Electrophysiological investigation of Parkinsonian and essential tremor

PhD theses
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INTRODUCTION

Tremor is a rhythmic, involuntary oscillatory movement of a body part, mainly of the upper limb\(^1\), which is the most common movement disorder. It arises from the interference of mechanical and reflex oscillations as well as from the activity of central neuronal circuits\(^2\).

Parkinsonian rest tremor (PT) has unilateral preponderance, it is inhibited by voluntary movement. Spontaneous oscillations within the basal ganglia, cerebello-thalamic circuits and motor cortex play role in its generation\(^3\).

Essential tremor (ET) is symmetric, postural or kinetic tremor of the hand and forearm, seldom solely of the head. ET is inhibited during rest and increased by intention or execution of the movement. It is related to the synchronized activity of the olivo-cerebellar neurons, which is transferred through the ventral intermediate nucleus of the thalamus and the reticulospinal\(^4\) and/or corticospinal\(^5\) projections to the lower motoneurons. It is not clarified yet, how the motor cortex contributes to the generation of ET.

Our aim was to examine the role of motor cortical areas in the generation of PT and ET by electroencephalography (EEG), accelerometry and electromyography.

Event-related power decrease (desynchronization) and increase (synchronization) of different EEG frequency bands are time-locked with individual latency to the evoking stimulus\(^6\). Increased beta (13-30Hz) oscillation following voluntary motor action is called post-movement beta synchronization\(^7\) (PMBS), which occurs 1-1.5s after movement offset. However its maximum can be detected at the contralateral primary motor cortex, it appears first over the midline structures suggesting a supplementary motor cortex (SMA) origin. The contribution of the sensory cortex and the afferent somatosensory inputs has also been revealed in its generation. It is hypothesized that PMBS indicates integrative information processing in the sensorimotor cortex or the termination processes of motor programming\(^8\), or it may show the idling state of the motor cortex\(^7\). Decreased PMBS was revealed in Parkinson’s disease (PD) compared to controls\(^9\).

Although PD is considered a disease-entity, pathomorphological studies support the existence of three subclasses: tremor dominant, akinetic-rigid and mixed forms\(^10\). This provides the bases for the hypothesis, that in these subtypes the pathophysiology may also be different. We examined the pathophysiology of tremor dominant subclass of Parkinson’s disease.
INVESTIGATIONS

1. PMBS in tremor dominant Parkinson’s disease

In most PD patients, tremor and rigor develop with unilateral preponderance that persists over the course of the disease. This asymmetry is most likely linked to the structural and/or functional deficit of the contralateral nigro-striato-cortical circuits. Therefore, we compared the PMBS after the movement of the more and less tremulous hand and instead of the right and left hand. The aim of the current study was to examine whether laterality of tremor exerts any effect on PMBS. Such a finding would suggest the involvement of tremor related neural networks in the genesis of this electrophysiological phenomenon.

Methods

We investigated 10 tremor dominant PD patients (age: 60.9±13.67 years, 5 male) and 8 healthy controls (age: 61.1±9.61 years, 4 male) using EEG. Subjects were in supine position, they were instructed to press an on-off switch with their thumb in a self-paced manner. The intertrial interval was 10-15s. On the EEG trigger signals marked the beginning (movement-on) and the end (movement-off) of button-press. Sessions consisted of at least 40 artifact-free trials with each hand.

Fifteen electrodes were placed above central and precentral areas based upon the MRI reconstruction of the cortical surface, according to the modified expanded 10-20 system. The electrode impedance was kept below 5 kΩ, the time constant was 0.3 s, and the upper cutoff frequency was 70 Hz. The reference electrode was mounted on the tip of the nose. For EEG analysis we used the common average reference method.

The EEG was digitized at a sample rate of 128 Hz. Four-second long EEG segments, triggered to movement-offset (2s before and 2s after the signal) were collected. Absolute power values within the 1.0-30 Hz frequency range were calculated by way of Fast Fourier Transformation using 1s long subsegments with Hahn window, overlapping at successive 125 ms intervals. Absolute power samples measured at the movement-reactive beta frequency (bandwidth 1Hz) were then averaged across at least 40 trials. The percentage values for PMBS were calculated using the following equation: PMBS%=(A-R)/R×100, where A is the absolute power at a given time, and R is the mean power of the reference interval. The reference interval in our study was the first 1s of the 2s period before movement offset. The maximum value of PMBS (maxPMBS) was computed over the contra- and ipsilateral hemispheres, in Parkinsonian patients after the more and less
affected hand movement, in controls after both right and left hand movement.

