SLEEPJ, 2022, 1–15

https://doi.org/10.1093/sleep/zsac010
Advance Access Publication Date: 12 January 2022
Original Article

ORIGINAL ARTICLE

Dyscoordination of non-rapid eye movement sleep oscillations in autism spectrum disorder

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Abstract

Study Objectives: Converging evidence from neuroimaging, sleep, and genetic studies suggest that dysregulation of thalamocortical interactions mediated by the thalamic reticular nucleus (TRN) contribute to autism spectrum disorder (ASD). Sleep spindles assay TRN function, and their coordination with cortical slow oscillations (SOs) indexes thalamocortical communication. These oscillations mediate memory consolidation during sleep. In the present study, we comprehensively characterized spindles and their coordination with SOs in relation to memory and age in children with ASD.

Methods: Nineteen children and adolescents with ASD, without intellectual disability, and 18 typically developing (TD) peers, aged 9–17, completed a home polysomnography study with testing on a spatial memory task before and after sleep. Spindles, SOs, and their coordination were characterized during stages 2 (N2) and 3 (N3) non-rapid eye movement sleep.

Results: ASD participants showed disrupted SO-spindle coordination during N2 sleep. Spindles peaked later in SO upstates and their timing was less consistent. They also showed a spindle density (#/min) deficit during N3 sleep. Both groups showed significant sleep-dependent memory consolidation, but their relations with spindle density differed. While TD participants showed the expected positive correlations, ASD participants showed the opposite.

Conclusions: The disrupted SO-spindle coordination and spindle deficit provide further evidence of abnormal thalamocortical interactions and TRN dysfunction in ASD. The inverse relations of spindle density with memory suggest a different function for spindles in ASD than TD. We propose that abnormal sleep oscillations reflect genetically mediated disruptions of TRN-dependent thalamocortical circuit development that contribute to the manifestations of ASD and are potentially treatable.

Statement of Significance

Converging lines of evidence implicate abnormal interactions between the thalamus and the cortex in the pathophysiology and manifestations of autism spectrum disorder (ASD). In the present study, we report a deficit in thalamically generated sleep spindles in ASD and provide the first demonstration of a disruption in their temporal coupling with cortical slow oscillations. Although these oscillations and their coupling mediate memory consolidation during sleep, only in typically developing participants did spindle activity predict better memory. We propose that abnormal sleep oscillations in ASD reflect genetically mediated disruptions of thalamocortical circuit development. Further study is needed to establish the functional significance of abnormal sleep physiology in ASD and its response to treatments that enhance sleep oscillations and their coordination.

Key words: autism spectrum disorder; spindles; slow oscillations; coupling; thalamocortical; memory consolidation; development

Submitted: 12 August, 2021; **Revised:** 13 December, 2021

Introduction

Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by social and communication impairments along with restricted and repetitive behaviors. Converging evidence from neuroimaging, sleep, and genetic studies suggest that dysregulation of thalamocortical interactions, mediated by the thalamic reticular nucleus (TRN), contribute to the expression of ASD (e.g. Refs. [1–3]). The most well-validated assays of TRN function are sleep spindles, defining EEG oscillations of stage 2 non-rapid eye movement (NREM) sleep (N2) consisting of brief bursts of approximately 10–15 Hz activity that are initiated in the TRN [4]. While the TRN can generate sleep spindles in isolation, their expression in the cortex reflects reciprocal interactions within thalamocortical feedback loops [4, 5]. Risk genes for ASD affect the TRN early in development and, when disrupted in mouse models, produce phenotypes resembling those seen in ASD, including attention impairments, sensory sensitivities, and sleep spindle deficits [2, 6, 7]. While numerous studies demonstrate disrupted sleep quality that correlates with core symptoms in children with ASD (e.g. [8–10]), relatively few have examined sleep oscillations. Studies of sleep spindles in ASD have produced inconsistent findings [1, 11–15]. The primary goal of the present study was to comprehensively characterize sleep spindles and their coordination with cortically generated slow oscillations (SOs) in children and adolescents with ASD, without intellectual disability.

Sleep spindles are temporally coordinated with cortical SOs and hippocampal sharp-wave ripples, an interregional dialogue that transfers memories from temporary indexing in the hippocampus to more permanent, distributed representation in the cortex [16, 17]. As reliable measurement of hippocampal ripples requires invasive recording, the present study focuses on SO-spindle interactions. SOs are large amplitude approximately 1 Hz oscillations that arise from the rhythmic depolarization (upstate) and hyperpolarization (downstate) of large populations of cortical pyramidal neurons [18]. Spindle and SO expression (initiation, development, and termination) and coordination depend on TRN-mediated thalamocortical feedback loops (for a review see Ref. [19]). SOs synchronize spindles, which preferentially occur during their upstates [20–22], and hippocampal ripples, which nest in the troughs of spindles [23–26]. Identifying sleep oscillation abnormalities in ASD may illuminate its pathophysiology and provide new electrophysiological targets for treating sleep, cognitive deficits, and symptoms.

The one previous study of SO-spindle coordination in children with ASD (9–12 years) reported no differences in coordination or spindles during NREM sleep [11]. SO-spindle coupling correlated with sleep-dependent picture recognition performance, but only in typically developing (TD) children (i.e. those without ASD meeting age-based developmental milestones). In the present study, we compared spindles, SOs, and their coordination in ASD and TD children and adolescents (9–17 years) and examined their relations with sleep-dependent consolidation of spatial memory. This was a reanalysis of data from our previous home-based overnight sleep study of ASD that reported no deficits in spindle density during N2 based on the visual identification of spindles at a single electrode (Cz) and did not investigate N3 or spindle coupling with SOs [13]. For the present study, we validated an automated spindle detector against visual identification in both groups and fully characterized spindles, SOs, and their coupling across all seven EEG electrodes. We examined N2 and N3 separately based on literature showing that both the physiology of these oscillations and their roles in memory consolidation differ by sleep stage [22, 27]. Since spindles are also thought to preserve sleep by suppressing sensory relay from the thalamus to the cortex to prevent arousals [28–30], we also examined the relations of spindle density to sleep maintenance.

Spindles and SOs undergo dramatic changes from childhood through adolescence [31–39] that parallel brain maturation [40, 41]. Alterations in their developmental trajectories may index atypical development [1, 42]. This age range is characterized by accelerated synaptic proliferation and pruning and the myelination of white matter tracts, which support the development of highly evolved cognitive and emotional capacities that are altered in ASD [43–45]. We investigated whether developmental changes in sleep oscillations are different in ASD by examining their relations to age.

Based on studies implicating TRN-mediated thalamocortical dysregulation in ASD, we hypothesized that sleep spindles would be reduced in ASD, consistent with the hypothesis of TRN dysfunction, and their coordination with SOs would be disrupted, suggesting abnormal thalamocortical interactions. We also expected spindle and SO-spindle coupling abnormalities to correlate with worse sleep-dependent memory consolidation, and reduced spindle density to be associated with worse sleep maintenance.

Methods

Participants

Data from 19 individuals with ASD, without intellectual disability or known genetic syndromes, and 18 TD controls, aged 9–17, were included in analyses. Since no females with ASD had polysomnography (PSG) data available, only males were included. Clinical evaluations were done by a licensed psychologist who conducted individual and parental interviews. ASD participants had clinical diagnoses of ASD and met ASD criteria on the Autism Diagnostic Observation Schedule [46] (ADOS) and the Autism Diagnostic Interview, Revised [47] (ADI-R). None of the participants met criteria for present comorbid psychiatric disorders. ASD participants scored higher than TD controls on parental ratings on the Child Behavior Checklist [48] (CBCL; Table 1) and the Social Responsiveness Scale [49] (SRS). Three ASD participants (16%) took stimulant medications and two (11%) took antipsychotics (see Supplement for details). Excluding medicated participants from analyses did not substantially change the results. None of the TD participants took medications. ASD and TD groups were matched for age. All participants had nonverbal intelligence quotients (NVIQ) ≥ 80 on the Differential Abilities Scales II [50] (DAS), but ASD participants showed a trend to lower NVIQ than TD (Table 1).

