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Beta Activity in the Subthalamic Nucleus During Sleep in Patients with Parkinson's Disease

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Abstract: The recordings of local field potentials in the subthalamic nucleus in patients with Parkinson's disease (PD), carried out through the stimulators implanted to treat the motor symptoms of the disease, show a prominent basal ("off") activity in the beta range, which is attenuated after dopaminergic therapy. A recent study described improvement of parkinsonian features during rapid eyes movements (REM) sleep. We describe, for the first time, the changes in activity of the subthlamic nucleus (STN) during different sleep stages in Parkinson's disease with special interest in the beta band. Ten patients with PD treated with deep brain stimulation of the STN were studied. Subthalamic local field potentials (LFPs) were recorded through the stimulation electrodes during wakefulness ("off" medication) and different sleep stages. In Stage 2 and slow-wave sleep, a significant decrease of beta activity was recorded. During REM sleep, beta power values were similar to wakefulness values or even higher. These findings indicate that STN activity is modulated and modified during different sleep stages. The increased beta activity during REM sleep is a new but unexpected finding, which requires further analysis. © 2008 Movement Disorder Society

Key words: Parkinson's disease; motor control; sleep; subthalamic nucleus; local field potentials (LFP)

The implantation of electrodes for deep brain stimulation in the internal part of the globus pallidus or in the subthalamic nucleus (STN) to treat motor complications in Parkinson's disease (PD) has provided a unique opportunity to record directly electrical activity from the human basal ganglia. A relatively typical pattern of oscillatory activities in different frequency bands has been described in the STN of PD patients. In the "off" medication state, the STN shows a prominent activity in the beta range (13–30 Hz), which is attenuated in the "on" medication state.[1–3] In the "on" state, oscillations in higher frequencies (high gamma band (60–90 Hz), or even as high as 300 Hz) can be recorded.[4–6] Finally, theta oscillations (4–10 Hz) associated to the presence of levodopa-induced dyskinesias have also been described.[7]

The oscillatory changes in the beta band appear particularly interesting. Because voluntary movement is preceded by significant reduction in their power both in the motor cortex[8,9] and STN,[10,11] it has been suggested that the subthalamic oscillations in the beta band may play a role in bradykinesia in PD.[12] However, there is no direct proof for such relationship yet.

Two recent studies suggest that during sleep there is an improvement of the motor disturbances observed in patients with Parkinson disease.[13,14] The pattern of the STN activity during sleep could help to explain the mechanism of this motor improvement in PD patients. Furthermore, a decrease in the beta band activity in STN during sleep would confirm the role of this activity in the motor state. To the best of our knowledge, there has not been any previous study of the effect of sleep on the oscillatory activity of the basal ganglia in

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PD patients. The aim of our study was to assess the influence of different stages of sleep on the oscillatory activity in the STN during the "off" motor state, with special focus on the beta band.

PATIENTS AND METHODS

Patients

Ten patients with PD who had undergone bilateral implantation of electrodes in the STN for treatment with DBS were included in the study. All the recordings were carried out between 2 and 4 days after the surgery, having ensured that the patients' general state was satisfactory. The sleep periods analyzed corresponded to naps during the early afternoon (after lunch) in 5 cases and whole night sleep in the remaining five. The study was integrated in the Parkinson's disease surgical protocol at our center. The institutional ethics committee approved this study and informed consent was obtained from each patient. The clinical characteristics of the patients are described in Table 1.

Surgical Procedure

Medtronic 3389 macroelectrodes (Medtronic Neurological Division, Minneapolis, MN) were bilaterally implanted into the STN in a single operation by a standard stereotactic approach.[15] The electrode contains four platinum-iridium cylindrical contacts, which were labeled 0, 1, 2, and 3 on the right STN, and 4, 5, 6, and 7 on the left STN, starting at the most caudal site. The STN was localized using a CT-MRI fusion-based technique (Stereoplan Radionics, Burlington, MA), through intraoperative microrecording and microstimulation, as performed routinely by our group.[16] The most ventral contact of each electrode was positioned to match the end of the STN as estimated by microrecording intraoperatively. Definitive placement of the macroelectrode within the STN was assessed by MRI 1–3 days after surgery.

