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Children with ASD show links between aberrant sound processing, social symptoms, and atypical auditory interhemispheric and thalamocortical functional connectivity

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ABSTRACT

Autism spectrum disorder (ASD) is a complex and prevalent neurodevelopmental disorder characterized by social and communicative deficits, as well as repetitive behaviors and atypical sensitivity to sensory stimulation. Alterations in network connectivity are widely recognized, but their interplay with social and sensory symptoms remains largely unclear. Here, functional magnetic resonance imaging and diagnostic and behavioral assessments were used in a cohort of children and adolescents with ASD (n = 40) and matched typically developing (TD, n = 38) controls to examine the relation between auditory processing, interhemispheric and thalamocortical network connectivity, and social-behavioral symptom severity. We found that atypical processing of sounds was related to social, cognitive, and communicative impairments. Additionally, severity of sensory processing deficits and lower verbal IQ were related to reduced interhemispheric connectivity of auditory cortices in ASD. Increased connectivity between the thalamus and auditory cortex in ASD, however, was associated with reduced cognitive and behavioral symptomatology, suggesting that thalamocortical overconnectivity might reflect a compensatory mechanism in ASD. These findings provide novel evidence for links between auditory sensory deficits and impairments in social interaction and communication.

1. Introduction

Sensory symptoms are common in autism spectrum disorders (ASDs; Baranek et al., 2006; Leekam et al., 2007), with atypical processing of sound afflicting up to 65% of individuals with ASD (Bishop et al., 2013; Chang et al., 2012). Only since the adoption of the DSM-5 (American Psychiatric Association, 2013), however, has unusual reactivity to sensory stimuli become part of the diagnostic criteria for ASD. Previous studies have shown that auditory deficits are associated with more severe social-behavioral symptoms of autism (Jao Keehn et al., 2016; Stewart et al., 2016; Watson et al., 2011), and two recent functional magnetic resonance imaging studies (fMRI) have found atypically increased activation of sensory cortices in ASD in response to sounds that is related to the degree of sensory oversensitivity (Green et al., 2013, 2016). Converging with these neuroimaging studies showing atypical responses of auditory cortex to sounds in ASD, genetic, post-mortem, molecular and animal model studies have also found atypical organization of auditory cortices in ASD (Figueiredo Anomal et al., 2015; Hoerder-Suabedissen et al., 2013; Stoner et al., 2014). The interaction between sensory symptoms, the social and behavioral manifestations of autism and alterations in functional brain organization, however, is not well understood. In this study, we therefore used fMRI and behavioral assessments to investigate how differences in functional connectivity of the auditory sensory network relate to atypical sensitivity to sounds, and to deficits in social cognition and communication in a cohort of children and adolescents with ASD.

Functional MRI has consistently revealed altered short and long-range connectivity in ASD (Anderson, 2014; Kana et al., 2011; Müller, 2014; Plitt et al., 2015; Vissers et al., 2012; Wass, 2011) but the organization of the auditory network is not well-studied even in healthy development. The auditory network can

Abbreviations: ASD, autism spectrum disorders; ADI-R, Autism Diagnostic Interview Revised; ADOS, Autism Diagnostic Observation Schedule; MRI, magnetic resonance imaging; HG, Heschl's Gyrus; IQ, intelligence quotient; SP, Sensory Profile; SRS, Social Responsiveness Scale; STG, superior temporal gyrus; TD, typically developing.

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be characterized by connectivity between the thalamus – relaying auditory information from the periphery – and auditory cortex, and connectivity between the auditory cortices in the left and right hemisphere (interhemispheric connectivity). Atypical interhemispheric (Anderson et al., 2011; Lee et al., 2016; Zhu et al., 2014) and thalamocortical (Cerliani et al., 2015; Mizuno et al., 2006; Nair et al., 2015, 2013) connectivity are, therefore of particular relevance for understanding the neural underpinnings of auditory sensory processing abnormalities in ASD and how they relate to social and behavioral symptomatology.

Interhemispheric connectivity between left and right auditory cortex is established early in development, with bilateral auditory resting state networks being present from birth (Fransson et al., 2009; Van Den Heuvel et al., 2015) and even in utero (Thomason et al., 2013). While fMRI studies have found interhemispheric connectivity to be reduced in ASD (Anderson et al., 2011; Lee et al., 2016; Zhu et al., 2014), these studies have typically focused on networks involved in complex cognition, such as the default mode network (Damarla et al., 2010; Just et al., 2007; Kleinhans et al., 2008; Mason et al., 2008; Weng et al., 2010). The importance of interhemispheric connectivity for early sensory processing is much less well understood, although two recent studies in healthy adults suggest that increased interhemispheric information transfer is beneficial to speech perception and phonetic categorization (Elmer et al., 2016; Steinmann et al., 2014). Furthermore, reduced interhemispheric connectivity of the superior temporal gyri in ASD was one of the main findings in a study by Anderson et al. (2011), but its relationship to sensory and social symptoms has not been addressed. We hypothesized that reduced interhemispheric connectivity of auditory cortical regions would be replicated in our sample of children and adolescents with ASD, and that the reduction in connectivity would be associated with atypical sound processing, as well as more severe social and cognitive outcomes.

