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Number of Alpha Peaks in the Electroencephalogram Is Associated With Clinical Phenotype and Copy Number Variants in Youths With Autism

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ABSTRACT

BACKGROUND: Electroencephalography (EEG) alpha-band neural activity has previously been reported to be altered in autism spectrum disorder (ASD), but no studies have addressed different parameters of alpha-band activity and their relationship to clinical phenotype and copy number variants (CNVs) in ASD.

METHODS: The study included 310 youths with and without ASD and consisted of resting-state EEG, behavioral phenotyping, and genome-wide CNV analysis.

RESULTS: First, the results revealed that alpha peak power was reduced in ASD, and younger-age autistic males had a higher number of peaks compared with younger-age autistic females. Second, a higher number of alpha peaks was related to lower language skills and a higher presence of autistic traits. Finally, a higher number of alpha peaks was related to a higher number of CNVs.

CONCLUSIONS: In this study, we explored a novel measure (number of peaks) associated with both clinical phenotype and genetic burden and provide evidence that supports alterations in alpha-band activity in ASD.

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Autism spectrum disorder (ASD), diagnosed based on difficulties in social communication/interaction and restricted and repetitive behaviors (RRBs), is a heterogeneous neurodevelopmental condition with a prevalence of 1 in 31 children (1,2). According to a number of studies, the neurobiology of ASD can be related to different mechanisms, including excitation/inhibition (E/I) imbalance, disruptions of the thalamocortical circuit, and altered attention systems (3–9). Electroencephalography (EEG) is a technique for recording neural activity, is well suited to biomarker development in neurodevelopmental conditions, and can be collected over brief recording periods (10).

Recent studies using noninvasive scalp EEG have implicated several metrics as being associated with the neurobiology of ASD, and one of those metrics is alpha-band (8–12 Hz in adults) neural activity. Abnormalities in different parameters of this neural activity have been detected in individuals with ASD compared with typically developing (TD) control individuals. For example, most studies have revealed alpha power reduction in autistic individuals (11–15), and this reduction was related to different mechanisms, such as E/I imbalance (16–19) due to abnormal functioning of the GABAergic (gamma-aminobutyric acidergic) inhibitory system (15), disruptions in the thalamocortical circuit in ASD (9,20), and involvement of children's attention to the task (21,22). Alpha peak frequency has also been reported to be atypical in ASD, tending to be lower compared with TD children and having an atypical developmental trajectory (23,24). Finally, frontal alpha asymmetry in autistic individuals/infants at risk for developing ASD had reverse pattern and atypical age-related change (25,26).

Given the significant contribution of genetics to some of the parameters of resting-state EEG spectral power (27), recent studies have investigated relationships between alpha oscillations and genetic markers in different clinical populations (28–30) using genome-wide copy number variant (CNV) and genome-wide association analyses. However, these studies have focused on raw alpha power consisting of both periodic and aperiodic neural activity and have not used other parameters (e.g., alpha peak frequency, number of alpha peaks). Only one study has addressed aperiodic-adjusted alpha-band parameters and genetic markers (CNVs), but in a mixed group of children with neurodevelopmental disorders (27). No such studies have been conducted with autistic individuals to examine interrelations among EEG aperiodic-adjusted alpha-

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band parameters, clinical phenotype, and genetic variables. We aim to fill this gap.

The main goal of the current study was to address alpha-band activity and its relation to clinical phenotype and genetics in a large group of youths with ASD by implementing a multimodal approach including resting-state EEG, behavioral phenotyping, and genome-wide CNV analysis. First, using a novel parameterization algorithm (31), we aimed to calculate aperiodic-adjusted alpha peak parameters (power, frequency, asymmetry, and additional parameters such as the number of peaks) by removing the aperiodic signal [which influences largely oscillatory component of the spectral power (32)] and compare these parameters in the ASD and TD groups. Second, in the autistic cohort, we aimed to assess the associations between alpha peak parameters and behavioral/clinical measures. Finally, we addressed the relationship between alpha peak parameters and genetic variables abstracted from genome-wide CNV analysis (total CNV size, number of genes within the CNVs, and number of CNVs). Therefore, this study focuses on comprehensive characterization of alpha peak parameters and their relationship with both behavioral and genetic markers in ASD.

METHODS AND MATERIALS

Participants

Two groups of participants (N = 310; ages 8–17 years) with valid EEG data were included in the analysis: 164 youths with ASD (72 female) and 146 TD youths (68 female). The data were collected from 4 sites as a part of the GENDAAR Autism Center for Excellence network, including Seattle Children's Research Institute, Boston Children's Hospital/Harvard Medical School, the University of California Los Angeles, and Yale University, with the data coordinating center located at the University of Southern California. Deidentified data were provided to the National Database of Autism Research (NDAR) (NDAR study #2021).

The study was performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all parents of children participating in the study; children provided written assent. Demographic information is presented in Table 1.

