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SHORT REPORT

Increased resting-state thalamocortical functional connectivity in children and young adults with autism spectrum disorder

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Abstract

There is converging evidence that abnormal thalamocortical interactions contribute to attention deficits and sensory sensitivities in autism spectrum disorder (ASD). However, previous functional MRI studies of thalamocortical connectivity in ASD have produced inconsistent findings in terms of both the direction (hyper vs. hypoconnectivity) and location of group differences. This may reflect, in part, the confounding effects of head motion during scans. In the present study, we investigated resting-state thalamocortical functional connectivity in 8–25 year-olds with ASD and their typically developing (TD) peers. We used pre-scan training, on-line motion correction, and rigorous data quality assurance protocols to minimize motion confounds. ASD participants showed increased thalamic connectivity with temporal cortex relative to TD. Both groups showed similar age-related decreases in thalamic connectivity with occipital cortex, consistent with a process of circuit refinement. Findings of thalamocortical hyperconnectivity in ASD are consistent with other evidence that decreased thalamic inhibition leads to increase and less filtered sensory information reaching the cortex where it disrupts attention and contributes to sensory sensitivity. This literature motivates studies of mechanisms, functional consequences, and treatment of thalamocortical circuit dysfunction in ASD.

Lay Summary

The thalamus is a deep brain structure that receives information from the senses and amplifies or inhibits its relay to the cortex via thalamocortical circuits. Using functional brain imaging, we found increased communication between the thalamus and specific cortical regions in children and young adults with autism spectrum disorder (ASD) compared with their typically developing peers. We hypothesize that increased thalamocortical communication in ASD reflects reduced thalamic inhibition of irrelevant sensory information from being relayed to the cortex, and contributes to attention deficits and sensory sensitivities.

KEYWORDS
autism spectrum disorder, functional connectivity, MRI, resting state, sensory sensitivity, thalamus

INTRODUCTION

Converging evidence from genetics, animal models, neuroimaging and sleep electrophysiology studies implicate thalamocortical circuit dysfunction in the pathophysiology of autism spectrum disorder (ASD). According to the "leaky thalamus" hypothesis, which is based on a genetic mouse model of ASD, deficits in filtering out

irrelevant sensory stimuli from being relayed to the cortex compromises attention and contributes to sensory sensitivities (Schmitt & Halassa, 2017). The present study investigated the hypothesis of unfiltered thalamocortical communication in ASD in childhood through early adulthood using resting-state functional connectivity magnetic resonance imaging (rs-fcMRI). We expected this unfiltered communication to be reflected by increased thalamocortical connectivity in individuals with ASD compared with their typically developing (TD) peers.

Several previous studies demonstrate abnormal thalamocortical connectivity in ASD (Ayub et al., 2021; Cerliani et al., 2015; Green et al., 2017; Linke et al., 2018; Linke et al., 2021; Mizuno et al., 2006; Nair et al., 2013; Nair et al., 2015; Woodward et al., 2017), but the direction and anatomical locations of group differences vary across studies. The primary culprits accounting for inconsistent findings in ASD neuroimaging research are small sample sizes, different sample characteristics (e.g., age), and head motion during scanning, which can lead to spurious findings (Van Dijk et al., 2012). The largest study utilized the publicly available Autism Brain Imaging Data Exchange (ABIDE) database ($n = 556$) (Woodward et al., 2017) and reported *increased* thalamocortical connectivity in temporal, sensorimotor and prefrontal cortices in ASD individuals from ages 6 through 40, with the strongest group differences in older adolescents. In contrast with other reports (Mizuno et al., 2006; Nair et al., 2013; Nair et al., 2015), there were no regions of decreased thalamocortical connectivity in ASD. In the present study, we minimized the potentially confounding effects of motion by using prescan training and acclimatization protocols, prospective motion correction during scanning, and rigorous quality criteria on acquired data.

