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The Electrophysiology of Tremor – Patterns of Neuronal Activity in Basal Ganglia, Thalamus and Cortex

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Eidesstattliche Erklärung

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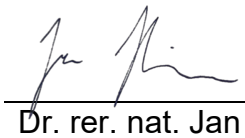

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Abstract

Tremor is defined as an involuntary, oscillatory movement of a body part. It occurs in several neurological disorders, such as Parkinson's disease or essential tremor. Although there are various causes and forms of tremor, it appears that there is a prototypical pattern of brain activity associated with tremor. Here, I will discuss this pattern based on a selection of five articles addressing different aspects of tremor pathophysiology. Study 1 investigated changes of subthalamic high frequency oscillations (HFO) associated with Parkinsonian rest tremor. During tremor episodes, subthalamic power shifted reliably from a very high (>300Hz) to a lower frequency range (<300 Hz). Together with three further power features, this novel marker of tremor allowed for accurate detection of Parkinsonian rest tremor by means of Hidden Markov modelling in study 2. Study 3 compared different phases of tremor episodes and found that tremor onset and tremor maintenance differ with respect to subthalamic oscillations. Study 4 revealed that HFO do not only occur in the subthalamic nucleus of PD patients but also in the motor thalamus of patients with other tremor syndromes. Study 5 assessed the cortical areas modulated by deep brain stimulation (DBS) in tremor patients. It showed that both thalamic and subthalamic DBS evoke electrophysiological responses in ipsilateral motor cortex. In summary, these studies demonstrate that tremor is associated with numerous changes of oscillatory activity. These might serve as feedback signals in novel closed-loop DBS devices for the treatment of tremor.

Zusammenfassung

Tremor ist definiert als eine unwillkürliche, rhythmische Bewegung eines Köperteils, die bei vielen Bewegungsstörungen auftritt. Trotz der vielfältigen klinischen Präsentationen des Tremors scheint es im Gehirn ein charakteristisches Muster für Tremor zu geben, das bei allen Formen des Tremors auftritt. Ziel dieser Arbeit ist es, dieses Muster anhand von fünf eigenen Studien zu beleuchten und die Implikationen für die Behandlung des Tremors aufzuzeigen. Studie 1 behandelt Tremor-assoziierte, hochfrequente Oszillationen im Nucleus subthalamicus (STN) von Parkinson-Patienten. Diese zeigen während des Ruhetremors eine charakteristische Verschiebung im Leistungsspektrum, ausgehend von sehr schnellen (>300 Hz) hin zu etwas langsameren Frequenzen (<300 Hz). Dieser neu entdeckte Tremor-Marker erlaubte es in Studie 2 ein automatisiertes Verfahren zur Detektion des Tremors zu entwickeln, welches basierend auf Methoden des maschinellen Lernens Tremor in Hirnsignalen erkennen kann. Studie 3 befasste sich mit den verschiedenen Phasen des Tremors und zeigte, dass sich der Beginn und die Aufrechterhaltung des Tremors hinsichtlich der neuronalen Oszillationen im STN unterscheiden. Studie 4 belegt, dass die in Studie 1 beschriebenen, hochfrequenten Oszillationen nicht nur im STN von Parkinson-Patienten sondern auch im motorischen Thalamus von Patienten mit anderen Tremorformen vorkommen. Studie 5 befasste sich mit den entfernten, kortikalen Zielen der Tiefen Hirnstimulation zur Tremor-Behandlung. Hier konnte gezeigt werden, dass sowohl die subthalamische als auch die thalamische Stimulation elektrophysiologische Antworten im ipsilateralen Motorkortex evoziert. Zusammen machen diese Studien deutlich, dass Tremor mit einer Reihe von elektrophysiologischen Veränderungen einhergeht. Diese Veränderungen könnten von THS-Systemen einer neuen Generation verwendet werden, um Tremor automatisch zu erkennen und bedarfsgerecht zu stimulieren.

1 Introduction

Tremor is defined as an involuntary, oscillatory movement of a body part (Bhatia et al., 2018). Different forms of tremor can be distinguished based on tremor features such as frequency or amplitude, its etiology and its modulation by drugs and context. The motor state provoking tremor is of particular importance. Neurologists differentiate between tremors occurring in a relaxed, “resting” state (rest tremor) and tremor occurring during action (action tremor). Action tremor is further subdivided into tremor occurring in a specific posture (postural tremor) and tremor occurring during movement (kinetic tremor). The latter is again subdivided into simple kinetic tremor, referring to a tremor that changes little in the course of a movement, and intention tremor, referring to a tremor that increases in amplitude as the hand approaches the target object (Bhatia et al., 2018).

1.1 Clinical aspects

1.1.1 Types of tremor

Various neurological diseases involve tremor. In the following, I will provide a brief overview over some of the most common types of tremor before discussing the electrophysiology in more detail.