Behavioral Assessment

All youths with ASD were diagnosed based on DSM-IV-TR or DSM-5 (1,33), and diagnoses were confirmed with the Autism Diagnostic Observation Schedule-Second Edition (ADOS-2) (34), Autism Diagnostic Interview-Revised (35), caregiver-reported developmental history, and expert clinical judgment. For both groups of participants, nonverbal IQ was assessed with the Differential Ability Scales-Second Edition (DAS-II) School Aged Cognitive Battery (36), and language skills were measured with the Clinical Evaluation of Language Fundamentals-4 (CELF-4) (37). Additional phenotypic characteristics were obtained from the Social Responsiveness Scale-2 (SRS-2) (38) and the Vineland Adaptive Behavior Scales-2 (VABS-2) (39).

Table 1. Demographic Characteristics of Study Participants

Characteristics	Group		Statistics
	ASD	TD	
Female/Male	72/92	68/78	–
Age, Months	[96.0–215.0] 151.0 (35.0)	[96.0–216.0] 156.6 (35.0)	$t_{303.6} = -1.41$, $p = .16$
Nonverbal IQ	[57.0–158.0] 100.2 (17.5)	[74.0–147.0] 109.1 (15.1)	$t_{307.7} = -4.83$, $p < .001$
CELF Core Language SS	[40.0–127.0] 91.4 (20.9)	[81.0–134.0] 110.7 (11.2)	$t_{179.6} = -8.82$, $p < .001$
VABS-2			
Communication SS	[49.0–122.0] 76.1 (11.8)	[67.0–135.0] 99.3 (13.2)	$t_{289.8} = -16.07$, $p < .001$
Socialization SS	[46.0–118.0] 72.6 (12.1)	[74.0–145.0] 101.2 (12.6)	$t_{297.6} = -20.20$, $p < .001$
Daily living skills SS	[51.0–119.0] 76.4 (13.8)	[58.0–130.0] 97.7 (14.1)	$t_{298.3} = -13.33$, $p < .001$
SRS Total T Score	[39.0–106.0] 75.3 (11.5)	[37.0–60.0] 43.8 (5.0)	$t_{206.15} = 30.39$, $p < .001$
ADOS-2			
CSS total	[4.0–10.0] 6.9 (1.8)	NA	–
CSS SA	[3.0–10.0] 7.0 (1.9)	NA	–
CSS RRB	[0.0–10.0] 6.4 (2.9)	NA	–
Ethnicity			
Hispanic or Latino	17 (10%)	20 (14%)	–
Not Hispanic or Latino	98 (60%)	94 (64%)	–
Other	2 (1%)	2 (1%)	–
Not Answered	47 (29%)	30 (21%)	–
Race			
Asian	4 (2%)	8 (5%)	–
Black or African American	6 (5%)	9 (6%)	–
Mixed Race	17 (10%)	12 (8%)	–
Other	4 (2%)	1 (1%)	–
White	86 (52%)	86 (59%)	–
Not Answered	47 (29%)	30 (21%)	–

Values are presented as n, [range] mean (SD), or n (%).

ADOS-2, Autism Diagnostic Observation Schedule, Second Edition; ASD, autism spectrum disorder; CELF, Clinical Evaluation of Language Fundamentals; CSS, calibrated severity score; NA, not applicable; RRB, Restrictive and Repetitive Behavior; SA, Social Affect; SRS, Social Responsiveness Scale; SS, standard score; TD, typically developing; VABS-2, Vineland Adaptive Behavior Scales-2.

Youths with ASD were excluded if they had known chromosomal syndromes related to ASD (e.g., fragile X syndrome), co-occurring neurological disorders (e.g., epilepsy), significant visual and auditory impairments, or sensorimotor difficulties that would prevent completion of study procedures. All participants with ASD had either verbal or nonverbal IQ $\geq$ 70. TD youths had no familial history of ASD and no elevation of autistic traits according to the SRS-2 (T score $\leq$ 60) or the Social Communication Questionnaire (40) (raw score $<$ 11), and all had normal nonverbal IQ (see Table 1).

