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Functional Neuroimaging of Sensory Over-Responsivity in Youth With Autism Spectrum Disorders

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Functional Neuroimaging of Sensory Over-Responsivity in Youth with Autism Spectrum Disorders

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Psychology

by

Shulamite Abra Green

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ABSTRACT OF THE DISSERTATION

Functional Neuroimaging of Sensory Over-Responsivity

in Youth with Autism Spectrum Disorders

by

Shulamite Abra Green

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2014

Professor Bruce L. Baker, Co-Chair

Professor Jeffrey J. Wood, Co-Chair

In addition to the core social and communication symptoms, individuals with autism spectrum disorders (ASD) have high rates of sensory over-responsivity (SOR). Despite the fact that over half of children and adolescents with ASD have SOR, very little is known about the neurobiological bases of this condition. SOR often co-occurs with anxiety disorders, which suggests a possible common biological basis for both SOR and anxiety in a subgroup of youth with ASD. The following studies used functional magnetic resonance imaging (fMRI) to examine brain response to mildly aversive sensory stimulation in youth with and without ASD, with a focus on brain areas responsible for primary processing of sensory information as well as those linked to anxiety and emotion regulation. Results suggest that youth with ASD and SOR have deficits in both primary sensory processing as well as in regulating emotional response to sensory information. These deficits are associated with reduced amygdala-prefrontal functional connectivity during exposure to sensory stimuli as well as reduced habituation to the stimuli. Findings can inform intervention, including better classification and targeted treatment for

subgroups of youth with ASD, and treatment focused on building coping skills for sensory stimulating environments.

The dissertation of Shulamite Abra Green is approved.

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SELECTED PRESENTATIONS

Green, S.A. et al. (2014, May). Neural responsivity to tactile and auditory sensory stimuli in youth with and without ASD. Paper presented at the International Meeting for Autism Research, Atlanta, GA.

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Green, S.A., Diep, J., & Baker, B.L. (2011, March). Maternal control and behavior problem trajectory: Differential effects on children with and without developmental delays. Paper presented at the biennial meeting for the Society for Research in Child Development, Montreal, Canada.

Introduction to Sensory Over-Responsivity in Autism Spectrum Disorders

Autism spectrum disorders (ASD) are characterized by impairments in social communication and repetitive or restrictive behaviors (American Psychiatric Association, 2013). The new Diagnostic and Statistical Manual of Mental Disoders (DSM-V), includes sensory over- and under-reactivity as a core symptom of ASD under the category of repetitive/restrictive behavior. Sensory over-responsivity (SOR), which causes children to react negatively to sensory stimuli such as noisy or visually stimulating environments, seams in their clothing, or being touched unexpectedly, is extremely common in ASD (Liss, Saulnier, Fein, & Kinsbourne, 2006). Rates of SOR in children with ASD are estimated to be 56-70% (Baranek, David, Poe, Stone, & Watson, 2006; Ben-Sasson et al., 2007b), compared to rates of 10-17% in typically developing TD children (e.g., Ben-Sasson et al., 2009; Ben-Sasson et al., 2007b). Furthermore, SOR is associated with increased functional impairment in children with ASD, including lower levels of social and adaptive skills (Liss et al., 2006; Pfeiffer, Kinnealey, Reed, & Herzberg, 2005), negative emotionality (Ben-Sasson et al., 2008), and overfocusing (Liss et al., 2006).

SOR has been linked to anxiety in children with ASD (Ben-Sasson et al., 2008; Liss et al., 2006; Pfeiffer et al., 2005), another clinical syndrome that is elevated in the ASD population (Gadow, DeVincent, Pomeroy, & Azizian, 2004; Kim, Szatmari, Bryson, Streiner, & Wilson, 2000; Weisbrot, Gadow, DeVincent, & Pomeroy, 2005). Anxiety is also quite impairing for children with ASD; it is related to greater deficits in social competence (Bellini, 2004, 2006; Pfeiffer et al., 2005; Sukhodolsky et al., 2008) and functional academics (Pfeiffer et al., 2005), as well as higher levels of externalizing behaviors (Kim et al., 2000). Thus, while ASD is a disabling disorder on its own, both SOR and anxiety may cause even greater deficits (e.g., Wood & Gadow, 2010), with potential implications for prognosis, hence necessitating targeted

interventions (e.g., Wood et al., 2009a,b). Examination of the link between these two syndromes therefore has potential implications for the treatment of children with ASD.

Despite recent findings that anxiety and SOR co-occur, the linking mechanism is still unknown. An association between anxiety and SOR in individuals with ASD suggests the possibility of a common biological basis, such as neural abnormalities that produce hyperarousal (Green & Ben-Sasson, 2010). While a number of investigators have proposed a hyperarousal hypothesis as an explanation for autism, these theories are largely unsupported (see Rogers & Ozonoff, 2005, for a review). However, there is emerging support for hyperarousal in a subgroup of children with ASD (e.g. Schoen, Miller, Brett-Green, & Hepburn, 2008a), which is consistent with findings of anxiety and SOR co-occurring in a subgroup (e.g., Liss et al., 2006). Thus, it may be that a particular neural dysfunction, such as amygdala hyperactivity, leads to hyperarousal in a subgroup of children with ASD, who are then at higher risk for developing both anxiety and SOR (Green & Ben-Sasson, 2010). Studying the neurobiological basis of SOR can inform understanding of heterogeneity within ASD and support individually targeted diagnosis and intervention.

SOR in ASD

Although it is well documented that individuals with ASD have higher rates of SOR than TD individuals (e.g., Ben-Sasson et al., 2009), the etiology, presentation, and course of these symptoms are not well understood. Most studies of SOR focus on parent-reported symptoms in young children with ASD (e.g., Ben-Sasson et al., 2008), although the few that have examined sensory symptoms in older children or adults indicate that SOR continues to be a significant problem for individuals with ASD throughout their lifespan (Kern et al., 2006). Interestingly, while TD/ASD group differences in SOR rates seem to decline on average after age 9 (Ben-

Sasson et al., 2009; Kern et al., 2006), there is some evidence that the correlation between SOR and anxiety increases as children get older (Pfeiffer et al., 2005); this suggests that children with ASD who continue to have high symptoms of SOR as they get older may be at a particularly high risk for developing anxiety disorders.

Studies in young and school-aged children indicate that sensory sensitivity is elevated in children with ASD across all sensory modalities (Baker, Lane, Angley, & Young, 2008; Leekam, Nieto, Libby, Wing, & Gould, 2007; Tomchek & Dunn, 2007). However, tactile sensitivity, which tends to be the most elevated in children with ASD, may best differentiate children with ASD from their chronological or mental age-matched TD or developmentally delayed peers (Kern et al., 2006; Leekam et al., 2007; Tomchek & Dunn, 2007).

SOR has been shown to be associated with increased functional impairment in children with ASD. First, SOR may be related to increased autism symptom severity. Hilton, Graver, and LaVesser (2007) found that SOR was strongly negatively correlated with scores on the Social Responsivity Scale, indicating that children with more symptoms of SOR were more socially impaired. Likewise, Kern et al. (2007) found that auditory and touch sensitivity were related to higher symptoms severity on the Child Autism Rating Scale (CARS). SOR is also associated with decreases in adaptive skills including daily living skills (Baker et al., 2008). Finally, SOR has been shown to correlated with a number of emotional and behavioral problems; in addition to anxiety, SOR is related to disruptive behavior, internalizing problems, and negative emotionality (Baker et al., 2008; Ben-Sasson et al., 2008; Liss et al., 2006).

Taken together, the literature on SOR in ASD indicates that SOR is present across sensory modalities, emerges early and persists over time, and is functionally impairing. However, most of these studies are correlational, which suggests a clear need for additional

experimental, longitudinal, and intervention research to increase the understanding of the causes, course, and treatment of SOR in individuals with ASD.

Study Goals

The two studies presented here are an investigation of the neurobiological basis of SOR. SOR is, by definition, a description of a behavioral response to sensory stimuli, because the underlying biological processes leading to that over-response are still unknown. Given the common co-occurrence with anxiety, SOR could be caused by abnormalities in how the brain assesses sensory stimuli as threatening and then how it interprets and regulates these assessments. Alternatively (or in addition), SOR could be caused by differences in the primary perception of sensory stimuli. The following studies clarify these questions by examining brain response to mildly unpleasant visual, auditory, and tactile sensory stimuli in relation to symptoms of SOR. The results contribute to the understanding of heterogeneity and comorbidity within ASD, and are discussed in terms of their implications for informing targeted intervention for youth with ASD.

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Study 1

Abstract

Objectives: Sensory over-responsivity (SOR), defined as a negative response to or avoidance of sensory stimuli, is both highly prevalent and extremely impairing in youth with autism spectrum disorders (ASD); yet, little is known about the neurological bases of SOR. This study aimed to examine the functional neural correlates of SOR by comparing brain responses to sensory stimuli in youth with and without ASD.

Method: Twenty-five high-functioning youth with ASD and 25 age- and IQ-equivalent typically developing (TD) youth were presented with mildly aversive auditory and visual stimuli during a functional magnetic resonance imaging (fMRI) scan. Parents provided ratings of children's SOR and anxiety symptom severity.

Results: Compared to TD participants, ASD participants displayed greater activation in primary sensory cortical areas as well as amygdala, hippocampus, and orbital-frontal cortex. In both groups, the level of activity in these areas was positively correlated with level of SOR severity as rated by parents, over and above behavioral ratings of anxiety.

Conclusions: This study demonstrates that youth with ASD show neural hyper-responsivity to sensory stimuli, and that behavioral symptoms of SOR may be related to both heightened responsivity in primary sensory regions as well as areas related to emotion processing and regulation.

Children with autism spectrum disorders (ASD) often display impairments in responding to sensory stimuli, in addition to the core symptoms of ASD, which include impairments in language and reciprocal social behavior. Sensory over-responsivity (SOR) is characterized by an extreme, negative response to, or avoidance of, sensory stimuli such as noisy or visually stimulating environments, sudden loud noises, seams in clothing, or being touched unexpectedly (Liss, 2006). About 56-70% of children with ASD meet criteria for SOR (Baranek, David, Poe, Stone, & Watson, 2006; Ben-Sasson et al., 2007) compared to 10-17% of typically developing (TD) children (Ben-Sasson, Carter, & Briggs-Gowan, 2009; Ben-Sasson et al., 2007). SOR is associated with increased functional impairment in children with ASD, including lower levels of social and adaptive skills (Liss, 2006; Pfeiffer, Kinnealey, Reed, & Herzberg, 2005), negative emotionality (Ben-Sasson et al., 2008), and anxiety (Ben-Sasson et al., 2008; Pfeiffer et al., 2005).

Despite the prevalence of and considerable impairment caused by SOR in children with ASD, there is a paucity of research on the neurobiological bases of SOR. Research in this area is critical to help explain heterogeneity within ASD, and can inform intervention targeted at specific subgroups of children with ASD. In one of the few functional MRI (fMRI) studies of response to non-social sensory stimuli in children with ASD, Gomot et al. (Gomot, Belmonte, Bullmore, Bernard, & Baron-Cohen, 2008) found that early adolescents with ASD responded faster to novel sounds than TD controls did, and had higher activation in prefrontal and inferior parietal regions but no differences in activation of auditory cortex. The authors theorized that novel auditory stimuli are initially processed normally but receive differential attention from the novelty detection circuit. Similarly, Hadjikhani, (2004) presented expanding circles of color to

adults with and without ASD, and found no between-group differences in visual cortex retinotopic maps. However, some EEG studies have found group differences in event-related potentials (ERPs) in response to tones, which may suggest an atypical response to sound in the primary auditory cortex (Marco, Hinkley, Hill, & Nagarajan, 2011).

The thalamus, which is considered the "gateway" that relays sensory information entering the brain to the cortex, could also be involved in SOR. For example, deficient thalamic gating could overload the sensory cortices; alternatively, thalamic dysfunction might result in a failure to integrate the sensory information appropriately. In support of this hypothesis, abnormally decreased metabolite (glutamate and glutamine) levels were found in the thalamus of individuals with ASD (Hardan et al., 2008) and these abnormalities related to sensory sensitivity. Although the thalamus has also been found to be smaller in high-functioning individuals with ASD compared to TD controls (Tsatsanis et al., 2003), functional connectivity between the thalamus and cortex has been shown to be greater in ASD (Mizuno, Villalobos, Davies, Dahl, & Müller, 2006). Mizuno et al. further suggest that thalamic hyperactivity during brain development may drive functional specialization in the cortex and could lead to cortical abnormalities such as reduced pruning and thalamo-cortical overconnectivity, which may ultimately put individuals at risk for SOR.

Other hypotheses on the neural basis of SOR posit heightened limbic responses to sensory stimuli, including the amygdala and hippocampus (Green & Ben-Sasson, 2010; Hitoglou, Ververi, Antoniadis, & Zafeiriou, 2010; Waterhouse, Fein, & Modahl, 1996). A number of correlational studies have shown that children with ASD and SOR also have high rates of anxiety symptoms (Ben-Sasson et al., 2008; Green & Ben-Sasson, 2010; Mazurek et al., 2013). Because SOR co-occurs frequently with anxiety symptoms, theories related to abnormal

amygdala and hippocampus functioning are particularly relevant given the role of these structures in anxiety. Functional MRI studies (fMRI) have consistently highlighted the amygdala's central role in detection and response to threat and fear conditioning (Davis, 1992; Garakani, Mathew, & Charney, 2006; Rauch, Shin, & Wright, 2003; Zald, 2003). Similarly, the hippocampus is thought to be associated with anxiety through its role in context conditioning, memory of threat-related events, and orienting to situations that could be threatening (Anagnostaras, Gale, Fanselow, & others, 2001; Bishop, 2007). As discussed in a review of fMRI studies on the amygdala by Zald (2003), the magnitude of amygdala activation in response to sensory input from the thalamus is found to correlate with the extent to which a stimulus is perceived as threatening or unpleasant. The amygdala can then trigger a response to these stimuli upon future exposure, including an enhanced sensory response that correlates with amygdala activation.

Limbic system abnormalities may increase the risk of SOR in children with ASD by decreasing ability to regulate in response to sensory input. There is evidence for functional amygdala abnormalities in ASD, though the evidence is mixed in terms of the direction of effect: early studies showed decreased amygdala activity in ASD (Baron-Cohen et al., 2000); however, Pierce et al. (Pierce, Haist, Sedaghat, & Courchesne, 2004) found no group differences in amygdala response to faces when stimuli were salient (e.g., family members). Furthermore, more recent studies have found that individuals with ASD show amygdala *hyperactivity* compared to TD controls during a face processing task (Dalton et al., 2005; Tottenham et al., 2013; Weng et al., 2011) and that the extent of activation was correlated with the amount of time ASD participants spent gazing at the eyes (Dalton et al., 2005; Tottenham et al., 2013). Therefore,

there is some evidence for abnormal amygdala function and possibly hyperactivity, but this has not been studied in the context of sensory sensitivity.

Few physiological or biological studies of sensory abnormalities in ASD have taken into account within-group heterogeneity in sensory symptoms, which may lead to null findings. For example, physiological studies examining a general hyperarousal in individuals with ASD have yielded few consistent findings (Rogers & Ozonoff, 2005), but the majority of these studies employed a small sample size and did not examine subgroups. Evidence from behavioral studies (Ben-Sasson et al., 2008; Liss, 2006) suggests the presence of SOR only in some children with ASD, whereas other children with ASD are actually under-responsive to sensory stimuli. Consistent with this, a recent study of electrodermal activity in children with ASD found two subgroups: one with high arousal and slow habituation and one with low arousal and fast habituation (Schoen, Miller, Brett-Green, & Hepburn, 2008). Furthermore, higher baseline arousal in children with ASD is related to greater physiological response to sensory stimuli and higher anxiety levels (Lane, Reynolds, & Dumenci, 2012). Similarly, the evidence for structural abnormalities in the amygdala and hippocampus in autism is mixed, with some studies finding smaller volumes (Aylward et al., 1999) and others finding larger volumes (Schumann et al., 2004; Sparks et al., 2002) than in TD individuals. This inconsistency could again be due to the heterogeneity of the ASD phenotype, and indeed amygdala volume in children with ASD has been found to be positively correlated with anxiety (Juranek et al., 2006). Therefore, it is important to account for within-group sensory characteristics when examining the neural bases of SOR, but as of yet there are no functional neuroimaging studies of response to sensory information in children who have both ASD and SOR.

It should be noted that, while physiological hyperarousal appears to be characteristic of both anxiety and SOR, these two conditions may be separate constructs. For example, in a large study of TD children, Carter et al. (Carter, Ben-Sasson, & Briggs-Gowan, 2011) found that about 25% of the sample had elevated rates of SOR and 75% of this group exhibited SOR without any known co-occurring psychiatric diagnosis. However, because of the common overlap of anxiety and SOR, we took a conservative approach in this study and controlled for anxiety symptoms to examine the unique correlation between SOR symptom severity and brain function.

The goal of the current study was to use fMRI to a) examine differences in brain responses to mildly aversive sensory stimuli in youth with and without ASD and b) identify the functional neural correlates of sensory over-responsivity in youth with and without ASD. Given the lack of research in this area, we took an exploratory, whole-brain approach, while also focusing on specific brain regions that have been implicated in anxiety and SOR. We hypothesized that, compared to TD controls, youth with ASD would display greater activation in areas related to sensory processing (thalamus and primary auditory and visual cortices) as well as areas related to anxiety (amygdala and hippocampus). Further, we predicted that amygdala and hippocampus activation would be correlated with severity of SOR symptoms within each group, given the role of these regions in processing threat-relevant stimuli.

Methods

Participants

Participants were 25 youth with ASD and 25 TD matched controls recruited through flyers posted around the University of California Los Angeles (UCLA) campus as well as through referrals from the UCLA autism clinic. Participants ranged in age from 8-17 years (M=13.13; SD=2.29) and all had a full-scale IQ within the normal range based on an assessment

with the Weschler Abbreviated Scales of Intelligence (WASI; Wechsler, 1999), or the Weschler Intelligence Scale for Children – 4th Edition (WISC; Wechsler, 2003). Original participants were 32 TD subjects and 35 ASD subjects, but 7 TD subjects and 10 ASD subjects were excluded due to maximum motion >2 mm. The final groups of 25 TD and 25 ASD did not differ significantly in age, FSIQ, performance IQ, verbal IQ, and mean or maximum head motion during fMRI (see Table 1). All ASD participants had a prior diagnosis of an autism spectrum disorder (i.e. Autistic Disorder, Pervasive Developmental Disorder Not Otherwise Specified, or Asperger's Disorder), which was confirmed using the Autism Diagnostic Interview – Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) and the Autism Diagnostic Observation Schedule – Generic (ADOS-G; Lord et al., 2000) (ADOS-G). Two participants met criteria only on the ADI but met DSM IV criteria based on clinical judgment. Two of the TD participants were taking psychoactive medications (psychostimulants), as were seven of the ASD participants including atypical antipsychotics (N=2), selective serotonin reuptake inhibitors (N= 1), psychostimulants (N=2), and multiple medications (N=3). No participants reported loss of consciousness for longer than 5 minutes or any neurological (e.g., epilepsy), genetic (e.g., Fragile X), or severe psychiatric disorder (e.g., schizophrenia) other than autism. T-tests were conducted comparing mean activation in children with and without medication in the a priori areas of interest (right and left hippocampus, amygdala, thalamus, and primary auditory (A1) and visual (V1) cortices). Out of 30 comparisons (the above 10 activations times 3 conditions), only one was significant (no more than would be expected by chance), indicating that medication status was unrelated to brain activation in response to the experimental task. T values ranged from -1.57 to 1.26; p= .07-.99, except for right thalamus in the auditory condition: T=-2.51; p=.016.

fMRI Sensory Task Paradigm

Participants were passively exposed to three mildly aversive stimulus conditions in an event-related paradigm (see Figure 1): an auditory stimulus, a visual stimulus, and the auditory and visual stimuli simultaneously (referred to as the "Joint" condition). The auditory stimulus was composed of white noise, which was set at the same volume for each participant. The volume increased linearly to the peak volume in the first .75 seconds of each 3-second presentation to minimize startle effects. The visual stimulus was a movie of a continually rotating color wheel (see Figure 1). Stimuli were chosen based on pilot testing with the Sensory Over-Responsivity Checklist indicating that these kinds of auditory and visual stimuli best differentiated the status groups. After completing the task, participants were asked to rate on a scale of 0-10 how "bad" each stimulus was. On average, both groups rated the auditory and joint conditions a 3 out of 10, and the visual condition a 2.2 out of 10. There were no significant group differences in aversiveness ratings. Each trial type was presented 12 times, in a randomized order, with each trial lasting 3 seconds. Inter-trial intervals were jittered between 1250 and 3500 ms. The total scan length was 3 minutes, 34 seconds including a 10-second final fixation.

MRI Data Acquisition

Scans were acquired on a Siemens Trio 3 Tesla magnetic resonance imaging scanner. A high-resolution structural T2-weighted echo-planar imaging volume (spin-echo, TR=5000 ms, TE=33 ms, 128x128 matrix, 20cm FOV, 36 slices, 1.56mm in-plane resolution, 3mm thick) was acquired coplanar to the functional scans in order to ensure identical distortion characteristics to the fMRI scan. Each functional run involved the acquisition of 107 EPI volumes (gradient-echo, TR=2000ms, TE=30ms, flip angle=90, 64x64 matrix, 20cm FOV, 33 slices, 3.125mm in-plane resolution, 3 mm thick). Visual and auditory stimuli were presented to the participant using 800x640 resolution magnet-compatible 3-D goggles and headphones under computer control

(Resonance Technologies, Inc.). The stimuli were presented using E-Prime. Participants wore earplugs and headphones to reduce interference of the auditory stimuli from the scanner noise. Participants were instructed to focus on the center of the screen for the duration of the task.

