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Tremor-correlated neuronal activity in the subthalamic nucleus of Parkinsonian patients

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ABSTRACT

Tremor in Parkinson's disease (PD) is generated by an oscillatory neuronal network consisting of cortex, basal ganglia and thalamus. The subthalamic nucleus (STN) which is part of the basal ganglia is of particular interest, since deep brain stimulation of the STN is an effective treatment for PD including Parkinsonian tremor. It is controversial if and how the STN contributes to tremor generation. In this study, we analyze neuronal STN activity in seven patients with Parkinsonian rest tremor who underwent stereotactic surgery for deep brain stimulation. Surface EMG was recorded from the wrist flexors and extensors. Simultaneously, neuronal spike activity was registered in different depths of the STN using an array of five microelectrodes. After spike-sorting, spectral coherence was analyzed between spike activity of STN neurons and tremor activity. Significant coherence at the tremor frequency was detected between EMG and neuronal STN activity in 76 out of 145 neurons (52.4%). In contrast, coherence in the beta band occurred only in 10 out of 145 neurons (6.9%). Tremor-coherent STN activity was widely distributed over the STN being more frequent in its dorsal parts (70.8–88.9%) than in its ventral parts (25.0–48.0%). Our results suggest that synchronous neuronal STN activity at the tremor frequency contributes to the pathogenesis of Parkinsonian tremor. The wide-spread spatial distribution of tremor-coherent spike activity argues for the recruitment of an extended network of subthalamic neurons for tremor generation.

Tremor is one of the core symptoms of Parkinson's disease (PD). It is assumed to be generated by a central oscillatory neuronal network consisting of cortex, basal ganglia and thalamus [10,11]. Cortical activity related to Parkinsonian tremor has been detected using recordings directly from the cortical surface as well as by EEG and MEG [2,14,35,36]. Tremor-related oscillatory activity in the basal ganglia was recorded during stereotactic neurosurgery in a number of subnuclei, in particular in the subthalamic nucleus (STN) [16,22,25,28] and in the internal globus pallidus [17]. Intraoperative recordings also provided evidence for the involvement of the thalamus [1,21].

In recent years, much attention in tremor research has been focused on one particular part of the basal ganglia, the STN. Lesioning the STN in an animal model of Parkinson's disease, i.e. monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), alleviated a number of Parkinsonian symptoms including tremor [4]. High frequency stimulation of the STN has become an established method to reduce tremor and other Parkinson-related deficits [12,18,23,24].

As yet, the pathophysiological mechanisms of tremor generation are not clearly understood. So-called 'tremor cells' firing at the tremor frequency have indeed been described in the STN [16,22,28]. However, coherence between subthalamic neurons and muscular activity at the tremor frequency seemed to be uncommon [22]. Subthalamic oscillatory activity in the beta frequency range seems to play a major role in Parkinsonian patients with predominant bradykinesia and rigidity [9,19,20,37]. However, a relationship between oscillatory activity in the beta frequency range and the amount of Parkinsonian tremor could not be found [19,37]. In all, the functional link between STN activity and tremor is unresolved.

In this study, we address this issue by analyzing neuronal STN activity in patients with Parkinsonian rest tremor who underwent stereotactic surgery for deep brain stimulation. We show that coherence between neuronal STN activity and muscular activity

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Table 1
Clinical data at the time of stereotactic operation and STN recording

Patient	Age (years)	Sex	Disease duration (years)	UPDRS motor score on/off (total 108)	Hoehn and Yahr Score in off	Number of neurons used for analysis within the right or left STN
B	40	M	7	30/37	2	R 23; L 0 (no tremor)
E	69	M	15	29/47	2	R 6; L 7
L	68	M	14	17/33	3	R 20; L 0 (thalamotomy)
M	60	M	7	28/37	2	R 16; L 23
P	70	M	27	22/35	3	R 0 (no tremor); L 12
S	53	M	9	27/36	3	R 0 (no tremor); L 23
W	50	F	8	26/37	2	R 0 (no tremor); L 15

M, male; F, female; R, right; L, left.

occurs predominantly at the tremor frequency, and only to a lesser extent in the beta frequency range.

