Central mechanisms in human enhanced physiological tremor

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The sites of the central nervous structures involved in enhanced physiological tremor (EPT) are still unclear. The syndrome of persistent mirror movements (PMM) is characterized by abnormal bilateral corticospinal projections. If a supraspinal mechanism is involved in EPT, the activity of EPT should be coherent between both sides in subjects with this abnormality. We investigated 3 PMM subjects and 3 normal controls. Focal transcranial magnetic stimulation (TMS) resulted in contralateral hand muscle responses in the controls. The PMM subjects, in contrast, had bilateral responses. Similarly, long-latency reflexes (LLR) in PMM could be recorded bilaterally, while the control subjects showed responses only on the stimulated side. EPT was evoked by i.v. salbutamol. EMG time series were recorded bilaterally from the wrist extensor muscles and cross spectra were calculated. If there was a significant right-left-coherence, phase analysis was performed. No control subject showed a significant right-left-coherence of tremor activity. In contrast, a significant coherence was found in PMM between 8 and 12 Hz. When the mechanical tremor frequency of one hand was reduced by loading, coherences and phase spectra of the EMGs remained unchanged. By comparing the results from TMS, LLR and cross spectral analysis we come to the conclusion, that the 8 to 12 Hz component of EPT is transmitted transcortically, most likely originating from two separate generators for both sides.

The contribution of peripheral versus central neuronal mechanisms to enhanced physiological tremor (EPT) is still under discussion. The "mechanical resonance component" [12] is thought to result mainly from the mechanical limb properties. It is obvious that the frequency-invariant component at about 8 to 12 Hz is of neuronal origin (for review see [6]). The present study was conducted in an attempt to identify central sites involved in the transmission of EPT.

The motor abnormality of persistent mirror movements (PMM) served as a model. Mirror movements are characterized by unintended activity contralateral to voluntary movements of homologous body parts. The exact neuropathological basis is still unknown. Several studies have shown abnormal bilateral responses on focal transcranial magnetic stimulation (TMS) of the motor cortex hand area. Thus, as a variant, comparable amounts of corticospinal fibres must project ipsi- and contralaterally. Assuming that a tremor underlies central mechanisms, using these abnormal pathways, EMG activity should be coherent between both hands in PMM in contrast to normal subjects with their separate pathways for transmission of motor commands to the right and left hand.

We examined 3 normal male subjects (aged 29, 30 and 38 years) and 3 unrelated subjects with PMM. A 30- year-old male (case 1) and a 31-year-old female (case 2) had inherited the disorder as an autosomal dominant trait without further neurological or endocrinological abnormalities. Case 3, a 28-year-old male had PMM in the context of Kallmann's syndrome. None of these subjects or the controls took regular medication or reported a history of tremor or any other relevant medical disorders. There were no contraindications for the application of salbutamol and the performance of TMS. All PMM subjects and controls were fully informed and gave consent to participate in the study.

To record tremor, subjects were seated in a chair with both forearms supported horizontally by armrests, allowing free mobility in the wrists. Accelerometers were fixed on the back of both hands. Surface electrodes were attached bilaterally over the wrist extensor muscles. The hands were extended horizontally. Tremor was recorded under two conditions before and after inducing EPT by salbutamol: First, no additional weight was added. In the second condition, a load of 1000 g was tied to the back of one hand. Accelerometer and EMG signals were recorded in periods of 30 seconds at a sampling rate of 1000 Hz and stored for offline analysis. Spectral and cross spectral analysis was performed (for detailed discussion of the methods see [13, 14]). Salbutamol was administered intravenously until a fine, just visible tremor developed. The required dosages ranged between 0.3 mg and 0.5 mg. Increase of tremor was always accompanied by mild hyperhydrosis and a moderate tachycardia at 90 to 130 bpm while blood pressure remained normal in all cases.

TMS was performed with a MagStim 200 (MagStim

Company). A butterfly-shaped coil was used for focal stimulation of the hand motor area of one hemisphere. Compound muscle action potentials (CMAP) of surface EMGs were recorded bilaterally from the abductor pollicis brevis muscles (APB). Long latency reflexes (LLR) were elicited by electrical stimulation of one median nerve as described by Deuschl and Lücking [3]. The CMAPs were recorded bilaterally from the thenar.

There were no relevant differences of tremor frequencies and amplitudes between controls and PMM subjects. In all subjects the amplitudes before medication were within the normal range defined from a large healthy population of our laboratory. After medication electromyographic and accelerometric amplitudes were elevated moderately in all cases (Tab. 1). Before mechanical loading there was a broad-band peak at about 5 to 12 Hz in the accelerometric recordings. When one hand was loaded with 1000g the so-called "mechanical" peak, which is without a correlate in EMG, became apparent at a lower frequency. A second peak remained at a frequency of about 12 Hz corresponding to the peaks in the EMG power spectra ("frequency invariant peak"; Fig 1). On the unloaded side, however, the frequency spectrum was unchanged in all cases (data not shown).

Table 1: The power of EMG activity and accelerometry is displayed before and after medication. Results of the right hands are shown. A clearcut rise in amplitude following medication can be seen in all controls and PMM subjects.

