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RESEARCH ARTICLE

The developmental trajectory of functional excitation-inhibition balance relates to language abilities in autistic and allistic children

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Abstract

Autism is a neurodevelopmental condition that has been related to an overall imbalance between the brain's excitatory (E) and inhibitory (I) systems. Such an EI imbalance can lead to structural and functional cortical deviances and thus alter information processing in the brain, ultimately giving rise to autism traits. However, the developmental trajectory of EI imbalances across childhood and adolescence has not been investigated yet. Therefore, its relationship to autism traits is not well understood. In the present study, we determined a functional measure of the EI balance (f-EIB) from resting-state electrophysiological recordings for a final sample of 92 autistic children from 6 to 17 years of age and 100 allistic (i.e., non-autistic) children matched by age, sex, and nonverbal-IQ. We related the developmental trajectory of f-EIB to behavioral assessments of autism traits as well as language ability. Our results revealed differential EI trajectories for autistic compared to allistic children. Importantly, the developmental trajectory of f-EIB values related to individual language ability. In particular, elevated excitability in late childhood and early adolescence was linked to decreased listening comprehension. Our findings provide evidence against a general EI imbalance in autistic children when correcting for non-verbal IQ. Instead, we show that the developmental trajectory of EI balance shares variance with autism trait development at a specific age range. This is consistent with the proposal that the late development of inhibitory brain activity is a key substrate of autism traits.

Lay Summary

An imbalance between the brain's excitatory (E) and inhibitory (I) systems has been proposed as an underlying neural mechanism in autism, potentially changing information processing. We show a different development of EI balance in autistic compared to allistic children and adolescents. Additionally, we find that the age trajectory of EI balance relates to language comprehension in both groups.

KEYWORDS
autism, autism symptoms, critical brain dynamics, excitation-inhibition ratio, language development, long-range temporal correlations, neural oscillations

INTRODUCTION

Autism is a neurodevelopmental condition characterized by restricted and repetitive patterns in behaviors and interests as well as persistent differences in social communication and language abilities (American Psychiatric Association, 2013). The precise nature and extent of the differences varies widely between autistic individuals (Barttfeld et al., 2013; Wang et al., 2013). This large heterogeneity within the autistic population has made it

notoriously difficult to understand the biological mechanisms underlying the condition. In recent years, the neuroscientific literature discusses a systems-level substrate of autism. Specifically, an imbalance between the brain's excitatory (E) and inhibitory (I) neurons and their connections has been suggested to be linked to autism (Rubenstein & Merzenich, 2003; Sohal & Rubenstein, 2019). Hence, the investigation of EI balance and its relation to autistic traits is of great importance for a unitary explanatory framework of this heterogenous condition.

Neurons can mainly be classified as excitatory and inhibitory neurons based on their effect on the activity of other neurons. Across neural networks, these two types of neurons are tightly coupled and cortical excitation is followed by proportional inhibition (Shu et al., 2003). This balance between excitatory and inhibitory systems ensures that the brain operates in a critical state (Avramiea et al., 2022; Shew et al., 2009) and is crucial for regulating the information flow through the brain (Poil et al., 2012). Evidence for an EI imbalance in autism comes from different measures of the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the brain. Postmortem tissue analyses have found anomalies in the biosynthesis and transmission of these neurotransmitters in autistic samples (Blatt & Fatemi, 2011; Fatemi et al., 2002, 2009, 2014; Oblak et al., 2009, 2010, 2011; Purcell et al., 2001; Shimmura et al., 2013; Yip et al., 2007). Magnetic resonance spectroscopy (MRS) provides the possibility to measure these neurotransmitter levels in vivo (for a review, see Rojas et al., 2015). MRS studies provided evidence for differences between autistic and allistic (i.e., non-autistic) individuals' resting levels of glutamate as well as its precursor glutamine (Bejjani et al., 2012; Bernardi et al., 2011; Brown et al., 2013; Corrigan et al., 2013; DeVito et al., 2007; Doyle-Thomas et al., 2014; Hassan et al., 2013; Horder et al., 2013; Page et al., 2006; Tebartz van Elst et al., 2014) and GABA (Gaetz et al., 2014; Rojas et al., 2014) in various brain regions, suggesting that EI differences are region-specific. However, findings regarding the specific location and even the direction of changes in neurotransmitter levels are mixed, making it currently difficult to draw specific conclusions on the differences between autistic and allistic individuals. In addition to MRS studies, genetic analyses have provided evidence for differential gene-expression within glutamatergic and GABAergic signaling pathway gene-sets between autistic and allistic individuals (Collins et al., 2006; Hollestein et al., 2023; Ramoz et al., 2004). A balanced interaction between glutamate and GABA is needed for the maturation of the brain's synapses and the refinement of neuronal circuitries during development (Dorrn et al., 2010; Luján et al., 2005; Sun et al., 2010). A deviation from this biochemical balance could consequently affect cognitive functions as well as social behavior (Cochran et al., 2015; DeLorey et al., 2008).

Recent advances in the mathematical quantification of nonlinear dynamics in neuroimaging time series now also allow for the assessment of EI balance from electroencephalography (EEG) recordings. In the current study, we quantified EI balance using a functional measure of the EI balance (f-EIB), which was recently introduced by Bruining et al. (2020). Although this functional measure indirectly estimates the EI balance from electrophysiological activity, it has been shown to relate to the structural EI balance, that is to the ratio of excitatory-to-excitatory and inhibitory-to-excitatory synapses in the brain. Bruining et al. (2020) further validated this method in vivo by showing that the f-EIB values are sensitive to pharmacological manipulation of GABA levels in healthy adults. The f-EIB value is computed based on the amplitude and temporal autocorrelation in the alpha frequency of resting-state electroencephalography (rs-EEG) recordings, which measure spontaneous neural activity reflecting task-unrelated cognitive functions. The short recording time and simple acquisition procedure (e.g., no stimulation, no behavioral task) of rs-EEG benefit practicality in clinical populations (Anderson & Perone, 2018) and the possibility to compute EI balance from rs-EEG thus allows to advance our understanding of the underlying neurobiological mechanisms of autism by including a wider range of children compared to other methods for assessing EI balance. To assess the relationship between EI balance and autism, Bruining et al. (2020) investigated f-EIB in a sample of 100 autistic and 29 allistic children between 7 and 16 years. As expected, allistic children displayed balanced f-EIB values, which is assumed to be optimal for information processing. The autistic group displayed a significantly larger variance in f-EIB values, which the authors interpreted as greater EI imbalance for autistic than allistic children. However, intelligence quotient (IQ) differences between the autistic and allistic group in the study by Bruining et al. (2020) could have influenced their results, as the two groups were not matched on IQ and previous research reported a relationship between IQ and EI balance where higher IQs associate with an EI balance closer to the optimum and thus having a smaller variance (Cochran et al., 2015; Robinson, 1989). Even though additional analyses by Bruining et al. (2020) did not find evidence for a relationship between f-EIB and IQ, direct comparisons between the two groups were difficult because of the large IQ differences. Moreover, it remains unclear how differences in f-EIB values develop across childhood and adolescence and whether their development may be linked to individual autism traits.

To fill these gaps, we here compare developmental trajectories of EI balance and their relationship to cognition and behavior in a group of autistic children and an allistic comparison group matched by age, sex, and nonverbal-IQ (nv-IQ). We analyzed rs-EEG recordings for a final sample of 92 autistic children from 6 to 17 years of age and 100 neurotypical children from the Healthy Brain Network (HBN) Biobank (Alexander

et al., 2017). In addition, we obtained cognitive measures of autism traits and language abilities for each participant. From the rs-EEG recordings, we quantified f-EIB values in the individual alpha frequency (IAF) for each participant. Since the developmental trajectory of the EIB has not been assessed yet, we first assessed the f-EIB across the age range. We then also examined the relationship between autism traits and the age trajectory of f-EIB values. Based on the potential IQ confound in prior work, we did not have a strong hypothesis on finding group differences in f-EIB values. However, we still expected a relationship between individual autism trait measures and the development of f-EIB values when performing statistics in a more continuous manner in a sample that displays a larger f-EIB range. In particular, we expected stronger autism traits to relate to higher EI imbalances.