Signal Recording

The recordings were acquired using the Harmonie long-term monitoring system (Stellate, Montreal, Canada). The montage included intracerebral depth electrodes implanted into the STN bilaterally, scalp electrodes, EOG and EMG of limb muscles. The local field potentials from the STN were recorded through the external connection of the implanted electrodes before the internalization of the system. A bipolar montage was used with contact pairs from the same

TABLE 1. *Clinical characteristics of the patients*

Age/ gender	Evolution time (years)	Dosage Pre (mg)	Dosage Post (mg)	UPDRS OFF pre	UPDRS ON pre	UPDRS OFF post (DBS ON)	UPDRS ON post (DBS ON)	CA1	CA2
60/M	12	2105	610	26	10	19	6	3 (−) 3.3 V-60 ms-185 Hz	7 (−) 6 (+) 3.5 V-60 ms-185 Hz
62/F	9	1625	1200	32	7	12	3	3(−) 3.5 V-120 ms-180 Hz	7(−) 6(−) 5(+) 3.5 V-120 ms-180 Hz
58/M	10	1275	250	29	13	20	14	2(−) 2.2 V-60 ms-185 Hz	6(−) 7(+) 2.5 V-60 ms-185 Hz
56/M	8	1400	375	31	12	12	7	2(−) 3(+) 3 V-60 ms-160 Hz	7(−) 3 V-60 ms-160 Hz
67/M	14	850	525	46	17	23	19	1 (−) 3.2 V-60 ms-140 Hz	7 (−) 3.2 V-90 ms-140 Hz
72/M	15	1800	1500	38	9	19	8	0(−) 2 V-60 ms-130 Hz	5(−) 7(+) 2.2 V-60 ms-130 Hz
61/M	25	2475	700	42	8		9	3(−) 2.5 V-60 ms-130 Hz	6(−) 2.5 V-60 ms-130 Hz
61/M	11	1300	500	28	6	7	5	3(−) 0(+) 4.5 V- 60 ms-185 Hz	6(−) 5(+) 4.5 V-60 ms-185 Hz
58/M	10	2150	675	39	14	6	2	2 (−) 1 (-) 3.0 V-60 ms-185 Hz	7 (−) 5 (+) 3.9 V-90 ms-180 Hz
67/M	9	775	200	33	10	17	11	1 (−) 0.7 V-60 ms-180 Hz	5 (−) 3.5 V-60 ms-180 Hz

M, male; F, female; Pre, presurgery; Post, postsurgery; Dosage, levodopa dose equivalent (mg); UPDRS, unified Parkinson's disease rating scale, part III (0-118); CA1, contacts that showed maximal benefit right STN; CA2, contacts that showed maximal benefit left STN.

side yielding a total of six STN channels (0–1, 1–2, and 2–3 in the right side, 4–5, 5–6, and 6-7 in the left side). Five (9 patients) or ten (1 patient) scalp Ag-AgCl electrodes were placed using the 10/10 system. The EEG channels were reformatted to a common average reference for analysis. The EMG was recorded with bipolar disposable surface electrodes (Neuroline, Spain) placed on both lower limbs (tibialis anteriors).

All channels were acquired with a sampling frequency of 200 Hz and default filters from the recording equipment (0.1 Hz low pass analog filter; ~70 Hz anti-aliasing digital filter).

Sample Selection and Analysis

Sleep staging was performed using the Rechtschaffen and Kales criteria.[17] Eighteen artifact-free segments of 10 s duration (totaling 3 minutes of recording) were selected from wakefulness (in "off" medication state) and sleep (3 minutes per stage, at least 3 hours after the last medication intake). The sleep segments obtained during Stage 2 of sleep, slow sleep, and REM sleep were analyzed separately. In the patients with early afternoon nap recordings, awake segments were obtained from the nearest "off" period to the nap according to the UPDRS values (the patients were explored periodically). In the patients with a whole night recording, awake segments were selected during a nocturnal awakening or at first hour in the morning before any drug intake.