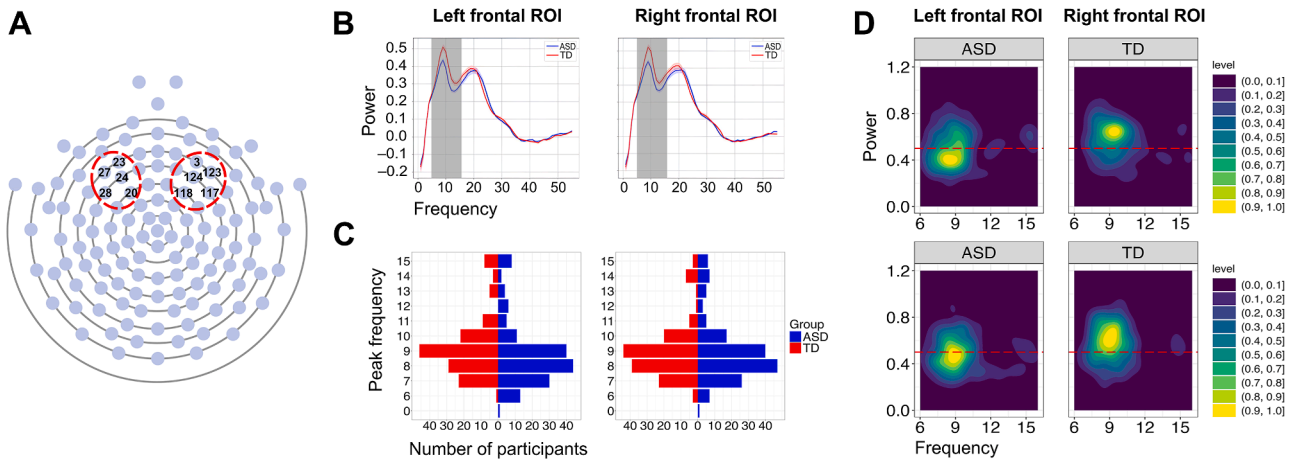

Figure 1. Alpha-band neural activity in the left and right frontal regions of interest (ROIs) in youths with autism spectrum disorder (ASD) and typically developing (TD) control participants. **(A)** Electroencephalography (EEG) cap with highlighted electrodes used for the analysis; **(B)** aperiodic-adjusted power spectra in the left and right ROIs at the alpha frequency range (6–15.99 Hz); **(C)** the distribution of central frequency in ASD and TD groups of youths; **(D)** heatmaps representing the distribution of alpha peak power in both groups of youths (dashed red line is set to 0.5 for visualization purposes).

EEG Data Acquisition, Processing, and Alpha Peak Identification

EEG data were collected with EGI 128-channel Net Amps 300 system with HydroCel nets (Magstim EGI Inc.), using Net Station 4.4.2, 4.5.1, or 4.5.2 with a standard Net Station acquisition template. Nets were available without outriders (eye electrodes 125, 126, 127, and 128) for participants with facial sensory sensitivities. Data were collected at 500-Hz sampling rate, referenced to Cz electrode (vertex), and impedances were $<$50 kΩ.

Resting-state EEG was acquired via an eyes-open condition. The recording session consisted of 3 runs of 6 $\times$ 16 second blocks of videos (dynamic screen saver–type images that had limited or slow movement). To calculate power spectral density (PSD), we used BEAPP (41) in MATLAB (version 2021a; The MathWorks, Inc.), consisting of 1) formatting the MFF file for MATLAB; 2) bandpass filtering 1 to 100 Hz; 3) downsampling from 500 Hz to 250 Hz; 4) implementation of the HAPPE module for artifact detection and rejection (42), including removal of 60-Hz line noise, rejection of bad channels, wavelet enhanced thresholding, independent component analysis with automated component rejection, bad channel interpolation, and rereferencing to average; 5) segmentation of the continuous file into 1-second epochs; 6) rejection of bad segments (±40 μV); and 7) calculation of the PSD using Hanning window on clean segments. A total of 10 electrodes over the frontal region were used for the analysis (electrodes 23, F3–24, 27, 28, 20 for the left regions of interest [ROIs]; 3, 117, 123, F4–124, 118 for the right ROI) (see Figure 1). PSD was calculated for each electrode and averaged within these ROIs. As the raw PSD includes both periodic and aperiodic components (31), we used the *specparam* toolbox (32) in Python version 3.10 to parametrize the neural spectral power and remove aperiodic component. This allowed us to estimate the alpha peak parameters without the non-oscillatory component of the PSD. We used the following settings to model aperiodic and periodic components: peak_width_limit = [1.5, 6], *n*_peaks = 6, peak_height = 0.10, peak_threshold = 2, and frequency_range = [1, 55]. We focused on the 6 to 15.99-Hz frequency range [the range from (43,44)] using the output of *specparam* modeling to identify individual alpha peak power, peak frequency, and the number of peaks for each participant. The model fits, R^2, and errors are provided in the Supplement—Specparam model fit parameters. The decision to extract the peak parameters from a slightly wider frequency range was motivated by the anticipated developmental changes in peak frequency in young children (44,45) as well as the absence of alpha peaks in the adult-like traditional frequency range in the large number of participants from our study (see the Supplement—Frequency ranges for alpha-band activity). If a participant had more than one peak in the alpha range, the power and peak frequency were taken for the most prominent/higher peak. The asymmetry was calculated as a difference between right and left ROI power. The groups of youths did not differ in the number of artifact-free epochs (ASD group: $\text{mean}_{\text{epoch}}$ = 101.06, range 62–123; TD group: $\text{mean}_{\text{epoch}}$ = 101.85, range 78–123; $t_{303.18} = -0.47$, $p = .63$).

Genotyping and CNV Detection

Blood samples were collected from the participants with ASD to obtain genomic DNA and processed by the Rutgers University Cell and Data Repository using standard protocols (Gentra Puregene Blood DNA extraction kit; Qiagen). All DNA samples were hybridized and genotyped by the HumanOmni2.5M-8 BeadChip microarray (Illumina) to minimize batch effects and variation. Genotyping data were analyzed with PLINK version 1.07 (46) using the forward stand and confirmed the reported sex of all participants.

CNV detection (duplications and deletions) was performed using 3 algorithms: PennCNV version 1.0.4, QuantiSNP version 1.1, and GNOSIS (47). Analysis and merging of CNV predictions used CNVision (47). All rare genic CNVs [≥50% of CNV at ≤1% frequency in the Database of Genomic Variants

(47)] (hereafter, CNVs) predicted by at least PennCNV and QuantiSNP and having a CNVision p_{CNV} of ≤.001, i.e., those considered high-quality predictions (48), were obtained for further analysis. Subsequent analyses combined duplications and deletions to maximize the number of CNVs available for examination; separating the 2 types led to low numbers and low statistical power.

