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Atypical EEG in autism spectrum disorder: comparing a dimensional and a categorical approach.

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Abstract

Myriad studies have found group differences in neural dynamics between people with and without autism spectrum disorder (ASD). However, the extent to which variation in neural dynamics is related to variation in the autism phenotype across the population is not known. Here we measured behavioral characteristics of autism alongside inter-trial phase coherence (ITC) and multi-scale entropy (MSE) computed from EEG in order to address this question. Data were obtained from ninety-nine adults, thirty-eight of whom had an ASD diagnosis. Phenotypic information was obtained from the Social Responsiveness Scale (Revised), the Repetitive Behavior Questionnaire, the WHO Adult ADHD Self-Report Scale Screener and the Beck Anxiety Inventory (Trait version). ITC and MSE were computed from EEG recorded during visual stimulation and eyes-closed rest. We found no evidence to suggest that population variance in autistic traits is underpinned by variance in neural dynamics, despite finding that ITC and MSE are more likely to be reduced in people with ASD than in those without. We conclude that there are likely to be multiple neural profiles underpinning ASD, and suggest that while individual differences in the autism phenotype exist across the population, their distribution is not underpinned by individual differences in neural dynamics.

Keywords: autism, inter-trial phase coherence, multi-scale entropy, EEG

General Scientific Summary: This study shows that while traits and behaviours associated with autism spectrum disorder (ASD) occur to a greater or lesser degree across the general population, this variation in autistic traits is not related to differences in brain activity. However, at a group-level, we found that brain activity differed between people with and without a diagnosis of ASD. This study supports the notion that there are likely to be multiple routes to the traits and symptoms of ASD, rather than a unique neurological difference that is common to all people with a diagnosis of ASD.

Atypical EEG in autism spectrum disorder: comparing a dimensional and a categorical approach

By definition, autism spectrum disorder (ASD) is a neurodevelopmental disorder (APA, 2013), albeit of unknown neural etiology. Although a number of recent studies have focussed on identifying potential neural biomarkers for ASD (Bosl, Tierney, Tager-Flusberg, & Nelson, 2011), no underlying neurobiological differences that consistently differentiate autistic and non-autistic brains have been identified. The search for a neural signature that distinguishes autism from non-autism assumes that there is a universally optimal neural profile within individuals without ASD. This assumption is likely to be incorrect (see Holmes & Patrick, 2018) but is prescient within ASD research given that traits associated with ASD are continuously distributed amongst the population (Skuse et al., 2009), reflecting the potential misnomer in the use of the term 'neurotypical' to describe people who are not autistic.

Two neural variables which have been shown to differ between people with and without ASD, and are the focus of this investigation, are inter-trial phase coherence (ITC) and multi-scale entropy (MSE). ITC is a measurement of the consistency of the phase angles of EEG oscillations across trials following events such as stimulus presentation (Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996). Many studies have found reduced ITC in ASD relative to controls, leading to the claim that reduced ITC could be an endophenotype of ASD (David et al., 2016). MSE characterises the degree of repetition within a timeseries across different temporal scales. In EEG data, entropy increases with increasing spatial scale, and higher entropy reflects greater complexity of the neural signal (Costa, Goldberger, & Peng, 2002). Changes to MSE have been reported in ASD (Catarino, Churches, Baron-Cohen, Andrade, & Ring, 2011), and reduced MSE in 9-month old infants, has been suggested as a potential biomarker for ASD (Bosl et al., 2011), although at other ages MSE did not distinguish so

clearly between infants who were at higher or lower risk for ASD. Collectively, ITC and MSE provide insight into a range of neural features including consistency of response and long-and short-range interaction between neural networks, all of which have been suggested to differ in ASD (Dinstein, Heeger, & Behrmann, 2015; Vissers, Cohen, & Geurts, 2012).

Claims that ITC and MSE may reflect endophenotypes or biomarkers of ASD highlight the importance of further investigations of neural dynamics, especially with respect to individual variability and the relationship between MSE, ITC and the autism phenotype. Previous investigations of these variables have taken a group-based approach, i.e. comparing ITC and MSE between relatively small groups of participants who either do, or do not, have a diagnosis of ASD. However, group-based analyses minimise the high degree of phenotypic overlap between autistic and non-autistic people (c.f. Holmes & Patrick, 2018). Numerous studies have shown that the traits of ASD, including differences in social communication and tendencies towards rigid and repetitive behavior vary continuously across the population (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001; Skuse et al., 2009). As such ASD is often considered to lie at the extreme end of the population distribution of autistic traits (Ronald, Happé, & Plomin, 2005). This continuum view is difficult to reconcile with research that aims to identify the particular neural etiology of autism that gives rise to the symptoms on which a diagnosis of ASD is based. Despite this, there is a paucity of studies which aim to investigate the extent to which individual differences in neural substrates underpin the continuous distribution of autistic traits. The majority of studies that have been carried out to address this question – typically by measuring autistic traits with the autism-spectrum quotient (AQ, Baron-Cohen et al., 2001) - do not include people at the extreme end of the distribution, i.e. people with a diagnosis of ASD, so do not fully address the question of whether these variables are continuously distributed across the population. Furthermore, using a single measure of ‘autistic traits’ may obscure some findings due to the fact that this

approach assumes ASD is a univariate construct, when in reality ASD is a complex, multivariate condition which is associated with multiple comorbidities including ADHD and anxiety (Gillberg, 2010). Furthermore, the domains on which ASD diagnosis are based – social communication and interaction (SCI) and repetitive behaviors and restricted interests (RBRI) - are dissociable (Happé & Ronald, 2008). It is possible, therefore, that stronger associations between phenotype and neurobiology may be observed by analysing these symptom domains in isolation rather than focussing only on general symptom severity.

Here we take a dimensional approach to the study of ASD by investigating ITC and MSE in a cross-section of adults who vary in the extent to which they express the autistic phenotype. We recruited adult participants as there are a growing number of people being diagnosed with ASD in adulthood (Brugha et al., 2011; Lai & Baron-Cohen, 2015) as evidenced by the development of ASD screening tools developed specifically for adults (Ritvo et al., 2011), yet there is a distinct lack of research in this population. In addition, we recruited participants without a diagnosis but who identify with a number of autistic traits, and participants who identify with very few autistic traits. Alongside computing ITC and MSE from EEG data, we measured SCI, RBRI, ADHD traits and dispositional anxiety with a view to identifying the extent to which individual variability in these domains is related to individual variability in MSE and / or ITC. In order to place our findings in the context of previous literature, we also compared MSE and ITC at a group level between participants with and without an ASD diagnosis. The implications of the findings from these two different analytic approaches will be considered in the context of the value of searching for neural biomarkers for ASD in light of population variability.

Materials and Methods

Participants

In total, 102 people were recruited to this study. Due to technical issues EEG was not obtained from three participants therefore all further descriptions refer to the remaining sample of 99 participants. Thirty-eight participants (19 female) had a diagnosis of ASD and sixty-one (32 female) did not. Hereafter, participant will be described as "diagnosed" and "undiagnosed" in order to avoid using the term neurotypical to describe the non-ASD group, and to acknowledge the range of factors that may influence whether or not someone has an ASD diagnosis. Diagnosis of ASD had previously been given by a clinical professional in the UK according to DSM-IV, DMS-V or ICD-10 criteria. All but two of the participants received their diagnosis of ASD when they were older than 18. For inclusion in the diagnosed group for group analysis, participants were required to have both a clinical diagnosis as described above and to obtain a RAADS-R (see below) score above the cut-off for ASD identified by Andersen et al., (2011). Diagnosed participants were recruited from our database of research volunteers and a local ASD outpatient assessment centre. Participants in the undiagnosed group were recruited via advertisements at local ASD-focussed public events, and mailing lists of volunteers. Participants lived in areas spanning the full range of 2015 English Indices of Deprivation (IMD), a measure provided by the UK Office of National Statistics based on neighbourhood employment, income, health provision, and housing. 27.8% of participants lived in areas with a score in the bottom three IMD deciles, a further 42.4% lived in deciles 4-7, with the remaining 29.8% living in the top three deciles.

