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Cortical correlates of the basic and first harmonic frequency of Parkinsonian tremor

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1. Introduction

Classical Parkinsonian resting tremor is very regular with a typical frequency between 3 and 6 Hz. However, in the power spectrum of the underlying rhythmic muscle activity we typically find a peak not only at the tremor frequency but also at double this frequency (Spieker et al., 1995; Deuschl et al., 1996; Milanov, 2000). This higher frequency peak is termed first higher harmonic, as it is a well known physical phenomenon that rhythmic processes with nonlinear or asymmetric wave forms produce peaks not only at their actual frequency (basic frequency) but also harmonic peaks at integer multiples of the basic frequency (Deuschl et al., 2000). In such cases the higher harmonic peaks can be considered to reflect a part of the same rhythmic process at the basic frequency. As wave form analyses have shown asymmetries in Parkinsonian tremor (Deuschl et al., 1995) its first higher harmonic peak has usually been interpreted in line with this physical rule. But this interpretation has been questioned recently. On the basis of MEG–EMG analyses it has been postulated that the first higher harmonic is the main corticospinal drive contributing to the peripheral tremor (Timmermann et al., 2003). A recent analysis in the time domain has lent further support to the view that the first harmonic peak may reflect an independent phenomenon (Sapir et al., 2003) rather than a mere effect of wave form asymmetry. However, the biological basis of such independent oscillations in Parkinsonian tremor remains obscure. One possible explanation would be separate central (cortical) generators as has been alluded to by (Volkmann et al., 1996). If this assumption was correct one would expect differing temporal and spatial patterns of the cortical correlates of the basic and higher harmonic frequencies in Parkinsonian tremor. We therefore examined the corticomuscular (EEG-EMG) coherence in such patients specifically looking for differences in the distribution of the coherences on the scalp and in their dynamics over time.

2. Methods

2.1. Patients

Twenty-one patients, 10 female and 11 male, were included in the study all of which fulfilled the diagnostic brain bank criteria for

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idiopathic Parkinson's disease (Hughes et al., 1992). Age ranged from 33 to 77 yrs. (mean: 65 ± 11.4). Disease duration was between 3 and 15 years (mean: 7.4 ± 3.5). All patients suffered from a tremor dominant disease with a classical type I Parkinsonian tremor (Deuschl et al., 1998). UPDRS rest tremor score (item 21) of the hand on the more affected side was 2 in 12, 3 in 7 and 1 in 2 of them. UPDRS total motor score ranged between 10 and 35 at the time of the recordings. All patients were taking dopaminergic medication, two patients were also under anticholinergics. All medications were continued at the time of the recordings. Three of the patients showed a mild leg tremor, none of them was suffering from facial or head tremor. The accelerometric hand tremor frequencies ranged between 4 and 6 Hz. All patients gave informed consent to a participation in the study which was approved by the local ethics committee.

2.2. Recordings

Patients were seated in a comfortable chair in a slightly supine position. Both forearms were supported by firm arm rests up to the wrist joints. Patients were asked to relax with their hands hanging freely from the arm rest during the recordings. They were asked to keep their eyes open and fix their eyes on a point about 2 m away.

Tremor was recorded by surface EMG from the more affected forearm flexors and extensors using silver chloride electrodes. EEG was recorded in parallel with a standard 64-channel recording system (Neuroscan, Herndon, VA, USA) using a linked mastoid reference. EEG and EMG were sampled at 1000 Hz and band pass filtered (EMG 30–200 Hz; EEG 0.05–200 Hz). Data were stored in a computer and analysed off-line.

Individual recordings were of 1–3 min duration. The amount of recordings performed in each patient varied between 2 and 4 depending on the way the patient tolerated the experimental setting (cap tautness).

