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EEG resting-state gamma power as a potential biomarker of excitation / inhibition imbalance in autism: Evidence from the Autism Biomarkers Consortium for Clinical Trials

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ABSTRACT

Identification of neural biomarkers is one of the central challenges in autism research as they could significantly advance our understanding of the brain mechanisms of symptom trajectories, serve as objective markers in clinical trials (e.g., for subgrouping children, or use for prognostic relationship), and lead to targeted treatment development. The Autism Biomarkers Consortium for Clinical Trials (ABC—CT) is a naturalistic longitudinal study assessing a set of candidate electroencephalographic (EEG) biomarkers, their change over time, utility for group discrimination, and relation to clinical phenotype. Here, we focused on one of the ABC—CT biomarkers – resting-state *gamma-band neural activity* – as a measure of excitation-inhibition balance, which is considered a key neurophysiological mechanism in autism. A total of 1597 EEGs were analyzed resulting in 399 autistic children and typically developing (TD) peers with resting-state EEG and behavioral measures at four timepoints: baseline, +6 weeks, +6 months, and +4 years. The results revealed a significantly increased gamma power in autistic children, suggesting an excitation-inhibition imbalance. This elevation was longitudinally associated with lower non-verbal IQ and memory for faces. Finally, males had higher gamma power in comparison to females and gamma power decreased with age in both groups. The study demonstrates that resting-state gamma power is related to cognitive ability across ages and timepoints of our study in autistic youth.

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1. Introduction

Autism Spectrum Disorder (ASD) is one of the most common neurodevelopmental conditions in pediatric population, affecting ~ 1 out of 31 children in the United States (Shaw et al., 2025). ASD is diagnosed based on behavioral symptoms in the domains of social communication and the presence of restricted and repetitive behaviors (American Psychiatric Association, 2013). Identification of neural biomarkers that have consistent relation to behavior is one of the central challenges in autism research as this may significantly advance our understanding of brain mechanisms of behavioral trajectories, serve as objective markers in clinical trials (e.g., for subgrouping children, or use for prognostic relationship), and lead to targeted intervention development (Hudac and Webb, 2024; Loth et al., 2016; McPartland, 2017; Webb et al., 2023). However, due to the high heterogeneity of the ASD population, relatively small sample sizes used in historical studies, variations in methodology, and a lack of longitudinal data, identifying replicable biomarkers has been challenging.

Electroencephalography (EEG) is particularly suitable for biomarker research in pediatric populations because it is non-invasive, provides high temporal resolution, and can be administered repeatedly across development (Hudac and Webb, 2024; Webb et al., 2020). Among candidate EEG measures, *gamma-band oscillatory activity* has been consistently reported as a non-invasive marker of excitation-inhibition balance (Buzsáki and Wang, 2012; Rhodes et al., 2025), which has been proposed as an important neurophysiological mechanism of autism (Gatto and Broadie, 2010; Levin and Nelson, 2015; Rubenstein and Merzenich, 2003; Sohal and Rubenstein, 2019; Yizhar et al., 2011). A number of studies in animal models of autism as well as studies in people with ASD have shown that the altered communication between glutamatergic (excitatory) and gamma-aminobutyric acidergic (GABAergic; inhibitory) neurotransmission causes a reduction in signal-to-noise ratio in key neural circuits (see Sohal and Rubenstein, 2019). This, in turn, results in elevated "noise" in the cortex, which impacts synaptic plasticity during development and leads to less effective information processing (Sohal and Rubenstein, 2019). Remarkably, studies with optogenetic manipulations in rats have demonstrated that shifting balance towards more excitation leads to social dysfunction and increased power in high-frequency (30–80 Hz) gamma oscillations, revealing a causal relationship between elevated excitation, increased gamma power, and alterations in social functioning (Yizhar et al., 2011).

Cellular studies in model systems, in combination with optogenetics, have revealed that gamma oscillations are mostly generated by the GABAergic interneurons expressing calcium-binding protein parvalbumin, i.e., PV+ inhibitory basket cells (Bartos et al., 2007; Cardin et al., 2009; Carlén et al., 2012; Sivarao et al., 2016; Sohal et al., 2009), and postmortem studies on autistic brain identified a reduction of the GABAergic PV+ interneurons (e.g., Hashemi et al., 2017). Gamma-band abnormalities in EEG, hypothetically due to excitation-inhibition imbalance, have been reported in a number of previous studies as a potential biomarker associated with both core and co-occurring conditions in ASD (Arutiunian et al., 2024; Cao et al., 2018; Gandal et al., 2010; Rojas and Wilson, 2014). A recent comprehensive meta-analysis of resting-state EEG in 1246 autistic and 1455 typically developing controls demonstrated significantly higher gamma power in the autistic group, confirming previous research in both animal models of autism and autistic individuals (Neo et al., 2023).

To summarize, studies on both animal models of autism and autistic individuals align to suggest that gamma oscillations may index excitatory-inhibitory neurocircuit systems dysfunction in ASD. While previous work from our group on the baseline data suggests that EEG resting-state gamma is unlikely to be a diagnostic biomarker (Webb et al., 2023), the longitudinal structure of the ABC—CT allows us to examine group differences in gamma power and its relation to behavior by age and timepoint.