Measures

The ADI-R, ADOS, WISC, and WASI were administered at a clinical assessment visit prior to the MRI scan. Parents completed the additional questionnaires and interviews listed below while the child was in the scanner.

Child Behavior Checklist for Ages 6-18 (CBCL; Achenbach & Rescorla, 2001). The CBCL is a parent-report measure of child problem behaviors. For the purposes of this study, the Anxiety Scale T-scores were used as a measure of severity of child anxiety symptoms.

Short Sensory Profile (SSP; Dunn, 1999). The SSP is a widely used, 38-item parent report measure of youth sensory dysregulation across a number of sensory modalities. Parents rate the frequency with which their child responds in an atypical way to sensory stimuli on a five-point Likert scale from "never" responds in this way to "always" responds in this way. This measure yields both a total score of sensory dysregulation as well as subscale scores for Tactile, Taste/Smell, Movement, and Auditory/Visual Sensitivity, Underresponsive/Seeks Sensation, Auditory Filtering, and Low Energy/Weak. For the purposes of this study, we used only the subscales relevant to the auditory and visual stimuli administered, namely the Auditory/Visual Sensitivity scores and the Auditory Filtering score. Higher scores on the SSP indicate *lower* impairment. On the Auditory/Visual Sensitivity subscale, a score of 19-25 is considered typical performance, a score of 16-18 is considered a "Probable Difference," and a score of 5-15 is considered a "Definite Difference." On the Auditory Filtering subscale, a score of 23-30 is considered typical performance, a score of 20-22 is considered a "Probable Difference," and a

score of 6-19 is considered a "Definite Difference." This measure has strong reliability and validity(McIntosh & Miller, 1999).

Sensory Over-Responsivity (SensOR) Inventory (Schoen, Miller, & Green, 2008). The SensOR Inventory is a parent checklist of sensory sensations that bother their child. For the purposes of this study, only the visual, and auditory subcales were used. The number of items parents rate as bothering their child has been shown to discriminate between TD children and children with SOR (Schoen et al., 2008). The SensOR inventory has been found to best differentiate children with SOR from TD children when at least four tactile *or* auditory items are present (Schoen et al., 2008b).

fMRI Data Analysis

Analyses were performed using FSL Version 4.1.4 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Preprocessing included motion correction to the mean image, spatial smoothing (Gaussian Kernel FWHM = 5mm), and high-pass temporal filtering (t > 0.01 Hz). Functional data were linearly registered to a common stereotaxic space by first registering to the in-plane T2 image (6 degrees of freedom) then to the MNI152 T1 2mm brain (12 degrees of freedom).

FSL's fMRI Expert Analysis Tool (FEAT), Version 5.98 was used for statistical analyses. Fixed-effects models were run separately for each subject, then combined in a higher-level mixed effects model to investigate within and between-group differences. Each experimental condition (auditory, visual, or both together) was modeled with respect to the fixation condition (during ISIs and the final fixation). Higher-level group analyses were carried out using FSL's FLAME (FMRIB's Local Analysis of Mixed Effects State) stage 1 and stage 2 (Beckmann, Jenkinson, & Smith, 2003; M. W. Woolrich, Behrens, Beckmann, Jenkinson, &

Smith, 2004; M. Woolrich, 2008). Within-group Z statistical images for each condition (vs. resting baseline) were thresholded at $Z > 2.3$ ($p<.01$) to define contiguous voxel clusters. FSL's cluster correction for multiple comparisons (Gaussian-random field theory based) was set at $p<.05$, whole brain correction (http://www.fmrib.ox.ac.uk/fsl). Between-group comparisons were then performed and also thresholded at $Z > 2.3$ ($p < .01$). Given the exploratory nature of the study and the focus on a priori regions of interest, these comparisons were not corrected for multiple comparisons. To evaluate the correlation of SOR with BOLD response, an SOR composite score was created by standardizing and averaging each relevant subscale of the SOR measures (SSP auditory/visual sensitivity, and auditory filtering scales and SensOR Inventory auditory and visual scores). To determine whether SOR predicted BOLD response over and above anxiety, regression analyses were performed with the de-meaned SOR composite as the independent variable and CBCL anxiety scores entered as covariates in the design matrix for the participants as a whole. These comparisons were also thresholded at $Z>2.3$, uncorrected. Parameter estimates for significant clusters in regions of interest (primary visual and auditory cortex, thalamus, amygdala, hippocampus, and orbitofrontal cortex), using functionally defined masks, were extracted from each participant and plotted in a graph to rule out the presence of outliers.

Results

Behavioral Results

Independent-sample t-tests were used to test for group differences in parent-reported SOR and anxiety data, including the SensOR Inventory visual and auditory scales, the Short Sensory Profile total and auditory/visual and auditory filtering subscales, as well as CBCL Anxiety T-scores. The ASD group was rated significantly higher on all of these measures (results

are displayed in Table 2). The correlation between CBCL Anxiety T-scores and the SOR composite was significant in both groups (TD: r=.50, p=.011; ASD: r=.59, p=.002).

fMRI Results

Within-group results. We first examined activity within each group in each of the three conditions. Results are displayed in Tables 2-4 and Figure 2; while whole-brain results are reported in the tables, only a priori regions of interest are reported in the text that follows. In the Auditory condition, the TD group showed significant activation in primary auditory cortex; in the Visual condition, the TD group showed significant activation in primary visual cortex. In the Joint condition, the TD group showed significant activation in both visual and auditory cortices. The ASD group showed significant activation in amygdala and auditory cortex in the Auditory condition, amygdala, visual cortex, lateral geniculate nucleus (LGN), and orbital frontal cortex in the Visual condition, and amygdala, visual and auditory cortex, thalamus (pulvinar), and orbital frontal cortex in the Joint condition.

Between-group results. We then directly compared activation patterns between ASD and TD groups for each contrast (see Tables 2-4 and Figure 2). The between-group contrasts indicated that the ASD group showed greater activation in the amygdala in the Auditory and Joint conditions, and greater prefrontal cortex in all three conditions. The ASD group also had greater primary auditory activation in the Auditory and Joint conditions and greater primary visual activation in the Joint condition. No significant differences were observed for the opposite comparisons (TD > ASD) in any of the a priori regions of interest.

Correlation with sensory over-responsivity severity. We examined SOR severity as a predictor of BOLD response above and beyond anxiety during the Joint condition by entering the SOR composite as a regressor of interest and CBCL anxiety T-scores as covariates. We

examined significant correlations in our a priori areas of interest as well as in the frontal orbital and medial cortices given the significant group differences found in these regions. There were significant positive correlations between the SOR composite and signal increases during the Joint condition in the amygdala, hippocampus, left orbital frontal cortex, frontal medial cortex, thalamus, and primary visual cortex (Figure 3). While we present results for the full sample, these correlations held when examined in each group separately, though in the ASD group, the correlation with activity in the amygdala was only significantly correlated at a Z threshold of 1.7. These regression results indicate that the between-group differences are likely due to differences in SOR, and that anxiety alone did not account for these group differences in BOLD response to sensory stimuli. Significant areas along with graphs of the correlations are presented in Figure 3; the MNI coordinates for all significant clusters are listed in Table 5.

Discussion

The aim of this study was to examine the neural correlates of sensory over-responsivity in children with and without ASD, with a focus on brain areas related to primary sensory processing as well as those related to anxiety and emotion regulation. As predicted, we found evidence for increased neural responses to mildly aversive sensory stimuli in youth with ASD compared to TD youth. In particular, the ASD group displayed greater activation in primary sensory areas (auditory and visual cortices) as well as in emotion processing regions (amygdala, hippocampus, and prefrontal cortex).

In terms of the primary sensory processing areas, although both groups engaged the primary auditory and visual cortices, the ASD group displayed greater activity in both primary sensory cortices as well as the thalamus. For all participants, visual cortex and thalamic activity was significantly correlated with SOR severity over and above anxiety.

We hypothesized that the neural bases of SOR might be similar to those previously found to be related to anxiety (i.e., amygdala, hippocampus, and prefrontal cortex), due to the consistent finding that SOR frequently co-occurs with anxiety (Ben-Sasson et al., 2008; Green & Ben-Sasson, 2010). Activity in these areas was also positively correlated with parent-rated SOR symptoms suggesting that group differences are related to greater SOR severity in the ASD group. Notably, SOR symptoms and brain activity were correlated over and above manifest anxiety symptoms, indicating that there may be a unique relationship between SOR and activity in these brain regions that is not fully mediated by anxiety level. This was a conservative approach, given the high co-occurrence of anxiety and SOR. This neural hyper-responsivity may reflect impairments in both bottom-up and top-down processing. The primary sensory cortices may be over-responsive to the stimuli and trigger an enhanced amygdala response, while simultaneously the amygdala may over-stimulate higher-level cortical regions. This is consistent with previous research showing that amygdala activation is correlated with level of behavioral response to sensory stimuli (Zald, 2003). The amygdala can then signal the hippocampus to retain memories of the stimuli, as well as the context in which the stimuli were presented, leading to context conditioning and generalization of the fear (Charney, Grillon, & Bremner, 1998). Furthermore, Liss (2006) found that children with ASD and SOR had over-focused attention and "exceptional memory," which could also be related to a hyperactive hippocampus encoding threat-relevant events.

Contrary to the typical negative relationship seen between the amygdala and PFC (Hariri, Bookheimer, & Mazziotta, 2000), in the ASD group we found higher amygdala activity co-occurring with higher PFC activation, which may reflect an immature or dysfunctional regulatory system. It is possible that the PFC is inhibiting the amygdala, and the amygdala

activation in the ASD group would be even stronger without modulation by the PFC. Alternatively, this finding could reflect a more immature connectivity pattern in the ASD group, as the negative connectivity between the amygdala and PFC develops with age (Pfeiffer et al., 2005). More research is needed on the development of the amygdala in ASD, especially given evidence that individuals with ASD have abnormally large amygdalae in childhood but not in adolescence, due to a lack of the typical amygdala volume increase normally seen in adolescence (Schumann et al., 2004).

To our knowledge, this is the first study to examine fMRI response to sensory stimuli in children with ASD while taking into account within-group heterogeneity in SOR severity and anxiety symptoms. Additionally, the stimuli presented in this study were rated by participants as being mildly aversive, as opposed to previous studies that failed to find group differences in response to more neutral stimuli, such as tones (Rogers & Ozonoff, 2005). Nevertheless, this study has a few limitations. The experimental paradigm included a limited number of trials per condition. For this reason, the power to find additional group differences may have been reduced. Despite this limitation, clear group differences were found in several a priori regions of interest; future studies should continue to examine how SOR severity relates to fMRI response in other brain areas. Another possible limitation is that participants who found the visual stimuli aversive could have shifted their gaze to avoid it, although we did find that all participants had significant increases in activation in visual cortex in the visual/both conditions compared to baseline. Future studies might combine the fMRI data with eyetracking to monitor participants' engagement with the stimuli. Additionally, it will be useful to examine brain response to tactile stimuli, which has been found to discriminate well between individuals with and without SOR (Schoen, Miller, & Green, 2008).

In addition, the findings of concurrent greater amygdala and PFC activity in the ASD group, which suggest a possible immature connectivity pattern in this group, need to be followed up on using functional connectivity analyses. Finally, future studies should examine the role that habituation in response to sensory stimuli may play in determining group differences. Evidence from the anxiety literature suggests that phobic subjects may have a more intense initial amygdala response to the feared stimulus and then look away, so their amygdala response quickly decreases, in comparison to control subjects who have a weaker but longer-lasting amygdala response (Larson et al., 2006). Additionally, Kleinhans et al. (2009) found reduced habituation in the amygdala in response to neutral faces. These findings highlight the importance of examining changes in the emotion regulation response across time, as averaging response over the entire task may mask important group differences in how the stimuli are processed.

In conclusion, we found that youth with ASD have a hyper-responsive BOLD response to mildly aversive sensory stimuli, particularly in areas related to sensory processing and emotion regulation. Activity in these regions was significantly related to parent-report symptoms of SOR in both groups even after controlling for anxiety, which indicates that group differences were not merely due to higher levels of anxiety in the ASD group. Overall, our findings suggest that SOR and anxiety may have a common neural basis in dysregulation of limbic system areas, particularly the amygdala and hippocampus. More research is needed to determine whether these neural abnormalities put youth with ASD at risk specifically for SOR and anxiety, or whether they simply contribute to overall emotional and behavioral dysregulation.

Tables and Figures

Table 1. Descriptive statistics.

	ASD	TD	t or χ^2
Age	13.10 (2.47)	13.15 (2.16)	0.09
Gender (% Male)	84% (n=21)	76% (n=19)	0.5
Handedness (% Right-Handed)	92% (n=23)	96% (n=24)	0.36
FSIQ	101.16 (15.95)	106.20 (11.78)	1.27
VIQ	102.00 (16.59)	105.60 (11.74)	0.89
PIQ	109.92 (15.27)	107.32 (11.39)	-0.68
Mean Absolute Motion	0.23 (.16)	0.22 (.18)	-0.12
Max Absolute Motion	0.58 (.40)	0.63 (.51)	0.4
Mean Relative motion	0.09 (.04)	0.08 (.04)	-0.63
Max Relative Motion	0.54 (1.04)	0.63 (.75)	-0.96
SensOR Visual Count	1.52 (1.83)	0.36 (.81)	-2.90**
SensOR Auditory Count	7.72 (6.67)	1.60 (2.66)	-4.26***
SSP Auditory/Visual	18.09 (4.46)	23.76 (1.74)	5.60***
SSP Auditory Filtering	17.09 (5.08)	26.12 (4.32)	6.58***
Auditory-Visual Composite	3.23 (4.63)	-3.23 (1.75)	-6.52***
CBCL Anxiety T-Score	61.16 (9.67)	51.56 (3.74)	-4.63***

**p<.01; ***p<.001.

Note: N=25 ASD, 25 TD except for SSP analyses where N=22 ASD, 25 TD.

Table 2. MNI coordinates for auditory condition as compared to baseline.

	ASD					TD					ASD>TD					TD>ASD				
	MNI peak (mm)			Max		MNI peak (mm)			Max		MNI peak (mm)			Max		MNI peak (mm)			Max	
	x	y	z	*Z*	vox	x	y	z	*Z*	vox	x	y	z	*Z*	vox	x	y	z	*Z*	vox
Right Lateral Occipital Cortex inferior division																38	-74	6	2.92	50
Left Supramarginal Gyrus											-60	-40	20	3.68	726					
Left Angular Gyrus																-40	-56	34	2.66	180
Right Cingulate Gyrus, Posterior Division											14	-28	36	3.71	344					
Left Cingulate Gyrus, Posterior Division											-8	-30	48	2.75	76					
Left Paracingulate Gyrus																-4	26	40	2.45	38
Left Insular Cortex											-44	0	6	3.02	290					
Right Precentral Gyrus											22	-24	78	2.46	52	60	-2	42	2.65	59
Left Postcentral Gyrus											-36	-34	58	3.39	683					
Left Amygdala											**-24**	**0**	**-18**	**2.54**	**34**					
Right Amygdala	**20**	**-4**	**-22**	**3.14**	**2834**															
Right Supramarginal Gyrus	62	-34	36	3.35																
Right Insular Cortex	42	-4	-12	4.24																
Right Inferior Temporal Gyrus	44	-54	-6	3.64																
Right Anterior Transverse Temporal Gyrus	54	18	-6	2.71																
Right Superior Temporal Gyrus	**54**	**-32**	**12**	**5.85**		**60**	**-40**	**10**	**5.31**	**2397**										
Right Fusiform Gyrus						38	-54	-14	3.81											
Right Heschl's Gyrus						**38**	**-28**	**6**	**3.87**		**56**	**-32**	**14**	**3.03**	**598**					
Right Postcentral Gyrus											48	-20	38	2.99						
Left Superior Temporal Gyrus	**-64**	**-30**	**22**	**3.78**	**1864**						**-66**	**-16**	**2**	**3.16**	**95**					
Left Heschl's Gyrus	**-44**	**-28**	**8**	**4.62**		**-48**	**-24**	**6**	**4.37**	**662**										
Left Thalamic Reticular Nucleus						**-22**	**-26**	**0**	**2.36**											
Right Middle Temporal Gyrus											60	-14	-28	2.64	117	68	-46	4	3.37	121
Left Middle Temporal Gyrus																-60	-48	4	2.57	109
Left Inferior Temporal Gyrus											-48	-66	0	2.70	46	-54	-44	-20	2.44	47
Left Temporal Pole																-40	4	-34	3.12	155
Left Superior Frontal Gyrus																-10	14	68	3.39	342
Right Middle Frontal Gyrus																44	18	50	2.68	53
Left Middle Frontal Gyrus																-40	12	54	2.91	107
Left Inferior Frontal Gyrus																-52	28	4	2.58	108
Right Frontal Medial Cortex											**4**	**48**	**-22**	**2.82**	**72**					
Right Frontal Orbital Cortex											**20**	**26**	**-22**	**2.71**	**58**					
Left Frontal Orbital Cortex											**-14**	**20**	**16**	**2.51**	**55**					
Right Frontal Pole											32	50	24	2.75	87					
Left Frontal Pole																-36	54	-8	2.55	84
Right Putamen											36	-12	-2	2.62	46					
Right Caudate tail											30	-36	6	2.61	66					
Cerebellum											-8	-62	-18	3.09	80	34	-40	-32	2.75	

Note: x, y, and z refer to the left-right, anterior-posterior, and inferior-superior dimensions, respectively; *Z* refers to the Z-score at those coordinates (local maxima or submaxima). k refers to cluster size in voxels; because FSL considers all contiguous voxels to be within the same cluster, some anatomical peaks fall within the same cluster size and are denoted with underlining the first peak listed in the cluster. Within-group analyses are cluster corrected for multiple comparisons, $Z>2.3$, $P<.05$; between-group analyses are thresholded at $Z>2.3$, uncorrected. A priori regions of interest are reported in bold font.

Table 3. MNI coordinates for visual condition as compared to baseline.

	ASD					TD					ASD>TD					TD>ASD				
	MNI peak (mm)			Max		MNI peak (mm)			Max		MNI peak (mm)			Max		MNI peak (mm)			Max	
	x	y	z	*Z*	vox	x	y	z	*Z*	vox	x	y	z	*Z*	vox	x	y	z	*Z*	vox
Right Occipital Pole	**24**	**-94**	**-6**	**8.99**	**18821**	**12**	**-96**	**-4**	**8.23**	**14981**										
Left Occipital Pole	**-18**	**-98**	**10**	**7.55**		**-30**	**-96**	**4**	**6.74**											
Right Lateral Occipital Cortex superior division	38	-86	12	6.69		-28	-70	24	3.58		32	-76	26	2.79	96					
Right Lateral Occipital Cortex inferior division	50	-68	-2	5.16		32	-86	8	8.52		48	-68	2	3.17	455					
Right Fusiform Gyrus	30	-48	-16	7.72		30	-70	-10	6.14		-20	-46	-16	2.95	91					
Left Fusiform Gyrus	-36	-68	-18	7.18		-22	-82	-14	7.20											
Left Parahippocampal Gyrus						-28	-30	-22	3.10											
Left Lateral Occipital Cortex superior division	30	-78	40	3.09																
Left Lateral Occipital Cortex inferior division	-42	-64	8	3.24																
Left Lingual Gyrus	0	-82	-2	6.26																
Right Insular Cortex	34	14	0	2.84																
Right Middle Temporal Gyrus	48	-16	-14	3.84												68	-46	4	3.06	126
Right Thalamus - lateral geniculate nucleus	**22**	**-28**	**-2**	**6.60**																
Right Amygdala	**26**	**-4**	**-16**	**3.73**																
Right Frontal Orbital Cortex	**38**	**36**	**-14**	**3.59**							**4**	**46**	**-24**	**2.94**	**128**					
Left Frontal Orbital Cortex											**-38**	**32**	**-12**	**3.04**	**90**					
Right Lingual Gyrus											2	-70	-4	2.82	137					
Right Precentral Gyrus																52	2	44	2.70	87
Right Superior Temporal Gyrus,											**48**	**-16**	**-14**	**3.54**	**3331**					
Right Temporal Pole											50	10	-16	2.64						
Precuneus											12	-50	18	2.72						
Right Caudate tail											30	-36	6	3.14						
Right Subthalamic Nucleus											12	-16	-8	2.98						
Cerebellum											14	-46	-16	2.46		36	-42	-36	2.60	39
Left Superior Temporal Gyrus											**-66**	**-14**	**-4**	**2.61**	**56**					
Right Inferior Temporal Gyrus											48	-44	-24	2.60	61					
Left Temporal Pole																-40	4	-34	2.49	95
Right Superior Frontal Gyrus											18	32	38	3.34	1801					
Right Frontal Pole											32	50	20	2.48						
Left Superior Frontal Gyrus																-10	14	70	2.90	138
Left Middle Frontal Gyrus																44	34	42	2.77	46
Left Frontal Pole																-20	68	-4	3.16	41
Left Putamen											-28	-10	6	2.83	87					

Note: x, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; *Z* refers to the *Z*-score at those coordinates (local maxima or submaxima). k refers to cluster size in voxels; because FSL considers all contiguous voxels to be within the same cluster, some anatomical peaks fall within the same cluster size and are denoted with underlining the first peak listed in the cluster. Within-group analyses are cluster corrected for multiple comparisons, $Z>2.3$, $P<.05$; between-group analyses are thresholded at $Z>2.3$, uncorrected. A priori regions of interest are reported in bold font.