METHODS

Participants

The participants of this study are part of the openly available HBN Biobank published by the Child Mind Institute in the United States (Alexander et al., 2017). The study was approved by the Chesapeake Institutional Review Board. For our study, we selected a subset of 125 individuals (19 female; 6–17 years old) who received a primary diagnosis of autism spectrum disorder. Clinical diagnoses in the HBN were made based on the computerized version of the Schedule for Affective Disorders and Schizophrenia—Children's version (KSADS-COMP) which was administered by a licensed clinician. This semi-structured psychiatric interview includes a child and a parent interview. In case of indications for autism, two additional diagnostic assessments, the Autism Diagnostic Interview—Revised (ADI-R) and the Autism Diagnostic Observation Schedule, second edition (ADOS-2), were additionally administered. ADI-R and ADOS-2 scores are not accessible in the HBN databank. To increase the representativeness of our sample, we included both autistic individuals with no secondary diagnoses ($n = 21$) and those with secondary diagnoses, as comorbidities are frequently reported in the autistic population (see Table S1; Mannion et al., 2013). We matched a comparison group of 125 neurotypical individuals to our autistic sample based on age, sex, and nv-IQ. We matched groups based on IQ to avoid differences in our outcome measure that are explained by differences in intelligence (see Cochran et al., 2015; Robinson, 1989), as lower IQ is not a core symptom of autism (American Psychiatric Association, 2013). Since we were investigating autism traits related to language, we matched on nv-IQ. Given that our sample did not include sufficient females to reliably examine sex differences and previous research found no evidence for sex-specific differences in inhibitory development (DeMayo et al., 2021), we here included both males and females in our analysis.

For a full set of in- and exclusion criteria to the HBN dataset, please refer to the original publication (Alexander et al., 2017). Most importantly for the current analysis, participation was not possible if serious cognitive impairment or neurological disorders prevented the completion of the experiments (e.g., IQ < 66, nonverbal autism, chronic epilepsy). Moreover, all participants were fluent in English. To be included in the current analysis, participants had to have completed the rs-EEG and their total EEG signal including all six paradigms had to have a minimum length of 500 s as required for the EEG preprocessing-pipeline employed here (Gabard-Durnam et al., 2018). They further had to have completed the Wechsler Intelligence Scale for Children—V (WISC–V for the computation of nv-IQ; Wechsler, 2014). Out of the 250 participants selected for the current analysis, a total of 58 participants ($n_{autistic} = 33$, $n_{allistic} = 25$) were excluded from the final analysis due to less than 40 artifact-free EEG epochs ($n_{autistic} = 19$, $n_{allistic} = 6$) or inability to compute long-range temporal correlations for the f-EIB computations ($n_{autistic} = 14$, $n_{allistic} = 19$). Descriptive statistics for the final sample are summarized in Table 1.

Data acquisition

Cognitive and behavioral measures

To quantify the participants' autism traits, language abilities as well as nv-IQ, their scores on six cognitive assessments were used. All participants were asked to complete all six assessments. Specific autism traits (i.e., specialized

TABLE 1 Demographics and cognitive assessment scores of the autistic and allistic participants included in the final analysis.

	Autistic ($n = 92$)	Allistic ($n = 100$)	p Value
Age (in years)	10.79 (2.88)	10.62 (2.94)	n.a.
Nonverbal-IQ	97.24 (19.89)	100.22 (15.67)	n.a.
Sex (f/m)	14/78	30/70	n.a.
ASSQ	20.1 (11.62)	2.57 (3.66)	<0.001
RBS	58.49 (37.87)	11.54 (17.41)	<0.001
SRS	90.24 (29.70)	30.35 (17.46)	<0.001
SCQ	13.23 (5.88)	5.59 (3.64)	<0.001
WIAT-LC	100.17 (16.68)	107.04 (15.77)	0.004

Note: Cognitive assessments included the Autism Spectrum Screening Questionnaire (ASSQ), Repetitive Behavior Scale (RBS), Social Responsiveness Scale (SRS), Social Communication Questionnaire (SCQ), and Wechsler Individual Achievement Test-Listening Comprehension (WIAT-LC). All assessments were done with all participants except for the RBS, which had not been included in the initial protocol. Standard deviations (SD) are given in brackets after the means. p Values for the matched variables age, nv-IQ, and sex are not applicable (n.a.; see e.g., Sassenhagen & Alday, 2016).

interests and repetitive behaviors, social interaction, social reciprocity, and language and communication) were assessed with four questionnaires completed by a participant's caregiver (Alexander et al., 2017): First, the Autism Spectrum Screening Questionnaire (ASSQ; Ehlers et al., 1999) captures general autism traits regarding social interaction, communication, and repetitive behavior. Second, the Repetitive Behavior Scale (RBS; Lam & Aman, 2007) quantifies specific autism traits concerning repetitive behaviors. Third, the Social Responsiveness Scale-2 (SRS-2; Constantino & Gruber, 2012) quantifies reciprocal social behavior as well as specialized interests and repetitive behaviors. Fourth, the Social Communication Questionnaire (SCQ—previously called Autism Screening Questionnaire; Rutter et al., 2003) is used to quantify specific autism traits concerning stereotyped body movements and gestures, language usage, and social interactions. Higher scores on any of these questionnaires indicate increased autism traits. Questionnaires were completed for all children, except for the RBS, which was only available for $n = 172$ children ($n_{autistic} = 75$, $n_{allistic} = 59$), as it was only added to the protocol later (Alexander et al., 2017).

In addition to the questionnaire scores, participants' scores on two behavioral assessments were included. Given the relationship between autism and language abilities (see Eigsti et al., 2011, for a review) and the potential relationship between EIB and language comprehension (Hegarty et al., 2018), we quantified receptive language abilities using the listening comprehension (LC) subtest of the Wechsler Individual Achievement Test-III (WIAT-III; Wechsler, 1992). The listening subtest contains vocabulary and oral discourse comprehension components and measures listening comprehension at the level of the word, sentence, and discourse. The test quantifies language ability using a standard score for age ($M = 100$, SD = 15). Participants' nv-IQ was quantified based on the WISC-V (Wechsler, 2014).

EEG data

Participants took part in one EEG session with a total duration of 90 min. The session consisted of six different EEG paradigms with the rs-EEG paradigm always conducted first. During the session, EEG was recorded continuously using a 129-channel EEG geodesic hydrocel system by Electrical Geodesics Inc. (EGI) at a sampling rate of 500 Hz. Cz served as online reference and impedances were kept below 40 kΩ during the recording. The rs-EEG lasted for 5 min in which participants were instructed to alternate five times between keeping their eyes open (20 s) and closed (40 s). In line with Bruining et al. (2020), only the eyes-closed rs-EEG was analyzed here, as it has been associated with functional balance in healthy adults compared to the eyes-open resting-state. To assess children's compliance with the eyes-closed instruction, we analyzed for group differences in the number of artifacts on the raw data for the eye channels (i.e., timepoints ± 125 μV). Both groups showed significantly more artifacts in the eyes-open than the eyes-closed condition (both $p < 0.003$) and there was no significant group difference in the number of artifacts for the eyes-closed condition ($t = -0.15$, $p = 0.88$), indicating high data quality and compliance with the instruction in both groups.

EEG preprocessing

Data preprocessing was done in MATLAB (The MathWorks, Inc., Natick, US) using the openly available toolboxes EEGLAB (Delorme & Makeig, 2004) and FieldTrip (Oostenveld et al., 2011). Preprocessing was done automatically using an adjusted version of the Harvard Automated Preprocessing Pipeline (HAPPE; Gabard-Durnam et al., 2018; Menn, Michel, et al., 2022). Although only the rs-EEG data was included in our analysis, we preprocessed the EEG signal of the 91 scalp electrodes (excluding external/face electrodes) for all paradigms to allow for a reliable independent component decomposition (Gabard-Durnam et al., 2018).

In line with HAPPE, the signal was high-pass (filter order: 16,500, pass-band: 1 Hz, −6 dB cutoff: 0.5 Hz) and low-pass (filter order: 166, pass-band: 50 Hz, −6 dB cutoff: 55 Hz) filtered with a noncausal finite impulse response filter. Next, channels were rejected if the normed joint probability of the average log power from 1 to 100 Hz exceeded a threshold of 3 standard deviations from the mean ($M_{autistic} = 6.43$, SD = 5.34; $M_{allistic} = 4.92$, SD = 3.26; $t(190) = 2.39$, $p = 0.018$; we have assessed the potential confound in a group difference in rejected channels in the analysis [see Section 3]). Artifacts were removed with wavelet-enhanced independent component analysis (Castellanos & Makarov, 2006) with a threshold of 3. Data was then decomposed using independent component analysis. Artifact components were automatically rejected using the multiple artifact rejection algorithm (MARA; $M_{autistic} = 43.88$, SD = 9.41; $M_{allistic} = 46.32$, SD = 10.09, $t = -1.73$, $p = 0.086$; Winkler et al., 2011). These rejection rates are comparable to manual validation approaches in developmental (Gabard-Durnam et al., 2018) and adult data (Winkler et al., 2011; Winkler et al., 2015). A randomly selected subset of these artifact components was visually inspected to ensure that non-artifact components were not rejected. Last, previously rejected channels were interpolated using spherical splines (Perrin et al., 1989) and the EEG data was re-referenced to an approximately zero reference with the reference electrode standardization technique (Dong et al., 2017).

