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Noemi Mazzoni, Eva-Maria Kurz, Nicola Cellini, Luciana Ciringione, Margherita Calderan, Giuseppe Gallitto, Simona Falco, Paola Venuti, Katharina Zinke, Jan Born & Andrea Caria

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“Aperiodic and periodic neural activity during sleep in autism spectrum disorders”

Noemi Mazzoni[1,2]*, Eva-Maria Kurz[3,4,5], Nicola Cellini[6], Luciana Ciringione[1], Margherita Calderan[6], Giuseppe Gallitto[7], Simona de Falco[1], Paola Venuti[1], Katharina Zinke[3,8], Jan Born[3,9,10,11], Andrea Caria[1]*

*corresponding authors

Corresponding authors:

Noemi Mazzoni

[1]Department of Psychology and Cognitive Science, University of Trento, Rovereto, Italy

[2]Department of Theoretical and Applied Sciences, eCampus University, Novedrate, Italy

E-mail: noemimax@gmail.com; noemi.mazzoni@unitn.it

Andrea Caria

[1]Department of Psychology and Cognitive Science, University of Trento, Rovereto, Italy

E-mail: andrea.caria@unitn.it

List of authors:

Noemi Mazzoni

[1]Department of Psychology and Cognitive Science, University of Trento, Rovereto, Italy

[2]Department of Theoretical and Applied Sciences, eCampus University, Novedrate, Italy

E-mail: noemi.mazzoni@unitn.it

Eva-Maria Kurz

[3] Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Tübingen, Germany

[4] Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany

[5] Department of Psychology, Development and Neurodiversity Lab, Uppsala University, Uppsala, Sweden

E-mail: eva-maria.kurz@uni-tuebingen.de

Nicola Cellini

[6] Department of General Psychology, University of Padua, Padua, Italy

E-mail: nicola.cellini@unipd.it

Luciana Ciringione

[1]Department of Psychology and Cognitive Science, University of Trento, Rovereto, Italy

E-mail: luciana.ciringione@unitn.it

Margherita Calderan

[6] Department of General Psychology, University of Padua, Padua, Italy

E-mail: margherita.calderan@unipd.it

Giuseppe Gallitto

[7] Department of Neurology, University Hospital Essen, 45147 Essen, Germany

E-mail: giuseppe.gallitto@uk-essen.de

Simona de Falco

[1]Department of Psychology and Cognitive Science, University of Trento, Rovereto, Italy

E-mail: simona.defalco@unitn.it

Paola Venuti

[1]Department of Psychology and Cognitive Science, University of Trento, Rovereto, Italy

E-mail: paola.venuti@unitn.it

Katharina Zinke

[3] Institute of Medical Psychology and Behavioural Neurobiology, University of Tübingen, Tübingen, Germany;

[8] Saxon State and University Library Dresden, Dresden, Germany

E-mail: katharina.zinke@slub-dresden.de

Jan Born

[3] Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Germany

[9] German Center for Diabetes Research (DZD), Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen (IDM), Tübingen, Germany

[10] Center for Integrative Neuroscience, Tübingen, Germany

[11] German Center for Mental Health (DZPG), Partner Site Tübingen, Germany

E-mail: jan.born@uni-tuebingen.de

Andrea Caria

[1]Department of Psychology and Cognitive Science, University of Trento, Rovereto, Italy

E-mail: andrea.caria@unitn.it

Aperiodic and periodic neural activity during sleep in autism spectrum disorders.

Noemi Mazzoni, Eva-Maria Kurz, Nicola Cellini, Luciana Ciringione, Margherita Calderan, Giuseppe Gallitto, Simona de Falco, Paola Venuti, Katharina Zinke, Jan Born, Andrea Caria

Abstract

Background: Influential theories propose that the complex and heterogeneous clinical and behavioral manifestations of autism spectrum disorder (ASD) arise from dysregulation of neural circuits driven by an imbalance between excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission. Building on this framework, and considering the role of homeostatic regulation of neuronal excitability in shaping sleep stages, we hypothesized that dysregulation of neuronal network activity—including altered ratios of excitatory drive to interneuronal inhibitory control—might manifest in sleep architecture. An elevated E/I ratio in ASD is expected to render the sleep EEG noisier, less synchronized, and less precisely timed, thereby compromising NREM sleep quality and disrupting memory-related oscillatory coordination.

Methods: To test this hypothesis, we examined sleep patterns in a homogeneous cohort of adults with ASD without intellectual disability and free from pharmacological treatment, compared with neurotypical (NT) controls. We specifically investigated electrophysiological sleep markers that may reflect alterations in cortical excitability and inhibition. Macro- and microstructural features of nocturnal sleep were assessed using in-home polysomnography (PSG), including analyses of periodic EEG components, such as slow oscillations and sleep spindles, and aperiodic metrics of EEG activity.

Results: Our findings revealed sleep-stage-specific PSG differences in ASD, characterized by increased N3 sleep, decreased N2 sleep, and heightened slope and offset of aperiodic EEG activity during NREM sleep relative to NT controls. Moreover, ASD participants showed elevated alpha power during N2, which positively correlated with ADOS total scores. We also observed a steeper slow-oscillation slope, a reduced anterior–posterior gradient in spindle density, and diminished spindle–slow oscillation coupling, collectively indicating atypical thalamo-cortical network dynamics in ASD. Overall, these spatially distributed and sleep-stage-dependent alterations reflect dysregulated neuronal dynamics, potentially pointing to increased inhibitory activity arising from altered thalamo-cortical regulation and compensatory mechanisms related to E/I imbalance.

Conclusions: Our study provides novel electrophysiological evidence for a nuanced, sleep-related dysregulation in ASD that varies by sleep stage and cortical region, and subtly diverges from patterns observed in NT controls. Given the mechanistic relevance of sleep for neurodevelopment and circuit homeostasis, these findings offer valuable insights into sleep-related neurophysiological dysregulation in ASD.

Keywords: Autism spectrum disorder, sleep, EEG, excitation/inhibition imbalance, spindles, aperiodic neural activity.

Background

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impairments in social communication, and restrictive and repetitive behaviors and interests (1). Sleep problems are among the most frequent and challenging comorbidities in ASD, to the extent that sleep abnormalities have been proposed as diagnostic indicators of this condition (2–4). Sleep disturbances are present in 50%-80% of individuals with ASD with no intellectual disability (5,6) and in approximately 80% of individuals with ASD and concurrent developmental delays (7). These disturbances negatively affect daytime behavior (8) and appear to exacerbate core symptoms of ASD, including repetitive behaviors, attentional difficulties, communication challenges, and socioemotional impairments (7,9–16) . They may also contribute to critical behaviors, like aggression and self-injury (17), and a bi-directional relationship has been suggested between the severity of sleep problems and the severity of ASD symptoms (18) .

A prominent mechanistic account proposes that the behavioral and symptom profiles characteristic of ASD arise from dysregulation within neural circuits driven by an imbalance between excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission (E/I imbalance). This imbalance is hypothesized to yield an elevated excitation/inhibition ratio across sensory, mnemonic, social, and emotional neural systems (19–24) (see Figure 1 for an illustrative picture of the relationship between brain networks, E/I balance, and sleep EEG activity in ASD).

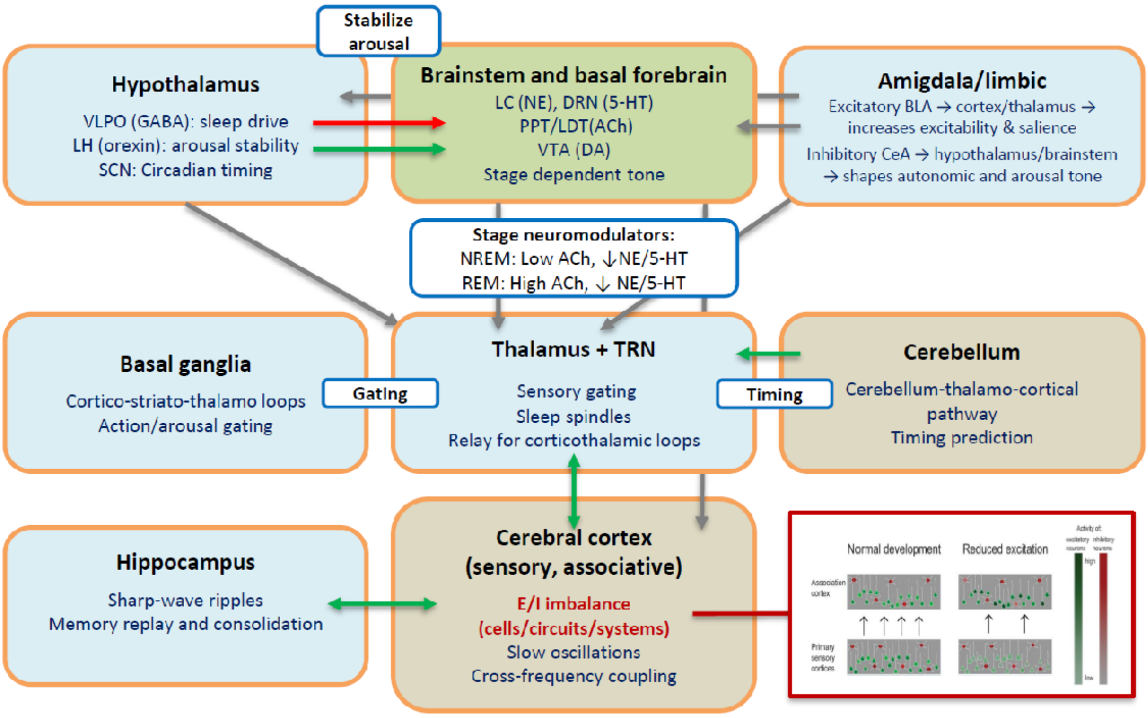

Figure 1. The relationship between brain networks, E/I balance, and sleep EEG activity in autism spectrum disorder.

