HHS Public Access

Author manuscript

Biol Psychiatry Cogn Neurosci Neuroimaging. Author manuscript; available in PMC 2023 January 14.

Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2023 January ; 8(1): 21–31. doi:10.1016/j.bpsc.2021.07.008.

Sleep Problems in Preschoolers With Autism Spectrum Disorder Are Associated With Sensory Sensitivities and Thalamocortical Overconnectivity

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Abstract

BACKGROUND: Projections between the thalamus and sensory cortices are established early in development and play an important role in regulating sleep as well as in relaying sensory information to the cortex. Atypical thalamocortical functional connectivity frequently observed in children with autism spectrum disorder (ASD) might therefore be linked to sensory and sleep problems common in ASD.

METHODS: Here, we investigated the relationship between auditory-thalamic functional connectivity measured during natural sleep functional magnetic resonance imaging, sleep problems, and sound sensitivities in 70 toddlers and preschoolers (1.5–5 years old) with ASD compared with a matched group of 46 typically developing children.

RESULTS: In children with ASD, sleep problems and sensory sensitivities were positively correlated, and increased sleep latency was associated with overconnectivity between the thalamus and auditory cortex in a subsample with high-quality magnetic resonance imaging data ($n = 29$). In addition, auditory cortex blood oxygen level–dependent signal amplitude was elevated in children

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

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2021.07.008.

with ASD, potentially reflecting reduced sensory gating or a lack of auditory habituation during natural sleep.

CONCLUSIONS: These findings indicate that atypical thalamocortical functional connectivity can be detected early in development and may play a crucial role in sleep problems and sensory sensitivities in ASD.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by sociocommunicative deficits, restricted and repetitive behaviors and interests, and sensory sensitivities (1). There is no known single etiology for ASD, but increasing evidence suggests that autism originates early in development, likely in utero (2–4). While a mechanism has not been established, atypical structural and functional brain organization is commonly observed in ASD (5–7). The formation and maturation of connections between the thalamus and cerebral cortex (i.e., thalamocortical connections), mediated by the subplate, play a crucial part in early cortical development (8–12). This process peaks during the third gestational trimester and, when disrupted, can result in distorted topographical cortical organization with cascading consequences for postnatal sensory processing, motor learning, and cognitive development [for reviews, see (13–16)]. Genetic predisposition (17–19) and, to a lesser extent, environmental factors such as maternal infection during pregnancy (20,21), prematurity, or other pregnancy or birth complications (22–24) constitute known risk factors for ASD and have been shown to interfere with subplate neuron function and development of thalamocortical projections (13,25–32). Abnormal function of subplate neurons during prenatal brain development has also been detected in autism (14,25,33–38), and focal laminar disorganization hypothesized to result from these early developmental disruptions has been observed in the majority of children with ASD (10 of 11) in one postmortem study, including in the posterior superior temporal cortices where the auditory cortex is located (34,39,40). Finally, distorted tonotopic maps in the primary auditory cortex have been found in animal models of autism (36,41).

The auditory system is one of the earliest to mature in the course of brain development. Functional connectivity (FC) between the thalamus and auditory cortices has been observed in neonates using in vivo functional magnetic resonance imaging (fMRI) (42,43), and interhemispheric FC between auditory cortices is already established in infants born prematurely and scanned before term-equivalent age (44) and in healthy fetuses undergoing fMRI in utero (45,46). Early maturation makes the auditory network vulnerable to disruption in utero or as a result of complications during birth (47). For instance, interhemispheric auditory FC has been shown to be reduced in fetuses before preterm birth (48). Rotem-Kohavi *et al.* (49) observed overconnectivity within the auditory network in neonates whose mothers took selective serotonin reuptake inhibitors to treat depression during pregnancy compared with those who did not.

Disruption to auditory cortical development likely results in atypical sound processing, with potentially cascading consequences for language and social development. In ASD, atypical cortical sound processing is evident from studies utilizing electroencephalography (50–52), magnetoencephalography (53), and fMRI (54–57), and atypical sensitivity to sounds constitutes one of the most frequent sensory symptoms reported, affecting up to 65% of

individuals with ASD (55,58). Atypical FC between the thalamus and cortex, in particular the auditory cortex, has been observed in multiple fMRI studies of children, adolescents, and young adults with ASD and has been linked to sensory and social deficits and repetitive behaviors (56,59–66).

In addition to guiding the early development of cortical topographical organization and relaying sensory information from the periphery to primary sensory cortices, the thalamus and thalamocortical connections play an important role in regulating sleep (67–70). Simultaneous fMRI-electroencephalography studies in adults show substantial changes in functional thalamocortical connectivity during the transition to sleep (71–77). In ASD, sleep problems are common, reported by 40% to 80% of individuals (78–84), and are associated with more severe ASD symptomatology and heightened sensory sensitivity (85–87). Together, these findings point toward disrupted thalamocortical connectivity as a possible mechanism underlying both sleep disturbances and sensory sensitivities in ASD. This study, therefore, investigated how thalamocortical connectivity, sleep problems, and atypical sensory processing relate in a cohort of toddlers and preschoolers with ASD.

We first aimed to examine links between sleep problems and sensory sensitivities in 15- to 65-month-old toddlers and preschoolers with ASD compared with an age-matched typically developing (TD) control group. Next, we assessed whether atypical FC (estimated from fMRI acquired during natural sleep) between the thalamus and auditory cortices could be observed in this age range and whether it was related to sleep problems and sensory sensitivities. Given the early development of connections between the thalamus and auditory cortex, we hypothesized that FC would be increased in preschoolers with ASD and that the strength of thalamocortical FC would be related to sleep problems and sensory sensitivities. Finally, we quantified the amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF) (88,89) in the primary auditory cortex and thalamus during resting-state fMRI. This index provides a measure of blood oxygen level–dependent (BOLD) activity, which has been observed to decrease in auditory regions but increase in the thalamus during sleep in healthy young adults (90). We hypothesized BOLD amplitude to be increased in the auditory cortex but decreased in the thalamus in children with ASD, potentially reflecting amplified sound processing and reduced thalamocortical gating, as has been observed in other neurodevelopmental disorders [e.g., schizophrenia (91)].

