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Oscillatory activity in the pedunculopontine area of patients with Parkinson's disease

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Abstract

The pedunculopontine nucleus (PPN) has recently been introduced as a new therapeutic target for deep brain stimulation (DBS) in patients suffering from Parkinson's disease (PD). In a recent case report it was demonstrated that alpha frequency oscillations appear in PPN after the administration of levodopa in PD, indicating a possible physiological role of these oscillations. Here we confirm this result and investigate the functional connectivity and reactivity of subcortical alpha activity by recording LFP activity from the PPN area and EEG in six patients with PD while at rest and in four of them while they performed ipsi- and contralateral self-paced joystick movements. Levodopa strongly promoted 7–11 Hz oscillatory synchronization in the region of PPN and coupling of this activity with similar activity in the cortical EEG. Such coupling was bidirectional. Moreover, the 7–11 Hz oscillatory synchronization in the PPN area increased about 3 s prior to self-paced movements, but only following levodopa treatment. These findings suggest that alpha oscillations in the PPN area may represent a physiological pattern of activity. The subcortical oscillations are coupled to cortical alpha activity and possibly allied to motor related attentional processes.

Keywords: Pedunculopontine nucleus; Deep brain stimulation; Local field potentials; Parkinson's disease; Alpha oscillations

Introduction

The pedunculopontine nucleus (PPN) is a key part of the reticular activating system and mesencephalic locomotor region (Pahapill and Lozano, 2000; Mena-Segovia et al., 2004; Mena-Segovia et al., 2005). It has extensive connections, including with the basal ganglia and thalamus. Recently, it has been introduced as a therapeutic target for deep brain stimulation (DBS) in patients suffering from Parkinson's disease (PD), particularly those with severe gait and postural impairment (Mazzone et al., 2005; Plaha and Gill, 2005; Lim et al., 2007; Stefani et al., 2007). Effective therapeutic stimulation in PPN is delivered at low frequencies, in line with studies in 1-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine treated primates where 10 Hz stimulation proved most efficient (Jenkinson et al., 2004). This contrasts with other basal ganglia targets, such as the subthalamic nucleus (STN) and the internal segment of the globus pallidus (GPi), where stimulation must be delivered at frequencies above 100 Hz to be therapeutic.

Just how and why this unique stimulation regime should work in the PPN in PD remains unclear. In a recent case report we showed that treatment with levodopa in a patient with PD implanted in Bristol (U.K.) lead to the appearance of alpha band activity in the local field potential (LFP) recorded from PPN (Androulidakis et al., 2008). This prompted the suggestion that

Abbreviations: a.u., arbitrary units; DBS, deep brain stimulation; GPi, globus pallidus interna; LFP, local field potentials; MRI, magnetic resonance imaging; PD, Parkinson's disease; PPN, pedunculopontine nucleus; STN, subthalamic nucleus; UPDRS, unified Parkinson's disease rating scale.

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alpha band synchronization is a physiological feature of PPN function and that this activity may be mimicked by low frequency stimulation of the PPN. Here we confirm our earlier result in a series of six more PD patients in whom the PPN area was implanted in Rome, and investigate the functional connectivity and reactivity of the subcortical alpha activity with the aim of deducing the possible role of this activity in behavioural performance in PD.

Methods

Patients and surgery

Six patients gave written informed consent to take part in this study which was approved by the local ethics committee. Cases 1 and 2 underwent bilateral implantation of the STN and PPN area, case 3 and 4 unilateral implantation of the STN and PPN area, case 5 unilateral implantation of the GPi and PPN area, and case 6 unilateral implantation of PPN area alone for the treatment of severe Parkinson's disease. Clinical findings in case 6 have been previously reported as case 3 in Stefani et al. (2007). Fig. 1 illustrates the post-operative MRI in case 4.

The targeting of PPN in this series merits some comment. It has been reported in detail elsewhere (Mazzone et al., 2005, 2007; Stefani et al., 2007). However, the precise nature of the target has been questioned (Yelnik, 2007; Zrinzo et al., 2007) and because of this, and the uncertainty regarding the definition of the limits of the extent of PPN (Mena-Segovia et al., 2005), we will adopt the conservative term 'PPN area' in describing our results.

