Neuroscience 250 (2013) 320–332

FUNCTIONAL AND EFFECTIVE CONNECTIVITY IN SUBTHALAMIC LOCAL FIELD POTENTIAL RECORDINGS OF PATIENTS WITH PARKINSON'S DISEASE

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Abstract—In Parkinson's disease (PD) levodopa-associated changes in the power and long-range temporal correlations of beta oscillations have been demonstrated, yet the presence and modulation of genuine connectivity in local field potentials (LFP) recorded from the subthalamic nucleus (STN) remains an open question. The present study investigated LFP recorded bilaterally from the STN at wakeful rest in ten patients with PD after overnight withdrawal of levodopa (OFF) and after a single dose levodopa administration (ON). We utilized connectivity measures being insensitive to volume conduction (functional connectivity: non-zero imaginary part of coherency; effective connectivity: phase–slope index). We demonstrated the presence of neuronal interactions in the frequency range of 10–30 Hz in STN–LFP without a preferential directionality of interactions between different contacts along the electrode tracks. While the direction of neuronal interactions per se was preserved after levodopa administration, functional connectivity and the ventral–dorsal information flow were modulated by medication. The OFF–ON differences in functional connectivity were correlated with the levodopa-induced improvement in clinical Unified Parkinson's Disease Rating Scale scores. We hypothesize that regional neuronal interactions, as reflected in STN–LFP connectivity, might represent a basis for the intra-nuclear spatial specificity of deep brain stimulation. Moreover, our results suggest the potential use of volume conduction-insensitive measures of connectivity in STN–LFP as a marker of clinical motor symptoms in PD.

Key words: basal ganglia, coherency, deep brain stimulation, levodopa, neuronal oscillations.

INTRODUCTION

Previous studies showed that neuronal oscillations in local field potential (LFP) recordings from the subthalamic nucleus (STN) of patients with Parkinson's disease (PD) are affected by levodopa particularly in the beta frequency range (approx. 13–35 Hz: Priori et al., 2004; Kühn et al., 2005; López-Azcárate et al., 2010; Marceglia et al., 2011): The abnormally elevated power of beta oscillations decreased after single-dose levodopa administration (Brown et al., 2001; Priori et al., 2004; Brown and Williams, 2005; Kühn et al., 2009) and the temporal dependency (or ''memory'') in the beta oscillations increased, as indicated by stronger long-range temporal correlations up to 50 s in the ON medication condition (Hohlefeld et al., 2012). Potential underlying mechanisms contributing to these findings are manifold, for instance levodopa-induced altered connectivity within the cortex–basal ganglia loop (Brown et al., 2001; Williams et al., 2002; Lalo et al., 2008) and, possibly, also altered neuronal synchronization between different regions within the STN, as addressed by the present study.

The investigation of connectivity in STN–LFP is highly relevant for a deeper understanding of basal ganglia functioning and of its potential importance in deep brain stimulation (DBS) (Benabid et al., 2009), since STN–DBS is characterized by a considerable spatial heterogeneity in the stimulation effects across electrode contacts and patients (McNeely et al., 2011; Whitmer et al., 2012). These findings could suggest a complex organization of the neuronal networks within STN (Lévesque and Parent, 2005), presumably associated with diverse connectivity patterns that remain to be investigated. To date there are only a few studies on functional connectivity showing that single cell activities, recorded intra-operatively in STN, show synchronization (Levy et al., 2000; Amtage et al., 2009; Lourens et al., 2013). However, single cell recordings can represent only a minor fraction of neuronal activity originating in STN and while a relationship between single cells and

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Abbreviations: COH, coherence; DBS, deep brain stimulation; iCOH, imaginary part of coherence; $iCOH_{sig}$, jackknife significance of iCOH; $iCOH_{sigav}$, averaged jackknife significance of iCOH; LFP, local field potentials; PD, Parkinson's disease; PSI, phase–slope index; PSI_{sig}, jackknife significance of PSI; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale.

0306-4522/13 $36.00
http://dx.doi.org/10.1016/j.neuroscience.2013.07.028

LFP has been demonstrated (Levy et al., 2002; Kühn et al., 2005) such a relation is not straightforward (Denker et al., 2011; Telenczuk et al., 2011). Importantly, LFP oscillatory dynamics, reflecting synchronous activity of neuronal populations within STN (Kühn et al., 2005; Schnitzler and Gross, 2005; Weinberger et al., 2009), were hypothesized to reflect a robust marker of pathological neurophysiologic processes in PD, especially in the case of neuronal beta oscillations (Wichmann and DeLong, 1999; Brown and Williams, 2005; Hammond et al., 2007). There is evidence for coherence within STN also from intra-operatively recorded LFP signals in the 8–12 Hz and 20–30 Hz frequency ranges, correlating with clinical motor scores (Pogosyan et al., 2010).

