The Central Oscillatory Network of Orthostatic Tremor

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Orthostatic tremor (OT) is a rare but unique tremor disorder that is characterized by 13- to 18-Hz oscillatory activity of the leg muscles while standing.[1] The tremor is hardly visible on clinical examination but is intricately connected to the main presenting symptom of a severe feeling of unsteadiness in the standing position.[2–4] Patients typically seek support or have to sit down after having maintained an upright position for some time. In contrast to all other common neurological tremors (eg, parkinsonian and essential tremor),[5] the muscle oscillations in OT are tightly coupled with all affected muscles of the body.[6] Because of these highly coherent oscillations throughout the body, a central origin of the tremor is to be expected.[7,8] However, the constituents of the central network contributing to OT are not clear. There is evidence for a contribution from the brainstem,[9] but oscillatory muscle activity similar to that in OT has been observed in paraspastic patients after spinal trauma, implying that the spinal cord may be involved in OT generation,[10] which seems to be supported by the partial effectiveness of spinal cord stimulation in OT.[11] Recently, the focus has shifted to supratentorial areas. In particular, the effective treatment of OT by high-frequency stimulation of the ventrolateral thalamus in 5 cases has shown that the thalamus is at least one part in the oscillating central network in OT. Furthermore, that cortical activation levels as measured by fluorodeoxyglucose positron emission tomography were reduced during effective thalamic stimulation in another case seems to indicate that the whole thalamocortical loop is influenced by the stimulation and may thus be an

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important constituent of the oscillating central network in OT,[12] similar to other tremor disorders. However, as far as it can be judged from the reported cases,[12–14] thalamic stimulation in OT is less effective than in essential or parkinsonian tremor. Whereas the latter tremor disorders are typically almost abolished by thalamic stimulation,[15,16] OT oscillations were only slightly reduced while the feeling of unsteadiness improved.[13] This difference in response to thalamic stimulation, the unique feature of widespread highly coherent muscle oscillations, and the improvement after spinal cord stimulation make it unlikely that the thalamocortical loop plays the same role in OT and in tremor of the hands (essential tremor [ET] and Parkinson's disease [PD]).

In this study we used coherent source analysis of simultaneous electroencephalography (EEG) and electromyography (EMG) recordings[17] to find out more about the role of these networks in OT. We chose this approach because it has greatly advanced our knowledge of the central networks of ET and PD in recent years.[18–20] To validate the results, we took advantage of 1 patient having a thalamic electrode, which enabled us to record local field potentials directly from the ventrolateral thalamus in parallel to the surface EEG.

Patients and Methods

Subjects

We analyzed 15 patients with OT (mean age, 67.6 years; range, 51-82 years; 9 women). The disease duration ranged from 5 to 25 years (mean, 9.8 years). The patient details are given in Table 1. Patients were seated in a comfortable chair in a slightly reclined position. Both forearms were supported by cushions to rest their arms up to the wrist joints. The experimental procedure consisted of having the subjects sit for the first 30 seconds and then stand for another 30 seconds to evoke the tremor and afterward sit down again.

The tremor was recorded by surface EMG from the tibialis anterior (TBA) and quadriceps (Q) muscles on both legs using silver chloride electrodes. EEG was recorded in parallel with a standard 64-channel recording system (Neuroscan, Herndon, VA), using a linked mastoid reference. Data were stored in a computer and analyzed offline. Individual recordings were of 1 to 2 minutes duration. The number of recordings performed in each patient varied between 1 and 2, depending on the patient's tolerance of the experimental procedure. In 1 patient, we were able to record monopolar local-field potentials (LFPs) simultaneously from all four contacts of the deep brain stimulated ventrolateral thalamus on both sides using EEG. Because of the small scar on this patient's scalp, we were able to place the leads tightly on the head in between the electrodes. This way we were able to record all 64 EEG channels; and some extra channels were used for the LFPs. No trepanation was performed. Instead a small burr hole in this part of the head was made to insert the macroelectrodes, but we did not see any changes in the EEG surrounding this region.