Recordings

Patients were studied 3–6 days post-operatively, in the interval between DBS electrode implantation and subsequent connection to a subcutaneous stimulator. The subjects were seated comfortably in a chair and recorded in the resting, awake state. Recordings were performed after overnight withdrawal of antiparkinsonian medication and again about 1 h after they had taken a minimum of 200 mg levodopa. Deep brain activity was recorded bipolarly from the adjacent four contacts of each DBS electrode (0–1, 1–2, 2–3), amplified (×100,000) and bandpass-filtered at 1–500 Hz (amplifier D160; Digitimer Ltd, Welwyn Garden City, Herts, UK). EEG activity was recorded monopolarly from FPz using a needle electrode and an ear reference and amplified and bandpass-filtered as before. For cases 1–3 and 5 (see Table 1) we recorded EEG and LFP activities from the PPN area (i.e. 6 sides) ON and OFF medication at rest. In case 6 we recorded the PPN area LFP activity in both states (1 side) and EEG activity only in the ON state and for case 4 we recorded the PPN area LFP activity only in the ON state. For cases 1–3 and 5 (i.e. 6 sides), we also recorded LFP activity from the PPN area while they made self-paced movements of a joystick forward and then immediately backward, repeated approximately every 10–15 s. This task was performed separately with left and right hands in both drug states. Recordings in the area of the subthalamic nucleus were only possible on 5 sides (3 patients) and are not considered further. All signals were recorded using a 1401 analogue-to digital converter (1401, Cambridge Electronic Design, Cambridge, UK) using Spike 2 software (Cambridge Electronic Design) and sampled at rates of 1–2 kHz.

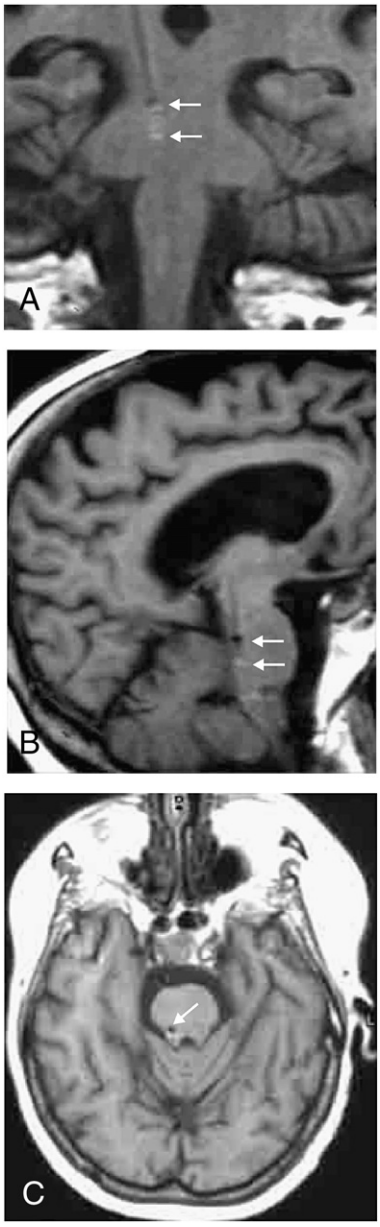

Fig. 1. Post-operative MRI in case 5. (A) Coronal (B) Sagital, and (C) Axial slices demonstrating position of DBS electrode in posterolateral pons. Arrows show approximate extent of artifact from electrode contacts.