The present study includes a more restricted age range (8–25 years) to examine functional connectivity from childhood to early adulthood. Adolescence is a period of rapid brain development including axonal growth, myelination and synaptic pruning. These changes are reflected in studies of structural connectivity and correlate with improved executive function (Goddings et al., 2021). In TD youth (8–20 years), functional and structural connectivity of the thalamus with prefrontal and parietal cortex increases with age, while temporal, sensorimotor and occipital cortices show an age-related decrease in connectivity, presumably reflecting circuit refinement (Alkonyi et al., 2011; Huang et al., 2021). In addition to characterizing group differences, we investigated whether individuals with ASD show different age-related changes in thalamocortical connectivity, which would suggest that altered circuit development continues beyond childhood.

METHODS

Participants

Eighty-seven individuals, aged 8–25, participated in the study (51 ASD, 36 TD). Table 1 shows the demographic characteristics of the sample before and after exclusion based on head motion. The final sample was comprised of 34 ASD and 35 TD participants (19 ASD participants

TABLE 1 Participant characteristics

All participants	**TD ($n = 36$)**	**ASD ($n = 51$)**	***t*(85)**	***p***
Age	14.4 ± 4.6	13.9 ± 3.8	0.55	0.58
Sex	6F/30M	7F/44M	$\chi^2 = 0.14$	0.76
Estimated IQ[a]	116.4 ± 16.3	113.7 ± 14.5	0.81	0.42
Handedness[b]	56.7 ± 54.2	40.9 ± 51.4	1.37	0.17
Mean parental education	16.1 ± 2.8	15.9 ± 2.2	0.33	0.74
Residual motion	0.062 ± 0.04	0.099 ± 0.07	−3.08	0.003
% Artifactual slices	5.8 ± 4.8	10.3 ± 9.1	−2.68	0.009
Motion-matched sample	**TD ($n = 35$)**	**ASD ($n = 34$)**	***t*(67)**	***p***
Age	14.6 ± 4.6	14.3 ± 3.8	0.21	0.83
Sex	6F/29M	6F/28M	$\chi^2 = 0.003$	0.99
Estimated IQ[a]	116.3 ± 16.5	114.9 ± 15.8	0.37	0.71
Handedness[b]	56.6 ± 55	42.5 ± 53	1.08	0.28
Mean parental education	16.2 ± 2.9	16.1 ± 2.2	0.22	0.83
Mean residual motion	0.058 ± 0.03	0.063 ± 0.03	−0.56	0.56
% Artifactual slices	5.4 ± 4.2	5.9 ± 4.3	−0.54	0.59

[a]Intelligence quotient (IQ), based on the full scale scores on the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).
[b]Based on the modified Edinburgh Handedness Inventory (Oldfield, 1971; White & Ashton, 1976) Laterality scores of −100 and +100 denote exclusive use of left or right hand, respectively.

took psychotropic medications, Table S1). Groups did not differ in age, sex or parental education, ASD participants were recruited from the Autism Consortium database (http://www.autismconsortium.org), excluding those with known genetic syndromes (e.g., tuberous sclerosis, fragile X, RETT syndrome). Diagnoses were made by experienced clinicians using the Autism Diagnostic Interview-Revised (Rutter et al., 2003) and the Autism Diagnostic Observation Schedule (Lord et al., 1999). All participants had an IQ ≥ 70 on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) and were screened to exclude substance abuse or dependence in the past 6 months and any contraindications for MRI. TD participants were recruited from the community through advertisements. The study was approved by the Partners Human Research Committee. After the procedures were explained, research staff obtained written informed consent from participants ≥ 18 years, and consent of the parent and assent of participants < 18 years. All participants were paid, children also received small gifts.

Imaging protocol

Preparation

Prior to their imaging session, participants received a link to a social story that prepared them for what to expect during their MRI visit (https://prezi.com/afxtce8yu65_/blastoff-manoach-lab-social-story/). They completed a mock scan to acclimate them to the confinement and sounds of the MRI environment and to practice lying still. Whenever possible the mock scan was conducted on a separate day from the actual scan. During both the mock and actual scan, participants wore earplugs (29 dB rating) and headphones to attenuate noise. They watched a movie of their choice during structural scans.

