Altered electroencephalogram complexity in autistic children shown by the multiscale entropy approach

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Autism spectrum disorder (ASD) is a severe neurodevelopment disorder. This study tests the hypothesis that children with ASD show atypical intrinsic complexity of brain activity. Electroencephalogram data were collected from boys with ASD and matching normal typically developing children while performing an observation and an imitation task. The multiscale entropy was estimated within the 0.5–30 Hz frequency band over 30 time scales using a coarse-grained procedure. A decreased electroencephalogram complexity was observed in the ASD children both during the observation and during the imitation tasks. On comparing the two tasks, significant differences were observed between groups in the right hemisphere, and also the central cortex for the observation task. Multiscale entropy could provide further evidence of the relationship between ASD and cerebral dysfunction.

Introduction

Autism spectrum disorder (ASD) is a severe neurodevelopmental disorder that begins at birth or within the first 2.5 years of life [1]. Most autistic children are characterized by deficits in communicative and social skills such as imitation, empathy, and shared attention, as well as restricted interests and repetitive patterns of behaviors [1]. The exact cause of autism is still unknown, although many studies have noted differences in the structure and function of brains of individuals with autism [2].

There is a growing consensus to suggest that ASD is associated with dysfunction of the brain, perhaps because of a functional deficit of the frontal mirror neuron system (MNS) [3], and a functional disconnect between brain regions or a functional deficit of the anterior cingulate cortex [4]. MNSs are primarily considered to be involved in comprehension and perception of motor actions, but they may also play a critical role in higher order cognitive processes such as the theory of the mind, imitation, empathy, and language [5]. Previous studies have found that individuals with ASD may have MNS impairments and dysfunction of the MNS that may lead to impaired self-other representations and imitation [3]. In addition, several pieces of evidence have also shown that ASD may

NeuroReport 28:169–173 Copyright © 2017 The Author(s).
Published by Wolters Kluwer Health, Inc.

NeuroReport 2017, 28:169–173

Keywords: autism spectrum disorder, complexity, electroencephalogram, multiscale entropy

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Received 21 November 2016 accepted 28 November 2016

be related to weak functional connectivity between remote brain regions, and an overabundance of functional connectivity within local cortical regions [6]. Although these recent developments have linked the key symptoms observed in ASD to a function defect of MNS and lack of integration between brain regions, further in-depth research is still required into the complex patterns of brain activity in heterogeneous samples.

The human brain is a complex nonlinear system, and its activity shows complex fluctuations, both in the spatial and in temporal domains. Computational and empirical studies have indicated that variations in functional connectivity may reflect specific cognitive and perceptual states and include the integration of information across detailed regions of the brain. The reciprocity of integration and functional regions can be quantified in particular in terms of neural complexity [7]; thus, it has been speculated that disconnections in the brain are associated with an increase in complexity. An unnatural level of complexity in neurophysiologic signals may represent an abnormal neural connectivity pattern in mental disorders [7]. Therefore, multiscale signal complexity can thus provide some indication of connectivity [8]. Over the past few decades, novel nonlinear approaches on the basis of entropy have been used widely to measure the complexity of physiological signals, including electroencephalogram (EEG) signal [9] and ECG signals [10]. Given its fine temporal resolution, low cost, and easy operation, EEG is particularly suitable for investigating

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inherently complex biological signals arising from brain systems.

Approximate entropy (ApEn) and sample entropy (SampEn) are two traditional methods of measuring complexity, which determine the probability of finding specific patterns or resemblance between time series to examine the irregularity or the predictability of one particular time series [11]. However, there is a limitation in the scope of traditional methods as they can only analyze short-range temporal dynamics. To address this limitation, Costa *et al.* [12,13] proposed multiscale entropy (MSE) as an extension of SampEn, which quantifies the complexity of physiological signals by measuring the entropy across multiple time scales using a coarse-graining procedure. This extension to larger temporal scales can be used to reflect information in long-range temporal dynamics [11]. An atypical MSE pattern could indicate disease conditions in the brain and provide useful information on the network controlling mechanisms underlying the physiological dynamics [13]. Because of these advantages, the MSE method has been used widely in the study of mental disorders. Mizuno *et al.* [11] has reported an increase in complexity at larger scale factors (SFs) in Alzheimer's disease, but the complexity is significantly reduced over smaller scales. An MSE study of drug-naïve schizophrenia has found elevated complexity at higher time scales in the centrottemporal region [8]. Some researchers have also found an association between autism disease and a significantly decreased MSE complexity [14,15]. Therefore, research into this complexity is vital to determine the intrinsically dynamic principles in the human brain.