Data Preprocessing and Spectral Analysis

EEG and EMG were sampled at 1,000 Hz and band-pass filtered (EMG, 30-200 Hz; EEG, 0.05–200 Hz). EMG was full-wave rectified; the combination of band-pass filtering and rectification is the common demodulation procedure for tremor EMG.[21] Each recording was segmented into a number of 1-second-long high-quality epochs (L), discarding all the data sections with visible artifacts. At the end, the total data length (N) of each of the recordings, which were restricted to thirty 1-second segments (M) while the subject was standing, were used for analysis such that $N = LM$. The coherence spectrum was estimated using the Welch periodogram method with disjoint segments, and the statistical significance of the coherence was calculated (as described in reference [22]). The dynamics of signals in the time and frequency domains were computed with the multitaper method.[23] The complete description of the method is explained elsewhere.[24]

Source Analysis

Dynamic imaging of coherent sources (DICS) was used to localize brain activity that is coherent with a peripheral EMG signal.[17] To locate the origin of a specific EEG activity seen on the scalp, two problems, the forward and inverse problems, needed to be solved. In our case the forward problem was solved by modeling the brain after a complex five-concentric-sphere model,[25,26] with a single sphere for each layer corresponding to the white matter, gray matter, cerebral spinal fluid, skull, and skin. The inverse problem was solved by a linear transformation carried out by a

TABLE 1. Patient Details

Patient Number	Age (Y)	Sex	Disease duration (Y)	Tremor frequency (Hz)
1	55	F	7	15
2	69	F	5	15
3	75	M	10	14
4	79	F	12	16
5	70	M	5	14
6	74	F	7	15
7	70	F	11	17
8	68	M	9	14
9	72	M	8	15
10	60	F	10	18
11	48	F	3	13
12	82	F	17	15
13	51	F	6	17
14	67	M	12	16
15	75	F	25	13

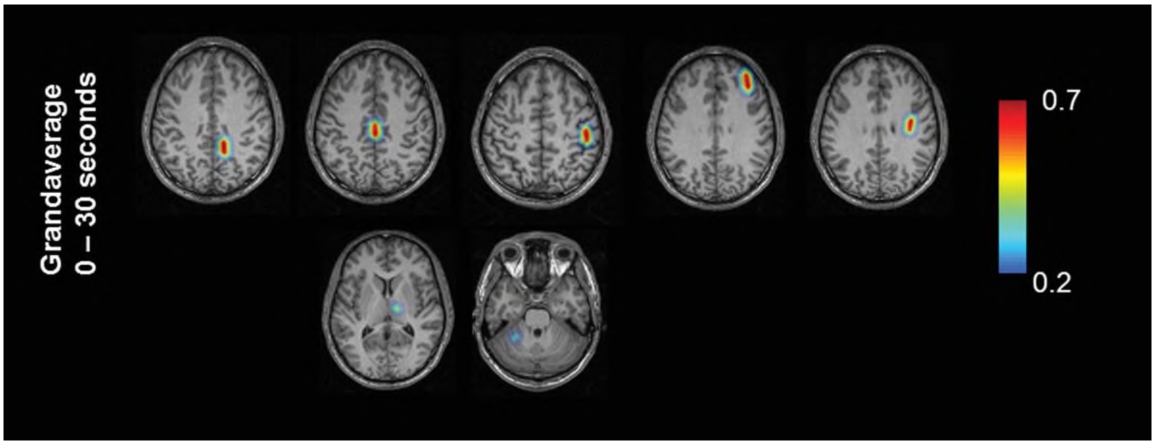

FIG. 1. The grand average network of sources for the whole segment 30 seconds at the tremor frequency for the tibialis anterior muscle. The color bar shows the overall coherence values.

spatial filter.[27] The complete description of the forward and the inverse solutions is described elsewhere.[28,29]

DICS is a beam-forming technique[30,31] that uses a spatial filter[27] to compute tomographic maps of cerebromuscular coherence at the frequency band of interest. The spatial filter was applied to a large number of voxels covering the entire brain. A voxel size of 5 mm was used in this study. The source in the brain with the strongest coherence to the EMG signal at the basic tremor frequency was identified. Because the coherence between the identified areas with itself is always 1, this region was projected out of the coherence matrix, and further coherent areas were identified[32] by taking the EMG as the reference

