

Alpha oscillations in the pedunculo pontine nucleus correlate with gait performance in parkinsonism

Wesley Thevathasan,^{1,2} Alek Pogosyan,¹ Jonathan A. Hyam,³ Ned Jenkinson,³ Tom Foltynie,⁴ Patricia Limousin,⁴ Marko Bogdanovic,² Ludvic Zrinzo,⁴ Alexander L. Green,³ Tipu Z. Aziz³ and Peter Brown^{1,2}

1 Nuffield Departments of Clinical Neurosciences, University of Oxford OX3 9DU, UK

2 Department of Clinical Neurology, John Radcliffe Hospital, Oxford OX3 9DU, UK

3 Nuffield Department of Surgical Sciences, University of Oxford OX3 9DU, UK

4 Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, London WC1N 3BG, UK

Correspondence to: Peter Brown,
Department of Clinical Neurology
University of Oxford
Level 6, West Wing
John Radcliffe Hospital
Oxford OX3 9DU, UK
E-mail: peter.brown@clneuro.ox.ac.uk

The pedunculo pontine nucleus, a component of the reticular formation, is topographically organized in animal models and implicated in locomotor control. In Parkinson's disease, pedunculo pontine nucleus stimulation is an emerging treatment for gait freezing. Local field potentials recorded from pedunculo pontine nucleus electrodes in such patients have demonstrated oscillations in the alpha and beta frequency bands, reactive to self-paced movement. Whether these oscillations are topographically organized or relevant to locomotion is unknown. Here, we recorded local field potentials from the pedunculo pontine nucleus in parkinsonian patients during rest and unconstrained walking. Relative gait speed was assessed with trunk accelerometry. Peaks of alpha power were present at rest and during gait, when they correlated with gait speed. Gait freezing was associated with attenuation of alpha activity. Beta peaks were less consistently observed across rest and gait, and did not correlate with gait speed. Alpha power was maximal in the caudal pedunculo pontine nucleus region and beta power was maximal rostrally. These results indicate a topographic distribution of neuronal activity in the pedunculo pontine nucleus region and concur with animal data suggesting that the caudal subregion has particular relevance to gait. Alpha synchronization, proposed to suppress 'task irrelevant' distraction, has previously been demonstrated to correlate with performance of cognitive tasks. Here, we demonstrate a correlation between alpha oscillations and improved gait performance. The results raise the possibility that stimulation of caudal and rostral pedunculo pontine nucleus regions may differ in their clinical effects.

Keywords: Parkinson's disease; gait freezing; pedunculo pontine nucleus; deep brain stimulation; neuronal oscillations

Abbreviations: FzCz = frontal zero central zero; PPN = pedunculo pontine nucleus; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

The pedunculo-pontine nucleus (PPN) is a reticular collection of neurons, located at the junction of midbrain and pons (Jacobsohn, 1911; Olszewski and Baxter, 1954; Alam *et al.*, 2011). The PPN, at least in animal models, appears to be topographically organized, with γ -aminobutyric acid expressing neurons predominating rostrally and cholinergic and glutamatergic neurons caudally (Martinez-Gonzalez *et al.*, 2011). In Parkinson's disease, cholinergic PPN neurons degenerate and this cell loss has been associated with gait dysfunction (Hirsch *et al.*, 1987; Zweig *et al.*, 1989; Rinne *et al.*, 2008; Karachi *et al.*, 2010). PPN neurons in Parkinson's disease may also be disrupted through their reciprocal connectivity with the basal ganglia (Breit *et al.*, 2001; Mena-Segovia *et al.*, 2004). In patients with Parkinson's disease, deep brain stimulation of the PPN region at low frequencies is an emerging treatment for postural instability and gait freezing (Plaha and Gill, 2005; Ferraye *et al.*, 2009; Moro *et al.*, 2010; Thevathasan *et al.*, 2011a).

The control of locomotion likely involves coordination between spatially segregated nervous system regions in order to modulate the rhythmic activity produced by spinal central pattern generators (Grillner *et al.*, 2008). Synchronized oscillatory neuronal activity is proposed to bind together such neuronal assemblies and enhance information representation—whilst also suppressing task irrelevant or competing processes (Fries, 2005; Schoffelen *et al.*, 2005; Jensen and Mazaheri, 2010). Local field potential recordings from deep brain stimulation electrodes implanted in the PPN in parkinsonian patients have variably been reported to demonstrate alpha or beta band oscillations, reactive to self-paced movement (Androulidakis *et al.*, 2008a, b; Tsang *et al.*, 2010). Whether these different oscillatory patterns conform to any topographic distribution or are relevant to locomotion is unknown.

In this study, we assessed local field potentials from parkinsonian patients implanted with PPN electrodes and assessed the spatial pattern of oscillatory activity in the region and its relationship to the performance of gait.

Materials and methods

Subjects and clinical assessments

Seven patients with Parkinson's disease implanted with deep brain stimulation electrodes in the PPN region were assessed (Table 1). Following their initial implantation, electrodes were attached to special extension cables 'externalized' through the scalp to permit connection with recording equipment. Final implantation of deep brain stimulation hardware was therefore deferred for the period of 'externalization' (3–7 days). Eleven PPN electrodes were recorded from the seven patients. Patients were recruited from hospitals in Oxford and London, UK. Local ethics committee approval was obtained from both centres and participants gave written informed consent. Reaction time results from one of the patients have been reported previously (Thevathasan *et al.*, 2010, 2011b).

The indication for PPN stimulation was severe gait freezing and postural instability, persisting even 'ON medication' and either causing frequent falls or precluding walking. In Parkinson's disease, gait freezing and postural instability become more frequent and less responsive to medication with disease progression (Giladi *et al.*, 2001; Bloem *et al.*, 2004). The overall prevalence of gait freezing and postural instability in Parkinson's disease is ~50% (Macht *et al.*, 2007). However, severe medication resistant gait freezing and postural instability as the predominant issue is unusual in Parkinson's disease and raises the question of atypical pathologies (Factor, 2008; Jankovic, 2008). As there is no definitive test in life, we stress that the diagnosis of Parkinson's disease in our series is presumptive.

Preoperative assessments included the motor subsection (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS; score/108). OFF medication assessments occurred after overnight withdrawal (> 12 h) of dopaminergic therapy. UPDRS was segmented into items 27–30 (IT27/30, score/16) assessing posture, gait and balance and residual items 1–26 (R-UPDRS, score/92) assessing bradykinesia, rigidity and tremor. Patients treated in Oxford also prospectively completed the Gait and Falls Questionnaire (score/64) which assesses Parkinsonian gait disturbance including gait freezing, festination and falls (Giladi *et al.*, 2000). The Freezing of Gait Questionnaire (score/24) and Falls Questionnaire (score/4) are components of the Gait and Falls questionnaire (Giladi *et al.*, 2000, 2009). For all motor scales, higher scores indicate worse function. The London patient was assessed with

