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Abnormally high EEG alpha synchrony during working memory maintenance in twins discordant for schizophrenia ☆

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Abstract

Background: The present analyses aimed to test the prediction that schizophrenia patients and their non-schizophrenic co-twins would display reduced efficiency of the neurocognitive mechanisms subserving active maintenance of spatial information in working memory.
Methods: Upper alpha frequency band EEG event-related desynchronization and synchronization (ERD/ERS) were calculated as percent changes in power relative to an inter-trial baseline across 4 memory loads in a spatial delayed-response task.
Results: During the delay, the diagnostic groups showed equivalent ERD/ERS activity over posterior scalp regions at the lowest memory load; however, as memory load increased, patients, and to an intermediate degree, their non-schizophrenic co-twins (monozygotic and dizygotic pairs collapsed together), showed significantly greater increases in ERD/ERS amplitude as compared with controls.
Conclusions: These findings demonstrate abnormally increased ERD/ERS amplitudes with increasing memory load in patients with schizophrenia and their co-twins, consistent with inefficiency of the neurocognitive mechanisms supporting active maintenance of information across a delay.

Keywords: Schizophrenia; Electrophysiology; Working memory; Twin; Efficiency; Alpha synchronization; Inhibition; Interference resolution

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1. Introduction

Schizophrenia patients and their first-degree relatives exhibit impaired working memory (WM) performance, possibly reflecting the disorder's genetic diathesis (Glahn et al., 2003). Attempts to determine the neural bases of these WM deficits suggest that reduced efficiency of certain critical neurocognitive mechanisms may be involved (Callicott et al., 2003; Manoach, 2003; Karlsgodt et al., 2007). Consistent with an inefficiency hypothesis, we demonstrated that compared to controls, patients and their non-schizophrenic co-twins exhibit relatively *larger* changes in the electrophysiological signatures of the stimulus-encoding and memory-consolidation stages of WM performance, per unit increase in memory demands (Bachman et al., submitted for publication). Along with encoding and consolidation, successful maintenance of information over a delay requires action of WM control functions, including suppression of potential interference when target stimuli are no longer displayed. Inhibiting cognitive processing of potential distracters is critical for preventing competition between task-relevant and task-irrelevant representations (Postle, 2005), and has been shown behaviorally to be differentially impaired in schizophrenia (Oltmanns and Neale, 1975).

Event-related desynchronization (ERD) and synchronization (ERS) of upper, or "fast," EEG alpha frequency band activity, a measure of power decrease (ERD) or increase (ERS) as a percentage of pre-stimulus power (Neuper and Pfurtscheller, 2001), have been associated consistently with individual differences in neurocognitive efficiency measured during performance of challenging cognitive tasks, including paradigms that place heavy demands on WM (Neubauer et al., 2006). Research into the mechanisms underlying these fluctuations in power has demonstrated that alpha ERD reflects increased excitability of active cerebral cortex, whereas, alpha *ERS* appears to reflect decreased excitability, or large-scale *inhibition*, of cortex (Neuper and Pfurtscheller, 2001).

Consistent with this inhibitory function, alpha ERS is evident during the delay period of WM tasks, correlates in magnitude with memory load, and peaks over cortical areas responsible for processing task modality-specific sensory information (Sauseng et al., 2005; Jensen et al., 2002). Collectively, these findings suggest that alpha ERS reflects 'top–down' gating of sensory areas to prevent encoding of goal-irrelevant stimuli while task-relevant information is held actively in mind (reviewed, Klimesch et al., 2007).

Fast alpha ERS, therefore, should be greater in amplitude during the delay period of a delayed-match-to-sample WM task among individuals less efficient at gating task-irrelevant stimuli. It was predicted that, across groups, delay-period ERS would increase with memory load; moreover, patients and their co-twins were expected to display stronger load effects than controls, reflecting a hypothesized decrease in neurocognitive efficiency. Alternatively, inefficient inhibition of posterior cortical areas not directly related to WM would be associated with increased posterior ERS among patients and their co-twins, in a manner insensitive to WM load.

