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Cortically evoked potentials in the human subthalamic nucleus

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HIGHLIGHTS

- We hypothesize that DBS in the STN motor area gives the optimal effect for PD.
- We perform motor cortex stimulation and measure the evoked potentials in the STN.
- We hypothesize that the cortically evoked potentials can identify the STN motor area.
- Cortically evoked potentials follow a specific spatial and temporal pattern in the STN.
- The evoked subthalamic potentials are partly related to the unit responses.

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ABSTRACT

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) alleviates motor symptoms in Parkinson's disease (PD) patients. However, in a substantial number of patients the beneficial effects of STN DBS are overshadowed by psychiatric side effects. We hypothesize that stimulation of the STN motor area will provide the optimal effect on the motor symptoms without inducing these side effects, and expect that motor cortex stimulation (MCS) evokes a spatially specific response within the STN, which identifies the STN motor area. We previously showed that MCS evokes responses in the unit activity specifically within certain areas of the STN. Unit activity is generally considered a measure of the output activity. To gain more insight into the neuronal input into the STN, we describe the results of cortically evoked subthalamic local field potentials (LFPs). We show that the cortically evoked LFPs follow a certain temporal and spatial pattern. The significant peaks of the evoked LFPs coincide with the timing of some of the inhibitions and excitations present in the unit responses. The spatial resolution of responses measured in the LFP to MCS is not high enough to identify the STN motor region. However, we believe that optimizing targeting techniques and the development of novel DBS electrodes will improve STN DBS therapy for PD patients.

1. Introduction

Neuronal recordings from the human subthalamic nucleus (STN) have become possible due to the surgical treatment for advanced Parkinson's disease (PD), such as deep brain stimulation (DBS) of the STN. STN DBS provides a remarkable improvement in the motor function of PD patients [6]. Unfortunately, STN DBS also induces unwanted behavioral changes, such as emotional disturbances and cognitive alterations [23]. These unwanted side-effects can be explained by the involvement of the STN in motor, associative and limbic behavior. Current spread to the associative area,

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which is located ventrolaterally, and to the limbic area in the most ventromedial tip of the nucleus is responsible for the psychiatric side effects [7,20,22]. Therefore, electrophysiological unit recordings are utilized to identify the STN and optimize electrode placement. Also local field potentials (LFPs) are often measured from the implanted DBS electrodes. The LFP shows pathologic ß oscillatory activity (12–30 Hz) in the STN of PD patients. This pathologic increase in ß activity is mainly observed within the dorsolateral motor region of the STN [13,19,24]. The LFP represents the summed postsynaptic potentials of a group of neurons [5], therefore it can be considered as the input activity. In contrast, the unit activity is a measure of the output activity. In human, the cortex is classically connected to the STN via the indirect pathway, which not only passes through the striatum and globus pallidus externa to the STN [20], but also via a monosynaptic pathway [4]. Previously, we have shown in human that motor cortex stimulation (MCS) evoked responses in the unit activity, which were not present outside the STN and differed spatially within the STN [11]. Strafella et al. [21] had similar findings when measuring subthalamic unit activity during transcranial magnetic stimulation. Considering the different neuronal origin of the LFP, a more detailed study of the response in the LFP to MCS will provide more insight into the subthalamic input activity and the pathways involved [16]. We hypothesized that the LFP is specifically responsive to MCS in the dorsolateral region of the STN, as this is the area believed to be involved in motor function [7]. Therefore, in this study we present the cortically evoked potentials in the LFP signal in the subthalamic region. As the LFP is believed to represent the neural input activity, it could provide an interesting tool for locating the STN motor area during stereotactic surgery. This potential use was studied by determining the temporal and spatial extent of the evoked LFPs. These results were also compared to the unit responses, which show a specific response to cortical stimulation in the dorsal STN [11].

2. Methods

Patients were enrolled based on the same criteria used for standard STN DBS. Five patients (ages 52–70 years) were included, but only the procedure and results of the last patient are described. The stimulation protocols used in the other patients did not result in an STN response due to saturation of the amplifier in the first two patients and suboptimal MCS protocols in the remaining two patients. The study, including five patients, was approved by the Medical Ethical Committee of the Maastricht University Medical Centre and all the patients gave written informed consent.