Table 1 Clinical details of the study participants

Patient	Age (years)	Parkinson's disease duration (years)	UPDRS III OFF/ON medication (score/108)	R-UPDRS OFF/ON medication (score/92)	IT27-30 OFF/ON medication (score/16)	GFQ (score/64)	FOGQ (score/24)	FallsQ (score/4)	L-dopa dose equivalent (mg/day)	Supportive for UK Brain Bank criteria ^a
1	55	14	35/24	28/18	7/6	55	22	4	1600	A, P
2	76	16	34/25	25/16	9/9	38	20	1	600	D, A, P
3	55	25	33/22	27/17	6/5	36	15	3	300	D, A, P
4	68	9	40/26	29/18	11/8	49	24	2	1650	A, P
5	70	20	35/22	29/17	6/5	36	13	3	900	D, A, T, P
6	71	20	37/19	27/14	10/5	NA	NA	2	1450	D, A, T, P
7	54	20	53/19	47/14	6/5	38	14	4	800	D, A, T, P

All patients were operated in Oxford except Patient 6 (London). All patients were male. FOGQ = Freezing of Gait Questionnaire (score/24); Falls Q = Falls Questionnaire (score/4); GFQ = Gait and Falls questionnaire; NA = not assessed. For all motor scales, higher scores indicate worse function. A = asymmetry persistent; D = dyskinesias; P = progressive disease course; T = tremor at rest.

a Additional to disease duration and L-dopa response as documented elsewhere in the table.

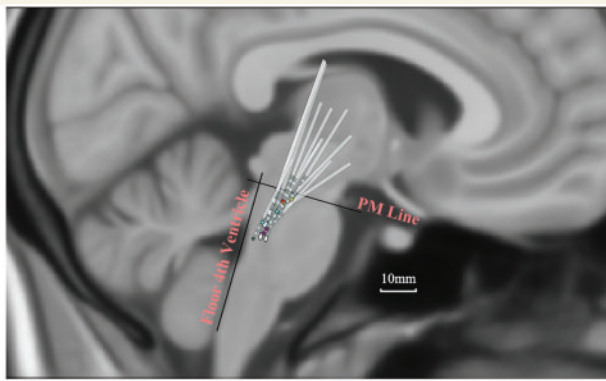


Figure 1 Localization of electrodes and contact locations represented in MNI space (sagittal view). The colouring of electrode tips identifies the electrodes of individual patients. PM = pontomesencephalic line connecting the pontomesencephalic junction to the caudal end of the inferior colliculi.

UPDRS (part II) items assessing gait, freezing and falls (combined score/16).

Techniques to target and implant electrodes in the PPN have been described previously (Pereira *et al.*, 2008; Zrinzo *et al.*, 2008; Foltynie and Hariz, 2010). In two early studies of stimulation in this vicinity, electrodes appeared to be placed lateral to the lemniscal system—in the peripeduncular nucleus rather than the PPN (Mazzone *et al.*, 2005; Stefani *et al.*, 2007; Yelnik, 2007; Zrinzo and Hariz, 2007; Zrinzo *et al.*, 2007). In the current study, the PPN was targeted medial to the lemniscal system and lateral to the superior cerebellar peduncle and its decussation. Electrodes (Medtronic) were configured with four active contacts each spanning 1.5 mm. Electrodes in six patients were model 3389 (0.5 mm spacing between contacts) and in one patient were model 3387 (1.5 mm spacing between contacts). Contact coordinates were assessed on postoperative MRI or postoperative CT fused with preoperative MRI and transformed onto Montreal Neurological Institute (MNI) space using the fMRIB Software Library (Smith *et al.*, 2004). Coordinates were calculated in millimetres from midline (laterality), ventrodorsal distance (*d*) from floor of the fourth ventricle and rostrocaudal distance (*h*) from a pontomesencephalic line connecting the pontomesencephalic junction to the caudal end of the inferior colliculi, as described previously (Ferraye *et al.*, 2009). Electrode locations are summarized in Fig. 1A.

Experiments and recordings

Experiments took place 2–6 days after electrode implantation. Assessments were performed ‘OFF medication’, after overnight withdrawal of dopaminergic medication, to limit variance from fluctuating dopaminergic state and to maximize gait disturbance.

There were two conditions: rest and gait. For rest recordings, patients sat comfortably with eyes open for 2–3 min. For gait recordings, patients walked at their preferred speed along an unobstructed path 10 m long, 10–30 times (depending on speed and fatigue).

Local field potentials were recorded in bipolar configuration from consecutive contacts (01, 12 and 23) of each electrode (Fig. 2A). Local field potentials were band-pass filtered between 0.5 and 500 Hz. Single channel EEG was recorded from FzCz (frontal zero central zero). In Patients 1–6, a triaxial accelerometer (TMSI) was firmly

fixed with tape over the spinous processes at the upper thoracic level to record trunk acceleration. A portable battery powered amplifier (Porti amplifier, TMSI) was attached with a waist belt. Data were sampled at 2048 Hz and recorded on a laptop (Porti32 software) via a long fibre-optic cable.

Data analysis and parameters

Data were analysed in Spike 2 (Cambridge electronic design) using routines therein. Unless stated otherwise, all frequency spectral analyses employed non-overlapping blocks of 4 s duration that afforded a resolution of 0.25 Hz (fast Fourier transform, Hanning window). The mean (\pm SEM) duration of recordings at rest was 222 ± 38 s and for gait was 253 ± 68 s.

Gait assessment with trunk accelerometer

Three dimensional trunk accelerometry is a validated method to assess spatiotemporal parameters of gait in healthy subjects and patients with Parkinson’s disease (Dijkstra *et al.*, 2008; Lord *et al.*, 2008; Senden *et al.*, 2009). Acceleration in the anteroposterior plane is predicted by an inverted pendulum model (MacKinnon and Winter, 1993). During single support after mid stance, forward acceleration increases as the body falls forwards and downwards (Zijlstra, 2004). Acceleration peaks at the point of foot contact after which there is sharp deceleration and ultimately reversal of body motion to upwards and backwards along with contralateral foot elevation. Thus the biggest transients in anteroposterior trunk acceleration oscillate in time with stepping.

Gait speed can be reliably estimated from the amplitudes of anteroposterior acceleration related to stepping (Cappozzo, 1982; Moe-Nilssen, 1998; Zijlstra and Hof, 2003; Zijlstra, 2004). The predominant frequency of stepping (cadence) within 4 s blocks is identifiable as the peak in spectral power over 1–3 Hz, corresponding to the ‘locomotor frequency band’ (Ichinoseki-Sekine *et al.*, 2006). This frequency band captures the typical ranges of cadences reported during unconstrained walking in healthy and parkinsonian subjects (MacDougall and Moore, 2005; Sofuwa *et al.*, 2005; Mirelman *et al.*, 2011). Relative gait speed can be derived from the power of the spectral peaks indicating cadence, as gait speed has a quadratic relationship with amplitudes of anteroposterior acceleration (Moe-Nilssen, 1998). The estimation of relative gait speed was considered sufficient for our purposes as we sought correlations between this parameter and local field potential activity within subjects. Estimation of absolute gait speed requires further assumptions, such as leg length helping predict step length. Such accelerometer based methods have been validated in both healthy subjects and parkinsonian patients and are substantially more accurate than the threshold crossing algorithms employed by pedometers (Ichinoseki-Sekine *et al.*, 2006; Dijkstra *et al.*, 2008; Lord *et al.*, 2008; Speelman *et al.*, 2011).