The figure illustrates key brain regions involved in sleep-wake regulation, including cortical areas (prefrontal and sensory cortices and cerebellum), subcortical structures (thalamus, hypothalamus, hippocampus, basal ganglia, and amygdala), and brainstem nuclei, with pathways showing excitatory, inhibitory and modulatory connections. Circuit block for hypothalamus: **V**entro**L**ateral **P**re**O**ptic nucleus (VLPO), **L**ateral **H**ypothalamus (LH), **S**upra**C**hiasmatic **N**ucleus (SCN)); block for brainstem modulators: the **L**ocus **C**eruleus (LC; Norepin**E**phrin), **D**orsal **R**aphe **N**ucleus (DRN; serotonin, 5-HT), **P**edunculo**P**ontine **T**egmental (PPT) and **L**atero**D**orsal **T**egmental (LDN) nuclei (cholinergic neurons, ACh), **V**entral **T**egmental **A**rea (VTA; Dopamine); block for thalamus + **T**halamic **R**eticular **N**ucleus (TRN).

Key pathways and interactions:

- Hypothalamus → brainstem/thalamus (sleep–wake gating, arousal stability)
- Brainstem → thalamus/cortex (stage-dependent neuromodulation)
- Cortex ↔ thalamus (SOs drive spindles; spindles entrain cortex)
- Cortex ↔ hippocampus (SOs ↔ ripples; memory replay)
- Basal ganglia → thalamus (gating) and cerebellum → thalamus (timing)
- Amygdala → brainstem/thalamus (neuromodulator release, arousal threshold, thalamo-cortical gain states)

These interactions modulate the E/I balance, which:

- drives periodic features (e.g., slow oscillations & delta/SWA, spindles (σ), K-complexes, ripple events, SO–spindle–ripple coupling).
- might be partially reflected in aperiodic 1/f slope and offset (e.g., steeper slope ↔ relatively more inhibition; flatter ↔ relatively more excitation).

- feeds back via homeostatic/plastic mechanisms

In autism, circuit-level differences may shift E/I, altering both periodic (spindles/SWA/ripple coupling) and aperiodic (1/f) measures during sleep.

Lower right panel modified from Nelson & Valakh 2015

Evidence for the E/I imbalance hypothesis in ASD has been reported in terms of both neuronal hyper-excitation and hypo-inhibition (25–27), and this heterogeneity may contribute to the broad variability in ASD behavioral manifestations (21,22,28–30). The complex relationships between E/I-related genetics and autism characteristics resulting in diverse alterations of glutamatergic and GABAergic activity (21) have been interpreted within a homeostatic framework of neural circuitry (22). Homeostatic regulation of neuronal excitability is achieved primarily through intrinsic network mechanisms, with inhibitory interneurons playing a central role in balancing excitatory and inhibitory synaptic input. Notably, interneuronal inhibition is thought to underlie both memory-related synaptic potentiation (local downscaling) during slow wave sleep (SWS), and global synaptic downscaling during rapid eye movements (REM) sleep, including synaptic pruning and reduced neural excitability (31–33). These plastic mechanisms, which share underlying neuronal processes, modulate the coordination of slow oscillations (SOs) and spindle events during non-rapid eye movements (NREM) sleep as well as theta activity during REM sleep.

Given the accumulating evidence for E/I imbalance in ASD and the critical role of homeostatic regulation of neuronal excitability across sleep stages, we hypothesized that dysregulation of neuronal network activity would manifest as alterations of sleep architecture. Earlier polysomnographic (PSG) studies demonstrated anomalies in individuals with ASD, including prolonged sleep onset latency (SOL), reduced total sleep time (TST), lower sleep efficiency (SE), reduced REM sleep and NREM sleep, and a lower REM density (11,34,35). Although these findings were primarily reported in children, sleep disturbances persist into adolescence and adulthood (12,36–42), and may change across developmental stages (6,43). Nonetheless, PSG findings in ASD remain limited and inconsistent, likely due to substantial phenotypic heterogeneity (6,34,40,44–50). The present study sought to clarify sleep macro- and microstructure in autistic adults and to investigate whether alterations in sleep EEG emerge from dysregulation of neural interactions, particularly the imbalance between excitatory activity and interneuronal inhibitory control. E/I imbalance in ASD was expected to render sleep EEG signals noisier, less synchronized, and less precisely timed, thereby affecting NREM sleep quality and memory-related oscillatory coordination. Specifically, we hypothesized that increased excitation or reduced inhibition would disrupt the neural circuits generating stable sleep rhythms, potentially leading to: (i) flatter aperiodic (1/f) slope, reflecting increased cortical activation, (ii) reduced slow-wave activity (SWA) and SOs due to impaired inhibitory synchrony, (iii) altered sleep spindles (e.g. lower density, shorter duration, reduced regularity), given their reliance on precise GABAergic signaling in the thalamic reticular nucleus (TRN), the primary sleep spindle pacemaker (51), and (iv) poorer SO–spindle coupling, which could disrupt hierarchical timing essential for memory consolidation (see Figure 2 for an integrative model linking genetic/neurobiological alterations, E/I imbalance, predicted sleep EEG alterations and behavioral manifestations). On the other hand, because E/I imbalance likely evolves from infancy through adulthood, some sleep architecture alterations may be partially compensated over development, potentially resulting in mitigated group differences relative to neurotypical controls.