Analysis of rest recordings

All analyses were performed offline in Spike 2 v6 and MatLab 7 (The Mathworks Inc., Lowell, MA, USA). Data were interpolated to a common sampling rate of 1 kHz. Spectral estimates of the power in the LFP and EEG signals from each contact pair were derived using the finite Fourier Transform for blocks of 1024 data points (frequency resolution ~1 Hz). The

Table 1
Clinical details in PD patients

Case	Age and sex (years)	Disease duration	Predominant symptoms	Motor UPDRS pre-operation (ON/OFF levodopa)	Motor UPDRS post-operation (OFF levodopa) ON/OFF DBS	Medication (daily dose) pre-operation	Contacts used in analysis
1	49/M	13	Freezing and rigidity	32/72	25/75	Levodopa 1250 mg	Left side: PPN01 Right side: PPN01
2	56/M	23	Freezing, rigidity, dyskinesia	44/72	30/70	Lisuride 9.6 mg Levodopa 500 mg	Left side: PPN23 Right side: PPN12
3	48/M	16	Freezing, rigidity, dyskinesia	44/72	30/72	Levodopa 1325 mg	PPN12
4	66/F	16	Freezing, dystonia, gait deficit	62/82	58/75	Levodopa 1325 mg	PPN01
5	51/M	8	Freezing, rigidity, dyskinesia	60/68	32/68	Levodopa 825 mg Entacapone 125 mg	PPN01
6	67/M	11	Freezing, rigidity, postural deficit	32/75	26/70	Levodopa 875 mg	PPN12

The clinical findings in case 6 have been previously reported as case 3 in Stefani et al. (2007).

first step was to identify the PPN area DBS contact pairs that afforded the highest mean power in the 7–11 Hz band. We then estimated the average power within the 7–11 Hz band across all trials in the ON and OFF conditions for the PPN area and the EEG and compared conditions by means of the Wilcoxon matched-pairs test. Thereafter we calculated the bivariate coherence between the PPN area LFP and EEG for the two drug states. We averaged the Fisher transformed coherence values across the 7–11 Hz band for each subject and performed Wilcoxon matched-pairs tests between the two drug states.

Significant power and coherence between the PPN region and EEG was only recorded in the ON medication state. The functional connectivity between the PPN area and cortex in this drug state was further investigated using the directed transfer function (DTF) implemented through the open source toolbox "FieldTrip" developed at the F. C. Donders Centre for Cognitive neuroimaging (http://www.ru.nl/fcdonders/fieldtrip) and the SPM toolbox (http://www.fil.ion.ucl.ac.uk/spm). A detailed description of the methodology and principles of the directed transfer function (DTF) can be found in Kaminski and Blinowska (1991), Korzeniewska et al. (2003) and Cassidy and Brown (2003). The DTF technique relies on the key concept of Granger causality between time series (Granger, 1969), according to which an observed time series $x(n)$ causes another series $y(n)$ if the knowledge of $x(n)$'s past significantly improves prediction of y(n). The latter relationship between time series is not reciprocal, i.e. x(n) may cause y(n) without y(n) necessarily causing x(n). This lack of reciprocity enables the evaluation of the direction of information flow between structures. To this end, the multiple autoregressive (MAR) model that best described the signals coming from the two regions of interest is determined. The MAR methodology is essential for the DTF, as the DTF is built directly from the MAR coefficients. The autoregressive coefficients can be used to construct a bounded, normalised measure (the DTF) that provides information on the effective direction of coupling.

The DTF has two potential advantages over spectral phase estimates. First, it does not assume unidirectional flow — an assumption that can potentially lead to erroneous physiological conclusions (Cassidy and Brown, 2003). On the other hand the DTF is relatively insensitive when phase/temporal differences between signals are small (Cassidy and Brown, 2003). There is no reason to think this is the case in the coupling between the LFP in the PPN area and EEG, given the indirect connectivity (see Discussion). Second, the estimation of temporal differences from phase spectra is best performed through linear regression analysis of phase over periods of significant coherence (Mima and Hallett, 1999; Grosse et al., 2002). This, in turn, requires peaks in coherence that are reasonably broad, to allow for several phase estimates. This was not the case with the present data set.

However, a general concern in all DTF analyses is whether spurious asymmetries of information flow can be generated through a poor signal to noise ratio (SNR) in one or more of the signals under consideration. This issue has been evaluated with respect to EEG where it has been noted that estimates are reasonable provided that SNRs ≥ 3 and ≥ 4800 data samples are available (Astolfi et al., 2005). Our data sets far exceeded this sample limit and the SNR of LFP signals likely exceeds that of EEG (Regan, 1989).

