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Resting state fMRI entropy probes complexity of brain activity in adults with ADHD

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ABSTRACT

In patients with attention deficit hyperactivity disorder (ADHD), quantitative neuroimaging techniques have revealed abnormalities in various brain regions, including the frontal cortex, striatum, cerebellum, and occipital cortex. Nonlinear signal processing techniques such as sample entropy have been used to probe the regularity of brain magnetoencephalography signals in patients with ADHD. In the present study, we extend this technique to analyse the complex output patterns of the 4 dimensional resting state functional magnetic resonance imaging signals in adult patients with ADHD. After adjusting for the effect of age, we found whole brain entropy differences ($P=0.002$) between groups and negative correlation ($r=-0.45$) between symptom scores and mean whole brain entropy values, indicating lower complexity in patients. In the regional analysis, patients showed reduced entropy in frontal and occipital regions bilaterally and a significant negative correlation between the symptom scores and the entropy maps at a family-wise error corrected cluster level of $P<0.05$ ($P=0.001$, initial threshold). Our findings support the hypothesis of abnormal frontal–striatal–cerebellar circuits in ADHD and the suggestion that sample entropy is a useful tool in revealing abnormalities in the brain dynamics of patients with psychiatric disorders.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common mental disorders of childhood, affecting 5–10% of all children. It frequently persists into adolescence, or even adulthood (Biederman, 1998), with a prevalence of approximately 4% (Biederman, 2005). Its core clinical symptoms include inattention, hyperactivity and impulsivity with the attentional deficit being usually the most functionally impairing symptom in adults (Barkley, 2003). Although the pathophysiology of ADHD remains unclear, some studies reported that the neural basis of this disorder resides mainly in anatomical and functional disturbances of frontal–striatal–cerebellar circuits (Giedd et al., 2001).

Many functional neuroimaging techniques have been explored to study the pathophysiology underlying ADHD. These techniques include single photon emission computed tomography (SPECT), positron emission tomography (PET) and blood oxygenation level dependent (BOLD) functional MRI (fMRI). Most SPECT and PET studies have probed the brain's resting-state to study the pathophysiology of ADHD. These studies reported abnormalities in the frontal cortex (Lee et al., 2005), striatum (Lou et al., 1990), anterior cingulate cortex (ACC) (Langleben, 2002), sensorimotor cortex (SMC) (Lee et al., 2005), occipital cortex (Schweitzer et al., 2003) and cerebellum (Lee et al., 2005). Task specific BOLD fMRI studies of ADHD have also been implemented but the results were found to be inconsistent. Both hypofrontality (Rubia et al., 1999) and hyperfrontality (Schulz et al., 2004) have been reported. The discrepancy could be a result of different tasks, ages and comorbidity in the studies. However, even studies using very similar tasks (Schulz et al., 2004; Tamm et al., 2004) have produced divergent results. Subtle differences in tasks and patients' performance strategies between the two studies might partly account for

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the discrepancies. Hence, it may be difficult to extract reliable markers of ADHD pathophysiology from task-based studies.

The resting-state (Raichle et al., 2001) fMRI approach has therefore been introduced as an alternative perspective on brain functional abnormalities in ADHD. Resting-state BOLD fMRI data allow for the analysis of functional connectivity patterns in brain networks and the temporal dynamics of their activity fluctuations (Rotarska-Jagiela et al., 2010). In children with ADHD, several studies have reported decreased amplitude of low-frequency fluctuations (ALFF) in the right inferior frontal cortex, the bilateral cerebellum and the vermis as well as increased ALFF in the right anterior cingulate cortex (Zang et al., 2007). Abnormal dorsal anterior cingulate cortex (dACC) functional connectivity patterns have been reported in adolescent ADHD patients (Tian et al., 2006). ADHD patients exhibited decreased regional homegeneity (ReHo) in frontal–striatal–cerebellar circuits but increased ReHo in the occipital cortex (Cao, 2006). Very few studies have applied this method to adult ADHD, but results of a study employing kernel principal component analysis to discriminate adults with ADHD from normal controls (Wang et al., 2011) are encouraging.

Nonlinear signal processing techniques such as approximate entropy (ApEn) (Pincus, 1991, 1995) and sample entropy (SampEn) (Richman and Moorman, 2000) provide a relatively new measure to probe the complexity of brain fMRI dynamics (Sokunbi et al., 2011). Entropy values reflect the number of times the patterns in a signal are repeated and thus measure the randomness and predictability of a stochastic process and in general increase with greater randomness. A lower value of SampEn thus indicates lower complexity of the signal or system. Recently, Gomez et al. (2011) applied SampEn to analyse the spontaneous MEG activity in ADHD patients. They performed five minutes of recording with a 148-channel whole-head magnetometer in 14 ADHD patients and 14 control subjects. They found that the SampEn values of the ADHD patients' MEGs were lower than those of the controls. Also, there were statistically significant differences ($P<0.01$, Student's t-test with Bonferoni's correction) at the five analysed brain areas: anterior, central, posterior, left lateral and right lateral. Until now the complex output patterns of the 4D blood oxygen level dependent (BOLD) signals in ADHD have remained unexplored.

