β-Band Peak in Local Field Potentials as a Marker of Clinical Improvement in Parkinson's Disease after Deep Brain Stimulation

P.D. Frangou[1], K.P. Michmizos[2], P. Stathis[3], D. Sakas[3], and K.S. Nikita[1]

[1] National Technical University of Athens, Athens, Greece
[2] Massachusetts Institute of Technology, Cambridge, MA, USA
[3] Evangelismos Hospital, National and Kapodistrian University of Athens, Greece

Abstract—**Although locating the stimulation contact in Deep Brain Stimulation (DBS) requires a sub-mm-precision, it remains a trial-and-error, patient-specific procedure that is usually the main cause of post-operational side-effects. In this work, we used microelectrode recordings from Parkinson's disease (PD) patients, acquired at the Neurosurgery Clinic, Evangelismos Hospital, Athens, Greece, to relate the β-band peak, a known neurophysiological signature of the sensorimotor pathways with the clinical outcome of DBS, as assessed by an expert neurologist after a follow-up of at least 1 year. By combining recordings from 5 microelectrodes, we estimated a summed β-band amplitude peak, per recording depth. We suggest that the maximum aggregate β-band peak is related to the stimulation target. We verified our method in 6 patients that responded well in a bilateral DBS treatment (average increase of Unified Parkinson's Disease Rating scale by 32.6 ± 5.4). In 7 out of 12 hemispheres, the distance between the stimulation depth and that of the maximum β-band peak was 0 and for the rest cases that distance was smaller than 2 mm which is a typical effective radius of a stimulation point. Our method needs to be further supported by data acquired from patients with good and poor clinical responses after DBS.**

Keywords—**Deep Brain Stimulation, Subthalamic Nucleus, microelectrode recordings, Parkinson's disease.**

I. INTRODUCTION

Parkinson's disease (PD) is estimated to affect 7 to 10 million people worldwide [1]. Although a combination of drugs such as Levodopa and Carbidopa is usually effective in alleviating most of the motor symptoms in PD, pharmaceutical treatment over a prolonged period of time becomes gradually less effective and other treatments need to be considered. Deep Brain Stimulation (DBS), initially developed in 1987 [2], has been used as an alternative invasive therapeutic approach in PD patients since 2002 [3]. The surgical procedure can briefly be described as the implantation of electrodes in the patient's brain, along with a pacemaker that regulates the stimulation, usually placed below the clavicle. DBS, when successful, moderates the need for pharmaceutical treatment. In some cases, DBS has no improvement of PD motor symptoms and sometimes is even related to side effects, such as psychiatric and speech disorders.

DBS outcome, which is largely based on the clinician's experience, entails some level of uncertainty. Clinical results are generally believed to be related to the accurate placement of the stimulation contact inside the dorsolateral area of the subthalamic nucleus (STN), where sensorimotor neurons are believed to predominate [4]. Selecting the stimulation contact is patient-specific and includes trial-and-error procedures that are discomforting for the patient and sometimes may cause side-effects. An expert neurologist initially locates the stimulation target combining preoperative magnetic resonance imaging (MRI) scans with microelectrode recordings (MERs) of the neuronal activity [5]. After the target is empirically confirmed, the final stimulation macroelectrode replaces the microelectrodes. The stimulation parameters are adjusted to avoid side-effects, while maximizing the improvement of motor symptoms, based on the sole judgement of the expert neurologist intraoperatively and during follow-up. Following a trial-and-error process, the neurologist decides on the stimulation contacts based on the amelioration of the motor symptoms and the absence of both long and short-term side-effects.

In this paper, we seek to develop a MER-driven clinical decision support system to guide the placement of the stimulation contact at the optimal, in terms of clinical results, point. Our ability to record the STN's neural activity as close to its generator as possible promises maximal spatial resolution and accuracy for the localization of the stimulation contact. MERs inside the STN have been used before to predict the spike activity from the local field potentials (LFPs) [6] and even the STN detection, per se [7]. We now seek to use the increased power and coherence observed in the β-band of the STN- LFPs in PD patients that are in «off-state» (known as the reduced medication efficacy state) [8,9]. In addition, previous studies rely on features acquired by a single microelectrode to determine the location of the STN [10]. In this study we propose the combination of features acquired from multiple microelectrodes.