The present study enhances our understanding of gamma power in autistic youth through the use of a longitudinal protocol and including 399 participants from 6 to 11.5 years (at baseline) followed through four timepoints with outcome age 8.7 to 16.8 years. *First,* we aim to calculate gamma power abstracted from the resting-state EEG and compare groups of children with and without ASD, as well as examine the development of gamma power across age, and in relation to sex, and timepoint (or repeated testing). Based on the previous studies, we hypothesize that gamma power will be elevated in the ASD group, pointing to a higher level of excitation-inhibition imbalance in the neocortex. *Second,* we focus on the relationships between gamma power and clinical phenotype in children with ASD, using all available data, to test if there is a robust relation between gamma power and clinical phenotype that is present across age and timepoint. We predict that higher gamma power will be related to more cognitive impairment (Arutiunian et al., 2024; Webb et al., 2023).

2. Experimental procedures

2.1. Participants

A total of 399 children participated in the study: 280 children with ASD (65 [23.2%] female, $M_{age} = 8.6$ years, $SD = 1.6$, range 6.0 – 11.5) and 119 demographically comparable TD children (35 [29.4%] female $M_{age} = 8.5$ years, $SD = 1.6$, range 6.0 – 11.5). The data were collected at five sites.

In accordance with the Declaration of Helsinki, the Yale University institutional review board and commercial IRB (Advarra) provided centralized oversight. Informed consent was obtained from guardians and assent from child participants after they had been given an explanation of the study procedures and an opportunity to ask questions.

2.2. Longitudinal design

The ABC—CT is a naturalistic longitudinal study of ASD and TD children that includes measurements at four timepoints: T1 = baseline, T2 = T1+6 weeks, T3 = T1+6 months, T4 = T1+~4 years. This design allows examination of short-term test-retest reliability (T1 to T2), developmental stability/change over a period consistent with a potential clinical trial (T1 to T3), and long-term developmental changes in both neural and behavioral measures (T1 to T4). We note that T1 to T3 were acquired from 2016 to 2019 and were a priori chosen timepoint intervals. T4 was added at a later stage of the project and start of the timepoint was delayed due to COVID-19, with data acquired between 2021 and 2023. Because of these factors, the time interval for return was significantly broader than earlier timepoints with a longer window between timepoints related to older age. Thus, we include both age and timepoint in our models to account for these factors. See more details about the whole ABC—CT protocol (McPartland et al., 2020; Webb et al., 2020, 2023).

2.3. Clinical and behavioral measures

The presence of ASD in the clinical group was confirmed with the Autism Diagnostic Observation Schedule – 2 (ADOS-2; Lord et al., 2012), Autism Diagnostic Interview-Revised (ADIS-R; Rutter et al., 2003), and expert clinical judgment based on the Diagnostic and Statistical Manual – Fifth Edition (DSM-5; American Psychiatric Association, 2013). TD children were screened for the presence of ASD (via ADOS-2) or a sibling with ASD (via parent report), and for the presence of emotional and behavioral disorders (with the Child and Adolescent Symptom Inventory – Fifth edition (CASI-5; Gadow and Sprafkin, 2013). Exclusion criteria for both groups of children were known genetic and neurological conditions (including history of epilepsy or current use of anti-epileptic medication), clinically significant visual and/or auditory impairments, sensory-motor difficulties that would limit participation in standardized assessments, prematurity or pre/perinatal birth injury or brain damage,

or severe environmental circumstances that would impact neural development.

Based on previous literature on the relationships between gamma power and cognitive abilities in ASD (Arutiunian et al., 2024; Webb et al., 2023), verbal and nonverbal IQ and the NEPSY face memory were our primary clinical variables. IQ was assessed with the Differential Ability Scales – 2 (DAS-2; Elliott, 2007). The NEPSY – 2 Memory for Faces standard score (Korkman et al., 2007) was calculated as an observational measure of social cognition. Additionally, we included exploratory analyses of adaptive skills using the Vineland Adaptive Behavior Scale (VABS) – 3 (Sparrow et al., 2016) Socialization, Communication, and Daily Living Skills Standard Scores (SS). Autistic behaviors were characterized via the Social Responsiveness Scale (SRS) – 2 (Constantino, 2012) T-scores for the Social Communication and Integration (SCI) and the Restricted Interests and Repetitive Behaviors (RRB) subscales; and the Pervasive Developmental Disorder Behavior Inventory (PDDBI; Cohen et al., 2003) T-Scores for the Social Approach Behaviors (SOCAPP) domain and the Repetitive, Ritualistic, and Pragmatic Problem (REPRIT) composite (calculated from the ritualisms/resistance to change, sensory/perceptual approach behaviors, and social pragmatic problems domains) (Table 1).

2.4. EEG data acquisition

Resting-state EEG was collected with a whole-head Magstim EGI 128-channel HydroCel Geodesic Sensor Net system from the Net Amps 300 series (three sites) or 400 series (two sites), with the following acquisition parameters: a 1000 Hz sampling rate, referenced to Cz, a 0.1–200 Hz band-pass filter, and impedances < 50kΩ.

The resting-state paradigm included three blocks of two 30-second videos, for a total of 180 s. Video stimuli were abstract non-social moving images subtending 8 × 6 degrees.

2.5. EEG data processing and excitation-inhibition balance measure abstraction

To calculate power spectral density (PSD) at the gamma frequency range (35–54.99 Hz) we used the Batch EEG Automated Processing Platform (Levin et al., 2018) uses the following steps: (1) formatting of the MFF file for Matlab; (2) band-pass filtering 1–100 Hz; (3) down sampling from 1000 Hz to 250 Hz (to improve performance of independent components analysis); (4) implementation of the Harvard Automated Preprocessing Pipeline for EEG (HAPPE) module for artifact

Table 1
Behavioral characterization of the ASD and TD groups (only for participants with the valid EEG data), M(SD). Significance is highlighted in bold.