MRI acquisition

Scanning was performed with a 3T Siemens Trio TIM whole-body-high-speed imaging device equipped with a 32-channel head coil. Head stabilization was achieved with cushioning. At the start of each scan, the Autoalign system aligned slice positioning (van der Kouwe et al., 2005). Anatomical images were acquired using a 3D multiecho magnetization-prepared rf-spoiled rapid gradient-echo MEMPRAGE (T1 weighted) sequence with EPI based volumetric navigators for real time motion correction (Tisdall et al., 2012; van der Kouwe et al., 2008) TR = 2530 ms, Flip Angle = 7°, TEs = 1.74 ms/3.6 ms/5.46 ms/7.32 ms, iPAT = 2; FOV = 56 mm; 176 in-plane sagittal slices; voxel size = 1 mm^3 isotropic; scan duration 6 m 12 s. Two rs-fcMRI scans were obtained with a gradient-echo T2*-weighted sequence for blood oxygen level–dependent (BOLD) contrast (TR = 3000 ms, flip angle = 85°, TE = 30 ms, 47 contiguous horizontal slices parallel to the intercommissural plane, voxel size = 3 × 3 × 3 mm, interleaved, scan duration = 6 min). The functional sequences included prospective acquisition correction (PACE) for head motion (Thesen et al., 2000).

MRI data analyses

Preprocessing

Resting state functional scans were preprocessed using SPM8 (Wellcome Department, London, UK) implemented in MATLAB. Anatomical images were segmented into white matter, gray matter, and cerebrospinal fluid masks, corrected for slice acquisition time, spatially realigned to the reference image, resliced, and coregistered with the functional images. The volumes were normalized to the Montreal Neurological Institute template and spatially smoothed using a Gaussian kernel with a full-width-at-half-maximum of 6 mm.

Quality assurance

Artifact Detection Tools (ART; http://www.nitrc.org/projects/artifact_detect/) were used to identify artifactual volumes (head displacement > 1 mm from the previous frame, or the global mean intensity > 3 SD above the entire functional scan). Residual head motion was calculated as the root-mean-square of translation parameters (Van Dijk et al., 2012). Participants with residual motion or number of artifactual volumes > 2 SD above the sample mean were excluded to minimize spurious correlations in resting-state networks (1 TD, 17 ASD).

Functional connectivity analyses

Subject-level analyses utilized the CONN Toolbox v17 implemented in Matlab (Whitfield-Gabrieli & Nieto-Castanon, 2012) using a component base noise reduction method, Anatomical CompCor (Behzadi et al., 2007), rather than global signal regression, to remove physiological and other noise (Chai et al., 2012). Preprocessing involved applying a temporal bandpass filter of 0.008 – 0.09 Hz to the time series. Residual head motion parameters were added as regressors and artifactual volumes (flagged by ART) were scrubbed in CONN.

We first quantified thalamic connectivity with the cortex using a large cortical mask that included somatosensory, motor, temporal and prefrontal regions. These regions were selected a priori based on findings of increased connectivity in ASD (Woodward et al., 2017). The thalamus was defined using the probabilistic FSL-Oxford-Thalamic-Connectivity-Atlas with a probability threshold of 25 (Behrens et al. 2003). We also quantified cortical connectivity with the thalamus using 6 bilateral

cortical seeds (prefrontal, motor cortex/supplementary motor area, somatosensory, temporal, posterior parietal, occipital) defined in prior studies (Woodward et al., 2017; Woodward & Heckers, 2016). For both of these complementary approaches, functional connectivity maps were generated for each participant by extracting the average time course of the BOLD signal from the seed region(s) and correlating it with every other gray matter voxel in the mask. The resulting Pearson coefficients were transformed into Fisher's z. The connectivity analyses for the two runs for each subject were averaged.

Group-level analyses were implemented in Permutation Analysis of Linear Models (PALM; Winkler et al., 2014) which uses nonparametric threshold-free cluster enhancement for type I error correction controlling the familywise-error (FWE) rate (10 k permutations; $p_{\text{FWE-corrected}} \leq 0.05$) (Smith & Nichols, 2009; Winkler et al., 2015; Winkler et al., 2016). We calculated linear regression models with factors for Age, Group, and Age x Group separately for both thalamic and cortical seed analyses.

Structural MRI analysis

Thalamic volume was estimated based on automated FreeSurfer subcortical segmentation (Fischl et al., 2002).