2.3. Data analysis

EMG was full wave rectified and the reference free current source density distributions (Hjorth transformation) were calculated for each EEG electrode (Hjorth, 1975). The combination of band pass filtering and rectification is the common demodulation procedure for tremor EMG (Journee, 1983; Timmer et al., 1998; Hurtado et al., 2005). Only 49 EEG electrodes were used. The boundary electrodes were used only for the Laplacian construction and not for the subsequent analysis. Each record was segmented into a number of 1 s high quality epochs discarding all those data sections with visible artefacts. Depending on the length of the recording and the quality of the data between 40 and 240 segments of 1 s were used for the analysis of one record. Following (Halliday et al., 1995) we calculated the periodogram of the power spectra and the cross spectrum for each of the 1 s segments independently using a Hanning window. These periodograms were then averaged over all the segments to get a reliable spectral and cross spectral estimate including confidence intervals with a frequency resolution of 1 Hz (Halliday et al., 1995). The coherence was then calculated as the ratio of the squared magnitude of the cross spectrum to the product of the power spectra. Coherence is a normalized linear measure, taking on a value of one in the case of a perfect linear dependence and zero in case of complete independence between the two processes. The statistical significance of coherence is assessed by the 99% confidence limit, which is derived under the hypothesis of linear independence (Halliday et al., 1995; Timmer et al., 1998) is given by

$$1 - (0.01)^{1/(L-1)}$$

where L is the number of disjoint sections (segments) used. Estimated values of coherence lying below this confidence limit are taken as an indication of a lacking linear dependence between the two processes. The coherence was calculated between each EEG electrode and the peripheral tremor EMG. In case of a mechanical transmission of the tremor oscillations from the arm to the head inducing rhythmic movement artefacts in the EEG we found a characteristic pattern of widespread bilateral coherence especially marked in the posterior electrodes. Those recordings are excluded from further analysis. This is in line with the observations and the procedure for movement artefact detection described by others (Timmermann et al., 2003).

The method of maximizing coherence was used to determine the direction of interaction and delay between the coherent EEG electrodes and peripheral EMG. The maximizing coherence method utilizes the fact that a delay between two signals introduces a time misalignment which slightly reduces the estimated coherence (Carter, 1987). In order to estimate the delay between the time series, one of them is time shifted backwards in time keeping the other constant. The coherence at a selected frequency (here: basic tremor frequency and first harmonic frequency) is estimated as a function of the shift. If there is a delay in this direction coherence will increase and reach a maximum value at the shift corresponding to the delay. The analysis is repeated by shifting the other time series (which was held constant in time in the above analysis) to estimate the delay, if any, in the other direction. Thus we can obtain the nature of coupling and the delay in both directions by this method. The significance of the delays was assessed by a surrogate test described elsewhere (Govindan et al, 2005). The delays and their standard deviations for all the coherent electrodes were weighted according to the strength of their coupling with the periphery (coherence) at the tremor frequency and then averaged. This weighted average was taken as a good approximation of the delay between the cortical correlates and the peripheral tremor. For a more detailed description of the method see (Govindan et al., 2005, 2006; Raethjen et al., 2007).

Among the recordings that showed a significant coherence at the tremor frequency and/or at the first harmonic frequency, long artefact free segments and completely artefact free recordings were selected, and a dynamical analysis of the corticomuscular coherence, the relative EMG and EEG power over time was performed for these recordings by calculating power and coherence spectra for moving 30 s windows with an overlap of 28 s resulting in an apparent time resolution of 2 s. For each of these 30 s windows the calculation followed the same procedure as for the recording as a whole described above (Halliday et al., 1995). For a detailed description and motivation of this method see (Raethjen et al., 2007). Subsequently these time courses were transformed into binary data sets with 1 indicating significant coherence and 0 indicating non-significant coherence. In this way the intermittent drops in coherence and their correlation between basic frequency and first harmonic could be analysed by calculating the Phi(φ)-coefficient and its level of significance. This is a correlation coefficient for binary data and can be interpreted analogous to other correlation coefficients.

3. Results

All 21 patients showed a significant corticomuscular coherence in the central area contralateral to the more affected hand at the basic tremor frequency and 14 of them also at the first harmonic frequency (Table 1). In 5 of the remaining 7 patients there were no visible peaks at the first harmonic frequency in the EMG power spectra, the other 2 did not show coherence despite visible peaks in the EMG spectrum.

Table 1
Characteristics of corticomuscular coherence for all patients.

