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Article type : Special Issue Article

Reviewers: Tal Kenet, Massachusetts General Hospital, Boston, USA
J. Christopher Edgar, The Children's Hospital of Philadelphia, USA

Journal section: Cognitive neuroscience

Peak alpha frequency is a neural marker of cognitive function across the autism spectrum.

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Running Title: Peak alpha frequency in autism

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ejn.13645

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Keywords: autism; electroencephalography; peak alpha frequency; cognitive function, spontaneous alpha.

Abstract

Cognitive function varies substantially and serves as a key predictor of outcome and response to intervention in autism spectrum disorder (ASD), yet we know little about the neurobiological mechanisms that underlie cognitive function in children with ASD. The dynamics of neuronal oscillations in the alpha range (6-12 Hz) are associated with cognition in typical development. Peak alpha frequency is also highly sensitive to developmental changes in neural networks which underlie cognitive function, and therefore it holds promise as a developmentally-sensitive neural marker of cognitive function in ASD. Here, we measured peak alpha band frequency under a task-free condition in a heterogeneous sample of children with ASD (N=59) and age-matched typically developing (TD) children (N=38). At a group level, peak alpha frequency was decreased in ASD compared to TD children. Moreover, within the ASD group, peak alpha frequency correlated strongly with non-verbal cognition. As peak alpha frequency reflects the integrity of neural networks, our results suggest that deviations in network development may underlie cognitive function in individuals with ASD. By shedding light on the neurobiological correlates of cognitive function in ASD, our findings lay the groundwork for considering peak alpha frequency as a useful biomarker of cognitive function within this population which, in turn, will facilitate investigations of early markers of cognitive impairment and predictors of outcome in high risk infants.

Introduction

Cognitive function contributes to the considerable phenotypic heterogeneity observed across the autism spectrum (Fombonne, 1999; Frazier *et al.*, 2014). Intellectual disability (ID) commonly co-occurs in autism spectrum disorder (ASD), with prevalence rates reported as high as 68% (Yeargin-Allsopp *et al.*, 2003). The degree of cognitive impairment varies widely across individuals, ranging from mild to severe (Charman *et al.*, 2011; Rivard *et al.*, 2015). Above average intelligence is also present in approximately 5% of children with ASD (Charman *et al.*, 2011; Rivard, 2015). Despite the vast range in cognitive function that exists across the autism spectrum, our understanding of the neurobiology which underlies these diverse developmental trajectories remains limited. Enhanced outcomes, such as greater levels of adaptive functioning, are seen in those with ASD who have higher cognitive function (Gabriels *et al.* 2007; Baghdadli *et al.*, 2012; Farley *et al.*, 2009). Cognitive function also predicts response to intervention, with higher pre-treatment cognition (as measured by intellectual quotient, or IQ) associated with more substantial gains and acquisition of skills during intervention (Ben-Itzhak & Zachor, 2007; Vivanti *et al.*, 2014). Despite the clinical relevance of cognitive impairment in ASD, few studies have examined the neural underpinnings of cognitive function across the autism spectrum.

Cognitive processes are mediated by large-scale synchronous neuronal activity which, due to its oscillatory nature, is well-suited to be studied using techniques such as magnetoencephalography (MEG) and electroencephalography (EEG). Using M/EEG, the spectral power changes that occur during typical brain development and accompany increases in cognitive capabilities have been quantified (Ward, 2003). Alpha oscillations (commonly defined as neural activity between 6-12Hz) show a well-defined developmental profile that are associated with maturation related increases in cognitive competence. Alpha band activity

is particularly relevant as a physiological assay of cognitive function, as the development of these oscillations provides an infrastructure for neural communication between increasingly distributed brain regions (Fries, 2005; Klimesch *et al.*, 2007). Enhanced neural communication underlies the sophisticated cognitive, sensory and motor processes that emerge during childhood (Fair *et al.*, 2009; Menon, 2013). Alpha activity reaches maximal amplitude when subjects are awake and relaxed with their eyes closed, and it dominates spontaneous EEG (recorded under task-free conditions). Spontaneous EEG measures are particularly valuable as they can be utilised across a wider range of participants than task-based paradigms, and reflect the underlying functional architecture of the brain (Northoff *et al.*, 2010; Cole *et al.*, 2014).

Previous studies of spontaneous alpha oscillations in ASD have focused on group-level differences in spectral power, employing samples that vary widely in terms of age and cognitive function. This discrepancy, perhaps unsurprisingly, has led to conflicting results, with evidence of increased (Cornew *et al.*, 2012; Mathewson *et al.*, 2012; Edgar *et al.*, 2015) decreased (Cantor *et al.*, 1986; Chan *et al.*, 2007; Sheikhan *et al.*, 2012) and unaltered alpha power (Coben *et al.*, 2008) in ASD, as compared to typically-developing (TD) comparison groups. Moreover, measures of alpha power may also be confounded by shifts in the peak frequency of alpha oscillations across development (Haegens *et al.*, 2014), highlighting the need for a more precise metric of alpha oscillations across the autism spectrum. Peak alpha frequency (PAF), the frequency at which oscillations in the alpha range demonstrate maximal power, serves as a more developmentally appropriate measure. PAF shows well-characterised increases with chronological age during childhood (Somsen *et al.*, 1997; Dustman *et al.*, 1999; Stroganova *et al.*, 1999; Chiang *et al.*, 2011; Cragg *et al.*, 2011; Miskovic *et al.*, 2015), most likely reflecting the fact that PAF indexes the development of

neural networks (Klimesch *et al.*, 2007; Valdés-Hernández *et al.*, 2010). In typical children, the development of these networks with age is closely tied to cognitive development. PAF also correlates with cognitive function in adults (Klimesch *et al.*, 1993; Richard Clark *et al.*, 2004; Grandy, Werkle-Bergner, Chicherio, Lövdén, *et al.*, 2013). The limited available literature suggests that PAF does not increase with chronological age in children with ASD (Edgar *et al.*, 2015). It may therefore be the case that PAF is instead more closely associated with developmental, or cognitive function in ASD, which does not consistently map onto chronological age in this population.