7 patients (6 male; 1 female) were included with a mean age of 59.1 ± 4.3 years and an average duration of Parkinson's disease of 12.4 ± 2.8 years by the time of stereotactic operation. They all met the criteria of the British Brain Bank for idiopathic Parkinson's disease. All patients presented a rest tremor ranging from 3.2 to 7.0 Hz of at least one upper limb. The patients were no longer sufficiently

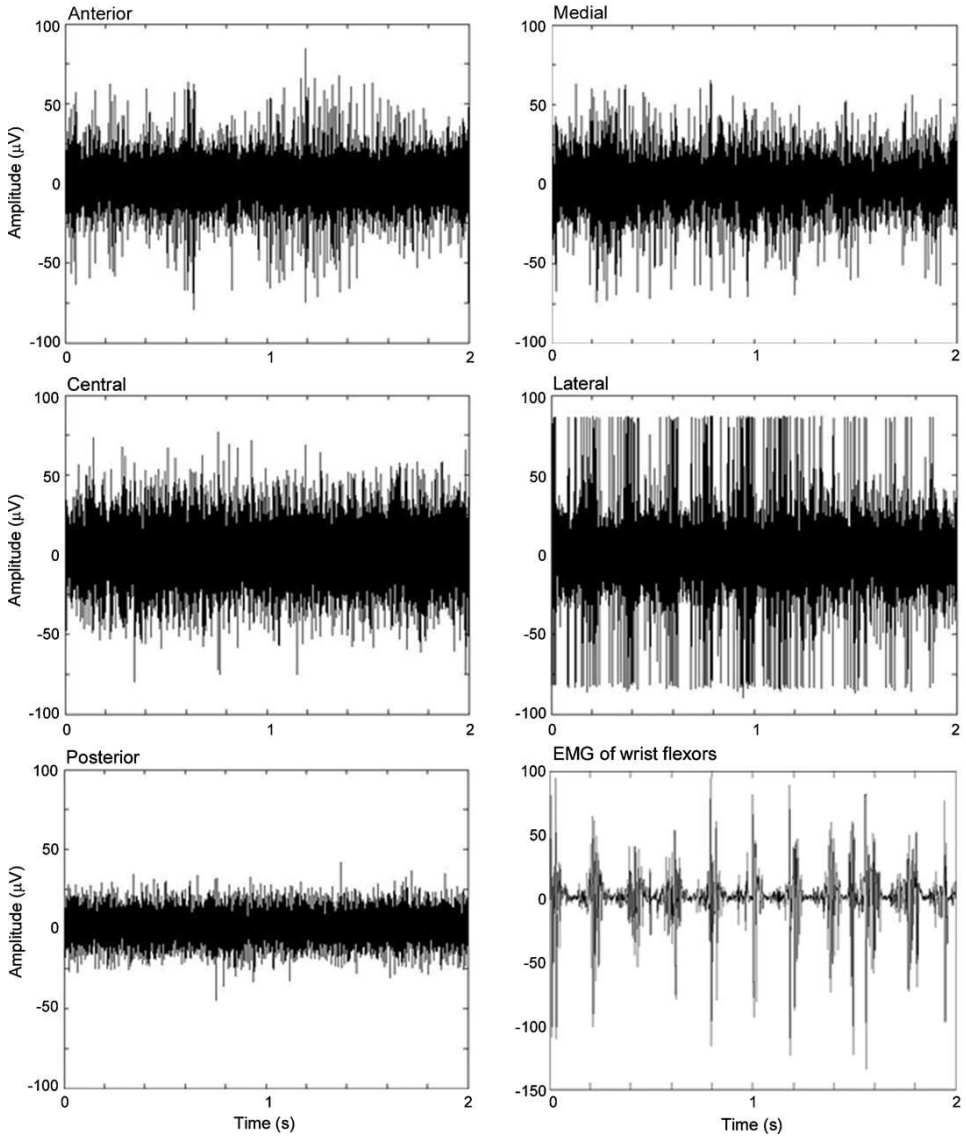

Fig. 1. Spike activity registered by five microelectrodes and simultaneously recorded surface EMG of the wrist flexors over a period of 2 s taken from one site of patient M.

