Clinical Neurophysiology 128 (2017) 2029–2036

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Parkinsonian rest tremor can be detected accurately based on neuronal oscillations recorded from the subthalamic nucleus

J. Hirschmann [a,b,*], J.M. Schoffelen [a], A. Schnitzler [b,c], M.A.J. van Gerven [a]

[a] Radboud University, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands
[b] Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich Heine University Düsseldorf, Germany
[c] Center for Movement Disorders and Neuromodulation, Medical Faculty, University Hospital Düsseldorf, Germany

ARTICLE INFO

Article history:
Accepted 25 July 2017
Available online 9 August 2017

Keywords:
Tremor detection
Parkinson's disease
Neuronal oscillations
Deep brain stimulation
Subthalamic nucleus
Hidden Markov Model

HIGHLIGHTS

- Tremor can be detected accurately in short segments of STN local field potential recordings.
- Four power estimates from a single DBS electrode contact pair suffice for successful detection.
- High frequency oscillations are the most useful feature for tremor detection.

ABSTRACT

Objective: To investigate the possibility of tremor detection based on deep brain activity.
Methods: We re-analyzed recordings of local field potentials (LFPs) from the subthalamic nucleus in 10 PD patients (12 body sides) with spontaneously fluctuating rest tremor. Power in several frequency bands was estimated and used as input to Hidden Markov Models (HMMs) which classified short data segments as either tremor-free rest or rest tremor. HMMs were compared to direct threshold application to individual power features.
Results: Applying a threshold directly to band-limited power was insufficient for tremor detection (mean area under the curve [AUC] of receiver operating characteristic: 0.64, STD: 0.19). Multi-feature HMMs, in contrast, allowed for accurate detection (mean AUC: 0.82, STD: 0.15), using four power features obtained from a single contact pair. Within-patient training yielded better accuracy than across-patient training (0.84 vs. 0.78, $p = 0.03$), yet tremor could often be detected accurately with either approach. High frequency oscillations (>200 Hz) were the best performing individual feature.
Conclusions: LFP-based markers of tremor are robust enough to allow for accurate tremor detection in short data segments, provided that appropriate statistical models are used.
Significance: LFP-based markers of tremor could be useful control signals for closed-loop deep brain stimulation.

1. Introduction

Deep brain stimulation (DBS) is a widely used treatment for patients with advanced Parkinson's disease (Perlmutter and Mink, 2006). While its efficacy is well established, its efficiency can potentially be optimized. Conventional DBS is applied continuously although motor symptoms are usually fluctuating. Moreover, the benefit of DBS is often compromised by side-effects, which can usually be alleviated by reducing stimulation power, i.e. the energy applied per unit of time. Suggested approaches to reduce power include electric field steering (Contarino et al., 2014), optimization of pulse patterning (Adamchic et al., 2014) and closed-loop stimulation (Priori et al., 2013).

In closed-loop DBS, stimulation is exclusively applied in the presence of symptoms rather than continuously. The approach has been demonstrated to reduce the occurrence of side-effects, such as dysarthria (Little et al., 2016). Furthermore, it is more energy-efficient than continuous DBS and thus expected to reduce the amount of surgeries for battery replacement (Rosin et al., 2011; Little et al., 2013; Cagnan et al., 2017). Finally, and most importantly, it was reported that closed-loop DBS may improve symptom suppression (Rosin et al., 2011; Little et al., 2013).

* Corresponding author at: Institute of Clinical Neuroscience and Medical Psychology, Moorenstr. 5, 40225 Düsseldorf, Germany.
E-mail address: Jan.Hirschmann@med.uni-duesseldorf.de (J. Hirschmann).

http://dx.doi.org/10.1016/j.clinph.2017.07.419
1388-2457/

In order to implement closed-loop DBS, it is necessary to first facilitate reliable symptom detection. Ideally, detection is achieved without the need to add further measurement channels to the DBS system, i.e. by online analysis of deep brain recordings. Obviously, such online monitoring makes sense only for symptoms which wax and wane dynamically. Furthermore, the symptom must have a known and robust neural correlate.

Rest tremor is a cardinal symptom of PD that fulfills both of these requirements. It is highly dynamic and well characterized with respect to its electrophysiology (Elble 2009; Raethjen and Deuschl, 2009; Helmich et al., 2012; Hallett 2014). Tremor-related activity occurs throughout the motor network, including the basal ganglia, thalamus, cerebellum, and primary motor cortex (Timmermann et al. 2003; Helmich et al., 2011). In the presence of tremor, these areas produce coherent neuronal oscillations at tremor frequency (3–7 Hz; Hirschmann et al., 2013a). Furthermore, beta power (13–30 Hz) and beta band coupling are reduced during tremor (Qasim et al., 2016). Finally, local field potential (LFP) recordings in the subthalamic nucleus (STN) have revealed an increase of low gamma power (31–45 Hz; Weinberger and Hutchison., 2009; Beudel et al., 2015) and a change in high frequency oscillations (HFOs). In particular, the ratio between slow HFO power (200–300 Hz) and fast HFO power (300–400 Hz) was reported to increase reliably during tremor (Hirschmann et al., 2016).

