Clinical Neurophysiology 129 (2018) 1001–1010

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Intra-operative characterisation of subthalamic oscillations in Parkinson's disease

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ARTICLE INFO

Article history:
Accepted 31 January 2018
Available online 27 February 2018

Keywords:
Intra-operative
Oscillation
Subthalamic nucleus (STN)
Parkinson's disease (PD)
Deep brain stimulation (DBS)

HIGHLIGHTS

- The 3-D visualized subthalamic area and the local field potential (LFP) oscillations were estimated intraoperatively.
- The resting and movement modulated oscillations had focal maxima in frequency bands.
- Movement related modulations showed differences in the scale and timing across frequency bands.

ABSTRACT

Objective: This study aims to use the activities recorded directly from the deep brain stimulation (DBS) electrode to address the focality and distinct nature of the local field potential (LFP) activities of different frequency.
Methods: Pre-operative and intra-operative magnetic resonance imaging (MRI) were acquired from patients with Parkinson's disease (PD) who underwent DBS in the subthalamic nucleus and intra-operative LFP recording at rest and during cued movements. Images were reconstructed and 3-D visualized using Lead-DBS® toolbox to determine the coordinates of contact. The resting spectral power and movement-related power modulation of LFP oscillations were estimated.
Results: Both subthalamic LFP activity recorded at rest and its modulation by movement had focal maxima in the alpha, beta and gamma bands. The spatial distribution of alpha band activity and its modulation was significantly different to that in the beta band. Moreover, there were significant differences in the scale and timing of movement related modulation across the frequency bands.
Conclusion: Subthalamic LFP activities within specific frequency bands can be distinguished by spatial topography and pattern of movement related modulation.
Significance: Assessment of the frequency, focality and pattern of movement related modulation of subthalamic LFPs reveals a heterogeneity of neural population activity in this region. This could potentially be leveraged to finesse intra-operative targeting and post-operative contact selection.

1. Introduction

There is growing interest in the nature of local field potential (LFP) activities recorded from the subthalamic nucleus (STN) of patients with Parkinson's disease (PD) undergoing neurosurgery for deep brain stimulation (DBS). This is fueled by the evidence that oscillatory activity in the beta frequency band is unduly synchronized and strong in these patients and that this relates to

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https://doi.org/10.1016/j.clinph.2018.01.075
1388-2457/

deficiency of dopamine in the basal ganglia (Hammond et al., 2007). Thus, the power of beta activity is correlated with the motor impairment in PD and the changes of power engendered by levodopa treatment or DBS correlate with improvements in bradykinesia and rigidity (Ray et al., 2008; Kühn et al., 2008, 2009; Eusebio et al., 2011). The same activities are modulated during the preparation, execution, and termination of voluntary movements (Kühn et al., 2004; Doyle et al., 2005; Klostermann et al., 2007; Joundi et al., 2012). However, the subthalamic LFP recorded in patients with Parkinson's disease also includes power in other frequency bands which are modulated by movement. Theta/alpha and gamma oscillations synchronise around the period of movement. Exaggerated theta/alpha activity has been related to the presence of dyskinesia and impulse control disorders (Alegre and Valencia, 2013; Rodriguez-Oroz et al., 2011). Similarly, gamma activity is associated with dyskinesias when it becomes exaggerated in the form of a finely tuned spectral peak (Fogelson et al., 2005; Swann et al., 2016).

The origin of these activities in the subthalamic area has been explored using intra-operative microelectrodes. This has led to the conclusion that beta activity is greatest in the dorsal 'motor' STN (Lourens et al., 2013; Verhagen et al., 2015). Importantly, these activities may also be evident in the LFP recorded directly from the definitive DBS electrode rather than from temporary microelectrodes. This has led to interest in exploiting LFP features to help improve functional targeting during surgery (Miyagi et al., 2009; Chen et al., 2006; Michmizos et al., 2015; Kolb et al., 2017; Yoshida et al., 2010), streamline the post-operative screening of electrode contacts (Tinkhauser et al., 2017) and form the basis of control signals in closed-loop DBS (Little et al., 2013). However, much still remains uncertain. To what extent are these subthalamic activities in different frequency bands focal when picked up by DBS electrodes rather than by microelectrodes? Are their sources separable in space? To what extent are spectral differences also associated with different patterns of modulation upon voluntary movement? Here we try to address these outstanding questions through an exploration of the spatial topography and movement-related reactivity of spectral features recorded directly from bilateral subthalamic DBS electrodes in eight patients with Parkinson's disease.