Selecting individual movement-reactive beta frequencies
PMBS is a subject- and task sensitive phenomenon, which is often present only in a narrow frequency band. The beta peak-power frequency derived from the mean power-spectra of the background EEG usually does not correspond to the movement sensitive frequency values (most reactive beta frequency, MRBF) within the 300-1200 ms post-movement period. To determine the individual movement-reactive beta frequency values, we constructed colour coded time-frequency-power maps in all subjects. The maps showed the distribution of the absolute power values 2s before and 2s after movement offset.

Averaging of peak PMBS values
The time delay between the end of movement and the maximum of the PMBS curves shows substantial inter-individual differences (range: 300-1500ms). Due to this latency variability averaging of PMBS curves across-subjects (grand-average) might render less pronounced, but important changes in maxPMBS values less detectable. Given our interest in delicate interhemispheric differences regarding size rather than the time course of PMBS, statistical analysis involved the average of the individual maxPMBS values of each subject rather than the peak values of the grand-average PMBS curves.

Results
In the control group the maxPMBS was similar after the right and left hand, and it was higher contralateral to the movement. In PT maxPMBS was significantly smaller over the contralateral hemisphere after the movement of the tremulous hand, compared to the movement of the non-tremulous hand, maxPMBS did not differ significantly over the ipsilateral hemisphere (p=0.059, significance level: p<0.0125). PMBS over the same hemisphere was smaller if it was recorded contralateral to the tremulous hand, and remarkably higher if it was recorded ipsilateral to the non-affected hand.

Discussion
In hemiparkinsonism, in the clinically affected hemisphere there is tonic hyperactivation of the motor cortical circuitry. This is supported by the fact that in PD patients 600-900ms after movement offset, the corticospinal excitability is above baseline. This overactivity might lead to disturbed post-movement deactivation, with reduced PMBS of the involved cortical areas in Parkinson-patients.
These results suggest that there are multiple PMBS generators and that the dysfunction of the tremor related subcortico-cortical connections might affect the activity of the cortical network responsible for PMBS.

2. PMBS in essential tremor

We examined the event related ERD and ERS power and latency parameters in essential tremor. Our aim was to investigate the difference of tremor generators in ET and PT. Studying the characteristics of movement related EEG changes under different pathological conditions might also help to elucidate their physiological functional importance.

Methods

We examined 10 patients with essential tremor, 10 patients with tremor-dominant Parkinson’s disease and 10 controls (ageET: 68,5±11,51 years, agePT: 59,4±11,69 years, ageC: 63,3±9,37 years; p=0,19, F2,29=1,75). The Parkinsonian patients of the present investigation did not participate in our previous study. In a preliminary session we determined the side with lower and higher tremor intensity (T+, T++ respectively), using accelerometry. Subjects were examined in supine position while their eyes closed. An on-off switch was placed in their hand lying comfortably beside their body. Surface electromyography (EMG) electrodes were placed over the forearm extensor and flexor muscles on both sides to record motor activity. Subjects pressed the on-off switch with their thumb in a self-paced manner, with an intertrial interval of 10-15s. Sessions consisted of at least 40 artifact-free trials with each hand. Electrodes were positioned according to the standard 10-20 system. Electrode impedance was kept below 5kΩ, the time constant was 0,03s, the upper cut-off frequency was 70Hz. The reference electrode was mounted on the tip of the nose. For EEG analysis we used the common average method.

We analyzed the EEG registered at C4, C3 electrodes corresponding to the primary sensorimotor area and Cz electrode, which corresponds to the medial anterior region including supplementary motor area. For EEG analysis we used the Brain Vision Analyzer program (Brain Products GmbH, Germany). The signal was digitized at a sample rate of 256Hz. After artifact rejection we placed markers to the end of each EMG burst indicating the end of button press movement. We rejected the trial in case of indefinite end of movement. Six-second long EEG segments, triggered to movement-offset (3s before and 3s after the marker) were collected. We determined the movement reactive beta frequency band using our previously described method and analyzed its power changes. After
averaging the segments of 40 trials, the percentage values for PMBS were calculated using the previously described equation. The reference interval in this study was the first 1s of the 3s period before movement offset. Due to the inter-individual differences of power change latencies instead of using the grand average method across the data set of different patients, we averaged the power series across trials and than the minimum value of beta desynchronization (minERD) and the maximum value of PMBS (maxPMBS) and their latencies were averaged across patients. We defined the latency of beta ERD/ERS as the time interval between movement offset and minimum/maximum beta power respectively.