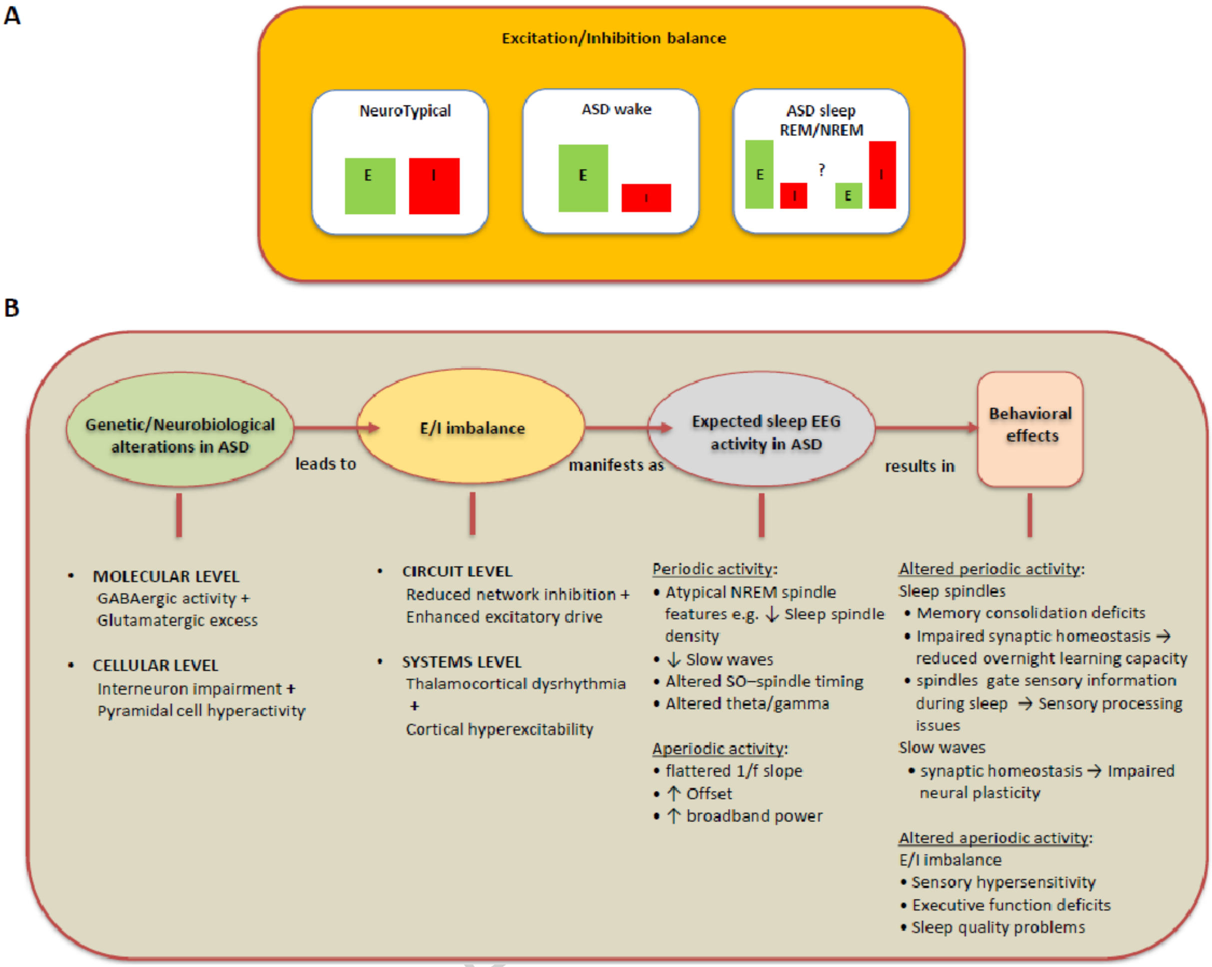

Figure 2. An integrative framework linking genetic/neurobiological alterations, E/I imbalance, altered sleep EEG patterns, and behavioral manifestations.
A - A visual representation of the E/I balance in typical and ASD brain states summarizing how GABAergic vs. glutamatergic tone might integrate circuit influences. Typical: balanced E/I tone across wake and sleep. ASD: region/age-dependent E/I shift during wake and sleep. During the awake state, an overall GABAergic decrease or glutamatergic tone increase has been hypothesized.
B - Four sections covering neurobiological mechanisms, E/I imbalance hypothesis in ASD, expected sleep EEG alterations, and behavioral implications for understanding ASD.

To test these hypotheses, we decomposed sleep EEG into periodic and aperiodic components to characterize SOs, sleep spindles, and aperiodic metrics, as well as their interrelationships in ASD. The aperiodic component (52)– an arrhythmic background signal contributing power across all frequencies and approximating a $1/f^{\beta}$ decay (53,54) – was indexed by the aperiodic offset and exponent. The offset reflects an overall shift in power across frequencies and is assumed to index global neuronal population firing rates (55,56), whereas the exponent β has been proposed as a noninvasive proxy of cortical E/I balance (52,57). Aperiodic dynamics vary systematically across wake, NREM, and REM sleep (58–61), and aperiodic activity during wakefulness has been suggested as an E/I maturation relevant for working memory development (62). However, the relationship between the aperiodic component and E/I balance remains debated (63,64), and results from pharmacological studies are mixed regarding how the E/I manipulations influence the slope (65–67). Notably, convergent multimodal evidence has demonstrated a tight coupling between glutamate–GABA ratios in human prefrontal cortex (via 7 Tesla Magnetic Resonance spectroscopy) and EEG-derived aperiodic measures (62). Aperiodic EEG metrics also differentiate ASD from NT children (68–71), and infant aperiodic activity has been proposed as a marker of later autism risk and language outcomes (71).

In the present study, we anticipated that SOs, sleep spindles, and aperiodic indices, would yield insights into the underlying neuronal dynamics of sleep in ASD. Furthermore, associations between oscillatory processes (e.g., sleep spindles) and 1/f activity have not yet been characterized in ASD. The present study seeks to fill this gap by examining potential relationships between periodic and aperiodic sleep components in autistic adults.

To minimize confounds related to developmental delay or variation in ASD symptoms severity (measured with Autism Diagnostic Observation Schedule - ADOS), we examined a rigorously selected and homogeneous cohort of adults with ASD without intellectual disability, free of neurological or psychiatric comorbidities, and not taking medication. Given the high sensitivity of autistic individuals to unfamiliar environments, which can increase stress and sensory reactivity, we conducted in-home PSG recordings to allow more naturalistic and ecologically valid sleep assessment. Subjective measures of sleep quality and sleepiness perception were also collected.

2. Methods

2.1 Participants

Thirty-one adults were recruited in the study, 15 with ASD (23.64±6.95 years, 1 female) and 16 neurotypical controls (NT, 23.40±2.67 years, 2 female). ASD participants were recruited through the Observation and Functional Diagnosis Lab (ODFLab) at the University of Trento. All ASD participants received diagnosis of ASD from expert clinicians using module 4 of the Autism Diagnostic Observation Schedule (ADOS) (72). Exclusion criteria included the presence of intellectual disabilities and the use of medication that may alter sleep architecture (e.g., benzodiazepines) which in adults with ASD is highly prevalent. NT participants were recruited through advertisements posted around the university campus and in social networks. Inclusion criteria were: (a) absence of any relevant psychiatric condition, as assessed by the Italian version of the Symptom Checklist-90 questionnaire (SCL-90) (73), (b) a lack of autistic symptoms, as attested by the Autism-spectrum Quotient questionnaire (AQ, Italian adaptation) (74), (c) a good self-reported sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI, Italian adaptation) (75) and (d) no medication use. These criteria aimed to recruit a NT reference group of individuals with potentially normative sleep quality.

The study was approved by the University of Tubingen ethical committee (ID: 720/2014BO1). All participants received a comprehensive explanation of the study procedures and provided written consent before participation. Participants were reimbursed for their participation in the study.

2.2 Experimental procedure

Before starting polysomnographic (PSG) recordings, participants completed the Pittsburgh Sleep Quality Index (PSQI) (76) and the Stanford Sleepiness Scale (SSS) (77) to track alertness and to assess sleep debt before going to bed. Sleep recordings were collected at the participant’s home using a portable EEG device (SOMNOscreenTM plus Neuro+, SOMNOmedics GmbH; Germany). The attachment of electrodes for recordings started at 9.00 p.m., and the participants were allowed to go to bed immediately afterwards. They were asked to push a button on the SOMNOmed device at the moment they switched off the light and decided to start sleeping. This button press applied a trigger on the EEG signal that was used as starting point for the visual sleep scoring. They should wake up the next morning spontaneously, i.e., without an alarm clock. The following morning, participants either returned to the lab or were visited by the experimenter to pick up the recording device.

2.3 PSG recordings

PSG recordings included 6 EEG electrodes (F3, F4, C3, C4, P3, P4) referenced to the linked mastoids, 2 electrooculogram (EOG) electrodes placed below the left and above the right canthi, and 2 electromyogram (EMG) electrodes placed over the left and right mentalis muscles. Electrodes were arranged according to the 10-20 system by experienced experimenters. The EEG and EOG signals were sampled at 256 Hz, high-pass filtered at 0.3 Hz, and low-pass filtered at 35 Hz, using a Butterworth IIR filter with model order 2. EMG signals were sampled at 256 Hz, high-pass filtered at 10 Hz, and low-pass filtered at 100 Hz, using a Butterworth IIR filter with model order 2. A 50-Hz notch filter was applied to all channels and data recordings. Sleep scoring (WAKE, N1, N2, N3, and REM) was visually performed on 30-sec EEG epochs from C3, in line with criteria (78). C4 was used whenever the signal from C3 was too noisy. We also calculated parameters related to sleep continuity (frequency and duration of awakenings) and stability (state transitions, frequency of microarousals) (Conte et al., 2021). Thirty-second epochs containing artefacts were marked during the scoring process and excluded from further analyses. For two participants, one channel each was excluded from further analyses (1 ASD: F4 and 1 NT: P3). Since for all parameters the average across frontal (F3, F4), central (C3, C4), and parietal (P3, P4) channels was used, data from the remaining electrode was considered for these two cases. Overall, the groups differed in the percentage of retained epochs (N2: mean ASD = 82%, SE ASD = 3.10, mean NT = 90 %, SE NT = 1.7, *t*(16.19) = -2.29, *p* = .036; N3: mean ASD = 89%, SE ASD =

3.92, mean NT = 97%, SE NT = 0.84, *t*(10.9) = -2.03, *p* = 0.067). The percentage of retained epochs was then included as covariate in the statistical analyses.

2.4 Analysis of spectral activity

Power spectral density (PSD) for artefact-free N2 and N3 epochs was calculated in MATLAB 2023b using the function *pwelch* (5-second segments with 50% overlap) and was averaged across frontal (F3, F4), central (C3, C4), and parietal channels (P3, P4). Power spectra were then subjected to the Python-based toolbox "fitting oscillations and one-over f" (fooof) (52) for the parameterization of aperiodic and oscillatory components in the frequency range of 0.5-25 Hz. No "knee" was fit, the peak width limit was set between 0.5 and 12 Hz, a maximum of 3 peaks could have been fit, and the minimum peak height was set to 0, though the height must exceed a threshold of 2 standard deviations (SDs) above the residual signal. The aperiodic fit was subtracted from the original power spectrum to determine for each individual the peak frequency in the fast spindle range (12-16 Hz), which was used as the center frequency for spindle detection. The aperiodic activity is characterized by an exponential decrease in power across frequencies with a $1/f^{\beta}$ distribution, whereby the β aperiodic exponent reflects the aperiodic power decrease across frequencies, equivalent to the negative slope of the power spectrum, and by an aperiodic offset representing the broadband spectrum's offset (52). In addition, mean alpha activity was obtained by averaging for each participant and channel across 8 to 12 Hz of the aperiodic corrected power spectrum, as for most participants, no individual frequency peak in the alpha range could be determined.

