

## Atypical EEG complexity in autism spectrum conditions: A multiscale entropy analysis

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### HIGHLIGHTS

- EEG complexity was compared between adults with autistic spectrum conditions (ASC) and control participants, whilst performing a social and a non-social task.
- The ASC group showed reduced complexity compared to the control group in both tasks, in parietal and occipital regions of the cortex.
- Both groups had relatively greater EEG complexity for the social, compared to the non-social task.

### ABSTRACT

**Objective:** Intrinsic complexity subserves adaptability in biological systems. One recently developed measure of intrinsic complexity of biological systems is multiscale entropy (MSE). Autism spectrum conditions (ASC) have been described in terms of reduced adaptability at a behavioural level and by patterns of atypical connectivity at a neural level. Based on these observations we aimed to test the hypothesis that adults with ASC would show atypical intrinsic complexity of brain activity as indexed by MSE analysis of electroencephalographic (EEG) activity.

**Methods:** We used MSE to assess the complexity of EEG data recorded from 15 participants with ASC and 15 typical controls, during a face and chair matching task.

**Results:** Results demonstrate a reduction of EEG signal complexity in the ASC group, compared to typical controls, over temporo-parietal and occipital regions. No significant differences in EEG power spectra were observed between groups, indicating that changes in complexity values are not a reflection of changes in EEG power spectra.

**Conclusions:** The results are consistent with a model of atypical neural integrative capacity in people with ASC.

**Significance:** Results suggest that EEG complexity, as indexed by MSE measures, may also be a marker for disturbances in task-specific processing of information in people with autism.

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### 1. Introduction

Physiological complexity, comprising the presence of non-random fluctuations over multiple time scales in the seemingly irregular dynamics of physiological outputs (Freeman, 1992; Glass and Mackey, 1992; Manor et al., 2010) is increasingly being recognized as contributing a novel descriptive approach to the investigation of typical and pathological developmental or degenerative

states (Costa et al., 2002, 2005; Fallani Fde et al., 2010; Ouyang et al., 2010). Whilst the interpretation of the meaning of changes in complexity varies according to the physiological parameters studied and the developmental or clinical condition being investigated, there is nevertheless increasing evidence that a variety of pathological processes are associated with atypical and often, but not always, reduced measures of physiological complexity (Escudero et al., 2006; McIntosh et al., 2008; Kang et al., 2009; Istenic et al., 2010; Manor et al., 2010; Mizuno et al., 2010; Takahashi et al., 2010; Bosl et al., 2011). Regarding brain activity specifically, electroencephalographic (EEG) activity provides fine temporal resolution, making it particularly suitable for investigating inherently

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complex biological signals arising from brain systems regulated by multiple sources interacting with each other over different time scales, mechanisms, couplings and feedback loops (Bhattacharya et al., 2005; Fallani Fde et al., 2010; Ouyang et al., 2010).

There are reasons to suspect that autism spectrum conditions (ASC) may be associated with atypical patterns of brain complexity. ASC are a set of pervasive neurodevelopmental conditions with onset in early childhood and a wide range of life-long signs and symptoms that suggest an association with atypical functioning at a relatively profound level of brain functioning. Core features of ASC include a restricted repetitive range of behaviours, interests and activities; impairments in reciprocal social interactions; and qualitative disturbances in communication (American Psychiatric Association, 2000). In addition to these characteristic social and cognitive features, atypical patterns of sensory and motor functioning and integration are also increasingly recognised as features of ASC, with evidence of atypical visual perception (Simmons et al., 2009), including perception of biological motion (Kaiser et al., 2010), auditory perception (Hitoglou et al., 2010), somatosensory integration (Russo et al., 2010), and motor functions (Gidley Larson, 2006) as well as impaired sensorimotor integration (Haswell et al., 2009), motor planning and control (Jansiewicz et al., 2006; Rinehart et al., 2006; Freitag et al., 2007) and reduced adaptability to environmental changes (Russo et al., 2007; Thakkar et al., 2008; Foley Nicpon et al., 2010). There is also evidence that motor deficits do not occur in isolation from the social and cognitive features of ASC (Dziuk et al., 2007). In attempting to explain this wide range of features of ASC several explanatory models of brain functioning that suggest disturbances of underlying brain complexity have been proposed, including atypical neural connectivity (Belmonte et al., 2004; Courchesne and Pierce, 2005; Just et al., 2007; Barttfeld et al., 2011; Wass, 2011) and disrupted temporal integration of information (Brock et al., 2002; Rippon et al., 2007). Supporting the possibility of atypical functional complexity in autism, it has been observed that, in those without ASC, improved adaptability to cognitive demands is associated with increasing physiological variability reflected by greater scalp EEG complexity (McIntosh et al., 2008; Sitges et al., 2010) and that altered neural connectivity may be associated with atypical signal complexity in schizophrenia (Friston, 1996) and Alzheimer's disease (Jeong, 2004). In addition, a recent study by Bosl et al. (2011) has shown a decrease in resting state EEG complexity in infants at high risk of ASC, when compared to normal controls, with low risk of ASC.

In order to examine whether ASC is associated with an atypical pattern of complexity of brain function we examined multiscale entropy (MSE) as a measure of physiological complexity in scalp-recorded EEG data in a group of adults with ASC and a matched typically developing control group. Entropy is a physical quantity that measures the order of a system. Regular systems have lower values of entropy, whilst totally irregular systems have very high values of entropy. However, regularity is not necessarily correlated with complexity. Random phenomena like white noise have very low regularity and will therefore present high values of entropy, but they do not have the structural richness of information over multiple spatial and temporal scales that characterises complex systems (Costa et al., 2002, 2005). In order to overcome this problem and differentiate between white noise and true complexity, Costa et al. (2002, 2005) introduced the method of MSE, which quantifies the complexity of a physiological signal by measuring the entropy across multiple time-scales, using a coarse-graining procedure. This model proposes that optimally functioning biological systems are modulated by multiple mechanisms which interact over multiple temporal scales. These processes generate complex data composed of overlapping signals from all the interrelating mechanisms. In these circumstances, MSE analysis will reveal a high value of entropy sustained for increasingly coarser

time-scales. For random noise signals however, the system will show a decrease in entropy values as the time-scales increase. This is because a random white-noise signal has information only on the shortest time-scale; as the time-scales increase, since no new structures are revealed, the standard deviation of the signal decreases, causing a progressive decrease in the values of entropy with time-scale (Costa et al., 2005).