Table 4. MNI coordinates for joint auditory+visual condition as compared to baseline.

	ASD					TD					ASD>TD					TD>ASD				
	MNI peak (mm)			Max		MNI peak (mm)			Max		MNI peak (mm)			Max		MNI peak (mm)			Max	
	x	y	z	*Z*	vox	x	y	z	*Z*	vox	x	y	z	*Z*	vox	x	y	z	*Z*	vox
Right Occipital Pole	**32**	**-90**	**14**	**6.58**	**18101**	**10**	**-96**	**-4**	**9.13**	**16254**	**8**	**-88**	**-4**	**2.53**	**61**					
Left Occipital Pole	**-20**	**-96**	**10**	**7.50**		**-18**	**-94**	**-12**	**6.74**											
Left Lateral Occipital Cortex superior division						-28	-72	26	3.42		0	-88	44	2.62	68					
Left Lateral Occipital Cortex inferior division	-44	-64	-2	3.33		-46	-78	-6	4.48											
Right Lateral Occipital Cortex superior division	26	-58	32	2.96																
Right Lateral Occipital Cortex inferior division	48	-72	2	5.60												36	-72	12	2.87	82
Right Fusiform Gyrus	12	-84	-10	10.10		30	-74	-10	6.14											
Left Fusiform Gyrus	-28	-76	-16	6.21		-24	-66	-16	5.94		-44	-68	-18	2.65	34					
Right Superior Temporal Gyrus,	**66**	**-10**	**2**	**4.26**		**60**	**-38**	**10**	**4.99**											
Right Heschl's Gyrus	**42**	**-30**	**12**	**4.70**		**36**	**-26**	**6**	**3.31**											
Right Supramarginal Gyrus	60	-38	26	2.82																
Right Frontal Orbital Cortex	**38**	**36**	**-8**	**3.50**							**30**	**28**	**-12**	**3.19**	**279**					
Right Thalamus - pulvinar	**20**	**-30**	**-2**	**6.87**																
Right Amygdala	**28**	**-2**	**-14**	**4.16**							**18**	**-2**	**-18**	**2.56**	**117**					
Cerebellum	-48	-52	-30	2.85												0	-48	-6	2.49	51
Right Temporal Pole	50	8	-16	3.16																
Left Temporal Pole																-40	4	-34	3.16	131
Right Insular Cortex						40	2	-16	3.30		46	-4	4	2.87	59					
Right Middle Temporal Gyrus						50	-54	-6	4.06							68	-46	4	3.48	108
Right Parahippocampal Gyrus						24	-34	-16	3.51		24	-28	-20	2.71	47					
Precuneus																18	-54	12	3.03	38
Left Heschl's Gyrus	**-42**	**-20**	**8**	**4.65**	**1101**	**-42**	**-30**	**8**	**4.48**	**508**										
Left Supramarginal Gyrus	-66	-42	22	3.29							-60	-40	20	3.33	533					
Right Cingulate Gyrus, Posterior Division											4	-40	8	2.46	95					
Left Insular Cortex											-32	20	-4	2.76	138					
Left Postcentral Gyrus																-22	-44	74	2.51	63
Left Superior Temporal Gyrus											**-64**	**-14**	**-4**	**3.09**	**257**					
Right Superior Frontal Gyrus											2	48	-24	2.88	102					
Left Superior Frontal Gyrus											-22	62	18	2.56	190					
Right Middle Frontal Gyrus																44	18	48	2.93	105
Left Middle Frontal Gyrus																-40	12	56	2.79	97
Right Frontal Pole											28	56	-6	2.55	195	16	72	-2	2.55	33
Left Frontal Pole																-20	68	-4	3.12	32
Left Putamen											-28	-12	4	2.71	74					
Right Caudate											16	18	12	2.99	102					
Right Caudate tail											30	-36	4	2.90	197					

Note: x, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; *Z* refers to the *Z*-score at those coordinates (local maxima or submaxima). k refers to cluster size in voxels; because FSL considers all contiguous voxels to be within the same cluster, some anatomical peaks fall within the same cluster size and are denoted with underlining the first peak listed in the cluster. Within-group analyses are cluster corrected for multiple comparisons, Z>2.3, P<.05; between-group analyses are thresholded at Z>2.3, uncorrected. A priori regions of interest are

Table 5. MNI coordinates for brain areas where BOLD response was correlated with SOR composite.

	MNI peak (mm)			Max	
	x	y	z	*Z*	k
Left Occipital Pole	**-2**	**-94**	**22**	**4.01**	**10778**
Right Lateral Occipital Cortex superior division	16	-82	38	3.45	
Left Lateral Occipital Cortex superior division	-46	-62	24	3.79	
Left Fusiform Gyrus	-32	-42	-24	2.32	
Right Lingual Gyrus	14	-64	-8	4.21	
Left Lingual Gyrus	-22	-56	-4	2.60	
Precuneus	-10	-70	32	3.72	
Right Cingulate Gyrus, Posterior Division	10	-36	38	3.17	
Left Cingulate Gyrus, Posterior Division	-6	-44	18	3.61	
Left Middle Temporal Gyrus	-60	2	-20	3.57	
Left Inferior Temporal Gyrus	-52	-20	-22	3.33	
Left Temporal Pole	-34	16	-36	2.54	
Left Hippocampus	**-28**	**-18**	**-18**	**3.10**	
Left Parahippocampal Gyrus	-38	-28	-16	2.60	
Left Lateral Occipital Cortex inferior division	-32	-86	-24	2.54	35
Right Fusiform Gyrus	42	-48	-24	2.89	80
Right Angular Gyrus	58	-52	26	3.11	352
Left Cingulate Gyrus, Anterior Division	0	20	20	2.76	38
Left Precentral Gyrus	-10	-20	64	2.49	193
Right Middle Temporal Gyrus	48	4	-30	3.02	198
Right Superior Frontal Gyrus	18	4	58	3.00	48
Left Superior Frontal Gyrus	-16	22	54	2.98	455
Left Inferior Frontal Gyrus	-36	4	20	3.66	104
Right Inferior Frontal Gyrus, pars triangluaris	50	26	0	2.94	65
Left Inferior Frontal Gyrus, pars triiangularis	-50	22	-4	2.95	163
Right Frontal Medial Cortex	**4**	**26**	**-28**	**3.02**	**96**
Left Frontal Medial Cortex	**-8**	**36**	**-24**	**2.83**	**34**
Left Frontal Orbital Cortex	**-24**	**34**	**-12**	**2.77**	**109**
Right Frontal Pole	14	48	48	3.04	284
Left Frontal Pole	-4	60	-2	3.58	949
Right Thalamus - Pulvinar	**8**	**-22**	**16**	**2.63**	**102**
Left Thalamus - Pulvinar	**-4**	**-24**	**12**	**2.89**	**82**
Right Hippocampus	**26**	**-14**	**-18**	**3.14**	**913**
Right Parahippocampal Gyrus	24	-26	-24	2.93	
Right Amygdala	**26**	**-2**	**-24**	**2.91**	
Cerebellum	10	-46	-30	3.47	

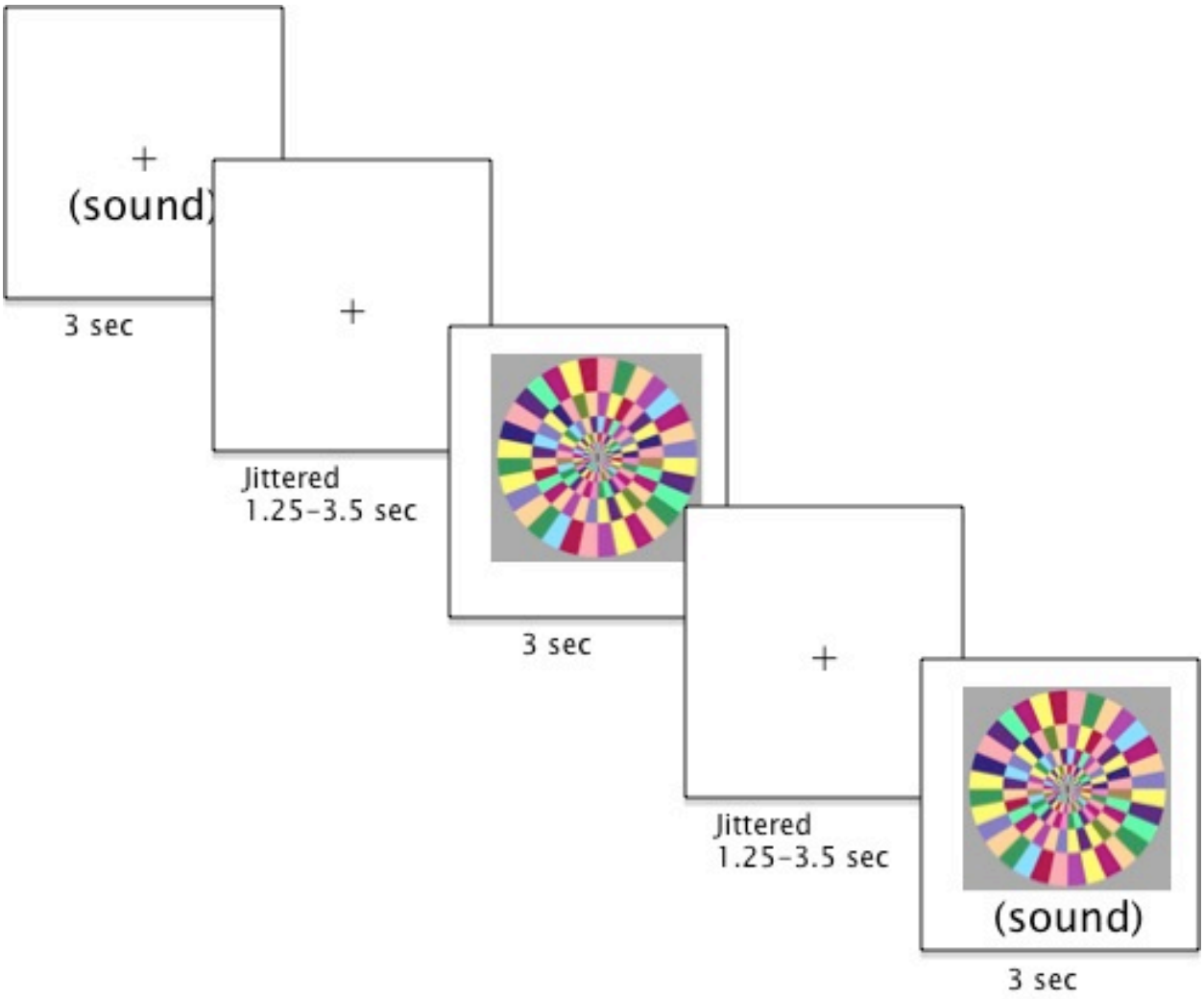
Note: x, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; *Z* refers to the *Z*-score at those coordinates (local maxima or submaxima). k refers to cluster size in voxels; because FSL considers all contiguous voxels to be within the same cluster, some anatomical peaks fall within the same cluster size and are denoted with indenting below the first peak listed in the cluster, which is underlined. Analyses are thresholded at $Z>2.3$, uncorrected. A priori regions of interest are reported in bold font.

Figure Legend

Figure 1. Experimental design.

Figure 2. Within- and between-group results: Joint auditory + visual condition. Within-group contrasts thresholded at $Z>2.3$, corrected ($p<.05$). Between-group contrasts thresholded at $Z>2.3$, uncorrected.

Figure 3. SOR severity as a predictor of BOLD response during the Joint condition. The horizontal axis displays the standardized residual SOR composite score after regressing out CBCL anxiety T-scores. The vertical axis displays the parameter estimate extracted from areas of significant activation. ASD participants are in blue; TD in red.



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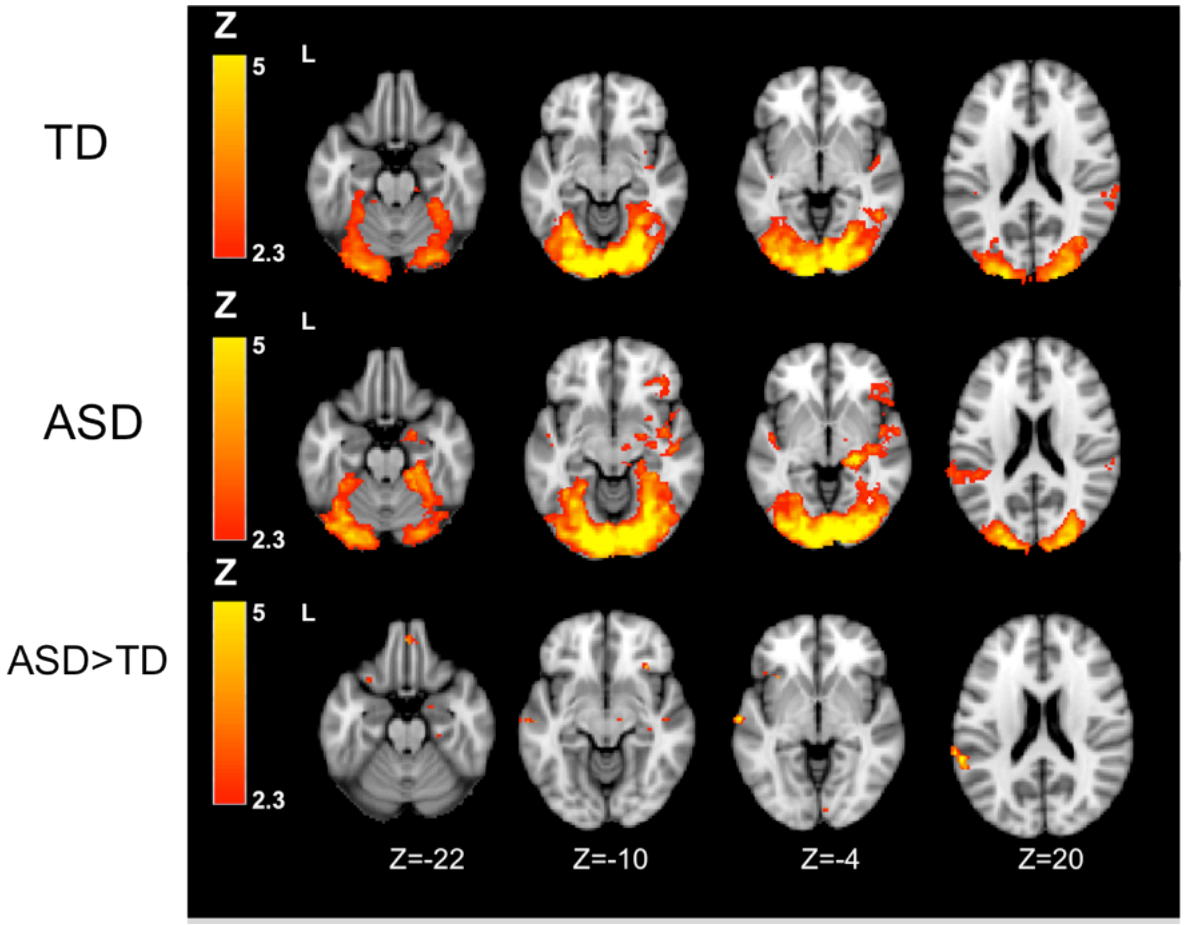

Figure 2. Within- and between-group results: Joint auditory + visual condition. Within-group contrasts thresholded at Z>2.3, corrected (p<.05). Between-group contrasts thresholded at Z>2.3, uncorrected.

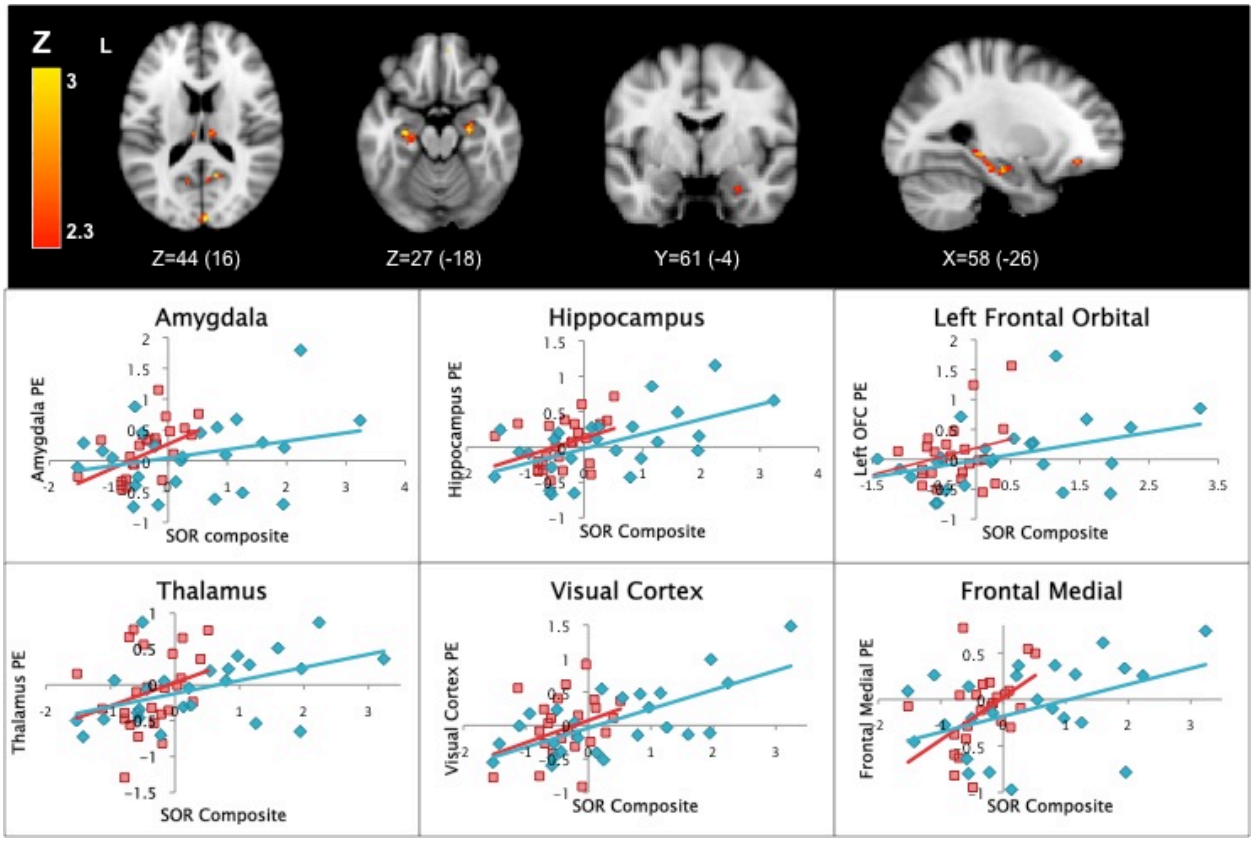

Figure 3. SOR severity as a predictor of BOLD response during the Joint condition. The horizontal axis displays the standardized residual SOR composite score after regressing out CBCL anxiety T-scores. The vertical axis displays the parameter estimates extracted from areas where significant correlations between SOR severity and brain activity were observed. ASD participants are in blue; TD in red.

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Rationale for Study 2

Study 1 was the first study to examine functional neural response to aversive sensory stimuli in children and adolescents with ASD. As such, the experimental paradigm was designed as a short pilot study, and many of the analyses were exploratory. The results clearly showed that children with ASD have more intense and widespread brain activation in response to mildly aversive visual and auditory stimuli compared to TD children. However, as discussed at the end of Study 1, the design had a number of limitations, and the results also left some questions unanswered regarding habituation, functional connectivity, and response to additional sensory modalities. Therefore, Study 2 was designed with the following aims:

1. Examine whether the results of Study 1 would replicate using a more powerful design, and thus allowing the ability to correct for multiple comparisons.

2. Examine brain response to tactile stimuli, which is one of the most common types of stimuli that children with ASD over-respond to.

3. Examine neural habituation across the scan to determine whether group differences are due to differences in initial response intensity or differences in sustained response across time.

4. Examine functional connectivity with a focus on group differences in amygdala-PFC connectivity to determine whether there are group differences in regulating amygdala response to sensory stimuli.

Study 2

Abstract

Objectives: Over half of youth with autism spectrum disorders (ASD) have sensory over-responsivity (SOR), an extreme negative reaction to sensory stimuli. The aim of this study was to examine the functional neural correlates of SOR by comparing brain responses to sensory stimuli in youth with and without ASD, and to investigate neural habituation and functional connectivity differences as potential causes for brain hyper-responsivity in SOR.

Method: Nineteen high-functioning youth with ASD and 19 age- and IQ-matched typically developing (TD) youth were presented with mildly aversive auditory and tactile stimuli during a functional magnetic resonance imaging (fMRI) scan. Parents provided ratings of children's SOR and anxiety symptom severity. Functional connectivity with amygdala and thalamus was conducted using a psycho-physiological interaction (PPI) analysis, and neural habituation across the scan was also examined.

Results: Compared to TD controls, ASD participants displayed greater activation in primary sensory cortical areas as well as amygdala and orbital-frontal cortex (OFC). Within the ASD group, the level of activity in sensory cortices and amygdala was positively correlated with level of SOR severity, over and above behavioral ratings of anxiety. The TD and ASD without SOR groups had faster and more extensive neural habituation than the ASD with SOR group, particularly in the amygdala and sensory cortices. Youth with ASD *without* SOR showed a pattern of down-regulation, with negative connectivity between amygdala and OFC.