2.5 Analysis of Sleep Spindles

Sleep spindles were automatically detected using the MATLAB-based open-source toolbox SleepTrip (https://sleeptrip.org/; RRID:SCR_017318), separately during artifact-free N2 and N3 epochs. For each individual, the signal was bandpass filtered (two-pass Butterworth filter, filter order 4) ± 1.5 Hz around the individually identified peak frequency. For each sample point, the root mean square (RMS) for 200-ms windows was calculated, which was further smoothed by another 200-ms RMS windows. Whenever the duration of the smoothed moving RMS lay between 0.5 and 3 seconds and exceeded the filtered signal in the respective channel by 1.5 SDs, a spindle was detected. For each participant and channel, spindle density (events/minute), duration (seconds), amplitude (µV, maximum peak to trough potential), and frequency (Hz) were calculated and averaged across frontal, central, and parietal channels.

2.6 Analysis of Slow Oscillations

Slow oscillations (SOs) were similarly detected using SleepTrip, separately during artifact-free N2 and N3 epochs. The signal was first high-pass (0.3 Hz, two-pass Butterworth, order 4) and then low-pass filtered (4 Hz, two-pass Butterworth, order 6). After marking all putative SOs (i.e., consecutive positive-to-negative zero crossings) in the filtered signal, a SO was detected when a) its frequency was between 0.5 and 1.25 Hz, b) the amplitude was 1.25 times greater than the mean amplitude of all putative SOs, and c) the trough potential was 1.25 times lower than the mean trough potential of all putative SOs. Density (events/minute), amplitude (µV), slope (µV/s), and duration (s) were computed for each individual and channel and then averaged across frontal, central, and parietal channels.

2.7 SO-spindle coordination

For each channel and individual, we first determined whether a spindle fell into the two positive-to-negative zero crossings of a SO and calculated the percentage of spindles co-occurring with a SO. In a second step, in order to calculate measures of SO-spindle coupling, the signal was filtered in the SO and spindle frequency ranges (using the same filter ranges as described above) using the MATLAB-based toolbox fieldtrip (79). The Hilbert transform was applied to obtain the instantaneous phase of the SO-filtered signal and the instantaneous amplitude of the spindle-filtered signal. For each spindle that coincided with a SO, the SO phase at the maximum spindle amplitude was extracted. Only channels with at least 20 co-occurring events were considered for the analysis (48) in order to calculate reliable coupling measures. Using the CircStat toolbox in MATLAB (80), we calculated for each channel the mean preferred phase of coupling and coupling consistency (vector length). The mean preferred phase of coupling and vector lengths were averaged across frontal, central, and parietal channels within an individual.

2.8 Statistical Analyses

Biographical data and sleep variables were compared between the groups using independent t-tests; Raven Matrices score was compared using Wilcoxon rank sum test with continuity correction, due to violation of normality distribution; and Cohen's d as a measure of effect size (Table 2). Differences in aperiodic activity, spindle and SO characteristics, ratio of spindles co-occurring with a SO and coupling consistency were analyzed using linear-mixed effects models (packages *lme4* and lmerTest) and Type III Analysis of Variance Table with Satterthwaite's method to test the significance of fixed effects (81,82) in R version 4.4.2 (83). Each model included participants as random effects and group (ASD, NT), sleep stage (N2, N3) and topography (frontal, central, parietal) as fixed effects. Additional covariates - age and percentage of retained epochs - were included as fixed effects to control for potential confounding influences. The Holm test was used for post-hoc comparisons using the *emmeans* package (84). Further statistical analyses of SO-spindle coupling were performed in MATLAB using the CircStat toolbox in order to determine the (non)uniformity of coupling and analyze group (ASD, NT) differences in the mean preferred phase of coupling. The level of significance was set at $p < 0.05$.

To examine associations between periodic and aperiodic EEG components, we computed separate Spearman's rank-order correlations (ρ) between periodic and aperiodic parameters (slope and offset). Spearman's method was chosen due to potential deviations from normality in the variables. Correlations were computed across participants and sleep stages. Similarly, we performed correlation analysis between sleep quality measures (PSQI, SSS, and sleep efficiency) and periodic and aperiodic components of the sleep EEG to assess relationships between subjective and objective aspects of sleep. Furthermore, to examine the potential association between autism symptom severity and electrophysiological markers, we computed Spearman's rank-order correlations between ADOS total scores and the periodic and aperiodic components.

3. Results

Seven participants were excluded from the analyses due to noisy sleep recordings. Of the remaining participants, 11 were in the ASD group (23.83±7.5 years, 1 female) and 13 in the NT group (23.92±2.43 years, 2 females). A post-hoc sensitivity analysis conducted using G*Power [version 3.1.9.7] (85) indicated that with our sample size, the study had >70% power to detect large effect sizes (Cohen's d ~1) for between-group comparisons at $\alpha = 0.05$ (two-tailed), critical t = 2.068. Our observed main effects were overall in line with this threshold; however, the study was underpowered to reliably detect small or medium effects.

3.1 Demographics and sleep macrostructure

There were no age differences between the two groups (overall sample: n=31, t=0.234, df=20.2, *p*=0.817; only analyzed participants: n=25, t=-0.039, df=13.12, *p*=0.969), nor between Raven Matrices score (See Table 1). Table 2 summarizes the characteristics of the microarchitecture of sleep in both the ASD group and the NT control group. Interestingly, ASD participants spent less time in N2 and more time in N3 - both in terms of minutes and proportion of TST- than the NT controls (full statistics are reported in Table 2).

Table 1. Psychometric measures

	ASD	NT	W	p	ES
Raven Matrices	122.42±9.78	120.583±9.615	76.5	0.810	0.054
ADOS total score	9.85±3.57	-	-	-	-

Table 1 shows means and standard deviations of Raven Matrices and ADOS total score. Notes. Data are presented as mean±standard deviations. W: Wilcoxon rank sum test with continuity correction; p: p-value; ES: effect size.

Table 2. Sleep questionnaires and polysomnographic parameters of sleep in both the ASD group and the NT control group.

	ASD	NT	*T*	*p*	ES
Sleep questionnaires					
Pittsburgh Sleep Quality Index	4.6±2.1	4.7±3.0	-0.10	.920	-0.04
Stanford Sleepiness Scale	3.4±1.4[↑]	2.2±1.3[§]	0.59	.563	0.27
Polysomnographic parameters					
Time in Bed (min)	452.0±71.3	462.7±47.6	-0.44	.664	-0.18
Total Sleep Time (min)	384.4±50.9	409±60.5	-1.07	.297	-0.44
Sleep Latency (min)	11.1±6.5	17.5±26.3	-0.79	.437	-0.32
WASO (min)	57.0±53.6	36.4±35.0	1.130	.272	0.46
Sleep Efficiency (%)	85.9±9.4	88.2±8.4	-0.63	.534	0.26
N1 (min)	22.3±10.9	24.3±12.2	-0.42	.680	-0.17
N2 (min)	**195.6±48.3**	**244.0±44.0**	**-2.56**	**.018**	**-1.05**
N3 (min)	**80.8±21.3**	**62.8±20.0**	**2.12**	**.045**	**0.87**
REM (min)	85.8±35.6	78.1±20.6	0.66	.516	0.27
N1 (%)	5.69±2.44	6.01±3.25	-0.27	.788	-0.11
N2 (%)	**51.1±11.3**	**59.4±4.46**	**-2.44**	**.023**	**-1.00**
N3 (%)	**21.3±5.9**	**15.5±4.78**	**2.65**	**.015**	**1.08**
REM (%)	21.9±7.3	19.1±3.74	1.24	.227	0.51
REM latency	136.2±86.8	130.7±51.1	0.19	.848	0.08
Total Awakening Frequency	2.27±1.49	3.19±0.90	-0.44	.661	-0.18
Brief Awakening Frequency	2.22±1.27	2.64±0.89	-0.95	.352	-0.39
Long Awakening Frequency	0.59±0.42	0.39±0.28	1.40	.174	0.58
Awakening Duration (min)	3.59±5.2	1.94±2.68	1.00	.328	0.41
Frequency of arousals	4.16±1.36	3.99±2.03	0.23	.817	0.10
State Transitions	14.79±4.99	15.66±4.04	-0.47	.640	-0.19

Notes. Data are presented as mean±standard deviations. REM: Rapid Eye Movement; WASO:

Wake After Sleep Onset; Long awakenings are > 2 min. ASD: autism spectrum disorder; NT: neurotypicals; ES: effect size; ↑: averaged on n=8; §: averaged on n=11. Parameters with significant (p < 0.05) differences are reported in bold case.

3.1 Aperiodic Activity

In the aperiodic signal of the PSD slope, both groups showed a steeper slope during N3 than N2 (all *p*holm < .001). Interestingly, in ASD we observed a steeper slope during N2 (t = 3.665 *p*holm = .0015), but not during N3 (t = 1.535, *p*holm = .133), with respect to NT (sleep stage*group interaction: *F*(1,119.98) = 12.21, *p* < .001; Figure 3B). Furthermore, the slope decreased from frontal to parietal sites in both groups (main effect channel: *F*(2,119.98) = 71.50, *p* < .001, Figure 3C). The aperiodic offset was higher in N3 than in N2, with this difference being greatest for more posterior sites in both groups (channel*stage interaction: *F*(2,119.98) = 4.57, *p* = .012). A trend for a greater sleep stage difference in NT than ASD was observed (group*stage interaction: *F*(1,119.98) = 2.97, *p* = .087). A greater offset was observed in ASD with respect to NT (main effect of group: *F*(1,26.48) = 4.23, *p* = .0498), with a trend of higher offset during N2 in ASD with respect to NT (t = 2.210, *p*holm = .07, see also Figure 3D).

