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Shared and distinct biological mechanisms for anxiety and sensory over-responsivity in youth with autism versus anxiety disorders

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Abstract

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INFORMED CONSENT

Informed consent/assent was obtained from all individual participants included in the study, as well as caregiver consent.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Sensory over-responsivity (SOR) is a prevalent cross-diagnostic condition that is often associated with anxiety. The biological mechanisms underlying the co-occurrence of SOR and anxiety symptoms are not well understood, despite having important implications for targeted intervention. We therefore investigated the unique associations of SOR and anxiety symptoms with physiological and neural responses to sensory stimulation for youth with anxiety disorders (ANX), autism spectrum disorder (ASD), or typical development (TD). Age/IQ-matched youth aged 8–18 years (22 ANX; 30 ASD; 22 TD) experienced mildly aversive tactile and auditory stimuli during functional magnetic resonance imaging and then during skin conductance response (SCR) and heart rate (HR) measurements. Caregivers reported on participants' SOR and anxiety symptoms. ASD/ANX youth had elevated SOR and anxiety symptoms compared to TD. ASD/ANX youth showed similar, heightened brain responses to sensory stimulation compared to TD youth, but brain responses were more highly related to SOR symptoms in ASD youth and to anxiety symptoms in ANX youth. Across ASD/ANX youth, anxiety symptoms uniquely related to greater SCR whereas SOR uniquely related to greater HR responses to sensory stimulation. Behavioral and neurobiological over-responsivity to sensory stimulation was shared across diagnostic groups. However, findings support SOR and anxiety as distinct symptoms with unique biological mechanisms, and with different relationships to neural over-reactivity dependent on diagnostic group. Results indicate a need for targeted treatment approaches.

Keywords

anxiety; autism spectrum disorders; fMRI; physiology; sensory over-responsivity

1 | INTRODUCTION

Atypical sensory processing, particularly sensory over-responsivity (SOR), has been observed across several psychiatric and neurodevelopmental groups. SOR, characterized by heightened responses to aversive environmental stimuli, has received the most attention in autism spectrum disorders (ASD; Balasco et al., 2019; Carson et al., 2021) with prevalences between 56% and 70% (Ben-Sasson et al., 2008). However, SOR has also been observed in individuals with anxiety disorders (ANX; Conelea et al., 2014; Hofmann & Bitran, 2007), posttraumatic stress disorder (PTSD; Engel-Yeger et al., 2013), bipolar disorder/schizophrenia (Brown et al., 2002), and attention deficit hyperactivity disorder (ADHD; Lane, Reynolds, et al., 2010). In addition to being highly prevalent across clinical groups, SOR is particularly impairing, as it has been associated with deficits in social functioning (Kojovic et al., 2019; Kotsiris et al., 2020) and daily living skills, as well as increased maladaptive behaviors (Lane, Young, et al., 2010) and internalizing problems (Istvan et al., 2020; Kotsiris et al., 2020).

SOR has been consistently related to anxiety symptoms across multiple groups, including in neurotypical adults (Engel-Yeger & Dunn, 2011; Ludlow et al., 2015), ASD (Green et al., 2012; Lidstone et al., 2014; Top Jr. et al., 2019), and individuals with elevated anxiety (Conelea et al., 2014; Top Jr. et al., 2019), but the neurobiological mechanisms underlying the co-occurrence of SOR and anxiety are not well understood. Green and Ben-Sasson (2010) proposed three theories for this co-occurrence: (1) SOR occurs as a byproduct

of anxiety, as increased hypervigilance and attentional biases may cause individuals to attend to certain aspects of their sensory environment and interfere with their ability to regulate a negative response to it; (2) SOR leads to an intolerance of unpredictability in the environment, resulting in hyperarousal and avoidance behaviors that may precede and exacerbate anxiety symptoms; or (3) an underlying shared neurobiological factor, such as atypical amygdala development, independently confers risk for both symptoms (Green & Ben-Sasson, 2010).

To date, there is some evidence that SOR may precede and exacerbate anxiety in ASD. Green et al. (2012) found that SOR around the age of 2 years positively predicted an increase in anxiety symptoms over 1 year, but anxiety did not predict increases in SOR (Green et al., 2012). In autistic youth, SOR mediates the relationship between anxiety and insistence on sameness (Lidstone et al., 2014), which may manifest as anxiety or hypervigilance. Atypical sensory processing may also confer a risk for the development of anxiety symptoms in other clinical groups. Children who had elevated SOR in preschool have greater co-occurrence of anxiety disorders in grade school (Carpenter et al., 2019), and childhood symptoms of Sensory Processing Disorder have been associated with a greater likelihood of receiving an anxiety disorder diagnosis in adulthood in a transdiagnostic sample of adults (McMahon et al., 2019). Taken together, these studies provide preliminary evidence that, in ASD, and possibly in other diagnostic groups, SOR is a primary symptom preceding increases in anxiety severity. However, this relationship has not been well explored, and the directionality or developmental timing of these symptoms may differ across groups.

There is also evidence for common neurobiological factors underlying both anxiety and SOR. Studies examining the neurobiological basis of SOR have found that in ASD, SOR is uniquely (over and above anxiety) associated with an over-active neural response to aversive sensory stimulation in sensory- and salience-processing brain regions (Green et al., 2013, 2015). In particular, autistic individuals with high SOR show reduced amygdala habituation and top-down prefrontal inhibition of the amygdala during sensory processing compared to autistic individuals with low SOR (Green et al., 2015, 2019). Similarly, individuals with ANX show heightened amygdala reactivity and reduced prefrontal regulation of the amygdala during threat processing (Kim & Kim, 2021; Monk et al., 2008) and at rest (Hamm et al., 2014), with amygdala hyperreactivity being associated with greater anxiety symptom severity (Monk et al., 2008). Amygdala hyperactivity and dysregulation in prefrontal–amygdala circuitry may thus be a common neural mechanisms underlying both anxiety symptoms (Liu et al., 2020) and SOR.

Physiological hyperarousal may play a similar role in the underlying etiology of both anxiety and SOR symptoms. Autistic individuals show overall hyperarousal, including higher heart rate (HR) and skin conductance responses (SCR), at rest and during aversive sensory stimulation (Jung et al., 2021). Additionally, this overactive autonomic profile is associated with elevated ASD, SOR, and anxiety symptoms (Bellato et al., 2021; Jung et al., 2021). In particular, a recent study found that while autistic children showed increased SCR to sensory stimulation compared to typically developing (TD) children, SOR was specifically related to increased HR responses but not SCR (Jung et al., 2021). Thus, during

sensory stimulation, elevated SCR may be an indicator of general hyperarousal, whereas elevated HR may be more specific to SOR. ANX is similarly associated with dysregulated physiological arousal (greater HR response, [Thayer et al., 2000], lower HR variability [Makovac et al., 2016], and greater SCR [Abend et al., 2021]) compared to individuals without ANX during periods of worry/threat and at rest (Chalmers et al., 2014). As SOR and anxiety co-occur so frequently and share similar underlying neural mechanisms, it can be difficult to understand to what extent they are truly unique symptoms that warrant distinct interventions. This study aimed to explore (1) whether SOR and anxiety are overlapping versus distinct symptoms and (2) to what extent SOR and anxiety relate to unique biological mechanisms versus a common underlying trait such as hyperarousal. These questions have important implications for individualized intervention such as determining what the primary focus of treatment should be for a particular individual.

To address these questions, we used functional magnetic resonance imaging (fMRI) and psychophysiological assessments to examine the unique contributions of SOR and anxiety symptoms to brain and physiological responses to sensory stimulation in youth with ANX, ASD, or TD. We predicted that ASD and ANX youth would have greater SOR and anxiety symptom severity than TD peers, and that these symptoms would be correlated within the diagnostic groups. We further predicted that both clinical groups would show hyperactive brain responses to sensory stimulation, but that SOR would be more strongly and uniquely correlated with brain responses to sensory stimulation in the ASD group, given prior evidence of neural hyperresponsivity in this group above and beyond the effects of anxiety (Green et al., 2013, 2015, 2019). We further hypothesized that anxiety symptoms would be more strongly and uniquely correlated with brain responses in the ANX group relative to the ASD group, as anxiety symptoms have been shown to relate to heightened neural responses (Lau et al., 2012) and disruptions in neural connectivity in ANX youth (Kujawa et al., 2016). Finally, we expected that anxiety symptoms would predict greater SCR to sensory stimulation, whereas SOR symptoms would predict greater HR responses across both clinical groups.

2 | METHODS

2.1 | Participants

Participants were children and adolescents with ANX (Generalized, Separation, or Social Anxiety Disorder; $N = 22$), ASD ($N = 30$), or TD ($N = 22$), ages 8.06–18.0 (mean = 13.7 years). This wide age range was selected due to evidence that atypical sensory processing symptoms are often present early in life (Green et al., 2012) and persist into adulthood (DuBois et al., 2017). The final sample for the neuroimaging analysis included 19 ANX, 25 ASD, and 20 TD participants; SCR analyses included 20 ANX, 28 ASD, and 20 TD participants; HR analyses included 19 ANX, 28 ASD, and 21 TD participants. Given the focus of this study on examining ANX youth to extend our prior work on ASD and TD youth (previously reported in Green et al., 2015, 2019; Jung et al., 2021), our participant sample included all ANX participants recruited for this study as well as a matched sample of ASD and TD youth that was kept as large as possible while still being statistically equivalent to the ANX group on proportions of males versus females. Four participants in the ASD

group reported having a formal anxiety diagnosis, although many more had elevated anxiety symptoms. See supplement for further details on the original sample, group matching, and exclusions.

Participants had a full-scale IQ (FSIQ) within the normal range or higher (>75) on the Wechsler Abbreviated Scales of Intelligence 2nd Ed. (WASI-II) and groups were matched on age, handedness, sex, FSIQ, and motion during the MRI scan (Table 1). Participants were 62% White, 30% Latine, 15% Multiracial, 7% Asian, and 9% Black or African American. The ANX group had significantly more Caucasian participants than the ASD or TD groups (See Table 1 for additional details regarding the racial backgrounds represented in the study). ASD participants had a diagnosis of ASD, confirmed with the Autism Diagnostic Interview–Revised (ADI-R; and/or the Autism Diagnostic Observation Schedule) (ADOS-2; Lord et al., 2012) and clinical judgment. ANX participants had either a prior clinical ANX diagnosis or had a suspected diagnosis confirmed with the Anxiety Disorders Interview Schedule (ADIS-IV; Silverman et al., 2001) which was completed by a study clinical psychologist with the child's parent. All diagnoses were also confirmed by parent report above the clinical cut-off on the Screen for Child Anxiety and Related Disorders (SCARED; Birmaher et al., 1999). All study procedures were approved by the University of California Los Angeles Institutional Review Board, and informed assent and consent were obtained from the participants and their caregivers.

Participants with ANX were recruited from a university anxiety disorders clinic. All families who were screened for the clinic and who met study eligibility criteria during the study period were contacted and enrolled if interested and eligible. ASD participants were recruited through a university autism clinic from families who indicated that they were interested in participating in research, as well as from community autism programs and schools. TD participants were recruited through flyers in the community, schools, and community programs such as recreation centers. ASD and TD participants were drawn from a larger sample to create matched groups on age, sex, and IQ with the ANX participants. A subset of the ASD and TD participants were included in two prior studies Green et al. (2019) (neuroimaging data) and Jung et al. (2021) (physiological data). See supplemental methods for full details on the original samples and group matching.

2.1.1 | Sensory paradigm—Participants received comparable sensory stimulation paradigms in two contexts: first while undergoing fMRI and afterward, outside of the scanner along with physiological (HR and SCR) measurement. The sensory paradigms included six 15-s blocks of mildly aversive auditory (various frequencies of pulsing colored [e.g., white] noise), tactile (scratchy materials rubbed on the left inner forearm), and joint (simultaneous auditory and tactile) stimulation (Green et al., 2019; Jung et al., 2021). Participants focused on a central fixation cross during inter-trial intervals (ITIs), with 12.5-s fixations before and between blocks during the fMRI scan and 9-s fixations during the psychophysiological assessment. Psychophysiological measures were also collected during an initial 2-min baseline fixation period while the participant sat quietly.

2.2 | Physiological measurements

Skin conductance and HR were acquired continually using BIOPAC MP150 and Acqknowledge 4.2 (BIOPAC Systems, Inc.) throughout the physiological part of the experiment while the subject rested in a sitting position. Two Lead110A leads and two EL507 11 mm Ag/AgCl electrodes were attached to the participant's distal phalanx of the index and the middle fingers of the right hand to record skin conductance, and two electrodes (one on the upper right chest and one between the left hip bone and bottom ribcage) was used to collect HR. Mean HR and SCL were calculated for the experimental baseline phase and across each stimulus trial. For the HR response analyses, average HR was calculated for all stimulus blocks, controlling for baseline HR. Skin conductance response (SCR) for each trial was calculated as the maximum value 1–6 s after stimulus onset minus the mean value during the 2 s prior to stimulus onset. See the supplement for additional details on SCR and HR measurements and exclusion criteria. Age was negatively related to skin conductance levels (SCL; $r = -.40$, $p = .03$) and had a trending negative relationship with SOR ($r = -.33$, $p = .09$) and anxiety ($r = -.37$, $p = .05$) in the ASD group. Additionally, in the ASD and ANX groups, greater FSIQ was significantly related to lower baseline HR ($r = -.34$, $p = .02$) and had a trending negative relationship with anxiety ($r = -.25$, $p = .09$). Therefore, both age and FSIQ were tested as covariates in all repeated-measures ANOVAs and included where significant at $p < .10$.

The IBM Statistical Package for the Social Sciences (SPSS) Version 27 was used for all statistical analyses using physiological and behavioral data. Repeated measure ANOVA models were used to examine the unique contributions of SOR and anxiety symptoms on physiological arousal (HR and SCR) during sensory processing. This method considers the covariance of repeated measures within subject across trials, adjusting the degrees of freedom as well as for multiple comparisons (Gelman & Hill, 2006) and is consistent with our prior work (Jung et al., 2021).

2.2.1 | NeuroMRI data—2.4.1 |Data Acquisition Scans were acquired on a Siemens Prisma 3-T MRI scanner. Each functional run involved the acquisition of 706 multiband echo planar imaging volumes (gradient-echo, TR = 720 ms, TE = 37 ms, flip angle = 52°, 104 × 90 matrix, 208 mm FOV, 72 slices, voxel size = 2 × 2 × 2 mm). The Siemens "prescan normalize" option was used after signal inhomogeneities were apparent in the first few scans, and there were no significant between-group differences in the percentage of participants who had the pre-scan normalization. Earplugs and noise-canceling headphones were used to reduce scanner noise (see Supplement for additional stimuli and acquisition details).

2.2.2 | fMRI data analysis—Analyses were performed using the FMRIB Software Library (FSL), version 6.0.10 (www.fmrib.ox.ac.uk/fsl). Preprocessing included motion correction to the mean image, spatial smoothing (Gaussian kernel full width at half maximum = 5 mm), and high-pass temporal filtering ($t > .01$ Hz). Functional data were linearly registered to a common stereotaxic space by registering to the MNI152 T1 2 mm template (12 degrees of freedom). FSL's fMRI Expert Analysis Tool (FEAT) was

used for statistical analyses, which were thresholded at $Z > 2.3$ and corrected for multiple comparisons at the cluster level ($p < .05$).

We first examined diagnostic differences in neural activation during aversive sensory exposure before entering SOR and anxiety symptoms as simultaneous bottom-up regressors in a whole-brain analysis to explore the unique contributions of each symptom to neural activation. This process allows for the examination of each symptom's specific contribution to neural activation while adjusting for the effects of covariates (Friston et al., 1995). These regression analyses were completed just for the ANX and ASD groups, as the TD group had very low levels of both SOR and anxiety. Age and FSIQ were covaried in analyses examining group differences to be consistent with psychophysiological analyses. See Supplement for further details on motion correction and fMRI analysis.

2.3 | Measures

The following questionnaires were completed by participants' parents:

2.3.1 | Sensory Over-Responsivity Inventory (SensOR Inventory)—

The SensOR Inventory (Schoen, Miller, & Green, 2008) is a 42-item checklist of potentially aversive sensations, with high internal consistency and discriminant validity (Schoen et al., 2016; Schoen, Miller, & Green, 2008). Each participant's SOR severity was determined by taking a count of the number of tactile and auditory items the parent endorsed as being bothersome for their child.

2.3.2 | Screen for Child Anxiety Related Disorders (SCARED)—

The SCARED (Birmaher et al., 1999) consists of 41 items measuring anxiety symptoms and has been found to have moderate to high internal consistency and test–retest reliability (Birmaher et al., 1999; Su et al., 2008). The total score was used to examine anxiety symptom severity for each participant.

3 | RESULTS

3.1 | Behavioral results

A one-way ANOVA showed significant diagnostic group differences in SOR ($F(2,73) = 12.2$, $p < .001$) and anxiety ($F(2,72) = 23.5$, $p < .001$) symptom severity. A Tukey HSD post-hoc analysis indicated that both the ANX and ASD groups had significantly greater SOR symptoms compared to the TD group, but were not significantly different from each other (Table 1). The ANX group had significantly greater anxiety symptoms compared to both the TD and ASD groups, while the ASD group only showed elevated anxiety symptoms relative to the TD group. A one-tailed Pearson correlation showed a significant positive relationship between SOR and anxiety symptoms in the ANX ($r = .57$, $p = .003$) and ASD ($r = .31$, $p = .046$) groups (Figure S1). Fisher's z-test of significance of correlation coefficients found no significant difference between these correlations ($z = 1.09$, $p = .27$) (Diedenhofen & Musch, 2015).

3.2 | Physiological results

3.2.1 | Baseline physiological arousal—One-way ANOVAs were conducted to compare the diagnostic groups on mean SCL and HR during the initial 2-min baseline fixation period. While there were no significant diagnostic-group differences ($F(2,65) = 1.66$, $p = .20$, $\eta^2 = .05$) in baseline SCL (Figure S2), there was a significant diagnostic group difference ($F(2,65) = 3.49$, $p = .04$, $\eta^2 = .10$) in baseline HR (Figure S3). A post-hoc Tukey HSD test indicated that the ASD group ($M = 83.81$, $SD = 13.07$) had significantly higher baseline HR than the TD group ($M = 74.17$, $SD = 13.22$; $t(47) = 2.55$, $p = .01$, $d = .74$), and there was a trend-level difference between the ANX ($M = 81.54$, $SD = 12.35$) and TD ($t(38) = 1.82$, $p = .08$, $d = .58$) groups. However, there was no significant difference between the ASD and ANX groups ($t(45) = -.60$, $p = .55$, $d = -.18$). Baseline HR was covaried in subsequent HR analyses to determine the differences in HR responses to aversive sensory stimulation over and above individual differences in baseline HR. SOR and anxiety were not significantly related to baseline HR or SCL in either the ASD (SOR & HR: $r = .05$, $p = .80$; SOR & SCL: $r = -.01$, $p = .95$; Anxiety & HR: $r = .20$, $p = .30$; Anxiety & SCL: $r = -.12$, $p = .56$) or ANX groups (SOR & HR: $r = .29$, $p = .24$; SOR & SCL: $r = -.21$, $p = .37$; Anxiety & HR: $r = .29$, $p = .22$; Anxiety & SCL: $r = -.30$, $p = .20$) using two-tailed tests. 3.2.2 | Skin conductance responses

Diagnostic group differences: A repeated-measures ANOVA showed significant linear ($F(1,65) = 24.18$, $p < .001$, $\eta_p^2 = .27$) and quadratic ($F(1,65) = 41.95$, $p < .001$, $\eta_p^2 = .39$) main effects of trials, indicating that for all groups, SCR to aversive sensory stimulation decreased over time and that the rate of change slowed over time. There was a trend-level main effect of diagnostic group ($F(2,65) = 2.65$, $p = .08$, $\eta_p^2 = .08$). A post-hoc analysis revealed the ANX group had higher mean SCR across all trials compared to the TD group ($F(1,38) = 5.08$, $p = .03$, $\eta_p^2 = .12$) (Figure 1a and Table S2). There were no other significant between-group differences in SCR.

Unique associations between SOR, anxiety symptoms, and SCR: An additional repeated-measures ANOVA was conducted to test the unique associations of anxiety and SOR symptoms with SCR within the ASD and ANX groups. There was a significant trial*anxiety interaction ($F(1,44) = 5.25$, $p = .03$, $\eta_p^2 = .11$) and a main effect of anxiety ($F(1,44) = 5.62$, $p = .02$, $\eta_p^2 = .11$), but no significant effect of SOR and no significant interactions with the diagnostic group. Thus, across both ANX and ASD groups, higher anxiety symptoms predicted higher SCR as well as faster habituation to aversive sensory stimulation over and above SOR (Figure 1b and Table S2).

3.2.3 | Heart rate responses

Diagnostic group differences: A repeated-measures ANOVA predicting HR responses showed that, after controlling for baseline HR, there was no significant main effect of diagnostic group, nor was there a significant diagnostic group*trial interaction, indicating that all three groups had comparable HR responses to aversive sensory stimulation (Figure 1c and Table S2). There was a significant main effect of baseline HR ($F(1,63) = 466.81$, $p < .001$, $\eta_p^2 = .88$) indicating that participants with higher baseline HR also showed higher HR

during sensory stimulation. Results were similar when age was not included as a covariate (see Table S3).

Unique associations between SOR, anxiety symptoms, and HR: SOR and anxiety symptoms were included in a subsequent repeated-measures ANOVA to examine their unique associations with HR responses within the ASD and ANX groups, over and above the effect of baseline HR. There was no main effect of SOR, but there was a significant stimulus*trial*SOR interaction ($F(1,42) = 10.56$, $p < .01$, $\eta_p^2 = .20$). A post-hoc analysis indicated that this three-way interaction was accounted for by a trial*SOR interaction that was larger for the Joint ($F(1,41) = 3.22$, $p = .08$, $\eta_p^2 = .07$) and Tactile ($F(1,41) = 4.45$, $p = .04$, $\eta_p^2 = 0.98$) stimuli than for the Auditory stimulus (Table S2). Thus, SOR predicted change over time in HR responses to Joint and Tactile trials over and above anxiety symptoms, whereby the participants with the highest levels of SOR displayed the steepest increases in HR responses across the stimulus trials (Figure 1d and Table S2).

3.3 | fMRI results

3.3.1 | Diagnostic group differences in neural responses to sensory stimulation

Within-group results: Compared to rest, all groups showed increased brain responses to aversive auditory and tactile stimulation in relevant sensory cortical regions, as well as the bilateral cerebellum, insula, and right temporal pole. Youth with ASD or ANX additionally showed activation in the left precentral gyrus, prefrontal regions (primarily right inferior frontal gyrus, medial prefrontal cortex (mPFC) and orbital frontal cortex (OFC)), and subcortical regions, including the amygdala, basal ganglia, hippocampus, and thalamus. The ASD group also showed activation in occipital and sensory association regions (Table S4 and Figure S5). Results without covariates are presented in the supplement.

Between-group comparisons: Compared to TD youth, sensory-evoked neural activation was significantly greater in the ANX and ASD groups in the operculum, insula, postcentral gyrus, and OFC. The ASD group specifically showed significantly greater activation compared to the TD group in widespread regions, including visual and sensorimotor cortices, the subcallosal cortex, and precuneus (driven by reduced deactivation in the ASD group compared to TD), insula and frontal regions (driven by increased activation in the ASD group relative to TD). Other regions of group differences, including the temporal pole, mPFC, and subcortical regions (amygdala and hippocampus), were driven by both increased activation in the ASD group and deactivation in the TD group. ASD youth also showed greater activity in the cerebellum compared to ANX or TD (Table S4 and Figure S5).

3.3.2 | Unique associations of SOR and anxiety symptoms with neural responses to aversive sensory stimulation—

We next examined regions where neural reactivity during sensory processing was uniquely related to symptoms of SOR and anxiety for ASD and ANX youth. Within both the ASD and ANX groups, SOR was uniquely related to increased activity in frontal regions, including the left frontal pole, superior frontal gyrus, paracingulate, and anterior cingulate cortex (ACC). Additionally, the ASD group showed widespread associations between SOR and brain responses to sensory stimulation, including

positive associations between SOR and activity across multiple frontal regions, occipital cortex, temporal cortex, right cerebellum, and bilateral precuneus, as well as negative associations with right inferior frontal gyrus, operculum, precentral gyrus, insula, and additional temporal regions (Figure 2 and Table 2). Between-group comparisons indicated that the relationship between SOR and neural responses was significantly stronger for the ASD group than for the ANX group, particularly in the posterior cingulate cortex (PCC) and precuneus. There were no regions where the relationship between SOR and neural reactivity was greater for ANX youth compared to ASD youth. (Figure 2 and Table 2).

Anxiety symptoms were uniquely related to neural activity in several regions for ANX and ASD youth during sensory exposure. Both groups showed a relationship between increased anxiety symptoms and greater activity in the right hippocampus, left lingual gyrus, and left cerebellum. Within the ANX group only, anxiety symptoms were also related to increased activity in multiple frontal regions (frontal pole, mPFC, and PCC), precuneus, and temporal fusiform cortex, as well as several subcortical regions (left hippocampus, parahippocampus, thalamus, right amygdala, nucleus accumbens, and putamen). Within the ASD group only, there was a positive relationship between anxiety symptoms and activity in the frontal operculum, right precentral gyrus, insula, left occipital fusiform, and multiple temporal regions. There were no regions that showed a negative relationship with anxiety symptoms for either diagnostic group.

Between-group comparisons revealed that compared to youth with ASD, youth with ANX showed a significantly stronger association between anxiety symptom severity and increased activity in multiple frontal regions, thalamus, precuneus, and intracalcarine/supracalcarine cortices (Figure 2 and Table 3). The results of these analyses without covariates are presented in the supplement (Figure S7).

4 | DISCUSSION

In this study, we examined differences in symptom profiles of SOR and anxiety for youth with ASD or ANX and their unique associations with neurobiological responses to aversive sensory stimulation. As expected, both ASD and ANX youth were reported to have more severe sensory and anxiety symptoms than peers without a diagnosis, and these symptoms were correlated within each group. Overall, ASD and ANX youth showed more similarities than differences in biological responses to sensory stimulation; both diagnostic groups showed hyperactive neural responses, as well as similar relationships between anxiety/SOR symptoms and peripheral measures of arousal. However, fMRI measures revealed distinct associations with symptom profiles between diagnostic groups, with SOR and anxiety symptoms showing unique relationships with brain responses in the ASD compared to ANX groups.

Consistent with prior research (Abend et al., 2021; Licht et al., 2009), both ASD and ANX youth showed elevated resting HR compared to TD youth. Furthermore, while there were no diagnostic group differences in HR responses to mildly aversive auditory and tactile sensory stimulation, across ANX and ASD groups, elevated SOR was uniquely related to increases in HR responses, over and above the effect of anxiety symptoms. SCR showed

a slightly different pattern: though there were no group differences in baseline SCL, ANX youth exhibited heightened SCR across the stimulus trials compared to TD youth. Elevated anxiety also predicted greater SCR during sensory stimulation in both ANX and ASD youth, controlling for SOR. These results are consistent with the ANX group showing the highest levels of anxiety symptoms and align with previous literature (Goodwin et al., 2006; Schoen, Miller, Brett-Green, et al., 2008). In contrast to HR, which may be better suited for tracking differences in SOR, SCR appeared to be related specifically to anxiety-related hyperarousal. It is also possible that the different relationships between SOR/anxiety and psychophysiological arousal may in part reflect differences in measurement. HR responses were an average response across the 15 s of a trial, while SCR is measured within the first 6 s of stimulation. It is possible that SOR reactions to sensory stimuli relate to heightened arousal over time, which is consistent with prior findings of reduced habituation to sensory stimuli in individuals with SOR (Green et al., 2015, 2019). In contrast, skin conductance response could be capturing an immediate startle response or more rapid initial increases in arousal.

Functional neuroimaging during a comparable sensory stimulation paradigm also demonstrated commonalities in sensory responses across both diagnostic groups. Overall, both the ANX and ASD groups showed hyperreactivity in a number of brain regions compared to the TD group when exposed to mildly aversive auditory and tactile stimuli. Though the ASD group showed more widespread between-group differences with TD youth compared to the ANX group, including in sensory, limbic, and frontal regions (in line with prior studies (Green et al., 2013, 2015, 2019)), there were few significant diagnostic differences in neural response during the task between the ASD and ANX groups. This is consistent with the high SOR and anxiety symptoms seen in both of these groups compared to the TD group, and suggests that neural hyperarousal to sensory stimulation may be common across ASD and ANX. Hyperresponsivity in sensory and limbic regions in youth with ASD during sensory processing has been replicated a number of times and been shown to relate to symptoms of SOR (Green et al., 2013, 2015, 2019). Youth with ASD and high SOR have also been shown to have reduced habituation in these brain regions, suggesting that SOR may be related to atypical, continued processing of, and increased affective responses to, extraneous sensory stimuli (see Green et al., 2015, 2019 for a full discussion of these mechanisms). During aversive sensory stimulation, youth with ASD and ANX also engage the OFC, a cognitive control area of the brain, to a greater extent than their TD peers; This may reflect greater effort to control SOR symptoms through increased downregulation of the amygdala, as seen in autistic youth with low SOR (Green et al., 2015, 2019).

Notably, one region of significant difference between the two diagnostic groups was in the cerebellum: compared to the ANX and TD groups, youth with ASD showed greater activation of cerebellar regions during sensory processing. The cerebellum is thought to operate under a forward internal model that coordinates our movement via the processing of prediction errors in our motor and sensory environments (Popa & Ebner, 2019). Disruptions in these internal predictive models of the environment may underlie some of the core symptoms of ASD, including SOR (van Laarhoven et al., 2020), and it is possible that SOR in ASD is due in part to an inability to predict changes in the sensory environment via

hyperresponsive error signals in the cerebellum. These prediction errors may be unique to SOR in ASD compared to other populations, but follow-up studies specifically examining the cerebellum and its role in predicting sensory inputs across diagnostic groups are necessary to further explore this hypothesis.

While the ASD and ANX groups both showed hyperactive neural responses to sensory information, SOR and anxiety symptoms were uniquely associated with brain responses within each group. SOR was significantly more correlated with neural response for the ASD group, while anxiety symptoms were more highly associated with neural response for the ANX group. Compared to youth with ANX, youth with ASD showed a significantly stronger relationship between SOR severity and increased activation in the PCC/precuneus, over and above anxiety. Interestingly, the opposite relationship was observed in the ANX group, where PCC/precuneus activation was associated with heightened anxiety symptoms over and above SOR. Hyperactivity of the precuneus during stimulus presentation of personally salient traumatic stimuli has been observed in patients with PTSD compared to control participants, and this is thought to underlie the self-referential retrieval of traumatic memories (Sartory et al., 2013). Identifying symptoms that are associated with activity in regions known to relate to trauma may influence treatment approaches and emphasizes the profound impact of SOR and anxiety in an individual's daily life.

Additionally, the ANX group showed a significantly greater relationship between anxiety symptoms and mPFC activation compared to the ASD group, whereas in the ASD group mPFC activation was more related to SOR than to anxiety symptoms. Activity in the mPFC has been shown to relate to developmental increases in emotional regulation (Klune et al., 2021), cognitive control, and reappraisal (Nelson et al., 2015). The mPFC may also be involved in directing attention to relevant social cues in the context of sensory distractions (Green et al., 2016; Patterson et al., 2021). It is possible that during aversive sensory stimulation, the mPFC plays a role in regulating responses, and as such is more related to the cause of such responses in each group—potentially anxiety in the ANX group and SOR in the ASD group. However, more research on sensory regulation across clinical groups is needed to explore this hypothesis.

Indeed, the degree to which SOR or anxiety symptoms uniquely relate to neural responses can be helpful in determining which symptom is “primary.” For example, SOR may develop first in ASD, leading to over-reactive behavioral responses to aversive sensory stimulation, and resulting in increased anxiety (Green et al., 2012). In contrast, in ANX, anxiety symptoms may develop first, and if heightened enough, may cause hypervigilance to sensory cues, thus being the primary cause of over-reactive behavioral responses (Green & Ben-Sasson, 2010). Differentiating which symptom is primary has important implications for treatment: while youth across multiple clinical diagnostic groups show SOR, different primary symptoms could indicate different treatment approaches. While the results of this study are preliminary, if replicated, they could suggest that when providing treatment for a child that has ANX and SOR, it may be more effective to first target their anxiety symptoms to indirectly alleviate SOR. In contrast, treatments that are specifically designed to target SOR symptoms may be more effective for youth with ASD, both in reducing SOR and in

secondarily reducing anxiety. However, these recommendations require further investigation, and all intervention would need to consider individual circumstances.

This sample provided a valuable opportunity to explore the unique contributions of symptom types to neurobiological responses to sensory stimulation in youth with ASD and ANX, which has significant implications for targeted treatment. However, some limitations should be noted. Though we matched groups for sex in the current study, the sample size did not allow for examination of sex differences. The rate of diagnosis of ASD or ANX is subject to significant sex differences; males are three times as likely to receive an ASD diagnosis compared to females (Loomes et al., 2017), and adolescent girls are approximately 1.5–3.5 times as likely to have some type of ANX compared to adolescent males (Merikangas et al., 2010). Sex differences in the relationship between neural connectivity and SOR has been observed in ASD (Cummings et al., 2020), suggesting that the way we process sensory information may be impacted by sex. Future research should directly examine potential sex differences using larger samples of youth with ASD and ANX. While there were no significant group differences in age in this study, the youth in this sample still represented a relatively large age range. Future research should be mindful of the potential impact of age on SOR and anxiety symptoms across the lifespan, especially because this may provide insight into mechanisms conferring risk and resilience during particular periods of development. Longitudinal designs may be especially important for identifying critical periods in the co-occurrence of these symptoms and providing insight into when treatments to alleviate anxiety and SOR should be administered for different groups. Another limitation of this study was that only caregiver report was used. Future research should also consider self-report, which may provide additional insights into symptomatology, especially as children get older, and may relate differently to biology compared to parent report.

To date, most studies that have examined difficulties with sensory processing have used predominantly ASD samples (Kotsiris et al., 2020); our results show that the relationship between anxiety and SOR extends beyond ASD and emphasize the need to study these symptoms across different populations. Compared to youth with ASD, youth with ANX showed greater anxiety symptoms, but similar SOR severity. It is important to note that the ANX participants were recruited primarily from youth seeking treatment at a UCLA anxiety clinic, who were characterized by particularly severe symptoms, with several of them unable to attend school due to their anxiety. It is possible that lower rates of SOR would be seen in a group with milder ANX, and there may be a threshold at which, if anxiety becomes high enough, it can cause SOR. Thus, further research on causal mechanisms and differential rates of SOR at different levels of anxiety may be necessary. Further, in this study we focused on SOR, but atypical sensory processing can manifest in other forms (e.g., sensory under-responsivity and increased sensation seeking) that may differentially relate to anxiety symptoms and neurobiology.

In summary, our results support the idea that SOR and anxiety are distinct, transdiagnostic symptoms with unique biological signatures. While behavioral and neurobiological over-responsivity to sensory stimulation was seen across diagnostic groups, distinct relationships between symptom profiles and neural responses in each group further suggests that SOR may be the primary contributor to this neural over-reactivity for youth with ASD, while

anxiety operates as the primary contributor for youth with ANX, indicating a need for targeted treatment approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The data used in this study are available from the corresponding author upon reasonable request.

Abbreviations:

ANX	anxiety disorder
ASD	autism spectrum disorder
SOR	sensory over-responsivity

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Significance

This study showed that youth with an autism (ASD) or an anxiety (ANX) diagnosis have elevated behavioral and neurobiological over-reactivity to sensory stimulation. Anxiety and sensory over-responsivity (SOR) symptoms had unique relationships with biological responses to sensory stimulation, suggesting that they are distinct symptoms with different biological signatures, despite their common co-occurrence. Hyperactive brain responses to aversive sensory stimulation were more highly related to SOR symptoms in ASD youth and to anxiety symptoms in ANX youth, emphasizing a need for targeted interventions that may address these symptoms differently depending on a child's diagnostic profile.

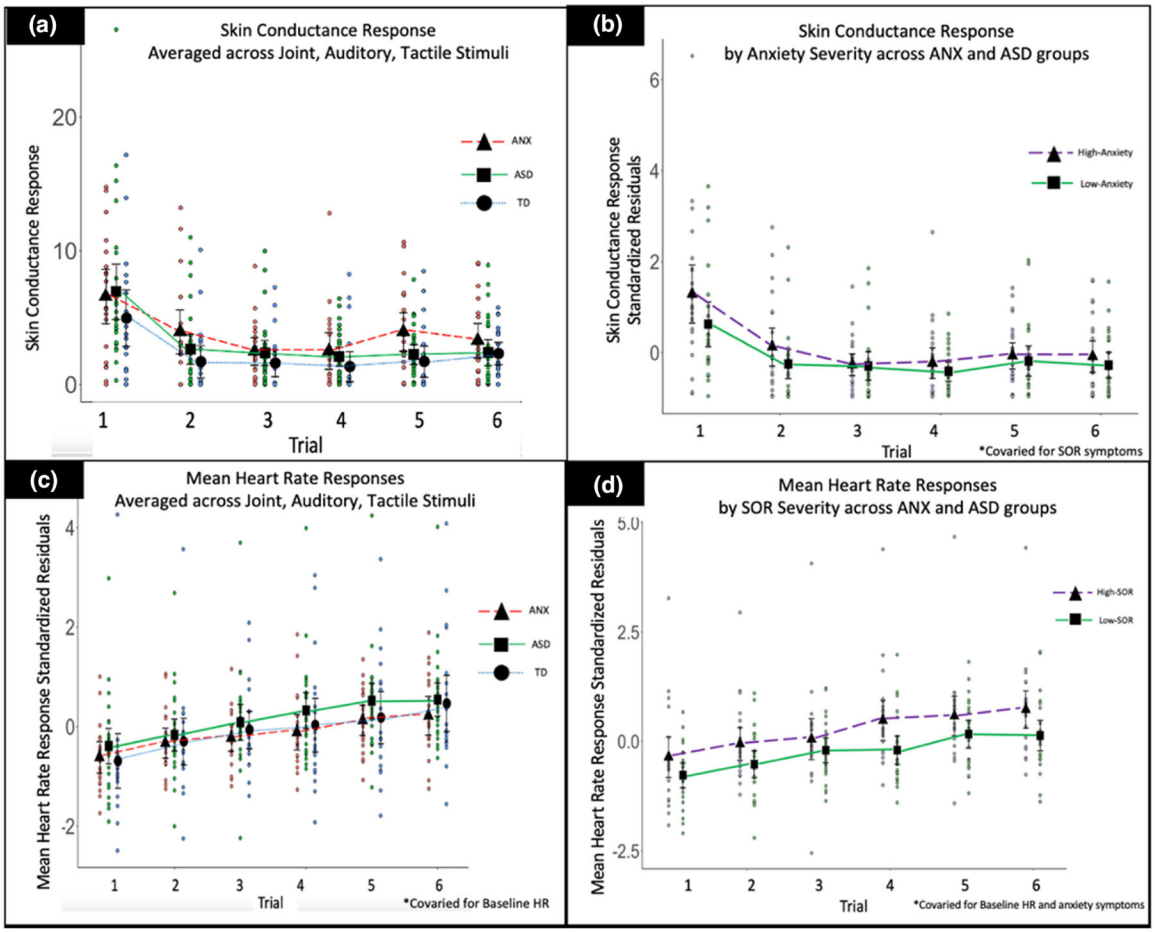

FIGURE 1.