Characteristics	T1		Diagnostics group effect	T2		Diagnostics group effect	T3		Diagnostics group effect	T4		Diagnostics group effect
	ASD (*N* = 242)	TD (*N* = 110)		ASD (*N* = 245)	TD (*N* = 105)		ASD (*N* = 228)	TD (*N* = 107)		ASD (*N* = 106)	TD (*N* = 66)	
Age, months	104.0 (19.6)	101.4 (18.9)	t(218.0) = 1.20, p = 0.23	104.7 (19.9)	104.5 (19.7)	t(198.0) = 0.11, p = 0.91	109.2 (19.6)	108.4 (19.8)	t(205.7) = 0.35, p = 0.72	152.7 (22.1)	151.4 (22.1)	t(138.1) = 0.38, p = 0.70
Sex, *N* of female participants	57	34	$\chi2(1) = 2.1$, p = 0.14	55	32	$\chi2(1) = 0.34$, p = 0.56	46	32	$\chi2(1) = 3.86$, p = **0.05**	21	17	$\chi2(1) = 0.83$, p = 0.36
Cognition												
DAS Nonverbal IQ	98.6 (16.8)	113.0 (13.7)	t(254.5) = –8.5, p < **0.001**	NA	NA	NA	100.0 (16.5)	115.9 (13.7)	t(245.9) = –9.3, p < **0.001**	101.5 (15.0)	113.1 (11.9)	t(160.7) = –5.6, p < **0.001**
DAS Verbal IQ	96.7 (20.7)	116.2 (10.6)	t(302.2) = –11.6, p < **0.001**	NA	NA	NA	97.3 (21.3)	118.3 (12.2)	t(319.9) = –11.3, p < **0.001**	99.5 (20.2)	113.9 (11.2)	t(168.0) = –6.0, p < **0.001**
NEPSY Memory for Faces SS	8.0 (3.6)	10.6 (3.5)	t(222.1) = –6.3, p < **0.001**	9.3 (4.2)	12.1 (3.1)	t(265.8) = –7.0, < **0.001**	9.8 (4.2)	13.0 (3.2)	t(261.6) = –7.5, p < **0.001**	8.9 (3.7)	11.7 (2.3)	t(170.0) = –6.1, p < **0.001**
Adaptive Skills												
VAB Communication SS	77.2 (15.4)	103.3 (9.2)	t(323.7) = –19.6, p < **0.001**	77.8 (15.3)	103.8 (13.2)	t(309.5) = –19.5, p < **0.001**	78.3 (14.7)	104.5 (9.2)	t(304.2) = –19.8, p < **0.001**	75.6 (14.8)	100.7 (9.1)	t(166.7) = –13.6, p < **0.001**
VAB Socialization SS	70.7 (16.0)	104.6 (9.1)	t(332.6) = –25.1, p < **0.001**	69.7 (16.5)	104.8 (9.5)	t(320.0) = –24.9, p < **0.001**	72.3 (17.0)	104.3 (9.6)	t(319.9) = –21.8, p < **0.001**	72.1 (15.0)	101.9 (9.8)	t(166.9) = –15.5, p < **0.001**
VAB Daily living skills SS	78.4 (11.9)	99.4 (9.9)	t(250.0) = –17.2, p < **0.001**	78.5 (11.9)	102.3 (9.8)	t(238.5) = –19.3, p < **0.001**	79.6 (12.2)	102.2 (10.8)	t(230.6) = –17.1, p < **0.001**	79.6 (15.1)	96.3 (9.0)	t(166.3) = –9.0, p < **0.001**
Autistic Behaviors												
SRS Social Communication and Integration T-score	72.2 (10.9)	42.7 (5.1)	t(347.7) = 34.3, p < **0.001**	71.4 (10.8)	42.5 (5.4)	t(339.3) = 33.1, p < **0.001**	70.1 (11.6)	42.7 (5.3)	t(332.0) = 29.6, p < **0.001**	71.3 (11.7)	43.5 (6.1)	t(163.9) = 20.2, p < **0.001**
SRS Restricted Interests and Repetitive Behaviors T-score	73.6 (11.9)	43.7 (3.8)	t(321.1) = 34.9, p < **0.001**	71.7 (12.6)	43.7 (3.5)	t(321.1) = 34.9, p < **0.001**	71.3 (12.8)	43.9 (3.6)	t(293.4) = 29.7, p < **0.001**	73.8 (12.9)	44.7 (4.6)	t(141.3) = 20.9, p < **0.001**
PDDBI Social Approach Behaviors T-score	55.0 (8.9)	69.9 (3.1)	t(324.5) = –22.9, p < **0.001**	55.0 (8.9)	70.0 (2.9)	t(323.7) = –23.5, p < **0.001**	55.2 (9.1)	70.0 (2.6)	t(292.5) = –22.3, p < **0.001**	54.0 (9.7)	67.2 (3.2)	t(127.9) = –12.4, p < **0.001**
PDDBI Repetitive, Ritualistic, and Pragmatic Problem T-score	49.2 (11.8)	28.1 (2.7)	t(283.6) = 26.1, p < **0.001**	48.0 (12.3)	27.7 (2.5)	t(283.3) = 24.5, p < **0.001**	47.1 (12.3)	27.5 (2.3)	t(256.7) = 23.0, p < **0.001**	44.0 (12.1)	27.5 (2.3)	t(111.8) = 13.3, p < **0.001**