In **Parkinson’s disease** (PD), rest tremor is one of the so-called cardinal, i.e. disease-defining symptoms, together with rigor and akinesia. Like the other cardinal symptoms, it is typically lateralized in the early stages of the disease. The frequency of Parkinsonian rest tremor ranges between 4 and 7 Hz. Movement leads to a transient reduction of tremor. **Essential tremor** (ET) is a bilateral action tremor of the upper limbs, not accompanied by other neurological signs. It is the most common type of tremor, is typically alcohol-responsive and heritable. **Cerebellar tremor** is a slow, broad intention tremor caused by cerebellar lesions. It is often accompanied by other manifestions of ataxia, such as dysarthria or nystagmus. **Holmes tremor** is a rare rest, postural and intention tremor resulting from midbrain lesions. It is relatively slow (2- 4 Hz) and of large amplitude. **Orthostatic tremor** is a fast (>12 Hz) postural tremor that, unlike the other tremor forms, predominantly affects the legs, appearing during standing or walking. **Dystonic tremor** is an action tremor occurring in dystonia. It is less rhythmic than the other forms and can often be reduced by touching the affected body part (geste antagoniste). **Enhanced physiological**

tremor is a pathological amplification of physiological tremor, a general characteristic of the motor system. It is comparably fast (~10 Hz), low-amplitude and can have diverse causes such as stress, hypoglycemia or hyperthyroidism.

1.1.2 Treatment of tremor

There are both pharmacological and surgical treatments of tremor. The drugs used for tremor treatment depend on the disease. PD rest tremor, for example, is often, but not always, responsive to levodopa and dopamine agonists (Elble, 2002). ET can be treated with propanolol, primidone or topiramate, for example, (Deuschl et al., 2011) which can also be helpful in other types of tremor. In many cases, however, tremor is not sufficiently controlled by medication. In these cases, patients can opt for surgical interventions, which often achieve excellent tremor control, even of pharmacoresistant tremors.

Deep brain stimulation (DBS) is an established treatment of tremor in PD and ET patients, and was reported to be effective in other types of tremor, too (Guridi et al., 2008; Kilbane et al., 2015; Tsuboi et al., 2020). In DBS, the target brain area is modulated by electric pulses delivered at high frequency (>100 Hz). The pulses are generated by an implantable stimulator and applied via chronically implanted macorelectrodes. In contrast to ablative techniques, DBS is reversible in the sense that stimulation can be turned off at any time. In addition, DBS is highly flexible. Once the system is implanted, a vast variety of settings can be tried in search for optimal tremor suppression. Ablative techniques are less flexible, but also have their advantages. Some techniques, such as high intensity focused ultrasound (FUS), for example, are less invasive than DBS. In FUS, a beam of high intensity ultrasound, guided by magnetic resonance imaging, selectively destroys tissue in the target brain area without harming skin, skull or surrounding brain tissue (Purrer et al., 2019). It is thus an attractive alternative when stereotactic brain surgery is not an option. Other ways of lesioning the thalamus are likewise effective, e.g. thermocoagulation or gamma radiation (Kondziolka et al., 2008).

1.2 The electrophysiology of tremor

Surgical treatments of tremor, and DBS surgery in particular, have facilitated electrophysiological recordings from tremor patients, opening a window into the patterns of brain activity associated with tremor. In the following, I will provide an

overview over the most important observations before discussing my own research in this context.

Several key observations point to the brain as the generator of tremor. In some cases, tremor is a direct consequence of brain injury (Raina et al., 2016). Regardless of the cause, brain surgery such as DBS or thalamotomy typically suppresses tremor. And finally, tremor-associated brain activity has been observed in many areas of the central motor system. In tremor patients, neuronal oscillations and/or spiking tend to adhere to the tremor rhythm, i.e. brain activity and tremulous muscle activity are synchronized. Such synchronous activity has been observed on the level of single cells in the thalamus (e.g. Zirh et al., 1998), on the level of local neuronal populations in the thalamus (e.g. Tan et al., 2019) and the basal ganglia (e.g. Wang et al., 2005), and on the level of brain-wide networks. Timmermann et al. have investigated the coherence between muscle activity and cortical activity in tremor-dominant PD patients by means of magnetoencephalography (MEG; Timmermann et al., 2003). Coherence can be considered the frequency-domain equivalent of correlation. They found distinct peaks of muscle-brain coherence at tremor frequency and twice the tremor frequency in multiple motor areas, such as primary motor cortex, posterior parietal cortex, pre-motor cortex and cerebellum. In my doctoral studies, I took a similar approach and investigated MEG synchronization with subthalamic activitiy recorded from DBS electrodes (Hirschmann et al., 2013). We compared episodes with rest tremor to spontaneous pauses of tremor and found that STN-cortex coherence at tremor frequency increased during tremor in a network comparable to the one reported by Timmermann et al. In addition, the severity of tremor correlated with the strength of STN-cortex coherence. These findings demonstrate that, in Parkinsonian rest tremor, a distributed cortico-subcortical network synchronizes at tremor frequency.

Importantly, synchronization at tremor frequency is not limited to Parkinsonian tremor. Similar findings have been made in ET patients (Hellwig et al., 2001; Schnitzler et al., 2009; Pedrosa et al., 2012, 2014) and patients with orthostatic tremor (Muthuraman et al., 2013). It has likewise been found in healthy participants imitating tremor (Pollok et al., 2004; Muthuraman et al., 2012), suggesting that system-wide synchronization at tremor frequency might be related to the specific

kinematics of tremulous movement without differentiating between voluntary and involuntary execution of that movement.

