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Quantitative electroencephalography as a biomarker for proneness toward developing psychosis

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ABSTRACT

The fully dimensional approach to the relationship between schizotypal personality traits and schizophrenia describes schizotypy as a continuum throughout the general population ranging from low schizotypy (LoS) and psychological health to high schizotypy (HiS) and psychosis-proneness. However, no biological markers have yet been discovered that reliably quantify an individual's degree of schizotypy and/or psychosis. This study aimed to evaluate quantitative electroencephalographic (qEEG) measures of power spectra as potential biomarkers of the proneness towards the development of psychosis in schizotypal individuals. The resting-state oscillatory brain dynamics under eyes-closed condition from 16 LoS and 16 HiS individuals were analysed for qEEG measures of background rhythm frequency, relative power in δ, θ, low-α, high-α, low-β, high-β and low-γ frequency bands, and the high-temporal cross-correlation of power spectra between low- and high-frequency bands observed by averaging signals from whole-head EEG electrodes. HiS individuals at rest locked the thalamocortical loop in the low-α band at a lower-frequency oscillation and displayed an abnormally high level of neural synchronisation. In addition, the high-α band was found to be positively correlated with both the high-β and low-γ bands unlike LoS individuals, indicating widespread thalamocortical resonance in HiS individuals. The increase of regional alpha oscillations in HiS individuals suggests abnormal high-level attention, whereas the pattern of correlation between frequency bands resembles the thalamocortical dysrhythmia phenomenon which underlies the symptomatology of a variety of neuropsychiatric disorders including schizophrenia. These qEEG biomarkers may aid clinicians in identifying HiS individuals with a high-risk of developing psychosis.

1. Introduction

Schizotypy describes a cluster of personality traits that include: a) unusual perceptual experience and magical thinking; b) bizarre behaviour and strange speech; and c) social anhedonia. These broadly correspond to the positive, disorganised and negative dimensions of schizophrenia (SZ) respectively (Compton et al., 2009; Fonseca-Pedrero et al., 2011; Nelson et al., 2013). The fully dimensional approach posits that schizotypal traits in the healthy population and SZ are fundamentally linked (Claridge and Beech, 1995; Nelson et al., 2013). This approach is also consistent with most current theories regarding SZ, which tend to describe continuity between clinical and non-clinical psychosis populations (Linscott and van Os, 2010). There is also good evidence that 'psychotic traits' and 'schizotypal traits' are convergent constructs (Claridge et al., 1996).

Despite intense study into the physiological correlates of schizotypal individuals in relation to SZ (Nelson et al., 2013), no biological markers have yet been discovered. As suggested by several authors, there is no test (biological or otherwise) that can reliably differentiate between individuals with and without psychosis (Wong and Van Tol, 2003; Beck et al., 2009; Wing and Agrawal, 2013). However, over recent decades, quantification of spontaneous electroencephalography (quantitative EEG, qEEG) has been used to predict the likelihood of developing psychiatric disorders, classify disease states and delineate the effects of pharmacological agents in a variety of disorders including SZ (Leiser et al., 2011). Neurobiologically, this approach is supported by the fact that the activity of a number of subcortical neurotransmitter systems from several brain regions outside the thalamus can directly impact cortical activity patterns (Leiser et al., 2011).

The general aim of the current investigation is to use qEEG measures of power spectra to distinguish low (LoS) from high schizotypy (HiS) individuals in the healthy population and gain a better understanding of the physiological mechanisms in schizotypy and their relation to SZ. Spectral power was chosen because it is the simplest quantifiable EEG measure and has long been studied in SZ (Boutros et al., 2008). Therefore the current investigation enables us to relate the physiological mechanisms of schizotypy to those studied in SZ and to elucidate the mechanisms underlying a construct whose relationship to SZ is generally poorly understood (see Nelson et al., 2013 for review). The qEEG measures employed in this study may be suitable biomarkers for classifying those individuals in the general population with a high risk of

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developing psychosis, complementing the conventional neuropsychological or psychometric approaches for the assessment of psychological dysfunction.

An electrophysiological conception considers the fundamental role of dysfunctional oscillations in patients (at rest or whilst performing a task) in the generation of cognitive deficits and symptomatology in a range of neurological and psychiatric disorders (Llinas et al., 1999; Uhlhaas and Singer, 2010; Schulman et al., 2011; Fuggetta and Noh, 2013). Dysfunctional neural activities have been studied using single unit recording from the human thalamus (Jeanmonod et al., 1996, 2003; Sarnthein et al., 2003, 2005; Sarnthein and Jeanmonod, 2007, 2008), whilst abnormal oscillatory activities have been assessed with magnetoencephalographic (MEG) (Llinas et al., 1999; Jeanmonod et al., 2001; Llinas and Ribary, 2001; Llinás et al., 2001; Schulman et al., 2001; Jeanmonod et al., 2003; Llinas et al., 2005; Schulman et al., 2011) and EEG (Sarnthein et al., 2003, 2005; Sarnthein and Jeanmonod, 2007, 2008) recordings in patients suffering from SZ, chronic psychosis, Parkinson's disease, epilepsy, neuropathic pain, tinnitus, major depression, and obsessive–compulsive, affective and impulse control disorders. These studies tested the hypothesis that the pathophysiological mechanism involved in the manifestation of symptoms in these disorders is the existence of abnormal, localized and protracted low-frequency spontaneous recurrent activation of the thalamocortical system. This condition has been labelled by Rodolfo Llinás thalamocortical dysrhythmia (TCD) (Llinas et al., 1999).

