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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 dysrhythma 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.

Key Words: Schizotypy; electroencephalography (EEG); resting-state oscillations; spectral analysis; thalamocortical dysrhythmia (TCD)

1. Introduction

Schizotypy describes a cluster of personality traits that include: a) unusual perceptual experience, magical thinking, b) bizarre behaviour, 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 (Beck, 2009; Wing, 2013; Wong and Van Tol, 2003). 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 better understand a condition that is largely misunderstood and often confused with SZ. The qEEG measures employed in this study may be suitable biomarkers for classifying those individuals in the general population with a high risk of 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 while performing a task) in the generation of cognitive deficits and symptomatology in a range of neurological and psychiatric disorders (Fuggetta and Noh, 2012; Llinas et al., 1999; Schulman et al., 2011; Uhlhaas and Singer, 2010). Dysfunctional neural activities have been studied using single unit recording from the human thalamus (Jeanmonod et al., 1996; Jeanmonod et al., 2003; Sarnthein and Jeanmonod, 2007, 2008; Sarnthein et al., 2003, 2005), while abnormal oscillatory activities have been assessed with magnetoencephalographic (MEG) (Jeanmonod et al., 2001; Jeanmonod et al., 2003; Llinas and Ribary, 2001; Llinás et al., 2001; Llinas et al., 2005; Llinas et al., 1999; Schulman et al., 2011; Schulman et al., 2001) and EEG (Sarnthein and Jeanmonod, 2007, 2008; Sarnthein et al., 2003, 2005) recordings in patients suffering from SZ, chronic psychosis, Parkinson's disease, epilepsy, neuropathic pain, tinnitus, major depression, 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; Jeanmonod et al., 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 (Jeanmonod et al., 2003; Llinas et al., 1999; 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 was found in both un-medicated 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 questionnaire (O-LIFE) (Mason and Claridge, 2006; Mason et al., 1995). 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 Disorganization' 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 artifacts. 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.

< Table 1 about here >

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 are suitable for tapping psychosis-proneness in healthy individuals, principally schizotypy (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, sound-attenuated room in a restful waking state. Participants were asked to close their eyes, remain awake, minimize body motion and eye movements, and to minimize 'mental wandering' for three minutes while EEG was recorded. 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).

2.4 EEG recording

Continuous EEG signals were recorded by a DC 32-channel amplifier (1-kHz sampling rate, 250 Hz high cut-off frequency; Brain Products Inc., Germany). EEG activity

was recorded via a Waveguard elastic cap, containing 64 unshielded and sintered Ag-AgCl electrodes (CAP-ANTWG64; ANT, Netherlands), with an electrode layout according to the international 10–5 electrode system. Twenty-six active electrodes were used (Fig 1). The right-earlobe electrode served as an on-line reference. EEG data were re-referenced off-line to the average of the right and left-earlobe electrodes. Two electrodes placed in a bipolar montage at approximately 1 cm from the outer canthi of both eyes served to record the horizontal electrooculogram (HEOG). The vertical electrooculogram (VEOG) and blinks were recorded from one electrode positioned below the right eye and referenced to the right earlobe. Electrode impedance was kept below 5 KΩ.

2.5 EEG analyses

The EEG data were processed off-line using commercial software (Vision Analyser, Brain Vision, Munich, Germany). Three minutes of continuous data were divided into forty-four consecutive, non-overlapping epochs of 4,096 data points. Subsequently, the data were digitally filtered with a band-pass of 0.5–45 Hz and a notch filter of 50 Hz. Epochs with eye movements and muscle or movement artefacts (as indicated by HEOG activity exceeding ±40 μV and activity at other electrodes exceeding ±70 μV) were excluded. A mean of 113.24±35.28 seconds of artefact-free epochs remained for analysis. This was considered sufficient for reliable spectral estimates in SZ (Boutros et al., 2008).

For each subject, a discrete fast fourier transform (FFT) of the epochs with a resolution of 0.244 Hz was computed for all electrodes and then averaged. Non-overlapping hamming-windows controlled spectral leakage. The FFT power value measurements within each frequency between 1.2 and 40.8 Hz were averaged to create 40 non-overlapping < 1 Hz frequency bins. The frequency bands of interest were defined as: δ (1.2-3.9 Hz), θ (4.2-7.8

Hz), Low α (8.1-10.0 Hz), High α (10.3-12.9 Hz), Low β (13.2-18.8 Hz), High β (19.0-29.8 Hz) and Low γ (30.0-40.8 Hz). Consequently, the frequency bands contained differing numbers of bins. Electrodes were grouped into regions of interest (ROIs) going from rostral to caudal (fronto-central, centro-parietal and parieto-occipital) for each hemisphere (Fig. 1).