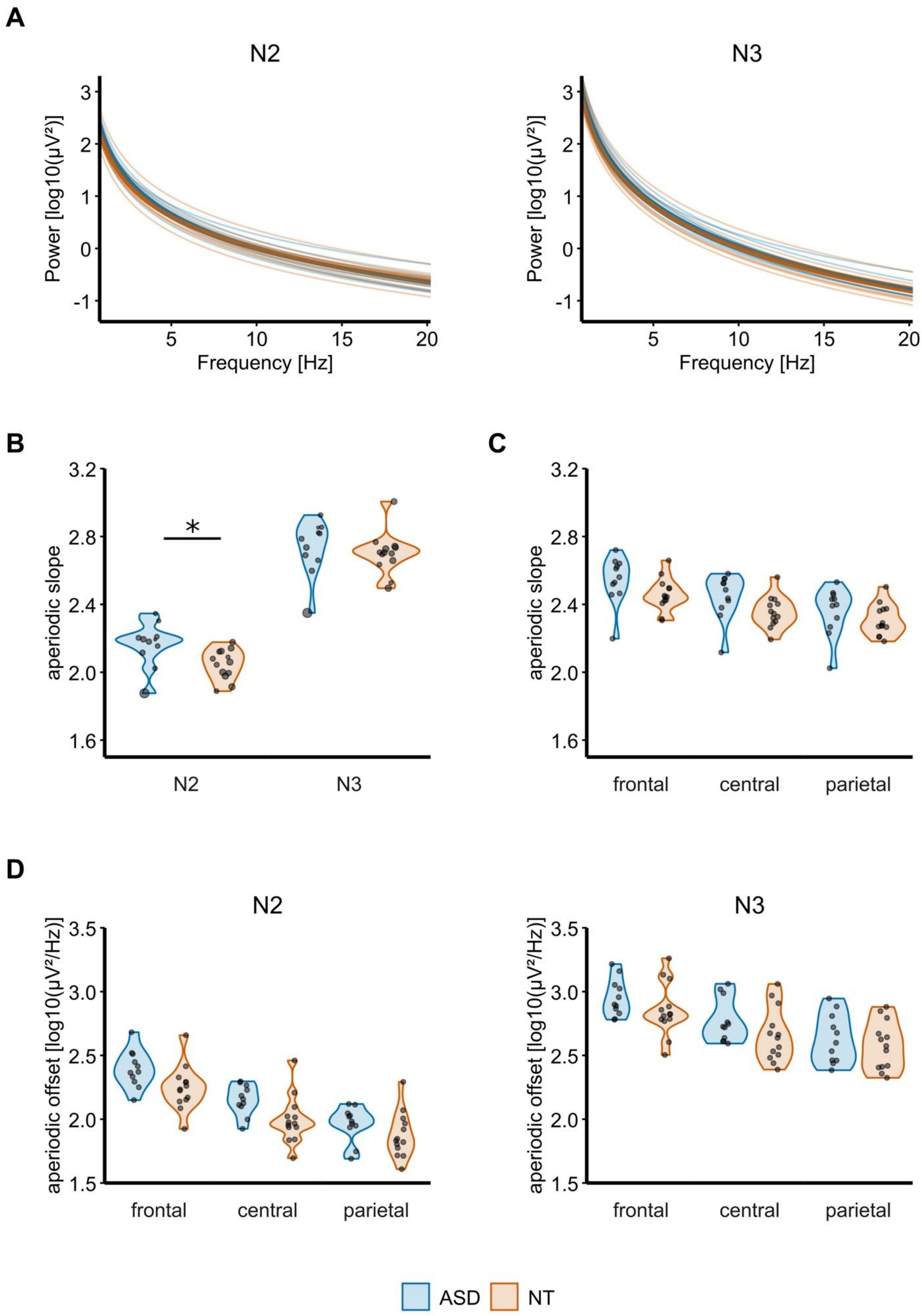

Figure 3. A. Individual values and means (bold lines) of the aperiodic power distribution across

frequencies for N2 and N3. **B.** Aperiodic slope as a function of sleep stage and group, dot size is proportional to the participants' age. **C.** Aperiodic slope as a function of channel and group. **D.** Aperiodic offset as a function of channel, separately during N2 and N3, in ASD and NT groups. Violin plots' width indicates the density of the data at each value (wider sections = higher density). Individual data points are overlaid. * $p < .05$ for pairwise comparisons.

3.2 Spindle Characteristics

NT showed greater channel differences in *spindle density* with respect to ASD (channel*group interaction: $F(2,119.98) = 4.016$, $p = .02$). The groups did not differ in their densities at any specific location (all *p*holm > .364 for pairwise comparisons; see also Figure 4A). *Spindle amplitude and frequency* did not show any group-specific differences (all $p > .083$). A trend of a greater difference between N2 and N3 *spindle duration* in NT as compared to ASD was observed (stage *group interaction: $F(1,120) = 3.34$, $p = .07$), but no group differences in either stage N2 or N3 emerged (all *p*holm > .202 for pairwise comparisons).

3.3 Slow Oscillation Characteristics

A trend of greater *SO amplitude* differences between channels in ASD with respect to NT was observed (channel*group interaction: $F(2,119.49) = 2.921$, $p = .058$). A direct channel-wise comparison of groups showed a higher amplitude in ASD than NT in frontal (*p*holm = .018) and central (*p*holm = .046) but not parietal channels (*p*holm > .09; see also Figure 4B). No interaction effects with group as factor, and main effects of group, in relation to *SO duration and density* (all $p > .261$) were found. A steeper SO slope was observed in ASD with respect to NT ($F(1,26.17) = 6.65$, $p = .016$, see Figure 4C).

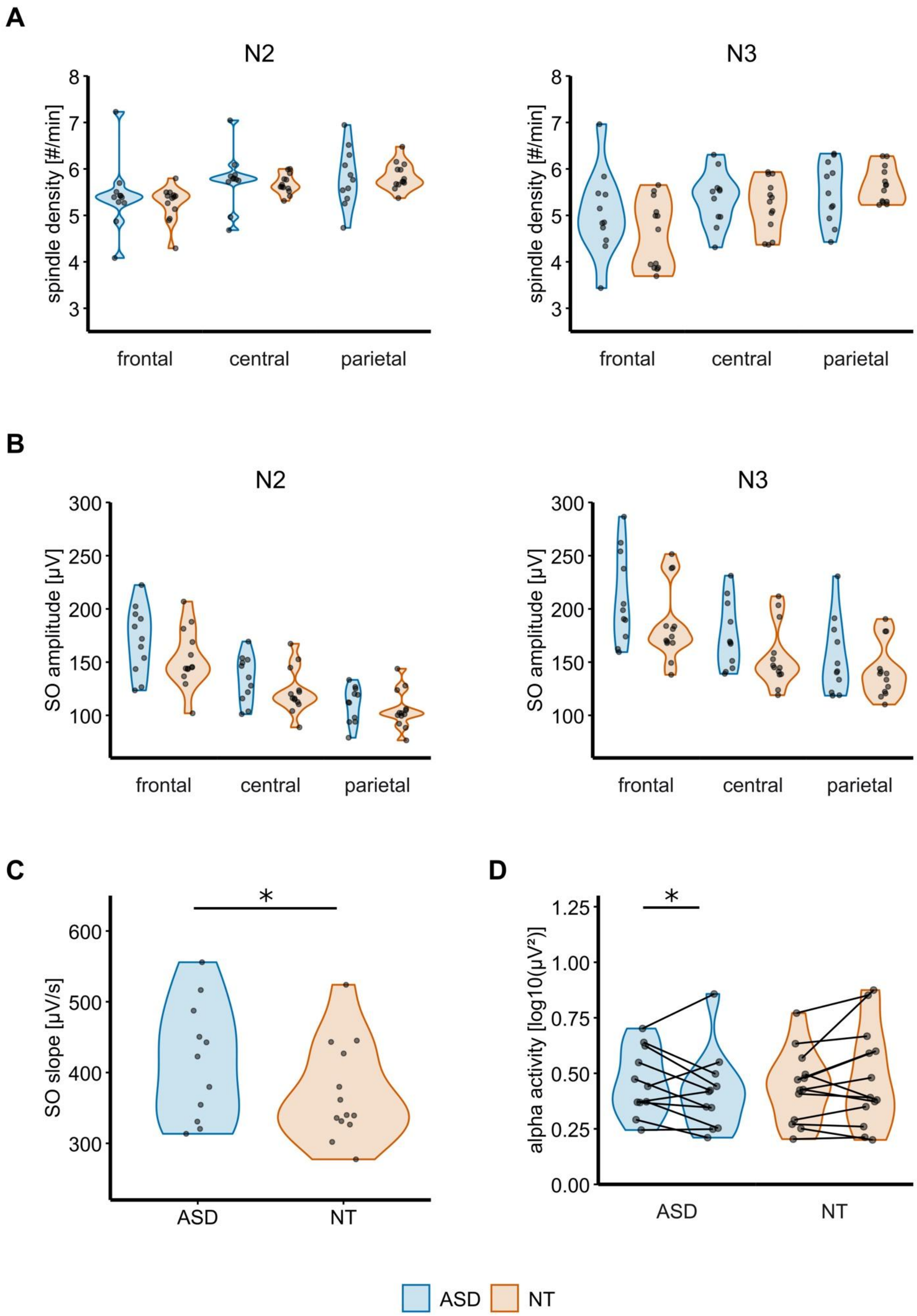

Figure 4. A. Violin plots of the spindle density as a function of channel and group, separately for

