Defective cortical drive to muscle in Parkinson’s disease and its improvement with levodopa

Stephan Salenius,1 Sari Avikainen,1 Seppo Kaakkola,2 Riitta Hari1,3 and Peter Brown4

1Brain Research Unit, Low Temperature Laboratory, Helsinki University of Technology, Espoo, 2Department of Neurology and 3Department of Clinical Neurophysiology, Helsinki University Central Hospital, Helsinki, Finland and 4Sobell Department of Neurophysiology, Institute of Neurology, London, UK

Correspondence to: Dr Stephan Salenius, Brain Research Unit, Low Temperature Laboratory, Helsinki University of Technology, FIN-02015 HUT, Espoo, Finland
E-mail: stephan@neuro.hut.fi

Summary
We recorded whole-scalp magnetoencephalographic (MEG) signals simultaneously with surface electromyographic (EMG) activity from eight patients with Parkinson’s disease after withdrawal and reinstatement of treatment with levodopa. Variations were seen in the coherence between the forearm extensor EMG and the MEG signal originating near or in the hand region of the primary motor cortex. As a group, the parkinsonian patients withdrawn from levodopa showed a reduction in the coherence at 15–30 Hz and 35–60 Hz, and a further three untreated patients had abnormally strong MEG–EMG coherence at 5–12 Hz compared with when medicated or with eight healthy age-matched control subjects. We conclude that the basal ganglia have a specific effect on the temporal organization of motor cortical activity during voluntary tonic contraction. Abnormalities in this aspect of basal ganglia function may directly contribute to bradykinesia and weakness in Parkinson’s disease.

Keywords: Parkinson’s disease; magnetoencephalography; coherence; motor cortex

Abbreviations: GPi = globus pallidus interna; MEG = magnetoencephalography; UPDRS = United Parkinson’s Disease Rating Scale

Introduction
Current theories of subcortico-cortical connectivity stress that voluntary limb movements depend on segregated, parallel loops funnelled through the globus pallidus interna (GPi) to the dorsolateral prefrontal cortex, the supplementary motor cortex and the anterior cingulate gyrus (Alexander et al., 1990). That fewer than 15% of neurones in GPi project to thalamic neurones which then project to the primary motor cortex (Hoover and Strick, 1999) supports the view that Parkinson’s disease particularly affects complex voluntary movements (Benecke et al., 1986, 1987; Flemingier, 1992; Georgiou et al., 1994). Nevertheless, a number of deficits in Parkinson’s disease may be largely caused by dysfunction in projections to the primary motor cortex. These projections include the direct dopaminergic innervation of the frontal cortex by the ventral tegmental area and projections from GPi relayed through the thalamus either directly to the primary motor cortex or to motor associational areas and thereby to the primary motor cortex. One particular parkinsonian deficit likely to reflect dysfunction of the primary motor cortex is the weakness found in some muscles, even when allowance is made for the slow development of maximal force (Stelmach et al., 1989; Yanagawa et al., 1990; Logigian et al., 1991; Corcos et al., 1996; Brown et al., 1997). This weakness may reflect the inability of the primary motor cortex to activate spinal motor neurones normally.

In healthy subjects, voluntary tonic contractions of the limbs are driven by three main descending activities, each characterized by its own pattern of rhythmicity. These are: (i) a 10 Hz drive, associated with the central elements of physiological postural tremor (McAuley et al., 1997; Halliday et al., 1999); (ii) a drive at around 20 Hz (Wollaston, 1810; Farmer et al., 1993; Conway et al., 1995; McAuley et al., 1997; Salenius et al., 1997; Brown et al., 1998); and (iii) a drive at 40 Hz (Piper, 1907; Hagbarth et al., 1983; Salenius et al., 1996; Brown, 1997; McAuley et al., 1997; Brown et al., 1998).

Of these, the 20 Hz drive characterizes weaker contractions whereas the 40 Hz or Piper drive is more evident in very strong contractions. Both rhythms may be represented in isometric contractions of moderate strength (Brown et al.,...
Tonic contraction in untreated Parkinson's disease is characterized by diminished EMG activity (Corcos et al., 1996; Brown et al., 1998) and by the tendency of motor units to discharge synchronously at a frequency of ~10 Hz (Hoefer and Putnam, 1940; Lance et al., 1963; Teräväinen and Calne, 1980), whereas EMG and muscle sound studies suggest that the 20 Hz and 40 Hz activities may be reduced (Brown, 1997; Brown et al., 1998). This may lead to an action tremor, the latter being separate from the more usual 4–6 Hz rest tremor seen in these patients (Lance et al., 1963). The action tremor persists during very strong contractions, where the synchronization of motor unit activity to a 10 Hz rhythm inevitably limits the ability to generate a fused muscle contraction, which, together with failure of motor unit recruitment, leads to reduced strength (Brown, 1997; Brown et al., 1998). To date the origin of the 10 Hz parkinsonian drive, like that associated with physiological tremor, remains unclear.

Muscle strength improves when parkinsonian patients are treated with levodopa (Corcos et al., 1996; Brown et al., 1998). To what extent the normal rhythmicity is restored remains uncertain, although recordings of muscle sound (Brown, 1997) and EMG (Brown et al., 1998, 1999) suggest that antiparkinsonian medication or therapeutic deep brain stimulation may return a Piper rhythm in strong tonic contractions. This would lead to a more fused muscle contraction and improved muscle strength (Brown, 1997).

Considered together, these observations suggest that levodopa may be able to restore normal rhythmic activity in the motor output. Here we show, by simultaneously recording MEG and EMG activity in patients with Parkinson’s disease, that normal rhythmicity is restored also in the primary motor cortex. We show that levodopa switches the primary motor cortex from a mode involving inefficient recruitment of motor units, often associated with the synchronization of cortical output at around 10 Hz, to one that involves improved motor unit recruitment and synchronous activity in the 15–30 Hz and 35–60 Hz bands.

**Methods**

We studied eight patients with Parkinson’s disease (mean age 49 years, range 41–70 years, three females, Hoehn and Yahr stage OFF medication I in three, II in two and III in three) and eight age-matched healthy subjects (mean age 48 years, range 37–77 years, three females). We excluded patients who had clinical evidence of other neurological disease, had dyskinesias or clinically severe rest or action tremor or United Parkinson’s Disease Rating Scale (UPDRS) motor scores \( \leq 10 \) when off treatment, or reductions in the UPDRS motor score \( \leq 20\% \) with treatment. All patients were taking levodopa preparations (mean daily dosage 860 mg). The mean UPDRS motor scores were \( 12 \pm 3 \) [mean ± SEM (standard error of the mean)] and 24 ± 3 with and without treatment, respectively. The worst affected hand was determined clinically and tested in each patient. Patients were recorded after overnight withdrawal of antiparkinsonian medication and again 1 h after treatment was restarted on the same day. All studies were performed with the approval of the Ethical Committee of The Helsinki University Central Hospital and the informed consent of each subject.

**Data collection**

We recorded whole-scalp MEG signals simultaneously with surface EMG from forearm extensor muscles during moderate isometric contraction (with mean rectified EMG levels 30–60% of those during maximal contraction). Recordings were performed in a magnetically shielded room with the subject supporting the head against the helmet-shaped bottom surface of a Neuromag-122™ magnetometer (Ahonen et al., 1993). EMG was picked up using bipolar surface electrodes. During the isometric contractions, the wrist was extended to \( \sim 30^\circ \) against a plastic constraint, while the forearm rested on a flat surface. The task was rehearsed prior to recording and care was taken to ensure that the hand did not move during contraction. Subjects were asked to look at a blank screen rather than their active hand. Contractions were continued for \( \sim 120 \) s and repeated twice after a rest of \( \sim 180 \) s. During recording, the hand was continuously inspected to detect movement. In five patients, the mean rectified EMG levels were similar OFF and ON levodopa. In the remaining three patients (Patients 6–8), the mean rectified EMG levels were 20–45% lower when recorded OFF than ON levodopa.

MEG and EMG signals were recorded with pass-bands of 0.03–200 Hz and 3–300 Hz, respectively, digitized at 600 Hz, and stored on magneto-optic disks for off-line analysis. The exact position of the head with respect to the sensor array was determined by measuring magnetic signals from three indicator coils placed on the scalp. The coil locations, with respect to three predetermined landmarks on the skull, were identified using a three-dimensional digitizer.

**Data analysis**

Power and coherence spectra between MEG and rectified EMG, calculated with a frequency resolution of 0.97 Hz, were averaged across trials for each subject (resulting in \( \sim 350 \) averaged epochs for each spectrum). Phase measurements were based on cross-spectra calculated with a frequency resolution of 0.24 Hz to enable linear regression analysis of phase slopes over relatively narrow frequency bands. To establish the noise level for the spectral values, coherence amplitudes were calculated with EMG signals shifted by 2 s (thus abolishing any true coherence). The significance level
of spectral peaks was defined so that these random coherences remained below it at 99% probability. We compared these significance levels with those derived on an a priori basis (Rosenberg et al., 1989). The latter gave lower significance levels and therefore a less conservative assessment than applied here. Coherences over different frequency bands were compared between treatment states, and between patients and healthy controls using paired and unpaired t-tests following Fisher’s z-transformation of the square root of the coherences (Rosenberg et al., 1989). Changes in coherence were also evaluated with repeated measures MANOVA (multiway analysis of variance) using the z-transformed coherences in three different frequency bands as dependent variables (3–12, 15–30 and 35–60 Hz).

Sources of oscillatory signals were modelled in time domain as equivalent current dipoles (Hämäläinen et al., 1993), found by a least squares search from the distribution of the strongest cross-correlogram peaks. Cross-correlograms were derived by inverse Fourier transformation of the averaged cross-spectra. The planar gradiometers in our whole scalp magnetometer show the largest signal above the cortical source current; therefore, we restricted our source analysis to sets of 30 detectors centred over the Rolandic area in each hemisphere. The locations, orientations and strengths of the equivalent current dipoles were determined at the strongest cross-correlogram peak; only sources that accounted for >85% of the field variance were accepted.

Results

Healthy subjects

Findings in the control group were similar to those previously reported (Conway et al., 1995; Salenius et al., 1997; Brown et al., 1998). Figure 1A shows the coherence spectrum between MEG and EMG for a normal subject during a moderate isometric contraction. The MEG was recorded over the left Rolandic cortex, contralateral to the dorsiflexed wrist. The spectrum reveals two distinct frequency bands, at about 20 and 45 Hz, with significant coherence. Figure 1B displays the distribution of the 20 Hz coherence on a schematic head. The distribution of the 45 Hz coherence was similar (data not shown). Source modelling of the major peaks in the cross-correlogram demonstrated dipoles in the region of the contralateral precentral cortex in or close to the motor hand area in all control subjects. The dipoles pointed anteriorly, perpendicular to the presumed orientation of the central sulcus. Figure 1C shows that the slope of the phase spectrum depended on frequency for the 20 Hz and 45 Hz peaks illustrated in Fig. 1A. Similar phase spectra were found in two other healthy controls. MEG led forearm extensor EMG by 6–13 ms, as previously reported (Brown et al., 1998). The remaining five subjects had relatively weaker coherence. All three subjects with the strongest coherence, for whom the phases could be most reliably estimated, displayed phase spectra with the phase linearly depending on frequency.

EMG and MEG power changes in parkinsonian patients

Changes in EMG power between the treated and untreated states are summarized in Fig. 2A for the three different frequency bands of interest. In line with previous reports (Brown, 1997; Brown et al., 1998), the relative EMG power in the 3–12 Hz band was significantly greater OFF treatment, while the converse was true over the 15–30 Hz and 35–60 Hz bands. Changes in MEG power recorded over the Rolandic area contralateral to the active limb are summarized in Fig. 2B for the three different frequency bands. Although MEG
power showed a tendency to change following levodopa in the same direction as EMG, no differences were significant.

Coherence in parkinsonian patients OFF and ON levodopa

The individual coherence spectra from all eight patients when OFF levodopa are shown in grey in Fig. 3. Only two patients (Patients A and D) showed a significant peak at around 20 Hz, and none had a peak in the 35–60 Hz band. Three patients (Patients F–H), however, had one or two peaks in the 3–12 Hz range. After treatment with levodopa (black traces in Fig. 3), six patients (A–D, F and G) displayed significant coherence in the 15–30 Hz band, and all but one (E) had significant coherence in the 35–60 Hz band. Two patients, A and C, displayed peaks at 5 Hz and 7–8 Hz, respectively, which were in both cases smaller than the 15–30 Hz coherence peak. The low frequency coherence in cases F–H was dramatically reduced following levodopa.