Secondly, we hypothesized that functional connectivity between thalamus and auditory cortices in ASD would be atypical and related to the severity of sensory symptoms and cognitive and communicative deficits. Thalamocortical projections begin to develop in utero, strengthen over the first years of life (Alcauter et al., 2014), and play an important role in early cortical differentiation (Kanold and Luhmann, 2010; O'Leary and Nakagawa, 2002). The thalamus not only relays information from the sensory periphery to cortex, but through top-down cortical modulations is also involved in attentional selection and suppression of sensory input (John et al., 2016). For example, a recent study using task-based fMRI (Green et al., 2016) showed increased activation of auditory and tactile cortices, emotional processing regions and the thalamus in a group of adolescents with ASD compared to TD controls when processing mildly aversive auditory and tactile stimuli. This increase in activation correlated with sensory symptom severity. The authors conclude that the increased activity might reflect a lack of attentional and emotional gating of aversive sensory stimuli. It is not clear how increased activation relates to strength of connectivity between two regions, but multiple other studies have found atypical connectivity between the thalamus and the temporal lobe in ASD (Cerliani et al., 2015; Nair et al., 2015, 2013). Mizuno et al. (2006) suggested that increased functional connectivity between the thalamus and cortex may serve to compensate for reduced long-range cortical connectivity in ASD. In line with these findings, Nair et al. (2015) found improved language and cognitive skills with increasing connectivity between the thalamus and the temporal lobe. Interestingly, increased input from the thalamus to maintain interhemispheric synchronization between sensory cortices has also been proposed in patients with agenesis of the corpus callosum, and in non-human species that lack a corpus callosum (Schmidt, 2003; Tyszka et al., 2011). We were therefore also interested in investigating the interaction between interhemispheric and thalamocortical connectivity in ASD and how different patterns of connectivity of the auditory network relate to atypical processing of sounds, and to deficits in social cognition and communication in ASD.

2. Materials and methods

2.1. Participants

High-functioning children and adolescents with ASD ($n = 40$) and typically developing control participants ($n = 38$) between the ages of 8–17 years were included in this study. Diagnoses of Autism Spectrum Disorder were confirmed with the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1989) and the Autism Diagnostic Interview Revised (ADI-R; Lord et al., 1994) based on criteria described by the DSM-5 (American Psychiatric Association, 2013). Participants with comorbid ASD-related medical conditions (e.g., Fragile-X syndrome, tuberous sclerosis, epilepsy), or other neurological conditions (e.g., Tourette syndrome), were excluded. Typically developing children were screened for any history of neurological, psychiatric, or developmental disorders. All participants were safety-screened for MRI contraindications (e.g., claustrophobia, ferrous material in body). Participants for this study were chosen from a larger cohort (ASD: $n = 93$, TD: $n = 67$), based on availability of both resting state data and the completed Sensory Profile Caregiver Questionnaire (SP; Dunn, 1999). 31 participants (18 ASD, 13 TD) did not have a complete Sensory Profile, and three ASD participants did not complete the resting state scan, and were thus excluded from this study. Motion during the resting state scan led to the exclusion of 29 participants (23 ASD, 6 TD; see criteria in section 2.3 below). Data from one TD participant was excluded due to sleepiness during the scan. FMRI data of five participants (1 ASD, 4 TD) were corrupted by scanning artifacts, four ASD participants did not meet diagnostic criteria, two TD participants were excluded due to ASD-related medical conditions, one TD participant was excluded because of a history of ASD in the family, one ASD participant was excluded because of a later disclosed seizure disorder, and five participants (3 ASD, 2 TD) were excluded due to structural brain abnormalities discovered after the MRI session. Groups of included subjects were matched on gender, handedness, nonverbal IQ, and in-scanner head motion (root-mean-square displacement [RMSD]) (Table 1). Informed assent and consent were acquired from all participants and their caregivers, and participants were compensated for their time. All study protocols were approved by the San Diego State University and University of California San Diego Institutional Review Boards.

2.2. Diagnostic measures and behavioral reports

The ADOS (Lord et al., 1989) and the ADI-R (Lord et al., 1994) were administered to the ASD participants, and the Wechsler Abbreviated Scale of Intelligence, 2nd edition (WASI-II; Wechsler, 2011), Social Responsiveness Scale (SRS; Constantino and Gruber, 2005), and Sensory Profile Caregiver Questionnaire (SP; Dunn, 1999) were administered or completed for all participants (see Table 1 for summary statistics). ADOS and ADI-R are standardized, semi-structured assessments that evaluate behaviors indicative of ASD symptomatology. Domain scores of each assessment relevant to the current study (ADOS Social Interaction and Communication Combined; ADOS Stereotyped Behaviors and Restricted Interests; ADI-R Social Interaction; ADI-R Communication; and ADI-R Repetitive Behaviors) were entered into correlational analyses.

The WASI-II (Wechsler, 2011) assesses overall cognitive capabilities. It was administered to all participants to obtain verbal, nonverbal, and full-scale IQ scores for initial groupwise match-

Table 1
Participant demographics.

	ASD (n = 40)		TD (n = 38)		$\chi^2(1)$, *p*-value	
Gender	8 female		6 female		0.23, $p = 0.63$	
Handedness	7 left		6 left		0.04, $p = 0.84$	
	Mean (SD)	Range	Mean (SD)	Range	$t(76)$, *p*-value	% diff
Age in years	14.02 (2.76)	9.20–18.00	13.66 (2.65)	8.10–17.70	0.59, $p = 0.56$	0.026
RMSD	0.06 (0.03)	0.02–0.12	0.06 (0.03)	0.02–0.14	0.21, $p = 0.83$	0.024
% Time points retained	99.00 (2.00)	94–100	99.00 (2.00)	92–100	0.43, $p = 0.67$	0.002
WASI-II						
Verbal IQ	102.90 (18.09)	59–147	107.00 (9.57)	87–127	1.24, $p = 0.22$	0.034
Nonverbal IQ	107.25 (20.94)	53–145	103.68 (13.30)	62–129	0.89, $p = 0.38$	0.034
Full-scale IQ	105.70 (18.70)	61–141	105.66 (10.75)	79–126	0.01, $p = 0.99$	<0.001
SRS						
Cognition	77.08 (13.18)	45–105	43.18 (5.63)	36–56	14.63, $p < 0.001$	0.785
Communication	80.73 (10.29)	62–105	43.18 (4.76)	36–55	20.45, $p < 0.001$	0.869
SP Auditory	3.41 (0.74)	1.65–4.75	4.74 (0.28)	3.90–5.00	10.38, $p < 0.001$	0.280
ADOS						
Social Interaction	7.93 (2.31)	3–13	–	–	–	–
Communication	3.95 (1.58)	0–7	–	–	–	–
Combined	11.88 (3.23)	7–19	–	–	–	–
Stereotyped Behav/Restricted Interests	2.15 (1.53)	0–5	–	–	–	–
ADI-R*						
Social Interaction	19.26 (4.40)	10–28	–	–	–	–
Communication	13.34 (5.05)	2–24	–	–	–	–
Repetitive Behavior	5.68 (2.30)	1–12	–	–	–	–