Conclusions: This study extends previous findings that youth with ASD and SOR show neural hyper-responsivity to sensory stimuli, in particular to multiple modalities presented

simultaneously. Results suggest that these brain differences may be due to lack of amygdala regulation by prefrontal regions as well as to slower habituation to aversive sensory stimulation.

The new diagnostic criteria for Autism Spectrum Disorder (ASD) includes hyper- or hypo-responsivity to sensory stimuli as part of the diagnostic criteria for autism (American Psychiatric Association, 2013). While not all children with ASD display sensory abnormalities, the vast majority do. In particular, at least 56-70% of children with ASD meet criteria for Sensory Over-Responsivity (SOR; Baranek, David, Poe, Stone, & Watson, 2006; Ben-Sasson et al., 2007), which is a severe and negative response to, or avoidance of, sensory stimuli such as noisy environments, unexpected loud noises, scratchy clothing, or being touched (Liss, 2006). By comparison, only 10-17% of typically developing (TD; Ben-Sasson, Carter, & Briggs-Gowan, 2009; Ben-Sasson et al., 2007) children meet criteria for SOR. Children with ASD who also have SOR display more functional impairment, including lower levels of social and adaptive skills and higher levels of negative emotionality and anxiety (Liss, 2006; Pfeiffer, Kinnealey, Reed, & Herzberg, 2005; Ben-Sasson et al., 2008).

Because SOR is so much more common in ASD compared to the general population, research examining its neurological bases can inform understanding of brain abnormalities in ASD. Furthermore, such research can contribute to our understanding of heterogeneity within ASD and help in targeting interventions towards individual needs. For example, individuals with SOR may constitute a subgroup of ASD with high biological arousal and high rates of anxiety disorders (Green & Ben-Sasson, 2010; Schoen, Miller, Brett-Green, & Hepburn, 2008).

While research on the neurological bases of SOR is still very new, results of a recent functional neuroimaging study suggest that SOR could be related to hyper-activity in brain areas involved in primary sensory processing as well as those involved in emotion regulation and response to threat. In this study, Green et al. (2013) presented mildly aversive auditory (white noise) and visual (a flashing checkerboard pattern) stimuli to children and adolescents with and

without ASD. They found that the ASD group had greater activation in the limbic system (amygdala and hippocampus), primary sensory cortices, thalamus, and prefrontal cortex compared to the TD group; furthermore, activity in these brain areas was correlated with parent reports of SOR in both groups. Interestingly, the heightened level of activity observed in the ASD group was most evident when both the auditory and visual stimulus were presented simultaneously. While previous fMRI studies had found no group differences in the primary auditory (Gomot, Belmonte, Bullmore, Bernard, & Baron-Cohen, 2008) and visual (Hadjikhani, 2004) cortices, these studies presented simple stimuli (tones and colored circles) that were not designed to be aversive. Given that Green et al. (2013) presented mildly aversive stimuli, their findings of over-activation in emotion regulation areas is consistent with the frequent co-occurrence between SOR and anxiety disorders (Green & Ben-Sasson, 2010) as well as recent findings of amygdala hyperactivity in response to faces in children with ASD compared to those with TD (Kleinhans et al., 2009; Tottenham et al., 2013). Additionally, thalamus hyperactivity could overload the sensory cortices, as suggested by Mizuno and colleagues (Mizuno, Villalobos, Davies, Dahl, & Müller, 2006).

The current study aimed to replicate and expand upon the results of the Green et al. (2013) study by comparing the following in youth with and without ASD: 1) fMRI response to auditory and tactile stimuli; 2) functional connectivity between the primary sensory processing areas and emotion regulation areas of the brain; and 3) habituation (i.e. decreased neural responses over the course of repeated stimulus presentation) to sensory stimuli.

Auditory and Tactile Over-Responsivity

Over-responsivity to auditory and tactile stimuli has been found to best distinguish individuals with and without SOR (compared to other sensory modalities; (Kern, 2006; Leekam,

Nieto, Libby, Wing, & Gould, 2006; Tomchek & Dunn, 2007); they are also among those most often reported in children with ASD (Rogers, Hepburn, & Wehner, 2003; Tomchek & Dunn, 2007). Despite this, most neurobiological studies of auditory functioning have examined either response to simple tones or discrimination between tones, neither of which represent the stimuli that individuals with SOR are usually reacting to (e.g., loud, sudden noises, environmental sounds, vacuum cleaners, etc.). There is some evidence from EEG studies that individuals with autism have abnormally high sensitivity to pitch changes and attend more to low-level characteristics of sound, which could lead to hypersensitivity to certain sounds and/or reduced attention to language (O'Connor, 2012). Likewise, in a functional imaging study, Gomot et al. (2008) found that adolescents with ASD had higher fMRI response to novel sounds in higher-level processing areas, including prefrontal and inferior parietal areas.

Two recent studies examined the relationship between neural response to tactile stimuli and autism in adults. Cascio et al. (2012) found that adults with ASD had greater activation in the posterior insula, posterior cingulate, and the pulvinar area of the thalamus compared to TD adults in response to unpleasant touch (a mesh material). However, in response to pleasant touch (a brush), they had greater activation only in the pulvinar and were overall underresponsive compared to the TD group. In another study comparing neurotypical adults' responses to affective (slow) touch versus fast touch, Voos, Pelphrey, & Kaiser (2013) found that individuals with more autistic traits had less responsiveness to affective touch relative to fast touch in the superior temporal sulcus and orbitofrontal cortex. Together, these studies suggest that individuals with ASD may have an over-reactive brain response to unpleasant touch specifically, and possibly a diminished response to pleasant or affective touch, further highlighting the importance of studying responsiveness to aversive sensory stimuli when examining SOR.

To our knowledge, other than Green et al. (2013), no studies have examined neural response to multiple sensory modalities simultaneously. However, this is likely to better represent real-world environments, which almost always present multiple modalities of sensory stimuli.

Habituation

SOR could reflect a higher initial response to sensory stimuli in ASD, but alternatively (or additionally) it could be due to reduced habituation to these stimuli in children with ASD compared to those with TD. Indeed, youth with ASD have been found to have decreased amygdala habituation to sad and neutral faces, and their level of habituation is correlated with autism symptom severity (Kleinhans et al., 2009; Swartz et al., 2013). In fact, Swartz et al. (2013) found that the children with ASD showed *increased* amygdala response to the faces over time. While decreased amygdala habituation to faces is correlated with anxiety in TD children (e.g., Hare et al., 2008), Swartz et al. (2013) did *not* find a relationship between anxiety and habituation in youth with ASD, suggesting that the group differences in habituation were not simply due to higher anxiety levels in the ASD group. In the current study, we hypothesized that TD youth would habituate more to sensory stimuli than would ASD youth, particularly in the amygdala and primary sensory cortices, and that extent of habituation in these areas would relate to levels of SOR symptoms within the ASD group.

Functional Connectivity

Green et al. (2013) found that SOR symptoms were correlated with hyperactivity in multiple brain areas, including amygdala, hippocampus, thalamus, primary sensory cortices, and orbitofrontal and medial prefrontal cortex (PFC), but they did not examine connectivity between these areas. Amygdala and PFC activity are usually negatively coupled such that PFC activation

is associated with a down-regulation of the amygdala in response to threat-relevant stimuli (e.g., Hariri, Bookheimer, & Mazziotta, 2000). Simultaneous overactivity between the amygdala and prefrontal cortex could indicate an ineffective emotion regulation system, in which the prefrontal cortex activates but fails to sufficiently down-regulate the amygdala, such as is found in social anxiety disorder (Sladky et al., 2013; Hahm et al.). Alternatively, this pattern could indicate an immature emotion regulation system similar to that of young children who display positive connectivity between amygdala and prefrontal cortex (e.g., Gee et al., 2013). Studies of functional connectivity in ASD have found reduced amygdala and thalamic connectivity with the fusiform gyrus (Kleinhans et al., 2008) and reduced amygdala connectivity with the ventromedial PFC (Swartz, Wiggins, Carrasco, Lord, & Monk, 2013) during response to emotional faces. There is also evidence of reduced structural connectivity (i.e. decreases in white matter) between the amygdala and OFC in ASD (Zalla & Sperduti, 2013), as well as reduced thalamo-cortical structural connectivity in Sensory Processing Disorder (Owen et al., 2013). In the present study, functional connectivity with amygdala and thalamus during exposure to sensory stimuli was examined, with a focus on connectivity between amygdala and OFC, to determine whether this reduced amygdala-PFC connectivity might also contribute to SOR in youth with ASD.

Methods

Participants

Participants were 19 youth with ASD and 19 TD matched controls recruited through flyers posted around the University of California Los Angeles (UCLA) campus as well as through referrals from the UCLA autism clinic. Participants ranged in age from 9-17.6 years (M=13.66; SD=2.11) and all had a full-scale IQ within the normal range as assessed with the

Weschler Abbreviated Scales of Intelligence (WASI; Wechsler, 1999), or the Weschler Intelligence Scale for Children – 4th Edition (WISC-IV; Wechsler, 2003). Original participants included 22 TD subjects and 22 ASD subjects, but 3 TD subjects and 3 ASD subjects were excluded due to maximum motion >2.5 mm. Volumes with motion > 2mm were removed for included subjects; a total of 3 ASD subjects (average volumes removed = 12.33), and 2 TD subjects (average volumes removed = 8.67) had volumes removed. The final groups of 19 TD and 19 ASD did not differ significantly in age, FSIQ, performance IQ, verbal IQ, and mean or maximum head motion during fMRI (see Table 1). All ASD participants had a prior diagnosis of Autism Spectrum Disorder which was confirmed using the Autism Diagnostic Interview – Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) and the Autism Diagnostic Observation Schedule – 2nd Edition (ADOS-2; Lord et al., 2012). Nine of the ASD participants were taking psychoactive medications including selective serotonin reuptake inhibitors (N= 1), psychostimulants (N=5), and multiple medications (N=3). No participants reported loss of consciousness for longer than 5 minutes or any neurological (e.g., epilepsy), genetic (e.g., Fragile X), or severe psychiatric disorder (e.g., schizophrenia) other than autism.

FMRI Sensory Task Paradigm

Participants were passively exposed to three mildly aversive stimulus conditions in a block design paradigm (see Figure 1): an auditory condition, a tactile condition, and a "joint" condition where the auditory and tactile stimuli were presented simultaneously. The auditory stimulus consisted of traffic noises (e.g., loud cars and trucks driving, honking), presented at the same volume for each participant. The tactile stimulus involved a scratchy wool fabric attached over a thin block of wood with a handle to form a brush used to rub the participants' inner arms. Stimuli were chosen based on pilot testing with the Sensory Over-Responsivity Checklist

indicating that these kinds of auditory and tactile stimuli best differentiated the ASD versus TD groups. After completing the scan, participants rated on a scale of 0-10 how "bad" each stimulus was. Out of 10, the average rating across both groups was 2.24 for the auditory condition, 1.58 for the tactile condition, and 2.45 for the joint condition. There were no significant group differences in these aversiveness ratings. Each trial type was presented 4 times, with each trial lasting 15 seconds and with 12.5 seconds of fixation cross in between trials. The total scan length was 5 minutes, 42.5 seconds including a 12.5-second initial and final fixation.

MRI Data Acquisition

Scans were acquired on a Siemens Trio 3 Tesla magnetic resonance imaging scanner. A high-resolution structural T2-weighted echo-planar imaging volume (spin-echo, TR=5000 ms, TE=33 ms, 128x128 matrix, 20cm FOV, 36 slices, 1.56mm in-plane resolution, 3mm thick) was acquired coplanar to the functional scans in order to ensure identical distortion characteristics to the fMRI scan. Each functional run involved the acquisition of 137 EPI volumes (gradient-echo, TR=2500ms, TE=30ms, flip angle=90, 64x64 matrix, 20cm FOV, 33 slices, 3.125mm in-plane resolution, 3 mm thick). Auditory stimuli were presented to the participant using magnet-compatible headphones under computer control (Resonance Technologies, Inc.). The stimuli were presented using E-Prime. Participants wore earplugs and headphones to reduce interference of the auditory stimuli from the scanner noise. Tactile stimuli were administered by a research assistant in the scanner room, who brushed the wool material along the participant's inner arm from wrist to elbow at the rate of one stroke per second. Light pressure was used so that the participant did not experience a tickling sensation. Pressure was standardized between research assistants. Participants were instructed to focus on the fixation cross in the center of the screen for the duration of the task.

Measures

The ADI-R, ADOS, WISC, and WASI were administered at a clinical assessment visit prior to the MRI scan. Parents completed the additional questionnaires and interviews listed below while the child was in the scanner.

Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994). The ADI-R is a 93-item semi-structured interview which takes about 2 hours to administer and which provides reliable and valid diagnoses of ASD for individuals with a mental age above 2 years. The algorithm focuses on three areas: communication, social, and restricted and repetitive behaviors, with established cut-off scores for each area. Based on these cut-off scores, an individual can meet criteria for autism, autism spectrum disorder, or no autism. Items are coded on a zero to three scale, with zero indicating no ASD-specific atypical behavior present, and three indicating extremely atypical behavior. Established cut-off scores for each area have been shown to adequately discriminate autistic individuals from a mental-age matched non-autistic comparison group of participants with language impairment and/or mental retardation (Lord et al., 1994). The measure yields acceptable internal consistency for each subscale: Social, alpha of .95; Restricted and Repetitive Behaviors, alpha of .69; Verbal alpha of .85; Communication alpha of .84. A classification of autism spectrum disorder is given to individuals who met criteria for autism on either the Social or Communication domains and are within two points on the other. A score of three or greater on the restricted and repetitive behaviors domain is required for a diagnosis of autism, but not for a diagnosis of autism spectrum disorder.

Autism Diagnostic Observation Schedule-Second Edition (ADOS-2; Lord et al., 2012). The ADOS-2 is a semi-structured, interactive observation designed to assess social and communicative functioning in individuals who many have an ASD. Youth in this study were

administered Module 3 (for children with fluent speech) which takes about 45 minutes to 1 hour to complete. The assessment involves a variety of social "presses" and questions about social relationships designed to elicit behaviors relevant to a diagnosis of autism. A standardized diagnostic algorithm is computed, composed of rated social and communicative behaviors, consistent with criteria in DSM-IV. Established cut-off scores are used to differentiate autism, autism spectrum disorder, and no autism. This assessment has high inter-rater reliability (k=.88), internal validity (ICC ranged from .84-.98 for the social-communication total), and test-retest reliability (Lord et al., 2000). The sensitivity and specificity for Module 3 differentiating any ASD from no ASD is 90 and 94, respectively (Lord et al., 2000).

Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1997). The SCARED is a 41-item report form of child anxiety symptoms. There are both parent-report and self-report versions with parallel items which ask the respondent to rate each symptom as "Not true or hardly ever true," "Somewhat true or sometimes true," or "Very true or often true." The total score was used in this study as a continuous measure of anxiety symptom severity. The SCARED has good internal consistency, test-retest reliability, and discriminative validity (Birmaher et al., 1997), and takes approximately 5 minutes to complete.

Short Sensory Profile (SSP; Dunn, 1999) The SSP is a widely used, 38-item parent report measure of youth sensory dysregulation across a number of sensory modalities. Parents rate the frequency with which their child responds in an atypical way to sensory stimuli on a five-point Likert scale from "never" responds in this way to "always" responds in this way. This measure yields both a total score of sensory dysregulation as well as subscale scores for Tactile, Taste/Smell, Movement, and Auditory/Visual Sensitivity, Underresponsive/Seeks Sensation, Auditory Filtering, and Low Energy/Weak. For the purposes of this study, we used only the

subscales relevant to the auditory and tactile stimuli administered, namely the Auditory/Visual Sensitivity, Auditory Filtering, and Tactile Sensitivity scores. Higher scores on the SSP indicate *lower* impairment. On the Auditory/Visual Sensitivity subscale, a score of 19-25 is considered typical performance, a score of 16-18 is considered a "Probable Difference," and a score of 5-15 is considered a "Definite Difference." On the Auditory Filtering subscale, a score of 23-30 is considered typical performance, a score of 20-22 is considered a "Probable Difference," and a score of 6-19 is considered a "Definite Difference." On the Tactile Sensitivity subscale, a score of 30-35 is considered typical performance, a score of 27-29 is considered a "Probable Difference," and a score of 7-26 is considered a "Definite Difference" This measure has strong reliability and validity (McIntosh & Miller, 1999).

Sensory Over-Responsivity (SensOR) Inventory (Schoen, Miller, & Green, 2008). The SensOR Inventory is a parent checklist of sensory sensations that bother their child. For the purposes of this study, only the auditory and tactile subcales were used. The number of items parents rate as bothering their child has been shown to discriminate between TD children and children with SOR (Schoen et al., 2008).

SOR Composite. An SOR composite score was created by standardizing and averaging each relevant subscale of the SOR measures (SSP auditory/visual sensitivity, tactile sensitivity, and auditory filtering scales and SensOR Inventory auditory and tactile scores). One TD child did not have SSP scores and two TD children did not have SensOR scores; for these children, their SOR composite was made up of only the alternative test scores. Children in the top 25th percentile of the composite were categorized as having elevated SOR.

fMRI Data Analysis

Analyses were performed using FSL Version 5.0.5 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Preprocessing included motion correction to the mean image, spatial smoothing (Gaussian Kernel FWHM = 5mm), and high-pass temporal filtering (t > 0.01 Hz). Functional data were linearly registered to a common stereotaxic space by first registering to the in-plane T2 image (6 degrees of freedom) then to the MNI152 T1 2mm brain (12 degrees of freedom).

FSL's fMRI Expert Analysis Tool (FEAT), Version 5.98 was used for statistical analyses. Fixed-effects models were run separately for each subject, then combined in a higher-level mixed effects model to investigate within and between-group differences. Single-subject models included six motion parameters as covariates. Each experimental condition (auditory, tactile, or joint condition) was modeled with respect to the fixation condition during rest. Higher-level group analyses were carried out using FSL's FLAME (FMRIB's Local Analysis of Mixed Effects State) stage 1 (Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004; Woolrich, 2008). Within-group Z statistical images for each condition (vs. fixation) were thresholded at Z > 2.3 ($p<.01$). FSL's cluster correction for multiple comparisons (Gaussian-random field theory based) was set at $p<.05$, whole brain correction (http://www.fmrib.ox.ac.uk/fsl). Between-group comparisons were then performed and thresholded at Z > 1.7 ($p < .05$), also corrected across the whole brain at $p<.05$. Age was covaried in each group analysis. Because of the a priori interest in the amygdala, and its small volume, we also used a small volume correction to correct for multiple comparisons within the amygdala, using FSL's cluster tool (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Cluster). The amygdala

was defined by the Harvard-Oxford probabilistic subcortical atlas, thresholded at 75%, for a total structure volume of 493 voxels.

Correlation with SOR scores. To determine whether SOR predicted BOLD response over and above anxiety, regression analyses were performed with the de-meaned SOR composite as the independent variable and the SCARED total anxiety scores entered as covariates in the design matrix for the participants as a whole. These comparisons were also thresholded at $Z>1.7$, corrected. Parameter estimates for significant clusters in regions of interest (primary somatosensory and auditory cortex, thalamus, amygdala, hippocampus, and orbitofrontal cortex), using functionally defined masks, were extracted from each participant and plotted in a graph to rule out the presence of outliers.

Neural habituation. Habituation in the Tactile and Joint conditions was assessed in two ways. First, a whole-brain analysis was conducted to examine group differences in brain regions that showed decreased BOLD response linearly across the scan. Second, a region-of-interest (ROI) analysis was conducted to examine more closely group differences across the scan in amygdala and primary sensory cortices. The focus was on the Tactile and Joint conditions because of the lack of significant group differences and relationships with SOR in the Auditory condition.

To conduct the whole-brain habituation analysis, regressors that modeled a linear decrease across the four blocks, (one regressor for each condition) were entered into the single-subject analysis. The original task regressors were also entered as covariates. The habituation regressors were de-meaned to prevent rank deficiency (i.e., being redundant with the task regressors). Single-subject analyses were then combined into a higher-level mixed-effects group analysis. Within-group analyses were thresholded at $Z>2.3$, corrected ($p<.05$), and between-

group analyses were thresholded at Z>1.7, corrected. As with the original analyses, we also conducted a small-volume correction within the amygdala.

For the ROI analysis, masks were created by drawing a sphere around the peak coordinate in the structure of interest in each group and then adding the spheres together. Masks were created separately for the Tactile and Joint conditions. Sphere size was 4mm for the amygdala, 6mm for the somatosensory cortex, and 10mm for the auditory cortex (Joint condition only). Amygdala peak coordinates are listed in table 5; somatosensory and auditory cortex coordinates are listed in Tables 3 and 4 (right postcentral gyrus and bilateral Heschl's gyrus). Parameter estimates were extracted from the masks from each of the four blocks of each condition. Repeated-measures ANOVAs were then used to examine group differences in change across the four blocks, as well as differences among the three SOR categories (ASD without SOR, ASD with SOR, and TD without SOR).