Here, we investigate alpha oscillations as a potential biomarker of cognitive function in ASD using EEG. We asked whether PAF would not only differentiate children with ASD from TD children, but also whether PAF relates to cognitive function within ASD. To accomplish this goal, we first compared spontaneous EEG power in the alpha range and PAF between age-matched cohorts of children with ASD and TD children. We then examined the relationship between PAF and both age and cognitive function in each cohort. We hypothesised that children with ASD, as a group, would exhibit lower PAF than TD children. We also hypothesised that PAF would relate not to chronological age, but to cognitive function, in children with ASD.

Method

Participants

61 children with ASD were enrolled in the present study. Children with ASD were recruited from the community through flyers, as well as through the UCLA Center for Autism Research and Treatment (CART) website and ongoing UCLA CART studies. Interested parents contacted the researchers via telephone or e-mail. Eligibility criteria

included a primary clinical diagnosis of ASD. Exclusionary criteria included other neurological abnormalities (including active epilepsy), birth-related complications and uncorrected vision or hearing impairment.

The study received ethical approval from the UCLA institutional review board. Parents provided informed written consent, in accordance with the declaration of Helsinki. Verbal assent was obtained from participants who had sufficient cognitive and language capabilities to understand and agree to the study procedures. All children entered the study with a prior clinical diagnosis of ASD, made through the California State Regional Center, independent clinical psychologists, child psychiatrist, and/or developmental pediatricians. Diagnoses were confirmed by UCLA psychologists based on DSM-IV criteria.

Two participants with ASD did not provide data of acceptable quality (determined as at least 30 seconds of artifact-free data; McEvoy et al., 2015), resulting in 59 participants with ASD undergoing analysis. Five of the participants with ASD had an additional diagnosis of attention-deficit/hyperactivity disorder (ADHD), one participant had additional diagnoses of obsessive compulsive disorder (OCD), ADHD and depression (based on parent report). At the time of the study six participants with ASD were taking medication, which included: anti-psychotic medication (N=2), medication for ADHD (N=3), and anti-depressants (N=1).

39 age-matched TD children were recruited by contacting the parents of children with targeted birthdates. Following an expression of interest, parents were contacted by telephone for screening before being admitted into the study. Exclusionary criteria for TD participants included a history of neurological abnormalities; birth-related complications; developmental delays; need for special services in school; diagnosis of psychiatric conditions; uncorrected

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vision or hearing impairment; or a first degree relative with an ASD diagnosis. Of the 39 TD participants who completed the EEG recording session, one participant did not have at least 30 seconds of artifact-free EEG data and was excluded from further analyses. No TD children were taking medication at the time of the study.

The final groups included 59 children with ASD and 38 TD children. The two groups did not differ on age or sex. Verbal and non-verbal IQ (as assessed with standardized tests, see section below) were significantly lower in the ASD group, as would be expected when representing the full spectrum of cognitive function in ASD. See table 1 for demographic variables.

Assessments

Cognitive and language assessments were tailored to the ability and age of the child. Standard scores (ratio IQ) were used to facilitate comparison across assessments. Assessments included the Mullen Scales of Early Learning (MSEL; Mullen, 1995), the Differential Abilities Scale-Second Edition (DAS-II; Elliott, 2007), and the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III; Wechsler, 2002). From these measures, ratio IQ scores for non-verbal IQ (NVIQ) and verbal IQ (VIQ) were calculated for each child and based on the age-equivalent score and chronological age. Ratio IQ 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 subscores. 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). 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 *et al.*, 2011; Harrison *et al.*, 2016; Hil *et al.*, 2014).

Paradigm

Children took part in a spontaneous EEG paradigm that involved displaying bubbles on the computer screen while EEG was recorded for two minutes in a dark, sound-attenuated room. Due to the young age of the children and the wide range of cognitive and language abilities, it was not possible to gather spontaneous data under ‘eyes-closed’ conditions. Therefore, consistent with many other studies in developmental populations, we presented the passive visual stimulus while recording EEG (Dawson *et al.*, 1995; Stroganova *et al.*, 1999; Tierney *et al.*, 2012; McEvoy *et al.*, 2015). Prior studies have supported the fact that reliable PAF values can be obtained for eyes-open as well as eyes closed conditions, and that PAF obtained under the two are highly correlated (Grandy, Werkle-Bergner, Chicherio, Lövdén, *et al.*, 2013; Grandy, Werkle-Bergner, Chicherio, Schmiedek, *et al.*, 2013).

EEG Acquisition and Processing

Continuous EEG data were recorded using a high density 128-channel HydroCel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR). Four electrodes positioned to record electrooculogram (EOG) (located below and lateral to the eyes) were removed from the net in order to increase comfort. Net Station 4.4.5 software was used to record from a Net Amps 300 amplifier, sampled at 500Hz. Data were filtered on line with a band pass of 0.1 to 100 Hz and referenced to vertex. Electrode impedances were kept below 100 K Ω .

All offline data processing and analyses were performed using EEGLAB (Delorme & Makeig, 2004), and in-house MATLAB scripts. Data were high pass filtered, to remove frequencies below 1Hz, and low pass filtered to remove frequencies above 100Hz, using a finite impulse response filter implemented in EEGLAB. Continuous data were then visually inspected, and noisy channels were removed. Following channel removal, data were interpolated to the international 10-20 system 25 channel montage (Jasper, 1958). Sections of data which showed electromyogram (EMG) or other non-stereotyped artifacts were then removed from the recording.