Figure 4 shows high resolution coherence and phase spectra for the three patients who, OFF levodopa, showed one or two peaks in the 3–12 Hz range. The slopes of the phase spectra depended on the frequency range, indicating that MEG leads EMG over 7–11 Hz by 15–38 ms, but that EMG leads MEG over 4–6 Hz. These frequency bands correspond to action and rest tremor, respectively; the different phases in the two bands would have been against a simple harmonic relationship in those cases in which two peaks were evident <12 Hz in the coherence spectra.

With one exception, the sources of the low frequency peaks observed in cases F–H (see Fig. 3) when untreated were consistent with a location in the region of the contralateral motor cortex (Fig. 5A). In the exceptional case, a reliable source could not be identified. This may reflect a contribution to the coherent activity from a subcortical source (see also Volkman et al., 1996).

Source modelling of the major peaks in the cross-correlogram and band-pass filtering the MEG signals to correspond to coherences in the 15–30 Hz and 35–60 Hz ranges demonstrated dipoles in the region of the contralateral precentral cortex, in or close to the motor hand area following treatment (Fig. 5B). Neither the mean x, y or z coordinates differed significantly between the 15–30 Hz and 35–60 Hz sources; the mean SEM distance between sources, as measured in three-dimensional space, was 6 ± 3 mm (Fig. 5B). The oscillatory currents were postero-anterior in orientation, perpendicular to the presumed orientation of the central sulcus, and similar to those found in the healthy subjects. In Patients A and B, the slopes of the phase spectra depended linearly on frequency within the 15–30 Hz band, so that MEG led EMG by 13 ± 7 ms and 7 ± 5 ms, respectively (Fig. 5C). These leads are similar to those previously reported (Brown et al., 1998) and found in our control subjects, although the intercept obtained with Patient A differed from that found in healthy subjects. Such non-zero intercepts are
believed to relate to a constant phase shift (Mima et al., 1999). Possibly this represents a residual abnormality of rhythmical cortex-muscle interaction, in this case not completely normalized by levodopa treatment.

Differences between MEG-EMG coherence in patients OFF and ON levodopa were confirmed by the mean data (Fig. 6). MANOVA revealed a significant difference between the treated and untreated conditions and a significant interaction between group and frequency \((P < 0.01)\). Coherence <12 Hz was reduced and that in the 15–30 Hz and 35–60 Hz bands increased following treatment \((P < 0.01)\). As a group, the treated patients did not differ significantly from the control subjects, except at a frequency of 3–12 Hz. Treatment with levodopa therefore effectively normalized the oscillatory interaction between the motor cortex and the spinal motor neurone pool during voluntary contraction.

Discussion

Parkinson’s disease is characterized by progressive degeneration of dopaminergic neurones in the substantia nigra pars compacta and, to a lesser extent, in the ventral tegmental area, leading to secondary dopamine depletion in the striatum and motor areas of the cerebral cortex (Gaspar et al., 1991). Dopamine deficiency and its functional consequences can be acutely annulled by levodopa, a dopamine precursor that temporarily restores brain dopamine levels, whilst having relatively little effect on noradrenergic or serotonergic systems in the brain (Bartholini and Plotscher, 1968; Scatton et al., 1983). Thus, the treatment of Parkinson’s disease with levodopa provides a reversible human model of basal ganglia dysfunction.

Here we have shown that exogenous dopamine in Parkinson’s disease is able to re-establish the normal
tendency of motor cortex output elements to synchronize at ~20 and 40 Hz. These rhythmicities are reflected in the MEG–EMG coherence spectra following treatment with levodopa. The coherent MEG signals originated in the area of the primary motor cortex contralateral to the active hand. The current dipoles pointed in the anterior direction and their activities preceded EMG activity, as reported in healthy subjects (Salenius et al., 1997; Brown et al., 1998).