In addition to changes at tremor frequency, many studies report a reduction of beta oscillations induced by tremor. Beta suppression has been observed locally in the STN (e.g. Wang et al., 2005) and in distributed basal ganglia-cortex networks (Qasim et al., 2016). Although this feature is highly sensitive to tremor, it is not specific to tremor. In fact, beta desynchronization shortly before and during movement, followed by a so-called “rebound”, i.e. a transient increase exceeding baseline levels, is a well-known phenomenon linked to movement in general, irrespective of the kinematics, occurring in many areas of the motor system (Pfurtscheller et al., 2003).

In summary, tremor is associated with a strengthening of neuronal oscillations at tremor frequency and a weakening of oscillations in the beta band. The former phenomenon, in particular, has inspired the “oscillation hypothesis”, stating that tremor is generated by pathological oscillations, which propagate through a tremor network, drive motor cortex and ultimately cause tremor. In support of this hypothesis, it was found that DBS at tremor frequency can entrain tremor, i.e. it can force tremor to adhere to the highly regular rhythm of stimulation (Cagnan et al., 2013, 2014). Similar observations have been made for transcranial alternating current stimulation (Brittain et al., 2013) and even median nerve stimulation has mild entrainment effects (Reis et al., 2021). In addition, single DBS pulses may either increase or reduce tremor amplitude, depending on their temporal alignment with the current tremor phase, testifying to constructive and destructive interference, respectively (Cagnan et al., 2013, 2014). In summary, these studies support the oscillation hypothesis by demonstrating phase-specific interactions between rhythmic brain stimulation and tremor.

The generators of putatively tremor-causing oscillations might be disease- or tremor-specific. A recent review proposes, for example, that ET, i.e. action tremor, might result from cerebellar oscillations whereas Parkinsonian rest tremor might be caused by oscillators in the basal ganglia (van der Stouwe et al., 2020). In line with this idea, a recent study found that transcranial magnetic stimulation of the cerebellum had an effect on postural, but not on rest tremor (Helmich et al., 2021).

2 Own work

In this work, I present five of my own studies on tremor. In all of these studies, I had either a first or a last author role. In study 5, first authorship was shared with Dr. Christian Hartmann. We acquired the data together, I analyzed the data, and Dr. Hartmann wrote the paper.

1) **Hirschmann J**, Butz M, Hartmann CJ, Hoogenboom N, Özkurt TE, Vesper J, Wojtecki L, Schnitzler A (2016) Parkinsonian Rest Tremor Is Associated With Modulations of Subthalamic High-Frequency Oscillations. Mov Disord 31:1551–1559.

2) **Hirschmann J**, Schoffelen JM, Schnitzler A, van Gerven MAJ (2017) Parkinsonian rest tremor can be detected accurately based on neuronal oscillations recorded from the subthalamic nucleus. Clin Neurophysiol 128:2029–2036.

3) **Hirschmann J**, Abbasi O, Storzer L, Butz M, Hartmann CJ, Wojtecki L, Schnitzler A (2019) Longitudinal Recordings Reveal Transient Increase of Alpha/Low-Beta Power in the Subthalamic Nucleus Associated With the Onset of Parkinsonian Rest Tremor. Front Neurol 10:145.

4) Schnitzler S, Hartmann CJ, Groiss SJ, Wojtecki L, Schnitzler A, Vesper J, **Hirschmann J** (2018) Occurrence of thalamic high frequency oscillations in patients with different tremor syndromes. Clin Neurophysiol 129:959–966.

5) Hartmann CJ*, **Hirschmann J*,** Vesper J, Wojtecki L, Butz M, Schnitzler A (2018) Distinct cortical responses evoked by electrical stimulation of the thalamic ventral intermediate nucleus and of the subthalamic nucleus. NeuroImage Clin 20:1246–1254. *equal contribution

2.1 Study 1: High-frequency oscillations – a novel marker of Parkinsonian tremor

Study 1 focused on subthalamic oscillations during spontaneous waxing and waning of Parkinsonian rest tremor. Subthalamic LFPs were recorded via DBS electrodes in 11 tremor-dominant PD patients in between electrode and stimulator implantation (a setting often referred to as “externalized leads”) after overnight withdrawal from

medication (OFF) and again after administration of levodopa (ON). As we had previously observed prominent oscillatory peaks in STN power around 240 Hz and 360 Hz, we were now interested in possible relationships with tremor. Thus, we compared epochs with rest tremor to tremor-free epochs, as identified in forearm EMG recordings.

All patients exhibited prominent spectral peaks around 240 Hz, which we termed slow high-frequency oscillations (sHFO), and/or peaks around 360 Hz, which we termed fast high-frequency oscillations (fHFO). Importantly, the ratio between sHFO and fHFO power increased consistently during tremor both OFF and ON medication, testifying to an involvement of high frequency oscillations in Parkinsonian rest tremor (Fig. 1A). The shift towards the sHFO range was highly consistent, occurring in 94% of the STNs. Other markers of tremor, such as power at individual tremor frequency or beta power, did not change as consistently (65% and 53% of STNs). Finally, we investigated the dynamics of HFO power in the tremor cycle and found that HFOs underwent cyclic modulation during tremor (Fig. 1B), consistent with HFO modulations reported for voluntary movements (Litvak et al., 2012).