For computing the DTF we used the multivariate autoregressive modeling toolbox distributed as a part of SPM (http://www.fil.ion.ucl.ac.uk/spm, in the subdirectory toolbox/spectral). This relies on a Bayesian estimation algorithm described by Penny and Roberts (2002). Before estimating the DTF, recordings were low-pass-filtered at 30 Hz (to avoid modeling line noise) and, resampled at 60 Hz and divided into trials of 3 s. A MAR model of order 5 (the optimal order according to Bayesian model comparison) was fitted to the data. In total, we analyzed 69 ± 10 trials in the ON state. An identical number of shift predictors were generated by analyzing the same dataset with one of the signals shifted by one trial. The DTF and shift predictor values for each direction were averaged across the 7–11 Hz band for each side. We performed Friedman's related sample test to assess the differences between DTF and shift predictor for each direction and post hoc Wilcoxon matched-pairs tests to confirm relevant differences.

Power was expressed in arbitrary units (a.u.). All statistical analyses were conducted using SPSS v12 (SPSS Inc. Chicago, IL, USA). Differences were considered statistically significant at $p < 0.05$. Results are presented as medians, where data were not normally distributed.

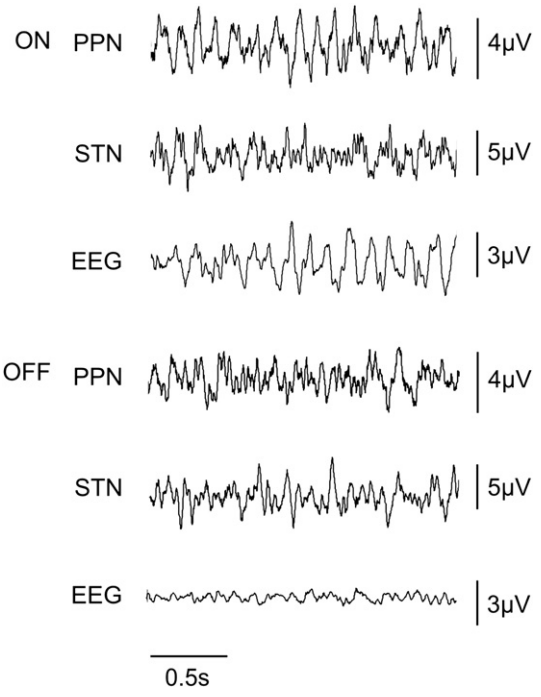

Fig. 2. Examples of the PPN area and STN LFP and EEG data taken from the right side of case 2 ON levodopa and after overnight withdrawal of medication.

Analysis of movement task recordings

Data were interpolated to a common sampling rate of 1 kHz. Using Spike 2 software, the onset of movements was detected from joystick position and marked. Movements were only marked when they were not preceded or followed by another movement within a period of 9 s. The mean number of movements marked was 14 (range, 9–18) and the mean duration of analyzed recordings was 330 s±19 s.

The first analysis step was to calculate the event-related spectral power for those contact pairs that afforded the highest mean power in the alpha band at rest (Table 1) for a period of 4 s before to 4 s after movement onset. Spectra were estimated using the discrete Fourier transform as outlined in Halliday et al. (1995). Records were divided into a number of sections of equal duration with a block size of 1024 data points, affording a frequency resolution of ~1 Hz. Spectra were estimated by averaging across sections and a Hanning window filter was used. Blocks were shifted by 10 ms and averaged again until the whole record length had been analyzed (using a modified Spike 2 script). Movement-related activity was estimated separately for left and right hand joystick movements in both the ON and OFF states for each implanted side (2 movement sides × 6 implanted sides) and defined as the percentage power change in relation to a pre-movement baseline (−4 s to −3.5 s) period. For visualization purposes, matrices of event-related percentage power changes were thresholded so that power values within the 99% confidence limits of the averaged baseline power were set to 100% (i.e. defined as no change). For quantitative analysis, we determined the frequency with the most pronounced mean event-related synchronization (ERS) between 3.5 s before to 4 s after movement onset over 6–12 Hz for each side from each patient, in accordance with the frequency distribution of the ERS in matrices of event-related power change of each patient.