PMM		baseline	salbutamol
Case 1	ACC (mg^2)	0.05	0.1
	EMG (μV^2)	27.6	89.8
Case 2	ACC (mg^2)	0.014	0.19
	EMG (μV^2)	20.1	56
Case 3	ACC (mg^2)	0.11	0.53
	EMG (μV^2)	171	236.7
Controls			
Case 1	ACC (mg^2)	0.07	0.17
	EMG (μV^2)	33.2	81
Case 2	ACC (mg^2)	0.02	0.12
	EMG (μV^2)	55.9	100.7
Case 3	ACC (mg^2)	0.014	0.15
	EMG (μV^2)	89	138

In the controls cross spectral analysis showed no significant coherence between both sides. In all PMM subjects coherences exceeded the level of significance (0.38 for $p < 0.05$), indicating a dependence of the processes driving tremor activity on both sides (Fig. 2).

The highest coherences were found between 6 and 12 Hz corresponding to the frequency-invariant peak. Phase spectra can only be interpreted within frequency bands

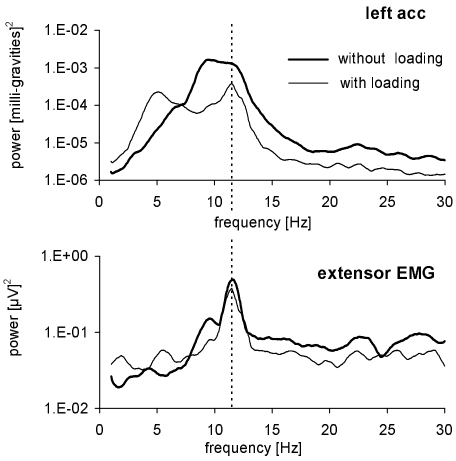

Figure 1: Power spectra from the left wrist extensor muscle of a normal subject with EPT. A: power spectra of the accelerometer recordings, B: EMG power spectra. Without loading (thick line) a broad-band frequency peak at around 10 Hz was found in the accelerometer recording accompanied by an EMG peak at about the same frequency. After loading with 1000g (thin line) an additional peak with reduced frequency ("mechanical component") separates from another, "frequency-invariant" peak. The peak in the EMG recording is unaffected by loading. This pattern was seen in all normals and PMM subjects.

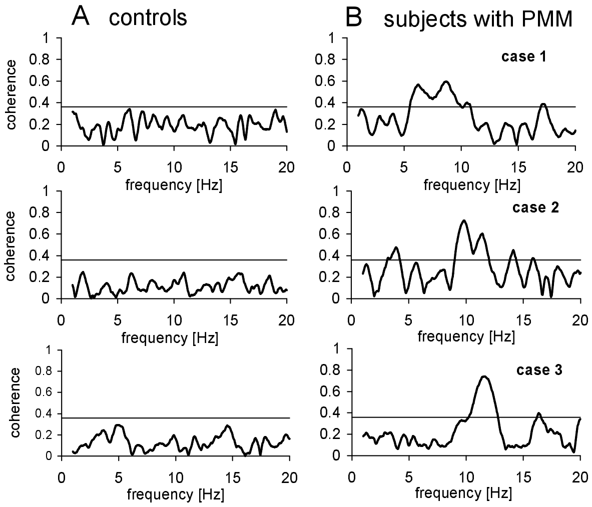

Figure 2: Cross spectra of the EMG time series from both wrist extensors. Values exceeding a level of 0.38 point to a significant side-to-side coherence in the respective range of frequencies. A: Three controls; the level of significance is not exceeded. B: All PMM subjects display a significant side-to-side coherence at about 6 to 12 Hz.

with a significant coherence [14]. Therefore, they were only evaluated in the PMM group where they revealed no phase shift, again between 6 and 12 Hz (Fig 3).

In TMS examination ipsilateral responses could only be evoked in the three cases with PMM in addition to the contralateral response usually found in normal subjects (Fig. 4; case 1).

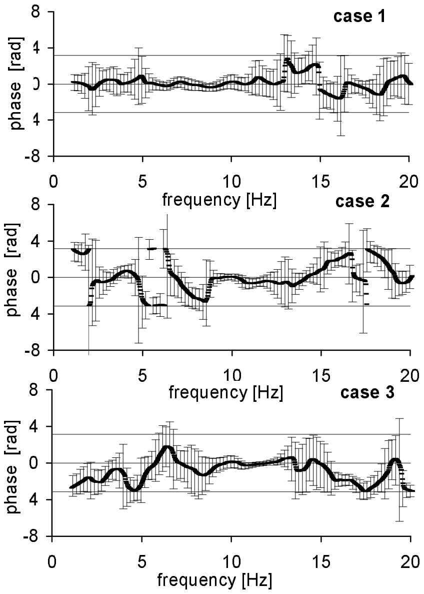

Figure 3: Phase spectra of the PMM subjects (black lines) do not show significant phase shifts. Below and above these regions the errors of the estimated phase are large due to a small coherence. No conclusion can be drawn for these frequency regions.

