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Frontal EEG alpha asymmetry in youth with autism: Sex differences and social-emotional correlates

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Abstract

In youth broadly, EEG frontal alpha asymmetry (FAA) associates with affective style and vulnerability to psychopathology, with relatively stronger right activity predicting risk for internalizing and externalizing behaviors. In autistic youth, FAA has been related to ASD diagnostic features and to internalizing symptoms. Among our large, rigorously characterized, sex-balanced participant group, we attempted to replicate findings suggestive of altered FAA in youth with an ASD diagnosis, examining group differences and impact of sex assigned at

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Conflict of Interest

James C. McPartland consults with Customer Value Partners, Bridgebio, Determined Health, and BlackThorn Therapeutics, has received research funding from Janssen Research and Development, serves on the Scientific Advisory Boards of Pastorus and Modern Clinics, and receives royalties from Guilford Press, Lambert, Oxford, and Springer. The remaining authors report no affiliations with or involvement in any organization or entity with any financial interest in the outcome of this project.

birth. Second, we examined relations between FAA and behavioral variables (ASD features, internalizing, externalizing) within autistic youth, examining effects by sex. Third, we explored whether the relation between FAA, autism features, and mental health was informed by maternal depression history. In our sample, FAA did not differ by diagnosis, age, or sex. However, youth with ASD had lower total frontal alpha power than youth without ASD. For autistic females, FAA and bilateral frontal alpha power correlated with social communication features, but not with internalizing or externalizing symptoms. For autistic males, EEG markers correlated with social communication features, and with externalizing behaviors. Exploratory analyses by sex revealed further associations between youth FAA, behavioral indices, and maternal depression history. In summary, findings suggest that individual differences in FAA may correspond to social-emotional and mental health behaviors, with different patterns of association for females and males with ASD. Longitudinal consideration of individual differences across levels of analysis (e.g., biomarkers, family factors, environmental influences) will be essential to parsing out models of risk and resilience among autistic youth.

Lay Abstract

A long history of research links asymmetry in EEG activity across left and right frontal brain regions with risk for mental health concerns, but very little research has explored these relations among youth with ASD. In a group of children and teens, we found that links between asymmetry, social communication, restricted/repetitive behavior, family history, and youth mental health differed for females versus males with an ASD diagnosis. Findings suggest that mental health risk factors may work differently for autistic females versus autistic males.

Keywords

autism; EEG; asymmetry; alpha; sex differences; internalizing; externalizing; maternal depression

Introduction

Youth diagnosed with autism spectrum disorder (ASD) represent a group at particular risk for internalizing and externalizing concerns throughout development. From early childhood, young children with ASD have higher levels of negative affect relative to peers (Garon et al., 2009), with heightened symptoms of depression by school age (Neuhaus, Bernier, & Beauchaine, 2014; Rieffe, De Bruine, De Rooij, & Stockmann, 2014; Simonoff et al., 2008) and further increases in adolescence (Brereton, Tonge, & Einfeld, 2006). Anxiety may be even more prevalent, with over 80% of autistic youth displaying symptoms of anxiety and over 50% meeting diagnostic criteria for an anxiety disorder (de Bruin, Ferdinand, Meester, de Nijs, & Verheij, 2007; (Muris, Steerneman, Merckelbach, Holdrinet, & Meesters, 1998). Externalizing behaviors are also common for children and adolescents on the autism spectrum, including physical aggression and other challenging behaviors (Gray et al., 2012; Mazefsky & White, 2014). Identification of biological and psychosocial factors conferring risk for internalizing and externalizing is critical, both for understanding the etiology of mental health concerns and to inform prevention and intervention efforts.

Frontal asymmetry as index of vulnerability

One particularly relevant biological factor is the construct of EEG frontal alpha asymmetry (FAA), as a rich history of research links individual differences in FAA with vulnerability to psychopathology among the general population (Coan & Allen, 2004; Davidson, 1998; Reznik & Allen, 2018). FAA represents the relative balance of resting-state neural activity within the alpha frequency range (8–12 Hz) occurring between the left and right frontal regions of the brain (Davidson, 1992). Because neural activity is inversely related to alpha power, FAA computed through differences scores (ln(right alpha power) – ln(left alpha power)) yields a continuous metric for which zero marks comparable activity bilaterally, larger values indicate relatively greater left-sided FAA, and smaller values (less than zero) indicate relatively greater right-sided FAA (Coan & Allen, 2004). Conceptually, theories describe greater left-sided FAA as reflecting an approach- or activation-oriented motivational style (Coan & Allen; 2003; Davidson, 1992; Harmon-Jones & Allen, 1997; Pizzagalli et al., 2005), underlying a tendency toward positive affect (Coan & Allen, 2004); in contrast, relatively greater right-sided FAA reflects a motivational style of withdrawal or inhibition, a characteristic feature of both anxiety and depression, and negative affect (Coan & Allen, 2004; Davidson, 1998; Jesulola, Sharpley, Bitsika, Agnew, & Wilson, 2015). Consistent with these models, an extensive literature among adults links relatively greater right-sided FAA with heightened risk for negative affect, depression, and anxiety (Reznik & Allen, 2018; Stewart, Bismark, Towers, Coan, & Allen, 2010; Thibodeau, Jorgensen, & Kim, 2006; Tomarken, Davidson, & Henriques, 1990). Moreover, FAA may index a relatively stable vulnerability to internalizing psychopathology over time (Coan & Allen, 2004), as relatively stronger right-sided FAA both predicts the onset of depression (Nusslock et al., 2011; Possel et al., 2008) and persists beyond an acute depressive episode (Henriques & Davidson, 1990).

Associations between FAA and mental health are more mixed among children and adolescents. Longitudinal findings during early childhood suggest that young children who are simultaneously high in negative emotionality and low in positive emotionality – a combination that confers risk for depression (Klein, Kotov, & Bufferd, 2011) – demonstrate decreasing left-sided FAA over time (Goldstein et al., 2019). Among school-age children, relatively greater right FAA has been associated with higher rates of internalizing disorders (Gatzke-Kopp, Jetha, & Segalowitz, 2014). In adolescents, greater right FAA may both correspond to the presence of comorbid depression and anxiety (Feldmann et al., 2018) and correlate with features of depression in non-clinical samples (Grunewald et al., 2018; Possel, Lo, Fritz, & Seemann, 2008). However, other studies suggest depression corresponds to relatively greater left FAA (e.g., Grunewald et al., 2018). Moreover, results from a 2014 meta-analysis spanning infancy through adolescence indicated only a marginally significant association between greater relative right FAA and internalizing symptoms (Peltola et al.), far less conclusive than the associations documented for adults (e.g., Thibodeau et al., 2006). Links between FAA and children's externalizing behaviors are similarly inconclusive in terms of the direction of effects. For example, multiple studies have found higher externalizing behaviors associated with relatively stronger right-sided FAA (Santesso, Reker, Schmidt, & Segalowitz, 2006), whereas externalizing symptoms were positively associated

with frontal left activity when controlling for concurrent internalizing symptoms (Gatzke-Kopp et al., 2014).