METHODS AND MATERIALS

Participants

A total of 70 young children with ASD and 46 TD children, ages 15 to 65 months, were enrolled in an ongoing longitudinal study of early brain markers of autism. Children with a (suspected) diagnosis of autism were referred from specialty autism clinics, state-funded early education and developmental evaluation programs, local pediatricians, service providers, and community clinics; TD children were recruited from the community. All participants were safety-screened for MRI contraindications (see the Supplement for exclusionary criteria).

Consent was acquired from caregivers, and families were compensated for their time. The research protocol was approved by the institutional review boards of the University of California San Diego and San Diego State University. MRI data were acquired during natural sleep, and after quality assessments, final fMRI analyses included 29 participants with ASD and 30 TD participants (see the Supplement). The groups did not differ on age, sex, or head motion during the fMRI scans. Demographics for all participants included in analyses are summarized in Table 1 and Table S1.

Diagnostic and Behavioral Assessments

All participants in the ASD group received a diagnosis of ASD [or clinical best estimate in children younger than age 3 years (92)], based on the DSM-5 criteria (1), supported by the Autism Diagnostic Observation Schedule, Second Edition (93) (Table 1), administered by research-reliable clinicians; the Autism Diagnostic Interview-Revised (for children older than 36 months); and expert clinical judgment. Parents also completed the Social Communication Questionnaire (current form) (94), a screener for ASD, with no TD participants exceeding the cut-off score of 15 (all TD scores ≤ 10). Measures summarizing sleep problems were obtained from the Child Behavior Checklist (CBCL) for ages 1.5 to 5 years (95) and from an in-house Sleep Questionnaire. The CBCL Sleep Problems T score, the 6 individual items it is derived from (96), and 7 items from the Sleep Questionnaire were included in analyses (see the Supplement). To quantify sensory symptoms and, in particular, sound sensitivities, the Toddler or Child Sensory Profile 2 (97) was administered to caregivers, and the Sensitivity Quadrant score and Auditory Processing score were used in analyses (with greater scores corresponding to greater impairment).

ASD and TD group differences in the CBCL Sleep Problems T score, individual CBCL sleep items, Sleep Questionnaire items, and Sensory Profile scores were tested using independent samples two-tailed Welch's t tests (to account for unequal variances) or likelihood ratio χ^2 tests for the full cohort and separately for the subgroup of children with fMRI data. Given the restricted range of scores in the TD group, Pearson correlations were carried out to test for a relationship between sensory sensitivities (Sensory Profile Sensitivity Quadrant and Auditory Processing score) and sleep problems (CBCL Sleep Problems T score) in the ASD group only. Additional analyses were carried out to assess potential confounds of gestational age at birth, sex, and socioeconomic status and are presented in the Supplement.

MRI Data

Natural sleep MRI data (see the Supplement) were collected at the University of California San Diego Center for fMRI on a GE 3T Discovery MR750 (GE Healthcare) scanner using a Nova Medical 32-channel head coil. A multiband echo-planar imaging (EPI) sequence allowing simultaneous acquisition of multiple slices was used to acquire 2 fMRI datasets (6-min duration each) with high spatial and temporal resolution (repetition time = 800 ms, echo time = 35 ms, flip angle 52°, 72 slices, multiband acceleration factor 8, 2 mm isotropic voxel size, 104 × 104 matrix size, field of view 20.8 cm, 400 volumes per run). Two separate 20-second spin-echo EPI sequences with opposing phase encoding directions were also acquired using the same matrix size, field of view, and prescription to correct for

susceptibility-induced distortions. After completion of the fMRI scans, a fast 3D spoiled gradient recalled T1-weighted sequence was used to acquire high-resolution structural images (0.8 mm isotropic voxel size, NEX = 1, echo time/inversion time = minimum full/1060 ms, flip angle 8°, field of view = 25.6 cm, matrix = 320 × 320, receiver bandwidth 31.25 Hz). Motion during structural acquisitions was corrected in real time using 3 navigator scans [real-time prospective motion correction (98)], and images were bias corrected using the GE Pure (GE Healthcare) option.

MRI data were preprocessed, denoised, and analyzed in MATLAB 2017b (The MathWorks, Inc.) using SPM12 (Wellcome Trust Centre for Neuroimaging, University College London), and the CONN toolbox v17f (NITRC). fMRI data were realigned, normalized to Montreal Neurological Institute template, bandpass filtered, and underwent nuisance regression to remove physiological noise and motion confounds (see the Supplement for detailed information on preprocessing and denoising procedures).

fMRI Analyses

Regions of Interest.—Analyses were carried out within left and right Heschl's gyrus (HG) and left and right thalamus regions of interest (ROIs) extracted from the Harvard-Oxford atlas provided by FSL and the CONN toolbox. Additional FC analyses included all cortical Harvard-Oxford atlas ROIs to determine whether atypical thalamocortical connectivity was specific to auditory cortices (see below).

FC Analysis.—BOLD time series were concatenated across the two EPI acquisitions and averaged across all voxels within each ROI. First, FC between the bilateral thalamus and HG was estimated using bivariate Pearson correlation standardized with a Fisher z-transform. Two-tailed independent samples *t* tests were used to assess differences in correlation magnitude between pairs of ROIs in the ASD compared with the TD group. Separate tests were also carried out for ipsilateral (average of intrahemispheric thalamus-HG) and contralateral (average of interhemispheric thalamus-HG) FC. FC (Fisher z) was Pearson correlated with age, separately in each group, to test for any age-related changes in auditory-thalamocortical connectivity. We hypothesized that auditory-thalamic FC would be elevated in toddlers and preschoolers with ASD. Results are reported at a threshold of $p < .05$ (Benjamini-Hochberg false discovery rate adjusted for multiple comparisons). To assess whether atypical thalamocortical connectivity was specific to sensory regions of the brain, a post hoc analysis also assessed whole-brain thalamocortical connectivity using the left and right thalamus as seeds and all Harvard-Oxford cortical ROIs as targets. Independent samples *t* tests of the Fisher z-transformed estimates of FC assessed differences between the ASD and TD groups. Finally, we assessed in an exploratory analysis whether atypical FC between HG and the thalamus was driven more strongly by specific regions within the thalamus involved in auditory processing (26,99,100). BOLD time series within the left and right HG were Pearson correlated with the time series of every voxel within the thalamus ROIs, and *t* tests carried out for the Fisher z-transformed correlation coefficient of each thalamic voxel to test for ASD-TD differences. To rule out that children in the ASD and TD groups might have been scanned during different sleep stages, which could confound FC estimates, a number of additional analyses were conducted and are described

in the Supplement. The influence of gestational age, sex, and socioeconomic status on auditory-thalamic FC were also assessed (see the Supplement).