< Figure 1 about here >

The background rhythm frequency (BRF) in each ROI was defined as the dominant frequency peak in the FFT average, determined by visual inspection. Additionally, the relative power (which reduces the effect of inter-subject variation in absolute power) at each frequency bin was also measured, by taking the power at each bin divided by the absolute power over the entire frequency range (1.2-40.8 Hz), as in previous MEG studies (Klassen et al., 2011; Osipova et al., 2005). The descriptive statistics for each combination of frequency bin, ROI and group are reported in Supplement 1.

2.6 Statistical Analysis

For all statistical tests, $p < .05$ was considered significant. For all ANOVAs, Greenhouse–Geisser epsilon adjustments for non-sphericity (assessed with Mauchly's test) were applied where appropriate. Post-hoc paired *t*-tests were Bonferroni corrected for multiple comparisons.

Several differences between the HiS and LoS groups were analysed: age using a *t*-test, both gender and handedness using chi-square tests and scores in each O-LIFE subscale using Mann-Whitney *U* tests. Moreover, each sub-scale and BRF in each ROI were cross-correlated using Pearson's product moment correlations (see Table 2). The BRF in each ROI was also submitted to a three-way repeated measures ANOVA with the factors: group (HiS and LoS),

rostral-caudal axis (fronto-central, centro-parietal, and parieto-occipital), and hemisphere (left and right).

To test for abnormal power excesses, as in clinical SZ, the participants' mean relative power was analysed with a series of four-way repeated measures ANOVAs, conducted separately for each frequency band, with the factors: 'Group' (HiS and LoS), 'Rostral-Caudal Axis' (fronto-central, centro-parietal, and parieto-occipital), 'Hemisphere' (left and right) and 'Frequency Bin'.

To test for abnormal correlations between low- and high-frequency bands, as in TCD, we calculated the cross-correlations of the relative power (averaged over all electrodes) for all 40 frequency bins between 1.2 and 40.8 Hz, similar to (Jeanmonod et al., 2003; Llinás et al., 2001; Llinas et al., 1999). Further, two-way hierarchical log-linear analyses by backward elimination tested for between-group differences in the frequency of significant Pearson's cross-correlations between *the lower-frequency bands* (δ, θ, low α, high α and the following low β frequency bands: 13.2-14.9, 15.1-16.8 and 17.1-18.8 Hz) and *the higher-frequency bands* (high β and low γ).

3. Results

Table 1 shows the main descriptive and comparative statistics for the LoS and HiS groups' associated O-LIFE subscale scores and qEEG measurements.

3.1 Subject characteristics

No significant group differences were found in age, gender or handedness. The HiS group scored higher on all four subscales of the O-LIFE questionnaire (See Table 1). All subscales were positively correlated, except 'Introvertive Anhedonia' and 'Unusual Experiences' (p = ns). These results accord with the reported extensive norms but show

stronger correlation coefficients, probably because the selected participants were extreme scores (Table 2).

< Table 2 about here >

Both Unusual Experiences and Impulsive Nonconformity were negatively correlated with BRF at bilateral fronto-central and centro-parietal ROIs. Also, Cognitive Disorganisation was negatively correlated with the right fronto-central ROI (Table 2).

3.2 Background Rhythm Frequency (BRF)

Fig. 2 displays each group's average relative power spectra for each frequency bin analysed.

< Figure 2 about here >

The BRF was significantly different between the two groups, $F_{(1,30)}= 9.2$, $p< .01$, $\eta^2p=.23$, with a shift to a slower α frequency in the HiS (9.35±0.75 Hz vs.10.27±0.96 Hz) group, particularly prominent at the caudal pole (Fig. 2).

3.3 Relative power

Only the Low-α band distinguished between the groups. Table 3 summarises the ANOVA results for the mean relative power for each frequency band.

< Table 3 about here >

3.3.1 δ (1.2–3.9 Hz)

Post-hoc comparisons for the significant Rostral-Caudal * Frequency Bin interaction showed increased power in fronto-central compared to centro-parietal and parieto-occipital regions at 1.2-2.0 Hz and 3.2-3.9 Hz bins.

3.3.2 θ (4.1–7.8 Hz)

An identical pattern of results to δ was obtained at 4.1-4.9 Hz at 5.1-5.9 Hz, at 6.1-6.8 Hz, and at 7.1-7.8 Hz bins.