Autism and frontal alpha asymmetry

Among autistic individuals, investigations of FAA are more limited, but suggest associations with the social communication and behavioral features of ASD as well as co-occurring emotional difficulties. From early in development, infants with an elevated likelihood of autism differed from their peers in resting FAA; whereas typically developing infants displayed greater right-sided FAA at 6 months of age that shifted to left-sided FAA within the second year of life (Gabard-Durnam et al., 2015), those with elevated autism likelihood displayed asymmetry scores close to zero at 6 months of age, which then trended toward right-sided asymmetry by 18 months (Gabard-Durnam et al., 2015). Cross-sectional studies have also documented group differences in FAA in response to social stimuli in the form of dynamic faces during childhood. Preschoolers with ASD showed a reversed pattern of FAA relative to children without ASD, with greater right-sided FAA in response to direct gaze when viewing faces (consistent with withdrawal) but greater left-sided FAA in response to downward gaze (consistent with approach) (Lauttia et al., 2019). Comparisons in older children have yielded similar findings with respect to open versus closed eyes (Kyllianinen et al., 2012), suggesting that social information may elicit different patterns of approach- and withdrawal-related activity in youth with and without ASD.

Associations with behavioral and emotional features among autistic youth are evident as well. Sutton and colleagues (2005) found that children with ASD (n=43, 9 to 14 years) displayed relatively stronger left FAA compared to peers without ASD, but also that stronger left asymmetry corresponded to fewer social difficulties but greater social anxiety, stress, and dissatisfaction. A larger sample studied by the same group (n=63, 8 to 15 years; Burnette et al., 2011) found no differences in asymmetry by diagnostic group, but found fewer social communication difficulties among those with greater left-sided FAA. Among adolescents with ASD, stronger left FAA was associated with fewer symptoms of anxiety by self-report (Schiltz et al., 2018). Finally, a study of social skills intervention for autistic youth found that greater right-sided FAA at baseline predicted worsening anxiety symptoms by self-report (though improvement in anxiety by parent-report) following treatment (Kang, Clarkson, Keifer, Rosen, & Lerner, 2019).

Differences by sex assigned at birth

Inconsistencies in the literature may stem in part from sex differences in FAA and its psychological correlates. Within ASD, Burnette et al. (2005) observed subtle changes in patterns of behavioral correlates of FAA when restricting their sample to only males, suggesting possible sex differences in associations between FAA and social, communication, and repetitive features of ASD. More broadly, studies of FAA and internalizing features find stronger associations between the two when study samples include a greater proportion of female participants (see meta-analysis by Peltola et al., 2014), and developmental and predictive effects of lower left FAA may be most prominent among women and girls (Baving, Laucht, & Schmidt, 2002; Stewart & Allen, 2018). A similar pattern emerges with regard to externalizing behaviors, as greater right-sided asymmetry may characterize girls

(but not boys) with significant externalizing symptoms, while greater left-side asymmetry is observed for non-externalizing girls (but not boys; Baving, Laucht, & Schmidt, 2003). Even very early in life, sex may moderate associations between FAA and infant temperament characteristics, potentially contributing to sex differences in the prevalence, presentation, and developmental course of internalizing and externalizing symptoms later in development (Gartstein, Bell, & Calkins, 2014; Rutter, Caspi, & Moffitt, 2003).

Current study goals

Considered together, data suggest that FAA may differ for youth with ASD relative to those without, individual differences in FAA may correspond to meaningful social and emotional features, and sex differences may modulate these effects. Accordingly, the primary goals of the current paper were two-fold. First, we aimed to consider FAA among children and adolescents with and without ASD in a large, rigorously characterized sample enriched for females, allowing the opportunity to disentangle the effects of sex from the effects of ASD. Because conventional FAA metrics do not provide insight into the contributions of individual hemispheres (Coan & Allen, 2003), we explored left and right alpha power as well throughout the current study. On the basis of existing research, we anticipated that autistic youth would display lesser left-sided FAA than nonautistic peers, as would youth higher on internalizing symptoms. We also anticipated that we would replicate our previous findings in this sample, such that decreased bilateral alpha power would be associated with ASD and with relatively older age (Neuhaus et al., 2021). Second, we aimed to investigate associations between FAA and social-emotional functioning among autistic youth, with particular attention to sex-specific associations between EEG and behavior. We anticipated that greater left-sided FAA would correspond to fewer internalizing difficulties, particularly among females, as well as lower scores on measures of social communication difficulties.

Over and above these findings, existing data suggest that FAA might interact with psychosocial factors in the development of psychopathology. Consequently, as an exploratory third aim, we sought to consider main and interactive effects of FAA and maternal depression history on social-emotional functioning for youth with autism, with a continued focus on potential sex differences. Maternal depression is a powerful familial risk factor for a range of emotional difficulties from very early in life, contributing to both increased likelihood of internalizing and externalizing concerns for youth (e.g., Forbes et al., 2006) and to altered patterns of EEG asymmetry relative to peers (Field & Diego, 2008; Goldstein et al., 2016; Peltola et al., 2014). For example, children with maternal history of depression display relatively stronger right FAA (Peltola et al., 2014), as well as a decreasing trajectory of left FAA during early childhood, in contrast to more stable FAA observed for those without such history (Goldstein et al., 2016). Again, effects may vary according to biological sex, with differential associations observed among females and males (Forbes et al., 2006; Peltola et al., 2014). Among children with ASD, heightened emotion dysregulation is observed when mothers have a history of internalizing symptoms (Mazefsky, Connor, & Oswald, 2010; Wiggins et al., 2019), but whether and how FAA and maternal history interact for autistic youth is thus far unexplored in the literature.

Method

Participants

The current analyses included EEG and phenotypic data for 280 youth with (n=142) or without (n=138) ASD who were enrolled in the Autism Center for Excellence (ACE) project Multimodal Developmental Neurogenetics of Females with ASD (R01MH100028), a multisite study of sex differences in ASD. Participants were enrolled at one of four sites throughout the U.S. (Seattle Children's Research Institute, Yale University, University of California Los Angeles, and Boston Children's Hospital), with data coordination through the University of Southern California. Caregivers and youth provided consent and assent, respectively, and procedures were approved by human subjects committees at each local site.

