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EEG Data Collection in Children with ASD: The Role of State in Data Quality and Spectral Power

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Abstract

Background: Electroencephalography can elucidate neurobiological mechanisms underlying heterogeneity in ASD. Studying the full range of children with ASD introduces methodological challenges stemming from participants' difficulties tolerating the data collection process, leading to diminished EEGdataretentionandincreasedvariabilityin participant 'state' during the recording. Quantifying state will improve data collection methods and aide in interpreting results.

Objectives: Observationally quantify participant state during the EEG recording; examine its relationship to child characteristics, data retention and spectral power.

Methods: Participants included 5–11 year-old children with D (N=39) and age-matched TD children (N=16). Participants were acclimated to the EEG environment using behavioral strategies. EEG was recorded while participants watched a video of bubbles. Participant 'state' was rated using a Likert scale (Perceived State Rating: PSR).

Results: Participants with ASD had more elevated PSR than TD participants. Less EEG data were retained in participants with higher PSR scores, but this was not related to age or IQ. TD participants had higher alpha power compared with the ASD group. Within the ASD group, participants with high PSR had decreased frontal alpha power.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Conclusions: Given supportive strategies, EEG data was collected from children with ASD across cognitive levels. Participant state influenced both EEG data retention and alpha spectral power. Alpha suppression is linked to attention and vigilance, suggesting that these participants were less 'at rest'. This highlights the importance of considering state when conducting EEG studies with challenging participants, both to increase data retention rates and to quantify the influence of state on EEG variables.

Keywords

autism spectrum disorder; intellectual disability; EEG; spectral power

Introduction

Although defined by core features of impaired social communication and the presence of restricted and repetitive patterns of behavior, autism spectrum disorder (ASD) includes a wide range of clinical characteristics and developmental courses. This heterogeneity stems, in part, from the fact that a range of etiologies and neural mechanisms contribute to the ASD phenotype (Chahrour et al., 2016; De Rubeis & Buxbaum, 2015; Jeste & Geschwind, 2014; Masi, DeMayo, Glozier, & Guastella, 2017). As a measure of synchronized post-synaptic neuronal activity, electroencephalography (EEG) provides a method to quantify neurophysiological characteristics underlying neurodevelopmental disorders such as ASD (Mohammad-Rezazadeh, Frohlich, Loo, & Jeste, 2016). EEG measures of neural activity (such as resting state oscillations) can potentially serve as powerful stratification biomarkers, linking genetic and biological mechanisms to clinical characteristics (Jeste, Frohlich, & Loo, 2015). Discovering sources of heterogeneity in ASD requires studying participants who represent the full range of the autism spectrum, including those with significant cognitive and/or language impairments (minimally verbal – MV) (McPartland, 2017). However, inclusion of this portion of the ASD population introduces methodological challenges rooted in participants' inherent difficulties understanding and complying with the data collection process, potentially leading to increased variability in participant 'state' during the recording. These challenges can contribute to both diminished EEG data quality (signal to noise ratio) and alterations in the EEG variables of interest (such as spectral power) (Webb et al., 2013). In this study, we created an observational rating system to quantify participant state during the EEG recording, and we applied it to a large, heterogeneous group of children with ASD as well as age matched typically developing participants (TD). Our state rating captured overt behavioral signs of vigilance and agitation, such as verbal protest or pulling on the EEG net. We examined the impact of child characteristics (cognitive and language level) and state on EEG data retention, as well as the relationship between our observational measure of state and EEG alpha spectral power.

EEG Data Collection in Pre-Verbal Children

Spontaneous EEG (also described as resting-state) is recorded in the absence of an overt task or event-related stimuli and reflects aspects of baseline neural function. In addition to representing intrinsic neuronal activity, spontaneous EEG also includes modulations induced by unconstrained behavior or 'state' (Duncan & Northoff, 2013). In studies of adults and typically developing children, spontaneous EEG is often recorded in an eyes-closed

condition, in order to approximate a true “resting state” and ensure that the EEG variables reflect underlying neurobiological traits. In studies of infants and young children, it is not be feasible to collect data under eyes-closed conditions, due to the child’s inability to understand and follow such directions, so other methods must be employed to reduce the impact of state (Figure 1).

Studies of these populations use non-social visual stimuli such as bouncing soap bubbles or spinning colored balls (e.g. Muller, Kühn-Popp, Meinhardt, Sodian, & Paulus, 2015; Mundy, Card, & Fox, 2000; Marshall, Bar-Haim, & Fox, 2002), which facilitate testing by providing a consistent, non-stimulating framework for the recording session. Additionally, participants are generally seated on a caregiver’s lap or in an infant car seat, in order to limit their movements (DeBoer, Scott, & Nelson, 2007). Finally, data processing includes strategies for removing periods of the recording where the participant does not appear to be in a state of rest. For example, Orekhova and colleagues (Orekhova, Stroganova, Posikera & Elam, 2006) report removing periods of “overt emotional expression” from the recording before analysis. These data collection strategies serve the dual purpose of reducing inter-participant variability in state as well as the amount of artifact (e.g. muscle movement) in the data. While these data collection methods provide a foundation for studying older participants with disabilities, additional considerations are necessary.

Similar to studies of pre-verbal infants, studies of older children with disabilities have also successfully used passive visual stimuli to collect resting-state EEG data (e.g. Dawson, Klinger, Panagiotides, Lewy, & Castelloe, 1995; Tierney, Gabard-Durnam, Vogel-Farley, Tager-Flusberg, & Nelson, 2012). Reducing movement can prove more challenging in this population, compared to infants and toddlers, due to physical size and challenging behaviors. Some studies have reported the successful use of behavior modification and desensitization strategies in order to increase compliance with the testing procedures (e.g. Cantiani et al., 2016; Roesler et al., 2013; Tager-Flusberg et al., 2016). Identifying periods of “non-rest” based on participant affect for removal from the dataset presents unique challenges. The high comorbidity of anxiety with ASD (van Steensel, Bögels, & Perrin, 2011; Vasa & Mazurek, 2015) and sensory sensitivities (Baum, Stevenson, & Wallace, 2015; Neil, Olsson, & Pellicano, 2016) may result in participants being more likely to experience agitation during the recording than typically developing toddlers, but due to increased exposure to intensive intervention this may manifest as relatively subtle signs of state differences (e.g. repeatedly touching the net, frequently turning to look at the experimenter). Finally, when studying the MV portion of the ASD population, any comparison group will likely have a better understanding of the testing situation. Thus discomfort with the EEG recording may systematically differ between groups, necessitating careful consideration.

Resting State EEG in ASD

Several studies have sought to quantify resting state EEG in children with ASD, with the primary goal of identifying patterns that might discriminate ASD from typically developing children. In a recent review, Wang and colleagues (Wang et al., 2013) compiled data from 14 studies of EEG in ASD and identified a possible “U shaped” profile of EEG power alterations, with excess power displayed in low and high frequency bands and reduced

power in mid frequency bands compared to typically developing (TD) individuals. The resting state paradigms varied across studies, including eyes open, eyes closed and passive visual stimuli. The majority of studies included only individuals with IQ's in the normal range, making it difficult to determine the effect of cognitive and language ability on EEG data retention (Table 1). This is a crucial issue, given that discovering clinically relevant stratification biomarkers in this heterogeneous population necessitates research with a wide range of participants.

One relatively consistent finding across studies was altered (primarily decreased) alpha band power in children with ASD compared with TD individuals. As an index of cortical inhibition (Mo, Liu, Huang, & Ding, 2013), alpha power likely reflects inhibitory top-down control (Klimesch, Sauseng, & Hanslmayr, 2007). Additionally, the alpha rhythm is thought to play an active role in the timing of cortical processes (Klimesch, 2012), as well as communication within and between brain regions (Edgar et al., 2015). Alpha oscillations show a well-defined developmental profile associated with cognitive competence, as the oscillations provide an infrastructure for neural communication between increasingly distributed brain regions (Fries, 2005; Klimesch et al., 2007). Recent research found that peak alpha power was associated with cognitive ability (rather than chronological age) in a heterogeneous sample of children with ASD (Dickinson, DiStefano, Senturk, & Jeste, 2017), suggesting that it may be a good candidate for a stratification biomarker. Alpha power is also strongly modulated by both cognitive and affective states. Alpha oscillations are dominant at rest (particularly in the eyes-closed condition) and during states of emotion regulation (Dennis & Solomon, 2010; Tortella-Feliu et al., 2014). Alpha attenuation occurs during tasks requiring attention, vigilance and memory (Edgar et al., 2015; Klimesch, 1999). Given its relationship to cognitive and emotional states, alpha power may be especially sensitive to the child's state during the EEG recording, thus limiting the interpretability of group differences. Careful characterization of participant state during the EEG recording will strengthen the conclusions that can be drawn.

In this study, we sought to quantify and examine state during the EEG recording in a heterogeneous group of children with ASD, through the development of a Likert Scale called the Perceived State Rating (PSR), and to compare the PSR in ASD to that of an age-matched group of TD children. We then asked whether child characteristics (age, IQ, language, diagnosis) and/or state during the recording affected EEG data quality (percent of data retained). Finally, we examined how state related to alpha spectral power, given its documented relationship with attention and emotion regulation. We hypothesized that as a group, children with ASD would demonstrate a more agitated state (higher PSR) during the EEG recording than TD children, and that state would be significantly related to data quality. Within the ASD group, we hypothesized that neither state nor data retention would be related to cognitive or language ability, given the use of supportive behavioral strategies (Figure 1). We also hypothesized that children with higher levels of agitation during the EEG recording session would show reduced alpha spectral power.

Methods

Participants

Data for this analysis were drawn from participants enrolled in ongoing studies at a large, university autism research center. Inclusion criteria included chronological age between 5–11 years and a primary clinical diagnosis of ASD (ASD group) or no neurodevelopmental diagnosis (TD group). Exclusionary criteria included other neurological abnormalities (including active epilepsy), birth-related complications and uncorrected vision or hearing impairment. Additional exclusionary criteria for the TD group included history of developmental delays, need for special services in school, diagnosis of psychiatric conditions, or a first-degree relative with an ASD diagnosis. All ASD participants had a prior clinical diagnosis of ASD, made through the California State Regional Center, independent clinical psychologists, child psychiatrist, and/or developmental pediatricians. Diagnosis was confirmed by the research team using the Autism Diagnostic Observation Schedule (ADOS) and Social Communication Questionnaire (described in the "Assessments" section below). All components of this study were approved by the University of California, Los Angeles Institutional eview Board. Informed consent was collected from parents of all participants. hild assent was collected from children who had sufficient language and cognitive abilities to understand the study procedures.

A total of 39 children with ASD and 16 TD children (age-matched) were included in this study. Of these, 34 children with ASD (Male = 28) and 16 TD children (Male = 12) provided sufficient EEG data to be included in analyses. The remaining 5 ASD participants were unable to complete the EEG recording due to behavioral dysregulation. The ASD group included children across a wide range of cognitive and language levels. Groups did not significantly differ on chronological age (t=0.96, p=0.35). The ASD group had a significantly lower verbal IQ (t=7.09, p<.001) and non-verbal IQ (t=5.16, p<.001).

Assessments

Cognitive and language assessments varied based on the ability and age of the child. Assessments included the Mullen Scales of Early Learning (MSEL; Mullen, 1995), Differential Abilities Scale-Second Edition (DAS-II; Elliot, 2007), and the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III; Wechsler, 2002). From these measures, ratio scores for full scale IQ (FSIQ), non-verbal IQ (NVIQ) and verbal IQ (VIQ) were calculated for each child and based on the age-equivalent score and chronological age. Ratio scores were used to account for the scores of children who performed outside of the standardized norms for their chronological age. For children who were tested with the WPPSI-III or DAS-II, NVIQ and VIQ were calculated from the protocol-specific sub-scores. For children who were administered the MSEL, VIQ was calculated using the average of the Receptive Language and Expressive Language subscale scores, and NVIQ was calculated using the average of the Visual Reception and Fine Motor subscale scores (Akshoomoff, 2006). Several studies have demonstrated the convergent validity of the WPPSI-III with other cognitive assessments such as the MSEL and the DAS-II, supporting the combination of assessments through standard scores (Bishop, Guthrie, Coffing, & Lord, 2011).

Perceived State Rating (PSR)

We developed a 5-point Likert scale to quantify the state of the participant during the EEG recording (Table 3), based on behavioral observation during the testing session.scoreof1indicatesthatthe participant appeared consistently calm and relaxed throughout the recording. Higher scores correspond to increasing levels of agitation, with a score of 5 indicating that a participant displayed a high level of agitation throughout the EEG recording. Similar Likert scale ratings have been developed to quantify pain in non-verbal children (Solodiuk & Curley, 2003), anxiety during dental visits (Venham, Gaulin-Kremer, Muster, Bengston-Audia, & Cohan, 1980) and agitation in elderly patients (Finkel, Lyons, & Anderson, 2015). Perceived state ratings (PSR) were drafted by a postdoctoral fellow (CD) and a research assistant (EB) experienced in collecting EEG data in children with ASD. Behavioral anchors were written to describe the range of behaviors observed during the EEG session. Ratings were then pilot tested by having additional staff rate sample videos of EEG sessions. Scores were discussed until consensus was reached, and revisions were made where necessary to clarify ratings. Once the rating system was finalized, undergraduate volunteers blind to participant diagnosis were then trained in the PSR and completed the ratings by watching a video of the EEG recording session. The rater watched the two-minute EEG recording and then assigned the PSR rating that best reflected the full segment. 20% of the sessions were rated by a second rater, and inter-rater reliability was calculated as percent agreement in ratings across the double coded sessions. Inter-rater reliability was 87%.

EEG Procedure

Behavioral strategies were used to acclimate participants to the testing environment, including modeling, incremental practice and positive reinforcement. Similar strategies have been described in previous EEG studies of children with ASD (Jeste et al., 2015b; Tager-Flusberg et al., 2016; Webb et al., 2015). Prior to the day of testing, parents of participants were interviewed regarding their child's preferences and interests so that the testing environment could be made as comfortable as possible with the child's preferred reinforcers available (e.g. a favorite snack). Pictures of a child undergoing EEG testing were also sent ahead of the session for parents to review with their child. On the day of testing, the following steps were followed:

1. **Initial acclimation**. Participants were free to explore the testing environment, while interacting with the examiner. A favorite movie was played on the testing monitor during this time and participants were given preferred reinforcers in the testing room. This step is crucial for building rapport between the child and experimenter, as well as reducing any anxiety to the testing environment.

2. **Netting**.Children were first shown a training EEG net, which mimics the tightness and feel of the actual EEG net, with plastic pedestals replacing the sensors. The parent or experimenter modeled putting it on, and the training net was then incrementally placed on the child's head, with reinforcement and praise after each step. After the child successfully wore the training net, the process was repeated with the actual EEG net. Throughout the netting process (including

adding electrolyte solution to sponges and final adjustments), the child watched a favorite move and received frequent reinforcement and praise.

3. **Recording**. During the EEG recording, an experimenter remained with the child to provide behavioral support (verbal and physical re-direction). The parent was given the option to sit with the child or remain behind the curtain. Many parents reported that their child would be distracted by their presence and so opted to stay out of view. Reinforcers were not available during the recording. However, if the child became agitated, the recording could be paused so that the child could briefly have a favorite snack or toy before continuing.

EEG Acquisition and Processing

Two minutes of resting G was recorded while children watched a video of bouncing soap bubbles in a dark, sound-attenuated room. The full EEG recording session lasted 10–15 minutes. video time-locked to the EEG was acquired in order to assist in subsequent data processing and was also used for PSR coding.

EEG data were recorded using a 128-channel HydroCel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR). To improve each child's comfort, four of the electrodes, channels 125–128 had been removed from the net. These electrodes were originally located below and lateral to the eyes. Placement of electrodes conformed to the International 10–20 System (Jasper, 1958). A combination of a Net Amps 300 amplifier and Net Station 4.4.5 software on a Macintosh Pro PC was used to record the EEG. The high impedance nature of this system allows us to accurately record a child's EEG while keeping impedances below 100 KΩ (Ferree, Luu, Russell, & Tucker, 2001). The EEG was sampled at 500 Hz. Data were referenced online to a vertical reference in a location equivalent to Cz.

All offline data processing and analyses were performed using EEGLAB (Delorme & Makeig, 2004), and MATLAB scripts. Data were high pass filtered to remove frequencies below 1Hz, and low pass filtered to remove frequencies above 120Hz, using a finite impulse response filter, as implemented in EEGLAB. Continuous data were then visually inspected, and any channels which were noisy throughout the recording were removed (e.g. periods of extremely high amplitude, characteristics artefactual activity such as 60Hz). Following channel removal, data were re-referenced to an average reference and interpolated to the international 10–20 system 25 channel montage. Data were again visually inspected for sections of data that showed electromyogram artifacts, and these sections were removed from the recording. EEG data retention was calculated as the length of the EEG recording following artifacts removal, divided by the length of the original recording for each participant. The experimenter was blinded to participant details throughout the data cleaning process.

Spectral Power Analysis

Four channels (F3, F4, O1 and O2) were selected for spectral power analysis, with each channel representing a distinct area of interest (left and right, frontal and occipital areas, respectively). Welch's method, using 2 second Hamming windows with 50% overlap, was used to compute spectral power. This method resulted in power spectrums with

approximately 0.5Hz frequency resolution for each of the four channels. Due to the influence of many non-neural anatomical factors on absolute power values (Nunez & Srinivasan, 2006), relative power values were instead used in all analyses in order to facilitate between-participant comparison of spontaneous EEG power. Relative spontaneous power was calculated by determining the proportion of total spectral power (1–55Hz) accounted for by each given frequency in the power spectrum of every channel. Relative power values were then summed for frequencies falling within the alpha range (8–12Hz).

Statistical Analysis

Perceived state ratings (PSR).—Due to the skewed distribution and low frequency of scores above 2, PSR scores were collapsed into two groups for analysis: low (rating = 1) and high (rating 2–5) groups. The frequency of high and low PSR scores were compared across groups using Fischer's exact test, in order to account for the low expected cell frequency of high PSR.

EEG data retention.—Separate analyses were carried out for each group. Pearson's correlations were used to test the relationships between EEG data retention (seconds remaining after artifact rejection/total seconds of recording x 100) and child characteristics (age, VIQ, NVIQ). T-tests were used to compare data retention between highandlowPSRgroups.

Spectral power.—Repeated measures ANOVA was used to compare spectral power in the alpha band, with group as the between subjects factor, hemisphere and region as within subjects factors. T-tests were used to compare regional alpha power between high and low PSR groups.

Results

EEG Data Retention

minimum of 2 minutes of resting EEG data were collected from 34 participants with ASD and 16 TD participants (87% of ASD participants, 100% of TD participants). An additional 5 ASD participants enrolled in the study but were unable to complete the EEG recording session, due to behavioral dysregulation. Figure 3 shows data retention rates by group. T-test results indicated that significantly more data were retained in the TD group (t=4.86, p<0.001, d=1.3). Additionally, significantly more channels were retained in the TD group compared with the ASD group (TD $M(SD)$=108(5.8), ASD $M(SD)$=97(10.9), t=4.82, p<.001, d=1.3).

Perceived State Rating

100% of participants in the TD group and 67% participants with ASD received a PSR score of 1. Given the skewed distribution of scores and the low frequency of scores above 2, PSR scores were collapsed into two groups for analysis: low (rating = 1) and high (rating 2–5) groups. Fisher's exact test was used to compare R scores (high vs. low) between groups. Participants with ASD were significantly more likely to have PSR scores above 1 than TD participants (p=0.002). Figure 4 displays the distribution of PSR scores in the ASD group. T-

tests were used to compare child characteristics between high and low PSR groups in the ASD group. Chronological age (t=0.46, p=0.65), NVIQ (t=1.84, p=0.08) and VIQ (t=2.10, p=.06) did not differ between high and low PSR groups, although there was a trend towards lower VIQ in the high PSR group. Spearman correlations indicated that PSR as rank-ordered variable (1–5) was also not significantly associated with age or IQ (verbal, non-verbal and full scale), consistent with the PSR group comparisons. Because all TD children had at PSR score of 1, it was not possible to compare the characteristics of TD children across PSR groups.

Factors Relating to EEG Data Retention

Pearson correlations were used to examine the relationships between percentage of data retained and child characteristics (chronological age, VIQ and NVIQ). To correct for multiple comparisons, p-values below 0.01 were considered significant. In both TD and ASD groups, percentage of data retained was not related to chronological age, VIQ or NVIQ (Tables 4, 5). Figure 5 displays EEG data retention by full-scale IQ in the ASD group. In the ASD group, significantly less data were retained in children with high PSR scores compared to those with low PSR scores (t=3.22, p=0.003, d=1.1).

Spectral Power

Repeated measures ANOVA was used to compare relative spectral power in the alpha band, with group (TD, ASD) as the between-subjects factor, and hemisphere (left, right) and region (frontal, occipital) as within-subjects factors. There was a main effect of region (F=33.40, p<0.001) on alpha band power, and a main effect of group (F=8.76, p=0.005). However, there was no main effect of hemisphere (F=0.74, p=.39) and no significant interactions (p-values 0.23–0.70). lpha power was therefore collapsed across hemispheres for the remaining analyses, resulting in two regions (frontal and occipital). Children in the TD group had significantly higher alpha power in both regions compared with children in the ASD group (Frontal t=3.41, p=0.003, d=1; Occipital t=2.37, p=0.02, d=0.7). In both groups, alpha power was higher in the occipital region compared with frontal (TD t=−2.16, p=0.04, d=0.2; ASD t=−3.05, p=0.01, d=0.4). Within the TD group, chronological age was associated with both frontal (r=0.82, p<0.001) and occipital alpha power (r=0.62, p=0.01). This association was not present in the ASD group (p-values 0.4–0.8). In the ASD group, there was a significant association between frontal alpha power and NVIQ (r=0.45, p=.01). There was no relationship between NVIQ and occipital alpha power, or VIQ and alpha power.

T-tests were used to compare regional alpha power between high and low PSR groups in ASD participants. Participants in the low PSR group had higher frontal alpha power compared to those in the high PSR group (t=2.49, p=0.02, d=0.6). Occipital alpha power did not differ between those in the high and low PSR groups (t=0.08, p=0.94). PSR as a rank-ordered variable (1–5) was significantly negatively associated with frontal alpha power (rho=−0.4, p=.02) but not occipital (rho=−0.02, p=.9), consistent with the results of the PSR group comparisons. Figure 7 displays regional alpha power in ASD (divided by PSR group) and TD participants.

Discussion

In this study, we developed an observational rating system to quantify participant state during the EEG recording. Our rating system captured overt behavioral signs of vigilance or agitation displayed by participants. We then examined factors relating to EEG data retention in a cohort of school-age children with ASD across a wide range of language and cognitive levels, and we compared them to age matched TD children. Supportive behavioral strategies were used to maximize participants' ability to complete the research protocol. We investigated how both state and child characteristics influenced EEG data retention, as well as how state and child characteristics related to each other. Finally, we examined the relationship between state during the EEG recording and alpha spectral power. Our study has three main findings: 1) Overall, children with ASD were more likely to have elevated (more agitated) state ratings compared to TD children, 2) EEG data retention was related to state during the recording (as measured by PSR), but not to age or IQ, and 3) Alpha power was reduced in children with ASD compared to TD children, with the greatest reduction in power occurring in the children who had elevated state ratings.

Given appropriate preparation and supportive strategies, EEG data were successfully collected in 87% of participants with ASD, including children with significant cognitive and language impairments. Although less data were retained in the ASD group as a whole, within the ASD group, age and IQ were not related to the percentage of EEG data retained. Instead, the percentage of EEG data retained related only to the child's state during the recording. Although not significant, there was a trend for children with lower VIQ to demonstrate more agitation during the EEG session, suggesting that while verbal ability was not directly related to data retention in our sample, it may nonetheless be a relevant factor. This may be due to the fact that children with more limited language have a difficult time understanding the testing environment, and are less able to express their feelings. Specialized behavioral strategies, such as the use of visual supports and social stories, are likely especially important for this subgroup of the population. Given the increasing interest in using EEG to study neurophysiological profiles in minimally verbal children with ASD, these encouraging results suggest that, with supportive behavioral strategies, most children with ASD can successfully complete a research protocol regardless of verbal ability.

In addition to an association with EEG data retention, we demonstrate that state during the EEG recording was inversely related to relative alpha power, with greater levels of perceived agitation and vigilance corresponding to reduced alpha power. Within the ASD group, frontal alpha power was also associated with non-verbal IQ. However, given that NVIQ did not differ based on state rating, this association cannot account for the reduced alpha power observed in participants with increased agitation. Alpha suppression has been consistently linked to attention and vigilance (Boiten, Sergeant, & Geuze, 1992; Klimesch, 1999), suggesting that our finding of reduced alpha power in children with an elevated state rating may reflect that these participants were less "at rest" during the EEG recording. Additionally, frontal alpha power has been related to emotional regulation, with higher power associated with more effective emotion regulation (Dennis & Solomon, 2010). Given that many individuals with ASD have difficulty with emotion regulation (Berkovits, 2016), the relationship between alpha power and level of agitation observed in our study may index

the capacity to self-regulate in the face of the specific demands of the EEG testing environment.

It is important to note that alpha power significantly differed between ASD and TD groups even when children with an elevated state rating were removed from the analysis, indicating that state did not exclusively drive the difference observed between ASD and TD groups. Researchers have consistently measured spontaneous alpha as a putative biomarker of healthy brain development, reflecting thalamo-cortical connectivity (Foxe & Snyder, 2011), and regulating the temporal structure of many basic cognitive processes (Klimesch, 2012). By quantifying and controlling for the potential confound of state during the recording, we can present a more compelling argument that the group differences in spontaneous alpha reported here do in fact reflect differences in basic neurophysiology.

There is rapidly growing interest in discovering clinical relevant biomarkers in neurodevelopmentaldisorderssuchas ASD, both for the purpose of stratifying participants and for detecting treatment effects. Projects such as European Autism Interventions – Multicentre Study for Developing New Medications (EU-AIMS), and the Autism Biomarkers Consortium for Clinical Trials (ABC-CT) are large-scale multi-site studies which seek to develop reliable and objective measures of social function and communication in people with ASD, laying the foundation for future clinical trials (Loth et al., 2017; McPartland et al., 2018). Along with careful clinical characterization and behavioral measures, these studies collect data on a wide variety of potential biomarkers (including eye tracking, EEG and brain imaging methodologies) in children with ASD, in order to identify clinical and biological meaningful subgroups and to inform treatment research. Despite standardization of data collection procedures across sites and across time points, there is the potential for variability in state both across participants, and across time within the same participant. For example, participants may become less anxious with repeated visits, affecting biomarker measurements. Good biomarker candidates are those that are either robust to variations in behavior during biomarker acquisition, or have a measurable and consistent relationship with confounding factors (McPartland, 2017). Observational characterization of state during biomarker acquisition will contribute towards this goal by elucidating the relationship between variations in participant state and the biomarker of interest.

Limitations and Future Directions

Although we observed a range of participant states during the EEG recording, most participants showed minimal levels agitation. This low rate of agitation reflects the effectiveness of our supportive behavioral strategies to prepare participants. Because participants were enrolled in ongoing studies, these strategies could not be altered to capture a more representative range of state. dditionally, we used a consistent set of behavioral strategies with all participants. Although this ensures a uniform testing situation, it precludes the possibility of ascertaining whether certain strategies differ in their effect on data retention and EEG variables. Further research, in which behavioral strategies are systematically manipulated, is needed to evaluate the effects of specific preparation and practice strategies on the participant’s state during the recording. This research will also

provide information on which strategies best match different participant needs. For example, participants with limited language may especially benefit from the use of visual supports, while participants with high levels of anxiety and sensory sensitivities may benefit more from incremental practice. Such research will facilitate the development of consistent strategies and protocols for recording EEG in challenging populations.

Within the ASD group, we found differences in alpha power between high and low PSR groups. However, high and low PSR groups also differed in terms of the amount of data retained. It is therefore possible that reduced data retention moderates the observed relationship between state and alpha power. We attempted to reduce the possibility of this confound by including only participants with at least 30 seconds of clean data, a threshold which should yield a stable estimate of spectral power. Additionally, we found that high and low PSR groups differed in frontal alpha power, but not occipital. If the group difference were an artifact of differences in data retention, we would expect all regions to be affected equally.

Our measure of state was based on observation of the child's behavior during the EEG session. Although a high level of inter-rater reliability was demonstrated for PSR scores, inclusion of a physiological marker of state (such as heart rate or galvanic skin response) would further strengthen the validity of these ratings. Additionally, such physiological measures may detect variability in state that cannot be captured by an observational rating system. Future research incorporating such physiological measures can provide additional detailed information about the relationship between participant state, EEG data retention and outcome variables.

Finally, it is important to note that to some degree, state can be a function of developmental traits, and therefore cannot be fully disentangled. For example, children with ASD who have increased sensory sensitivities may show increased arousal during the EEG recording, in which case variation in state is indexing an underlying behavioral trait. Although state was not associated with child characteristics in this sample, further research that includes measures of additional characteristics such as sensory sensitivity, repetitive behavior or anxiety can further clarity the extent to which observed state differences may reflect underlying developmental traits.

Implications

EEG has the potential to serve as a powerful biomarker in neurodevelopmental disorders such as ASD by elucidating neurobiological mechanisms (such as excitation/inhibition imbalance and disrupted network formation) that may underlie and even precede the variability observed in clinical characteristics. Given that 30% of the ASD population remains minimally verbal, it is crucial that research investigating neurobiological mechanism include these participants, as they may represent unique genetic and neurobiological etiologies.

In this study, we documented that language and cognitive impairment were not significant factors influencing the success of EEG data collection, while state during the recording was significantly related to data retention. Given that cognitive and affective states can also

influence EEG variables of interest (as in the case of alpha spectral power), consistent use of specialized behavioral strategies to increase participant success in the testing environment, coupled with characterization of the participant's state during the EEG recording itself will strengthen the quality of the information gathered and the conclusions that can be drawn from this line of research.

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Highlights

- In children with ASD, ‘state’ during the EEG recording influences the amount of EEG data retained.
- Children showing a more agitated state had reduced alpha spectral power, suggesting that they were less “at rest”.
- Amount of EEG data retained was not related to language or cognitive ability.

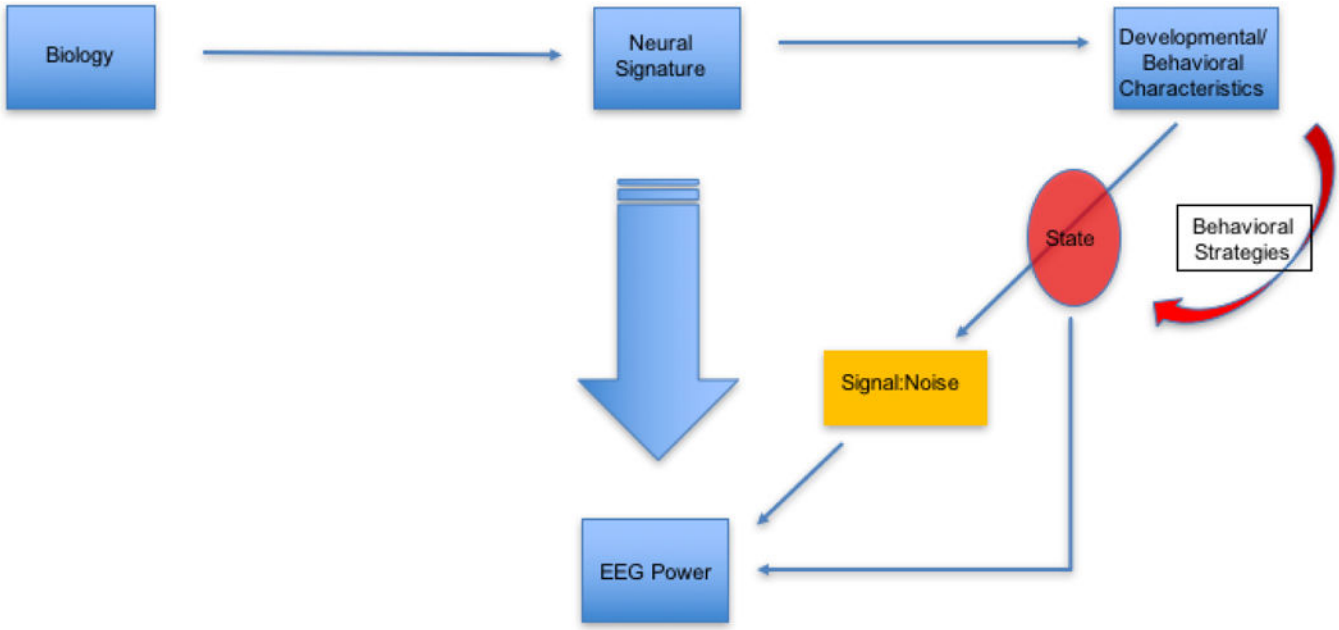

Figure 1: Conceptual outline of factors contributing to the EEG signal

Caption: As a measure of synchronized, post-synaptic neural activity, EEG is a method to assay neural mechanisms, which are thought to serve as intermediary between biological processes and observed behavioral characteristics. In order for the EEG signal to be interpretable, there needs to be a sufficient signal-to-noise ratio. Several studies have outlined specialized behavioral strategies suitable for acclimating participants to the EEG environment and therefor increasing successful EEG data acquisition. Participant 'state' during the EEG recording has the potential to contribute to the EEG signal as well, serving as a confound when drawing conclusions about underlying neurobiological traits. Although state may also be modulated through the use of behavioral strategies, measuring state during the recording is necessary in order to understand its relationship to data quality and contribution to the observed EEG signal.

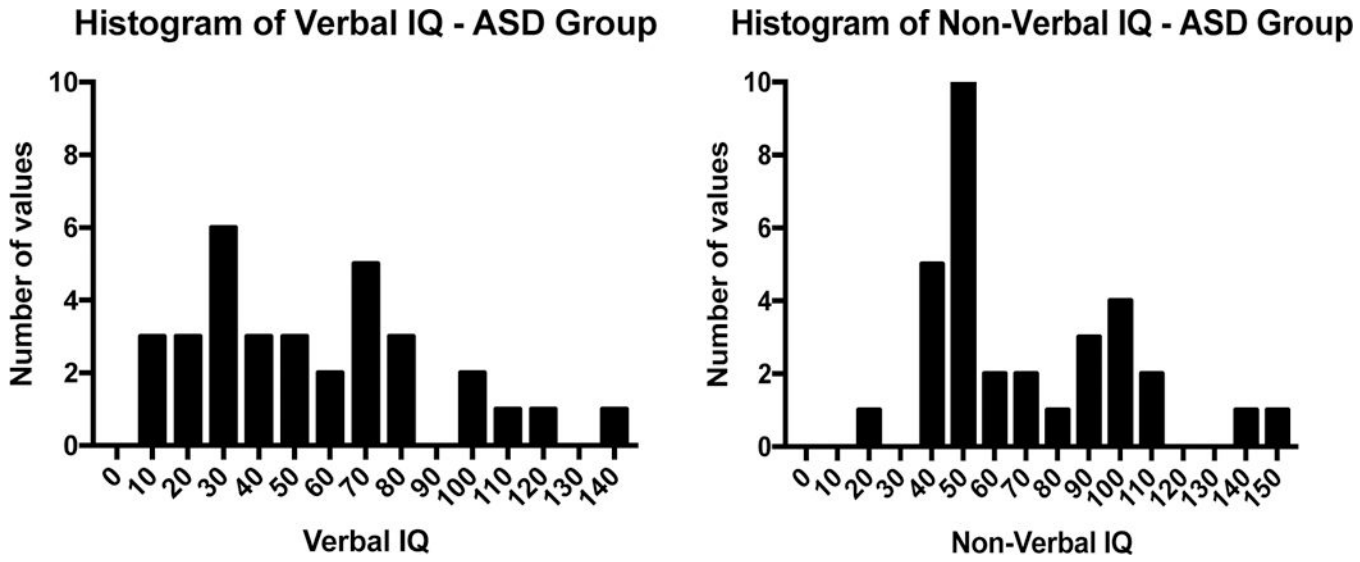

Figure 2: Histograms of verbal and non-verbal IQ scores in the ASD group

Caption: Histograms demonstrating the range of verbal and non-verbal IQ scores in the SD group. The ASD group included participants with a wide variety of verbal and non-verbal cognitive abilities.

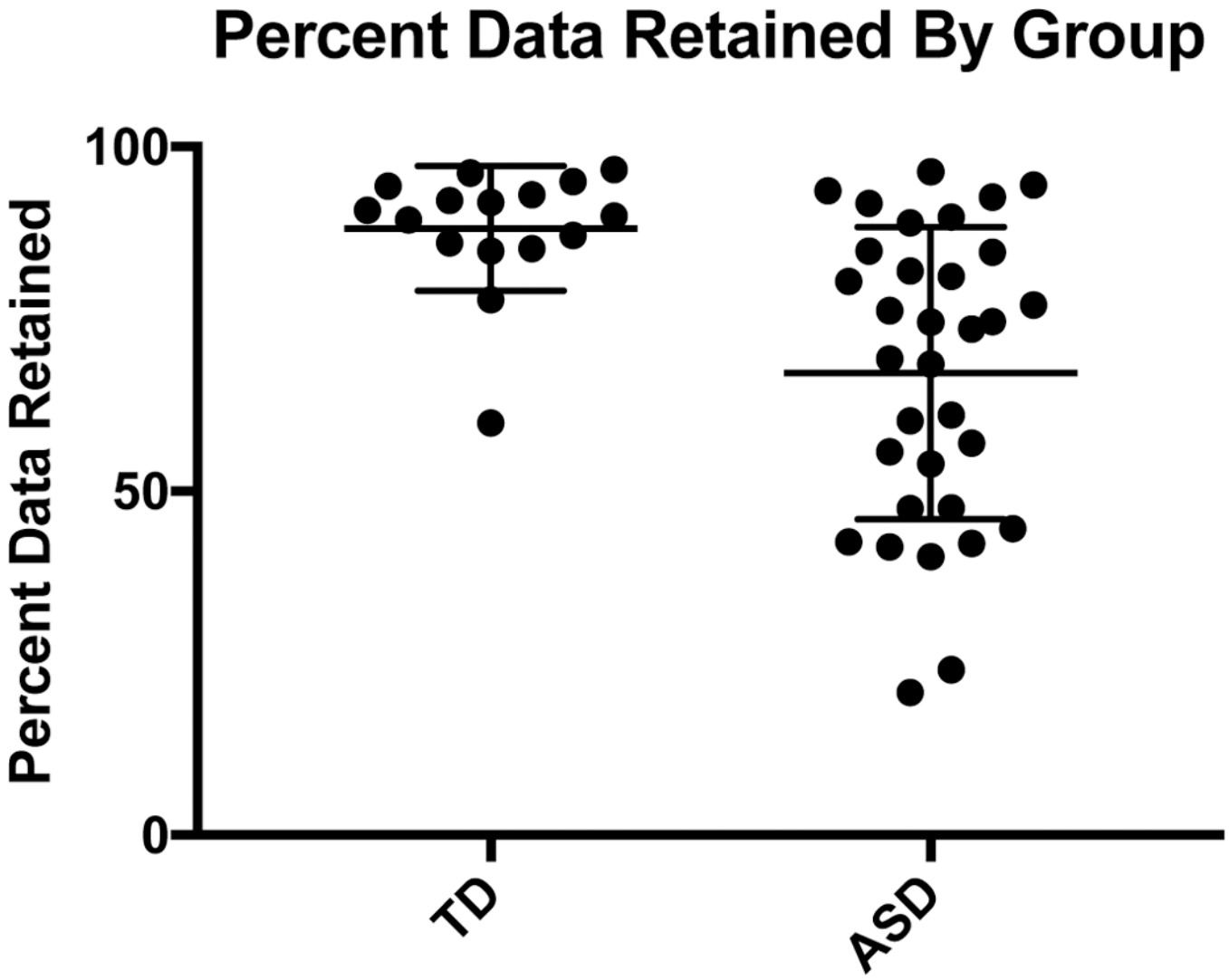

Figure 3: Percentage of EEG data retained by group

Caption: Scatterplot showing the percentage of EEG data retained (seconds remaining after artifact rejection/total seconds of recording x 100) by group (TD, ASD). Significantly more data was retained in the TD group (t=4.86, p<0.001). Additionally, there was more variability present in the ASD group.

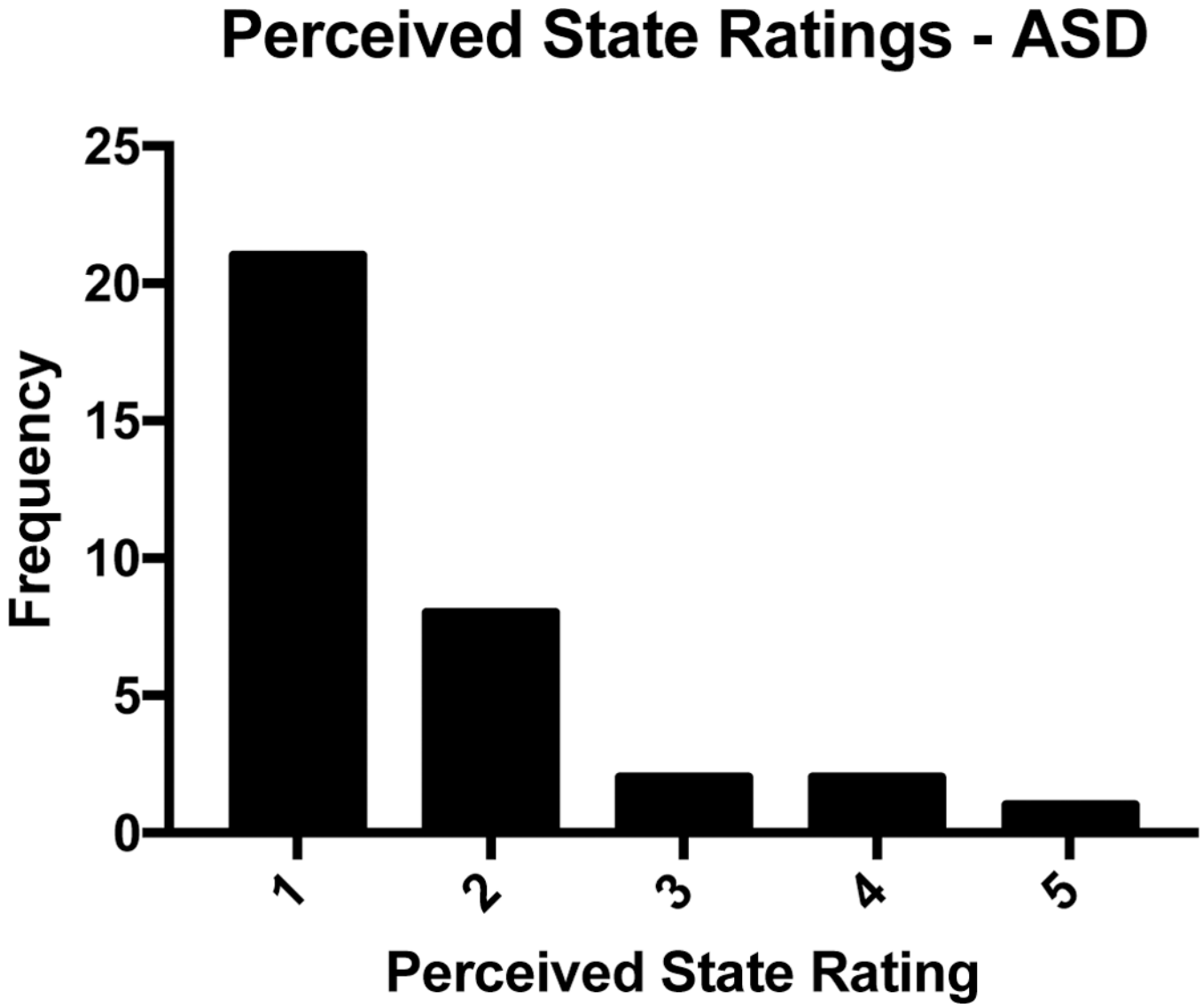

Figure 4: Frequency of Perceived State Ratings in the ASD group

Caption: Bar graph showing the frequency of Perceived State Ratings in the ASD group. PSR 1 indicates that the child showed no or very minimal signs of agitation during the recording. Higher ratings correspond to increasing levels of agitation. 67% of participants in the ASD group were rated as having a PSR of 1.