Independent component analysis (ICA), a statistical blind source separation technique (Makeig *et al.*, 1997), was implemented to remove EOG and other stereotyped artifacts from the data. After decomposing the data into maximally independent components (IC), the scalp topography and time course of each IC was visually inspected. Any IC that represented a non-neural source (including EMG, EOG and line noise) was removed from the data. Data were then re-referenced to an average of all channels.

The first 38 seconds of cleaned data for each participant were then selected for spectral power analysis. Thirty-eight seconds of data represented the minimum amount of artifact free data available across participants, and it was deemed an appropriate minimum threshold to gain reliable estimates of the characteristics of spontaneous EEG in line with previous literature (Gudmundsson *et al.*, 2007). In order to establish the reliability of PAF measurements from 38 seconds of data, we compared central PAF measured from the first and second 38 seconds of data in participants who had at least 76 seconds of artifact-free data (N=60). Measurements of central PAF obtained from the first 38 seconds of data (M=9.29, SD=0.92) did not differ significantly from central PAF obtained from the second 38 seconds

of data ($M= 9.27$, $SD= 0.95$, $t(59)= -0.485$, $P=0.629$). The experimenter was blinded to participant details throughout the data cleaning process.

Spectral Power Analysis

Welch's method, implemented using 2 second Hamming windows with 50% overlap, was used to compute spectral power for six channels (F3, F4, C3, C4, O1 and O2) which defined three regions of interest (frontal, central and occipital). The resulting power spectra

Peak frequency

To measure PAF, we first modelled the $1/f$ trend of the log-transformed power spectrum (1-55Hz) using a least-squares method (see figure 1a). The $1/f$ trend was then subtracted from the data (Nikulin & Brismar, 2006; Haegens *et al.*, 2014); see figure 1b). This approach facilitates the identification of the spectral peak without bias towards lower frequencies within the alpha range (Neto *et al.*, 2015). A robust curve fitting procedure was then used to fit a Gaussian curve to the spectra within the alpha range in order to select a representative peak (see figure 2). This approach resulted in less ambiguity than simply choosing the local maxima, especially in subjects for whom it was difficult to identify the local maxima or for whom the data showed two local maxima (double peak). If the robust curve-fitting procedure failed, this was taken to represent a lack of modulation in the alpha range for that particular region, and the data were omitted from further analysis. Ten participants had at least one region omitted from analysis. Examples of this peak selecting procedure in three different participants are shown below.

Results

A repeated measures ANOVA was first used to determine whether there were any differences in alpha power between the two groups. There was no significant effect of group ($F(1, 96)=2.03, P=0.16$), and also no significant group x region interaction effect on alpha power ($F(2,192)= 0.38, P=0.68$). There was a significant effect of region on alpha power ($F(2,192)=64.52, P<0.001$), with central alpha power significantly higher than both frontal alpha power ($t(97)=-9.85, P<0.001$) and occipital alpha power ($t(97)=8.20, P<0.001$). There was no significant difference between occipital and frontal alpha power ($t(97)=0.34, P=0.74$).

A repeated measures ANOVA was also used to determine whether there were any differences in PAF between the two groups. Due to missing PAF for at least one region in ten participants, these participants were excluded from this portion of the analyses. There was a significant effect of group on peak alpha frequency ($F(1, 84)=6.41, P=0.01$), where PAF values were significantly lower in the ASD group compared to the TD group. There was no significant group x region interaction effect on peak alpha frequency ($F(2,168)=.92, P=0.40$), implying that group differences existed across scalp regions. There was a significant effect of region on PAF ($F(2,168)=3.68, P=0.027$).

In order to include all possible data and study regional differences, each region was investigated separately in the follow-up analyses. PAF was significantly lower in children with ASD compared to TD in frontal ($t(89)=2.71, P=0.008$; see figure 3a) and central regions ($t(93)=2.50, P=0.014$; see figure 3b), and it approached significance for the occipital region ($t(92)=1.92, P=0.058$; see figure 3c). PAF and relative alpha power values are described in table 2.

Association between PAF, age and cognitive function

In order to determine whether there were significant associations between age and PAF, and whether this association varied by group, we performed regression analyses for frontal, central and occipital PAF separately. Age, group and age x group interaction were entered as predictors. Age ($P<0.001$), group ($P = 0.002$) and group x age interaction ($P<0.001$) all contributed significantly to a model which significantly predicted frontal PAF ($F(3, 87)=14.945, P<0.001, R^2=0.34$). Similarly, age ($P<0.001$), group ($P=0.039$) and group x age interaction ($P=0.002$) all contributed significantly to a model which significantly predicted central PAF ($F(3, 91)=12.14, P<0.001, R^2=.286$). For occipital PAF, both age

($P=0.002$) and group x age interaction ($P=0.038$) contributed significantly to a model which significantly predicted occipital PAF ($F(3, 90)=8.343$, $P<0.001$, $R^2 = 0.218$). Group did not contribute significantly to this model ($P=0.172$). These regression models demonstrate that there are significant effects of age on peak alpha frequency in each region of interest, and that these effects differ significantly between the two groups. There was a positive association between age and PAF in the TD group, while this association was absent for the ASD group, as will be described in more detail in the group-specific analyses. Similar analyses could not be performed by simultaneously regressing PAF on both cognitive function and group, since both VIQ and NVIQ are significantly lower in the ASD group than TD participants. Hence, there was an almost perfect separation of groups based on the cognitive function variables.

To further investigate the association between age and PAF in each group, and to examine associations between cognitive function and PAF, we performed regression procedures separately in each group. Age, VIQ, and NVIQ were entered as predictors of PAF into a forward step-wise regression procedure for TD and ASD separately. This model was repeated for PAF in frontal, central and occipital regions.

For all three regions of interest, age was the first and only significant predictor in the regression of PAF for TD children (Frontal: $R^2=0.57$, $F(1,37)=49.12$, $P<0.001$; Central: $R^2=0.56$, $F(1,37)=47.9$, $P<0.001$; Occipital: $R^2=0.41$, $F(1,37)=25.25$, $P<0.001$; see Figure 4). Introduction of VIQ and NVIQ as predictors did not significantly improve the prediction of the model, where neither variable had significant correlations with frontal (VIQ: $R=0.01$, $P=0.93$; NVIQ: $R=0.04$, $P=0.81$), central (VIQ: $R=0.01$, $P=0.96$; NVIQ: $R=0.05$, $P=0.77$), or occipital PAF (VIQ: $R=-0.80$, $P=0.63$; NVIQ: $R=-0.18$, $P=0.28$).

In children with ASD, non-verbal IQ was the first and only predictor in the regression of PAF in frontal and central regions (Frontal: $R^2=0.14$, $F(1,48)=7.74$, $P=.000$; Central: $R^2=0.11$, $F(1,52)=5.66$, $P=0.013$; see Figure 5) and the introduction of age and VIQ did not significantly improve the prediction of these models for either frontal (age: $R=-0.03$, $P=0.85$; VIQ: $R=0.28$, $P=0.05$) or central PAF (age: $R=0.13$, $P=0.35$; VIQ: $R=0.26$, $P=0.06$). For the occipital region, neither age ($R=0.18$, $P=0.18$), VIQ ($R=0.10$, $P=0.46$) or NVIQ ($R=0.16$, $p=0.26$), was a significant predictor of PAF.

Discussion

Here, we examined PAF and its relationship to chronological age and cognitive function in a heterogeneous group of children with ASD, across a wide developmental range. PAF was examined in comparison to TD age-matched children and within the autism spectrum. Confirming our hypothesis, we found that PAF was decreased in children with ASD. Moreover, in ASD, PAF correlated strongly with non-verbal cognitive function, but not with chronological age.

The relationship demonstrated here between PAF and age in TD children consistent with previous literature (Chiang et al., 2011; Cragg et al., 2011; Dustman et al., 1999; Miskovic et al., 2015; Somsen et al., 1997; Stroganova et al., 1999; Thorpe et al., 2016). PAF represents one of the key developmental changes in spectral power during childhood (Valdes et al., 1990), indexing neural maturation (Segalowitz *et al.*, 2010) and likely represents the development of large-scale oscillatory networks during childhood that promote enhanced and efficient connectivity (Segalowitz *et al.*, 2010; Rodríguez-Martínez *et al.*, 2017). However, the foundation of our understanding of alpha oscillations is based on studies in typical

development, where neural maturation and cognitive development map onto chronological age.

We found that children with ASD did not show the typical increase in PAF with age (see also, Edgar et al., 2015). The absence of a relationship between markers of neural maturation and chronological age has previously been reported in studies of both structural and functional brain development in ASD. For instance, Courschene and colleagues (2011) found that brain volume increases demonstrated in TD children during childhood do not show the same trajectory of development in children with ASD (Courschene et al., 2011). In addition, typical increases in functional connectivity in the default mode network seen during adolescence are reported to be absent in ASD (Washington et al., 2014). Consistent with these findings, the results presented here also suggest that, as a group, PAF does not follow a typical trajectory with chronological age in children with ASD, based on cross sectional data. However, our results highlight that delays in certain neural maturation processes (such as those represented by PAF) are more closely associated with cognitive function across the autism spectrum than the presence of ASD itself.

While the link between cognitive function and PAF has been reported previously in typical adults (Grandy, Werkle-Bergner, Chicherio, Lövdén, *et al.*, 2013), the present study is the first to report that PAF is a robust marker of non-verbal cognitive function in children with ASD. Discrepancies between verbal and non-verbal IQ have been noted in children with ASD, with many individuals showing higher non-verbal skills, particularly in early childhood (Charman et al., 2011; Joseph, Tager-Flusberg & Lord, 2002). Given the characteristic communication impairments in ASD, verbal IQ scores are likely reflective of the language deficits that represent core features of ASD (Joseph et al., 2002). Therefore, we posit that nonverbal IQ scores may be serve as a more independent estimate of underlying cognitive

ability. It is notable that NVIQ accounts for less variability in PAF in the ASD group than chronological age does in the control group. We hypothesize that inaccuracy of measurement and contribution of other factors are the reason non-verbal IQ does not account for a larger proportion of the variance in PAF. There are many challenges to accurately assessing abilities in children with ASD (e.g. difficulty understanding with or complying with directions, difficulty adjusting to the testing environment), which may reduce the accuracy of their scores (Kasari et al., 2014). Additionally, although non-verbal IQ is a better overall measure for this population than verbal IQ, it is likely that our measure of non-verbal IQ does not fully capture the variability in cognitive development that is related to PAF.

The results observed in the current study support the contention that PAF assays network development, as cognitive function is linked to both the structural and functional aspects of neural networks (Lee et al., 2017). Therefore, the development and integrity of neural networks is likely to be reflected in both PAF and cognitive function (Jann et al., 2012), and it may mediate the relationship between PAF and cognitive function reported here in ASD.

Accordingly, network-level brain activity has previously been reported to be atypical in ASD (Courchesne & Pierce, 2005; Wass, 2011), likely due to disruptions in white matter development, with reports suggesting accelerated development under the age of two in ASD, which is then followed by delays throughout childhood (Courchesne, 2004; Courchesne *et al.*, 2007). The development of white matter provides the structural basis for the communication of neural information in large-scale brain networks, playing an important role in the development of both structural and functional connectivity during childhood (Hagmann *et al.*, 2010), and is accordingly an early predictor of cognitive function (Lee *et al.*, 2017).