RESULTS

Thalamic seed analyses

Relative to TD participants, those with ASD showed greater thalamic connectivity with lateral temporal cortex bilaterally that survived FWE correction only in the right hemisphere, spanning the anterior portions of the middle and superior temporal gyri (Figure 1 & Table 2; also see Figure S1 for uncorrected statistical maps). No brain regions showed reduced thalamic functional connectivity in ASD, even at an uncorrected threshold of $p = 0.05$. There were no significant effects of age or age by group interaction.

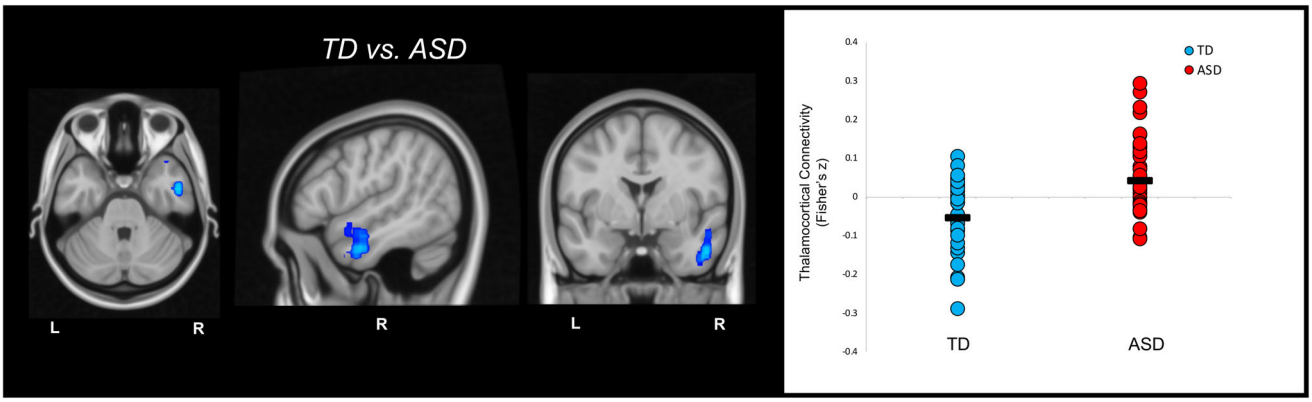

FIGURE 1 Thalamic seed analyses of thalamocortical functional connectivity. Left: statistical map of the group differences in the connectivity of the thalamus with the cortex, displayed on the template brain at $p_{\text{FWE-corrected}} \leq 0.05$. Greater connectivity in autism spectrum disorder (ASD) is depicted in blue. There were no regions of significantly greater connectivity in typically developing (TD). Right: dot plot of averaged thalamocortical connectivity in the group difference cluster: blue dots represent TD, red dots represent ASD, and black bars represent group means

TABLE 2 Maxima and locations of clusters showing significant group differences in thalamocortical functional connectivity

Region	Voxels	MNI coordinates			BA	z value (max)
		x	y	z		
Thalamic seed analyses						
R middle temporal gyrus	574	52	−1	−30	21	4.43
R superior temporal gyrus		52	−4	−18	38	
R fusiform gyrus		52	−5	−32	20	
Cortical seed analyses						
Temporal Cortex seed						
R mediodorsal nucleus	216	4	−8	6		3.45
R pulvinar		8	−26	10		

Note: All reported clusters have $p_{\text{FWE-corrected}} \leq 0.05$. There were no clusters where TD subjects showed significantly greater functional connectivity than ASD. Local maxima within the clusters (indented) are listed only if they fell in a different Brodmann area (BA) than the global maximum.
Abbreviations: MNI: Montreal Neurological Institute; R: right.

Cortical seed analyses

Compared with TD, ASD participants exhibited increased positive connectivity of temporal cortex with a large thalamic cluster encompassing bilateral mediodorsal and pulvinar nuclei (Figure 2, Table 2). Both groups showed decreased connectivity of the occipital cortex with bilateral pulvinar and lateral geniculate nuclei of the thalamus with age (Figure 3a,b, [−22,-31,0], 200 voxels). There were no significant effects for other cortical seeds.

