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Basic visual dysfunction allows classification of patients with schizophrenia with exceptional accuracy

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ABSTRACT

Basic visual dysfunctions are commonly reported in schizophrenia; however their value as diagnostic tools remains uncertain. This study reports a novel electrophysiological approach using checkerboard visual evoked potentials (VEP). Sources of spectral resolution VEP-components C1, P1 and N1 were estimated by LORETA, and the band-effects (BSE) on these estimated sources were explored in each subject. BSEs were Z-transformed for each component and relationships with clinical variables were assessed. Clinical effects were evaluated by ROC-curves and predictive values. Forty-eight patients with schizophrenia (SZ) and 55 healthy controls participated in the study. For each of the 48 patients, the three VEP components were localized to both dorsal and ventral brain areas and also deviated from a normal distribution. P1 and N1 deviations were independent of treatment, illness chronicity or gender. Results from LORETA also suggest that deficits in thalamus, posterior cingulum, precuneus, superior parietal and medial occipitotemporal areas were associated with symptom severity. While positive symptoms were more strongly related to sensory processing deficits (P1), negative symptoms were more strongly related to perceptual processing dysfunction (N1). Clinical validation revealed positive and negative predictive values for correctly classifying SZ of 100% and 77%, respectively. Classification in an additional independent sample of 30 SZ corroborated these results. In summary, this novel approach revealed basic visual dysfunctions in all patients with schizophrenia, suggesting these visual dysfunctions represent a promising candidate as a biomarker for schizophrenia.

1. Introduction

Disturbances of neurofunctional processing can be studied using both structural and functional imaging as well as neurophysiological measures such as EEG and event-related potentials (Javitt et al., 2008; Keshavan et al., 2008; Carter et al., 2011). To date, many research efforts in schizophrenia (SZ) have been devoted to the assessment of evoked responses extracted from EEG measures. These investigations have proven useful in providing genetic vulnerability, pathophysiological, and progression markers of possible ongoing cognitive and cortical deterioration. Recently, these results have been used to evaluate clinical trials focused on the improvement of cognition (van der Stelt and Belger, 2007; Butler et al., 2012).

Despite these promising results, there is still a large gap between the advances at the neurobiological, genetic, and electrophysiological level and the possibility of clinical interventions in SZ. Currently, no generally accepted biomarkers exist for SZ that can be used as standards in clinical practice. The visual system is a good candidate system since numerous visual processes have been identified as being altered in SZ (Butler et al., 2008). In particular, studies involving visual evoked potentials (VEPs) have consistently demonstrated that patients with SZ exhibit severe deficits of visual sensory processing (Foxe et al., 2001; Yeap et al., 2006, 2008a, 2008b; Lalor et al., 2012). One of the shortcomings of these studies is that group results do not allow for diagnostic specificity and sensitivity on an individual level. Therefore, measures of individual results are urgently required to improve diagnostic specificity and treatment assignments.

The mechanisms underlying the neurobiological dysfunctions in SZ remain controversial (Foxe et al., 2005; Butler et al., 2008). Several researchers have begun to look toward the lower visual regions to assess dysfunctions in the early stages of sensory processing (Butler et al., 2008). To date, it is generally accepted that such early-stage dysfunctions represent a critical pathophysiological component in SZ

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(Doniger et al., 2002; González-Hernández et al., 2006; Butler et al., 2008). However, the distribution of deficits within patient and control groups usually show considerable overlap, a fact that clearly restricts the utility of visual-based measures as diagnostic or risk assessment tools on an individual level.

Early visual processing deficits in SZ have been mostly seen in the VEP positive component P1 (Doniger et al., 2002; Yeap et al., 2006; Martínez et al., 2012). P1 is widely considered to arise from generators inside the dorsal and ventral extra striate cortex (Martinez et al., 1999; Di Russo et al., 2005). Abnormal P1 can result from a variety of dysfunctions (Haenschel et al., 2007; Butler et al., 2008). The other two VEP components, C1 (≈75 ms) and N1 (≈145 ms) have been less systematically studied in SZ. The C1 component seems to have sources distributed along the (circum) striate cortex while the N1 emerges mainly from ventral area (Foxe et al., 2001; Foxe and Simpson, 2002; Yeap et al., 2006). In most cases, these locations have been inferred from surface evoked responses, analogies with animal studies or by compiling results of separate studies. Deficits associated with the symptoms have been inconsistent (Yeap et al., 2008a). Most of the studies failed to find correlation between P1 amplitude measures and clinical symptoms (Butler et al., 2005; Schechter et al., 2005). However relationships were seen when the visual evoked response was assessed through brain oscillation analysis (Spencer et al., 2004). Despite the progress in localizing neural dysfunctions within the visual system and related areas, there is an urgent need for a more consistent definition of the frequency of basic visual deficits, their reliability and the association with clinical variables. This would considerably improve the utility of VEPs in the classification of patients versus controls. Here, we investigated one candidate method.