Statistical Analysis

Statistical analysis was performed in R (49) using the *lme4* package (50), and the data were plotted with *ggplot2* (51). A correction for multiple comparisons (false discovery rate [FDR]) was applied to each set of analyses, and *p* values were corrected with *p.adjust.method* in R.

RESULTS

Descriptive Summary of EEG Measures

In almost all participants, we were able to identify the alpha peak, except in 2 cases (one participant with ASD did not have a peak in the left ROI, and another participant with ASD did not have a peak in the right ROI). The shape of PSD for each ROI as well as alpha peak frequency and peak power distribution across participants are shown in Figure 1. Individual PSDs for both groups of children can be found in the Supplement. Most participants had alpha peak in a canonical adult-like frequency range (mean frequency, left ROI = 9.5 Hz, right ROI = 9.5 Hz) (Figure 1C). The range of the peak number was 1 to 3, with a mean of 1.6 for each group and ROI.

Between-Group Comparisons on Alpha Peak Parameters and Asymmetry

To perform between-group comparisons for the left and right frontal ROIs in alpha peak power, peak frequency, and the number of peaks, we fitted linear models with the EEG measures as dependent variables and tested for main effects of group, sex, and age.

The outputs of the models are presented in Table 2. To summarize, first, alpha peak power was significantly reduced in the ASD group in both ROIs (Figure 2); no sex or age effects were identified. Second, for the alpha peak frequency, no significant effects were shown (Figure 2). Third, the number of alpha peaks was related to sex and age, such that the males had a higher number of peaks in comparison with females, and there was an age-related decrease in the number of peaks in the left ROI. Finally, the frontal alpha asymmetry increased with age, reflecting possible maturational changes in the frontal brain regions associated with executive functions (Figure 2).

Sex and Age Effects in the Number of Alpha Peaks

As the number of alpha peaks was related to both sex and age, we conducted the follow-up exploratory analysis in both ASD and TD youths. We fitted generalized liner models within each group with the number of peaks as a dependent variable and the effect of sex nested within the age window (Age1 = 8–11 years, Age2 = 12–15 years, Age3 = 16–18 years).

In the TD group, there was no relationship between the number of peaks and sex in any time window in either ROI (left ROI: Age1, $\beta = 0.65$, SE = 0.63, $z = 1.04$, $p = .30$; Age2, $\beta = 0.37$, SE = 0.54, $z = 0.68$, $p = .49$; Age3, $\beta = 0.29$, SE = 0.73, $z = 0.39$, $p = .70$; right ROI: Age1, $\beta = 0.41$, SE = 0.57, $z = 0.73$, $p = .46$; Age2, $\beta = 0.70$, SE = 0.55, $z = 1.28$, $p = .20$; Age3, $\beta = -0.25$, SE = 0.73, $z = -0.34$, $p = .73$) (Figure 3).

In contrast, in the ASD group, in both the left and right ROIs, there was a relationship between sex and the number of peaks in the 8- to 11-year-old group, such that ASD males had a higher number of peaks in comparison with ASD females (left ROI: $\beta = 1.50$, SE = 0.51, $z = 2.94$, FDR–corrected $p = .006$; right ROI: $\beta = 1.36$, SE = 0.49, $z = 2.74$, FDR-corrected $p = .006$). In other age windows, there were no significant effects (left ROI: Age2, $\beta = 0.05$, SE = 0.52, $z = 0.10$, $p = .92$; Age3, $\beta = 0.50$, SE = 0.76, $z = 0.66$, $p = .51$; right ROI: Age2, $\beta = 0.30$, SE = 0.53, $z = 0.58$, $p = .56$; Age3, $\beta = -0.14$, SE = 0.76, $z = -0.18$, $p = .85$) (see Figure 3).

Relationship Between Alpha Peak Parameters and Clinical Phenotype in Youths With ASD

To examine the relationships between alpha peak parameters and clinical phenotype in the ASD group, we fitted linear models for the left and right ROIs with the EEG measures as dependent variables and included 6 predictors: nonverbal IQ, language skills (CELF-4 Core Language standard score [SS]), a measure of RRB (SRS-2 RRB T score), and social skills (VABS-2 Socialization SS) and included age and sex as covariates.

After correction for multiple comparisons, 2 effects remained statistically significant, including the relationship between the number of alpha peaks and language skills ($\beta = -0.05$, SE = 0.01, $z = -3.03$, $p = .004$) and between the number of alpha peaks and RRB ($\beta = 0.08$, SE = 0.02, $z = 3.10$, $p = .002$) in the right ROI (Table 3 and Figure 4). A higher number of peaks was associated with lower language skills and a higher presence of autistic traits. As the number of alpha peaks was also related to age, we conducted a follow-up Pearson's correlation analysis between behavioral measures (CELF Core Language SS and SRS RRB T score) and age to confirm that the observed brain-behavior relationships were not driven by the age effect. None of the behavioral measures were correlated with age (CELF: $r = 0.29$, FDR-corrected $p = .28$; RRB: $r = 0.10$, FDR-corrected $p = .18$).