Brain activity in typical development from childhood to adulthood has been associated with increasing MSE (McIntosh et al., 2008), and in a study of adults with schizophrenia increased MSE has been observed in fronto-central and parietal regions (Takahashi et al., 2010) whereas age-related response to photic stimulation in typical individuals (Takahashi et al., 2009), and treatment of schizophrenia with antipsychotics, have been associated with reduced MSE. Alzheimer's disease has been associated with several patterns of EEG complexity, with earlier studies reporting lower MSE (Escudero et al., 2006; Park et al., 2007) whilst more recently Mizuno et al. (2010) reported relatively decreased complexity over smaller timescales but relatively increased complexity at coarser timescales, possibly reflecting different modulating effects by separate neuropathophysiological mechanisms. Additionally, Bosl et al. (2011) have recently shown a decrease in resting state EEG complexity, at several stages of development, for infants at high risk of ASC, when compared to infants at low risk of ASC.

Whilst some MSE studies have analysed data collected during resting states (Escudero et al., 2006; Hornero et al., 2009; Takahashi et al., 2010; Bosl et al., 2011), others have employed activation or stressor tasks to explore responses to stimuli of relevance to the physiological or clinical process of interest (Takahashi et al., 2009; Manor et al., 2010; Sitges et al., 2010). Previous event-related potential (ERP) studies have found that face processing in some circumstances is impaired in people with ASC (O'Connor et al., 2005; Jemel et al., 2006; Churches et al., 2010) and in this study we analysed EEG recorded whilst participants observed images of faces and other objects.

In this investigation the first aim is to determine whether typical controls and a group with ASC have similar or differing patterns of MSE. We predict that those with ASC will have an atypical pattern of complexity, as reflected by significantly different MSE values at coarser time scales compared to controls. Secondly, given the reduced behavioural adaptability observed in ASC (Russo et al., 2007; Thakkar et al., 2008; Foley Nicpon et al., 2010), and the observation that in the general population greater adaptability is associated with higher MSE values (McIntosh et al., 2008), along with findings of reduced complexity in infants at high risk of ASC by Bosl et al. (2011), we hypothesise that MSE will be reduced over coarser time scales in the ASC group, when compared to MSE in the control group, during performance of a visual matching task. To address the question of the extent to which differences in EEG complexity may relate to group differences in EEG power spectra, we also conducted a traditional power analysis using the same EEG data. Based on results from previous studies (Milne et al., 2009; Rymaekers et al., 2009) we did not expect to find any differences in EEG power spectra between the ASC and the control groups.

## 2. Materials and methods

This study was approved by the School of Psychology Research Ethics Committee at the University of Cambridge and all participants gave informed written consent.

### 2.1. Participants

Fifteen patients with ASC and fifteen typical controls were recruited for this study. All ASC participants were diagnosed with

**Table 1**

Age, verbal IQ, performance IQ, full-scale IQ and autism questionnaire (AQ) scores for each group.

Participants characteristics							
	Controls (n = 15)			AS (n = 15)			Group comparison
	Mean	s.d.	Range	Mean	s.d.	Range	
Age	29.38	4.63	21.50–37.77	31.44	6.71	23.79–42.34	$t_{28} = -.980$ ; $p = .335$
Verbal <sup>a</sup>	114	16	77–133	119	11	101–134	$t_{27} = -1.034$ ; $p = .310$
Performance IQ <sup>a</sup>	119	11	93–134	115	14	93–132	$t_{27} = 834$ ; $p = .412$
Full-Scale IQ <sup>a</sup>	119	14	93–134	119	13	98–136	$t_{27} = -.081$ ; $p = .936$
AQ <sup>b</sup>	16	7	4–27	35	7	21–46	$t_{27} = -7.573$ ; $p < .0005$

<sup>a</sup> IQ scores were not available for one control participant.<sup>b</sup> AQ scores were not available for one control participant.

ASC by a professional experienced with the diagnosis of ASC based on international criteria (American Psychiatric Association, 2000). Exclusion criteria for ASC participants were uncorrected impairment in eyesight or hand movement, a personal or family history of any psychological or genetic condition apart from ASC or a period of unconsciousness in the last 5 years. Exclusion criteria for control participants were similar, with the addition of any personal or family history of an ASC. All participants were male and were right-handed, as measured by the Edinburgh Handedness Inventory (Oldfield, 1971).

Participants were administered the Wechsler Abbreviated Scale of Intelligence (WASI; (Wechsler, 1999) for IQ assessment and the Autism Spectrum Quotient (AQ; (Baron-Cohen et al., 2001)). Higher scores on the AQ reflect a greater number of traits indicative of ASC. The ASC group (mean = 35, s.d. = 7) scored significantly higher than the typical control group (mean = 16, s.d. = 7,  $t_{27} = -7.573$ ;  $p < .0005$ ). The participant groups were matched for age and IQ. Participants' demographic details and their IQ and AQ scores are presented in Table 1.