Patient	Significant corticomuscular coherence		Maximal coherence (EEG electrode)		Sign. coherence over time			More affected hand
					Constant coherence	Binary correl. BF – FH		
	BF	FH	BF	FH	BF = FH	φ	p	
1	X		C1	–		–	–	Right
2	X		FC3	–		–	–	Right
3	X		C1	–		–	–	Right
4	X		CP2	–		–	–	Left
5	X		C1	–		–	–	Right
6	X		CP1	–		–	–	Right
7	X		FC5	–		–	–	Right
8	X	X	C5	C3		−0.5	<0.00	Right
9	X	X	C3	FC3		−0.4	<0.00	Right
10	X	X	FCZ	C3		−0.5	<0.05	Right
11	X	X	FC3	CP3		−0.3	<0.05	Right
12	X	X	C1	CP3		−0.8	<0.00	Right
13	X	X	C2	C4		−0.3	<0.05	Left
14	X	X	FC2	C4		−0.3	<0.01	Left
15	X	X	FC1	C3		−0.2	<0.05	Right
16	X	X	C2	C4		−0.5	<0.00	Left
17	X	X	FC1	FC3		−0.3	<0.05	Right
18	X	X	FCZ	CP3	X	–	–	Right
19	X	X	FC3	CP3	X	–	–	Right
20	X	X	FC3	C3	X	–	–	Right
21	X	X	FC2	C4	X	–	–	Left

BF, basic (tremor) frequency; FH, first harmonic frequency; –, not applicable; φ, Phi-coefficient = correlation coefficient for two binary (coherent/not coherent) data sets; p, level of significance of binary correlation.

3.1. Topography of the coherence on the scalp

The EEG electrodes showing the maximal corticomusuclar coherence with the contralateral EMG were mostly in the central lateral area (Table 1). However, in all of the patients with coherence at both frequencies the maxima were located in different electrodes for the basic as compared to the first harmonic frequencies. The difference in the distribution of the coherence for the two frequencies on the scalp are exemplified in Fig. 1 displaying all the corticomuscular coherence spectra for the relevant cortical electrodes in a schematic way for one recording in one patient. It becomes visible that the maximal coherences and their surrounding 'fields' are different for the basic and first harmonic frequencies. The electrode showing maximal coherence was well reproducible in repeated recordings during the same session in the same patient. The EMG power spectrum and the EEG power and the corticomuscular coherence spectra for two neighbouring electrodes are given in Fig. 2. Whereas one of the electrodes shows significant coherence only at the first harmonic the other shows coherence at both frequencies. The EEG power spectra, however, look very similar with comparable noise levels at both frequencies and for both electrodes.

3.2. Time course of significant of coherence

Only in 4 of the 14 patients with corticomuscular coherence at both frequencies this was constantly significant throughout the recordings. In the remaining 10 patients the times at which there was significant coherence at the basic frequency did not necessarily overlap with the times with significant coherence at the first harmonic. The phi-coefficients and the significance levels of the binary correlation analysis between the time courses of the significant coherence at the basic and the first harmonic frequencies reveal that there is a weak but significant ($p < 0.05$ for all 10 patients) and clearly negative correlation between the two (Table 1). This indicates that there is not a parallel but rather anti-parallel occurrence of significant corticomuscular coherence at the basic frequency and first harmonic.

Two examples of the coherence over time are displayed together with the relative EMG and EEG power over time in Fig. 3. It can be seen that the coherence at the basic frequency remains significant during the whole recording in A whereas the coherence at the higher harmonic frequency drops below the significance level intermittently. In B the tendency of an anti-parallel run of the coherence at both frequencies can be seen. The basic frequency only becomes coherent during the later part of the recording, at the same time the coherence at the first harmonic frequency drops below the significance level. The course of these coherence curves were not paralleled by changes in the relative EMG and EEG power in all instances. Only the drop in the relative EMG power at the first harmonic frequency in the last third of the recording in A was directly reflected in a drop of corticomuscular coherence at this frequency.