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Table 1 Motor evaluation of the patients in terms of UPDRS (III) score, before and after the operation in «off state» (reduced medication efficacy) (mean UPDRS(III) score improvement: 32.67 ± 5.4).

Patient ID	Age	UPDRS (III) preoperative "off state"	UPDRS (III) postoperative "off state"
101	62	75	38
105	65	60	35
109	50	66	28
110	62	70	41
113	53	61	24
122	64	78	48

II. MATERIALS AND METHODS

A. Patient Recordings

Six male PD patients with average age of 59 ± 6 years old were included in this study. Patients underwent a bilateral DBS implantation procedure according to the CAPSIT-PD protocol [11], in the Neurosurgery Clinic of Evangelismos Hospital, Athens, Greece. Following the operation and for a period of at least 1-year, the patients presented an average UPDRS (Unified Parkinson's Disease Rating Scale) (III) scale improvement of 32.67 (± 5.4). The motor evaluation for all patients is presented in Table I. No mental disorders were reported in follow-up psychiatric evaluations.

DBS implantation was guided by an expert neurologist (co-author of this study, P.S.) by listening to MERs sent to an audio scope. MERs were acquired on spontaneous STN activity, defined as the neuronal activity acquired during periods in which the PD patient lied down immobile in the operational table. No electrical stimulation was performed during recordings. Neither active nor passive movements were executed during analyzed MERs.

Analysis of MERs was conducted separately for each hemisphere. Both hemispheres were considered to contribute equally to the patient's clinical responses. Therefore, each clinical result was mapped to 2 STN, one at each side of a patient's brain. MERs were acquired using a Ben Gun formation, consisting of five microelectrodes in a cross formation, namely central, anterior, posterior, medial, lateral. The distance between the central and the surrounding electrodes was 2 mm and the signals recorded from each electrode lasted 10s each [12].

The permanent DBS lead (Medtronic®) had 4 contacts that were 0.5mm apart and had a diameter of 1.5mm. Stimulation was either monopolar or bimonopolar (i.e. two contacts with the same negative polarity).

Stimulation parameters (contact, pulse amplitude, width and frequency) were also chosen by neurologist (P.S.) for optimal clinical benefit intraoperatively and during follow-up. In both cases, the neurologist had no access to the β-peak information acquired from MER data. Hence, contact point and stimulation parameters were only based on clinical outcome.

B. Identifying the Stimulation Target

Each of the 5 electrodes entered and exited the STN at different depths. The STN entrance and exit for each trajectory was determined off-line by P.S., after visual inspection of MERs. Signals outside the STN were excluded from this study.

Power spectral density (PSD) for each MER, normalized by its electrode impedance, was estimated using the Welch's modified periodogram with a data window length of 0.68 s and 50% overlap. The β-band [12 – 30 Hz] is considered to be a neurophysiological signature of the location of sensorimotor neurons in non-moving patients [13]. That is why we isolated the amplitude peaks in that range.

The stimulation seems to be effective within a spherical area of 3mm radius around the stimulation contact [14]. Knowing the final position of the stimulation contact, we estimated the 3mm spherical area where the DBS signal had an effect.

We calculated the β-band amplitude peaks and compared the maximum aggregate β-band peak with the 3mm sphere. Our hypothesis was that the depth where the maximum β-band amplitude peak was present coincided with the optimal stimulation target [15]. We tested our hypothesis by estimating the distance, in mm, between stimulation point and maximum aggregate β-peak in vertical direction, as shown in Figure 1. For each STN we identified the suggested stimulation target as the depth where the sum of the five β-band amplitude peaks was maximum.