3.3.3 Low α (8.1–10.0 Hz)

A broadly opposite trend to δ and θ was obtained. Specifically, there was decreased power in fronto-central regions compared to centro-parietal regions at 8.1-8.8 Hz and at 9.0-10.0 Hz bins. The power in parieto-occipital regions was increased compared to both fronto-central and centro-parietal regions at the 9.0-10.0 Hz bin.

Importantly, the HiS group showed a greater overall power increase (13.6 vs. 8.4 %, $p<.05$). This effect was greatest at the parieto-occipital ROI at the 9.0-10.0 Hz bin (25.4 vs. 11.9%, $p<.05$), as revealed by post-hoc comparisons for the significant Rostral-caudal * Frequency bin * group interaction. Post-hoc comparisons for the significant Hemisphere * Group interaction revealed slightly increased power in the right compared to left hemisphere in HiS (13.9 vs. 13.4%, $p<.05$) but not LoS individuals (8.4 vs. 8.5 %, p = ns).

3.3.4 High α (10.2–12.9 Hz)

Similar to low-α, there was a significant decrease in power in fronto-central regions compared to both centro-parietal and parieto-occipital regions at all frequency bins.

3.3.5 Low β (13.2–18.8 Hz)

Post-hoc comparisons for the significant Rostral-Caudal * Hemisphere * Frequency bin interaction showed, as in high- and low-α, decreased power rostrally. This effect was more robust in the left hemisphere. Specifically, the left hemisphere displayed increased power in parieto-occipital compared to fronto-central and centro-parietal regions at the 13.2-13.9 bin. There was increased power in parieto-occipital compared to centro-parietal regions at the 14.2-14.9 Hz bin. There was increased power in the left hemisphere for centro-parietal regions at all three 13.2 to 15.9 Hz bins.

3.3.6 High β (19.0–29.8 Hz)

Post-hoc comparisons for the significant Hemisphere * Frequency bin interaction showed increased power in the left hemisphere at bins from 24.2 to 29.8 Hz.

3.3.7 Low γ (30.0–40.8 Hz)

Post-hoc comparisons for the significant main factor of frequency bin revealed a progressive attenuation of power at higher-frequency bins.

3.4 Power spectra cross-correlation

Figure 3 shows each group's power spectra cross-correlation between lower and higher frequency bands.

< Figure 3 about here >

Table 4 summarises the results of the hierarchical log-linear analyses which test for between-group differences in the frequency of significant cross-correlations between power in the lower- and higher-frequency bands.

< Table 4 about here >

Figure 3 shows that for both LoS and HiS groups, the 'high-β + low-γ' band displayed very few correlations with the δ, θ and low α bands. However, there are clear group differences in the correlations with high-α and low-β bands.

The Significant Group * Correlation Count (Absent vs. Present) interaction indicated that in the LoS group, the 'high-β + low-γ' band showed almost absent correlations with the high-α (10.2-12.9 Hz) and low-β (13.2-18.8 Hz) bands (0% and 1.1%, respectively). However, for the HiS group, there were many positive correlations (31.8% and 46.6%, respectively).

Interestingly, the group differences are reversed for the low-β bands (15.1-16.8 Hz and 17.1-18.8 Hz), indicated by significant Group * Correlation Count (Absent vs. Present) interaction. This time for the LoS group, the 'high-β + low-γ' band showed many positive correlations with both the low-β bands (34.1% and 31.8%, respectively). Conversely, the HiS group showed barely any correlations (2.3% and 1.1%, respectively).

4. Discussion

The results of this qEEG investigation into the neurophysiological correlates of schizotypal personality organization suggest the presence of an attenuated form of

thalamocortical dysfunction in HiS compared with LoS individuals. This may represent a parallel to TCD in clinical SZ. Overall, these results are in agreement with previous neurobiological, neuropsychological, social and environmental investigations, which demonstrated abnormalities in schizotypy similar to, but less pronounced than, those in SZ (Nelson et al., 2013). In particular, our group of HiS individuals 1) locked the thalamocortical loop in the low-α band at a lower-frequency oscillation, as measured with individual BRF; 2) displayed an abnormally high level of neural synchronisation in the same low-frequency rhythm, indicated by increased relative EEG power; and, 3) the high-α band was found to be positively correlated with both the high-β and low-γ bands. Overall, these abnormalities in cortical oscillations resemble a mild version of TCD, which has been associated with the pathophysiology of various neuropsychiatric disorders including SZ and psychosis (Jeanmonod et al., 2001; Jeanmonod et al., 2003; Llinas et al., 1999; Schulman et al., 2011).