EEG data analysis

All f-EIB values were computed within each participant's IAF. To prepare the IAF analysis, the total 200 s of preprocessed EEG signal corresponding to eyes-closed rs-EEG was segmented into two-second epochs with 50% overlap leading to a potential maximum of 195 epochs. As suggested by HAPPE, all epochs with amplitudes exceeding ±40 μV were excluded. On average, 158.28 artifact-free epochs per participant were analyzed ($M_{\text{autistic}} = 158.47$, SD = 42.07; $M_{\text{allistic}} = 158.83$, SD = 40.54).

As a next step, we quantified each participant's IAF as the alpha center of gravity of the smoothed power spectra following the algorithm by Corcoran et al. (2018). Since the alpha band (canonical: 8–12 Hz) is often slower in developmental samples (Cellier et al., 2021), we extended the frequency band of interest to 4–14 Hz. The participants' IAF range was defined as the range from 4 Hz below the alpha center of gravity to 2 Hz above (Klimesch, 1999).

Finally, we calculated the f-EIB from the preprocessed eyes-closed rs-EEG signal in the IAF for each participant. Computations were done using the original MATLAB code published by Bruining et al. (2020) based on long-range temporal correlations and alpha amplitudes within the signal on five-second epochs with 80% overlap. Inhibition-dominated networks are characterized by an f-EIB value < 1, excitation-dominated networks display an f-EIB value > 1 and balanced networks will have an f-EIB value = 1.

In line with Bruining et al. (2020), we excluded all participants with detrended fluctuation analysis exponents below 0.6 from the final analysis, as amplitude and fluctuation function have been shown to not co-vary in neural networks with low long-range temporal correlations, leading to unreliable estimates of f-EIB values.

Statistical analysis

The relationship between f-EIB values and autism was assessed using mixed-effects models ('lme'; Bates et al., 2015) in R (v. 4.1.2; R. C. Team, 2021) with RStudio (1.2.5042; R. Team, 2020). The *p* values for the mixed-effects models were computed using Satterthwaite approximation ('lmerTest'; Kuznetsova et al., 2017) and graphics were created using 'ggplot2' (Wickham, 2016).

To test differences in the f-EIB values between the two groups, we conducted a two sample *t*-test and a Levene's test to assess the equality of variances. Since previous studies have found EI differences in the brain to be region-specific, which may manifest into different topographies at the scalp-level, we clustered the electrodes into four regions of interest (ROI; left-anterior, left-posterior, right-anterior, right-posterior) according to their caudality and laterality (see Figure S1). To test whether there were differences in the age trajectory of f-EIB values between the groups, we conducted a mixed-effects model using the f-EIB values as dependent variable and group (autistic, allistic), a quadratic term for age, and the ROI as well as their interactions as predictors. All continuous predictors were standardized for the analysis. Group was contrast coded with autistic as reference level coded as −0.5 and ROI was deviation coded, meaning that f-EIB values for each level of ROI were compared to the overall mean. Significant interactions were followed-up with separate analyses within the ROI implicated in the significant interaction term, followed by group comparisons. To assess the relationship between the developmental trajectory of f-EIB values and the individual level of autism traits, we conducted five separate mixed-effects models each replacing the autism group predictor in the model described above by the individual's score on the respective autism characteristic assessment (ASSQ, SCQ, SRS, RBS, and WIAT). Given that autism is seen as a spectrum with a varying degree of autistic traits present in the general population, these analyses were conducted across both participant groups. To correct for multiple comparisons, we used Bonferroni-correction (adjusted-$\alpha = 0.01$) for all analyses and follow-up analyses assessing the relationship between f-EIB values and individual autism traits.

RESULTS

f-EIB differences for autistic and allistic children

There was no significant difference in mean f-EIB values between the autistic ($M = 1.05$) and the allistic ($M = 1.07$) group across all electrodes, $t(190) = 0.67$, $p = 0.5$ (Figure 1a), or within any ROI (all $ps > 0.33$). This result remained after controlling for the number of rejected channels and the number of rejected channels did not relate to f-EIB values (all $ps > 0.08$), indicating that the group difference in numbers of rejected channels did not confound our EI balance estimates. There was also no significant difference in the variance of f-EIB values between the two groups across electrodes, $p = 0.2$, or within the ROIs (all $ps > 0.07$). Numerically, the allistic group had a higher variance (SD = 0.19) than the autistic group (SD = 0.16).

Our analysis testing for different developmental trajectories of f-EIB values between autistic and allistic children showed a significant increase of f-EIB values with age, $t = 2.3$, $p = 0.023$. Importantly, the analysis revealed a significant interaction between group, age, and ROI for the left-anterior region, $t = 2.3$, $p = 0.022$. Follow-up regression analyses for this ROI confirmed the linear increase of f-EIB values with age, $t = 2.27$, $p = 0.024$, and revealed a significant interaction between group and the quadratic term for age, $t = 2.02$,

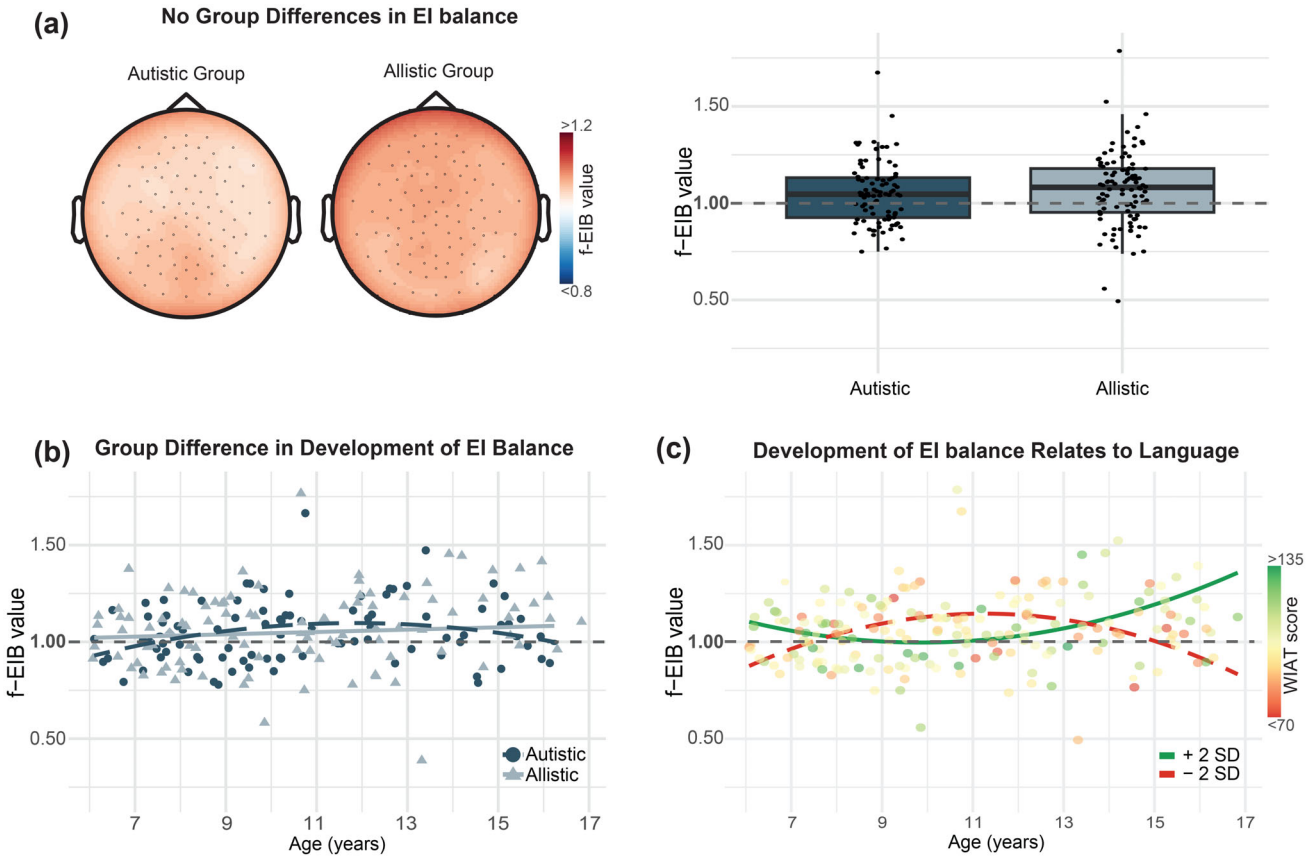

FIGURE 1 Overview of our main results. (a) No significant group difference between the autistic and the allistic group. Topographical distributions of f-EIB values displayed on the left, mean f-EIB values across all electrodes on the right. Dots indicate individual data points. (b) The age trajectories of the f-EIB values differ between the autistic and allistic group for the left-frontal region of interest (ROI). The autistic group (dark) showed an inverse u-shaped age trajectory for f-EIB values whereas the allistic group (bright) showed a (marginally significant) linear trajectory. (c) The age trajectory of f-EIB values relates to WIAT Listening Comprehension (WIAT-LC) scores. Note that we used listening comprehension as a continuous measure in the analysis. A grouping (lines indicate trajectory for children ± 2 SD from the mean) was applied for visualization only. Individual dots are colored according to the WIAT score.

