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Sex Differences in Salience Network Connectivity and its Relationship to Sensory Over-Responsivity in Youth with Autism Spectrum Disorder

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Abstract

Individuals with autism spectrum disorder (ASD) are significantly more likely to experience sensory over-responsivity (SOR) compared to neurotypical controls. SOR in autism has been shown to be related to atypical functional connectivity in the salience network (SN), a brain network thought to help direct attention to the most relevant stimuli in one's environment. However, all studies to date which have examined the neurobiological basis of sensory processing in ASD have used primarily male samples so little is known about sex differences in the neural processing of sensory information. This study examined the relationship between SOR and resting-state functional connectivity in the SN for 37 males and 16 females with autism, ages 8–17 years. While there were no sex differences in parent-rated SOR symptoms, there were significant sex differences in how SOR related to SN connectivity. Relative to females with ASD, males with ASD showed a stronger association between SOR and increased connectivity between the salience and primary sensory networks, suggesting increased allocation to sensory information. Conversely, for females with ASD, SOR was more strongly related to increased connectivity between the SN and prefrontal cortex. Results suggest that the underlying mechanisms of SOR in ASD are sex specific, providing insight into the differences seen in the diagnosis rate and symptom profiles of males and females with ASD.

Lay Summary:

Sensory over-responsivity (SOR) is common in autism. Most research on the neural basis of SOR has focused on males, so little is known about SOR or its neurobiology in females with autism spectrum disorder. Here despite no sex differences in SOR symptoms, we found sex differences in how SOR related to intrinsic connectivity in a salience detection network. Results

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Conflict of interest

All authors declare that there is no conflict of interest.

Supporting Information

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

show sex differences in the neural mechanisms underlying SOR and inform sex differences seen in diagnosis rates and symptom profiles in autism.

Keywords

autism spectrum disorder; resting-state fMRI; salience network; sensory; sex differences

Introduction

Individuals with autism spectrum disorder (ASD) are commonly affected by atypical sensory processing, often expressed as sensory over-responsivity [SOR; e.g., Liss, Saulnier, Fein, & Kinsbourne, 2006; Ben-Sasson et al., 2009; Tavassoli, Miller, Schoen, Nielsen, & Baron-Cohen, 2014]. SOR is characterized as a heightened aversive response to sensory stimuli, such as loud noises, scratchy fabrics, or bright lights [Green et al., 2013, 2015; Kientz & Dunn, 1997; Klintwall et al., 2011]. It is estimated that at least 70% of individuals with ASD experience atypical sensory processing [Baker, Lane, Angley, & Young, 2008; Baranek, David, Poe, Stone, & Watson, 2006], and these symptoms have been found to correlate with autism-related social difficulties [Hilton et al., 2010; Taylor et al., 2018]. SOR is impairing; it has been shown to correlate with maladaptive behavior, impaired daily living skills [Baker et al., 2008] problem behaviors [O'Donnell, Deitz, Kartin, Nalty, & Dawson, 2012], sleep problems [Mazurek & Petroski, 2015] and anxiety [Green & Ben-Sasson, 2010; Hofmann & Bitran, 2007; Jerome & Liss, 2005]. The most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (fifth edition, DSM-5; American Psychiatric Association, 2013) incorporated atypical sensory processing as a core feature of ASD, recognizing the importance of these symptoms to the ASD phenotype. Yet the neurobiological underpinnings of sensory issues in ASD are still vastly understudied.

Studies examining the neural basis of SOR have found that youth with ASD show increased activation and reduced habituation in the amygdala and sensory processing regions of the brain (primary auditory and somatosensory cortices) during exposure to mildly aversive sensory stimuli [Green et al., 2013, 2015, 2019]. Further, activity in these regions correlate with parent-reported SOR severity. The role of the amygdala in determining what is salient and what an individual should attend to [e.g., Zheng et al., 2017; Anderson & Phelps, 2001; Sander, Grafman, & Zalla, 2003] suggests that SOR may be related to an over-attribution of salience to extraneous sensory information. Indeed, sensory-evoked activity in the amygdala and primary somatosensory cortex is correlated with greater resting-state functional connectivity between these regions and the anterior insula [Green, Hernandez, Bookheimer, & Dapretto, 2016], the hub of an intrinsic brain network known as the salience network [SN; Seeley et al., 2007].

The SN plays a role in determining which of many internal and/or external stimuli require attention [Menon & Uddin, 2010; Seeley et al., 2007]. Atypical resting-state functional connectivity in the SN is well documented in ASD [e.g., Chen et al., 2017; Elton, Di Martino, Hazlett, & Gao, 2016; Uddin, 2015; von dem Hagen, Stoyanova, Baron-Cohen, & Calder, 2013], and has been shown to discriminate between ASD and TD participants

[Uddin, Supekar, & Menon, 2013]. The anterior insula has been shown to be hypoactive in ASD individuals [for review, see Uddin & Menon, 2009; Di Martino et al., 2009], and decreased activity in this region relates to impairments in emotional awareness often seen in those with the disorder [Silani et al., 2008]. There is also evidence that the anterior insula is overactive in individuals with ASD during the processing of sensory information [Di Martino et al., 2009; Green et al., 2015]. Increased SN connectivity with the amygdala and primary auditory and somatosensory cortices is associated with increased behavioral symptoms of SOR in addition to hyperactivity in these regions during exposure to mildly aversive stimuli [Green et al., 2016], suggesting that altered salience attribution may be one of the predominant factors in SOR. This prior study, like most imaging studies examining autism, featured a predominantly male sample, however, leaving little information on how females with ASD process information.

Three to four males are diagnosed with ASD for every female diagnosed [e.g., Baio et al., 2018; Loomes, Hull, & Mandy, 2017], and this likely explains why most ASD studies only have a small fraction of females, if any [for review, see Lai, Baron-Cohen, & Buxbaum, 2015; Philip et al., 2012]. Nonetheless, the results of these studies are often generalized to all individuals with ASD, although they may not be accurately reflecting females with the diagnosis. There are several well-known theories explaining why more males than females are diagnosed with ASD. One theory is that there are female-specific protective factors that allow girls to tolerate more of an etiological load before reaching clinical thresholds for ASD [Robinson, Lichtenstein, Anckarsäter, Happé, & Ronald, 2013]. Another theory is that cognitive and behavioral differences seen in males and females with ASD may result in under-diagnosis of females [Frazier, Georgiades, Bishop, & Hardan, 2014; McFayden, Antezana, Albright, Muskett, & Scarpa, 2019]. A third theory suggests that females are underdiagnosed because of their ability to mask their symptoms. This “camouflage” hypothesis states that young girls with ASD may shield their social shortcomings more effectively than males because of how they interact with their peers, staying in close proximity to their classmates as they shift between different activities while ASD boys tend to draw more attention as they play alone [Dean, Harwood, & Kasari, 2017]. This can affect diagnosis rates when one is examining a disorder that relies on observations of behavioral symptoms [Rynkiewicz et al., 2016]. Even if males and females with ASD show similar social and behavioral impairments, parents tend to rate their daughters as being more affected than their sons [Holtmann, Bölte, & Poustka, 2007], potentially reflecting different expectations for females than males.

At the neural level, there is evidence that males and females on the autism spectrum display different patterns of brain activity and connectivity which in turn differ from those seen in neurotypical (NT) controls [for review, see Lai et al., 2017]. For example, females with ASD generally show hyperconnectivity compared to males (i.e., greater number of brain regions fluctuating together during rest and/or a higher degree of correlation between the brain regions fluctuating together), whereas in NT individuals the opposite pattern is evident [Alaerts, Swinnen, & Wenderoth, 2016]. However, results are mixed, and a recent study found no sex differences in SN connectivity in children and adolescents with ASD [Lawrence et al., 2020]. To our knowledge, few if any studies have examined sex differences in the associations between behavior and brain connectivity in ASD. Studies that have

examined task-related brain activity in ASD have also found evidence of sex differences in neural activity underlying visuospatial [Beacher et al., 2012] and socially relevant processes [Coffman, Anderson, Naples, & McPartland, 2015]. It is possible that ASD results in atypical sex differences, such that females and males show different neural signatures and symptom profiles compared to each other and to what is observed in males and females in the NT population.

Given the prevalence of and impairment caused by sensory processing difficulties in ASD, and that girls as well as boys experience these difficulties [Moseley, Hitchiner, & Kirkby, 2018], more research is needed on sex differences in the neurobiology underlying SOR in autism. Some studies have even suggested that females with ASD show greater sensory processing difficulties compared to males with ASD [Kumazaki et al., 2015; Lai et al., 2011], furthering the need to examine SOR in this population. If there is a significant difference in the neurobiological mechanisms of SOR in females versus males, this could have an impact on many aspects of their functioning and potentially help explain differential manifestations of ASD at the behavioral level. Thus, this study aimed to examine sex differences in the relationship between SOR and resting-state functional connectivity of the SN in females versus males with ASD.

Methods

Participants

Participants were 53 (16F) youth and adolescents with ASD (mean age, 13.7 years; range, 8.2–17.9 years). Each participant had a full-scale IQ within the normal range according to the Weschler Abbreviated Scales of Intelligence [Wechsler, 1999]. Each had a formal autism diagnosis according to the Autism Diagnostic Interview—Revised [ADI-R, Lord, Rutter, & Le Couteur, 1994], and/or the Autism Diagnostic Observation Schedule—second edition [ADOS-2; Lord, Rutter, DiLavore, Risi, & Bishop, 2012], and clinical judgment. Females and males with ASD did not differ significantly on full-scale IQ (FSIQ-$t[51] = -1.2$, $p = 0.26$), age ($t[51] = -1.5$, $p = 0.14$), handedness (X^2 [1, $N = 53$] = 0.9, $p = 0.34$) or mean relative or absolute motion during the scan ($t[51] = 0.2$, $p = 0.84$; $t[51] = 1.8$, $p = 0.08$; Table 1). Additionally, there were no significant differences in overall autism symptomatology, as assessed through the ADOS ($t[50] = -1.2$, $p = 0.23$) or parent report on the ADI-R for the Social Interaction ($t[49] = -0.7$, $p = 0.45$), Communication ($t[49] = 0.3$, $p = 0.78$), or Restrictive and Repetitive Behaviors ($t[49] = 0.2$, $p = 0.88$) subscales. The only difference in the ADI-R between males and females was on the fourth subscale, Abnormality of Development Evident at or Before 36 months, with ASD males showing more signs of autism at an earlier age compared to diagnosed females ($t[49] = -2.2$, $p = 0.03$). Of the original sample of 57 ASD participants, three (1 female, 2 males) were excluded due to motion, and 1 male was excluded due to an echo-planar imaging (EPI) artifact. Subjects with a mean absolute motion greater than 1 mm and mean relative motion greater than 0.25 mm were excluded from all analyses. All study procedures were approved by the University of California Los Angeles Institutional Review Board.

Measures

The following questionnaires were completed by participant's parents.

Sensory Over-Responsivity Inventory.—The Sensory Over-Responsivity Inventory [Schoen, Miller, & Green, 2008] is a checklist of sensations that one may find aversive and was used to determine SOR severity. Each participant's SOR score was calculated by taking a count of the number of tactile, visual, and auditory items the parent endorsed as being bothersome for their child. The SOR total score used in this study was highly correlated with each of the modality subscales (with Auditory SOR: $r = 0.93$, $p = 0.01$; Visual SOR: $r = 0.56$, $p = 0.01$; Tactile SOR: $r = 0.87$, $p = 0.01$), thus the total score was used in analyses.

Screen for Child Anxiety-Related Disorders.—The Screen for Child Anxiety Related Disorders [SCARED; Birmaher et al., 1999] measures anxiety symptoms and categorizes them into different subscales in order to screen for specific anxiety disorders. The total score was used to examine general anxiety severity for each participant.

Magnetic Resonance Imaging Data Acquisition

Functional magnetic resonance imaging (fMRI) resting-state scans were completed on a Siemens Prisma 3 Tesla scanner with a 64-channel head coil. This scan was the first functional scan administered as part of a larger protocol, to ensure no contamination from task-based scans. Participants fixed their gaze on a white crosshair on a black background, presented using a pair of 800 × 640 resolution magnet-compatible 3D goggles under computer control (Resonance Technologies, Inc.). Scans were acquired using an EPI multiband acquisition lasting 8 min and covering the entire cerebral volume (repetition time (TR) = 720 ms, field-of-view (FOV) = 208 mm, echo time (TE) = 37 ms, flip angle = 52, in-plane voxel size = 2 mm^2, 72 slices).

Data Preprocessing and Analysis

The fMRI data were analyzed using the FMRIB Software Library (FSL), Version 5.0.10 (www.fmrib.ox.ac.uk/fsl). The preprocessing pipeline included spatial smoothing (Gaussian kernel full width at half maximum = 5 mm), bandpass filtering ($0.1 \text{ Hz} > t > 0.01 \text{ Hz}$), and the regression of mean white matter, cerebrospinal fluid, and global signal times series. Independent Component Analysis—Automatic Removal of Motion Artifacts [Pruim, Mennes, Buitelaar, & Beckmann, 2015] was used to remove potential confounds resulting from head motion by regressing out single-subject components labeled as motion or noise. Each participant's data was then registered to the MNI152 T1 2-mm template brain (12 degrees of freedom).

A fixed-effects model was run for each individual subject using FSL's fMRI Expert Analysis Tool (FEAT, Version 6.0) before they were combined in a higher-level mixed-effects model to examine within- and between-group differences. Higher-level group analyses were conducted using FSL's Local Analysis of Mixed Effects State (FLAME 1 + 2). Research examining the SN supports a right dominance, as hubs of the network have been shown to be more connected to regions on the right hemisphere compared to the left [Cauda et al., 2011; Seeley et al., 2007; Zhang et al., 2019] in addition to activating more in

response to salient stimuli [Sridharan, Levitin, & Menon, 2008]. Therefore, a 5-mm sphere in the right anterior insula (rAI; Montreal Neurological Institute [MNI] coordinates 38, 26, −10) was used as the seed for the SN [Seeley et al., 2007]. Single-subject connectivity maps were created by isolating the time-series from this region in individual subject space and correlating it with the activity of every other voxel in the brain in order to find regions of synchronous activity. Fischer's *r*-to-z transformation was then used to create *z*-statistic maps prior to conducting group-level analyses. All whole-brain contrasts were corrected for multiple comparisons using Gaussian random-field theory in FSL with a voxel-wise threshold of $z > 2.3$ and corrected cluster threshold of $p < 0.05$. To examine how SN connectivity related to SOR, SOR scores were entered as a bottom-up regressor in the whole-brain analysis. Anxiety symptoms were used as a covariate in these analyses because of their high comorbidity with SOR [Green & Ben-Sasson, 2010; Ben-Sasson et al., 2008], and their correlation with SOR in the ASD sample ($r = 0.31$, $p = .05$). While not a primary focus of this paper, we also show within-group and sex differences in SN connectivity in the supplement (Figure S1, Table S1).

Results

Behavioral

An independent samples *t* test showed that there were no significant sex differences in total SOR score ($t[51] = -0.4$, $p = 0.67$). Females with ASD had significantly higher anxiety compared to males with ASD ($t[51] = 3.1$, $p = 0.003$).

Connectivity

Sex differences in SOR correlations with SN connectivity.—In males with ASD, SOR was positively correlated with connectivity between the rAI and temporal regions involved in auditory and language processing, including the planum temporale, temporal pole, and temporal gyrus, as well as the left hippocampus, and inferior frontal gyrus. SOR was also negatively correlated with connectivity between the SN seed and the posterior cingulate, right thalamus, precuneus, and occipital regions of the brain.

In females with ASD, SOR was positively correlated with connectivity between the rAI and frontal regions, including the frontal pole, superior frontal gyrus (dorsal lateral prefrontal cortex, dlPFC), paracingulate (dorsal medial prefrontal cortex, dmPFC), and anterior cingulate cortex (ACC). In this group, SOR was negatively correlated with connectivity between the rAI and sensory-motor regions including precentral and postcentral gyri and auditory cortex. Additionally, SOR was negatively correlated with rAI connectivity with the insular/opercular cortex and additional higher-level sensory processing regions including the planum temporale, planum polare, and supramarginal gyrus.

Between-group contrasts demonstrated that, compared to females with ASD, males showed a more positive correlation between SOR and rAI connectivity with sensory regions including temporal cortex and postcentral gyrus. This group difference was accounted for both by a negative correlation with SOR in females as well as a positive correlation in males, although this was only visible at lower thresholds (i.e., $z > 1.7$), suggesting opposite effects

in males compared to females. In contrast, compared to males with ASD, in females, SOR was more strongly related to connectivity between the rAI and dlPFC/dmPFC/ACC (Figure 1, Table 2).

Parameter estimates were extracted from regions where there were significant sex differences in SN connectivity as a function of SOR to illustrate the direction of effects and ensure that correlations were not driven by outliers (Figure 2). Finally, to ensure that these effects were due to real sex differences, rather than differences in power due to unequal male and female sample sizes, we reran these analyses with a subset of 16 males that were matched on age, SOR, anxiety, FSIQ, and motion to the original group of 37 (Table S2). Results from the original analysis were replicated and showed stronger within-group connectivity in the male sample (Figure S2, Table S3).

Discussion

In this study, we aimed to identify whether males and females with ASD differ in the neurobiology underlying sensory over-responsivity. To do so, we examined sex differences in SOR symptoms and the relationship between SOR and SN connectivity. We found that despite sharing similar behavioral profiles, males and females with ASD differ in how SN connectivity relates to SOR symptoms.

At the behavioral level, we found that males and females with ASD did not show sex differences in SOR symptom severity, which is consistent with a number of other studies [Mandy et al. 2012; Bitsika et al., 2018; Nguyen & Ronald, 2014]. Although one study [Kumazaki et al., 2015] reported greater sensory issues in females compared to males with ASD, these participants were younger than in the current study, suggesting a need to examine sex differences in sensory processing across development.

Importantly, although males and females with ASD did not differ in SOR symptomatology, they differed significantly in how SOR related to SN connectivity. Only in males with ASD, higher SOR was associated with greater SN connectivity with sensory processing regions and reduced connectivity with regions important for social processing such as the precuneus. Furthermore, in the current study, SOR was significantly *more* correlated with primary sensory cortices in males than in females. These results may reflect a lack of functional segregation between the salience and sensory networks in males with ASD, which is consistent with our previous findings of SOR associations with SN connectivity in a predominantly male ASD sample (Green et al., 2016). In addition, they are in line with prior reports, also in predominantly male samples, that SOR is associated with overactive brain responses to sensory stimuli in both sensory processing regions as well as regions implicated in salience and attention [i.e., amygdala and insula;Green et al., 2013, 2015]. These results support the theory that, at least in males with ASD, SOR may result from the mis-attribution of salience to external sensory stimuli.

Notably, SOR related quite differently to SN connectivity in ASD females compared to ASD males, suggesting that females with ASD may engage different neural networks in response to aversive sensory stimuli. SN connectivity with sensory cortices was actually correlated

with reduced SOR in females. In contrast, increased SN connectivity with prefrontal regions including dmPFC, dlPFC, and ACC was associated with higher SOR in females with ASD.

The distinct relationships observed between SOR and SN connectivity in males versus females with ASD may reflect sex differences in how SOR and other sensory processing atypicalities are experienced, or in how SOR relates to other symptoms such as social functioning [Head, McGillivray, & Stokes, 2014; Lai et al., 2011]. Activity in medial prefrontal regions, including in the dorsal medial prefrontal cortex/anterior cingulate cortex and in dorsolateral prefrontal cortex, as seen in this study, as well as in more ventral regions has been implicated in emotional regulation [Ochsner, Silvers, & Buhle, 2012]. It is possible that females compared to males with ASD may extend more effort toward regulating negative emotions in relation to aversive sensory stimuli. This finding could indicate that girls with higher levels of SOR are working harder to regulate and reduce sensory-related behaviors in order to fit in better, as in the camouflage hypothesis [Dean et al., 2017]. This process of masking sensory symptoms may require prefrontal top-down regulation, and there is evidence to suggest that for women with autism, enhanced camouflaging is associated with increased activation in the prefrontal cortex during a self-representation task [Lai et al., 2018]. However, the prefrontal region found in Lai et al. was more ventral than that seen in this study, and more research is necessary to determine how and whether prefrontal down-regulation during sensory stimulation might be associated with camouflaging.

The dmPFC/ACC regions seen here to be related to SOR also overlap with regions associated with pain perception [Bräscher, Becker, Hoeppli, & Schweinhardt, 2016; Woo et al., 2017; Woo, Roy, Buhle, & Wager, 2015]. It is possible that SOR is more highly associated with the pain network for females with ASD and the somatosensory network in males with ASD. Finally, activity in the vmPFC and ACC has also been shown to relate to reward processing in autism, specifically in relation to the individual's own restricted interests [Dichter et al., 2012]. Research on sensory subgroupings within ASD suggests that SOR and sensory seeking actually cluster together in those most severely affected by sensory processing challenges [Ausderau et al., 2014; Liss et al., 2006]. Accordingly, the observed greater SN connectivity with mPFC in ASD females might also be associated with sensory seeking and actually represent a higher reward value of sensory stimuli to this group. Future research should examine sex differences in the internal experience of different types of sensory stimuli and how these relate to distinct neural profiles in males and females with ASD.

Sensory processing difficulties can span across several domains, including SOR, sensory under responsivity, and sensory seeking [Ben-Sasson et al., 2009; Liss et al., 2006]. These atypical sensory processing symptoms often cluster together according to severity as opposed to sensory processing style [e.g., Ausderau et al., 2014; Elwin, Schröder, Ek, Wallsten, & Kjellin, 2017], such that individuals with autism often experience difficulties across domains and modalities. Given the high correlation between the SOR composite score used in this study with each of the subscales (auditory, tactile, visual), we decided to use the SOR composite for all analyses. The strongest correlation in scores was for the auditory and tactile subscales, possibly because these sections of the SOR Inventory contain more items than the visual subscale, or possibly because auditory and tactile are

the most commonly cited modalities of over-responsivity in general [Schoen et al., 2008] and in autism [Mikkelsen, Wodka, Mostofsky, & Puts, 2016; Tavassoli et al., 2014]. Future research examining sensory processing should consider examining specific modalities of SOR in order to determine whether SOR in any particular domain has differential effects on brain response or behavior. Further, while we examined here the unique effect of SOR after controlling for anxiety symptoms, future research should examine the specificity of the relationship between SN connectivity and SOR in general, for example determining whether SN connectivity is predictive of SOR over and above autism symptom severity.

While this study did have a higher proportion of affected females compared to many other autism imaging studies, the female sample size was still relatively small, and future studies should aim to replicate these results with a larger sample size. Future studies should also examine atypical sensory processing using more robust sensory questionnaires and behavioral assessments across development in ASD in order to determine the stability and generalizability of sex differences in SOR symptomatology. If there are sex differences in sensory processing in young children with ASD that diminish with development, neuroimaging can provide insight into why this may occur.

Results inform potential avenues for sex-specific sensory therapies for youth with ASD. For example, a therapeutic approach that involves consciously thinking about one's external world and engages prefrontal areas, such as cognitive behavioral therapy [Mason, Peters, Williams, & Kumari, 2017; van der Straten, Huyser, Wolters, Denys, & van Wingen, 2018], may be an effective treatment plan for females with ASD and SOR, as they may already be engaging prefrontal regions to regulate their responses to sensory stimuli. In males with ASD, meanwhile, SOR appears to be related to attributing increased salience to extraneous sensory stimuli, potentially at the cost of attention to key social stimuli and cues. Therefore, interventions that help to redirect attention either by reducing salience of extraneous sensory stimuli or increasing salience of social stimuli may be particularly helpful for males with SOR. There is some evidence for the effectiveness of this technique: Green, Hernandez, Bowman, Bookheimer, and Dapretto [2018] found that distracting sensory stimuli disrupted neural processing of social cues for primarily male ASD youth, and this effect was mitigated by instructing participants to direct their attention to key social cues. Additionally, if SOR is related to different internal experiences in females compared to males, such as a greater perception of pain versus an increase in the amount of effort and attention put in to processing sensory information, this too would inform targeted treatment approaches.

To the best of our knowledge, this study is the first to examine sex differences in brain connectivity as it relates to sensory symptoms in ASD. The observed sex differences in the associations between SN connectivity and SOR support the need for imaging studies in autism to examine sex as a moderator and indicate that prior findings from predominantly male samples cannot necessarily be generalized to females with autism. Research focused on the role of sensory processing and its relationship to social functioning should also keep in mind the need to study females and males separately.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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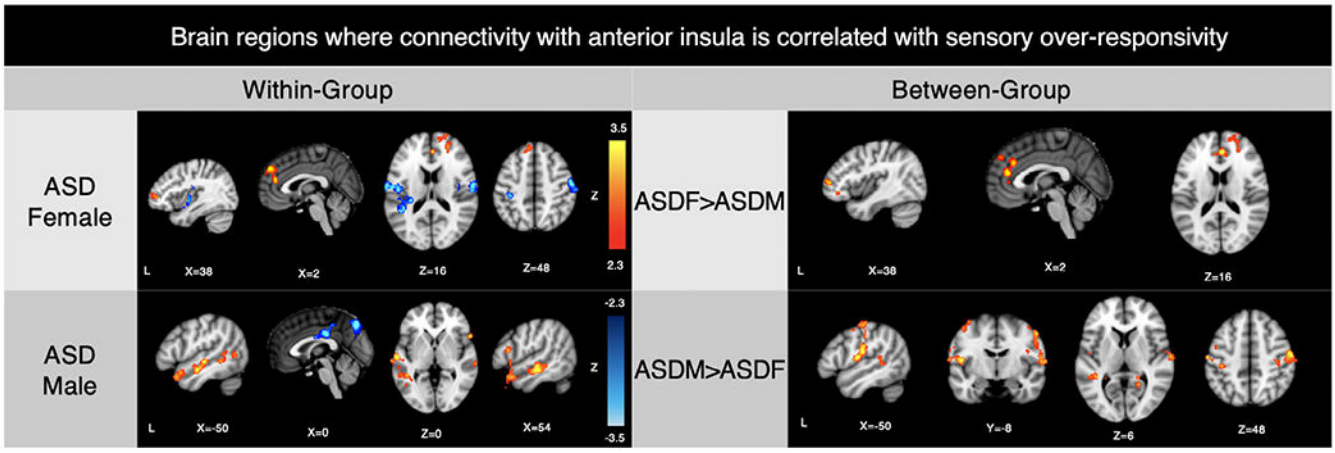

Figure 1.

Within- and between-group results: Sex differences in salience network connectivity related to SOR in the autism group. *Note*. Within- and between-group contrasts thresholded at $z > 2.3$, corrected ($p < 0.05$). ASD, autism spectrum disorder; SOR, sensory over-responsivity

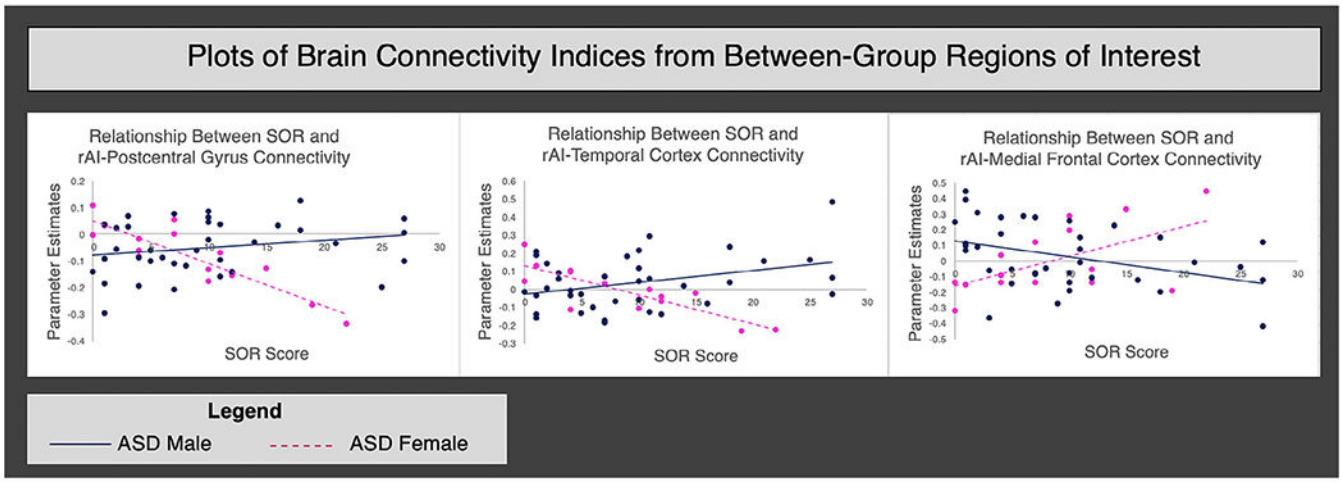

Figure 2.

The relationship between sensory over-responsivity (SOR) severity and connectivity with the right anterior insula (rAI) for males and females with autism spectrum disorder (ASD). *Note*: The horizontal axis displays the SOR score and the vertical axis displays the parameter estimates extracted from areas where significant correlations between SOR severity and connectivity with the rAI were observed in the between-group contrasts

Table 1.

Descriptive Statistics

	Female mean (SD)	Male mean (SD)	Female versus male *p* values
N	16	37	–
Age (years)	12.84 (2.6)	14.10 (2.9)	0.14
Full-scale IQ	100.63 (19.2)	106.76 (13.6)	0.26
Handedness (R/L)	16/0	35/2	0.34
Behavioral measures			
ADOS[a]	5.75 (1.6)	6.33 (1.6)	0.23
ADI-R[b]: Social Interaction	17.67 (5.3)	19.03 (5.9)	0.45
ADI-R[b]: Communication	16.60 (4.1)	16.19 (4.9)	0.78
ADI-R[b]: Restrictive/Repetitive Behaviors	6.20 (2.3)	6.08 (2.5)	0.88
ADI-R[b]: Abnormality of Development	2.67(1.2)	3.53 (1.3)	0.03*
SOR total score	8.63 (6.5)	9.59 (8.0)	0.67
SCARED total score	25.44 (12.7)	15.24 (10.2)	0.003**
Scanner measures			
Mean absolute motion (mm)	.50 (.2)	.40 (.2)	0.08
Mean relative motion (mm)	.13 (.1)	.13 (.1)	0.84
Components removed	104.31 (33.5)	113.86 (33.1)	0.34

Note. Higher SOR/SCARED scores indicate higher symptom severity. *N* = 16 ASD females, 37 ASD males.

Abbreviations: ADI-R, Autism Diagnostic Interview—Revised; ADOS, Autism Diagnostic Observation Schedule; SCARED, Screen for Child Anxiety-Related Disorders; SOR, sensory over-responsivity.

[a] *N* = 16F, 36 M.

[b] *N* = 15F, 36 M.

* $p < 0.05$;

** $p < 0.01$;

*** $p < 0.001$.

Table 2.

Montreal Neurological Institute (MNI) Coordinates for Brain Areas where Connectivity with the Right Anterior Insula (rAI) Correlated with Sensory Over-Responsivity (SOR)

	ASD female					ASD male					ASD female>ASD male					ASD male>ASD female				
	MNI peak (mm)					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**	**Voxels**	***x***	***y***	***z***	**Max Z**
Superior frontal gyrus	1266	4	48	38	3.65															
ACC/paracingulate/superior frontal gyrus		*2*	*42*	*20*	*3.61*						582	4	40	16	4.04					
Middle frontal gyrus		*42*	*52*	*8*	*3.15*						883	40	50	6	3.64					
Right OFC												*28*	*26*	*−10*	*3.25*					
Right postcentral gyrus	**1373**	**52**	**−24**	**60**	**7.7**											1230	58	−18	54	4.6
Left operculum/insula	**1321**	**−48**	**−16**	**20**	**4.87**											1068	−48	−16	20	4.3
Left postcentral gyrus																	*−56*	*−16*	*52*	*4.26*
Lingual gyrus																	*20*	*−48*	*−4*	*3.63*
Left superior temporal gyrus						1174	−60	−16	−2	4.21							*−44*	*−42*	*2*	*3.76*
Right superior temporal gyrus/middle temporal gyrus						605	54	−20	−10	3.71										
Right planum polare						747	48	26	−22	4.26										
Left temporal fusiform gyrus						643	−42	−38	−18	4.07										
Precuneus						**1149**	**−2**	**−74**	**46**	**4.19**										
Posterior cingulate gyrus						**525**	**2**	**−26**	**32**	**4.27**										

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 with SOR and functional connectivity with the right anterior insula seed or a negative correlation with SOR (in bold). Between-group coordinates indicate clusters where the one group had a significantly correlation between SOR and rAI connectivity with that region relative to the other group. Peak coordinates were found in similar regions when anxiety was not covaried, except for the frontal regions positively associated with SOR for ASD females (Figure S4).

Abbreviations: ASD, autism spectrum disorder; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex.