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P50 sensory gating in panic disorder

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Abstract

Previous studies with prepulse inhibition in panic disorder (PD) have suggested that the early stages of sensory information processing are abnormal in patients with PD. To further investigate sensory gating function in panic disorder we performed a case-control study in a sample of 28 patients with PD, compared to 28 normal subjects and 28 schizophrenic subjects evaluating auditory mid-latency evoked potential P50 in a double-click paradigm as a measure of sensory gating. PD subjects showed weaker sensory gating as evidenced by higher P50 ratios as compared to normal subjects (62.5% vs. 45.4%, $p = 0.03$) and higher S2 (test) amplitude (3.5 μV vs. 2.1 μV, $p = 0.01$). Schizophrenic subjects when compared to healthy controls showed higher P50 ratios as compared to normal subjects (79.2% vs. 45.4%, $p < 0.01$) and higher S2 amplitude (3.3 μV vs. 2.1 μV, $p = 0.01$), but were not statistically different from PD subjects ($p > 0.1$). The present study corroborates recent findings of sensory gating dysfunction in PD. Further studies are still necessary to better understand the pathophysiology of this neurophysiological dysfunction and its nature as a trait or a state marker.

Keywords: Panic disorder; Sensory gating; EEG; Anxiety

1. Introduction

Auditory brain evoked potentials and other neurophysiological examinations have been performed in panic disordered patients in order to understand its underlying pathophysiology. Panic disordered patients were found to exhibit significantly larger N1 amplitudes associated initially to abnormal temporal processing (Knott et al., 1991) and N3 latency abnormalities, correlated to pontine activation, probably through *locus ceruleus* (Levy et al., 1996). These patients also showed enlarged prefrontal P300 in response to stimulus change, related to prefrontal-limbic pathways that could affect the processing of incoming information, supposedly disrupted in panic disorder (PD) (Clark et al., 1996; Turan et al., 2002) or even related to reticulothalamic structures plus septohippocampal limbic system (Gordeev et al., 2003). A standard two-tone discrimination task study (oddball task) showed amplitudes that are also suggestive of alteration of early information processing in PD, specifically N1 and N2 amplitudes for target tones and the N1 amplitude for non-target tones were significantly larger in the PD patients (Iwanami et al., 1997). Another odd-ball study replicated findings of an

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abnormal N2 in PD (Wang et al., 2003). More recently, studies focusing sensory gating based in the pre-pulse inhibition (PPI) were carried out in PD. Panic disorder patients in remission exhibited normal startle reactivity, reduced habituation and significantly reduced pre-pulse inhibition (PPI) and these alterations were more pronounced in patients with high trait and state anxiety (Ludewig et al., 2002). Increased startle response and decreased habituation were found in PD patients that were not under treatment and correlated significantly with higher cognitive dysfunction scores, but this was not the case for PPI (Ludewig et al., 2005).

The suppression of the P50 component of the auditory event-related potential has been used as an index of sensory gating in neuropsychiatric research (Freedman et al., 1983; Adler et al., 1998). The P50 wave is a small amplitude, positive wave occurring about 50 ms after an auditory stimulus. In the P50 suppression paradigm, when two stimuli are presented 500 ms apart, the amplitude of the second peak (S_2), compared to the first (S_1), is usually attenuated in healthy subjects (S_2/S_1 ratio <0.5), whereas in patients with schizophrenia, acute mania or post-traumatic stress disorder this suppression is impaired (S_2/S_1 ratio > 0.5) (Adler et al., 1998; Ghisolfi et al., 2004). The hippocampus, as well as structures of brainstem and temporal cortex have been suggested as mediators of P50 suppression and it is generally assumed that impaired suppression due to an inhibitory deficit, which leads to an overflow of information and diminished capacity to filter out irrelevant stimuli (Adler et al., 1998). The neurochemical basis of P50 suppression is not yet completely understood, but cholinergic, GABAergic and monoaminergic systems have been proposed to modulate this phenomenon (Adler et al., 1998; Hershman et al., 1995; Light et al., 1999) and more recently adenosine has been implicated in P50 dysfunction (Ghisolfi et al., 2002).

Despite the cumulative evidence for the involvement of auditory sensory processing and for disturbed sensory gating in PD, studies on P50 auditory gating are lacking, as far as we know. This work was designed to compare P50 auditory gating between PD patients and control healthy volunteers as well as schizophrenic patients as an additional control group.

2. Materials and methods

2.1. Subjects

This study was approved by the Institutional Review Board of Hospital de Clínicas de Porto Alegre. Participants were recruited and signed an informed consent form after complete explanation about the protocol, the purpose and potential risks of this study.

Twenty-eight PD outpatients, previously diagnosed according to DSM-IV criteria assessed by clinical interview and the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), were included (10 men and 18 women, mean age of 43.3 ± 10.1 years). At the time of P50 measurements, six PD subjects were not on pharmacological treatment, 11 were on antidepressants alone and 11 were on combined treatment with antidepressants and benzodiazepines. Characteristics of PD subjects are shown on Table 1. Twenty-eight healthy volunteers were recruited for this study among university students and local hospital employees (10 men and 18 women, mean age of 39.7 ± 7.8 years, all non-smokers). As an additional comparison group, 28 schizophrenia outpatients, previously diagnosed according to DSM-IV were included (12 men and 16 women, mean age of 37.5 ± 7.4 years). The three groups did not differ regarding age and gender. Healthy volunteers were screened by psychiatrists using a structured clinical interview. Exclusion criteria for healthy volunteers were a DSM-IV axis I diagnosis of any disorder, clinical illness and any current pharmacotherapy, current use of alcohol and drugs of abuse, except for nicotine and oral contraceptives. No control subjects were currently taking psychotropic medication, but some PD patients were on pharmacological treatment. Subjects with family history of schizophrenia or other psychotic disorders, in first or second degree, were also excluded. Participants could not use tobacco in the preceding 2 h, neither caffeine nor any beverages containing methylxanthines over the 4 h preceding the recordings. All schizophrenic patients were on treatment with typical antipsychotics, which do not correct P50 sensory gating deficit (Adler et al., 1998).

2.2. Electrophysiological recordings

The method for electrophysiological recordings was based on previously described protocols, with slight modifications (Nagamoto et al., 1996) as used by our group in previous works that replicated the classical findings for schizophrenia (Ghisolfi et al., 2002) and post-traumatic stress disorder (Ghisolfi et al., 2004). In brief, subjects were recorded seated, relaxed, and awake with eyes open and fixed on a distant target to decrease drowsiness during the recording. Electroencephalographic activity was recorded from a disk electrode (positive reference) affixed to the vertex (Cz) and referenced to both ears. Electroencephalogram (EEG) was provided using a Nihon–Kohden MEM-4104K system in 4 channels for recording of evoked responses integrated with auditory stimulator. The mean signal was registered in two channels (A_1 and A_2), one for each mastoid and amplified 20,000 times with a bandpass filter between 1 Hz and 10 kHz. EEG was collected for 1000 ms for each paired stimulus presented. Additional channels were used to record the electro-oculogram