The procedure has been previously described in detail by Janssen et al. [11]. In short, subdural MCS with a strip of four electrodes (Model TS04R-SP10X-000; ADTech, Racine, WI, USA) was performed on the hand area of the motor cortex (stimulation settings: bipolar, monophasic, 0.2 ms, 7 or 15 mA, 200 stimuli). Concurrently, neuronal activity in and around the STN was measured using five microelectrodes (MicroMacroElectrode; InoMed, Emmendingen, Germany). Only local anesthesia was used. The stimulation amplitudes were determined based on the amplitude needed to obtain a motor evoked potential (MEP, 7 mA).

In order to obtain LFPs from the raw signals, the signals were filtered using a non-causal second order band pass Butterworth filter between 3 and 95 Hz; 50 Hz noise was removed using a notch filter. Subsequently, the signals were divided into epochs from 100 ms before stimulation until 200 ms after stimulation. All epochs belonging to the same location and resulting from the same stimulation settings were averaged. Significant deflections in the average LFPs were determined when five successive samples exceeded a threshold of plus or minus two times the standard deviation of the signal measured during 15 mA stimulation. LFP responses were compared to the responses in the unit activity. The unit responses were evaluated by peri-stimulus time histograms (PSTHs) in which significant changes were found by the change point analysis. A detailed description of the analysis of the unit activity is previously described [11].

3. Results

LFP recordings in the anterior and lateral trajectories were made from 1.5 and 0.5 mm above the target until 1 and 2.5 mm below the target. These trajectories were inside the STN from 2 mm above the target until 2.5 mm below the target. Fig. 1 shows the LFPs and peri-stimulus time histograms (PSTHs) constructed using the responses in the unit activity [11] after cortical stimulation. The LFPs show a positive deflection around 43 ± 3 ms. This peak is present at all heights in the lateral trajectory and at -1.5 and -0.5 mm in the anterior trajectory. Subsequently, negative peaks are present at 78 ms in the anterior trajectory and at 81 ms in the lateral trajectory at a height of -1.5 mm. At -0.5 mm above the calculated target, this negative peak has disappeared. At +1 mm in the anterior and lateral trajectory and at +2.5 mm in the lateral trajectory, a positive peak is seen at ~75 ms after stimulation. Finally, a significant negative peak is visible in the anterior trajectory at +2.5 mm. In the central and medial trajectory, the LFP response did show some significant peaks, but no specific pattern was visible. The LFP results did not correspond with the changes in the PSTH, which showed little to no response to stimulation [11].

Responses were only visible in the LFPs when 15 mA stimulation was applied, but not when a stimulus amplitude of 7 mA was used; except for the responses shown at +2.5 mm. This was in agreement with the fact that no significant responses to MCS were visible in the PSTHs while using an amplitude of 7 mA for MCS [11].

The positive peak at 43 ms corresponds with the start of the first inhibitory period found in the PSTHs at heights -1.5 and -0.5 mm. The negative peaks at 78 and 81 ms at a height of -1.5 mm in the anterior and lateral trajectory are within the period of increased firing rate in the PSTHs from about 63–100 ms after stimulation. The positive peaks in the anterior and lateral trajectories at ~75 ms are not seen in the PSTHs at these levels.

4. Discussion

In this study, for the first time evoked LFPs in the STN region following MCS in a PD patient have been described. We showed that evoked LFPs follow a specific pattern in the dorsal STN, namely first a positive deflection around 43 ms followed by a negative deflection around 80 ms. The positive deflection is seen in the entire STN, but the negative deflection seems specific to the dorsolateral STN region. Some of the evoked LFP peaks are temporally and spatially linked to the unit responses to MCS.

We showed that the cortical input to the human STN can be visualized in the LFP. However, the temporal response in the LFP is not as clear-cut as in the rodent, although the LFP was averaged over many stimuli, which was not necessary in rodents [16]. In contrast to the animal data, the deflections in the LFP caused by the mono-synaptic cortico-subthalamic pathway and the indirect cortico-striato-pallido-subthalamic pathway were not found. This could be due to difference in the size of the dendritic fields between species and a prominent lower cell density in the human compared to the rodent STN [8,17]. Nonetheless, a clear positive deflection around 43 ms and a negative deflection around 80 ms were observed. The positive deflection was seen through the full ventro-dorsal axis of the STN and has a similar latency as observed in the rodents, which is the start of the long-lasting inhibitory period that may be caused by cortical disfacilitation [16]. The