General exclusion criteria were significant hearing or vision loss; unstable chronic medical conditions; other neurological conditions including seizure disorder; and a diagnosed sleep disorder based on interviews and a review of medical records. TD controls had no history of neuropsychiatric or neurodevelopmental disorders. The study was approved by the Boston Children's Hospital Institutional Review Board. All participants provided assent and their parents gave written informed consent.

Procedures

Overview. One week prior to the first experimental session, participants visited Boston Children's Hospital for informed consent and clinical and cognitive assessments. Experimental sessions (Sleep, Wake) were conducted in the participants' homes at least 1 week apart and the order was counterbalanced within each group. The present report focuses on the Sleep session.

During the Sleep session a subset of participants trained on a spatial memory task and had an immediate test at night, an hour before their habitual bedtime. They were then wired for PSG and were retested in the morning after electrode removal. During the Wake session, participants trained and were tested on the task in the morning, 30 min after their habitual wake time, and were retested 10 h later, after a day of wakefulness. Participants engaged in their normal daily activities and were instructed not to nap. Fourteen ASD and 14 TD participants completed the spatial memory task.

Spatial memory task

The spatial memory task is similar to the children's game known as "Concentration." The stimuli are 15 pairs of colored images of animals and common objects arranged in a 5 × 6 array and presented on a laptop computer. Participants were instructed to learn the locations of each pair, after which they were tested for immediate recall. (See Supplemental Methods for a more detailed task description.) We calculated memory consolidation using two published methods: the percent change in correct pairs from (1) the last training trial to the retest trial [13, 51], and (2) the immediate test to the retest trial [27]. Memory consolidation on this task benefits more from sleep than wake in children and young adults [51, 52] and correlates with N2 spindle density (#/min) in TD children [27].

PSG

Data were acquired at 200 Hz using an Embla A-10 ambulatory PSG system (Medcare Systems, Buffalo, NY) with a standard montage including seven EEG (F3, F4, C3, Cz, C4, O1, O2), two electrooculography (EOG), and two electromyography (EMG) electrodes. PSG data were pre-processed and analyzed using BrainVision Analyzer 2.0 (BrainProducts, Germany) and Matlab R2018 (Mathworks, Natick, MA). Data were filtered at 0.3–35Hz referenced to the linked mastoids and artifacts were visually identified and removed. Electrodes with artifacts throughout the recording were excluded from analysis (total number of electrodes excluded: TD: 18 [14%]; ASD: 20 [15%]). Cardiac artifacts were removed using Independent Component Analysis implemented in fieldtrip (runICA) [53].

Sleep architecture and quality

Each 30s epoch of PSG was visually scored according to standard criteria [54] as WAKE, REM, N1, N2, or N3 by expert raters blind to diagnosis. Sleep stages were calculated as total minutes and percent of total sleep time (TST). Two subjects (1 ASD, 1 TD) were excluded from sleep architecture analyses due to noisy EOG and EMG electrodes, rendering the distinction between wake and REM scoring unreliable. We quantified sleep quality in terms of time in bed (TIB), TST, sleep efficiency (TST/TIB), sleep onset latency (SOL), and wake time after sleep onset (WASO). We also obtained parental ratings of participants' sleep quality on the Children's Sleep Habits Questionnaire (CSHQ; Table 1) [55]. 13/18 ASD and 4/18 TD for whom it was available, met criteria for clinically significant sleep problems based on a score > 40 on the CSHQ.

Spindle detection

Spindles were automatically detected at each electrode in N2 and N3 using a well-validated wavelet-based algorithm [56, 57]. The peak frequency of the wavelet was based on each individual's spindle frequency at Cz with a fixed bandwidth of ±1.5 Hz. Spindle frequency was defined separately for N2 and N3 as the frequency with maximum power in the 9–15 Hz range [58]. To facilitate detection of spectral peaks, power estimates were obtained from the temporal derivative of the EEG signal [59] using Welch's method with 10 s windows and 50% overlap. The vast majority of participants had a single peak in the fast spindle frequency range in both N2 and N3 (> 12 Hz; Figure S1). In the few cases (N2: 1 TD, 0 ASD; N3: 4 TD, 4 ASD) where two

Table 1. Participant characteristics

	TD (n = 18)	ASD (n = 19)		
	$M \pm SD$	M ± SD	t	P
Age (years)	13 ± 2	12 ± 2	1.28	.21
NVIQ	115 ± 17	106 ± 11	1.95	.06
SRS total score	45 ± 7	78 ± 11	−10.98	**<.001***
CBCL total problems score	43 ± 11	64 ± 8	−6.79	**<.001***
CSHQ scores				
Bedtime resistance	6.5 ± .6	7.4 ± 1.7	−2.32	**.04***
Sleep onset delay	1.4 ± .6	1.9 ± .8	−2.06	**.047***
Sleep duration	3.9 ± 1.1	4.6 ± 1.8	−1.34	.19
Sleep anxiety	4.2 ± .6	6.1 ± 1.7	−4.62	**<.001***
Nocturnal wakenings	3.2 ±. 5	3.4 ±. 8	−1.26	.22
Parasomnias	8.0 ± 1.3	8.8 ± 1.6	−1.61	.12
Disordered breathing	3.1 ± .3	3.3 ± .6	−1.39	.17
Daytime sleepiness	10.2 ± 2.4	12.6 ± 3.5	−2.33	**.03***
Total score	38.5 ± 4.2	45.7 ± 6.6	−3.89	**<.001***

Means, standard deviations, and group comparisons of demographic, clinical, and cognitive measures. Bold values with asterisks are significant at $P < .05$.

peaks were detected, the higher frequency peak was chosen. The threshold for spindle detection—nine times the median signal amplitude of artifact-free epochs—was chosen to maximize between-class ("spindle" vs. "non-spindle") variance [21, 60]. A spindle was detected whenever the wavelet signals exceeded threshold for a minimum of 400 ms.

This method was validated in TD and ASD samples by calculating spindle density (#/min) based on visual detection by expert scorers and correlating this with algorithmically detected spindle density in N2, at Cz in ten randomly selected participants from each group (TD: r = .74, p = .02, slope = 1.06; ASD: r = .85, p = .002, slope = 1.07; Figure S2A). The ratio of visually detected to algorithmically detected spindles did not differ between groups (TD: 1 to 1.68 ± .63, ASD: 1 to 1.76 ± .38; $t(18)$ = .37, p = .71). There was also good agreement between algorithmically detected and visually detected spindles within subjects [57] (Supplemental Methods; Figure S2B).

We measured spindle density and individual spindle morphology—peak amplitude, duration, peak frequency—based on 2 s epochs centered on the point of spindle detection. Peak amplitude was the maximal voltage following band-pass filtering of each individual's spindle frequency range; peak frequency was the spectral peak of the spindle following fast Fourier transform (FFT); and the duration of each spindle was the half-height width of the wavelet coefficients.