Fractional ALFF.—ALFF measures the power of the BOLD signal within a low-frequency range and is thought to reflect the amplitude of regional neural activity. ALFF was calculated as:

$$ALFF = \sqrt{\frac{1}{N}\sum_{t}\left(h(t) * BOLD(x,t)^2\right)}$$

as implemented in the CONN toolbox, with N = the number of volumes, BOLD(x,t) = original BOLD time series before bandpass filtering, and $h(t)$ = bandpass filter (see https://web.conn-toolbox.org/measures/other for more detail). fALFF was developed to better protect against noise and is a measure of the relative contribution of low-frequency fluctuations to the entire frequency range detectable by BOLD-optimized EPI (88,89). It was calculated as the power within the low-frequency range (0.01–0.1 Hz) divided by the total power of the entire frequency spectrum, again using the implementation included with the CONN toolbox:

$$fALFF = \sqrt{\frac{\sum_{t}\left(h(t) * BOLD(x,t)\right)^2}{\sum_{t} BOLD(x,t)^2}}$$

ALFF and fALFF were calculated for each voxel in the brain and averaged for the left and right HG and thalamus ROIs. We hypothesized that *f*(ALFF) would be increased in HG but decreased in the thalamus in the ASD group, which was tested using independent samples two-tailed *t* tests. Additional analyses of covariance (controlling for root-mean-square deviation) tested for an association between *f*(ALFF) in HG and the thalamus and between the two regions and averaged HG-thalamus FC.

Relationship Between FC, Sleep Problems, and Sensory Sensitivities

Partial correlations (correcting for average head motion [root-mean-square deviation] and age) tested for a relationship between HG-thalamus FC and sensory sensitivities (Sensory Profile Sensitivity Quadrant and Auditory Processing score), the CBCL Sleep Problems T score, and those Sleep Questionnaire items that showed significant ASD-TD group differences in the fMRI cohort. To reduce the number of multiple comparisons, correlations were only conducted for contralateral and ipsilateral FC. Due to the narrow distribution of CBCL and Sensory Profile scores in the TD group, correlations where only assessed for children with ASD. We hypothesized that elevated FC between the thalamus and HG would be related to greater sensory sensitivity and more severe sleep problems in the ASD group. Given the relatively small sample size for detecting robust brain-behavior relationships, these results are presented as preliminary and uncorrected for multiple comparisons and need to be interpreted with caution.

RESULTS

Sleep Problems in Preschoolers With ASD Are Associated With Sensory Sensitivities

Sleep problems were significantly more pronounced in children with ASD compared with TD children (CBCL Sleep Problems T score, $t_{98} = -3.82$, $p < .001$) (Figure 1A), and those with ASD were reported to have more trouble sleeping ($\chi^2_2 = 16.4$, $p < .001$) and were more likely to resist bedtime ($\chi^2_2 = 15.3$, $p < .001$), to wake up at night ($\chi^2_2 = 11.0$, $p = .004$), and to be overtired ($\chi^2_2 = 5.99$, $p = .05$) and sleepless ($\chi^2_2 = 12.03$, $p = .001$). In addition, toddlers and preschoolers with ASD were reported to take significantly longer to fall asleep (sleep latency/time to fall asleep: ASD mean = 30.3 min [SD = 30.1], TD mean = 19.7 min [SD = 14.4], $t_{109} = -2.2$, $p = .03$) (see Table S2).

As expected, the Sensory Sensitivities score and the Auditory Processing score from the Toddler or Child Sensory Profile 2 (97) were significantly higher in the ASD than the TD group ($p < .001$) (Figure 1B). The CBCL Sleep Problems T score positively correlated with the Sensory Profile 2 Sensory Sensitivity quadrant in the ASD group ($r = 0.35$, $p = .008$, controlling for age) (Figure 2A; Table S2), with higher scores on each scale corresponding to greater impairment. This association remained significant when additionally controlling for ASD symptom severity (the Autism Diagnostic Observation Schedule, Second Edition total scores; $r = 0.36$, $p = .007$). The correlation with the Sensory Profile 2 Auditory Processing score was not significant ($r = 0.12$, $p = .37$, controlling for age) (Table S3).

Children with successful fMRI scans did not significantly differ on any of the included Sensory Profile or CBCL sleep measures from those without MRI in the ASD and TD groups (Table S4). As in the full cohort, children with ASD and successful fMRI scans had more sleep problems than TD peers as measured using the CBCL (Sleep Problems T score: $t_{52} = -2.62$, $p = .012$; trouble sleeping: $\chi^2_2 = 9.62$, $p = .008$; resists bedtime: $\chi^2_2 = 9.73$, $p = .008$; and, marginally, wakes up at night: $\chi^2_2 = 4.95$, $p = .08$). Similarly, sleep latency was prolonged in children with ASD (ASD mean = 26.9 min [SD = 16.1], TD mean = 17.4 min [SD = 10.4], $t_{53} = -2.6$, $p = .011$) (Figure 1C).

Children with ASD in the fMRI cohort also showed greater sensory sensitivities and more severe auditory processing symptoms as assessed using the Sensory Profile 2 (both $p < .001$) (Figure 1D; Table S2). Similarly, the correlation between the Sensory Profile 2 Sensory Sensitivity Quadrant score and the CBCL Sleep Problems T score was positive ($r = 0.39$, $p = .057$), consistent with the full cohort data (Figure 2B). The correlation between the Sensory Profile 2 Auditory Processing score and the CBCL Sleep Problems T score was not significant ($r = 0.23$, $p = .28$, partial correlations controlling for age) (Table S3).