Associations of Alpha Peak Parameters With Rare Genic CNVs in Youths With ASD

The last set of analyses addressed the relationships between EEG measures and the genetic variables abstracted from genome-wide CNV analysis in the ASD group. We calculated Spearman's correlations between EEG measures (alpha peak power, the number of alpha peaks, and the asymmetry) and genetic measures (total CNV size, number of genes within the CNVs, number of CNVs per individual). Peak frequency was excluded from the analysis because we did not find a between-group difference in this variable or the relationships with the clinical phenotype and age.

The summary of results is presented in Table 4. We identified a significant correlation between the number of alpha peaks in the left ROI and the number of CNVs. A greater

Table 2. Between-Group Comparisons in Electroencephalography Alpha Peak Parameters

			Analysis	
Measure	ASD	TD	Predictor	Model Output
Left Frontal ROI				
Peak Power	0.49 (0.15)	0.57 (0.15)	Group	$\beta = 0.09$, SE = 0.02, $t_{306} = 4.93$, $p < .001$***
			Sex	$\beta = 0.02$, SE = 0.02, $t_{306} = 1.94$, $p = .38$
			Age	$\beta = -0.00$, SE = 0.01, $t_{306} = -1.77$, $p = .16$
Peak Frequency, Hz	9.27 (2.26)	9.81 (2.09)	Group	$\beta = 0.55$, SE = 0.25, $t_{306} = 2.21$, $p = .06$
			Sex	$\beta = 0.35$, SE = 0.25, $t_{306} = 1.38$, $p = .17$
			Age	$\beta = -0.00$, SE = 0.00, $t_{306} = -0.15$, $p = .88$
Number of Peaks	1.63 (0.62)	1.66 (0.58)	Group	$\beta = 0.19$, SE = 0.24, $z = 0.80$, $p = .74$
			Sex	$\beta = 0.61$, SE = 0.24, $z = 2.57$, $p = .01$*
			Age	$\beta = -0.01$, SE = 0.00, $z = -2.48$, $p = .02$*
Right Frontal ROI				
Power	0.49 (0.15)	0.58 (0.16)	Group	$\beta = 0.00$, SE = 0.00, $t_{306} = 5.32$, $p < .001$***
			Sex	$\beta = 0.00$, SE = 0.00, $t_{306} = 0.87$, $p = .38$
			Age	$\beta = 0.00$, SE = 0.00, $t_{306} = 0.08$, $p = .93$
Peak Frequency, Hz	9.49 (2.25)	9.47 (1.83)	Group	$\beta = -0.03$, SE = 0.23, $t_{306} = -0.13$, $p = .89$
			Sex	$\beta = 0.42$, SE = 0.23, $t_{306} = 1.79$, $p = .14$
			Age	$\beta = 0.00$, SE = 0.00, $t_{306} = 1.42$, $p = .30$
Number of Peaks	1.61 (0.63)	1.65 (0.64)	Group	$\beta = 0.08$, SE = 0.23, $z = 0.34$, $p = .74$
			Sex	$\beta = 0.57$, SE = 0.23, $z = 2.48$, $p = .01$*
			Age	$\beta = -0.00$, SE = 0.00, $z = -0.52$, $p = .60$
Asymmetry	−0.00 (0.10)	0.01 (0.11)	Group	$\beta = 0.01$, SE = 0.01, $t_{306} = 0.53$, $p = .60$
			Sex	$\beta = -0.00$, SE = 0.01, $t_{306} = -0.46$, $p = .64$
			Age	$\beta = 0.00$, SE = 0.00, $t_{306} = 2.65$, $p < .008$**

Values are presented as mean (SD). All p values are false discovery rate corrected.
*$p < .05$, **$p < .01$, ***$p < .001$.
ASD, autism spectrum disorder; ROI, region of interest; TD, typically developing.

number of peaks was related to a higher number of CNVs ($r = 0.26$, FDR-corrected $p = .04$) (Figure 4).

Sex Differences in Clinical Measures in Younger Autistic Individuals

We identified that a greater number of alpha peaks was related to lower language skills and a higher presence of autistic traits as well as a higher number of peaks in autistic males in comparison with autistic females at younger ages (8–11 years). In addition, we showed that a greater number of peaks was associated with a higher number of CNVs. This exploratory follow-up analysis aimed to reveal whether younger-age male and female autistic individuals are different in their clinical/behavioral characteristics.

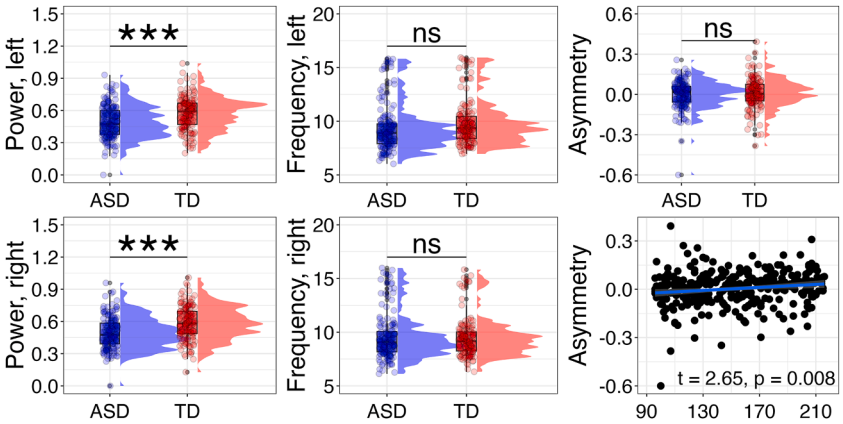

Figure 2. Between-group comparisons of the alpha peak parameters and age-related changes in the frontal alpha asymmetry (across the autism spectrum disorder [ASD] and typically developing [TD] groups; age in months). Significance is labeled with ***$p < .001$. All p values are false discovery rate corrected. ns, nonsignificant.