N2 (left) and N3 (right) sleep. **B.** Violin plots of the SO amplitude as a function of channel and group, separately for N2 (left) and N3 (right) sleep. **C.** SO slope distribution in ASD and NT groups. **D.** Alpha activity in ASD and NT separately for N2 (each left) and N3 (each right). Violin plots' width indicates the density of the data at each value (wider sections = higher density). Individual data points are overlaid. * *p* < .05 for pairwise comparisons.

3.4 SO-spindle coordination

Regarding the percentage of spindles co-occurring with SO, we observed a small decrease of the percentage of SO-spindle co-occurrences in N2 in ASD with respect to NT, and a small increase in N3 (group*stage interaction: *F*(1,120) = 4.34, *p* = .039); no main group differences at either sleep stage emerged (all *p*holm > .1; Figure 5A).

For further analysis of SO-spindle coupling, we considered channels with at least 20 co-occurring events. We first checked whether each participant showed a non-uniform distribution of spindle amplitude maxima across the SO cycle using the Rayleigh test. During N2, four participants (1 ASD, 3 NT) and during N3, two participants (1 ASD, 1 NT) showed a uniform distribution. Using the V-test, we then checked whether the mean preferred phases of coupling within a group were directed towards the SO upstate (0°), which was the case for each sleep stage and site (all *p* < .001). Using the Watson-Williams test, we found that the groups did not differ in their mean preferred phases of coupling at any site during any sleep stage (all *p* > .372; see also Figure 5C).

Overall, spindles were more consistently coupled towards the same SO phase during N3 (*M* = 0.69, *SEM* = 0.012) than N2 (*M* = 0.59, *SEM* = 0.014; *F*(1,136.84) = 31.97, *p*< .001). Regarding coupling consistency, NT showed channel differences (smallest consistency frontally), whereas no channel differences were observed in ASD (channels*group interaction: *F*(2,113.36) = 3.33, *p* = .039; Figure 5B); no effect of group emerged (all *p*holm > .999) at any site (see also Figure 5C).

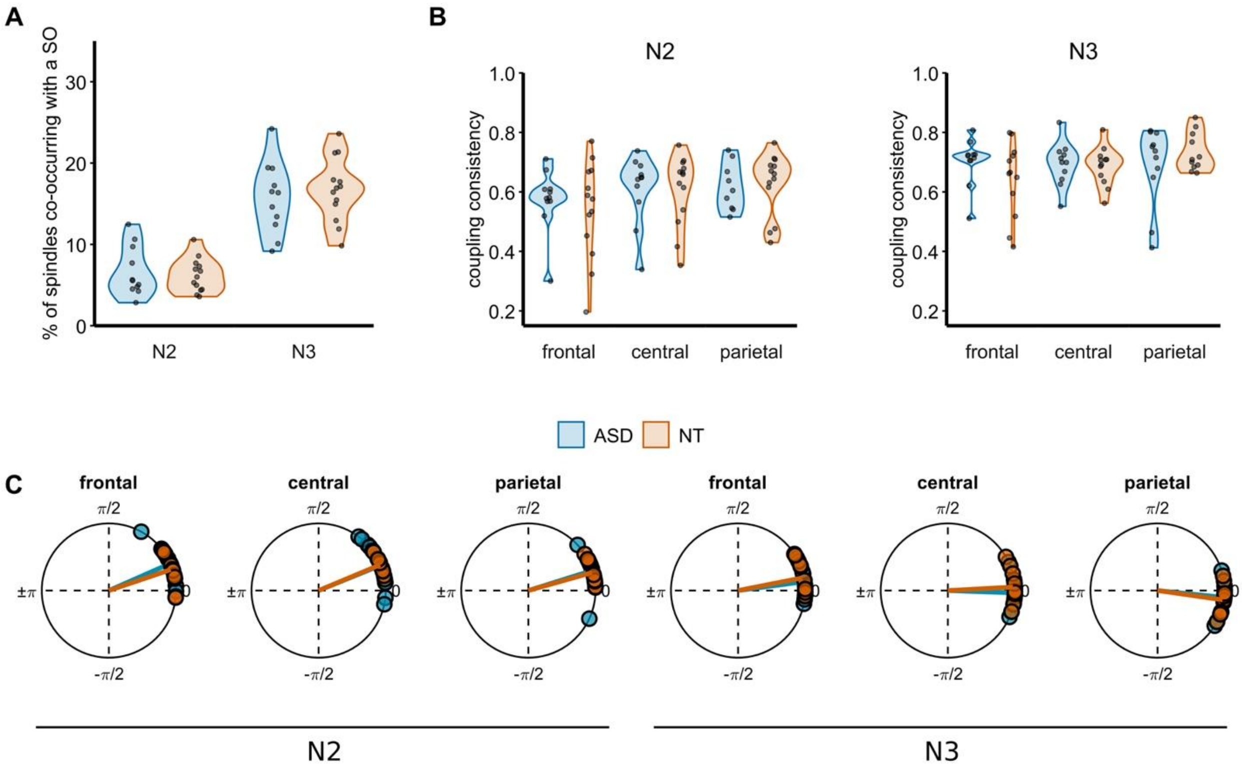

Figure 5. A. Percentage of spindles co-occurring with a SO as a function of group and sleep stage. **B.** Consistency of SO-spindle coupling as a function of group and channel, separately for N2 and N3. **C.** Mean preferred phases of coupling separately for N2 and N3 sleep and channels. Violin plots show the distribution of the spindle co-occurring with a SO as a function of channel, separately during N2 and N3, in ASD and NT groups. Violin plots' width indicates the density of the data at each value (wider sections = higher density). Individual data points are overlaid. * *p* < .05 for pairwise comparisons.

3.5 Alpha activity

A group x stage interaction (F(1,119.91) = 10.37, *p* = .002) revealed greater alpha activity during N2 with respect to N3 in ASD (*p* = .019) but not in NT (*p* = .999). In addition, alpha activity was greater at frontal channels (*p* < .023), similar centrally (*p* = .694), and smaller parietally during N3 with respect to N2 (*p* < .001, channel*stage interaction: F(2,119.91) = 21.41, p < .001).

3.6 Correlations between periodic and aperiodic components

Aperiodic offset

The aperiodic offset was positively correlated with SO density in NT in the central (ρ = 0.74, $p < .001$) and parietal channels during N2 (ρ = 0.79, $p < .001$) but not in ASD (central ρ = 0.54, $p = .093$; parietal ρ = 0.37, $p = .261$), while a positive correlation was observed in ASD in the central (ρ = 0.74, $p < .001$) and frontal channels (ρ = 0.76, $p = .009$) during N3 but not in NT (central ρ = 0.53, $p = .064$; frontal ρ = 0.49, $p = .092$). A positive correlation between the aperiodic offset and spindle mean amplitude was observed in the central (ρ = 0.8, $p = .002$) and parietal (ρ = 0.7, $p = .009$) channels during N3 in NT but not in ASD (central ρ = 0.09, $p = .797$; parietal ρ = 0.31, $p = .356$).

Aperiodic slope

The aperiodic slope positively correlated with SO density in the central (ρ = 0.8, $p = .005$) and frontal channels (ρ = 0.78, $p = .007$) during N3 in ASD but not in NT (central ρ = 0.51, $p = .081$; frontal ρ = 0.46, $p = .115$). The aperiodic slope positively correlated with SO mean amplitude in the frontal (ρ = 0.77, $p = .008$) and parietal channels (ρ = 0.61, $p = .05$) during N2 in ASD but not in NT (frontal ρ = 0.46, $p = .115$; parietal ρ = 0.53, $p = .067$), as well as in the frontal (ρ = 0.85, $p = .001$), central (ρ = 0.89, $p < .001$) and parietal (ρ = 0.83, $p = .003$) channels during N3 in ASD but not in NT (frontal ρ = 0.31, $p = .297$; central ρ = 0.41, $p = .163$; parietal ρ = 0.49, $p = .092$). The aperiodic slope positively correlated with SO slope the frontal channels (ρ = 0.83, $p = .003$) during N2 in ASD but not in NT (ρ = 0.37, $p = .217$), as well as in the frontal (ρ = 0.85, $p = .002$) and parietal (ρ = 0.75, $p = .011$) channels during N3 in ASD but not in NT (frontal ρ = 0.21, $p = .493$; parietal ρ = 0.09, $p = .751$). The aperiodic slope positively correlated with spindles density in the parietal channels during N3 (ρ = 0.57, $p < .05$) in NT but not in ASD (ρ = -0.26, $p = .435$).