Combining source detection techniques with evoked responses under appropriate stimulus conditions can contribute to the detection of the pathophysiological mechanisms in SZ (Di Russo et al., 2005; Foxe et al., 2005; González-Hernández et al., 2009). Similarly, current sources estimated from averaged VEPs, which were band-pass filtered using several different filters showed differences between specific mental states (Haupt et al., 2008; González-Hernández et al., 2009). This novel band-source effect (BSE) has yet not been systematically addressed in SZ research.

The foremost aim of the present study was to uncover VEP alterations at the individual level in patients drawn from a large patient sample ($N = 48$). Secondarily, this study aimed to map these neural correlates to illness related symptoms by using the BSE approach. This work differs from previous studies (Haupt et al., 2008; González-Hernández et al., 2009) by using the computed difference among bands—F value—and its voxel-based distribution (Z-transformation) instead of addressing specific paired band differences (i.e. post-hoc analysis), and by evaluating individualized results. In this context Z value also reflects the differences among bands. We combined a full-field checkerboard stimulus with a dense EEG recording array and VEP with spectral resolution (González-Hernández et al., 2009). Using a standard brain, sources were estimated at the peak of C1, P1, and N1 components. After calculating the BSE in each subject, the patient's data was Z-transformed, 3D-plotted and significant deviations were then assessed in relation to the independent variables. In this work, the terms 'dorsal and ventral' not only refer to posterior areas involved in visual processing as in typical visual studies. We chose a passive visual contrast task because contrast processing, as a basic visual function, is a precursor for most visual tasks. Manipulation of ongoing EEG (i.e. spectral resolution VEP) may become sensitive enough to yield neurobiological dysfunctions specific to SZ and may provide clinical evidence for a neurophysiological index that could help guide clinical decision-making.

2. Subjects

Forty-eight patients with schizophrenia (Table 1) were drawn from both outpatient and inpatient facilities including the Corynthia Primary Health Care Center, the Department of Psychiatry of Hermanos-Ameijeiras Hospital and the Manuel-Fajardo Hospital, all of which were situated in Havana City, Cuba. Patients were diagnosed according to DSM-IV(R) based on consensus conferences by psychiatric experts considering all available clinical data. For psychopathological symptoms, 29 patients were assessed on the Positive and Negative Syndrome Scale (PANSS) (Kay, 1987). Exclusion criteria included any history of neurological disorders and current drug/alcohol abuse. Patients were medicated at the time of testing. Fifty–five medication free volunteers (Table 1) without any history of psychiatric or neurological diseases or drug/alcohol abuse were also studied. All subjects had normal or corrected to normal vision and gave informed consent for their participation. The study was conducted in accordance with the Declaration of Helsinki concerning human experimentation and approved by the Ethical Committee of the Hermanos-Ameijeiras Hospital.

Table 1
Clinical and demographic characteristics of the groups.

	Schizophrenia ($n = 48$)	Controls ($n = 55$)
Age (years)	30.66 ± 9.59	31.20 ± 9.2
Males: females	31: 17	30: 25
Education duration (years)	12.60 ± 3.77	16.70 ± 2.8
Onset age (years)	23.66 ± 6.35	
Illness duration (years)	9.27 ± 8.61	
PANSS score ($n = 29$)		
-positive symptoms	20.62 ± 8.89	
-negative symptoms	23.13 ± 8.41	
Neuroleptic type		
Typical: Atypical	23: 25	

3. Visual task

Subjects were seated in a comfortable chair in a dimly lit, air conditioned room. Subjects were instructed to fixate a central point on a monitor and to refrain from excessive movement and blinking. A full-field black–white checkerboard stimulus, subtending 60 arc/min of visual angle, with a spatial frequency 1.15 cpd (Mind Tracer, Neuronic SA, Havana), was presented on a 19″ Flat monitor (HP) located 0.9 m from the subjects. Checkerboard reversal rate was 1 Hz (stimulus: 400 ms, post-interval: 100 ms). A total of 240 stimulus presentations were equally separated into two blocks of 120 to avoid patient disengagement. Luminance was constant and the checkerboard contrast was 100%. Viewing was monocular, but collected from all participants from one eye and then also from the other one, choosing randomly the first eye.

4. Electrophysiology

An electrode cap with 58 monopolar channels was fitted to the participant's head with the ground electrode at the middle anterior frontal site and the references at the earlobes. For analysis, data were re-referenced to an average reference. Recording, digitization, and processing of the EEG were performed with a Medicid-5-64 data acquisition system and the EP-Workstation recording software (Neuronic, SA). Amplifier specifications of this system were gain 1000 dB, low cut at 0.5 Hz and high cut at 70 Hz, with a 60-Hz notch filter. Sampling rate was 500 Hz and all electrode impedances were kept bellow 5 kΩ. Marks corresponding to the stimuli were co-registered and stored with the amplified and digitized raw EEG for subsequent off-line analysis.

The EEG data were analyzed for evoked activity by the EP-Workstation analyzer software (Neuronic, SA). The continuous EEG was epoched from −100 to 260 ms, linearly detrended and DC corrected (subtraction of the mean pre stimulus activity). Each EEG was visually inspected and trials with EEG signals greater than 100 μV