Results

PPN area alpha band power and reactivity

Raw data showed a prominent 7–11 Hz activity in the LFP from the PPN area but only after treatment with levodopa (8 and 7 sides studied ON and OFF, respectively; Figs. 2 and 3A). Power between 7–11 Hz was significantly higher in the ON (median=0.14 a.u.) than in the OFF state (median=0.078 a.u.; $z=2.36$, $p=0.018$, Wilcoxon test; Fig. 3B). For each DBS electrode, alpha power showed a well-defined peak at one contact pair in the ON state. This peak was arbitrarily distributed between contact pairs (see Table 1) with a mean gradient of alpha power at the remaining contact pairs of 45±16%. This is consistent with a fairly local origin, and similar to the decrement previously reported across contacts in the STN (Kuhn et al., 2006). However, we found no evidence of polarity reversal in the alpha band across the contact pairs. There was no difference in power in the 7–11 Hz band in the EEG between the two drug states.

Grand averages of event-related power changes demonstrated a significant alpha ERS which started about 3 s prior to movement and persisted for more than 2 s thereafter in the ON but not in the OFF state (Figs. 4A, B). Time-evolving grand averages of the most reactive frequencies over the 6–12 Hz band (mean most reactive frequencies: ON state, 8.4±0.7 Hz; OFF state, 8.2±0.6 Hz) showed that the alpha ERS in the ON state was higher compared to the reactivity over the same band in the OFF state (Fig. 4C). Time-evolving Wilcoxon tests confirmed that this difference was significant prior to movement ($p<0.05$, Fig. 4D).

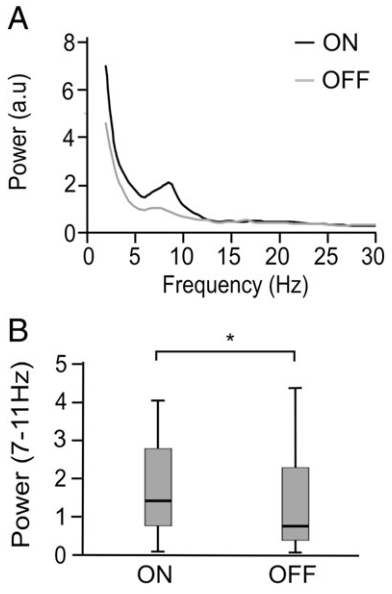

Fig. 3. Group medians of PPN area LFP spectral power ON (black lines) and OFF (grey lines) medication and [B] corresponding boxes of 7–11 Hz power of PPN area LFP ($n=7$ sides). The boxes show the median (marked by a horizontal line), the inter-quartile range, and the extreme values of power in both drug states. * $p=0.018$.