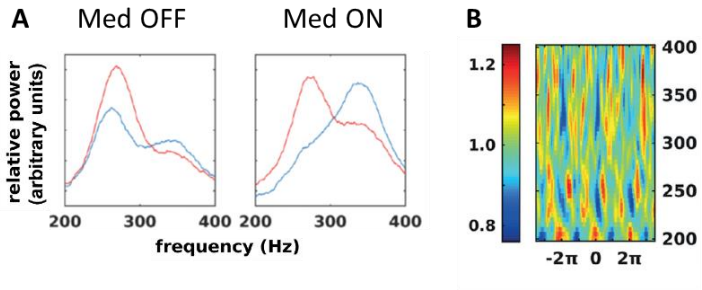

Fig. 1: *Tremor-associated modulations of STN power*. A: Group-average STN power spectra in medication OFF and ON (red: tremor episodes, blue: tremor-free episodes). B: Cyclic modulation of HFO power. Relative power change with respect to the mean over the entire cycle is color-coded. Tremor cycles were derived from forearm EMG recordings. From (Hirschmann et al., 2016). Reused with permission.

Study 1 established HFO as a novel and highly reliable marker of tremor. Tremor induced a shift of STN power from fHFO to sHFO. Interestingly, administration of levodopa was reported to induce a shift in the opposite direction (Özkurt et al., 2011).

It is possible that this effect reflects levodopa-induced tremor reduction. DBS, however, has recently been reported to reduce rather than increase HFO peak frequency, despite its ability to reduce tremor (Wiest et al., 2020).

2.2 Study 2: A LFP-based tremor detector

Besides their implications for tremor generation, tremor-associated changes of neuronal oscillations are interesting from an engineering perspective, as they could help refining DBS therapy. By combing stimulation with deep brain recordings, future DBS systems could detect tremor by recognizing the associated brain activity. This would enable stimulation on demand, i.e. only in the presence of tremor. Such an adaptive protocol would account for the dynamic nature of tremor, and might be as effective as the continuous protocols while causing less side-effects (Arlotti et al., 2016).

Study 2 aimed at constructing a LFP-based tremor detector. To this end, the data of Study 1 were re-analyzed and subjected to various machine learning techniques, such as elastic-net logistic regression (Zou and Hastie, 2005), Kalman filtering (Welch and Bishop, 2006) and Hidden Markov Modelling (HMM; Rabiner and Juang, 1986). In our hands, the HMM approach achieved the best results, although a recent study obtained even higher accuracy with Kalman filtering (Yao et al., 2020). The HMM is a probabilistic, generative model which accounts for auto-correlation in the data. For this reason, it is well suited for the analysis of times series, which typically depend on their own past.

Based on a set of four STN power features (power at individual tremor frequency, beta power, low gamma power and the sHFO/fHFO power ratio), the HMM achieved a detection accuracy of 84% when trained and tested on distinct datasets belonging to the same patient (see Fig. 2 for examples). When the model was trained and tested on data from different patients, group-average accuracy was lower (73%) but the prediction was still good in many cases. The latter finding is important because LFP-based detectors should work without training on individual data, as LFP recordings are not part of clinical routine in most centers and therefore not available for the standard case. Another important finding was that models operating on single features performed worse than multi-feature models, undermining the advantage of monitoring multiple markers simultaneously. This result might inspire engineers of real closed-loop DBS systems which are mostly based on single-feature classification

so far (Little et al., 2013, 2016; Piña-Fuentes et al., 2017; Arlotti et al., 2018). In accordance with study 1, the sHFO/fHFO power ratio was the best performing single feature.

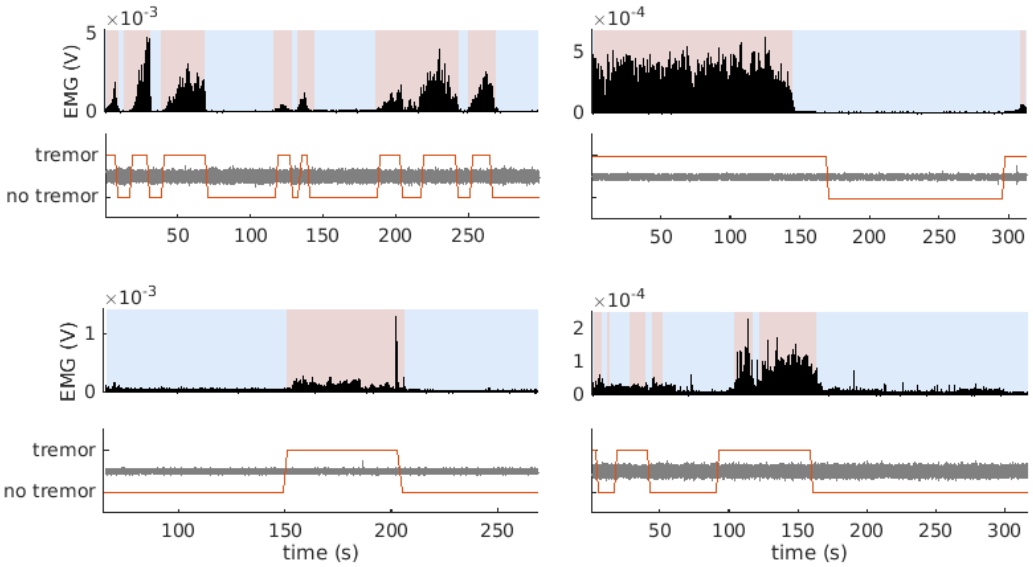

Fig. 2: *Four examples of LFP-based detection of Parkinsonian rest tremor.* Upper panel: Labeled EMG trace (red: episodes with tremor, blue: tremor-free episodes). Lower panel: Model output in orange and LFP signal in gray. The model input consisted of four power features derived from the LFP signal. From (Hirschmann et al., 2017). No permission required for reuse in thesis.