PAF has been shown to be related to white matter architecture through diffusion tensor imaging (DTI), with increases in PAF are associated with increased white matter (axonal growth/myelination) in TD populations (Jann *et al.*, 2012), including the development of corticothalamic connections (Valdés-Hernández *et al.*, 2010). In particular, the role of the thalamus in resting state alpha oscillations is well documented (e.g. Larson *et al.*, 1998), thus supporting the contention that altered PAF in ASD indicates abnormalities in corticothalamic projections, which may contribute to previous reports of altered alpha power in this population, as well as the atypical relationship between thalamic volume and resting alpha power reported in ASD (Edgar *et al.*, 2015). Therefore, measuring PAF using functional methods such as EEG offers a means to functionally track the structural processes underlying large-scale network development in larger and more heterogeneous samples, and in a way that is more feasible than conventional structural imaging techniques such as magnetic resonance imaging (MRI) and DTI. Although here we use high-density EEG to collect data, we demonstrate that analyzing data from as few as six electrodes can capture PAF across the scalp effectively.

Future Directions

This study highlights the promise of PAF as a marker of cognitive function within the ASD population. However, there are some areas that require further examination in order to determine how PAF can be utilized practically. For instance, PAF could potentially be used longitudinally from an early age to highlight children in need of early intervention, and track change through intervention. White matter development is regulated not only by underlying genetic and neurobiological factors, but also by environment and experience (Als *et al.*, 2004; Scholz *et al.*, 2009). PAF may therefore provide a sensitive longitudinal marker of cognitive

development which can be modulated through ASD intervention. If this is the case, PAF may provide insight into mechanisms of change through intervention (Goldani *et al.*, 2014). In addition, it may be that differences in PAF predict cognitive outcomes (Vivanti *et al.*, 2013). PAF as a predictor of intervention outcomes, and as a marker of cognitive gains through intervention, will be explored in future research.

Limitations

One limitation of the current study is the lack of additional measures measuring ASD symptoms. While diagnoses were confirmed via psychologist clinical determination, we are unable to evaluate whether PAF is related to variability in ASD symptoms. Given the relationship between PAF and neural network development, we would predict that PAF is related to cognitive function, and is not specific to ASD symptoms. Future research is needed to confirm this hypothesis.

Conclusion

Our results support the promise of investigating PAF as an assay of cognitive function during development, both typical and atypical. In the context of previous literature, the relationship between PAF and cognitive function suggests that network-level dysfunction underlies cognitive impairment in ASD. Therefore, PAF also serves as a useful metric to assay the integrity of network-level neural activity, as deviations in this development may precede and predict cognitive impairment. The field of neurodevelopmental disorders is in tremendous need for biomarkers that inform clinical heterogeneity and facilitate prediction of outcomes. Future studies using PAF, a scalable and mechanistically informed physiological marker, will examine early development in order to examine changes with intervention and predict cognitive outcome in infants at heightened risk for ASD.

Acknowledgements

The authors wish to thank all of the children and families who participated in the study. The authors are also grateful to Dr Nicole McDonald and Dr Megan Freeth for their helpful comments on the manuscript. This work was supported by Autism Speaks (Meixner Postdoctoral Fellowship in Translational Science, PI Charlotte DiStefano); the National Institutes of Mental Health (K23MH094517, PI Shafali Jeste); the National Institute of General Medical Sciences (R01 GM111378-01A1, PI Damla Senturk); the National Institute of Health (ACE 2P50HD055784-06, PI Susan Bookheimer).

Conflict of interest statement

The authors report no conflicts of interest.

Data Accessibility

All data collected through NIH funding is available in the national database for autism research (NDAR). Due to the size of raw data files, they are not publicly archived. Please contact the corresponding author to obtain raw data files or data processing/analysis materials.

Author Contributions

Conception of the work: AD & SJ; Data collection: CD; EEG analyses: AD; Statistical analyses: AD & DS; First Draft of manuscript: AD & SJ; Critical revision of manuscript: AD, CD, DS & SJ; Approval of final manuscript: AD, CD, DS & SJ.

Abbreviations

Attention-deficit/hyperactivity disorder (ADHD); Autism spectrum disorder (ASD); Center for Autism Research and Treatment (CART); Differential Abilities Scale-Second Edition (DAS-II); Diffusion tensor imaging (DTI); Electroencephalography (EEG); Electromyogram (EMG); Electrooculogram (EOG); Independent component analysis (ICA); Independent components (IC); Intellectual disability (ID); magnetic resonance imaging (MRI); Magnetoencephalography (MEG); Mullen Scales of Early Learning (MSEL); Non-verbal IQ (NVIQ); Obsessive compulsive disorder (OCD); Peak alpha frequency (PAF); Typically-developing (TD); Verbal IQ (VIQ); Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III).

References

- Akshoomoff, N. (2006) Use of the Mullen Scales of Early Learning for the assessment of young children with Autism Spectrum Disorders. *Child Neuropsychol.*, **12**, 269–277.
- Als, H., Duffy, F.H., McAnulty, G.B., Rivkin, M.J., Vajapeyam, S., Mulkern, R. V, Warfield, S.K., Huppi, P.S., Butler, S.C., Conneman, N., Fischer, C. & Eichenwald, E.C. (2004) Early experience alters brain function and structure. *Pediatrics*, **113**, 846–857.
- Baghdadli, A., Assouline, B., Sonié, S., Pernon, E., Darrou, C., Michelon, C., Picot, M.-C., Aussilloux, C. & Pry, R. (2012) Developmental Trajectories of Adaptive Behaviors from Early Childhood to Adolescence in a Cohort of 152 Children with Autism Spectrum Disorders. *J. Autism Dev. Disord.*, **42**, 1314–1325.
- Ben-Itzhak, E. & Zachor, D.A. (2007) The effects of intellectual functioning and autism severity on outcome of early behavioral intervention for children with autism. *Res. Dev. Disabil.*, **28**, 287–303.
- Bishop, S.L., Guthrie, W., Coffing, M. & Lord, C. (2011) Convergent Validity of the Mullen

Scales of Early Learning and the Differential Ability Scales in Children With Autism Spectrum Disorders. *Am. J. Intellect. Dev. Disabil.*, **116**, 331–343.

