Received: 6 December 2022 | Revised: 14 June 2023 | Accepted: 28 July 2023

DOI: 10.1002/dev.22415

Developmental Psychobiology WILEY

RESEARCH ARTICLE

Pubertal maturation and timing effects on resting state electroencephalography in autistic and comparison youth

Hannah M. Rea[1] | Ann Clawson[2] | Caitlin M. Hudac[3] | Megha Santhosh[4] | Raphael A. Bernier[1] | Rachel K. Earl[1] | Kevin A. Pelphrey[5,6,7] | Sara Jane Webb[1,4] | Emily Neuhaus[1,4] | the GENDAAR Consortium[1]

[1]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington, USA

[2]Department of Neuropsychology, Children's National Hospital, Washington, DC, USA

[3]Department of Psychology, University of South Carolina, Columbia, South Carolina, USA

[4]Center on Child Health, Behavior and Development, Seattle Children's Research Institute, Seattle, Washington, USA

[5]Brain Institute, Department of Neurology, University of Virginia, Charlottesville, Virginia, USA

[6]Department of Psychology, University of Virginia, Charlottesville, Virginia, USA

[7]School of Education and Human Development, University of Virginia, Charlottesville, Virginia, USA

Correspondence
Emily Neuhaus, Department of Psychiatry and Behavioral Sciences, University of Washington, M/S CAC, PO Box 5371, Seattle, WA 98145-5005.
Email: eneuhaus@uw.edu

Funding information
National Institutes of Health, Grant/Award Numbers: R01 MH10028, R01 MH100047

Abstract

Autistic and comparison individuals differ in resting-state electroencephalography (EEG), such that sex and age explain variability within and between groups. Pubertal maturation and timing may further explain variation, as previous work has suggested alterations in pubertal timing in autistic youth. In a sample from two studies of 181 autistic and 94 comparison youth (8 years to 17 years and 11 months), mixed-effects linear regressions were conducted to assess differences in EEG (midline power for theta, alpha, and beta frequency bands). Alpha power was analyzed as a mediator in the relation between pubertal maturation and timing with autistic traits in the autistic groups to understand the role of puberty in brain-based changes that contribute to functional outcomes. Individuals advanced in puberty exhibited decreased power in all bands. Those who experienced puberty relatively early showed decreased power in theta and beta bands, controlling for age, sex, and diagnosis. Autistic individuals further along in pubertal development exhibited lower social skills. Alpha mediated the relation between puberty and repetitive behaviors. Pubertal maturation and timing appear to play unique roles in the development of cognitive processes for autistic and comparison youth and should be considered in research on developmental variation in resting-state EEG.

Abbreviations: ADI-R, Autism Diagnostic Interview—Revised; ASD, autism spectrum disorder; CI, confidence interval; DAS-II, Differential Ability Scales—Second Edition; EEG, electroencephalography; ICC, intraclass correlation coefficient; PDS, Pubertal Development Scale; RRB, restricted and repetitive behavior; SCQ, Social Communication Questionnaire; SRS-2, Social Responsiveness Scale, Second Edition; VABS-II, Vineland Adaptive Behavior Scales, Second Edition.

KEYWORDS
autism spectrum disorder, electroencephalography (EEG), pubertal maturation, pubertal timing, resting state, spectral power

1 | INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by social–communication differences and restricted and repetitive behaviors (RRBs) (American Psychiatric Association, 2013). Neural biomarkers may elucidate mechanisms of ASD to provide more objective measures of functioning for stratification in clinical trials (McPartland et al., 2020). Resting-state electroencephalography (EEG) may be a primary biomarker given that autistic individuals [1] differ from comparison individuals in resting-state power frequencies (Neuhaus et al., 2021). Maturational changes (age) and sex[2] account for some variability between groups and studies, but the nature of diagnostic group differences is not yet fully understood (Gorday & Meyer, 2018; Wang et al., 2013). Recent work in functional and structural neuroimaging suggests that pubertal processes may enhance understanding of factors, beyond age, that impact neural functioning (Murray et al., 2016; Walsh et al., 2021). Examining puberty (maturation and timing) may account for developmental changes that contribute to variability across groups and relate to autistic traits; also, ongoing research is needed on characteristics that impact variation in EEG findings (Neuhaus et al., 2021).

1.1 | EEG in ASD

EEG reflects postsynaptic potentials of pyramidal neurons in the neocortex with high temporal resolution (Jeste et al., 2015; Kirschstein & Köhling, 2009), with state and trait functioning captured in EEG spectral frequency. Theta (4–8 Hz) reflects focused attention, effort, stimulus processing, memory, and recall (Pizzagalli, 2007). Alpha (8–13 Hz) increases during relaxation, while decreases are associated with inhibition, attention, and sensory control (Schürmann & Başar, 2001). Beta (13–30 Hz) relates to task engagement, motor control, and alertness (Neuper & Pfurtscheller, 2001). Research indicates differences between autistic and comparison individuals in EEG power within each of these frequency bands when "at rest" or engaging in calm viewing. Autistic individuals show increased power at lower (theta) and higher (beta) frequencies, with reduced power in midrange (alpha) frequencies (Wang et al., 2013). Most consistently observed are alpha power reductions, which have been found in large studies in autistic children and adults and across a broad range of intellectual functioning (Dawson et al., 1995; Murias et al., 2007; Neuhaus et al., 2021). As a result, alpha band activity in particular has been proposed as a marker of altered neural activity in autism, with evidence that power reductions are related to the social and emotional autism traits (Shephard et al., 2018; Wang et al., 2013; Wantzen et al., 2022).

Across studies, differences in sample characteristics—including age and sex ratios—may account for inconsistencies in resting-state differences between autistic and nonautistic individuals. For example, few studies have been well-powered to investigate sex differences in ASD research. In a large sex-balanced sample of autistic and nonautistic adolescents, males had significantly greater power values in all five frequency bands in the central and posterior regions, with no interaction with diagnostic group. Within the autistic group, lower power in theta, alpha, and beta bands was related to better social skills in autistic males but not in autistic females (Neuhaus et al., 2021). While there is evidence that age and sex may play a role in diagnostic group differences in resting-state EEG, no studies have explored the separate yet overlapping impact of puberty, a potentially important source of individual difference.

1.2 | Puberty and neural functioning

Puberty is a nonlinear process involving complex, interrelated physiological, behavioral, and cognitive processes that occur from early childhood through adolescence (Dorn et al., 2006). Given this complexity, it is important to examine not only an individual's *progress* through pubertal stages (referred to as maturation in the current paper) but also relative pubertal *timing* (Dorn & Biro, 2011). Pubertal timing represents the *relative* deviation of an individual's pubertal stage compared to the average stage for their age and sex (Dooley et al., 2022). Though age and pubertal maturation are often correlated, age alone does not fully account for individual variability in pubertal maturation and timing, suggesting the need for a more nuanced understanding of developmental change (Blakemore et al., 2010; Fung et al., 2020; Sisk & Foster, 2004).

Indeed, age and puberty likely have separable influences on neural, cognitive, and physical development (Dorn & Biro, 2011; Shirtcliff et al., 2009). Puberty is a sensitive period in neurodevelopment, eliciting both temporary changes in neural activity and permanent alterations to neural structure (Byrne et al., 2017; Herting & Sowell, 2017; Vijayakumar et al., 2018). Evidence of brain-based pubertal effects comes primarily from structural and functional neuroimaging studies in humans and animals (Mendle et al., 2019; Vijayakumar et al., 2018) and indicates that pubertal hormones trigger reductions in gray matter, increases in white matter density (Herting & Sowell, 2017), and changes in functional connectivity (Gabard-Durnam et al., 2014; Peters et al., 2015). Further, puberty-driven changes are critical in facilitating the development of cognitive, social, and emotional functions

[1] "Identity-first language" will be used based on consultation with self-advocates and preferences by autistic people, as identity-first language is considered less stigmatizing than person-first language (Bottema-Beutel et al., 2021; Kenny et al., 2016).
[2] Sex will refer to sex designated at birth throughout the article.

(Blakemore et al., 2010; Corbett et al., 2020; Fung et al., 2020; Pfeifer et al., 2013; Whitehouse et al., 2011). For example, nonautistic males who were early to mature performed better on visuospatial cognitive tasks, compared to males who were late to mature (Shirazi et al., 2020), although the same pattern was not found for females (Beltz & Berenbaum, 2013). In the general population, early puberty has been linked to increased risk for psychopathology (Ullsperger & Nikolas, 2017) and puberty-driven changes in brain development may play a role in mental health outcomes (Byrne et al., 2017). Despite these links, much remains to be learned about whether and how changes in brain activity mediate the association between biochemical changes associated with puberty and functional outcomes such as social–emotional functioning (Murray et al., 2016; Ullsperger & Nikolas, 2017). For example, although pubertal rises in reproductive hormones have been theorized to enhance development in the prefrontal and temporal cortices (regions that support social awareness and self-evaluation [Jankowski et al., 2014; Pfeifer et al., 2013]), existing data are incomplete, particularly among autistic youth.

1.3 | Puberty and ASD

Relatively little is known about puberty in autistic individuals. Autistic populations experience earlier puberty and growth spurts than comparison groups (Corbett et al., 2020; Pohl et al., 2014), with inconclusive findings on menarche (Corbett et al., 2020; Hergüner & Hergüner, 2016; Whitehouse et al., 2011). It has been proposed that prenatal changes in neural development may alter sensitivity to puberty-related activation and organization (Picci & Scherf, 2015). Pubertal timing may also be altered for autistic individuals, with consequences for brain development and social–emotional trajectories (Picci & Scherf, 2015). Behavioral studies with autistic individuals reveal poorer mental health and adaptive functioning following puberty (Billstedt et al., 2005) and that relatively early puberty was associated with deteriorations of functioning and loss of therapeutic gains (Ayres & Mailloux, 1983; Gillberg & Schaumann, 1982). Given this paucity of research, further work is necessary to understand (1) whether puberty has a unique, additive effect on brain functioning beyond age and (2) in what ways puberty plays a role in the brain-based vulnerabilities that contribute to functional outcomes in ASD.

1.4 | Current study aims

The current study investigated whether pubertal *maturation* and *timing* explain developmental variation (over and above age, sex, and diagnosis) in EEG power in the alpha, beta, and theta frequency bands. Because pubertal processes contribute to sex-based dimorphism, we also considered the differential interaction effects of puberty (maturation and timing) with diagnosis and sex designated at birth. The direction of effects was exploratory.

As a secondary goal, we hypothesized that EEG frequency in the alpha band would mediate the association between puberty (maturation and timing) and autistic functioning (social communication and RRBs) for autistic youth and that there would be sex differences in these processes. We chose to explore alpha band frequencies in mediation models given the literature suggesting that reduced alpha band activity may reflect neural differences associated with autism traits, and given that puberty has been shown to impact brain development in neural regions that show relationships with autistic traits (Neuhaus et al., 2021). We also examined similar mediation models in the theta and beta bands as exploratory aims.

2 | MATERIALS AND METHODS

2.1 | Participants

Youth with and without ASD contributed data through two studies, described below. Individuals in the ASD group had a prior clinical or research diagnosis of ASD, which was confirmed by research-reliable clinicians using the Autism Diagnostic Interview—Revised (ADI-R), Autism Diagnostic Observation Schedule (ADOS-2), and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). For some participants, scores in the clinical ASD range on the Social Responsiveness Scale, Second Edition (SRS-2) and the Social Communication Questionnaire (SCQ) were substituted for the ADI-R ($n = 7$). For the comparison group of youth without ASD, children did not have first- or second-degree relatives with ASD, and they did not have elevated concerns for ASD per parent (SRS-2 total *T*-score <60; SCQ raw score <11) or clinician report. Comparison participants also did not have diagnoses of learning/intellectual disability or other developmental or psychiatric disorder.

For both groups, we restricted criteria for inclusion in this analysis to participants aged 8 years to 17 years and 11 months with a full-scale IQ above 70. Participants were excluded if they had a history of a known single-gene condition related to ASD (e.g., Fragile X; assessed through parent-reported medical history), a medical condition likely to be etiological (e.g., focal epilepsy), a history of active seizures within the past year, clinically significant visual or auditory impairment after correction, sensory–motor difficulties or an active tic disorder that would preclude valid use of the diagnostic instruments or neuroimaging, or any neurological disorders involving pathology above the brainstem. Participants were also excluded if they had a history of significant prenatal/perinatal/birth injury or neonatal brain damage, gestation less than 36 weeks or birthweight less than 2000 g, Neonatal Intensive Care Unit hospital stay over 3 days, and any environmental circumstances that might account for behaviors related to autism (e.g., severe nutritional or psychosocial deprivation). Participants were excluded if they currently used benzodiazepines, barbiturates, or antiepileptic medication or if they changed medications within 6 weeks before enrolling in the study.

2.1.1 | Study 1: The Autism Center for Excellence project Multimodal Developmental Neurogenetics of Females with ASD (MH100028) "GENDAAR"

Data collection occurred at Boston Children's Hospital, Seattle Children's Research Institute, the University of California Los Angeles,

and Yale University, with data coordination at the University of Southern California. Parent consent and adolescent assent were obtained. De-identified data were provided to the National Database of Autism Research (NDAR #2021). Additional exclusion criteria included that participants could not be twins.

2.1.2 | Study 2: Phenotypic Characterization of Gene Disrupting Mutations in ASD (R01MH100047) "ZEBRA"

Data collection occurred at the University of Washington. Parent consent and adolescent assent were obtained. De-identified data were provided to the National Database of Autism Research (NDAR #2101). Additional inclusion criteria included youth with ASD with a known genetic etiology as well as individuals without a known genetic etiology ("idiopathic" ASD or unconfirmed genetic status).

2.1.3 | Final sample

The current study included EEG data from 275 participants (32.4% female, M_{age} = 147.83 months). For participants who completed both Study 1 and Study 2 (n = 5), data were included from the first study completed. In the final combined sample, there were 181 autistic individuals (n = 103 from Study 1, n = 78 from Study 2, 31.5% female, M_{age} = 145.37) and 94 comparison individuals (n = 94 from Study 1, 47.9% female, M_{age} = 152.55). There was a significant sex (χ^2 = 7.12, p = .008) but not age difference ($t(168)$ = 1.96, p = .05) between the autistic and comparison groups. Additional details on the full sample characteristics are in Table 1, and reasons for data loss are in the Supporting Information.

2.2 | Measures

2.2.1 | Behavioral phenotype

Cognitive ability was measured using the Differential Ability Scales—Second Edition (DAS-II) (Elliot, 2007). The DAS-II includes Verbal, Nonverbal, and Spatial reasoning standard scores, as well as a General Conceptual Ability (GCA), which is a measure of full-scale IQ.

Social skills were measured using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) caregiver interview (Sparrow et al., 2005). The VABS-II includes communication, daily living, and social subscale scores. Only the social subscale was used in the current study as the focus of the study was on autism-related social skill differences. The subscale is a standard score with an average of 100 and a standard deviation of 15.

Restricted repetitive behaviors and interests (RRBs) were measured using the Social Responsiveness Scale, Second Edition (SRS-2) parent report (Constantino, 2012). The SRS-2 RRB subscale is commonly used to characterize RRBs in autistic populations. Scores can be converted to T-scores with a mean of 50 and a standard deviation of 10. Here, we use the RRB subscale T-scores, which include items related to inflexibility of behaviors, coordinated behaviors, and unusual sensory behaviors.

2.2.2 | Pubertal development

Pubertal development was measured using the Pubertal Development Scale (PDS; Petersen et al., 1988). On the PDS, individuals or their caregivers use a 4-point Likert scale (1 = *not started*; 4 = *complete*) to rate the onset and progression of five key pubertal indicators: changes to height, body hair, skin, facial hair and voice (males), and breast development (females). For females, ratings are also given on menarche (1 = *not begun*; 4 = *started*). Only parent report was used for the current study. PDS scores have been shown to relate to physical exams and hormone levels (Hibberd et al., 2015; Schmitz et al., 2004; Shirtcliff et al., 2009). The PDS has been used effectively with autistic youth (May et al., 2017) and with the GENDAAR study sample (Clawson et al., 2020).

Pubertal maturation was measured using the total PDS score, which is an average of all items for each participant.

Pubertal timing was calculated by regressing pubertal maturation (measured using average scores on the PDS) on age for males and females separately, and then using the residuals to approximate variation in pubertal timing. Negative residuals indicate later-than-average development relative to other same-aged and same-sex youth in the sample, and positive residuals correspond to earlier-than-average development relative to same-aged and same-sex youth in the sample (Dooley et al., 2022; Dorn et al., 2003).

2.3 | EEG protocol

EEG data were collected using the EGI 128-channel Net Amps 300 system (Study 1) and Net Amps 400 system (Study 2) with 128-channel HydroCel nets (Electrical Geodesics Inc.). Electrode sensor performance was validated monthly. Data were collected using Net Station 4.4.2, 4.5.1, or 4.5.2 using a standard Net Station acquisition template of 500 Hz recording rate, referenced to Cz (vertex), and with starting impedances <50 kΩ.

2.3.1 | Acquisition of resting-state data

For the eyes-open resting state, EEG participants were instructed to watch a series of short and colorful screensaver-like calm videos with limited or slow movement presented via E-Prime 2.0. All experiment-specific instructions were presented as text with an audio recording reading the instructions to ensure equivalent directions across participants. During EEG acquisition, research staff coded participant behavioral compliance during the task, and segments during which the participant was talking, moving, or nonattentive were discarded during EEG processing. Data analyzed here consisted of three experimental runs of six 16-s blocks of videos. (Eyes-closed data were collected as well but are not in the current paper.) Videos were

TABLE 1 Participant descriptive information.

	Total N = 277	ASD N = 181		Comparison group N = 94		Diagnostic group effect
		Female = 57	Male = 124	Female = 45	Male = 49	
Age in months *M*	147.83	144.77	145.65	148.60	156.18	$t(273) = 1.59, p = .114$
SD	34.34	31.43	33.40	39.10	35.06	
Range	96–215	97–207	96–215	97–214	101–213	
DAS-II GCA *M*	104.92	100.11	101.77	112.07	111.96	$t(273) = 11.63, p < .001$
SD	18.9	19.68	20.11	14.36	15.05	
Range	70–167	70–156	70–167	79–142	79–138	
VABS-II Socialization *M*	80.61	71.85	74.30	104.20	99.46	$t(223) = 14.30, p < .001$
SD	17.85	13.80	11.85	15.58	11.89	
Range	45–145	45–118	50–107	77–145	82–127	
SRS-2 RRB *M*	66.66	77.12	72.03	44.69	45.52	$t(220) = 1–24.86, p < .001$
SD	16.96	14.05	12.69	3.04	4.51	
Range	41–108	46–108	41–101	42–54	41–57	
Time between EEG and PDS data collection in months *M*	−0.82	−0.72	−1.73	0.31	0.33	$t(273) = 4.71, p < .001$
SD	3.87	3.23	5.03	1.41	1.35	
Range	−27 to 14	−13 to 9	−27 to 14	−4 to 6	−3 to 7	

Abbreviations: EEG, electroencephalography; GCA, General Conceptual Ability; PDS, Pubertal Development Scale; SRS-2, Social Responsiveness Scale, Second Edition; VABS-II, Vineland Adaptive Behavior Scales, Second Edition.

displayed at a visual angle of 5.5–6.7 to 7.5–8.5° to reduce eye movements. Resting runs were interwoven between other experiments that were different for Study 1 and Study 2; however, the first resting run was the first experiment in both studies.

2.3.2 | Signal processing

Preprocessing procedures were identical across both Study 1 and Study 2. EEG data were bandpass filtered at 0.1 and 100 Hz with a 60-Hz notch filter. Data were segmented in 2048-ms segments. Segments with poor attention and behavioral noncompliance were removed. Bad channels were identified as any electrode with a >100 microvolt difference between its lowest and highest points. Segments with more than 24 bad electrodes (including eye electrodes) were removed. Manualized hand editing was then performed to remove segments with remaining significant eye movements and eye artifacts. Segments were rejected for eye artifacts if (American Psychiatric Association, 2013) the first two rows of frontal electrodes (Fung et al., 2020; Herting & Sowell, 2017; Jeste et al., 2015; Kirschstein & Köhling, 2009; Murias et al., 2007; Shephard et al., 2018; Sisk & Foster, 2004) were all rejected by the Net Station 4.5.6 bad channel algorithm, or (McPartland et al., 2020) the first two rows of frontal electrodes were partially rejected by the bad channel algorithm and the third row of frontocentral electrodes (Dorn & Biro, 2011; Neuhaus et al., 2021; Pizzagalli, 2007; Shirtcliff et al., 2009; Wantzen et al., 2022) still showed the morphology of a blink or eye artifact. On the remaining good segments, bad electrodes were interpolated with signal from adjacent electrodes. Data were re-referenced to an average reference. Participants were required to have 10 segments (20 s) with valid, artifact-free data to be included in the study (Neuhaus et al., 2021). The amount of data retained differed by group ($t(1, 271) = -3.58, p < .001$): the comparison group had more remaining artifact-free trials ($n = 89.57$, $SD = 43.84$) than the ASD group ($n = 75.29$, $SD = 22.06$).

The time-domain EEG signal was transformed to the frequency domain using Welch's power spectral density estimate (MATLAB, PWELCH function; Frohlich et al., 2016; McEvoy et al., 2015). Fast Fourier Transfers for each 2048-ms sample segment were calculated on 512-point Hamming windows with 50% overlap resulting in a 0.5-Hz frequency resolution. Absolute power was calculated for theta (4–7 Hz), alpha (8–12 Hz), and beta (13–29 Hz) frequency bands. Regions of interest were created to improve signal-to-noise estimates by averaging the absolute power across the electrodes in each region: (1) frontal medial (5, FZ-11, 12, 16), (2) central medial (7, 31, 80, 106), and (3) posterior medial (Pz-62, 71, 72, 76). To normalize the distribution, values were then natural logarithm transformed. Medial regions were of focus to decrease the number of analyses run and as medial regions previously showed the greatest differences by diagnostic group (Neuhaus et al., 2021).

2.4 | Statistical methods

Mixed-effects linear regression models were conducted in R to assess differences in power in the theta, alpha, and beta frequency bands in the anterior medial, central medial, and posterior medial regions

associated with pubertal maturation and timing. Separate models were run for each frequency–region combination and for pubertal maturation and timing separately. Nested random effects were considered for site and family (as some participants were biologically related), but preliminary models across all frequency bands and all sites indicated only small variance related to site (intraclass correlation coefficient [ICC] = 0.34%) and this was not included in the final model. As there was a modest amount of variance accounted for by family effects (ICC = 4.36%), nested random effects were retained for family. Age, autism diagnosis, and sex were included as covariates. We sequentially tested for two-way interactions (sex × age, sex × group) and three-way interactions (sex × age × group) but interactions among covariates (e.g., age × sex) were not included as they were not significant, and the goal of the current paper was to investigate additive effects. Effect sizes are presented and may be interpreted as small ($\eta^2 = .01$), medium ($\eta^2 = .06$), or large ($\eta^2 = .14$). For each regression, we planned a priori testing of simple slopes for males and females, as well as autistic and comparison groups, given the importance of probing sex and diagnostic effects.

Mediation models for the autistic group were run using Process Macro in SPSS using the approach recommended by Shrout and Bolger (2002) and were run for the autistic group only as they focused on autistic traits that would have little variability in nonautistic groups. Mediation models were also run separately by sex. For males and females, separate models were run for each frequency-region combiation as mediators, for pubertal maturation and timing as separate independent variables, and for social skills EEG frequency was the mediator, and (VABS-3 Social Skills), and RRBs (SRS-2 RRBs) as separate dependent variables. Mediation analyses were run in the alpha band as that is the frequency that most consistently distinguishes between autistic and comparison groups (Wang et al., 2013), however results in the theta and beta bands are presented in the supplemental section.

3 | RESULTS

Distributions of pubertal maturation and timing are presented in Figure 1. There was no difference between youth with and without ASD on pubertal maturation ($t(273) = 0.52$, $p = .300$), but there was a difference in pubertal timing ($t(273) = -2.87$, $p = .002$) such that autistic individuals ($M = 0.12$, $SD = 0.08$) matured earlier compared to comparison individuals ($M = -0.24$, $SD = 0.91$). There was also a difference between males and females on pubertal maturation ($t(273) = -4.53$, $p < .001$) such that females ($M = 2.47$, $SD = 0.98$) were further along in puberty compared to males ($M = 1.94$, $SD = 0.86$). There was no sex difference in pubertal timing, suggesting that males and females did not differ in estimates of the relative timing of pubertal development compared to other same-ages and same-sex youth in this sample ($t(273) = -0.07$, $p = .942$).

3.1 | Pubertal maturation

There were main effects of pubertal maturation in the theta band in the central medial region ($F(1, 272) = 8.15$, $p < .001$), alpha band in the posterior medial region ($F(1, 265) = 4.52$, $p = .03$), and beta band in all regions (Anterior: $F(1, 272) = 8.15$, $p < .001$; Central: $F(1, 270) = 12.89$, $p < .001$; Posterior: $F(1, 260) = 5.32$, $p = .02$), as presented in Table 2. All were small effects. Individuals who were further along in pubertal maturity showed decreased power in all regions, over and above age, sex, and diagnosis. See other main effects in Table 3.

Per our a priori statistical plan, we explored sex and diagnostic differences in the relations between pubertal maturation and resting-state power. Figures 2 and 3 depict simple slopes of pubertal maturation by sex and diagnosis, respectively. Slope beta values and significance (i.e., significant difference from a slope = 0) are reported within the figures. Broadly, slopes were negative, indicating that with increasing pubertal maturation, spectral power was reducing. As seen in Figure 2, the simple slopes for males and females were always in the same direction, although the slopes were significant for females but not males in the theta band anterior region, and the slopes were significant for males but not females in the beta band posterior region.

Figure 3 shows that the simple slopes were significant for the autistic group in almost all bands and regions, except in the theta band anterior region or beta band posterior region. The slopes for the comparison group were only significant in the beta band in all regions.

3.2 | Pubertal timing

There were main effects of pubertal timing in the theta band in the anterior ($F(1, 275) = 8.51$, $p < .001$) and central regions ($F(1, 263) = 8.17$, $p < .001$), as well as in the beta anterior ($F(1, 275) = 8.10$, $p < .001$) and central regions ($F(1, 273) = 9.96$, $p < .001$). There were also main effects of sex and age broadly, with some main effects of diagnoses, presented in Table 3.

Figure 4 depicts simple slopes of pubertal timing by sex. Again, slopes were broadly negative, indicating that with relatively earlier pubertal maturity, spectral power was reducing. Simple slopes were significant for males in all regions except for the theta band anterior region, and slopes were only significant for females in the theta band anterior and central regions.

Figure 5 shows simple slopes of pubertal timing by diagnosis. Again, slopes were generally negative, indicating that with relatively early pubertal maturity, spectral power was reducing. Simple slopes were significant for the autistic group in all bands and all regions, except for alpha central, and slopes were not significant for the comparison group in any bands in any regions.

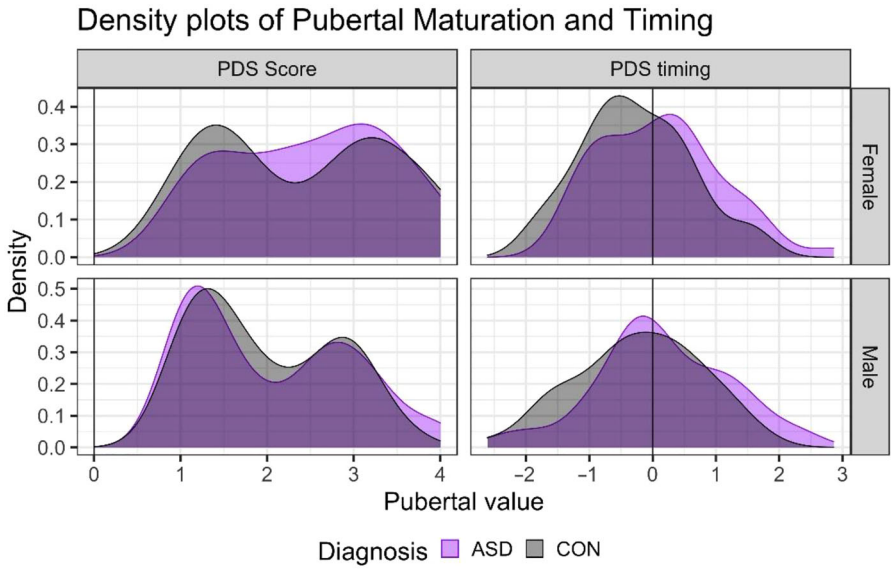

FIGURE 1 Distributions of pubertal maturation and timing by sex.

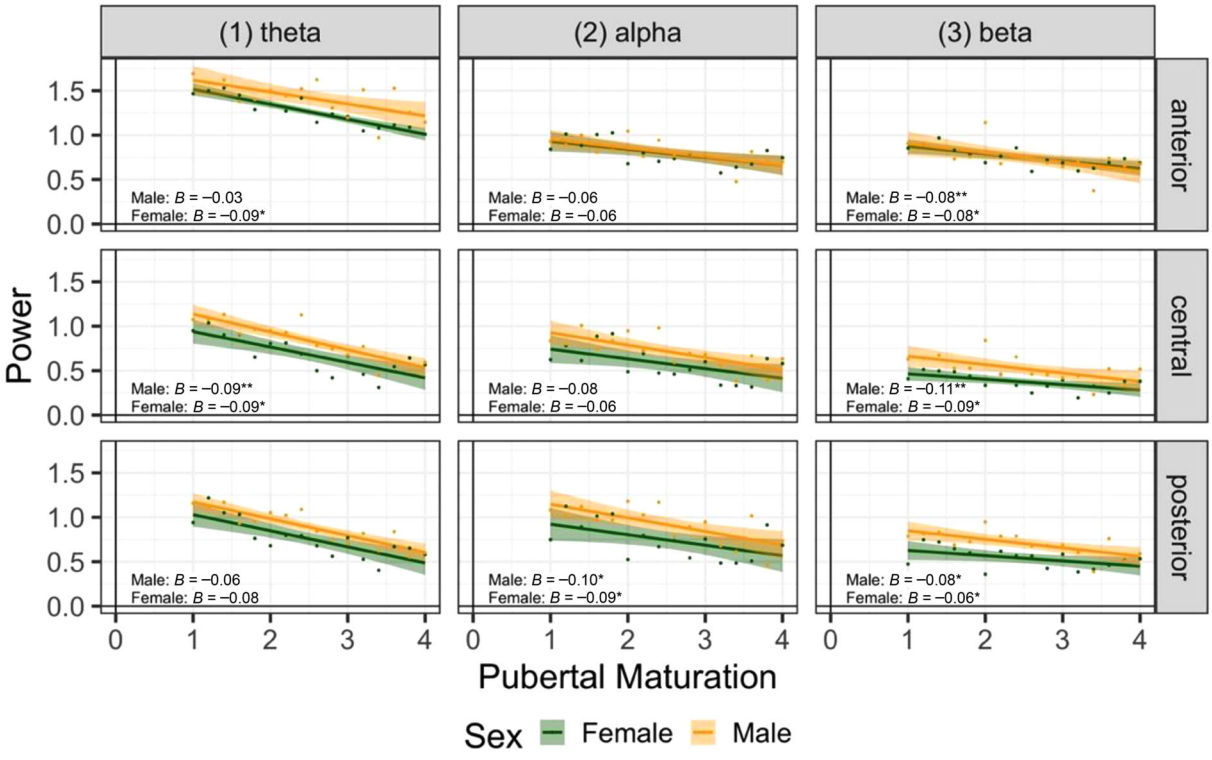

FIGURE 2 Electroencephalography (EEG) power in theta, alpha, and beta by region for males (yellow) and females (green) in relation to pubertal maturation.

3.3 | Relation to behavior

We investigated whether EEG frequency in the alpha band would mediate the association between puberty (maturation and timing) and social communication and RRBs for autistic youth. Mediation analyses were conducted in the autistic group in the alpha band. Mediation analyses in the theta and beta bands are in the Supporting Information.

3.3.1 | Pubertal maturation

Social skills

Figure 6 shows mediation models for pubertal maturation predicting social skills, mediated by alpha for the autistic group, and Figure 8 shows a forest plot of all mediation effects. There was a significant direct effect of pubertal maturation on social

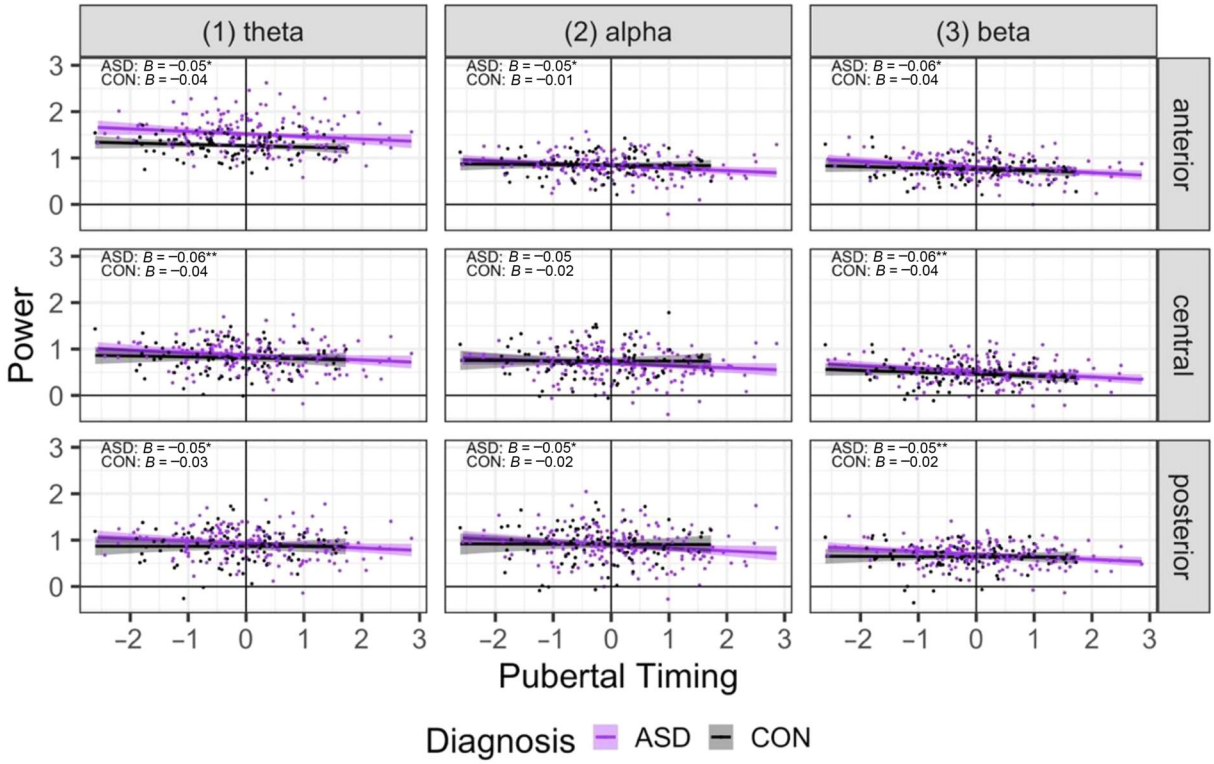

FIGURE 3 Electroencephalography (EEG) power in the theta, alpha, and beta bands by region for the autistic group (purple) and the comparison group (black) in relation to pubertal maturation.

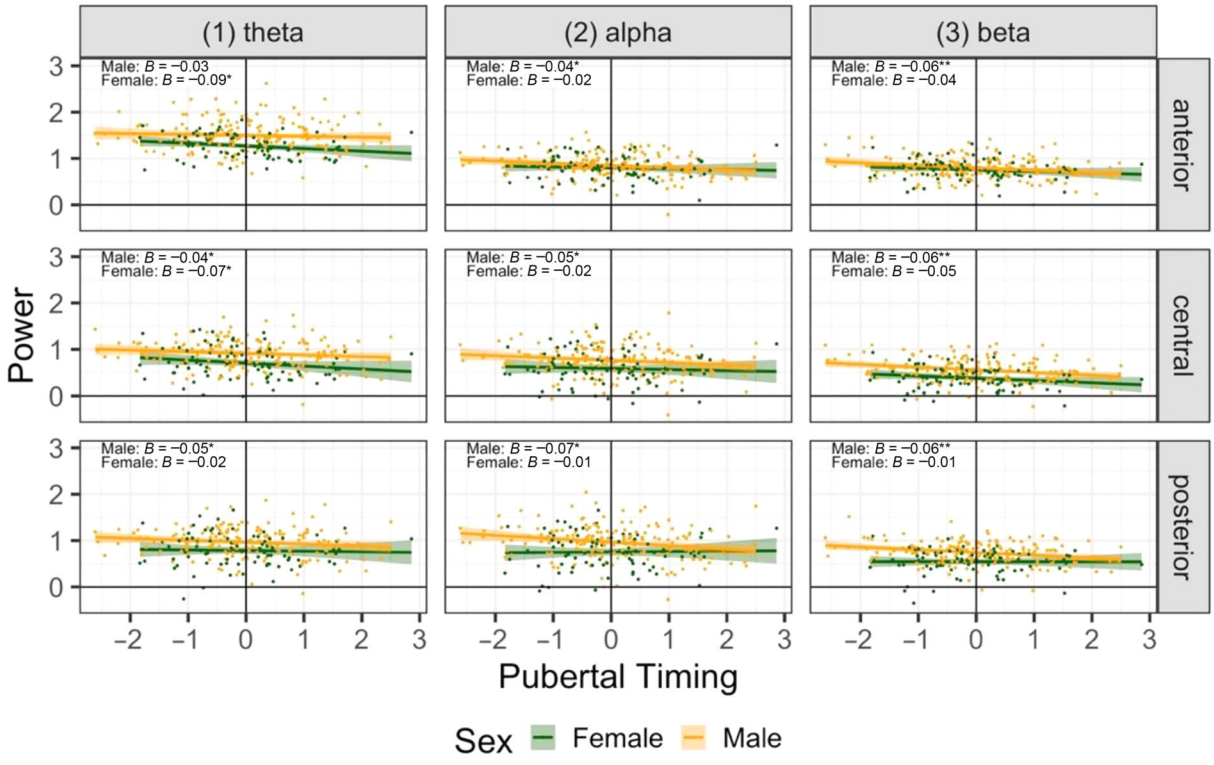

FIGURE 4 Electroencephalography (EEG) power in theta, alpha, and beta by region for males (yellow) and females (green) in relation to pubertal timing.

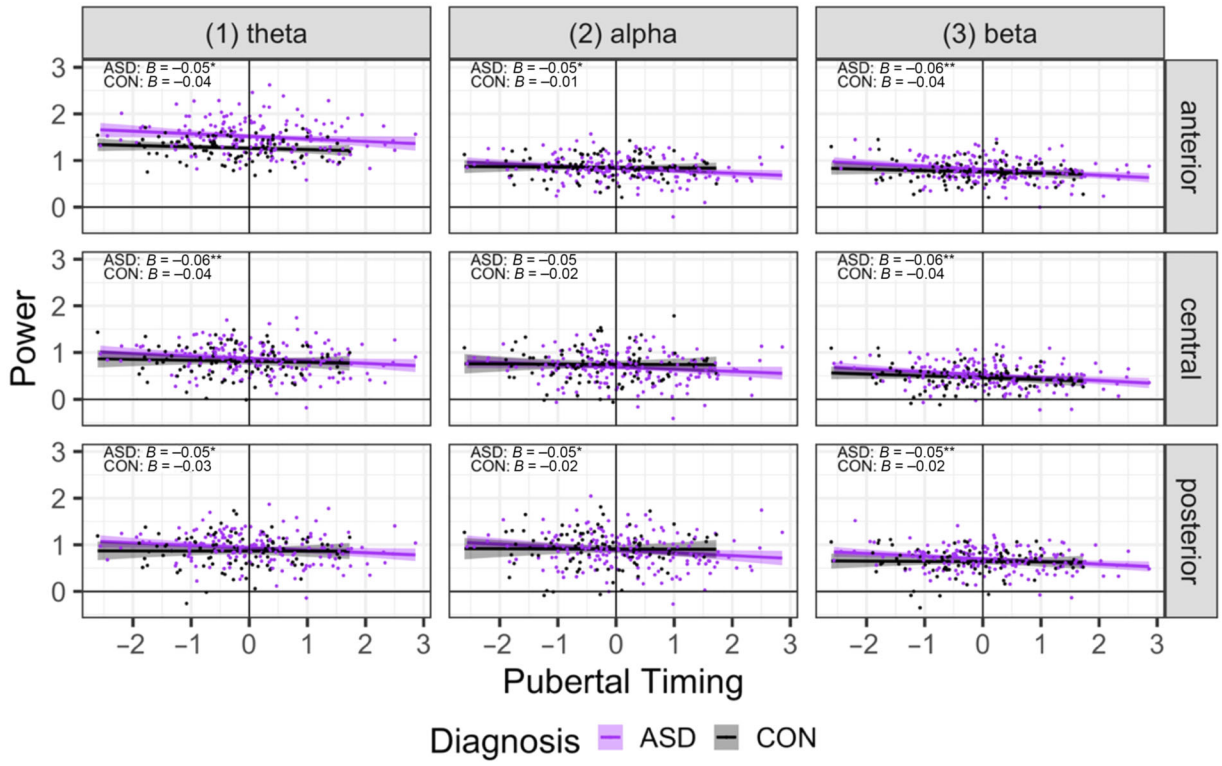

FIGURE 5 Electroencephalography (EEG) power in the theta, alpha, and beta bands by region for the autistic group (purple) and the comparison group (black) in relation to pubertal timing.

skills, such that individuals further along in pubertal development exhibited social skills that were lower compared to age- and sex-matched peers. Alpha did not mediate the relation between pubertal maturation and social skills in the anterior, central, or posterior regions.

When males and females were analyzed separately, alpha did not mediate the relation between pubertal maturation and social skills and there was no direct effect of pubertal maturation on social skills for either sex.

Restricted and repetitive behaviors

Figure 6 shows mediation models for pubertal maturation predicting RRBs, mediated by alpha for the autistic group, and Figure 8 shows a forest plot of all mediation effects. Alpha mediated the relation between pubertal maturation and RRBs in the anterior region, although there was not a direct effect of pubertal maturation on RRBs, as shown in Figure 6. Alpha did not mediate the relation between pubertal maturation and RRBs in the central or posterior regions.

For males only, alpha mediated the relation between pubertal maturation and RRBs in the anterior region ($b_{boot} = -1.19$, $SE_{boot} = 0.62$, 95% confidence interval [CI] [−2.59 to −0.15]), although there was not a direct effect of pubertal maturation on RRBs ($B = 0.09$, $SE = 1.41$, $t(117) = 0.06$, $p = .95$, 95% CI [−2.71 to 2.88]), and alpha did not mediate this relation in the central or posterior regions for males. Alpha did not mediate the relation between pubertal maturation and RRBs for females in any region.

3.3.2 | Pubertal timing

Social skills

Figure 7 shows mediation models for pubertal timing predicting VABS-II social skills, mediated by alpha for the autistic group. Alpha did not mediate the relation between pubertal timing and VABS-II social skills in any region in the alpha band.

Findings were consistent among both males and females that alpha did not mediate the relation between pubertal timing and VABS-II social skills in the anterior, central, or posterior region.

Restricted and repetitive behaviors

Figure 7 shows mediation models for pubertal timing predicting SRS-2 RRBs, mediated by alpha for the autistic group, and Figure 8 shows a forest plot of mediation effects. Alpha in the anterior region significantly mediated the relation between pubertal timing and SRS-2 RRBs as shown in Figure 7. Individuals who were at earlier stages of puberty for their age and sex, relative to other youth in the sample, exhibited higher alpha power and individuals with higher alpha power exhibited more SRS-2 RRBs. Alpha did not mediate the relation between pubertal timing and SRS-2 RRBs in the central or posterior region.

Alpha mediated the relation between pubertal timing and SRS-2 RRBs for males in the anterior region ($b_{boot} = -0.76$, $SE_{boot} = 0.41$, 95% CI [−1.68 to −0.11]), although there was not a significant direct effect ($B = 0.76$, $SE = 1.19$, $t(119) = 0.63$, $p = .528$, 95% CI [−1.61 to 3.12]).

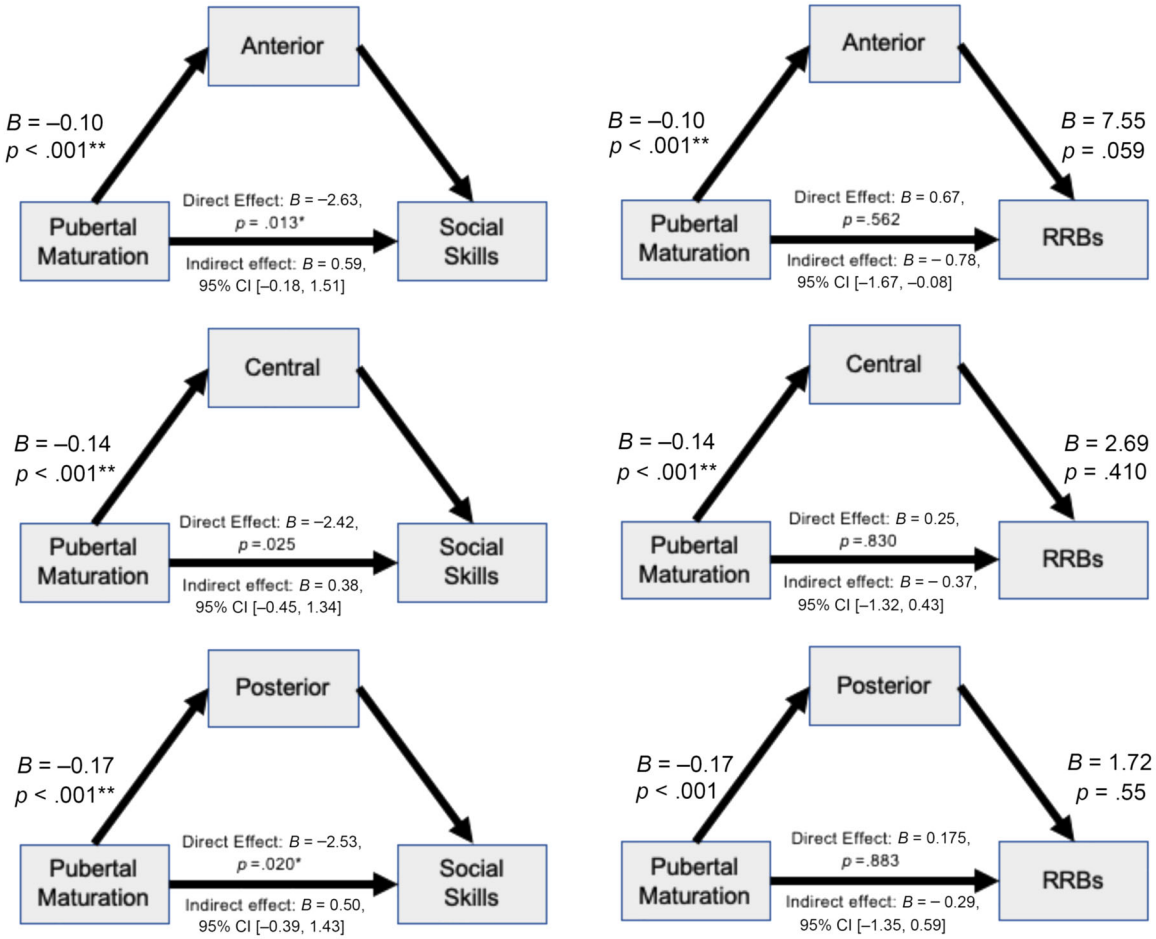

FIGURE 6 Anterior alpha mediating pubertal maturation and social skills and restricted and repetitive behaviors (RRBs) for the autistic group.

In contrast, alpha did not mediate the relation between pubertal timing and SRS-2 RRBs for females in the anterior region (Direct effect: $B = 1.80$, $SE = 1.82$, $t(54) = 0.99$, $p = .327$, 95% CI [−1.86 to 5.47]; Indirect effect: $b_{boot} = -0.07$, $SE_{boot} = 0.36$, 95% CI [−1.14 to 0.25]). As with the combined autistic sample, alpha did not mediate the relation between pubertal timing and SRS-2 RRBs for males or females in the central or posterior region.

Mediation analyses for the other frequency bands were exploratory and are included in the Supporting Information.

4 | DISCUSSION

We investigated whether pubertal maturation and timing explained developmental variation in EEG power in the theta, alpha, or beta frequency bands in autistic and comparison youth. We explored sex and diagnostic differences in these models. For the autistic youth, we also examined EEG power in the alpha band as a mediator in the relation between pubertal maturation and timing with ASD-related traits (i.e., social skills and restricted repetitive behaviors and interests; RRBs) for the whole autistic group and for autistic males and females separately.

4.1 | Main effects of puberty

Our hypotheses that there would be a main effect of both pubertal maturation and timing on resting-state EEG power were supported. Findings indicate that, in addition to age, pubertal maturation and timing also exert specific effects on resting-state EEG and should therefore be considered in future research. Individuals further along in pubertal maturation showed decreased power in the beta band across all regions, as well as decreased power in the theta band in the central region and alpha band in the posterior region. Similarly, individuals who were relatively "early bloomers" (i.e., at a later pubertal stage compared to same-aged and same-sex peers in this sample) showed decreased power in the theta band in all regions and in the beta band in the anterior and central regions. Our findings extend previous research documenting decreases in power with increasing age by suggesting that pubertal development may play a unique additional role in the development of more efficient information processing and executive functioning (Kharitonova et al., 2013; Tamnes et al., 2013). As increased beta and theta are associated with greater attention, findings suggest that individuals with less advanced and slower pubertal maturity showed increased cognitive engagement during resting state

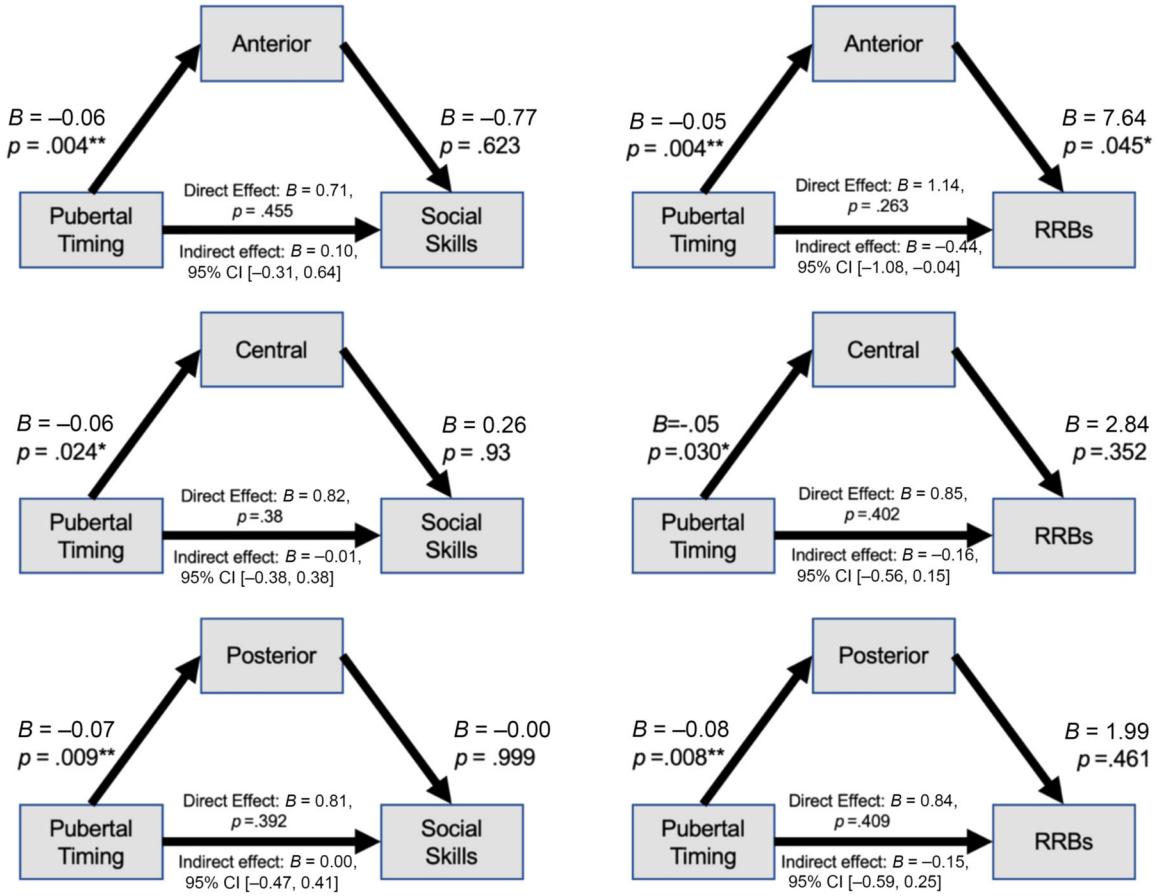

FIGURE 7 Anterior alpha mediating pubertal timing and Vineland Adaptive Behavior Scales, Second Edition (VABS-II) social skills and Social Responsiveness Scale, Second Edition (SRS-2) restricted and repetitive behaviors (RRBs) for the autistic group.

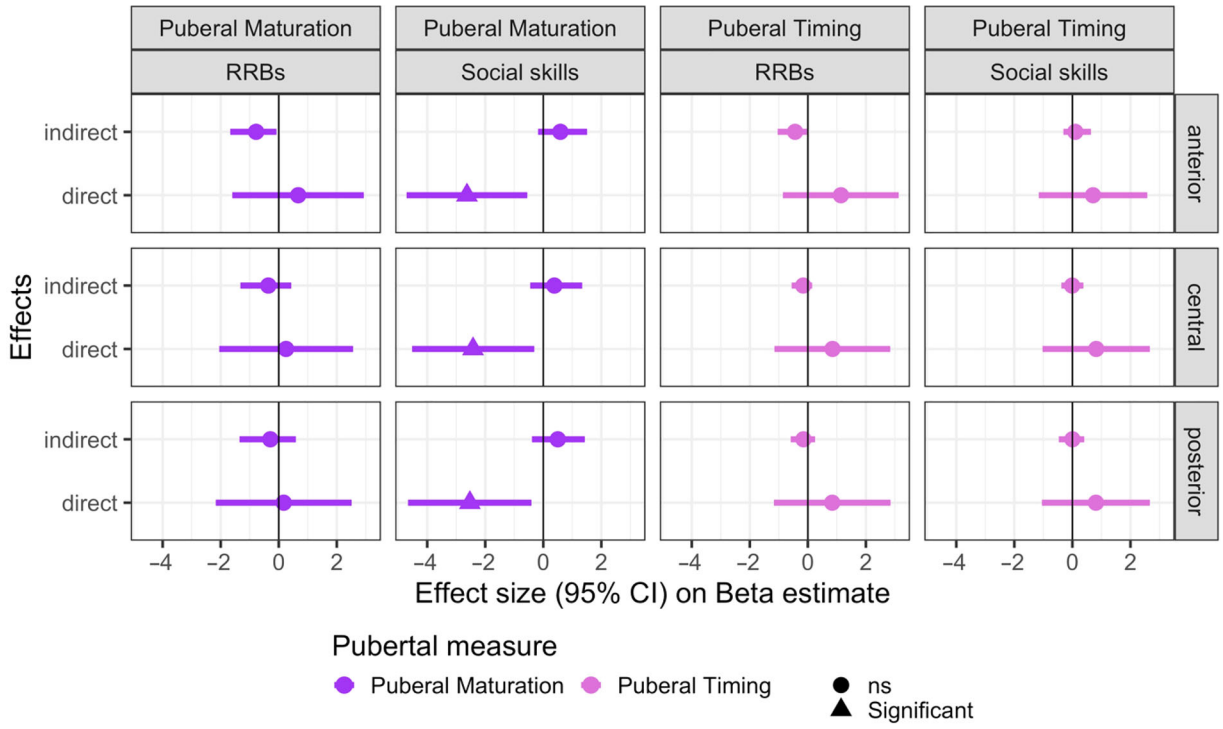

FIGURE 8 Forest plot of all mediation effects for the alpha band for the autistic group.

TABLE 2 Effects of pubertal maturation reported as *F* values, with effect sizes (η^2) in parentheses.

	Theta			Alpha			Beta		
	Anterior medial	Central medial	Posterior medial	Anterior medial	Central medial	Posterior medial	Anterior medial	Central medial	Posterior medial
Sex	0.33 (.002)	3.65 (.02)	2.18 (.01)	0.15 (.0006)	3.79 (.01)	2.67 (.01)	0.07 (.0003)	5.10* (.02)	5.32* (.02)
Diagnosis	7.33* (.03)	0.53 (.002)	1.59 (.01)	0.01 (.0000)	0.83 (.003)	0.00 (.0000)	0.37 (.001)	0.15 (.0005)	0.04 (.0001)
Age	16.18** (.06)	14.90** (.05)	25.73** (.09)	2.25 (.01)	1.93 (.007)	1.02 (.004)	0.95 (.003)	0.59 (.002)	0.00 (.0000)
Pubertal maturation	2.80 (.01)	7.50* (.03)	3.66 (.01)	3.62 (.01)	3.37 (.01)	4.52* (.02)	8.15** (.03)	12.89** (.05)	6.00* (.02)
Sex × Pubertal maturation	1.75 (.01)	0.04 (.0002)	0.16 (.001)	0.02 (.0000)	0.12 (.0005)	0.01 (.0000)	0.08 (.0003)	0.64 (.003)	0.25 (.001)
Diagnosis × Pubertal maturation	0.77 (.003)	1.02 (.004)	2.11 (.01)	0.32 (.001)	0.10 (.0004)	0.57 (.002)	0.08 (.0003)	0.06 (.0002)	0.01 (.0000)

Note: Effect sizes may be interpreted as small ($\eta^2 = .01$), medium ($\eta^2 = .06$), or large ($\eta^2 = 0.14$).
*$p < .05$; **$p < .01$.

TABLE 3 Effects of pubertal timing reported as *F* values, with effect sizes (η^2) in parentheses.

	Theta			Alpha			Beta		
	Anterior medial	Central medial	Posterior medial	Anterior medial	Central medial	Posterior medial	Anterior medial	Central medial	Posterior medial
Sex	32.21** (.11)	49.71** (.18)	36.23** (.12)	5.39* (.02)	28.76** (.10)	27.15** (.10)	2.12 (.01)	35.83** (.12)	39.57** (.13)
Diagnosis	23.86** (.17)	0.31 (.001)	0.09 (.0004)	2.83 (.01)	9.72** (.04)	4.16* (.02)	0.68 (.003)	0.08 (.0003)	0.00 (.0000)
Age	89.88** (.27)	119.83** (.30)	144.93** (.35)	31.10** (.10)	28.41** (.09)	26.27** (.09)	37.90** (.12)	17.48** (.06)	15.35** (.05)
Pubertal timing	8.51** (.03)	8.17** (.03)	3.00 (.01)	2.58 (.01)	1.37 (.005)	0.88 (.003)	8.10** (.03)	9.96** (.04)	2.37 (.009)
Sex × Pubertal timing	2.15 (.01)	0.73 (.003)	0.36 (.001)	0.43 (.002)	0.47 (.002)	2.38 (.009)	0.12 (.0004)	0.07 (.0002)	2.27 (.008)
Diagnosis × Pubertal timing	0.09 (.0003)	0.27 (.001)	0.31 (.001)	1.17 (.005)	0.51 (.002)	0.61 (.002)	0.68 (.003)	0.42 (.002)	1.06 (.004)

Note: Effect sizes may be interpreted as small ($\eta^2 = .01$), medium ($\eta^2 = .06$), or large ($\eta^2 = .14$).
*$p < .05$; **$p < .01$.

relative to peers (Pizzagalli, 2007; Wang et al., 2013). While counterintuitive, these participants may find resting stimuli more engaging or may expend more cognitive energy during refractory or preparatory periods than peers. To delineate between these possibilities, it would be helpful to utilize a variety of contrasting conditions (e.g., resting state vs. task-active state) to better understand patterns and implications of pubertal development.

Additionally, while research in nonautistic populations has suggested that earlier pubertal maturation may be a risk factor for mental and physical health challenges (Hoyt et al., 2020), it may be beneficial for cognitive development (Chaku & Hoyt, 2019). There may be interactions between neurobiological changes (e.g., thinning gray matter and synaptic pruning of the prefrontal cortex) and social consequences (e.g., increased responsibility of youth who look more mature) that facilitate development in executive functioning and other cognitive processes (Chaku & Hoyt, 2019). Alternatively, precocious puberty may truncate important periods of early learning and plasticity, or at least alter the timing and magnitude of growth (Piekarski et al., 2017). This may be particularly impactful for autistic children with language challenges, as areas of the brain associated with language development exhibit less plasticity after puberty (Piekarski et al., 2017). Given the potential that puberty may convey both risk as well as benefits for youth, follow-up work will be needed across multiple behavioral domains.

4.2 | Sex differences

The interactions between puberty and sex were not significant, which is consistent with recent research that shows relatively similar outcomes for males and females who develop early (Chaku & Hoyt, 2019; Hoyt et al., 2020). However, there were some notable sex differences in patterns of simple slopes. For pubertal maturation, males and females showed significant effects in most of the same regions. Females showed a unique significant association between theta and pubertal maturation in the anterior region, while males showed a unique significant association with beta in the posterior region. For pubertal timing, males showed a significant association with almost all frequency bands in almost all regions, while females only showed a significant correlation in the theta band in the anterior and central regions. One possible explanation for the stronger association for females in the theta band may be that males show a slower decrease in theta over the course of development, compared to females (Clarke et al., 2001).

Clarifying the relation between sex, puberty, brain, and behavioral functioning may benefit from direct measures of hormone levels, particularly testosterone. Our findings for females may be consistent with functional magnetic resonance imaging research that found a stronger association between testosterone and gray matter, as well as cortical thickness in the frontal region, for females as compared to males (Bramen et al., 2012; Nguyen et al., 2017). In contrast, males, but not females, had an association between testosterone levels and executive function (Nguyen et al., 2017).

4.3 | Diagnostic differences

Again, there was not a significant interaction between diagnosis and puberty, but there were notable differences in patterns of simple slopes. Both pubertal maturation and timing were related to all EEG resting-state frequencies across most regions for the autistic group, whereas the association was only significant in the beta region for the comparison group for pubertal maturation. Little research has examined neurodevelopmental functioning in relation to puberty for autistic *and* comparison individuals, but it is possible that puberty has a differential effect on autistic individuals and may therefore show stronger relations between puberty and brain development. Additionally, the timing of puberty may be more impactful for autistic individuals, particularly as puberty-related biological and environmental changes may confer additional challenges to autistic individuals. Alternatively, as there is more variability in pubertal timing for autistic individuals (Picci & Scherf, 2015), there may be a stronger correlation between age and puberty for comparison individuals, so puberty may not provide as much additional information above and beyond age for these comparison individuals.

4.4 | Autism traits and pubertal development

Mediation analyses with the autistic sample extended previous research on nonautistic individuals that found that brain abnormalities (e.g., size) mediated the relation between puberty and mental health (Murray et al., 2019). In the current autistic sample and analysis of medial areas, alpha only mediated the relation between pubertal maturation and timing with RRBs in the anterior region. RRBs are related to challenges with response inhibition and cognitive flexibility (Faja & Nelson Darling, 2019; Mostert-Kerckhoffs et al., 2015), and executive functions in the prefrontal cortex that undergo substantial changes in puberty due to changes in neural capacity in that region (Tyborowska et al., 2016; Zhou et al., 2016). Although the role of puberty in executive functioning and trait presentation in autism remains largely unstudied, our findings fit with broader literature indicating that puberty may drive executive functioning-related behaviors, including RRBs (Blakemore et al., 2010; Nguyen et al., 2017). Also, given that mediation analyses were significant for both pubertal maturation and timing analyses, our findings highlight the need to better understand how alterations in pubertal maturation and relative timing impact behavioral trajectories across development.

When sex differences were probed, alpha mediated the relation with RRBs for males only. Although we did not directly measure hormone levels, prior work suggests that adolescents with higher testosterone showed more adult-like patterns of anterior prefrontal cortex activity, while controlling emotional reactions, and, as previously mentioned, testosterone appears to exert unique effects on males during puberty (Nguyen et al., 2017; Tyborowska et al., 2016). Further, findings of sex differences in the associations of EEG resting-state power are consistent with comparable resting-state research on

autistic samples and further support the need to include and separately consider females in biomarker research (Neuhaus et al., 2021). Our findings of complete mediation indicate that the relation between puberty and autism traits is entirely accounted for by the impact of puberty on brain development and functioning, although future research may investigate mediation models in other brain regions and in longitudinal data.

4.5 | Limitations and future directions

Our measure of pubertal development was based on parent report. The PDS is a practical, easy-to-administer, less invasive measure of puberty (Koopman-Verhoeff et al., 2020), although it may underrepresent gonadal development and is a less precise measure overall (Vijayakumar et al., 2018). To understand which aspects of puberty are contributing to the relationships between brain and behavior, more nuanced mechanistic information will be important (e.g., hormones, physical characteristics, etc.).

The current sample was also composed of individuals with relatively high cognitive skills; thus, we cannot conclude that our findings extend to individuals with intellectual disability and autism. The impact of co-occurring disorders on these relations will also require consideration, due to high rates of co-occurring anxiety, attention-deficit/hyperactivity disorder, and other mental and physical health challenges with autism that impact puberty and resting EEG power (Clarke et al., 2001; Newson & Thiagarajan, 2019). Our project was also largely exploratory, and confirmation through other projects will be necessary.

Lastly, sociodemographic differences also influence puberty and will be particularly important to consider. The age of pubertal onset is earlier in Black and Hispanic children, as well as those in families of lower socioeconomic status in the United States (Piekarski et al., 2017). The COVID-19 pandemic further altered the average age of puberty, in part due to increases in stress (Belsky, 2012), body mass index, screen time, and other factors (Stagi et al., 2020). There may be important environmental risk factors for precocious puberty that also interact with age, sex, cognition, and developmental outcomes. As autistic youth are more likely to be obese and less likely to engage in physical activity, they may be more impacted by these patterns of lifestyle changes that decrease the age of onset of puberty (McCoy et al., 2016).

Gender identity was also not included in our analyses and will be an important next step, particularly given heightened rates of the co-occurrence of gender diversity and ASD (Nobili et al., 2020; Pasterski et al., 2014). Gender-diverse youth, particularly those with co-occurring ASD, report experiencing unique social and environmental stressors that compound the more commonly experienced challenges (Strang et al., 2018). Thus, the interplay of gender identity and puberty on neurodevelopment is complex but must be considered in addition to designated sex at birth.

5 | CONCLUSIONS

In summary, findings presented here demonstrate the impact of pubertal maturation and timing on resting-state neural functioning. This work further underscores the importance of considering sex when investigating brain–behavioral correlates. Our findings also identify the potential for neural functioning as a mediator in the relation between puberty and behavioral outcomes in autistic populations.

AUTHOR CONTRIBUTIONS

Hannah M. Rea: Conceptualization; data curation; formal analysis; methodology; writing—original draft. **Ann Clawson**: Conceptualization; methodology; writing—original draft. **Caitlin M. Hudac**: Conceptualization; data curation; formal analysis; investigation; methodology; visualization; writing—original draft. **Megha Santhosh**: Conceptualization; data curation; investigation; methodology; project administration; resources; writing—original draft. **Raphael A. Bernier**: Conceptualization; funding acquisition; project administration; resources; methodology; supervision; writing—reviewing and editing. **Rachel K. Earl**: Conceptualization; data curation; investigation; methodology; project administration; resources; supervision; writing—reviewing and editing. **Kevin A. Pelphrey**: Conceptualization; data curation; funding acquisition; methodology; project administration; resources; supervision; writing—reviewing and editing. **Sara Jane Webb**: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; writing—original draft. **Emily Neuhaus**: Conceptualization; formal analysis; investigation; methodology; project administration; supervision; writing—original draft.

ACKNOWLEDGMENTS

We wish to thank the families, parents, and children who participated in the GENDAAR study at the four data collection sites, as well as those who participated in the ZEBRA study at the University of Washington and Seattle Children's Research Institute. Funding was provided by the NIMH R01 MH10028 ACE Network (to K.A.P.) and by the NIMH R01 MH100047 (to R.A.B.).

The ACE GENDAAR Consortium includes contributions from Kevin A. Pelphrey PhD (PI), Katy Ankeman MSW, Elizabeth Aywlard PhD, Raphael A. Bernier PhD, Susan Bookheimer PhD, Sarah Corrigan MA, Mirella Dapretto PhD, Daniel Geschwind MD, Abha Gupta PhD, Allison Jack PhD, Zack Jacokes, Erin Libsack, Jennifer Lowe PhD, Desiree Lussier PhD, Shafali Jeste MD, Anna Kresse MPH, James McPartland PhD, Adam Naples PhD, Charles Nelson PhD, Emily Neuhuas PhD, Megha Santhosh MHA, Matthew State MD, Catherine Sullivan, Carina Torgenson, Jack Van Horn PhD, Pamela Ventola PhD, and Julie Wolf PhD.

The ZEBRA Study research team includes contributions from Raphael A. Bernier PhD, Sara Jane Webb PhD, Evan Eichler PhD, Jennifer Gerdts PhD, Arianne Wallace PhD, Rachel K. Earl PhD, Caitlin Hudac PhD, Trent DesChamps PhD, Brianna Cairney MA, Monique

Mahony, Anne Arnett PhD, Sandy Trinh PhD, Jennifer Beighley PhD, Jessica Berg PhD, Megan Frye PhD, Evangeline Kurtz-Nelson PhD, Tracey Ward PhD, Micah Pepper MPH, and Alana Peters-Whiting.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Repository data are available through the National Database for Autism Research (NDAR) study #2021 for the GENDAAR data and the ZEBRA data are available from the authors upon request.

ORCID

Hannah M. Rea https://orcid.org/0000-0002-3786-9725

REFERENCES

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Author.

Ayres, A. J., & Mailloux, Z. K. (1983). Possible pubertal effect on therapeutic gains in an autistic girl. *The American Journal of Occupational Therapy*, *37*(8), 535–540. https://doi.org/10.5014/ajot.37.8.535

Belsky, J. (2012). The development of human reproductive strategies: Progress and prospects. *Current Directions in Psychological Science*, *21*(5), 310–316. https://doi.org/10.1177/0963721412453588

Beltz, A. M., & Berenbaum, S. A. (2013). Cognitive effects of variations in pubertal timing: Is puberty a period of brain organization for human sex-typed cognition? *Hormones and Behavior*, *63*(5), 823–828. https://doi.org/10.1016/j.yhbeh.2013.04.002

Billstedt, E., Gillberg, C., & Gillberg, C. (2005). Autism after adolescence: Population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. *Journal of Autism and Developmental Disorders*, *35*(3), 351–360. https://doi.org/10.1007/s10803-005-3302-5

Blakemore, S. J., Burnett, S., & Dahl, R. E. (2010). The role of puberty in the developing adolescent brain. *Human Brain Mapping*, *31*(6), 926–933. https://doi.org/10.1002/hbm.21052

Bottema-Beutel, K., Kapp, S. K., Lester, J. N., Sasson, N. J., & Hand, B. N. (2021). Avoiding ableist language: Suggestions for autism researchers. *Autism in Adulthood*, *3*(1), 18–29. https://doi.org/10.1089/aut.2020.0014

Bramen, J. E., Hranilovich, J. A., Dahl, R. E., Chen, J., Rosso, C., Forbes, E. E., Dinov, I. D., Worthman, C. M., & Sowell, E. R. (2012). Sex matters during adolescence: Testosterone-related cortical thickness maturation differs between boys and girls. *PLoS ONE*, *7*(3), e33850. https://doi.org/10.1371/journal.pone.0033850

Byrne, M. L., Whittle, S., Vijayakumar, N., Dennison, M., Simmons, J. G., & Allen, N. B. (2017). A systematic review of adrenarche as a sensitive period in neurobiological development and mental health. *Developmental Cognitive Neuroscience*, *25*, 12–28. https://doi.org/10.1016/j.dcn.2016.12.004

Chaku, N., & Hoyt, L. T. (2019). Developmental trajectories of executive functioning and puberty in boys and girls. *Journal of Youth and Adolescence*, *48*(7), 1365–1378. https://doi.org/10.1007/s10964-019-01021-2

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (2001). Age and sex effects in the EEG: Development of the normal child. *Clinical Neurophysiology*, *112*(5), 806–814. https://doi.org/10.1016/S1388-2457(01)00488-6

Clawson, A., Strang, J. F., Wallace, G. L., Gomez-Lobo, V., Jack, A., Webb, S. J., Pelphrey, K. A., & GENDAAR Research Consortium. (2020). Parent-child concordance on the pubertal development scale in typically developing and autistic youth. *Research in Autism Spectrum Disorders*, *77*, 101610. https://doi.org/10.1016/j.rasd.2020.101610

Constantino, J. N. (2012). *Social Responsiveness Scale, Second Edition (SRS-2)*. Western Psychological Services.

Corbett, B. A., Vandekar, S., Muscatello, R. A., & Tanguturi, Y. (2020). Pubertal timing during early adolescence: Advanced pubertal onset in females with autism spectrum disorder. *Autism Research*, *13*(12), 2202–2215. https://doi.org/10.1002/aur.2406

Dawson, G., Klinger, L. G., 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*(5), 569–583. https://doi.org/10.1007/BF01447662

Dooley, N., Ruigrok, A., Holt, R., Allison, C., Tsompanidis, A., Waldman, J., Auyeung, B., Lombardo, M. V., & Baron-Cohen, S. (2022). Is there an association between prenatal testosterone and autistic traits in adolescents? *Psychoneuroendocrinology*, *136*, 105623. https://doi.org/10.1016/j.psyneuen.2021.105623

Dorn, L. D., & Biro, F. M. (2011). Puberty and its measurement: A decade in review. *Journal of Research on Adolescence*, *21*(1), 180–195. https://doi.org/10.1111/j.1532-7795.2010.00722.x

Dorn, L. D., Dahl, R. E., Woodward, H. R., & Biro, F. (2006). Defining the boundaries of early adolescence: A user's guide to assessing pubertal status and pubertal timing in research with adolescents. *Applied Developmental Science*, *10*(1), 30–56. https://doi.org/10.1207/s1532480xads1001_3

Dorn, L. D., Susman, E. J., & Ponirakis, A. (2003). Pubertal timing and adolescent adjustment and behavior: Conclusions vary by rater. *Journal of Youth and Adolescence*, *32*(3), 157–167. https://doi.org/10.1023/A:1022590818839

Elliot, C. D. (2007). *Differential Ability Scales, Second Edition*. The Psychological Corporation.

Faja, S., & Nelson Darling, L. (2019). Variation in restricted and repetitive behaviors and interests relates to inhibitory control and shifting in children with autism spectrum disorder. *Autism*, *23*(5), 1262–1272. https://doi.org/10.1177/1362361318804192

Frohlich, J., Senturk, D., Saravanapandian, V., Golshani, P., Reiter, L. T., Sankar, R., Thibert, R. L., DiStefano, C., Huberty, S., Cook, E. H., & Jeste, S. S. (2016). A quantitative electrophysiological biomarker of duplication 15q11.2-q13.1 syndrome. *PLoS ONE*, *11*(12), e0167179. https://doi.org/10.1371/journal.pone.0167179

Fung, M. H., Taylor, B. K., Frenzel, M. R., Eastman, J. A., Wang, Y. P., Calhoun, V. D., Stephen, J. M., & Wilson, T. W. (2020). Pubertal testosterone tracks the developmental trajectory of neural oscillatory activity serving visuospatial processing. *Cerebral Cortex*, *30*(11), 5960–5971. https://doi.org/10.1093/cercor/bhaa169

Gabard-Durnam, L. J., Flannery, J., Goff, B., Gee, D. G., Humphreys, K. L., Telzer, E., Hare, T., & Tottenham, N. (2014). The development of human amygdala functional connectivity at rest from 4 to 23years: A cross-sectional study. *Neuroimage*, *95*, 193–207. https://doi.org/10.1016/j.neuroimage.2014.03.038

Gillberg, C., & Schaumann, H. (1982). Infantile autism and puberty. *Journal of Autism and Developmental Disorders*, *11*(4), 365–371. https://doi.org/10.1007/BF01531612

Gorday, J. Y., & Meyer, A. (2018). Linking puberty and error-monitoring: Relationships between self-reported pubertal stages, pubertal hormones, and the error-related negativity in a large sample of children and adolescents. *Developmental Psychobiology*, *60*(4), 483–490. https://doi.org/10.1002/dev.21625

Hergüner, A., & Hergüner, S. (2016). Association between age at menarche and autistic traits in Turkish university students. *American Journal of Human Biology*, *28*(1), 44–47. https://doi.org/10.1002/ajhb.22739

Herting, M. M., & Sowell, E. R. (2017). Puberty and structural brain development in humans. *Frontiers in Neuroendocrinology*, *44*, 122–137. https://doi.org/10.1016/j.yfrne.2016.12.003

Hibberd, E. E., Hackney, A. C., Lane, A. R., & Myers, J. B. (2015). Assessing biological maturity: Chronological age and the pubertal development scale predict free testosterone in adolescent males. *Journal of Pediatric Endocrinology and Metabolism*, *28*(3–4), 381–6.

Hoyt, L. T., Niu, L., Pachucki, M. C., & Chaku, N. (2020). Timing of puberty in boys and girls: Implications for population health. *SSM - Population Health*, *10*, 100549. https://doi.org/10.1016/j.ssmph.2020.100549

Jankowski, K. F., Moore, W. E., Merchant, J. S., Kahn, L. E., & Pfeifer, J. H. (2014). But do you think I'm cool?: Developmental differences in striatal recruitment during direct and reflected social self-evaluations. *Developmental Cognitive Neuroscience*, *8*, 40–54. https://doi.org/10.1016/j.dcn.2014.01.003

Jeste, S. S., Frohlich, J., & Loo, S. K. (2015). Electrophysiological biomarkers of diagnosis and outcome in neurodevelopmental disorders. *Current Opinion in Neurology*, *28*(2), 110–116. https://doi.org/10.1097/WCO.0000000000000181

Kenny, L., Hattersley, C., Molins, B., Buckley, C., Povey, C., & Pellicano, E. (2016). Which terms should be used to describe autism? Perspectives from the UK autism community. *Autism*, *20*(4), 442–462. https://doi.org/10.1177/1362361315588200

Kharitonova, M., Martin, R. E., Gabrieli, J. D. E., & Sheridan, M. A. (2013). Cortical gray-matter thinning is associated with age-related improvements on executive function tasks. *Developmental Cognitive Neuroscience*, *6*, 61–71. https://doi.org/10.1016/j.dcn.2013.07.002

Kirschstein, T., & Köhling, R. (2009). What is the source of the EEG? *Clinical EEG and Neuroscience*, *40*(3), 146–149. https://doi.org/10.1177/155005940904000305

Koopman-Verhoeff, M. E., Gredvig-Ardito, C., Barker, D. H., Saletin, J. M., & Carskadon, M. A. (2020). Classifying pubertal development using child and parent report: Comparing the pubertal development scales to tanner staging. *Journal of Adolescent Health*, *66*(5), 597–602. https://doi.org/10.1016/j.jadohealth.2019.11.308

May, T., Pang, K. C., O'Connell, M. A., & Williams, K. (2017). Typical pubertal timing in an Australian population of girls and boys with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *47*, 3983–3993.

McCoy, S. M., Jakicic, J. M., & Gibbs, B. B. (2016). Comparison of obesity, physical activity, and sedentary behaviors between adolescents with autism spectrum disorders and without. *Journal of Autism and Developmental Disorders*, *46*(7), 2317–2326. https://doi.org/10.1007/s10803-016-2762-0

McEvoy, K., Hasenstab, K., Senturk, D., Sanders, A., & Jeste, S. S. (2015). Physiologic artifacts in resting state oscillations in young children: Methodological considerations for noisy data. *Brain Imaging Behaviour*, *9*(1), 104–114. https://doi.org/10.1007/s11682-014-9343-7

McPartland, J. C., Bernier, R. A., Jeste, S. S., Dawson, G., Nelson, C. A., Chawarska, K., Earl, R., Faja, S., Johnson, S. P., Sikich, L., Brandt, C. A., Dziura, J. D., Rozenblit, L., Hellemann, G., Levin, A. R., Murias, M., Naples, A. J., Platt, M. L., Sabatos-DeVito, M., … Autism Biomarkers Consortium for Clinical Trials. (2020). The Autism Biomarkers Consortium for Clinical Trials (ABC-CT): Scientific context, study design, and progress toward biomarker qualification. *Frontiers in Integrative Neuroscience*, *14*, 16. https://www.frontiersin.org/article/10.3389/fnint.2020.00016

Mendle, J., Beltz, A. M., Carter, R., & Dorn, L. D. (2019). Understanding puberty and its measurement: Ideas for research in a new generation. *Journal of Research on Adolescence*, *29*(1), 82–95. https://doi.org/10.1111/jora.12371

Mostert-Kerckhoffs, M. A. L., Staal, W. G., Houben, R. H., & de Jonge, M. V. (2015). Stop and change: Inhibition and flexibility skills are related to repetitive behavior in children and young adults with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *45*(10), 3148–3158. https://doi.org/10.1007/s10803-015-2473-y