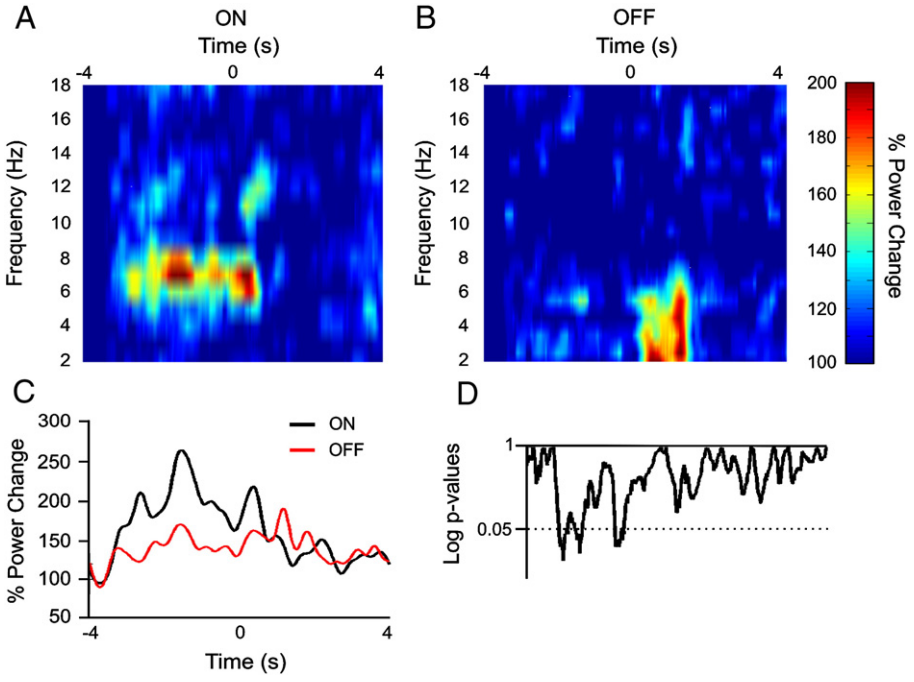

Fig. 4. Movement-related spectral power change in the ON (A) and OFF (B) states. Averaged color coded time-evolving power relative to baseline period (4 to 3.5 s prior to movement). For visualization purposes, the matrices were thresholded at 99% CL of the averaged baseline power. (C) Grand averages of time-evolving mean most reactive frequencies 6–12 Hz movement-related changes ON (black line) and OFF (red line) levodopa. (D) Time-evolving significance of the difference in percentage power change in the most reactive frequencies over the 6–12 Hz band between ON state and OFF state. Horizontal interrupted line is $p=0.05$ and y-axis is logged. Alpha reactivity is episodically significantly higher in the ON than in the OFF state.

Functional connectivity of PPN area alpha activity

The 7–11 Hz activity in the PPN area LFP was coherent with EEG, but only in the ON drug state (6 sides studied ON and OFF levodopa with EEG; Fig. 5A). Accordingly, coherence in the 7–11 Hz band between the PPN area LFP and EEG was higher ON (median=0.022) than OFF medication (median=0.008; $z=2.2$, $p=0.028$, Wilcoxon test; Fig. 5B).

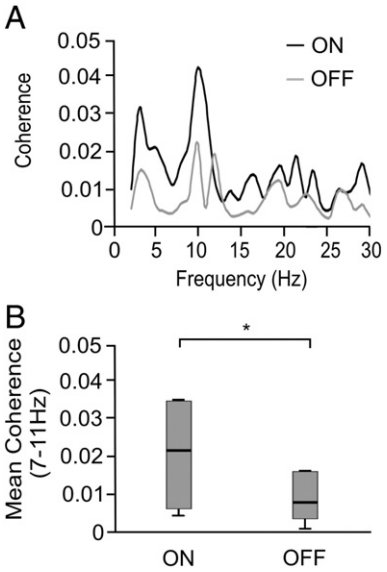

Fig. 5. Bivariate coherence estimates. [A] Group medians ($n=6$ sides) of coherence between PPN area LFP–EEG and [B] corresponding box plots of 7–11 Hz coherence ($n=6$ sides). The boxes show the median (marked by a horizontal line), the inter-quartile range, and the extreme values of coherence in both drug states. * $p=0.028$.