Thalamic volumetry analyses

Groups did not differ in thalamic volume normalized to total brain volume (left: $t(67) = -0.69$, $p = 0.49$; right: t

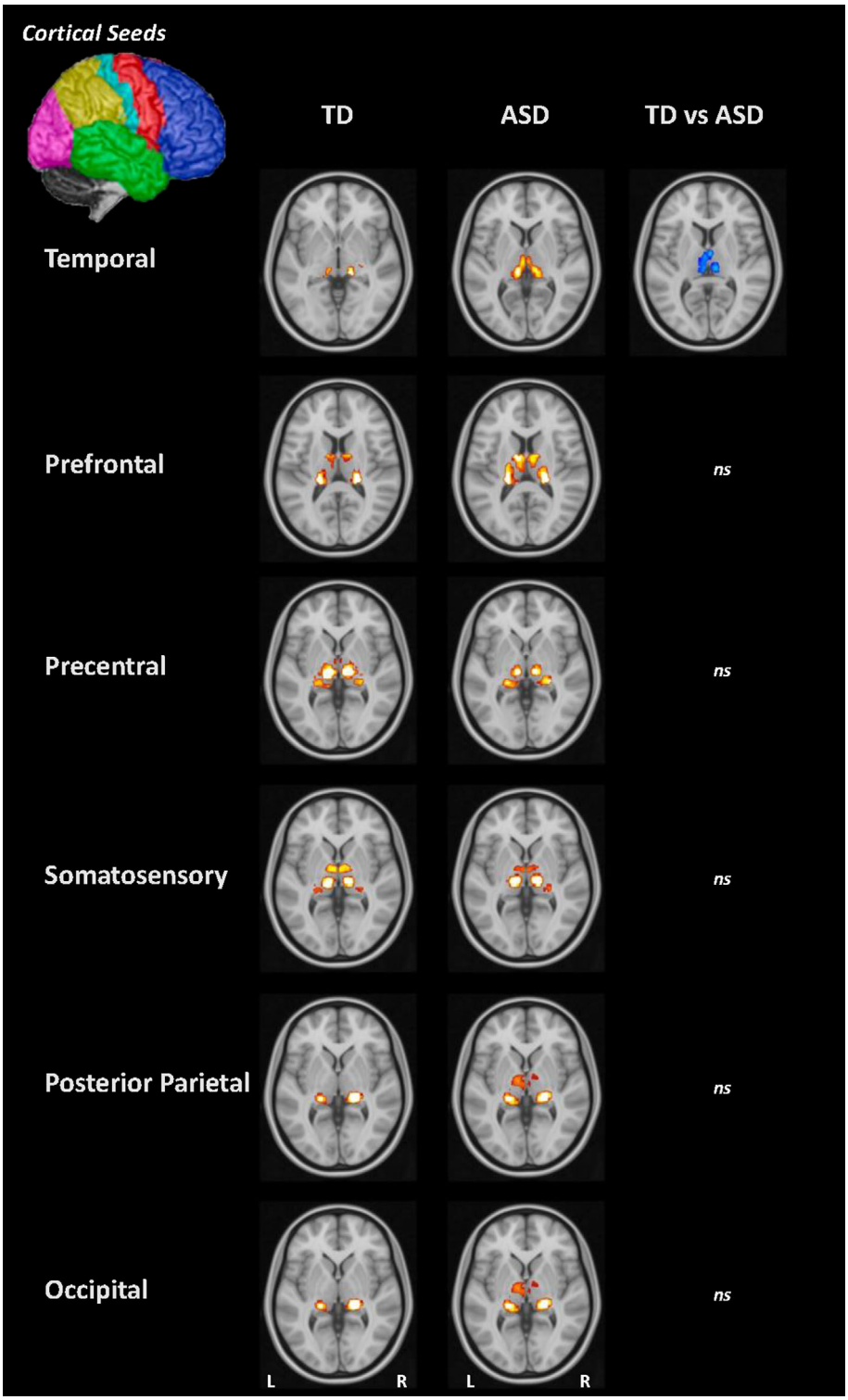

FIGURE 2 Cortical seed analyses of thalamocortical functional connectivity. The cortex was parcellated into six non-overlapping seeds. Statistical maps of thalamic connectivity of each seed are displayed on the template brain for typically developing (TD) and autism spectrum disorder (ASD) groups separately. The third column corresponds to the statistical map of group differences displayed on the template brain at $p_{FWE\text{-}corrected} \leq 0.05$. Greater connectivity in ASD is depicted in blue. There were no regions of significantly greater connectivity in TD (ns: non-significant)