TCD is based on the concept that in the intact brain, the thalamus and cortex are interconnected and support recurrent functional loops. In an awake resting-state, the thalamus oscillates at around 10 Hz, driving the cortex to oscillate at the same rate (Dossi et al., 1992). This thalamocortical resonance is a prerequisite for normal cognition (Llinas and Ribary, 2001; Llinás et al., 2001). With TCD, low-threshold calcium spike (LTS) bursts in the thalamus have an inter-burst frequency of ~4 Hz in awake resting-state patients (Jeanmonod et al., 1996, 2003; Llinas and Steriade, 2006). This in turn exerts an increased neural synchronisation at the ~4 Hz frequency in thalamo-cortical modules which can be measured with EEG (Sarnthein and Jeanmonod, 2007, 2008) and MEG (Llinas et al., 1999). It is this increased neural synchronisation within the θ band, in conjunction with a widespread increase in correlation between θ and both high-β and γ frequency oscillations, that may underpin the positive symptoms in a various clinical disorders (Llinas et al., 1999; Jeanmonod et al., 2003; Schulman et al., 2011).

A meta-analysis conducted to assess studies where spectral power was compared between SZ patients and healthy control subjects in a resting-state, eyes-closed condition found abnormal differences in the EEG power (i.e. neural synchronisation) of several widespread frequency rhythms (Boutros et al., 2008). Specifically, an increase in δ and θ, a decrease in α, and an increase in β and γ were found in both unmedicated and medicated SZ patients (Boutros et al., 2008). Based on the available literature, it was concluded that the δ power excess (and to a lesser extent the θ excess) is a strong biological marker of SZ (Boutros et al., 2008).

The TCD framework seems an ideal candidate to provide a better understanding of the physiological mechanisms underlying the cluster of personality traits in schizotypy and their relation to SZ. However, previous research has not investigated whether the TCD model could also be extended to schizotypy. Thus the aim of the present study is to use a series of qEEG measures to evaluate whether HiS individuals show an associated perturbation of the thalamo-cortical activation system. Given that it is known that such individuals are prone to developing psychosis, this is an important question that needs addressing.

2. Material and methods

This study was approved by the School of Psychology ethics committee at the University of Leicester in accordance with the Declaration of Helsinki. All participants gave written informed consent and received course credit for participating. Participants were fully debriefed about the purpose of the study.

2.1. Subjects

An initial group of 165 (140 females, 18–26 years) undergraduate psychology students from the University of Leicester completed the Oxford–Liverpool Inventory of Feelings and Experiences (O-LIFE) questionnaire (Mason et al., 1995; Mason and Claridge, 2006). Participants scoring outside the inter-quartile range, for their given age and gender-specific psychometric distribution of normative data (Mason and Claridge, 2006), in either the 'Unusual Experiences' or 'Cognitive Disorganisation' subscale of the O-LIFE, took part in the experimental stage of the study and were classified as being LoS or HiS individuals. Of the initial group, 38 subjects participated in the experimental stage of this study. Six participants were excluded due to EEG artefacts. Therefore, EEG data from 16 LoS (18–22 years) and 16 HiS participants (18–25 years) were analysed. Subject characteristics for both groups are detailed in Table 1. All participants reported no use of medication, history of chemical dependency or neurological, psychiatric/psychological disorders or closed head injuries.

2.2. Self-report measure

The O-LIFE is a four-scale self-report measure of 104 items with a binary response format. Its items show high internal consistency (all alphas between 0.77 and 0.89; Mason et al., 1995), and good test–retest reliability (0.70; Burch et al., 1988). The construct validity of the scale as a measure of schizotypy has been established in studies across many fields of interest (see Mason and Claridge, 2006 for review), and it is seen as an effective tool for assessing psychosis-proneness and schizotypy in healthy individuals (Mason and Claridge, 2006).

2.3. Procedure

Participants were naïve to the purpose of the investigation. All were tested individually and were presented with instructions to complete the O-LIFE questionnaire in conventional paper-and-pencil form. At a later date, 38 participants underwent the experimental stage, which lasted approximately 30 min. After the approximately 25 min EEG setup procedure, participants sat in a comfortable chair in a darkened and sound-attenuated room. In the current study, we have followed the recommendations of procedures put forward by Boutros et al. (2008) employed by majority of EEG studies on schizophrenia adopting a "resting-state" experimental design. The "resting state" needs to be clearly defined. By definition resting wakefulness state is the absence of specific mental activity (Boutros et al., 2008). Therefore, taking into account the above definition, subjects were given the following instructions prior to baseline recording:

Your brain activity at rest will be recorded for 3 min. You are asked to close your eyes, remain awake, and minimize 'mental wandering'. Because muscle tension and movement can affect the data we are most interested in, we would like you to remain as still and relaxed as you can, especially the muscles in your face and scalp. Please remember that it is very important that you minimize body motion and especially avoid eye movements as this will affect the data.

During the recordings, participants' body motions as well as eye movements and muscle activities were continuously monitored. It seems that all participants have followed the instructions given. However it is impossible to make precise assumptions concerning subjects' mental states. The eyes-closed procedure had the effect of maximising occipital alpha oscillation and thus its influence on prefrontal alpha oscillation and prefronto-thalamic circuits (Llinás et al., 2001).