Table 2
Auditory items of the Sensory Profile.

Threshold	Auditory Processing Item
Low	Responds negatively to unexpected or loud noises
Low	Holds hands over ears to protect ears from sound
Low	Has trouble completing tasks when the radio is on
Low	Is distracted or has trouble functioning if there is a lot of noise around
Low	Can't work with background noise
High	Appears to not hear what you say
High	Doesn't respond when name is called but you know the child's hearing is OK
High	Enjoys strange noises/seeks to make noise for noise's sake
High	Seems oblivious within an active environment

ing, and verbal IQ scores for further analyses. The SRS (Constantino and Gruber, 2005) is a caregiver questionnaire that measures social abilities in children and adolescents, and is comprised of 5 social domains (Awareness, Cognition, Communication, Motivation, and Autism Mannerisms). Responses are scored on a 4-point Likert scale (1 = not true, 2 = sometimes true, 3 = often true, 4 = almost always true); higher scores indicate greater severity. Two specific domains of the SRS were examined in the current study: Social Cognition (SRS-COG), which assesses the ability to interpret social cues, and Social Communication (SRS-COM), which includes expressive forms of social communication.

The Sensory Profile (SP; Dunn, 1999) assesses sensory responsivity and reactivity as reported by a caregiver, and consists of 125 items that target several modalities including auditory, visual, tactile, and olfactory processing. Nine items are classified as specific to the auditory modality – 5 low threshold items measure hypersensitivity, and 4 high threshold items measure hyposensitivity (see Table 2 for specific items). Caregiver responses are scored on a 5-point Likert scale (1 = always, 2 = frequently, 3 = occasionally, 4 = seldom, 5 = never); lower scores indicate greater sensory symptomatology.

This questionnaire was used to measure auditory processing abnormalities (see subsections 2.4 and 4.4 for a brief discussion). An independent samples *t*-test assessed whether there were any differences in the resulting auditory Sensory Profile (A-SP) scores between the TD and ASD groups. Additionally, for the ASD group, the auditory Sensory Profile scores were correlated with the other available neuropsychological assessment scores (WASI-II, ADI-R, ADOS, and SRS) described above, in order to test for any relationships between atypical processing of sounds, and behavioral and social symptoms of ASD.

2.3. MRI acquisition and image preprocessing

Imaging data were acquired on a GE 3T Discovery MR750 scanner using an 8-channel head coil at the University of California San Diego Center for Functional MRI (CFMRI). A standard FSPGR T1-weighted sequence was used to acquire high-resolution structural images (172 slices; repetition time [TR] = 8.136 ms; echo time [TE] = 3.172 ms; flip angle = 8°; field of view [FOV] = 25.6 mm; matrix = 256 × 256; resolution = 1 mm^3). Functional images were obtained using a single-shot gradient-recalled, echo-planar image pulse sequence. During the resting state scan, 180 whole-brain volumes were acquired (TR = 2000 ms; TE = 30 ms; slice thickness = 3.4 mm; flip angle = 90°; FOV = 22.0 mm; matrix = 64 × 64; in-plane resolution = 3.4 mm^2) over the duration of 6 min. Participants were instructed: "Keep your eyes on the cross. Let your mind wander, relax, but please stay as still as you can. Do not to fall asleep." Participants' adherence to the instructions to remain awake, with eyes open, was monitored with an MR-compatible videocamera. A separate mock scan session prior to the actual scan acclimated the participants to the MR environment and allowed them to practice staying still.

Data were processed and analyzed using Analysis of Functional NeuroImages (AFNI; Cox, 1996) and FMRI software library (FSL; Smith et al., 2004). Imaging data underwent a standard preprocessing pipeline of field map correction, slice-timing correction, motion correction, and spatial-smoothing with a Gaussian kernel of 6 mm FWHM. Structural images were normalized to the MNI152 template; functional images were coregistered to the structural images and resampled to 3 mm isotropic voxels. Functional time series data were bandpass-filtered (0.008 < f < 0.08 Hz) with a second-order