SO detection

SOs were automatically detected at each electrode in N2 and N3 using a modified version of a previously published method [26]. The raw EEG was filtered at 0.5–4 Hz using a two-way least-squares finite impulse response filter implemented in EEGLAB [61]. Consecutive positive-to-negative zero crossings occurring within 0.8 and 2 s of one another (corresponding to 0.5–1.25 Hz) were marked as candidate SOs. Those with peak-to-peak amplitudes in the upper 25th percentile were defined as SOs [17, 21, 25]. We measured SO density, duration, and absolute peak-to-peak amplitude. To control for irrelevant factors that influence EEG amplitude (e.g. electrode impedance, skull thickness) and that vary over the age range of our sample, we also calculated the relative peak-to-peak amplitude of the detected SOs for each participant. To calculate relative amplitude, we normalized the peak amplitude by dividing it by the standard deviation of the filtered EEG signal (0.5–4 Hz) at each electrode. The standard deviation of the EEG signal was calculated after excluding all candidate SOs to ensure that the relative amplitude reflected SO deviation from background EEG activity and was not driven by the presence of SOs. The results did not change when we calculated relative SO amplitude without excluding candidate SOs.

SO-spindle coordination

We measured the density of SO-spindle coupled events (events in which a spindle peaked during a SO), the SO phase at the spindle peak, and the consistency of this phase relationship. The instantaneous phase of the SO was derived from the Hilbert transform of the EEG trace filtered between 0.5 and 4 Hz. The mean phase of the SO at the spindle peak was calculated for each participant at each electrode using the circular statistics toolbox in MATLAB [62]. The length of the mean SO phase vector indexes the consistency of the SO-spindle phase relationship. To increase reliability of these measures, coupling parameters were calculated only at electrodes with at least 20 coupled events [21, 22].

Statistical analysis

All statistical analyses were carried out in Matlab (R2021a; Mathworks, Natick, MA). Spindle, SO, and SO-spindle coordination measures were averaged across frontal (F3, F4), central (C3, Cz, C4), and occipital electrodes (O1, O2) [11]. Unless otherwise specified, for all analyses we used linear mixed effects models that included Group (TD, ASD), Location (Frontal, Central, Occipital), and their interaction as fixed effects and Subject as a random effect. The results of the mixed effects models are presented in the tables. The figures show the effects broken down by Group and Location. Although the groups were well-matched for age, given the large range, we re-ran our main analyses on the 13 TD and ASD participants who could be matched for age on a one-to-one basis. Our main results were unchanged (see Supplemental Methods and Results).

Group differences in sleep parameters. Sleep quality and architecture were compared between groups using two sample t-tests. Spindle, SO, and SO-spindle coordination parameters were compared across groups using linear mixed effects models. To evaluate the effects of Group, Location, and their interactions on the SO phase at the spindle peak we used a two-way circular ANOVA [62].

Spatial memory in relation to spindles and SO-spindle coordination. We evaluated the relations of spindle density, coupled spindle density, coupling consistency, and SO phase at spindle peak with overnight memory consolidation using linear mixed effects models that included Overnight Improvement and its interactions as fixed effects. To interpret group differences in the relations of overnight improvement with spindle density we regressed memory consolidation against spindle density at each location using robust linear regression models.

Spindles in relation to sleep maintenance. To examine the role of spindles in sleep protection from arousals and transitions to lighter sleep, we regressed spindle density against WASO and the percent of TST spent in N1 using linear mixed effects models.

Sleep parameters in relation to age. To investigate the relation of sleep oscillation parameters and their coordination with age we used linear mixed effects models that included Age and its interactions as fixed effects. To interpret group differences in the relations of sleep oscillation parameters with age we used robust linear regression models at each location.

Correction for multiple comparisons. All effects in the models were corrected for multiple comparisons based on the number of sleep parameters in both sleep stages using False Discovery Rate (FDR) correction with the false positive rate set to .10 [63, 64].

Results

Sleep architecture and quality

While TST did not differ by Group (Table 2), ASD participants spent more TIB and had worse sleep quality as indexed by lower sleep efficiency, increased WASO, and increased SOL. ASD

Table 2. Sleep quality and architecture measures

Sleep quality	TD (*M* ± *SD*)	ASD (*M* ± *SD*)	*t*	*P*
TST (min)	483 ± 47	492 ± 51	.54	.59
Sleep efficiency (%)	95 ± 2	91 ± 7	−2.45	**.02***
TIB (min)	521 ± 45	576 ± 58	3.13	**.004***
WASO (min)	24 ± 11	51 ± 42	2.59	**.01***
SOL (min)	14 ± 10	32 ± 26	2.90	**.007***
N1	3 ± 2	4 ± 3	1.96	.06
N2	46 ± 8	47 ± 9	.56	.58
N3 Sleep architecture (%)	29 ± 6	34 ± 17	1.21	.24
REM	23 ± 4	20 ± 6	−1.59	.12
Sleep architecture (min)				
N1	14 ± 7	21 ± 12	2.16	**.04***
N2	221 ± 47	232 ± 46	.67	.51
N3	138 ± 28	167 ± 84	1.36	.19
REM	110 ± 23	99 ± 34	−1.08	.29

*Bold values with asterisks are significant at $P < .05$

Means, standard deviations, and group comparisons.

ASD, autism spectrum disorder; TD, typical developing controls; TST, total sleep time; TIB, time in bed; SOL, sleep onset latency; SE, sleep efficiency; WASO, wake after sleep onset; N1, stage 1 non-rapid eye movement (NREM) sleep; N2, stage 2 NREM sleep; N3, stage 3 NREM sleep; REM, rapid eye movement sleep.

participants spent more time in N1 than did TD, but otherwise, sleep architecture did not differ.

Spindles

N2 spindle density did not differ by Group (Figure 1; Table 3), but ASD participants had 30% and 32% lower spindle density at frontal and central locations respectively in N3 (Group: $p = .03$, Group by Location: $p = .007$; *post hoc* tests: Frontal: $t(31) = 2.34$, $p = .03$; Central: $t(34) = 2.30$, $p = .03$; Occipital: $t(32) = -.66$, $p = .51$). ASD participants had increased spindle duration in N2 (Group: $p = .048$), but this difference did not pass multiple comparisons correction. Spindle amplitude and frequency did not differ by Group in either N2 or N3.

SOs

Because SOs are generated frontally [65], their amplitude is significantly lower at occipital locations, which renders their identification less reliable. All Group and Group by Location effects were primarily driven by the occipital location. When these analyses omitted the occipital location, there were no significant group differences or interactions. Including the occipital location in the analyses ASD participants had higher SO density than TD in both N2 ($p = .02$; Figure S3; Table S1) and N3 ($p = .03$) and this did not significantly differ by Location. Neither absolute nor relative SO amplitude differed by Group, but there was a significant Group by Location interaction for relative SO amplitude during N2 ($p < .001$) reflecting that group differences were similar at frontal and central (ASD < TD) versus occipital (ASD > TD) locations, but did not reach significance at any location. There was also a significant Group by Location interaction for SO duration in N2 ($p = .01$), driven by longer SOs in ASD at the occipital location ($t(33) = -2.44$, $p = .02$).

SO-spindle coordination

The occipital location was omitted from these analyses because too few participants met the reliability criterion of >20 coupled spindles per electrode (N2: 6 TD, 15 ASD; N3: 1 TD, 0 ASD).

Coupled SO-spindle density did not differ by Group in N2 (Table 4; Figure 2A), but was reduced in ASD participants during N3 (Group: $p = .03$; Figure 2B). We attribute this reduction to lower spindle density in ASD since the percent of spindles coupled with SOs in N3 did not differ by Group (TD: Frontal: 8 ± 3%, Central: 9 ± 3%; ASD: Frontal: 8 ± 3%, Central: 8 ± 4%).