In accordance with the above, relative gait speed was computed as follows. The accelerometer channel detecting acceleration in the anterior–posterior axis was selected for analysis. Periods marked during experiments as other than unconstrained walking (e.g. turning, standing) were spliced out. Cadence was identified for every non-overlapping 4 s block as the peak frequency in acceleration over 1–3 Hz. In each patient, depending on the variability of cadence, a span of 4–6 spectral bins (1.0–1.5 Hz) was identified to cover the predominant spectrum of cadences over all blocks. Power within this individualized frequency band computed for every 4 s block of walking yielded the relative gait speed.

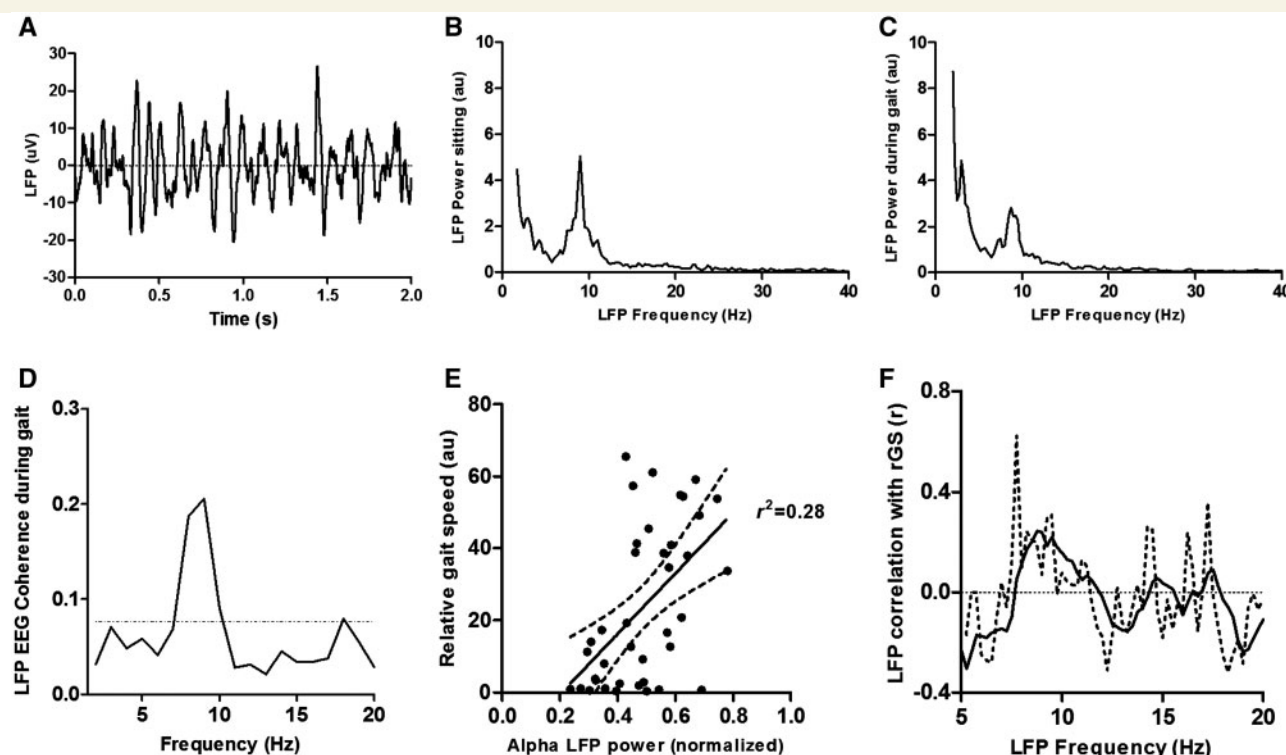


Figure 2 Example data from Patient 3, left PPN electrode at contact pair 01. (A) Raw local field potential (LFP) during rest. (B) Local field potential autospectrum averaged over the period (127 s) of rest. Note peak at 9 Hz ('peak rest local field potential'). (C) Autospectrum of local field potential averaged over the period of unconstrained walking. Note peak at 8 Hz ('peak gait local field potential'). (D) Spectra of coherence between the local field potential and EEG (FzCz) during the period of walking. Horizontal line is the 95% confidence limit. Note the peak in coherence at 8–9 Hz. (E) Peak alpha power (sum of normalized power over 6–10 Hz) correlation with relative gait speed (rGS). Linear regression line and its 95% confidence limit are shown. (F) Cross frequency local field potential (normalized) correlation with relative gait speed. Dotted line is the raw correlation and continuous line is the 6-point (backwards) moving average. Note the peak in correlation in the alpha band.

Local field potential analysis

Local field potentials during rest and gait

Local field potential frequency spectra from each bipolar contact pair (01, 12 and 23) were derived for the periods of sitting and walking (Fig. 2B and C). The frequency and power of spectral peaks was assessed. Peaks were identified as local elevations in power spanning at least five contiguous 0.25 Hz bins with a minimum rise of two and fall of three adjacent bins [the asymmetry in criteria necessary given the background ($1/f$) decrease of local field potential power with frequency, f]. Where several peaks occurred within a broader based power elevation, the peak frequency was defined as the midpoint of this activity. Spectral peaks were sought over 7–100 Hz and identified in the alpha (defined here as 7–12 Hz) and beta (13–30 Hz) bands. Where more than one discrete peak occurred within a given frequency band, the most prominent peak was selected for analyses. Power in each spectral peak was calculated as the sum of power around the centre of the peak, spanning 4 Hz for alpha and 2 Hz for beta (the differing ranges reflecting the relative sizes and skirt-widths of these peaks). For rest recordings, log power of local field potential peaks was used in analyses. To limit the effects of any movement artefact, local field potential power during walking was normalized (as was rest local field potential power when compared with walking local field potential power). Alpha power was expressed as per cent of total power over 5–40 Hz and beta power expressed as per cent of total power over

15–40 Hz. The more restricted range for beta aimed to exclude reciprocal effects from higher amplitude alpha activity, whereby the generally larger changes in the alpha band might have obscured changes in the beta band. This approach was considered reasonable as no direct comparison was made between frequency bands.

Localization of local field potential power

The centre of each bipolar recording site was calculated from the coordinates derived for electrode contacts (described above). For rest recordings, the mean un-normalized local field potential spectral log power in the alpha band could be assessed over 4-mm subregions spanning the entire rostrocaudal extent of recordings. For recordings during gait (including all beta band analyses, as fewer beta peaks necessitated collapsing data at rest and during gait), the smaller gradients afforded by normalizing local field potential power meant that power in spectral peaks was simply compared between sites below and above a point 2 mm below the pontomesencephalic line, used to define the 'caudal PPN' and 'rostral PPN' regions.

Coherence between local field potential and electroencephalography

Coherence was sought between local field potentials and single channel EEG at FzCz (Fig. 2D). This was estimated using non-overlapping data blocks of 1 s, affording 1 Hz resolution, using standard techniques (Grosse *et al.*, 2002). Peaks in coherence were sought at the

frequency of the local field potential spectral peaks, at the contact pairs expressing the highest power at these peaks. Coherence was considered relevant where there was significant coherence spanning at least two contiguous bins in a 4 or 2 Hz band corresponding to the local field potential spectral peak in the alpha and beta bands, respectively.

Correlation between local field potential and relative gait speed

Local field potential power spectra from each bipolar contact pair were derived from consecutive, non-overlapping 4 s blocks during walking. Cadence varied insufficiently to assess for correlations with local field potential. Correlations between the relative gait speed and local field potential were assessed as follows.

Spectral peak local field potential correlation with relative gait speed

Normalized local field potential power at spectral peaks was assessed (from the bipolar pair expressing the highest power in each electrode) for each 4 s block during walking and correlated with the relative gait speed from corresponding sections (Fig. 2E).

Across frequency local field potential correlation with relative gait speed

Normalized local field potential power across different frequencies was correlated with relative gait speed yielding correlation spectra. Thereby, the frequency of local field potential that correlated most strongly with the gait index could be identified (Fig. 2F). We could therefore test the assumption that correlations were strongest at the frequency of the peak in local field potential power spectra.

Local field potential power averaged to gait freezing episodes

In Patient 6, discrete freezing episodes were sufficient in number to allow local field potential activity to be averaged to the onset of gait freezing. Freezing onset was determined by thresholding the root mean square of the anteroposterior accelerometer signal over 1.0–3.0 Hz. Local field potential power was derived from non-overlapping data blocks of 1 s, affording a 1 Hz spectral resolution. Power at the alpha peak and flanking two spectral bins at the contact pair expressing highest alpha power was aligned to freezing onset according to change-point analysis, using commercial software (Change-Point Analyser 2.0 shareware program, Taylor Enterprises Inc., <http://www.variation.com>) and techniques described previously (Cassidy *et al.*, 2002). Change-point analysis iteratively uses time varying cumulative sum charts and bootstrapping to detect changes in time series (Taylor, 2000). For this analysis, cumulative sum charts were determined by plotting the sequentially summed deviation of each spectrum from the average determined for the whole record (total of 11 s). Ten thousand bootstraps were performed and only changes with probabilities of >95% were highlighted.

Statistics

The Kolmogorov–Smirnov Test demonstrated that the distribution of normalized peak local field potential power and relative gait speed was not different from the normal. Normalized local field potential power in specific frequency bands was compared between conditions and/or recording sites using paired *t*-tests. Differences in normalized local field potential power across a range of frequencies were assessed with serial *t*-tests performed for each frequency. Correlations (Pearson's) were sought between peak local field potential frequencies across conditions

and between normalized local field potential power and relative gait speed. Level of significance was $P < 0.05$.

Results

Gait assessment

Following electrode implantation and without stimulation, all patients experienced a reduction in gait freezing, which persisted up to 6 weeks—a time course consistent with 'stun effect' (Koop *et al.*, 2006). Preoperatively, when 'OFF medication', every patient experienced frequent, long duration freezing. However, post-operatively when 'OFF medication' during experiments, freezing in five patients was infrequent and then typically brief (<3 s). In two patients (who were both implanted unilaterally), freezing had improved but remained clinically severe. In one of these patients (Patient 6) discrete freezing episodes were identifiable while in the other (Patient 2) freezing was almost continuous. Festination was not observed during experiments. The mean cadence (\pm SD) across patients for every 4 s block of walking was 1.81 Hz (\pm 0.28). Relative gait speed coefficients of variation ranged from 40 to 308% between patients, consistent with some degree of gait disturbance, despite the stun effect. Cadence was less variable, with coefficients of variation ranging from 6 to 21% between patients.

Local field potentials and their relationship to electroencephalography and gait

Spectral analysis during rest and gait

A discrete peak in the alpha band was present in all electrode recordings during rest and gait (Fig. 2B and C). A discrete peak in the beta band was observed in 6/11 electrodes (5/7 patients). Beta peaks occurred inconsistently across rest and gait, being present across both conditions in only two electrodes. Gamma band peaks were not identified in any recordings, at rest or during gait.

Alpha band activity

Activity during rest and gait

The frequencies of alpha peaks during rest (mean 8.2 Hz, range 7–10 Hz) and gait (mean 8.4 Hz, range 7–10 Hz) correlated strongly ($r = 0.90$, $P < 0.001$) across patients (Figs 2A–C and 3A), suggesting that the peaks were homologous across the two states. Alpha peaks were relatively focal to one bipolar contact pair. Normalized peak alpha (\pm SEM) power dropped in the remaining two contact pairs by 15.6% (\pm 2.5) at rest and 14.2% (\pm 2.8) during gait. Even so, these values likely underestimate the gradient across contacts due to the normalization procedure. At rest, where there was no potential contamination by movement artefact, the un-normalized peak alpha (\pm SEM) power dropped in the remaining two contact pairs by 42.7% (\pm 9.0). In all but one electrode, the normalized alpha power during rest and gait was maximal at the same (7/11 electrodes) or an adjacent

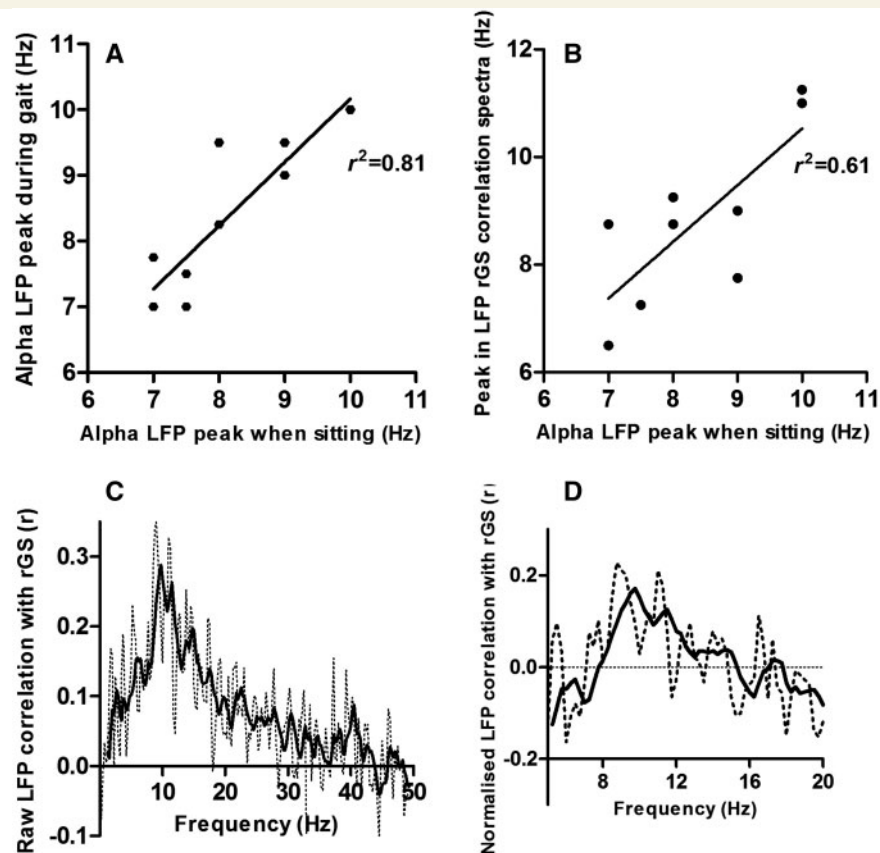


Figure 3 (A) Relationship between the peak rest local field potential (LFP) and peak gait local field potential. The strong correlation ($r = 0.90$, $P < 0.001$) suggests that the two local field potential peaks may be related. (B) Relationship between the peak rest local field potential and the frequency of the peak in the local field potential–relative gait speed (rGS) correlation spectra. The strong correlation ($r = 0.779$, $P = 0.013$) suggests that the peak rest local field potential may be relevant to the performance of gait. (C) Group average un-normalized local field potential and relative gait speed correlation spectra demonstrating a peak in correlation in the alpha band. Dotted line is the average correlation and continuous line is the 6-point (backwards) moving-average. (D) Group averaged normalized (across 5–40 Hz) local field potential and relative gait speed correlation spectra demonstrating persistence of the peak in correlation in the alpha band. Dotted line is the average correlation and continuous line is the 6-point (backwards) moving-average. Correlations were Fisher transformed prior to averaging in C and D.

(3/11 electrodes) contact pair. Normalized peak alpha power did not significantly differ between rest and gait.

Localization

Normalized alpha peak power during gait was significantly greater at caudal (deeper than 2 mm below the pontomesencephalic junction) compared with rostral recording sites [$t(31) = 4.183$, $P < 0.001$; Fig. 4A]. During rest, normalized alpha peak power was also significantly greater in caudal compared with rostral recording sites [$t(31) = 3.359$, $P < 0.001$].

For rest recordings, which did not require normalization, we were able to follow un-normalized log alpha peak power across recording depth (Fig. 4B). The resting un-normalized log alpha peak power was divided according to the depth of each recording site into subregions spanning 4 mm along a rostrocaudal axis. An ANOVA revealed a significant difference in log alpha peak power across these subregions [$F(4,28) = 7.873$, $P < 0.001$] (Fig. 4B). Resting un-normalized log alpha peak power was maximal in the caudal PPN subregion between 2 and 6 mm below the pontomesencephalic junction, falling significantly at rostral

subregions [−2 to −6 mm versus −2 to +2 mm, $t(10) = 3.177$, $P = 0.010$ and −2 to −6 mm versus +2 to +6 mm $t(8) = 4.793$, $P = 0.003$] and caudal subregions [−2 to −6 mm versus −6 to −10 mm, $t(14) = 2.845$, $P = 0.013$ and −2 to −6 mm versus −10 to −14 mm $t(11) = 2.667$, $P = 0.022$]. These subregions along the rostrocaudal axis are represented in Fig. 4C in standard MNI space. For Patient 3's left electrode (used as the individual example for local field potentials in Fig. 2) the highest resting peak alpha power was at 2.5 and 4.2 mm below the pontomesencephalic line—reflecting findings from the grouped analysis. For this patient, to give an example of the anatomy of the region expressing highest alpha power, axial MRI slices across this and flanking regions are displayed in the Supplementary material.

Coherence with EEG

In 7/11 electrodes, significant local field potential EEG coherence spanning at least two consecutive 1 Hz bins was observed within the alpha peak range during rest and/or walking (Fig 2D).

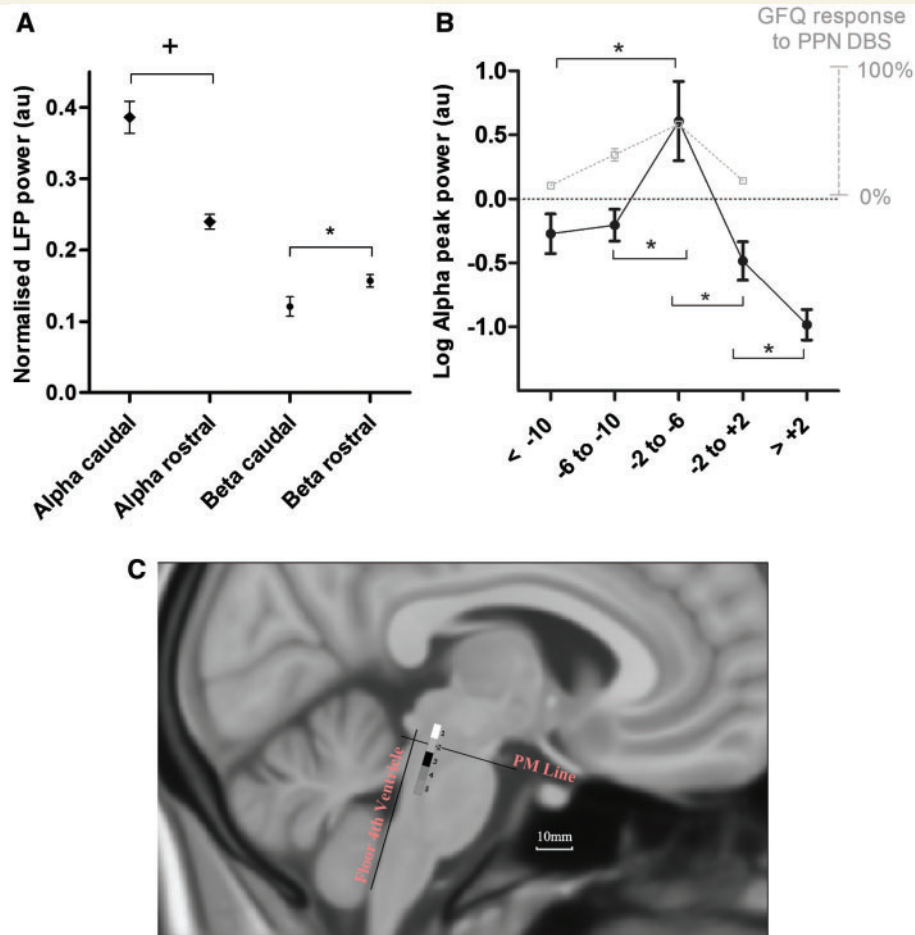


Figure 4 (A) Normalized power (mean \pm SEM) of alpha peaks during gait and beta peaks during rest or gait grouped according to caudal (deeper than 2 mm below the pontomesencephalic junction) or rostral recording site. Alpha peak power was greater caudally and beta power was greater rostrally. (B) Log alpha peak power at rest (mean \pm SEM) divided according to recording site depth into 4-mm subregions (denoted on the x-axis in mm relative to the pontomesencephalic junction). Log alpha peak power is maximal in the -2 to -6 mm region, falling significantly at surrounding sites. $*P < 0.05$. In grey has been superimposed a plot of the variation in per cent improvement in the Gait and Falls questionnaire (GFQ) postoperatively according to stimulation depth at most recent follow-up [depth selected blinded to the local field potential (LFP) data]. One data point was available from each subject (Table 2), with the exception of the patient from London, where the Gait and Falls questionnaire was not assessed. Three of these data points fell -6 to -10 mm below the pontomesencephalic junction, so that here the SEM is also displayed. (C) Representation of the rostrocaudal location of peak un-normalized alpha power at rest, which correlated strongly in frequency and location with peak alpha power that correlated with gait (but which required normalization to remove movement artefact thereby also diminishing power gradients). Relative log alpha power is represented in grey-scale intensity whereby black is highest and white lowest alpha power. Regions relative to the pontomesencephalic line are numbered as follows: 1, $+2$ to $+6$ mm; 2, -2 to $+2$ mm; 3, -6 to -2 mm; 4, -10 to -6 mm; and 5, -14 to -10 mm. Alpha power was maximal at location 3 (-6 to -2 mm below the pontomesencephalic line). Beta power was highest in regions 1 and 2 combined. Note: no inference is made regarding location in ventrodorsal or mediolateral planes. DBS = deep brain stimulation; GFQ = Gait and Falls questionnaire; LFP = local field potential; PM = pontomesencephalic line connecting the pontomesencephalic junction to the caudal end of the inferior colliculi.

Relationship with relative gait speed

In eight of nine electrodes where local field potential and trunk acceleration were simultaneously recorded, normalized peak alpha power correlated significantly with the relative gait speed. In these electrodes, the mean correlation was $r = 0.433$, $P < 0.01$ (see Fig. 2E for an example from a single electrode). Local field potential relative gait speed correlation spectra in all electrodes revealed that the correlation peaked in the alpha band (see Fig. 2F for an example from a single electrode). The frequency of this peak

correlated strongly with the peak local field potential during gait ($r = 0.782$, $P = 0.013$) and peak local field potential at rest ($r = 0.779$, $P = 0.013$; Fig. 3B). When averaged across recordings, spectra of the Fisher transformed correlations between local field potential power and relative gait speed demonstrated a discrete positive peak in correlation at 7–10 Hz, regardless of whether local field potential power was raw (Fig. 3C) or normalized (Fig. 3D). Note that normalization inevitably induced a negative correlation at frequencies below 7 Hz.

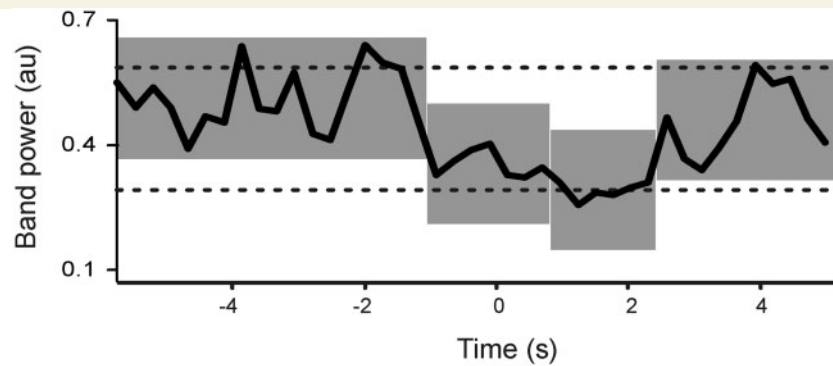


Figure 5 Change-point analysis of the time series of mean local field potential power over 7–9 Hz averaged to onset (0 s) of freezing episodes ($n = 24$) in Case 6. Horizontal dotted lines are the 95% confidence limit of the whole record and the grey blocks represent stable periods between changes in power as defined by change-point analysis. There is a significant drop in 7–9 Hz power ~ 1 s before the onset of freezing, and 7–9 Hz activity continues to be attenuated for just over 2 s thereafter.

Averaged to gait freezing episodes

Patient 6 had 24 discrete freezing episodes identifiable during recordings and a local field potential alpha peak during gait at 8 Hz. Local field potential power over 7–9 Hz averaged to the onset of the freezing episodes is represented in Fig. 5. There is a significant associated attenuation in alpha power, which begins around 1 s prior to the onset of freezing and continues for over 2 s thereafter.

Beta band activity

Activity during rest or gait

Beta peaks (mean 21.1 Hz, range 17.3–28.5) were relatively focal to one bipolar contact pair, with normalized peak beta (\pm SEM) power dropping by 15.4 (± 2.4)% at the remaining two contact pairs of each electrode. At rest, the un-normalized peak beta (\pm SEM) power dropped in the remaining two contact pairs by 45.6 (± 11.1)%.

Localization

In the six electrodes demonstrating a beta peak (during rest or gait), normalized beta peak power was significantly greater in rostral (higher than 2 mm beneath the pontomesencephalic junction) than caudal contacts [$t(16) = -2.232$, $P = 0.040$; Fig. 4]. There were insufficient beta peaks at rest to compare un-normalized beta peak power with location.

Coherence with EEG

In only one of the six electrodes demonstrating a beta peak, was there significant coherence spanning at least two consecutive 1 Hz bins between the local field potential at beta peak frequency and FzCz.

Relationship with relative gait speed

Normalized beta peak power did not significantly correlate with relative gait speed. Similarly, spectra of correlations between normalized local field potential at each frequency and relative gait speed did not reveal discrete peaks in correlation at the frequencies corresponding to beta peaks.

Therapeutic impact of chronic stimulation on gait

Therapeutic outcomes from chronic PPN region stimulation are presented in Table 2. Pre- and postoperative Gait and Falls questionnaire scores were available in all six cases operated in Oxford, affording six estimates of therapeutic impact. Gait and Falls questionnaire scores in these six patients improved with PPN stimulation [mean 42.0–29.8, $t(5) = 4.425$, $P = 0.007$]. The location where stimulation was applied along the rostrocaudal axis was calculated relative to the pontomesencephalic line. Where stimulation was bilateral, stimulation depth was the mean from both sides. The overall improvement of Gait and Falls questionnaire scores with PPN stimulation was only moderate. However, closer examination within this small sample suggests a possible relationship between stimulation depth and percentage improvement in the Gait and Falls questionnaire with the best outcome being achieved when stimulation was applied at the level of maximal alpha activity (Fig. 4B). Thus, a relationship was sought between power in the alpha band where stimulation was applied and therapeutic outcomes. With monopolar stimulation, alpha power was taken as the mean power recorded from the two flanking bipolar pairs. A correlation between mean log alpha power at rest and per cent postoperative Gait and Falls questionnaire improvement confirmed a correspondence between these measures ($r = 0.85$, $P = 0.033$). The picture was similar if the per cent improvement (20%) in UPDRS II items scoring freezing, falls and gait was included from the London patient in whom these measures were used to assess outcome ($r = 0.81$, $P = 0.027$).

Discussion

In parkinsonian patients, we found alpha oscillations in a network involving the caudal subregion of the PPN and the cerebral cortex. Synchronization of PPN alpha activity in the caudal PPN region correlated with the performance of gait. Beta oscillations were found in the rostral PPN subregion but this activity did not correlate with gait.

Table 2 Pedunculopontine nucleus region stimulation and therapeutic outcomes

Patients	Rostrocaudal stimulation location (mm to PM line)	Stimulation settings (Hz/V/ μ s)		Preoperative GFQ (score/64)	Postoperative GFQ (score/64)	Improvement in GFQ (%)	Time post operation (months)
1	−7.65	Bilateral	35/3.5/60	55	38	30.9	2
2	−12.7	Unilateral	35/2.3/60	38	34	10.5	13
3 ^a	−5.5	Bilateral	30/2.5/60	36	15	58.3	9
4	−1.5	Bilateral	40/1.8/60	49	42	14.3	7
5	−8.9	Bilateral	35/2.2/60	36	28	22.2	2
6 ^b	+0.4	Unilateral	30/3.0/60	NA	NA	NA ^b	NA
7	−7.0	Bilateral	20/2.5/60	38	22	42.1	2

Where bilateral stimulation was applied, voltage reflects the mean of both sides.

a Stimulation remains under titration and cycled between off and on, with postoperative GFQ score the best result so far.

b Outcome in this patient was assessed with UPDRS II items scoring freezing, falls and gait with the combined score being 5/16 preoperatively and 4/16 postoperatively (on medication).

GFQ = Gait and Falls questionnaire; NA = not available; PM = pontomesencephalic.

Topographical distribution of oscillations

A rostrocaudal topographical organization of the PPN is supported by extensive data from animal research (Martinez-Gonzalez *et al.*, 2011). Rostral PPN neurons predominantly express γ -aminobutyric acid and are strongly interconnected with the basal ganglia including subthalamic nucleus and internal pallidum (Mena-Segovia *et al.*, 2004; Ros *et al.*, 2010; Martinez-Gonzalez *et al.*, 2011), which exhibit beta activity in untreated Parkinson's disease (Hammond *et al.*, 2007). Caudal PPN neurons express predominantly acetylcholine and glutamate (Martinez-Gonzalez *et al.*, 2011). Cholinergic neurons arborize widely, including to cortex and locomotor centres (Skinner *et al.*, 1990; Mena-Segovia *et al.*, 2008). It is therefore congruent that we found beta oscillations in the rostral PPN region and a distinct oscillatory activity in the caudal PPN region, alpha activity, coherent with cortex and associated with locomotion. This interpretation is also supported by the one previous study in which PPN local field potentials were assessed in parkinsonian patients according to recording site depth (Weinberger *et al.*, 2008). In that study, beta oscillations were recorded in an area corresponding to what is here defined as the rostral PPN region. In an example local field potential recording, a spectral peak can also be identified in the alpha band in what is defined here as the caudal PPN region (1–4 mm below the inferior colliculus). Of further interest, neurons considered by the authors as likely cholinergic (having long duration action potentials and low firing rates) were found predominantly in the caudal PPN region (Weinberger *et al.*, 2008). Such topography could explain why different centres have reported different dominant oscillatory patterns, in the alpha or beta frequency bands, from PPN recordings—as this would be determined by the depth of the implanted electrodes (Androulidakis *et al.*, 2008a, b; Weinberger *et al.*, 2008; Tsang *et al.*, 2010).

The origin of the focal alpha activity in the PPN region needs consideration. The distribution of electrode contacts in this study was broad—and this facilitated the relationship between oscillatory power and location to be recognized. Some contacts lie more

caudal than any described location of the PPN but these were not the ones expressing alpha at highest power across patients. Across patients, un-normalized peak alpha power at rest, which correlated strongly in frequency and location with alpha power during gait, was maximal between 2 mm and 6 mm beneath the pontomesencephalic junction. The spatial accuracy of this finding is limited by the bipolar nature of the local field potential recordings and the averaging of data across patients. However, with this limitation in mind, a key question is whether this region corresponds to the PPN. The PPN comprises a well-defined 'pars compacta' subregion but also a reticular 'pars dissipata' with indistinct boundaries (Olszewski and Baxter, 1954). The atlas of Olszewski and Baxter (1982) identifies the PPN based on cytoarchitectural methods. Later, cholinergic PPN neurons were identified in humans by immunohistochemical labelling of choline acetyltransferase (Mesulam *et al.*, 1989; Manaye *et al.*, 1999). Although these latter studies do not provide stereotactic coordinates, their relevance has been heightened by the involvement of cholinergic PPN neurons in gait and its dysfunction (Karachi *et al.*, 2010) and several observations are of localizing value. While cholinergic PPN neurons were clustered most densely in the pars compacta, the pars dissipata accounts for the greater proportion of cholinergic neurons (Manaye *et al.*, 1999). Cholinergic PPN neurons span at least 7 mm in the rostrocaudal plane being at highest density 2.5 mm under the rostral pole (as defined by choline acetyltransferase staining, so potentially missing any rostral component not expressing choline acetyltransferase; Manaye *et al.*, 1999). Cholinergic PPN neurons were noted to lie where the 'superior cerebellar peduncle ascends towards the dorsolateral pons towards its decussation' with the pars compacta located at the level of the decussation (Mesulam *et al.*, 1989; Manaye *et al.*, 1999). Identifying these anatomical landmarks on the axial images of Patient 3 suggests that the levels 2–4 mm below the pontomesencephalic line would therefore correspond to the caudal PPN region. Other gait related entities also exist in the PPN region including the cuneiform and subcuneiform nuclei, which together with the PPN comprise the mesencephalic locomotor region (Alam *et al.*, 2011). Both the PPN and cuneiform nucleus are activated during fast imagined gait in functional MRI studies in healthy

subjects (Karachi *et al.*, 2010). Microelectrode recordings have suggested that neurons that modulate firing in response to imagined gait actually tend to be located in the subcuneiform region dorsal to the PPN (Piallat *et al.*, 2009). However, boundaries between these various nuclei are indistinct—potentially confounding precise determination of the source of neuronal recordings and of the structures responsible for clinical effects of stimulation in this region. On the other hand neurons of the PPN, but not the cuneiform or subcuneiform, are reported to degenerate in association with falls in Parkinson's disease (Karachi *et al.*, 2010). Furthermore, cytoarchitectural atlases suggest that the cuneiform and subcuneiform nuclei do not extend as caudally as the zone where we recorded maximal alpha band activity (Olszewski and Baxter, 1982).

The distribution of PPN oscillatory activity concurs with previous work in Parkinson's disease suggesting that alpha and beta oscillatory networks are segregated (Litvak *et al.*, 2010). The functional nature of alpha and beta oscillations in Parkinson's disease also appears distinct. Beta band activity is pathologically increased in Parkinson's disease, is suppressed by L-dopa and high-frequency subthalamic stimulation and correlates with deficits of bradykinesia and rigidity (Silberstein *et al.*, 2005; Kuhn *et al.*, 2006; Eusebio *et al.*, 2010). Alpha power in the PPN tends to increase with L-dopa, suggesting that it could be pathologically attenuated in Parkinson's disease (Androulidakis *et al.*, 2008a, b). It now also appears that attenuation of PPN alpha activity is associated with gait freezing whilst increases in PPN alpha power in Parkinson's disease correlated with improved gait.

Pedunculopontine nucleus alpha oscillations and locomotor function

A potential confound needs consideration; that the correlation between alpha power and gait speed could be due to movement artefact. Several factors militate against this. First, our local field potential recordings were bipolar, so a signal common across contacts should have been subtracted out. Second, the relative gait speed correlated maximally with alpha oscillations (7–10 Hz), which differed in frequency from the accelerometer frequencies used to derive gait speed (1–3 Hz). Third, correlation with the relative gait speed was relatively specific to alpha local field potential activity, evidenced by the peak in correlation spectra at alpha frequencies and the lack of any correlation with beta power. Fourth, correlations were present even when local field potential power was normalized to broad band activity, which effectively eliminated any common artefact from movement.

An important qualification is that the correlation between gait speed and alpha power does not necessarily imply causation and the relationship could be epiphenomenal. For example, alpha power may be permissive for higher gait speeds or reactive to it. However, correlations were found within a brain area that is functionally relevant to gait disturbance, as evidenced by the potential for improvement upon PPN stimulation. Furthermore, the positive nature of the correlation between alpha synchronization and increasing gait speed, concurs with the synchronization of alpha power observed with L-dopa (Androulidakis *et al.*, 2008a, b),

which also tends to improve gait. Yet, even if PPN alpha oscillations are mechanistically important in gait disturbance, the relationship does not appear obligatory or exclusive. The mean correlation was 0.43, so that fluctuations in alpha power only predicted ~20% ($r^2 = 0.19$) of the variance in relative gait speed. A further question is whether this alpha activity also relates specifically to gait freezing. Due to the reduction in freezing post-operatively due to a possible stun effect, we could only compare freezing episodes with alpha power in a single patient, who was implanted unilaterally. This demonstrated an attenuation of alpha activity related to the onset of freezing. This suggests that higher gait speeds could have, at least partly, resulted from relief of freezing related deficits even if discrete freezing episodes did not frequently occur. For example, patients with gait freezing are reported to have continuous background deficits in gait, including reduced gait velocity, step length and increased spatiotemporal variability (Hausdorff *et al.*, 2003b; Chee *et al.*, 2009; Snijders *et al.*, 2011). It is notable that attenuation of alpha local field potential power preceded freezing onset. However, this latter finding should be interpreted cautiously given the limited accuracy in determining when exactly freezing begins.

Thus, a particular limitation of the current study was the limited characterization of gait performance in terms of relative gait speed and the analysis of freezing in only one patient. Gait dysfunction in Parkinson's disease is complex, with varying involvement of features such as gait initiation, turning, postural instability and gait velocity (Bloem, 1992; Morris *et al.*, 1994; Hausdorff *et al.*, 2003b; Sofuwa *et al.*, 2005). The failure to capture these features might also help explain why fluctuations in alpha power only predicted ~20% of the variance in relative gait speed.

By what mechanism could PPN alpha activity relate to gait performance, as indexed by relative gait speed? Gait speed reduces in healthy subjects, elderly fallers and in Parkinson's disease during the performance of a second, unrelated task ('dual tasking') (Hausdorff *et al.*, 2003a; Springer *et al.*, 2006; Lamothe *et al.*, 2011). In elderly subjects, an inability to 'walk whilst talking' predicts falls (Lundin-Olsson *et al.*, 1997). Such findings implicate 'attention' and the effective allocation of processing resources that flows from it, as a potentially important factor influencing gait speed. In Parkinson's disease, attentional deficits are common and there is also impaired automaticity of movement so that processing demands are higher (Wu and Hallett, 2005, 2008). Parkinsonian patients with gait freezing are reported to have even more attentional deficits than those without gait freezing (Amboni *et al.*, 2008; Yogeve-Seligmann *et al.*, 2008). Dual tasking can worsen gait freezing, as can other precipitants that are thought to 'distract' attention away from gait (Giladi and Hausdorff, 2006).

There is increasing evidence that alpha activity has an important role in attention and the allocation of processing resources. The synchronization of occipital alpha with eye closure was once interpreted to reflect passive 'idling' (Berger, 1929; Pfurtscheller *et al.*, 1996). However, alpha activity is now considered to support active suppression of task irrelevant processes (Jensen and Mazaheri, 2010). For example, during working memory tasks, cortical alpha power in visual and motor-sensory areas increases and the degree of synchronization correlates with the number of items

recalled (Jensen *et al.*, 2002; Haegens *et al.*, 2010). Correlation of performance with oscillatory power in task irrelevant regions suggests suppression rather than mere idling. It has been proposed that within the motor system, suppression of competing processes with alpha could aid the smooth execution of motor programmes (Pfurtscheller and Neuper, 1994; Suffczynski *et al.*, 2001). Regions such as the subthalamic nucleus and caudal PPN that have distributed functional connectivity, including with cerebral cortical areas, would be placed to operationalize this putative role. Thus PPN deep brain stimulation is able to increase blood flow in an extensive network of subcortical and cortical areas involved in balance and motor control (Strafella *et al.*, 2008; Ballanger *et al.*, 2009).

Clinical relevance to pedunculopontine nucleus stimulation

Gait freezing improved following electrode implantation in the absence of any stimulation in all patients, although this was less pronounced in patients implanted unilaterally. Gait freezing is notorious for improving during medical assessments, perhaps due to attentional or placebo effects. However, we observed that the improvement in gait freezing persisted for up to 6 weeks post-implantation—a time course arguably more consistent with a stun effect. In the subthalamic nucleus, the ‘stun’ or ‘microlesion’ effect of surgery is usually attributed to suppression of beta activity in the target nucleus by acute tissue disruption from electrode implantation (Chen *et al.*, 2006; Koop *et al.*, 2006). However, in the caudal PPN, alpha activity persisted despite the apparent stun effect and correlated positively with gait performance. Accordingly, we speculate that stun effects in PPN surgery might predominately arise from microlesioning inhibitory supraspinal influences along the electrode trajectory. Excessive inhibition of the PPN (for example from the internal pallidum) has been considered a pathophysiological factor causing gait and postural disturbance in Parkinson’s disease, in addition to PPN neuronal degeneration (Aziz *et al.*, 1998). Consistent with this reasoning, in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model of Parkinson’s disease, the microinjection of a γ -aminobutyric acid antagonist into the PPN improved mobility (Nandi *et al.*, 2002). Microlesioning inhibitory afferents to the PPN would be expected to have analogous effects. If this reasoning is correct, then the occurrence of a possible stun effect would not necessarily indicate accurate electrode placement within the PPN, nor necessarily portend benefit from stimulation.

The topographic arrangement of oscillations in the PPN region along the rostrocaudal axis raises the possibility that caudal and rostral PPN stimulation could have different therapeutic effects. Alpha and beta oscillatory activity could provide functional biomarkers for these different subregions. Alpha and beta activity in the PPN region were focal, evidenced by un-normalized oscillatory power at rest dropping by an average of 42% for alpha activity and 45% for beta activity across bipolar recording sites. This is similar to the gradients of beta activity reported across the dorso-lateral subthalamic nucleus that can be detected in intraoperative

and postoperative recordings and used to guide deep brain stimulation electrode implantation (Chen *et al.*, 2006).

Only the alpha activity recorded in the caudal PPN region was demonstrated to be functionally related to gait and gait freezing. Therapeutic outcomes from PPN region stimulation were variable between patients as were the locations along the rostrocaudal axis where stimulation was applied. Interestingly, the best outcome was achieved when stimulation was applied at the level of maximal alpha activity, 2–6 mm below the pontomesencephalic junction, so that per cent improvement in Gait and Falls questionnaire score at different depths closely correlated with the alpha power recorded at the same depths. We take this to be an encouraging preliminary finding, noting that patient numbers were small, unilateral and bilateral stimulation were mixed, postoperative periods were relatively short and our outcome measure was not objective. Accordingly, it is important that future studies examine whether the efficacy of PPN stimulation relates to stimulation location ‘within’ patients, preferably using objective gait measures. Still, the current study is important in providing physiological evidence, supported by consistent clinical findings, that the site of stimulation along the rostrocaudal axis of the PPN region might be a factor determining therapeutic outcomes.

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Supplementary material

Supplementary material is available at *Brain* online.

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