## 2.2. EEG recording

EEG data was acquired as part of an ERP protocol (Churches et al., 2010) using 28 standard scalp electrodes placed in accordance with the International 10–20 System (Klem et al., 1999). Reference was the tip of the nose with ground at Fpz. Eye-movements were monitored using bi-polar channels with electrodes above and below the left eye (vertical electro-oculogram) and 1 cm from the outer canthus of each eye (horizontal electro-oculogram). Impedances at all sites were maintained below 5 k $\Omega$ . EEG data was obtained at a sampling frequency of 1000 Hz, with a .1–50 Hz input bandpass filter, and using a 32-channel Synamps apparatus (Compumedics Neuroscan, Charlotte, NC, USA). Consistent with previous MSE studies (Escudero et al., 2006; Hornero et al., 2009; Takahashi et al., 2010), the data was not subjected to other pre-processing steps (i.e., filtering, artefact removal or data reconstruction algorithms) since this could distort the data and influence the MSE analysis results. Instead artefact free segments of data were chosen for analysis.

The EEG was recorded whilst participants performed a face and chair detection task. They were seated in a darkened room approximately 60 cm from the computer screen, on which the stimuli were presented. Stimuli consisted of 30 pictures of neutral faces (15 male, 15 female) and 30 pictures of chairs.

Participants viewed two blocks of stimuli between which only the order of the images varied. In each block, all 60 pictures (30 faces, 30 chairs) were presented three times pseudorandomly without immediate repetition. Each image was presented for 500 ms, with an interstimulus interval that varied randomly between 1200 and 1400 ms. Thus each block lasted for about 5.5 min. In one of the blocks, the subject's attention was directed

to the chairs, and in the other block their attention was directed to the faces pictures. To do this, 10 images of faces (5 male, 5 female) and 10 images of chairs were inserted as immediate repetitions. At the start of each block, participants were asked to attend to one of the categories of stimulus (faces or chairs) and to press a response button whenever they saw an immediate repetition of an image of that category, while ignoring all stimuli in the other category. The purpose of this instruction was to direct the participants' attention to a given category. Response times and accuracy were measured for each participant. Each block began with a practice run of 10 stimuli. The order of the two blocks, the attended category and the hand used to respond were counter-balanced across participants. Participants rested for approximately 5 min between blocks.

## 2.3. Signal analysis

The first 180 s of EEG recording of all participants during each visual task were extracted for analysis. From these 180 s, segments free of artefacts such as eye movements, blinks, muscle movements or other artefacts were visually identified and selected for analysis. MSE and power analyses were run for each participant for the first 40,000 data points (40 s) of the EEG signal resulting from all the artefact free segments. This is the default number of data points analysed by the MSE algorithm (available at <http://www.physionet.org/physiotools/mse/mse.c>, (Goldberger et al., 2000)). Analyses were run separately for the chairs and for the face tasks. There were no significant between group differences in the number of pictures included in the 40 s period chosen for analysis (chair task: control = 17 (standard deviation (s.d.) = 3), AS = 16 (s.d. = 4),  $t = .783$ ,  $p = .440$ ; face task: control = 18 (s.d. = 3), AS = 17 (s.d. = 4),  $t = .422$ ,  $p = .676$ ). Electrodes Fp1, Fp2 and Fz were excessively affected by eye movement artefacts and were removed from the analysis. Technical problems affected electrodes F3 and O2 during data acquisition for some participants. Therefore electrode pairs F3/F4 and O1/O2 were also excluded from the analysis.

## 2.4. Multiscale entropy (MSE)

The MSE method quantifies the complexity of a time-series by calculating the sample entropy ( $S_E$ ) over several time scales, using a coarse-graining procedure (Costa et al., 2002, 2005). The  $S_E$  is a measure of irregularity of a time-series. Considering an EEG time-series  $x = \{x_1, x_2, \text{etc.}\}$ ,  $S_E$  can be defined as the negative of the logarithmic conditional probability that two similar sequences of  $m$  consecutive data points will remain similar at the next point ( $m + 1$ ) (Richman and Moorman, 2000; Richman et al., 2004):  $S_E(m, r, N) = -\ln\left(\frac{C_{m+1}(r)}{C_m(r)}\right)$  where  $C_m(r) =$

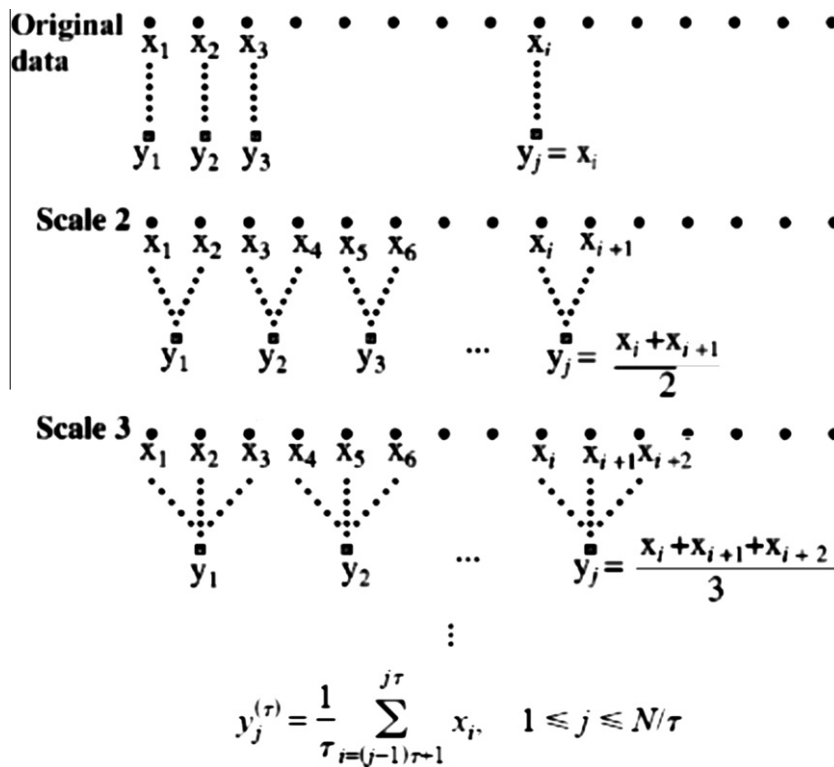


Fig. 1. Coarse graining procedure. Schematic illustration of the coarse-graining procedure. Adapted from Costa et al., 2005.

