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Neural correlates of lexical decisions in Parkinson's disease revealed with multivariate extraction of cortico-subthalamic interactions

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- Parkinsonian patients with subthalamic electrodes for deep brain stimulation.
- Maximized cortico-subthalamic i-coherency (MIC) in 14–35 Hz oscillations.
- Positive correlation between MIC and accuracy in lexical decisions.

A B S T R A C T

Objective: Neural interactions between cortex and basal ganglia are pivotal for sensorimotor processing. Specifically, coherency between cortex and subthalamic structures is a frequently studied phenomenon in patients with Parkinson's disease. However, it is unknown whether cortico-subthalamic coherency might also relate to cognitive aspects of task performance, e.g., language processing. Furthermore, standard coherency studies are challenged by how to efficiently handle multi-channel recordings.
Methods: In eight patients with Parkinson's disease treated with deep brain stimulation, simultaneous recordings of surface electroencephalography and deep local field potentials were obtained from bilateral subthalamic nuclei, during performing a lexical decision task. A recent multivariate coherency measure (maximized imaginary part of coherency, MIC) was applied, simultaneously accounting for multi-channel recordings.
Results: Cortico-subthalamic synchronization (MIC) in 14–35 Hz oscillations positively correlated with accuracy in lexical decisions across patients, but not in 7–13 Hz oscillations. In contrast to multivariate MIC, no significant correlation was obtained when extracting cortico-subthalamic synchronization by "standard" bivariate coherency.
Conclusions: Cortico-subthalamic synchronization may relate to non-motor aspects of task performance, here reflected in lexical accuracy.
Significance: The results tentatively suggest the relevance of cortico-subthalamic interactions for lexical decisions. Multivariate coherency might be effective to extract neural synchronization from multi-channel recordings.

1. Introduction

Neural interactions between cortex and basal ganglia structures, such as the subthalamic nucleus (STN), have been frequently demonstrated in 7–35 Hz oscillations in patients with Parkinson's disease (PD) being treated with deep brain stimulation: In simultaneous recordings of STN local field potential recordings (LFP) and electroencephalography (EEG) or magnetoencephalography,

Abbreviations: DBS, deep brain stimulation; EEG, electroencephalography; iCOH, imaginary part of coherency; LFP, local field potentials; MCOHp, absolute value of coherency corresponding to MIC; MEG, magnetoencephalography; MIC, maximized imaginary part of coherency; PD, Parkinson's disease; ROI, region of interest; SD, standard deviation; SEM, standard error of the mean; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale.

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cortico-subthalamic coherency was revealed at rest (Fogelson et al., 2006; Hirschmann et al., 2011; Litvak et al., 2011) and it was correlated with the severity of motor symptoms (Hirschmann et al., 2013; Kato et al., 2015). Moreover, cortico-subthalamic coherency was modulated by movement performance (Klostermann et al., 2007; Hirschmann et al., 2013; Litvak et al., 2012), movement inhibition (Alegre et al., 2013), dopaminergic medication (Hirschmann et al., 2013; Lalo et al., 2008; Williams et al., 2002), and DBS (Kühn et al., 2008).