$p = 0.045$. Within this ROI, the autistic group showed a significant quadratic age effect on f-EIB values, $t = -2.36$, $p = 0.021$, whereas the allistic group showed a marginally significant linear effect of age on f-EIB values, $t = 1.94$, $p = 0.055$. Note that there were five potential outliers (z-scores > 2.5 or < −2.5; $n_{allistic} = 4$; $n_{autistic} = 1$). The exclusion of these data points did not affect the overall pattern of results reported in this manuscript, except that it led to a significant linear effect of age on f-EIB values in the allistic group $t = 2.41$, $p = 0.018$. This indicates different patterns in developmental trajectories of EI balance between autistic and allistic children. Inspection of the regression estimates suggests that in the left-anterior ROI relative excitation peaks between 11 and 13 years of age for autistic children and decreases in adolescence whereas relative excitation shows an increase across childhood and adolescence for the allistic group (Figure 1b). To follow-up on the group × age interaction, we evenly divided participants into three age groups (children: 6–9 years, $n_{autistic} = 29$, $M_{autistic} = 1.07$, $n_{allistic} = 36$, $M_{allistic} = 1.11$; young adolescents: 9–12 years, $n_{autistic} = 31$, $M_{autistic} = 1.08$, $n_{allistic} = 32$, $M_{allistic} = 1.07$; older adolescents: 13–17 years, $n_{autistic} = 32$, $M_{autistic} = 1.07$, $n_{allistic} = 32$, $M_{allistic} = 1.12$). We did not observe a statistically significant between-group difference in any individual age group (children: $t = -1.44$, $p = 0.154$; young adolescents: $t = 0.13$, $p = 0.895$; older adolescents: $t = -0.78$, $p = 0.439$), suggesting that the different pattern of EI development may not manifest into significant group differences in EI balance at any age point in childhood.

Relationship f-EIB trajectory to autism traits

The five assessments of autism traits were significantly different between the two groups (Table 1; Wilcoxon rank-sum tests: all ps ≤ 0.004) and none showed evidence for age bias (all ps ≥ 0.238). Results for all separate models investigating the relationship between autism traits and f-EIB trajectory can be found in Supplementary Tables S2–S7. We here only discuss the effects involving autism traits that remained significant after multiple-comparisons correction.

The analyses with parental questionnaires ASSQ, SCQ, and SRS showed significant interactions between the respective test score and age for the left-anterior ROI (ASSQ: $t = -2.83$, $p = 0.005$; SCQ: $t = -2.78$, $p = 0.006$; SRS: $t = -2.98$, $p = 0.003$). This tentatively suggests that individual differences in the degree of autism traits relate to the developmental trajectory of f-EIB values in the left-anterior ROI. However, none of the follow-up analyses within this ROI showed a significant interaction between the respective test score and age (all $ps \geq 0.08$). For the RBS, we observed a significant interaction between test scores and ROI, which was also specific to the left-anterior channels, $t = -2.81$, $p = 0.005$. However, follow-up analyses within the left-anterior ROI showed no significant relationship between repetitive behavior and f-EIB values, $t = -1.34$, $p = 0.184$.

Importantly, for the listening comprehension subscale of the WIAT, we found a significant interaction between test scores and the quadratic age term on f-EIB values, $t = 2.75$, $p = 0.007$ (see Figure 1c). In line with the group analysis reported above, model estimates indicate that lower listening comprehension scores are related to an inverse-u shaped age trajectory of f-EIB values with a peak in relative excitation between 11 and 13 years of age. Higher listening comprehension scores, on the other hand, associate with a u-shaped trajectory of f-EIB values with a trough in relative excitation between 8 and 10 years of age followed by an increase in relative excitation across adolescence. Including the group factor to this model provided no evidence that the relationship between listening comprehension and age on f-EIB values was different for the two groups (interaction WIAT $\times$ Age^2 $\times$ Group: $t = -0.26$, $p = 0.796$). To control for a potential impact of language impairments (other than the language differences typically observed in autism) on the relationship between EI balance and language abilities, we repeated the analysis excluding all participants with any language-related secondary diagnosis ($n = 16$). The interaction between the listening comprehension score and the quadratic age term remained significant, $t = 2.9$, $p = 0.004$.

Control analysis: Relationship f-EIB with IQ

In contrast to the results reported by Bruining et al. (2020), we find no evidence for differences in f-EIB variance between the two nv-IQ-matched groups in our sample. Control analyses showed no significant relationship between IQ and f-EIB values, $t = 0.76$, $p = 0.447$, in our sample. We also found no evidence that the developmental trajectory of f-EIB values relates to IQ (linear term: $t = 0.06$; $p = 0.95$; quadratic term: $t = 0.03$; $p = 0.978$; see Supplementary Table S8). Note that both groups had IQ values in the normal range. A second methodological difference between our study and the study by Bruining et al. (2020) was that we computed f-EIB values in the IAF. Control analyses showed no evidence that IAF affected the results reported here (see Supplement D).

DISCUSSION

In a large cross-sectional sample, we identified differences in the developmental trajectory of EI balance between autistic and age-, sex-, and nv-IQ-matched allistic children over left-anterior channels in rs-EEG recordings. In this ROI, autistic children showed a quadratic trajectory of f-EIB values, in contrast to a linear trajectory for allistic children. Moreover, our analysis shows that the developmental trajectory of EI balance relates to individual differences in language abilities: Children with lower listening comprehension scores showed an inverse u-shaped trajectory of EI balance with peak relative excitation around 11–13 years of age. Children with higher listening comprehension showed a u-shaped trajectory of f-EIB values with a trough in relative excitation between 8 and 10 years of age. This finding mirrors the group differences in the developmental trajectory of EI balance observed for left-anterior channels. Tentative relationships between other autism traits assessed via parental report and the EI balance trajectory were also observed for left-anterior channels, but follow-up analyses were not significant. While the reliability of parental reports of autism is generally high (Frazier et al., 2023), future research should investigate whether participant-led assessments may allow for more reliable relationships between autism traits and f-EIB values.

In contrast to recent reports by Bruining et al. (2020), we did not find evidence for a general EI imbalance as indicated by higher variance in the autistic compared to the allistic group. This discrepancy likely stems from differences in the statistical treatment of participants' IQ. In particular—and in contrast with the current study—, Bruining et al. (2020) report a significant group difference in IQ that can explain the observed difference in f-EIB. While their autistic group was comparable to ours ($IQ_{autistic} = 101.4$ vs. 97.24), their allistic group differed from ours ($IQ_{allistic} = 120.6$ vs. 100.22). EIB and IQ are known to covary in both allistic and autistic people (Cochran et al., 2015; Orekhova et al., 2008; Said et al., 2013). Specifically, IQs > 130 associate with optimal EI balance (Robinson, 1989). Since the allistic participants in the study by Bruining et al. (2020) had a high mean IQ around 120, they are expected to exhibit low variance in f-EIB. In addition to this gross difference, the low IQ cutoff of 55 employed by Bruining et al. (2020) might have further inflated EIB variance; in contrast, the HBN cutoff is 66 (Alexander et al., 2017). Future work needs to consider IQ when comparing EI balance across groups.

Our findings portraying a pattern in which f-EIB values are elevated for autistic adolescents is in line with

previous reports of cortical hyperexcitability in autistic individuals (Canitano, 2007; Chez et al., 2006; Lewine et al., 1999). It is important to note that our use of f-EIB values from scalp-level EEG means that we can only interpret our findings in terms of EI balance on a system level (see Ahmad et al., 2022, for a review), as a ratio between excitatory and inhibitory systems. We cannot distinguish whether increased f-EIB values reflect increased excitatory activity or decreased inhibitory activity on a neuronal level. Nevertheless, our result of a peak in relative excitation in autistic pre-adolescents is in line with previous findings showing major developments in the inhibitory (GABAergic) system during (early) adolescence (Arain et al., 2013; Kilb, 2012; Silveri et al., 2013) and evidence for GABAergic differences in autistic children (DeMayo et al., 2021). Adding to these previous studies reporting EI imbalances in autism, we here show a developmental change of EI imbalance across childhood and adolescence for autistic individuals and further provide evidence that the trajectory is associated with individual differences in the degree of autism characteristics.