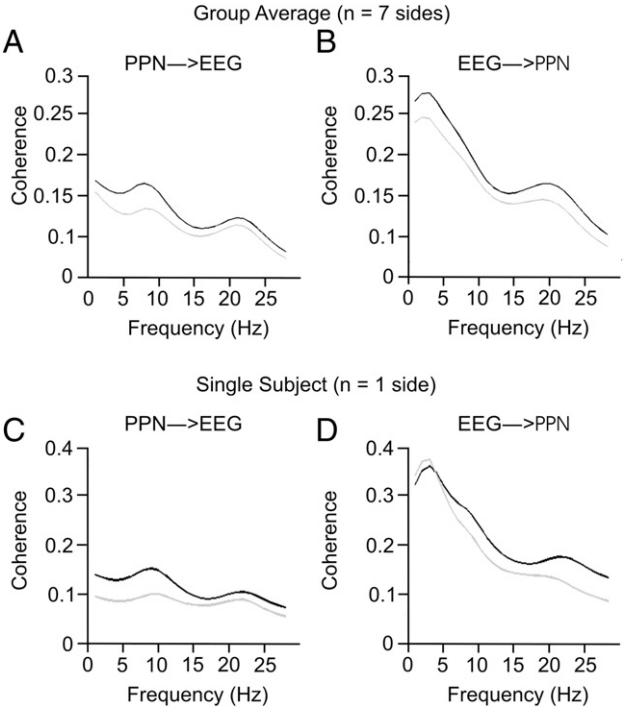

Fig. 6. [A–B] Group averages ($n=7$ sides) of directed coherence in the ON drug state. Plots demonstrate the mean directed coherence of all subjects (black line) and the corresponding shift predictor (grey line) in each direction. [C–D] Examples of directed coherence from the left hemisphere of case 1.

The directed coherence between cortex and the PPN area was estimated to characterize bidirectional interactions between these levels. Friedman tests demonstrated significant differences between DTF and shift predictors from the PPN area to cortex and vice versa (7 sides studied ON levodopa with EEG; $\chi^2=8.65$, $p=0.034$). Post hoc Wilcoxon tests confirmed that interactions between activities in the PPN area and cortex were significant in the ON medication state both from the PPN area to cortex (medians: 0.15 vs. 0.13; $z=2.2$, $p=0.028$; Fig. 6A) and from cortex to the PPN area (medians: 0.21 vs. 0.16; $z=2.37$, $p=0.018$; Fig. 6B). An example of the DTF between these sites is shown for case 1 in Fig. 6C, D. These findings suggest that there is a bidirectional flow of information between the PPN area and cortex in the 7–11 Hz range.

Discussion

In this series of patients with Parkinson's disease we found that levodopa promoted 7–11 Hz oscillatory synchronization in the region of PPN, in accordance with our previous case report (Androulidakis et al., 2008). Moreover, we showed that this oscillatory activity in the PPN area was coherent with similar activity in the cortical EEG, but only after treatment with levodopa. Estimation of the directed coherence revealed that this coupling between the PPN area and cortex was bidirectional, perhaps involving connections with the basal ganglia and thalamus (Pahapill and Lozano, 2000; Mena-Segovia et al., 2004; Mena-Segovia et al., 2005). The data are broadly in keeping with the hypothesis that prominent synchronization at low frequencies may have a physiological role in PPN (Androulidakis et al., 2008) and in the communication between PPN and cortex.

However, before considering the significance of these findings in greater detail it would be circumspect to describe the limitations of our data set. First, there is, without post-mortem histology, no way of currently confirming the precise structure or structures targeted in this series. Accordingly, we have used the conservative term PPN area to describe our target, thereby acknowledging the debate about the precise targeting of PPN (Mazzone et al., 2005, 2007; Stefani et al., 2007; Yelnik, 2007; Zrinzo et al., 2007) and the difficulty in transcribing the anatomical details of this region to the human when, even in animal studies, the extent of the PPN remains unclear (Mena-Segovia et al., 2005). Nevertheless, we would stress that the therapeutic effects of stimulation of the target selected here are so far indistinguishable from those of other reports of PPN stimulation in Parkinson's disease (Plaha and Gill, 2005; Lim et al., 2007), and the central finding of increased spectral 7–11 Hz power in the PPN region upon treatment with levodopa has been previously reported in a single patient implanted in PPN, where surgery was performed by another group in Bristol (Androulidakis et al., 2008). A second consideration is the extent to which the present findings might be representative of Parkinson's disease. Patients were selected for DBS in the PPN area on the basis of gait freezing that was unresponsive to medication and/or postural instability (Stefani et al., 2007), —symptoms that tend to mark advanced PD and are not indications for more conventional STN DBS in isolation. Accordingly, the present findings may be representative of only a subset of parkinsonian patients. A further limitation of the present data is the limited sampling of the EEG, dictated by surgical constraints. We could only record over FPz. As such we elected to use a monopolar signal so that our EEG signal was as representative of distributed cortical activity as possible. Finally, the small number of patients ($n=6$) reported in this study should be stressed.