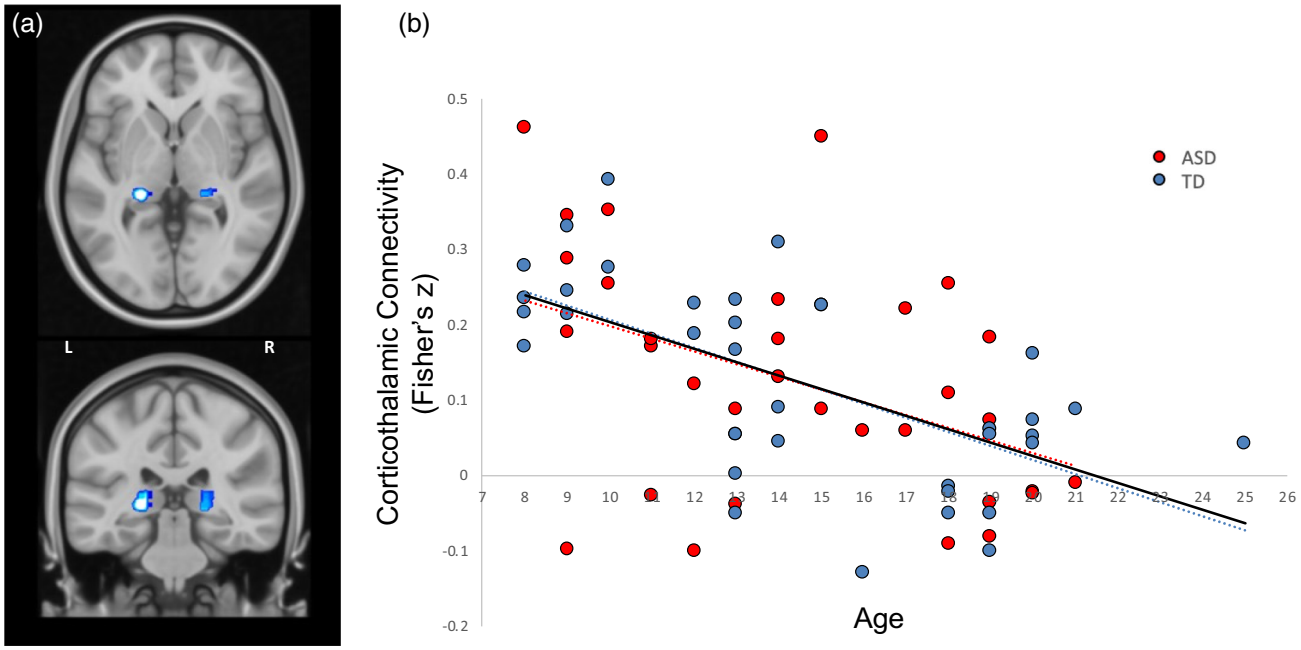

FIGURE 3 Age effects in thalamocortical functional connectivity (cortical seed analysis). (a) Statistical map of the main effect of age on the connectivity of the occipital cortex seed with the thalamus displayed on the template brain at $p_{\text{FWE-corrected}} \leq 0.05$. Negative relationship is depicted in blue, there were no regions of age-related increases in thalamocortical connectivity or any significant age-relations with the rest of the cortical seeds. (b) Scatterplot of the relations between occipital thalamocortical connectivity and age in the age effect mask: blue dots and regression lines represent typically developing, red dots regression lines represent autism spectrum disorder, black line represents the regression line for the main effect of age

(67) = −1.30, $p = 0.20$). Age did not correlate with thalamic volume.