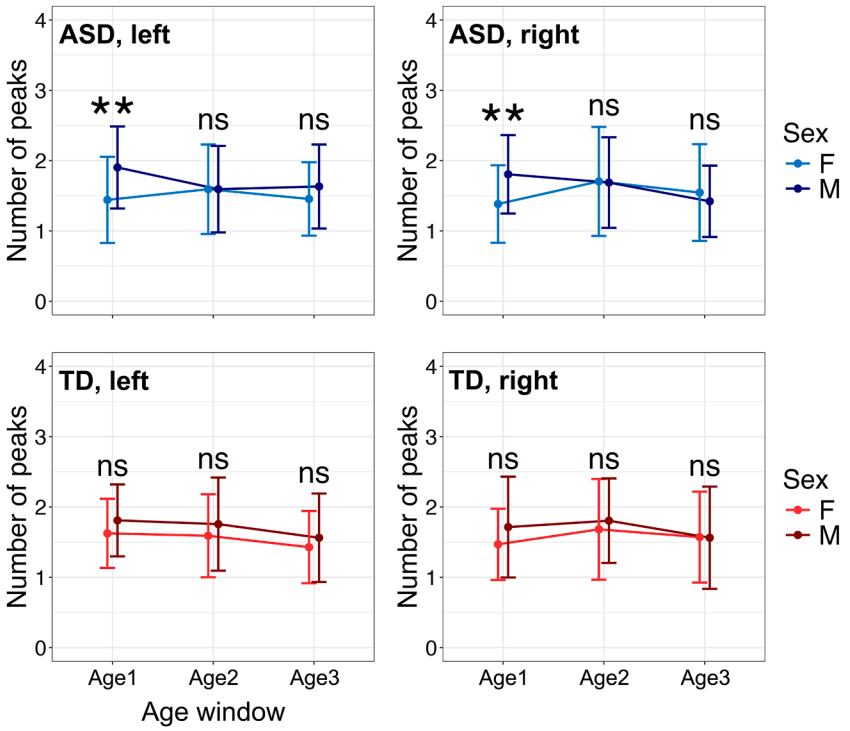

Figure 3. Sex differences in the number of alpha peaks in youths with and without autism spectrum disorder (ASD) at 3 age windows: T1 = 8 to 11 years, T2 = 12 to 15 years, T3 = 16 to 18 years. The significance is labeled with $^{**}p < .01$. All p values are false discovery rate corrected. F, female; M, male; ns, nonsignificant; TD, typically developing.

We fitted a generalized linear model with sex as the dependent variable and included all behavioral measures used before as well as the ADOS-2 calibrated total severity score as main effects. The results showed no difference between male and female ASD individuals on any measure (nonverbal IQ: $\beta = 0.01$, SE = 0.02, $z = 0.61$, $p = .543$; CELF-4 Core Language SS: $\beta = -0.00$, SE = 0.02, $z = -0.38$, $p = .702$; SRS-2 RRB T score: $\beta = 0.01$, SE = 0.03, $z = 0.43$, $p = .670$; VABS-2 Socialization SS: $\beta = -0.02$, SE = 0.03, $z = -0.70$, $p = .482$; ADOS-2 calibrated total severity score: $\beta = 0.18$, SE = 0.17, $z = 0.97$, $p = .33$).

DISCUSSION

The current study focused on alpha-band neural activity and its relationship with clinical phenotype and copy number variation in a large sample of youths with ASD. In general, the study replicated the previous findings of a broad reduction in alpha power in autistic individuals while revealing a novel measure (a number of alpha peaks) associated with both clinical phenotype and genetic markers.

Between-group comparisons in alpha peak parameters demonstrated that youths with ASD had reduced peak power compared with TD participants. This corresponds to previous findings that showed a similar alpha power reduction during rest in autistic individuals (11–15,52). Abnormalities in resting-state alpha power can be related to cortical E/I imbalance and altered thalamocortical connections in ASD (3–9), and the reduction of alpha power during rest can reflect increased level of activation in the neural circuits. Different studies with animals and humans have revealed that GABAergic inhibitory neurotransmission is crucially involved in the generation of alpha oscillations, and it has been established that alpha power can be impacted during different GABA-related pharmacological manipulations with thalamus (53–56). Therefore, we propose that the reduction in alpha power in autistic individuals could reflect shifted neural balance toward more excitation (18,19) and atypical thalamic activity (53,56) related to possible dysfunction of the GABAergic system. It is important to note that although the autistic group had reduced alpha power in comparison with the TD group, the asymmetry and pattern of the age-related increase of alpha asymmetry were similar in the 2 groups, perhaps reflecting structural age-related changes in frontal brain regions (57).