Functional connectivity. A psychophysiological interaction (PPI) analysis was used to examine functional connectivity during the Joint condition. This analysis examines the interaction between task (psychological context) and the time series of a seed region (physiological context) to identify brain regions where activity is more correlated with the seed region during the task than during baseline. The right amygdala and pulvinar nucleus of the thalamus were used as seed regions; these regions were a priori regions of interest (ROIs) to focus on sensory and emotion regulatory networks. The right amygdala seed region was functionally defined by areas of the right amygdala that were active in either group during the Joint condition; the right amygdala was chosen because both groups had significant activation in the right, but not left amygdala. The pulvinar seed was defined by masking a 5mm sphere around the peak coordinate of activation in each group during the Joint condition (at Z>1.7) and adding

the two masks (TD peak coordinates: x=18, y=-26, z= 8; ASD peak coordinates: x=14, y=-16, z=12). Within- and between-group-level analysis were performed and cluster corrected at Z>1.7, corrected for multiple comparisons at p<.05. Both positive and negative connectivity (areas showing increased and decreased activity as function of increased activity in the seed region) were examined.

Results

Behavioral Results

Independent-sample t-tests were used to test for group differences in parent-reported SOR and anxiety data, including the SensOR Inventory tactile and auditory scales, the Short Sensory Profile tactile, auditory/visual and auditory filtering subscales, SOR composite, as well as the SCARED anxiety total score. The ASD group was rated as significantly more severe on all of these measures except for the SensOR tactile count (results are displayed in Table 2; note that lower SSP scores indicate more severe sensory differences). The correlation between SCARED anxiety total and the SOR composites (tactile, auditory, and both, respectively) were significant in both groups (TD: *r*=.59, .49, and .56, p<.05; ASD: *r*=.74, .60, .69, p<.01).

A total of nine children in the ASD group and one child in the TD group had elevated SOR. A one-way analysis of variance (ANOVA) was used to compare the SOR composite and SCARED anxiety totals for the ASD-SOR, ASD-no SOR, and TD-no SOR groups. In both cases, the overall F was significant (SOR composite F(2,34)=65.20, p<.001; SCARED F(2.34)=20.61, p<.001). Post-hoc LSD tests showed that the ASD-SOR group had significantly higher SOR composite scores (M=1.27, SD=.64) than either the ASD-no SOR group (M=-0.29, SD=.27, p<.001) or the TD group (M=-0.55, SD=.29, p<.001). Similarly, the ASD-SOR group had significantly higher SCARED scores (M=21, SD=8.78) than either the ASD-no SOR group

(M=7.40, SD=3.50, p<.001) or the TD group (M=5.11, SD=5.83, p<.001). For both the SOR composite and the SCARED scores, there were no significant differences between the ASD-no SOR and the TD groups.

Finally, to determine whether the ASD-no SOR group was an underresponsive or sensory seeking group, an ANOVA was used to examine differences in the SSP underresponsive/seeks sensation scale among the ASD-no SOR, ASD-SOR, and TD-no SOR groups. All three groups significantly differed from each other in under-responsiveness (F(2.33)=12.88, p<.001), with the ASD-SOR group (mean=22.78, SD=7.51) being more underresponsive than the ASD-no SOR group (mean=29.80, SD=7.70, p=.009), which, in turn, was more underresponsive than the TD group (mean=34.35, SD=1.32, p=.047).

fMRI Results

Within-group results. We first examined activity within each group in each of the three conditions. Results are displayed in Tables 2-5 and Figures 2-4. In the Auditory condition, both groups had significant activation in bilateral temporal lobes including auditory cortex, right insula, and right inferior frontal gyrus (IFG). The TD group also had significant activation in the left insula. The TD group had significant activation in the left amygdala and the ASD group in the right amygdala. In the Tactile condition, both groups had significant activation in bilateral somatosensory cortex, supramarginal gyrus, precentral gyrus, operculum, and insula, as well as right IFG and right putamen. Both groups also had significant bilateral amygdala activation. Additionally, the TD group had significant activation in left IFG and right planum temporale. The ASD group had significant activation in bilateral superior parietal lobule, right posterior cingulate, right middle frontal gyrus, left orbital frontal cortex (OFC), left putamen, and pulvinar. In the Joint condition, both groups had significant activation in bilateral somatosensory cortex,

right precentral gyrus, bilateral auditory cortex, right operculum, right insula, and right amygdala. Additionally, the ASD group had widespread activation throughout the brain including bilateral frontal lobes, bilateral OFC, left operculum, bilateral basal ganglia (putamen, caudate, right pallidum), thalamus, and bilateral amygdala.

Between-group results. We then directly compared activation patterns between ASD and TD groups for each contrast (see Tables 2-5 and Figures 2-4). There were no significant group differences in the Auditory condition. In the Tactile Condition, the ASD group had greater activation in bilateral somatosensory cortex, left superior parietal lobule, right precentral gyrus, and right posterior cingulate. In the Joint condition, the ASD group had significantly greater activation in bilateral somatosensory cortex, left superior temporal gyrus, right OFC, bilateral basal ganglia, right thalamus, left hippocampus, bilateral amygdala, as well as frontal lobes and occipital cortex. No significant differences were observed for the opposite comparisons (TD > ASD).

Correlation with sensory over-responsivity severity. We examined SOR severity within the ASD group as a predictor of BOLD response above and beyond anxiety by entering the SOR composite as a regressor of interest and parent-reported SCARED total scores (as well as age) as covariates. Correlations were examined within each condition, and separate Auditory and Tactile SOR composites were created as regressors for the Auditory only and Tactile only conditions, respectively. The full SOR composite with both tactile and auditory scores was used as the regressor for the Joint condition. There were no brain regions significantly correlated with the auditory SOR composite in the Auditory condition. In the Tactile condition, tactile SOR scores were significantly positively correlated with bilateral somatosensory cortices, left superior parietal lobule, left supramarginal gyrus, and left insula, as well as bilateral amygdala. In the

Joint condition, SOR scores were significantly positively correlated with signal increases in the bilateral somatosensory cortices and precentral gyri, right superior parietal lobule, left supramarginal gyrus, left temporal lobe (including auditory cortex), and left insula, as well as bilateral amygdala. Parameter estimates for clusters in areas of interest (amygdala, thalamus, and sensory cortices) were extracted and plotted to ensure correlations were not driven by outliers. These areas, along with graphs of the correlations in the Joint condition are presented in Figure 5; the MNI coordinates for all significant clusters are listed in Table 3 for the Tactile condition and Table 4 for the Joint condition.

Habituation. Clusters that decreased significantly across the scan in the whole-brain habituation analyses are presented in Figures 7 and 8 and peak coordinates are listed in Tables 6 and 7. We also conducted a small-volume correction within the amygdala; these results are reported in Table 8. These analyses showed that the TD group showed widespread habituation across the brain in both the Tactile and Joint conditions, including somatosensory cortex, frontal lobes, prefrontal cortices, cingulate gyrus, temporal lobes (including auditory cortex), insula, occipital lobes, basal ganglia, hippocampus/parahippocampal gyri, and bilateral amygdala. The ASD group showed far fewer areas of habituation; in the tactile condition the ASD group showed significant habituation in the bilateral somatosensory cortex, right superior parietal lobule, middle temporal gyrus, insula, and right lateral occipital cortex. The ASD group displayed more areas of habituation in the Joint condition, including bilateral somatosensory cortex and precentral gyri, orbital frontal cortex, parietal and occipital cortex, cingulate, bilateral insula, bilateral temporal lobes (including auditory cortex), and bilateral amygdala.

In the Tactile condition, most of the regions with significant habituation in the TD group also habituated significantly more in the TD group compared to the ASD group, including

bilateral amygdala (though not somatosensory cortex); see Tables 6 and 8 for details. In the Joint condition, the TD group had greater habituation in the right amygdala, right precentral gyrus, frontal cortex, right superior parietal lobule, occipital cortex, and anterior cingulate. There were no brain regions in either condition that habituated more in the ASD compared to the TD group.

ROI analyses -Tactile condition. Results for the Region-of-Interest habituation analyses are displayed in Tables 9-10 and Figures 9-10. For the amygdala ROI, there was a main effect of time such that amygdala activation significantly decreased for both groups linearly across the four tactile blocks. There was also a significant diagnosis by time interaction indicating that the amygdala activity in the TD group decreased more quickly across the scan than in the ASD group. There was no main effect of diagnosis on amygdala activity. However, follow-up independent t-tests examining group differences for each block indicated that the TD group had higher initial amygdala activation (mean=.57, SD=.44) than the ASD group (mean=.12, SD=.21; $t(36)=4.01$, $p<.001$), but by the second block the ASD group (mean=.17, SD=.32) had higher activation than the TD group (mean=-.04, SD=.28). In the ANOVA comparing amygdala activation across the three SOR category groups (including TD-no SOR, ASD-no SOR, and ASD-SOR), there was both a linear and quadratic significant time by SOR category such that the TD group started out higher and decreased faster than either the ASD no SOR or ASD SOR groups. There was no significant main effect of SOR category.

The ANOVA modeling primary somatosensory cortex activation across the scan indicated a main effect of time: somatosensory cortex activity decreased linearly across the scan. There was a significant time by diagnosis quadratic interaction indicating that the TD group decreased more quickly than the ASD group. There was no significant main effect for diagnostic group. There was also no significant time by SOR category interaction or overall main effect for

SOR category. However, a post-hoc LSD test indicated that the ASD SOR group had overall higher activation across the scan than the ASD no SOR group (mean difference=.26, std. error=.12, p=.04).

ROI analyses -Joint condition. There was a main effect for time such that amygdala activation decreased significantly and the rate of decrease slowed across the four Joint condition blocks. There was no main effect of diagnostic group, but there was a significant diagnosis by time interaction for the cubic slope parameter reflecting that for the ASD group, amygdala activation began to rise again towards the second half of the scan, whereas the TD group continued to decrease. There was a marginally significant main effect of SOR category (p=.075), and a significant SOR category by time interaction for the cubic slope parameter. A post-hoc LSD test indicated that there was a significant difference between the ASD SOR group and both the ASD no SOR group (mean difference=.24, std error=.11, p=.04) and the TD group (mean difference=.20, std. error=.10, p=.047). There was no significant difference between the ASD no SOR and the TD groups.

For the somatosensory cortex, there was a significant linear decrease across the scan, but no main effect of diagnostic status. There was a marginally significant (p=.057) diagnosis by time interaction for the quadratic slope term indicating that, for the ASD group, somatosensory cortex activation decreased more slowly across the scan compared to the TD group. There was no significant main effect of SOR category or category by time interaction. However, a post-hoc LSD test indicated that the ASD SOR group activation was marginally higher than that in the ASD no SOR group (mean difference=.28, std. error=.15, p=.07) and that in the TD group (mean difference=.28, std. error=.14, p=.05).

Finally, an analysis of habituation in the primary auditory cortex indicated a significant

linear and quadratic decrease across the scan, but there were no significant differences among diagnostic status groups or among SOR category groups. Taken together, these results show that there were group differences in habituation in the amygdala and somatosensory cortices, but not in the auditory cortex. The TD group tended to have initial activation as high as or even higher than the ASD group, but quickly decreased activation, whereas the ASD group decreased much more slowly or inconsistently. The differences between the TD and ASD group generally tend to be due to the higher activation and slower decreases specifically in the ASD group *with* SOR.

Functional connectivity. Regions showing significant connectivity with the right amygdala seed are displayed in Figure 10 and peak coordinates for all significant clusters are listed in Table 11. Within the TD group, the right amygdala was found to have positive functional connectivity with the left middle frontal gyrus (MFG), bilateral OFC, and left superior temporal gyrus (STG). Within the ASD group, the amygdala had positive functional connectivity with the right STG and right hippocampus. The between-group analyses indicated that there were significant group differences in connectivity between the amygdala and left OFC, left MFG, right postcentral gyrus (somatosensory cortex), and posterior cingulate. Extraction of parameter estimates for these significant clusters showed that the ASD group had significant negative connectivity with left OFC and left MFG whereas the TD group had significant positive connectivity. The TD group had significant negative connectivity with the right somatosensory cortex and posterior cingulate, whereas the ASD group did not have significant connectivity with the somatosensory cortex, and had significant positive connectivity with the posterior cingulate.

To further examine differences in amygdala-prefrontal connectivity among the three SOR category groups, we conducted a one-way ANOVA using the parameter estimates of connectivity between the amygdala and OFC (see Figure 11). There were significant differences

between all three groups (MS=0.55, F(2)=16.96, p<.001). A post-hoc LSD test indicated that the ASD-no SOR group (M=-0.32, SD=.29) had significantly greater negative connectivity than the ASD-SOR group (M=-0.13, SD=.07, p=.03), and the TD-no SOR group (M=0.09, SD=.14, p<.001). The TD group had significantly positive connectivity and was also significantly different from the ASD-SOR group (p=.006), which had significant negative connectivity. In summary, the ASD-no SOR group had the most strongly negative connectivity, the ASD-SOR group had lesser, though significant negative connectivity, and the TD group had slight positive connectivity between right amygdala and OFC.

Regions showing significant functional connectivity with the right thalamus pulvinar seed are displayed in Figure 12 and coordinates are listed in Table 12**.** The PPI analyses with the thalamus seed region showed positive connectivity within the TD group in right MFG, right IFG, bilateral STG, right middle temporal gyrus, and primary visual cortex. The ASD group did not show any significant connectivity with the pulvinar. There were significant group differences in connectivity in bilateral somatosensory cortex, right precentral gyrus, and left superior parietal lobule. Extraction of parameter estimates indicated that the TD group had significant, negative connectivity within each of these regions, whereas the ASD group did not have significant connectivity.

Finally, to investigate potential connectivity between the sensory processing and emotion regulation systems, we examined whether there was significant pulvinar connectivity to the amygdala seed, and vice versa (a small volume correction – i.e., correcting for multiple comparisons only within the right thalamus and amygdala, respectively – was applied for these ROI analyses). Within the amygdala seed analysis, there was a significant group difference in negative connectivity with the pulvinar (peak coordinate=16,-28,4, val=3.00, p<.0001,

voxels=65), with the TD group showing significant negative connectivity and the ASD group showing no significant connectivity. Within the thalamus seed analysis, the ASD group had significant positive connectivity with the right amygdala (peak coordinate=20,-8,-16, val=2.92, p<.0001, voxels=2.92).

Discussion

The aim of this study was to investigate the functional neurobiological basis of SOR through comparing brain response to aversive sensory stimuli in TD youth and ASD youth with and without SOR. We explored additional brain abnormalities potentially related to these group differences by examining functional connectivity and neural habituation during exposure to the sensory stimuli, with a focus on brain areas related to primary sensory processing as well as those related to emotion regulation.

As hypothesized, results indicated that youth with ASD have a greater neural response to mildly aversive sensory stimuli compared to TD youth. Differences were greatest during exposure to two simultaneous stimuli (auditory and tactile). In fact, there were no group differences in response to the auditory stimuli alone, which suggests this stimulus was not particularly aversive to either group (especially given that Green et al. (2013) found group differences in response to a more unpleasant white noise sound). The tactile condition, conversely, elicited group differences in primary somatosensory (SMS) cortex, and extent of activation in this area was correlated with parent-reported SOR symptoms. There were no ASD-TD group differences in emotion-processing regions in response to the tactile stimulus, but, within the ASD group, SOR symptoms were correlated with increased response in secondary somatosensory processing regions (operculum and superior parietal lobule) as well as the insula and amygdala. The insula is involved in interoception and emotional processing of sensory

stimuli, including touch, and receives inputs from the amygdala based on the perceived saliency of touch (Paulus & Stein, 2006; Wei & Bao, 2013). Furthermore, over-reactive insula response during emotion processing is associated with anxiety (Simmons, Strigo, Matthews, Paulus, & Stein, 2006; Stein, Simmons, Feinstein, & Paulus, 2007), which is consistent with the common co-occurrence of SOR and anxiety.

The greatest differences between youth with and without ASD occurred in response to the Joint condition (simultaneous auditory and tactile stimuli). Here, the ASD group had a stronger neural response in sensory processing regions, including auditory and tactile sensory cortices and thalamus, as well as in emotional processing regions, including amygdala and orbital frontal cortex (OFC). Additionally, the extent of activation in sensory cortices, amygdala, and insula, was correlated with parent-reported SOR scores within the ASD group.

Habituation analyses, examining decreases in neural response across the scan, demonstrated greater habituation within the TD group compared to the ASD group, particularly during the Tactile condition. The TD group had greater linear decreases across most areas of the brain during this condition, which is consistent with the theory that the TD group quickly assessed the tactile stimulus and found it to be neither particularly threat-relevant nor salient. An ROI analysis of habituation within the amygdala and somatosensory cortex showed that both groups decreased over time in these regions, but the TD group habituated more quickly. This group difference was mainly accounted for by the youth with ASD and SOR, whereas the ASD-no SOR group had habituation more similar to the TD group. Group differences were not so extensive in the Joint condition, though the TD group did show greater habituation than the ASD group. This could be because the main group differences were not linear, as modeled in the whole-brain analysis, but quadratic and cubic, as shown in the ROI analyses. The ROI analysis

of the amygdala and sensory cortices showed that there were significant group differences in amygdala and somatosensory cortex habituation, with both groups starting off with similar activation, but the ASD group habituating more slowly and inconsistently. Again, this difference was accounted for by the ASD-SOR group, which not only habituated more slowly, but also ended the scan with higher activity levels than the TD group. There were no group differences in habituation during the auditory condition, which is consistent with the previous results indicating that the auditory stimuli were not significantly aversive.

To further understand how emotion regulation might relate to SOR, we examined functional connectivity with the amygdala during the Joint condition, with a focus on the amygdala-OFC connection. We found a group difference in connectivity, with the ASD group demonstrating a significant negative correlation between amygdala and OFC activation, and the TD group demonstrating a significant positive correlation. When we broke this down further, we found that the ASD youth *without* SOR had the most significant negative amygdala-OFC connectivity, with the ASD-SOR group having slightly negative connectivity, and the TD group having slightly positive. Negative connectivity between the prefrontal cortex and amygdala is usually associated with down-regulation of the amygdala during emotion processing and behavioral regulation (Hariri et al., 2000; Kim et al., 2011). Our results suggest that youth with ASD and no SOR may have an exaggerated amygdala response to sensory information but are able to compensate through prefrontal down-regulation of the amygdala and thus do not display the behavioral responses seen in youth with SOR. The TD group, on the other hand, may not perceive the stimuli as particularly aversive and do not have an over-reactive amygdala response, so they do not require prefrontal down-regulation. Positive amygdala-OFC activity in the TD group could simply reflect emotional processing and learning; for example, positive connectivity

between the amygdala and PFC has been found during resting state and is thought to relate to identifying the emotional significance of stimuli without activating effortful regulation (e.g., Roy et al., 2009).

Interestingly, the TD group but not the ASD group had significant negative connectivity between the amygdala and somatosensory cortex, whereas both groups had significant positive connectivity between amygdala and auditory cortex. This could reflect the potentially greater aversiveness of the tactile compared to the auditory stimulus; perhaps the TD group is able to activate a negative feedback loop between the sensory processing and emotion regulation brain systems, allowing them to prevent overloading of the sensory cortices and inhibit a behavioral response. The TD group also had significant negative connectivity between the pulvinar area of the thalamus and the amygdala. This is consistent with evidence from emotion processing tasks in neurotypical populations of negative connectivity between amygdala, thalamus, and sensory cortex, suggesting neuromodulation of response (Williams et al., 2006).

Overall, we found evidence for greater pulvinar connectivity within the TD group compared to the ASD group. The TD group showed negative pulvinar connectivity with somatosensory cortex and association areas and positive connectivity with frontal regions and with auditory and visual sensory cortex, whereas none of these areas showed significant connectivity within the ASD group. These findings are consistent with a recent study demonstrating decreased structural connectivity with the thalamus in children with sensory processing disorder (Owen et al., 2013). The pulvinar is a unique thalamic nucleus in that it mainly receives input from and outputs to cortical regions, and thus is thought to aid in interpretation and integration of sensory information (e.g., Sherman & Guillery, 1996). Pulvinar underconnectivity in the ASD group, particularly during the joint condition of two simultaneous

sensory stimuli, could reflect difficulties in sensory integration in the ASD group, and potentially could help explain the lesser somatosensory cortex habituation in this group, though these hypotheses are speculative and require further investigation.

While the ASD group displayed overall thalamus under-connectivity, this group did have significant (positive) connectivity between the pulvinar and right amygdala. Positive pulvinar and amygdala connectivity has been found during subconscious (i.e., masked) face processing tasks, and is thought to relate to disruption in inhibitory cortical feedback (Williams et al., 2006). While the sensory task in this study was not subconscious, it is possible that the positive amygdala-pulvinar activity in the ASD group is related to lack of cortical inhibition, especially as the ASD group lacked the negative amygdala and pulvinar connectivity with the somatosensory cortex as seen in the TD group.

Taken together, results of this study confirm previous findings of over-reactive brain response to sensory stimuli in youth with ASD (Green et al., 2013), and further extend these findings to show that SOR in youth with ASD is related to decreased habituation in amygdala and sensory cortex as well as absence of amygdala-prefrontal negative connectivity. These findings are consistent with previous studies of amygdala over-reactivity and reduced habituation in ASD in response to faces (Kleinhans et al., 2008; Swartz et al., 2013); however, results of this study suggest that amygdala abnormalities in ASD are not limited to social contexts. Rather, youth with ASD may have more general amygdala hyperactivity and/or difficulty determining saliency and threat-relevance of stimuli. Reduced top-down regulation from the prefrontal cortex in youth with ASD and SOR could contribute to deficits in using context to determine saliency of stimuli (Zalla & Sperduti, 2013).