FC Between the Thalamus and HG Is Increased in Preschoolers With ASD

FC between the thalamus and HG was significantly increased between the right HG and right and left thalamus in the ASD compared with the TD group ($t_{57} = -2.7$, $p = .01$ and $t_{57} = -2.8$, $p = .007$, respectively) (Figure 3A). FC was also higher between the left HG and left and right thalamus in the ASD group, but the group difference was not significant ($t_{57} = -1.3$, $p = .19$ and $t_{57} = -1.76$, $p = .08$, respectively). Ipsilateral and contralateral FC between HG and the thalamus were significantly elevated in the ASD group ($t_{57} = -2.5$, p

= .015 and t_{57} = −2.32, p = .024, respectively). In many TD children, FC estimates were close to zero or negative, in line with previous reports of decreasing thalamocortical FC with anticorrelations frequently observed during deep sleep (71). These results remained similar when global signal regression was included during fMRI data denoising, with FC between the left HG and left and right thalamus additionally showing significant group differences after global signal regression (Figure S1). There was no significant correlation between FC strength and age in the ASD or TD group or when carrying out correlations across the combined cohort for any of the auditory-thalamic FC estimates (all r < 0.2, p > .2). Sleep latency correlated positively with contralateral HG-thalamus FC (partial correlation controlling for root-mean-square deviation and age, r = 0.49, p = .016; ipsilateral FC: r = 0.37, p = .08) (Figure 2C). Results remained largely unchanged when controlling for gestational age at birth, socioeconomic status, or sex in models testing for group differences in FC or associations between FC and sleep latency (see the Supplement).

To assess whether overconnectivity was specific to auditory regions, seed-to-ROI analysis was carried out using the left and right thalamus as a seed and all cortical Harvard-Oxford ROIs as targets. Based on the pattern of group differences in FC (Figure 3B), results suggest that overconnectivity between the thalamus and cortex is most pronounced in the temporal lobe around the primary auditory cortex, with the right HG having the highest effect size among all comparisons for the left thalamus seed (Cohen's d = 0.73). Left HG similarly was among the highest effect sizes for both left and right thalamus seeds (Cohen's d = 0.46 and d = 0.34, respectively).

Finally, we assessed whether overconnectivity between thalamus and primary auditory cortex was driven by specific thalamic subregions. Results are shown in Figure 3C, with the pattern of FC suggesting that overconnectivity is strongest for the posterior regions of the thalamus, potentially overlapping with the medial geniculate nucleus, and corresponding to the functional parcellations of the thalamus derived from functional thalamocortical connectivity patterns previously, including in infants (26,99,100).

BOLD Signal Amplitude Is Increased in the Auditory Cortex During Natural Sleep in Toddlers and Preschoolers With ASD

ALFF (t_{57} = 2.4, p = .02) and fALFF (t_{57} = 1.9, p = .06) were higher in HG in the ASD compared with the TD group (Figure S3), but no significant differences were observed for thalamus ALFF (t_{57} = −0.65, p = .52) or fALFF (t_{57} = −0.52, p = .61). fALFF in the thalamus and HG were negatively correlated ($F_{1,55}$ = 5.1, p < .05) (Figure S4A). In addition, HG-thalamus FC was negatively associated with thalamus fALFF ($F_{1,55}$ = 10.5, p < .005) and ALFF ($F_{1,55}$ = 17.2, p < .001) (Figure S4B). There were no significant relationships between HG (*f*)ALFF and FC. Neither ALFF nor fALFF correlated significantly with Sensory Profile Sensory Sensitivity or Auditory Processing scores or with the CBCL Sleep Problems T score in children with ASD.

DISCUSSION

We investigated the relationship between auditory-thalamocortical FC, sleep problems, and sensory sensitivities in toddlers and preschoolers with ASD. Elevated sleep problems and

sensory sensitivities, as reported by caregivers, were positively correlated in children with ASD, and increased sleep latency was associated with higher thalamocortical connectivity during natural sleep. Our findings support a model of both atypical sensory processing and sleep problems being linked to early neurodevelopmental disturbances of thalamocortical connectivity.

Atypical Thalamocortical FC May Underlie Both Sensory Sensitivities and Sleep Problems in Young Children With ASD

Sensory overresponsivity can interfere with sleep (101,102), potentially accounting for correlations reported between sleep problems and sensory sensitivities in ASD (87). The mechanisms behind sensory sensitivities and sleep problems, however, remain unclear. In this study, we focused specifically on investigating FC between the thalamus and auditory cortex and its association with sleep problems and sensory sensitivities for a number of reasons: 1) connections between the thalamus and auditory cortex are established early in development (42,43) making them particularly vulnerable to disruption in utero (47); 2) the formation of tonotopic maps in the auditory cortex is guided by thalamocortical connections in utero, and its disruption can result in atypical sound processing, as has been shown in animal models of ASD (36,41); 3) altered sensitivity to and atypical cortical processing of sounds is very common in ASD and has been linked to reduced modulation of thalamocortical FC (56); and 4) a relationship between atypical sensory gating by the thalamus during sleep, as reflected by increased thalamocortical connectivity and elevated BOLD amplitude, was likely to be most obvious in the auditory cortex given that sleep fMRI is collected in the presence of substantial noise produced by the MRI scanner.

Similar to findings in older children and adolescents with ASD who underwent resting-state fMRI while awake (60,65,66), auditory-thalamic FC was elevated in toddlers and preschoolers with ASD scanned during natural sleep in this study. While auditory-thalamic FC was positively associated with sleep problems, particularly the time it takes children to fall asleep, it did not correlate with sensory sensitivities. The Sensory Profile may not have quantified atypical auditory processing in ASD with high reliability (103), because it relies on caregiver report and some questions targeting modality-specific processing also tap into non-sensory aspects of behavior. Previous studies employing sensory stimulation fMRI designs [e.g., (56)] have found thalamocortical overconnectivity in ASD to be associated with sensory overresponsivity [quantified as a composite score derived from the Short Sensory Profile (104) and Sensory Overresponsivity Inventory (105)]. The lack of a relationship between sensory sensitivities as broadly assessed with the Sensory Profile and auditory-thalamocortical FC is thus likely to reflect the Sensory Profile psychometric limitations.