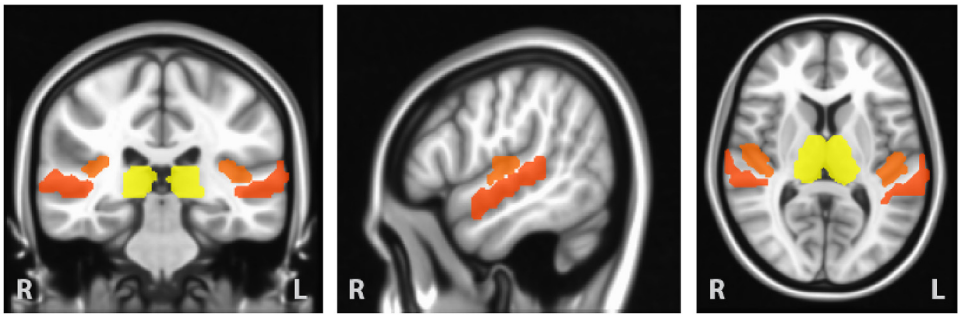

Fig. 1. Auditory and thalamic regions of interest from the Harvard-Oxford anatomical atlas. Primary auditory regions (Heschl's Gyrus) are shown in orange, secondary auditory regions (Superior Temporal Gyrus) are shown in red, and the thalamic ROIs are shown in yellow. Average timecourses for the functional connectivity analyses were derived from grey-matter masked left and right hemisphere ROIs separately. In an initial analyses step, average timecourses were derived from the combined "auditory" HG and STG ROIs. Post-hoc analyses then assessed whether results differed between primary and secondary auditory cortical regions.

Butterworth filter. White matter and lateral ventricles were segmented, and the average time series data from these segmentations were then extracted and served as nuisance regressors along with their first order derivatives. The 6 rigid-body motion parameters (3 rotation, 3 translation) and their first order derivatives were used as additional nuisance regressors. To minimize any effects of head motion (Power et al., 2012; Van Dijk et al., 2012), these parameters were also used to censor time points with motion exceeding 0.5 mm. No participants in the current study suffered >10% data loss due to censoring, and groups did not differ in the amount of censored time points (Table 1). Finally, global signal regression, a controversial tool used for noise reduction in functional connectivity data, was not implemented so as to avoid spurious deactivation effects (Fox et al., 2009; Jones et al., 2010; Murphy et al., 2009; Weissenbacher et al., 2009).

2.4. Functional connectivity analyses

Left and right hemisphere ROIs were created for auditory cortical regions by combining grey-matter masked Heschl's Gyrus (HG) and superior temporal gyrus (STG) ROIs from the Harvard-Oxford atlas (Desikan et al., 2006), as shown in Fig. 1, and were resampled to EPI space. Average timecourses were extracted from the two auditory ROIs, and from left and right thalamus (as defined in the Harvard-Oxford atlas). Interhemispheric connectivity was assessed by correlating the timecourses from the left and right auditory cortical ROIs for each subject. All correlation coefficients were Fisher *z*-transformed. An independent samples *t*-test was used to test for differences in auditory interhemispheric connectivity between the TD and ASD groups. Similarly, average timecourses from left and right thalamus were Pearson correlated with those extracted from the left and right auditory cortical ROIs. A repeated measures ANOVA with group (TD, ASD) as a between subject factor revealed that there were no significant hemispheric differences in thalamocortical connectivity ($F(2.34,178.15) = 2.78$, *ns*, Greenhouse-Geisser sphericity corrected), nor any significant hemisphere by group interactions. The main effect of group was significant ($F(1,76) = 8.02$, $p < 0.01$). Thalamocortical connectivity was, therefore, averaged across the four possible ipsi- and contralateral comparisons for each subject. Differences in mean auditory thalamocortical connectivity between the TD and ASD groups were then assessed using an independent samples *t*-test. In a post-hoc test, the auditory cortical ROIs were split into primary (HG) and secondary (STG) ROIs to examine whether any differences found were driven by auditory regions implicated in more basic sensory (HG) vs. higher-order (STG) processing of sound.

Next, we assessed whether strength of interhemispheric and thalamocortical connectivity (as measured by the Fisher *z*-transformed correlation coefficients) was related to sensory and sensory-related social symptoms in ASD. Correlations were carried out across all participants irrespective of ASD diagnosis for verbal IQ (WASI-II) and the auditory Sensory Profile scores. The relationship between functional connectivity and the two relevant SRS subscales (Cognitive [SRS-COG] and Communicative [SRS-COM]) was assessed separately for the TD and ASD group, due to the design of the SRS scales and inherently non-overlapping distribution of scores between the two groups. Additional analyses including the two relevant ADOS subscales (Social Interaction and Communication Combined, and Stereotyped Behaviors and Restricted Interests), which were not available for the TD participants, were carried out for the ASD group only. In-scanner motion (as measured by RMSD) and age were partialled out in all correlation analyses as developmental effects on functional connectivity were not the focus of this study. A separate analysis of age effects revealed that the only significant correlation (partialling out motion) was between age and HG (but not STG) thalamocortical connectivity in the TD (HG: $r(36) = -0.35$, $p < 0.05$, STG: $r(36) = -0.24$, $p = 0.15$) but not in the ASD group (HG: $r(38) = -0.08$, $p = 0.61$, STG: $r(38) = 0.11$, $p = 0.51$).

Lastly, the relationship between interhemispheric and thalamocortical connectivity was assessed. Pearson correlations were performed to test whether atypical interhemispheric and thalamocortical connectivity were independent, or present in the same individuals, the latter suggesting a shared developmental origin or compensatory neural mechanisms. To test this further, participants with ASD were split into subgroups based on their pattern of interhemispheric and thalamocortical connectivity. A median-split on interhemispheric and thalamocortical connectivity yielded four subgroups: low interhemispheric – low thalamocortical connectivity ($n = 12$), low-high ($n = 8$), high-low ($n = 8$) and high–high ($n = 12$). The TD participants formed a fifth group. A one-way ANOVA tested for differences in auditory Sensory Profile scores between the five groups.