Results

Beta ERD
The minimum power of desynchronization and its latency was similar in the three groups, and the side of movement also did not affect it.

Beta ERS
The maxPMBS power was the smallest in the PT and the highest in the control group, but the difference was not significant. In ET the amplitude of maxPMBS was higher contralateral to the movement of the T++ compared to the T+ hand, but the difference was not significant. In the PT group maxPMBS was significantly smaller contralateral to the movement of the more compared to the less tremulous hand. In the C group maxPMBS power was similar after the movement of the right and left hand. The latency of PMBS did not differ in the three groups. In the ET group maxPMBS latency was significantly longer after the movement of the more tremulous compared to the less tremulous hand. In PT the latency of the maxPMBS was similar after the movement of the more and less affected side. In C the latency of maxPMBS was also similar regardless that the right or left hand was moved.

Discussion
In the present study we examined the correlation between tremor severity and the latency and power of beta ERD and ERS in essential tremor and compared the data to that of Parkinsonian patients and healthy controls. The power and latency of ERD preceding voluntary movement was similar in all three groups, however PMBS was affected in PT and ET as well. This suggests, that essential tremor and Parkinson’s disease may not interfere
with the generators of beta ERD, and also confirms that the sources and/or mechanisms of ERD and ERS are probably different.

In ET the maximum power of PMBS was not significantly different from that of controls. This suggests that in ET the functional integrity of neuronal networks generating PMBS is preserved, and are probably not a part of the tremor circuit. This finding is in line with the results of transcranial magnetic stimulation studies, which show that the excitability of cortical neurons in essential tremor is normal.

In contrast to Parkinson’s disease, where the attenuated beta ERS appeared without delay, the PMBS latency in ET was significantly longer after the movement of the more tremulous hand. This increased latency in ET but not in Parkinson’s disease can be due to the fact, that ET is facilitated while PT is suppressed by motor action. The enhancement of tremor during movement may delay PMBS because tremor interfering with voluntary motor action increases the overall EMG activity.

3. The effect of contralateral hand movement on Parkinsonian and essential tremor

Transcranial magnetic stimulation studies show that motor cortex activation during voluntary movement of one hand leads to concurrent inhibition of the homologous contralateral motor area, which action is transmitted by the corpus callosum and/or cortico-subcortical pathways. Anatomical studies provide evidence that the main source of callosal input to both parts of SMA is the corresponding motor region of the other hemisphere, however the pre-SMA is more densely interconnected than the SMA-proper. The primary motor cortex (M1) receives a minor callosal input from the homologous contralateral area. It is known that during self-paced motor action pre-SMA is activated earlier than in externally triggered movements.

In our present investigation we examined the impact of externally triggered and self-paced voluntary hand movement on the tremor of the non-moving hand in Parkinson’s disease and essential tremor, in order to study the effect of physiological transcallosal motor cortex inhibition and the function of different motor areas in the genesis of tremor.

Methods

We examined 9 patients with parkinsonian rest tremor and 7 subjects with ET (age: 64.4 ± 8.49 and 73.7±3.86 years respectively, p=0.368; 3 women in each group), they did not participate in our previous study. Unidirectional accelerometer was positioned on the both hands in the dominant direction of the tremor. Electromyography (EMG) electrodes
were placed over the wrist flexor and extensor muscles on both sides to monitor their motor activity. In a preliminary session we determined the side with more intense tremor (tremulous hand). During the experiment tremor power changes of the tremulous hand were analysed while patients were instructed to perform triggered and self-initiated movements with the other hand (active hand). The tremulous hand of PT patients was in rest position. The lower arm of ET patients was supported, while the hand was extended against gravity and the fingers were adducted.