detection and rejection (Gabard-Durnam et al., 2018), including a reduction of the array to 18 channels (electrode # 9, 11, 22, 24, 33, 36, 45, 52, 58, 62, 70, 83, 92, 96, 104, 108, 122, 124; based on the 10–20 system and excluding Cz, see Fig. 1A) to avoid overlearning during ICA, removal of 60 Hz line noise, rejection of bad channels, wavelet enhanced thresholding, ICA with automated component rejection, bad channel interpolation, and re-referencing to average; (5) segmentation into 1 s segments; and (6) rejection of files based on HAPPE (Gabard-Durnam et al., 2018) quality metrics (set at 3 SD): >80% good channels remaining, <30%mean retained artifact probability, <35% median retained artifact probability, <84%percent of independent components rejected as artifact, and >32% percent of EEG signal variance retained after artifact removal. On the remaining valid participant files: (7) discarding un-attended segments; and (8) calculating the PSD using a Hanning window on clean segments without high-amplitude artifact. Valid signal was defined as ≥ 40 s of usable data. PSDs were calculated across the entire scalp (averaged over 18 electrodes) and normalized with log10 transformation for further statistical analysis.

This frequency range (35–54.99 Hz) was retained to maintain consistency with the pre-specified gamma-band definition used in previous ABC—CT analyses (Webb et al., 2023). The upper boundary of 54.99 Hz also minimizes potential effects of 60-Hz line noise and its removal during EEG preprocessing (Arutiunian et al., 2024).

In total, 1597 EEG files were analyzed across the four timepoints. Based on the quality metrics described above, 387 resting-state EEG sessions were excluded from the analysis (N_{ASD} = 300, N_{TD} = 87). Children with ASD had fewer artifact-free epochs in comparison to TD children: T1, M_{ASD} = 143.7 (SD = 25.1) vs. M_{TD} = 161.6 (SD = 9.4), t(341.2) = –9.7, p < 0.01; T2, M_{ASD} = 144.4 (SD = 26.9) vs. M_{TD} = 160.4 (SD = 10.7), t(346.5) = –8.0, p < 0.01; T3, M_{ASD} = 146.4 (SD = 25.2) vs. M_{TD} = 162.4 (SD = 8.7), t(313.3) = –8.6, p < 0.01; T4, M_{ASD} = 156.3 (SD = 17.0) vs. M_{TD} = 161.4 (SD = 11.6), t(168.6) = –2.3, p = 0.02.

2.6. Statistical modeling

Statistical analyses were performed in R (R Core Team, 2019). Specifically, we used *psych* package (Revelle, 2025) to calculate short-term (6 weeks) stability of log gamma power, the *lme4* package (Bates et al.,

Table 2
Group and sex differences in gamma power and its developmental changes. Significance is labeled with *p < 0.05, **p < 0.01, ***p < 0.001 and highlighted in bold.

Predictors	Gamma power			
	Estimate	*Standard error*	*t*	*p*
(Intercept)	−1.77	0.02	−77.39	**<0.001*****
Group, ASD	0.05	0.02	2.58	**0.010***
Sex, male	0.07	0.02	3.41	**0.001****
T2	−0.00	0.01	−0.25	0.801
T3	−0.02	0.01	−1.57	0.117
T4	0.10	0.03	3.68	**<0.001*****
Age	−0.00	0.00	−6.99	**<0.001*****
Random Effects				
σ^2	0.03			
$\tau_{00\ ID}$	0.02			
ICC	0.45			
$N_{\ ID}$	391			
Observations	1209			
Marginal R^2 / Conditional R^2	0.101 / 0.507			