An additional sleep segment selection was carried out in REM sleep after the first analysis of the results to obtain segments of REM sleep with and without muscle atonia in 3 of the patients.

The samples were saved in text format and transferred to Spike2 software (Cambridge Electronic Design, Cambridge, UK) by means of a custom-made script.

Measurement of Beta Band Power by Spectral Analysis

The power spectrum was determined using the fast Fourier transform (FFT) function in the Spike 2 software. Using a FFT length of 1,024 (window of 512 points per epoch, Hamming window, nonoverlapping epochs), a frequency resolution of 0.1953 Hz was attained given the 200 Hz sampling rate. The signal power was converted to log-scale to obtain a more Gaussian distribution.[18] The beta band was defined between 15 and 30 Hz. Frequencies between 13 and 15 Hz were excluded due to the coincidence with the frequency of sleep spindles that were identified during Stage 2 of sleep in eight STN from five patients (Fig. 1).

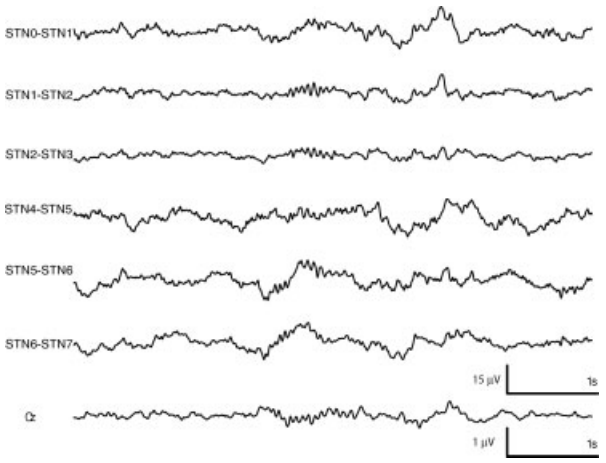

FIG. 1. Examples of a sleep spindle simultaneously observed in STN channels and the scalp electrode Cz. Note that the scales in STN channels and Cz are different.

All the power spectra were visually reviewed to identify peaks at different frequencies. The channels showing the clearest peak in the beta band during the "off" medication state, in each STN, were selected for additional analysis.

Measurement of Cortical-STN Coherence

The coherence between the STN channels showing the clearest peaks and the cortex (Cz) was computed in Spike 2 software using blocks of 1,024 points. The coherence was calculated from the *cross spectral density* or csd between the two waveforms normalized by the *power spectral density* or psd of each waveform. The coherence at some frequency f was given by:

$$\mathrm{coh}(f) = \frac{|\sum \mathrm{csd}_{ab}(f)|^2}{\sum \mathrm{psd}_a(f) \sum \mathrm{psd}_b(f)}$$

Statistics

Paired Student t-tests were used to compare the power of the beta band between wakefulness (in "off") and different sleep stages in the STN channels. An ANOVA test with Bonferroni posthoc comparisons was used to compare the results obtained including all the channels, the channels with the clearest beta peak and the channels without beta peak during wakefulness.