DISCUSSION

Using complementary analysis techniques and rigorous methods to minimize motion confounds we found increased thalamic functional connectivity with temporal cortex in children and young adults, aged 8–25, with ASD compared with their TD peers. This hyperconnectivity in ASD occurred in the context of normal age-related reductions in thalamic functional connectivity with occipital cortex, suggestive of circuit refinement. These findings are consistent with genetic and sleep studies that implicate thalamocortical interactions in ASD. We interpret increased connectivity to reflect increased communication between brain regions (e.g., Al-Aidroos et al., 2012; Honey et al., 2007) and less filtered thalamic relay of auditory sensory information to temporal cortex.

Our findings of hyperconnectivity in superior and middle temporal gyri replicate those of previous studies (Linke et al., 2018; Nair et al., 2013; Woodward et al., 2017). We hypothesize that hyperconnectivity of the thalamus with temporal cortex reflects reduced thalamic inhibition of irrelevant and redundant auditory input from the periphery that may interfere with its processing and integration with information from other sensory modalities. A deficit in thalamic inhibition may contribute to sensory gating deficits, sensory sensitivity and overload as well as selective attention deficits (Chen et al., 2015; Green et al., 2017; McAlonan et al., 2006; Wimmer et al., 2015). This hypothesis is consistent with findings that in ASD, lower concentrations of the inhibitory neurotransmitter GABA in the thalamus predict sensory sensitivities and increased thalamic functional connectivity with sensory cortices (Wood et al., 2021). Reduced thalamic inhibition in ASD may also contribute to reduced sleep spindles in ASD (Tessier et al., 2015), oscillations that require powerful inhibition of thalamocortical relay neurons for their generation (Steriade, 2003), and reduced spindle coordination with cortical slow oscillations (Mylonas et al., 2022; Tessier et al., 2015), which relies on thalamocortical circuitry. Our findings that in both health and schizophrenia sleep spindle rate inversely correlates with thalamocortical connectivity with regions in sensorimotor cortex and superior and middle temporal gyri support the hypothesis that both measures reflect the degree of thalamic inhibition (Baran et al., 2019). Hyperconnectivity of the thalamus with sensory cortices is also seen in major depressive disorder (Brown et al., 2017) and social anxiety disorder (Arnold Anteraper et al., 2014). Convergent findings (e.g., sleep spindle deficits) would help constrain hypotheses about the locus of impairment in this complex circuitry.

In this cross-sectional sample that captures the transition from childhood to adulthood, we observed an age-related reduction in thalamic connectivity with occipital cortex. This finding is in line with previous work in typical adolescent development; however, these studies also reveal other age-related changes in thalamocortical

connectivity (Alkonyi et al., 2011; Fair et al., 2010; Steiner et al., 2020), which we did not replicate. Nor, did we observe any group differences in age effects. To our knowledge, no other study has directly compared the developmental trajectory of thalamocortical connectivity in ASD and TD. Considering recent findings of altered thalamocortical connectivity in preschoolers with ASD compared to TD (Linke et al., 2021), and in infant siblings of individuals with ASD compared to low familial-risk infants (Nair et al., 2021), it is possible that developmental differences arise much earlier than our study was able to capture or that due to interindividual variability larger or longitudinal samples are needed to capture these effects. Another potential limitation of the present study is that it was restricted to individuals without intellectual disability who could cooperate with scanning procedures and this may limit generalizability. Further, because our analyses of age effects focused only on linear relationships, our results may not fully capture dynamic developmental differences between ASD and TD participants. Finally, due to the limited number of volumes per subject (i.e., 240), we may have been underpowered to capture all clinically relevant group differences.

Implementing protocols to minimize the potentially confounding effects of head motion- on functional neuroimaging data, we demonstrate thalamic hyperconnectivity with temporal cortex in ASD. These findings are in line with a growing body of work that implicates abnormal thalamocortical interactions in the manifestations of ASD. Collectively, this work motivates further studies of mechanisms, functional consequences, and treatment of thalamocortical circuit dysfunction in ASD.

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CONFLICT OF INTEREST

The authors report no biomedical financial interests or potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The study was approved by the Mass General Brigham Institutional Review Board (IRB) and conforms to the US Federal Policy for the Protection of Human Subjects. After the procedures were explained, research staff obtained written informed consent from participants ≥18yr, and consent of the parent and assent of participants <18yr.

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SUPPORTING INFORMATION

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

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