It is important to note that the above-listed power differences between rest tremor and tremor-free rest relate to temporal averages (tens to hundreds of seconds). It is unclear whether LFP-based markers of tremor are robust enough to allow for a moment-by-moment detection of tremor. Here, we show that such that detection in short data segments is indeed possible, provided that appropriate statistical methods are used.

2. Methods

2.1. Patients

This study is a re-analysis of a dataset collected previously (Hirschmann et al., 2013a, 2016). In order to have a sufficient amount of data, we selected those patients with at least two continuous data epochs, containing at least 12 s of tremor-free rest and 12 s of rest tremor each. Recordings from 10 patients (12 STNs) met this inclusion criterion. Patient S10 was the only patient not included in earlier studies.

All patients were diagnosed with idiopathic PD, experienced waxing and waning rest tremor, and were selected for DBS surgery. Clinical details are provided in Table 1. The study was approved by the ethics committee of the Medical Faculty of the Heinrich Heine University Düsseldorf (Study No. 3209), was carried out in accordance with the Declaration of Helsinki and required written informed consent.

2.2. Recordings

Patients were recorded one day after electrode implantation. Patients S01-S09 were off oral dopaminergic medication for $\geq$12 h. Patient S10 had received 200 mg of levodopa 3.5 h before the measurement started to avoid painful upper limb cramps. Subcutaneous apomorphine administration was paused 1.5 to 2 h before measurements started.

Each patient underwent two sessions containing rest (5 min) followed by one of two motor tasks: static forearm extension or self-paced fist-clenching at approximately 1 Hz (Hirschmann et al., 2013b). Patients S08 and S09 were only recorded at rest for 20 min and 15 min, respectively. Movements were performed with the symptom-dominant body side in five 1-min blocks which were interleaved by 1 min pauses to avoid fatigue. Except for the analysis of voluntary movement in Section 3.2, we exclusively consider the rest condition in this paper.

Local field potentials (LFPs) from the STN, the magnetoencephalogram (MEG; Elekta Oy, Helsinki, Finland) and the surface electromyogram (EMG) of the *extensor digitorum communis* and *flexor digitorum superficialis* muscles of both upper limbs were recorded simultaneously. Here, we concentrated on LFPs because they are in principle available to implanted DBS systems with sensing capacity and could therefore be used to control closed-loop DBS.

The sampling rate was 2000 Hz. Externalized, non-ferromagnetic leads connected DBS electrodes to the amplifier of the MEG system. Electrode contacts were referenced to the left mastoid and rearranged to a bipolar montage offline by subtracting signals from neighboring contacts. EMG electrodes were referenced to surface electrodes at the muscle tendons. A hardware filter was applied with a pass-band of 0.1–660 Hz. EMG preprocessing consisted of the application of a high-pass filter with a cut-off frequency of 10 Hz and signal rectification. Individual tremor frequency was defined as the highest peak of the EMG power spectrum during tremor.

Table 1
Information on patients. Columns 7 and 8 show that deep brain stimulation generally reduced the contralateral upper limb rest tremor score of the Unified Parkinson's Disease Rating Scale. OFF/OFF = medication off/stimulation off. B = 8-contact, non-segmented electrode by Boston Scientific. M = 4-contact, non-segmented electrode by Medtronic (model 3389). S = 4-contact, non-segmented electrode by St. Jude Medical.

Patient	Gender	Age (y)	Disease duration (y)	Tremor frequency (Hz)	Electrode model	Tremor side	Upper limb tremor score control OFF/OFF	Upper limb tremor score control OFF/ON	Tremor-free rest (min)	Tremor (min)	Tremor-free, voluntary movement ipsilat. to tremor (min)
S01	m	65	8	4	M	left	3	2	4.67	5.63	5.23
S02	m	69	6	3.5	M	left	3	2	8.77	4.77	–
						right	3	3	8.07	5.47	–
S03	m	68	11	3	M	left	1	0	4.60	0.63	–
S04	m	68	2	4	S	right	1	0	6.40	2.50	–
S05	m	52	11	6	S	right	2	0	5.60	4.47	4.50
S06	m	53	12	5	M	left	3	2	7.80	1.20	2.53
S07	m	59	6	4.5	M	right	3	1	7.47	2.73	–
S08	m	52	7	5	B	left	3	0	6.23	6.50	–
						right	1	0	6.33	6.40	–
S09	m	53	6	5	B	right	3	0	7.00	5.27	–
S10	f	75	14	4	M	right	1	0	3.07	1.47	3.57
Mean		61.40	8.30	4.40			2.25	0.83	6.33	3.92	3.96
Std		8.60	3.62	0.88			0.97	1.11	1.65	2.10	1.17