The idea behind TCD in clinical populations is that sustained, abnormal, internally-generated δ and θ oscillations in thalamic neurons impose a slow rhythmicity on the thalamocortical loops, leading to disruption of the normal, state-dependent flow of information within the thalamo–cortico–thalamic network (Jeanmonod et al., 2003). This increase in slow rhythmic activity, whilst awake and at rest, leads to disturbances of sensation, cognition and motor performance (Jeanmonod et al., 2003; Llinás et al., 2001; Llinas et al., 1999; Schulman et al., 2011; Schulman et al., 2001; Whitwell et al., 2011). One crucial organising feature of the cortex is its system of inhibitory GABAergic interneurons, which mediate reciprocal cortico-cortical networks (Llinas et al., 2005; Llinas et al., 1999). It has been proposed that since thalamo-cortical modules interact via these cortico-cortical inhibitory interneurons, excessive thalamo-cortical θ oscillations reduce lateral inhibitory drive in the cortex (Llinas et al., 2005). This in turn leads to increased synchronisation of both β and γ rhythms observed in EEG and MEG recordings and is thought to underlie

positive symptoms in various clinical disorders (Llinás et al., 2001; Sarnthein et al., 2003).

Enhanced low-frequency oscillations normally occur during sleep and cognitive tasks (Kahana et al., 2001). The thalamocortical activity in TCD has two main characteristics which distinguish it from the α oscillations present in waking states. First is a sustained, increased, low-frequency thalamocortical resonance. Second is an abnormal correlation between the low- and high-frequency bands (Llinás et al., 2001; Llinas et al., 1999). In this study, we found that HiS individuals displayed both of these characteristics in an attenuated form. Specifically, they showed an increased synchronisation at a slightly lower frequency and an abnormal correlation between the medium- and high-frequency bands. So it appears that a mild form of TCD is at play in schizotypy.

Thus we propose that the manifestation of schizotypy, which includes bizarre behaviour, strange speech, magical thinking, unusual perceptual experience and social anhedonia, ultimately relates to the specific alterations of oscillatory activity in the α band and its abnormal interaction with higher frequency bands. We also propose that thalamocortical resonance is not only a prerequisite for normal cognition, but that its slight perturbation (e.g. dysrhythmia) can underlie the schizotypal personality organization.

4.1 Background Rhythm Frequency

The BRF results of the current study are consistent with previous reports of slower resting-state neural oscillations within the α band in schizophrenic patients (Clementz et al., 1994; Omori et al., 1995). That similar changes were detected in a non-clinical group of HiS, makes it tempting to speculate that these alterations may present themselves at the preclinical stages of SZ spectrum disorder, and thus may precede the onset of the symptomatology.

Longitudinal studies have suggested that HiS is a forerunner of schizophrenia (Chapman et al., 1994).

We also found that high scores in both the Unusual Experiences and Impulsive Nonconformity subscales were associated with a slower BRF in fronto-central and centro-parietal regions. Thus, the BRF could represent a qEEG biomarker which may complement neuropsychological and psychometric testing in studying HiS incidence in the normal population.

4.2 Relative power

In comparison with the abnormal increase in synchronisation of neural oscillations of the δ and θ rhythms described in SZ patients, the widespread synchronisation within the low-α rhythm (in the 9.0–10.0 Hz frequency bin) in HiS individuals represents only a mild alteration of brain oscillatory dynamics (Boutros et al., 2008). In SZ, slow wave abnormalities (mainly increases in δ are generally localized to frontal lobe regions (Winterer et al., 2000). However, several studies have also found spectral EEG abnormalities localized to the more posterior regions of the brain (Begic et al., 2011; Clementz et al., 1994; Miyauchi et al., 1990; Sponheim et al., 2000; Sponheim et al., 1997). A previous study comparing the EEG power spectra between LoS and HiS individuals demonstrated that HiS individuals may exhibit increased power in the δ rhythm in frontal regions and increased power between the low-α and low-γ rhythms in occipital regions (Tcheslavski, 2008). Our HiS group exhibited increased low-α power in frontal, central and occipital regions, therefore the results of the current study are in partial agreement with previous findings. The differences may reflect heterogeneities between the recruited schizotypal groups.