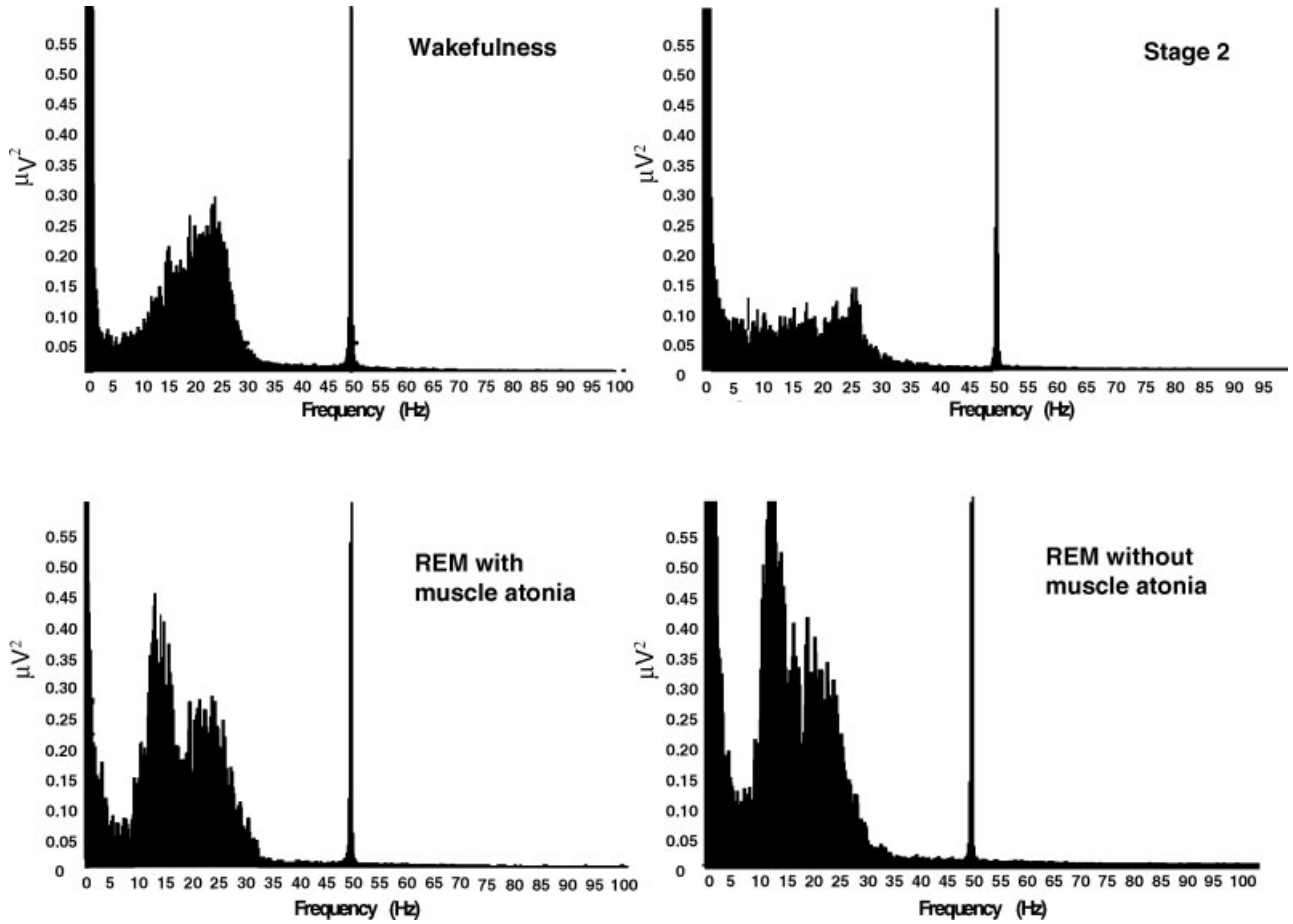

FIG. 2. Spectral analysis of a STN channel during wakefulness and the different sleep stages in a patient. Typical changes during the different stages. REM sleep has been divided in REM sleep with muscle atonia and REM sleep without atonia.

RESULTS

In the "off" medication state during wakefulness, the spectral findings in the STN were similar in all patients. Seventeen of the 20 analyzed STN nuclei, including at least one nucleus from every patient, showed a well-defined peak in the beta band (15–30 Hz) (Fig. 2), indicating that all the segments were selected during the "off" motor state. The beta peak was seen in 1 to 3 channels per nucleus (30 of 60 analyzed channels); 73% of them were dorsal.