$\frac{\{\text{number of pairs}(i,j)\text{with}|x_i^m - x_j^m| < r, i \neq j\}}{\{\text{number of all probable pairs} = \frac{N(N-1)}{2}\}}$  where  $|x_i^m - x_j^m|$  denotes the distance between vectors  $x_i^m$  and  $x_j^m$ , of dimension  $m$ ,  $r$  is the tolerable distance between two vectors (in terms of fraction of the standard deviation of the time-series) and  $N$  is the length of the time-series. Therefore, for more regular series  $C_{m+1}(r) \approx C_m(r) \Rightarrow \frac{C_{m+1}(r)}{C_m(r)} \rightarrow 1 \Rightarrow S_E(m, r, N) \rightarrow 0$ . On the other hand, for completely irregular time-series  $C_{m+1}(r) \ll C_m(r) \Rightarrow \frac{C_{m+1}(r)}{C_m(r)} \ll 1 \Rightarrow S_E(m, r, N) \gg 1$ .

For MSE analysis, the original EEG time-series  $\{x_1, \dots, x_i, \dots, x_N\}$  is coarse-grained into consecutive time-series  $\{y^{(\tau)}\}$ , corresponding to the scale factor (SF)  $\tau$ : first the original time-series is divided into non-overlapping windows of length  $\tau$ , and then the data points inside each window are averaged, so each coarse-grained time-series is defined by  $y_j^{(\tau)} = (\frac{1}{\tau}) \sum_{i=(j-1)\tau+1}^{j\tau} x_i, 1 \leq j \leq \frac{N}{\tau}$ . The length of each coarse-grained sequence is  $\tau$  times shorter than the length  $N$  of the original series.  $S_E$  is calculated for each time-series  $\{y^{(\tau)}\}$ . Fig. 1 shows a schematic illustration of the coarse-graining procedure (adapted from Costa et al., 2005).

Previous studies have proved that  $S_E$  has a good statistical validity for  $m = 1$  or  $m = 2$  and  $.1 \leq r \leq .25$  times the s.d. of the time series (Lake et al., 2002; Richman et al., 2004). In this study we used  $m = 2, r = .15 \times \text{s.d.}, N = 40,000$  data points and 40 scale factors, so that for the shortest coarse-grained time-series we still have  $N/\tau = 40\,000/40 = 1000$  data points, which is enough to obtain reliable estimation of the  $S_E$  value (Richman and Moorman, 2000).

2.5. Power analysis

It is possible that differences in complexity values are correlated with differences in EEG power spectra (Takahashi et al., 2009). In order to investigate this we performed a conventional power analysis in the first 40 s of artefact free EEG data for each

participant. This analysis was performed using a built in function (pwelch) in MATLAB software (version 7.10.0). The data were divided into eight sections of equal length, each with 50% overlap. Each segment was then windowed with a Hamming window and spectral density (power/frequency) was calculated using a fast Fourier transform (FFT). Four standard band frequencies were studied: theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–40 Hz). The relative power at each frequency band was calculated as the power in each frequency band divided by total power across all frequency bands.

2.6. Statistical analysis

Statistical analyses were carried out using SPSS Statistics v17.0 software for Microsoft Windows. The alpha significance value was set at .05. To test for differences in behavioural results, a 2-way repeated-measures analysis of variance (ANOVA) was done for accuracy and response time, with group (AS vs. controls) as a between-subjects factor, and task (chair vs. face) as a within-subjects factor. In order to reduce the skewness in the distributions, response time data was transformed using a logarithmic function ( $f(x) = \ln(x)$ ) and proportional accuracy was transformed using an arcsin function ( $f(x) = \arcsin(\sqrt{x})$ ).

Distribution normality of MSE values was confirmed using the Kolmogorov–Smirnov normality test as well as by examination of skewness and kurtosis values, for each electrode and each group. To test for group differences in complexity a 4-way repeated-measures ANOVA was performed, with group (AS vs. controls) as a between-subjects factor, and task (chair vs. face), SF ( $\tau$ : 40 scales) and electrode (21 electrodes: C3, C4, Cp3, Cp4, F7, F8, Fc3, Fc4, Ft7, Ft8, P3, P4, P7, P8, T7, T8, Tp7, Tp8, Cz, Oz, Pz) as within-subjects factors. To test for group differences in EEG power spectra a 4-way repeated-measures ANOVA was used, with group as a between-subjects factor, and task, electrode and frequency band (4 frequency bands: theta, alpha, beta, gamma) as within-subjects

**Table 2**  
Accuracy (out of 10) and response times (in msec) for both tasks, for each group.

Behavioural results	Controls ( <i>n</i> = 15)		AS ( <i>n</i> = 15)	
	Mean	s.d.	Mean	s.d.
Chair task				
Accuracy (out of 10)	9.73	.59	9.60	.91
Response time (m s)	479.01	83.43	514.10	70.47
Face task				
Accuracy (out of 10)	9.73	.46	8.80	1.47
Response time (m s)	493.12	88.46	515.34	84.36

factors. The Greenhouse–Geisser adjustment was applied to the degrees of freedom for all analyses and the Bonferroni correction was applied for all post hoc tests.