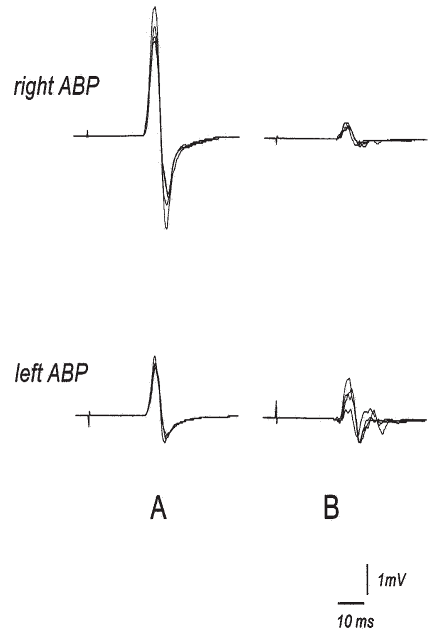

Figure 4: Unilateral focal TMS over the hand motor area in PMM case 1. CMAPs were recorded from both abductor pollicis brevis muscles (APB) simultaneously. Upon stimulation of the right (A) as well as the left hemisphere (B) there were simultaneous responses on both sides.

This finding supports the concept, that uncrossed corticospinal fibers play a role in PMM.

On LLR studies all subjects displayed an early (H-reflex) and a late response (long-latency reflex II, LLR II after about 50 msec) in the ipsilateral thenar. The PMM subjects showed additional potentials contralaterally. These occured at identical latencies as the ipsilateral LLR II. The H-reflex of all PMM subjects was present only ipsilaterally.

We examined subjects with the inborn motor abnormality of PMM in order to define possible sites where the nervous system contributes to EPT. The synchronous responses on both sides in PMM found in our TMS and LLR studies are compatible with the concept, that corticospinal fibres from one hemisphere project to both the ipsilateral and the contralateral arm in comparable amounts. Cross spectral analysis of the EMG time series recorded from both wrist extensor muscles showed a significant coherence of EMG activity without a time delay in all PMM cases.

The congruence between the results of TMS, LLR as well as cross spectral analysis in PMM suggests that the pathways transmitting tremor from the central nervous system are identical with the motor pathways involved in TMS and LLR responses. In contrast to the PMM cases, we did not find a significant coherence in controls, which is in line with accelerometric studies by Marsden [10]. It can be concluded, that in normal subjects both sides receive separate inputs from the central nervous system while they share common inputs in PMM, probably via corticospinal fibers.

A transmission of cortical inputs to both sides could be explained by the following hypotheses:

1. On a spinal segmental level homologous muscles on both sides could be innervated by lateralized motor neurons, e. g. via interneurons or axon collaterals. Our experiments showed the degree and the frequency range of the side-to-side-coherence unchanged, when one hand was loaded. A coherence based on a segmental mechanism would be expected to change its frequency or even to disappear under this condition. Furthermore, the absence of a contralateral H-reflex in the PMM cases in LLR studies argues against a spinal segmental mechanism connecting both sides.

2. One single central oscillator giving input to descending pathways of both sides would result in coherent EMG activity on both sides without a phase shift. This possibility can be ruled out since the controls do not show a significant coherence.

3. Our findings can best be explained by the presence of independent generators, conveying tremor activity exclusively to one side under normal conditions. In PMM a bilateral spread of descending pathways from the motor cortex of one side causes coherent EMG activity of both sides.

As TMS and LLR involve corticospinal pathways, the frequency invariant component of EPT, in analogy, is likely to be conducted transcortically, descending via the same corticospinal tracts to the arms.

For pathological tremors evidence was previously found favouring the involvement of the cerebral cortex: TMS lead to a phase resetting of essential and parkinsonian postural tremor [1, 11] pointing to cortical mechanisms. Evidence for a transcortical pathway could be found by MEG studies for parkinsonian tremor where cortical and diencephalic structures showed coherent activity [15]. Moreover lesioning the motor cortex was found to abolish parkinsonian resting tremor [2]. These studies suggest a functional involvement of the cerebral cortex in central tremor mechanisms. It is still under discussion, whether the pathological essential tremor and EPT are distinct entities or rather represent two - quantitatively different - expressions of the same process [4]. Thus it is possible, that the central component of EPT and pathological tremors share common mechanisms including transcortical pathways.

The primary oscillator in EPT is still not identified. A connection of this bilateral oscillator to the hemispheral cortices must be assumed from our results. Examples of such oscillatory structures are the basal ganglia, the thalamus, brainstem raphe and reticular nuclei and others [5]. The inferior olive is one of the structures with the ability to generate oscillations [9]. It is closely linked to the cerebellum and was found to play a role in postural tremor at frequencies similar to those in EPT [7]. Via various projections it is linked to the hemispheral cortices. However, this pathway involves also the thalamic nuclei, which themselves may be able to produce oscillations at various frequencies and are thought to play a role at least in parkinsonian tremor [8].

In summary our data suggest the presence of bilateral and independent generators of EPT, each of which is responsible for tremor generation in one hand in normal subjects. In subjects with PMM both oscillators are connected with both hands. A transcortical transmission of EPT to the corticospinal tract is likely.

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