The finding that higher f-EIB values (i.e., lower relative inhibition) in childhood associate with lower listening comprehension scores is consistent with earlier findings suggesting a relationship between GABA and language ability (Gaetz et al., 2014) and previous reports of reduced GABA concentrations in language areas for autistic children and their siblings (Rojas et al., 2014). Noteworthy, Hegarty et al. (2018) reported a relationship between an EI imbalance in the cerebellum and listening comprehension in autistic individuals. Given the uncertainty regarding the assessment of cerebellar activity in EEG recordings (e.g., Andersen et al., 2020), it is unclear in how far EI imbalances in the cerebellum could have contributed to our scalp-level EEG measures. Our data also suggests that f-EIB values were especially sensitive to individual differences in language ability during primary school years and thus at a developmental period during which children acquire new knowledge in multiple language domains, including syntax and reading. GABA may be especially relevant during such learning periods by establishing newly acquired knowledge in memory (Barron, 2021; Shibata et al., 2017). In a recent study, Frank et al. (2022) showed that GABA concentrations dynamically increase during a perceptual learning task in children but not in adults, which may explain why children are more efficient learners than adults. Some limited evidence from aphasic patients suggests that GABA concentrations may also contribute to an optimal learning environment for language learning (Harris et al., 2019). The association between EI development and language ability in our data may thus reflect an impact of GABA on language learning during childhood and early adolescence. Another possible explanation is that the relationship between EI development and language ability in our sample may reflect differences in auditory processing based on differences in EI development during earlier development already. Animal studies have shown that EI balance is crucial for the spectro-temporal response tuning of neurons in the auditory cortex during early development (Sun et al., 2010; Wehr & Zador, 2003). Deviations in EI development in human infants could thus impact the processing of spectro-temporal speech information, which is, amongst others, crucial for phonemes (i.e., speech sounds) and pitch (involved in speech prosody and intonation). Some recent evidence suggests that autism is related to differences in EI balance already during infancy (Carter Leno et al., 2022), which could thus affect acoustic fine-tuning of the auditory cortex. It has recently been shown that electrophysiological processing of acoustic-phonological information in infancy predicts later language development (Menn, Ward, et al., 2022). Future longitudinal studies are needed to assess how the developmental trajectory of EI balance in adolescence relates to EI development during infancy and whether greater deviances from the typical EI development during childhood and adolescence associate with greater deviances in infancy already. Importantly, the identification of a relationship between EI balances and language ability in the current study thus not only offers compelling evidence supporting the relevance of EI imbalances in contributing to language differences observed in individuals with autism, but it also lays a crucial foundation for future investigations within the broader domain of language acquisition, where the intricate interplay between EI balance and language development has received limited attention yet (also see Menn et al., 2023).

Tentatively, our findings of a relationship between the developmental trajectory of f-EIB values and autism in the left-anterior ROI is in line with previous reports indicating altered prefrontal GABA concentrations for autistic compared to allistic adults (Maier et al., 2022) as well as reduced GABA concentrations in the (left prefrontal) language areas for autistic children (Rojas et al., 2014). However, it is important to note that since EEG is measured at the scalp-level, our ability to draw inferences about the specific brain regions underlying our findings is limited. Hence, future research is needed to establish novel techniques enabling the reconstruction of the neural sources of f-EIB values assessed on the scalp level. Additionally, we cannot draw conclusions about the direction of the relationship between EI balance and autism from this correlational cross-sectional design. While it is plausible that deviances from the typical EI balance trajectory lead to autism (e.g., Rubenstein & Merzenich, 2003), it has also been suggested that EI differences between autistic and allistic groups may reflect some compensatory mechanism of autistic individuals aiming to mask autistic traits (Chan et al., 2022). Interestingly, the inverted u-shape trajectory for the autistic group and the potentially linear trajectory for the allistic group in our data suggests hyperexcitability for autistic individuals during pre-adolescence and a possible reversal of this pattern for older adolescents, when the allistic

group may display higher relative excitation than the autistic group. Elevated inhibition for autistic adults is in line with a recent study reporting higher GABA concentrations in the prefrontal cortex for autistic compared to allistic adults (Fung et al., 2021). However, a linear trajectory of f-EIB values for allistic individuals into adulthood is biologically implausible and not in line with findings showing that GABA concentrations plateau during adulthood after improving over adolescence (Caballero et al., 2021; Spielberg et al., 2015). In addition, Bruining et al. (2020) observed balanced f-EIB values in an allistic adult group. It is thus likely that the seeming shift in elevated relative excitability between the autisitc and allistic group is caused by sparser sampling of older adolescents in our sample, leading to higher uncertainty of the estimates at this age.

CONCLUSION

We show that the developmental trajectory of EI balance during childhood and adolescence differs between autistic and allistic children and that these differences can be measured on the systems level using cheap and noninvasive resting-state EEG recordings. On an individual level, the developmental trajectory of functional EI balance relates to a general measure of language ability. These findings are consistent with a differential development of the inhibitory neurotransmitter GABA in autistic versus allistic children and the proposed role of GABA for (language) learning.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Child Mind Institute healthy brain network at http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/index.html after signing of a data usage agreement.

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REFERENCES

Ahmad, J., Ellis, C., Leech, R., Voytek, B., Garces, P., Jones, E., Buitelaar, J., Loth, E., Dos Santos, F. P., Amil, A. F., Verschure, P. F. M. J., Murphy, D., & McAlonan, G. (2022). From mechanisms to markers: Novel noninvasive eeg proxy markers of the neural excitation and inhibition system in humans. *Translational Psychiatry*, *12*(1), 1–12. https://doi.org/10.1038/s41398-022-02218-z

Alexander, L. M., Escalera, J., Ai, L., Andreotti, C., Febre, K., Mangone, A., Vega-Potler, N., Langer, N., Alexander, A., Kovacs, M., Litke, S., O'Hagan, B., Andersen, J., Bronstein, B., Bui, A., Bushey, M., Butler, H., Castagna, V., Camacho, N., … Milham, M. P. (2017). An open resource for transdiagnostic research in pediatric mental health and learning disorders. *Scientific Data*, *4*(1), 1–26. https://doi.org/10.1038/sdata.2017.181

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed.). American Psychiatric Publishing.

Andersen, L. M., Jerbi, K., & Dalal, S. S. (2020). Can EEG and MEG detect signals from the human cerebellum? *NeuroImage*, *215*, 116817. https://doi.org/10.1016/j.neuroimage.2020.116817

Anderson, A. J., & Perone, S. (2018). Developmental change in the resting state electroencephalogram: Insights into cognition and the brain. *Brain and Cognition*, *126*, 40–52. https://doi.org/10.1016/j.bandc.2018.08.001

Arain, M., Haque, M., Johal, L., Mathur, P., Nel, W., Rais, A., Sandhu, R., & Sharma, S. (2013). Maturation of the adolescent brain. *Neuropsychiatric Disease and Treatment*, *9*, 449. https://doi.org/10.2147/NDT.S39776

Avramiea, A.-E., Masood, A., Mansvelder, H. D., & Linkenkaer-Hansen, K. (2022). Long-range amplitude coupling is optimized for brain networks that function at criticality. *Journal of Neuroscience*, *42*(11), 2221–2233. https://doi.org/10.1523/JNEUROSCI.1095-21.2022

Barron, H. C. (2021). Neural inhibition for continual learning and memory. *Current Opinion in Neurobiology*, *67*, 85–94. https://doi.org/10.1016/j.conb.2020.09.007

Barttfeld, P., Amoruso, L., Ais, J., Cukier, S., Bavassi, L., Tomio, A., Manes, F., Ibanez, A., & Sigman, M. (2013). Organization of brain networks governed by long-range connections index autistic traits in the general population. *Journal of Neurodevelopmental Disorders*, *5*(1), 1–9. https://doi.org/10.1186/1866-1955-5-16

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*(1), 1–48. https://doi.org/10.18637/jss.v067.i01

Bejjani, A., O'Neill, J., Kim, J. A., Frew, A. J., Yee, V. W., Ly, R., Kitchen, C., Salamon, N., McCracken, J. T., Toga, A. W., Alger, J. R., & Levitt, J. G. (2012). Elevated glutamatergic compounds in pregenual anterior cingulate in pediatric autism spectrum disorder demonstrated by ^{1}H MRS and ^{1}H MRSI. https://doi.org/10.1371/journal.pone.0038786

Bernardi, S., Anagnostou, E., Shen, J., Kolevzon, A., Buxbaum, J. D., Hollander, E., Hof, P. R., & Fan, J. (2011). In vivo ^{1}H-magnetic resonance spectroscopy study of the attentional networks in autism. *Brain Research*, *1380*, 198–205. https://doi.org/10.1016/j.brainres.2010.12.057

Blatt, G. J., & Fatemi, S. H. (2011). Alterations in GABAergic biomarkers in the autism brain: Research findings and clinical implications. *The Anatomical Record*, *294*(10), 1646–1652. https://doi.org/10.1002/ar.21252

Brown, M. S., Singel, D., Hepburn, S., & Rojas, D. C. (2013). Increased glutamate concentration in the auditory cortex of persons with autism and first-degree relatives: A ^{1}H-MRS study. *Autism Research*, *6*(1), 1–10. https://doi.org/10.1002/aur.1260

Bruining, H., Hardstone, R., Juarez-Martinez, E. L., Sprengers, J., Avramiea, A.-E., Simpraga, S., Houtman, S. J., Poil, S.-S., Dallares, E., Palva, S., Oranje, B., Matias Palva, J., Mansvelder, H. D., & Linkenkaer-Hansen, K. (2020).