### 3. Results

#### 3.1. Behavioural performance

Regarding accuracy, there was no significant group-by-task interaction ( $F_{1, 28} = 3.661, p = .066$ ) or effect of group ( $F_{1, 28} = 2.409, p = .132$ ), but there was a significant effect of task ( $F_{1, 28} = 4.898, p = .035$ ). Regarding response time, no significant effects of group ( $F_{1, 28} = 1.214, p = .280$ ) or task ( $F_{1, 28} = .606, p = .443$ ) were observed. The group-by-task interaction was also non-significant ( $F_{1, 28} = .740, p = .397$ ). Further details on the participants' accuracy and response times can be found in Table 2.

#### 3.2. MSE analysis

The results of the MSE analysis show a main effect of group in which the sample entropy was higher in the control group (mean = 1.33, s.d. = .23) than the ASC group (mean = 1.12, s.d. = .29,  $F_{1, 28} = 4.859, p = .036$ ). This was qualified by a significant group-by-scale factor interaction ( $F_{1, 936, 54.195} = 4.914, p = .012$ ). This means that collapsing across task and electrode the sample entropy curves of each group presented a different slope as the scale factor increases. Specifically, relative to the Control group, there is a decrease in the values of sample entropy in the ASC group as the scale factor increases (see Figs. 2 and 3). Hence, Figs. 2 and 3 reflect group differences in sample entropy for increasing scale factors, in each task. Although the difference between groups is not noticeable for smaller scale factors, the curves for both groups become distinguishable for higher scale factors, representing greater group differences in sample entropy at higher scale factors. It is this difference in curve profile between groups for smaller and higher scale factors that drives the significant group-by-scale factor interaction found.

The results also showed a significant main effect of task ( $F_{1, 28} = 6.719, p = .015$ ), with higher entropy associated with the faces (mean = 1.28, s.d. = .31) than the chairs task (mean = 1.17, s.d. = .29), for both groups. However, there was no significant interaction between task and participant group ( $F_{1, 28} = .067, p = .797$ ).

There was also a significant group-by-SF-by-electrode interaction ( $F_{7, 637, 213.829} = 4.262, p < .0005$ ). Although independence of measurement cannot be assumed for each electrode, this interaction was investigated further with 2-way ANOVAs (group-by-SF) for each electrode. These results are shown in Table 3. A significant group-by-SF interaction was found in electrode sites C3, C4, Cp3, Cp4, T7, T8, Tp7, Tp8, P3, P4, P7, P8, Pz and Oz, as shown in Fig. 4. After correcting for multiple statistical testing, using the Bonferroni correction ( $p_{\text{corrected}} = p_{\text{uncorrected}} \times 21$  electrodes), a significant group-by-SF interaction was still evident in electrodes Tp7,

Tp8, P7 and P4, in which entropy was lower in the ASC group at coarser time scales. The results presented in Fig. 4 represent sites where significant group-by-scale factor interactions, collapsed across tasks, were found. These arise from differences between groups in sample entropy curves profiles, i.e. significant group differences will be present when the curves for each group have different characteristics (e.g. curves that start together for both groups but have different slopes for higher scale factors, as can be seen for example in the graph for electrode T7 in Fig. 2). These should not be confused with between group differences in mean sample entropy, calculated from the average of sample entropy values across scale factors for each group.

#### 3.3. Power analysis

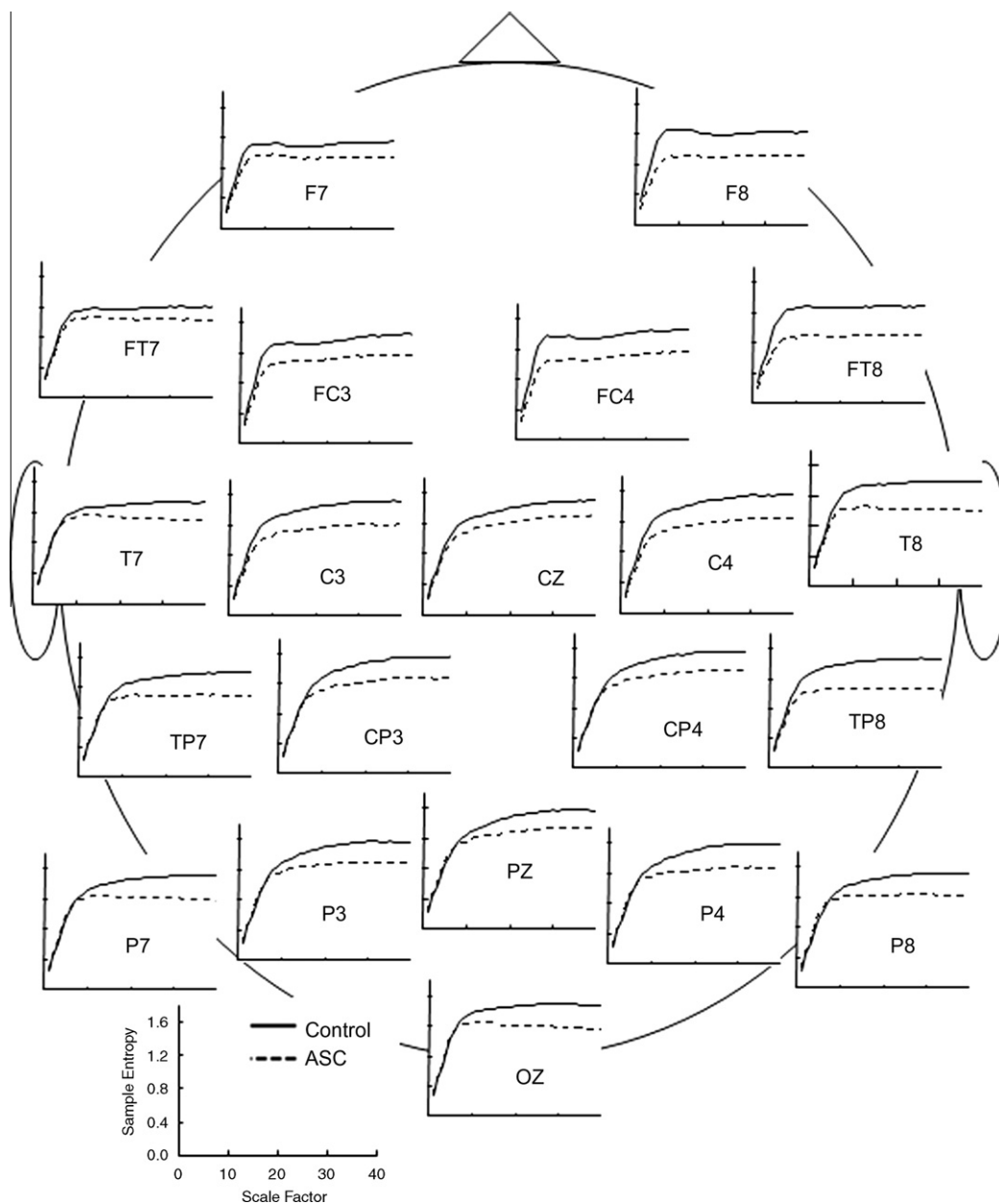
No significant effects of group ( $F_{1, 28} = 1.895, p = .180$ ) or task ( $F_{1, 28} = .082, p = .776$ ) were found. Group-by-frequency band ( $F_{1, 949, 54.584} = 1.545, p = .223$ ) and task-by-frequency band ( $F_{2, 170, 60.765} = 2.074, p = .131$ ) interactions were also not significant.