With the above provisos in mind, what might be the relevance of the findings presented here? The appearance of oscillatory electric fields over 7–11 Hz after levodopa may predominantly reflect synchronized oscillatory input to the PPN area, as LFPs tend to be dominated by such inputs (Boraud et al., 2005). This synchronized oscillatory input following dopaminergic stimulation may potentially be exerted via the major afferents to the PPN from the basal ganglia output nuclei, GPi and substantia nigra pars reticulata (Mena-Segovia and Giordano, 2003; Mena-Segovia et al., 2005). In PD this would mean a reduction in the inhibitory input to PPN from the latter nuclei.

There is reasonable evidence to suggest that oscillatory electric fields, such as the LFP in the PPN area following treatment with levodopa, may influence the emergent properties of neuronal networks both locally (Deans et al., 2007) and at subsequent projection targets. This seems to be the case with respect to pathological beta oscillations in the STN area which are locked to population activities at projection targets (Brown et al., 2001) and may even shape the firing probability of local neurons (Kuhn et al., 2005; Weinberger et al., 2006). Indeed, experiments in brain slices suggest that the influence of oscillatory fields increases as their frequency drops so that the lower frequency oscillations in the PPN area after dopaminergic therapy may potentially have even greater effects (Deans et al., 2007). The notion that the 7–11 Hz oscillations in the PPN area after dopaminergic therapy may be both physiological and influential is further supported by the effects of local DBS. In contrast to STN, where DBS is performed at high frequencies, stimulation of the PPN area at low frequencies results in symptomatic improvement in parkinsonian symptoms (Jenkinson et al., 2004; Mazzone et al., 2005; Plaha and Gill, 2005; Stefani et al., 2007). The increase in 7–11 Hz activity in the PPN region upon treatment with levodopa suggests that DBS at low frequency may be partly mimicking this spontaneous activity by direct driving of neural elements in the region of stimulation (Androulidakis et al., 2008). This, however, remains to be established.

The present data also provide clues as to the function of the subcortical oscillatory activity over 7–11 Hz. This activity was only significant after treatment with levodopa, and may therefore represent a more physiological type of activity. Moreover, it increased prior to self-paced movements. This increase was sustained for several seconds suggesting that it was more likely to be related to attentional processes than any parameterization of movement. Furthermore, the activity was coherent with oscillatory activity at the cerebral cortical level in the alpha band. Alpha oscillations are thought to play an important role in attentional processes, particularly when these tend to occur over the lower frequencies in the alpha range, as here (Klimesch, 1999; Palva and Palva, 2007). In particular, it has been suggested

that alpha activity may indicate that attention is actively suppressing cortical activity related to distracters as a part of the process of focusing attention on important targets (Ward, 2003). For example, alpha power increases with memory load in the Sternberg memory-scanning task, reflecting an increase in the need to suppress distraction (Jensen et al., 2002). Moreover, when attention is directed internally towards mental imagery, alpha power at attention-relevant scalp sites is greater than during externally directed, information-intake tasks, reflecting suppression of external input during the imagery task (Cooper et al., 2003). In the same study, alpha power increased with increasing external task load, reflecting the need to suppress competing information sources. Extrapolation of these data leads to the speculation that the PPN area may have a function in supporting the network subserving internal attention and characterized and perhaps underpinned by alpha oscillatory activity. The posited role of PPN in internal attention might also help explain why PPN DBS can ameliorate freezing, by improving the focusing of internal attention on the motor task (Okuma, 2006; Giladi and Hausdorff, 2006). The above schema would be consistent with the position of the PPN area as part of the reticular activating system (Pahapill and Lozano, 2000; Mena-Segovia et al., 2004, 2005).

In conclusion, levodopa strongly promotes 7–11 Hz oscillatory synchronization in the region of PPN and coupling of this activity with similar activity in the cortical EEG in patients with PD. The 7–11 Hz activity is further increased prior to self-paced movement and the coupling between the PPN area and cortex in the same band is bidirectional. These findings suggest that alpha oscillations in the PPN area may represent a physiological pattern of activity. The subcortical oscillations are coupled to cortical alpha activity and may possibly be allied to motor related attentional processes.

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