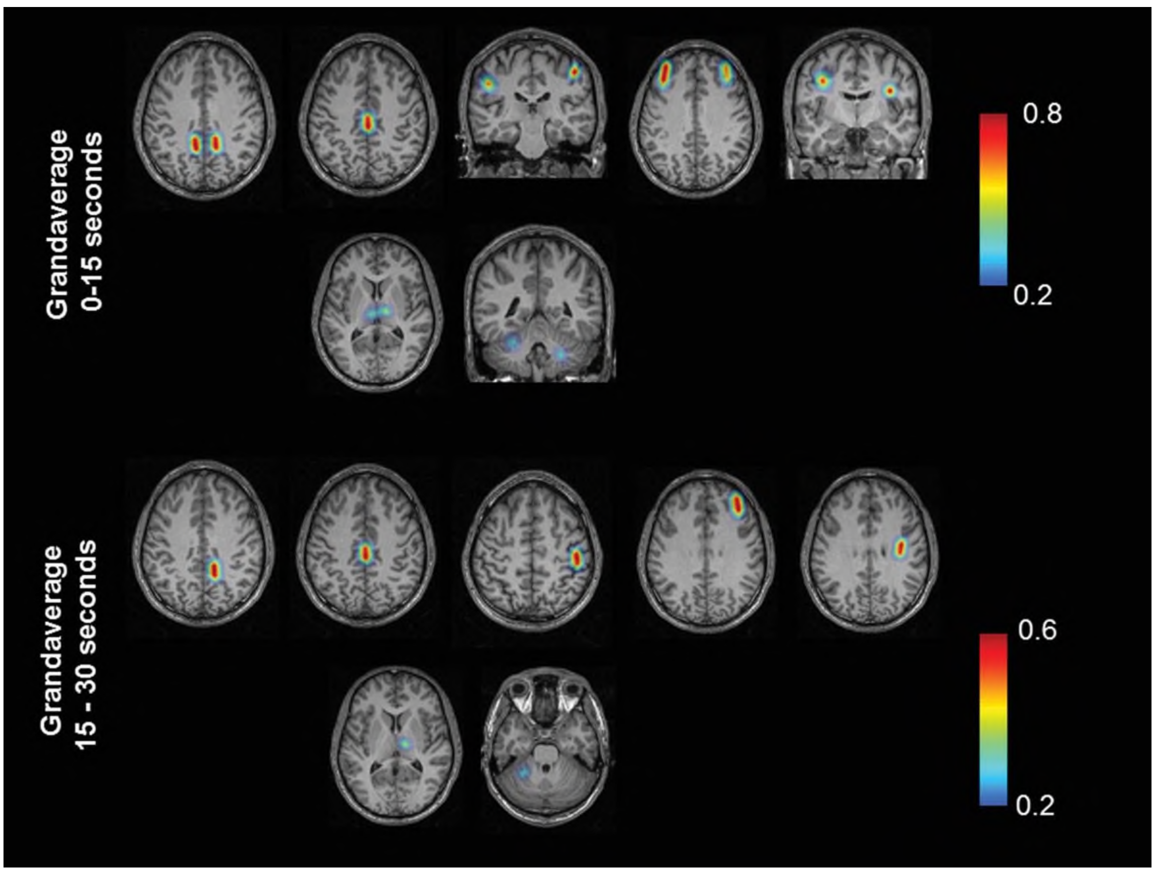

FIG. 2. The grand average for the 2 segments 0–15 and 15–30 seconds separately at the tremor frequency for the left tibialis anterior muscle. It is evident that bilateral sources can be identified during the first period, whereas in the second period the coherence is limited to the contralateral network only. The color bar shows the overall coherence values.

signal. Once coherent brain areas were identified, their activity was extracted by the spatial filter.[27] In a further analysis, all the original source signals for each source were combined to acquire a pooled source signal estimate. This can be done by pooling the individual second-order spectra using a weighting scheme and estimating the pooled estimate of coherence as previously described.[33,34] The criterion used to identify the areas was computed by a within-subject surrogate analysis to define the significance level that was the limit for projecting out and identifying other areas in the brain. The individual maps of the strongest cerebromuscular coherence were spatially normalized, averaged, and displayed on a standard Montreal Neurological Institute template brain in statistical parametric mapping (SPM2). Local maxima in the resulting maps represent areas that have the strongest coherence to the reference signal.

Statistical Analysis

The significance of the sources was tested by a within-subject surrogate analysis. The surrogates were estimated by a Monte Carlo random permutation, 100 times shuffling of 1-second segments within each subject.[20] The P value was estimated for each of these 100 random permutations. The percentile difference of the source coherence values from the first segment (0–15 seconds) to the second segment (15–30 seconds), obtained in the standing position, between the primary leg area, the thalamus, and the cerebellum with the muscles as well as between the muscles were included in a nonparametric n-related sample Friedman test ($P < 0.01$). It was followed by the post hoc related sample Wilcoxon test, which was performed separately for each pair. The same tests were repeated for the absolute power and root mean square (RMS) values of the TBA muscles on both legs.

