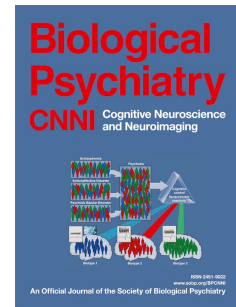


# Journal Pre-proof

Number of alpha peaks in the electroencephalogram is associated with clinical phenotype and copy number variation in youths with autism

Vardan Arutiunian, PhD, Morgan Opdahl, Catherine A.W. Sullivan, MS, Megha Santhosh, MHA, Emily Neuhaus, PhD, Heather Borland, MS, Raphael A. Bernier, PhD, Susan Y. Bookheimer, PhD, Mirella Dapretto, PhD, Allison Jack, PhD, Shafali Jeste, MD, James C. McPartland, PhD, Adam Naples, PhD, John D. Van Horn, PhD, Kevin A. Pelphrey, PhD, Sara Jane Webb, PhD, Abha R. Gupta, MD PhD



PII: S2451-9022(25)00302-7

DOI: <https://doi.org/10.1016/j.bpsc.2025.10.001>

Reference: BPSC 1508

To appear in: *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*

Received Date: 13 May 2025

Revised Date: 20 September 2025

Accepted Date: 5 October 2025

Please cite this article as: Arutiunian V., Opdahl M., Sullivan C.A.W., Santhosh M., Neuhaus E., Borland H., Bernier R.A., Bookheimer S.Y., Dapretto M., Jack A., Jeste S., McPartland J.C., Naples A., Van Horn J.D., Pelphrey K.A., Webb S.J. & Gupta A.R., Number of alpha peaks in the electroencephalogram is associated with clinical phenotype and copy number variation in youths with autism, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (2025), doi: <https://doi.org/10.1016/j.bpsc.2025.10.001>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2025 Published by Elsevier Inc on behalf of Society of Biological Psychiatry.

# Number of alpha peaks in the electroencephalogram is associated with clinical phenotype and copy number variation in youths with autism

## *EEG alpha in relation to behavior and genetics in ASD*

### Authors

|                             |       |
|-----------------------------|-------|
| Vardan Arutiunian PhD       | 1     |
| Morgan Opdahl               | 1     |
| Catherine A. W. Sullivan MS | 6     |
| Megha Santhosh MHA          | 1     |
| Emily Neuhaus PhD           | 1,2,3 |
| Heather Borland MS          | 1     |
| Raphael A. Bernier PhD      | 2     |
| Susan Y. Bookheimer PhD     | 4,5   |
| Mirella Dapretto PhD        | 4,5   |
| Allison Jack PhD            | 9     |
| Shafali Jeste MD            | 10    |
| James C. McPartland PhD     | 7     |
| Adam Naples PhD             | 7     |
| John D. Van Horn PhD        | 11,12 |
| Kevin A. Pelphrey PhD       | 13    |
| Sara Jane Webb PhD*         | 1,2,3 |
| Abha R. Gupta MD PhD*       | 6,7,8 |

\*Equal contribution

1. Center for Child Health, Behavior and Development, Seattle Children's Research Institute, Seattle, WA, USA; 2. Department of Psychiatry and Behavioral Science, University of Washington, Seattle, WA, USA; 3. Institute on Human Development and Disability, University of Washington, Seattle WA, USA; 4. Center for Autism Research and Treatment, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA; 5. Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA; 6. Department of Pediatrics, Yale School of Medicine, Yale University, New Haven, CT, USA; 7. Yale Child Study Center, Yale School of Medicine, Yale University, New Haven, CT, USA; 8. Department of Neuroscience, Yale School of Medicine, Yale University, New Haven, CT, USA; 9. Department of Psychology, George Mason University, Fairfax, VA, USA; 10. Department of Pediatrics and Neurology, USC Keck School of Medicine, Children's Hospital of Los Angeles, Los Angeles, CA, USA; 11. School of Data Science, University of Virginia, Charlottesville, VA, USA; 12. Department of Psychology, University of Virginia, Charlottesville, VA, USA; 13. Department of Neurology, School of Medicine, University of Virginia, Charlottesville, VA, USA

**Correspondence:** Sara Jane Webb, Center for Child Health, Behavior and Development, Seattle Children's Research Institute, 1920 Terry Ave., Seattle, WA 98101, United States of America, Email: [sara.webb@seattlechildrens.org](mailto:sara.webb@seattlechildrens.org)

**ABSTRACT**

**Background:** EEG alpha-band neural activity has been previously reported to be altered in Autism Spectrum Disorder (ASD), but no studies have been done addressing different parameters of alpha-band activity, their relation to clinical phenotype and copy number variation (CNV) in ASD.

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

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

**Conclusions:** The study explored a novel measure (number of peaks) associated with both clinical phenotype and genetic burden and supports alterations in alpha-band activity in ASD.

## INTRODUCTION

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

Recent studies using non-invasive scalp EEG have implicated several metrics associated with the neurobiology of ASD, and one of those metrics is alpha-band (8–12Hz in adults) neural activity. Abnormalities in different parameters of this neural activity have been detected in ASD compared to typically developing (TD) controls. For example, most studies have revealed *alpha power* reduction in autistic individuals (11–15), and this reduction was related to different mechanisms, such as excitation/inhibition imbalance (16–19) due to abnormal functioning of the gamma-aminobutyric acidergic (GABAergic) inhibitory system (20); disruptions of thalamocortical circuit in ASD (9,21); and involvement of children's attention to the task (22,23). *Alpha peak frequency* has also been reported to be atypical in ASD tending to be lower compared to TD children and had atypical developmental trajectory (24,25). Finally, *frontal alpha asymmetry* in autistic individuals/infants at risk for developing ASD had reverse pattern and atypical age-related change (26,27).

Given the significant contribution of genetics to some of the parameters of resting-state EEG spectral power (28), recent studies have investigated relationships between alpha oscillations and genetic markers in different clinical populations (29–31) 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). There is only one study addressing aperiodic-adjusted alpha-band parameters and genetic markers (CNVs) but in a mixed group of children with neurodevelopmental disorders (28). No such studies have been conducted in autistic individuals to examine interrelations among EEG aperiodic-adjusted alpha-band parameters, clinical phenotype, and genetic variables. We aim to fill this gap.