However, previous coherency studies were challenged by one or more of the following three open questions, which will be addressed simultaneously by the present study: (i) How to effectively extract neural synchronization from multi-channel recordings, (ii) how to overcome artifacts due to volume conduction (Nolte et al., 2004; Srinivasan et al., 2007), and (iii) whether cortico-subthalamic synchronization is relevant for task performance beyond the motor domain. While volume conduction artifacts in cortico-subthalamic synchronization were effectively ruled out in a previous study (Litvak et al., 2011), the "multi-channel-challenge" (i.e., tens or hundreds of possible connections between sensors) is usually met by manual selection of a few connections only (e.g., Fogelson et al., 2006; Hirschmann et al., 2013; Klostermann et al., 2007; Kühn et al., 2008; Lalo et al., 2008; Litvak et al., 2012; Toledo et al., 2014) or by prior source localization (Litvak et al., 2011, 2012). Those previous approaches either did not allow considering data from many connections simultaneously or were not aimed at analytically identifying the maximal neural synchronization between the sensors. If those aspects were achieved simultaneously, spatial resolution and signal-to-noise ratio could be optimized. In order to meet these requirements, we applied a recently developed spatial decomposition method based on maximizing the imaginary part of coherency (MIC; Ewald et al., 2012): MIC indicates time-lagged neural interactions and therefore is insensitive to volume conduction artifacts, and MIC optimizes the extraction of coherency from multi-channel recordings (Ewald et al., 2012; Nolte et al., 2004). In the present study we provide a detailed and accessible explanation of the use of MIC for EEG-LFP recordings. Importantly, in contrast to previous studies we aimed at studying the involvement of cortico-subthalamic neural synchronization during the performance of a primarily non-motor, e.g., language-related, task. For this purpose, MIC was applied on EEG-LFP recordings of eight deep brain stimulation patients with PD during the performance of a lexical decision task (Ehlen et al., 2013; Krugel et al., 2014; Rubenstein et al., 1970). Specifically, we investigated a possible relation between the accuracy in lexical decisions and cortico-subthalamic coherency estimated by MIC in 7–13 Hz (alpha) and 14–35 Hz (beta) oscillations. These frequency ranges were selected, since cortico-subthalamic synchronization was demonstrated primarily in both, the alpha (at rest and motor preparation: Fogelson et al., 2006; Hirschmann et al., 2011; Klostermann et al., 2007) and beta frequency ranges (at rest, movement performance, motor preparation: Alegre et al., 2013; Hirschmann et al., 2011, 2013). In general, clinical deep brain stimulation studies often involve only small number of patients (⩽10; e.g., Fogelson et al., 2006; Hirschmann et al., 2013; Hohlefeld et al., 2012; Kühn et al., 2006; Litvak et al., 2010; Williams et al., 2002); yet a demonstration of the feasibility of applying MIC in the clinical domain, and a possible relation to lexical performance, would provide evidence for advancing the extraction of clinically relevant biomarkers in Parkinson's Disease. Notably, while previous electrophysiological studies of language processing were based on cortical and subthalamic evoked potentials (Krugel et al., 2014; Wahl et al., 2008), the present study complements previous findings by directly investigating neural interactions between cortex and STN.

2. Methods

2.1. Patients and surgery

Eight patients (five males; mean age 54 years, range 31–77 years; 4 left-handed according to self-report) diagnosed with idiopathic PD (mean disease duration 7 years, range 2–13 years) and eligible for DBS participated in the present study. Written informed consent was obtained from all participants. All patients were native German speakers (monolingual) without clinical hearing impairment (no formal hearing assessment). The experimental procedures were approved by the local ethics committee (Charité – University Medicine Berlin), in accordance with the Declaration of Helsinki (Rickham, 1964). The DBS electrodes were bilaterally implanted in the STN (Model 3389, Medtronic Neurological Division, Minneapolis, MN, USA). For more details on the surgery cf. Hohlefeld et al. (2012). Details on the reconstruction of the electrode coordinates were reported elsewhere (cf. Hohlefeld et al., 2015; Horn and Kühn, 2015). The post-surgery motor condition was assessed by an experienced clinician with the Unified Parkinson's Disease Rating Scale (UPDRS, part III) in the ON levodopa state. The clinical details are summarized in Table 1. The present data are part of an accompanying study that investigated neural correlates of language processing in patients with movement disorders (cf. Hohlefeld et al., 2015; Tiedt et al., 2014, 2016) and were addressed in the present study with the primary objective of investigating the relation between cortico-subthalamic coherency and accuracy of lexical decisions.

2.2. Experimental task

Eight patients performed a lexical decision task requiring a button press with the dominant hand (or non-dominant hand, if the dominant hand was affected by tremor and/or dyskinesia) if a gen-

Table 1
Summary of patient clinical details.

Patient #	Age (years) at surgery, sex	Disease duration (years)	UPDRS III (on medication)	Medication (LED)	Handedness	Response hand*
1	31, f	4	8	1103	Right	Right
2	47, f	4	23	400	Left	Right
3	51, m	13	26	580	Left	Left
4	69, m	4	20	1332	Left	Left
5	53, m	9	25	950	Right	Left
6	77, f	2	26	250	Right	Right
7	49, m	5	21	510	Left	Right
8	52, m	10	7	1304	Right	Right
Mean	54	6	20	804		
SD	14	4	8	422		

UPDRS III — motor Unified Parkinson's Disease Rating Scale, post-surgery, on medication.
* Response hand: Three subjects had to use the non-dominant hand for the button press (if dominant hand affected by tremor and/or dyskinesia). F — female; LED — daily levodopa equivalent dose; m — male; SD — standard deviation.