3.7 Correlations between sleep quality measures (PSQI, SSS, and sleep efficiency) and periodic and aperiodic components

No significant correlations were observed between either PSQI or SSS with SO slope, spindle density and aperiodic slope and offset in both ASD and NT (all $p > .0.5$). Sleep efficiency positively correlated with SO density during N3 in the frontal ($\rho = 0.74$, $p = .01$) and central ($\rho = 0.69$, $p < .05$) channels in ASD but not in NT (frontal $\rho = 0.31$, $p = .306$; central $\rho = 0.11$, $p = .723$).

3.8 Correlations between behavioral and electrophysiological measures in ASD

Spearman's correlation revealed that ADOS total score positively correlated with alpha activity during N2 in the frontal ($\rho = 0.79$, $p = .010$) and central ($\rho = 0.64$, $p = .006$) channels, and during N3 in the frontal channels ($\rho = 0.9$, $p = .001$). No significant correlations were found between ADOS scores and the aperiodic components (all $p > .10$).

Discussion

On the basis of growing evidence indicating an E/I imbalance in ASD and the role of homeostatic regulation of neuronal excitability in mediating different sleep stages (21,22,28–30,57), we hypothesized that neuronal dysregulation, encompassing both excitatory activity and interneuronal inhibitory control, would be reflected in alterations of sleep architecture in ASD, affecting both periodic and aperiodic components and their interrelationships.

Our main findings revealed subtle but significant differences in individuals with ASD compared to NT controls including: i) altered sleep macrostructure, with increased N3 and reduced N2 sleep, ii) modified neuronal population dynamics as evidenced by a steeper aperiodic slope and increased offset and slope during NREM, iii) steeper SO slope, and a flattened anterior-posterior topography in spindle density and SO-spindle coupling during N3, and iv) elevated alpha power during N2, which positively correlated with ADOS total scores.

On one hand, the observed sleep EEG pattern in ASD, seemingly contrary to expected hyperarousal effects, suggests a deepening rather than a flattening of sleep. On the other hand, specific variations in periodic and aperiodic EEG features, along with their correlations, may reflect the impact of an

E/I imbalance, partially confirming predicted disturbances in the interplay between background cortical excitability and structured rhythmic activity during sleep. The increased inhibition and deepening of sleep may reflect adaptive compensatory mechanisms of cortical hyperexcitation, but alternatively may also indicate maladaptive overcompensation, where inhibitory circuits respond excessively to hyperexcitable cortical states, potentially reducing thalamo-cortical flexibility.

Sleep macrostructure analysis showed that ASD participants spent less time in N2 (in both absolute minutes and as a percentage of total sleep time), but more time in N3 compared to NT controls. These findings align with early actigraphy sleep studies showing a trend of decreased N2 and increased N3 in ASD participants with respect to healthy controls (49,86) and with more recent reports of increased N3 and reduced REM in children with ASD (40). In this latter study, a higher slow wave sleep ratio, alongside a lower REM sleep ratio, was associated with more severe core ASD symptoms, and was interpreted as indicative of neuronal immaturity. Additional studies in similar age cohorts have also reported longer slow wave sleep in ASD than NT (87). Interestingly, increased N3 sleep has also been observed in ADHD (attention deficit and hyperactivity disorder) (88), a neurodevelopmental condition that shares traits, symptoms and genetic architecture with ASD (89).

Conversely, Limoges and colleagues (46) reported increased N1 duration and decreased NREM and slow-wave sleep in ASD adults. A subsequent study by the same group also found increased N1 duration, decreased NREM, no differences in N2, and reduced SWS and sleep efficiency in ASD (12). Lower SWS ratios were likewise reported in a younger ASD cohort (90) . These discrepancies may be ascribable to methodological differences: in our study and those by Tani et al. (49) and Kwai et al. (40), PSG recordings were conducted at home, whereas Limoges et al.(12,46) and Lehoux et al. (90) recorded sleep in a laboratory. In-laboratory recordings may contribute to lighter sleep and reduced deep sleep in sensitive individuals such as those with ASD, as evidenced by decreased N3 relative to NT.

In addition to macrostructural changes, EEG-based microstructural differences between ASD and

NT participants also emerged. In particular, analysis of aperiodic activity revealed a steeper (more negative) spectral slope during N2 in ASD. This suggests enhanced, slower network dynamics, greater power in low frequencies and reduced power in high frequencies, reflecting low-frequency synchronization (lower cortical activation), and possibly heightened inhibition indicative of increased sleep pressure (58,91). A steeper 1/f slope may also indicate greater temporal coordination of asynchronous activity, potentially involving longer timescale correlations in population firing and more balanced network dynamics allowing compensatory inhibition. At the same time, ASD participants exhibited a greater aperiodic offset during NREM, suggesting elevated background activity potentially linked to cortical hyperexcitability.

Aperiodic EEG components are considered proxy markers of the E/I balance (62,92,93). In early computational models, reduced inhibition was associated with a flattened slope in power spectral density (57). However, recent studies using pharmacological manipulations to alter the E/I balance have shown conflicting results: both increased excitation and increased inhibition were associated with a steepened slope (65–67). A more nuanced interpretation arises from recent biophysical modelling, suggesting that changes in E/I balance also reflect synaptic kinetics and other physiological mechanisms (94). On the other hand, magnetic resonance spectroscopy studies in humans have shown that decreases in the glutamate-GABA asymmetry mediate decreases in the slope steepness (62). Thus, the observed increase in both slope steepness and offset in ASD during NREM may suggest E/I imbalance with a shift toward increased inhibition and altered neuronal population dynamics. Similar patterns of enhanced negative spectral slope during N2 have also been observed in NT children and adolescents (58), and age-related changes typically involve spectral slope flattening from childhood to adulthood. This suggests that the ASD sleep profile may also reflect delayed neurophysiological maturation.

Notably, elevated alpha power during N2 was observed in ASD, which, in addition, positively correlated with ADOS total scores, suggesting that individuals with more severe ASD symptoms exhibited greater alpha activity. This may reflect incomplete cortical deactivation and heightened arousal during NREM, pointing to potential cortical hyperarousal or sleep instability, possibly stemming from incomplete disengagement from wakefulness or impaired thalamic gating. Alternatively, persistent alpha activity in N2 may also reflect developmentally atypical retention of wake-like features into early NREM**,** consistent with theories of delayed neural state differentiation in ASD (46,95,96). Such abnormal alpha activity may also trigger compensatory inhibitory mechanisms (adaptive or maladaptive), reflected in the observed increase in aperiodic slope and slow wave activity.

Indeed, slow wave activity analyses indicated increased SO slope and a trend toward larger amplitude differences across channels in ASD, possibly indicating increased sleep pressure. No significant differences were found in SO duration and density, although density correlated with sleep efficiency in ASD, possibly suggesting that increased inhibitory tone underlies both SO generation and sleep stability. Previous findings on periodic sleep features in ASD adults are heterogenous: some report no significant differences in SW components (49), while others find reduced SWS (12,46). In children, a trend of higher SO power (6), and greater delta relative power during NREM were reported (40), although others noted decreased delta power in a large ASD sample (97). These inconsistencies may reflect ASD heterogeneity, comorbidities, medication effects, and methodological differences, particularly between home-based and in-lab PSG. Notably, higher SO was observed in home recordings (6,40), whereas lower SO was associated with in-lab sleep studies (12,46,97).

Correlational analyses between periodic and aperiodic components in ASD revealed a recurrent positive correlation between aperiodic slope and SO amplitude, density, and slope during N2 and N3, these correlations were not significant in NT. An apparently divergent correlation pattern was also found between aperiodic offset and SO density during N2 and N3 in ASD, possibly suggesting that altered background activity in ASD may modulate slow-wave generation through different mechanisms.

Spindle analyses revealed group differences in spindles density. NT participants showed a typical pattern of a lower frontal and higher parietal spindle density, whereas ASD participants exhibited no such topographical variation. No differences were found in spindle amplitude, frequency, or duration. However, ASD patients exhibited stronger SO-spindle coupling in N2, and more consistent but reduced coupling in N3, relative to NT. Moreover, the fronto-parietal gradient of SO-spindle coupling, prominent in NT during N3, was flattened in ASD, mirroring the pattern seen in spindle density distribution. These findings, consistent with previous heterogenous results in ASD (12,46,49,98–103) may indicate disrupted thalamo-cortical regulation during deep sleep (104,105). This could reflect sleep-stage dependent mechanisms regulating E/I balance (33,106–108). Background E/I balance might indeed steepen to compensate for altered spindle-generating mechanisms. Critically, spindle activity in ASD did not correlate with aperiodic slope or offset during N3, further suggesting atypical thalamo-cortical coupling and a decoupling of background cortical from spindle generation.