In focusing attention on specific targets, oscillatory α activity probably reflects the active suppression of distracter-related cortical activity (Klimesch, 2012; Ward, 2003). Moreover, α power at attention-relevant scalp sites is greater during internal attentional tasks, involving mental imagery, than during external attentional tasks (Cooper et al., 2003). This reflects the need for suppression of external input in the mental imagery task (Cooper et al., 2003). Topographically widespread lower α synchronization (approximately the 6–10 Hz range) is thought to be especially indicative of general task demands and attentional processes (Klimesch, 1999). Pfurtscheller and colleagues (Pfurtscheller and Lopes da Silva, 1999) proposed that, at α frequencies, higher levels of attentional suppression would recruit greater numbers of interconnected neurons (increased EEG power) and lower frequency oscillations (decreased EEG frequency). If correct, it may be that increased power at low-α oscillations in central and parietal regions in our HiS participants indicate abnormally high levels of attention.

The current study's finding of a hemispheric asymmetry, in the low-α frequency band, for HiS compared to LoS individuals represents another minor deviation in the electrophysiological profile of HiS individuals. Whilst this is only a small effect, it is consistent with previous reports of long-term stability in EEG α asymmetry, at frontal and parietal regions in outpatients with schizophrenia during resting states (Jetha et al., 2009). Moreover, a study assessing EEG power in HiS compared to LoS individuals found more pronounced differences in the left hemisphere at high-α, high-β, and low-γ frequencies (Tcheslavski, 2008), consistent with previous reports (Kidd and Powell, 1993; Raine et al., 2002).

4.3 Power spectra cross-correlation

If the frequency spectrum is plotted against itself, a cross-correlation plot of power between frequencies is obtained. In normal controls, such cross-correlation plots yield a well-defined image, showing strong links with high-β to low-γ frequencies, but not between δ to low-β (13.2-14.9 Hz) and both high-β to low-γ frequencies (Llinás et al., 2001). In our study, as expected, LoS individuals showed this familiar pattern of cross-correlation (figure 3). Conversely, in HiS individuals, in addition to the usual high frequency cross-correlations, the high-α (10.2-12.9 Hz) to low-β (13.2-14.9 Hz) band was also positively cross-correlated with the high-β to low-γ frequency bands, indicating that whenever there was a time epoch with high-α power, this epoch was most likely also to display high-β and low-γ power. In other words, periods of neural synchronisation at the medium frequencies and at high frequencies coincided.

These results, using the average signal of many EEG electrodes from schizotypal individuals, resemble the results reported using the average signal of many MEG sensors from clinical SZ individuals (Jeanmonod et al., 2001; Jeanmonod et al., 2003; Llinas and Ribary, 2001; Llinás et al., 2001; Llinas et al., 1999; Sarnthein et al., 2003) and the interpretation is that there exists a slight, but widespread, perturbation of thalamocortical resonance (TCD) in individuals who exhibit the cluster of personality traits associated with schizotypy.

4.4 Conclusions

Overall, the finding that HiS individuals display a mild perturbation of thalamo-cortical activation systems (TCD) support the fully dimensional model, which posits that varying levels of schizotypal personality traits throughout the general population lie on a continuum of SZ spectrum disorders (Claridge and Beech, 1995; Nelson et al., 2013; Vollema

and Hoijtink, 2000). Interruptions of distinct thalamic arousal systems that deal with external stimuli and their level of allocated attention, ranging from minor asynchrony to complete uncoupling, could give rise to many forms of anomalous processing and so form the basis of the continuum linking schizotypy and SZ (Gruzelier, 2003).

With the results of this study, we support the current opinion in functional neuroimaging literature that the application of a "resting-state" experimental design, which is not dependent on subject compliance or on task-specific factors, is suitable for studying both neuropsychiatric disorders (Greicius, 2008; Hinkley et al., 2011) and healthy subjects (Fuggetta and Noh, 2012). Our results also suggest that qEEG measures of spectral power (in combination with psychometric measures) have potential use in clinical settings as biological markers of an increased likelihood of later psychosis. This may prove especially valuable for those individuals who have gone undetected by conventional assessments of psychological dysfunction.

References

Beck, A.T., Rector, N.A., Stolar, N., Grant, P.,, 2009. Schizophrenia: Cognitive Theory, Research, and Therapy. The Guilford Press, New York.

Begic, D., Popovic-Knapic, V., Grubisin, J., Kosanovic-Rajacic, B., Filipcic, I., Telarovic, I., Jakovljevic, M., 2011. Quantitative electroencephalography in schizophrenia and depression. Psychiatr Danub 23(4), 355-362.

Boutros, N.N., Arfken, C., Galderisi, S., Warrick, J., Pratt, G., Iacono, W., 2008. The status of spectral EEG abnormality as a diagnostic test for schizophrenia. Schizophr Res 99(1-3), 225-237.