In this study, we were able to reveal a novel EEG biomarker associated with age, sex, clinical phenotype, and genetics. Specifically, the results showed age-related decreases in the number of alpha peaks. It is largely unknown what neurobiological mechanism is represented by the number of peaks in the EEG frequency bands. In infants, it has been shown that the number of peaks in the low-frequency range (4–12 Hz, theta/alpha) decreases during the first year of age (20), but this is the first report of age-related changes in peaks during childhood and adolescence. In a sample of healthy adults, multiple alpha peaks and the variability in the number of alpha peaks have been associated with 2 or more independent brain sources that generated alpha-band activity simultaneously (58). If multiple sources are generating alpha-band activity, perhaps the decrease in the number of peaks is related to structural changes and shapes of the cortex, so that older participants have a more dominant source that contributed to

Table 3. The Relationships Between Electroencephalography Alpha Peak Parameters and Clinical Phenotype in Youths With Autism Spectrum Disorder

	Analysis	
Measure	Predictor	Model Output
Left Frontal ROI		
Peak Power	Nonverbal IQ	β = −0.00, SE = 0.00, t_{99} = −1.53, p = .13
	CELF-4 core language SS	β = 0.00, SE = 0.00, t_{99} = 1.00, p = .31
	SRS-2 RRB T score	β = 0.00, SE = 0.00, t_{99} = 0.80, p = .42
	VABS-2 socialization SS	β = −0.00, SE = 0.00, t_{99} = −0.06, p = .95
	Age	β = 0.00, SE = 0.00, t_{99} = 0.21, p = .83
	Sex	β = 0.03, SE = 0.37, t_{99} = 0.82, p = .41
Peak Frequency, Hz	Nonverbal IQ	β = 0.02, SE = 0.01, t_{99} = 1.33, p = .18
	CELF-4 core language SS	β = −0.01, SE = 0.01, t_{99} = −0.69, p = .48
	SRS-2 RRB T score	β = 0.03, SE = 0.02, t_{99} = 1.48, p = .14
	VABS-2 socialization SS	β = 0.01, SE = 0.02, t_{99} = 0.51, p = .60
	Age	β = 0.01, SE = 0.00, t_{99} = 1.48, p = .14
	Sex	β = 0.46, SE = 0.58, t_{99} = 0.79, p = .42
Number of Peaks	Nonverbal IQ	β = −0.00, SE = 0.01, z = −0.20, p = .83
	CELF-4 core language SS	β = 0.00, SE = 0.01, z = 0.12, p = .90
	SRS-2 RRB T score	β = 0.00, SE = 0.01, z = 0.44, p = .65
	VABS-2 socialization SS	β = −0.00, SE = 0.02, z = −0.22, p = .82
	Age	β = −0.00, SE = 0.00, z = −0.35, p = .72
	Sex	β = 0.33, SE = 0.48, z = 0.70, p = .48
Right Frontal ROI		
Power	Nonverbal IQ	β = −0.00, SE = 0.00, t_{99} = −1.71, p = .09
	CELF-4 core language SS	β = 0.00, SE = 0.00, t_{99} = 0.93, p = .35
	SRS-2 RRB T score	β = 0.00, SE = 0.00, t_{99} = 0.89, p = .37
	VABS-2 socialization SS	β = −0.00, SE = 0.00, t_{99} = −1.10, p = .27
	Age	β = 0.00, SE = 0.00, t_{99} = 0.40, p = .68
	Sex	β = 0.01, SE = 0.03, t_{99} = 0.33, p = .73
Peak Frequency, Hz	Nonverbal IQ	β = −0.00, SE = 0.01, t_{99} = −0.34, p = .93
	CELF-4 core language SS	β = 0.00, SE = 0.01, t_{99} = 0.08, p = .93
	SRS-2 RRB T score	β = 0.00, SE = 0.02, t_{99} = 0.12, p = .90
	VABS-2 socialization SS	β = −0.00, SE = 0.02, t_{99} = −0.19, p = .85
	Age	β = 0.01, SE = 0.00, t_{99} = 1.39, p = .16
	Sex	β = 0.91, SE = 0.54, t_{99} = 1.67, p = .09
Number of Peaks	Nonverbal IQ	β = 0.02, SE = 0.01, z = 1.42, p = .15
	CELF-4 core language SS	β = −0.05, SE = 0.01, z = −3.03, p = .004**
	SRS-2 RRB T score	β = 0.08, SE = 0.02, z = 3.10, p = .002**
	VABS-2 socialization SS	β = 0.03, SE = 0.02, z = 1.33, p = .18
	Age	β = 0.01, SE = 0.00, z = 1.28, p = .19
	Sex	β = 0.18, SE = 0.54, z = 0.34, p = .72

Significant p values are false discovery rate corrected.

**$p < .01$.

ASD, autism spectrum disorder; CELF-4, Clinical Evaluation of Language Fundamentals-4; CSS, calibrated severity score; ROI, region of interest; RRB, Restrictive and Repetitive Behavior; SA, Social Affect; SS, standard score; TD, typically developing; VABS-2, Vineland Adaptive Behavior Scales-2.

most of the scalp signal. Understanding why peak number decreases with age will require additional information from imaging or model systems.

