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Are the subthalamic nucleus, internal globus pallidus and thalamus involved in thinking?

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ABSTRACT

Introduction: The aim was to compare event-related potentials and event-related de/synchronisations between the P300 and mismatch negativity paradigms, both recorded in the subcortical structures and thus illustrate conscious cognition process in these structures. The second aim was to uncover if the mismatch negativity can be found in subcortical structures.

Methods: We included patients with Parkinson's disease, generalised dystonia, essential tremor and epilepsy in the deep brain stimulation program. The electrodes were implanted into the subthalamic nucleus, internal globus pallidus, then in the anterior and ventral intermediate nucleus of the thalamus bilaterally. We were interested in local oscillations.

Results: We found a significant P300 - mismatch negativity difference at 250–400 ms latency in the basal ganglia and thalamus in event-related potentials in 7 out of 8 patients. There was also a significant difference in event-related de/synchronisations at 500–1500 ms latency in 7 out of 8 patients in the beta band and desynchronisation in the subthalamic nucleus plus the internal globus pallidus and synchronisation in the anterior thalamic nucleus. When the mismatch negativity protocol was processed we found a significant outcome in event-related potentials (100–250 ms latency) in the internal globus pallidus and the ventral intermediate nucleus of the thalamus in 4 out of 6 patients.

Conclusion: The results suggest that the subthalamic nucleus, internal globus pallidus and maybe also the thalamus are involved firstly in the subconscious cognitive process 100–250 ms after the stimuli, then in the conscious cognitive processes at the level of the afferent information processing network at 250–400 ms and finally they affect conscious cognitive activity at a time of large brain neuronal network 500–1500 ms after stimuli.

1. Introduction

Mismatch negativity (MMN) is the electrophysiological recording of changes in automatic sensory memory activity. The brain registers the repetitive stereotyped stimuli unconsciously and when a change in that signal occurs, brain activity changes as well. Using averaged electroencephalography (EEG) we are able to detect a difference between stereotype stimuli and changed stimuli. The generators of MMN are in the temporal and frontal cortex. But it is likely that the neuronal net included in this response is wider – an MMN-like response was

Abbreviations: ATN, anterior thalamic nucleus; DBS, deep brain stimulation; Dys, generalised dystonia; EEG, electroencephalography; ERD, event-related desynchronisations; ERD/S, event-related de/synchronisations; ERP, event-related potentials; ERS, event-related synchronisations; GPI, internal globus pallidus; ICE, intracerebral electrodes; MMN, mismatch negativity; MMN-like, mismatch negativity-like potentials; PD, Parkinson's disease; P300, P300 wave; pP300, pure P300 wave; STN, subthalamic nucleus; VIM, ventral intermediate nucleus of the thalamus

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recently discovered in the nucleus subthalamicus [1] and animal studies suggest that there could be other subcortical sources of this phenomenon [2–6]. The same oddball paradigm that we use with MMN is used for recording the **P300 wave** (P300). The only difference between using the standard MMN and the P300 paradigm can be that in the case of the P300 protocol (the proband pays attention to this paradigm - he/she follows the signal change. P300 reflects the electrophysiological activity of the brain involved in the conscious process and P300 generators are probably multiple, relatively independent or P300 is generated by the central integrated system with widespread connections and impact throughout the brain [7–9–12].

P300 is a more complex response than MMN and it corresponds to the change in time after stimuli in the EEG - if MMN can be best subtracted from the signal at 100 to 250 ms, then P300 has a peak at 300 ms or later [7]. MMN and P300 are examples of the electrophysiological recording of brain activity that in addition to being time-locked is also phase-locked to the event. Potentials are generated by synchronised oscillation summation of neuronal potentials involved primarily in afferent pathways [13,14]. We talk about **event-related potentials** (ERP). In contrast, the **event-related de/synchronisations** (ERD/S) are changes in brain oscillations, which are also time-locked to the event, but not phase-locked. They are a reflection of the increased or decreased activity of neuronal populations in wide networks of the cortex. In the case of event-related desynchronisations (ERD) we are talking about desynchronisation manifested by decreased power, and with event-related synchronisations (ERS) about increased power. ERD/S are used for the study of sensory, motor or cognitive tasks [13,14] and recently they have been studied in the context of the cognitive activity of subcortical structures [15–17].