3.3. Corticomuscular delays

Using the new maximizing coherence method we analyzed the delays at the basic and first harmonic frequency separately. We found significant delays (delays that passed the surrogate test) in 65 recordings from 20 of the 21 patients. In 55 recordings from those 20 patients we could estimate a significant delay at both frequencies, whereas 10 recordings from the 20 patients only showed a significant delay at one of the two frequencies. All recordings with significant delays showed a bidirectional interaction (EEG–EMG and EMG-EEG). The delays for all these recordings are displayed for both directions (positive = EEG–EMG, negative = EMG–EEG) both recorded muscles (flexor and extensor) and both sides separately. Whereas there were no significant differences between the delays from contralateral cortex to flexor EMG and extensor EMG or between left sided and right sided muscles, the corticomuscular delays for the higher harmonic frequency was visibly longer than for the basic frequency and this difference was statistically significant ($p < 0.001$; basic frequency: EEG–EMG 16.58 ± 2.12 ms, EMG–EEG 13.86 ± 4.86 ms; first harmonic: EEG-EMG 19.45 ± 2.85 ms, EMG–EEG 18.24 ± 3.20 ms; Fig. 4).

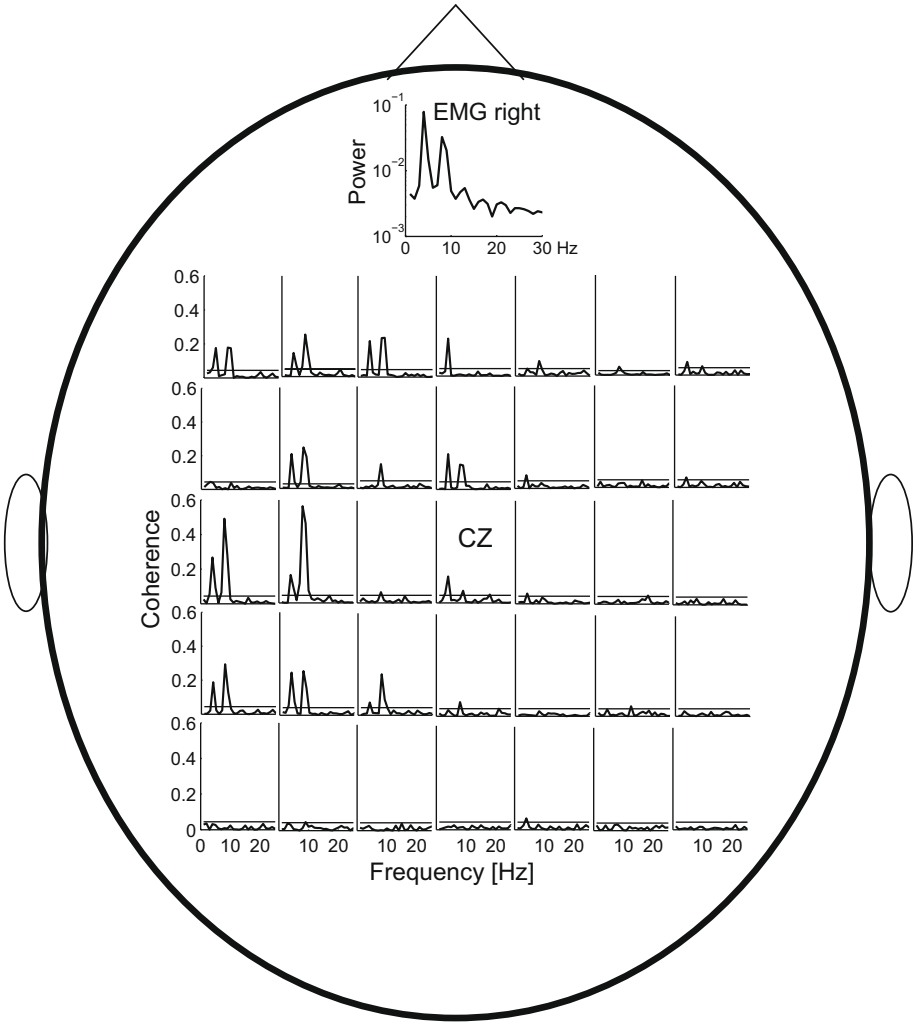

Fig. 1. Corticomuscular coherence spectra for the relevant EEG electrodes. The horizontal line indicates the level of significance. Approximate location of the electrodes on the scalp is indicated by the schematic head drawing surrounding the figures. The respective EMG power spectrum of the right forearm extensor muscle is given at the top. It can be seen that the magnitude and distribution of the coherences on the scalp differs between the basic and first harmonic frequencies.

