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Auditory P3a and P3b neural generators in schizophrenia: An adaptive sLORETA P300 localization approach

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ABSTRACT

The present study investigates the neural substrates underlying cognitive processing in schizophrenia (Sz) patients. To this end, an auditory 3-stimulus oddball paradigm was used to identify P3a and P3b components, elicited by rare-distractor and rare-target tones, respectively. Event-related potentials (ERP) were recorded from 31 Sz patients and 38 healthy controls. The P3a and P3b brain-source generators were identified by time-averaging of low-resolution brain electromagnetic tomography (LORETA) current density images. In contrast with the commonly used fixed window of interest (WOI), we proposed to apply an adaptive WOI, which takes into account subjects' P300 latency variability. Our results showed different P3a and P3b source activation patterns in both groups. P3b sources included frontal, parietal and limbic lobes, whereas P3a response generators were localized over bilateral frontal and superior temporal regions. These areas have been related to the discrimination of auditory stimulus and to the inhibition (P3a) or the initiation (P3b) of motor response in a cognitive task. In addition, differences in source localization between Sz and control groups were observed. Sz patients showed lower P3b source activity in bilateral frontal structures and the cingulate. P3a generators were less widespread for Sz patients than for controls in right superior, medial and middle frontal gyrus. Our findings suggest that target and distractor processing involves distinct attentional subsystems, both being altered in Sz. Hence, the study of neuroelectric brain information can provide further insights to understand cognitive processes and underlying mechanisms in Sz.

1. Introduction

Alterations in cognitive processing in schizophrenia (Sz) have long been assessed using electroencephalographic (EEG) recordings (Roach and Mathalon, 2008). In particular, it is usual to obtain the event-related potentials (ERP) as the average of EEG epochs time-locked to repeated external stimulus or events. Reduced P300 amplitude during an auditory oddball paradigm is one of the most consistent findings in schizophrenia (Sz) (Bramon et al., 2004); however, the neural bases of this amplitude reduction are incompletely understood. In this regard, the analyses focused on the localization of neural generators can contribute to elucidate possible sources of altered information processing in Sz (Mulert et al., 2004).

The oddball paradigm is a common experimental design used in ERP analyses to obtain the P300 wave. The 3-stimulus variant of the auditory-oddball paradigm is characterized by infrequent-distractor stimuli interspersed randomly into a sequence of frequent-standard and rare-target. This paradigm allows the examination of cognitive processing as response to both relevant and irrelevant stimuli (Polich, 2007). The resulting P300 wave includes two components: the P3a, evoked by distractor stimuli for which no subject-response is expected; and the P3b, elicited by target stimuli for which the subject is instructed to respond. The neural processing as a response to auditory distractor tones has been related to bottom-up attentional mechanisms; hence, P3a may be generated whether sufficient attentional focus is engaged. In contrast, P3b seems to be related to conscious top-down target processing, likely contributing to processing the stimulus information and performing cognitive response (Polich, 2007; Strobel et al., 2008). In previous reports, we found a blunted ERP modulation in Sz as

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response to both target (Bachiller et al., 2014) and distractor (Bachiller et al., 2015b) tones during an oddball paradigm. Thus, the analysis of the differences in neural pattern generators between Sz patients and healthy controls becomes an interesting research topic to clarify the neural substrate of reduced P300 amplitude in Sz.

Source imaging techniques may help to detect neural generators that contribute to the scalp recorded ERPs, resulting in an acceptable compromise between spatial and temporal resolutions. The inverse solution (i.e. the computation of 3-D intracerebral images of electric neuronal activity based on scalp-recorded EEG) would provide useful information on the time course and localization of brain functions (Pascual-Marqui, 2002). There is no unique solution to the inverse problem; nevertheless, the low-resolution brain electromagnetic tomography (LORETA) is one of the most reliable methods for localizing ERP electrical activity and it is associated with relatively low error rates (Pascual-Marqui, 2002; Jung et al., 2012). LORETA has been widely used for source localization in psychiatric disorders, such as Sz or depression (Kawasaki et al., 2004; Mientus et al., 2002). Moreover, auditory P3a and P3b source localization has been previously addressed in healthy controls using LORETA and functional magnetic resonance imaging (fMRI). P3a generators are localized in anterior cingulate, frontal area and parietal cortices (Polich, 2007; Strobel et al., 2008; Volpe et al., 2007), whereas P3b sources include a more distributed network, involving superior and medial temporal, posterior parietal, hippocampal, cingulate and frontal structures (Polich, 2007; Strobel et al., 2008; Volpe et al., 2007; Wronka et al., 2012).

It is noteworthy that the previous LORETA findings are influenced by one important technical shortcoming: although ERP analyses show a considerable inter-subject variability of P300 latency (Campanella et al., 1999), LORETA source imaging studies commonly used a large fixed post-stimulus window of interest (WOI), like [250 500] ms (Higuchi et al., 2008; Kawasaki et al., 2007; Sumiyoshi et al., 2006), [280 450] ms (Wang et al., 2003, 2010), [240 420] ms (Pae et al., 2003), [227 383] ms (Volpe et al., 2007), or [400 700] ms (Wronka et al., 2012).