Participant characteristics are presented in Table 1, and also provided in Neuhaus et al. (2021). Youth were between the ages of 8 and 17 years (mean=12.8 years, SD=2.9) at enrollment and were invited to the study with the goal of creating a sample balanced by sex. Note that inclusion was based on caregiver-reported sex assigned at birth (hereafter, "sex"), and gender identity was not assessed at the time of enrollment. Across the four study locations, participant ethnic background was as follows: 14.3% of Hispanic or Latino descent, 77.1% not of Hispanic or Latino descent, and 8.6% who declined to answer. In addition, participant racial background was as follows: 4.3% Asian, 4.3% Black or African American, 0.4% Hawaiian or Pacific Islander, 71.1% white, 11.8% who endorsed more than one race, and 8.2% who declined to answer. Median annual household income was reported in increments, with the median income for the sample falling at approximately $125,000.

ASD group: All children and teens in our ASD group (N=142, 43% female) met criteria for autism according to DSM-IV-TR criteria (American Psychiatric Association, 2000), assessed through research-reliable administration of the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2; Lord et al., 2012) and Autism Diagnostic Interview – Revised (ADI-R; Rutter, LeCouteur, & Lord, 2003). Participants for whom ADI-R data were not available instead met clinical thresholds on parent report on the Social Responsiveness Scale, 2nd Edition (SRS-2; Constantino, 2012) or Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003). Enrollment inclusion also included verbal fluency and a standard score over 70 on at least one subtest of the Differential Ability Subscales, 2nd Edition (DAS-II; Elliott, 2007).

Neurotypical (NT) group: Youth in our non-ASD comparison group (N=138, 49% female) were included if they had no parent-reported concerns or diagnoses of ASD, learning disorder, intellectual disability, developmental or psychiatric concerns, or schizophrenia. Inclusion criteria for this group also included a total T-score below 60 on the SRS-2, a score below 11 on the SCQ, and the absence of ASD within their first- and second-degree relatives.

For both groups, exclusion criteria included twin status, history of a known single-gene event associated with ASD (e.g., Fragile X); recent history of active seizures; medical or neurological conditions likely to be causal for ASD (e.g., focal epilepsy); significant prematurity or perinatal events; significant environmental adversity; and sensory-motor

difficulties that would interfere with diagnostic or neuroimaging methods. In addition, participants were not using benzodiazepine, barbiturate, or anti-epileptic medications, and had not made medication changes within the six weeks prior to EEG collection.

EEG markers

Eyes-open resting state EEG was collected as participants viewed dynamic videos similar to screen savers, presented via EPrime. Participants completed three runs, in which each run contained approximately 64 seconds (32 trials of 2048 msec each) of eyes-open resting, for a total of approximately 192 seconds (96 trials of 2048 msec each) across the experiment. High density EEG was collected using the EGI 128-channel Net Amps 300 system with HydroCel nets (EGI Inc, Eugene OR) and a standard Net Station acquisition template. Sampling occurred at 500 Hz with signals referenced to vertex (Cz) and impedances below 50KOhms. Behavioral support was provided to minimize movement and promote attention, and instances of motion and inattention to stimuli were monitored and marked by staff for removal during post-processing.

Following acquisition, EEG data were filtered (bandpass filter at .1–100 Hz, with a notch filter of 60Hz) and segmented into 2048 msec segments. Bad channels and artifacts (e.g., eye blinks) were identified and addressed through NetStation tools and manualized hand editing. Please refer to Neuhaus et al. (2021) for full processing details, including detailed procedures for artifact detection. Next, spectral power was estimated using the Welch periodogram method in MATLAB (PWELCH function; see Frohlich et al., 2016; McEvoy et al., 2015), and FFTs were calculated to yield power estimates across a range of regions and frequency bands (Neuhaus et al., 2021).

Relevant to the current analyses, alpha was calculated as absolute power (μV_2) within the 8–12 Hz frequency band for the frontal left (electrodes 23, F3–24, 27, 28) and frontal right (electrodes 3, 117, 123, F4–124) regions. Values were natural logarithm-transformed, and frontal alpha asymmetry was then computed as recommended by Smith, Reznick, Stewart, and Allen (2017) as follows: frontal alpha asymmetry = ln(right alpha power) −ln(left alpha power). Because alpha power is inversely related to neural activity, lower FAA scores corresponded to relatively stronger right activity whereas higher FAA scores corresponded to relatively stronger left activity. Left alpha power, right alpha power, and frontal alpha asymmetry were all retained for analyses as continuous variables. FAA did not differ according to handedness among the participants with available handedness data, $F(1,201)=0.05$, $p=.83$.

Behavioral measures

Phenotypic characteristics of interest were assessed through two well-established instruments. In the ASD group, we assessed social communication behaviors with the Social Affect calibrated severity score (SA CSS) from the ADOS-2 (Hus, Gotham, & Lord, 2014). This score is derived from each participant's social affect score, on which higher scores indicate more social communication difficulties. The SA CSS provides a standardized score within a continuum from 1 (fewer difficulties observed) to 10 (more difficulties observed). Similarly, we utilized the Restricted/repetitive behaviors CSS (RRB

CSS), reflecting features related to restricted interests as well as sensory-oriented, repetitive, or ritualized behaviors.

From the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001), we extracted the Internalizing and Externalizing broadband *T*-scores (mean of 50, SD of 10). The Internalizing scale is composed of the Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints subscales, and the Externalizing scale is composed of the Aggressive Behavior and Rule-Breaking Behavior subscales. For both broadband scales, *T*-scores below 60 are within the "Normal" range, *T*-scores from 60 to 63 are within the "Borderline" range, and *T*-scores at or exceeding 64 are within the "Clinical" range.

Participants' primary caregivers completed interviews with clinical staff to report on family history of neurodevelopmental (e.g., cerebral palsy, neurofibromatosis) and mental health (e.g., depression, anxiety disorders) diagnoses. For each diagnosis, caregivers reported whether it was absent or present for the participants' biological parents and any siblings. Because the majority of caregiver reporters were mothers, we considered maternal history to be self-report, whereas paternal history was considered to be other-reported and so potentially less reliable. As a result, we did not include paternal mental health history in our analyses. On the basis of caregiver responses, we then classified participants as having a positive or negative maternal history of depression. Note that the interview did not differentiate within the broad category of depression nor between more specific conditions (e.g., postpartum depression, dysthymia).

Please see Table 1 for descriptive statistics by group for the full sample of 280 participants. Sample sizes varied for the three aims of the study as described next, and additional descriptive statistics are provided.

Analytic approach

Aim 1: We first sought to characterize frontal EEG alpha power for children and adolescents with ASD relative to those without ASD. Although study goals related primarily to FAA, left and right alpha power were analyzed in order to provide insight into the component processes (i.e., lateralized alpha activity) contributing to the FAA. To evaluate group differences in left and right frontal alpha power, we first conducted a repeated measures ANCOVA containing a within-subject term for hemisphere (left frontal, right frontal) and between-subjects terms for diagnostic group (ASD, NT) and sex assigned at birth. Because we wished to consider effects of group and sex over and above associated emotional features, we also included CBCL Internalizing and Externalizing T-scores as covariates. Age at assessment was included as well, given developmental shifts in EEG alpha power over development (Anderson & Perone, 2018; Clark, Barry, McCarthy, & Selikowitz, 2001).

To examine effects on frontal alpha asymmetry, we then conducted an ANCOVA with asymmetry as the outcome, diagnostic group and sex as between-subjects factors, and age, CBCL Internalizing, and CBCL Externalizing as covariates.

Aim 2: We then examined links between EEG measures (frontal alpha power and asymmetry) and behavioral variables specifically within our ASD group. Utilizing partial correlations controlling for age, we examined associations between our EEG variables and four behavioral domains, operationalizing autism features via the ADOS-2 SA and RRB CSS and mental health via the CBCL Internalizing and Externalizing domains. Analyses were conducted separately for female and male participants to consider sex-specific associations.

Aim 3: Third, we considered the role of familial depression history in youth social-emotional functioning for autistic females and males. Maternal depression data were available for 124 of the participants with ASD, and there were no differences between those with and without such data with respect to sex ratio, $\chi^2(1)=.14$, $p=.457$, age, $F(1,140)=0.85$, $p=.358$, left frontal alpha, $F(1,140)=0.25$, $p=.617$, right frontal alpha, $F(1,140)=0.01$, $p=.912$, frontal alpha asymmetry, $F(1,140)=0.685$, $p=.409$, ADOS-2 SA CSS, $F(1,140)=2.71$, $p=.102$, ADOS-2 RRB CSS, $F(1,140)=0.01$, $p=.926$, CBCL Internalizing, $F(1,115)=0.05$, $p=.823$, or CBCL Externalizing, $F(1,115)=0.00$, $p=.975$.

Chi-square analyses were conducted to examine rates of maternal depression history to determine whether frequency of maternal depression differed for ASD females versus ASD males. Next, ANOVAs were conducted to investigate whether EEG frontal alpha power differed according to maternal history. Finally, ANCOVAs (with child age as covariate) were conducted to consider main and interactive effects of EEG frontal alpha power and maternal depression history on autistic youth functioning.

In accordance with recommendations from Pedhazur (1997), we interpret interactions effects over main effects when both were present. Throughout analyses, a conventional significance threshold of $p<.05$ was applied.

Results

Aim 1: Frontal EEG alpha power and asymmetry by group

Data were available for 252 participants. Number of trials of EEG data did differ by group, with fewer trials of EEG data retained by the group with ASD (mean = 66.63, SD = 27.07) than the group without ASD (mean = 81.58, SD = 23.98; $F(1,246)=20.50$, $p<.001$, but there was no effect of sex, $F(1,246)=0.16$, $p=.69$, and no sex x group interaction on EEG data retention, $F(1,246)=0.16$, $p=.69$. For the full sample, number of EEG trials retained was positively correlated with participant age, $r=.22$, $p<.001$, and negatively with internalizing, $r=-.13$, $p=.04$, and externalizing, $r=-.14$, $p=.027$, features, but was not significantly correlated with left alpha power, $r=-.01$, $p=.860$, right alpha power, $r=-.07$, $p=.260$, or frontal alpha asymmetry, $r=-.11$, $p=.078$.

Consistent with hypotheses and our previous analyses (Neuhaus et al., 2021), the ANCOVA for frontal alpha power revealed significant effects of diagnostic group and age, such that greater alpha power was found in participants in the NT group compared to those with ASD, as well as in participants who were younger compared to those who were older. See Figure 1. The effect of sex did not reach significance, and there were no effects of hemisphere,

internalizing, or externalizing. Complete main and interaction statistical effects are presented in Table 2. Overall, given the inverse relationship between alpha power and neural activity, the pattern of results indicated increased neural activity in the autistic youth compared to the group without ASD.

With regard to frontal alpha asymmetry, the overall ANCOVA was not significant. There were no differences in asymmetry according to diagnosis, age, sex, internalizing or externalizing. This absence of effects contrasted with our hypotheses, as we had anticipated effects of diagnostic group and internalizing symptoms on FAA.

Aim 2: EEG and behavioral correlates among youth with ASD

Valid EEG frontal alpha power and behavioral data were available for 142 participants with ASD (61 female, 43%). Associations between EEG measures and behavior are presented in Table 3.

For autistic females, contrary to expectations, FAA did not correlate with social communication or internalizing features. Right (r=.36, p=.005) and left (r=.26, p = .045) frontal alpha power were positively correlated with the social-affect severity score on the ADOS-2. Females with greater alpha power (indicating less neural activity) bilaterally tended to have more social communication difficulties during the ADOS-2. EEG measures were not significantly associated with restricted/repetitive behaviors scores on the ADOS-2, nor with internalizing or externalizing on the CBCL.

In autistic males, frontal alpha asymmetry correlated positively with social communication difficulties (r=.23, p=.037). In addition, externalizing symptoms were negatively correlated with frontal alpha asymmetry scores (r=−.32, p=.008); males displaying fewer externalizing symptoms also displayed relatively stronger left-sided FAA.

Aim 3: Maternal depression history in ASD

Relation to internalizing and externalizing.—Among autistic females, 38.9% of mothers endorsed a personal history of depression and 30.0% of mothers of autistic males endorsed a history of depression. The rate was not significantly different by child sex, $\chi^2(1)=1.08$, p=.300. Participants' frontal alpha power and asymmetry did not differ according to maternal depression history for either females or males (ps>.14). See Table 4.

Results from ANCOVAs examining frontal alpha power (left, right, asymmetry) in relation to maternal depression are presented separately by sex in Table 5.

For females with ASD, models containing left alpha power, right alpha power, and frontal asymmetry were significant with respect to internalizing symptoms. The model for left alpha power was driven by a significant main effect for maternal depression history, $F(1,42)=4.55$, p=.039, partial η^2 =.10, such that autistic females had higher internalizing scores when mothers had a history of depression. For the model pertaining to right alpha power, none of the individual predictors within the model were individually significant despite the overall model significance. For frontal asymmetry, the main effect of maternal depression history was again significant, $F(1,42)=12.79$, p<.001, partial η^2=.233.

For autistic males, models for externalizing behavior were significant for left and right frontal power as well as for frontal asymmetry. See Table 5. For left and right alpha power, no individual predictors emerged as statistically significant. However, within the frontal asymmetry model, the interaction of maternal depression history and frontal asymmetry was significant, $F(1,56)=8.46$, $p=.005$, partial $\eta^2=.13$, as were the main effects of maternal depression, $F(1,56)=8.83$, $p=.004$, partial $\eta^2=.14$ and asymmetry, $F(1,56)=4.44$, $p=.04$, partial $\eta^2=.07$. These effects were such that lower asymmetry scores (reflecting relatively greater right hemisphere activity) corresponded to more externalizing behaviors for males only when mothers *did not* endorse a history of depression.

Relation to autistic behaviors.—The model pertaining to right alpha power and social affect features on the ADOS-2 was also significant for autistic females (see Table 5). Within the model, there was a main effect of right alpha power on social affect scores, $F(1,49)=10.08$, $p=.003$, partial $\eta^2= .17$, such that greater right frontal alpha power corresponded to more social communication difficulties on the ADOS-2, consistent with the significant positive correlation reported earlier (Table 3).

In addition, among males with ASD, models containing alpha power for left and right frontal regions were both significant with regard to restricted/repetitive behaviors. For both, there was a significant interaction between alpha power and maternal depression (left: $F(1,65)=7.09$, $p=.010$, partial $\eta^2=.10$; right: $F(1,65)=9.13$, $p=.004$, partial $\eta^2=.12$). The interaction was consistent in both hemispheres, such that greater left or right alpha power corresponded to more restricted/repetitive behaviors only for males whose mothers endorsed a history of depression.

Discussion

The overarching objective of the current study was to consider frontal alpha power and asymmetry in relation to sex, age, and social-emotional features among children and adolescents with and without ASD. Previous findings from our group and others have identified decreased resting alpha power (indicating increased alpha activity) among samples of autistic children and adolescents, older participants, and females (Neuhaus et al., 2021; Wang et al., 2013) although not found in younger autistic children (Webb et al., 2023). Effects were largely consistent in the current paper, which included re-analysis of our data to examine effects of internalizing and externalizing symptoms, indicating that alpha differences by diagnostic group and age were robust over and above concurrent internalizing and externalizing features. In a shift from our previous report, however, the effect of sex in models of frontal alpha power no longer met conventional thresholds for significance (see Table 2) when accounting for co-occurring internalizing and externalizing behaviors.

In contrast to hypotheses, we did not observe differences in frontal alpha asymmetry within the current sample, suggesting that group differences in alpha power were comparable across left and right frontal regions for our participants. Although greater left-sided FAA corresponds to stronger social approach under experimental conditions in ASD (Kyllianinen et al., 2012; Lauttia et al., 2019), published findings with direct comparisons of resting-state FAA in ASD are quite limited, with one study (Sutton et al., 2005) revealing

relatively stronger left asymmetry among children with ASD, and a related study finding no differences by diagnosis (Burnette et al., 2011). An important component moving forward will be to disentangle potential effects of diagnosis and sex, as both of these published study groups were comprised primarily of males (83% and 91% male, respectively, compared with 57% here). Findings regarding FAA and social-emotional features in the general population have been sensitive to sample sex ratios (Peltola et al., 2014), and it may be that group comparisons of FAA are similarly sensitive.

Brain-behavior correlates

The second aim of the current study was to examine associations between EEG markers and social-emotional features for autistic youth, separately by sex assigned at birth. Increased alpha power (indicating decreased neural activity) was associated with increased social communication features of ASD on the ADOS-2 for females. This finding differs from those of our original analysis in which frontal alpha was unrelated to social skills as measured by the Vineland Adaptive Behavior Scales (Vineland-II; Sparrow, Cicchetti, & Balla, 2005), and may stem from methodological differences in reporter (caregiver report on the Vineland-II versus clinician assessment during the ADOS-2), type of social behavior assessed (skills versus difficulties), and population in which the measure was developed (community versus clinically-recruited).

With regard to asymmetry, relatively stronger right-sided FAA corresponded to both more externalizing behaviors and fewer social communication difficulties for males with ASD. Both correlations are somewhat counter-intuitive. As discussed earlier, prevailing motivational models for FAA link right-sided FAA with withdrawal behaviors (predicting fewer externalizing symptoms and greater social communication difficulties) and stronger left-sided FAA with approach behaviors (predicting more externalizing behaviors and fewer social communication difficulties) (Coan & Allen, 2004; Davidson, 1998; Thibodeau et al., 2006). Our findings suggest a need to more fully characterize motivation in ASD in relation to social communication and externalizing. Specifically, the traditional model assumes an approach function for externalizing behaviors (e.g., aggression or rule-breaking to obtain a goal), but fails to consider the possibility of a withdrawal, avoidance, or anxiety-driven function of externalizing behaviors which would include reactive aggression, oppositional behavior or tantrums reflecting efforts to escape an event or activity, or active avoidance of challenging or anxiety-provoking situations (Matson et al., 2011). From that perspective, withdrawal motivation may drive externalizing behaviors, particularly in the context of communication difficulties in autistic youth (Neuhaus et al., 2022). Although this possibility is speculative, links between asymmetry and externalizing have been inconsistent in studies of nonautistic youth (e.g., Gatzke-Kopp et al., 2014; Peltola et al., 2014; Santesso et al., 2006), and assessing the function of externalizing behavior may aid in clarifying that inconsistency.

Similarly, our finding of fewer social communication difficulties with relatively stronger right-sided FAA is surprising. Reframed as stronger left-sided FAA (approach-related) in the context of more social-communication difficulties, this pattern might suggest unique approach styles or unconventional interaction strategies among autistic youth. ADOS-2

items comprising the social affect score assess the quality of social approach, interpersonal rapport, and reciprocal communication. Though not exclusively, higher scores on these items can capture difficulty modulating how one expresses social interest. For example, an individual who expresses interest in the clinician by repeatedly introducing a preferred topic, asking overly personal questions, or offering contextually inappropriate humor might receive elevated scores that actually result from unconventional social strategies in combination with intact social approach motivation. Together, these findings highlight the need to consider social *motivation* and social *skill* as overlapping but separable variables.