treatable with medication due to adverse effects, severe motor fluctuations or persisting tremor under therapy. Therefore, they were selected for deep brain stimulation in the STN by a committee of neurologists and neurosurgeons. All patients were preoperatively evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS motor score), which had a mean value of 37.4 ± 1.7 of 108 points in the defined "off" state after absence of dopaminergic drugs for at least 12 h. The best "on" state was achieved by a dosage of 250 mg of rapidly effective and soluble levodopa (Madopar LT®, Hoffman-La Roche, Grenzach-Wyhlen, Germany). The rating for the "on" condition took place 30 min and 1 h after oral application, yielding a mean of 25.6 ± 1.7 points based on the best score obtained. For the UPDRS tremor subscore (items 20 and 21) the mean value in the "off" state of 10.9 ± 1.0 out of 28 points improve to 6.4 ± 1.3 points in the "on" condition. In all, nine STN could be used for offline analysis. The remaining five STN were not evaluated since tremor was unilateral in four patients and suppressed by thalamotomy in one patient. Detailed patient information can be gathered from Table 1. This study was approved by the local ethical committee; all procedures were conducted in accordance with the Declaration of Helsinki. Patients' informed consent for surgery including microelectrode recording and EMG was obtained prior to surgery.

After adjustment of a modified frame-based Riechert-Mundinger system, a contrast-enhanced stereotactic computerized tomography (CT) was performed. Images were fused with preoperative magnetic resonance imaging (T1-weighted contrast-enhanced 1 mm MP-Rage and T2-weighted 2 mm images) using STP4 software (Stryker-Leibinger, Freiburg, Germany). The target coordinates in relation to the mid commissural point ($x = 12$ mm, $y = -2.5$ mm, $z = -3$ mm) were calculated. Trajectories were adapted with respect to the patients' individual gyral and vascular configuration. Electrode implantation was carried out under local anesthesia without sedation and in a defined "off" condition after >12 h discontinuation of dopaminergic medication.

Bilateral 14 mm burr holes were applied. For microelectrode recording the MeKIT® system (inomed GmbH, Teningen, Germany) was used, consisting of five cannula and microelectrodes (MicroMacroelectrodes®) with a tip diameter of 4 μm. These microelectrodes were arranged 2 mm anterior, medial, lateral and posterior to the calculated central electrode. Microelectrode recording was started 5–10 mm dorsal to the calculated target. Microelectrodes were advanced simultaneously in 1 mm steps using a manual MicroDrive® (inomed GmbH, Teningen, Germany). Microelectrode recordings (ISIS MER®, inomed GmbH, Teningen, Germany) were sampled at 25 kHz and were registered over a period of 30–120 s. Simultaneously, electromyography (EMG) of the contralateral forearm flexors and extensors was recorded using surface electrodes (Kendall Soft-E®, TYCO Healthcare Group LP, Mansfield, MA, USA) and sampled at 2500 Hz. Recordings were assumed to be within the STN when neuronal spike activity matched the criteria for STN neurons previously described [16]. As an example, Fig. 1 shows a 2-s section of an original recording from patient 'M'.

After systematic test stimulation (OSIRIS BrainStimulator®, inomed GmbH, Teningen, Germany) of the target structure, the quadripolar macroelectrode (Medtronic® 3389, Minneapolis, MN, USA) was implanted at the position of best clinical effect. The final position of the bilateral electrodes was confirmed by a stereotactic CT and computer-based fusion with the preoperative plan. The implantation of a dual channel neurostimulator (Kinetra™, Medtronic®, Minneapolis, MN, USA) was realized under general anesthesia on the same day.

EMG data were band-pass filtered between 30 Hz and 1 kHz and full-wave rectified. Each recording of neuronal activity was preprocessed using a wavelet-based spike sorting algorithm [31] to separate the action potentials of different neurons recorded by one microelectrode. The maxima of the action potentials determined the firing time which were used for further analysis.

To assure stationarity of the data, recordings entered the analysis only if the tremor EMG was strong and continuous and the STN spike trains showed stable activity. For spike activity, a firing rate of more than 10 spikes/s over a duration of at least 30 s was demanded as an inclusion criterion.

Cross-spectral analysis was used to investigate the interrelation between signals [33]. The spectral coherence measures the interrelation between the frequency components of the analysed signals. As a normalized measure for the correlation, the spectral coherence was estimated by smoothing and rescaling of the cross-periodogram. This procedure is a standard technique in time series analysis [8].

For the analysis of neuronal activity, cross-spectral analysis is adapted to spike trains which are mathematically well described by point processes. The entire information of point processes is encoded by the times of the occurrence of events, i.e. the occurrence of the action potentials.