During Stage 2 of sleep, the activity recorded from the STN nuclei was dominated by theta-alpha rhythms. Spindles (Fig. 2) and K-complexes were recorded from 8 STN nuclei (6 patients). The spectra showed an increase in the power of delta, theta, and alpha bands respect to wakefulness. In the beta band, there was a significant decrease in the power from "off" wakefulness to Stage 2 ($P < 0.0001$) (Fig. 3). In fact, a beta peak (markedly attenuated) could only be observed in this stage in four STN nuclei (3 patients), which also showed a pronounced peak in this frequency range during wakefulness (Fig. 2). An additional small peak at 12–14 Hz was seen in seven of the eight nuclei showing spindles. No peaks in frequencies over 30 Hz were observed in the STN. The direct observation of the STN traces in the patients with prominent beta activity showed that the beta reduction occurred immediately after sleep onset.

Samples of Stage 4 were obtained in 6 patients (12 STN, 36 channels), all of them with a marked beta peak during wakefulness but not during Stage 2. During slow-sleep, the activity recorded from the STN nuclei was dominated by delta and theta activity. In three of the STN nuclei (2 patients), the spindles present in Stage 2 did not disappear completely during Stage 4 and a peak at 12 Hz could be seen in the spectra. The power of the beta band was similar to that observed during Stage 2 of sleep ($P > 0.05$) (Fig. 3);

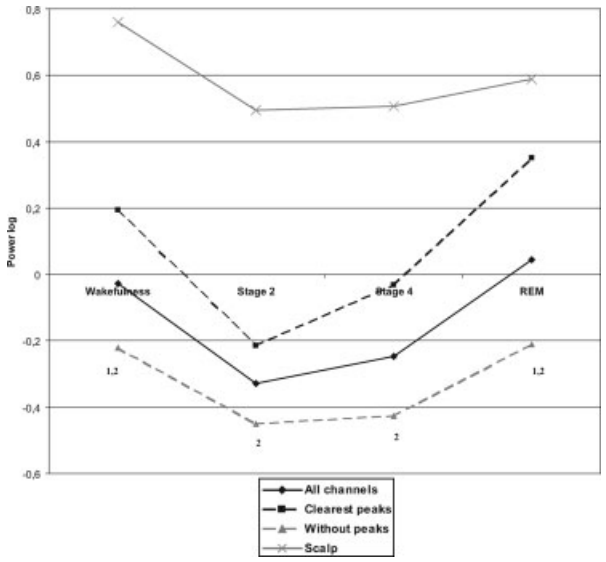

FIG. 3. Beta power during wakefulness and different sleep stages in the subthalamic nucleus and neocortex. Differences between the results analyzing all the STN channels and the STN channels with the best beta peaks were not statistically significant.[1] Statistically significant differences with the average of all the channels.[2] Statistically significant differences with the average of the channels with the clearest peaks.

however, in two STN nuclei (2 patients) there was a peak in the beta band in Stage 4 but not in Stage 2. The peaks were similar to the peaks observed during wakefulness in the same electrodes but with lower amplitude. The power of the beta band during Stage 4 was significantly lower than during wakefulness ($P < 0.0001$, n = 36) (Fig. 3). As in Stage 2, no peaks in the gamma band (>30 Hz) were seen.

Samples of REM sleep were obtained in 5 patients (10 STN, 30 channels), who also had samples available from all other sleep stages. During REM sleep, low amplitude beta activity was seen in the recordings from the STN nuclei. No spindles were observed. The beta power in the STN was slightly higher than during wakefulness ($P = 0.002$, n = 30), and clearly higher than during Stages 2 and 4 ($P < 0.0001$, n = 30) (Fig. 3). The power increase observed during REM sleep affected almost exclusively the high beta range (20–30 Hz), remaining the power in the low-beta range (13–20 Hz) lower than during wakefulness. An evident peak in the power of the beta band was seen in 4 of the 5 patients (7 STN) (Fig. 2). Two of these patients had beta peaks during wakefulness and Stage 4 of sleep, and the other 2 patients had beta peaks exclusively during wakefulness. The patient without the beta peak in REM sleep had a clear peak during wakefulness, in both STN nuclei.