Evidence for Early Development of Atypical Auditory-Thalamocortical FC

Auditory-thalamic FC did not correlate with age, suggesting that the observed overconnectivity reflects early neurodevelopmental disruptions preceding toddler age. Postmortem histology and studies in autism animal models provide evidence for altered establishment of thalamocortical projections and topographical sensory maps in utero, potentially as a result of atypical subplate function (25,34,36,38,40,47,106–108). Recent

findings from an infant sibling fMRI study support this interpretation, showing increased FC between the thalamus and somatosensory cortex in 6-week-old infants at high familial risk of ASD, which was associated with increased ASD symptoms at 36 months (109). Relatedly, in a large group of at-risk infant siblings, Swanson *et al.* (110) reported that thalamus volumes at 12 months differentially predicted language skills at 24 months in those with ASD compared with those with language delay or without familial risk. Abnormalities in auditory cortical processing (111) and increased prevalence of sleep problems (112,113) tied to differences in brain development (114) have also been observed in infant sibling studies of ASD, further strengthening the notion that underlying neurodevelopmental disruptions occur very early.

Possible Mechanisms: Atypical Modulation of Thalamocortical FC During Awake and Sleep States and Reduced Sensory Gating

Unlike in older children and adults scanned awake, average FC between the auditory cortex and the thalamus was close to zero or negative in TD toddlers and preschoolers in our study, with overconnectivity in the ASD group driven by a positive shift in correlation magnitudes. FC between the cortex and subcortical structures changes substantially during sleep, with a reduction in thalamocortical connectivity observed in fMRI studies conducted during deep sleep in adults (71). Mitra *et al.* (77) scanned young children (from 6 to 24 months) asleep and compared the lag pattern of FC with that of adults scanned awake and asleep. During N3 sleep, the BOLD responses of the thalamus and cortex showed increased lag compared with wakefulness, in both sleeping 2-year-olds and sleeping adults. While the authors did not report zero-lag FC of the thalamus, increased lag of thalamic BOLD time series during N3 sleep is likely to result in negative or reduced thalamocortical FC compared with wakefulness. Increased FC in the ASD group observed in this study may therefore reflect a lack of thalamocortical modulation during sleep. It is not possible to discern from this study whether those children with increased thalamocortical connectivity during deep sleep would also show heightened thalamocortical connectivity while awake. However, findings from previous studies show that thalamocortical overconnectivity in ASD is also present in the awake state (60,65,66). Similarly, in schizophrenia, thalamocortical overconnectivity during the awake state has been observed in multiple studies (115–117) and is associated with reduced sleep spindle density (118), which has also been observed in 2- to 6-year-old children with ASD (119). In addition, BOLD signal amplitude in HG was significantly higher during sleep in toddlers and preschoolers with ASD in our study. Across groups, HG BOLD signal amplitude correlated negatively with BOLD signal amplitude in the thalamus, mirroring an observation of increased thalamic but decreased auditory BOLD activity during sleep in healthy young adults (90). Increased (*f*)ALFF in the thalamus was further associated with reduced HG-thalamus FC. Together, these findings suggest heightened ongoing sound processing in the auditory cortex or a lack of habituation to the scanner noise and support an explanation of atypical thalamocortical modulation and reduced sensory gating during sleep in ASD.

Given the consequences that disrupted sensory processing and sleep might have on development, understanding the relationship between mechanisms underlying sleep problems and the emergence of core ASD symptomatology early in life is of crucial

importance. This study is limited by the use of parent-report measures to assess and quantify sensory symptoms and sleep problems. Given the frequency of sleep problems in young children with ASD and the likely influence on neurodevelopment, neuroimaging studies that also collect more direct measures of sleep quality are urgently needed. Ideally, this would include polysomnography and long-term sleep tracking using actigraphy. In addition, despite the modest sample size used for the fMRI analyses, secondary to the practical and methodological challenges associated with obtaining natural sleep MRI data in young children with ASD, our results replicate previously reported associations between sleep problems and sensory sensitivities (85–87), as well as elevated auditory-thalamic FC in older children and adolescents (60,65,66). Our findings extend this previous literature and suggest that early developmental abnormalities of thalamocortical connectivity in ASD are linked to both sleep disturbances and sensory problems, laying out a pathway for mechanistic models and ultimately targeted neurobehavioral interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the National Institutes of Health (Grant No. R01 MH107802 [to IF]).

ACL, MK, and IF designed the study; ACL, BC, LO, CI, CF, SR, MA, MK, and IF collected the data; ACL, BC, and LO conducted fMRI and behavioral analyses; and ACL, R-AM, and IF drafted the manuscript.

We thank Lisa Mash, M.S. (San Diego State University), and Tiffany Wang, M.S. (University of California San Diego), for invaluable assistance with data collection. Our strongest gratitude goes to the children and families who so generously dedicated their time and effort to this research.

A previous version of this article was published as a preprint on bioRxiv: https://www.biorxiv.org/content/10.1101/2021.01.15.426899v1.

The data that support the findings presented in this manuscript are available in the National Institute of Mental Health Data Archive, a National Institutes of Health–funded data repository (https://nda.nih.gov/). Software used for all analyses are available to researchers for replication.