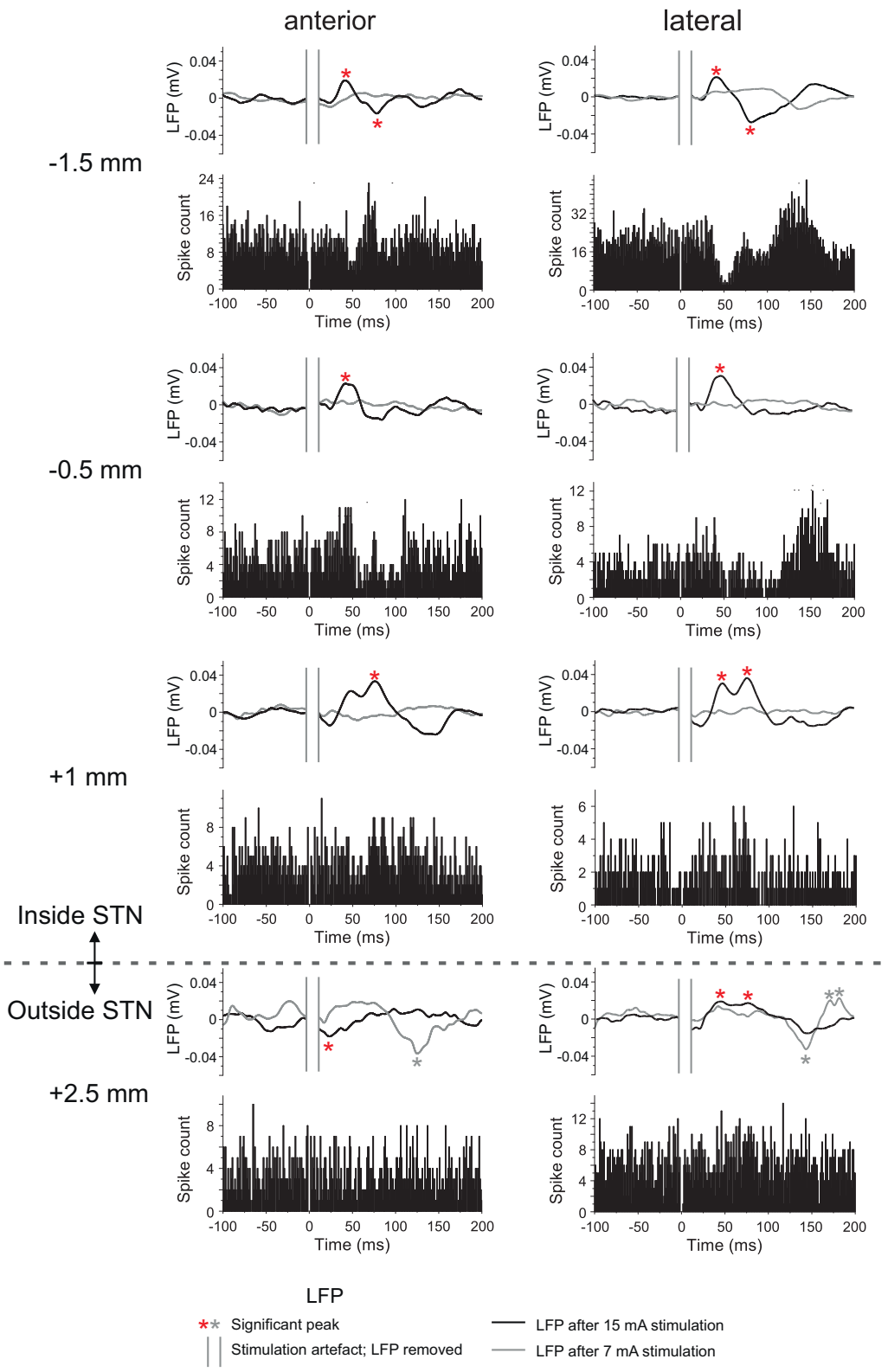

Fig. 1. The cortically evoked LFPs using a stimulation amplitude of 7 and 15 mA are plotted as well as the PSTHs of the anterior and lateral electrode starting 0.5 mm after the electrode first enters the STN (1.5 mm above target) until it leaves the STN (2.5 mm below target). The PSTHs using 7 mA stimulation did not show any significant responses, therefore only the PSTHs obtained with 15 mA are plotted. LFP: LFPs were averaged over all trials. An asterisk indicates a significant LFP peak, which is determined by exceeding a threshold of ±2 times the standard deviation from the signal during 15 mA stimulation. The PSTHs are partially adapted from Janssen et al. [11].

negative deflection, which was only observed in the dorsal region of the STN, can be explained as a sensor response caused by muscular contraction induced by MCS [9]. Movement related neuronal activity of the STN has earlier been described [1,10].