However, the existence of genuine connectivity in STN–LFP remains an open question, since studying LFP interactions is strongly challenged by the interfering effect of volume conduction, which is particularly pronounced for very closely spaced electrode contacts (typical for DBS recordings). Under such circumstances volume conduction unavoidably leads to the detection of spurious neuronal interactions, as is the case with the traditional coherence measure. However, recently developed methods, based on the imaginary part of coherency (i.e., excluding the zero-phase lag part), allow circumventing the problem of volume conduction and thus provide reliable approaches to the detection of genuine neuronal interactions (Nolte et al., 2004, 2008). We investigated the existence of neuronal connectivity in STN–LFP recorded from patients with severe idiopathic PD. In addition, we assessed possible modulations of connectivity by dopaminergic medication and correlated it to changes in clinical motor scores.

EXPERIMENTAL PROCEDURES

Patients and surgery

Ten patients (six males; mean age 61 years, range 47–71 years) diagnosed with idiopathic PD (mean disease duration 10 years, range 5–20 years) participated in the study, as described in our previous study (Hohlefeld et al., 2012), where further details about the patients were reported (see Table 1 therein). This data set was reanalyzed for the purposes of the present study. For all patients informed consent was obtained and the experimental procedures were approved by the local ethics committee in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964). The pre-surgery motor Unified Parkinson's Disease Rating Scale (UPDRS) scores were assessed by an experienced clinician (see Table 1 in Hohlefeld et al., 2012) for OFF and ON levodopa (scores available in nine patients). Additionally, the body side being more strongly affected was also evaluated by the clinician, and was furthermore confirmed by the pre-surgery UPDRS hemibody scores OFF levodopa (in seven out of 10 patients, in which the hemibody scores were available).

The DBS electrodes were implanted bilaterally in the STN (Model 3389, Medtronic Neurological Division, Minneapolis, MN, USA), where contact 0 was the lowermost and contact three 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 and electrode localization please refer to Hohlefeld et al. (2012).

Data recordings

Briefly, the patients were studied post-operatively (range 2–6 days) while the DBS electrodes were still externalized. The recordings were performed after overnight withdrawal of levodopa, referred to as ''OFF'', and ~30–45 min after the 1–2× usual morning dose (100–200 mg) of oral levodopa (Madopar LT, Roche Pharma AG, Grenzach-Wyhlen, Germany), referred to as ''ON''. One patient received apomorphine (9.5 mg/h) instead of levodopa. The recordings were performed during wakeful rest (while sitting, eyes open and fixated) in two blocks of 7 min each, separated by a break. The OFF and ON conditions were recorded on separate days (1 day between recording conditions in seven out of 10 patients; 2 days in one patient, and two patients were recorded on the same day). In four patients the OFF condition was recorded first and in another four patients the ON condition was recorded first (in data recordings for two performed on the same day, OFF was recorded first). LFP were recorded bipolarly from the adjacent contact pairs 01, 12, and 23 (referred to as ''channels'') of the macroelectrode in the left and right STN, where channel pair 01 was the lowermost and pair 23 was the uppermost. By these terms and by ''upward–downward'' connectivity we refer throughout the text to the relative position of the channels along the electrode tract. Prior to the analysis the data were carefully inspected for segments containing artifacts, which were excluded from further processing. Channels containing an excessive amount of noise, as determined by visual inspection, were also excluded from further evaluation. For the analysis of connectivity, the bipolar channels were grouped into pairs, with three channel pairs for the connections in each STN (left STN: L01–12, L12–23, and L01–23; right STN: R01–12, R12–23, and R01–23). Notably, in comparison to other studies of connectivity involving STN (e.g., Klostermann et al., 2007; de Solages et al., 2010; Hirschmann et al., 2011; Litvak et al., 2011) an advantage of the present study is that we used an anatomical reconstruction of the electrode trajectory (Schönecker et al., 2009) for analyzing only those bipolar channels with at least one contact in STN (see Hohlefeld et al., 2012, for details and for the justification of including contact pairs in the analysis). The present selection approach ensures that if in a given bipolar channel (e.g., channel 23) both contacts were outside of STN (for channel 23 this would mean that the dorsal end of the electrode track being out of STN), then this channel was excluded and no coherence was calculated between this channel and others.

Notably, despite this careful electrode selection, and because of the limited accuracy of the post-operative imaging method in the average range of 1–2 mm (Schönecker et al., 2009), one cannot exclude the