An additional peak in the limit between the alpha and beta bands (10–15 Hz) appeared in 4 of the 5 patients in this stage (Fig. 2). This peak was not observed during wakefulness or other sleep stages. No peaks in the gamma band were seen.

In 3 of the 5 patients with REM sleep, there were 3–8 seconds length segments with muscle activity in the EMG during REM sleep instead of the characteristic atonia. No clear body movements where observed in the video recording during these periods. In these 3 patients, we reanalyzed separately samples of REM sleep differentiating segments without and with muscle activity in the EMG. For the samples of REM without muscle atonia, 10 s-segments with muscle activity in more than 50% of the time were selected. We found in the 3 patients that the beta power during REM sleep was higher when muscular activity was present (beta power log: 0.56) than when there was muscle atonia (beta power log: 0.07, $P < 0.001$, n = 18), with a clear beta peak in the spectra. The power increase included the low and high beta ranges. The 10–15 Hz peak found between the alpha and beta bands also had higher amplitude.

Channels with Clear Beta Peaks versus Channels Without Beta Peak

When only the channels with the highest beta peak during wakefulness in each nucleus were included in the analysis, the changes between wakefulness and the different sleep stages studied were more pronounced than those observed when all the channels were included, but with a similar tendency and statistical significance (Fig. 3). From these channels (n = 17), 14 (82%), included dorsal contacts and were active in the stimulation.

On the other hand, the analysis limited to the channels without beta peaks during the off-medication wakefulness showed smaller differences between the different stages, which did not reach statistical significance (n = 12) (Fig. 3).

Subthalamic Nucleus versus Cortex

Figure 3 compares the mean power obtained in the STN and the cortex in different sleep stages. The changes in cortex had the same direction as in the STN but proportionally they were much less prominent.

Cortico-STN coherence during off-medication wakefulness showed a peak in the beta range in 11 nuclei from 8 patients. Maximal coherence values ranged between 0.18 and 0.48 (mean = 0.31). The frequency of the peak ranged between 18 and 30 Hz (mean: 25 Hz). During Stage 2 and Stage 4 of sleep, coherence was reduced in the beta range, but increased at lower

frequencies. The maximum coherence in the beta band during Stage 2 of sleep ranged between 0.07–0.29 (mean = 0.15; n = 11) and during Stage 4 of sleep ranged between 0.05–0.21 (mean= 0.13; n = 7).

During REM sleep, coherence results were not consistent. Two patients showed a beta peak with maximum values lower than during wakefulness (0.32 during REM sleep vs. 0.38 during wakefulness in the first patient; and of 0.24 during REM sleep vs. 0.34 during wakefulness in the second patient). The frequency of the peak was similar during REM sleep and wakefulness (22 Hz in the first patient and 30 Hz in the second patient). Both patients also had clear beta peaks in the power spectra during REM sleep. In other 2 patients the cortico-subthalamic coherence in the beta range remained low during REM sleep (maximum <0.12), without identifiable peaks. One of these patients did not show beta power peaks in the spectra during REM sleep and the other one showed a weak beta power peak.

None of the STN nuclei that did not show a beta peak in cortico-subthalamic coherence during wakefulness showed coherence peaks during sleep. These nuclei were excluded from the analysis.

DISCUSSION

We describe changes in the power of the beta activity of LFP recorded in the STN and cortico-STN coherence during different sleep stages in PD patients with respect to wakefulness in the "off" medication state. To the best of our knowledge, this is the first study assessing STN oscillatory activity during different sleep stages in PD.