4. Discussion

Our finding of a tremor-related corticomuscular coherence in the contralateral hemisphere confirms numerous previous studies that have clearly demonstrated a cortical correlate of Parkinsonian tremor (Volkmann et al., 1996; Hellwig et al., 2000; Salenius et al., 2002; Timmermann et al., 2003). All of these studies reported coherence at both the tremor frequency and its first harmonic which is in keeping with the first harmonic peak typically observed in the peripheral tremor spectra (Deuschl et al., 1996).

The different topography of the corticomuscular coherence at both frequencies found in almost all our patients likely indicates a spatially distinct origin of these two oscillations, and this finding is in keeping with single examples displayed in previous studies (Volkmann et al., 1996; Timmermann et al., 2003). One methodological problem in these analyses is the difference in signal-to-noise ratio between different frequency bands and different EEG electrodes as has recently been pointed out by (Wang et al., 2006). We have therefore looked at the EEG power spectra for each electrode and typically found a clear difference in the coherence spectra without much difference in the EEG power spectra, making a purely methodological artefact unlikely. However, the spatial resolution of the electrode array does not allow for a localisation of the exact origin of the oscillations. The maxima given in Table 1 seem to suggest that the basic frequency usually originates from slightly more medial and possibly more frontal areas then the first harmonic frequency mainly originating from central lateral areas. These locations may suggest medial premotor areas (e.g. SMA) as the main origin for the basic frequency whereas the location of the maximal coherence for the first harmonic frequency would be in keeping with the primary sensorimotor area. This is in agreement with previous MEG studies which have used coherent source analysis and have identified primary sensorimotor and premotor areas as part of the oscillating network of Parkinsonian tremor (Timmermann et al. 2003; Volkmann et al. 1996). However, none of these studies have looked for a systematic difference between the cortical representations of the basic and first harmonic frequencies. One recent paper on the distribution of tremor-related activity in the subthalamic nucleus alludes to different representations of the basic and first harmonic frequencies of Parkinsonian tremor in the basal ganglia (Reck et al. 2009), thus the different cortical representations found in the present study may belong to separate subcortico-cortical loops for both frequencies.

The hypothesis of a different origin of the basic and first harmonic frequencies is further supported by the significant difference in the corticomuscular delays, with significantly longer delays of the first harmonic oscillation. Thus these two oscillations seem to also reach the muscle via different pathways. The delays