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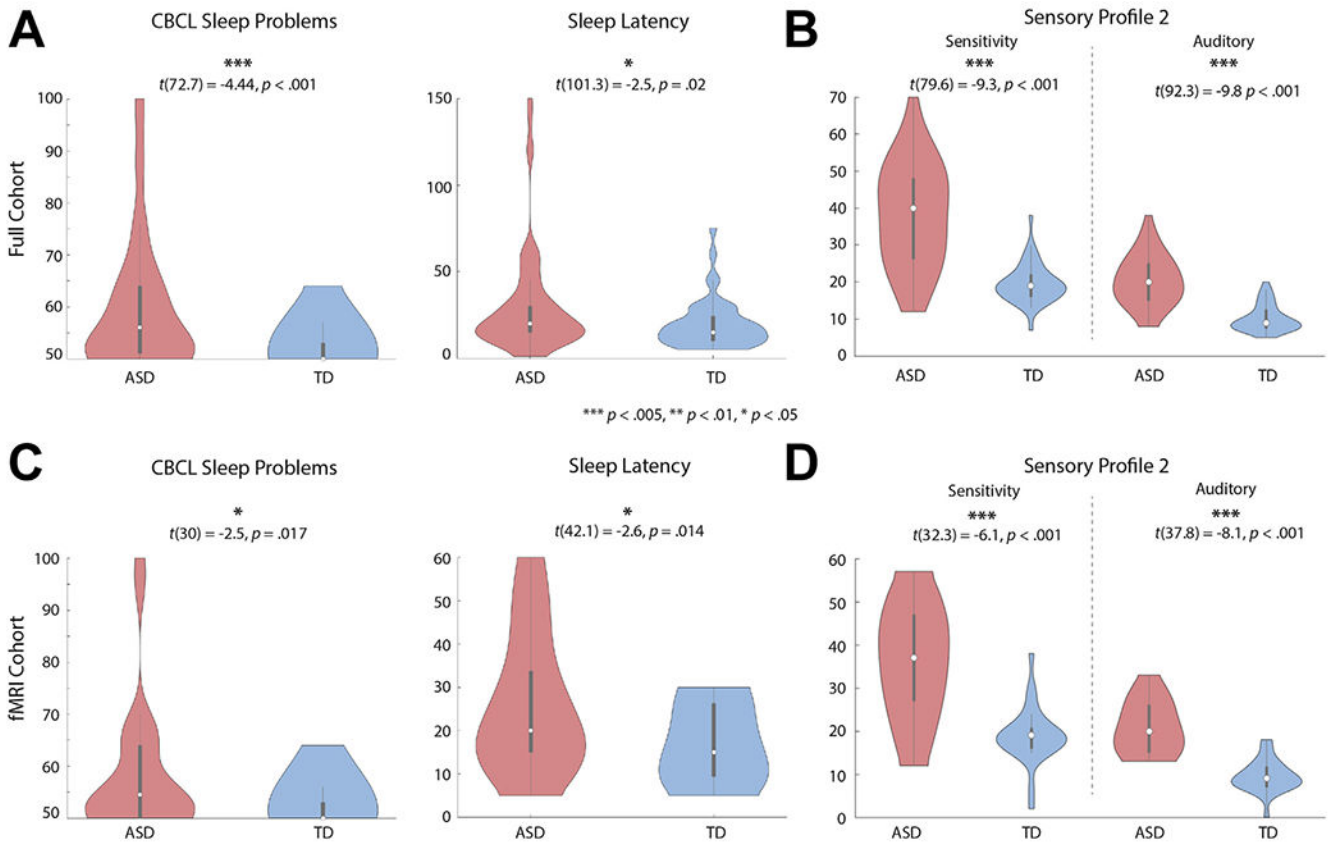

Figure 1.

Greater sleep problems and sensory sensitivity, including auditory sensitivity, in toddlers and preschoolers with autism spectrum disorder (ASD). **(A, C)** More severe sleep problems (as measured using the Child Behavior Checklist [CBCL] Sleep Problems scale, T scores) and prolonged sleep latency (time [in min] it takes a child to fall asleep, as reported on an in-house Sleep Questionnaire that asked caregivers about their child's sleep habits in the past few weeks prior to participating in the study) are reported for young children with ASD compared with age- and sex-matched typically developing (TD) children, in **(A)** the full cohort and **(C)** the subgroup of children with successful functional magnetic resonance imaging (fMRI) scans (fMRI cohort). **(B, D)** Toddlers and preschoolers with ASD show greater sensory sensitivity and more severe auditory processing symptoms, as measured using the Sensory Profile 2 (T scores), in **(B)** the full cohort and **(D)** the subgroup of children with successful fMRI scans (fMRI cohort). These results remained significant when controlling for gestational age at birth and socioeconomic status, and no significant effects of sex (or sex × diagnosis interactions) were observed (see the Supplement).