2. Methods and materials

2.1. Sample ascertainment and assessment

Participants were recruited from the cohort of same-sex twin pairs born in Finland between 1940 and 1957 and in which one cotwin received a DSM-III-R diagnosis of schizophrenia and the other did not meet criteria for any psychotic disorder. Additional subject identification and recruitment details are provided elsewhere (Cannon et al., 1998). Twenty-nine of these discordant pairs participated, although factors including hardware problems and noise, movement, and apparent electromagnetic inference – likely related to construction nearby the laboratory – rendered data from 16 twin sets unusable. Since only intact twin pairs were included, patients and their non-schizophrenic co-twins were eliminated from the study sample at equivalent rates. Another 4 discordant pairs were excluded because their behavioral performance fell below chance, leaving 9 discordant pairs. After screening for any psychotic disorder, Cluster A diagnosis, or history of psychosis-related treatment or work disability in any first-degree relatives, 9 demographically-matched, control twin pairs were recruited from the same database. The data contamination discussed above did not affect the discordant and control pairs differentially (16 discordant sets and 14 control sets eliminated).

Pairs did not differ in age (discordant: $M=47.97$ years; control: $M=48.67$; $F[1,35]=0.066$, $p=0.936$) or sex (4 female pairs per group), and all were right-handed and white. Substance abuse histories were also matched. Zygosity type was collapsed due to the size of the overall sample.

After the study was described, written informed consent was obtained. The study protocol was approved by the ethics committees or Institutional Review Boards of the Universities of Helsinki, Pennsylvania, and California, Los Angeles, and the Uusimaa Hospital District in Helsinki.

2.2. Behavioral task

The match-to-sample task (Glahn et al., 2003) consists of 2000 ms exposure to a memory set of 1, 3, 5, or 7 locations arrayed around a fixation point, followed by a 3000 ms delay during which only the fixation point is visible, and then a single-probe dot prompting the participant to decide whether it matches the location of any stimuli in the memory set. 50% of trials were true positive and 50% were true negative; trial sequence was ordered randomly. Participants received feedback during initial practice trials.

2.3. EEG recording and signal conditioning

EEG was recorded in a magnetically-shielded room using a whole-head EEG/MEG instrument (Elekta Neuromag, Ltd.). Signals were obtained from 66 equally-spaced Ag/AgCl electrodes referenced to the nose (Virtanen et al., 1996), and digitized at 500 Hz, with a 0.01–160 Hz band-pass filter. Vertical and horizontal electro-oculograms (EOG) were recorded with a bandpass of 0.5–30 Hz.

Continuous data were subjected to independent components analysis (ICA; Jung et al., 2000) for identification and removal of artifacts. On average, 16.1% (S.E.M. = 1.3%), 14.0% (S.E.M. = 1.9%), and 14.3% (S.E.M. = 1.9%) of components were removed from the control, cotwin, and patient data, respectively, with no significant difference between the groups, $F(2,35) = 0.55$, $p = 0.58$. Conditioning of the EEG data included band-pass filtering (zero-phase shift, 0.01–70 Hz). Epochs were sorted for accuracy and only correct trials were retained.

As recommended by Klimesch (1999), peak individual alpha frequency (IAF) was ascertained for each subject. Each participant's fast alpha band ranged from IAF at the lower bound to (IAF + 2 Hz) at the upper bound. ERD/ERS was calculated as a percentage of power decrease (ERD) or increase (ERS), relative to the 200 ms pre-stimulus baseline (Neuper and Pfurtscheller, 2001). Consistent with published reports (Neubauer et al., 2006), electrodes were collapsed into linearly-derived channels (created from clusters of 7 contiguous EEG channels) representing grossly-defined brain regions (see Fig. 1).