During N2, SO-spindle coupling was abnormal in ASD. Spindles peaked later in the SO upstate (Group: $p = .002$; 31° average delay across locations; Figure 2C) and the phase of the SO at which spindles peaked was less consistent at the central location (Group by Location: $p < .001$; Central: $t(34) = 2.43$, $p = .02$; Figure 2A). In N3 the SO phase at spindle peak and the consistency of this coupling did not differ by Group (Figure 2, B and D).

Relations of spindles and SO-spindle coordination with overnight memory consolidation

For both measures of memory consolidation, both groups performed better after an interval of sleep than wake. Group differences in memory consolidation are reported in the Supplemental Results; Figure S4. We report relations for overnight memory consolidation calculated as the percent change from the last training trial to retest. These relations were similar for memory consolidation calculated as the percent change from the immediate test to retest (Supplemental Results; Figure S5).

The relations of spindle density with overnight improvement differed by Group in both N2 ($F(2,70) = 5.83$, $p = .02$) and N3 ($F(2,70) = 16.30$, $p < .001$). This reflected that, as expected, in TD participants higher spindle density predicted better overnight memory consolidation, but the opposite was true for ASD (Figure 3). There was a significant Group by Overnight Improvement by Location interaction in N3 ($F(2,70) = 4.43$, $p = .02$) reflecting that unlike frontal and central locations, spindle density did not correlate with memory in TD participants at the occipital location. Surprisingly, SO-spindle density did not significantly predict memory consolidation in either group, location, or sleep stage (all *p*s > .11). There were no correlations of SO-spindle coordination parameters with overnight memory consolidation.

Relations of spindles with sleep maintenance

The correlations of N2 spindle density with both WASO and the N1 percent differed by Group (at a trend level for WASO

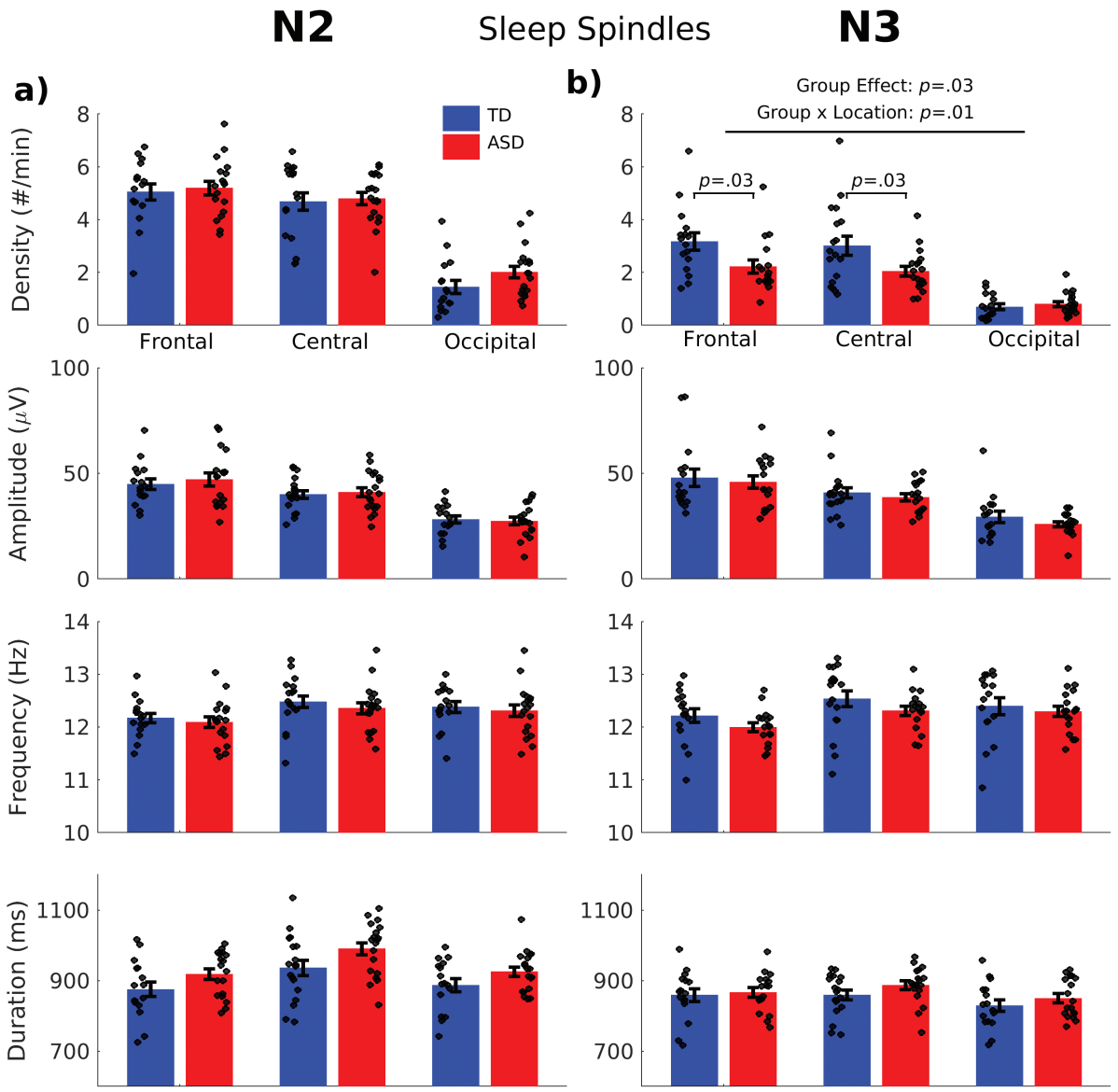

Figure 1. Sleep spindles. (A) Bar graphs of mean spindle parameters for each group at each location with standard error bars in N2 and (B) N3. Black circles represent data points for each individual.

($F(1,89) = 2.84$, $p = .09$)) and significantly for N1 ($F(1,89) = 4.50$ $p = .04$), reflecting that in ASD only, higher spindle density correlated with better sleep quality (i.e. less WASO and lower N1 percent; Figure S6). The correlation of N3 spindle density with N1 percent also differed significantly by Group ($F(1,89) = 4.42$, $p = .04$; Figure S6), reflecting that in TD higher spindle density correlated with increased N1 percent (Figure S6).

Relations of sleep oscillations with age

Consistent with previous studies of this age range [33, 34, 37, 38], N2 spindle density ($p = .006$) and spindle frequency in both N2 ($p < .001$) and N3 ($p < .001$) increased with age and this did not differ by Group or Location (Figure 4A and B; Table 5). There were no significant relations of age with spindle amplitude or duration.

Although SO density did not change with age, SO amplitude in N3 decreased with age in both groups ($p = .005$; Figure 4C), replicating previous studies of this age range [36, 39]. (Note that the slope of this relation was consistently shallower in ASD than TD—at all locations, in both sleep stages—but this group difference reached significance only at the occipital location for N3, suggesting that we may have been underpowered to detect these differences.) Relative SO amplitude significantly correlated with age, and these relations nominally differed by Group in N3 but did not reach statistical significance (Group by Age: $p = .051$; $ps < .001$ for all *post hoc* robust regressions of age by group at each location). While TD participants showed significant increases in N3 relative SO amplitude with age (Frontal: $r = .70$, $p = .002$; Central: $r = .68$, $p = .002$; Occipital: $r = .71$, $p = .002$; Figure 4D), ASD participants showed nonsignificant decreases (Frontal: $r = -.50$, $p = .08$; Central: $r = -.41$, $p = .25$; Occipital: $r = -.52$, $p = .14$). Similarly, while SO duration in both N2 and N3 increased with age in TD, it decreased with age in ASD (Group by Age: N2: $p=.02$; N3: $p=.03$), but these interactions did not pass correction for multiple comparisons.