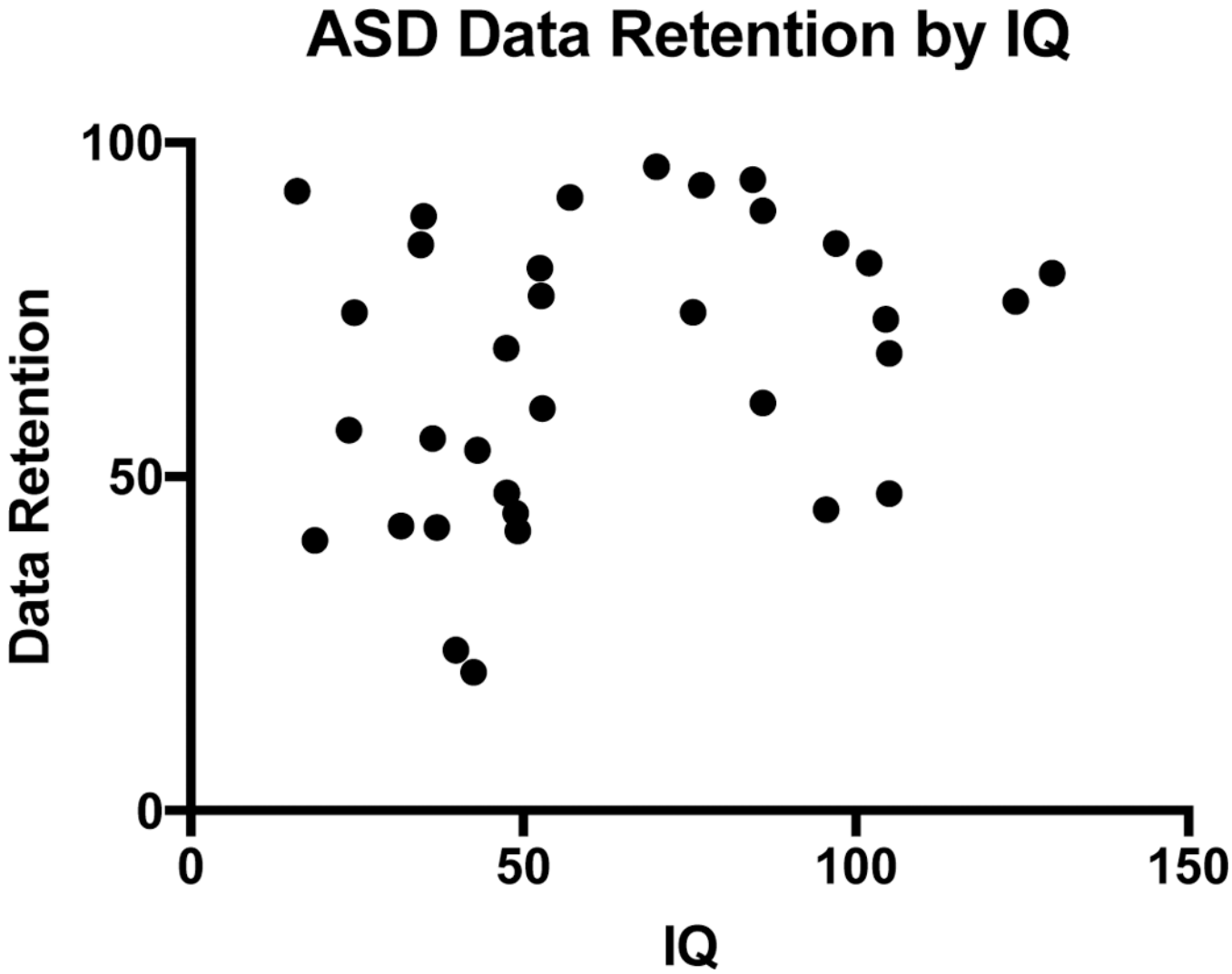

Figure 5: Relationship between EEG data retention and IQ in the ASD group

Caption: Scatter plot showing EEG data retention (percent of data retained after artifact rejection) by IQ score in the ASD group. EEG data retention was not significantly related to IQ in the ASD group, after correcting for multiple comparisons (r=0.39, p=0.03).

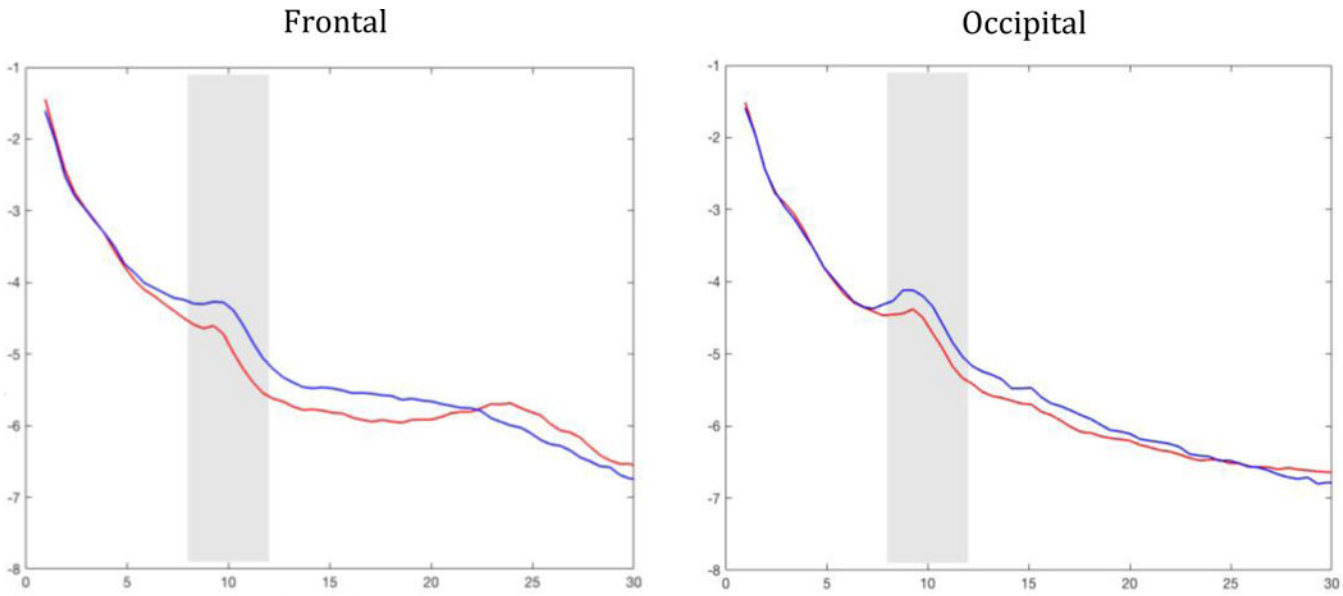

Figure 6: Power spectral density plots by region and group

Caption: Average relative power spectral density for ASD group (red), and TD group (blue), shown for frontal and occipital regions with the alpha band highlighted. Children in the TD group had significantly higher alpha power in both regions compared with children in the ASD group (Frontal t=3.41, p=0.003, d=1; Occipital t=2.37, p=0.02, d=0.7).

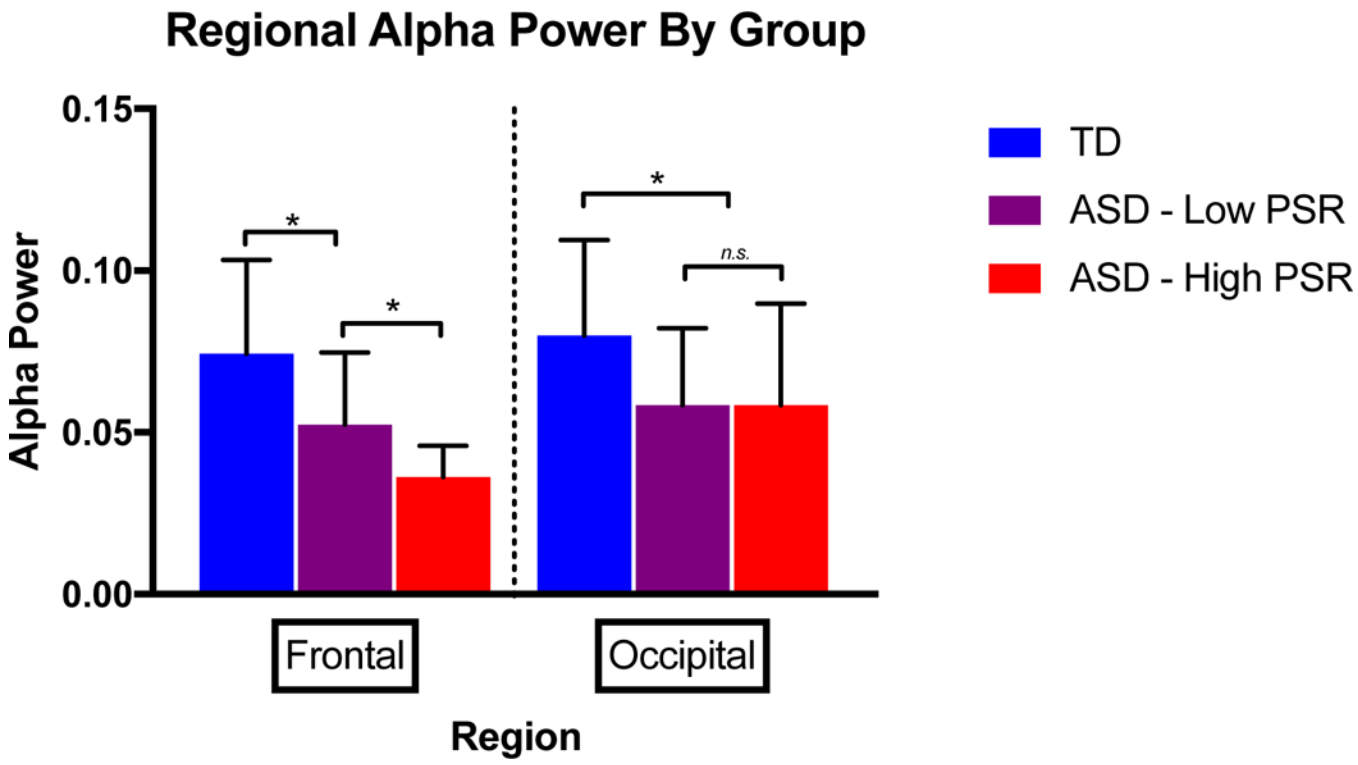

Figure 7: Relative alpha spectral power by region and group

Caption: Bar graph showing relative alpha spectral power in frontal and occipital regions, in the TD group, ASD group with low PSR scores and ASD group with high PSR scores. Children in the TD group had significantly higher alpha power in both regions compared to children with ASD (regardless of PSR score; *p*-values 0.003–0.036). Within the ASD group, participants in the low PSR group had higher frontal alpha power compared to those in the high PSR group (t=2.49, p=0.02). Occipital alpha power did not differ between those in the high and low PSR groups (t=0.08, p=0.94).

Table 1:

Resting State Paradigms Used in EEG Studies of ASD

Study	Resting State Paradigm	Participant Characteristics		
		N	Age (years) *M(SD)*	IQ *M(SD)*
Barttfeld et al., 2011	Eyes closed	10	23.8(7.6)	101(15)
(Burnette et al., 2011)	Eyes open and eyes closed (averaged)	35	12.2(.2)	105(15)
(Cantor, Thatcher,Hrybyk, & Kaye, 1986)	Eyes open	9	7.9(2)	37(11)
(Chan, Sze, & Cheung,2007)	Eyes open, visual stimuli (fish swimming animation on a monitor)	66	9.7(3)	83(22)
(Coben, Clarke,Hudspeth, & Barry,2008)	Eyes closed	20	8.9(2.3)	93(17)
(Daoust, Limoges,Bolduc, Mottron, &Godbout, 2004)	Eyes closed, in bed prior to sleep EEG	10	22.2(4)	>80
(Dawson et al., 1995)	Live bubbles being blown	28	11(4)	60(24)
(Duffy & Als, 2012)	“Awake and alert” (no other information)	463	Range 1–18	Not reported
(Lazarev, Pontes, &deAzevedo, 2009)	Eyes closed	14	9.7(2.3)	91(28)
(Murias, Webb,Greenson, & Dawson,2007)	Eyes closed	18	22.7(4.4)	107(14)
(Orekhova et al., 2007)	Visual stimuli (bubbles/fish swimming animation on a monitor)	20	5.7(1.4)	“% mental delay” 20(24)
		20	4.6(1.1)	27(19)
(Pop-Jordanova,Zorcec, Demerdzieva,& Gucev, 2010)	Eyes open, eyes closed	9	4.9(1.4)	Not reported
(Stroganova et al.,2007)	Visual stimuli (bubbles and fish swimming animations on a monitor)	20	5.7(1.4)	“% mental delay” 20(24)
		20	4.6(1.1)	27(19)
(Sutton et al., 2005)	Eyes open and eyes closed (averaged)	23	11.4(1.5)	110(21)

Table 2:

Participant Characteristics

	Age (months)		**VIQ**		**NVIQ**	
Group	*M(SD)*	Range	*M(SD)*	Range	*M(SD)*	Range
TD	90.60(21.01)	59–126	116.81(16.22)	95–146	113.25(16.18)	88–141
ASD	84.39(20.86)	55–126	55.05(32.79)	12–137	69.37(31.88)	20–145

Table 3:

Perceived State Rating

Score	Characteristics
1	-Content/happy for over 90% of session -No verbal/non-verbal protests -Attentive
2	-Mildly annoyed during 10–30% of session -Brief verbal/non-verbal protests -May briefly touch net in irritation -Easily re-directed
3	-Agitated for 30–50% of the session -Periodic verbal/non-verbal protests with long periods of calm in between -May touch net in irritation -Can eventually be redirected
4	-Consistently agitated for 50–70% of the session -Repeatedly touches/pulls at net in irritation Frequent verbal/non-verbal protests -Difficult to redirect
5	-Agitated for over 70% of the session -Frequently attempts to remove net -Continual verbal/non-verbal protests without any sustained periods of calm -Not able to fully re-direct

Table 4:

Correlations between Data Retention and Child Characteristics – TD Group

	1	2	3
1. Age	—		
2. VIQ	0.43	—	
3. NVIQ	−0.48	0.29	—
4. Percent Data Retained	0.27	−0.26	−0.15

Table 5:

Correlations between Data Retention and Child Characteristics – ASD Groups

	1	2	3
1. Age	—		
2. VIQ	0.41	—	
3. NVIQ	−0.32	0.80**	—
4. Percent Data Retained	0.17	0.43	0.29

** $p<.01$