Magill et al. [16] showed that a negative deflection in the LFP (input) coincides with an excitation shown in the PSTH (output) and vice versa. We clearly see that the positive peaks in the averaged LFP coincided with the long lasting inhibitory periods found

in the PSTH. This positive LFP peak was also present at a height of +1 mm, at which the inhibition was no longer present in the PSTH. In this PD patient, the LFPs, thus, extended to a broader area than the unit responses. There can be different reasons for this. First, it should be considered that the LFP reflects the summed postsynaptic potentials of a group of neurons [5], while multi-unit activity reflects the action potentials measured in one or just a few neurons. Changes in the synaptic activity do not always lead to an action potential. Furthermore, LFPs exhibit strong low-pass filtering properties [3], which could account for a larger responsive region of the low frequency LFP signal as compared to the high frequency spike signal. It has been argued that LFPs are volume conducted over a radius of 0.25 mm [12]. As the measurement at +2.5 mm was just outside of the STN (+2 mm was still inside of the STN), it might be that the LFPs originating from STN activity were volume conducted outside the STN. The negative peak in the LFPs at a height of −1.5 mm around 80 ms coincided with an increased firing rate shown in the PSTHs. However, the remaining PSTH was not reflected in the LFP. Additionally, we found significant deflections in the LFPs when no significant changes in the PSTH were found (Fig. 1: +2.5 mm). These were probably caused by a low signal to noise ratio outside the STN, since also at 7 mA significant peaks were found.

Finally, we only observed a response after MCS while using a stimulation amplitude of 15 mA, but not after 7 mA stimulation. Moreover, in the LFP no excitatory monosynaptic response could be observed. This is not in line with what we expected, as our modeling study shows activation of pyramidal axons at 7 mA [26]. A reason for this discrepancy could be suboptimal placement of the stimulation electrode or it could be that the synaptic strength from the cortical afferents is less strong than thus far assumed. To our knowledge no quantitative studies exist on the number of synapses in the STN with a cortical origin. This would imply that a STN response is only present when a high number of pyramidal neurons is activated. On the other hand a strong coherence is present between the prefrontal cortex and the STN, which implicates a strong cortico–subthalamic connectivity [15]. Furthermore, the duration of the stimulation artifact overlapped with the expected timing of the monosynaptic response, which could have made this response invisible. We believe, despite the small sample size, that our results are important from a clinical perspective. In literature, it is being debated whether additional invasive procedures are warranted to improve the quality of the DBS procedure [2]. We believe that neurophysiological recordings can be helpful to increase the accuracy of the implantation of DBS electrodes. Accurate targeting is the limiting step in achieving maximal benefit on motor symptoms and minimizing side effects on behavior and cognition. Here we showed that the evoked LFPs were not restricted to a certain area of the STN and also extended beyond STN borders. Thus, the evoked LFPs did not have a spatial resolution high enough to locate the STN motor area. Further adaptation of the stimulation and recording protocol will decrease surgery time and will be of additional value to the standard used intra-operative tests to define the optimal site of implantation. To achieve this goal, computational models of cortical stimulation should be made to predict the optimal cortical stimulation site, electrode size and stimulation parameters [26]. Moreover, since MCS had an unexpectedly high risk of inducing seizures [11], alternative non-invasive techniques, such as high resolution imaging, and other electrophysiological markers, such as the ß activity, should be further investigated to explore their possibilities to target the motor part of the STN [14,25]. Imaging techniques can be combined with intra-operative electrophysiological information providing a more precise indication of which area of the STN should be stimulated. The next step then would be to develop DBS electrodes that are able to stimulate a selective area [18]. Combining the improved identification of the STN motor region and the development of DBS electrodes with a higher spatial resolution will optimize DBS therapy for PD patients.

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