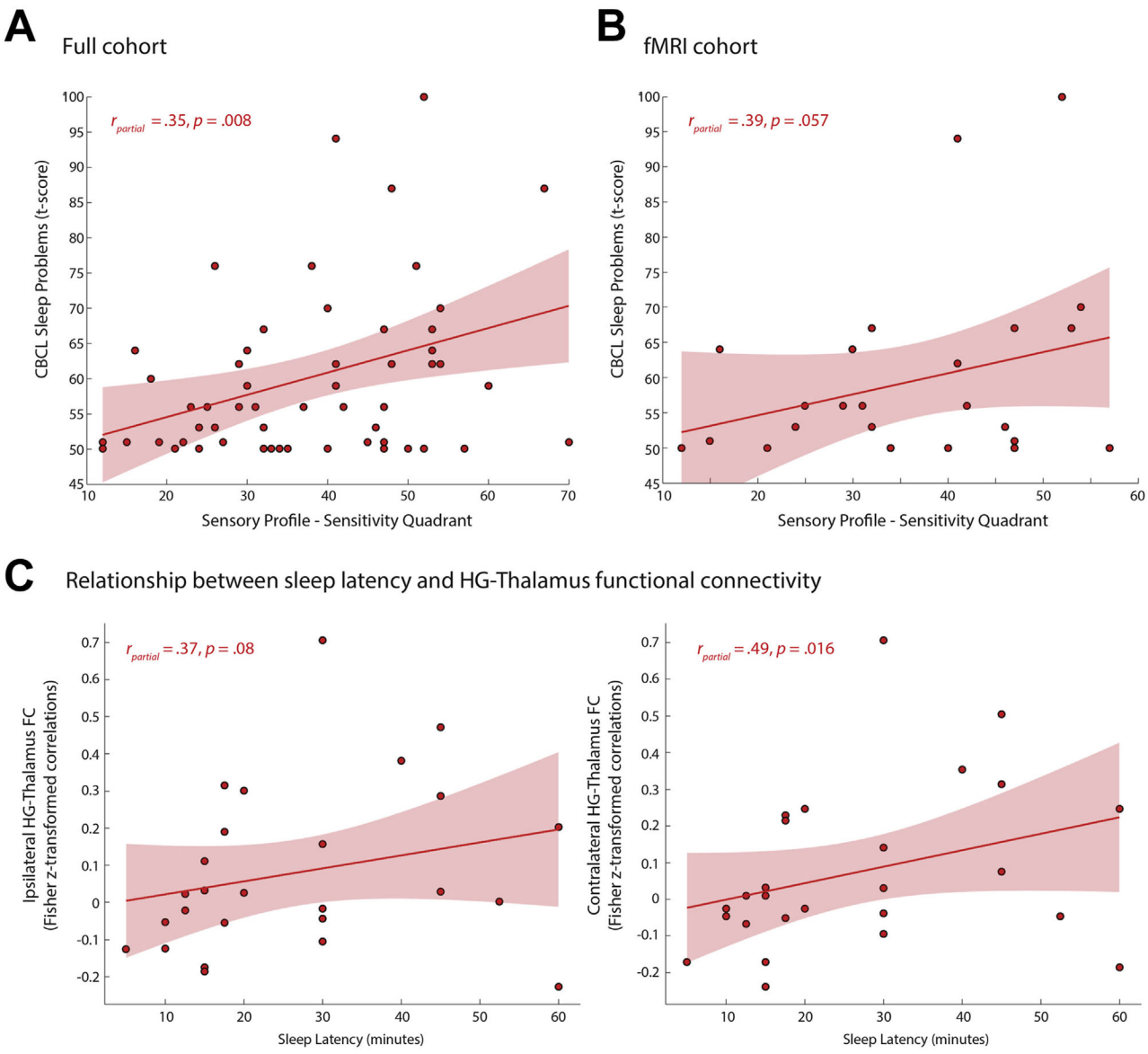

Figure 2.

Correlations between sensory sensitivity, sleep problems, and Heschl's gyrus (HG)–thalamus functional connectivity (FC). **(A, B)** The Sensory Profile Sensitivity score correlates positively (partial correlation controlling for age) with sleep problems as quantified using the Child Behavior Checklist (CBCL) Sleep Problems T score in the **(A)** full and **(B)** functional magnetic resonance imaging (fMRI)–only autism spectrum disorder groups. This association between sensory sensitivity and sleep problems remained significant when controlling for gestational age or socioeconomic status, with no sex differences observed (see the Supplement). Correlations were not assessed for the typically developing group due to the narrow distribution of scores in typically developing children for these measures. **(C)** Sleep latency correlates positively (partial correlations controlling for in-scanner head motion [root-mean-square deviation] and age) with contralateral FC between the thalamus and HG in the autism spectrum disorder group. See the Supplement

for additional analyses testing the effects of gestational age, socioeconomic status, sex, and sleep stage on HG-thalamus FC. All scatterplots show zero-order correlations. Robust linear regressions as implemented in MATLAB (2017b; The MathWorks, Inc.) with the robustfit function were conducted as post hoc analyses to minimize the potential influence of outliers. The association between the Sensory Profile Sensitivity score and CBCL Sleep Problems T score (controlling for age) remained significant in the full cohort ($t = 2.04$, $p < .05$; fMRI cohort $t = 1.6$, $p = .12$). Similarly, the relationship between sleep latency and contralateral HG-thalamus FC (controlling for age and root-mean-square deviation) remained significant ($t = 2.5$, $p < .05$; ipsilateral FC: $t = 1.7$, $p = .1$).

