



Research report

Complexity analysis of brain activity in attention-deficit/hyperactivity disorder: A multiscale entropy analysis

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ABSTRACT

The multiscale entropy (MSE) is a novel method for quantifying the intrinsic dynamical complexity of physiological systems over several scales. To evaluate this method as a promising way to explore the neural mechanisms in ADHD, we calculated the MSE in EEG activity during the designed task. EEG data were collected from 13 outpatient boys with a confirmed diagnosis of ADHD and 13 age- and gender-matched normal control children during their doing multi-source interference task (MSIT). We estimated the MSE by calculating the sample entropy values of delta, theta, alpha and beta frequency bands over twenty time scales using coarse-grained procedure. The results showed increased complexity of EEG data in delta and theta frequency bands and decreased complexity in alpha frequency bands in ADHD children. The findings of this study revealed aberrant neural connectivity of kids with ADHD during interference task. The results showed that MSE method may be a new index to identify and understand the neural mechanism of ADHD.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with cardinal signs of inattention, impulsivity, and hyperactivity. About 5–8% of children are estimated to meet the diagnosis of ADHD worldwide (Bush, 2010). And ADHD is 2.3 times more common in boys than girls (Bauermeister et al., 2007). ADHD children are at high risk of having learning disability and delinquency problems, which is a huge burden to the society, family and the children (Konrad and Eickhoff, 2010).

Various sources have been used to illustrate that ADHD is associated with an atypical neurodevelopmental process, including neuroimaging, neuropsychological, genetics and neurochemical (Bush, 2010). Structural magnetic resonance imaging (sMRI) studies in ADHD children have observed abnormalities in late developing fronto-striatal, fronto-temporo-parietal and fronto-cerebellar network (Cubillo et al., 2012). Similar to that, functional magnetic resonance imaging (fMRI) studies have provided plenty of

evidences on prefrontal cortex dysfunction (Smith et al., 2008), dorsal anterior midcingulate cortex (daMCC) abnormal (Bush, 2009), parietal cortex underactivated (Tamm et al., 2006), cerebellum dysfunction (Durstun et al., 2007), and abnormal activation of stratum (Scheres et al., 2007). These findings offered ample demonstrations that ADHD is related to disconnection and dysfunctions of brains. The human brain is a complex nonlinear system. Its activity exhibits complex fluctuations, both in spatial and temporal (Takahashi et al., 2009).

Electroencephalogram (EEG) is the recording of electrical activity of the brain along the scalp, and it is believed to have the finest temporal resolution. With its easy operation and low cost, EEG is particularly suitable for investigating inherently complex biological signals arising from brain systems. Earlier EEG studies revealed the differences between children with ADHD and normal controls. Willis et al. demonstrated theta activity was increased while alpha and beta activities were decreased in ADHD (Willis and Weiler, 2005). Meanwhile, the increased theta/beta power ratio (TBR) was reported as a meaningful EEG feature of ADHD (Barry et al., 2003). However, Arns et al. concluded from their meta-analysis that the TBR cannot be considered as a reliable diagnostic measure for ADHD (Arns et al., 2012). The inconsistent research conclusions might come from the power analysis's internal deficit of being influenced

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by noise from outside and inside body easily, i.e., EOG, MEG, the machine itself and so on. Therefore, only power analysis can hardly reveal the inherent neural mechanism of ADHD.

Over the past decades, novel nonlinear approached based on entropy have been widely used to measure the complexity of physiological signal, including EEG signal (Fernández et al., 2013), electrocardiographic (ECG) (Šliupaitė et al., 2015) and biological codes (Costa et al., 2005). Approximate entropy calculates the probability of new mode emerging in the signal along with the changing to evaluate the system complexity (Pincus and Huang, 1992; Richman et al., 2004). The sample entropy is more accurate to measure the probability of newly emerged mode, which is an advanced method of approximate entropy algorithm (Pincus and Huang, 1992; Richman et al., 2004). These traditional methods determine the probability of finding specific patterns or resemblance in a time series, thereby examine the irregularity or predictability in only one time series (Mizuno et al., 2010). Although widely used, the two methods are limited in their scope to only short-range temporal dynamics (Costa et al., 2005). Costa et al. proposed Multiscale entropy (MSE) as an extension of sample entropy, quantifying the complexity of physiological signal by measuring the entropy across multiple time scales by coarse-graining procedure (Costa et al., 2005, 2002). This extension to larger temporal scales may reflect information of long-range temporal dynamics (Mizuno et al., 2010). The atypical MSE pattern may reflect disease condition of the brain and provide useful information into the network controlling mechanisms underlying physiological dynamics (Costa et al., 2002). Due to those advantages above, MSE method has been widely used on studies of mental disorders. Tomoyuki et al. demonstrated the complexity increased at larger scales factors in Alzheimer's but significantly reduced over smaller scales (Mizuno et al., 2010). Autism disease has been associated with significantly decreased MSE complexity (Catarino et al., 2011). And MSE study of drug-naïve schizophrenia found elevated complexity at higher time scales in centro-temporal (Takahashi et al., 2010). It has been successfully employed as a useful biomarker for early detection of risk for autism spectrum disorder abnormalities in infants' cognitive development (Catarino et al., 2011; Bosl et al., 2011). And also, atypical cortical dynamics in schizophrenia was found to be easily characterized and understood by MSE analytic method. (Takahashi et al., 2010).