To characterize the complexity pattern of brain function of ASD and the control samples, we collected the EEG of all participants during the performance of observation and imitation tasks. To test the hypothesis that children with ASD would show atypical intrinsic complexity of brain activity, we calculated and compared the MSE of the EEG activity during the designed tasks.

Participants and methods

Participants

The study included 20 outpatient boys diagnosed with ASD (age range, 5–8 years; 6.5 ± 1.17 years; right-handed) and 20 age-matched and sex-matched normal control children (age range, 5–10 years; 7.5 ± 1.98 years; right-handed). All participants had full-scale and verbal IQ scores above 70 (WISC-IV). All participants' parents filled out the Symptoms Autism Diagnostic Observational Scale and the Autism Diagnostic Interview – Revised. An experienced child psychiatrist and a health care psychologist made the diagnosis of age of childhood onset. The criteria for ASD included the following: (i) being within the scale's diagnostic boundaries; (ii) no history of stimulant medication usage, severe brain injury, or other neuropsychiatric disorders; and (iii) able to cooperate with the

EEG data acquisition process. Normal controls were excluded if they were diagnosed with ASD or they had a history of using stimulant medication, a severe brain injury, other neuropsychiatric disorders, cognitive deficits, learning disabilities, or communication problems.

Task description

The experimental procedure used for this research was based on the experimental program of Oberman *et al.* [16] and included the following: (i) Observation tasks: watching a video of a moving hand. The participants viewed a black-and-white video of an individual opening and closing their right hand with their fingers and thumb held straight. The video was 80 s in length and moved at a rate of 1 Hz, and the distance between the participants and the monitor was 85 cm; (ii) Imitation tasks: moving their own hand. Participants were asked to imitate the video action 80 times at a rate of ~ 1 Hz and to maintain this action throughout the duration of the task. Their hands were held at eye level and at a comfortable viewing distance. To ensure that participants paid attention to the video stimuli while watching the hand movement video, they were asked to count the number of times the stimulus occurred and report this number at the end of the experiment. All conditions were presented twice to obtain enough clean EEG data for analyses.

Electroencephalogram data acquisition and recording

EEGs were recorded from 18 electrodes at the following scalp locations of the 10–20 system: FP1, FP2, F3, FZ, F4, F7, F8, FT7, FT8, T7, T8, C3, C4, CZ, P3, P4, O1, and O2 (Neuroscan; Compumedics Limited, Charlotte, North Carolina, USA). The electrode impedance was below 5 k Ω . A reference electrode was placed at the left mastoid and a ground electrode was placed between Fpz and Fz. The vertical electrooculogram was recorded from electrodes attached above and below the left eye, and the horizontal electrooculogram was recorded from the outer canthi of both eyes. The EEG was sampled at 24 bits of accuracy and an analogue/digital sampling rate of 1000 Hz. All participants were seated inside an acoustically and electromagnetically shielded room and were asked to minimize all movement during the experiments. Thirty seconds (30 000 samples, continuous data) of artifact-free data (no ocular or muscular artifacts) were selected off-line from the results obtained from each participant. Filter analysis (FIR bandpass filter) was carried out on every EEG data segment, and the MSE was calculated across the 0.5–30 Hz frequency band for each participant.

Multiscale entropy

The MSE method was developed by Costa *et al.* [12,13] and can be used to quantify the complexity of a signal by calculating the SampEn over multiple temporal scales, which is realized by a coarse-grained procedure. The ApEn was proposed by Pincus [17]. SampEn measures

the regularity of a time series and is a modified version of ApEn [18].

Given a one-dimensional EEG discrete time series $x = [x_1, \dots, x_N]$ and SF τ , the time series is calculated for consecutive and nonoverlapping time series y^τ using a coarse-grained procedure: $y^\tau = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i$, $1 \leq j \leq N/\tau$. The

first scale is simply the original time series representing the short-range temporal scale and the larger SFs represent longer temporal scales. SampEn is calculated for each series y^τ and is defined as the negative value of the logarithmic condition probability that two similar sequences of m consecutive data points will remain similar at the next point ($m+1$) [14,17]: $\text{SampEn}(m, r, N) = -\ln [C^{m+1}(r)/C^m]$, where $C^m = [\text{number of pairs } (i, j) \text{ with } |x_i^m - x_j^m| < r, i \neq j] / [\text{number of all probable pairs} = (N-m+1)/(N-m)]$, where $|x_i^m - x_j^m|$ denotes the distance between vectors x_i^m and x_j^m , m is the dimension of the vectors x_i^m and x_j^m , r is the tolerable distance between the two vectors, and N represents the length of the time series. When $m=1$ or $m=2$ and r is between 0.1 and 0.25 times, the SD of the time series has the best statistical validity [17]. In this study, we used the parameters $m=2$, $r=0.15 \times \text{SD}$, $N=30\,000$ data points, and we set the SF to 30. After the coarse-grained procedure, there are still $30\,000/30=1000$ data points, which have been shown to be enough to obtain a reliable estimation of the SampEn value.