Also, we showed that the number of alpha peaks differed between males and females; specifically, autistic males had higher number of peaks in comparison with autistic females during the younger age period (8–11 years). Differences between male and female autistic individuals have been demonstrated in previous neuroimaging studies (52,59,60). Our results are also consistent with the findings from studies on children and youths with attention-deficit/hyperactivity disorder that showed differences between male and female individuals (61) with evidence of later maturation of different brain areas in males in comparison with females (62). We confirmed this, showing the age-related decrease in the number of alpha peaks and that autistic males have a higher number of peaks in comparison with autistic females at younger ages.

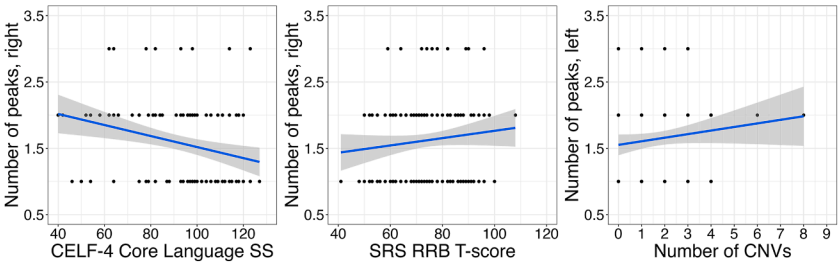

Figure 4. The relationships between the number of alpha peaks and clinical phenotype/genetic markers. CELF-4, Clinical Evaluation of Language Fundamentals-4; RRB, Restrictive and Repetitive Behavior; SRS, Social Responsiveness Scale; SS, standard score.

Our analysis of the relationship between alpha peak parameters and clinical phenotype in autistic youth has revealed a specific association between the number of alpha peaks and behavioral measures. Higher number of peaks was related to greater autistic traits on one of the core domains, i.e., RRBs. Also, higher number of peaks was associated with lower language skills, which is one of the most common features in ASD (60). Again, the neural mechanisms of the number of peaks are still unknown; however, based on our findings, it is clear that the higher number of peaks in autistic individuals is related to difficulties in specific domains of functioning. Importantly, although the number of peaks was also related to age and sex at a young age, we did not find any relationships between age and behavioral measures, and there were no sex differences on clinical/behavioral measures in youths with ASD. This means that the relationship between the number of peaks and behavioral measures in autistic individuals is not driven by age or sex and rather represents a distinct phenomenon.

An important insight into the biology of alpha peak parameters comes from our EEG-genomic analysis. Rare genic CNVs are genomic duplications or deletions that are a significant source of genetic disorders (63). Larger CNVs are related to behavioral and brain abnormalities in different psychiatric and neurological disorders (64–67). In our study, we revealed a relationship between the number of CNVs and the number of alpha peaks in autistic youth, wherein the higher number of CNVs (and, thus, larger genomic alterations) was related to a higher likelihood of more than one alpha peak.

We acknowledge some limitations of the current study. First, although this large sex-balanced dataset combines neural functioning, behavioral/clinical phenotyping, and genome-wide CNV analysis in ASD, it included mostly average-to-high cognitive ability individuals. Inclusion of individuals with lower cognitive ability would reveal whether this neural measure is related to functioning in the full spectrum of autistic individuals. Second, our sample included 8- to 17-year-old youths, and given the increase in the number of alpha peaks with age, it would be beneficial to address preschoolers and young adults to determine whether the shape of the maturational pattern changes. Finally, further studies are needed to replicate the findings and confirm that the results are not driven by the methodological specificity of the study (e.g., broader alpha frequency range).

Table 4. Correlations Between Alpha Peak Parameters and Genetic Measures

	Genetic Variables					
	Total CNV Size[a]		Number of CNVs[b]		Number of Genes Within CNVs[c]	
Frontal Alpha	*r*	*p*	*r*	*p*	*r*	*p*
Left Frontal ROI						
Power	0.02	.82	0.02	.97	0.19	.13
Number of peaks	−0.04	.82	0.26	.04*	0.18	.13
Right Frontal ROI						
Power	0.12	.47	−0.02	.97	0.19	.13
Number of peaks	−0.11	.47	−0.00	.97	0.04	.65
Asymmetry	0.14	.47	−0.02	.97	0.05	.65

All *p* values are false discovery rate corrected.

*$p < .05$.

CNV, copy number variation; max, maximum; min, minimum; ROI, region of interest.

[a]Mean = 250,089.1, range = 909–4,050,194.

[b]Mean = 2.33, range = 1–8.

[c]Mean = 4.07, range = 1–21.

Conclusions

We used a multimodal approach combining EEG neural functioning, genome-wide CNV analysis, and behavioral phenotyping in a large cohort of youths with and without ASD to investigate EEG alpha-band neural activity and its relationship with behavior and genetics in autistic youths. Our study demonstrated that a higher number of peaks was related to a worse behavioral phenotype and larger genomic alterations. The neurobiology of peaks in EEG frequency bands is largely unknown; therefore, future studies should address this EEG parameter through multimodal assessments and clarifying mechanisms in animal models.

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The behavioral and EEG data from the current study are available via the NIMH Data Archive Data Collection #2021. All genetic and biospecimen data from ACE study participants were contributed to the NIMH Repository and Genomics Resource (https://www.nimhgenetics.org) as well as archived through Sampled, Inc. (http://sampled.com), Infinity BiologiX/RUCDR. The code for statistical analysis is available in the Supplement.

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