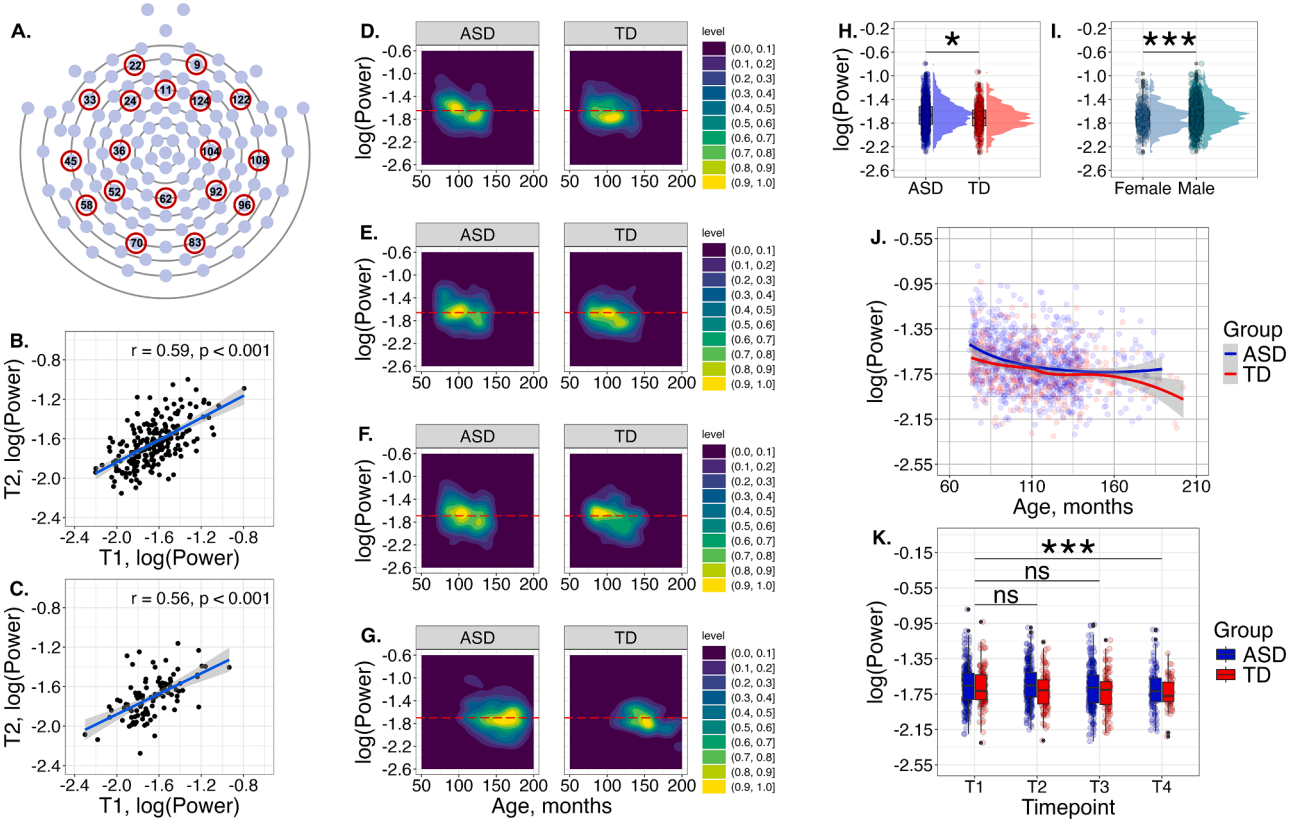

Fig. 1. Group differences (ASD = Autism Spectrum Disorder, TD = typically developing) and developmental changes in gamma power: A) EEG cap with highlighted electrodes used for the analysis; Pearson's correlation analysis between T1 and T2 in gamma power for the B) ASD and C) TD groups of children; Heatmaps representing distribution of gamma power in the ASD and TD groups based on age at D) T1, E) T2, F) T3 and G) T4; H) Between-group comparisons in gamma power; I) Sex differences in gamma power; J) Age-related changes in gamma power; K) Between-timepoint comparisons in gamma power. The significance is labeled with *p < 0.05, **p < 0.01, ***p < 0.001, ns = non-significant.

2015) for the main linear mixed-effects models using, the *sjPlot* package (Lüdecke, 2020) to create the tables for model outcomes (Table 2,3), and *gglot2* (Wickham, 2016) for the figures. Our analytic strategy included two types of modeling: (1) To examine developmental changes and group differences in resting-state EEG, we utilized a linear mixed-effects model with log gamma power as the outcome, diagnostic group (TD and ASD, with TD as the reference) and sex (female and male with female as the reference) as a between subjects factors, timepoint (T1, T2, T3, and T4, with T1 as the reference) as a within-subjects factor, and age as a continuous within subject predictor. Random intercepts were included to account for the differences between participants at baseline. (2) To model longitudinal associations between gamma power and clinical measures as well as developmental changes in behavioral skills in children with ASD, we fit parallel linear mixed-effects models with each of the clinical measures as the dependent variable and gamma power as an additional time-varying covariate. Of note, to capture possible effects of repeated experience with the assays and the COVID-19 pandemic, in addition to the index of chronological age, we included indicators for study measurement point (timepoint). A lack of significance of timepoint would imply that subjects of the same age had comparable gamma power at all measurement points, whereas significant effects would imply that there were sequencing patterns beyond age-based-development.

Data availability

The dataset(s) supporting the conclusions of this article is(are) available in the National Database for Autism Research repository, ID: #2288, https://ndar.nih.gov/

3. Results

3.1. Short-term (6 weeks) reliability of gamma power

For both the ASD and TD groups, we calculated interclass correlation (ICC) coefficients using two-way random effects models (absolute agreement) to evaluate short-term (T1 ~ T2, 6 weeks) reliability of gamma power. The values indicated *moderate* reliability in both groups: ASD, ICC = 0.59 [0.56, 0.62]; TD, ICC = 0.55 [0.50, 0.60] with a statistically significant correlation between T1 and T2: ASD, $r = 0.59$, $p < 0.001$, TD, $r = 0.56$, $p < 0.001$ (Figs. 1B,C).

3.2. Group and sex differences in gamma power and its developmental changes

Figs. 1D–G represent the distribution of gamma power in each group at each timepoint as a function of age (with the dashed red lines indicates the mean gamma power). The mixed effects model showed that children with ASD had significantly elevated gamma power when compared to TD children, estimated mean difference = 4.914e-02, SE = 1.903e-02, $t = 2.58$, $p = 0.01$ (Fig. 1H), pointing to an increased excitation-inhibition ratio in the ASD group (see Table 2 with the model outputs). The magnitude of this between-group difference did not vary according to concurrent CNS medication use in autistic participants (see Supplementary data). A main effect of sex was also identified with the evidence of higher power in males, estimated mean difference = 6.930e-02, SE = 2.032e-02, $t = 3.41$, $p < 0.001$ (Fig. 1I).