3. Results

3.1. Sensory profile

Clear differences in Sensory Profile auditory scores (mean of nine auditory items) were observed between the TD and ASD groups ($t(76) = -10.38$, $p < 0.001$; Fig. 2A). Additionally, while four of the items were designated as indexing "hypersensitivity" and five as measuring "hyposensitivity" to sound, there was a high positive correlation between the two categories ($r(76) = 0.73$, $p < 0.001$; this was true within the ASD group when assessed separately as well: $r(38) = 0.48$, $p < 0.005$). For this reason, we averaged across all nine items to yield an overall auditory Sensory Profile (A-SP) score for each subject that was subsequently used in all further analyses. Cor-

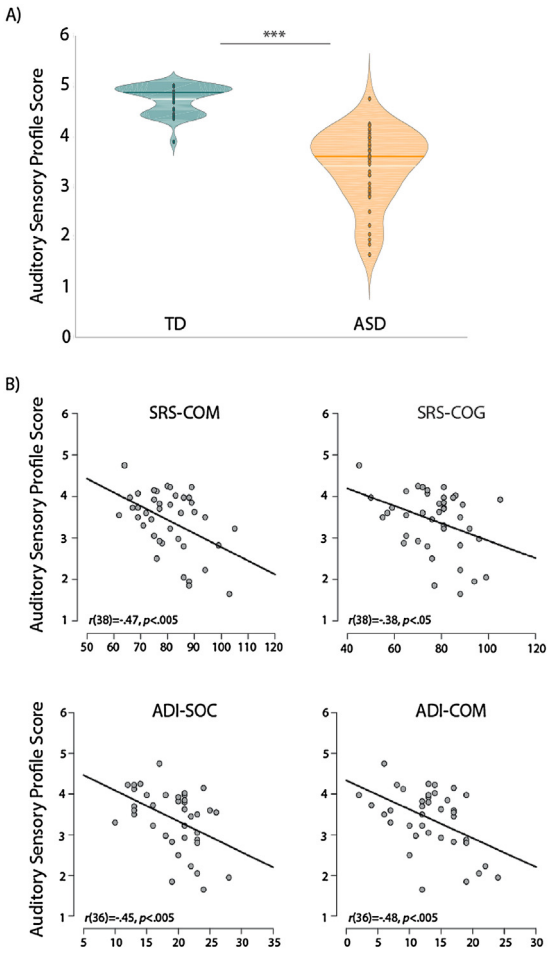

Fig. 2. (A) Significant difference in auditory Sensory Profile scores (average of all auditory items) between the TD and ASD groups (*** indicated $t(76) = -10.38$, $p < 0.001$;,dark horizontal line = median, white horizontal line = mean). Lower scores indicate greater auditory processing deficits. (B) Significant correlations between auditory Sensory Profile scores and SRS and ADI-R subscales for the ASD group.

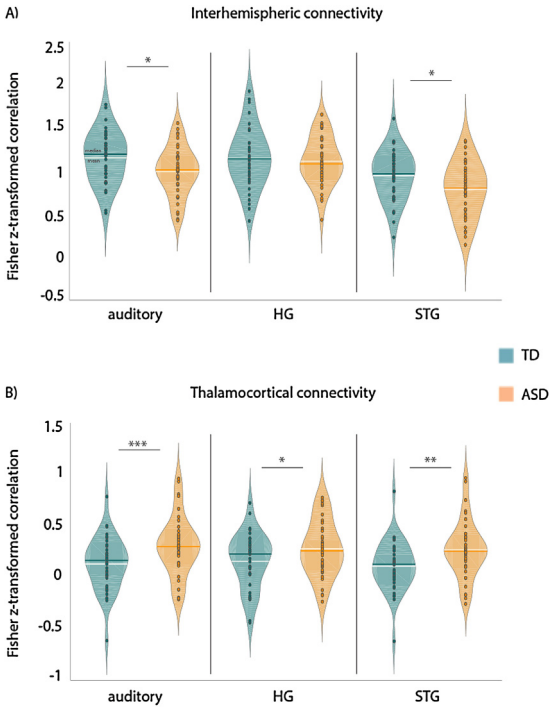

Fig. 3. Differences in interhemispheric (A) and thalamocortical (B) functional connectivity between the TD (green) and ASD (orange) groups, for the combined "auditory" ROI, and split into primary (HG) and secondary (STG) auditory cortical regions. Correlations were Fisher z-transformed, dark horizontal line = median, white horizontal line = mean, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$.

relations with symptom severity measures were carried out for the ASD group only, showing significant relationships between auditory sensory deficits and higher SRS-COM ($r(38) = -0.46$, $p < 0.005$), SRS-COG ($r(38) = -0.38$, $p < 0.05$), ADI-R communication (ADI-COM: $r(36) = -0.48$, $p < 0.005$) and social interaction scores (ADI-SOC: $r(36) = -0.45$, $p < 0.005$; Fig. 2B). Note that lower A-SP scores indicate great sensory deficits. This suggests that atypical auditory processing in ASD as measured by the Sensory Profile is related to more severe sociocommunicative symptoms.

3.2. Interhemispheric connectivity

Interhemispheric connectivity of the left and right auditory combined ROI was significantly lower in the ASD than TD group ($t(76) = -2.40$, $p < 0.05$, Fig. 3A). A post-hoc split of the ROI into a primary auditory cortex (HG) ROI and a "secondary auditory" ROI covering the superior temporal gyrus (STG) revealed that this difference was driven by weaker interhemispheric connectivity of secondary auditory areas in ASD ($t(76) = -2.37$, $p < 0.05$), while interhemispheric connectivity of HG did not differ significantly between the ASD and TD groups ($t(76) = -0.56$, *ns*). Next, we assessed the relationship between the strength of interhemispheric connectivity, atypical auditory processing (as measured by the A-SP) and social-behavioral symptom severity.