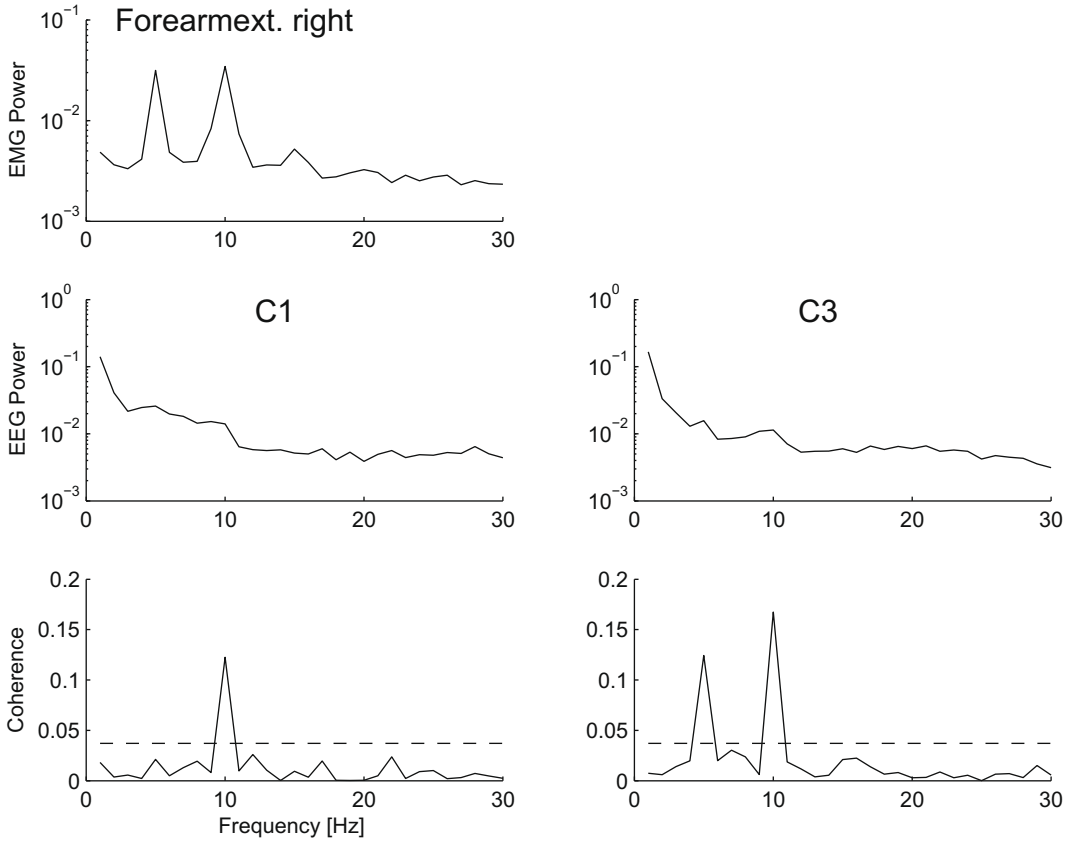

Fig. 2. EMG power spectrum from right forearm extensor (top), EEG power spectra from two neighbouring electrodes in the contralateral hemisphere (middle, C1 left, C3 right) and respective corticomuscular coherence spectra (bottom, C1-EMG left, C3-EMG right). Although the power spectra of the recordings from two neighbouring electrodes are very similar and the EMG power spectrum clearly contains peaks at both frequencies only one of the electrodes (C3) shows coherence at both frequencies whereas the other (C1) is only coherent at the first harmonic frequency.

for both frequencies would be principally in keeping with transmission via fast corticospinal pathways (Rothwell et al., 1991) and feedback from the periphery, but the exact ways to the muscle remain obscure especially in view of the difference between the two frequencies.

The analysis of the coherence over time indicates that whenever one of the frequencies was coupled to the contralateral cortex the other tended not to be, again supporting separate oscillations at both frequencies. The differences in the relative EEG and EMG power (signal-to noise ratio) could not fully account for the drops or increases in the coherences, making a purely methodological artefact unlikely.

So far three different hypotheses have been put forward as to how the peaks at higher harmonic frequency emerge.

The first and most straight forward physical explanation is based merely on the non-linearity of the waveforms in Parkinsonian tremor (Deuschl et al., 1995). This has been the most accepted view for a long time. It does not allow for any biological interpretation as it regards the higher harmonic peak(s) as a purely physical/methodological effect which is directly related to and part of the tremor oscillation. In this case one would expect identical central representations and identical dynamics of the basic and first harmonic frequencies. The clear differences in the topography of the cortical representations, the corticomuscular delays and the dynamics of the corticomuscular coherence at both frequencies clearly argues against this physical phenomenon being the only explanation.

The second hypothesis has been put forward on the basis of the first MEG study of Parkinsonian tremor which has shown that the mostly reciprocal alternating bursts of antagonistic hand muscles are represented as a temporal sequence in the cortical tremor-related activity (Volkmann et al., 1996). In a subsequent analysis of the phase-synchronisation between the cortical and peripheral tremor signals the same group found a preference of a 2–1 coupling (Tass et al., 1998). Thus the main cortical representation of the tremor may be at double its frequency which is distributed to antagonistic muscles in the periphery and may contribute to the typical reciprocal alternating pattern of activity (Timmermann et al., 2003). This concept is biologically interesting. However, the clear peak at double the tremor frequency in the EMG and the intermittent disappearance of coherence at the first harmonic frequency while the basic frequency coherence comes up is difficult to reconcile with the view that the first harmonic frequency is the main and dominant central drive in Parkinsonian tremor.