The rationale for studying resting state data of psychiatric patients with complexity measures is that complex output patterns of a system can give an indication of the health and robustness of the system (Goldberger et al., 2002a). Therefore, the characterization and analysis of the brain's output in terms of its complexity may reveal a better understanding of an individual's adaptive capacity, the ability to respond to unpredictable perturbations and stresses, which is presumed to be impaired in mental disorders. Complex organic systems such as the human brain have evolved to maximise adaptive capacity (Wolf and Linden, 2012). The degradation of these processes with age and disease is associated with loss of complexity in the dynamics of complex physiological systems (Lipsitz, 2004). Chaotic and complex behaviours indicate a healthy system whereas more predictable behaviours would be linked to pathological states (Pool, 1989).

The aim of the present study was to investigate differences in the complex output patterns of resting state fMRI signals in adult ADHD patients when compared to age-matched healthy controls. Current models of ADHD posit funcitonal deficits in the frontal cortex, striatum, cerebellum, and occipital cortex of the brain (Seidman et al., 1998; Swanson et al., 1998). We expected the functional physiological complexity of ADHD patients (as reflected in the entropy values) to be reduced, and this reduction to scale with symptom severity.

2. Materials and methods

2.1. Participants

We recruited 17 ADHD patients (8 female, mean (standard deviation; SD) age 29.65 (± 10.19)) from National Health Service (NHS) out-patient clinics in Swansea and 13 age- and gender-matched controls (8 female, mean (SD) age 29.69 (± 8.39)). The study was approved by the South West Wales Research Ethics Committee. Exclusion criteria were inability to give informed consent and MRI contraindication.

A detailed written and verbal explanation of the purpose and design of the study was provided to all the participants and written informed consent obtained prior to the commencement of the study.

Patients were receiving psychotropic medication for ADHD at the time of scanning (dose): Methylphenidate 32 mg (6 patients), D-amphetamine 70 mg (2 patients), Atomoxetine 80 mg (1 patient), Risperidone 0.5 mg, (1 patient), and benzodiazepines (1 patient). One patient was treated with Acamprosate 666 mg for alcohol dependence and was currently abstinent. Three patients were additionally treated with antidepressant medication. Five patients were not on any medication.

All patients and control participants completed the Conners' Adult ADHD Rating Scales (CAARS), a standardized self-rating for adults undergoing evaluation for ADHD (Conners et al., 1999a, 1999b; Erhardt et al., 1999). CAARS are a set of easily administered instruments consisting of self-reports and observer ratings allowing for the multimodal assessment of adult ADHD symptoms and behaviours. The CAARS subscales include inattention/memory problems, hyperactivity/restlessness, impulsivity/emotional liability, problems with self-concept and ADHD index. The mean (± 2 SD) ADHD score for the control and ADHD groups are listed in Table 1.

2.2. Resting state fMRI acquisition

Functional MR images were acquired with a T_2* weighted gradient echo echo-planar imaging sequence (EPI) in the axial plane using a GE Medical Systems twin-speed Signa HDx 3T MRI scanner. A total of 31 axially orientated 4 mm thick contiguous sequential slices were obtained for each of 100 volumes using a TR of 3000 ms, TE of 35 ms, flip angle of 90°, field of view of 240 × 240 mm and matrix 64 × 64. The first three volumes were discarded to allow for transient effects. The fMRI images were acquired using a 16 channels head coil without a task or stimulus ('resting state').

2.3. Image pre-processing

The image pre-processing was performed on the fMRI data using version 8 of Statistical Parametric Mapping software (SPM8; The Wellcome Department of Imaging Neuroscience, UCL, London, UK). The fMRI data were realigned using Realign (Est & Res) from the Spatial pre-processing section of SPM8 to correct for head movement distortion. Temporal high pass filtering (128 s) was performed from Specify 1st-level of the model specification, review and estimation section to reduced low frequency noise. Each voxel time series was standardized to a mean of zero and standard deviation of unity to allow data set with different amplitudes to be compared (Richman and Moorman, 2000).

2.4. Estimation of input parameters for calculating SampEn

Richman and Moorman (2000) developed sample entropy (SampEn) from the modification of the approximate entropy (ApEn) algorithm (Pincus, 1991, 1995) to reduce the bias of ApEn, where self-matches were excluded from the ApEn algorithm, $(i \neq j)$ and $(1 \leq i \leq N\text{-}m)$ i.e. vectors are not compared to themselves. SampEn has the advantage of being less dependent on time series length, and showing relative consistency over a broader range of possible r, m, and N values under circumstances where ApEn does not (Richman and Moorman, 2000). SampEn is the negative logarithm of the conditional probability that two sequences remain similar at the next point, where self matches are not included in calculating the probability.

The same input parameters of m, r, N and τ used in calculating ApEn are also applicable to SampEn. The SampEn for a given N-dimensional time series $(x_1, x_2, \ldots\ldots, x_N)$ is defined as

$$\mathrm{SampEn}(m,r,N) = -\ln\left[\frac{U^{m+1}(r)}{U^{m}(r)}\right]$$

$$U^{m}(r) = [N-m\tau]^{-1}\sum_{i=1}^{N-m\tau} C_i^m(r) \quad (1)$$

where

$$C_i^m(r) = \frac{B_i}{N-(m+1)\tau}$$

$$B_i = \text{number of } j \text{ where } d|X_i, X_j| \leq r \quad (2)$$

$$X_i = (x_i, x_{i+\tau}, \ldots\ldots, x_{i+(m-1)\tau}) \quad (3)$$

$$X_j = (x_j, x_{j+\tau}, \ldots\ldots, x_{j+(m-1)\tau})$$
$$1 \leq j \leq N-m\tau, j \neq i \quad (4)$$

In Eq. (1), N is the number of time points, m specifies the pattern length, r defines the tolerance value and τ is the time delay. The two patterns i and j of m