How neuronal activity of the basal ganglia is modified during sleep is not well defined. Early studies of the dopaminergic system in the rat and cat suggested that the substantia nigra neurons did not modify their firing rate and pattern during sleep.[19,20] However, a recent microdialysis study in monkeys showed a significant reduction of striatal dopamine concentrations at night.[21] In our patients, the STN LFP power in the beta band during Stage 2 and 4 of sleep was lower than the power during wakefulness, with a fast transition, and increased during the REM stage. This is the first evidence of a modulation of neuronal activity during sleep in main basal ganglia nuclei in humans. This observation is conceptually important because the basal ganglia have been traditionally thought to keep a fairly permanent level of activity, regarding both the dopaminergic system and the neuronal firing of the output nuclei, including the STN.

Our findings are also clinically relevant although, admittedly, more difficult to define precisely. The FFT of the LFP activity recorded during wakefulness from the STN showed peaks in the beta range in all the patients. The abnormal oscillatory LFP activity in the beta range recorded from the STN in "off" PD patients has been previously reported by several groups.[3,5,7,22] There is a positive correlation between the amount of beta activity in the STN in "off" and the motor improvement of the patients with dopaminergic therapy (difference between "off" and "on" UPDRS scores).[1,23] Thus, the abnormal subthalamic beta activity might be considered a marker of dopaminergic depletion. PD patients usually complain of reduced mobility during nocturnal sleep but this generally refers to periods of wakefulness during the night. The fast transition in the power of the beta activity from wakefulness to sleep and viceversa sustains this interpretation. Moreover, some studies suggest that in fact there is a partial alleviation of the akinesia and rigidity during sleep,[24,25] which is congruent with the reduction in beta activity during Stages 2 and 4 of sleep. A recent study has also described that the firing pattern of single neurons recorded from the STN of PD patients during spontaneous sleep (Stage 2) resembles the one found after amelioration of parkinsonian features by administration of apomorphine.[14]

The beta power during REM sleep increased to levels higher than those observed during wakefulness, which at first, may appear to conflict with a recent study describing the restoration of an apparently normal motor control during REM sleep in PD patients with REM behavior disorder (RBD).[13] There are however, several points to take in consideration when discussing this apparent discrepancy. First, the motor state of PD patients during REM sleep is difficult to evaluate due to the muscle atonia characteristic of this sleep stage. The mechanisms of the muscle atonia during REM sleep, although not perfectly known, seem mainly mediated by structures of the brainstem and the role played by the interaction with the forebrain is unclear.[26] Secondly, none of our patients had obvious behavioral disturbances during REM sleep, although three did show increased muscle activity. This is an electrophysiologic finding required for the diagnosis of RBD but it is not synonymous of RBD. In fact, we did not undertake any direct evaluation of the motor state in those patients and therefore, can not establish a concrete relationship between beta activity and parkinsonian state. Moreover, it is possible that the increased muscle activity seen in our patients could reflect rigidity or be mediated by mechanisms bypassing the basal

ganglia. Finally, it has previously been hypothesized that there might be, within the broad beta band, more specific patterns of activity.[3,27] Interestingly, in our study, the power increase observed during REM sleep with atonia affected almost exclusively the high-beta range, which is less influenced by anti-Parkinsonian medication,[3] while the power of the low-beta range only increased when muscle activity was observed. In addition, a new peak appeared during REM sleep in the limit between the alpha and beta bands (10–20 Hz). In our opinion, the possible relationship between this peak and motor control is supported by two facts: on one hand this peak was more evident when there was muscle activity in the EMG and, on the other hand, the STN channels showing this 10–20 Hz peak during REM sleep coincided with the channels showing the increase in the beta LFP power during wakefulness.

In summary, LFP activity in the STN in "off" PD patients is modified by sleep. In Stages 2 and 4, a reduction in the abnormal beta activity can be observed affecting all STN contact pairs but more significant in those channels showing a prominent basal beta peak. In REM sleep, beta activity surpasses the "awake" values, especially during REM without atonia, although the effects may be different for the low and high beta bands. These findings raise new questions about the motor control mechanisms operating in PD during sleep. The significance of increased beta activity during REM sleep requires further analysis but, we believe, represent an important first step to better understand RBD in PD.

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