Chapman, L.J., Chapman, J.P., Kwapil, T.R., Eckblad, M., Zinser, M.C., 1994. Putatively psychosis-prone subjects 10 years later. J Abnorm Psychol 103(2), 171-183.

Claridge, G., Beech, T., 1995. Fully and quasi-dimensional constructions of schizotypy, in: A., R., T., L., S.A., M. (Eds.), Schizotypal Personality. Cambridge: Cambridge University Press, pp. 192-216.

Claridge, G., McCreery, C., Mason, O., Bentall, R., Boyle, G., Slade, P., Popplewell, D., 1996. The factor structure of "schizotypal' traits: a large replication study. Br J Clin Psychol 35 (Pt 1), 103-115.

Clementz, B.A., Sponheim, S.R., Iacono, W.G., Beiser, M., 1994. Resting EEG in first-episode schizophrenia patients, bipolar psychosis patients, and their first-degree relatives. Psychophysiology 31(5), 486-494.

Compton, M.T., Goulding, S.M., Bakeman, R., McClure-Tone, E.B., 2009. Confirmation of a four-factor structure of the Schizotypal Personality Questionnaire among undergraduate students. Schizophrenia Research 111(1–3), 46-52.

Cooper, N.R., Croft, R.J., Dominey, S.J., Burgess, A.P., Gruzelier, J.H., 2003. Paradox lost? Exploring the role of alpha oscillations during externally vs. internally directed attention and the implications for idling and inhibition hypotheses. Int J Psychophysiol 47(1), 65-74.

Dossi, R.C., Nunez, A., Steriade, M., 1992. Electrophysiology of a slow (0.5-4 Hz) intrinsic oscillation of cat thalamocortical neurones in vivo. J Physiol 447, 215-234.

Fonseca-Pedrero, E., Paino, M., Lemos-Giraldez, S., Sierra-Baigrie, S., Muniz, J., 2011. Measurement invariance of the Schizotypal Personality Questionnaire-Brief across gender and age. Psychiatry Res 190(2-3), 309-315.

Fuggetta, G., Noh, N.A., 2012. A neurophysiological insight into the potential link between transcranial magnetic stimulation, thalamocortical dysrhythmia and neuropsychiatric disorders. Exp Neurol.

Greicius, M., 2008. Resting-state functional connectivity in neuropsychiatric disorders. Curr Opin Neurol 21(4), 424-430.

Gruzelier, J.H., 2003. Theory, methods and new directions in the psychophysiology of the schizophrenic process and schizotypy. Int J Psychophysiol 48(2), 221-245.

Hinkley, L.B., Vinogradov, S., Guggisberg, A.G., Fisher, M., Findlay, A.M., Nagarajan, S.S., 2011. Clinical symptoms and alpha band resting-state functional connectivity imaging in patients with schizophrenia: implications for novel approaches to treatment. Biol Psychiatry 70(12), 1134-1142.

Jeanmonod, D., Magnin, M., Morel, A., 1996. Low-threshold calcium spike bursts in the human thalamus. Common physiopathology for sensory, motor and limbic positive symptoms. Brain 119 (Pt 2), 363-375.

Jeanmonod, D., Magnin, M., Morel, A., Siegemund, M., Cancro, A., Lanz, M., Llinás, R., Ribary, U., Kronberg, E., Schulman, J., Zonenshayn, M., 2001. Thalamocortical dysrhythmia II.: Clinical and surgical aspects. Thalamus & Related Systems 1(3), 245-254.

Jeanmonod, D., Schulman, J., Ramirez, R., Cancro, R., Lanz, M., Morel, A., Magnin, M., Siegemund, M., Kronberg, E., Ribary, U., Llinas, R., 2003. Neuropsychiatric thalamocortical dysrhythmia: surgical implications. Thalamus & Related Systems 2(2), 103-113.

Jetha, M.K., Schmidt, L.A., Goldberg, J.O., 2009. Resting frontal EEG asymmetry and shyness and sociability in schizophrenia: a pilot study of community-based outpatients. Int J Neurosci 119(6), 847-856.

Kahana, M.J., Seelig, D., Madsen, J.R., 2001. Theta returns. Curr Opin Neurobiol 11(6), 739-744.

Kidd, R.T., Powell, G.E., 1993. Raised left hemisphere activation in the non-clinical Schizotypical Personality. Personality and Individual Differences 14(5), 723-731.