Coupled spindle density did not change with age. The SO phase at the spindle peak decreased with age in N3 for both

Table 3. Spindle parameters

N2		Electrode		
		Frontal	Central	Occipital
Density (#/min)	**TD**	5.1 ± 1.2	4.7 ± 1.4	1.5 ± 1.0
	ASD	5.2 ± 1.1	4.8 ± 1.0	2.0 ± 1.0
Group: $F(1,100)=.56$, $p=.46$		**Electrode:** $F(2,100) = 151.09$, $\mathbf{p < .001}$*		**Interaction**: $F(2,100) = .70$, $p=.50$
Amplitude (μV)	**TD**	45.1 ± 10.1	40.2 ± 8.0	28.4 ± 7.1
	ASD	47.2 ± 13.2	41.2 ± 9.5	28 ± 7.5
Group: $F(1,100) = .21$, $p = .65$			**Electrode**: $F(2,100) = 123.38$, $\mathbf{p < .001}$*	**Interaction**: $F(2,100) = .42$, $p = .66$
Frequency (Hz)	**TD**	12.2 ± .4	12.5 ± .5	12.4 ± .4
	ASD	12.1 ± .4	12.4 ± .4	12.3 ± .5
Group: $F(1,100) = .49$, $p = .48$			**Electrode**: $F(2,100) = 133.90$, $\mathbf{p < .001}$*	**Interaction**: $F(2,100) = 1.22$, $p = .30$
Duration (ms)	**TD**	876 ± 82	937 ± 93	888 ± 74
	ASD	919 ± 64	991 ± 76	926 ± 58
Group: $F(1,100) = 4.01$, $p = .048$			**Electrode**: $F(2,100) = 23.57$, $\mathbf{p < .001}$*	**Interaction**: $F(2,100) = .35$, $p = .70$
N3		**Electrode**		
		Frontal	**Central**	**Occipital**
Density (#/min)	**TD**	3.2 ± 1.3	3.0 ± 1.5	.7 ± .5
	ASD	2.2 ± 1.0	2.1 ± .8	.8 ± .4
Group: $F(1,97) = 4.67$, $\mathbf{p = .03}$*		**Electrode**: $F(2,97) = 98.70$, $\mathbf{p < .001}$*		**Interaction**: $F(2,97) = 5.20$, $\mathbf{p = .007}$*
Amplitude (μV)	**TD**	48.1 ± 16.8	41.0 ± 10.3	29.6 ± 10.7
	ASD	46.0 ± 12.1	38.8 ± 7.3	26.1 ± 5.3
Group: $F(1,97) = .40$ $p = .53$		**Electrode**: $F(2,97) = 102.92$, $\mathbf{p < .001}$*		**Interaction**: $F(2,97) = .05$, $p = .95$
Frequency (Hz)	**TD**	12.2 ± .5	12.5 ± .6	12.4 ± .6
	ASD	12.0 ± .3	12.3 ± .4	12.3 ± .4
Group: $F(1,97) = 1.51$, $p = .22$		**Electrode**: $F(2,97) = 81.48$, $\mathbf{p < .001}$*		**Interaction**: $F(2,97) = .79$, $p = .46$
Duration (ms)	**TD**	860 ± 71	860 ± 59	830 ± 66
	ASD	868 ± 56	888 ± 53	851 ± 55
Group: $F(1,97) = .1.61$, $p = .21$		**Electrode**: $F(2,97) = 6.29$, $\mathbf{p = .002}$*		**Interaction**: $F(2,97) = .40$, $p = .67$

Means and standard deviations by group and location, and group level statistics.
*Bold values with asterisks meet FDR correction for significance.

groups (p = .004; Figure S7A), reflecting that spindles peaked earlier (closer to the SO upstate) in older participants. Coupling consistency in N2 and N3 increased with age in both groups (N2: p = .005; N3: p = .02; Figure S7B).

Discussion

Our primary finding is that children and adolescents with ASD show disrupted coordination of thalamically generated spindles with cortical SOs during N2 sleep, consistent with neuroimaging evidence of dysregulated thalamocortical interactions [3, 66, 67]. During N2 sleep, spindles peaked later in the SO phase and were less consistent in this timing. These coupling abnormalities occurred in the context of normal N2 spindle density and morphology. ASD participants did, however, show a spindle density deficit in N3, consistent with genetic evidence implicating the TRN in pathophysiology [2, 6, 7]. Contrary to expectations, SO-coupled spindles did not correlate with memory in either group.

Consistent with a large body of literature in healthy individuals (e.g. Ref. [68]), spindle density in TD correlated with better sleep-dependent memory consolidation. Surprisingly, in ASD, although their memory benefited from sleep, spindle density correlated with worse memory consolidation. These relations differed significantly by Group, suggesting that spindles function differently in ASD. In addition to mediating memory consolidation, spindles are also believed to protect sleep by suppressing sensory relay to the cortex [28–30]. As in prior studies [8], ASD participants showed worse sleep quality than TD, including greater WASO. Higher N2 spindle density correlated with lower WASO and percent of TST spent in N1 in ASD participants only, suggesting that in the context of disrupted sleep, spindles may serve to prevent arousals and transitions to lighter sleep.

The spindle density deficits seen in N3 add to the genetic evidence of TRN dysfunction in ASD [2, 6]. The TRN is the major inhibitory nucleus of the thalamus and it modulates thalamocortical interactions during both wake and sleep [69]. During wake, the TRN inhibits thalamocortical neurons to gate the relay of sensory information to the cortex, suppressing irrelevant and redundant input while amplifying relevant information [70–72]. A deficit in TRN function in ASD could contribute to sensory gating deficits, sensory sensitivities, and impaired selective

Table 4. Slow oscillation-spindle coordination parameters

		Electrode	
N2		Frontal	Central
Coupled density (#/min)	**TD** **ASD**	.49 ± .16 .56 ± .17	.40 ± .13 .47 ± .16
Group: $F(1,67) = 1.80$, $p = .18$		**Electrode:** $F(1,67) = 15.39$, $\mathbf{p < .001}$*	**Interaction**: $F(1,67) = .05$, $p = .82$
Phase (°)†	**TD** **ASD**	34 ± 36 75 ± 52	18 ± 36 40 ± 42
Group: $\chi^2 = 10.22$, $\mathbf{p = .006}$*		**Electrode**: $\chi^2 = 6.11$, $p = .05$	**Interaction**: $\chi^2 = .1.42$, $p = .23$
Consistency	**TD** **ASD**	.22 ± .09 .25 ± .14	.30 ± .11 .21 ± .12
Group: $F(1,65) = .98$, $p = .33$		**Electrode**: $F(1,65) = 1.03$, $p = .31$*	**Interaction**: $F(1,65) = 13.09$, $\mathbf{p < .001}$
N3		**Electrode**	
		Frontal	**Central**
Coupled density (#/min)	**TD** **ASD**	.27 ± .21 .17 ± .11	.30 ± 21 .18 ± .13
Group: $F(1,65) = 4.81$, $\mathbf{p = .03}$*		**Electrode:** $F(1,65) = .94$, $p = .34$	**Interaction**: $F(1,65) = .06$, $p = .81$
Phase (°)†	**TD** **ASD**	13 ± 30 -2 ± 31	9 ± 16 20 ± 33
Group: $F(1,50) = .46$, $p = .50$		**Electrode**: $F(1,48) = .94$, $p = .34$	**Interaction**: $F(1,48) = 2.28$, $p = .14$
Consistency	**TD** **ASD**	.45 ± .14 .52 ± .18	.46 ± .10 .41 ± .16
Group: $F(1,50) = .02$, $p = .88$		**Electrode**: $F(1,48) = 2.09$, $p = .16$	**Interaction**: $F(1,48) = 2.49$, $p = .12$

Means and standard deviations by group and electrode, and group level statistics.
*Bold values with asterisks meet FDR correction for significance.
†χ^2, F and p values were derived using a circular two-way ANOVA.