Despite prior evidence suggesting a relationship, frontal alpha asymmetry did not correlate with internalizing symptoms for autistic participants. Both developmental and methodological factors may have contributed to the lack of association. Developmentally, our participant group spanned a broad range with a mean age around 12 years, and associations between FAA and internalizing symptoms may emerge over time, as rates of depression increase during adolescence (Gotham, Brunwasser, & Lord, 2015). Methodologically, the CBCL broadband Internalizing score (Achenbach & Rescorla, 2001) used here includes items indexing withdrawal, depression, and anxiety features, and FAA among individuals with depression can be altered by the presence of significant anxiety, and even by the particular dimensions of anxiety (e.g., worry, panic, anxious apprehension) experienced (Jesulola et al., 2015; Nusslock et al., 2018). Items within the Internalizing domain may also overlap with features of ASD (e.g., perceived shyness, preference to be alone), and investigations with measures that disentangle that overlap may yield different insights.

Maternal depression in relation to EEG

In our third aim, we observed associations between EEG and behavioral features in exploratory analyses investigating the role of maternal depression history. For females with ASD, we observed a main effect of maternal depression history on youth internalizing, with higher internalizing scores in the context of positive depression history. Among males with ASD, maternal depression related primarily to externalizing and restricted/repetitive behaviors. Stronger right asymmetry corresponded to more externalizing for males whose mother did not endorse depression, while greater alpha power bilaterally corresponded to more restricted/repetitive behavior for males whose mothers endorsed a positive history of depression. Although these analyses were exploratory and included only the subset of participants for whom parental history data were available, they suggest the need for in-depth exploration of sex-based effects in mental health outcomes in ASD. Mechanisms through which maternal mental health are associated with child EEG and behavioral outcomes can include shared genetic liability, environmental stressors, and other factors, and clearer understanding of these processes over the course of development warrant further study.

Limitations

Although our sample was large and rigorously characterized, it did not include autistic individuals without verbal fluency, with intellectual disability, or for whom EEG data collection was not feasible. As such, we cannot determine whether findings extend across

the full spectrum of individuals with ASD. Additionally, diagnostic groups differed in the number of EEG trials included in the current analyses, with fewer trials corresponding to diagnosis of ASD, younger age, and lower internalizing and externalizing scores. As a result, findings may be less robust for individuals with those features. Importantly, our EEG analyses were limited to frontal power and asymmetry in the alpha frequency band, but diagnostic group differences and social-emotional correlates of activity in other regions and frequency bands may be important as well. For example, parietal asymmetry also corresponds to approach-inhibition traits in ASD (Schiltz et al., 2018), and increases in left-sided gamma-band asymmetry have been observed following social skills intervention, corresponding to increased social engagement and knowledge among autistic youth (Van Hecke et al., 2015). Similarly, different methods of computing FAA may yield varying associations with social-emotional processes, particularly in the context of development over time (Vincent et al., 2021). Absolute (rather than relative) FAA was used here for consistency with previous literature, but alternative approaches may prove valuable, particularly when considering developmental processes (Vincent, Xie, & Nelson, 2021). Cautious interpretation is also warranted given our use of conventional statistical thresholds (rather than correcting for number of analyses), an approach selected to preserve statistical power as one of the few investigations of the moderating effects of EEG asymmetry on behavior in a sex-balanced sample of autistic youth.

There are additional considerations related to our clinical assessment. Maternal depression history relied on mothers' self-report, without confirmation through health records or clinical assessment. While in-depth assessment was not available, a comprehensive meta-analysis linking youth FAA with maternal history of depression found no difference in effect size between studies with maternal self-report of depression versus those with clinical assessment of maternal depression (Peltola et al., 2014), reinforcing the utility of self-report. Similarly, we cannot distinguish between mothers with depression at the time of data collection and those with historical depression, nor can we estimate the impact that any current depressive symptoms might have had on their report of youth behavior. Finally, the current data did not include any self-report measures of internalizing, externalizing, social communication, or restricted/repetitive behavior among youth with ASD. Firsthand perspectives on these constructs would be helpful moving forward in order to more fully represent internal experiences that are not accessible to caregiver report.

Conclusions

Broadly, our findings suggest that youth with and without ASD do not differ on resting frontal alpha asymmetry, but that individual differences in FAA may (1) correspond to social-emotional outcomes, and (2) interact with risk factors influencing those outcomes among autistic youth. Continued consideration of individual differences across levels of analysis (e.g., biomarkers, family factors, environmental influences) will be essential to parsing out models of risk and resilience among autistic youth, as well as to informing efforts at prevention and intervention for mental health concerns. Within this work, the literature stemming from youth without ASD provides a rich basis from which to build, and intentional exploration of moderators and mechanisms of outcomes specifically among individuals on the autism spectrum will be needed in order to understand shared versus

unique processes and provide appropriate supports (Mundy, Henderson, Inge, & Coman, 2007).

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Data Availability Statement

The data that support the findings of this study are openly available in NIMH Data Archive at https://nda.nih.gov/edit_collection.html?id=2021.

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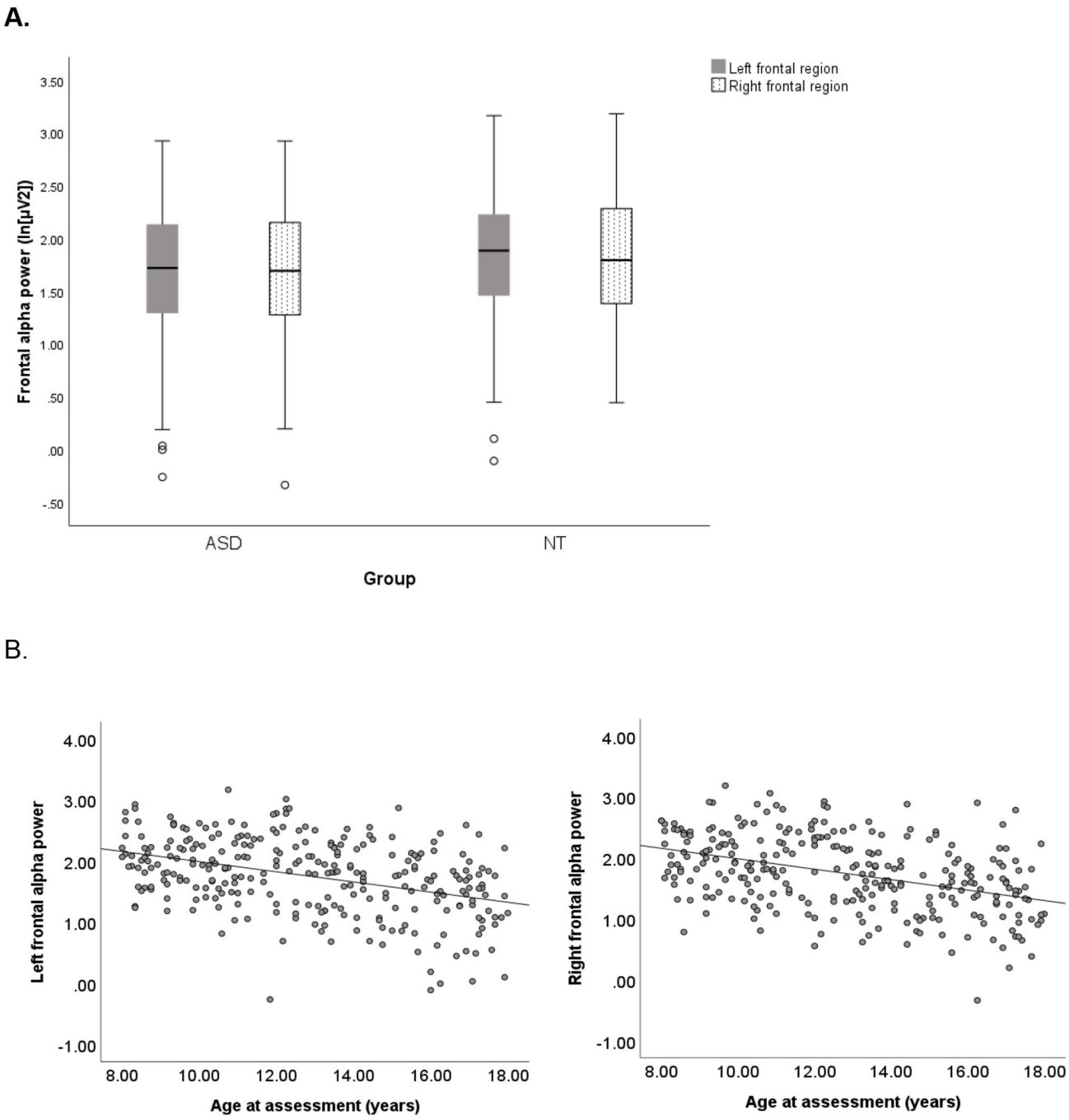

Figure 1: Alpha power in left and right frontal regions by diagnostic group (upper panel) and age at assessment (lower panel)

Table 1:

Descriptive statistics for EEG and social-emotional measures for the full sample.

	Female		***Male***	
	ASD	**NT**	**ASD**	**NT**
N=280	61	68	81	70
Age (years)	12.46 (2.9) range: 8.08–17.67	13.17 (3.07) range: 8.0–18.0	12.21 (2.85) range: 8.0–17.92	13.45 (2.76) range: 8.25–17.92
Left Alpha (ln[μV2])	1.61 (0.64) range: −0.26–2.93	1.76 (0.64) range: −0.11–2.87	1.77 (0.59) range: 0.0–2.85	1.88 (0.57) range: 0.49–3.17
Right Alpha (ln[μV2])	1.59 (0.60) range: 0.20–2.78	1.73 (0.63) range: 0.45–3.18	1.78 (0.60) range: −0.34–2.29	1.86 (0.57) 0.71–3.06
Frontal alpha asymmetry	−0.02 (0.34) range: −0.90–1.33	−0.03 (0.44) range: −0.80–1.86	0.01 (0.26) range: −0.76−.73	−0.02 (0.25) range: −0.78–0.44
CBCL Internalizing T-Score	62.9 (12.31) range: 39–83	46.11 (9.47) range: 33–71	59.84 (8.45) range: 40–76	43.86 (9.05) range: 34–70
CBCL Externalizing T-Score	56.82 (11.47) range: 34–82	42.85 (7.70) range: 34–61	55.19 (10.48) range: 33–77	40.50 (6.74) range: 33–55
ADOS-2 SA CSS	6.61 (1.79) range: 3–10	--	7.28 (1.89) range: 3–10	--
ADOS-2 RRB CSS	6.84 (2.59) range: 1–10	--	6.54 (2.59) range: 1–10	--
N with Maternal Depression History	14 (N = 41)	--	16 (N = 53)	

Notes: CBCL, Child Behavior Checklist; ADOS-2, Autism Diagnostic Observation Schedule, 2nd Edition; SA, Social Affect; RRB, Restricted and Repetitive Behavior; CSS, Calibrated Severity Score.

Table 2.

Main and interactive effects of diagnostic group, sex, age, internalizing and externalizing on EEG power and frontal alpha asymmetry

	Frontal alpha power	Frontal alpha asymmetry	Summary
Omnibus	--	$F(1,245) = 0.40$, $p = .881$ partial $\eta^2 = .01$	
Group	$F(1,245) = 6.21$, $p = .013$ partial $\eta^2 = .03$	$F(1,245) = 0.81$, $p = .369$ partial $\eta^2 = .00$	Greater alpha power among NT group
Sex	$F(1,245) = 3.34$, $p = .076$ partial $\eta^2 = .01$	$F(1,245) = 0.28$, $p = .595$ partial $\eta^2 = .00$	
Age	$F(1,245) = 48.90$, $p < .001$ partial $\eta^2 = .17$	$F(1,245) = 0.51$, $p = .477$ partial $\eta^2 = .00$	Greater alpha power among younger participants
Internalizing	$F(1,245) = 0.25$, $p = .616$ partial $\eta^2 = .00$	$F(1,245) = 0.47$, $p = .495$ partial $\eta^2 = .00$	
Externalizing	$F(1,245) = 0.04$, $p = .841$ partial $\eta^2 = .00$	$F(1,245) = 0.12$, $p = .727$ partial $\eta^2 = .00$	
Hemisphere	$F(1,245) = 1.30$, $p = .256$ partial $\eta^2 = .01$	--	
Group × Sex	$F(1,245) = 0.10$, $p = .757$ partial $\eta^2 = .00$	$F(1,245) = 0.05$, $p = .821$ partial $\eta^2 = .00$	
Hem. × Group	$F(1,245) = 0.81$, $p = .369$ partial $\eta^2 = .00$	--	
Hem. × Sex	$F(1,245) = 0.28$, $p = .595$ partial $\eta^2 = .00$	--	
Hem. × Age	$F(1,245) = 0.51$, $p = .477$ partial $\eta^2 = .00$	--	
Hem. × Int.	$F(1,245) = 0.47$, $p = .495$ partial $\eta^2 = .00$	--	
Hem. × Ext.	$F(1,245) = 0.12$, $p = .727$ partial $\eta^2 = .00$	--	
Hem. × Group × Sex	$F(1,245) = 0.05$, $p = .821$ partial $\eta^2 = .00$	--	

Notes: Hem., Hemisphere; Int., Internalizing; Ext., Externalizing.

Table 3:

Partial correlations between EEG alpha power and behavioral measures for female and male youth with ASD

	Left frontal alpha power	Right frontal alpha power	Frontal alpha asymmetry
Females			
CBCL Internalizing	$r = .13$ $p = .386$	$r = .08$ $p = .595$	$r = -.09$ $p = .56$
CBCL Externalizing	$r = .13$ $p = .389$	$r = .15$ $p = .311$	$r = .03$ $p = .861$
ADOS-2 SA CSS	$r = .26$ $p = .045$	$r = .361$ $p = .005$	$r = .14$ $p = .29$
ADOS-2 RRB CSS	$r = -.13$ $p = .317$	$r = -.06$ $p = .677$	$r = .15$ $p = .26$
Males			
CBCL Internalizing	$r = .02$ $p = .882$	$r = -.04$ $p = .728$	$r = -.12$ $p = .334$
CBCL Externalizing	$r = .11$ $p = .39$	$r = -.06$ $p = .642$	$r = -.32$ $p = .008$
ADOS-2 SA CSS	$r = -.01$ $p = .919$	$r = .10$ $p = .376$	$r = .233$ $p = .037$
ADOS-2 RRB CSS	$r = .10$ $p = .391$	$r = .03$ $p = .792$	$r = -.14$ $p = .218$

Notes: CBCL, Child Behavior Checklist; ADOS-2, Autism Diagnostic Observation Schedule, 2nd Edition; SA, Social Affect; RRB, Restricted and Repetitive Behavior; CSS, Calibrated Severity Score. Correlations control for age at time of assessment.

Table 4:

Mean scores (SD, ranges) for EEG measures by maternal depression history for female and male youth with ASD

	Maternal History of Depression		***F***
	Absent	**Present**	
Females (N = 54)	n = 33	n = 21	
Left frontal alpha power	1.67 (0.64) range: −0.26–2.93	1.56 (0.67) range: 0.04–2.52	$F(1,52) = 0.38$, $p = .54$ partial $\eta^2 = .01$
Right frontal alpha power	1.60 (0.55) range: 0.38–2.78	1.58 (0.69) range: 0.20–2.47	$F(1,52)=0.01$, $p = .917$ partial $\eta^2 = .00$
Frontal alpha asymmetry	−0.08 (0.39) range: −0.90–1.33	0.02 (0.23) range: −0.46–0.54	$F(1,52) = 1.0$, $p = .323$ partial $\eta^2 = .02$
Males (N = 70)	n = 49	n = 21	
Left frontal alpha power	1.73 (0.62) range: 0.00–2.85	1.86 (0.52) range: 1.06–2.78	$F(1,68) = 0.73$, $p = .397$ partial $\eta^2 = .01$
Right frontal alpha power	1.71 (0.64) range: −0.34–2.92	1.94 (0.52) range: 0.90–2.92	$F(1,68) = 2.13$, $p = .149$ partial $\eta^2 = .03$
Frontal alpha asymmetry	−0.02 (0.26) range: −0.76–0.73	0.08 (0.28) range: −0.52–0.55	$F(1,68) = 2.08$, $p = .154$ partial $\eta^2 = .03$

Table 5:

Omnibus results for models of EEG measures, maternal depression history, and their interaction in relation to youth outcomes

	Left Alpha	Right Alpha	Frontal Asymmetry
Females			
CBCL Internalizing	$F(4,42) = 3.89$, $p = .009$ partial $\eta^2 = .27$	$F(4,42) = 3.38$, $p = .017$ partial $\eta^2 = .24$	$F(4,42) = 3.74$, $p = .011$ partial $\eta^2 = .26$
CBCL Externalizing	$F(4,42) = 1.67$, $p = .175$ partial $\eta^2 = .14$	$F(4,42) = 2.13$, $p = .094$ partial $\eta^2 = .17$	$F(4,42) = 1.36$, $p = .264$ partial $\eta^2 = .12$
ADOS CSS SA	$F(4,49) = 1.30$, $p = .283$ partial $\eta^2 = .10$	$F(4,49) = 2.74$, $p = .039$ partial $\eta^2 = .18$	$F(4,49) = 1.65$, $p = .177$ partial $\eta^2 = .12$
ADOS CSS RRB	$F(4,49) = 0.63$, $p = .644$ partial $\eta^2 = .05$	$F(4,49) = 0.66$, $p = .625$ partial $\eta^2 = .05$	$F(4,49) = 0.92$, $p = .461$ partial $\eta^2 = .07$
Males			
CBCL Internalizing	$F(4,56) = 1.40$, $p = .245$ partial $\eta^2 = .09$	$F(4,56) = 1.86$, $p = .131$ partial $\eta^2 = .12$	$F(4,56) = 1.78$, $p = .147$ partial $\eta^2 = .11$
CBCL Externalizing	$F(4,56) = 2.67$, $p = .041$ partial $\eta^2 = .16$	$F(4,56) = 2.66$, $p = .042$ partial $\eta^2 = .16$	$F(4,56) = 8.24$, $p < .001$ partial $\eta^2 = .37$
ADOS CSS SA	$F(4,65) = 0.29$, $p = .882$ partial $\eta^2 = .02$	$F(4,65) = 0.37$, $p = .830$ partial $\eta^2 = .02$	$F(4,65) = 1.77$, $p = .145$ partial $\eta^2 = .10$
ADOS CSS RRB	$F(4,65) = 2.94$, $p = .027$ partial $\eta^2 = .15$	$F(4,65) = 3.30$, $p = .016$ partial $\eta^2 = .17$	$F(4,65) = 1.86$, $p = .129$ partial $\eta^2 = .10$

Notes: CBCL, Child Behavior Checklist; ADOS-2, Autism Diagnostic Observation Schedule, 2nd Edition; CSS, Calibrated Severity Score; SA, Social Affect; RRB, Restricted and Repetitive Behavior.