Statistical analysis

The statistical analysis was carried out using SPSS 13.0 (SPSS Inc., Chicago, Illinois, USA) for Windows. A Kolmogorov–Smirnov normality test was used to confirm the normal distribution of MSE values for every group and every channel. Mauchly's test of sphericity was used to test whether the data were appropriate for the analysis of variance (ANOVA) or whether a data correction is needed, and then the Greenhouse–Geisser adjustment was applied to each degree of freedom for all of the analyses. The significance value was set as P less than 0.05 for the repeated ANOVA. For the MSE analysis, we applied a four-way repeated-measure ANOVA to test the differences in the two groups (ASD vs. control) in terms of the between-participants factor, the SF ($\tau=30$), the tasks (observation and imitation task) as well as the channels (FP1, FP2, F3, FZ, F4, F7, F8, T7, T8, FT7, FT8, CZ, C3, C4, P3, P4, O1, O2) as well as the within-participants factors. For every task, we then tested the differences in the two groups (ASD vs. control) in terms of the between-participants factor, and SF ($\tau=30$), and the channels (FP1, FP2, F3, FZ, F4, F7, F8, T7, T8, FT7, FT8, CZ, C3, C4, P3, P4, O1, O2) as well as the within-participants factors. For every electrode, ANOVA was then repeatedly measured for the two groups (ASD

vs. control) for the between-participant factor and SF ($\tau=30$) as well as the within-participant factor.

Results

The MSE results showed a significant main effect of group difference ($F_{1,16}=8.426$, $P=0.011$) for the four-way ANOVA. The mean SampEn value of the ASD group (mean=1.324, SD=0.044) was significantly lower than that of the normal control group (mean=1.491, SD=0.037).

The results also showed group-by-SF-by-channel interactions. The group-by-SF interaction was further explored using two-way ANOVA for each channel for the two tasks. The results are shown in Table 1 and Fig. 1. For the observation task, a significant group-by-SF interaction was found in C3, C4, CZ, P3, P4, O1, O2, F3, F8, FT8, and T8, where the ASD group was significantly lower than the control group. For the imitation task, a significant group-by-SF interaction was only found in C3, P3, T8, and O1, where the ASD group was significantly lower than the control group.

Discussion

MSE can characterize the complexity of a physiological signal at multiple temporal scales using a coarse-graining procedure [12,13]. As such, MSE can measure the inherent complexity of signal dynamics [11]. An atypical MSE pattern may reflect a disease condition of the brain and can be used as a reliable index of some mental disorders, such as Alzheimer's [11] and schizophrenia [8]. Similarly, more recent studies have applied MSE to investigate the complexity of electrical brain activity in autism. Bosl *et al.* [15] was the first to find a pattern of reduced complexity for infants at high risk of autism,

Table 1 Group-by-scale factor interaction significance values (autism spectrum disorder vs. control) for each channel in the observation and imitation tasks

Channels	Group-by-scale factor interaction	
	Observation task	Imitation task
C3	$F_{1,16}=6.573$, $P=0.022^*$	$F_{1,16}=5.878$, $P=0.028^*$
C4	$F_{1,16}=14.417$, $P=0.002^{**}$	$F_{1,16}=2.367$, $P=0.145$
Cz	$F_{1,16}=8.189$, $P=0.01^*$	$F_{1,16}=2.691$, $P=0.122$
F3	$F_{1,16}=6.165$, $P=0.025^*$	$F_{1,16}=3.579$, $P=0.078$
F4	$F_{1,16}=1.797$, $P=0.200$	$F_{1,16}=2.340$, $P=0.147$
F7	$F_{1,16}=2.688$, $P=0.122$	$F_{1,16}=0.237$, $P=0.634$
F8	$F_{1,16}=7.917$, $P=0.013^*$	$F_{1,16}=4.089$, $P=0.061$
FT7	$F_{1,16}=2.382$, $P=0.144$	$F_{1,16}=0.222$, $P=0.644$
FT8	$F_{1,16}=6.939$, $P=0.019^*$	$F_{1,16}=4.268$, $P=0.057$
FP1	$F_{1,16}=3.345$, $P=0.087$	$F_{1,16}=1.614$, $P=0.223$
FP2	$F_{1,16}=1.156$, $P=0.299$	$F_{1,16}=3.873$, $P=0.068$
FZ	$F_{1,16}=2.859$, $P=0.112$	$F_{1,16}=3.937$, $P=0.066$
O1	$F_{1,16}=13.854$, $P=0.002^{**}$	$F_{1,16}=6.897$, $P=0.019^*$
O2	$F_{1,16}=16.998$, $P=0.001^{**}$	$F_{1,16}=4.253$, $P=0.057$
P3	$F_{1,16}=8.634$, $P=0.010^*$	$F_{1,16}=7.034$, $P=0.018^*$
P4	$F_{1,16}=21.577$, $P=0.001^{**}$	$F_{1,16}=3.810$, $P=0.070$
T7	$F_{1,16}=1.975$, $P=0.180$	$F_{1,16}=0.176$, $P=0.681$
T8	$F_{1,16}=12.427$, $P=0.003^{**}$	$F_{1,16}=12.668$, $P=0.003^{**}$