### 4. Discussion

The present study found reduced sample entropy in EEG signals acquired during a visual matching task in people with ASC, relative to controls, at higher scale factors, as indexed by the significant scale factor-by-group interaction. This difference in curve behaviour serves as an index for measuring signal complexity: systems with higher complexity will present higher values of sample entropy, sustained over increasing values of SF (Costa et al., 2002, 2005). This is because values of sample entropy sustained over increasing values of SF suggest the existence of a power-law scaling property, which is a characteristic of nonlinearity and intrinsic complexity in physiological systems (Takahashi et al., 2009). This supports the hypothesis that the complexity of electrical brain activity is reduced in people with ASC, possibly in association with relatively reduced long-range temporal correlations in brain activity (Takahashi et al., 2009) in response to the visual task employed in this study.

The lack of significant differences in EEG power spectra between groups or tasks establishes a distinction between complexity measures and power spectrum analysis; changes in complexity values are not a reflection of changes in EEG power spectra. This is in accordance with previous studies reporting the absence of abnormal patterns in EEG power spectra in individuals with ASC (Milne et al., 2009; Raymaekers et al., 2009).

ASC have long been associated with atypical patterns of neural connectivity (Belmonte et al., 2004; Courchesne and Pierce, 2005; Just et al., 2007; Barttfeld et al., 2011; Wass, 2011). Given that previous research has demonstrated that changes in local complexity may be related to brain connectivity (Friston, 1996; Sakkalis et al., 2008), we hypothesize that our findings may be associated with atypical neural connectivity in ASC. Supporting this is the work by Bosl et al. (2011), that shows a pattern of reduced EEG complexity for infants at high-risk of ASC, at early stages of brain development (6–24 months). Those authors considered that local neural connectivity, which undergoes rapid changes during early brain development, may be reflected in variation in EEG signal complexity at these early stages, and suggest the possibility of EEG complexity being used in the future as a biomarker for ASC risk. Our results can be considered complementary to those reported by Bosl et al. (2011). Whilst their findings indicated decreased complexity in resting state EEG in infants at risk of developing autism, (by virtue of having an older sibling with a diagnosis of autism), in the current study we demonstrate the presence of reduced EEG complexity in adults with a confirmed diagnosis of ASC, relative to