The **subthalamic nucleus** (STN), **internal globus pallidus** (GPI) and **thalamus** are subcortical grey matter structures and are connected in the basal ganglia circuit in motor and sensory functions. STN precedes GPI in the indirect pathway and GPI as one of output structures in the basal ganglia system (output nuclei) influences the thalamus, and the thalamus mainly projects into the cortex. Initially STN, GPI and the thalamus were considered exclusively as motor (STN and GPI) or sensory (thalamus) structures [18]. Gradually, however, ample evidence of the non-motor or non-sensory functions of these structures has emerged. Firstly, for STN with the deep brain stimulation program (DBS), undesirable side effects on cognitive abilities such as attention, executive abilities and verbal memory were observed [19]. Later there were several studies published which in turn reported an improvement in cognitive performance of patients with DBS – e.g. executive functions or "cognitive flexibility" [20,21]. Recently its modulatory role in cognitive functions [22] has been talked about. For example GPI work has been published about engaging in sensorimotor sequence learning [23] and an improvement in depression symptoms after DBS [24], while DBS thalamus works are about a decrease in depression, anxiety, memory and obsessive compulsive symptoms [25–27]. Therefore it appears that the role of subcortical structures is wider than previously thought and that they extend into the "territory" of cortical (cognitive) functions.

1.1. Aim of this study

In our previous experiment, we recorded the MMN paradigm in STN and got MMN-like potentials in this subcortical structure [1]. Given that it was the first recording of the MMN protocol in STN, we wanted to make sure that we really got potentials associated with MMN and not with P300. So after the MMN protocol we applied exactly the same protocol under the same conditions, only with the addition of the attention of proband and got P300 and so we were able to compare these two potentials. After the publication of our study we thought we could use these two protocols and subtract one from the other and gain "a purely conscious" cognitive component in the EEG recording. MMN recording of brain activity includes automatic and subconscious changes arising from the stimulus even though the proband does not pay attention to the signal. For P300 we obtain an electrophysiological signal that corresponds to the cognitive process – the proband follows the protocol with his/her attention involving other cognitive functions. However the automatic changes from an unconscious level are also present in the record of P300 (e.g. potential MMN as an automatic change in the unaffected brain can always be present - no matter whether the proband is paying attention to the task or is asleep). So if we analyse the difference between the MMN protocol and the P300 protocol this difference means a "purely conscious answer" – for this article's purpose let us call it **pure P300 (pP300)**. Thus one could determine whether the subcortical structures are involved in consciousness – whether they are participating in the "conscious mind" at the time of the stimuli. We expanded the number of patients from the original five [1] and recorded other subcortical structures. The aim of the study was to answer the hypothetical question of whether subcortical structures are involved in the **conscious cognitive process.** The second aim of this study was to find out if there are other **MMN-like** potentials such as the ERP in subcortical structures other than only in the STN – namely in the GPI and in the anterior thalamic nucleus (ATN) and ventral intermediate nucleus (VIM) of the thalamus.

2. Materials and methods

The study protocol was approved by the Ethics Committee of St. Anne's Hospital in Brno and conformed to the Declaration of Helsinki. All participants gave their written informed consent and there were no adverse events during our study. ***In short*** – in the course of this study, patients who were included in the DBS program were evaluated neurologically and psychologically, they were implanted with deep brain electrodes in certain targets and before internalisation (before linking the electrodes to the stimulator) the MMN and P300 protocols were applied and the EEG recorded. Subsequently, the data was processed statistically. Important characteristics of the individual steps of this study are described below.

2.1. Characteristics of the patients

All the patients underwent a battery of neuropsychological tests that included the assessment of cognitive functions and depression [28–33]. None of the patients showed symptoms of dementia or clinically significant signs of cognitive deterioration according to the results of neuropsychological tests, but three patients showed signs of partial cognitive deterioration. None of the patients showed clinically significant signs of depression or anxiety disorders based on the DSM-IV criteria. Several patients showed a mild level of depression, but with no impact on cooperation or motivation during the protocols. For detailed results of neuropsychological tests see the Supplementary material 1. From each patient's history, neurological examination and a test of both ears, we had no reason to suspect any hearing loss. During the study we included twelve consecutive patients (seven of them men). The patients were included in the deep brain stimulation program (DBS) with planned bilateral implantation of intracerebral electrodes. Six patients had advanced Parkinson's disease (PD) and DBS was targeted in the subthalamic nucleus (STN), four patients had generalised dystonia and DBS was targeted into the internal globus pallidus (GPI). One patient had essential tremor with DBS in the ventral intermediate nucleus (VIM) of the thalamus and one patient had epilepsy and DBS was guided into the anterior thalamic nucleus (ATN). All the patients except one (with PD) had bilateral electrodes implanted. A summary of patients and their target structures is stated in Table 1.

2.2. Characteristics of the process and the protocol

During the DBS program patients were implanted with intracranial depth electrodes into the targets (STN, GPI, ATN and VIM), 11 of them bilaterally, one of them unilaterally. For details of the neurosurgical