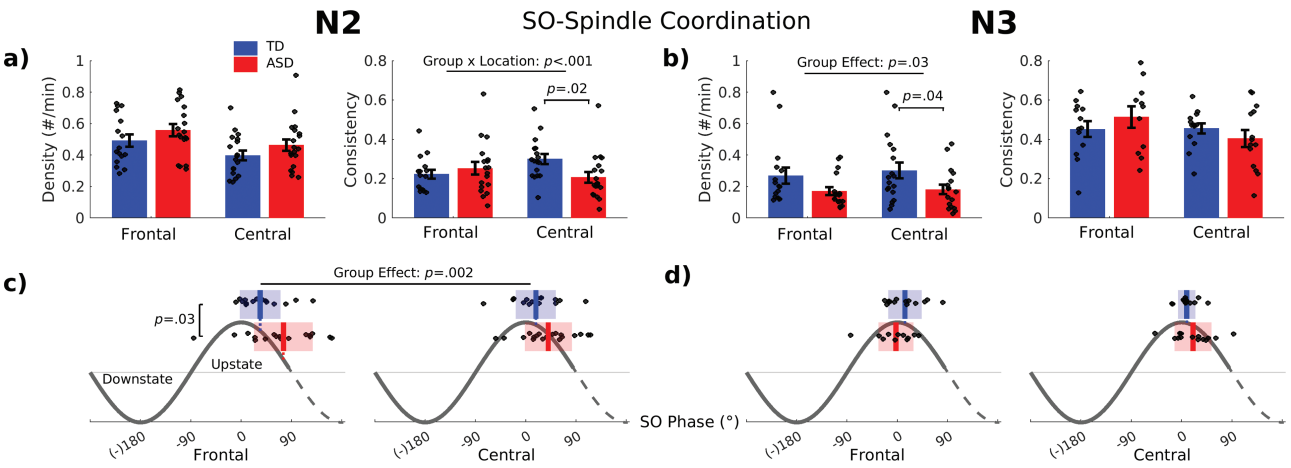

Figure 2. SO-spindle coordination. (A) Mean coupled spindle density and coupling consistency for each group at frontal and central locations with standard error bars in N2 and (B) N3. In ASD spindles peaked significantly later in the SO upstate than TD. Black circles represent data points for each individual. (C) Mean and standard deviation of SO phase superimposed on a schematic representation of a SO in N2 and (D) N3.

attention. During sleep, the TRN powerfully inhibits thalamocortical neurons resulting in the rebound burst firing that generates spindles [4]. By leading to a reduction of spindles, deficient TRN inhibition in ASD could contribute to sleep disruption.

Spindle activity is highly heritable [37, 73, 74] and genetic studies have identified ASD risk genes that by affecting the TRN early in development, may contribute to both spindle deficits and the waking manifestations of ASD. *Ptchd1*, which is selectively expressed in the TRN early in postnatal development, is mutated in approximately 1% of individuals with ASD [75–77]. Humans with *Ptchd1* deletion or truncating mutations exhibit ASD phenotypes [78]. Deletions of this gene in mice attenuate TRN activity and cause spindle, attention, and sensory gating deficits. Importantly, these deficits can be rescued by

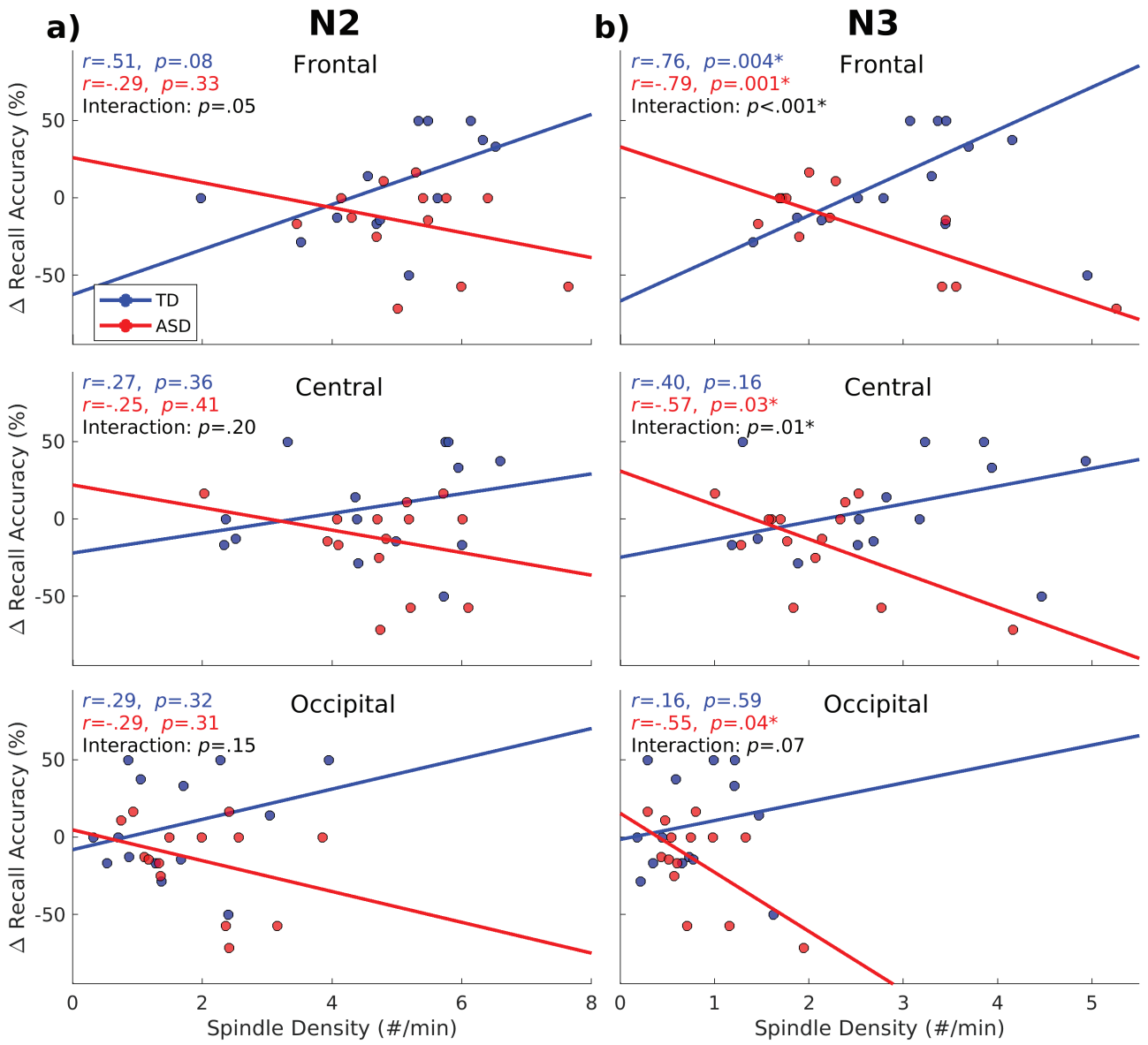

Figure 3. Relations of spindle density to overnight memory consolidation. (A) Spindle density at each location plotted against overnight change in recall accuracy calculated as the percent change from the last training trial to retest in N2 and (B) N3 with regression lines for each group.

a compound that corrects TRN function [2]. *Gabrb3* (GABA receptor beta 3), another ASD risk gene, is expressed in the thalamus and primarily in the TRN [79]. *Gabrb3* gene-deficient mice have reduced expression of *Gabrb3* in the TRN 6, 7] and show both deficits in social behavior [80, 81] and increased auditory and tactile sensory sensitivities. These findings raise the possibility that genetically mediated TRN dysfunction may contribute to the development and manifestations of ASD, and may be treatable.