Klassen, B.T., Hentz, J.G., Shill, H.A., Driver-Dunckley, E., Evidente, V.G., Sabbagh, M.N., Adler, C.H., Caviness, J.N., 2011. Quantitative EEG as a predictive biomarker for Parkinson disease dementia. Neurology 77(2), 118-124.

Klimesch, W., 1999. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Brain Res Rev 29(2-3), 169-195.

Klimesch, W., 2012. alpha-band oscillations, attention, and controlled access to stored information. Trends Cogn Sci 16(12), 606-617.

Leiser, S.C., Dunlop, J., Bowlby, M.R., Devilbiss, D.M., 2011. Aligning strategies for using EEG as a surrogate biomarker: a review of preclinical and clinical research. Biochem Pharmacol 81(12), 1408-1421.

Linscott, R.J., van Os, J., 2010. Systematic reviews of categorical versus continuum models in psychosis: evidence for discontinuous subpopulations underlying a psychometric continuum. Implications for DSM-V, DSM-VI, and DSM-VII. Annu Rev Clin Psychol 6, 391-419.

Llinas, R., Ribary, U., 2001. Consciousness and the brain. The thalamocortical dialogue in health and disease. Ann N Y Acad Sci 929, 166-175.

Llinás, R., Ribary, U., Jeanmonod, D., Cancro, R., Kronberg, E., Schulman, J., Zonenshayn, M., Magnin, M., Morel, A., Siegmund, M., 2001. Thalamocortical dysrhythmia I.: Functional and imaging aspects. Thalamus & Related Systems 1(3), 237-244.

Llinas, R., Urbano, F.J., Leznik, E., Ramirez, R.R., van Marle, H.J., 2005. Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci 28(6), 325-333.

Llinas, R.R., Ribary, U., Jeanmonod, D., Kronberg, E., Mitra, P.P., 1999. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci U S A 96(26), 15222-15227.

Llinas, R.R., Steriade, M., 2006. Bursting of thalamic neurons and states of vigilance. J Neurophysiol 95(6), 3297-3308.

Mason, O., Claridge, G., 2006. The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE): further description and extended norms. Schizophr Res 82(2-3), 203-211.

Mason, O., Claridge, G., Jackson, M., 1995. New scales for the assessment of schizotypy. Personality and Individual Differences 18(1), 7-13.

Miyauchi, T., Tanaka, K., Hagimoto, H., Miura, T., Kishimoto, H., Matsushita, M., 1990. Computerized EEG in schizophrenic patients. Biol Psychiatry 28(6), 488-494.

Nelson, M.T., Seal, M.L., Pantelis, C., Phillips, L.J., 2013. Evidence of a dimensional relationship between schizotypy and schizophrenia: a systematic review. Neurosci Biobehav Rev 37(3), 317-327.

Omori, M., Koshino, Y., Murata, T., Murata, I., Nishio, M., Sakamoto, K., Horie, T., Isaki, K., 1995. Quantitative EEG in never-treated schizophrenic patients. Biol Psychiatry 38(5), 305-309.

Osipova, D., Ahveninen, J., Jensen, O., Ylikoski, A., Pekkonen, E., 2005. Altered generation of spontaneous oscillations in Alzheimer's disease. Neuroimage 27(4), 835-841.

Pfurtscheller, G., Lopes da Silva, F.H., 1999. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol 110(11), 1842-1857.

Raine, A., Venables, P.H., Mednick, S., Mellingen, K., 2002. Increased psychophysiological arousal and orienting at ages 3 and 11 years in persistently schizotypal adults. Schizophr Res 54(1-2), 77-85.

Sarnthein, J., Jeanmonod, D., 2007. High thalamocortical theta coherence in patients with Parkinson's disease. J Neurosci 27(1), 124-131.

Sarnthein, J., Jeanmonod, D., 2008. High thalamocortical theta coherence in patients with neurogenic pain. Neuroimage 39(4), 1910-1917.

Sarnthein, J., Morel, A., von Stein, A., Jeanmonod, D., 2003. Thalamic theta field potentials and EEG: high thalamocortical coherence in patients with neurogenic pain, epilepsy and movement disorders. Thalamus & Related Systems 2(3), 231-238.

Sarnthein, J., Morel, A., von Stein, A., Jeanmonod, D., 2005. Thalamocortical theta coherence in neurological patients at rest and during a working memory task. Int J Psychophysiol 57(2), 87-96.