In Henschel et al. [15], it was suggested to perform the spectral analysis of point processes directly on the sequences of times when

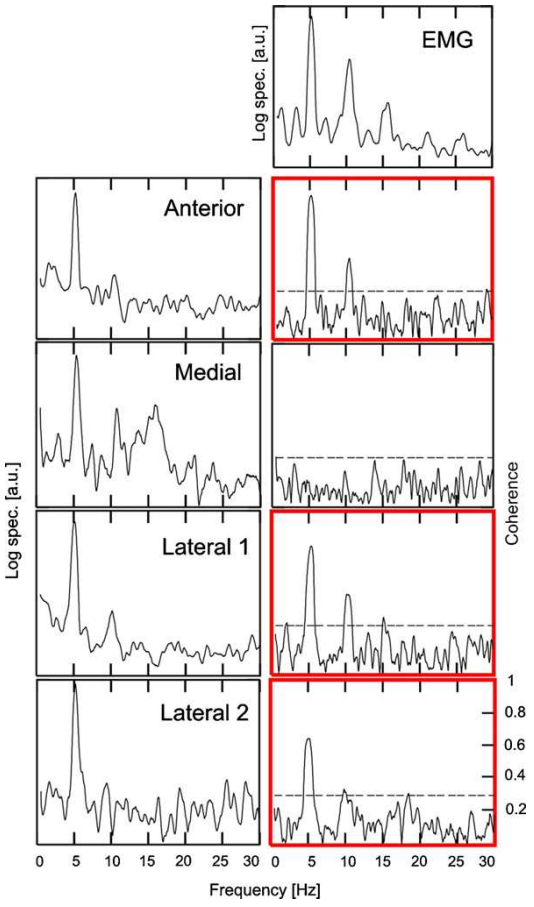

Fig. 2. Illustration of frequency spectra of four subthalamic neurons (anterior, medial, and two lateral neurons) and tremor surface-EMG as well as the coherence analyses between neurons and EMG. The horizontal dashed line indicates the level of significance ($p < 0.01$). Panels with significant coherences at the tremor frequency and/or its first harmonic are highlighted by a red frame. Spec., spectrum; a.u., arbitrary units.

action potentials are generated. The Fourier transform of such a sequence of events dN_t reads:

$$\mathrm{FT}(dN_t)(w) = \sum_s e^{-iwT_s}$$

where T_s denotes the times of the occurrence of the s event in the spike train. The estimation of the spectrum, cross-spectrum and coherence can now be performed in analogy to the procedure for time series [8].

Both the neuronal activity as well as the EMG data were tapered using a triangular window to avoid leakage prior to the spectral analysis [15]. The periodograms were smoothed using a triangular kernel with a smoothing width of 1 Hz.

To test for the statistical significance of the coherence values obtained, the pointwise 99% significance level was calculated. This significance level allows for testing the significance of coherence at one particular frequency which is usually the tremor frequency or its first higher harmonic. If coherence is tested for several frequencies or for a range of frequencies, the significance level has to be corrected. This is due to the increased likelihood of a significant coherence if more than one frequency is considered. In this multiple testing situation the significance level was Bonferroni adjusted to $(1 - 0.01/n)$, where n denotes the number of independent frequencies under investigation. Considering the beta frequency band (15–30 Hz), the significance level has to be 99.95% according to our estimation procedure [7,34]. This ensures that each individual crossing of the significance level can be assumed to be statistically significant at 99%.

Data was collected from nine STN in seven patients (see Table 1). Recordings from 42 sites each corresponding to one defined depth within an STN were considered for analysis. By application of the criteria described above, between 2 and 6 neurons per site were selected.

In all, 145 neurons were analyzed. As an example, Fig. 1 shows a 2-s section of an original recording. Fig. 2 illustrates the statistical analysis of this recording in a matrix with frequency spectra and coherence analyses. All recordings were analyzed as in Fig. 2.

In 76 out of 145 neurons (52.4%), we found significant coherence between neuronal STN activity and the EMG at the tremor frequency or its first harmonic (Fig. 3). Tremor-coherent neurons were widely distributed over the whole STN. Their percentage was lower in the ventral parts of the STN (25.0–48.0%) than in its dorsal parts (70.8–88.9%). Within one site, tremor-coherent STN activity could be observed at up to four microelectrodes simultaneously.

In contrast to coherence analysis at the tremor frequency in which one particular frequency is considered, coherence in the beta band may be significant in a broad frequency range between 15 and 30 Hz. This means that, for coherence analysis in the beta band, the level of significance has to be adjusted to higher values (for details of this argument, see above). Applying this correction to our data, only 10 out of 145 neurons (6.9%) show coherence to the EMG in the beta frequency range.