Results

Power and Coherence

The EMG power spectra of the TBA and the Q muscles of both legs showed clear tremor-related peaks between 13 and 18 Hz, followed by their harmonics, for all subjects while standing. The tremor activity as recorded from the TBA and Q muscles on both legs was significantly coherent to both contralateral and ipsilateral EEG electrodes at the tremor frequency. The coherence was stronger in the contralateral side compared with the ipsilateral side. The absolute EMG power and the RMS of the TBA muscle from both sides were computed for both segments (0–15 and 15–30 seconds) separately. The absolute power at the tremor frequency and the root mean square values did not significantly differ between these two segments ($P = 0.42$).

Coherent Network Sources of OT

In all the OT patients, the source analysis identified the coherent network responsible for the tremor at the main frequency. First, the source analysis was performed for the whole segment after standing 0–30 seconds. The network for the tremor frequency was unilateral and consisted of the primary leg area, the supplementary motor area, the primary sensory cortex, two prefrontal/premotor sources, the thalamus, and the cerebellum. The sources were statistically significant for each of the subjects. The grand average of all the 15 patients is shown in the normalized brain of Figure 1.

Network Changes Over Time

Second, the source analysis was repeated separately for both segments, obtained in the standing position (0–15 and 15–30 seconds). The major difference in the network of sources between these two segments was that in the second segment the network of sources was only contralateral to the analyzed muscle. This is illustrated in the group statistics maps of the grand average of the OT patients for the TBA left muscle (Fig. 2).

The identified sources were statistically significant ($P = 0.003$) based on the Monte Carlo random permutation test across all 15 subjects, which justifies that the sources were found in all subjects. To investigate the difference between the first and the second segment analysis, coherence values at the tremor frequency were computed between the spatially filtered source signals of the tremor frequency sources, namely, the primary leg area, the thalamus, and the cerebellum with that of the muscles (for right and left separately) and also between the muscles. The four pairs that were taken into account for all the above sources were contralateral source–muscle right, contralateral source–muscle left, ipsilateral source–muscle right, and ipsilateral source–muscle left. The percentile difference in coherence at the tremor frequency between the two segments was tested with an N-related sample test ($P < 0.05$), followed by the post hoc related sample Wilcoxon test. In all the pairs, for the sources primary leg area and thalamus, the coherence was significantly higher in the first segment (0–15 seconds—a; a > b; $P = 0.005$) compared with the second segment (15–30 seconds—b). These percentile differences are illustrated in Figure 3. In the case of the cerebellum right with the right-sided muscles, the coherence value in the second segment was significantly higher compared with the first segment (b > a; $P = 0.009$). For the coherence value of the cerebellum left, there was no significant difference when using the right or left tibialis anterior muscle ($P = 0.34$).