With the exception of epilepsy, additional diagnoses were not considered as exclusion criteria. This approach is consistent with the Research Domain Criteria (RDoC) project which calls for research that spans diagnostic boundaries and focuses on symptoms rather than clinical labels (Insel, 2014). Four participants from the undiagnosed group had been

diagnosed with depression and /or anxiety, two had dyslexia, one had PTSD and another had borderline personality disorder. Three people in the undiagnosed group were taking medication that we considered relevant due to potential effects on neurotransmission (i.e. anti-anxiety medication). Within the diagnosed group, co-occurring diagnoses and medication use were common: eleven participants had additional diagnoses of anxiety and / or depression, three participants were dyslexic and nine had additional diagnoses of ADHD. Sixteen were taking relevant medication.

Group comparisons were based on comparing indices from unmedicated diagnosed participants (N = 22, 9 female) and a matched subsample of unmedicated undiagnosed participants (N = 22, 12 female). Selection of the undiagnosed participants for the comparison group was based on obtaining RAADS-R score below 72, being in the appropriate age-range to match the diagnosed sample, and not taking relevant medication. Within the unmedicated diagnosed sample, three participants had ADHD, five had depression and three were dyslexic. None of the participants in the matched undiagnosed sample had any diagnoses. Correlation analyses were based on the entire sample, although the results of correlation analyses with subgroups of participants, i.e. unmedicated participants, and the diagnosed and undiagnosed participants separately, are presented in Supplementary material. Participant details are given in table 1.

Ethical approval was given by the regional NHS Research Ethics Committee, overseen by the Health Research Authority in the UK, and the Institutional Psychology ethics subcommittee. All participants provided written informed consent before participating. The study complied with the APA ethical principles regarding research with human participants.

Procedure

The protocol included EEG recording, administration of the matrix reasoning sub-task from the WASI (Weschler, 1999), and completion of the questionnaires described below.

Ritvo Autism Asperger's Diagnostic Schedule (RAADS-R, Ritvo et al., 2011). The RAADS-R is an 80-item questionnaire that was developed to assist in the diagnosis of ASD in adults. Each item is answered on a four-point scale with the options ''never true'', ''true only when I was young (before the age of 16)'', ''true only now'' and ''true now and when I was young''. Possible scores range from 0 to 240. Two clinical cut-offs for ASD have been identified: Ritvo et al. (2011) suggested that a score of 65 or above is consistent with a diagnosis of ASD, whereas a score of 72 was recommended when sensitivity and specificity were given equal priority (Andersen et al., 2011).

Social Responsiveness Questionnaire (SRS-2, Constantino & Gruber, 2012). This 65-item instrument asks participants to rate the extent to which their behavior and experiences have reflected the autism phenotype in the last 6 months. Responses are given on a four-point scale ranging from "not true" to "almost always true". Possible t-scores range from 30 to 90. We created a separate raw score comprising items that measure SCI (see Appendix B of Constantino & Gruber, 2012) and used this scale to measure the DSM-V domain of SCI. Cronbach's alpha of the SCI scale in this sample was .96. There are two versions of the SRS-2 – a self-report and an other-report. In addition to administering the self-report version we asked each participant to nominate someone who could complete the other-report. Other reports were returned for sixty-two participants.

Adult Repetitive-Behaviors Questionnaire (RBQ-2A, Barrett et al., 2015). The RBQ-2A is a 20 item questionnaire that measures restricted and repetitive behavior in adults. Participants are asked to rate the frequency or severity of particular behaviors on a three-point scale. Total mean score, ranging from 1 to 3, was computed. Cronbach's alpha in this sample was .88.

Beck Anxiety Inventory - Trait (BAIT, Kohn, Kantor, DeCicco, & Beck, 2008). This 21 item scale asks participants to rate the extent to which they are affected by the

physical symptoms of anxiety on a day to day basis. Responses are given on a four-point scale ranging from “Never / rarely” to “Almost Always”. Scores range from 0 to 63. Cronbach’s alpha in this sample was .93.

WHO Adult ADHD Self-Report Scale Screener, Part A (ASRS Screener, Kessler et al., 2005). The ASRS Screener (Part A) is a six-item screening questionnaire that asks participants to rate how they have conducted themselves in the past six months in relation to DSM-IV criterion A symptoms of ADHD. Responses are given on a 5-point Likert scale from ‘never’ to ‘very often’. The instrument has been shown to have strong concordance with clinicial diagnoses of ADHD. Total scores are computed as the sum of all items. Scores range from 0 to 24. Cronbach’s alpha in this sample was .72.

Information about missing data points is given in supplemental information.

EEG acquisition and processing. EEG was acquired via BioSemi ActiveTwo in an electrically shielded chamber during visual stimulation and eyes-closed rest. Data were filtered online with a band-pass of 0.01-140 Hz and digitised at a sampling rate of 2048 Hz. All channel offsets were kept below 25 kΩ. Visual stimulation involved presenting a black and white checkerboard, generated within Psychtoolbox (Brainard & Vision, 1997) on a 20-inch LCD screen within Matlab (The Mathworks, Inc. Natick, MA). The checkerboard subtended 13.5° x 11.5°, each check subtended 0.4°. Participants were asked to maintain fixation on a red cross that was present in the centre of the screen throughout the task, and instructed to press the spacebar at checkerboard offset. Each checkerboard remained on screen for an average of 2000 ms, jittered between 1500 and 2500 ms. The mean inter-stimulus interval was 2000 ms, jittered between 1500 and 2500 ms. Two blocks of 100 trials were presented, interspersed by a self-timed break. After 200 trials, resting state data were acquired: participants remained seated and were asked to close their eyes while EEG was recorded for 150 s **(**see Figure 1).

Insert Figure 1 here

Offline processing was carried out using EEGLAB v14.1.1 (Delorme & Makeig, 2004) and customised MATLAB scripts. Data were downsampled to 512 Hz and referenced to channel Cz. For the majority of participants (N=81) a 64-sensor montage was used to acquire data. For the remaining participants, a 128-sensor montage was used. Prior to analysis, channels were systematically removed from the 128-sensor montage datasets so that the remaining sensors were located in the same, or very similar locations to the 64-sensor montage. Continuous data were filtered using the eegfiltnew function within EEGLAB, transition bandwidth and passband edges were both 1Hz. Channels and segments of data contaminated by gross artifacts were identified via visual inspection and removed. Data were decomposed into independent components (IC) using the runica algorithm within EEGLAB. In order to obtain good quality decomposition from ICA it is important to ensure that the ratio of data points to channels is sufficient. The estimated minimum number of data points required to perform ICA is (number of channels^2) x 30. In this study, the number of channels entered to ICA ranged from 48 to 63, suggesting that the minimum length of data required would range from 69,120 to 119,070 data points. Here the number of data points entered to ICA ranged from 311,982 to 549,888 and was therefore well above the recommended minimum. Components reflecting eye-movements or blink artifacts were removed, and missing channels were interpolated. Continuous data containing ICA weights were then segmented into two separate files: visual evoked data from which ITC was computed, and resting state data from which MSE was computed.

Computation of ITC. Epochs from -1s to 1.5s around stimulus onset were extracted and corrected to the 1s 'baseline' prior to stimulus onset. The mean number of epochs retained for each participant was 193.4 (SD = 13.8). Time-frequency analysis was performed by the EEGLAB function, newtimef (see Delorme & Makeig, 2004), using wavelets with 3

cycles at the lowest frequency and 12.5 cycles at the highest frequency with a window size of 556.56 ms. Spectral estimates at 200 evenly spaced time-points (from -721.5 to 1221.5ms) and 47 evenly spaced frequencies (from 4 to 50Hz) were returned as complex vectors in phase space. After normalising the magnitude of each trial activity vector to 1, the complex average of each trial activity vector was averaged. ITC values were returned as absolute values from these complex averages. For each time point of the epoch and each frequency an ITC value between 0 and 1 was obtained, with 0 representing an absence of synchronisation across trials and 1 representing perfect inter-trial phase synchrony. The frequency associated with the maximum ITC value for each subject (typically between 4-9 Hz) was used for subsequent analysis.

