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CORRELATION BETWEEN CORTICAL AND SUBCORTICAL NEURAL DYNAMICS ON MULTIPLE TIME SCALES IN PARKINSON'S DISEASE

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Abstract—Complex amplitude dynamics of dominant alpha oscillations (8–13 Hz) in the cortex can be captured with long-range temporal correlations (LRTC) in healthy subjects and in various diseases. In patients with Parkinson's disease (PD), intra-nuclear coherence was demonstrated in dominant beta rhythms (10–30 Hz) in the basal ganglia. However, so far the relation between cortical LRTC (across tens of seconds) and subcortical coherence (millisecond scale) is unknown. We addressed these ''multiscale interactions'' by simultaneous recordings of surface electroencephalography (EEG) and deep local field potentials (LFP) from the bilateral subthalamic nucleus (STN) in eight patients with severe PD eligible for deep brain stimulation, who performed a lexical decision task on medication. In the continuous data set LRTC up to 20 s were calculated in the amplitude envelope of 8–13-Hz EEG oscillations (across whole scalp), and subcortical coherence was assessed with measures being insensitive to volume conduction artifacts (imaginary part of coherency; iCOH) in 10–20 and 21–30-Hz oscillations in STN–LFP. We showed a significant positive correlation across patients between cortical LRTC (8–13 Hz) and subcortical iCOH selectively in 10–20-Hz oscillations in the left STN. Our results suggest a relation between neural dynamics in the most dominant rhythms in the cortex and basal ganglia in PD, extending across multiple time scales (milliseconds vs. tens of seconds). Furthermore, the investigation of multiscale interactions might contribute to our understanding of cortical–subcortical neural coupling in PD. © 2015 Published by Elsevier Ltd. on behalf of IBRO.

Key words: connectivity, deep brain stimulation, detrended fluctuation analysis, imaginary part of coherency, long-range temporal correlations, oscillations.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease mediated by a loss of dopaminergic neurons in the substantia nigra, resulting in profound alterations of local and distant neural dynamics in the basal ganglia, thalamus, and cortex. A large number of studies demonstrated excessive neural synchronization primarily in beta oscillations (approx. 10–30 Hz) in local field potential (LFP) recordings from the subthalamic nucleus (STN) of patients with PD eligible for deep brain stimulation (DBS; review: Brown and Williams, 2005; Hammond et al., 2007; Eusebio et al., 2012). However, the contribution of distant neural interactions to PD pathology, e.g., between the cortex and STN, is far less understood (Hirschmann et al., 2013); yet they might be of particular relevance, given the direct anatomical connection between both structures via the hyperdirect pathway (Brunenberg et al., 2012; Whitmer et al., 2012). The hyperdirect pathway is assumed to contribute to excessive oscillatory beta activity in the STN under dopamine depletion in PD, due to an increased propagation of rhythmic cortical activity, as shown in animals (Magill et al., 2001). Electrophysiological data confirmed the cortical–subthalamic coupling in humans by demonstrating coherence in beta oscillations (10–30 Hz) between the cortex (electroencephalography, EEG; magnetoencephalography) and STN: cortex–STN beta coherence was primarily pronounced between STN and the ipsilateral sensorimotor cortices (Hirschmann et al., 2011, 2013; Litvak et al., 2011), with the motor cortex leading the STN (Marsden et al., 2001; Williams et al., 2002; Litvak et al., 2012). Moreover, cortex–STN beta coherence was found to be modulated by levodopa (Williams et al., 2002; Lalo et al., 2008; Litvak et al., 2011, 2012; Hirschmann et al., 2013), movement performance (Marsden et al., 2001; Kühn et al., 2006; Klostermann et al., 2007; Lalo et al., 2008), and DBS (Kühn et al., 2008). While previous studies of cortex–STN coherence suggested a substantial role of such long-distance neural interactions for PD pathology, the present study

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Abbreviations: DBS, deep brain stimulation; EEG, electroencephalography; ERD, event-related desynchronization; iCOH, imaginary part of coherency; $iCOH_d$, detectability of imaginary part of coherency; $iCOH_{dav}$, detectability of imaginary part of coherency averaged within designated frequency band; LFP, local field potential; LRTC, long-range temporal correlations; $LRTC_{av}$, averaged within region of interest; PD, Parkinson's disease; ROI, region of interest; SEM, standard error of the mean; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale.