The main goal of the present study is to address alpha-band activity and its relation to clinical phenotype and genetics in a large group of youth with ASD by implementing a multi-modal approach including resting-state EEG, behavioral phenotyping, and genome-wide CNV analysis. First, using a novel parameterization algorithm (32), we aim to calculate aperiodic-adjusted alpha peak parameters (power, frequency, asymmetry and additional parameter such as the number of peaks) by removing the aperiodic signal (which influences largely oscillatory component of the spectral power (33)) and compare these parameters between the ASD and TD groups. Second, in the autistic cohort, we aim to assess the associations between alpha peak parameters and behavioral / clinical measures. Finally, we address the relationship of 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 to both behavioral and genetic markers in ASD.

## **METHODS AND MATERIALS**

### **Participants**

Two groups of participants ( $N = 310$ , aged 8 to 17 years) with valid EEG data were included in the analysis: 164 youth with ASD (72 female) and 146 TD youth (68 female). The data were

collected from four 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 in Los Angeles, and Yale University, with the data coordinating center located at the University of Southern California (USC). De-identified data were provided to the National Database of Autism Research (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 the Table 1.

(Table 1)

### **Behavioral assessment**

All youth with ASD were diagnosed based on the DSM-IV-TR or DSM-5 (1,34), and the diagnosis was confirmed with the Autism Diagnosis Observation Schedule – Second Edition (35), Autism Diagnostic Interview – Revised (36), 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 (37), and the language skills were measured with the Clinical Evaluation of Language Fundamentals-4, CELF-4 (38). Additional phenotypic characteristics have been obtained from the Social Responsiveness Scale-2, SRS-2 (39) and the Vineland Adaptive Behavior Scales-2, VABS-2 (40).

Youth 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 sensory-motor difficulties that would prevent completion of study procedures. All ASD participants had either verbal or non-verbal IQ  $\geq 70$ .

TD youth had no familial history of ASD, no elevation of autistic traits according to SRS-2 (T-score  $\leq 60$ ) or the Social Communication Questionnaire (41) (raw score  $< 11$ ), and all had normal nonverbal IQ (see Table 1).

### **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., Eugene OR), 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  $< 50 \text{ k}\Omega$ .

Resting-state EEG was acquired via an eyes open condition. The recording session consisted of three 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 the Batch EEG Automated Processing Platform, BEAPP (42) in MATLAB 2021a, consisting of: (1) format the MFF file for Matlab; (2) band-pass filter 1–100 Hz; (3) down sampling from 500 Hz to 250 Hz; (4) implementation of the Harvard Automated Preprocessing Pipeline for EEG (HAPPE) module for artifact detection and rejection (43), including removal of 60 Hz line noise, rejection of bad channels, wavelet enhanced thresholding, Independent Component Analysis (ICA) with automated component rejection, bad channel interpolation, and re-referencing to average; (5) segmentation of the continuous file into 1 second epochs; (6) rejection of bad segments ( $\pm 40 \text{ }\mu\text{V}$ ); (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 ROI; 3, 117, 123, F4-124, 118 for the right ROI, see Figure 1). PSD was calculated for each electrode and averaged within these regions of interest. As the raw PSD includes both periodic and aperiodic components (32), we used the

*specparam* toolbox (33) in Python v3.10 to parametrize the neural spectral power and to remove aperiodic component. This allowed to estimate the alpha peak parameters without 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 – 15.99Hz frequency range (the range from 44,45) 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, R2 and errors can be seen in Supplementary materials – 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 (45,46) 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 about it Supplementary materials – 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 ROIs power. The groups of youth did not differ in the number of artifact-free epochs: *ASD*,  $M_{\text{epoch}} = 101.06$ , range 62–123; *TD*,  $M_{\text{epoch}} = 101.85$ , range 78–123,  $t(303.18) = -0.47$ ,  $p = 0.63$ .

### **Genotyping and copy number variant (CNV) detection**

Blood samples were collected from the ASD participants to obtain genomic DNA and processed by the Rutgers University Cell and Data Repository (RUCDR) 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 by PLINK v1.07 (47) using the forward stand and confirmed the reported sex of all subjects.

CNV detection (duplications and deletions) was performed using three algorithms: PennCNV v1.0.4, QuantiSNP v1.1, and GNOSIS (48). Analysis and merging of CNV predictions used CNVision (48). All rare genic CNVs ( $\geq 50\%$  of CNV at  $\leq 1\%$  frequency in the Database of Genomic Variants (48); hereafter, CNVs) predicted by at least PennCNV and QuantiSNP and having a CNVision pCNV of  $\leq 0.001$ , i.e., those considered high-quality predictions (49), were obtained for further analysis. Subsequent analyses combined duplications and deletions to maximize the number of CNVs available for examination; separating the two types led to low numbers and low statistical power.

### **Statistical analysis**

Statistical analysis was performed in R (50) using the *lme4* package (51) and the data were plotted with *ggplot2* (52). A correction for multiple comparisons (false discovery rate, FDR) was applied to each set of the analyses, and *p*-values were corrected with the *p.adjust.method* in R.

### **Data availability**

The behavioral and EEG data from the current study are available via the National Institute of Mental Health 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.

### **Code availability**

The code for statistical analysis is available in Supplementary materials.

## RESULTS

### Descriptive summary of EEG measures

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

(Figure 1)

### 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 the 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 and age effects were identified. *Second*, for the alpha peak frequency, no significant effects were shown (Figure). *Third*, the number of alpha peaks was related to sex and age, such that the males had 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).

(Table 2)

(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 youth. 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 = aged 8–11 years, Age2 = aged 12–15 years, Age3 = aged 16–18 years old).

In the TD group, there was no relationship between the number of peaks and sex in any time window in both ROIs: *left ROI*, Age1,  $\beta = 0.65$ , SE = 0.63,  $z = 1.04$ ,  $p = 0.30$ , Age2,  $\beta = 0.37$ , SE = 0.54,  $z = 0.68$ ,  $p = 0.49$ , Age3,  $\beta = 0.29$ , SE = 0.73,  $z = 0.39$ ,  $p = 0.70$ ; *right ROI*, Age1,  $\beta = 0.41$ , SE = 0.57,  $z = 0.73$ ,  $p = 0.46$ , Age2,  $\beta = 0.70$ , SE = 0.55,  $z = 1.28$ ,  $p = 0.20$ , Age3,  $\beta = -0.25$ , SE = 0.73,  $z = -0.34$ ,  $p = 0.73$  (Figure 3).