Rodent studies provide clues to potential mechanisms by which early TRN dysfunction could contribute to the development of ASD. The TRN plays a crucial role in establishing and refining thalamocortical circuits. During gestation, axons connecting the thalamus to the cortex all pass through the TRN, which helps guide them to their terminations [82]. As early as the first postnatal week, spindle bursts, generated by the TRN, appear [83] and refine reciprocal thalamocortical connections [84–86]. This leads to the hypothesis that genetically mediated TRN dysfunction, by disrupting the development of this circuitry, set the stage for ASD.

Although the TRN can generate sleep spindles when isolated from the rest of the thalamus and the cortex [4, 87], their synchronization with cortical SOs requires reciprocal thalamocortical interactions [5, 88]. This suggests that SO-spindle coordination deficits reflect abnormal thalamocortical communication in ASD. This hypothesis is supported by functional connectivity MRI findings of abnormally high thalamic connectivity with auditory, somatosensory, and motor cortex in ASD that correlates with sensory sensitivities [3, 66, 67, 89–94]. Theoretically, reduced TRN-mediated thalamocortical inhibition in ASD could result in both spindle deficits and increased unfiltered sensory relay as reflected in thalamic "hyperconnectivity" with sensory cortices. In support of this hypothesis, in both health and schizophrenia, spindle density inversely correlates with thalamocortical connectivity with somatosensory and motor cortices, suggesting that both measures index the integrity of

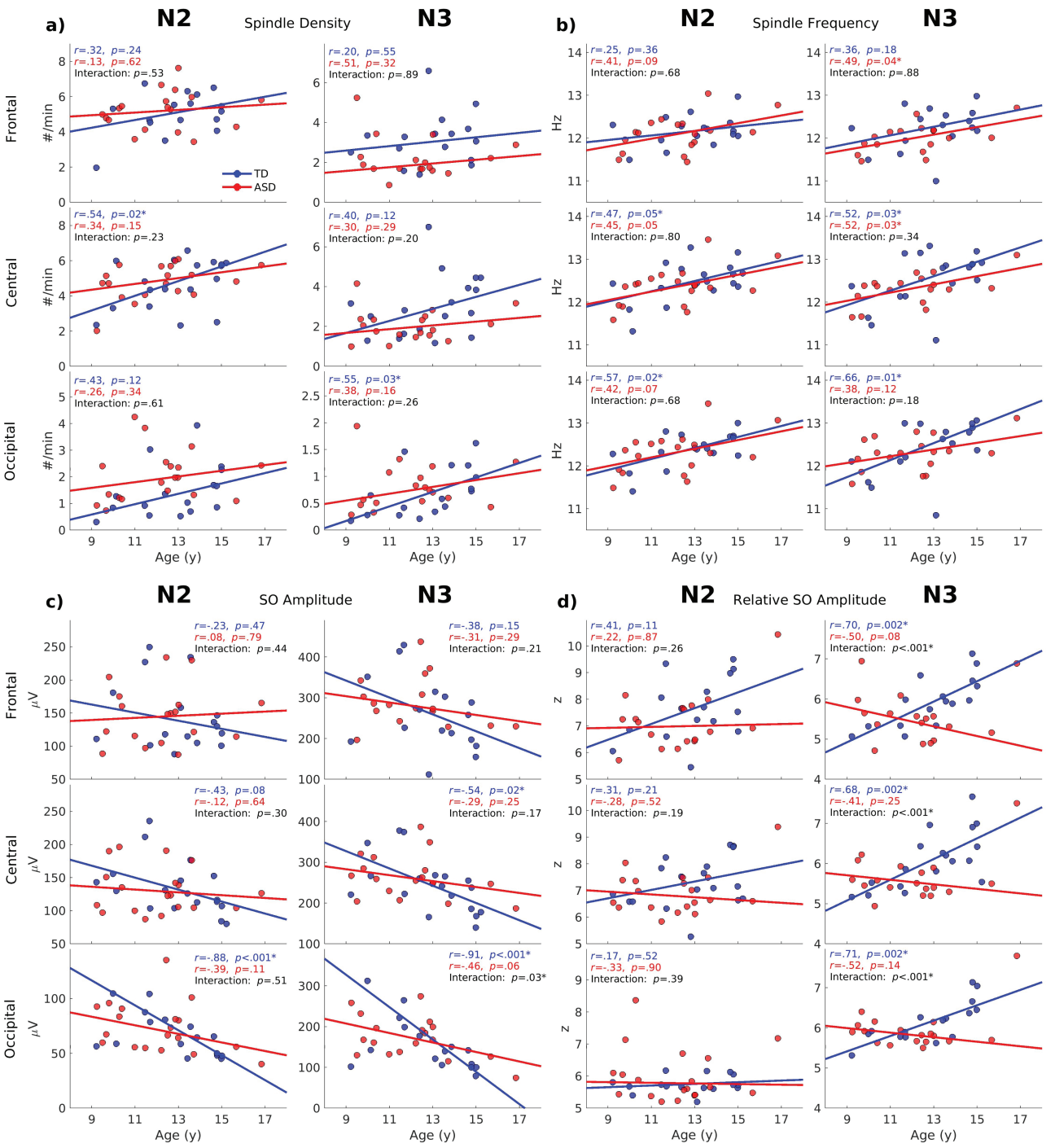

Figure 4. Relations of spindle and SO parameters with age. (A) Spindle density, (B) spindle frequency, (C) SO amplitude, and (D) relative SO amplitude at each location plotted against age during N2 and N3 with regression lines for each group. Circles represent data points for each individual.

TRN-mediated thalamocortical inhibition [95]. Based on these findings one might expect that in ASD spindle deficits will correlate with thalamic hyperconnectivity with sensory and motor cortices and sensory sensitivities.

While N2 spindle density and morphology did not differ in ASD compared with TD, we found a reduction of spindles in N3. Studies including ASD participants within this age range have reported both reduced [15, 96] and similar 11, 97] spindle density. The largest (n = 135) study of children with ASD [1] (aged 2 to 6 years, including those with intellectual disability), showed reduced spindle density and duration based on visual inspection of 5 min epochs of N2 across the night. Our finding of abnormal SO-spindle coupling in ASD during N2 sleep also seems to be inconsistent with the one previous study of SO-spindle coupling in children with ASD [11], which reported no differences, but this may reflect that they combined N2 and N3 and the different range of ages. The present finding of coupling deficits only in N2 may reflect that the higher amplitude SOs of N3 provide a stronger drive to the TRN, allowing them to more consistently align spindles in their upstates. This interpretation is supported