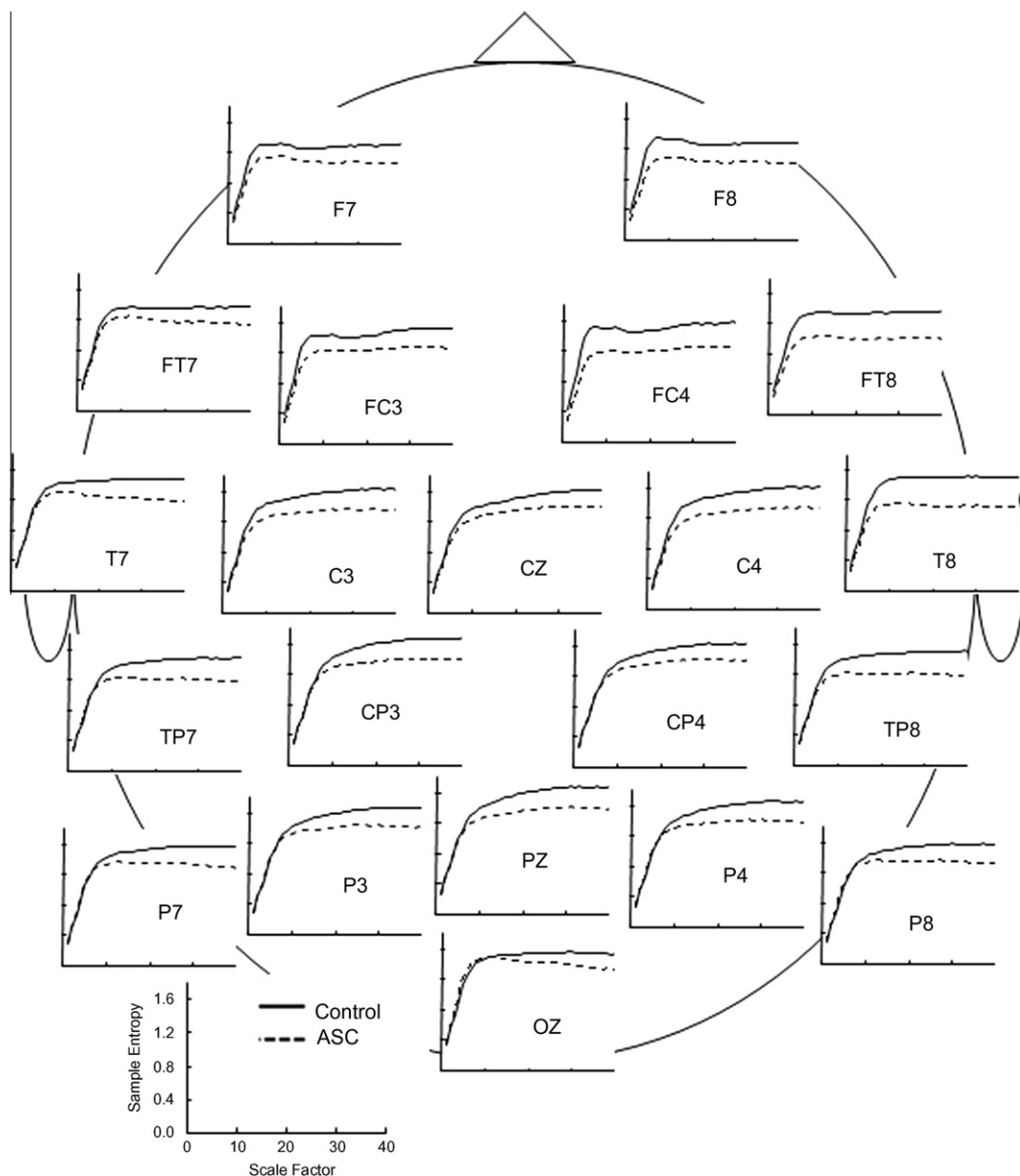


**Fig. 2.** Group differences in the chair task. Sample entropy by scale factor (SF) graphs for the chair task, for each electrode, for each group (full line – Control group, dashed line – ASC group).

typical controls, supporting the hypothesis that EEG complexity, as an index for neural processing of information and neural connectivity, is sensitive to the presence of an autistic condition.

Electrical activity measured in a single scalp electrode may not have its origin in the cortex area directly underneath the electrode (Picton et al., 2000), so it is not possible to localize the differences observed as arising from any specific regions. Nevertheless, in the current study post hoc analysis of the significant group-by-scale factor-by-electrode interaction suggests that the differences between groups are more evident in temporo-parietal and occipital regions of the cortex (see Fig. 4). These posterior areas are known to subserve integrative functions during the processing of visual information (Belmonte et al., 2004). These results are also in accordance with functional imaging studies of visuospatial processing in ASC, where differences have been found between ASC and controls in the temporo-parietal junction and occipital regions of the cortex (Di Martino and Castellanos, 2003; Billington et al., 2008; Sahyoun

et al., 2010). In addition, the observation from an earlier ERP analysis of EEG data which included the data employed in the current study, that the N170 ERP face response in posterior sites (P7 and P8) was less modulated by attention in the participants with ASC than in a neurotypical control group (Churches et al., 2010), is compatible with the suggestion that the current MSE results may reflect a decrease in integrative capacity in the participants with ASC. It is of interest to note that Bosl et al. (2011), who compared resting state EEG complexity of infants at high risk and low risk of ASC, reported a pattern of reduced complexity for infants at high-risk of ASC particularly in frontal regions of the brain. This is in contrast to our own findings, in which group differences in EEG complexity measured during performance of a visual matching task likely to involve temporo-parietal brain regions (Corbetta et al., 1993; Schultz et al., 2000; Deffke et al., 2007) were greater in posterior brain regions. This suggests that EEG complexity, as indexed by MSE measures, may be a marker for local disturbances in



**Fig. 3.** Group differences in the face task. Sample entropy by scale factor (SF) graphs for the face task, for each electrode, for each group (full line – Control group, dashed line – ASC group).

task-specific processing of information as well as for more non-specific associations of pervasive developmental disorders.

As well as potentially reflecting task-related neuronal activity, our results suggest the possibility that MSE may also be sensitive to how demanding a task is. In support of this proposition, it was noted that the face task was performed, across both groups, a little less accurately than the chair task, whilst at the same time, although overall entropy levels were lower in the ASC group, the analysis revealed an increase in complexity of the EEG signal for the face task relative to the chair task across both the participant groups. It is therefore possible that the decreased accuracy observed reflected increased difficulty in the face task compared to the chair task and that the increased MSE during performance of the face task was a reflection of brain response to greater task demands associated with attending to faces compared to non-face objects. It should be noted however that this possible interpretation of our facts is speculative, and limited by the absence of a direct correlation between MSE indices and behavioural task