(Figure 3)

By contrast, in the ASD group in both left and right ROI there was a relationship between sex and the number of peaks in the 8 to 11 year group, such that ASD males had higher number of peaks in comparison with ASD females: *left ROI*,  $\beta = 1.50$ , SE = 0.51,  $z = 2.94$ , FDR-corrected  $p = 0.006$ , *right ROI*,  $\beta = 1.36$ , SE = 0.49,  $z = 2.74$ , FDR-corrected  $p = 0.006$ . In other age windows, there were no significant effects: *left ROI*, Age2,  $\beta = 0.05$ , SE = 0.52,  $z = 0.10$ ,  $p = 0.92$ , Age3,  $\beta = 0.50$ , SE = 0.76,  $z = 0.66$ ,  $p = 0.51$ ; *right ROI*, Age2,  $\beta = 0.30$ , SE = 0.53,  $z = 0.58$ ,  $p = 0.56$ , Age3,  $\beta = -0.14$ , SE = 0.76,  $z = -0.18$ ,  $p = 0.85$  (see Figure 3).

**Relation of alpha peak parameters to clinical phenotype in youth 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 six predictors: nonverbal IQ, language skills (CELF-4 Core Language Standard Score, SS), a measure of restricted and repetitive behavior (SRS-2 RRB T-score), social skills (VABS-2 Socialization SS) and included age and sex as covariates.

After correction for multiple comparisons, two effects remained statistically significant, including the relation between the number of alpha peaks and language skills,  $\beta = -0.05$ ,  $SE = 0.01$ ,  $z = -3.03$ ,  $p = 0.004$ , and between the number of alpha peaks and restricted and repetitive behavior in the right ROI,  $\beta = 0.08$ ,  $SE = 0.02$ ,  $z = 3.10$ ,  $p = 0.002$  (Table 3, Figure 4). Higher number of peaks was associated with lower language skills and 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 correlated with age: CELF,  $r = 0.29$ , FRD-corrected  $p = 0.28$ ; RRB,  $r = 0.10$ , FRD-corrected  $p = 0.18$ .

(Table 3)

(Figure 4)

### **Associations of alpha peak parameters with rare genic CNVs in youth 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 between-group difference in this variable, not 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. Greater number of peaks was related to higher number of CNVs,  $r = 0.26$ , FRD-corrected  $p = 0.04$  (Figure 4).

(Table 4)

### **Sex differences in clinical measures in young age autistic individuals**

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

We fitted a generalized linear model with the sex as a dependent variable and included all behavioral measures used before as well as ADOS-2 Calibrated Total Severity Score as main effects. The results showed no difference between male and female ASD individuals in any measure: *nonverbal IQ*,  $\beta = 0.01$ ,  $SE = 0.02$ ,  $z = 0.61$ ,  $p = 0.543$ ; *CELF-4 Core Language SS*,  $\beta = -0.00$ ,  $SE = 0.02$ ,  $z = -0.38$ ,  $p = 0.702$ ; *SRS-2 RRB T-score*,  $\beta = 0.01$ ,  $SE = 0.03$ ,  $z = 0.43$ ,  $p = 0.670$ ; *VABS-2 Socialization SS*,  $\beta = -0.02$ ,  $SE = 0.03$ ,  $z = -0.70$ ,  $p = 0.482$ ; *ADOS-2 Calibrated Total Severity Score*,  $\beta = 0.18$ ,  $SE = 0.17$ ,  $z = 0.97$ ,  $p = 0.33$ .

## **DISCUSSION**

The present study focused on alpha-band neural activity and its relation to clinical phenotype and copy number variation in a large sample of youth 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 youth with ASD had reduced peak power in comparison with TD participants. This corresponds to previous findings that showed a similar alpha power reduction during rest in autistic individuals (11–15,53). 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 on animals and humans have revealed that GABAergic inhibitory neurotransmission is crucially involved in the generation of alpha oscillations, and it is established that alpha power can be impacted during different GABA-related pharmacological manipulations with thalamus (54–57). 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 (54, 57) 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 sample, the asymmetry and the pattern of the age-related increase of alpha asymmetry were similar in both groups, perhaps reflecting structural age-related changes in the frontal brain regions (58).

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 number of peaks in the EEG frequency bands. In infants it has been shown that the number of peaks in the low-frequency range (4–12Hz, theta/alpha) decreases during first year of age (21), but this is the first report of age-related changes in peaks in 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 two or more independent brain sources that generated alpha-band activity simultaneously (59). 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 more dominant source that contributed to most of the scalp signal. Differentiating 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, particularly, autistic males had higher number of peaks in comparison with autistic females at younger age period (8–11 years). Differences between male and female autistic individuals have been demonstrated in previous neuroimaging studies (53,60,61). Our results are also in line with the findings from the studies on children and youth with Attention Deficit Hyperactivity Disorder (ADHD) that showed differences between male and female individuals (62) with evidence of later maturation of different brain areas in males in comparison with females (63). We confirmed this, showing the age-related decrease in the number of alpha peaks and that autistic males have higher number of peaks in comparison with autistic females at younger age.

Our analysis of the relationship between alpha peak parameters and clinical phenotype in autistic youths have 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., restricted and repetitive behaviors. Also, higher number of peaks was associated with lower language skills, which is one of the most common features in ASD (61). Again, the neural mechanisms of the number of peaks are yet 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 were also related to age and sex at young age, we did not find any relationships between age and behavioral measures as well as there was no sex difference in clinical / behavioral measures in youth 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 represent a distinct

phenomenon.

An important insight into 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 (64). Larger CNVs are related to behavioral and brain abnormalities in different psychiatric and neurological disorders (65–68). In our study, we revealed a relationship between the number of CNVs and the number of alpha peaks in autistic youth, so that the higher number of CNVs (and, thus, larger genomic alterations) was related to a higher likelihood of more than one alpha peak.