The findings ON treatment were relatively consistent across subjects. The findings OFF treatment, although different from the treated state, were far less homogeneous. In three patients withdrawn from medication, one or two peaks below 12 Hz were evident in MEG–EMG coherence spectra. A further two had a peak in EMG spectra at action tremor frequency, but no significant MEG–EMG coherence. These differences from the treated state were unlikely to be caused by differences in the force of contraction between conditions, as the mean rectified EMG levels only differed in three subjects. Furthermore, in healthy subjects coherence varies little with force at the weak to moderate contraction strengths used in the present study (Mima et al., 1999). EMG power changes in particular frequency bands could also not explain changes in coherence between treatment states. Mean power changed in the same direction as coherence between conditions, so that changes reflected alterations in the absolute degree of coupling and could not be explained purely by differences in non-linear components of the signals.

In two out of the three untreated patients with prominent coherence <12 Hz, sources were identified in the region of the contralateral primary motor cortex, consistent with previous reports (Volkmann et al., 1996; Hellwig et al., 2000). MEG led EMG by 15–38 ms at action tremor frequencies (7–10 Hz). These lags were longer than those seen at higher frequencies in patients and healthy controls, suggesting that slowly conducting pyramidal pathways were involved in the generation of parkinsonian action tremor or that motor cortex drives action tremor indirectly, perhaps through the brainstem or that the brainstem drives tremor and sends internal re-afference signals (effenter copies) to the motor cortex. Some patients showed coherence at the frequency of parkinsonian rest tremor (3–6 Hz) which, when marked, may encroach upon tonic contraction (Lance et al., 1963). In these cases, the EMG activity in the forearm preceded MEG activity by ~30 ms, consistent with peripheral re-afference. Volkmann et al. (1996) found that precentral activity dominated at a similar interval following rest tremor EMG. The different MEG–EMG phase lags during resting and action tremor suggest that these two activities are separate and driven by different mechanisms (Lance et al., 1963).

It is important to consider whether the presence of tremor could have masked MEG–EMG coherence at higher frequencies through movement of the limb during the task. However, this seems unlikely. In Patients F and H, levodopa greatly decreased coherence at rest and action tremor frequencies, but increases in coherence >15 Hz were much less than in Patients A–D in whom there was no coherence at tremor frequencies. Indeed, in Patient A, MEG–EMG coherence at rest tremor frequency actually appeared, together with coherence at higher frequencies, for the first time following levodopa. Finally, tremor may coexist with MEG–EMG coherence in the 15–30 Hz range in other tremulous conditions (Halliday et al., 2000).

In summary, our results in parkinsonian patients imply that dopaminergic basal ganglia systems are necessary to support synchronization of output elements of the motor cortex at high frequencies, as has been previously suggested (Brown and Marsden, 1998). Without this subcortical input, the motor cortex activity (as reflected by the pattern of muscle discharge) is either arrhythmic or synchronized at low frequencies.

**Mechanisms by which cortical rhythmicity may be modulated by the basal ganglia**

Current theories of parkinsonism suggest that an exaggeration of pallidal output is a critical element in the pathophysiology of bradykinesia (DeLong, 1990). The over-activity of neurones in GPi in parkinsonism consists of two elements: an increase in the firing rate and a change in the pattern of firing (Filion and Tremblay, 1991; Sterio et al., 1994; Bergman et al., 1994; Nini et al., 1995; Hutchison et al., 1997, 1998; Merello et al., 1999). Normally, most GPi
neurones tend to fire evenly and independently, with the vast majority of the remaining 5% or so oscillatory neurones bursting with a frequency of >20 Hz (Filion and Tremblay, 1991; Bergman et al., 1994). In parkinsonian monkeys and patients, the GPi neurones have a much greater tendency for burst discharge and synchronization, and this can be reversed by dopamine agonists (Filion and Tremblay, 1991; Bergman et al., 1994). The frequency of the abnormal synchronous and oscillatory activity is ~4–10 Hz (Nini et al., 1995). Stimulation rates of this range in the inner division of the pallidum of animals lead to synchronization of the EEG in cortical motor areas and to gradual slowing and eventual cessation of spontaneous movements (Hassler and Dieckmann, 1967; Dieckmann, 1968). Comparable effects have been provisionally reported following low frequency stimulation of the human subthalamic nucleus (Demeret et al., 1999).