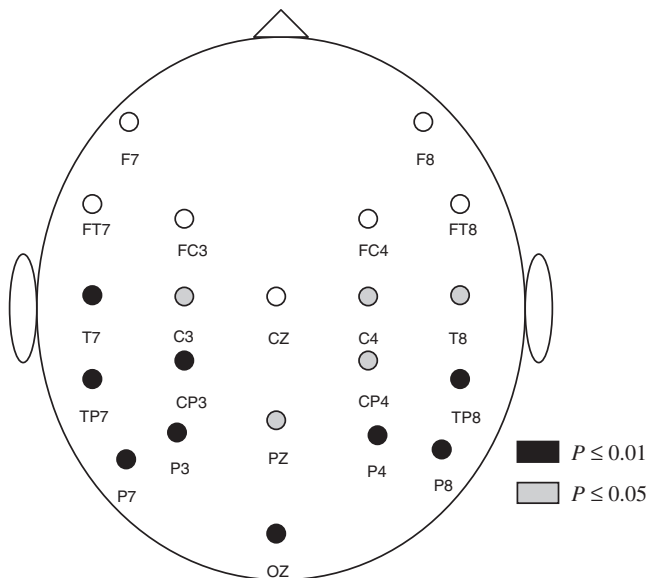
performance as well as confounded by the nature of the tasks, in that while both required visual matching, the more 'difficult' task involved faces whilst the easier task involved chairs. In addition, we do not have subjective ratings of the perceived difficulty of the two tasks by the participants. All these issues should be explored during future research in this topic. However, the proposition is in line with the conclusion reported by Takahashi et al. (2009), who interpreted higher MSE values following photic stimulation in their healthy younger participants as reflecting the cortical response to the stimuli, and the decrease in MSE values for the elderly group as representative of an attenuated cortical response to photic stimulation. Thus, whilst those with ASC manifest overall lower entropy than the Control group, this group difference was not differentially modulated by the precise nature of the visual task and the ASC group, like the controls, responded to the faces with an increase in EEG complexity. A possible implication of these results is that the widely recognised atypical social and communication behaviour that characterise ASC are not the result of isolated

**Table 3**

Group-by-SF interaction significance values for each electrode site. Electrode sites in bold showed a significant ( $p \leq .05$ ) group-by-SF interaction.

Group-by-SF anova Electrode	Group-by-SF interaction
C3	$F_{1,982, 55.502} = 4.432; p = .017$
C4	$F_{1,799, 50.360} = 3.629; p = .038$
Cp3	$F_{1,832, 51.293} = 6.405; p = .004$
Cp4	$F_{1,675, 46.897} = 5.071; p = .014$
F7	$F_{2,465, 69.023} = 1.060; p = .363$
F8	$F_{2,174, 60.870} = 1.160; p = .323$
Fc3	$F_{2,306, 64.560} = 1.467; p = .237$
Fc4	$F_{2,207, 61.805} = 1.730; p = .183$
Ft7	$F_{2,265, 63.432} = 1.267; p = .291$
Ft8	$F_{1,915, 53.609} = 3.085; p = .056$
P3	$F_{1,692, 47.378} = 6.047; p = .007$
P4	$F_{1,641, 45.941} = 8.268; p = .002^a$
P7	$F_{1,997, 55.927} = 7.748; p = .001^a$
P8	$F_{1,659, 46.445} = 6.844; p = .004$
T7	$F_{2,246, 62.875} = 4.806; p = .009$
T8	$F_{1,742, 48.780} = 5.028; p = .013$
Tp7	$F_{2,234, 62.542} = 8.217; p < .0005^a$
Tp8	$F_{2,092, 58.584} = 6.930; p = .002^a$
Cz	$F_{1,873, 52.452} = 2.153; p = .129$
Pz	$F_{1,579, 44.206} = 5.691; p = .010$
Oz	$F_{1,756, 49.158} = 5.843; p = .007$

<sup>a</sup> These electrode sites showed a significant ( $p \leq .05$ ) group-by-SF interaction after Bonferroni correction ( $p_{\text{corrected}} = p_{\text{uncorrected}} \times 21$  electrode sites).



**Fig. 4.** Group-by-scale factor interaction. Electrodes that presented a significant group-by-scale factor (SF) interaction. For electrode sites shaded gray, the group-by-SF interaction had significance values  $p \leq .05$ , whilst for electrode sites shaded black, significance values for this interaction were  $p \leq .01$ . Electrode sites Tp7, P7, Tp8 and P4 presented significant ( $p \leq .05$ ) group-by-SF interaction after being subject to Bonferroni correction ( $p_{\text{corrected}} = p_{\text{uncorrected}} \times 21$  electrode sites).

disturbances in selective brain functions. Rather, they may reflect an overall change in brain functioning but, since social, emotional and language functions make greater demands on neural networks and on relationships between neural networks (Minshew and Williams, 2007), these behaviours may be particularly vulnerable to deficits in integrative capacity.

Considering the methods employed in this study, there are several approaches used to examine auto-correlations in complex physiological time series including the Hurst exponent (Lai et al.,

2010), power spectral density analysis, the rate of moment convergence and multiscale entropy methods. In a comparison of these four approaches Crevecoeur et al. (2010) concluded that MSE was the most appropriate method for examining long-range correlations in time series with more than 512 points and in the current study we examined time series comprising a total of 40,000, with a minimum of 1000 points for the shortest coarse-grained time-series. We suggest that future MSE studies of EEG data in ASC should also use resting state EEG data. Although some MSE studies have investigated physiological complexity in resting conditions (Escudero et al., 2006; Hornero et al., 2009; Takahashi et al., 2010), others have employed activation or stressor tasks to explore complexity responses to stimuli or clinical process of interest (Takahashi et al., 2009; Sitges et al., 2010). Whilst there have been no MSE studies so far analysing resting state EEG from adults with a confirmed diagnosis of ASC, our results, together with those of Bosl et al. (2011), seem to suggest that the pattern of group differences observed in the current study is related to the fact that we recorded EEG signal during a visual task. If future studies confirm MSE measures as indexing task-specific patterns of EEG complexity, this might provide a new tool for the investigation of the temporal organization of neural networks subserving specific cognitive processes, and their possible perturbation in neurocognitive disorders.

## 5. Conclusions

Overall, our results show a significant difference in complexity between the ASC and the Control group. Particularly, our results show that there is a decrease in EEG complexity in the ASC group, when compared to the Control group, in occipital and parietal regions of the cortex. This supports the model of an inherent alteration in neuronal integration in people with ASC, in response to a visual matching task, which may be associated with relatively reduced long-range temporal correlations in EEG and atypical neural connectivity in people with ASC.

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