2.3 Study 3: A marker of tremor onset

Although studies 1 and 2 have revealed a set of useful markers for tremor detection, they do not provide all of the information we need for closed-loop DBS. For a satisfactory treatment of tremor, it is not sufficient to know whether tremor is currently present or not. Ideally, we want to suppress tremor before it occurs. So far, however, no study has succeeded in predicting tremor ahead of time. Alternatively, one could aim at suppressing tremor at the very onset when it is not interfering with daily activities yet, possibly before it is noticed by the patient. The goal of study 3 was to find a LFP marker of tremor onset that could support such a strategy.

The endeavor is challenging because the identification of event-markers in a noisy signal typically requires many repetitions of the event. In case of PD rest tremor onset, this is difficult to achieve because the tremor state changes slowly and

recording time is limited. To overcome this limitation, we used a special DBS system capable of recording and transferring LFP data after implantation (Medtronic PC+S), in combination with scalp electroencephalography. Importantly, we studied a patient capable of pausing tremor voluntarily. In this case, tremor mainly affected the legs and a sudden repositioning of the feet led to transient tremor arrest. With this setting, we were able to measure 100 tremor onset events in four different sessions. Next, we examined the EMG traces all of the onset events, seeking to define the exact start time of tremor. This was possible in 38 of 100 episodes.

A statistical comparison of LFP power before and after tremor onset revealed a transient increase of power between 8 and 15 Hz and 1.15 to 1.4 s relative to tremor onset. At this stage, tremor was still gaining momentum, as evidenced by the EMG trace (Fig. 3A). Interestingly, power changed in the opposite direction after the build-up was complete. When comparing all epochs to pre-tremor baseline instead of tremor onset only, we observed a decrease of subthalamic beta power (Fig. 3B), as reported by previous studies (Wang et al., 2005; Qasim et al., 2016).

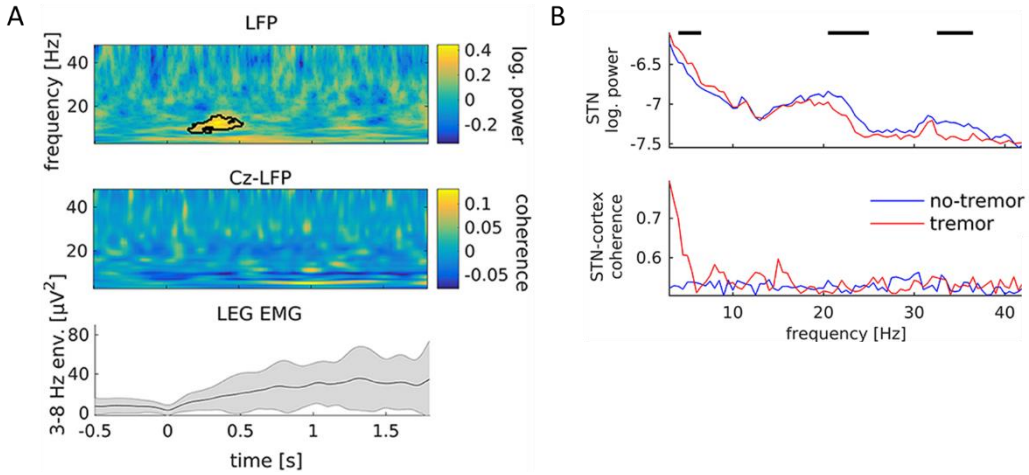

Fig. 3: *STN power changes during tremor onset and tremor maintenance.* A: Tremor onset. Top: Time-frequency spectrum of LFP power around tremor onset (time 0). Power difference to baseline is color-coded. The black outline marks statistical significance. Middle: Time-frequency spectrum of coherence between the Cz electrode and STN LFP. Bottom: Temporal evolution of EMG power at tremor frequency. B: Tremor maintenance. Time-average spectrum of STN power (top) and STN-cortex coherence (bottom). Note that STN beta power is suppressed during

tremor maintenance whereas it is transiently increased in the alpha/low-beta range around tremor onset. From (Hirschmann et al., 2019). No permission required (CC BY license).

These results are interesting because they suggest different patterns of STN activity for tremor onset and tremor maintenance, in line with recently proposed scheme termed the “dimmer-switch hypothesis” (Helmich et al., 2012). According to this hypothesis, tremor onset and tremor maintenance are two distinct processes governed by two different circuits. The onset mechanism (the switch) is believed to reside in the basal ganglia whereas the mechanism for tremor modulation during maintenance (the dimmer) resides in the cerebello-thalamo-cortical loop (Helmich et al., 2011). The STN is connected to both circuits (Bostan et al., 2010), and might thus take part in both processes. The temporal pattern of activity described here might distinguish between subthalamic engagement in the “dimmer” circuitry and engagement and the “switch” circuitry. A recent study combining STN LFP recordings with electrocorticography in PD patients reached a similar conclusion, although the authors found the biggest differences between tremor onset and tremor maintenance in STN theta (4-7 Hz) rather than beta oscillations (Lauro et al., 2021).