This study had a number of strengths, including examination of multiple modalities of

sensory stimuli, accounting for within-group heterogeneity in SOR, and investigating brain over-reactivity from multiple perspectives (e.g., habituation, functional connectivity). There were also some limitations, including the relatively small sample size, which left reduced power to examine within-group differences. However, the pattern of results was consistent in showing greater over-reactivity and reduced habituation in the ASD group with elevated SOR and future research should continue to examine this subgroup with larger samples. Future research should also examine in more detail youth with ASD *without* SOR, as our findings that this group has significant negative amygdala-OFC connectivity suggests that youth with ASD and no SOR may have developed unique coping strategies to inhibit sensory response.

Future research should also follow up on the role of the posterior cingulate cortex (PCC), insula and basal ganglia in SOR. While not a priori areas of interest, we did find greater response to sensory stimuli in these areas in the ASD group. Cascio et al. (2012) also found increased PCC and insula response to an unpleasant mesh texture in adults with ASD, which they hypothesized was related to increased attention towards determining affective significance of the tactile stimuli in the ASD group. In this study, as well as in Green et al. (2013), we found increased basal ganglia (i.e., caudate and putamen) response to sensory stimuli in the ASD group. The basal ganglia plays an important role in selecting objects for attention by releasing inhibition on the thalamus, and is also involved in a negative feedback loop suppressing cortical activity; excessive basal ganglia signaling to the thalamus could thus lead to over-activation of sensory cortical areas in SOR (Koziol, Budding, & Chidekel, 2011).

Finally, further research is needed on how laterality of amygdala response might be related to SOR. We found that while the ASD group activated bilateral amygdala more than the TD group in response to both simultaneous stimuli, the TD group did not have significant

activation in the left amygdala at all. The right amygdala is thought to be more involved in rapid stimuli assessment, whereas the left is involved in more extensive evaluation (Sergerie, Chochol, & Armony, 2008). It is possible that the TD group activated the right but not left amygdala because the youth in this group were able to quickly evaluate the stimulus, determine the saliency to be relatively low, and then decrease amygdala response, whereas the ASD group continued to evaluate the stimulus across the scan.

These findings have a number of implications for intervention. First, we found the greatest over-responsiveness occurred in response to multiple simultaneous stimuli. This suggests that limiting stimulus type could help youth with ASD cope with their SOR. For example, a child might be more tolerant of being touched in a quiet house than in a noisy movie theater. Second, youth with ASD and no SOR appear to have some initial over-reactivity to stimuli but are then able to down-regulate their response. This may indicate that the focus of intervention for SOR should be on building coping strategies rather than on normalizing sensory processing. Successful interventions for teaching coping strategies to reduce anxiety in ASD already exist (e.g., Wood et al., 2009) and, particularly given the high co-occurrence of anxiety and SOR in ASD (Green & Ben-Sasson, 2010), it may be possible to adapt these interventions to target SOR.

Tables and Figures

Table 1. Descriptive statistics.

	ASD	TD	t or χ^2
Age	13.71 (1.60)	13.61 (2.57)	0.13
Gender (% male)	84% (n=16)	84% (n=16)	0
Handedness (% right-handed)	95% (n=18)	100% (n=19)	0.31
FSIQ	104.63 (13.22)	107.37 (15.06)	-0.59
VIQ	103.74 (13.49)	107.63 (13.17)	-0.9
PIQ	103.70 (14.47)	105.76 (16.00)	-0.42
Mean Absolute Motion	0.33 (.17)	0.31 (.23)	0.21
Max Absolute Motion	0.94 (.64)	0.87 (.97)	0.29
Mean Relative motion	0.09 (.04)	0.13 (.20)	-0.9
Max Relative Motion	0.80 (.63)	0.61 (1.15)	0.62
SensOR Tactile Count	4.79 (5.57)	2.76 (4.12)	1.22
SensOR Auditory Count	6.89 (7.06)	1.56 (3.90)	2.87**
SSP Auditory/Visual	19.32 (5.10)	24.28 (2.11)	-3.90**
SSP Auditory Filtering	17.42 (6.00)	26.11 (4.01)	-5.20***
SSP Tactile Sensitivity	27.32 (6.19)	32.89 (3.64)	-3.31**
SOR Composite	0.45 (.93)	-0.45 (.51)	3.71**
SCARED Anxiety Total	13.84 (9.44)	5.47 (5.88)	3.28**

**p<.01; ***p<.001.

Note: N=19 ASD, 19 TD except for SSP analyses where N=19 ASD, 18 TD, and SensOR analyses where N=19 ASD, 17 TD.

Table 2. MNI coordinates for the auditory condition as compared to baseline.

	TD				ASD			
	MNI Peak (mm)			Max	MNI Peak (mm)			Max
	x	y	z	*Z*	x	y	z	*Z*
Right Precentral Gyrus	44	8	26	3.11				
Right IFG	58	26	26	4.23	46	40	6	3.14
Right Heschl's gyrus	52	-20	8	6.53	48	-16	8	6.36
Left Heschl's gyrus	-44	-20	2	6.44	-52	-22	8	6.14
Right Superior Temporal Gyrus	66	-42	14	5.40	66	-32	6	4.58
Left Superior Temporal Gyrus	-62	-30	10	4.52	-66	-18	-4	3.25
Right Planum Temporale					62	-18	12	6.60
Left Planum Temporale	-48	-36	12	5.39	-36	-36	16	4.57
Right Planum Polare	42	0	-16	3.43				
Right Temporal Pole	54	8	-8	2.73	52	22	-14	3.45
Right Middle Temporal Gyrus	60	-56	10	2.96	48	-40	10	3.59
Right Central Opercular Cortex					60	-6	14	4.01
Right Insula	48	-10	-4	5.51	-54	-6	4	4.31
Left Insula	-32	-34	16	4.85				
Cerebellum					-28	-56	-46	3.79

Note: x, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; *Z* refers to the Z-score at those coordinates (local maxima or submaxima Within-group analyses are cluster corrected for multiple comparisons, $Z>2.3$, $p<.05$.

Table 3. MNI coordinates for the tactile condition as compared to baseline.

	TD				ASD				ASD>TD				Regress Tact ASD			
	MNI Peak (mm)			Max	MNI Peak (mm)			Max	MNI Peak (mm)			Max	MNI Peak (mm)			Max
	x	y	z	*Z*	x	y	z	*Z*	x	y	z	*Z*	x	y	z	*Z*
Right Postcentral Gyrus	22	-42	68	4.98	24	-38	64	5.63	14	-30	76	3.77	30	-38	56	3.67
Left Postcentral Gyrus	-56	-22	26	4.63	-26	-40	64	4.01	-54	-22	52	2.86	-20	-40	58	2.80
Right Precentral Gyrus	28	-16	66	3.57	62	6	6	4.33	12	-16	78	3.37				
Left Precentral Gyrus	-58	10	26	4.26	-58	4	28	4.59								
Right Middle Frontal Gyrus					32	-4	58	2.77								
Right Inferior Frontal Gyrus	42	-30	24	5.70	48	14	0	2.91								
Left Inferior Frontal Gyrus	-46	12	4	2.85												
Left Frontal Orbital Cortex					-30	16	-20	3.18								
Right Operculum	48	-16	16	4.38	44	-22	18	5.88								
Left Operculum	-46	-36	22	4.05	-44	-30	22	4.49					-58	-30	20	3.21
Right Insula	36	-16	14	5.40	32	0	12	4.83								
Left Insula	-40	6	-2	3.65	-34	-2	14	4.16					-34	-6	12	3.85
Right Supramarginal Gyrus	62	-44	26	2.52	66	-22	24	4.81								
Left Supramarginal Gyrus	-56	-46	34	2.88	-58	-28	24	5.90					-50	-34	32	2.93
Posterior Cingulate					16	-24	42	3.74	16	-20	38	2.68				
Right Superior Parietal Lobule					20	-50	72	4.02								
Left Superior Parietal Lobule					-40	-46	64	3.99	-16	-50	74	3.47	-34	-44	64	3.08
Right Planum Temporale	64	-32	20	5.73												
Right Putamen	26	4	-4	3.23	26	6	-4	4.39								
Left Putamen					-24	8	-10	4.72								
Right Thalamus - Pulvinar					14	-22	14	3.67								

Note: x, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; Z refers to the Z-score at those coordinates (local maxima or submaxima Within-group analyses are cluster corrected for multiple comparisons, $Z>2.3$, $p<.05$; between-group and regression analyses are thresholded at $Z>1.7$, corrected. Between-group analyses are masked by regions of significant activation in either within-group analysis, at the liberal threshold of $Z>1.7$, uncorrected. Regression results show clusters with activation significantly correlated with SOR composite, within the ASD group, over and above age and anxiety symptoms.

Table 4. MNI coordinates for the joint (auditory and tactile) condition as compared to baseline.

	TD				ASD				ASD>TD				Regress With SOR			
	MNI Peak (mm)			Max	MNI Peak (mm)			Max	MNI Peak (mm)			Max	MNI Peak (mm)			Max
	x	y	z	Z	x	y	z	Z	x	y	z	Z	x	y	z	Z
Right Postcentral Gyrus	26	-38	66	4.98	24	-38	68	6.5772	50	-16	36	4.6256	30	-38	58	3.6437
Left Postcentral Gyrus	-52	-22	24	3.64	-22	-42	68	4.4852	-60	-10	40	3.4697	-62	-26	30	2.4741
Right Precentral Gyrus	28	-16	66	3.30	26	-14	64	4.01	58	8	36	3.4192	34	-10	70	4.30
Left Precentral Gyrus					-62	6	26	4.41					-56	4	24	3.70
Right Supplementalry Motor Cortex					6	-10	56	2.82	6	6	50	3.3113	6	-12	58	2.7361
Right Inferior Frontal Gyrus					58	16	-4	4.79								
Left Inferior Frontal Gyrus					-48	10	16	3.50	-48	12	16	2.50				
Right Superior Frontal Gyrus									4	22	46	2.4483				
Right Middle Frontal Gyrus									54	20	38	3.5788				
Right Frontal Pole					12	50	46	4.11	38	50	16	4.434				
Right Frontal Orbital Cortex					42	22	-14	4.29	42	22	-14	2.7195				
Left Frontal Orbital Cortex					48	14	46	3.15								
Right Heschl's Gyrus	52	-20	10	6.62	48	-20	12	7.10								
Left Heschl's Gyrus	-46	-14	4	5.79	-42	-22	0	5.34								
Right Superior Temporal Gyrus	62	-34	18	6.151	62	-20	12	6.61								
Left Superior Temporal Gyrus	-40	-32	14	5.90	-54	-8	4	5.99	-52	10	-16	3.4486	-66	-32	18	4.9216
Left Temporal Pole													-48	10	-8	3.3058
Right Middle Temporal Gyrus					54	14	-16	3.15	62	-20	-14	3.90				
Left Middle Temporal Gyrus													-52	-56	8	2.361
Right Operculum	48	10	0	3.4476	40	-26	22	6.18	-54	-6	4	3.0684	58	-28	26	4.3112
Left Operculum					-40	-32	18	7.15					-40	-4	16	3.4623
Right Insula	38	-20	0	4.9054	38	-20	0	5.43								
Left Insula					-38	-4	-12	4.60					-34	-16	8	2.80
Left Supramarginal Gyrus					-64	-30	20	5.53	-64	-36	32	3.1245	-62	-52	18	3.2661
Posterior Cingulate									-2	-36	24	4.9117	0	-26	26	3.4423
Right Superior Parietal Lobule					18	-50	74	5.2794	18	-52	74	3.3595	20	-50	70	2.6534
Left Superior Parietal Lobule					-34	-46	64	4.0425								
Left Fusiform									-28	-74	-18	3.8136				
Right Caudate					14	-2	18	3.19	16	18	10	3.1537				
Left Caudate					-12	12	12	3.22	-18	26	4	2.6905				
Right Putamen					28	10	2	4.87	28	10	0	3.0591				
Left Putamen					-26	6	-6	3.97	-24	12	2	3.1668				
Right Pallidum									20	-8	0	3.00				
Right Thalamus - Ventral Nucleus					14	-16	12	3.78	-10	-12	4	2.3135				
Right Thalamus - Pulvinar					16	-26	2	3.64	14	-28	14	3.1345				
Left Hippocampus/Parahippocampal Gyrus									-28	-12	-22	3.8371				
Cerebellum					34	-78	-42	3.63	-42	-60	-46	4.2906	-10	-70	-38	3.466

Note: x, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; Z refers to the Z-score at those coordinates (local maxima or submaxima). Within-group analyses are cluster corrected for multiple comparisons, Z>2.3, p<.05; between-group and regression analyses are thresholded at Z>1.7, corrected. Between-group analyses are masked by regions of significant activation in either within-group analysis, at the liberal threshold of Z>1.7, uncorrected. Regression results show clusters with activation significantly correlated with SOR composite, within the ASD group, over and above age and anxiety symptoms.

Table 5. MNI coordinates for significant amygdala clusters in each condition compared to baseline.

		Right Amygdala						Left Amygdala					
		MNI Peak (mm)			Max	Size	p-value	MNI Peak (mm)			Max	Size	p-value
		x	y	z	*Z*	(voxels)		x	y	z	*Z*	(voxels)	
Auditory	TD							-20	-10	-10	2.78	17	p = 0.0024
	ASD	20	-8	-14	2.89	25	p = 0.0002						
	ASD>TD												
Tactile	TD	20	-4	-12	3.61	68	p < 0.0001	-22	-10	-12	2.68	59	p < 0.0001
	ASD	22	-2	-10	2.73	20	p = 0.0008	-22	0	-14	3.58	26	p = 0.0001
	ASD>TD												
	ASD Regress Tactile	22	-4	-14	2.96	92	p < 0.0001	-24	-4	-26	2.75	142	p < 0.0001
Joint	TD	20	-6	-12	2.24	23	p = 0.0003						
	ASD	22	-12	-10		199	p < 0.0001	-32	2	-18	2.90	145	p < 0.0001
	ASD>TD	32	-2	-18	2.30	10	p = 0.03	-28	-6	-24	2.62	109	p < 0.0001
	ASD Regress Both	20	-4	-14	2.16	29	p < 0.0001	-14	-10	-14	2.33	14	p = 0.0075

Note: x, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; Z refers to the Z-score at those coordinates (local maxima). Analyses are cluster-corrected using a small volume correction within the amygdala. Regression results show clusters with activation significantly correlated with SOR composite, within the ASD group, over and above age and anxiety symptoms.

Table 6. MNI coordinates for clusters significantly decreasing in activation intensity across the four tactile blocks.

	TD				ASD				TD>ASD			
	MNI Peak (mm)			Max	MNI Peak (mm)			Max	MNI Peak (mm)			Max
	x	y	z	*Z*	x	y	z	*Z*	x	y	z	*Z*
Right Postcentral Gyrus	52	-20	14	4.47	56	-14	36	3.72				
Left Postcentral Gyrus	-28	-40	56	3.31	-44	-28	44	3.48				
Right Precentral Gyrus	48	-2	52	3.63								
Left Precentral Gyrus	-10	-24	44	5.22					-22	-22	66	3.173
Right Paracentral Lobule	8	-8	54	3.435								
Right Frontal Pole	26	46	28	4.15					32	56	6	3.499
Left Frontal Pole	-24	48	32	2.99					-22	62	10	3.528
Right Superior Frontal Gyrus	20	20	60	3.55					20	36	50	3.666
Left Superior Frontal Gyrus	-2	54	30	3.92					0	22	58	3.669
Right Middle Frontal Gyrus									48	22	38	3.415
Left Middle Frontal Gyrus	-36	0	60	3.52					-30	18	46	4.337
Right Inferior Frontal Gyrus	50	26	2	3.18								
Right Orbital Frontal Cortex	28	8	-14	4.27					36	20	-8	3.287
Left Orbital Frontal Cortex	-36	34	-14	3.52								
Medial Prefrontal Cortex	-2	48	-8	3.26					-2	50	-8	3.156
Right Superior Temporal Gyrus	64	-32	12	4.826					50	-22	-4	3.085
Left Middle Temporal Gyrus	-52	-8	-18	4.354	-48	-60	8	3.932	-64	-30	-10	3.526
Right Temporal Pole	48	8	-16	3.912								
Left Temporal Pole	-44	16	-26	4.29								
Right Operculum	36	18	14	4.123	56	-30	20	4.161				
Left Operculum	-46	-36	18	5.04	-46	-30	22	3.90	-56	-34	18	2.335
Left Insula	-38	-10	0	4.88	-36	-4	-8	4.279	-34	14	-4	3.39
Left Supramarginal Gyrus	-60	-30	38	4.50								
Paracingulate Gyrus	-10	40	16	4.265					0	38	30	3.987
Anterior Cingulate	6	-6	34	4.361					10	2	42	2.622
Posterior Cingulate	-6	-46	30	4.291					-2	-26	40	4.338
Right Superior Parietal Lobule	28	-48	64	3.35	34	-42	70	2.91				
Left Superior Parietal Lobule	-14	-54	70	2.565								
Right Lateral Occipital Cortex	40	-64	16	4.271	40	-62	18	3.539	48	-54	50	4.371
Left Lateral Occipital Cortex	-42	-72	34	3.967					-50	-68	40	3.912
Lingual Gyrus	6	-86	-10	3.574								
Right Precuneus	4	-54	14	4.514					4	-54	12	3.959
Left Precuneus	-14	-68	28	3.915					-6	-64	28	4.669
Right Intracalcarine Cortex/V1	10	-74	12	2.814					10	-74	12	3.209
Left Fusiform	-36	-12	-32	4.416					-36	-12	-32	3.384
Left Caudate	-12	-2	12	4.20					-14	4	-2	2.814
Thalamus - Ventral Anterior Nucleus	8	-12	-2	4.90					8	-12	-2	4.168
Right Parahippocampal Gyrus/Hippoca	22	-8	-30	3.486					26	-40	0	2.761
Left Hippocampus									-22	-22	-16	2.705
Cerebellum	-24	-40	-28	4.409	-16	-64	-44	4.459				

Note: x, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; *Z* refers to the *Z*-score at those coordinates (local maxima or submaxima). Within-group analyses are cluster corrected for multiple comparisons, $Z>2.3$, $p<.05$; between-group and regression analyses are thresholded at $Z>1.7$, corrected.

Table 7. MNI coordinates for clusters significantly decreasing in activation intensity across the four joint (auditory and tactile) blocks.

	TD				ASD				TD>ASD			
	MNI Peak (mm)			Max	MNI Peak (mm)			Max	MNI Peak (mm)			Max
	x	y	z	*Z*	x	y	z	*Z*	x	y	z	*Z*
Right Postcentral Gyrus	18	-36	58	2.69	60	-14	22	4.24				
Left Postcentral Gyrus	-22	-44	62	3.82	-24	-40	56	3.94				
Right Precentral Gyrus	46	0	44	5.05	32	-24	60	3.96	46	0	44	3.90
Left Precentral Gyrus	-40	-14	50	4.28	-52	-2	24	4.04				
Right Frontal Pole	28	50	22	3.99					4	4	68	3.278
Right Superior Frontal Gyrus	6	4	60	4.24								
Left Superior Frontal Gyrus	-2	54	30	3.18								
Right Middle Frontal Gyrus	44	44	10	3.07					26	22	46	3.336
Right Inferior Frontal Gyrus	46	24	18	4.18								
Left Inferior Frontal Gyrus					-56	24	8	4.13				
Right Orbital Frontal Cortex	48	28	-6	3.63								
Left Orbital Frontal Cortex					-42	22	-14	4.37				
Right Superior Temporal Gyrus	64	-42	10	4.675	62	-34	14	4.259				
Left Superior Temporal Gyrus					-64	-38	14	4.187				
Left Planum Polare	-48	2	-4	4.357								
Right Middle Temporal Gyrus					50	-48	6	3.736				
Left Middle Temporal Gyrus					-62	-12	-22	3.374				
Right Operculum	64	-22	18	4.427	44	-34	26	3.567				
Left Operculum	-60	-20	14	4.088								
Right Insula	28	22	-2	3.443	38	-10	2	3.66				
Left Insula	-44	-34	14	4.909	-36	-2	-10	4.186				
Right Supramarginal Gyrus	62	-42	36	3.91	64	-42	36	3.10				
Left Supramarginal Gyrus	-54	-32	46	3.23	-56	-40	42	4.07				
Anterior Cingulate	6	14	32	4.575	2	-8	36	2.833	8	8	40	3.48
Posterior Cingulate	12	-22	42	4.253								
Right Superior Parietal Lobule	36	-46	60	3.49					38	-48	58	2.535
Left Superior Parietal Lobule					-44	-46	60	2.36				
Right Lateral Occipital Cortex	58	-64	14	4.28	56	-66	16	2.95	16	-78	54	2.839
Left Lateral Occipital Cortex	-46	-68	8	3.60	-48	-78	6	3.34	-12	-90	34	2.627
Lingual Gyrus	-10	-88	-2	2.963					8	-60	-2	2.977
Left Precuneus	-2	-48	50	4.093					-6	-74	48	3.088
Left Fusiform					-38	-22	-22	3.286				
Left Putamen	-26	-22	8	4.22								
Left Parahippocampal Gyrus					-24	-36	-16	3.661				
Cerebellum	-2	-56	-14	3.256								

Note: x, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; *Z* refers to the *Z*-score at those coordinates (local maxima or submaxima. Within-group analyses are cluster corrected for multiple comparisons, $Z>2.3$, $p<.05$; between-group and regression analyses are thresholded at $Z>1.7$, corrected.

Table 8. MNI coordinates for amygdala clusters decreasing in activation across the scan.