Because ICA unmixes signals from independent sources it acts as a spatial filter to EEG data and generates signals (components) that are less contaminated by artifacts than those measured from channels. When measuring a variable such as ITC which could be influenced by transient fluctuations from other neural and non-neural sources, analysing data in source space (components) rather than sensor space (channels) is recommended (Milne, 2011). Here, we report ITC obtained from ICs rather than from channels, although data obtained from channels is included for comparison in supplementary material. ITC values across the timeseries were computed at each frequency (4 to 50 Hz) from every IC. Within each participant, an IC showing very strong ITC could be clearly identified. The weights of the unmixing matrix of these components projected to electrodes positioned over posterior cortex, suggesting that the sources of these components were in visual cortex. Scalp topographies of the ICs that showed maximum ITC are shown in supplementary figure S2. The ERP of each of these components also showed features of the visual evoked potential (e.g. C1, P1 or N1 deflections), further confirming that the IC which shows the highest ITC reflects the activity of a neural source associated with visual information processing.

Maximum ITC value, from any component and from any frequency band was extracted within matlab and used for subsequent analysis.

Computation of MSE. MSE was computed using the algorithm of Liang et al., (2014) and can be found at http://www.psynetresearch.org/tools.html. Resting state data were re-filtered with cut-offs of 1.5Hz and 50Hz, and split into 5 second epochs (corresponding to 2560 data points), with no baseline correction. MSE analysis was performed on the 2nd to the 20th epoch and then averaged to yield a single MSE value for each scale and each channel. The MSE analysis on scale factors 1–20 for each channel for each epoch was calculated in two steps. First, the algorithm creates course grained timeseries by progressively down-sampling the EEG timeseries $\{x_1,\ldots, x_i,\ldots, x_N\}$. For scale factor τ, the coarse-grained timeseries $\{y(\tau)\}$ is obtained by averaging data points within non-overlapping windows of length τ. The timeseries associated with scale factor 1 is simply the original data and scale factor 2 is the average of consecutive pairs of data points and so forth for increasing scales. As such, the element of a coarse-grained timeseries, j, is calculated according to:

$$(1)\ yj^{(\tau)} = \frac{1}{\tau}\sum_{i=(j-1)\tau+1}^{j\tau} X_i\,, 1 \le j \le \frac{N}{\tau}$$

where N is the length of the timeseries. Second, the algorithm computes the sample entropy for each coarse-grained timeseries. Sample entropy is defined by the negative natural logarithm of the conditional probability that a timeseries of length (N/τ), having repeated itself within a tolerance r (similarity factor) for m points (pattern length), will also repeat itself for m + 1 points, without allowing self-matches. As in Liang et al., (2014), the pattern length, m, was set to 1; that is, one data point was used for pattern matching. The similarity factor, r, was set to 0.30; that is, data points were considered to be indistinguishable if the absolute amplitude difference between them was ≤ 30% of the standard deviation of the timeseries. Data points of 10^m or 20^m have been shown to be of sufficient length to calculate entropy (Pincus & Goldberger, 1994; Richman & Moorman, 2000), therefore, the 2560 data points used here are

well above that suggested previously. As there was no a priori reason to select particular ICs for the analysis of MSE, MSE analyses were based on channel data.

Results

Histograms showing the range of scores on variables that reflect the ASD phenotype and the range of ITC and MSE (averaged overall scales and all electrodes) are given in figure 2. Table 1 shows the mean scores obtained from the questionnaires for the whole sample and from the subsamples of medicated and unmedicated participants.

Insert Table 1 about here please

Insert Figure 2 about here please

Bayes Factors evaluating strength of evidence in support of the null hypothesis (two-tailed BF_{01}) were computed within JASP (JASP team, 2018). We adopted the convention for evaluating the strength of evidence in favour of a particular hypothesis via Bayes factors which states that BF <3 = weak evidence; BF >3<10 = moderate evidence and BF >10 = strong evidence.

Dimensional Approach

Correlations between ITC, MSE at fine- mid- and coarse-scales, and phenotypic variables are reported in table 2. As our sample included a greater proportion of people with an ASD diagnosis than would be expected in the general population, non-parametric correlations were performed. Commensurate with previous work showing that aging is associated with a shift towards smaller-scale network dynamics and away from longer-range interactions (McIntosh et al., 2013), in the undiagnosed sample MSE at fine scales was positively correlated with age and MSE at coarse-scales was negatively correlated with age. It is interesting to note that there was no relationship between age and MSE in the diagnosed participants. No other correlations involving EEG variables were significant. This pattern of results remained consistent when data from only unmedicated participants or from only

diagnosed or undiagnosed participants was analysed (see supplemental tables S1, S2 and S3). Scatterplots showing the relationships between the variables are shown in supplemental figure S3.

Insert Table 2 about here please

As described in the Method section, we obtained SRS-2 other reports for sixty-two participants (forty of whom were undiagnosed). The correlation between SRS-2 t-scores given by self or other report was high, rho = .680, p<.001, 95% CI = [.506 .801], B_{01} = <.001. Furthermore, when SCI obtained from the other-report was entered into correlation analyses as described above, the significance of all results remained stable, i.e. SCI was not significantly related to any of the EEG variables and remained significantly related to RBS-2A, ASRS and BAIT scores. Results from these correlations are presented in supplemental material.

Group Comparisons

All group comparisons included data from the subsample of 44 unmedicated participants only. Effect sizes for group comparisons are reported as A_w which is a non-parametric estimate of common-language effect size (see Li, 2016). A_w is calculated as follows:

$$(2)\ A_w = [\#(p>q) + .5\#(p=q)]/n_p n_q,$$

where p and q represent two groups (e.g. diagnosed and undiagnosed participants), and # represents the count function, e.g. counting the number of times that each value in distribution p is larger than each value in distribution q plus 0.5 x the number of times each value in distribution p is equal to each value in distribution q. The resulting output indicates the probability of a randomly selected value in distribution p being larger than a randomly selected value in distribution q. Because A_w is unaffected by sampling distributions and has been shown to be one of the most robust measures of effect size (Li, 2016), A_w is presented

regardless of whether parametric or non-parametric statistics were used to evaluate the significance of group differences. A_w = values of .56, .64 and .71 are considered small, medium and large respectively. 95% confidence intervals for Aw were calculated from the distributions of 5000 bootstrapped values.

Analysis of ITC. ITC data are shown in Figure 3. The frequency of maximum ITC ranged from 4 to 9 Hz, and did not differ significantly between groups, $\chi^2(5) = 3.54$, p = .62, Cramer's V = .284. Maximum ITC was not normally distributed, therefore group comparisons were performed using Mann-Whitney U. Maximum ITC was significantly lower in the diagnosed participants (Median = .898, 25 and 75 centiles = [.856 .929]) than the undiagnosed participants (Median = .937, 25 and 75 centiles = [.905 .969]), Mann-Whitney U = 186, p =.005, A_w = .75, 95% CI for A_w = [.585 .870], BF_{01} = 0.073. Conversely, Bayes factor in favour of the alternate hypothesis (BF_{10}) was 13.762.

Given that ITC is sensitive to data quality, we investigated whether the groups differed in indices that reflect data quality including number of data points entered into ICA, the difference between the number of data points entered into ICA and the recommended number of data points based on the number of channels available, and the number of epochs from which ITC was calculated. No group differences were found (see supplemental material)**.**

Insert Figure 3 about here please

Analysis of MSE. MSE values are shown in figures 4A and 4B. For analysis, data were collapsed into variables reflecting coarse scales, medium scales and fine scales by averaging scales 1 – 5, scales 6 – 13 and scales 14 – 20 respectively, and into three regions of interest (frontal, central and parietal / occipital) by averaging across channel-groups as shown in supplemental figure S3.

Data were analysed using a repeated measures ANOVA with group (diagnosed or undiagnosed) as a between-subject factor, and location (frontal, central or parietal) and scale (fine, mid or coarse) as within-subjects variables. Greenhouse–Geisser adjustment was applied. Results revealed a main effect of scale, $F(1.28, 53.73) = 532.9$, $p<.001$, $\eta^2 = .927$, 90% CI for $\eta^2 = [.909\ .956]$; a main effect of location, $F(1.69, 70.92) = 13.80$, $p<.001$, $\eta^2 = .296$, 90% CI for $\eta^2 = [.109\ .445]$; and a main effect of group, $F(1,42) = 4.18$, $p = .047$, $A_w = .66$, CI for $A_w = [.509\ .796]$ MSE was lower in diagnosed ($M = 1.22$, $SD = .059$) than in undiagnosed participants ($M = 1.25$, $SD = .039$), $BF_{01} = 0.649$. Bayesian statistics indicated only weak evidence ($BF_{10} = 1.541$) in support of a group difference in MSE.