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

We acknowledge some limitations of the present 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 8-17-year-old youth and given the increase in the number of alpha peaks with age, it would be beneficial to address preschoolers and young adults to determine if the shape of the maturational pattern changes. Finally, future studies are needed to replicate the findings and to confirm that the results are not driven by the methodological specificity of the study (e.g.,

broader alpha frequency range).

Journal Pre-proof

**Competing interests**

James C. McPartland consults or has consulted with Customer Value Partners, Bridgebio, Determined Health, Apple, and BlackThorn Therapeutics, has received research funding from Janssen Research and Development, serves on the Scientific Advisory Boards of Pastorius and Modern Clinics, and receives royalties from Guilford Press, Lambert, Oxford, and Springer. The remaining authors report no biomedical financial interests or potential conflicts of interest.

**Funding**

Funding was provided by the R01MH10028 (NIMH ACE Network, Pelphrey), R01MH117982 (Dapretto/Pelphrey), and the University of Washington Intellectual and Developmental Disabilities Research Center (U54HD083091).

**Acknowledgement**

We wish to thank the families, parents, and children who participated in our study at our four data collection sites. The ACE GENDAAR Network additionally included contributions from: Katy Ankenman MSW, Elizabeth Aylward PhD, Veronica Kang PhD, Erin J. Libsack PhD, and Désirée Lussier-Lévesque PhD who were formerly at Seattle Children's Research Institute; Sarah Corrigan MA and Waylon Howard PhD who are currently at Seattle Children's Research Institute; Laura A. Edwards PhD and Jack Keller who were formerly at Boston Children's Hospital; Rachael Tillman PhD who was formerly at Yale Child Study Center; Scott Huberty PhD who was formerly at UCLA; Zachary Jacokes who is currently at University of Virginia; Carinna Torgerson who is currently at USC; and Charles Nelson who is currently at Boston Children's Hospital and Harvard Medical School.

**Supplement Description:**

Supplement Methods, Results, Figures S1-S2, and Code

## References

1. American Psychiatric Association (2013): *Diagnostic and statistical manual of mental disorders: DSM-5 (5th ed.)*. Washington, DC; London: American Psychiatric Publication.
2. Shaw KA, *et al.* (2025): Prevalence and Early Identification of Autism Spectrum Disorder Among Children aged 4 and 8 years – Autism and Developmental Disabilities Monitoring Network, 16 sites, United States, 2022. *Surveillance Summaries* 74(2): 1–22.
3. Antoine MW, Langberg T, Schnepel P, Feldman DE (2019): Increased Excitation-Inhibition Ratio Stabilizes Synapse and Circuit Excitability in Four Autism Mouse Models. *Neuron* 101(4): 648–661.
4. Gatto CL, Broadie K (2010): Genetic controls balancing excitatory and inhibitory synaptogenesis in neurodevelopmental disorder models. *Frontiers Synaptic Neuroscience* 2: 4.
5. Cona G, *et al.* (2020): Theta and alpha oscillations as signatures of internal and external attention to delayed intentions: A magnetoencephalography (MEG) study. *NeuroImage* 205: 116295.
6. Hanslmayr S, *et al.* (2011): The role of alpha oscillations in temporal attention. *Brain Research Reviews* 67: 331–343.
7. Rubenstein JLR, Merzenich MM (2003): Model of autism: increased ratio of excitation / inhibition in key neural systems. *Genes, Brain and Behavior* 2: 255–267.
8. Sohal VS, Rubenstein JLR (2019): Excitation-inhibition balance as a framework for investigating mechanisms of neuropsychiatric disorders. *Molecular Psychiatry* 24: 1248–1257.
9. Woodward ND, *et al.* (2017): Thalamocortical dysconnectivity in autism spectrum disorder: An analysis of the Autism Brain Imaging Data Exchange. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 2(1): 76–84.

10. Webb SJ, *et al.* (2023): The Autism Biomarkers Consortium for Clinical Trials: Initial Evaluation of a Battery of Candidate EEG Biomarkers. *American Journal of Psychiatry* 180: 41–49.
11. Arutiunian V, *et al.* (2024): Abnormalities in both stimulus-induced and baseline MEG alpha oscillations in the auditory cortex of children with Autism Spectrum Disorder. *Brain Structure and Function* 229(5): 1225–1242.
12. Dawson G, Klinger LG, Panagiotides H, Lewy A, Castelloe P (1995): Subgroups of autistic children based on social behavior display distinct patterns of brain activity. *Journal of Abnormal Child Psychology* 23: 569–583.
13. Edgar JC, *et al.* (2015): Resting-State Alpha in Autism Spectrum Disorder and Alpha Associations with Thalamic Volume. *Journal of Autism and Developmental Disorders* 45: 795–804.
14. Neuhaus E, *et al.* (2021): Resting state EEG in youth with ASD: age, sex, and relation to phenotype. *Journal of Neurodevelopmental Disorders* 13: 33.
15. Wang J, Barstein J, Ethridge LE, Mosconi MW, Takarae Y, Sweeney J (2013): Resting state EEG abnormalities in autism spectrum disorders. *Journal of Neurodevelopmental Disorders* 5: 24.
16. Mathewson KE, Lleras A, Beck DM, Fabiani M, Ro T, Gratton G (2011): Pulsed out of awareness: EEG alpha oscillations represent a pulsed-inhibition of ongoing cortical processing. *Frontiers in Psychology* 2: 99.
17. Thies M, Zrenner C, Ziemann U, Bergmann TO (2018): Sensorimotor mu-alpha power is positively related to corticospinal excitability. *Brain Stimulation* 11: 1119–1122.
18. Chapeton JJ, Haque R, Wittig JH, Inati SK, Zaghloul KA (2019): Large-Scale Communication in the Human Brain Is Rhythmically Modulated through Alpha Coherence. *Current Biology* 29: 2801–2811.

19. Jensen O, Mazaheri A (2010): Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Frontiers in Human Neuroscience* 4: 186.
20. Wang J, Barstein J, Ethridge LE, Mosconi MW, Takarae Y, Sweeney J (2013): Resting state EEG abnormalities in autism spectrum disorders. *Journal of Neurodevelopmental Disorders* 5: 24.
21. Wilkinson CL, *et al.* (2024): Developmental trajectories of EEG aperiodic and periodic components in children 2–44 months of age. *Nature Communications* 15: 5788.
22. Händel BF, Haarmeier T, Jensen O (2011): Alpha Oscillations Correlate with the Successful Inhibition of Unattended Stimuli. *Journal of Cognitive Neuroscience* 23: 2494–2502.
23. Klimesch W (2012): Alpha-band oscillations, attention, and controlled access to stored information. *Trends in Cognitive Sciences* 16: 606–617.
24. Dickinson A, DiStefano C, Senturk D, Jeste SS (2018): Peak alpha frequency is a neural marker of cognitive function across the autism spectrum. *European Journal of Neuroscience* 47(6): 643–651.
25. Finn CE, Han GT, Naples AJ, Wolf JM, McPartland JC (2023): Development of peak alpha frequency reflects a distinct trajectory of neural maturation in autistic children. *Autism Research* 16(11): 2077–2089.
26. Gabard-Durnam L, Tierney AL, Vogel-Farley V, Tager-Flusberg H, Nelson CA (2015): Alpha asymmetry in infants at risk for autism spectrum disorders. *Journal of Autism and Developmental Disorders* 45(2): 473–480.
27. Laauttia J, Helminen TM, Leppanen JM, Yrttiaho S, Eriksson K, Hietanen JK, Kylliainen A (2019): Atypical pattern of frontal EEG asymmetry for direct gaze in young children with autism spectrum disorder. *Journal of Autism and Developmental Disorders* 49: 3592–3601.

28. Dubois AEE, *et al.* (2025): Genetic modulation of brain dynamics in neurodevelopmental disorders: the impact of copy number variations on resting-state EEG. *Translational Psychiatry* 15: 139.
29. Borlot F, Regan BM, Bassett AS, Stavropoulos DJ, Andrade DM (2017): Prevalence of Pathogenic Copy Number Variation in Adults With Pediatric-Onset Epilepsy and Intellectual Disability. *JAMA Neurology* 74(11): 1301–1311.
30. Malone SM, Burwell SJ, Vaidyanathan U, Miller MB, McGue M, Iacono WG (2014): Heritability and molecular-genetic basis of resting EEG activity: a genome-wide association study. *Psychophysiology* 51(12): 1225–1245.
31. Smit DJA, *et al.* (2018): Genome-wide association analysis links multiple psychiatric liability genes to oscillatory brain activity. *Human Brain Mapping* 39(11): 4183–4195.
32. Donoghue T, *et al.* (2020): Parameterizing neural power spectra into periodic and aperiodic components. *Nature Neuroscience* 23: 1655–1665.
33. Ostlund B, *et al.* (2022): Spectral parameterization for studying neurodevelopment: How and why. *Developmental Cognitive Neuroscience* 54: 101073.
34. American Psychiatric Association (2000): *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*. Washington, DC: Author.
35. Lord C, Rutter, M, DiLavore PC, Risi S, Gotham K, Bishop S (2012): *Autism Diagnostic Observation Schedule, second edition (ADOS-2) manual (part I): modules 1–4*. Torrance, CA: Western Psychological Services.
36. Rutter M, Le Couteur A, Lord C (2003): *ADI-R: Autism Diagnostic Interview-Revised (ADI-R)*. Los Angeles, CA: Western Psychological Services.
37. Elliott CD (2007): *Differential Ability Scales, second edition*. San Antonio, TX: The Psychological Corporation.
38. Semel E, Wiig EH, Secord WA (2003): *Clinical evaluation of language fundamentals*,

- fourth edition (CELF-4)*. Toronto: The Psychological Corporation / A Harcourt Assessment Company.
39. Constantino JN (2012): *Social Responsiveness Scale, second edition (SRS-2)*. Torrance, CA: Western Psychological Services.
  40. Sparrow S, Cicchetti D, Balla D (2005): *Vineland Adaptive Behavior Scales, second edition (Vineland-II)*. Circle Pines, MN: American Guidance Service.
  41. Rutter ML, Bailey A, Lord C (2003): *Social Communication Questionnaire*. Torrance, CA. Western Psychological Services.
  42. Levin AR, Méndez Leal AS, Gabard-Durnam LJ, O’Leary HM (2018): BEAPP: The Batch Electroencephalography Automated Processing Platform. *Frontiers in Neuroscience* 12, 513.
  43. Gabard-Durnam LJ, Méndez Leal AS, Wilkinson CL, Levin AR (2018): The Harvard Automated Processing Pipeline for Electroencephalography (HAPPE): Standardized Processing Software for Developmental and High-Artifact Data. *Frontiers in Neuroscience* 12: 97.
  44. Caffarra S, *et al.* (2024): Development of the Alpha Rhythm Is Linked to Visual White Matter Pathways and Visual Detection Performance. *The Journal of Neuroscience* 44(6): e0684232023.
  45. Turner C, *et al.* (2023): Developmental changes in individual alpha frequency: Recording EEG data during public engagement events. *Imaging Neuroscience* 1: 1–14.
  46. Freschl J, Azizi LA, Balboa L, Kaldy Z, Blaser E (2022): The development of peak alpha frequency from infancy to adolescence and its role in visual temporal processing: A meta-analysis. *Developmental Cognitive Neuroscience* 57: 101146.
  47. Purcell S, *et al.* (2007): PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analysis. *American Journal of Human Genetics* 81(3): 559–

- 575.
48. Sanders SJ, *et al.* (2011): Multiple Recurrent De Novo CNVs, Including Duplications of the 7q11.23 Williams Syndrome Region, Are Strongly Associated with Autism. *Neuron* 70: 863–885 (2011).
  49. Sanders SJ, *et al.* (2015): Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci. *Neuron* 87: 1215–1233.
  50. R Core Team (2019): *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. Vienna <https://www.R-project.org/>
  51. Bates D, Mächler M, Bolker BM, Walker SC (2015): Fitting linear mixed-effects models using *lme4*. *Journal of Statistical Software* 67: 1–48.
  52. Wickham H (2016): *ggplot 2: Elegant Graphics for Data Analysis*. New York: Springer-Verlag.
  53. Neuhaus E, *et al.* (2023): Frontal EEG alpha asymmetry in youth with autism: Sex differences and social-emotional correlates. *Autism Research* 16(12): 2364–2377.
  54. Ahveninen J, *et al.* (2007): MRI-constrained spectral imaging of benzodiazepine modulation of spontaneous neuromagnetic activity in human cortex. *NeuroImage* 35(2): 577–582.
  55. Lorincz ML, Kékesi KA, Juhász G, Crunelli V, Hughes SW (2009): Temporal framing of thalamic relay-mode firing by phasic inhibition during the alpha rhythm. *Neuron* 63(5): 683–696.
  56. Lozano-Soldevilla D, ter Huurne N, Cools R, Jensen O (2014): GABAergic modulation of visual gamma and alpha oscillations and its consequences for working memory performance. *Current Biology* 24(24): 2878–2887.
  57. Schreckenberger M, *et al.* (2004): The thalamus as the generator and modulator of EEG alpha rhythm: a combined PET/EEG study with lorazepam challenge in humans.

- NeuroImage* 22(2): 637–644.
58. Zhou D, Lebel C, Evans A, Beaulieu C (2013): Cortical thickness asymmetry from childhood to older adulthood. *NeuroImage* 83: 66–74.
  59. Olejarczyk E, Bogucki P, Sobieszek A (2017): The EEG Split Alpha Peak: Phenomenological Origins and Methodological Aspects of Detection and Evaluation. *Frontiers in Neuroscience* 11: 506.
  60. Andrews DS, *et al.* (2024): Sex differences in trajectories of cortical development in autistic children from 2–13 years of age. *Molecular Psychiatry* 29: 3440–3451.
  61. Arutiunian V, *et al.* (2024): The relationship between gamma-band neural oscillations and language skills in youth with Autism Spectrum Disorder and their first-degree relatives. *Molecular Autism* 15: 19.
  62. Villemonteix T, *et al.* (2015): Grey matter volume differences associated with gender in children with attention-deficit/hyperactivity disorder: A voxel-based morphometry study. *Developmental Cognitive Neuroscience* 14: 32–37.
  63. Mahone EM, Wodka EL (2008): The neurobiological profile of girls with ADHD. *Developmental Disabilities Research Review* 14(4): 276–284.
  64. Auwerx C, *et al.* (2024): Rare copy-number variants as modulators of common disease susceptibility. *Genome Medicine* 16(1): 5.
  65. Cooper GM, *et al.* (2011): A copy number variation morbidity map of developmental delay. *Nature Genetics* 43: 838–846.
  66. Gupta AR, *et al.* (2017): Neurogenetic analysis of childhood disintegrative disorder. *Molecular Autism* 8: 19.
  67. Jack A, *et al.* (2021): A neurogenetic analysis of female autism. *Brain* 144(6): 1911–1926.
  68. Mefford HC, *et al.* (2010): Genome-Wide Copy Number Variation in Epilepsy: Novel Susceptibility Loci in Idiopathic Generalized and Focal Epilepsies. *PLoS Genetics* 6:

e1000962.

Journal Pre-proof

**Table 1.** Demographic information. Range, M(SD).

| Characteristics           | Group                    |                         | Statistics                     |
|---------------------------|--------------------------|-------------------------|--------------------------------|
|                           | ASD (72 female, 92 male) | TD (68 female, 78 male) |                                |
| Age, months               | 96.0–215.0, 151.0(35.0)  | 96.0–216.0, 156.6(35.0) | $t(303.6) = -1.41, p = 0.16$   |
| Nonverbal IQ              | 57.0–158.0, 100.2(17.5)  | 74.0–147.0, 109.1(15.1) | $t(307.7) = -4.83, p < 0.001$  |
| CELF Core Language SS     | 40.0–127.0, 91.4(20.9)   | 81.0–134.0, 110.7(11.2) | $t(179.6) = -8.82, p < 0.001$  |
| VABS-2                    |                          |                         |                                |
| Communication SS          | 49.0–122.0, 76.1(11.8)   | 67.0–135.0, 99.3(13.2)  | $t(289.8) = -16.07, p < 0.001$ |
| Socialization SS          | 46.0–118.0, 72.6(12.1)   | 74.0–145.0, 101.2(12.6) | $t(297.6) = -20.20, p < 0.001$ |
| Daily living skills SS    | 51.0–119.0, 76.4(13.8)   | 58.0–130.0, 97.7(14.1)  | $t(298.3) = -13.33, p < 0.001$ |
| SRS total T-score         | 39.0–106.0, 75.3(11.5)   | 37.0–60.0, 43.8(5.0)    | $t(206.15) = 30.39, p < 0.001$ |
| 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, <i>N</i>       |                          |                         |                                |
| Not Hispanic or Latino    | 98(60%)                  | 94(64%)                 | –                              |
| Hispanic or Latino        | 17(10%)                  | 20(14%)                 | –                              |
| Other                     | 2(1%)                    | 2(1%)                   | –                              |
| Not answered              | 47(29%)                  | 30(21%)                 | –                              |
| Race, <i>N</i>            |                          |                         |                                |
| White                     | 86(52%)                  | 86(59%)                 | –                              |
| Black or African American | 6(5%)                    | 9(6%)                   | –                              |
| Asian                     | 4(2%)                    | 8(5%)                   | –                              |
| Mixed race                | 17(10%)                  | 12(8%)                  | –                              |
| Other                     | 4(2%)                    | 1(1%)                   | –                              |
| Not answered              | 47(29%)                  | 30(21%)                 | –                              |

**Table 2.** Between-group comparisons in EEG alpha peak parameters. ASD = Autism Spectrum Disorder, TD = typically developing. The significance is labeled with \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  and highlighted in bold. All  $p$ -values are FDR-corrected.

| Measure                  | ASD   |      | TD   |      | Analysis  |                                                                     |
|--------------------------|-------|------|------|------|-----------|---------------------------------------------------------------------|
|                          | Mean  | SD   | Mean | SD   | Predictor | Model output                                                        |
| <i>Left frontal ROI</i>  |       |      |      |      |           |                                                                     |
| Peak power               | 0.49  | 0.15 | 0.57 | 0.15 | Group     | $\beta = 0.09$ , SE = 0.02, $t = 4.93$ , $p < \mathbf{0.001^{***}}$ |
|                          |       |      |      |      | Sex       | $\beta = 0.02$ , SE = 0.02, $t = 1.94$ , $p = 0.38$                 |
|                          |       |      |      |      | Age       | $\beta = -0.00$ , SE = 0.01, $t = -1.77$ , $p = 0.16$               |
| Peak frequency, Hz       | 9.27  | 2.26 | 9.81 | 2.09 | Group     | $\beta = 0.55$ , SE = 0.25, $t = 2.21$ , $p = 0.06$                 |
|                          |       |      |      |      | Sex       | $\beta = 0.35$ , SE = 0.25, $t = 1.38$ , $p = 0.17$                 |
|                          |       |      |      |      | Age       | $\beta = -0.00$ , SE = 0.00, $t = -0.15$ , $p = 0.88$               |
| Number of peaks          | 1.63  | 0.62 | 1.66 | 0.58 | Group     | $\beta = 0.19$ , SE = 0.24, $z = 0.80$ , $p = 0.74$                 |
|                          |       |      |      |      | Sex       | $\beta = 0.61$ , SE = 0.24, $z = 2.57$ , $p = \mathbf{0.01^*}$      |
|                          |       |      |      |      | Age       | $\beta = -0.01$ , SE = 0.00, $z = -2.48$ , $p = \mathbf{0.02^*}$    |
| <i>Right frontal ROI</i> |       |      |      |      |           |                                                                     |
| Power                    | 0.49  | 0.15 | 0.58 | 0.16 | Group     | $\beta = 0.00$ , SE = 0.00, $t = 5.32$ , $p < \mathbf{0.001^{***}}$ |
|                          |       |      |      |      | Sex       | $\beta = 0.00$ , SE = 0.00, $t = 0.87$ , $p = 0.38$                 |
|                          |       |      |      |      | Age       | $\beta = 0.00$ , SE = 0.00, $t = 0.08$ , $p = 0.93$                 |
| Peak frequency, Hz       | 9.49  | 2.25 | 9.47 | 1.83 | Group     | $\beta = -0.03$ , SE = 0.23, $t = -0.13$ , $p = 0.89$               |
|                          |       |      |      |      | Sex       | $\beta = 0.42$ , SE = 0.23, $t = 1.79$ , $p = 0.14$                 |
|                          |       |      |      |      | Age       | $\beta = 0.00$ , SE = 0.00, $t = 1.42$ , $p = 0.30$                 |
| Number of peaks          | 1.61  | 0.63 | 1.65 | 0.64 | Group     | $\beta = 0.08$ , SE = 0.23, $z = 0.34$ , $p = 0.74$                 |
|                          |       |      |      |      | Sex       | $\beta = 0.57$ , SE = 0.23, $z = 2.48$ , $p = \mathbf{0.01^*}$      |
|                          |       |      |      |      | Age       | $\beta = -0.00$ , SE = 0.00, $z = -0.52$ , $p = 0.60$               |
| Asymmetry                | -0.00 | 0.10 | 0.01 | 0.11 | Group     | $\beta = 0.01$ , SE = 0.01, $t = 0.53$ , $p = 0.60$                 |
|                          |       |      |      |      | Sex       | $\beta = -0.00$ , SE = 0.01, $t = -0.46$ , $p = 0.64$               |
|                          |       |      |      |      | Age       | $\beta = 0.00$ , SE = 0.00, $t = 2.65$ , $p < \mathbf{0.008^{**}}$  |

**Table 3.** The relationships between EEG alpha peak parameters and clinical phenotype in youths with ASD. The significance is labeled with  $*p < 0.05$ ,  $**p < 0.01$ ,  $***p < 0.001$  and highlighted in bold. Significant  $p$ -values are FDR-corrected.