Measurement of excitation-inhibition ratio in autism spectrum disorder using critical brain dynamics. *Scientific Reports*, *10*(1), 1–15. https://doi.org/10.1038/s41598-020-65500-4

Caballero, A., Orozco, A., & Tseng, K. Y. (2021). Developmental regulation of excitatory-inhibitory synaptic balance in the prefrontal cortex during adolescence. *Seminars in Cell & Developmental Biology*, *118*, 60–63. https://doi.org/10.1016/j.semcdb.2021.02.008

Canitano, R. (2007). Epilepsy in autism spectrum disorders. *European Child & Adolescent Psychiatry*, *16*(1), 61–66. https://doi.org/10.1007/s00787-006-0563-2

Carter Leno, V., Begum-Ali, J., Goodwin, A., Mason, L., Pasco, G., Pickles, A., Garg, S., Green, J., Charman, T., Johnson, M. H., Jones, E. J. H., the EDEN & STAARS Teams. (2022). Infant excitation/inhibition balance interacts with executive attention to predict autistic traits in childhood. *Molecular Autism*, *13*(1), 1–13. https://doi.org/10.1186/s13229-022-00526-1

Castellanos, N. P., & Makarov, V. A. (2006). Recovering EEG brain signals: Artifact suppression with wavelet enhanced independent component analysis. *Journal of Neuroscience Methods*, *158*(2), 300–312. https://doi.org/10.1016/j.jneumeth.2006.05.033

Cellier, D., Riddle, J., Petersen, I., & Hwang, K. (2021). The development of theta and alpha neural oscillations from ages 3 to 24 years. *Developmental Cognitive Neuroscience*, *50*, 100969. https://doi.org/10.1016/j.dcn.2021.100969

Chan, M. M., Choi, C. X., Tsoi, C., Zhong, J., & Han, Y. M. (2022). Heightened functional excitation-inhibition ratio as a compensatory mechanism in autism spectrum disorder (asd): An EEG study. https://doi.org/10.21203/rs.3.rs-2207767/v1

Chez, M. G., Chang, M., Krasne, V., Coughlan, C., Kominsky, M., & Schwartz, A. (2006). Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. *Epilepsy & Behavior*, *8*(1), 267–271. https://doi.org/10.1016/j.yebeh.2005.11.001

Cochran, D. M., Sikoglu, E. M., Hodge, S. M., Edden, R. A., Foley, A., Kennedy, D. N., Moore, C. M., & Frazier, J. A. (2015). Relationship among glutamine, γ-aminobutyric acid, and social cognition in autism spectrum disorders. *Journal of Child and Adolescent Psychopharmacology*, *25*(4), 314–322. https://doi.org/10.1089/cap.2014.0112

Collins, A. L., Ma, D., Whitehead, P. L., Martin, E. R., Wright, H. H., Abramson, R. K., Hussman, J. P., Haines, J. L., Cuccaro, M. L., Gilbert, J. R., & Pericak-Vance, M. A. (2006). Investigation of autism and GABA receptor subunit genes in multiple ethnic groups. *Neurogenetics*, *7*(3), 167–174.https://doi.org/10.1007/s10048-006-0045-1

Constantino, J. N., & Gruber, C. P. (2012). *Social responsiveness scale: Srs-2*. Western Psychological Services Torrance.

Corcoran, A. W., Alday, P. M., Schlesewsky, M., & Bornkessel-Schlesewsky, I. (2018). Toward a reliable, automated method of individual alpha frequency (IAF) quantification. *Psychophysiology*, *55*(7), e13064. https://doi.org/10.1111/psyp.13064

Corrigan, N. M., Shaw, D. W., Estes, A. M., Richards, T. L., Munson, J., Friedman, S. D., Dawson, G., Artru, A. A., & Dager, S. R. (2013). Atypical developmental patterns of brain chemistry in children with autism spectrum disorder. *JAMA Psychiatry*, *70*(9), 964–974. https://doi.org/10.1001/jamapsychiatry.2013.1388

DeLorey, T. M., Sahbaie, P., Hashemi, E., Homanics, G. E., & Clark, J. D. (2008). Gabrb3 gene deficient mice exhibit impaired social and exploratory behaviors, deficits in non-selective attention and hypoplasia of cerebellar vermal lobules: A potential model of autism spectrum disorder. *Behavioural Brain Research*, *187*(2), 207–220. https://doi.org/10.1016/j.bbr.2007.09.009

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

DeMayo, M. M., Harris, A. D., Song, Y. J. C., Pokorski, I., Thapa, R., Patel, S., Ambarchi, Z., Thomas, E. E., Hickie, I. B., & Guastella, A. J. (2021). Age-related parietal GABA alterations in children with autism spectrum disorder. *Autism Research*, *14*(5), 859–872. https://doi.org/10.1002/aur.2487

DeVito, T. J., Drost, D. J., Neufeld, R. W., Rajakumar, N., Pavlosky, W., Williamson, P., & Nicolson, R. (2007). Evidence for cortical dysfunction in autism: A proton magnetic resonance spectroscopic imaging study. *Biological Psychiatry*, *61*(4), 465–473. https://doi.org/10.1016/j.biopsych.2006.07.022

Dong, L., Li, F., Liu, Q., Wen, X., Lai, Y., Xu, P., & Yao, D. (2017). Matlab toolboxes for reference electrode standardization technique (REST) of scalp eeg. *Frontiers in Neuroscience*, *11*, 601. https://doi.org/10.3389/fnins.2017.00601

Dorrn, A. L., Yuan, K., Barker, A. J., Schreiner, C. E., & Froemke, R. C. (2010). Developmental sensory experience balances cortical excitation and inhibition. *Nature*, *465*(7300), 932–936. https://doi.org/10.1038/nature09119

Doyle-Thomas, K. A., Card, D., Soorya, L. V., Wang, A. T., Fan, J., & Anagnostou, E. (2014). Metabolic mapping of deep brain structures and associations with symptomatology in autism spectrum disorders. *Research in Autism Spectrum Disorders*, *8*(1), 44–51. https://doi.org/10.1016/j.rasd.2013.10.003

Ehlers, S., Gillberg, C., & Wing, L. (1999). A screening questionnaire for asperger syndrome and other high-functioning autism spectrum disorders in school age children. *Journal of Autism and Developmental Disorders*, *29*(2), 129–141. https://doi.org/10.1023/A:1023040610384

Eigsti, I.-M., de Marchena, A. B., Schuh, J. M., & Kelley, E. (2011). Language acquisition in autism spectrum disorders: A developmental review. *Research in Autism Spectrum Disorders*, *5*(2), 681–691. https://doi.org/10.1016/j.rasd.2010.09.001

Fatemi, S. H., Halt, A. R., Stary, J. M., Kanodia, R., Schulz, S. C., & Realmuto, G. R. (2002). Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. *Biological Psychiatry*, *52*(8), 805–810. https://doi.org/10.1016/S0006-3223(02)01430-0

Fatemi, S. H., Reutiman, T. J., Folsom, T. D., Rustan, O. G., Rooney, R. J., & Thuras, P. D. (2014). Downregulation of $GABA_A$ receptor protein subunits $\alpha6$, $\beta2$, δ, ϵ, $\gamma2$, θ, and $\rho2$ in superior frontal cortex of subjects with autism. *Journal of Autism and Developmental Disorders*, *44*(8), 1833–1845. https://doi.org/10.1007/s10803-014-2078-x