Could this abnormal low frequency, synchronous oscillatory activity in GPi act, via the thalamus, to hold the motor cortex in the idling state in Parkinson’s disease? Neuronal activity in the specific and non-specific thalamic nuclei tends to oscillate with a frequency of ~40 Hz upon depolarization (Steriade et al., 1991), and GPi overactivity and low frequency bursting in Parkinson’s disease might diminish these fast oscillations and their action on the cortex. This could be brought about by GABA (γ-aminobutyric acid)-induced hyperpolarization of thalamo-cortical neurones and deinactivation of low threshold calcium channels, triggering short bursts of very high frequency action potentials synchronized by and phase-locked to the pallidal bursts, in much the same way as phasic GABAergic inputs from nucleus reticularis thalami may drive sleep spindles (Steriade et al., 1993). The result would be a pervasive synchronization of cortical activity at frequencies of 4–10 Hz. Action tremor

---

**Fig. 5** (A) Coherence spectrum and MEG contour map in Patient H OFF levodopa. Field patterns (steps of 0.03) correspond to the strongest peak in the cross-correlogram of MEG and EMG pass band filtered between 8 and 20 Hz to reflect the 10 Hz peak in the coherence spectrum. Resolution of coherence spectrum 0.97 Hz. (B) Coherence spectrum and MEG contour map (steps of 0.02) in Patient A following levodopa. Field patterns correspond to the strongest peak in the cross-correlogram of MEG and EMG pass band filtered between 8 and 45 Hz to reflect the 20 Hz peak in the coherence spectrum. White arrows indicate the orientation of the corresponding dipolar sources in A and B. EMG was recorded from the contralateral forearm extensors during isometric contraction. The head is viewed from the side. The contour maps are superimposed on a schematic sensor array. Both maps are consistent with a Rolandic source contralateral to the contracted wrist. Resolution of coherence spectrum 0.24 Hz. (C) Phase spectrum corresponding to the boxed section of the high resolution coherence spectrum in B (Patient A). (D) Cross-correlogram between MEG and EMG (Patient A). Dashed lines indicate upper and lower 99% confidence limits based on the assumption of independence.
might then result from the involvement of pyramidal neurones in these synchronized low frequency oscillations, with consequent driving of muscle.

Consequences of abnormal cortical rhythmicity in Parkinson’s disease
The abnormal pattern of oscillatory cortical activity in Parkinson’s disease may lead to inefficiencies at two non-mutually exclusive levels. First, synchronization at low frequency, as seen in some patients, leads to a sub-optimal unfused pattern of muscle activation, thereby slowing the onset of voluntary actions and decreasing contraction strengths (Brown et al., 1998). The restoration of an essentially normal basal ganglia input enables cortical motor elements to oscillate at higher frequencies. Muscles can then be activated at high frequencies, reversing bradykinesia and weakness. Secondly, it has been suggested that coherence of motor cortical elements at frequencies >20 Hz could be associated with higher order aspects of motor control, e.g. providing a mechanism for favouring, and therefore selecting and binding together those distributed cortico–cortical activities necessary for the prompt and successful execution of a movement (Brown and Marsden, 1998, 1999; Brown, 1999). In this case, one would predict an association between bradykinesia and the failure to shift cortical activity to higher frequencies in motor areas both with and without major projections to the spinal cord. This should be particularly evident in complex movements, which are especially difficult in Parkinson’s disease, and has been confirmed in parkinsonian subjects performing manual tracking or combined and sequential motor tasks ON and OFF levodopa (Brown and Marsden, 1999; Wang et al., 1999). Nevertheless, a role for synchronization at high frequency in higher order aspects of motor control remains speculative (Hari and Salenius, 1999).

In conclusion, the basal ganglia seem to influence the temporal organization of motor cortical activity. Abnormalities in this aspect of basal ganglia function may directly contribute to bradykinesia and weakness in Parkinson’s disease.

Acknowledgements
We thank V. JousmaÈki and M. Illman for help in the experiments. This study was supported financially by the Academy of Finland and by the EU Human Capital and Mobility Programme through the Large Scale Facility BIRCH at the Low Temperature Laboratory, Helsinki University of Technology.

References


McAuley JH, Rothwell JC, Marsden CD. Frequency peaks of tremor, muscle vibration and electromyographic activity at 10 Hz, 20 Hz and 40 Hz during human finger muscle contraction may reflect rhythmicities of central neural firing. Exp Brain Res 1997; 114: 525–41.


Received December 21, 2000. Revised September 21, 2001. Accepted October 8, 2001