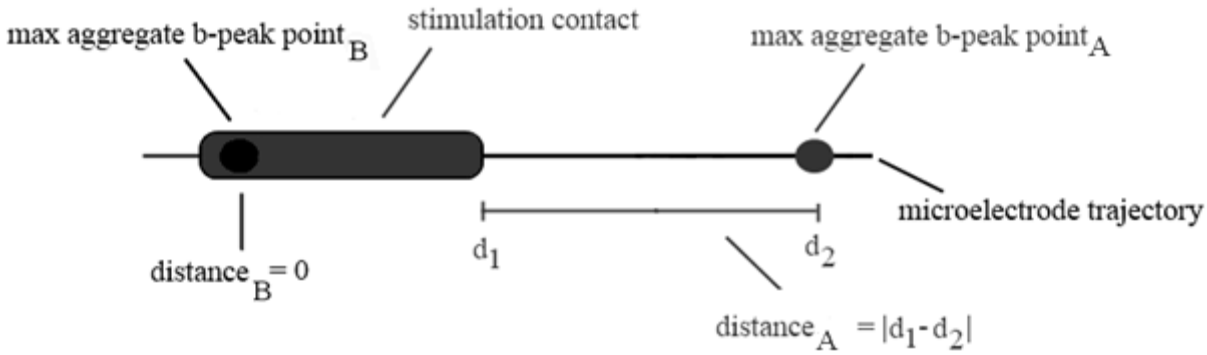

Fig 1 In case A, the distance between the stimulation contact and the maximum aggregate β-peak in vertical direction is calculated as the absolute value of the difference between the depth of the maximum aggregate β-peak (point A) and the depth of the contact's tip that is closest to point A. In case B, the maximum aggregate β-peak lies inside the clinically selected stimulation contact, hence the distance is 0.

III. Results

The measured distances for the 12 cases are presented in Figure 2. In 7 cases the distance was 0, meaning that the maximum aggregate β-band peak lied inside the clinically selected stimulation contact. In the other 5 cases, that distance ranged from 1 to 2mm, as measured from the closest tip of the stimulation contact. In all 12 STN from patients with good clinical response, the distance was always smaller than 3mm. In other words, the suggested stimulation depth was within the spherical area of effective stimulation. Overall, the distance between the suggested stimulation depth and the actual stimulation contact had an average value of 0.67 mm (± 0.86).

IV. Conclusions

In this paper, we introduced a method that combines the β-band peak from 5 electrodes to propose a location for the optimal stimulation depth inside the STN of PD patients. Considering the β-band amplitude peaks as a neurophysiological signature of the location of sensorimotor neurons in non-moving patients, we found that the stimulation at the depth where the sum of β-band amplitude peaks was maximum was related to a good clinical response, in terms of UPDRS(III) score improvement and psychiatric evaluation, in all 6 patients.

These encouraging results call for an extended study on more patients, in order to verify our hypothesis. Specifical-

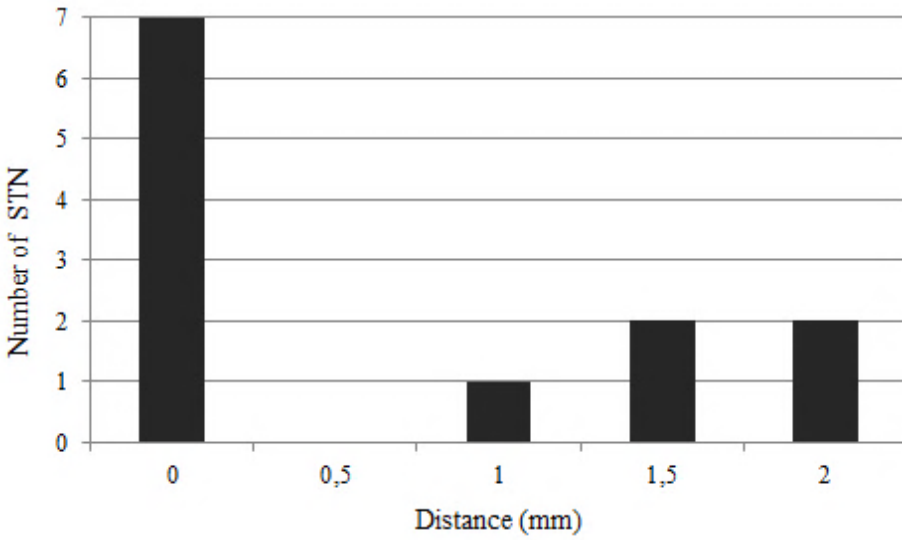

Fig 2 Distribution of the distance values in the 12 STN.

ly, we aim to verify our hypothesis on patients that developed side-effects after DBS implantation. We seek to relate the poor outcome of the DBS procedure to stimulation of an STN area that is farther than 3 mm away from the maximum β-peak. Another interesting application of this work would be to test how the stimulation of each hemisphere contributes separately to the patient's clinical response, under the scope of the hemispheric preponderance of Parkinson's disease. This way, we can possibly determine whether unilateral stimulation determines the final clinical response of the patient or not.

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Polytimi D. Frangou

National Technical University of Athens
Iroon Polytechniou 9
Athens, Greece
pfrangou@biosim.ntua.gr