2.4. ERD/ERS calculation

Data analysis employed a general linear mixed model ANOVA (SAS Institute, Cary, NC), with set size entered as a repeated measure and twin-pair membership entered as a random variable (Satterthwaite option used to correct for non-independence of observations). Group differences and Group × Set Size interactions were tested for accuracy (% correct), reaction time (RT), and fast

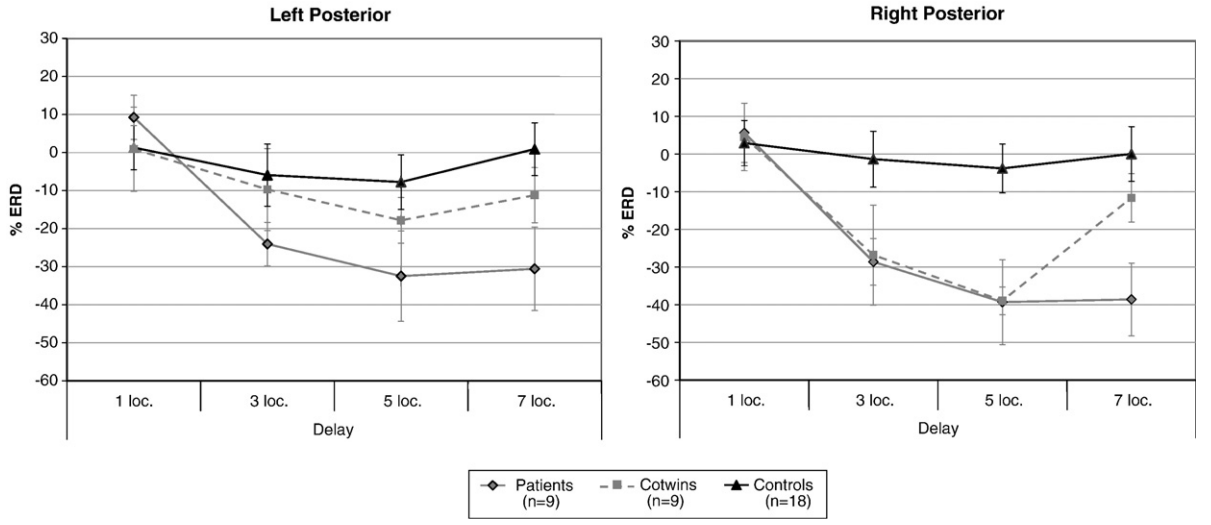

Fig. 1. Fast alpha band ERD/ERS during delay period of spatial working memory task. Event-related desynchronization (positive values) and synchronization (negative values) of fast alpha band EEG activity during the information maintenance period of the spatial match-to-sample task. Left Posterior and Right Posterior regions were derived linearly from combinations of electrodes over corresponding areas of the scalp. Referring to our approximated International 10–20 System (Jasper, 1958) electrode locations, the Left Posterior channel consists of: P1', P3', P5', P7', PO3', PO7', and O1'. The Right Posterior channel consists of: P2', P4', P6', P8', PO4', PO8', and O2'. For both derived channels, the diagnostic groups showed equivalent ERD/ERS activity at the lowest memory load; however, as memory load increases, schizophrenia patients, and to an intermediate degree, their non-schizophrenic co-twins, showed a relatively more dramatic increase in ERD/ERS amplitude.

alpha ERD/ERS magnitude. Hypotheses were modeled as contrast statements within the ANOVA.

3. Results

3.1. Behavioral findings

There were significant effects of group, $F(2,27)=3.75$, $p=0.036$, and memory set size, $F(3,105)=50.90$, $p<0.001$, on accuracy. Consistent with studies using the same task (e.g., Glahn et al., 2003), Group × Set Size was not significant, $F(6,105)=1.32$, $p=0.255$. RT results paralleled the accuracy data with significant effects of group, $F(2,28)=9.09$, $p=0.009$; and memory set size, $F(3,106)=49.65$, $p<0.001$; but not Group × Set Size, $F(6,105)=0.33$, $p=0.920$.