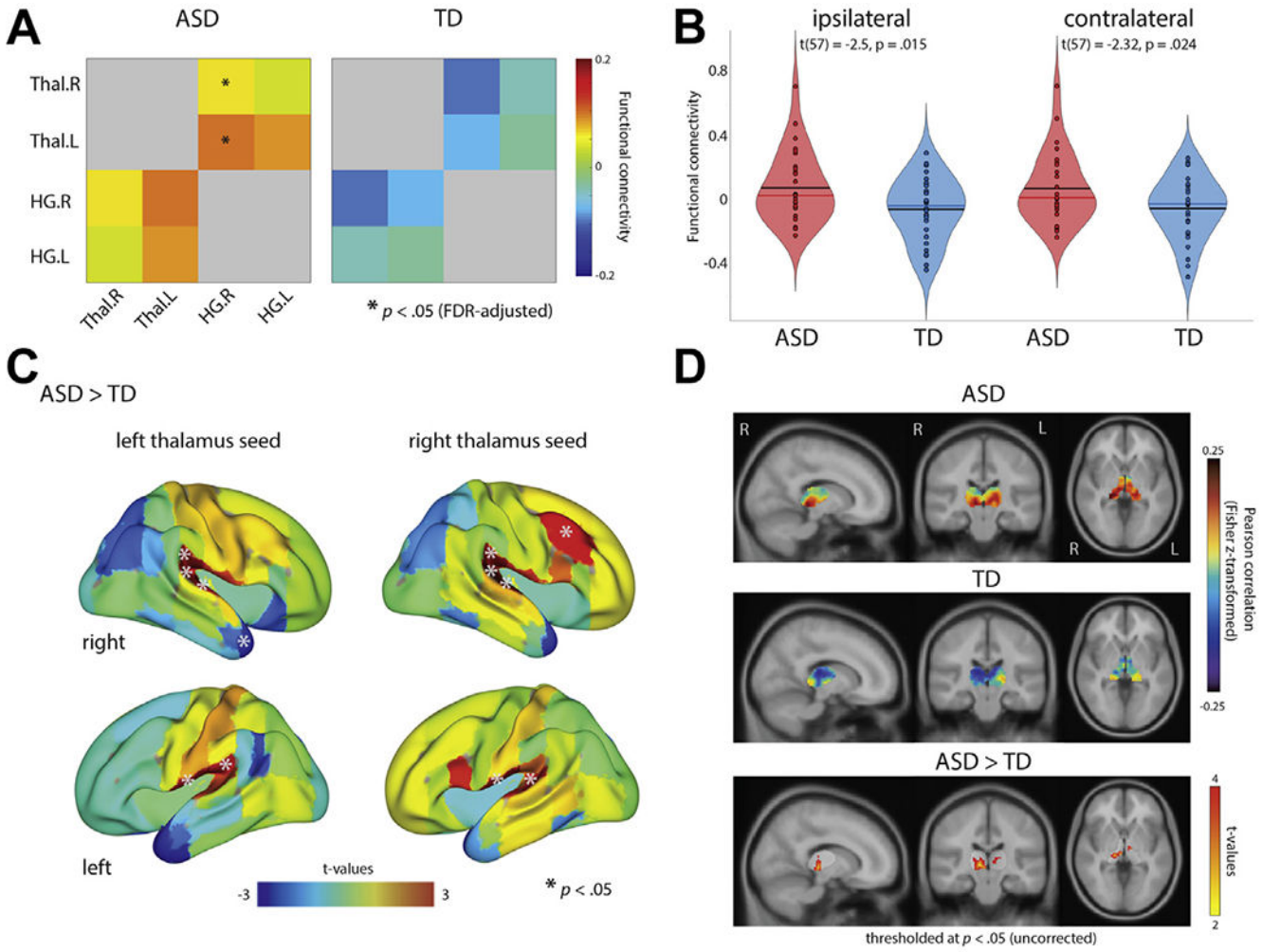

Figure 3.

Thalamic (Thal)–Heschl's gyrus (HG) overconnectivity in young children with autism spectrum disorder (ASD). **(A)** Toddlers and preschoolers with ASD show overconnectivity between the thalamus and HG during natural sleep functional magnetic resonance imaging compared with age-, motion-, and sex-matched typically developing (TD) children (* in the ASD matrix mark region of interest [ROI] pairs with significant group differences, $p < .05$, Benjamini-Hochberg false discovery rate (FDR)–adjusted for multiple comparisons). Functional connectivity was significantly different from zero for HG.R-Thal.L (one-sample t test: $t_{28} = 2.3$, $p = .03$) in the ASD group (but t values for all ROI pairs were positive) and for HG.R-Thal.R ($t_{29} = -2.4$, $p = .03$) in the TD group (with t values for all ROI pairs negative). **(B)** Ipsilateral and contralateral functional connectivity was similarly elevated in toddlers and preschoolers with ASD and used for behavioral correlations in subsequent analyses. **(C)** Seed-to-ROI analyses show that thalamocortical overconnectivity is most pronounced for auditory regions. Left (L) and right (R) thalami were used as seeds and all cortical Harvard-Oxford atlas ROIs as targets. t values for the ASD > TD comparison are shown with * marking significant ($p < .05$, uncorrected) group differences in functional connectivity. **(D)** Thal-HG overconnectivity in the ASD group appears to be driven by the

posterior section of the thalamus. Left and right HG were used as seeds and all voxels in the thalamus as targets.

Table 1.

Demographics for Full and fMRI Cohorts

	Full Cohort			fMRI Cohort		
Demographics	**ASD, *n* = 70**	**TD, *n* = 46**	**Statistic**	**ASD, *n* = 29**	**TD, *n* = 30**	**Statistic**
Gestational Age at Birth, Weeks	38.4 ± 2.6 [31–43]	39.7 ± 1.1 [37–42]	$t_{103} = 3.1$; $p < .05$	38.5 ± 2.5 [31–43]	39.5 ± 1.2 [37–42]	$t_{54} = 1.84$; $p = .07$
Age at Behavioral Assessment, Months	34.7 ± 12.4 [17–64]	32.6 ± 15.2 [15–64]	$t_{114} = -0.82$; $p = .42$	33.3 ± 9.8 [17–54]	34.1 ± 14.3 [15–64]	$t_{57} = 0.25$; $p = .81$
Age at MRI Scan, Months	N/A	N/A	N/A	34.7 ± 10.1 [18–56]	34.5 ± 14.8 [16–65]	$t_{57} = -0.05$; $p = .96$
Sex, Female, *n* (%)	16 (23%)	21 (46%)	$\chi^2 = 6.58$; $p = .01$	9 (31%)	13 (43%)	$\chi^2 = 0.96$; $p = .33$
ADOS-2 SA	11.8 ± 4.6 [3–20]	N/A	N/A	12.0 ± 4.9 [3–19]	N/A	N/A
ADOS-2 RRB	3.3 ± 2.1 [0–8]	N/A	N/A	3.5 ± 2.2 [0–8]	N/A	N/A
ADOS-2 Total	15.0 ± 5.5 [4–26]	N/A	N/A	15.5 ± 5.7 [6–26]	N/A	N/A
RMSD Run1	N/A	N/A	N/A	0.12 ± 0.04 [0.047–0.188]	0.11 ± 0.04 [0.046–0.172]	$t_{57} = -1.04$; $p = .30$
RMSD Run2	N/A	N/A	N/A	0.12 ± 0.045 [0.046–0.24]	0.10 ± 0.03 [0.05–0.176]	$t_{57} = -1.18$; $p = .24$

Values are presented as mean ± SD [range] unless otherwise indicated. The ASD and TD groups were matched on age, sex, and in-scanner head motion (RMSD). Information on exact gestational age at birth was missing for 8 children with ASD (2 of 8 known to be born at term) and 3 TD children; this includes 2 ASD children (1 known to be born at term) and 1 TD child in the fMRI cohort.

ADOS-2, Autism Diagnostic Observation Schedule, Second Edition; ASD, autism spectrum disorder; fMRI, functional magnetic resonance imaging; N/A, not applicable; RMSD, root-mean-square deviation; RRB, restricted and repetitive Behavior; SA, social affect; TD, typically developing.