In accordance with a number of previous findings, we found a linear age-related decrease in EEG gamma power across the ASD and TD groups, age slope β = –2.990e-03, SE = 4.274e-04, $t = –6.99$, $p < 0.001$ (Fig. 1J). Although there is a between-group difference in gamma power, visual examination of the mean trajectory showed similar changes in both ASD and TD groups. We found no difference in age-adjusted gamma power between T1 and T2 (6 weeks; β = –3.106e-03, SE = 1.230e-02, $t = –0.25$, $p = 0.80$) or T1 and T3 (6 months; β = –1.984e-02, SE = 1.264e-02, $t = –1.57$, $p = 0.11$). However, at T4, subjects showed significantly higher gamma power than would be expected for their age based on the earlier timepoints (β = 9.596e-02, SE = 2.607e-02, $t = 3.68$, $p < 0.001$) (Fig. 1K).

We conducted a *posthoc* analysis, modeling gamma power in the ASD and TD group separately including the same predictors, i.e., sex, age, and timepoint. The results of the models confirmed the results of the main model with the exception of the timepoint effect: we identified that the significant elevation of gamma power from T1 to T4 was presented only in the ASD group (Table 3).

3.3. Longitudinal changes of clinical measures and their relation to gamma power in children with ASD

Three linear mixed-effects models were fit in the ASD sample to assess the relationships between cognitive measures and gamma power, as well as a function of age, sex, and study timepoint.

The results revealed statistically significant relationships between gamma power and nonverbal IQ and memory for faces: lower nonverbal IQ (β = –6.43, SE = 2.10, $t = –3.06$, $p < 0.01$) and lower memory for faces (β = –1.50, SE = 0.55, $t = –2.74$, $p < 0.01$) were associated with higher gamma power (Fig. 2, Table 4). Adaptive and autistic behavior metrics were not associated with gamma power (see a set of additional exploratory results in Supplementary data).

4. Discussion

The present longitudinal study focused on EEG gamma power (as a measure of excitation-inhibition balance) as a function of chronological age, sex, and timepoint, as well as its relation to clinical phenotype, in a large sample of children with and without ASD. The results of the study

Table 3
Developmental changes in gamma power in relation to sex and age in children with and without ASD. Significance is labeled with $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ and highlighted in bold.

Predictors	TD group				ASD group			
	Estimate	*Standard error*	*t*	*p*	*Estimate*	*Standard error*	*t*	*p*
(Intercept)	−1.76	0.03	−58.73	**<0.001*****	−1.73	0.03	−68.33	**<0.001*****
Sex, male	0.07	0.03	2.28	**0.023***	0.07	0.03	2.60	**0.009****
T2	−0.04	0.02	−1.70	0.091	0.01	0.02	0.74	0.460
T3	−0.03	0.02	−1.52	0.129	−0.01	0.02	−0.93	0.354
T4	0.07	0.04	1.58	0.115	0.11	0.03	3.31	**<0.001*****
Age	−0.00	0.00	−4.01	**<0.001*****	−0.00	0.00	−5.68	**<0.001*****
Random Effects								
σ^2	0.02				0.03			
$\tau_{00\ ID}$	0.02				0.02			
ICC	0.44				0.46			
$N_{\ ID}$	118				273			
Observations	388				821			
Marginal R^2 / Conditional R^2	0.110 / 0.500				0.085 / 0.503			

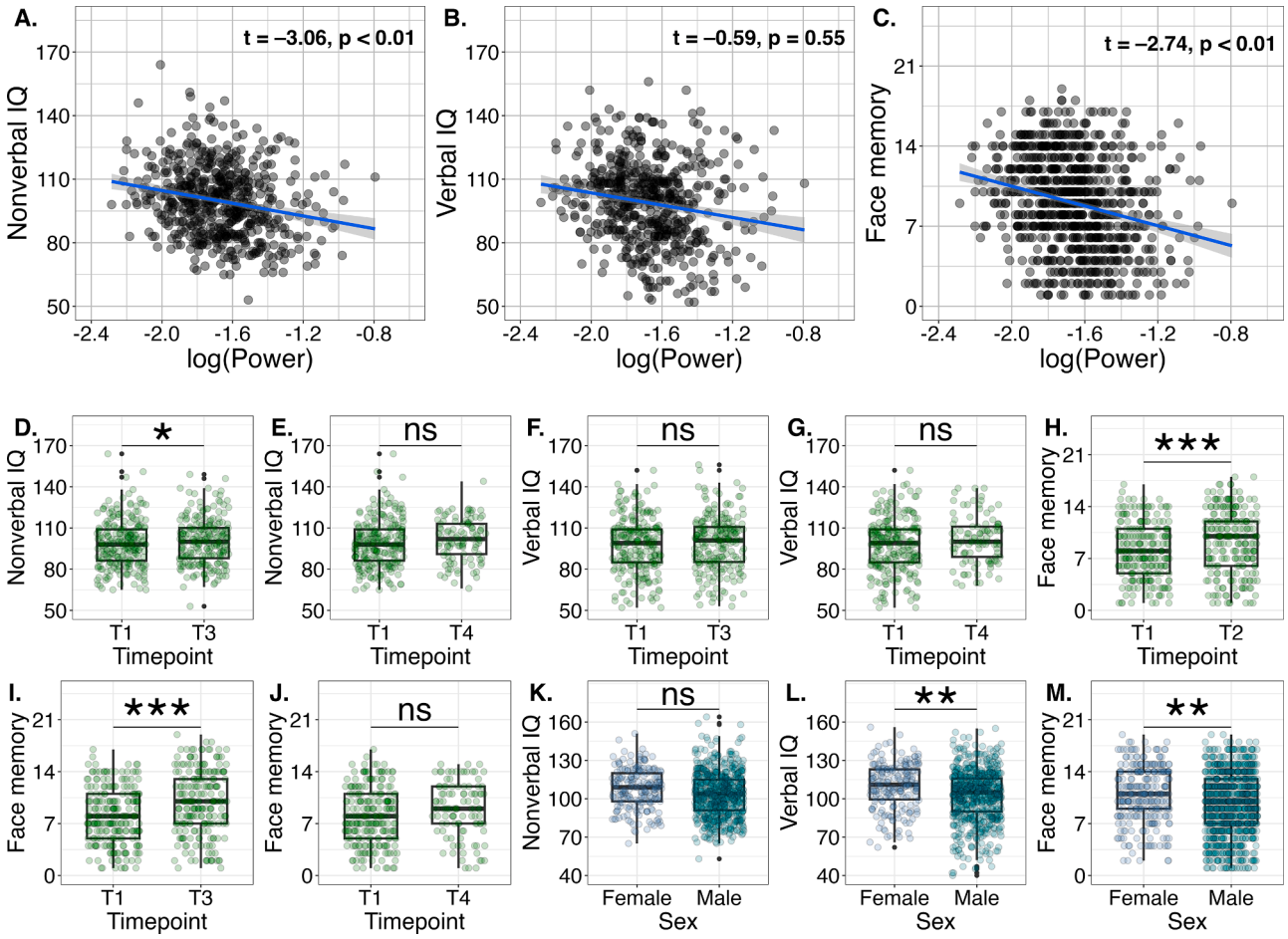

Fig. 2. Relationships between gamma power and cognitive measures at different timepoints and sex differences in children with Autism Spectrum Disorder: Gamma power as a predictor of A) nonverbal IQ, B) verbal IQ, C) face memory; Timepoint effects for D), E) nonverbal IQ, F),G) verbal IQ, H–J) face memory; Sex differences in K) nonverbal IQ, L) verbal IQ, M) face memory. The significance is labeled with $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

confirmed the findings of previous research and extended understanding of the development of neural excitation-inhibition balance in ASD and its relationship to the clinical phenotype.

Between-group comparisons revealed a significant difference in gamma power across the full age range/set of study measurement points, with elevated spectral power in the ASD group. This is consistent with a number of previous studies (Neo et al., 2023; Sohal and Rubenstein, 2019) that have shown increased spectral power in the gamma frequency range reflecting elevated excitation-inhibition neural balance (e.g., Sohal and Rubenstein, 2019). This atypical elevation of gamma power is hypothesized to result in increased neural 'noise' in the cortex, impacting synaptic plasticity during development and resulting in less effective neural processing, including influencing regulatory and homeostatic processes as well as perceptual and cognitive functioning (Contractor et al., 2021; Sohal and Rubenstein, 2019; Tang et al., 2021). Cellular studies have shown that gamma-band neural activity is primarily associated with the GABAergic activity, and the dysregulated interplay between excitation and inhibition is likely due to GABA dysfunction (Levin and Nelson, 2015). Critically, GABA-related drugs have been used recently in clinical trial studies of ASD (e.g., Veenstra-VanderWeele et al., 2017). Our results support continued investigation of gamma-band neural activity as a potential index of GABA functioning and a potential neural marker of target engagement in clinical trials. As well, baseline differences in gamma power may be useful in identifying a subgroup of autistic group based on their excitation-inhibition neural balance.

We showed that the elevation of gamma power in children with ASD had clinical relevance: higher spectral power was associated with lower nonverbal IQ and lower memory for faces longitudinally. This is consistent with a number of previous findings in autistic individuals, demonstrating that elevated gamma power is related to social function, language impairments, and intellectual disability (Arutiunian et al., 2024; Cao et al., 2018; Gandal et al., 2010; Rojas and Wilson, 2014). Our longitudinal design contributed to the previous findings by showing that this brain-behavior relationship in autistic children is consistent across development despite the age-related changes in gamma power and the repeated nature of testing.

We demonstrated an age-related decrease in resting-state gamma power in both ASD and TD children, consistent with the previous cross-sectional studies in the same age range (e.g., Tierney et al., 2013). This decrease may be associated with maturational changes in GABAergic neurotransmission and developmental changes in excitation-inhibition balance with the evidence of lower excitatory activity in older children (Cho et al., 2015). This development starts very early: in the neonate brain, GABA receptors switch from a depolarizing to hyperpolarizing action (Ben-Ari, 2002, 2014; Cherubini et al., 1991). GABAergic PV+ neurons (the main generators of gamma oscillations) also mature relatively late in development (Gao et al., 1999). In addition, it has been demonstrated that GABA regulates synapse elimination and axonal pruning in the developing brain (Gomez-Castro et al., 2021; Wu et al., 2012) and, perhaps, gamma-band neural activity is reflecting the maturation of the inhibitory system. Generally, there is a drop of synaptic density after 10 years of age and lower neural 'noise' in the cortex (e.g., Huttenlocher and Dabholkar, 1997; Ponton et al., 2000;

Table 4
Developmental changes of cognitive measures and their relation to gamma power and sex in children with ASD. Significance is labeled with *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ and highlighted in bold.

