Neuroscience 332 (2016) 170–180

PARKINSON SUBTYPE-SPECIFIC GRANGER-CAUSAL COUPLING AND COHERENCE FREQUENCY IN THE SUBTHALAMIC AREA

ESTHER FLORIN,[a,b*] JOHANNES PFEIFER,[c] VEERLE VISSER-VANDEWALLE,[d] ALFONS SCHNITZLER[b] AND LARS TIMMERMANN[a*]

[a] *Department of Neurology, University Hospital Cologne, Kerpener Strasse 62, 50937 Köln, Germany*

[b] *Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine University Düsseldorf, Germany*

[c] *Department of Economics, University of Mannheim, Germany*

[d] *Department of Stereotaxy and Functional Neurosurgery, University Hospital of Cologne, Germany*

Abstract—Previous work on Parkinson's disease (PD) has indicated a predominantly afferent coupling between affected arm muscle activity and electrophysiological activity within the subthalamic nucleus (STN). So far, no information is available indicating which frequency components drive the afferent information flow in PD patients. Non-directional coupling e.g. by measuring coherence is primarily established in the beta band as well as at tremor frequency. Based on previous evidence it is likely that different subtypes of the disease are associated with different connectivity patterns. Therefore, we determined coherence and causality between local field potentials (LFPs) in the STN and surface electromyograms (EMGs) from the contralateral arm in 18 akinetic-rigid (AR) PD patients and 8 tremor-dominant (TD) PD patients. During the intraoperative recording, patients were asked to lift their forearm contralateral to the recording side. Significantly more afferent connections were detected for the TD patients for tremor-periods and non-tremor-periods combined as well as for only tremor periods. Within the STN 74% and 63% of the afferent connections are associated with coherence from 4–8 Hz and 8–12 Hz, respectively. However, when considering only tremor-periods significantly more afferent than efferent connections were associated with coherence from 12 to 20 Hz across all recording heights. No difference between efferent and afferent connections is seen in the frequency range from 4 to 12 Hz for all recording heights. For the AR patients, no significant difference in afferent and efferent connections within the STN was found for the different frequency bands. Still, for the AR patients dorsal of the STN significantly more afferent than efferent connections were associated with coherence in the frequency range from 12 to 16 Hz. These results provide further evidence for the differential pathological oscillations and pathways present in AR and TD Parkinson patients.

Key words: deep brain stimulation, connectivity, directionality, coherence, human, subthalamic nucleus.

INTRODUCTION

Parkinson's disease (PD) is characterized by pathological oscillations within the subthalamic nucleus (STN) and motor cortex (Volkmann et al., 1996; Timmermann et al., 2003; Kühn et al., 2006; Brown, 2007). Much of the previous work has either focused on analyzing the frequency components of these pathological oscillations (Kühn et al., 2006; Reck et al., 2009b; Hirschmann et al., 2013) or the directionality of such a pathological coupling (Florin et al., 2010b). In particular, with coherence-based analysis different pathological frequency ranges have been found for the different Parkinson subtypes, akinetic-rigid (AR) and tremor-dominant (TD). In the case of AR patients, excessive beta oscillations (12–30 Hz) are a pathological hallmark (Brown et al., 2001; Silberstein et al., 2003; Kühn et al., 2004; Chen et al., 2007). For TD patients the oscillations are increased in the tremor (4–8 Hz) and double-tremor frequency range (Timmermann et al., 2003; Reck et al., 2009b, 2010). These two different findings indicate that subtype-specific pathophysiological changes are found in PD.

Furthermore, our own previous work has indicated that the coupling between affected arm muscle activity and electrophysiological activity within the STN is predominantly afferent during the main motor symptom of the particular Parkinson subtype (Florin et al., 2010b, 2012). Additionally, an optogenetic study in Parkinsonian rodents has shown that stimulation of the afferent axons projecting to the STN alleviates the motor symptoms (Gradinaru et al., 2009). However, so far no information on the frequency specificity of the afferent connections has been provided. This stems from a limitation of Granger based causality measures, which are often used to determine the directionality of the coupling. Due to a low determined model order of the autoregressive

*Corresponding authors. Address: Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine University Düsseldorf, Germany (E. Florin). Fax: +49-221-87512 (L. Timmermann).

E-mail addresses: Esther.Florin@hhu.de (E. Florin), Lars.Timmermann@uk-koeln.de (L. Timmermann).

Abbreviations: AR, akinetic-rigid; DBS, deep brain stimulation; EDC, M. extensor digitorum communis; EMG, electromyogram; FDI, first dorsal interosseous muscle; FDL, M. flexor digitorum superficialis; fMRI, functional magnetic resonance imaging; LFPs, local field potentials; LOOM, leave one out method; MVAR, multivariate autoregression; PD, Parkinson's disease; sPDC, squared partial directed coherence; STN, subthalamic nucleus; TD, tremor-dominant.

http://dx.doi.org/10.1016/j.neuroscience.2016.06.052
0306-4522/

model – on which the estimation of Granger causality is often based – the frequency resolution in many real data applications is not high enough to distinguish the physiological frequency ranges (Schlögl and Supp, 2006). The aim of the present study is to provide insights into the frequency specificity of directional information with respect to different subtypes of PD by jointly studying the relationship between coherence and directionality.