Insert Figure 4 about here please

Can diagnosed and undiagnosed participants be identified by their EEG data?

Discriminant function analysis (DFA) entering average MSE (collapsed over electrode and scale) and ITC as predictors of group membership (diagnosed and undiagnosed) was performed. The association between group and predictors was significant, $\chi^2(2) = 12.09$, *Wilks* $\Lambda = .75$, $p = .002$. However, while 18 out of 22 (81.8%) undiagnosed participants were correctly classified, only 12 out of 22 (54.5%) diagnosed participants were correctly classified. Additional DFAs were performed to identify how well the groups could be classified by either ITC or MSE alone. The association between group and ITC was significant, $\chi^2(1) = 7.99$, *Wilks* $\Lambda = .825$, $p = .005$, with 81.8% of the undiagnosed participants being correctly classified, and 50% of the diagnosed participants being correctly classified. The association between group and MSE was also significant, $\chi^2(1) = 4.34$, *Wilks* $\Lambda = .90$, $p = .037$, however only 63.6% of the undiagnosed participants and 59.1% of the diagnosed participants were correctly classified. Two of the undiagnosed participants and five of the diagnosed participants were incorrectly classified in both DFAs. Only seven of the twenty-two autistic participants were correctly classified by both DFAs, six were correctly classified

by the MSE analysis and not the ITC analysis, and four were correctly classified by the ITC analysis and not the MSE analysis. With a view to establishing whether there was any evidence of particular subgroups characterised by atypical EEG, we scrutinised questionnaire scores, matrix reasoning scores and categorical variables including gender and co-occurring diagnoses in the participants with particularly low MSE and / or ITC scores. Based on visual inspection, we found no evidence to suggest that the participants with reduced MSE and / or ITC represented a distinct phenotypic cluster.

Discussion

The aim of this study was to establish whether individual differences in neural dynamics, as indexed by ITC and MSE, are related to individual differences in autistic traits. In order to place this study in the context of previous work suggesting that ITC and MSE may represent biomarkers or endophenotypes of ASD we also compared ITC and MSE between a subsample of unmedicated undiagnosed and diagnosed participants. As expected, and as shown in figure 2, individual differences in autistic traits were seen in both the diagnosed and undiagnosed participants. Individual differences in ITC and MSE were also evident, but were unrelated to phenotypic variability. In light of Happé's call to "give up on a single explanation of autism" (Happé, Ronald, & Plomin, 2006), we investigated relationships between EEG and symptom-domains, rather than global ASD severity. However, even when analysed in isolation, ASD symptom-domains were not related to either MSE or ITC.

At a group level, ITC and MSE were significantly reduced in the diagnosed participants. Such group differences are in line with previous work showing reduced ITC and reduced MSE in ASD (Catarino et al., 2011; Milne, 2011). However, there was substantial overlap between diagnosed and undiagnosed participants in both variables, and Bayes factors provided only weak evidence for a group difference in MSE. Furthermore, discriminant function analysis showed that EEG variables did not clearly distinguish diagnosed from

undiagnosed participants. The lack of clarity in group-based classifications highlights the heterogeneous nature of ASD and the observation made recently by Holmes and Patrick (2018) that there is no optimal neural profile in 'typical' development. Many authors have proposed that the current diagnostic label of ASD comprises a number of sub-types with different genetic profiles (Geschwind & Levitt, 2007). Indeed, there are a number of genetic variants that can give rise to symptoms and behaviors that meet diagnostic criteria for ASD (Betancur, 2011). Despite this, there is a tacit assumption in much autism research that the diagnostic label of ASD represents a neurobiological boundary and that therefore a distinct neural signature which identifies the condition should be found.

The work presented here shows that while neural differences are more likely to be seen in people with a diagnosis of ASD than in people without a diagnosis of ASD, autistic traits and behaviors are not underpinned by a unique and distinct neural etiology, at least in so far as is reflected by ITC and MSE. Instead, just as has been shown by genetic studies, there are likely to be multiple routes to a diagnosis of ASD which are underpinned by multiple neural profiles. Indeed, it is possible that in some people, a diagnosis of ASD represents one end of a continuous distribution of particular traits in the absence of specific neural etiology, whereas in other people a diagnosis of ASD reflects alteration to specific neural circuitry which may give rise to autistic traits and symptoms. Alteration to both ITC and MSE have been reported in other conditions including schizophrenia and Tourette's syndrome (Koh et al., 2011; Takahashi et al., 2010, Weng et al., 2017), suggesting - as RDoC proposes - that neural differences do not necessarily reflect clinical boundaries imposed by current diagnostic criteria, and that reduced ITC and MSE are not specific to ASD. The data presented here can be viewed in the context of the Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) framework, which suggests that neurodevelopmental disorders are not necessarily "discrete disorders or syndromes, but […]

brain dysfunctions/neurodevelopmental problems that reflect circuitry breakdown, network dysfunctions and decreased/aberrant/increased connectivity…" (Gilberg, 2010, pp 1549). In this context, differences in neural dynamics as reflected by reduced ITC and / or MSE may represent underlying vulnerabilities for a number of neurodevelopmental and psychiatric conditions that, as shown here, occur in a subgroup of individuals with ASD, but need not necessarily be related to particular traits within the population.

ITC represents consistency of the phase angles of EEG oscillations across trials therefore reduced ITC is indicative of more irregular, and less consistent neural responses. This is commensurate with increased neural variability and unreliable neural responses in ASD (Dinstein et al., 2012), which could originate from increased neural noise (Weinger, Zemon, Soorya, & Gordon, 2014), or inconsistent and inefficient neural transmission as has been suggested in ADHD (Russell et al., 2006). MSE represents the integration of activations across varying time scales and provides an index of the complexity of the EEG signal; lower MSE reflects reduced complexity of the signal. To the best of our knowledge this study is the first to measure both ITC and MSE in the same participants. We found no evidence of a correlation between MSE and ITC (see table 2) suggesting that the neural processes being measured by these two variables are distinct, and that both variables are unlikely to be measuring a single construct.

EEG complexity has been associated with neural connectivity. For example, model-based analyses show that reduced connectivity increases complexity (Friston, 1996), therefore, reduced complexity, as found here in the diagnosed participants, may suggest increased connectivity in these participants. Figure 4 shows a trend towards reduced MSE in ASD being most evident at fine scales, although the interaction between group and scale did not reach statistical significance. Given that sample entropy at fine-scales reflects local, short-range dynamics and sample entropy at coarse-scales reflects longer-range interactions

(McIntosh et al., 2013), reduced MSE at fine scales would be in-line with previous suggestion of increased short-range connectivity in ASD (Belmonte et al., 2004), although, as discussed above not all diagnosed participants showed reduced MSE.

The increase in ITC that is seen following the presentation of a visual stimulus has been suggested by some to be due to phase re-setting of on-going alpha-band oscillations (Gruber, Klimesch, Sauseng, & Doppelmayr, 2004; Makeig et al., 2002), which play a functional role in controlling the timing of information processing. Specifically, it has been proposed that the visual P1 deflection of the ERP represents the inhibitory-phase of the alpha-band oscillation and acts as an inhibitory filter, increasing signal to noise ratio during stimulus encoding and facilitating top-down integrative processes (Klimesch, Sauseng, & Hanslmayr, 2007). Although we did not find a relationship between ITC and autism traits, reduced ITC may be associated with features of ASD not measured here such as atypicalities of perception, a suggestion which is intriguing in light of recent work carried out in our lab showing that reduced ITC is associated with anomalous perception (Milne, Dunn, Zhao, & Jones, 2019).

There are a number of limitations to this study. Firstly, a large minority of the diagnosed participants were taking medication that may exert an effect on EEG. For group comparisons these participants were excluded from analyses. This reduces the generalizability of our findings and is a non-trivial problem for research of this nature, where prescribed medication use is a common feature of autism in adulthood. However, the correlation analyses remained stable when participants who were taking medication were excluded from the analysis, suggesting that our conclusion that the traits and symptoms of ASD are not related to either ITC or MSE across the population is not affected by medication use within the sample. A second limitation concerns the difficulty in confirming ASD diagnoses in research participants. Although observational tools, e.g. the ADOS, are available

for this purpose, these tools may not be sensitive enough to measure autistic behaviors in adults. This is particularly relevant here as many of the diagnosed participants did not receive a diagnosis of ASD until adulthood and reported developing strategies that enabled them to mask their autistic traits. Because of this, we did not administer the ADOS and instead used the RAADS-R to confirm the presence of ASD symptomatology (Andersen et al., 2011; Ritvo et al., 2011). As the RAADS-R was administered face-to-face with all participants, anecdotal information provided during the administration of the RAADS-R suggested that this instrument provided a sensitive way to measure experiences and behaviors (including masking behaviors) in autistic participants.

A third limitation is the use of self-report measures. In an attempt to overcome this, we administered the other-report version of the SRS wherever possible. There was a relatively high degree of concordance between the self- and other reports, and the pattern of correlations obtained using SCI calculated from other-report was similar to the pattern of correlations obtained using SCI calculated from self-report, providing confidence in the use of self-report measures. Nevertheless, some degree of measurement error is inevitable with the use of questionnaires, which may impact on the results of the correlations presented here.

A fourth limitation concerns the fact that we analysed only two EEG variables. It is possible that had other variables been investigated, a relationship between neural features and autistic traits would be seen (c.f. Elton, Di Martino, Hazlett, & Gao, 2016). However, MSE and ITC were selected for analysis specifically because they reflect integrity of a broad range of neural features, and are sensitive to variation in neural structure and function (e.g. changes to MSE associated with aging reported by McIntosh et al., 2013, and found here in the undiagnosed sample). Furthermore, both variables were sensitive enough here to differ between the participants with and without ASD at a group level.

A final consideration is the extent to which the diagnosed participants are representative of the autistic population. Given that the aim of this study was to investigate the extent to which alterations to neural dynamics that have previously been reported in ASD are related to the autism phenotype across the population, we purposefully recruited diagnosed participants who were similar in intellectual level and socio-economic status to the undiagnosed participants. However, many autistic people have additional needs which would preclude them from taking part in a study such as this, therefore it is important to acknowledge that these data reflect only a subsection of autistic adults**.** The mean RAADS-R score for the unmedicated diagnosed participants on which group comparisons are based was 116.9. Compared with two other papers that have recruited large samples of participants with ASD, this mean score is lower than the mean RAADS-R score of 133.8 reported by Ritvo et al., and similar to the mean score of 118.7 reported by Andersen et al., 2011. It is possible that different patterns of results would be found if we repeated this study in a different population, for example in autistic children, infants at high risk for being diagnosed with ASD (c.f. Bosl, Tager-Flusberg, & Nelson, 2018**),** or in autistic adults who score more highly on the RAADS-R.

To summarise, these data support previous findings of individual differences within the general population of the traits associated with ASD. However, we found no evidence to suggest that the distribution of autistic traits in the population is underpinned by individual differences in neural dynamics: EEG variables that have been reported by others, and found here, to differ between people with and without ASD were unrelated to ASD traits. This conclusion is tempered by the fact that we measured only two EEG variables and obtained data from only one neuroimaging method. Nevertheless, ASD is defined as a neurodevelopmental disorder, implying a neural etiology of the condition. By combining a categorical and a dimensional approach to analysis, this study suggests that neural etiology is

seen in some, but not all, people who are diagnosed with ASD, and that there are likely to be multiple neural profiles underlying the condition. These data have implications for studies that aim to find distinct neural biomarkers for ASD, and highlight the difficulties involved in research that is aimed at identifying the neural etiology of diagnostic constructs that are defined by behavior alone.

References

Andersen, L. M., Näswall, K., Manouilenko, I., Nylander, L., Edgar, J., Ritvo, R. A., . . . Bejerot, S. (2011). The Swedish version of the Ritvo Autism and Asperger Diagnostic Scale: revised (RAADS-R). A validation study of a rating scale for adults. Journal of autism and developmental disorders, 41(12), 1635-1645.

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high-functioning autism, malesand females, scientists and mathematicians. Journal of autism and developmental disorders, 31(1), 5-17.

Barrett, S. L., Uljarević, M., Baker, E. K., Richdale, A. L., Jones, C. R., & Leekam, S. R. (2015). The Adult Repetitive Behaviours Questionnaire-2 (RBQ-2A): a self-report measure of restricted and repetitive behaviours. Journal of autism and developmental disorders, 45(11), 3680-3692.

Belmonte, M. K., Allen, G., Beckel-Mitchener, A., Boulanger, L. M., Carper, R. A., & Webb, S. J. (2004). Autism and abnormal development of brain connectivity. Journal of Neuroscience, 24(42), 9228-9231.

Betancur, C. (2011). Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting. Brain research, 1380, 42-77.

Bosl, W., Tierney, A., Tager-Flusberg, H., & Nelson, C. (2011). EEG complexity as a biomarker for autism spectrum disorder risk. BMC medicine, 9(1), 18.

Bosl, W. J., Tager-Flusberg, H., & Nelson, C. A. (2018). EEG analytics for early detection of autism spectrum disorder: a data-driven approach. Scientific reports, 8(1), 6828.

Brainard, D. H., & Vision, S. (1997). The psychophysics toolbox. Spatial vision, 10, 433-436.

Brugha, T. S., McManus, S., Bankart, J., Scott, F., Purdon, S., Smith, J., . . . Meltzer, H. (2011). Epidemiology of autism spectrum disorders in adults in the community in England. Archives of general psychiatry, 68(5), 459-465.

Catarino, A., Churches, O., Baron-Cohen, S., Andrade, A., & Ring, H. (2011). Atypical EEG complexity in autism spectrum conditions: a multiscale entropy analysis. Clinical neurophysiology, 122(12), 2375-2383.

Constantino, J. N., & Gruber, C. P. (2012). Social responsiveness scale (SRS): Western Psychological Services Torrance, CA.

Costa, M., Goldberger, A. L., & Peng, C.-K. (2002). Multiscale entropy analysis of complex physiologic time series. Physical review letters, 89(6), 068102.

David, N., Schneider, T. R., Peiker, I., Al-Jawahiri, R., Engel, A. K., & Milne, E. (2016). Variability of cortical oscillation patterns: A possible endophenotype in autism spectrum disorders? Neuroscience & Biobehavioral Reviews, 71, 590-600.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. Journal of neuroscience methods, 134(1), 9-21.

Dinstein, I., Heeger, D. J., & Behrmann, M. (2015). Neural variability: friend or foe? Trends in cognitive sciences, 19(6), 322-328.

Dinstein, I., Heeger, D. J., Lorenzi, L., Minshew, N. J., Malach, R., & Behrmann, M. (2012). Unreliable evoked responses in autism. Neuron, 75(6), 981-991.

Elton, A., Di Martino, A., Hazlett, H. C., & Gao, W. (2016). Neural connectivity evidence for a categorical-dimensional hybrid model of autism spectrum disorder. Biological psychiatry, 80(2), 120-128.

Friston, K. J. (1996). Theoretical neurobiology and schizophrenia. British medical bulletin, 52(3), 644-655.

Geschwind, D. H., & Levitt, P. (2007). Autism spectrum disorders: developmental disconnection syndromes. Current opinion in neurobiology, 17(1), 103-111.

Gillberg, C. (2010). The ESSENCE in child psychiatry: early symptomatic syndromes eliciting neurodevelopmental clinical examinations. Research in developmental disabilities, 31(6), 1543-1551.

Gruber, W. R., Klimesch, W., Sauseng, P., & Doppelmayr, M. (2004). Alpha phase synchronization predicts P1 and N1 latency and amplitude size. Cerebral Cortex, 15(4), 371-377.

Happé, F., & Ronald, A. (2008). The 'fractionable autism triad': a review of evidence from behavioural, genetic, cognitive and neural research. Neuropsychology review, 18(4), 287-304.

Happé, F., Ronald, A., & Plomin, R. (2006). Time to give up on a single explanation for autism. Nature neuroscience, 9(10), 1218.

Holmes, A. J., & Patrick, L. M. (2018). The myth of optimality in clinical neuroscience. Trends in cognitive sciences.

Insel, T. R. (2014). The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry. American Journal of Psychiatry, 171(4), 395-397.

JASP Team (2018). JASP (Version 0.9)[Computer software].

Kessler, R. C., Adler, L., Ames, M., Demler, O., Faraone, S., Hiripi, E., . . . Spencer, T. (2005). The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. Psychological medicine, 35(2), 245-256.

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition–timing hypothesis. Brain research reviews, 53(1), 63-88.

Koh, Y., Shin, K. S., Kim, J. S., Choi, J.-S., Kang, D.-H., Jang, J. H., . . . Kwon, J. S. (2011). An MEG study of alpha modulation in patients with schizophrenia and in subjects at high risk of developing psychosis. Schizophrenia research, 126(1-3), 36-42.

Kohn, P. M., Kantor, L., DeCicco, T. L., & Beck, A. T. (2008). The Beck Anxiety Inventory–Trait (BAIT): A measure of dispositional anxiety not contaminated by dispositional depression. Journal of Personality Assessment, 90(5), 499-506.

Lai, M.-C., & Baron-Cohen, S. (2015). Identifying the lost generation of adults with autism spectrum conditions. The Lancet Psychiatry, 2(11), 1013-1027.

Li, J. C.-H. (2016). Effect size measures in a two-independent-samples case with nonnormal and nonhomogeneous data. Behavior research methods, 48(4), 1560-1574.

Liang, W.-K., Lo, M.-T., Yang, A. C., Peng, C.-K., Cheng, S.-K., Tseng, P., & Juan, C.-H. (2014). Revealing the brain's adaptability and the transcranial direct current stimulation facilitating effect in inhibitory control by multiscale entropy. Neuroimage, 90, 218-234.

Makeig, S., Westerfield, M., Jung, T.-P., Enghoff, S., Townsend, J., Courchesne, E., & Sejnowski, T. J. (2002). Dynamic brain sources of visual evoked responses. Science, 295(5555), 690-694.

McIntosh, A., Vakorin, V., Kovacevic, N., Wang, H., Diaconescu, A., & Protzner, A. (2013). Spatiotemporal dependency of age-related changes in brain signal variability. Cerebral Cortex, 24(7), 1806-1817.

Milne, E. (2011). Increased intra-participant variability in children with autistic spectrum disorders: evidence from single-trial analysis of evoked EEG. Frontiers in psychology, 2, 51.

Milne, E., Dunn, S., Zhao, C., & Jones, M. (2019). Altered neural dynamics in people who report spontaneous out of body experiences. Cortex, 111, 87 - 99.

Pincus, S. M., & Goldberger, A. L. (1994). Physiological time-series analysis: what does regularity quantify? American Journal of Physiology-Heart and Circulatory Physiology, 266(4), H1643-H1656.

Richman, J. S., & Moorman, J. R. (2000). Physiological time-series analysis using approximate entropy and sample entropy. American Journal of Physiology-Heart and Circulatory Physiology, 278(6), H2039-H2049.

Ritvo, R. A., Ritvo, E. R., Guthrie, D., Ritvo, M. J., Hufnagel, D. H., McMahon, W., . . . Attwood, T. (2011). The Ritvo Autism Asperger Diagnostic Scale-Revised (RAADS-R): a scale to assist the diagnosis of autism spectrum disorder in adults: an international validation study. Journal of autism and developmental disorders, 41(8), 1076-1089.

Ronald, A., Happé, F., & Plomin, R. (2005). The genetic relationship between individual differences in social and nonsocial behaviours characteristic of autism. Developmental science, 8(5), 444-458.

Russell, V. A., Oades, R. D., Tannock, R., Killeen, P. R., Auerbach, J. G., Johansen, E. B., & Sagvolden, T. (2006). Response variability in attention-deficit/hyperactivity disorder: a neuronal and glial energetics hypothesis. Behavioral and Brain Functions, 2(1), 30.

Skuse, D. H., Mandy, W., Steer, C., Miller, L. L., Goodman, R., Lawrence, K., . . . Golding, J. (2009). Social communication competence and functional adaptation in a general population of children: preliminary evidence for sex-by-verbal IQ differential risk. Journal of the American Academy of Child & Adolescent Psychiatry, 48(2), 128-137.

Takahashi, T., Cho, R. Y., Mizuno, T., Kikuchi, M., Murata, T., Takahashi, K., & Wada, Y. (2010). Antipsychotics reverse abnormal EEG complexity in drug-naive schizophrenia: a multiscale entropy analysis. Neuroimage, 51(1), 173-182.

Tallon-Baudry, C., Bertrand, O., Delpuech, C., & Pernier, J. (1996). Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human. Journal of Neuroscience, 16(13), 4240-4249.

Vissers, M. E., Cohen, M. X., & Geurts, H. M. (2012). Brain connectivity and high functioning autism: a promising path of research that needs refined models, methodological convergence, and stronger behavioral links. Neuroscience & Biobehavioral Reviews, 36(1), 604-625.

Weinger, P. M., Zemon, V., Soorya, L., & Gordon, J. (2014). Low-contrast response deficits and increased neural noise in children with autism spectrum disorder. Neuropsychologia, 63, 10-18.

Weng, W.-C., Chang, C.-F., Wong, L. C., Lin, J.-H., Lee, W.-T., & Shieh, J.-S. (2017). Altered resting-state EEG complexity in children with Tourette syndrome: A preliminary study. Neuropsychology, 31(4), 395.

Weschler, D. (1999). Weschler abbreviated scale of intelligence (WASI). London: Psychological Corporation.

Table 1.

Descriptive variables and questionnaire scores for the full sample, and for the sub-sample of un-medicated diagnosed and undiagnosed participants used in group analysis.

	Full Sample (N = 99)		Un-medicated diagnosed (N = 22)		Matched undiagnosed (N = 22)					
	Mean	SD	Mean	SD	Mean	SD	t[a]	p	Aw[c]	CI
Age	37.5	13.5	42.1	14.0	37.2	10.7	-1.28	.21	.608	[.415 .767]
MR t-score	59.5	7.3	59.4	7.8	59.1	6.7	-.130	.90	.538	[.315 .731]
IMD	5.73	2.7	5.8	2.9	5.7	2.7	.446	.658	.466	[.218 .688]
RAADS-R score	72.4	53.3	116.9	27.9	24.3	19.9	-11.83[b]	<.001	1	[1 1]
SRS-R t-score	58.0	14.3	66.3	9.9	44.8	4.3	-9.40[b]	<.001	.979	[.923 .997]
SCI score	51.1	32.3	69.3	21.6	21.0	9.8	-9.55[b]	<.001	.978	[.910 .996]
RBQ-2A score	1.7	0.4	1.9	0.3	1.3	0.3	-6.72	<.001	.924	[.831 .970]
BAIT score	14.4	10.9	16.1	10.5	8.3	6.3	-2.98[b]	.005	.725	[.522 .869]
ASRS score	12.3	4.7	13.9	4.3	9.4	4.2	-3.50	.001	.798	[.657 .897]

Note. MR = matrix reasoning; IMD = Index of Multiple Deprivation; RAADS-R = Ritvo Autism Asperger Diagnostic Scales – Revised; SRS-R = Social Responsiveness Scales, Revised; SCI = social communicative interaction subscale from the SRS-R; RBQ-2A = Adult Repetitive Behaviour Questionnaire-2A; BAIT = Beck Anxiety Inventory – Trait version; ASRS = World Health Organisation Adult ADHD Self-Report Scale Screener Part A.

[a] Comparison of the subsample of un-medicated diagnosed participants and the matched undiagnosed participants.

[b] degrees of freedom adjusted due to between-group inequality of variance

[c] Aw presented as probability of score from the diagnosed group being larger than score from the undiagnosed group. CI = 95% confidence intervals around Aw

Table 2.

Correlation coefficients (Spearman's rho) between MSE, ITC and questionnaire scores.

N = 99[a]	MSE fine	MSE mid	MSE coarse	ITC	SCI	RBRI	ASRS	BAIT
MSE mid	.190							
95% CI	[-.007 .374]							
B_{01}	1.059							
MSE coarse	**-.639****	**.386****						
95% CI	**[-.743 -.505]**	**[.204 .542]**						
B_{01}	**< 0.001**	**0.004**						
ITC	.039	-.052	-.048					
95% CI	[-.166 .241]	[-.253 .153]	[-.249 .157]					
B_{01}	7.144	6.673	6.529					
SCI	.028	-.043	-.087	-.077				
95% CI	[-.171 .224]	[-.238 .156]	[-.279 .113]	[-.276 .129]				
B_{01}	7.347	6.860	5.194	5.998				
RBRI	-.005	-.108	-.128	-.019	**.827****			
95% CI	[-.202 .193]	[-.299 .091]	[-.318 .071]	[-.222 .185]	**[.752 .881]**			
B_{01}	7.621	4.137	3.454	7.288	**< 0.001**			
ASRS	-.031	-.047	-.019	-.199	**.609****	**.587****		
95% CI	[-.227 .167]	[-.242 .152]	[-.216 .179]	[-.387 .005]	**[.468 .720]**	**[.441 .703]**		
B_{01}	7.288	6.816	7.471	1.038	**< 0.001**	**< 0.001**		
BAIT	.079	.048	-.096	-.130	**.632****	**.595****	**.553****	
95% CI	[-.120 .272]	[-.151 .243]	[-.288 .103]	[-.325 .075]	**[.497 .737]**	**[.450 .709]**	**[.399 .677]**	
B_{01}	5.771	6.681	4.695	3.967	**< 0.001**	**< 0.001**	**< 0.001**	
AGE	**.389****	**.**069	**-.361****	-.067	.197	.136	-.026	**.249***
95% CI	**[.207 .544]**	[-.130 .263]	**[-.521 -.176]**	[-.267 .139]	[.000 .380]	[-.060 .325]	[-.223 .172]	**[.055 .426]**
B_{01}	**0.004**	6.120	**0.014**	6.158	1.336	2.706	7.499	**0.344**

Note. CI = Confidence interval; B_{01} = Bayes Factor in favour of the null hypothesis; MSE = multi-scale entropy; ITC = inter-trial coherence; SCI = social communicative interaction subscale from the SRS-R; RBRI = score from the Adult Repetitive Behaviour Questionnaire-2A; BAIT =

Beck Anxiety Inventory – Trait version; ASRS = World Health Organisation Adult ADHD Self-Report Scale Screener Part A. Significant correlations are indicated by bold font.
[a] with the exception of correlations involving ITC where N = 93.
* = p<.05, ** = p< .01

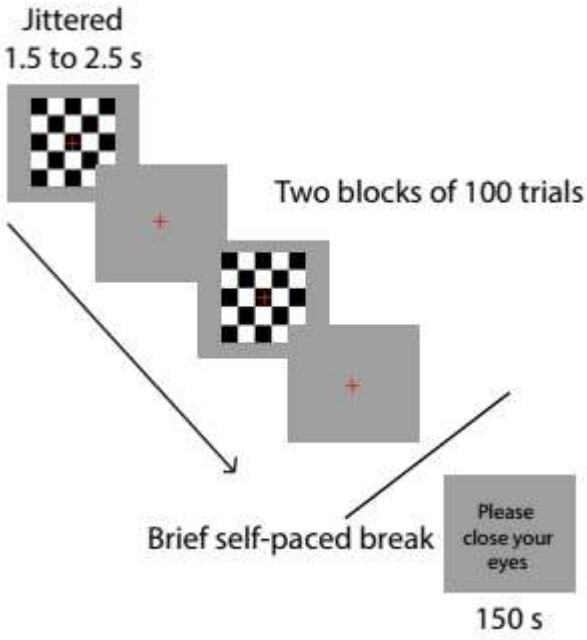

Figure 1. Schematic illustration of the EEG procedure.

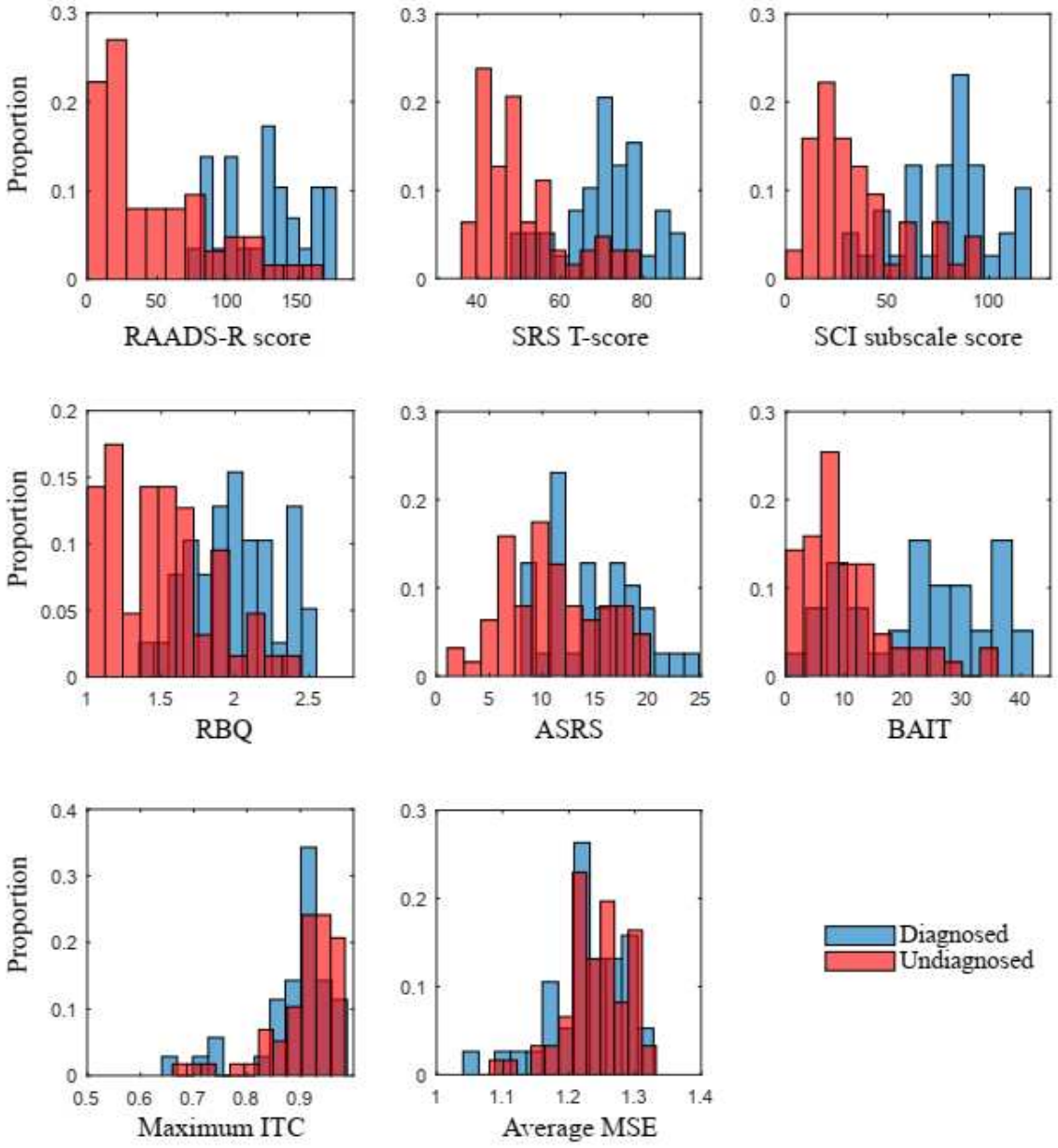

Figure 2. Histograms showing the distribution of scores obtained from the questionnaires and EEG variables in the diagnosed (N = 38) and undiagnosed (N = 61) participants. See the online article for the color version of this figure.

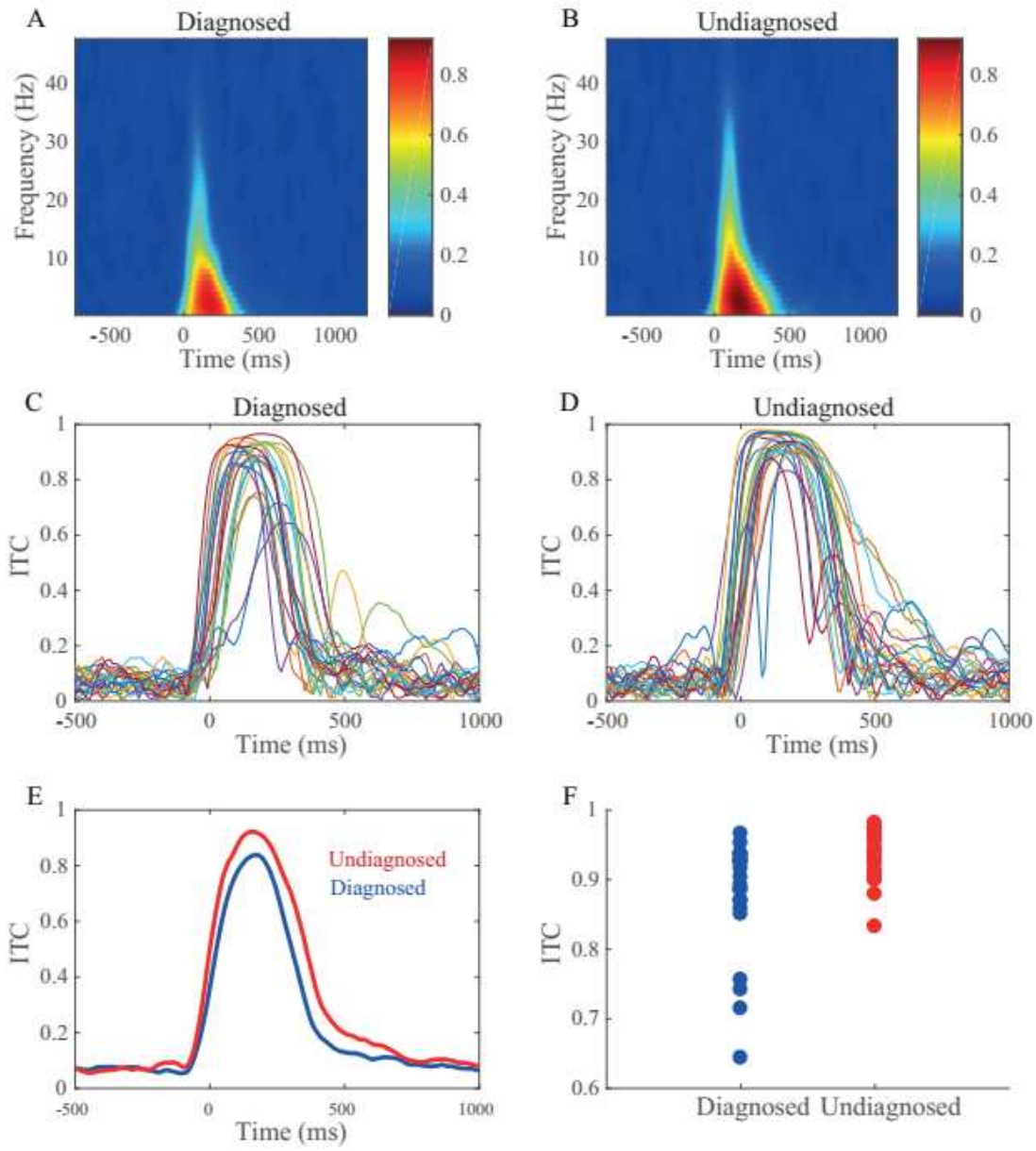

Figure 3. ITC values in the unmedicated subsample of diagnosed and undiagnosed participants. Top panel shows time/frequency plots of ITC values in the diagnosed (A) and undiagnosed (B) samples. Middle panel shows the timeseries at the frequency at which maximum ITC occurred from each participant in the diagnosed (C) and undiagnosed (D) samples. E shows the average of the timeseries depicted in C and D, and F shows the maximum ITC value in the diagnosed and undiagnosed groups. Note that if the five participants who show clearly reduced ITC values (four from the diagnosed group and one

from the undiagnosed group) are excluded from analysis, there is still a significant group difference between the diagnosed and undiagnosed participants (Mann-Whitney U = 104, p =.016, BF_{10} = 5.92). See the online article for the color version of this figure.

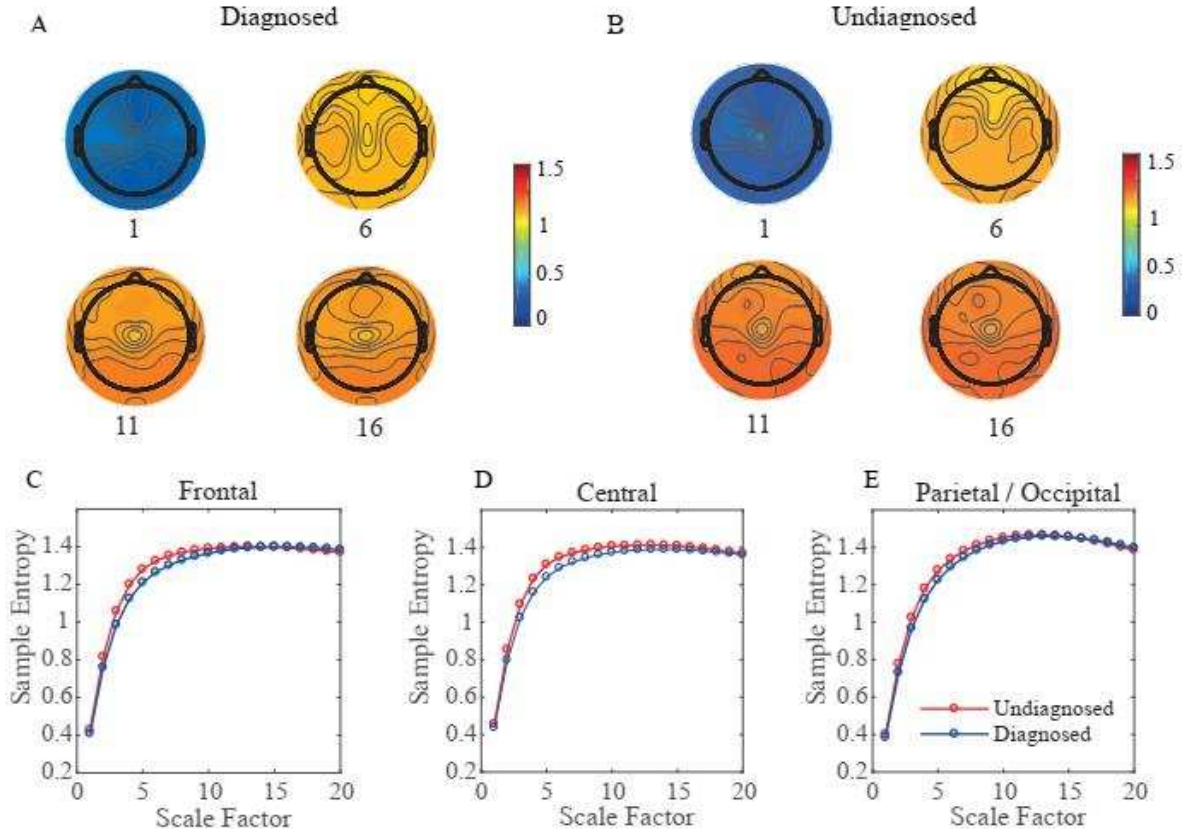

Figure 4. MSE values in the unmedicated subsample of diagnosed and undiagnosed participants. Sample entropy at each electrode and at a selection of scale factors (1,6,11 & 16) is shown in each headplot. (A) shows mean sample entropy for the diagnosed participants and (B) shows mean sample entropy for the undiagnosed participants. C, D and E show mean sample entropy at each scale factor in the diagnosed and undiagnosed participants computed from frontal (C), central (D) and parietal / occipital (E) electrodes. See the online article for the color version of this figure.