* $P < 0.05$.

** $P < 0.01$.

Fig. 1

Group-by-scale factor interaction significance values (autism spectrum disorder vs. control) for each channel in the observation and imitation tasks. The gray solid circle indicates $P < 0.05$.

particularly in the frontal regions of the brain. Catarino *et al.* [14] then further reported a reduction of EEG signal complexity within the temporoparietal and occipital regions in an autistic group during a visual matching task. Ghanbari *et al.* [19] then showed lower complexity in ASD in the frontal regions in the delta band and the occipital-parietal regions in the alpha band. This study also found notably descended EEG SampEn in individuals with autism during both observation tasks and imitation tasks, which was in agreement with other previous complexity studies of ASD. As previous research has shown that changes in local complexity may be associated with atypical neural connectivity [19,20] and that these atypical patterns are related to autism [21,22], EEG complexity can be used as a sensitive method for distinguishing early symptoms of autism as an index for neural processing of information and neural connectivity.

In the current study, a significant group-by-SF-by-electrode interaction suggests that compared with the imitation task, the observation task results in evidently reduced MSE for more regions of the cortex, especially in the right hemisphere and the central brain regions. Although an atypical structural [23] and functional [24] asymmetry phenomenon has been observed in ASD patients, further investigation is needed to determine what this precisely reflects. A previous study discovered that atypical hemispheric asymmetries shift toward the right hemisphere in the ASD group in the visual, auditory, motor, executive, language, and attentional networks, suggesting that atypical asymmetry might be a

pervasive feature of functional brain organization in ASD [25]. Our results should be considered to be complementary to this previous research.

Moreover, the complexity of the two groups showed significant differences in the central regions during the observation task, but no statistical difference in most of the central regions during the imitation task. These findings were consistent with the study by Oberman *et al.* [16], who found that the ASD group showed significant μ -suppression during self-performed hand movements, but not while observing hand movements in the central regions. Mirror neurons are a kind of sensory-motor neurons. Its typical feature is that the MNS is activated in the observation and interpretation of movements by others [16]. Cook *et al.* [26] reported that mirror neurons play a key role in understanding the movement of others, which is especially important for social skills. Interestingly, the primary sensorimotor cortices are located in the central brain region. Thus, the present study infers that the lower complexity in the ASD group during the observation task in the central regions is indicative of a possible dysfunction in the MNS in patients with ASD. Furthermore, the lack of a statistical difference in complexity during the imitation task between the two groups suggests normal functioning of other motor systems involved in self-performed actions in the ASD group. The growing consensus indicates that a dysfunction in the MNS early in development could result in a cascade of impairments that are characteristic of ASD [27], such as deficits in imitation, language, theory of mind, empathy,

and social communication. Given that ASD is defined by behavioral deficits in many of these areas, the results of this study provide evidence that the altered complexity in central brain regions during observation tasks may contribute toward the behavioral deficits in children with ASD.

In this study, we explored the MSE method to analyze the EEG signals of children with and without ASD during an observation task and an imitation task. The results of this study showed an altered complexity pattern for ASD children compared with normal controls for both tasks. In addition, compared with the imitation task, the complexity of the ASD group in the right hemisphere and the central cortex regions showed a significant decline during the observation task. These findings, which were consistent with previous ASD studies, provide further evidence of the relationship between ASD and cerebral dysfunction.

Acknowledgements

The authors would like to thank the following funding organizations for support: the National Natural Science Foundation of China (Grant 61503295), the China Postdoctoral Science Foundation (Grant 2015M570840), the Natural Science Foundation of Shaanxi Province (Grant 2015JQ8318), and the Science and Technology Project of Guangdong Province (Grant 2014A020215032).

Tian Liu: conceived and designed the experiments, carried out the data analysis, and wrote the manuscript; Yanni Chen: conducted the experiments; Desheng Chen: contributed materials and analysis tools; Chenxi Li: analyzed the data; Yusheng Qiu: revised the manuscript; Jue Wang: approved the final version.

Conflicts of interest

There are no conflicts of interest.

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