2.4 Study 4: HFOs in other types of tremor

Studies 1-3 have shed some light on subthalamic activity associated with Parkinsonian rest tremor. In particular, they have established STN HFO as a tremor marker. Next, we were curious to see whether HFO occur in other brain areas, too, and whether they occur in other diseases. To answer these questions, study 4 evaluated LFPs obtained from the motor thalamus in patients suffering from different types of tremor (16 ET, 3 PD, 2 Holmes tremor and 1 dystonic tremor). Unlike the previous studies, this study did not use externalized DBS leads, but intraoperative recordings with combined micro-macro-electrodes performed for target identification. A circle-like configuration of up to five electrodes recorded neural activity from 5 mm above to 2 mm below the planned target point in the ventral intermediate nucleus of the thalamus (VIM) in steps of 1 mm. The electrode configuration is depicted in Fig. 4. At each height, we recorded for 1-2 min while patients were at rest.

sHFO (150-300 Hz) and/or fHFO (>300 Hz) peaks occurred in all 40 thalami and, thus, in all studied tremor syndromes (Fig. 4 A-D). sHFO were detected mainly by

macroelectrodes whereas fHFO appeared in both micro- and macro-electrode recordings. Using a clustering algorithm, we identified peaks re-occurring in several recording depths and observed that sHFO covered a much larger area than fHFO. Finally, sHFO were most frequent in anterior-medial locations above target. fHFO, in contrast, clustered around the target point (Fig. 4E and 4F).

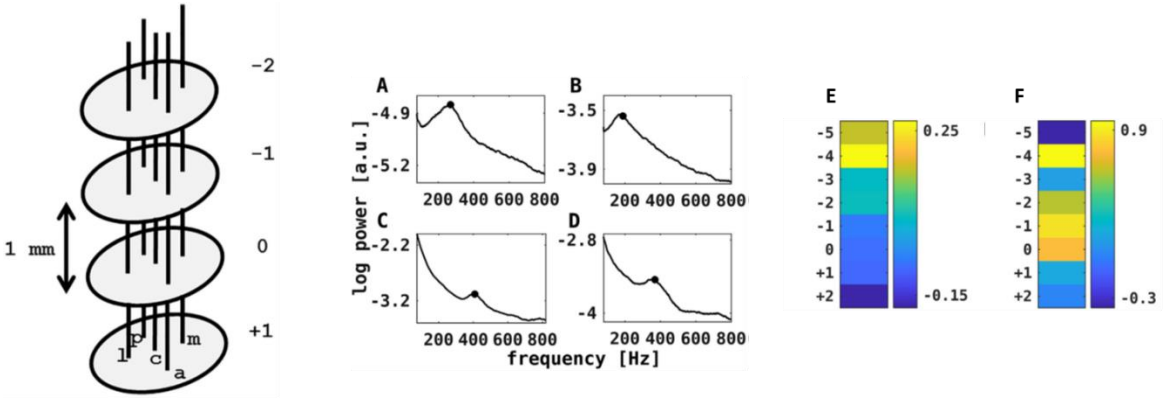

Fig. 4: *HFO of the motor thalamus in different types of tremor*. **Left**: Spatial configuration of micro-macro-electrodes. Height 0 indicates the DBS target. **Middle**: Power spectrum for a patient with Holmes tremor (A), dystonic tremor (B), essential tremor (C) and Parkinsonian tremor (D). Dots mark the automatically detected peak frequency. **Right**: Depth profile of HFO power for macroelectrodes (E), which detected mainly sHFO, and microelectrodes (F), which detected mainly fHFO. From (Schnitzler et al., 2018). No permission required for reuse in thesis.

Study 4 demonstrates that HFO are neither restricted to PD patients nor the STN. Instead, they occur in the thalamus of patients with different tremor types. Hence, HFO could be a general feature of (subcortical) nodes in the tremor network. Alternatively, they could be part of normal electrophysiology, i.e. not tremor-specific. Notably, study 4 emphasizes the need to distinguish between sHFO and fHFO. fHFO appear to be a local phenomenon whereas sHFO could be far-field potentials picked up by macroelectrodes or reflect the activity of an oscillatory network of large spatial extent.

2.5 Study 5: Cortical responses to subthalamic and thalamic DBS

The studies presented so far dealt with subcortical LFP recordings. Study 5 approached tremor from a different angle by comparing the electrophysiological effects of stimulating two different structures commonly targeted in tremor patients:

the STN and the VIM. Both STN and VIM DBS effectively suppress tremor, yet the VIM is preferred in the absence of Parkinsonism. Given that the modulation of remote areas in the cortex was proposed to be a key factor in DBS (Gradinaru et al., 2009), we wondered whether STN and VIM DBS modulate common cortical targets.

To study cortical modulation, we measured the MEG of 7 PD and 7 ET patients implanted with a DBS system and localized the electrophysiological responses evoked by single DBS pulses by means of dipole fitting. PD patients received STN stimulation and ET patients received thalamic stimulation.

Both STN and VIM stimulation evoked highly consistent, yet clearly distinct cortical responses. The prototypical response to VIM stimulation consisted of a sharp deflection at 13 ms, followed by a broader peak in the opposite direction around 40 ms (Fig 4A). This first wave was followed by second wave of similar shape, with peaks around 77 and 116 ms. Interestingly, the second wave was slower and of lower amplitude than the first, such that the entire response resembled a two-cycle, damped beta oscillation. Dipole fits were performed for each peak, and all of the dipoles localized to the central sulcus ipsilateral to the stimulated VIM, close the hand knob of primary motor cortex. In 3 patients, we observed an additional response originating from the contralateral cerebellum.