More recently the third hypothesis has been put forward stating that both the basic and higher harmonic frequencies in Parkinsonian tremor may indeed be separate oscillations (Sapir et al., 2003). The most likely explanation would be separate central generators (Volkmann et al., 1996) both of which may contribute to the peripheral tremor. Our data with different topography of the central representations, the difference in corticomuscular delays and in the dynamics of the corticomusuclar interaction at both frequency clearly support this last hypothesis. However, the exact origins of the two oscillations in Parkinsonian tremor are not clear and possible modes of interaction between these two frequencies contributing to the same peripheral symptom remain obscure. Further studies are warranted here.

Interestingly, corticomuscular coherence in Essential Tremor (ET) patients as shown in previous studies was only rarely found

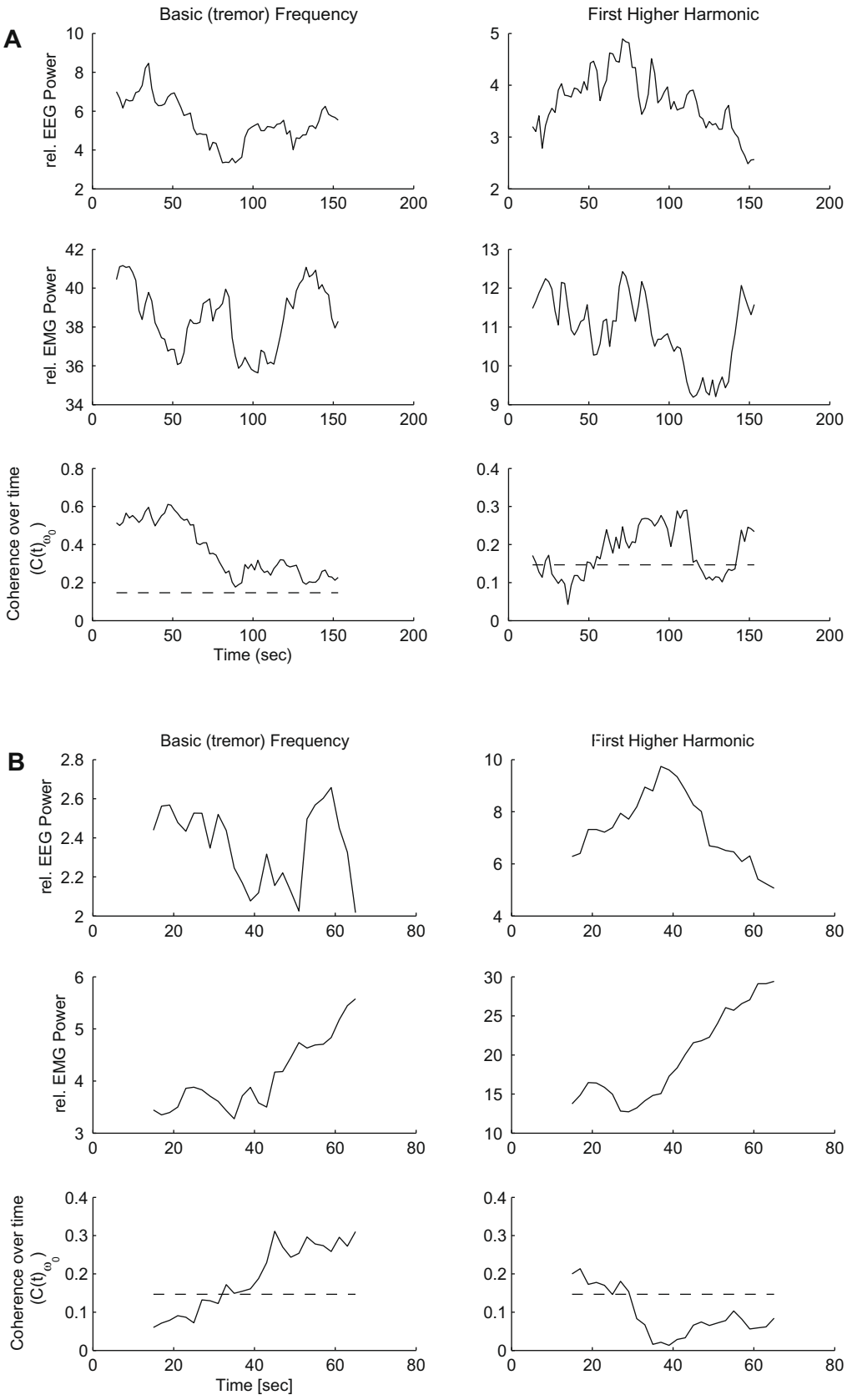

Fig. 3. Relative EEG and EMG power (top and middle) and coherence (bottom) over time for two representative patients and recordings (A/B). The dotted horizontal line indicates the level of significance for the coherence ($p = 0.01$). In both cases it is obvious that the coherence does not run in parallel over time for both frequencies and the relative EEG and EMG power show non-parallel changes in both cases. The second example (B) illustrates the tendency of an anti-parallel occurrence of the coherence at both frequencies. Whereas significant corticomuscular coherence at the first