Interhemispheric connectivity between auditory regions was positively correlated (after partialling out effects of motion and age) with verbal IQ ($r(74) = 0.27$, $p < 0.05$), and negatively with the A-SP score ($r(74) = 0.23$, $p < 0.05$), indicating that reduced interhemispheric connectivity of auditory cortical areas was related to greater deficits in auditory sensory processing and lower verbal IQ. In order to assess whether the correlation of auditory interhemispheric connectivity with atypical sensory processing scores was modality specific, we also assessed the correlations between auditory interhemispheric connectivity and the average visual and tactile Sensory Profile scores of the same participants. Neither of these correlations was significant (visual: $r(74) = 0.12$, *ns*; tactile: $r(74) = 0.13$, *ns*). As there was a significant difference in A-SP scores between the TD and ASD groups (see section 3.1), we also performed the correlation analysis between interhemispheric connectivity and A-SP scores for the ASD group only. This correlation was not significant, suggesting that the significantly higher A-SP scores and significantly higher interhemispheric connectivity of the TD subjects drove the result seen for the whole group.

3.3. Thalamocortical connectivity

The ASD group showed significantly higher connectivity between auditory cortical regions and thalamus ($t(76) = 2.77$, $p < 0.005$, Fig. 3B). This was true for both HG ($t(76) = 2.0$, $p < 0.05$) and the STG ROI ($t(76) = 2.71$; $p < 0.01$). In order to assess how increased thalamocortical connectivity relates to ASD symptom severity, we correlated strength of connectivity with the A-SP scores and ADOS and SRS subscales. For the ASD participants, the strength of thalamocortical connectivity correlated negatively (partialling out effects of motion and age) with the ADOS repetitive behavior subscale (ADOS-REP: $r(30) = -0.39$, $p < 0.05$), the cognitive SRS subscale (SRS-COG: $r(36) = -0.38$, $p < 0.05$), and marginally with the communicative SRS subscale (SRS-COM: $r(36) = -0.32$, $p = 0.054$).

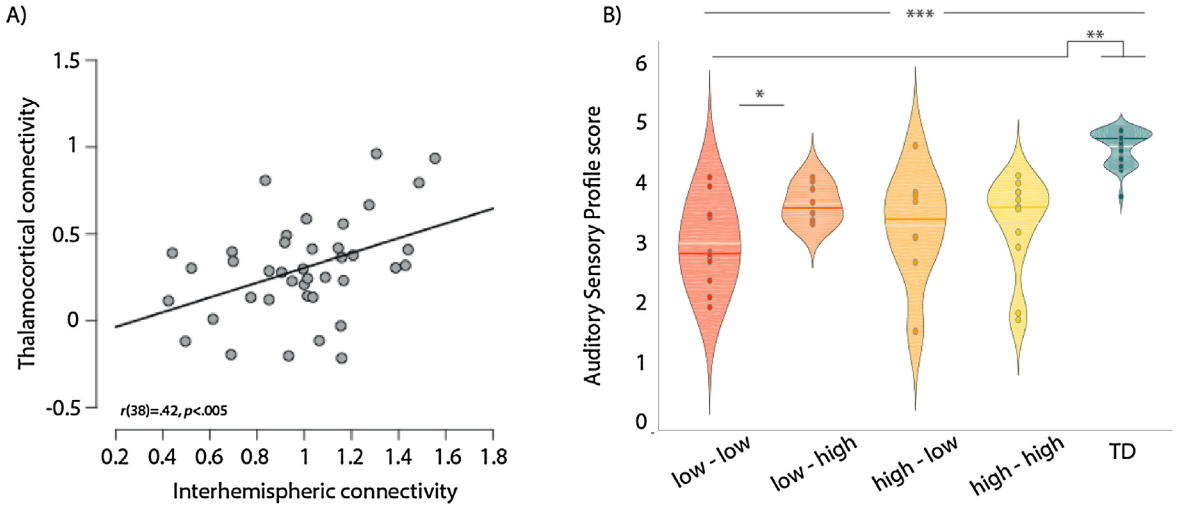

Fig. 4. (A) Positive correlation between interhemispheric (left and right auditory cortex) and auditory thalamocortical connectivity. (B) Auditory Sensory Profile scores for ASD subjects split by their pattern of interhemispheric and thalamocortical connectivity (low – low: low interhemispheric, low thalamocortical connectivity; low – high: low interhemispheric, high thalamocortical connectivity; high – low: high interhemispheric, low thalamocortical connectivity; high – high: high interhemispheric, high thalamocortical connectivity). Lower auditory Sensory Profile scores indicate more atypical sound processing. Dark horizontal line = median, white horizontal line = mean; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$.

SRS subscale scores were also available for the TD group, but correlations with strength of thalamocortical connectivity were not significant.

Increased thalamocortical connectivity was not related to auditory sensory deficits (A-SP scores) in the ASD group ($r(36) = 0.18$, *ns*). Together with the negative correlations of thalamocortical connectivity with the ADOS-REP, SRS-COG, and SRS-COM measures indicating improved functioning with higher thalamocortical connectivity, this suggests that atypically increased thalamocortical connectivity might reflect a compensatory mechanism. We next assessed whether the same ASD participants who showed increased auditory thalamocortical connectivity also showed increased interhemispheric connectivity between left and right auditory cortex. The strength of interhemispheric connectivity correlated positively (partialling out effects of motion and age) with the strength of thalamocortical connectivity in the ASD group ($r(38) = 0.42$, $p < 0.005$). Interestingly, this was not true for the TD group ($r(36) = 0.28$, *ns*). Despite the significant positive correlation in the ASD group, the pattern of connectivity seen in each subject varied, with some subjects also showing high thalamocortical connectivity but low interhemispheric connectivity, or low thalamocortical but high interhemispheric connectivity (Fig. 4A). To investigate the interaction between thalamocortical and interhemispheric connectivity of the auditory network further, we split the ASD participants by their pattern of interhemispheric and thalamocortical connectivity. This revealed a significant main effect of group ($F(4,73) = 30.245$, $p < 0.001$, Fig. 4). Post-hoc *t*-tests showed significant differences between the ASD and TD groups, but also between those subjects with low interhemispheric and low thalamocortical connectivity compared to the ASD subjects who had low interhemispheric but increased thalamocortical connectivity ($t(18) = -2.53$, $p < 0.05$).

4. Discussion

Many previous studies have reported altered sensory processing in autism (Marco et al., 2011), especially in the auditory domain (O'Connor, 2012). In the current study, we showed that this is reflected in Sensory Profile scores with greater deficits in the ASD compared to the TD group for the auditory modality. Importantly, these auditory deficits were related to symptom severity in ASD, particularly within the domain of social and communicative behavior. Greater auditory sensory deficits were also related to reductions in interhemispheric functional connectivity between auditory regions. Finally, increased auditory thalamocortical functional connectivity was not related to auditory sensory deficits, but was correlated with decreased repetitive behaviors and fewer social symptoms in the ASD group, suggesting a possible compensatory mechanism. Overall, these findings suggest that sensory impairments, specifically in the auditory domain, are related to core symptomatology in ASD.

4.1. Relationship between sensory and social features in ASD

The ability to acquire and filter incoming sounds is fundamental to the development of language and communication (Benasich et al., 2002), which are inherently social. Impairments in auditory processing may have cascading effects on higher-level social and communicative abilities. Our results showed that greater auditory sensory deficits in ASD were linked to increased symptom severity in several social domains including social interaction, social cognition, and communication and language. These findings suggest a connection between sensory and social features in ASD.

Atypical responses to auditory stimuli have been well documented in ASD (Dahlgren and Gillberg, 1989; Hilton et al., 2010; Tomchek and Dunn, 2007). On the one hand, individuals with ASD have been reported to show greater proficiency in tasks involving simple, low-level auditory stimuli (e.g., pitch discrimination) compared to their TD peers (Bonnel et al., 2010). On the other hand, there are reports of impairments in the processing of complex auditory stimuli often present in social environments such as speech in those with ASD (for a review, see O'Connor, 2012). Further auditory deficits in ASD have included weaker performance in auditory filtering tasks compared to TD (Lane et al., 2010; Tomchek and Dunn, 2007; Wiggins et al., 2009), as well as slower responses in orienting to social (and nonsocial) auditory stimuli than TD controls (Baranek et al., 2013; Dawson et al., 2004). These findings of atypical auditory processing, particularly in social contexts, may have an impact on language development and contribute to communicative difficulties (Tomchek et al., 2014). In our study, reported auditory abnormalities as measured by the Sensory Profile were

highly related to the severity of social and communicative symptoms.

Our findings of increased auditory deficits associated with greater autism symptomatology are also consistent with recent evidence linking specific sensory abnormalities to socio-communicative deficits (Jao Keehn et al., 2016; Liss, 2006; Stewart et al., 2016; Watson et al., 2011), as well as stereotyped and restricted behaviors in children with ASD (Gabriels et al., 2008; Hilton et al., 2010; Kern et al., 2007a,b; Wiggins et al., 2009). Although deficits in overall sensory processing have been correlated with impairments in social responsiveness and interaction (Baker et al., 2008; Ben-Sasson et al., 2009; Matsushima and Kato, 2013), this is to our knowledge the first study in ASD that has examined both auditory sensory processing abnormalities and intrinsic functional connectivity between auditory regions (see subsections 4.2 and 4.3), in relation to social features of autism.

4.2. Reduced interhemispheric connectivity in ASD

Analyses examining interhemispheric connectivity between auditory cortices showed weaker connectivity in ASD compared to TD participants, in accordance with our hypothesis. This finding was largely driven by altered connectivity between secondary auditory areas (STG), rather than primary regions (HG). Previous studies have provided similar evidence of decreased interhemispheric connectivity in STG (Anderson et al., 2011; Lo et al., 2011). While this region has been implicated in both abnormal auditory processing (Anderson et al., 2011) and social intelligence (Baron-Cohen et al., 1999), the relationship between reduced interhemispheric connectivity and sensory and social symptoms had not previously been tested directly. Our results show that lower interhemispheric connectivity was associated with greater sensory deficits in children with ASD, suggesting less robust communication between auditory cortical areas for processing sensory information.

It is important to note that modality-specific items on the Sensory Profile may not be exclusively sensory as many of the items concern behaviors that are social and sensory. Moreover, they may not exclusively tap into a single sensory modality (even when labeled "auditory," "visual," etc.) and are not age-normed. With this caveat in mind, interhemispheric functional connectivity in auditory areas was correlated with the A-SP scores, while correlations between interhemispheric connectivity and visual and tactile sensory processing scores were not significant. Combined, these results imply that the Sensory Profile can measure modality-specific deficits, and more importantly, that auditory processing impairments are reflected in reduced functional connectivity between the two hemispheres.

Our results further indicated that reduced interhemispheric connectivity between auditory cortical areas was correlated with lower verbal IQ. These findings are consistent with previous research examining neuropsychological outcomes in children and adolescents with corpus callosum abnormalities (CCA, which include agenesis, partial agenesis, hypoplasia, hyperplasia, and dysgenesis). In one study, CCA were frequently associated with intellectual disabilities, and 6.6% of the sample also presented with diagnoses of ASD (Margari et al., 2016). A multitude of studies investigating CCA in autism have reported a reduction in the total or partial volume of the corpus callosum (Aoki et al., 2013; Barbeau et al., 2015; Frazier and Hardan, 2009; Travers et al., 2012). These findings suggest that atypical structural development of the corpus callosum may impede interhemispheric functional interactions between brain regions.