Fatemi, S. H., Reutiman, T. J., Folsom, T. D., & Thuras, P. D. (2009). $GABA_A$ receptor downregulation in brains of subjects with autism. *Journal of Autism and Developmental Disorders*, *39*(2), 223–230. https://doi.org/10.1007/s10803-008-0646-7

Frank, S. M., Becker, M., Qi, A., Geiger, P., Frank, U. I., Rosedahl, L. A., Malloni, W. M., Sasaki, Y., Greenlee, M. W., & Watanabe, T. (2022). Efficient learning in children with rapid GABA boosting during and after training. *Current Biology*, *32*(23), 5022–5030. https://doi.org/10.1016/j.cub.2022.10.021

Frazier, T. W., Whitehouse, A. J., Leekam, S. R., Carrington, S. J., Alvares, G. A., Evans, D. W., Hardan, A. Y., & Uljarević, M. (2023). Reliability of the commonly used and newly-developed autism measures. *Journal of Autism and Developmental Disorders*, 1–12. https://doi.org/10.1007/s10803-023-05967-y

Fung, L. K., Flores, R. E., Gu, M., Sun, K. L., James, D., Schuck, R. K., Jo, B., Park, J. H., Lee, B. C., Jung, J. H., Kim, S. E., Saggar, M., Sacchet, M. D., Warnock, G., Khalighi, M. M., Spielman, D., Chin, F. T., & Hardan, A. Y. (2021). Thalamic and prefrontal GABA concentrations but not $GABA_A$ receptor densities are altered in high-functioning adults with autism spectrum disorder. *Molecular Psychiatry*, *26*(5), 1634–1646. https://doi.org/10.1007/s10803-023-05967-y

Gabard-Durnam, L. J., Mendez Leal, A. S., Wilkinson, C. L., & Levin, A. R. (2018). The Harvard automated processing pipeline for electroencephalography (HAPPE): Standardized processing software for developmental and high-artifact data. *Frontiers in Neuroscience*, *12*, 97. https://doi.org/10.3389/fnins.2018.00097

Gaetz, W., Bloy, L., Wang, D., Port, R. G., Blaskey, L., Levy, S., & Roberts, T. P. (2014). GABA estimation in the brains of children

on the autism spectrum: Measurement precision and regional cortical variation. *NeuroImage*, *86*, 1–9. https://doi.org/10.1016/j.neuroimage.2013.05.068

Harris, A. D., Wang, Z., Ficek, B., Webster, K., Edden, R. A., & Tsapkini, K. (2019). Reductions in GABA following a tDCS-language intervention for primary progressive aphasia. *Neurobiology of Aging*, *79*, 75–82. https://doi.org/10.1016/j.neurobiolaging.2019.03.011

Hassan, T. H., Abdelrahman, H. M., Fattah, N. R. A., El-Masry, N. M., Hashim, H. M., El-Gerby, K. M., & Fattah, N. R. A. (2013). Blood and brain glutamate levels in children with autistic disorder. *Research in Autism Spectrum Disorders*, *7*(4), 541–548. https://doi.org/10.1016/j.rasd.2012.12.005

Hegarty, J. P., Weber, D. J., Cirstea, C. M., & Beversdorf, D. Q. (2018). Cerebro-cerebellar functional connectivity is associated with cerebellar excitation–inhibition balance in autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *48*(10), 3460–3473. https://doi.org/10.1007/s10803-018-3613-y

Hollestein, V., Poelmans, G., Forde, N. J., Beckmann, C. F., Ecker, C., Mann, C., Schaefer, T., Moessnang, C., Baumeister, S., Banaschewski, T., Bourgeron, T., Loth, E., Dell'Acqua, F., Murphy, D. G. M., Puts, N. A., Tillmann, J., Charman, T., Jones, E. J. H., Mason, L., … Naaijen, J. (2023). Excitatory/inhibitory imbalance in autism: The role of glutamate and GABA gene-sets in symptoms and cortical brain structure. *Translational Psychiatry*, *13*(1), 18. https://doi.org/10.1038/s41398-023-02317-5

Horder, J., Lavender, T., Mendez, M., O'Gorman, R., Daly, E., Craig, M., Lythgoe, D., Barker, G., & Murphy, D. (2013). Reduced subcortical glutamate/glutamine in adults with autism spectrum disorders: A [1H] MRS study. *Translational Psychiatry*, *3*(7), e279. https://doi.org/10.1038/tp.2013.53

Kilb, W. (2012). Development of the GABAergic system from birth to adolescence. *The Neuroscientist*, *18*(6), 613–630. https://doi.org/10.1177/1073858411422114

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Research Reviews*, *29*(2–3), 169–195. https://doi.org/10.1016/S0165-0173(98)00056-3

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2017). lmerTest package: Tests in linear mixed effects models. *Journal of Statistical Software*, *82*(13), 1–26. https://doi.org/10.18637/jss.v082.i13

Lam, K. S., & Aman, M. G. (2007). The Repetitive Behavior Scale-Revised: Independent validation in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *37*(5), 855–866. https://doi.org/10.1007/s10803-006-0213-z

Lewine, J. D., Andrews, R., Chez, M., Patil, A.-A., Devinsky, O., Smith, M., Kanner, A., Davis, J. T., Funke, M., Jones, G., Chong, B., Provencal, S., Weisend, M., Lee, R. R., & Orrison, W. W. (1999). Magnetoencephalographic patterns of epileptiform activity in children with regressive autism spectrum disorders. *Pediatrics*, *104*(3), 405–418. https://doi.org/10.1542/peds.104.3.405

Luján, R., Shigemoto, R., & López-Bendito, G. (2005). Glutamate and GABA receptor signalling in the developing brain. *Neuroscience*, *130*(3), 567–580. https://doi.org/10.1016/j.neuroscience.2004.09.042

Maier, S., Düppers, A. L., Runge, K., Dacko, M., Lange, T., Fangmeier, T., Riedel, A., Ebert, D., Endres, D., Domschke, K., Perlov, E., Nickel, K., & Tebartz van Elst, L. (2022). Increased prefrontal GABA concentrations in adults with autism spectrum disorders. *Autism Research*, *15*(7), 1222–1236. https://doi.org/10.1002/aur.2740

Mannion, A., Leader, G., & Healy, O. (2013). An investigation of comorbid psychological disorders, sleep problems, gastrointestinal symptoms and epilepsy in children and adolescents with autism spectrum disorder. *Research in Autism Spectrum Disorders*, *7*(1), 35–42. https://doi.org/10.1016/j.rasd.2012.05.002

Menn, K. H., Männel, C., & Meyer, L. (2023). Does electrophysiological maturation shape language acquisition? *Perspectives on Psychological Science*, 174569162311515. https://doi.org/10.1177/17456916231151584

Menn, K. H., Michel, C., Meyer, L., Hoehl, S., & Männel, C. (2022). Natural infant-directed speech facilitates neural tracking of prosody. *NeuroImage*, *251*, 118991. https://doi.org/10.1016/j.neuroimage.2022.118991

Menn, K. H., Ward, E. K., Braukmann, R., Van den Boomen, C., Buitelaar, J., Hunnius, S., & Snijders, T. M. (2022). Neural tracking in infancy predicts language development in children with and without family history of autism. *Neurobiology of Language*, *3*(3), 495–514. https://doi.org/10.1162/nol_a_00074

Oblak, A. L., Gibbs, T. T., & Blatt, G. J. (2009). Decreased $GABA_A$ receptors and benzodiazepine binding sites in the anterior cingulate cortex in autism. *Autism Research*, *2*(4), 205–219. https://doi.org/10.1002/aur.88

Oblak, A. L., Gibbs, T. T., & Blatt, G. J. (2010). Decreased $GABA_B$ receptors in the cingulate cortex and fusiform gyrus in autism. *Journal of Neurochemistry*, *114*(5), 1414–1423. https://doi.org/10.1111/j.1471-4159.2010.06858.x

Oblak, A. L., Gibbs, T. T., & Blatt, G. J. (2011). Reduced $GABA_A$ receptors and benzodiazepine binding sites in the posterior cingulate cortex and fusiform gyrus in autism. *Brain Research*, *1380*, 218–228. https://doi.org/10.1016/j.brainres.2010.09.021

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J. M. (2011). FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational intelligence and neuroscience*, *2011*, 1–9. https://doi.org/10.1155/2011/156869

Orekhova, E. V., Stroganova, T. A., Prokofyev, A. O., Nygren, G., Gillberg, C., & Elam, M. (2008). Sensory gating in young children with autism: Relation to age, IQ, and EEG gamma oscillations. *Neuroscience Letters*, *434*(2), 218–223. https://doi.org/10.1016/j.neulet.2008.01.066