To characterize the complexity pattern of brain function of ADHD and Control, we tested the subjects' attention related performance using multi-source interference task (MSIT) (Bush et al., 2003). The multi-source interference task (MSIT) combines multiple dimensions of cognitive interference in a single task (i.e., Stroop tasks, Eriksen Flanker-type tasks, and Simon effect task variants) (Bush and Shin, 2006). It is known as an effective way to activate the network of brain regions involving attention and cognitive control with decision-making, target detection, response selection, stimulus/response competition and so on (Bush and Shin, 2006). Various studies using MSIT have been reported in patients with ADHD (Matsubara et al., 2014; Nakashima et al., 2014); for instance, children with ADHD showed abnormal prefrontal activation in response to multiple interference control (Nakashima et al., 2014).

In the present study, first, our aim was to investigate the MSE pattern of EEG in a population of ADHD children and healthy control subjects. We hypothesize that ADHD group will present significantly changed MSE pattern compared to control group. Second, we conduct a traditional power analysis and try to explore relevancy between MSE and power spectrum at different frequencies. To test this hypothesis, EEG was used to calculate the complexity and power spectrum of children with ADHD and normal Control during the MSIT performance.

2. Materials and methods

2.1. Participants

EEG data were collected from 13 outpatient boys with a confirmed diagnosis of ADHD (age range, 6–13 years; mean age, 8.5 ± 3.17 years; mean IQ score, 93 ± 16.8) and 13 age- and gender-matched healthy control children (age range, 6–13 years; mean age, 7.9 ± 1.98 years; mean IQ score, 98 ± 18.3). All the participants are right handed. According to the Declaration of Helsinki, all parents of participants were informed with written consent. The study was approved by ethics committees of Xi'an Jiaotong University School of Medicine. All participants were given full-scale and verbal IQ test with scores >80 (Wechsler Intelligence Scale for Children, Fourth Edition). All the 26 parents filled translated versions of the Conner's Parent Rating Scales-Revised and the ADHD Rating Scale-VI for current and childhood-onset ADHD symptoms. The ADHD Rating Scale-IV is linked directly to the diagnostic criteria for ADHD of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (Dupaul et al., 2006), which has been widely used as a reliable method to diagnose ADHD (Konrad et al., 2012; Uddin et al., 2008). ADHD group had higher DSM-IV scores (mean, 13.23 ± 3.22) than that of typical control group (mean, 5.23 ± 2.09) ($P < 0.01$). Subjects with higher DSM-IV scores suffer from more serious ADHD. The ADHD children were included if they had (1) ≥ 6 of 9 DSM-IV symptoms of inattention as well as ≥ 6 of 9 symptoms of hyperactivity/impulsivity; (2) no record of brain injuries, medical history, and other neuropsychiatric disorders; and (3) no signs of cognitive deficit, learning disabilities, as well as communication problems. Exclusion criteria for normal control group were the same, and also they do not have ADHD disease or have individuals in their families.

2.2. Task description

The multi-source interference task (MSIT) is believed to have the ability activating the cingulo-fronto-parietal (CFP) network (Stroop, 1935). The MSIT task is designed using system STIM2 provided by Neuroscan company. The operation is practicable for the both groups and can be finished within 15 min. Subjects were given a button with two keys, of which the left one and right one respectively represented the number 1 and 2. In this study, the interference trials were included only. In the trials, there are 3 numbers on the screen combined by 1 and 2, the total set of the number combinations are 112, 212, 221 and 211. During the interference task, subjects were instructed to use the index and middle finger of right hand to respond to the target number among the three, the target numbers were never placed congruently with their button box (Stroop effect (Eriksen and Eriksen, 1974)), and the Flanker stimuli (Bush and Shin., 2006) were always potential target. One example of the stimuli in a single trial is shown in Fig. 1. Before the experiment, each subject underwent some adaptive exercises. All the interference trials would appear at the center of the screen every 3 s with 15 s of fixation (a white dot in the center of the screen). During fixation, subjects completed 80 random trials.

2.3. EEG data collection

EEG data was acquired from 19 electrodes using the International ten-twenty system. The scalp locations are: Fp1, Fp2, F3, F4, F7, F8, Fz, T3, T4, T7, T8, C3, Cz, P3, P4, Pz, O1 and O2 (Neuroscan; Compumedics Limited, Charlotte, NC). The impedance of all sites was $<5 \text{ k}\Omega$. Reference electrode was at the left mastoid, and the ground electrode was between Fpz and Fz. Eye-movement were monitored vertically and horizontally separately, the vertical electro-oculogram was recorded from electrode attached above and below the left eye, and a horizontal electro-oculogram was

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