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investigated two crucial features of cortex–STN interactions that have not been addressed so far:

(i) *Relevance of different time scales.* Coherence quantifies neural interactions on very short time scales with millisecond precision (Nunez et al., 1997; Nolte et al., 2004; Srinivasan et al., 2007) and is an established biomarker of PD in both cortex (Silberstein et al., 2005) and STN (Amtage et al., 2009; Pogosyan et al., 2010; Lourens et al., 2013; Hohlefeld et al., 2013a). Furthermore, neural dynamics were also shown to be correlated over very long time scales, up to hundreds of seconds, also termed long-range temporal correlations (LRTC), which are an established finding in cortical recordings (Linkenkaer-Hansen et al., 2001, 2007; Montez et al., 2009; Nikulin et al., 2012a) and were shown to be also present in STN–LFP (Hohlefeld et al., 2012). Moreover, studies demonstrated the interdependence of neural dynamics on short-term vs. long-term scales in healthy subjects in the context of motor performance (Palva et al., 2013), excitation–inhibition balance (Poil et al., 2012), and information coding capacities (Shew et al., 2011) in neural networks.

(ii) *Relevance of cross-frequency relations.* Previous studies of cortex–STN beta coherence were limited to investigate neural interactions within the same frequency band. However, neural interactions are not necessarily limited to the same frequency range (Canolty and Knight, 2010), as shown for cortical data (e.g., Palva et al., 2005; Nikulin et al., 2012b) and in STN–LFP (Fogelson et al., 2005; Marceglia et al., 2006; López-Azcárate et al., 2010; Özkurt et al., 2011), thus broadening the interaction between neural populations that generate oscillations with distinct frequencies. In the cortex, alpha oscillations (approx. 8–13 Hz) represent the most pronounced rhythm (Berger, 1929; Niedermeyer, 1997; Nunez et al., 2001; Palva and Palva, 2007), whereas in the basal ganglia/STN of patients with PD beta oscillations (approx. 10–30 Hz) are the dominant rhythm (Brown and Williams, 2005; Hammond et al., 2007; Eusebio et al., 2012). Therefore, a demonstration of cross-frequency relations between the temporal dynamics in alpha oscillations in the cortex and beta oscillations in the basal ganglia would provide evidence for an additional mode of interaction between these two major brain regions, here in the context of PD.

Consequently, in the present study we addressed the question whether there might be a relationship between neural dynamics on the millisecond scale in the STN and long-range temporal dynamics in the cortex, expressed in the subcortically dominant beta rhythms and cortically dominant alpha rhythm. We refer to this phenomenon as ‘‘multiscale interactions’’. For this purpose, we investigated the relation between LRTC (up to 20 s) in cortical alpha oscillations (8–13 Hz, EEG) and subcortical coherence in STN–LFP (milliseconds; volume conduction-free: Nolte et al., 2004) in low (10–20 Hz) and high (21–30 Hz) beta oscillations. LRTC in the alpha frequency range was chosen as *cortical* biomarker, since several studies demonstrated alterations of cortical long-range correlations in patients (e.g., Alzheimer’s disease and schizophrenia: Montez et al., 2009; Nikulin et al., 2012a) and during thalamic DBS (Hohlefeld et al., 2013b). Intra-nuclear coherence in STN–LFP within beta frequency ranges was chosen as *subcortical* biomarker, since several studies showed its presence in PD (Alavi et al., 2013; Lourens et al., 2013) and its sensitivity to levodopa and correlation with motor symptoms (Pogosyan et al., 2010; Hohlefeld et al., 2013a). Low and high beta oscillations were investigated since previous findings suggested a functional distinction between both frequency ranges, regarding spectral power (Priori et al., 2004; Kühn et al., 2006; López-Azcárate et al., 2010; Marceglia et al., 2011; Hohlefeld et al., 2013a) and STN–LFP coherence (Little et al., 2013; Hohlefeld et al., 2013a, 2014). Furthermore, we hypothesized these multiscale interactions to be hemispheric-specific (i.e., differentially expressed in the left vs. right STN). This was based on previous studies suggesting distinct functional roles of both STN for motor performance and language processing in healthy subjects (Aron and Poldrack, 2006; Forstmann et al., 2012; Schurz et al., in press; Weiss et al., in press), as it was also suggested by LFP recordings of patients with PD in resting state (de Solages et al., 2010; Hohlefeld et al., 2013a) and for emotional processing (Eitan et al., 2013), and by DBS-induced worsening of speech and language (Schulz et al., 2012).

EXPERIMENTAL PROCEDURES

Patients and surgery

Eight patients (five males; mean age 54 years, range 31–77 years; four 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. The patients had no further neurological or psychiatric disorders (e.g., alcohol or drug abuse, apathy, dementia, depression or psychosis, according to the criteria of the German Manual for Psychopathological Diagnosis (AMDP, 2007). All patients were native German speakers. 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). Contact 0 was the lowermost and contact 3 the uppermost (contact length 1.5 mm, contact-to-contact separation 0.5 mm; total contact separation 7.5 mm). For more details on the surgery cf. Hohlefeld et al. (2012). 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 (score available in six patients). The clinical details are summarized in Table 1. The

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