Dysfunction of the TRN - a shell of GABAergic neurons that provides the major inhibition to thalamocortical neurons (109,110) - has been implicated in sensory processing anomalies, attentional deficits, and altered sleep in both schizophrenia and ASD (111–115). Abnormal TRN function has also been linked to disrupted spindle activity in both disorders (102,103,114,116,117).

Collectively, our findings align with the “leaky thalamus” hypothesis, which posits that reduced thalamic filtering capacity leads to cortical sensory overload, resulting in increased perceptual sensitivity and attentional impairment in ASD (118,119). However, it is equally plausible that such thalamocortical dysregulation reflects impaired developmental tuning of inhibitory feedback circuits during critical periods, with consequences that extend into adulthood.

Dysregulation of thalamocortical interactions, demonstrated by converging evidence from genetics, animal models, neuroimaging, and electrophysiology, has been proposed as a core mechanism in ASD (99,120–128). Strong evidence supports thalamocortical hyperconnectivity in both children and adults with ASD (128,129).

Given reduced thalamic gating, increased slow-wave activity during N2 may thus reflect a compensatory need for greater synaptic downscaling, possibly linked to elevated sensory sensitivity and attentional load during wakefulness. This form of sleep-dependent plasticity, predominantly regulated by inhibitory interneurons (31–33), may result in increased cortical inhibition.

In summary, our findings suggest a deepening of sleep in adults with ASD, characterized by increased N3, heightened inhibition (as evidenced by a steeper aperiodic slope and increased offset during N2), and atypical thalamo-cortical regulation, as indicated by increased alpha power, flattened spindle topographies, and altered SO–spindle coupling. Overall, while some sleep EEG features in ASD resemble those of NT individuals, the observed alterations support the E/I imbalance hypothesis in ASD. Our findings may possibly reflect compensatory mechanisms that preserve network stability (130,131); however, alternative interpretations should be equally considered. Specifically, the observed enhancement in slow-wave activity and increased inhibition during N2 may indicate maladaptive overcompensation by inhibitory circuits. Such overcompensation could interfere with typical thalamo-cortical dynamics, leading to network rigidity and impairments in synaptic plasticity, rather than an adaptive homeostatic response. Additionally, neuronal hyperexcitation in ASD may also trigger excessive inhibition and increased GABAergic tone in several key brain regions (132,133). In fact, sleep-related activity is extensively modulated by subcortical structures, such as the locus coeruleus and hypothalamus. The former, via norepinephrine release, influences sleep–wake transitions and memory-related processes (134,135), and recent work suggests altered locus coeruleus function in ASD children (136). The hypothalamus, central to sleep and social homeostasis (137,138) may also be implicated in ASD symptoms due to its role in state switching deb(139–141), homeostatic sleep regulation (142) , and socioemotional behavior (143–146).

In short, the maladaptive overcompensation interpretation suggests that the observed sleep-related neural dynamics may reflect dysregulated developmental processes, rather than functionally adaptive compensatory mechanisms. This perspective is consistent with broader neurodevelopmental models of ASD (147–150), which posit that disrupted maturation of inhibitory systems contributes to both cognitive and behavioral phenotypes.

In conclusion, framed within the E/I imbalance hypothesis, our findings reveal a deepening of sleep and multiple EEG alterations in adults with ASD that may be consistent with adaptive homeostatic regulation, yet they could equally reflect maladaptive compensatory processes. Clarifying this distinction will require further studies designed to disentangle true compensatory adaptations from enduring developmental immaturity or circuit-level dysfunction.

Limitations

A main limitation of the study is the reduced statistical power due to the limited sample size, which was a direct consequence of strict inclusion criteria: specifically, the inclusion of only participants not undergoing pharmacological treatment, which is highly prevalent among adults with ASD. Furthermore, several recording segments and participants had to be excluded due to corrupted or incomplete PSG data, primarily resulting from participant discomfort. Another potential limitation is the use of a single-night recording session without an adaptation night, as implemented in some previous studies. This may have affected participants’ comfort and familiarity with the sleep setting, potentially influencing sleep quality. However, the use of a single-night PSG also prevented any carry-over effects of discomfort or distress from a prior night, which could have altered sleep architecture in subsequent recordings. Finally, we acknowledge that the limited number of EEG electrodes, used to reduce participant discomfort during sleep, may have impacted the spatial resolution of the EEG results. Nonetheless, this approach is consistent with most previous PSG studies in similar populations.

Conclusions

Our study provides novel electrophysiological evidence of nuanced, sleep-related alterations in ASD, modulated by sleep stage and cortical region, which subtly diverge from patterns observed in neurotypicals. Given the mechanistic relevance of sleep to neurodevelopment and circuit homeostasis, our findings offer valuable insights into the sleep-related dysregulation of neurophysiological processes in ASD, conceivably involving alterations in E/I balance, and contribute to the relatively limited literature exploring the multifaceted architecture of sleep in this population. However, confirmation of these findings in larger cohorts is essential, given the limited sample size of the present study. Despite this limitation, an important contribution of this study lies in revealing an association between oscillatory dynamics, including sleep spindles, and 1/f activity in autistic adults. We proposed integration of sleep research in ASD within the E/I imbalance framework - linking molecular and cellular dysfunction to observable electrophysiological signatures - that offers a unifying explanatory model for the sleep difficulties frequently reported in ASD. Further research is needed to determine whether the sleep-stage-dependent alterations observed in ASD reflect adaptive or maladaptive mechanisms, and to establish more direct associations between atypical sleep EEG patterns and E/I imbalance. In particular, it remains unclear whether the observed dysregulation of sleep-related neuronal dynamics mirrors the E/I imbalance present during wakefulness, or instead reflects compensatory processes aimed at counteracting such dysregulation. Future studies may also elucidate whether the associations between altered EEG patterns and E/I imbalance during sleep are directly shaped by the atypical cognitive, affective, and social behaviors expressed during wakefulness, or whether they reflect broader physiological consequences of the genotypic and phenotypic traits characteristic of ASD. Ultimately, if confirmed in larger validation cohorts, the observed alterations in periodic and aperiodic EEG features during sleep could contribute to the identification of objective biomarkers for ASD subtypes and inform the development of targeted, circuit-level interventions.

List of abbreviations (in alphabetical order): Attention deficit and hyperactivity disorder (ADHD); Autism Diagnostic Observation Schedule (ADOS); Autism-spectrum Quotient questionnaire (AQ, Italian adaptation); Autism spectrum disorder (ASD); Central EEG channels (C3, C4); Cholinergic neurons (ach); Dorsal Raphe Nucleus (DRN); Effect size (ES);

Electroencephalogram (EEG); Electrooculogram (EOG); Electromyogram (EMG); Excitation/inhibition (E/I); First, second and third stages of non-REM sleep (N1, N3, N2); Frontal channels (F3, F4); Lateral Hypothalamus (LH); Latero Dorsal Tegmental Nucleus (LDN); The Locus Ceruleus (LC); Neurotypical participants (NT); Non-rapid eye movements (NREM sleep); P-value (p); Parietal channels (P3, P4); Pedunculo Pontine Tegmental Nucleus (PPT); Pittsburgh Sleep Quality Index (PSQI); Pittsburgh Sleep Quality Index (PSQI, Italian adaptation); Polysomnography (PSG); Power spectral density (PSD); Rapid eye movements (REM sleep); Root mean square (RMS); Sleep efficiency (SE); Sleep onset latency (SOL); Slow oscillations (SO); Slow wave (SW); Slow wave sleep (SWS); Slow-wave activity (SWA); Standard error (SE); Stanford Sleepiness Scale (SSS); Suprachiasmatic Nucleus (SCN); Symptom Checklist-90 questionnaire (SCL-90); Thalamic Reticular Nucleus (TRN); Thalamic reticular nucleus (TRN); Total sleep time (TST); Ventral Tegmental Area (VTA); Ventrolateral preoptic nucleus (VLPO); Wake After Sleep Onset (WASO); Wilcoxon rank sum test with continuity correction (W).

Declarations

- **Ethics approval and consent to participate:** The study was approved by the University of Tubingen ethical committee (ID: 720/2014BO1). All participants received a comprehensive explanation of the study procedures and provided written consent before participation. Participants were paid for reimbursed for their participation in the study.
- **Consent for publication:** Not applicable, this manuscript does not contain any individual person’s data in any form.
- **Data availability:** Derived data supporting the findings of this study are available from the corresponding authors upon reasonable request.
- **Competing interests:** The authors declare that they have no competing interests

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- **Authors' contributions: conception:** J.B., A.C., S.D.F, and P.V. conceptualized and discussed the original idea of the project; J.B., K.Z., and E.M.K. designed the work; N.M., L.C., and G.G. collected the data; N.C., M.C., E.M.K., and N.M. analysed the data; A.C., N.M., N.C., and J.B. interpreted the data; P.V., S.D.F., A.C., K.Z., and J.B. supervised the work; N.M., A.C., E.M.K., N.C., and M.C. drafted the manuscript, N.M., A.C., and J.B. revised the article; all the authors read and approved the final manuscript.

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- **Authors' social media handles:** Margherita Calderan BlueSky account is: @marcald.bsky.social

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