In this study we proposed a new LORETA approach based on P300 wave ('P300 latency adaptive WOI') to properly localize P300 brain-source generators in each subject. To the best of our knowledge, this is the first study that analyzes the sources of both P3a and P3b in Sz using LORETA. Hence, this research is aimed at: (i) analyzing the performance of the adaptive WOI method in comparison to conventional fixed WOI analysis; and (ii) applying the adaptive WOI method to analyze the differences of auditory P3a and P3b underlying cortical sources between Sz patients and healthy controls.

2. Materials and methods

2.1. Subjects

Thirty-one patients with paranoid Sz (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, DSM-IV-TR, criteria) and 38 healthy controls were recruited. Sz group was composed by 20 chronic stably treated patients, 7 fist-episode patients and 4 patients who had dropped their medications for a period longer than 6 months. Chronic patients were previously treated with atypical antipsychotics. First-episode patients have not been received previous antipsychotic treatment, except for a brief time interval of less than 72 h prior to EEG acquisition. No medications were administered to the patients during the 12 h preceding the EEG recording. Controls were initially assessed by a semi-structured psychiatric interview to discard major psychiatric antecedents and treatments. Detailed description of treatments and doses, as well as exclusion criteria are detailed in previous reports (Bachiller et al., 2015a, 2015b). Symptoms were scored using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Socio-demographic and clinical characteristics for both groups are shown in Table 1.

Table 1
Socio-demographic and clinical characteristics of the cohort of subjects enrolled in the study. Values are shown as 'mean ± standard deviation, SD'. Post-stimulus P300 latency was calculated over a target response using a 9-sample moving average. P3a and P3b amplitudes were obtained from distractor and target responses, respectively. Significance of between-group comparisons is shown in the first column (Kruskal–Wallis test, * $p < 0.05$; ** $p < 0.001$). aWOI adaptive window of interest, CP chronic patients, MTP minimally treated patients, M male, F female, NA not applicable.

	Sz patients	Controls
Age (years)	36.25 ± 9.62	33.35 ± 12.26
Gender (M:F)	21:10	23:15
PANSS-Positive	19.19 ± 4.81	NA
PANSS-Negative	19.52 ± 5.69	NA
PANSS-Total	73.19 ± 15.94	NA
Duration of the illness (months)	79.73 ± 103.37	NA
Number of artifact-free epochs	88.85 ± 16.15	84.47 ± 9.32
P300 latency at Pz (ms)	435.23 ± 67.82	413.05 ± 72.95
aWOI length (ms)	124.26 ± 61.66	117.47 ± 47.53
aWOI lower limit (ms)	375.48 ± 68.11	357.79 ± 66.33
aWOI upper limit (ms)	499.74 ± 85.76	475.26 ± 91.94
P3a amplitude at Pz (μV)**	0.70 ± 0.82	1.62 ± 1.21
P3b amplitude at Pz (μV)*	2.16 ± 1.18	3.10 ± 1.47

The research boards of the Hospitals of Valladolid and Salamanca (Spain) endorsed the study according to The Code of Ethics of the World Medical Association (Declaration of Helsinki). Moreover, written informed consent was obtained from patients, their caregivers and healthy volunteers.

2.2. EEG recording procedure

EEG recordings were performed while subjects underwent a 3-stimulus auditory-oddball paradigm. Participants heard a random series of 600 binaural tones (90 dB; 50 ms duration; 5 ms rise and fall-time) consisting on standard (2000 Hz tone), distractor (1000 Hz tone) and target tones (500 Hz tone) with probabilities of 0.6, 0.2 and 0.2, respectively (Bachiller et al., 2015a).

For each subject, 13 min of EEG activity and stimulus markers were continuously recorded using a 17-channel (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T5, T6, Fz, Pz and Cz) EEG system (BrainVision®, Brain Products GmbH; Munich, Germany). Electrodes were placed according to the revised 10/20 International System. Participants were relaxed and with their eyes closed. EEG data were recorded at a sampling frequency of 250 Hz and referenced over Cz electrode. Electrode impedance was always kept under 5 kΩ.

Each EEG recording was off-line re-referenced to the common average (Bledowski et al., 2004) and digitally filtered using a [0.5 40] Hz finite impulse response filter. Then, a three-step artifact rejection method was applied. Firstly, an independent component analysis was performed to decompose EEG signals (Delorme and Makeig, 2004). After a visual inspection of the scalp maps and their temporal activation, components related to eyeblinks were discarded. In a second step, continuous EEG data were segmented from −100 ms before target stimulus onset to 900 ms after onset. In a third step, artifacts were automatically rejected using an adaptive thresholding method (Bachiller et al., 2015a).

Finally, the responses to distractor and target tones were baseline-corrected by subtracting the 100 ms pre-stimulus mean and they were averaged across time-locked trials to obtain ERP data for each channel (Pae et al., 2003).

2.3. Identification of ERP components

The P300 wave is an ERP component commonly used to assess the neural underpinnings of cognition (Polich, 2007). P300 amplitude was obtained from ERP data as the most positive voltage between 250 and 550 ms, whereas P300 latency was defined as the time point from stimulus onset at which the peak amplitude is found (Polich, 2007).