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Dopaminergic mechanisms of target detection — P300 event related potential and striatal dopamine

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ABSTRACT

The P300 is a cortically generated event related potential (ERP) widely used in neurophysiological research since it is related to cognitive functions and central information processing. Intracerebral recordings and functional neuroimaging studies have demonstrated that this potential is generated by various brain regions including frontal, temporal and parietal cortices. Regarding the neurochemical background, clinical and genetic investigations suggest that dopaminergic neurons could be involved in the generation of the P300. However, there is no direct evidence in vivo that P300 amplitudes and latencies are related to dopaminergic parameters. The aim of this study was to further elucidate dopaminergic aspects of the P300 ERP by combining neurophysiological and nuclear medicine assessments in vivo. Patients with a major depressive episode underwent both P300 recordings and dynamic [^{123}I] IBZM SPECT for the evaluation of striatal dopamine D_2/D_3-receptor availability. There were statistically significant positive correlations of the striatal dopamine D_2/D_3-receptor status with P300 amplitudes and significant negative correlations with P300 latencies. Using this combined approach, the study presents direct evidence in vivo that the central dopaminergic system might play an important role in the generation of the P300 and that central dopaminergic activity could be involved in the modulation of P300 parameters. This association might be of relevance for the interpretation of P300 studies in psychiatric disorders.

1. Introduction

The P300 is an event related potential (ERP), occurring with a latency of about 300 ms (250 to 500 ms) after presentation of task-relevant stimuli, e.g. within an oddball paradigm, discriminating target from non-target stimuli (Sutton et al., 1965; Dierks and Maurer, 1989; Halgren et al., 1995a, 1995b; Hegerl and Frodl-Bauch, 1997; Frodl-Bauch et al., 1999). In neuropsychiatry, this potential is of particular interest because it is generated by different cortical and limbic structures including frontal, temporal and parietal regions (McCarthy and Wood, 1987; Halgren et al., 1998). The P300 has been proposed as a marker of different cognitive processes including attention, information processing, orienting, memory related processes or decision making (Donchin and Coles, 1988; Verleger, 1988). Electroencephalographic scalp recordings of the P300 show a maximum of the amplitudes over midline electrodes; electromagnetic tomography techniques (LORETA) and functional magnetic resonance imaging (fMRI) revealed that the distribution of elicited activations is in line with intracranial recordings (Kiehl et al., 2001; Mulert et al., 2004a,b).

The P300 has been investigated in various neuropsychiatric disorders, where reductions in amplitudes and increases in latencies have been described (Pfefferbaum et al., 1984, 1991; Polich et al., 1994; Hegerl et al., 1995; Gallinat et al., 2001).

Reductions of P300 amplitudes and, less consistently, increases in peak latencies are also common findings in patients with depression (Gangadhar et al., 1993; Kayser et al., 2000; Urretavizcaya et al., 2003; Kawasaki et al., 2004). Heterogeneous results might be due to depressive subtypes or the variability of the patients' clinical presentation, since marked reductions in P300 amplitudes were found especially in patients with more severe depression and with melancholic features (Gangadhar et al., 1993; Santosh et al., 1994; Kemp et al., 2009, 2010). There is evidence of a state-related aspect of P300 parameters in patients with depression. Gangadhar et al. (1993) showed an increase in P300 amplitudes in melancholic patients upon

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recovery under ECT treatment, and Neuhaus et al. (2007) were able to demonstrate that treatment responders to vagus nerve stimulation showed increases in P300 amplitudes that were significantly correlated with the course of clinical symptoms (Gangadhar et al., 1993; Neuhaus et al., 2007).

However, the clinical implications of P300 studies are a matter of discussion since reductions in amplitudes seem to be rather unspecific findings. In addition, the physiological context of the P300 potential remains to be further elucidated. Regarding clinical relevance, the neurochemical background is of special interest. P300 potentials recorded on the scalp result from intracortical currents induced by postsynaptic potentials. For the electrogenesis of the P300, glutamatergic activity via NMDA receptors might be of major relevance (Frodl-Bauch et al., 1999). However, according to clinical and genetic studies, there is evidence of a contribution of dopaminergic systems to the generation of the P300. Patients with Parkinson's disease exhibited prolonged P300 latencies that decreased under dopaminergic treatment (Stanzione et al., 1991; Sohn et al., 1998). It has been shown that P300 amplitudes are associated with polymorphisms in dopamine D_2 and D_3 receptor genes (Noble et al., 1994; Berman et al., 2006; Mulert et al., 2006) and that they can be modulated by a challenge with amphetamine (McKetin et al., 1999) and other dopaminergic agents (Takeshita and Ogura, 1994; Nishimura et al., 1995). These associations are of interest and could be the basis for the recognition of the P300 as an intermediate phenotype (Mulert et al., 2006). Under these assumptions changes in P300 amplitudes as robust findings in patients with schizophrenia (Ford et al., 1992; Juckel et al., 1996; Frodl et al., 2002b) could be well explained by the dopamine hypothesis of this disorder. Besides mesolimbic dopaminergic hyperactivity, associated with positive schizophrenic symptoms, a prefrontal hypoactivity of the dopamine system has been postulated which might be involved in the development of negative symptoms, cognitive deficits, and attentional alterations (Shelley et al., 1997; Duncan et al., 1999; Kahkonen et al., 2001). In depression, there is some evidence of a differential contribution of neurotransmitter systems to the presentation of depressive symptoms. Dopaminergic dysfunction could contribute to the presence of melancholia, including features such as anhedonia or psychomotor disturbances (Malhi et al., 2005), which in turn might be associated with alterations of event related potentials (Kemp et al., 2010). Whereas alterations of early sensory processing reflected by an exaggeration of the P200 potential could be the consequence of serotonergic dysfunction (Kemp et al., 2010), pronounced P300 abnormalities in patients with melancholic features provide at least indirect evidence of the P300 being influenced by the dopaminergic system (Malhi et al., 2005; Kemp et al., 2010).