Psychophysiological results: (a) Skin conductance response (SCR) averaged across joint, tactile, and auditory trials did not show significant diagnostic group differences. (b) For illustration purposes, ASD and ANX participants were combined and re-divided into low- and high-anxiety groups using a median split on the parent-reported total anxiety score. Higher anxiety symptoms predicted higher SCR and faster habituation to aversive sensory stimuli over and above SOR across the stimulation trials. (c) Mean heart rate (HR) responses, measured by taking the average HR across joint, tactile, and auditory trials and controlling for baseline HR, did not show significant diagnostic group differences. (d) For illustration purposes, ASD and ANX participants were combined and divided into low- and high-SOR groups using a median split on parent-reported SOR. Higher SOR symptoms predicted a steeper increase in mean heart rate responses (mean heart rate during sensory stimulation, controlling for baseline HR) over and above anxiety across the trials. Individual data points represent the raw mean skin conductance (a, b) and raw mean heart rate responses for each subject in each trial. Black triangles, squares, and circles represent the estimated mean for each group (a, c: ANX, ASD, TD, respectively; b: High-anxiety, Low-anxiety, respectively; d: High-SOR, Low-SOR, respectively) while controlling for covariates. Error bars display 2 times the standard error of each mean.

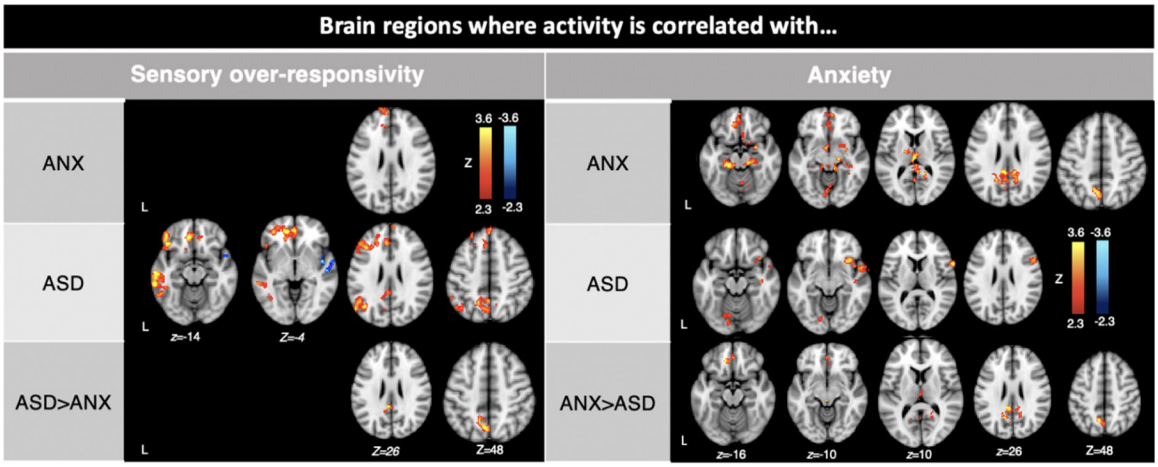

FIGURE 2.

Unique associations between sensory-evoked neural activation with sensory over-responsivity and anxiety symptoms in the ASD and ANX groups. Contrasts thresholded at $z > 2.3$, corrected ($p < .05$). ANX, anxiety group; ASD, autism spectrum disorder group.

TABLE 1

Participant demographics.

	ASD			ANX versus ASD	ANX versus TD	ASD versus TD
	ANX	***N***	**TD**	**χ^2, *p*-value**		
Total	22	30	22			
Sex (female/male)	15/7	14/16	10/12	.12	.13	.93
Handedness (R/L)	19/3	29/1	20/2	.17	.64	.38
Race/Ethnicity						
Caucasian, not Latine	15	12	7	.04	.02	.55
Asian, not Latine	0	1	3	.39	.07	.17
Black or African American, not Latine	2	2	1	.75	1	.75
Multiracial, not Latine	1	4	2	.29	.55	.64
Caucasian, Latine	2	6	4	.28	.38	.87
Asian, Latine	0	0	1	–	.31	.24
Black or African American, Latine	0	1	1	.39	–	.39
Multiracial, Latine	0	2	2	.22	.15	.75
Latine	0	2	1	.22	.31	.75
Not reported	2	0	0	.09	.15	–
	Mean (SD)				***t*-test, *p*-value**	
Age (years)	13.69 (3.3)	13.42 (2.9)		14.11 (2.9)	.95	.89	.7
Full scale IQ[a]	105 (11.0)	107.1 (15.7)		109.18 (11.1)	.84	.55	.84
Behavioral measures						
SOR total score	7.12 (7.7)	10.77 (7.8)		1.32 (1.6)	.19	.012	<.001
SCARED total score[a]	32.02 (14.7)	22.27 (13.2)		6.45 (7.1)	.017	<.001	<.001
Scanner motion[b]						
Mean absolute motion (mm)	.47 (.3)	.45 (.3)		.42 (.2)	.84	.53	.66
Mean relative motion (mm)	.13 (.04)	.14 (.06)		.12 (.06)	.67	.47	.31

Note: Higher SOR/SCARED scores indicate greater symptom severity.

Abbreviations: SCARED, Screen for Child Anxiety Related Disorders; SOR, sensory over responsivity.

[a] *N* = 21 ANX, 30 ASD, 22 TD.

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[b] N = 19 ANX, 25 ASD, 20 TD.

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TABLE 2

Montreal Neurological Institute (MNI) coordinates for brain areas where activity during joint condition was correlated with sensory over-responsivity.

	Sensory over-responsivity														
	ANX					**ASD**					**ASD > ANX**				
		MNI peak (mm)					**MNI peak (mm)**					**MNI peak (mm)**			
	Voxels	***x***	***y***	***z***	**Max *Z***	**Voxels**	***x***	***y***	***z***	**Max *Z***	**Voxels**	***x***	***y***	***z***	**Max *Z***
Superior frontal gyrus	*409*	*−8*	*58*	*24*	*3.26*	559	0	40	54	3.64					
Left frontal pole	409	−28	66	12	3.55		*−8*	*38*	*54*	*3.39*					
Right frontal pole							*6*	*62*	*24*	*3.23*					
Middle frontal gyrus						4061	−38	26	28	5.32					
Left paracingulate/ACC		*−6*	*40*	*28*	*2.86*		*−2*	*46*	*0*	*4.36*					
Left OFC/inferior frontal gyrus							*−42*	*28*	*−14*	*4.76*					
Left temporal pole							*−30*	*20*	*−28*	*3.81*					
Left lateral occipital/superior parietal						1343	−10	−64	66	3.66					
Posterior cingulate cortex							*0*	*−50*	*16*	*3.52*	907	−4	−44	28	4.42
Left precuneus							*−8*	*−56*	*34*	*3.5*		*−2*	*−66*	*46*	*4.18*
Right precuneus/lateral occipital cortex							*6*	*−64*	*60*	*3.38*		*10*	*−66*	*36*	*2.85*
Right STG/MTG						**505**	**52**	**−16**	**−6**	**4.79**					
Right planum polare/insula/Heschel's gyrus							***46***	***−4***	***−4***	***3.99***					
Right temporal pole							***54***	***10***	***−22***	***2.99***					
Inferior frontal gyrus							***54***	***16***	***0***	***3.8***					
Operculum; precentral gyrus							***50***	***6***	***2***	***3.12***					
Left lateral occipital cortex/angular gyrus						1219	−40	−66	28	4.43					
Supramarginal gyrus							*−46*	*−56*	*56*	*3.58*					
Left MTG/ITG						1097	−62	−20	−16	5.11					
Right cerebellum						1033	32	−74	−54	4.32					

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). Voxels indicates cluster size; coordinates in italics are local maxima within the same cluster as the coordinates above them. Within- and between-group analyses are cluster corrected for multiple comparisons, $z > 2.3$, $p < .05$.

Within-group coordinates indicate either a positive or negative (in bold) correlation between SOR and neural response during all conditions (Joint, Auditory, and Tactile aversive sensory stimulation) compared to rest. SOR and anxiety scores were included as bottom-up regressors in a whole brain analysis to assess the unique contributions of SOR, over and above anxiety. Between-group coordinates indicate clusters where the ASD group had a significantly greater correlation between SOR and neural response in each region relative to the ANX group. There were no regions where neural response showed a stronger relationship with SOR in the ANX compared to the ASD group.

Abbreviations: ACC, anterior cingulate cortex; ANX, anxiety disorder; ASD, autism spectrum disorder; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; OFC, orbitalfrontal cortex; STG, superior temporal gyrus; TD, typically-developing.

TABLE 3

Montreal Neurological Institute (MNI) coordinates for brain areas where activity during joint condition was correlated with anxiety.

	Anxiety														
	ANX					ASD					ANX > ASD				
		MNI peak (mm)					MNI peak (mm)					MNI peak (mm)			
	Voxels	*x*	*y*	*z*	Max *Z*	Voxels	*x*	*y*	*z*	Max *Z*	Voxels	*x*	*y*	*z*	Max *Z*
Left mPFC/white matter	428	−12	38	−14	3.72						775	−10	38	−14	4.63
Left frontal pole		*−2*	*56*	*−16*	*3.64*							*−2*	*60*	*12*	*2.5*
Right frontal pole		*6*	*56*	*−10*	*3.45*							*2*	*54*	*−6*	*2.52*
Left paracingulate/ACC												*−10*	*42*	*0*	*4.2*
Right Paracingulate/ACC		2	36	−10	2.95							*10*	*46*	*16*	*3.3*
Right mPFC												*2*	*42*	*−16*	*3.12*
Right subcallosal cortex		*4*	*32*	*−12*	*3.09*							*6*	*32*	*−12*	*3.07*
Right nucleus accumbens		*10*	*6*	*−14*	*2.86*										
Left frontal gyrus											499	−26	24	44	4.85
Right orbital frontal cortex						724	36	20	−12	4.99					
Right insula							32	14	−12	4.15					
Left parahippocampal gyrus	4369	−20	−30	−18	5.1										
Left posterior cingulate cortex		*−4*	*−44*	*24*	*4.46*						1875	−4	−48	20	4.37
Left precuneus		*−2*	*−64*	*50*	*4.57*							*−8*	*−60*	*50*	*3.99*
Right posterior cingulate cortex		*14*	*−52*	*−42*	*4.08*							*8*	*−46*	*22*	*3.72*
Supracalcarine/intracalcarine cortices												*−22*	*−62*	*14*	*3.29*
Brain stem		*2*	*−36*	*−2*	*3.68*							*0*	*−30*	*−12*	*3.54*
Thalamus		*0*	*−16*	*8*	*5.05*							*0*	*−18*	*10*	*2.9*
Left hippocampus		*−8*	*−38*	*4*	*3.52*							*−8*	*−42*	*4*	*3.02*
Right hippocampus							*38*	*−18*	*−16*	*3.12*					
Right amygdala		*26*	*0*	*−16*	*3.75*										
Right putamen		*30*	*−2*	*−4*	*3.71*										
Right precuneus		*6*	*−48*	*14*	*3.63*										
Right STG/MTG							*56*	*−18*	*−6*	*4.08*					
Right planum polare							*46*	*−2*	*−4*	*3.81*					

	Anxiety														
	ANX					ASD					ANX > ASD				
		MNI peak (mm)					MNI peak (mm)					MNI peak (mm)			
	Voxels	*x*	*y*	*z*	Max *Z*	Voxels	*x*	*y*	*z*	Max *Z*	Voxels	*x*	*y*	*z*	Max *Z*
Heschel's gyrus							*46*	*−4*	*0*	*3.59*					
Right temporal pole							*52*	*6*	*−12*	*3.36*					
Right hippocampus							*38*	*−18*	*−16*	*3.12*					
Right precentral gyrus						866	64	14	12	5.2					
Right inferior frontal gyrus							*52*	*10*	*4*	*4.26*					
Right middle frontal gyrus							*52*	*14*	*44*	*2.95*					
Left occipital fusiform						645	−12	−84	−18	3.49					
Left lateral occipital cortex							*−22*	*−90*	*−22*	*3.38*		*−12*	*−62*	*56*	*3.12*
Left lingual gyrus		*−2*	*−74*	*−4*	*3.74*		*−12*	*−84*	*−14*	*3.48*					
Right lingual gyrus		*12*	*−50*	*−4*	*3.45*										
Left cerebellum							−24	−74	−28	3.34					
Right cerebellum		*2*	*−56*	*−28*	*3.69*						550	28	−54	−60	4.56

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). Voxels indicates cluster size; coordinates in italics are local maxima within the same cluster as the coordinates above them. Within- and between-group analyses are cluster corrected for multiple comparisons, $z > 2.3$, $p < .05$.

Within-group coordinates indicate either a positive correlation between anxiety and neural response during all conditions (Joint, Auditory and Tactile aversive sensory stimulation) compared to rest. Sensory over-responsivity (SOR) scores were included as bottom-up regressors in order to assess the unique contributions of anxiety, over and above SOR. Between-group coordinates indicate clusters where the ANX group had a significantly greater correlation between anxiety and neural response in each region relative to the ASD group. There were no regions where neural response showed a stronger relationship with anxiety in the ASD compared to the ANX group.

Abbreviations: ACC, anterior cingulate cortex; ANX, anxiety disorder; ASD, autism spectrum disorder; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; STG, superior temporal gyrus; TD, typically-developing.