		Right Amygdala						Left Amygdala					
		MNI Peak (mm)			Max	Size	p-value	MNI Peak (mm)			Max	Size	p-value
		x	y	z	*Z*	(voxels)		x	y	z	*Z*	(voxels)	
Tactile	TD	16	-10	-14	4.12	398	p < 0.0001	-26	-4	-18	4.54	401	p < 0.0001
	ASD	26	-2	-24	2.59	158	p < 0.0001	-26	-4	-22	2.45	55	p < 0.0001
	TD>ASD	18	2	-18	2.29	13	p = 0.01	-20	-8	-20	2.62	181	p < 0.0001
Joint	TD	18	-4	-12	4.51	291	p < 0.0001	-16	-10	-12	3.18	191	p < 0.0001
	ASD	24	-2	-14	2.83	38	p < 0.0001	-28	-10	-12	3.85	174	p < 0.0001
	TD>ASD	14	-8	-14	2.69	34	p < 0.0001						

Note: x, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; Z refers to the Z-score at those coordinates (local maxima). Analyses are cluster-corrected using a small volume correction within the amygdala.

Table 9. Repeated-measures ANOVA predicting changes in amygdala and sensory cortex activation across the scan by diagnostic status.

		Right Amygdala		Somatosensory Cortex		Auditory Cortex	
		MS	F	MS	F	MS	F
Tactile	**Main effect of time**						
	Linear	3.35	19.97***	1.22	9.94**		
	Quadratic	--	--	--	--		
	Main effect of dx	0.34	1.98	0.27	0.94		
	TimeXdx						
	Linear	0.13	0.76	0.036	0.29		
	Quadratic	2.27	12.98**	0.61	5.55*		
Joint	**Main effect of time**						
	Linear	1.27	12.25**	0.79	5.05*	0.93	17.35***
	Quadratic	0.54	7.42*	--	--	0.24	8.52**
	Main effect of dx	0.23	0.34	0.69	1.47	0.02	0.16
	TimeXdx						
	Linear	0.05	0.48	0	0	0.05	0.88
	Quadratic	0.08	1.15	0.32	3.85+	--	--
	Cubic	0.41	10.58**	--	--	--	--

+p<.10; *p<.05; **p<.01; ***p<.001.

Note: Dx indicates a comparison of the two diagnostic groups, ASD vs. TD.

Table 10. Repeated-measures ANOVA predicting changes in amygdala and sensory cortex activation across the scan by SOR category.

		Right Amygdala		Somatosensory Cortex		Auditory Cortex	
		MS	F	MS	F	MS	F
Tactile	**Main effect of time**						
	Linear	2.87	19.65***	1.3	10.48**		
	Quadratic	--	--	--	--		
	Main effect of SOR	0.19	1.07	0.13	0.41		
	TimeXSOR						
	Linear	0.57	3.92*	0.07	0.56		
	Quadratic	1.37	8.84**	0.53	5.19		
Joint	**Main effect of time**						
	Linear	1	9.43**	0.78	5.07*	0.98	17.40***
	Quadratic	0.35	4.60*	--	--	0.16	5.35*
	Cubic	0.21	5.22*				
	Main effect of SOR	0.64	2.80^{+}	1.07	2.4	0.03	0.22
	TimeXSOR						
	Linear	0.6	0.56	0.05	0.29	0.03	0.61
	Quadratic	0.04	0.53	--	--	--	--
	Cubic	0.21	5.15*				

$^{+}$p<.10; *p<.05; **p<.01; ***p<.001.

Note: SOR indicates a comparison of the three SOR category groups: ASD-no SOR, ASD-SOR, and TD-no SOR.

Table 11. MNI coordinates for brain regions where activation is significantly correlated with amygdala seed activation.

	TD+				ASD+				TD>ASD +				ASD>TD +			
	MNI Peak (mm)			Max	MNI Peak (mm)			Max	MNI Peak (mm)			Max	MNI Peak (mm)			Max
	x	y	z	*Z*	x	y	z	*Z*	x	y	z	*Z*	x	y	z	*Z*
Right Postcentral Gyrus													30	-34	48	2.81
Left Middle Frontal Gyrus	-38	18	26	3.825					-42	16	30	3.70				
Right Inferior Frontal Gyrus																
Right Orbital Frontal Cortex	22	32	-12	3.988												
Left Frontal Orbital Cortex	-42	34	-6	3.70					-42	36	-6	3.08				
Medial Prefrontal Cortex																
Right Superior Temporal Gyrus					52	-4	-12	3.323								
Left Superior Temporal Gyrus	-44	-18	-4	4.835												
Right Posterior Cingulate													6	-32	34	3.518
Right Hippocampus					32	-30	-16	3.513								

Note: x, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; *Z* refers to the *Z*-score at those coordinates (local maxima or submaxima). Within-group and between-group analyses are cluster corrected for multiple comparisons, $Z>1.7$, $p<.05$. Within-group coordinates indicate positive connectivity; between-group coordinates indicate that one group has greater positive connectivity than the other.

Table 12. MNI coordinates for brain regions where activation is significantly correlated with pulvinar seed activation.

	TD+				ASD+				ASD>TD+			
	MNI Peak (mm)			Max	MNI Peak (mm)			Max	MNI Peak (mm)			Max
	x	y	z	*Z*	x	y	z	*Z*	x	y	z	*Z*
Right Postcentral Gyrus									16	-36	66	2.50
Left Postcentral Gyrus									-32	-32	56	2.64
Right Precentral Gyrus									28	-22	66	3.663
Right Middle Frontal Gyrus	38	8	46	3.11								
Right Inferior Frontal Gyrus	54	28	10	3.19								
Right Superior Temporal Gyrus	52	-8	-12	3.92								
Left Superior Temporal Gyrus	-54	-2	-6	3.97								
Right Middle Temporal Gyrus	62	-46	4	3.21	58	-46	0	3.37				
Left Superior Parietal Lobule									-16	-54	68	3.085
Occipital Pole/V1	-8	-104	12	4.50								
Right Hippocampus					32	-32	-16	3.99				

Note: x, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; Z refers to the Z-score at those coordinates (local maxima or submaxima). Within- and between-group analyses are cluster corrected for multiple comparisons, $Z>1.7$, $p<.05$. Within-group coordinates indicate positive connectivity; between-group coordinates indicate that one group has greater positive connectivity than the other.

Figure Legend

Figure 1. Experimental design.

Figure 2. Within-group results: Auditory condition. Within-group contrasts thresholded at $Z>2.3$, corrected ($p<.05$).

Figure 3. Within- and between-group results: Tactile condition. Within-group contrasts thresholded at $Z>2.3$, corrected ($p<.05$). Between-group contrasts thresholded at $Z>1.7$, corrected. Between-group maps are masked by regions active in either within-group condition at $Z>1.7$, uncorrected.

Figure 4. Within- and between-group results: Joint auditory + tactile condition. Within-group contrasts thresholded at $Z>2.3$, corrected ($p<.05$). Between-group contrasts thresholded at $Z>1.7$, corrected. Between-group maps are masked by regions active in either within-group condition at $Z>1.7$, uncorrected.

Figure 5. SOR severity as a predictor of BOLD response during the Joint condition. The horizontal axis displays the standardized residual SOR composite score after regressing out SCARED total scores and age. The vertical axis displays the parameter estimate extracted from areas of significant activation.

Figure 6. Within- and between-group results: Tactile habituation. Within-group contrasts thresholded at $Z>2.3$, corrected ($p<.05$). Between-group contrasts thresholded at $Z>1.7$, corrected.

Figure 7. Within- and between-group results: Joint auditory + tactile habituation. Within-group contrasts thresholded at $Z>2.3$, corrected ($p<.05$). Between-group contrasts thresholded at $Z>1.7$, corrected.

Figure 8. Amygdala and sensory cortex habituation by diagnostic group.

Figure 9. Amygdala and sensory cortex habituation by SOR category.

Figure 10. PPI results: Areas of significant connectivity with right amygdala seed region.

Figure 11. Amygdala-Orbital Frontal Cortex (OFC) connectivity by SOR category.

Figure 12. PPI results: Areas of significant connectivity with right pulvinar seed region.

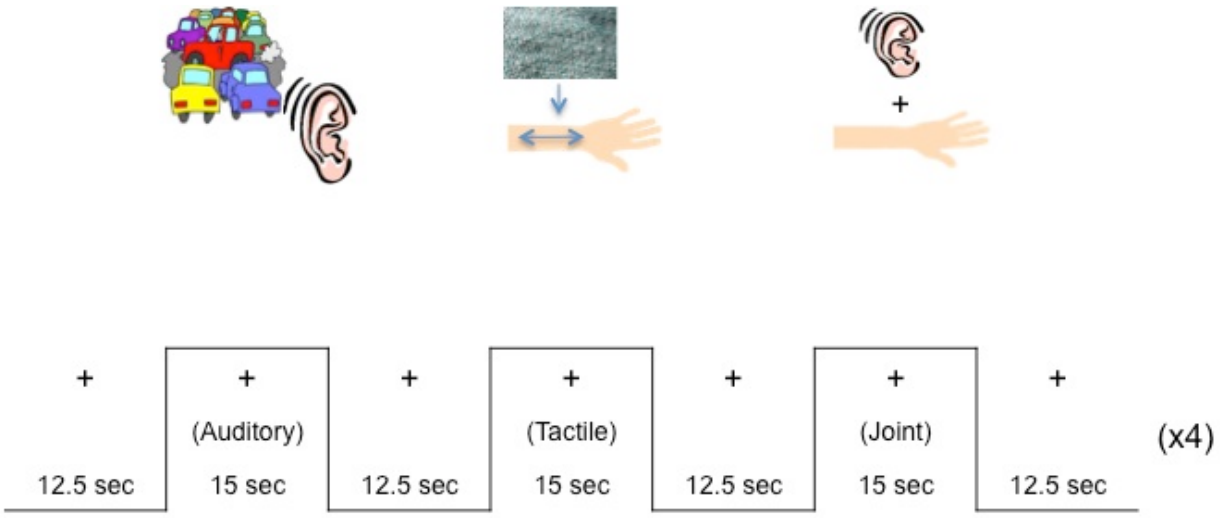


Figure 1. Experimental design.

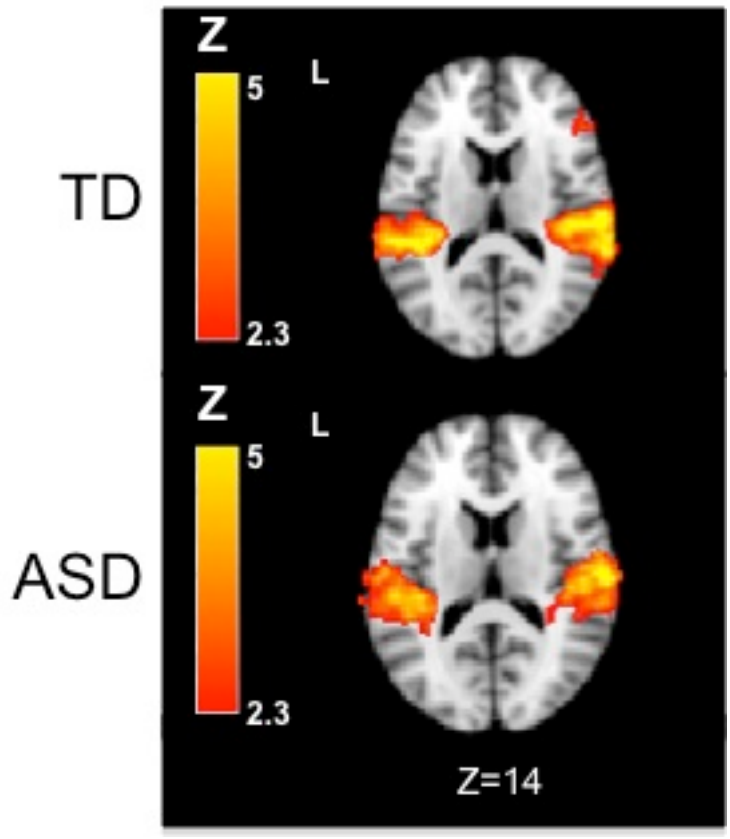


Figure 2. Within-group results: Auditory condition. Within-group contrasts thresholded at Z>2.3, corrected (p<.05).

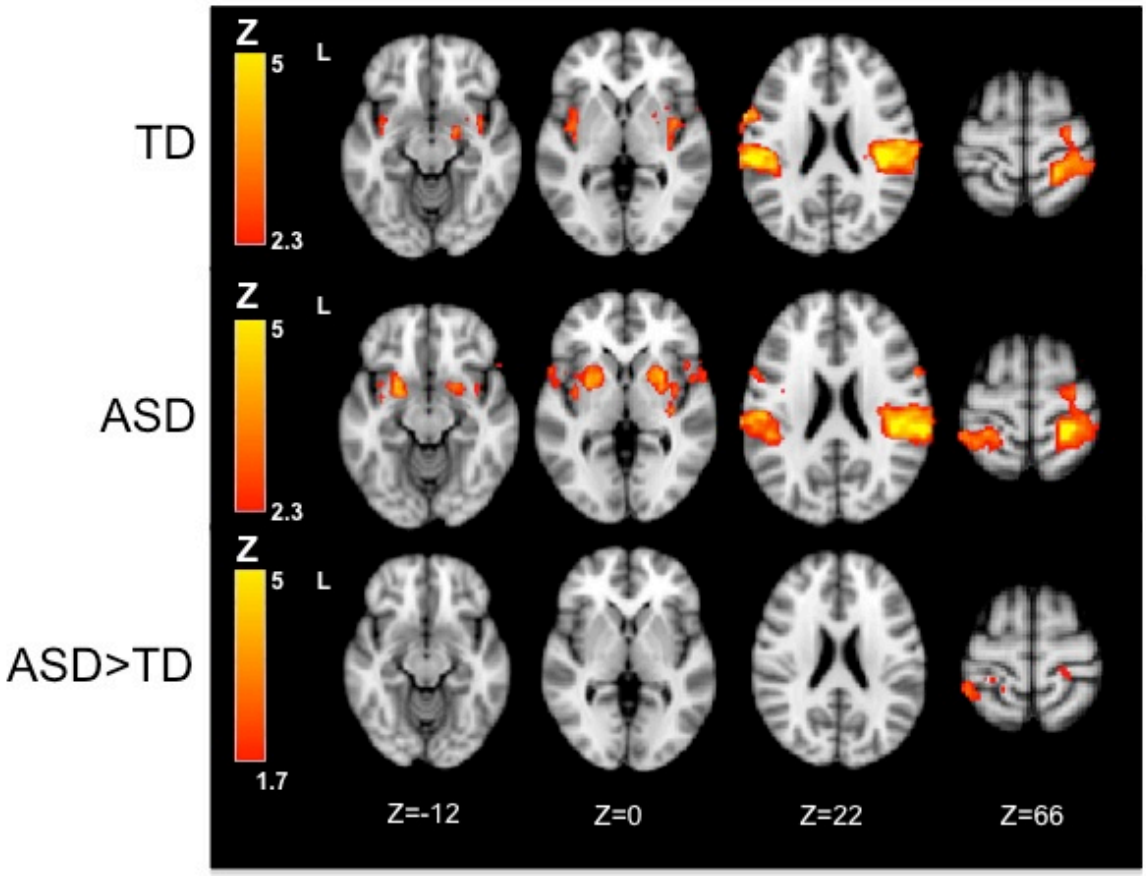


Figure 3. Within- and between-group results: Tactile condition. Within-group contrasts thresholded at Z>2.3, corrected (p<.05). Between-group contrasts thresholded at Z>1.7, corrected. Between-group maps are masked by regions active in either within-group condition at Z>1.7, uncorrected.

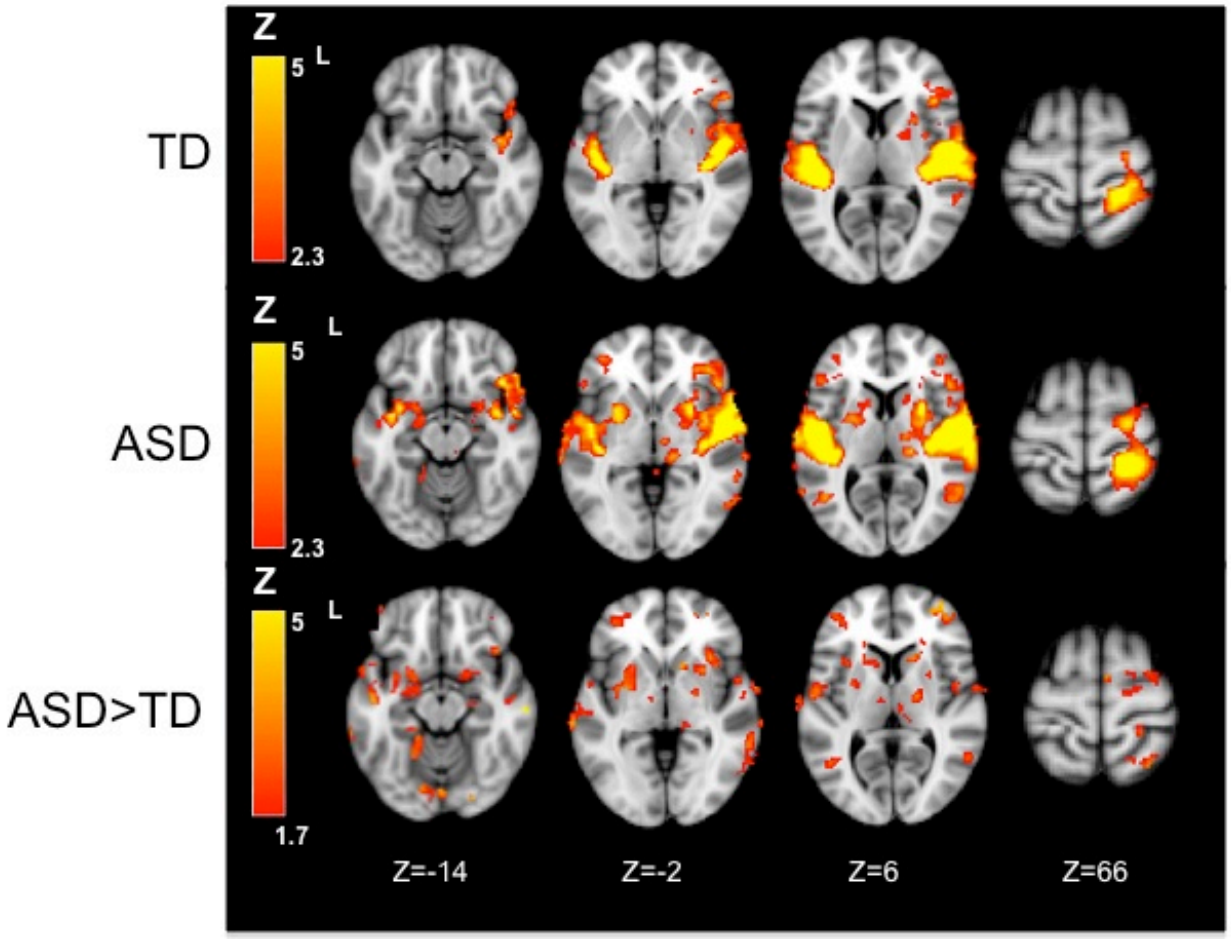
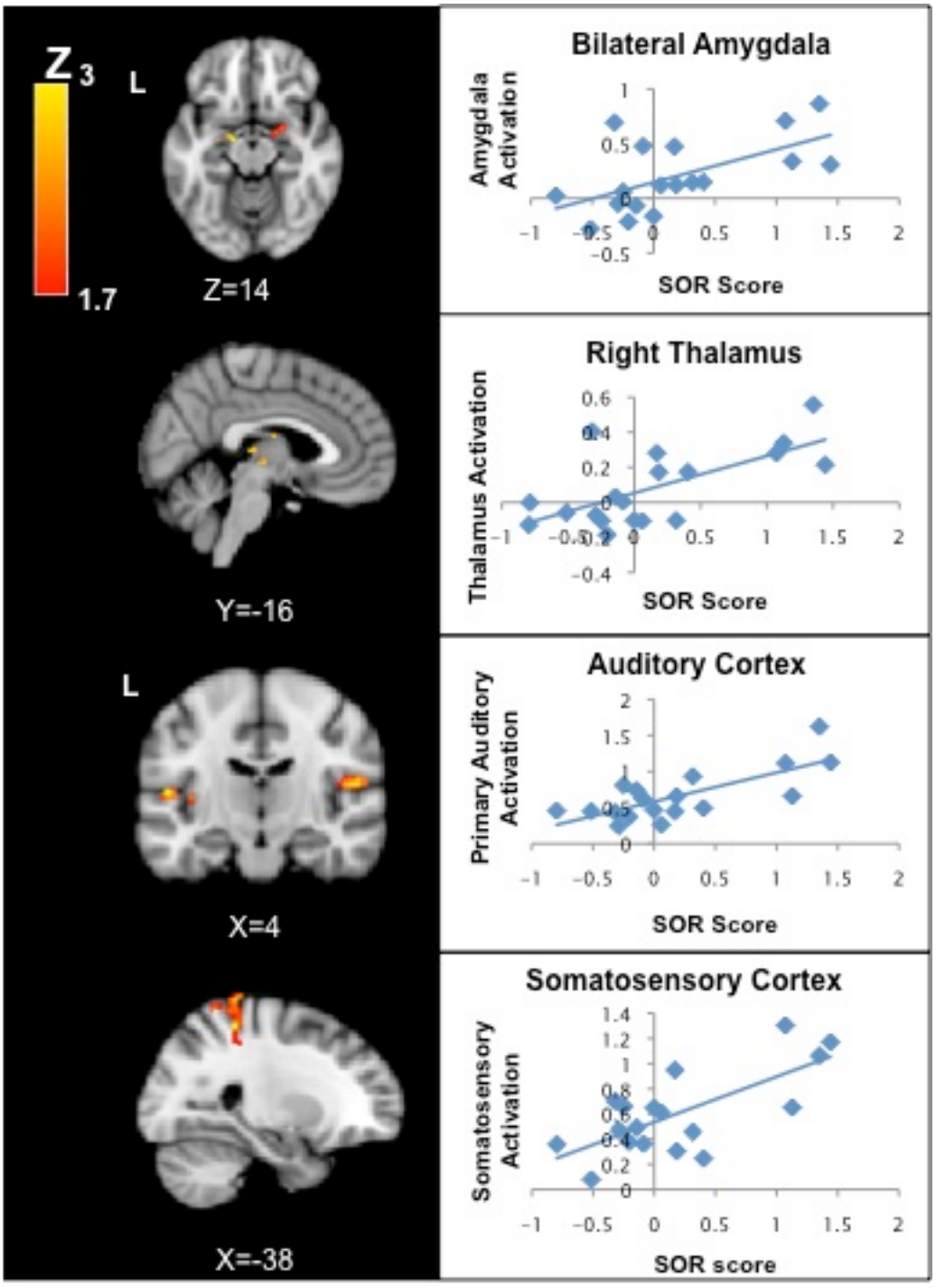


Figure 4. Within- and between-group results: Joint auditory + visual condition. Within-group contrasts thresholded at Z>2.3, corrected (p<.05). Between-group contrasts thresholded at Z>1.7, corrected. Between-group maps are masked by regions active in either within-group condition at Z>1.7, uncorrected.