Schulman, J.J., Cancro, R., Lowe, S., Lu, F., Walton, K.D., Llinas, R.R., 2011. Imaging of thalamocortical dysrhythmia in neuropsychiatry. Front Hum Neurosci 5, 69.
Schulman, J.J., Horenstein, C.I., Ribary, U., Kronberg, E., Cancro, R., Jeanmonod, D., Llinas, R.R., 2001. Thalamocortical dysrhythmia in depression and obsessive-compulsive disorder. NeuroImage 13(6, Supplement), 1004.
Sponheim, S.R., Clementz, B.A., Iacono, W.G., Beiser, M., 2000. Clinical and biological concomitants of resting state EEG power abnormalities in schizophrenia. Biol Psychiatry 48(11), 1088-1097.
Sponheim, S.R., Iacono, W.G., Clementz, B.A., Beiser, M., 1997. Season of birth and electroencephalogram power abnormalities in schizophrenia. Biol Psychiatry 41(10), 1020-1027.
Tcheslavski, G.V., 2008. Effects of tobacco smoking and schizotypal personality on spectral contents of spontaneous EEG. Int J Psychophysiol 70(1), 88-93.
Uhlhaas, P.J., Singer, W., 2010. Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci 11(2), 100-113.
Vollema, M.G., Hoijtink, H., 2000. The multidimensionality of self-report schizotypy in a psychiatric population: an analysis using multidimensional Rasch models. Schizophr Bull 26(3), 565-575.
Ward, L.M., 2003. Synchronous neural oscillations and cognitive processes. Trends Cogn Sci 7(12), 553-559.
Whitwell, J.L., Avula, R., Master, A., Vemuri, P., Senjem, M.L., Jones, D.T., Jack, C.R., Jr., Josephs, K.A., 2011. Disrupted thalamocortical connectivity in PSP: a resting-state fMRI, DTI, and VBM study. Parkinsonism Relat Disord 17(8), 599-605.
Wing, J.K., Agrawal, N.,, 2013. Concepts and classification of schizophrenia, in: Hirsch, S.R., W., D.R. (Eds.), Schizophrenia. Blackwell, Maiden, pp. 3-14.
Winterer, G., Ziller, M., Dorn, H., Frick, K., Mulert, C., Wuebben, Y., Herrmann, W.M., 2000. Frontal dysfunction in schizophrenia--a new electrophysiological classifier for research and clinical applications. Eur Arch Psychiatry Clin Neurosci 250(4), 207-214.
Wong, A.H.C., Van Tol, H.H.M., 2003. Schizophrenia: from phenomenology to neurobiology. Neuroscience & Biobehavioral Reviews 27(3), 269-306.

Table/Figure Legends

Table 1.Demographic information, and qEEG measures of subjects with varying levels of schizotypal personality traits

Table 2.Correlations between sub-scales of the O-LIFE questionnaire and Background Rhythm Frequency (N=32)

Table 3. ANOVA statistical results of relative EEG power for δ, θ, low α, high α, low β, high β and low γ frequency bands.

Table 4. Hierarchical log-linear analyses of temporal correlations between spectral powers at low (δ, θ, low α, high α and low β) vs. high frequency (high β (19.0-29.8 Hz) and low γ (30.0-40.8 Hz)) bands.

Figure 1. Clustering of EEG electrodes into regions of interest (ROI) above the major cortical areas. Middle electrodes Fz, Cz, Pz, and Oz have been excluded from power spectra analysis. L = Left, R = Right, FC = fronto-central, CP = centro-parietal, PO = parieto-occipital.

Figure 2. Line charts showing superposition of mean (± SEM) relative power averaged over (A) Fronto-Central, (B) Centro-Parietal, and (C) Parieto-Occipital electrodes for High Schizotypy (N = 16) and Low Schizotypy (N = 16) groups in the 1.2 to 40.8 Hz frequency range. Note the differences in frequency distribution between the two groups of individuals especially at parieto-occipital sites. In particular, a peak shift in the low α domain accompanied with a relative power increase is found in high schizotypal individuals.

Figure 3. Pearson's product moment cross-correlation of relative power spectra over a period of ~ 3 min. The plot shows temporal correlations between spectral powers at different frequencies between 1.2 and 40.8 Hz. Note in particular the large number of significant correlations between high-α & low-β and high-β & low-γ bands, i.e. more widely separated frequencies, in the High Schizotypy (N=16) compared with the Low Schizotypy group (N = 16). Hierarchical log-linear analyses revealed a significant difference between the two groups

in the significant correlations between the 'high-β + low-γ' and the both high-α (10.2-12.9 Hz) and low-β (13.2-18.8 Hz) frequency bands.

Supplementary data

Supplementary material cited in this article is available online at http://