2. Material and methods

2.1. Subjects and surgery

Eight patients (six males, age 54.6 ± 7.1 years) with Parkinson's disease underwent bilateral STN implantation of DBS electrodes at the General Hospital of PLA, Beijing, China. All patients gave written informed consent to take part in this study, which was agreed by the local ethics committees. The pre-operative Unified Parkinson's Disease Rating Scale part III – motor exam was evaluated one week before surgery (Table 1). Surgeries were performed after overnight withdrawal of levodopa in all patients.

All patients underwent stereotactic-framed pre-operative 3.0 T magnetic resonance imaging (MRI) scans the day before the surgery. The DBS electrodes were targeted at the dorsolateral area of the STN. The targets and trajectory of electrode implantation were calculated and determined using the Frame link planning station (Medtronic, Minneapolis, MN, USA). The DBS electrodes were Medtronic 3389 (Medtronic, Minneapolis, MN, USA) with four platinum-iridium cylindrical surface contacts. Each contact was 1.27 mm in diameter and 1.5 mm in length, and separated by 0.5 mm. The most caudal contact was contact 0 and the most rostral was contact 3. Subjects had local anesthesia and were awake during the operation to allow for intraoperative movement and stimulation assessments. The placement of DBS electrodes was confirmed intra-operatively by 1.5 T MRI (Cui et al., 2016) and macrostimulation effects.

2.2. Paradigm and recording

Bipolar LFPs were intraoperatively recorded from the adjacent four contacts (contact pairs: 01, 12, 23) of each DBS electrode. The recordings were made after the implantation of DBS electrodes on each side. All LFPs were band-pass filtered in the range of 0.1–500 Hz, amplified with a gain of 10,000, and sampled at 1000 Hz (EEG100C, BIOPAC Inc., USA). The signals were displayed online, saved onto a hard disk (Acqknowlege 4.2, BIOPAC Inc., USA), and exported for further analysis in MATLAB (MathWorks Inc., Natick, MA, USA).

Patients underwent recording at rest and during auditory-cued movement. Patients were instructed to avoid speaking during the tasks. During the movement task, patients were asked to hold a joystick handle with a button on top in the hand contralateral to the LFP recording. An auditory cue was delivered at random intervals ranging from 5 to 6 s. The patients were asked to click on the button using the thumb as fast as possible following the cue. The cueing sound was 100 ms spindle shaped white noise with 10% voltage ramp at the beginning and at the end. It was delivered through a speakerphone, adjusted so as patients volunteered that they could hear the cue clearly but did not feel it uncomfortable. The cue onset time was defined as the time of 50% of the ramp up. The response time was defined as the time of button press. The cue and button click were recorded by analog channels on the amplifier (UIM100C, BIOPAC Inc., USA). At least forty trials were performed for off-line analysis.

2.3. Signal processing

Data analyses were performed offline with custom developed scripts in MATLAB (MathWorks Inc., Natick, MA, USA). LFP signals were band-pass filtered over 3–90 Hz and adaptively band-stop filtered to reject 50 Hz line noise. The adaptive filter applied here used the power ratio of the stop-band and of reference side-bands to adjust the attenuation of the stop-band to avoid over-filtering. A continuous 60 s at rest and 30 trials of movement,

Table 1
Clinical summary.

Case	Age/sex	Dominant symptoms	Duration of disease (years)	UPDRS part-III (pre-operative off medication)
1	50/M	Right side rigidity and tremor; left side rigidity	4	38
2	55/M	Left side rigidity and tremor	10	52
3	49/M	Tremor, rigidity and bradykinesia	2	53
4	65/F	Rigidity, mobility and gait impairment	7	54
5	52/M	Rigidity and bradykinesia	5	40
6	45/F	Bradykinesia and gait impairment	N/A	41
7	64/M	Tremor	N/A	N/A
8	57/M	Rigidity, tremor and dyskinesia	4	57

UPDRS = Unified Parkinson's disease rating scale. Part – III: Motor Exam.