The response to STN stimulation had a different time course than the response to VIM stimulation and was smaller by an order of magnitude. It consisted of two sharp peaks in the same direction around 4 and 11 ms, respectively, followed by a broader peak in the opposite direction around 27 ms. Several peaks followed thereafter, but these were highly variable across patients. Dipole locations were much more variable than for VIM stimulation, including several cortical and subcortical areas. The ipsilateral motor cortex was the most consistent dipole source (Fig. 4B).

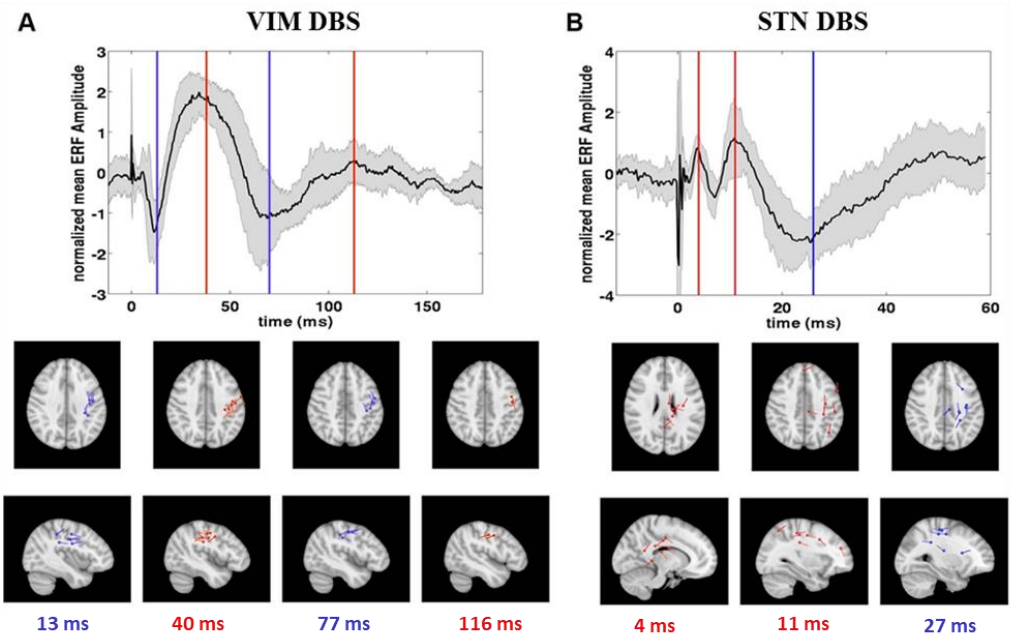

Fig. 4: *Responses evoked by VIM and STN DBS.* Upper panel: Group-average responses to single DBS pulses on sensor-level. Grey shading indicates standard deviation across patients. Vertical lines mark time points for dipole fitting. Lower panel: Dipole locations and orientations. A) VIM stimulation. B) STN stimulation. From (Hartmann, Hirschmann et al., 2018). No permission required for reuse in thesis.

These results demonstrate that STN and VIM DBS share the ipsilateral motor cortex as a common remote target, which might contribute to the tremor suppression achieved by both treatments. In line with this idea, invasive and non-invasive electrical stimulation of the motor cortex can reduce tremor (Moro et al., 2011; Brittain et al., 2013). The fact that VIM DBS elicited stronger and more consistent responses in motor cortex can be explained by the presence of prominent thalamo-cortical projections. The STN lacks such monosynaptic output routes to motor cortex and evoked activity travels along different paths, resulting in a different response shape.

3 Discussion

The studies presented here shed some light on the electrophysiology of tremor and tremor treatment by DBS. In summary, tremor is associated with numerous changes

of neural activity and with changes of HFO in particular. These could be useful feedback signals for future closed-loop DBS devices.

3.1 The nature of HFO

A key challenge for future research is to clarify the electrophysiological basis of HFO. Since these oscillations are very fast, it is natural to consider action potentials as the possible cause. The literature, however, is inconclusive on this question, with some studies reporting a correlation between spiking and HFOs (Meidahl et al., 2019) and others not (Wang et al., 2014; Yang et al., 2014). In this context, it might be helpful to remember that spikes are recorded by a low number of microelectrodes in patient studies. These can only track a few neurons, which appear to contribute to HFO either temporarily or not at all. Computational studies suggest, however, that HFO reflect the degree of spike synchronicity in large populations (Foffani et al., 2007; Ibarz et al., 2010), implying that weak, stochastic contributions of individual neurons might go unnoticed, except for moments of strong intra-network spike synchronization (Meidahl et al., 2019). Confirming this hypothesis experimentally would require recording many neurons simultaneously. While this is difficult in patients, it might be possible in animal models of PD.

3.2 Closed-loop DBS

With regard to closed-loop DBS for tremor, the next important milestones is to demonstrate the clinical advantage afforded by closed-loop systems. These could operate on LFPs from the subcortical stimulation target, as suggested by studies 1-4, brain signals from other areas involved in tremor, such as the primary motor cortex (Opri et al., 2020), or use peripheral feedback signals such as accelerometer output (Malekmohammadi et al., 2016; Cernera et al., 2021). While the risk of unwanted interference increases with additional hardware, peripheral sensing has the advantage of measuring tremor directly instead of inferring it from brain signals, which is typically more error-prone.