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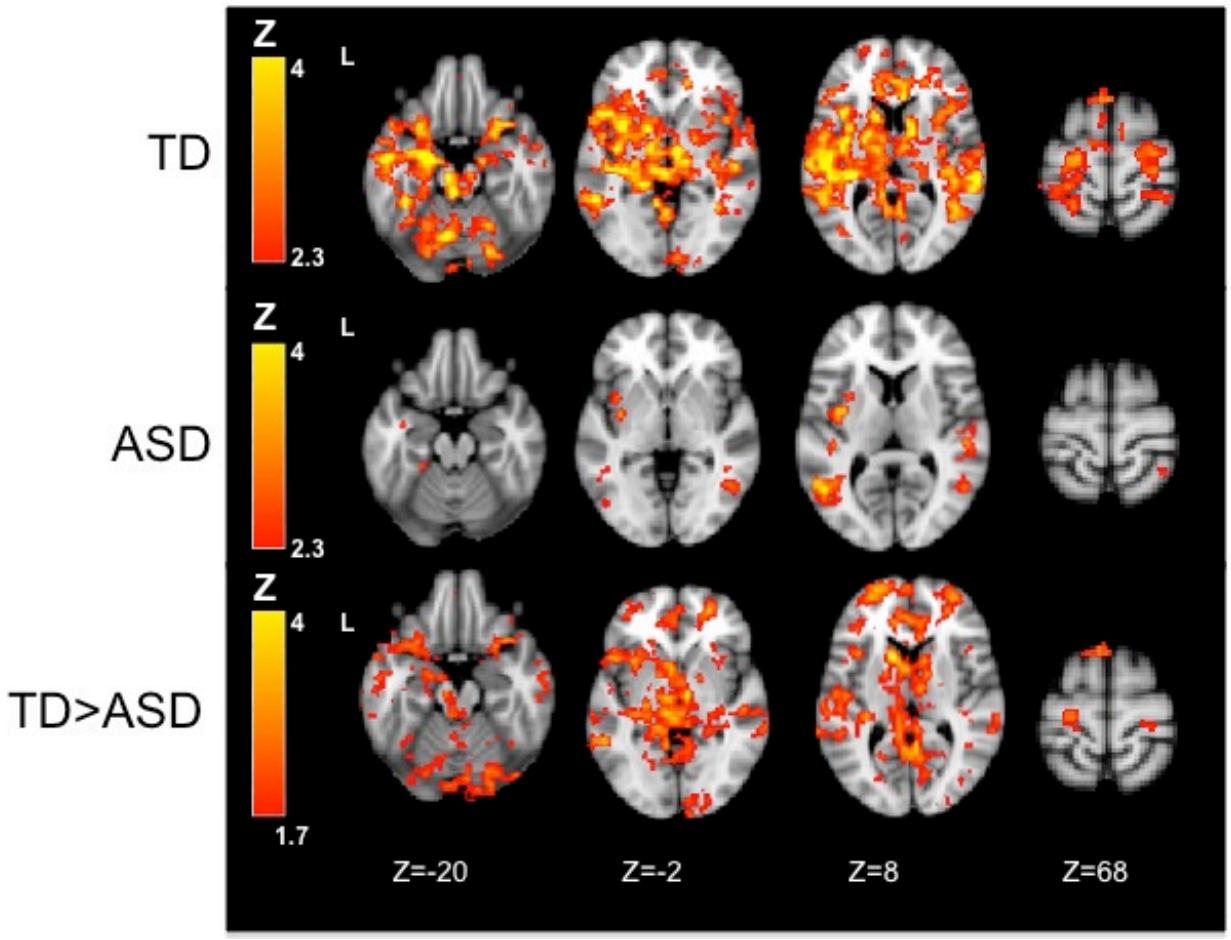

Figure 6. Within- and between-group results: Tactile habituation. Within-group contrasts thresholded at Z>2.3, corrected (p<.05). Between-group contrasts thresholded at Z>1.7, corrected.

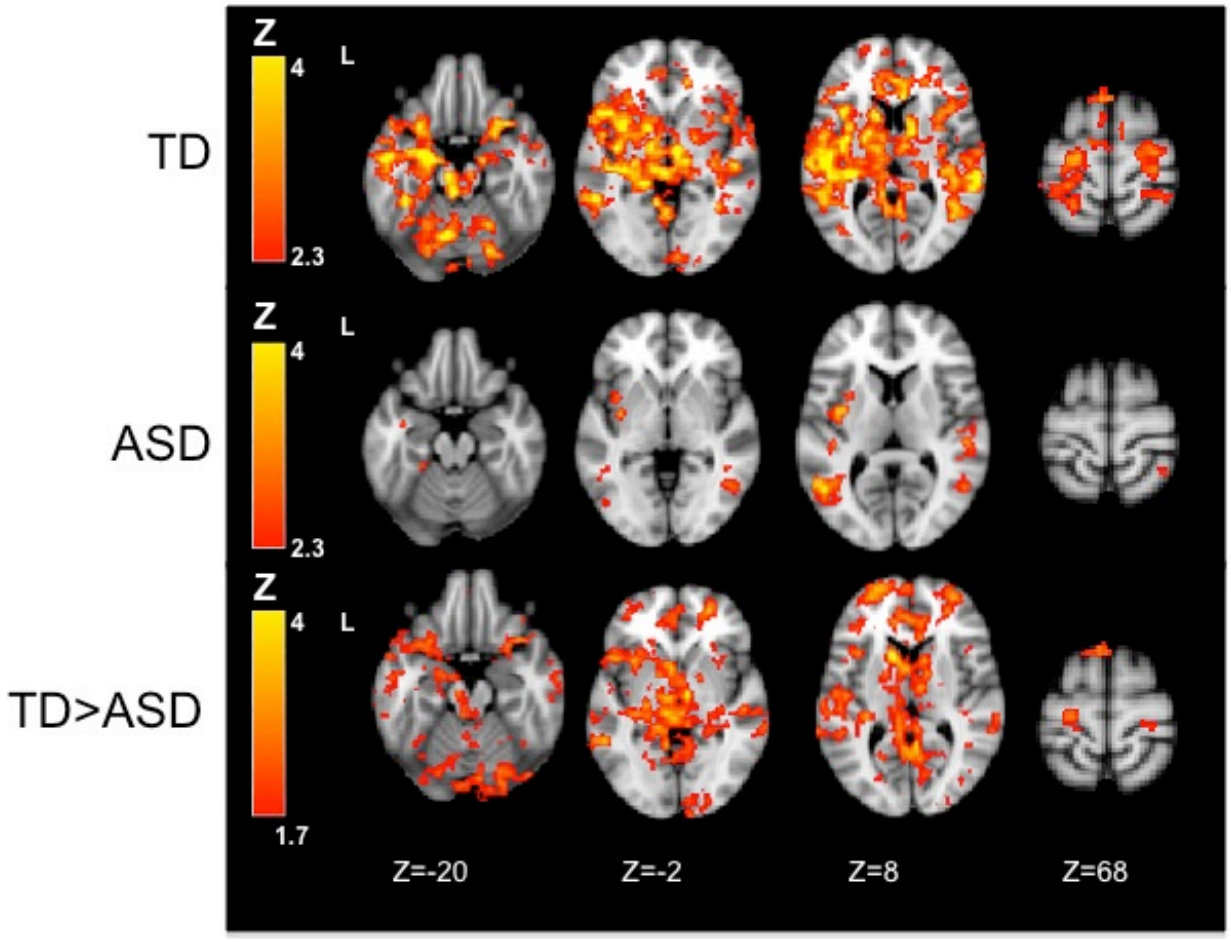

Figure 7. Within- and between-group results: Joint auditory + tactile habituation. Within-group contrasts thresholded at Z>2.3, corrected (p<.05). Between-group contrasts thresholded at Z>1.7, corrected.

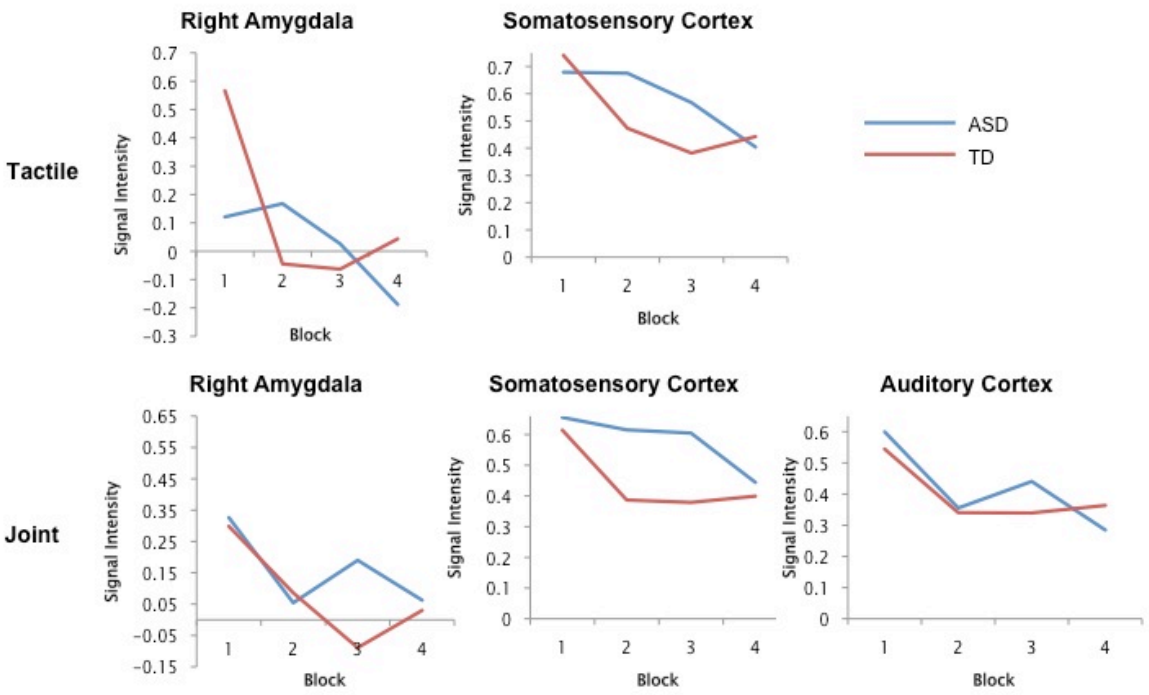

Figure 8. Amygdala and sensory cortex habituation by diagnostic group. Vertical axis represents ROI parameter estimates during the Tactile or Joint condition compared to baseline. Horizontal axis represents each block of the condition.

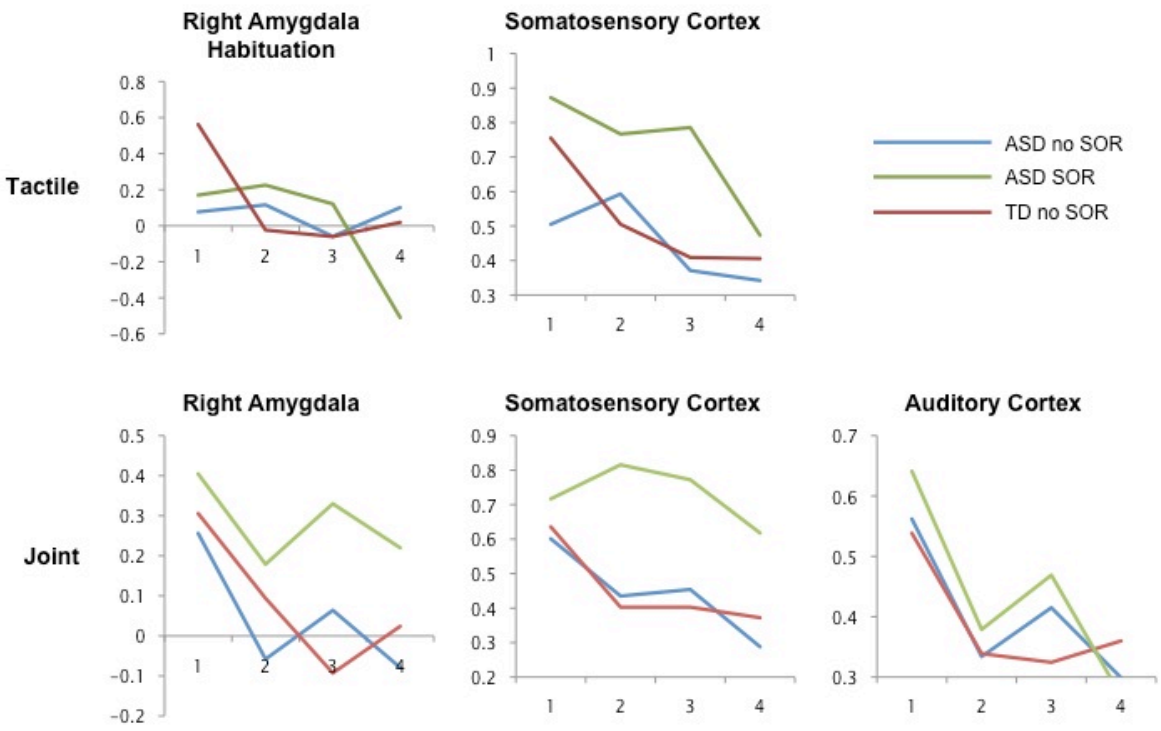

Figure 9. Amygdala and sensory cortex habituation by SOR category. Vertical axis represents ROI parameter estimates during the Tactile or Joint condition compared to baseline. Horizontal axis represents each block of the condition.

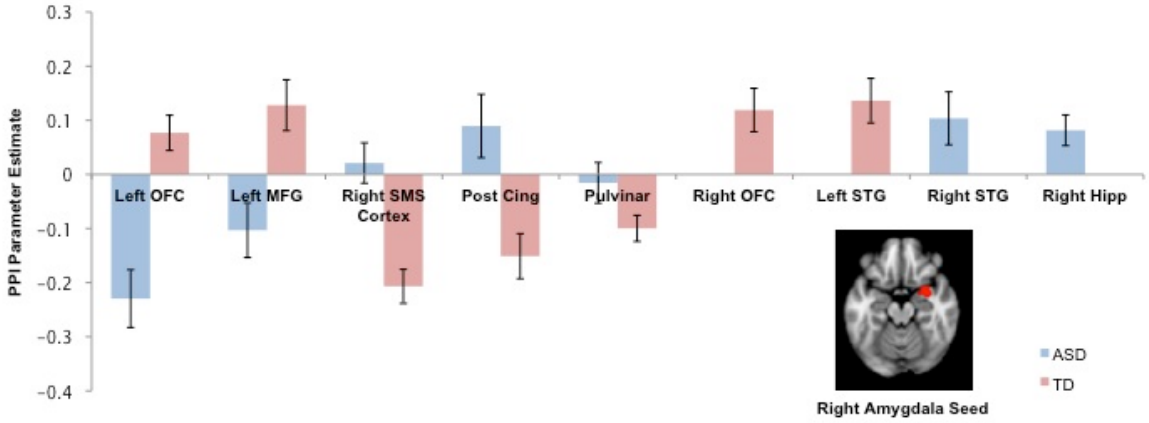

Figure 10. PPI results: Areas of significant functional connectivity with right amygdala seed region.

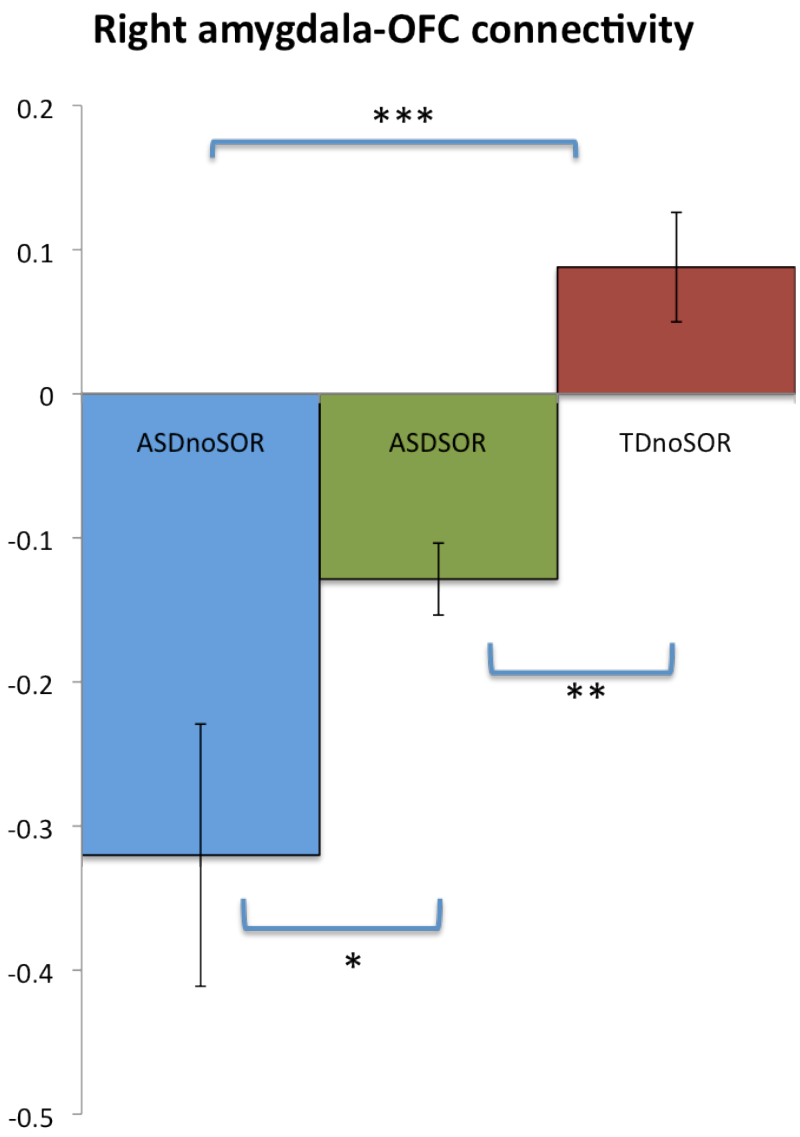

Figure 11. Amygdala-Orbital Frontal Cortex (OFC) connectivity by SOR category.

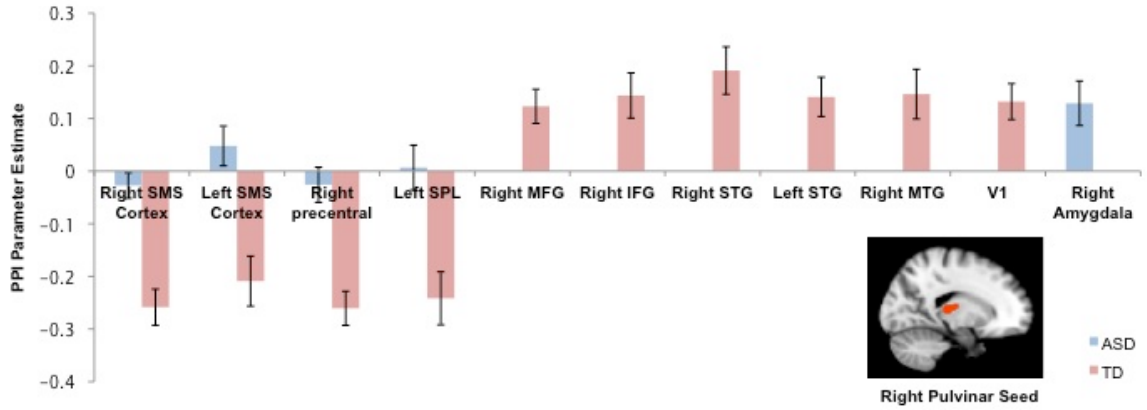

Figure 12. PPI results: Areas of significant connectivity with right pulvinar seed region.

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