The study protocol consisted of consecutive 3 tasks.
1. Flash (F): using a photo stimulator random flash stimulus was delivered. Subjects did not perform any voluntary movement during this task.
2. Flash triggered movement (FM): Subjects were instructed to press the on-off button after a random flash stimulus with the active hand as quickly as they could.
3. Self-paced movement (SPM): Subjects pressed the on-off button with the active hand in a self-paced manner.

In each task at least 40 trials were collected.

The bandpass filter for data acquisition was set to 1-120Hz for both accelerometry and EMG. Accelerometry signal was digitized at a sample rate of 128Hz. Four-second long segments triggered to flash or button press markers (±2 s) were collected. Absolute power values within the 1.0-30 Hz frequency range were calculated by way of Fast Fourier Transformation using 1s long subsegments overlapping at successive 125 ms intervals. Tremor peak frequency in the selected epochs was determined using colour coded time-frequency-power maps in all subjects. Absolute peak frequency power values of each of the 30 segments were converted into relative power values, the reference interval was the first second of the 2s prestimulus period. We collected and averaged the maximum (in case of increased tremor intensity after movement) or minimum (in case of decreased tremor intensity after movement) power values of the individual 30 segments in each task.

Results
The intraindividual variability of tremor power change during FM and SPM was minimal in PT patients, while it was remarkably high in ET. In the PT group the flash stimulus without movement did not change the tremor power, but it decreased significantly in FM and SPM compared to F. There was no statistical difference between FM and SPM. Relative power changes of ET were not significantly different in the various tasks. In 2 ET patients tremor power decreased in both motor task similarly to the profile of PT power changes. In 2/7 patient tremor increased in both
motor task, while in 3/7 ET patients tremor was influenced variably by triggered and self-paced movement.

Discussion
We hypothesised that transcallosal inhibition evoked by externally- and internally triggered contralateral voluntary hand movement influences different tremors depending on how the various motor areas are integrated in the given tremor generator circuitry.

Both externally triggered and self-paced movements inhibit contralateral parkinsonian rest tremor, suggesting that higher order motor areas, responsible for movement planning and initiation are invariably part of the generator system. In ET the remarkable intra- and interindividual variability of tremor intensity caused by both internally- and externally triggered movement suggests stochastically interacting multiple oscillators, which are not inevitably related to the activity of the higher order cortical motor areas. These results also imply that essential tremor might not be considered an unique disease entity, rather a clinical phenomenon produced by different functional and/or structural systems.

SUMMARY, CONCLUSIONS

We analysed the post-movement beta synchronization and the interhemispheric inhibition of tremor in Parkinson’s disease and in essential tremor to investigate the role of different motor areas in the generation of tremor.

Our finding are the followings:
1. We used a new method for the analysis of PMBS. While the latency of PMBS is individually different, we averaged only the maxPMBS values of the most reactive beta frequency band instead of the whole PMBS curves across subjects (grand average). With this method the less pronounced, specific power changes related to the side of clinical symptoms could be statistically proved.
2. Based upon pathomorphological findings, we suggested that electrophysiological examinations in Parkinson’s disease should be carried out in rigorously selected patient subgroups. Examining the tremor dominant subtype of Parkinson’s disease we could demonstrate specific electrophysiological findings related to the clinical symptomatology.
3. Pfurtscheller et al. published that PMBS is impaired in Parkinson’s disease. We showed that the impairment of PMBS is related to the side of tremor in tremor dominant PD.
4. It has not been previously established, that the dysfunction of the motor cortex in PD is primary, or it is caused by disturbed subcortico-cortical connections. We proved that PMBS above the same cortical area is impaired after the movement of the tremulous hand, and normal after the movement of the non-affected hand. These results preclude the possibility of primary dysfunction of the motor cortex and suggest that there are multiple PMBS generators, and they are affected by the tremor related subcortico-cortical connections.

5. The analysis of PMBS in essential tremor was first carried out by our group. In ET the power of PMBS was normal, so the generator circuit is not affected by the tremor related network. In ET, the latency of PMBS is longer after the more tremulous hand, presumably because of the interference of voluntary and involuntary motor programs.

6. It is a clinical observation that PT is inhibited by voluntary movement of the contralateral hand. We confirmed this observation using accelerometry and showed that the changes of ET-power have intra- and interindividual variability. Our results indicate that the intracortical pathways of tremor generators are different in Parkinson’s disease and in essential tremor. ET is probably not a unique disease entity.
REFERENCES

PUBLICATIONS


Abstracts: