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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-

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