4.3. Increased thalamocortical connectivity in ASD

ASD participants showed increased thalamocortical connectivity compared to TD participants for both primary and secondary auditory regions. These findings are consistent with previous studies demonstrating atypical thalamocortical connectivity in ASD (Nair et al., 2013, 2015). Unexpectedly, however, increased functional connectivity in ASD did not correlate with auditory Sensory Profile scores. Thalamocortical connectivity was inversely related to social symptomatology. While it could be argued that early abnormalities of auditory processing are likely to have downstream effects on social abilities, it is also conceivable that auditory thalamocortical overconnectivity is compensatory. A recent study demonstrated similar associations between increased temporal lobe thalamocortical connectivity and improved communication and language skills (Nair et al., 2015). This notion is substantiated by our findings of increased thalamocortical connectivity, which was related to fewer symptoms in social cognition and communication, as well as fewer repetitive behaviors within the ASD group only; there was no relationship between thalamocortical connectivity and social and communicative behavior in the TD group. Critically, the more atypical thalamocortical connectivity was in ASD, the more typical (closer to TD norms) the manifested symptoms were.

We further assessed the relation between interhemispheric and thalamocortical connectivity in ASD. Results indicated an overall significant positive correlation between interhemispheric and thalamocortical connectivity in which participants with increased interhemispheric connectivity also showed atypically high thalamocortical connectivity (high–high), and participants with atypically reduced interhemispheric connectivity also showed low thalamocortical connectivity (low–low). Some participants, however, had a more mixed pattern (low interhemispheric connectivity paired with high thalamocortical connectivity [low-high] and vice versa [high–low]). Importantly, auditory sensory deficits were more severe in the low–low ASD subgroup compared to the subgroup with low interhemispheric connectivity but high thalamocortical connectivity. This supports the hypothesis that in some cases of ASD increased auditory thalamocortical connectivity may reflect a compensatory mechanism for sensory processing when interhemispheric connectivity is reduced. One possible explanation for this mechanism is that with disrupted or reduced interhemispheric connectivity, thalamocortical connections strengthen to maintain synchrony between the two hemispheres (Schmidt, 2003; Tyszka et al., 2011). The sub-group of ASD participants with high interhemispheric and increased thalamocortical connectivity, on the other hand, did not show reduced sensory symptom severity. This suggests that the interaction between interhemispheric and thalamocortical connectivity is complex, and likely influenced by the developmental trajectory of other brain regions. It is plausible that increased thalamocortical connectivity is a compensatory response to a lack of interhemispheric synchronization – as observed in patients with agenesis of the corpus callosum – while increased thalamocortical connectivity in the presence of normal interhemispheric connectivity may reflect a different developmental trajectory that does not share the same compensatory function. Future studies are needed to unravel the complex interactions of brain network development by implementing longitudinal designs to track neural and behavioral development from infancy through early childhood.

4.4. Considerations and concerns

Several considerations and general concerns for the current study must be taken into account. Firstly, the constraints of scanning a clinical and developmental population such as ASD necessitated the inclusion of primarily high-functioning partici-

pants who were able to keep still during scanning. It remains unclear whether our findings would extend to lower functioning segments of the autism spectrum.

Secondly, it is important to consider that most of the significant correlations were based on parent-report measures, with the exception of repetitive behaviors, which were measured by the clinician's observations during ADOS. Given such a context, there may be discrepancies between the observed sensory and social behaviors and the actual processing that contribute to the scores. These parent report measures are nevertheless informative, at least until a better means of directly recording neural and behavioral processing in realistic social environments becomes available.

Thirdly, unusual sensory responses have generally been characterized in the ASD literature as following one of two behavioral response patterns: hypersensitivity and hyposensitivity (Baranek et al., 2006; O'Neill and Jones, 1997; Rosenhall et al., 1999). Individuals who show hypersensitivity have a low threshold for, and are over-stimulated by sensory stimuli (e.g., avoidance of loud sounds); those who show hyposensitivity have a high threshold for, and are under-stimulated by sensory stimuli (e.g., diminished response to loud sounds). This distinction, however, was less clear in our sample assessed with the Sensory Profile, due to the high positive correlation between auditory hypersensitivity and hyposensitivity items, which could be ascribed to the tendency of some Sensory Profile items to be more social than sensory in nature (see subsection 4.2). Additionally, while some researchers have supported a prevalence of hyposensitive behaviors in children with ASD (Baranek et al., 2006, 2013; Ben-Sasson et al., 2009; Rogers and Ozonoff, 2005), others have suggested coexisting response patterns of hypersensitivity and hyposensitivity, as well as reliable differences between ASD and TD for both (Hirstein et al., 2001; Kern et al., 2007a,b). Future studies could examine the relation between auditory processing and thalamocortical functional connectivity—which would most likely reflect early auditory processing—more directly by assessing sensory thresholds with psychophysics.

4.5. Conclusions

Using diagnostic assessments, observational reports of sensory and social behaviors, and functional neuroimaging, we showed strong correlations between auditory sensory processing and symptom severity in ASD. Moreover, reduced interhemispheric functional connectivity in ASD was linked to increases in both sensory and social symptomatology, suggesting less robust communication between auditory cortices for processing and interpreting sensory input. Increased thalamocortical functional connectivity between thalamus and auditory cortices, however, was associated with decreased repetitive behaviors and social deficits, indicating a possible compensatory mechanism in ASD that may serve to ameliorate these symptoms. Together, these findings suggest that sensory deficits are linked to impairments in the core features of autism, specifically, social interaction and communication.

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Conflict of interest

None.

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