimaging work has detected signs of a "neural endophenotype" of autism; atypical patterns of brain structure and function that are shared between children with ASD and their unaffected siblings (UAS; Barnea-Goraly et al., 2010; Belmonte et al., 2010; Dalton et al., 2007; Kaiser et al., 2010; Spencer et al., 2011). One study investigating brain responses to biological motion found trait-level hypoactivation shared between children with ASD and UAS in regions including right inferior temporal gyrus, left dorsolateral prefrontal cortex, and bilateral fusiform gyrus (Kaiser et al., 2010). Because UAS do not share in the ASD clinical phenotype or the experience of growing up with ASD, these common neural profiles are thought to be a result of the strong genetic basis for the disorder (for review see Gupta and State, 2007). Supporting this claim, behavioral assessments of UAS of children with ASD have found largely normal patterns of social support, social competence, and psychosocial development (Kaminsky and Dewey, 2002; Macks and Reeve, 2007; Pilowsky et al., 2004; Rodrigue and Geffken, 1993). Thus, while some neural profiles are common among the two groups, the experience of social victimization and isolation in youth with ASD does not seem to be shared by their healthy siblings.

To investigate atypical neural responses to social rejection in children with ASD and UAS that may represent trait-level biological vulnerabilities to developing autism, we used functional magnetic resonance imaging (fMRI) to measure brain responses to discrete periods of social exclusion. To this end, we used a modification of the Cyberball task (Williams et al., 2000) during which participants play an online ball-tossing game with two other ostensibly-real children. The game alternates between periods of fair play, where the participant receives the ball on one-third of the throws, and social exclusion, where the participant does not receive any throws. While it is extremely difficult to assess neural activation during actual peer rejection because of methodological constraints, this study utilized an experimental model of peer rejection that has been developed in an attempt to marry a naturalistic social experience of rejection with necessary controls on presentation (Williams et al., 2000). The hope is that for each participant, brain responses to the experience of social exclusion during Cyberball will mirror brain responses during a natural occurrence of peer rejection.

The current study utilized a two-step analysis approach to identify brain regions where both children with ASD and UAS showed differential activation to Social Exclusion vs. Fair Play compared to TD controls. First, the two groups of healthy children (the UAS and the TD controls) were compared in order to identify regions where UAS showed abnormal brain activation during social exclusion. Next, activation in each of these regions was assessed in a third group of children with ASD. Regions where the ASD group also significantly diverged from the TD controls in the same direction as the UAS were considered regions of trait-level difference. This two-step analysis strategy is fundamentally important. As it is tempting to only compare UAS and TD youth and conclude that differences reflect some sub-symptom genetic abnormality in the UAS, the potential remains that differences found between the two groups may be due to coincidental differences between the samples that prevented a full study replication. However, the use of a third, independent participant group (ASD) allowed us to confirm that certain regions where activation differed between TD and UAS groups represented meaningful, trait-level abnormalities.

2. Methods

2.1. Participants

Participants in the current study were children and adolescents ranging from 7 to 18 years of age. Individuals were excluded from participation in the current study if parents reported that the child had experienced neurological problems or abnormalities (unrelated to autism). In addition, if the child ever experienced seizures, epilepsy, hearing or vision loss, motor impairment, or severe allergies, then he or she was excluded from participation. Participants in the current study were recruited as three separate groups. Typically developing (TD) children had no parents, siblings, or half siblings with an autism spectrum disorder. In addition, these children had no diagnosis of an intellectual disability or learning disability. UAS were healthy children with a full sibling diagnosed with an autism spectrum disorder. One UAS was excluded from analyses when the diagnosis of the proband sibling (not in the current study) was not confirmed by study clinicians. Children with an ASD were diagnosed using one or both the autism diagnostic interview-revised (ADI-R; Lord et al., 1994) and the autism diagnostic observation schedule (ADOS; Lord et al., 2000), as well as expert clinical judgment based on DSM-IV-TR criteria (APA, 2000). All children (except for one ASD participant) had their social responsiveness level assessed by parent report using the social responsiveness scale (SRS; Constantino and Todd, 2003). Any TD child or UAS with an SRS standardized score within the "severe" range (t-score > 75) was excluded from the current study (two TD children were excluded for this reason). The data from the ASD group in the current study has been previously reported (Bolling et al., 2011b). In addition, data from the TD group in the current investigation is a subset of a sample, which has been previously reported (two TD children with elevated SRS scores were removed for the current investigation; Bolling et al., 2011a,b). The UAS in the current study are a novel group of participants, and thus the current study focuses on the UAS in comparison to TD and ASD children.

Following exclusions for head motion and task performance (thresholds described below), 19 TD controls (12.96 ± 2.7 years, 14 male), 16 youth with ASD (12.36 ± 4.2 years, 10 male), and 15 UAS (11.88 ± 3.2 years, 9 male) were included in analyses. Only 2