Cantor, D.S., Thatcher, R.W., Hrybyk, M. & Kaye, H. (1986) Computerized EEG analyses of autistic children. *J. Autism Dev. Disord.*, **16**, 169–187.

Chan, A.S., Sze, S.L. & Cheung, M. (2007) Quantitative electroencephalographic profiles for children with autistic spectrum disorder. *Neuropsychology*, **21**, 74–81.

Chan, A.S., Sze, S.L. & Cheung, M.-C. (n.d.) Quantitative Electroencephalographic Profiles for Children With Autistic Spectrum Disorder.

Charman, T., Pickles, A., Simonoff, E., Chandler, S., Loucas, T. & Baird, G. (2011) IQ in children with autism spectrum disorders: data from the Special Needs and Autism Project (SNAP). *Psychol. Med.*, **41**, 619–627.

Chiang, A.K.I., Rennie, C.J., Robinson, P.A., van Albada, S.J. & Kerr, C.C. (2011) Age trends and sex differences of alpha rhythms including split alpha peaks. *Clin. Neurophysiol.*, **122**, 1505–1517.

Coben, R., Clarke, A.R., Hudspeth, W. & Barry, R.J. (2008) EEG power and coherence in autistic spectrum disorder. *Clin. Neurophysiol.*, **119**, 1002–1009.

Cole, M.W., Bassett, D.S., Power, J.D., Braver, T.S. & Petersen, S.E. (2014) Intrinsic and Task-Evoked Network Architectures of the Human Brain. *Neuron*, **83**, 238–251.

Cornew, L., Roberts, T.P., Blaskey, L. & Edgar, J.C. (2012) Resting-state oscillatory activity in autism spectrum disorders. *J Autism Dev Disord*, **42**, 1884–1894.

Courchesne, E. (2004) Brain development in autism: Early overgrowth followed by premature arrest of growth. *Ment. Retard. Dev. Disabil. Res. Rev.*, **10**, 106–111.

Courchesne, E., Campbell, K. & Solso, S. (2011) Brain growth across the life span in autism: age-specific changes in anatomical pathology. *Brain research*, **1380**, 138–145.

Courchesne, E. & Pierce, K. (2005) Why the frontal cortex in autism might be talking only to

itself: local over-connectivity but long-distance disconnection. *Curr. Opin. Neurobiol.*, **15**, 225–230.

Courchesne, E., Pierce, K., Schumann, C.M., Redcay, E., Buckwalter, J.A., Kennedy, D.P. &

Morgan, J. (2007) Mapping Early Brain Development in Autism. *Neuron*, **56**, 399–413.

Cragg, L., Kovacevic, N., McIntosh, A.R., Poulsen, C., Martinu, K., Leonard, G. & Paus, T.

(2011) Maturation of EEG power spectra in early adolescence: a longitudinal study.

Dev. Sci., **14**, 935–943.

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. *J. Abnorm. Child Psychol.*, **23**, 569–583.

Abnorm. Child Psychol., **23**, 569–583.

Delorme, A. & Makeig, S. (2004) EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods*,

134, 9–21.

Dustman, R.E., Shearer, D.E. & Emmerson, R.Y. (1999) Life-span changes in EEG spectral amplitude, amplitude variability and mean frequency. *Clin. Neurophysiol.*, **110**, 1399–1409.

Edgar, J., Heiken, K., Chen, Y. & Herrington, J. (2015) Resting-state alpha in autism

spectrum disorder and alpha associations with thalamic volume. *J. Autism Dev. Disord.*,

45, 795–804.

Elliott, C.D. (2007). Differential ability scales (2nd ed.). San Antonio,

TX: Harcourt Assessment.

Fair, D.A., Cohen, A.L., Power, J.D., Dosenbach, N.U.F., Church, J.A., Miezin, F.M.,

Schlaggar, B.L. & Petersen, S.E. (2009) Functional Brain Networks Develop from a

“Local to Distributed” Organization. *PLoS Comput. Biol.*, **5**, e1000381.

Farley, M.A., McMahon, W.M., Fombonne, E., Jenson, W.R., Miller, J., Gardner, M., Block,

- H., Pingree, C.B., Ritvo, E.R., Ritvo, R.A. & Coon, H. (2009) Twenty-year outcome for individuals with autism and average or near-average cognitive abilities. *Autism Res.*, **2**, 109–118.
- Fombonne, E. (1999) The epidemiology of autism: a review. *Psychol. Med.*, **29**, 769–786.
- Frazier, T.W., Georgiades, S., Bishop, S.L. & Hardan, A.Y. (2014) Behavioral and Cognitive Characteristics of Females and Males With Autism in the Simons Simplex Collection. *J. Am. Acad. Child Adolesc. Psychiatry*, **53**, 329–340.e3.
- Fries, P. (2005) A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn. Sci.*,
- Goldani, A.A.S., Downs, S.R., Widjaja, F., Lawton, B. & Hendren, R.L. (2014) Biomarkers in autism. *Front. psychiatry*, **5**, 100.
- Grandy, T.H., Werkle-Bergner, M., Chicherio, C., Lövdén, M., Schmiedek, F. & Lindenberger, U. (2013) Individual alpha peak frequency is related to latent factors of general cognitive abilities. *Neuroimage*, **79**, 10–18.
- Grandy, T.H., Werkle-Bergner, M., Chicherio, C., Schmiedek, F., Lövdén, M. & Lindenberger, U. (2013) Peak individual alpha frequency qualifies as a stable neurophysiological trait marker in healthy younger and older adults. *Psychophysiology*, **50**, 570–582.
- Gudmundsson, S., Runarsson, T.P., Sigurdsson, S., Eiriksdottir, G. & Johnsen, K. (2007) Reliability of quantitative EEG features. *Clin. Neurophysiol.*, **118**, 2162–2171.
- Haegens, S., Cousijn, H., Wallis, G., Harrison, P.J. & Nobre, A.C. (2014) Inter- and intra-individual variability in alpha peak frequency. *Neuroimage*, **92**, 46–55.
- Hagmann, P., Sporns, O., Madan, N., Cammoun, L., Pienaar, R., Wedeen, V.J., Meuli, R., Thiran, J.-P. & Grant, P.E. (2010) White matter maturation reshapes structural connectivity in the late developing human brain. *Proc. Natl. Acad. Sci. U. S. A.*, **107**,

19067–19072.

- Harrison, A.J., Lu, Z.L., McLean., R.L. & Sheinkopf, S.J. (2016) Cognitive and adaptive correlates of an ADOS-derived joint attention composite. *Res Autism Spectr Disord.*, **29**, 66-78.
- Hill, A.P., Zuckerman, K.E., Hagen, A.D., Kriz, D.J., Duvall, S.W., van Santen, J., Nigg, J., Fair, D. & Fombonne, E. (2014) Aggressive Behavior Problems in Children with Autism Spectrum Disorders: Prevalence and Correlates in Large Clinical Sample. *Res Autism Spectr Disord.*, **8**, 1121-1133.
- Jann, K., Federspiel, A., Giezendanner, S., Andreotti, J., Kottlow, M., Dierks, T. & Koenig, T. (2012) Linking Brain Connectivity Across Different Time Scales with Electroencephalogram, Functional Magnetic Resonance Imaging, and Diffusion Tensor Imaging. *Brain Connect.*, **2**, 11–20.
- Jasper, H.H. (1958) The ten-twenty electrode system of the International Federation. *Electroencephalogr Clin Neurophysiol*, **10**, 371-375.
- Kasari, C., Brady, N., Lord, C. & Tager-Flusberg, H. (2013) Assessing the minimally verbal school-aged child with autism spectrum disorder. *Autism res*, **6**, 479-493.
- Klimesch, W., Sauseng, P. & Hanslmayr, S. (2007) EEG alpha oscillations: The inhibition–timing hypothesis. *Brain Res. Rev.*, **53**, 63–88.
- Klimesch, W., Schimke, H. & Pfurtscheller, G. (1993) Alpha frequency, cognitive load and memory performance. *Brain Topogr.*, **5**, 241–251.
- Larson, C.L., Davidson, R.J., Abercrombie, H.C., Ward, R.T., Schaffer, S.M., Jackson, D.C., Holden, J.E. & Perlman, S.B. (1998) Relations between PET-derived measures of thalamic glucose metabolism and EEG alpha power. *Psychophysiology*, **35**, 162-169.
- Lee, S.J., Steiner, R.J., Yu, Y., Short, S.J., Neale, M.C., Styner, M.A., Zhu, H. & Gilmore, J.H. (2017) Common and heritable components of white matter microstructure predict

cognitive function at 1 and 2 y. *Proc. Natl. Acad. Sci. U. S. A.*, **114**, 148–153.

Makeig, S., Jung, T.P., Bell, A.J., Ghahremani, D. & Sejnowski, T.J. (1997) Blind separation of auditory event-related brain responses into independent components. *Proc. Natl. Acad. Sci. U. S. A.*, **94**, 10979–10984.

Mathewson, K.J., Jetha, M.K., Drmic, I.E., Bryson, S.E., Goldberg, J.O. & Schmidt, L.A. (2012) Regional EEG alpha power, coherence, and behavioral symptomatology in autism spectrum disorder. *Clin. Neurophysiol.*, **123**, 1798–1809.

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 Behav.*, **9**, 104–114.

McLaughlin, K.A., Fox, N.A., Zeanah, C.H. & Nelson, C.A. (2011) Adverse Rearing Environments and Neural Development in Children: The Development of Frontal Electroencephalogram Asymmetry. *Biol. Psychiatry*, **70**, 1008–1015.

Menon, V. (2013) Developmental pathways to functional brain networks: emerging principles. *Trends Cogn. Sci.*, **17**, 627–640.

Miskovic, V., Ma, X., Chou, C.-A., Fan, M., Owens, M., Sayama, H. & Gibb, B.E. (2015) Developmental changes in spontaneous electrocortical activity and network organization from early to late childhood. *Neuroimage*, **118**, 237–247.

Mullen, E. M. (1995). *Mullen Scales of Early Learning* (AGS ed.). Circle Pines, MN: American Guidance Service Inc.

Neto, E., Allen, E.A., Aurlien, H., Nordby, H. & Eichele, T. (2015) EEG Spectral Features Discriminate between Alzheimer's and Vascular Dementia. *Front. Neurol.*, **6**, 25.

Nikulin, V.V. & Brismar, T. (2006) Phase synchronization between alpha and beta

oscillations in the human electroencephalogram. *Neuroscience*, **137**, 647–657.

Northoff, G., Qin, P. & Nakao, T. (2010) Rest-stimulus interaction in the brain: a review.

Trends Neurosci., **33**, 277–284.

Nunez, P.L. & Srinivasan, R. (2006) *Electric Fields of the Brain*. Oxford University Press.

Oberman, L.M., Ramachandran, V.S. & Pineda, J.A. (2008) Modulation of mu suppression in

children with autism spectrum disorders in response to familiar or unfamiliar stimuli:

The mirror neuron hypothesis. *Neuropsychologia*, **46**, 1558–1565.

Richard Clark, C., Veltmeyer, M.D., Hamilton, R.J., Simms, E., Paul, R., Hermens, D. &

Gordon, E. (2004) Spontaneous alpha peak frequency predicts working memory

performance across the age span. *Int. J. Psychophysiol.*, **53**, 1–9.

Rivard, M., Terroux, A., Mercier, C. & Parent-Boursier, C. (2015) Indicators of Intellectual

Disabilities in Young Children with Autism Spectrum Disorders. *J. Autism Dev. Disord.*,

45, 127–137.

Rodríguez-Martínez, E.I., Ruiz-Martínez, F.J., Barriga Paulino, C.I. & Gómez, C.M. (2017)

Frequency shift in topography of spontaneous brain rhythms from childhood to

adulthood. *Cogn. Neurodyn.*, **11**, 23–33.

Scholz, J., Klein, M.C., Behrens, T.E.J. & Johansen-Berg, H. (2009) Training induces

changes in white-matter architecture. *Nat. Neurosci.*, **12**, 1370–1371.

Segalowitz, S.J., Santesso, D.L. & Jetha, M.K. (2010) Electrophysiological changes during

adolescence: A review. *Brain Cogn.*, **72**, 86–100.

Sheikhani, A., Behnam, H., Mohammadi, M.R., Noroozian, M. & Mohammadi, M. (2012)

Detection of Abnormalities for Diagnosing of Children with Autism Disorders Using of

Quantitative Electroencephalography Analysis. *J. Med. Syst.*, **36**, 957–963.

Somsen, R.J., van't Klooster, B.J., van der Molen, M.W., van Leeuwen, H.M. & Licht, R.

(1997) Growth spurts in brain maturation during middle childhood as indexed by EEG

power spectra. *Biol. Psychol.*, **44**, 187–209.

Stroganova, T.A., Orekhova, E. V, & Posikera, I.N. (1999) EEG alpha rhythm in infants.

Clin. Neurophysiol., **110**, 997–1012.

Tierney, A.L., Gabard-Durnam, L., Vogel-Farley, V., Tager-Flusberg, H. & Nelson, C.A.

(2012) Developmental Trajectories of Resting EEG Power: An Endophenotype of Autism Spectrum Disorder. *PLoS One*, **7**, e39127.

Valdes, P.A., Biscay, R., Galán, L., Bosch, J., Száva, S. & Virués T. (1990) High resolution spectral norms for topography. *Brain Topography*, **32**, 281–282.

Valdés-Hernández, P.A., Ojeda-González, A., Martínez-Montes, E., Lage-Castellanos, A.,

Virués-Alba, T., Valdés-Urrutia, L. & Valdes-Sosa, P.A. (2010) White matter architecture rather than cortical surface area correlates with the EEG alpha rhythm.

Neuroimage, **49**, 2328–2339.

Vivanti, G., Barbaro, J., Hudry, K., Dissanayake, C. & Prior, M. (2013) Intellectual

development in autism spectrum disorders: new insights from longitudinal studies.

Front. Hum. Neurosci., **7**, 354.

Vivanti, G., Prior, M., Williams, K. & Dissanayake, C. (2014) Predictors of outcomes in

autism early intervention: why don't we know more? *Front. Pediatr.*, **2**, 58.

Ward, L.M. (2003) Synchronous neural oscillations and cognitive processes. *Trends Cogn.*

Sci., **7**, 553–559.

Washington, S.D., Gordon, E.M., Brar, J., Warburton, S., Sawyer, A.T., Wolfe, A., Mease-

Ference, E.R., Girton, L., Hailu, A., Mbwana, J. & Gaillard, W.D. (2014) Dymaturation of the default mode network in autism. *Human brain mapping*, **35**, 1284-1296.

Wass, S. (2011) Distortions and disconnections: Disrupted brain connectivity in autism.

Brain Cogn., **75**, 18–28.

Wechsler, D. (2002). The Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III). San Antonio, TX: The Psychological Corporation.

Yeargin-Allsopp, M., Rice, C., Karapurkar, T., Doernberg, N., Boyle, C. & Murphy, C. (2003) Prevalence of Autism in a US Metropolitan Area. *JAMA*, **289**, 49–55.

Figures

Figure 1. (a) an example power spectra (solid line) with computed 1/f trend (dashed line) (b) Power spectra following removal of linear trend.

Figure 2. Example of curve fitting (dashed line) power spectra (dashed line) and how it can provide an accurate estimation of spectral peaks for (a) conventional alpha peak and (b) participants with double alpha peaks.

Figure 3. Dot plots demonstrating peak alpha frequency (with group mean and SD) for both ASD and TD participants in (a) frontal, (b) central and (c) occipital regions.

Figure 4. Scatter plots demonstrating the relationship between age and PAF for ASD (blue) and TD (red) participants in (a) frontal, (b) central and (c) occipital regions.

Figure 5. Scatter plots demonstrating the relationship between NVIQ and PAF for ASD (blue) and TD (red) participants in (a) frontal, (b) central regions.

Table 1. *Demographic variables of participants.*

Measure	ASD	TD	Group Comparison
	M(<i>SD</i>), range or number (%)	M(<i>SD</i>), range or number (%)	Student's <i>t</i> or χ^2 <i>P</i> value
Age (months)	69.44(24.12), 25–126	71.56(26.58), 29-146	0.68
Sex (N females)	13 (22)	13 (33.3)	0.16
VIQ	68.96(34.35), 12-160	121.12(19.42), 82-168	0.000
NVIQ	74.67(33.82), 10-145	112.55(12.07), 88-156	0.000

Table 2. *Relative alpha power and peak alpha frequency in ASD and TD children.*

	Relative Alpha Power			PAF (Hz)		
	Frontal	Central	Occipital	Frontal	Central	Occipital
ASD						
Mean (<i>SD</i>)	0.14 (0.05)	0.18 (0.07)	0.15 (0.05)	8.72 (0.92)	8.92 (0.95)	8.91 (0.91)
TD						
Mean (<i>SD</i>)	0.16 (0.04)	0.20 (0.07)	0.16 (0.05)	9.29 (1.07)	9.41 (0.95)	9.27 (0.91)
<i>P</i> value	0.086	0.228	0.272	0.008	0.014	0.058