3.2. EEG results

During the delay, there were significant effects of group, $F(2,33)$ 4.92, $p=0.014$, memory load, $F(3,511)=11.72$, $p<0.001$, and scalp region, $F(3,511)=3.19$, $p=0.024$ (anterior vs. posterior, not included) on fast alpha ERS. Critically, the Group × Memory Load interaction was significant, $F(6,511)=4.16$, $p=0.004$, as was the contrast predicting that patients and their co-twins would show greater ERS than controls, most markedly at higher load levels, $F(1,511)=14.11$, $p<0.001$. Despite this increased load-sensitivity among patients and their co-twins, topographic distribution of ERS activity did not differ as evidenced by the absence of Group × Scalp Region, $F(6,511)=0.93$, $p=0.473$, Memory Load × Scalp Region, $F(9,511)=0.60$, $p=0.797$, or Group × Load × Scalp Region, $F(18,511)=0.48$, $p=0.966$, effects.[1] There were no significant associations between electrophysiological measures and symptom severity or medication exposure.

4. Discussion

Schizophrenia patients and their co-twins were found to display a larger increase in ERS magnitude with increasing memory loads, relative to controls. Given that delay-period alpha ERS likely reflects the activity of a 'top–down' (Klimesch et al., 2007) interference control mechanism serving to buffer task-relevant information against competition from potential distracters (Klimesch et al., 2007; Jensen et al., 2002), these results suggest an increased physiological cost of screening out potentially-interfering information among patients and their co-twins. Therefore, rather than failing to inhibit encoding of task-irrelevant stimuli, interference control appears to function in affected groups, but at greatly reduced efficiency.

Although these conclusions rely upon a relatively small sample, several safeguards were implemented in order to preserve our inferential power. These include use of ICA to remove non-cerebral artifacts while leaving EEG signals unaltered (Jung et al., 2000), reliance on a minimum number of accurate, artifact-free epochs per condition, and implementation of statistical tests that do not assume equal variance between groups. Finally, exclusion of subjects performing below chance at two or more memory loads and inclusion of only correct trials removed any uncertainty inherent in consideration of cognitive processes leading to incorrect responses.

The necessity of combining monozygotic and dizygotic co-twins into a single category precludes stating conclusively that genetic factors account for patients' and their co-twins' apparently homologous decrements in neurocognitive efficiency. The presence of these abnormalities among patients' co-twins, however, does suggest that they occur independently of diagnosis-related factors, such as antipsychotic medication exposure, significant symptom expression, and history of institutionalization.

Thus, present results provide an electrophysiological perspective on WM capacity limitations associated with schizophrenia and its inherited diathesis, demonstrating that patients and their non-schizophrenic co-twins suffer from a reduction in neurocognitive efficiency during the process of active information maintenance, in addition to decreased efficiency evident during the late perceptual encoding period (Bachman et al., submitted for publication).

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Contributors

Drs. Kim and Cannon designed the study protocol, and collaborated with Drs. Lönnqvist, Kaprio, and Huttunen, and with Mr. Therman and Mr. Manninen, to recruit participants. Dr. Näätänen provided laboratory facilities for Mr. Therman's and Mr. Manninen's administration of the study protocol. Dr. Kim cooperated with Mr. Therman and Mr. Manninen to import and format the raw EEG data,

[1] On an exploratory basis, we did compare group averaged data (correct trials only) including subjects performing at or below chance with group data excluding those same subjects, and found virtually no difference in the pattern of ERS magnitude results.

and with Dr. Bachman to carry out initial data processing. Under the guidance of Drs. Yee and Cannon, Dr. Bachman completed data processing, performed statistical analyses, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest

The authors report no conflicts of interest.

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