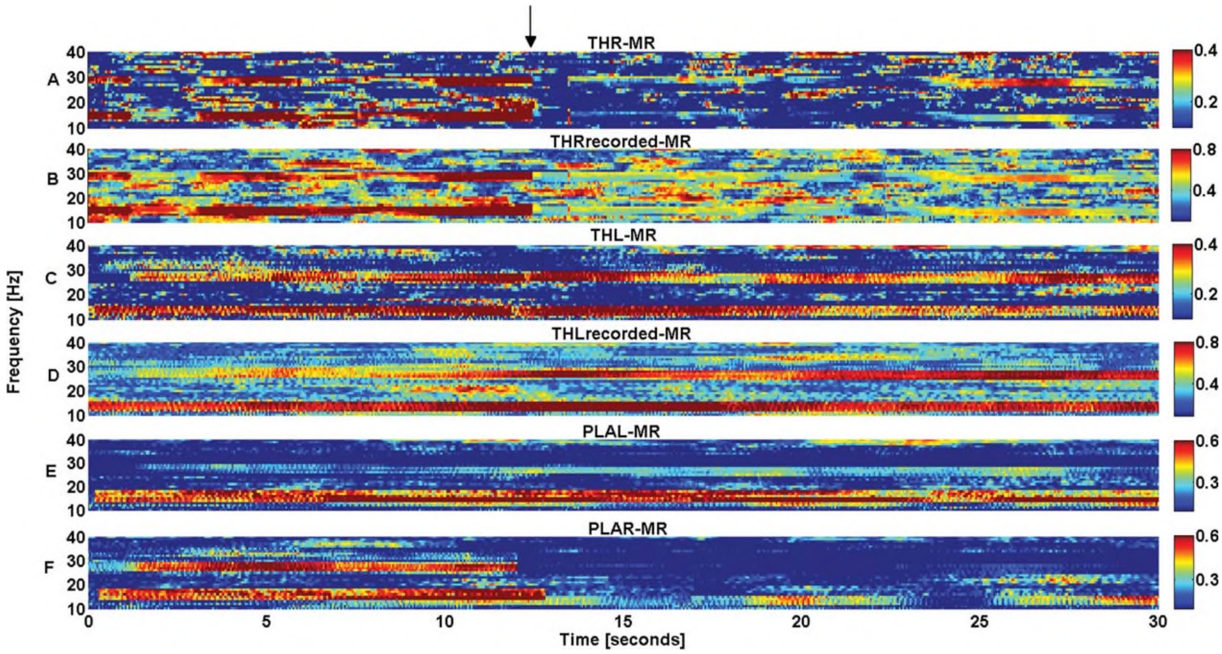

FIG. 3. Change in coherence of the second 15 seconds in percentage of the coherence during the first 15 seconds illustrating the qualitative changes of the coherence patterns. Each open circle represents 1 patient. The reduction in coherence is seen for the ipsilateral leg area and the ipsilateral thalamus, whereas the contralateral coherences remain stable MR, tibialis muscle right; ML, tibialis muscle left; PLAR, primary leg area right; PLAR, primary leg area right; THR, thalamus right; thalamus right.

The dynamics of the tremor frequency oscillation over time was analyzed by applying the multitaper method.[24] In this analysis, only the primary leg area sources and thalamus sources on both sides together with the TBA muscle right were taken into account. A representative example of the patient with intracerebral electrodes is shown in Figure 4. The ipsilateral thalamus and the primary leg area sources remained coherent with that of the muscle for the first segment (0–15 seconds) and became less coherent in the second segment (15–30 seconds). However, the contralateral thalamus and the contralateral primary leg area sources remained coherent for the whole 30 seconds. The coherence between the thalamus source signal and the muscle was weaker compared with the coherence of the primary leg area with the muscle. In addition, with regard to the single stimulated patient, the coherence of the thalamus source signal with the muscle followed the same dynamics as the actual recorded thalamus signal. The coherence values were higher in the recorded signal compared with the estimated signal because the estimated source signal was taken from the EEG, which has a lower signal-to-noise ratio compared with the recorded signal. We estimated the coherence for all the different bipolar combinations and selected the combination that had the highest coherence with the EMG and the highest correlation with the source signal. The bipolar combination for the middle (1-2) contacts had the highest mean coherence and correlation for the ipsilateral side (0.624 ± 0.23; $r = 0.51$) and for the contralateral side (0.745 ± 0.14; $r = 0.64$) at the tremor frequency. The other 14 patients had the same dynamics over time as that illustrated in the stimulated patient.

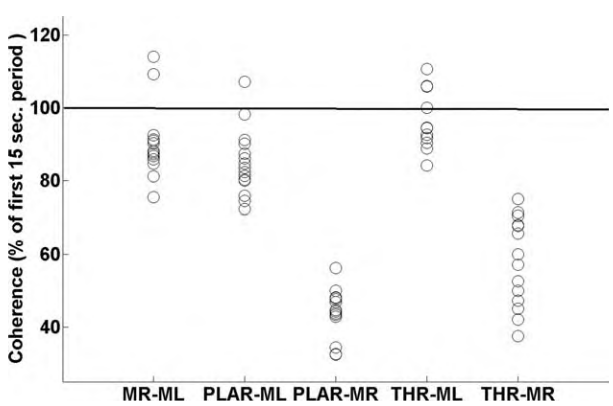

FIG. 4. Recordings from a patient with thalamic deep brain electrode. The time frequency dynamic coherence plots for different connections are shown for the whole 30-second recording period after standing up. After 13 seconds the coherence changes: the ipsilateral coherence between muscle and ipsilateral leg area (**F**) or thalamus (**A, B**) is reduced, whereas they are maintained for the contralateral connections (**E, C, D**). **B, D:** Frequency analysis from the recorded LFP signal of the thalamic deep brain electrode. **A, C:** Estimated signal with our source analysis.