We analyzed recordings from Parkinson patients who underwent an implantation of deep brain stimulation (DBS) electrodes. During this implantation of DBS electrodes we simultaneously recorded local field potentials (LFPs) from above and within the STN and electromyographic (EMG) activity from affected contralateral arm muscles. We combined coherence and causality analysis to gain additional information on the connections between LFPs and affected arm muscles. For the causality analysis we used the squared partial directed coherence (sPDC) (Astolfi et al., 2006). While causality and coherence in principle analyze different temporal components (temporal shift vs. contemporaneous), their joint behavior is nonetheless informative about the connection between arm-muscle activity and LFPs in the STN.

Based on the subtype-specific frequency changes in PD (Brown et al., 2001; Silberstein et al., 2003; Kühn et al., 2004; Chen et al., 2007), the two specific hypotheses tested are (1) that the detected causalities in the case of AR patients co-occur with coherence in the beta band and (2) that in the case of TD patients the co-occurrence is mainly in the tremor-frequency range. The frequency specificity within these hypotheses is based on the previous literature on oscillatory activity in PD.

EXPERIMENTAL PROCEDURES

Patients

For this study we included all Parkinson patients from 2005 to 2008 who (i) underwent DBS implantation in the STN at our center and (ii) had recordings of LFPs during an isometric hold condition. The clinical preoperative decision for the implantation of DBS electrodes was made in accordance to the guidelines in Lang et al. (2006) and Hilker et al. (2009). After excluding patients with incomplete clinical information (no pre- and postoperative UPDRS), 18 AR PD patients with 24 recorded hemispheres and 8 TD PD patients with 9 recorded hemispheres were included for this study. We have analyzed data from these patients in our previous studies (Reck et al., 2009a, 2009b, 2010; Florin et al., 2010b, 2012, 2013a, 2013b), but focused on different aspects in the recordings than in the current study. The Parkinson patients were classified as AR, TD and mixed type based on their UPDRS score according to Spiegel et al. (2007). The mixed type and TD patients were grouped together, because all these patients had a higher tremor than akinesia score. A summary of preoperative data is given in Table 1.

All patients gave written informed consent to the implantation of electrodes and the micro- and macroelectrode recordings. The study was approved by the local ethics committee (study no. 2459 and 08-158) and conducted in accordance with the Declaration of Helsinki.

Implantation and intra-operative recordings

The implantation and intra-operative recording procedure has been described in detail in Florin et al. (2012). Dopaminergic medication was withdrawn for at least 12 h before operation to minimize its influence during the operation. Clinically this allows for testing the stimulation parameters during the operation without confounds from the medication. During implantation, LFPs were recorded with up to five combined micro- and macroelectrodes using the INOMED ISIS MER-system (INOMED corp., Teningen, Germany). Less than five micro–macroelectrodes were used in patients where the individual anatomy and blood vessels did not allow for all five electrodes. Simultaneously, surface EMGs were recorded of the M. extensor digitorum communis (EDC), M. flexor digitorum superficialis (FDL), and the first dorsal interosseous muscle (FDI) with the INMOED ISIS MER-system. Patients were asked to lift their forearm contralateral to the recording side for at least 30 s. For the tremor patients we included periods both with and without postural tremor. In a subanalysis we further separated these recordings into periods with postural tremor and without tremor. The sampling rate of the EMG and LFP signals was 2500 Hz. During the recording a high-pass filter of 0.5 Hz and a low-pass filter of 1 kHz was used. The LFPs were recorded from at most 9 mm above the target point in the STN. The recording was continued in steps of 1 mm downwards until up to 1 mm below the target point within the STN. An example recording is displayed in Fig. 1. Based on the discharge pattern from the microelectrode recording the location was either classified as within the STN or above the STN. For details on this please refer to Reck et al. (2010).

Statistical causality analysis with squared partial directed coherence (sPDC)

After the implantation, macroelectrode and EMG recordings from each patient were visually reviewed to detect artifacts. In the case of an artifact the respective sequences were excluded from further analysis. Only consecutive sequences of at least 10 s were used. The EMGs were 2 Hz high-pass filtered to remove drifts due to movements. Both LFPs and EMGs were 50 Hz notch filtered to remove potential electric artifacts. These filter settings are in accordance with our previous simulation study, where we demonstrated their compatibility with statistical causality analysis (Florin et al., 2010a), and are the same as in Florin et al. (2012). In addition the recordings were *z*-scored to normalize the amplitudes between EMG and LFP. Matlab (version 8.2., The MathWorks, Inc., Natick, MA, USA) and the Biosig-toolbox (version 1.97) (http://biosig.sourceforge.net) were used for the analysis.

For the statistical causality analysis we used a multivariate extension of Granger causality (Granger, 1969) in the spectral domain: the sPDC (Astolfi et al.,