| Measure                         | Analysis                 |                                                                      |
|---------------------------------|--------------------------|----------------------------------------------------------------------|
|                                 | Predictor                | Model output                                                         |
| <b><i>Left frontal ROI</i></b>  |                          |                                                                      |
| Peak power                      | Nonverbal IQ             | $\beta = -0.00$ , SE = 0.00, $t = -1.53$ , $p = 0.13$                |
|                                 | CELFS-4 Core Language SS | $\beta = 0.00$ , SE = 0.00, $t = 1.00$ , $p = 0.31$                  |
|                                 | SRS-2 RRB T-score        | $\beta = 0.00$ , SE = 0.00, $t = 0.80$ , $p = 0.42$                  |
|                                 | VABS-2 Socialization SS  | $\beta = -0.00$ , SE = 0.00, $t = -0.06$ , $p = 0.95$                |
|                                 | Age                      | $\beta = 0.00$ , SE = 0.00, $t = 0.21$ , $p = 0.83$                  |
|                                 | Sex                      | $\beta = 0.03$ , SE = 0.37, $t = 0.82$ , $p = 0.41$                  |
| Peak frequency, Hz              | Nonverbal IQ             | $\beta = 0.02$ , SE = 0.01, $t = 1.33$ , $p = 0.18$                  |
|                                 | CELFS-4 Core Language SS | $\beta = -0.01$ , SE = 0.01, $t = -0.69$ , $p = 0.48$                |
|                                 | SRS-2 RRB T-score        | $\beta = 0.03$ , SE = 0.02, $t = 1.48$ , $p = 0.14$                  |
|                                 | VABS-2 Socialization SS  | $\beta = 0.01$ , SE = 0.02, $t = 0.51$ , $p = 0.60$                  |
|                                 | Age                      | $\beta = 0.01$ , SE = 0.00, $t = 1.48$ , $p = 0.14$                  |
|                                 | Sex                      | $\beta = 0.46$ , SE = 0.58, $t = 0.79$ , $p = 0.42$                  |
| Number of peaks                 | Nonverbal IQ             | $\beta = -0.00$ , SE = 0.01, $z = -0.20$ , $p = 0.83$                |
|                                 | CELFS-4 Core Language SS | $\beta = 0.00$ , SE = 0.01, $z = 0.12$ , $p = 0.90$                  |
|                                 | SRS-2 RRB T-score        | $\beta = 0.00$ , SE = 0.01, $z = 0.44$ , $p = 0.65$                  |
|                                 | VABS-2 Socialization SS  | $\beta = -0.00$ , SE = 0.02, $z = -0.22$ , $p = 0.82$                |
|                                 | Age                      | $\beta = -0.00$ , SE = 0.00, $z = -0.35$ , $p = 0.72$                |
|                                 | Sex                      | $\beta = 0.33$ , SE = 0.48, $z = 0.70$ , $p = 0.48$                  |
| <b><i>Right frontal ROI</i></b> |                          |                                                                      |
| Power                           | Nonverbal IQ             | $\beta = -0.00$ , SE = 0.00, $t = -1.71$ , $p = 0.09$                |
|                                 | CELFS-4 Core Language SS | $\beta = 0.00$ , SE = 0.00, $t = 0.93$ , $p = 0.35$                  |
|                                 | SRS-2 RRB T-score        | $\beta = 0.00$ , SE = 0.00, $t = 0.89$ , $p = 0.37$                  |
|                                 | VABS-2 Socialization SS  | $\beta = -0.00$ , SE = 0.00, $t = -1.10$ , $p = 0.27$                |
|                                 | Age                      | $\beta = 0.00$ , SE = 0.00, $t = 0.40$ , $p = 0.68$                  |
|                                 | Sex                      | $\beta = 0.01$ , SE = 0.03, $t = 0.33$ , $p = 0.73$                  |
| Peak frequency, Hz              | Nonverbal IQ             | $\beta = -0.00$ , SE = 0.01, $t = -0.34$ , $p = 0.93$                |
|                                 | CELFS-4 Core Language SS | $\beta = 0.00$ , SE = 0.01, $t = 0.08$ , $p = 0.93$                  |
|                                 | SRS-2 RRB T-score        | $\beta = 0.00$ , SE = 0.02, $t = 0.12$ , $p = 0.90$                  |
|                                 | VABS-2 Socialization SS  | $\beta = -0.00$ , SE = 0.02, $t = -0.19$ , $p = 0.85$                |
|                                 | Age                      | $\beta = 0.01$ , SE = 0.00, $t = 1.39$ , $p = 0.16$                  |
|                                 | Sex                      | $\beta = 0.91$ , SE = 0.54, $t = 1.67$ , $p = 0.09$                  |
| Number of peaks                 | Nonverbal IQ             | $\beta = 0.02$ , SE = 0.01, $z = 1.42$ , $p = 0.15$                  |
|                                 | CELFS-4 Core Language SS | $\beta = -0.05$ , SE = 0.01, $z = -3.03$ , $p = \mathbf{0.004^{**}}$ |
|                                 | SRS-2 RRB T-score        | $\beta = 0.08$ , SE = 0.02, $z = 3.10$ , $p = \mathbf{0.002^{**}}$   |
|                                 | VABS-2 Socialization SS  | $\beta = 0.03$ , SE = 0.02, $z = 1.33$ , $p = 0.18$                  |
|                                 | Age                      | $\beta = 0.01$ , SE = 0.00, $z = 1.28$ , $p = 0.19$                  |
|                                 | Sex                      | $\beta = 0.18$ , SE = 0.54, $z = 0.34$ , $p = 0.72$                  |

**Table 4.** Correlations between alpha peak parameters and genetic measures. The significance is labeled with \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  and highlighted in bold. All  $p$ -values are FDR-corrected.

| Frontal alpha            | Genetic variables                                                |          |                                                |              |                                                                 |          |
|--------------------------|------------------------------------------------------------------|----------|------------------------------------------------|--------------|-----------------------------------------------------------------|----------|
|                          | Total CNV size<br>(Mean = 250,089.1, min = 909, max = 4,050,194) |          | Number of CNVs (Mean = 2.33, min = 1, max = 8) |              | Number of genes within CNVs<br>(Mean = 4.07, min = 1, max = 21) |          |
| <i>Left frontal ROI</i>  | <i>r</i>                                                         | <i>p</i> | <i>r</i>                                       | <i>p</i>     | <i>r</i>                                                        | <i>p</i> |
| Power                    | 0.02                                                             | 0.82     | 0.02                                           | 0.97         | 0.19                                                            | 0.13     |
| Number of peaks          | -0.04                                                            | 0.82     | 0.26                                           | <b>0.04*</b> | 0.18                                                            | 0.13     |
| <i>Right frontal ROI</i> |                                                                  |          |                                                |              |                                                                 |          |
| Power                    | 0.12                                                             | 0.47     | -0.02                                          | 0.97         | 0.19                                                            | 0.13     |
| Number of peaks          | -0.11                                                            | 0.47     | -0.00                                          | 0.97         | 0.04                                                            | 0.65     |
| Asymmetry                | 0.14                                                             | 0.47     | -0.02                                          | 0.97         | 0.05                                                            | 0.65     |

## Figure legends

**Figure 1.** Alpha-band neural activity in the left and right frontal regions of interest (ROIs) in youth with Autism Spectrum Disorder (ASD) and typically developing (TD) controls: A) 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 the ASD and TD groups of youth; D) heatmaps representing the distribution of alpha peak power in both groups of youth (dashed red line is set to 0.5 for visualization purposes).

**Figure 2.** Between-group comparisons on the alpha peak parameters and age-related changes in the frontal alpha asymmetry (across the ASD and TD group, age in months). The significance is labeled with  $*p < 0.05$ ,  $**p < 0.01$ ,  $***p < 0.001$ , ns = non-significant. All  $p$ -values are FDR-corrected. ASD = Autism Spectrum Disorder, TD = typically developing.

**Figure 3.** Sex differences in the number of alpha peaks in youth with and without Autism Spectrum Disorder at three age windows: T1 = 8–11 years old, T2 = 12–15 years old, T3 = 16–18 years old. The significance is labeled with  $*p < 0.05$ ,  $**p < 0.01$ ,  $***p < 0.001$ , ns = non-significant. All  $p$ -values are FDR-corrected.

**Figure 4.** The relationships between the number of alpha peaks and clinical phenotype / genetic markers.