Discussion

In the present study we analyzed the central oscillatory network components of OT using high-resolution EEG and coherent source analysis. We have shown that the typical 13- to 18-Hz oscillations of the leg muscles in OT[1] are represented in a bilateral supratentorial motor network including many primary and secondary cortical and subcortical sources. All these sources in the central oscillating network are similar to those of other pathological tremors,[18–20] but they change from bilateral to unilateral coherence. EEG-coherence analysis in OT is reported here for the first time. Compared with other tremors,[18,19,28,29] this is more consistent for OT and has been found in every single patient. Furthermore, in 1 patient the local field potential was recorded from the thalamus in parallel with EEG, and thus we were able to verify that the signal extracted from the thalamic source by spatial filtering of the EEG showed great similarities to the actual recorded thalamic activity. This confirms that the applied source analysis methods have the power to extract tremor-related signal components with the surface EEG originating from the depth of the brain. This has been inferred from previous mathematical modeling studies,[32] and DICS has been widely used to detect the cortical and subcortical (eg, thalamic) parts of tremor networks.[17–20] We present the first direct comparison with deep brain recordings, markedly improving the validation of DICS for the detection of subcortical sources of tremor-related activity.

The involvement of a widespread thalamocortical and cerebellar network in OT seems to challenge the view that OT arises from an oscillator in the brainstem[9,35] or even on the spinal level.[10] Such an oscillator on lower levels of the central nervous system was found to be in accordance with the strong coupling of the tremor oscillations between different limbs,[4,10,35,36] as it may act simultaneously on the pathways for both sides and different limbs that run in the close vicinity of these regions. However, the characteristic coupling between the left and right leg oscillations in OT could also be produced by a bilaterally coherent oscillatory network in supratentorial structures, and our data seem to support this at first sight. However, when analyzing the first 15 seconds and the second 15 seconds of the recordings separately, we found a clear difference, with the bilateral network changing after the first period to a unilateral oscillatory network during the final 15 seconds. At the same time the coherence between the two legs remained strong and changed only to a minor degree when the patients reported an increasing sense of instability while standing.

This feeling of unsteadiness has been analyzed in detail by Fung et al,[37] who showed that it increases severely from the first to the second 15 seconds of standing duration. We propose that the change in the coherence pattern may be related to the increase of unsteadiness. Despite the physiology of the peripheral tremor oscillations remaining virtually unchanged, unsteadiness as the main symptom of OT even increases. The current hypothesis assumes that the proprioceptive feedback from the periphery is synchronized at the tremor pattern, which increases unsteadiness.[37] The present data show that the oscillatory cerebello-thalamo-cortical network is even being confined to one side of the body, adding to the hypothesis that the necessary feedback from proprioception even becomes uncoupled from both sides. This can seemingly be overcome in case of rocking movements of the body or during gait,[7,37] which is close to normal in OT patients, but once the patients are standing, this proprioceptive feedback becomes synchronized and hypothetically causes unsteadiness.

In fact, our data in conjunction with previous evidence[9,10,35] would be in accordance with a theory of a brainstem oscillator or even spinal oscillator remaining active while the subject is standing and thus leading to the increasing unsteadiness.[37] The pathophysiological role of the bilateral cerebello-thalamo-cortical network right after standing and the unilateral continuation after some standing time is not yet clear but might add to the increase of unsteadiness. High-frequency thalamic stimulation has a beneficial effect on the feeling of unsteadiness in OT patients, which has been documented in 6 cases[12–14] including 1 such case in the present series. Our patient also reported clear improvement of the unsteadiness. But according to our experience and others, the effect is much less beneficial than for other tremors.[12–14] It has been reported that the tremor rhythm of OT remains unchanged even during thalamic deep brain stimulation,[14] which was also found in our case. The present observation of two strong and separated cerebello-thalamo-cortical networks may provide a tentative explanation for this, as only the feedback loop is stimulated by thalamic stimulation, whereas the hypothetical brainstem oscillator remains unaffected. This hypothesis needs to be tested in more elaborate tests of patients with parallel EEG/EMG recordings and with more advanced analysis tools, for example, time-resolved analysis of network interactions, which are currently being developed.

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