harmonic frequency was mainly present during the first part of the recording the coherence at the basic frequency became coherent only in the second part. Most of the drops and rises in coherence are not paralleled by changes in the relative power. Thus the changes over time are not a pure effect of changes in the signal-to-noise ratios.

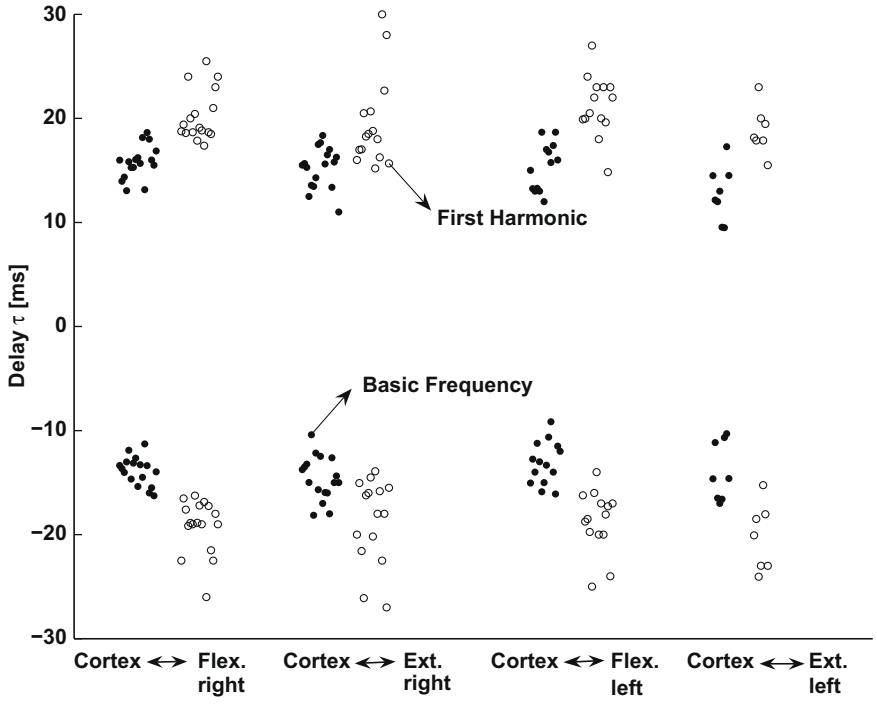

Fig. 4. Corticomuscular delays for flexor and extensor on the left and right side at the basic tremor frequency and the first harmonic frequency. The time delays from cortex to muscle (EEG-EMG: positive values) and from muscle to cortex (EMG-EEG: negative values) are displayed for forearm flexor and extensor muscles on each side and at the basic tremor and first harmonic frequency separately. Each dot represents one recording. The delays in both directions did not differ significantly between flexor and extensor muscles and the left and right side. However the delays at the first harmonic frequency was significantly longer than at the basic frequency in both directions ($p < 0.001$).

at the first harmonic frequency although many of the analysed ET patients showed a strong peak in the EMG power spectrum also at the first harmonic frequency (Raethjen et al., 2007; Hellwig et al., 2001), and in advanced ET we often find a reciprocal alternating pattern between antagonistic muscles as well (Deuschl et al., 1996). Thus there seems to be a difference between the cortical representation of Essential and Parkinsonian tremor.

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