Murias, M., Webb, S. J., Greenson, J., & Dawson, G. (2007). Resting state cortical connectivity reflected in EEG coherence in individuals with autism. *Biological Psychiatry*, *62*(3), 270–273. https://doi.org/10.1016/j.biopsych.2006.11.012

Murray, C. R., Simmons, J. G., Allen, N. B., Byrne, M. L., Mundy, L. K., Seal, M. L., Patton, G. C., Olsson, C. A., & Whittle, S. (2016). Associations between dehydroepiandrosterone (DHEA) levels, pituitary volume, and social anxiety in children. *Psychoneuroendocrinology*, *64*, 31–39. https://doi.org/10.1016/j.psyneuen.2015.11.004

Murray, E., Sharma, R., Smith, K. B., Mar, K. D., Barve, R., Lukasik, M., Pirwani, A. F., Malette-Guyon, E., Lamba, S., Thomas, B. J., Sadeghi-Emamchaie, H., Liang, J., Mallet, J.-F., Matar, C., & Ismail, N. (2019). Probiotic consumption during puberty mitigates LPS-induced immune responses and protects against stress-induced depression- and anxiety-like behaviors in adulthood in a sex-specific manner. *Brain, Behavior, and Immunity*, *81*, 198–212. https://doi.org/10.1016/j.bbi.2019.06.016

Neuhaus, E., Lowry, S. J., Santhosh, M., Kresse, A., Edwards, L. A., Keller, J., Libsack, E. J., Kang, V. Y., Naples, A., Jack, A., Jeste, S., McPartland, J. C., Aylward, E., Bernier, R., Bookheimer, S., Dapretto, M., Van Horn, J. D., Pelphrey, K., Webb, S. J., & the ACE GENDAAR Network. (2021). Resting state EEG in youth with ASD: Age, sex, and relation to phenotype. *Journal of Neurodevelopmental Disorders*, *13*(1), 33. https://doi.org/10.1186/s11689-021-09390-1

Neuper, C., & Pfurtscheller, G. (2001). Evidence for distinct beta resonance frequencies in human EEG related to specific sensorimotor cortical areas. *Clinical Neurophysiology*, *112*(11), 2084–2097. https://doi.org/10.1016/S1388-2457(01)00661-7

Newson, J. J., & Thiagarajan, T. C. (2019). EEG frequency bands in psychiatric disorders: A review of resting state studies. *Frontiers in Human Neuroscience*, *12*, 521. https://www.frontiersin.org/article/10.3389/fnhum.2018.00521

Nguyen, T. V., Lew, J., Albaugh, M. D., Botteron, K. N., Hudziak, J. J., Fonov, V. S., Collins, D. L., Ducharme, S., & McCracken, J. T. (2017). Sex-specific associations of testosterone with prefrontal-hippocampal development and executive function. *Psychoneuroendocrinology*, *76*, 206–217. https://doi.org/10.1016/j.psyneuen.2016.12.005

Nobili, A., Glazebrook, C., Bouman, W. P., Baron-Cohen, S., & Arcelus, J. (2020). The stability of autistic traits in transgender adults following cross-sex hormone treatment. *International Journal of Transgender Health*, *21*(4), 431–439. https://doi.org/10.1080/26895269.2020.1783738

Pasterski, V., Gilligan, L., & Curtis, R. (2014). Traits of autism spectrum disorders in adults with gender dysphoria. *Archives of Sexual Behavior*, *43*(2), 387–393. https://doi.org/10.1007/s10508-013-0154-5

Peters, S., Jolles, D. J., Duijvenvoorde, A., Crone, E. A., & Peper, J. S. (2015). The link between testosterone and amygdala–orbitofrontal cortex connectivity in adolescent alcohol use. *Psychoneuroendocrinology*, *53*, 117–126. https://doi.org/10.1016/j.psyneuen.2015.01.004

Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of Youth and Adolescence*, *17*(2), 117–133. https://doi.org/10.1007/BF01537962

Pfeifer, J. H., Kahn, L. E., Merchant, J. S., Peake, S. J., Veroude, K., Masten, C. L., Lieberman, M. D., Mazziotta, J. C., & Dapretto, M. (2013). Longitudinal change in the neural bases of adolescent social self-evaluations: Effects of age and pubertal development. *Journal of Neuroscience*, *33*(17), 7415–7419. https://doi.org/10.1523/JNEUROSCI.4074-12.2013

Picci, G., & Scherf, K. S. (2015). A two-hit model of autism: Adolescence as the second hit. *Clinical Psychological Science*, *3*(3), 349–371. https://doi.org/10.1177/2167702614540646

Piekarski, D. J., Johnson, C. M., Boivin, J. R., Thomas, A. W., Lin, W. C., Delevich, K., Galarce, E. M., & Wilbrecht, L. (2017). Does puberty mark a transition in sensitive periods for plasticity in the associative neocortex? *Brain Research*, *1654*, 123–144. https://doi.org/10.1016/j.brainres.2016.08.042

Pizzagalli, D. A. (2007). Electroencephalography and high-density electrophysiological source localization. In J. T. Cacioppo, L. G. Tassinary, & G. G. Berntson (Eds.), *Handbook of psychophysiology* (3rd ed., pp. 56–84). Cambridge University Press.

Pohl, A., Cassidy, S., Auyeung, B., & Baron-Cohen, S. (2014). Uncovering steroidopathy in women with autism: A latent class analysis. *Molecular Autism*, *5*(1), 27. https://doi.org/10.1186/2040-2392-5-27

Schmitz, K. E., Hovell, M. F., Nichols, J. F., Irvin, V. L., Keating, K., Simon, G. M., Gehrman, C., & Jones, K. L. (2004). A validation study of early adolescents' pubertal self-assessments. *The Journal of Early Adolescence*, *24*(4), 357–384. https://doi.org/10.1177/0272431604268531

Schürmann, M., & Başar, E. (2001). Functional aspects of alpha oscillations in the EEG. *International Journal of Psychophysiology*, *39*(2), 151–158. https://doi.org/10.1016/S0167-8760(00)00138-0

Shephard, E., Tye, C., Ashwood, K. L., Azadi, B., Asherson, P., Bolton, P. F., & McLoughlin, G. (2018). Resting-state neurophysiological activity patterns in young people with ASD, ADHD, and ASD + ADHD. *Journal of Autism and Developmental Disorders*, *48*(1), 110–122. https://doi.org/10.1007/s10803-017-3300-4

Shirazi, T. N., Self, H., Cantor, J., Dawood, K., Cárdenas, R., Rosenfield, K., Ortiz, T., Carré, J., McDaniel, M. A., Blanchard, R., Balasubramanian, R., Delaney, A., Crowley, W., Breedlove, S. M., & Puts, D. (2020). Timing of peripubertal steroid exposure predicts visuospatial cognition in men: Evidence from three samples. *Hormones and Behavior*, *121*, 104712. https://doi.org/10.1016/j.yhbeh.2020.104712

Shirtcliff, E. A., Dahl, R. E., & Pollak, S. D. (2009). Pubertal development: Correspondence between hormonal and physical development. *Child Development*, *80*(2), 327–337. https://doi.org/10.1111/j.1467-8624.2009.01263.x

Shrout, P. E., & Bolger, N. (2002). Mediation in experimental and nonexperimental studies: new procedures and recommendations. *Psychological Methods*, *7*(4), 422.

Sisk, C. L., & Foster, D. L. (2004). The neural basis of puberty and adolescence. *Nature Neuroscience*, *7*(10), 1040–1047. https://doi.org/10.1038/nn1326

Sparrow, S., Cicchetti, D., & Balla, D. (2005). *Vineland Adaptive Behavior Scales* (2nd ed.). Pearson Assessments.

Stagi, S., De Masi, S., Bencini, E., Losi, S., Paci, S., Parpagnoli, M., Ricci, F., Ciofi, D., & Azzari, C. (2020). Increased incidence of precocious and accelerated puberty in females during and after the Italian lockdown for the coronavirus 2019 (COVID-19) pandemic. *Italian Journal of Pediatrics*, *46*(1), 165. https://doi.org/10.1186/s13052-020-00931-3

Strang, J. F., Powers, M. D., Knauss, M., Sibarium, E., Leibowitz, S. F., Kenworthy, L., Sadikova, E., Wyss, S., Willing, L., Caplan, R., Pervez, N., Nowak, J., Gohari, D., Gomez-Lobo, V., Call, D., & Anthony, L. G. (2018). "They thought it was an obsession": Trajectories and perspectives of autistic transgender and gender-diverse adolescents. *Journal of Autism and Developmental Disorders*, *48*(12), 4039–4055. https://doi.org/10.1007/s10803-018-3723-6

Tamnes, C. K., Walhovd, K. B., Dale, A. M., Østby, Y., Grydeland, H., Richardson, G., Westlye, L. T., Roddey, J. C., Hagler, D. J., Jr., Due-Tønnessen, P., Holland, D., Fjell, A. M., & Alzheimer's Disease Neuroimaging Initiative. (2013). Brain development and aging: Overlapping and unique patterns of change. *Neuroimage*, *68*, 63–74. https://doi.org/10.1016/j.neuroimage.2012.11.039

Tyborowska, A., Volman, I., Smeekens, S., Toni, I., & Roelofs, K. (2016). Testosterone during puberty shifts emotional control from pulvinar to anterior prefrontal cortex. *Journal of Neuroscience*, *36*(23), 6156–6164. https://doi.org/10.1523/JNEUROSCI.3874-15.2016

Ullsperger, J. M., & Nikolas, M. A. (2017). A meta-analytic review of the association between pubertal timing and psychopathology in adolescence: Are there sex differences in risk? *Psychological Bulletin*, *143*(9), 903–938. https://doi.org/10.1037/bul0000106

Vijayakumar, N., Op de Macks, Z., Shirtcliff, E. A., & Pfeifer, J. H. (2018). Puberty and the human brain: Insights into adolescent development. *Neuroscience & Biobehavioral Reviews*, *92*, 417–36.

Walsh, M. J. M., Wallace, G. L., Gallegos, S. M., & Braden, B. B. (2021). Brain-based sex differences in autism spectrum disorder across the lifespan: A systematic review of structural MRI, fMRI, and DTI findings. *NeuroImage: Clinical*, *31*, 102719. https://doi.org/10.1016/j.nicl.2021.102719

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

Wantzen, P., Clochon, P., Doidy, F., Wallois, F., Mahmoudzadeh, M., Desaunay, P., Christian, M., Guilé, J.-M., Guénolé, F., Eustache, F., Baleyte, J.-M., & Guillery-Girard, B. (2022). EEG resting-state functional connectivity: Evidence for an imbalance of external/internal information integration in autism. *Journal of Neurodevelopmental Disorders*, *14*(1), 47. https://doi.org/10.1186/s11689-022-09456-8

Whitehouse, A. J. O., Maybery, M. T., Hickey, M., & Sloboda, D. M. (2011). Brief report: Autistic-like traits in childhood predict later age at menarche in girls. *Journal of Autism and Developmental Disorders*, *41*(8), 1125–1130. https://doi.org/10.1007/s10803-010-1129-1

Zhou, X., Qi, X. L., & Constantinidis, C. (2016). Distinct roles of the prefrontal and posterior parietal cortices in response inhibition. *Cell Reports*, *14*(12), 2765–2773. https://doi.org/10.1016/j.celrep.2016.02.072

SUPPORTING INFORMATION

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

How to cite this article: Rea, H. M., Clawson, A., Hudac, C. M., Santhosh, M., Bernier, R. A., Earl, R. K., Pelphrey, K. A., Webb, S. J., & Neuhaus, E., the GENDAAR Consortium. (2023). Pubertal maturation and timing effects on resting state electroencephalography in autistic and comparison youth. *Developmental Psychobiology*, *65*, e22415. https://doi.org/10.1002/dev.22415