Clinical variable	Predictors			
	Gamma power	Age	Sex (Female vs. Male)	Timepoint (T1 vs. T2, T3, T4)
Nonverbal IQ	β = –6.43, t = –3.06, $p <$ **0.01****	β = 0.04, t = 0.89, $p =$ 0.37	β = –2.12, t = –0.92, $p =$ 032	NA
				β = 1.61, t = 2.31, $p =$ **0.02***
				β = –0.55, t = –0.23, $p =$ 0.81
Verbal IQ	β = –1.37, t = –0.59, $p =$ 0.55	β = –0.08, t = 1.45, $p =$ 0.13	β = –8.67, t = –2.97, $p <$ **0.01****	NA
				β = 1.53, t = 1.90, $p =$ 0.06
				β = –2.80, t = –0.98, $p =$ 0.32
Face memory	β = –1.50, t = –2.74, $p <$ **0.01****	β = 0.01, t = 1.93, $p =$ 0.06	β = –1.30, t = –2.63, $p <$ **0.01****	β = 1.36, t = 6.09, $p <$ **0.001*****
				β = 1.94, t = 8.34, $p <$ **0.001*****
				β = –0.14, t = –0.25, $p =$ 0.80

Note: Verbal and nonverbal IQ scores are not available for T2, thus, the comparisons have been conducted for T1 vs. T3, T4.

Poulsen et al., 2009), which could underly the age-related changes in gamma power.

We revealed a significant effect of sex, such that males had higher gamma power in comparison to females. Our results are consistent with a prior study of N > 300 autistic and neurotypical 8 to 18 year olds (with a sex-balanced sample) that showed elevated gamma power in males during a speech perception task (Arutiunian et al., 2024) and elevated broad-band (including gamma) neural activity in males in EEG resting-state (Neuhaus et al., 2021). It is not yet clear what neurobiological mechanisms are associated with this sex difference. However, hypothesizing the relation of gamma oscillations to the GABA system, it is important to mention that several studies have shown later maturation of the GABAergic inhibitory system in males (e.g., Nuñez and McCarthy, 2007; Silveri et al., 2013).

A noted limitation to our work is the reduction of sample size from T3 to T4. There were no significant differences in those who returned vs. did not return, confirming that our T4 sample was representative of the original cohort (Shic et al., unpublished; Webb, et al., unpublished). As noted, T4 was added in the renewal of the project, with COVID-19 impacting our timeline for recruitment and likely suppressing return rates. Several studies have shown that COVID-19 significantly impacted brain development with neural-regression in both typical and atypical pediatric populations (Chagas and Serfaty, 2024; Deoni et al., 2022; Tso et al., 2022); our finding that participants showed higher gamma power than would be expected for their age based on the earlier timepoints is consistent with a potential impact of COVID-19 on brain development. However, the combination of these factors (age at return, time window between T3 and T4, and reduced sample) limits our ability to eliminate other potential confounds.

In conclusion, we investigated changes in gamma power (as a measure of neural excitation-inhibition balance) in a naturalistic longitudinal study with children entering the study between 6 and 11 years and followed across 4 timepoints. Gamma power showed a significant differences between the ASD and TD groups (albeit with a small effect size) and demonstrated relation to sex and cognitive phenotype in a large sample of children with and without ASD. The results of the study revealed a significant elevation of gamma power in the ASD group, pointing to a higher level of excitability in the brain, and the association between this elevation and lower non-verbal IQ and memory for faces in autistic children. In general, our study showed a high potential of EEG resting-state gamma power as a biomarker that is related to phenotypic variability in autistic youth, with the potential for indexing excitatory/inhibitory processes in future pharmacological clinical trial studies.

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Author contributions

All authors contributed to the design of the study. AN, MS, HB, JB, RAB, KC, GD, JD, SF, SJ, NK, MSdV, JMCP were involved in data acquisition. VA, CS, GH, DS, and SJW were involved in data analytics. VA, CS, AL, SJW contributed to interpretation and draft revision. All authors read and approved the final manuscript.

Conflict of interest

Geraldine Dawson is on the scientific advisory boards of the Nonverbal Learning Disability Project, Bristol Myers Squibb, Ignite BioMedical, Tris Pharma, and YAMO Pharmaceuticals; is a consultant for Guidepoint Global, LLC; and receives book royalties from Guilford Press, Oxford University Press, and Springer Nature. Shafali Jeste is a consultant for Roche Pharmaceutical Company. James C. McPartland consults or has consulted with Customer Value Partners, Bridgebio, Determined Health, Apple, Neumarker, and BlackThorn Therapeutics, has received research funding from Janssen Research and Development, serves on the Scientific Advisory Boards of Pastorus and Modern Clinics, and receives royalties from Guilford Press, Lambert, Oxford, and Springer. Frederick Shic is a consultant for MindMed LLC., Roche Pharmaceutical Company, and Janssen Research. All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential competing interest.

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The main study (presented here) was conducted from 2014 to 2019; with a confirmation study ongoing (2021–2026). Consortium members also include the ABC—CT Data Coordinating Core: Lisa Nanamaker, Laura Simone; Project Management Team: Julia Holub, Taylor Hoffman, & Helen Seow; Data Analytic and Analysis EEG Core: Adham Atyabi, Carter Carlos, Sophie Cramer-Benjamin, Iris Emerman, Diogo Fortes, Simone Hasselmo, Kelsey Macdonald, Takumi McAllister, Michael Murias, Dylan Stahl; and EEG Site Staff: Melody Altschuler, Elizabeth Baker, Brenna Boyd, Brianna Cairney, Amanda Cremone, Cassandra Franke, Rachel Fung, Caitlin Hudac, Marie Johnson, Molly Joseph, Laura Macias, Samantha Major, Nicole Nadwodny, Laura Nelson, Sharon Ornelas, Margarita Orozco, Julie Trapani.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2026.113864.

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