Table 5. Relationship of sleep oscillations with age

N2	Age effect		Age by group		Age by location		Age by group by location	
Spindles	*F*(1,94)	*P*	*F*(1,94)	*P*	*F*(2,94)	*p*	*F*(2,94)	*P*
Density	8.02	**.006***	.86	.36	.52	.60	.03	.97
Amplitude	.44	.51	.25	.62	.67	.51	.07	.93
Frequency	13.00	**<.001***	.03	.86	.24	.79	1.38	.26
Duration	.48	.49	3.61	.06	.36	.70	1.89	.16
Slow oscillations	***F*(1,94)**	***P***	***F*(1,94)**	***P***	***F*(2,94)**	***P***	***F*(2,94)**	***P***
Density	1.98	.16	2.11	.15	3.01	.054	.28	.75
Amplitude	2.79	.10	1.44	.23	1.28	.28	.77	.47
Relative amplitude	3.51	.06	.03	.86	14.62	**<.001***	.05	.96
Duration	.43	.51	5.32	.02	4.93	.01	.27	.76
Coordination	***F*(1,63)**	***P***	***F*(1,63)**	***P***	***F*(1,63)**	***P***	***F*(1,63)**	***P***
Coupled density	.68	.41	.01	.94	1.31	.26	.69	.41
Phase	.73	.40	.61	.44	1.11	.30	.71	.40
Coupling consistency	8.54	**.005***	2.30	.13	.41	.53	.70	.40
N3								
Spindles	***F*(1,91)**	***P***	***F*(1,91)**	***p***	***F*(2,91)**	***P***	***F*(2,91)**	***P***
Density	1.56	.22	1.51	.22	1.27	.29	.26	.77
Amplitude	3.67	.06	1.23	.27	2.66	.08	.70	.50
Frequency	12.43	**<.001***	.76	.39	.34	.71	2.98	.06
Duration	1.13	.29	2.44	.12	.56	.57	.98	.38
Slow oscillations	***F*(1,91)**	***P***	***F*(1,91)**	***P***	***F*(2,91)**	***P***	***F*(2,91)**	***P***
Density	.001	.99	.34	.56	.02	.98	.05	.95
Amplitude	8.16	**.005***	1.44	.23	.99	.38	.37	.69
Relative amplitude	11.46	**.001***	3.90	.051	2.35	.10	2.36	.10
Duration	.81	.37	4.86	.03	.14	.87	.54	.58
Coordination	***F*(1,61)**	***P***	***F*(1,61)**	***P***	***F*(1,61)**	***P***	***F*(1,61)**	***P***
Coupled density	.70	.40	.43	.52	.12	.73	.24	.62
Phase	9.36	**.004***	.78	.38	.14	.71	4.20	.046
Coupling consistency	6.37	.02	2.09	.16	.02	.88	4.44	.04

*Bold values with asterisks meet FDR correction for significance.

by previous findings that higher SO amplitude is associated with greater coupling consistency [11, 21]. Inconsistencies across studies likely reflect myriad factors including small sample sizes, which limit power and generalizability; different sample composition in terms of age, level of intellectual function, and the presence of seizures; the heterogeneity of ASD; as well as methodological differences (for review see Ref. [98]).

The precise timing of spindles with SOs correlates with better memory consolidation in TD children [99], adults [100], and individuals with schizophrenia [20], whereas disruption in this timing is associated with forgetting in older adults [101]. In this study, memory consolidation did not correlate with SO-spindle coordination in either group. Paradoxically, a previous study reported an inverse correlation of coupling consistency with sleep-dependent gist extraction in children with ASD [11]. Given the lack of relationship of SO-spindle coordination parameters with memory in our study, and that sleep benefited memory in ASD, the functional significance of abnormal coupling is unclear.

Our findings of age-related differences in sleep oscillations from childhood to adolescence are consistent with the developmental literature and, with the exception of relative SO amplitude, did not differ significantly by group. Spindle density and frequency increased with age [32, 34, 102–104]. The increase of spindle density has been proposed to reflect the maturation of thalamocortical circuitry [34, 105] and, in a longitudinal study, correlated with better sleep-dependent memory consolidation [32]. SO amplitude declined with age, consistent with a body of literature showing decreased slow-wave activity and sleep depth during adolescence [35, 36, 39] that has been hypothesized to reflect the functional optimization of cortical circuits through a process of synaptic refinement that increases the specificity of connections [42, 106, 107]. Relative SO amplitude, which reflects the SO amplitude relative to background EEG activity, increased with age in TD, but declined in ASD, a group difference that reached significance in N3. This finding is novel and requires replication, but we interpret this difference to reflect atypical cortical circuit maturation in ASD. Finally, with increasing age, in both groups spindles peaked closer to the SO upstate and this phase relationship became more consistent. A prior study also reported an age-related increase of SO-spindle coupling consistency in TD individuals that correlated with better sleep-dependent memory consolidation [99].

Several limitations of the present study merit consideration. The small sample size and cross-sectional design may leave us underpowered to detect subtler group differences in sleep oscillations and their development, as well as non-linear relations with age (e.g. Ref. [33, 37]). Our findings also may not generalize beyond the age group studied or to individuals with intellectual disabilities. Larger longitudinal studies are warranted to understand whether and how the developmental trajectories of sleep oscillations differ in ASD, which has implications for understanding cortical and thalamocortical circuit development.

The memory task employed gave different results depending on which of the published measures of consolidation was used to measure group differences. This did not affect our conclusions since both measures showed similar relations with sleep parameters. As there was no non-memory control night we cannot exclude the possibility that spindle density correlated with memory in TD, not because spindles mediate memory consolidation, but because spindles correlate with cognitive ability more generally [68]. In the present study, however, spindles did not correlate with IQ. Our hypothesis that spindles mediate memory in TD is based on literature highlighting the critical role of spindles in memory consolidation (e.g. Refs. [17, 108–110]). Other potential concerns are that the novelty of the study procedures, including PSG, was more disruptive to sleep in ASD, and that the higher rate of periodic leg movements reported in ASD [111] may have also diminished sleep quality. While we lack data to evaluate these possibilities, if true, it is not clear whether and how they would affect sleep oscillations. Finally, the sparse EEG montage of the present study limits our ability to make inferences about group differences in the topography of sleep oscillations.

Since spindles are the most well-validated assay of TRN function, and their coordination with SOs indexes thalamocortical communication, large-scale studies of sleep in genetically characterized ASD samples using well-validated automated spindle and SO detectors could provide opportunities to advance our understanding of the genetic architecture and pathophysiology of thalamocortical dysfunction in ASD and illuminate its mechanisms. Such discoveries could guide the development of mechanistically targeted treatments. Importantly, dysfunction related to abnormal TRN-mediated thalamocortical interactions in ASD may be treatable using available interventions. Recent findings in humans demonstrate that pharmacologic approaches and noninvasive neuromodulation (electrical and auditory stimulation) can increase spindles, SOs, and their coupling and improve memory presumably by normalizing thalamocortical interactions (for review see Ref. [112]).

In summary, we found a disruption of the coordination of spindles with SOs during N2 sleep in children and adolescents with ASD, consistent with neuroimaging and other evidence of abnormal thalamocortical interactions. We also found a spindle density deficit during N3, consistent with genetic evidence implicating the TRN in ASD pathophysiology. The functional significance of these abnormalities remains to be established. We propose that sleep oscillations can index abnormal brain development from childhood to adolescence and that genetically mediated dysfunction of the TRN, and the thalamocortical circuitry it modulates, contribute to both the waking and sleeping manifestations of ASD, and are potentially treatable.

Supplementary Material

Supplementary material is available at *SLEEP* online.

Funding

This work was supported by a grant from the Simons Foundation to the Simons Center for the Social Brain at MIT (DSM) and Autism Speaks (RS; Grant #6213).

Acknowledgments

The authors thank Hannah Holbrook and Ellen Hanson for their help with characterizing participants and data acquisition, as well as all families for their participation.

Disclosure Statement

Financial disclosure: None.

Nonfinancial disclosure: None.

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