Although rarely tested for tremor specifically, the experimental closed-loop systems evaluated so far achieved good motor improvement in general (Rosin et al., 2011; Little et al., 2013; Piña-Fuentes et al., 2017), justifying an optimistic view on the effectivity of closed-loop DBS. Whether closed-loop DBS will be of considerable advantage over continuous DBS, however, is less clear to date. Well-placed DBS electrodes may reach, but do not exceed the clinical effect of levodopa, suggesting

that standard DBS is already at the limit of what is possible. Hence, improving the clinical effect of DBS might turn out to be difficult. In line with this view, studies testing closed-loop DBS for tremor reported an efficacy comparable to standard DBS at best, albeit with lower energy consumption (Cagnan et al., 2017; Opri et al., 2020; Cernera et al., 2021).

Side-effects, however, are another matter. It has been shown, for example, that closed-loop DBS reduces stimulation-induced dysarthria in PD patients (Little et al., 2016). This “side-effect advantage” might play and even bigger role for tremor, as closed-loop DBS might counter habituation. Habituation is a problem in ET patients, in particular, who adapt to the stimulation over time, resulting in a shrinking therapeutic window (Paschen et al., 2019). Pausing DBS whenever possible is one way of tackling this multi-faceted problem (Fasano and Helmich, 2019). Hence, closed-loop DBS could potentially lead to a substantial improvement of long-term tremor control in ET.

3.3 Voluntary vs. involuntary movement

Even though tremor is readily dissociable from rest based on electrophysiological markers, none of these markers distinguishes between true, involuntary tremor and similar voluntary movement such as mimicked tremor (Pollok et al., 2004; Muthuraman et al., 2012; Hirschmann et al., 2016, 2017). Although one study has proposed directed connectivity between cerebellum and sensorimotor cortex (Muthuraman et al., 2018), even the directed connectivity profiles, which are quite susceptible to bias (Haufe et al., 2013), are remarkably similar between true and mimicked tremor. Thus, the factors causing involuntary movement remain a mystery. Are voluntary and involuntary movements different with respect to their generating mechanism, or does the post-movement comparison of the expected and the actual sensory feedback decide whether a movement is experienced as voluntary (Hallett, 2007)? Questions like these are not only of neurological interest, but touch the longstanding philosophical debate on free will. Due to its high prevalence and the possibility to perform intracranial recordings in a sub-group of patients, tremor is an excellent model system for tackling such questions. Understanding the differences between voluntary and mimicked tremor in terms of brain activity might help us gain some intuition about how the brain constructs a sense of agency.

3.4 The tremor mechanism

The question of volition is closely linked to the tremor mechanism. If the electrophysiological processes discussed so far simply reflect that a rhythmic movement is being performed, what makes these processes start? Although we still do not known the answer, we do know that there are most likely multiple causes of tremor. Neurodegeneration of the basal ganglia, as occurring in PD, appears to be one possible cause, but does not seem to be a requirement, since tremor also occurs in disorders lacking basal ganglia neurodegeneration, such as ET (Deuschl and Elble, 2009). Notably, neurodegeneration is probably not even the immediate cause of tremor in PD, since some patients lack tremor altogether and tremor appears to become less prominent the course of PD despite progressing neurodegeneration (Coelho et al., 2010).

In the discussion about tremor mechanisms, electrical engineering might provide important hints. It is well known that unwanted, so-called parasitic oscillations can emerge in several kinds of circuits, and avoiding them is a field of its own (Fettweis and Meerkötter, 1977). The situation might be similar in the brain, i.e. the avoidance of parasitic oscillations might require a delicate balance of excitation and inhibition, which can be perturbed in many ways. This thought aligns well with the heterogeneity seen in many tremor syndromes, particularly in ET (Louis, 2014). One common theme in these patients could be that inappropriate titration of inhibition ultimately leads to volleys of excitation cycling through a loop involving primary motor cortex. The thalamus appears to be a key structure in this loop, being the major target of all surgical therapies for tremor. Thalamic DBS might interrupt transmission through this node by synaptic vesicle depletion (Rosenbaum et al., 2014), whereas thalamotomy simply destroys the relay.

In ET, at least, the concept of impaired inhibition is supported by multiple lines of evidence. First, the density of GABA-receptors in the cerebellum was found to be reduced in ET patients (Paris-Robidas et al., 2012). Second, GABA-α1 knockout mice exhibit action tremor (Kralic et al., 2005). An third, antiepileptica such as topiramate and primidone are successfully used for treating tremor (Deuschl et al., 2011). Scrutinizing the role of inhibition could thus be a promising avenue for future research, in ET and other tremor syndromes.

4 Conclusion

Tremor has a characteristic electrophysiological signature expressed in a distributed motor network, which can be leveraged to develop next-generation, adaptive DBS systems. The basal ganglia might be particularly important for triggering tremor. Since different tremor disorders and even mimicked tremor are similar, the characteristic electrophysiological pattern in tremor is most likely related to the characteristic movement pattern rather than its involuntary nature. Finding the reason why tremor cannot be stopped at will remains a major challenge for clinical neuroscience.

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6 Original Articles

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