Our results demonstrate that synchronization at the tremor frequency is an outstanding feature of STN neurons in PD. More than 50% of the neurons analyzed here showed significant tremor coherence. This percentage might seem surprisingly large. Yet, our findings correspond well to the clinical appearance of patients whose motor activity during stereotactic recordings consisted essentially of rest tremor.

In accordance with previous reports [22,37] we show that synchronization in the beta frequency band does occur in the STN of patients with Parkinsonian tremor. However, in our study, coherence in the beta frequency range was considerably less prominent than synchronization at the tremor frequency. This supports prior findings in which a relationship between beta oscillatory activity and the amount of tremor could not be demonstrated [37]. A number of reports provide evidence for a relation of beta synchronization in the STN with bradykinesia [9,19,20]. In our study, we interpret the synchronization at the beta frequency in this respect, since the patients were not purely tremor dominant but suffered from bradykinesia as well.

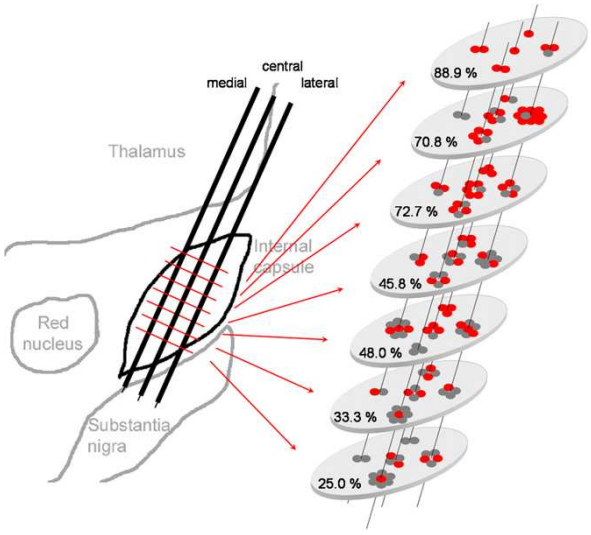

Fig. 3. (A) Schematic frontal section of the right subthalamic nucleus (black) and neighboring structures (grey). The positions of the medial, central and lateral microelectrodes are indicated by black lines. Recordings of neuronal STN activity took place in different depths separated by 1 mm (red lines). (B) Schematic illustration of sections through the STN at different recording depths indicated by the red lines in (A). The results for 145 neurons are displayed. Red dots: neurons coherent with the tremor EMG. Grey dots: neurons without coherence at the tremor frequency. The numbers on the left indicate the percentage of tremor-coherent neurons per section.

The proportion of tremor-coherent neurons diminishes in the ventral direction consistent with the observation that the ventromedial STN corresponds to the associative-limbic subdivision of this nucleus [3,13]. Otherwise, tremor-coherent neurons seem to be widely and isotropically distributed (Fig. 3b), in accordance with the homogeneous anatomical appearance of the STN [39].

The question remains whether the high amount of tremor coherence in the STN found in this study is of functional significance. It has been questioned if basal ganglia circuits are involved in the pathogenesis of parkinsonian tremor [32]. Tremor activity in the STN may simply reflect proprioceptive input without contributing actively to tremor generation. Moreover, tremor-related oscillations in the internal globus pallidus, the primary target for projections from the STN, continue when the STN is lesioned in the MPTP-monkey model of PD [38]. Finally, the cerebellum which is assumed to be part of the tremor network in essential tremor [10], is likely to be involved in parkinsonian tremor as well [26,27,32].

Thus, the present findings do not prove that the STN is the pacemaker for tremor in Parkinson's disease. However, the finding that more than 50% of the STN neurons are tremor coherent is unlikely to be an epiphenomenon. Subthalamic neurons have indeed the intrinsic property of firing in rhythmic bursts [5,6]. Moreover, oscillatory activity in the STN can be maintained by forming functional loops with other centers, in particular the cerebral cortex and the external globus pallidus [29,30]. Thus, both the intrinsic properties of subthalamic neurons and the coupling of the STN to other struc-

tures in the loop consisting of cortex, basal ganglia and thalamus may contribute to tremor generation.

In conclusion, spatially distributed synchronization at the tremor frequency is a key feature of the functional organization of the STN in patients with Parkinsonian tremor. Activity in the beta frequency range is less important for tremor and may be predominantly related to bradykinesia [9,19,20].

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