However, direct evidence of a dopaminergic modulation of the P300 is lacking and several studies reported the P300 being unaffected by dopaminergic drugs or stimuli (Juckel et al., 1996; Luthringer et al., 1999; Oranje et al., 2006). Therefore the aim of this study was to further explore the relationship between dopaminergic neurotransmission and neurophysiological variables with a multimodal approach combining different techniques. We investigated depressed patients by recording the P300 and determining dopamine D_2/D_3-receptor availability with single photon emission computed tomography (SPECT) and the dopamine D_2/D_3-receptor radioligand [^{123}I] IBZM. This concept allows direct and objective comparisons of P300 recordings and activity of the dopaminergic system in vivo. Hence, our focus was not to contribute to the pathophysiology of depression but to investigate potential dopaminergic meachnisms of neurophysiological techniques.

2. Methods

The investigations were part of a research project on the neurobiological background of neurophysiological tools and interventions such as event related potentials and transcranial magnetic stimulation. The study was reviewed and approved by the local ethics committee of the Ludwig-Maximilian-University of Munich and by the federal regulatory authorities regarding the use of radioactive agents. All subjects gave written informed consent for participation in this study, after the procedures had been fully explained.

2.1. Subjects

Seven patients (age 50 to 69 years, 4 females, 3 males) with moderate to severe major depressive episodes (DSM IV: 296.xx, ICD10: F31-33, Hamilton Rating Scale for Depression-HRSD score $\geq$18) were included. Exclusion criteria were comorbid psychiatric disorders (DSM IV-axis I), neurological disorders, especially Parkinsonian syndromes, and any psychotropic medication known to interfere with [^{123}I] IBZM binding. Other psychotropic drugs were withdrawn starting 7 days before inclusion in the study, and patients remained medication-free during the study procedures. After the washout period, the subjects received neurophysiological assessments (EEG, P300) and [^{123}I] IBZM SPECT twice, at baseline and again after a 3-week treatment with repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex with the following stimulation parameters per session: application of 3000 stimuli in 30 trains of 10 s with a 30-s intertrain interval at 10-Hz stimulation frequency and with 100% stimulation intensity related to individual resting motor threshold. The last rTMS session was performed at least 24 h before the second imaging and neurophysiological studies (Pogarell et al., 2006). In order to investigate acute effects of exogenous challenges on dopaminergic activity, the SPECT study was performed according to a bolus and constant infusion protocol as proposed by Laruelle et al. (1995, 1996). These data are reported elsewhere (Pogarell et al., 2006).

2.2. P300 recordings and analyses

2.2.1. P300 paradigm

The subjects in our study underwent EEG recordings under stimulation with an auditory oddball paradigm with 80% frequent (non-target) stimuli and 20% target stimuli (400 pure tones at 500 Hz, 100 pure tones at 1000 Hz, respectively) presented binaurally via headphones in a pseudo-randomised order (80-dB sound pressure level, 40-ms duration with 10-ms rise and fall time, interstimulus interval 1.5 s). Subjects were instructed to press a button with their dominant hand upon recognition of the target stimuli. Prior to the recording, auditory dysfunction was excluded by auditory testing of hearing thresholds using a Phillips audiometer.

2.2.2. EEG recording and averaging

Subjects were seated in a slightly reclined comfortable armchair with a headrest in a sound attenuated and electrically shielded room. They were instructed to avoid movements and to keep their eyes closed during the recording. Electroencephalographic (EEG) activity and event related potentials were recorded using a Neuroscan SynAmps system with 32 tin electrodes placed via electrocaps according to the International 10–20 System with Cz as reference and Fpz as ground electrode. Additional electrodes (above the left eye and the left ocular canthus) were used to monitor ocular artefacts (EOG). Impedances were kept at 5 kΩ or below. EEG was digitised at a sample rate of 250 Hz and band-pass filtered with a filter range from 0.16 to 70 Hz. EEG epochs of 1000 ms (from 200 ms pre-stimulus to 800 ms post-stimulus) were averaged. For artefact rejection, an amplitude criterium ($\pm$50 μV) was used involving all of the 32 EEG channels and the EOG at any time point during the averaging period. At least 50 artefact-free sweeps for target and non-target and non target stimuli were obtained for averaging.