Page, L. A., Daly, E., Schmitz, N., Simmons, A., Toal, F., Deeley, Q., Clin, A. D., Psych, F., McAlonan, G. M., Murphy, K. C., & Murphy, D. G. (2006). In vivo ^{1}H-magnetic resonance spectroscopy study of amygdala-hippocampal and parietal regions in autism. *American Journal of Psychiatry*, *163*(12), 2189–2192. https://doi.org/10.1176/ajp.2006.163.12.2189

Perrin, F., Pernier, J., Bertrand, O., & Echallier, J. F. (1989). Spherical splines for scalp potential and current density mapping. *Electroencephalography and Clinical Neurophysiology*, *72*(2), 184–187. https://doi.org/10.1016/0013-4694(89)90180-6

Poil, S.-S., Hardstone, R., Mansvelder, H. D., & Linkenkaer-Hansen, K. (2012). Critical-state dynamics of avalanches and oscillations jointly emerge from balanced excitation/inhibition in neuronal networks. *Journal of Neuroscience*, *32*(29), 9817–9823. https://doi.org/10.1523/JNEUROSCI.5990-11.2012

Purcell, A., Jeon, O., Zimmerman, A., Blue, M., & Pevsner, J. (2001). Postmortem brain abnormalities of the glutamate neurotransmitter system in autism. *Neurology*, *57*(9), 1618–1628. https://doi.org/10.1212/WNL.57.9.1618

Ramoz, N., Reichert, J. G., Smith, C. J., Silverman, J. M., Bespalova, I. N., Davis, K. L., & Buxbaum, J. D. (2004). Linkage and association of the mitochondrial aspartate/glutamate carrier SLC25A12 gene with autism. *American Journal of Psychiatry*, *161*(4), 662–669. https://doi.org/10.1176/appi.ajp.161.4.662

Robinson, D. L. (1989). The neurophysiological bases of high IQ. *International Journal of Neuroscience*, *46*(3–4), 209–234. https://doi.org/10.3109/00207458908986260

Rojas, D. C., Becker, K. M., & Wilson, L. B. (2015). Magnetic resonance spectroscopy studies of glutamate and GABA in autism: Implications for excitation-inhibition imbalance theory. *Current Developmental Disorders Reports*, *2*, 46–57. https://doi.org/10.1007/s40474-014-0032-4

Rojas, D. C., Singel, D., Steinmetz, S., Hepburn, S., & Brown, M. S. (2014). Decreased left perisylvian GABA concentration in children

with autism and unaffected siblings. *NeuroImage*, *86*, 28–34. https://doi.org/10.1016/j.neuroimage.2013.01.045

Rubenstein, J., & Merzenich, M. M. (2003). Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior*, *2*(5), 255–267. https://doi.org/10.1034/j.1601-183X.2003.00037.x

Rutter, M., Bailey, A., & Lord, C. (2003). *The social communication questionnaire: Manual*. Western Psychological Services.

Said, C. P., Egan, R. D., Minshew, N. J., Behrmann, M., & Heeger, D. J. (2013). Normal binocular rivalry in autism: Implications for the excitation/inhibition imbalance hypothesis. *Vision Research*, *77*, 59–66. https://doi.org/10.1016/j.visres.2012.11.002

Sassenhagen, J., & Alday, P. M. (2016). A common misapplication of statistical inference: Nuisance control with null-hypothesis significance tests. *Brain and Language*, *162*, 42–45. https://doi.org/10.1016/j.bandl.2016.08.001

Shew, W. L., Yang, H., Petermann, T., Roy, R., & Plenz, D. (2009). Neuronal avalanches imply maximum dynamic range in cortical networks at criticality. *Journal of Neuroscience*, *29*(49), 15595–15600. https://doi.org/10.1523/JNEUROSCI.3864-09.2009

Shibata, K., Sasaki, Y., Bang, J. W., Walsh, E. G., Machizawa, M. G., Tamaki, M., Chang, L.-H., & Watanabe, T. (2017). Overlearning hyperstabilizes a skill by rapidly making neurochemical processing inhibitory-dominant. *Nature Neuroscience*, *20*(3), 470–475. https://doi.org/10.1038/nn.4490

Shimmura, C., Suzuki, K., Iwata, Y., Tsuchiya, K. J., Ohno, K., Matsuzaki, H., Iwata, K., Kameno, Y., Takahashi, T., Wakuda, T., Nakamura, K., Hashimoto, K., & Mori, N. (2013). Enzymes in the glutamate-glutamine cycle in the anterior cingulate cortex in postmortem brain of subjects with autism. *Molecular Autism*, *4*(1), 1–7. https://doi.org/10.1186/2040-2392-4-6

Shu, Y., Hasenstaub, A., & McCormick, D. A. (2003). Turning on and off recurrent balanced cortical activity. *Nature*, *423*(6937), 288–293. https://doi.org/10.1038/nature01616

Silveri, M. M., Sneider, J. T., Crowley, D. J., Covell, M. J., Acharya, D., Rosso, I. M., & Jensen, J. E. (2013). Frontal lobe γ-aminobutyric acid levels during adolescence: Associations with impulsivity and response inhibition. *Biological Psychiatry*, *74*(4), 296–304. https://doi.org/10.1016/j.biopsych.2013.01.033

Sohal, V. S., & Rubenstein, J. L. (2019). Excitation-inhibition balance as a framework for investigating mechanisms in neuropsychiatric disorders. *Molecular Psychiatry*, *24*(9), 1248–1257. https://doi.org/10.1038/s41380-019-0426-0

Spielberg, J. M., Galarce, E. M., Ladouceur, C. D., McMakin, D. L., Olino, T. M., Forbes, E. E., Silk, J. S., Ryan, N. D., & Dahl, R. E. (2015). Adolescent development of inhibition as a function of ses and gender: Converging evidence from behavior and fMRI. *Human Brain Mapping*, *36*(8), 3194–3203. https://doi.org/10.1002/hbm.22838

Sun, Y. J., Wu, G. K., Liu, B.-H., Li, P., Zhou, M., Xiao, Z., Tao, H. W., & Zhang, L. I. (2010). Fine-tuning of pre-balanced excitation and inhibition during auditory cortical development. *Nature*, *465*(7300), 927–931. https://doi.org/10.1038/nature09079

Team, R. C. (2021). *R: A language and environment for statistical computing*. R foundation for statistical computing.

Team, R. (2020). Rstudio: Integrated development for R. rstudio.

Tebartz van Elst, L., Maier, S., Fangmeier, T., Endres, D., Mueller, G. T., Nickel, K., Ebert, D., Lange, T., Hennig, J., Biscaldi, M., Riedel, A., & Perlov, E. (2014). Disturbed cingulate glutamate metabolism in adults with high-functioning autism spectrum disorder: Evidence in support of the excitatory/inhibitory imbalance hypothesis. *Molecular Psychiatry*, *19*(12), 1314–1325. https://doi.org/10.1038/mp.2014.62

Wang, J., Barstein, J., Ethridge, L. E., Mosconi, M. W., Takarae, Y., & Sweeney, J. A. (2013). Resting state EEG abnormalities in autism spectrum disorders. *Journal of Neurodevelopmental Disorders*, *5*(1), 1–14. https://doi.org/10.1186/1866-1955-5-24

Wechsler, D. (1992). *Wechsler individual achievement test*. The Psychological Corporation, Harcourt Brace.

Wechsler, D. (2014). *Wisc-v: Technical and interpretive manual*. NCS Pearson.

Wehr, M., & Zador, A. M. (2003). Balanced inhibition underlies tuning and sharpens spike timing in auditory cortex. *Nature*, *426*(6965), 442–446. https://doi.org/10.1038/nature02116

Wickham, H. (2016). *Ggplot2: Elegant graphics for data analysis*. Springer.

Winkler, I., Debener, S., Müller, K.-R., & Tangermann, M. (2015). On the influence of high-pass filtering on ICA-based artifact reduction in EEG-ERP. In *2015 37th annual international conference of the IEEE engineering in medicine and biology society (EMBC)*, pp. 4101–4105. https://doi.org/10.1109/EMBC.2015.7319296

Winkler, I., Haufe, S., & Tangermann, M. (2011). Automatic classification of artifactual ICA-components for artifact removal in EEG signals. *Behavioral and Brain Functions*, *7*(1), 1–15. https://doi.org/10.1186/1744-9081-7-30

Yip, J., Soghomonian, J.-J., & Blatt, G. J. (2007). Decreased GAD67 mRNA levels in cerebellar Purkinje cells in autism: Pathophysiological implications. *Acta Neuropathologica*, *113*(5), 559–568. https://doi.org/10.1007/s00401-006-0176-3

SUPPORTING INFORMATION

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

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