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Gamma activity and reactivity in human thalamic local field potentials

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Abstract

Depth recordings in patients with Parkinson's disease on dopaminergic therapy have revealed a tendency for oscillatory activity in the basal ganglia that is sharply tuned to frequencies of ~70 Hz and increases with voluntary movement. It is unclear whether this activity is essentially physiological and whether it might be involved in arousal processes. Here we demonstrate an oscillatory activity with similar spectral characteristics and motor reactivity in the human thalamus. Depth signals were recorded in 29 patients in whom the ventral intermediate or centromedian nucleus were surgically targeted for deep brain stimulation. Thirteen patients with four different pathologies showed sharply tuned activity centred at ~70 Hz in spectra of thalamic local field potential (LFP) recordings. This activity was modulated by movement and, critically, varied over the sleep–wake cycle, being suppressed during slow wave sleep and re-emergent during rapid eye movement sleep, which physiologically bears strong similarities with the waking state. It was enhanced by startle-eliciting stimuli, also consistent with modulation by arousal state. The link between this pattern of thalamic activity and that of similar frequency in the basal ganglia was strengthened by the finding that fast thalamic oscillations were lost in untreated parkinsonian patients, paralleling the behaviour of this activity in the basal ganglia. Furthermore, there was sharply tuned coherence between thalamic and pallidal LFP activity at ~70 Hz in eight out of the 11 patients in whom globus pallidus and thalamus were simultaneously implanted. Subcortical oscillatory activity at ~70 Hz may be involved in movement and arousal.

Introduction

Several types of oscillatory activity may be recorded from subcortical nuclei in the human (Brown & Williams, 2005). Many are considered pathological, but there is one type of activity that may particularly relate to normal function, even though it has necessarily been recorded in patients with movement disorders who have had electrodes implanted in the basal ganglia for subsequent therapeutic stimulation (Brown *et al.*, 2001; Cassidy *et al.*, 2002; Williams *et al.*, 2002; Alegre *et al.*, 2005; Alonso-Frech *et al.*, 2006; Devos *et al.*, 2006; Fogelson *et al.*, 2006; Pogosyan *et al.*, 2006; Trottenberg *et al.*, 2006; Androulidakis *et al.*, 2007). This activity is focused in the gamma band, and often manifests as a sharply tuned spectral peak between about 60 and 95 Hz. Subcortical gamma activity may be functionally related to the gamma activity picked up over motor cortical areas, as the two activities are phase coupled (Cassidy *et al.*, 2002; Williams *et al.*, 2002) and both increase with voluntary movement (Crone *et al.*, 1998; Androulidakis *et al.*, 2007; Ball *et al.*, 2008; Cheyne *et al.*, 2008). In parkinsonian patients basal ganglia gamma activity is increased by treatment with dopaminergic therapy, in tandem with improvement in motor performance (Brown *et al.*, 2001; Alonso-Frech *et al.*, 2006). These observations have lead to the suggestion that synchronization of the activity of populations of basal ganglia neurons in the gamma band may facilitate motor processing (Brown, 2003).

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This facilitation may relate to specific coding of movement-related parameters (Brown, 2003; Brown & Williams, 2005), paralleling the role posited for gamma band synchronization in the cerebral cortex, or some supporting role, such as arousal or shifting of attention to the motor task (Buzsáki & Draguhn, 2004). Although most studies of gamma activity in the cerebral cortex relate to sensory areas and generally involve oscillations at a lower frequency (40–60 Hz) than the finely tuned gamma activity reported in basal ganglia-cortical loops, they still do suggest a positive linear relationship between arousal and levels of gamma activity (Gross & Gotman, 1999). Similarly, there is a relationship between attention and enhanced gamma frequency synchronization among cortical neurons (Steinmetz *et al.*, 2000; Fries *et al.*, 2001, 2008). Consistent with the above, gamma activity in the subthalamic nucleus (STN) disappears as patients become drowsy (Brown *et al.*, 2001). In fact the basal ganglia have in the past been considered extensions of the reticular activating system as it relates to executive as opposed to perceptual function, an idea promoted by Hassler (1978) and reinvoked by Brown & Marsden (1998). The anti-parkinsonian effects of direct stimulation of the brainstem reticular activating system in the form of the pedunculo-pontine (PPN) nucleus would encourage reappraisal of this old notion.

One way to explore the possible role of the gamma activity identified in recordings of the basal ganglia activity is to seek similar activity in the thalamus, which is heavily and reciprocally connected with the basal ganglia (Sidibé *et al.*, 2002), integrating as it does the activities of the ascending arousal system (Hallanger *et al.*, 1987). Therefore, by seeking gamma activity in the thalamus with similar reactivity to that in the basal ganglia we sought to clarify whether this activity might be involved in arousal processes and by demonstrating its existence across different pathologies infer a common physiological function for this activity. This approach was aided by consideration of spectral changes induced by startle or movement and those related to sleep, particularly rapid eye movement (REM) sleep in which gross physiological patterns in the forebrain resemble those of waking state (Siegel, 2005).

Materials and methods

Patients and surgical targets

Twenty-nine patients participated in the study with informed consent and the agreement of the local ethics committees according to the Declaration of Helsinki. Of these, 13 showed discrete and significant gamma frequency band peaks in spectra of thalamic local field potential (LFP) recordings (see later for definition of significance of spectral peaks). Their clinical details are given in Table 1. The target structures in the thalamus were the ventral intermediate nucleus (VIM) in patients with dystonia (cases 1–8), myoclonic epilepsy (case 9) and

TABLE 1. Clinical details of subjects with discrete and significant gamma frequency band peaks recorded postoperatively

Case	Age/sex	Pathology	Surgical centre	Pre-op medication	Task	Thalamic targets	Gamma activity
1	29/M	Myoclonic dystonia (DYT-11-positive)	Berlin	None	Rest awake, startle, sleep, movement	VIM bilaterally	R: 66–80 Hz L: 66–80 Hz
2	28/F	Myoclonic dystonia (DYT-11-positive)	Berlin	None	Rest awake	VIM bilaterally	R: – L: 78 Hz
3	68/M	Segmental dystonia	Mannheim	none	Rest awake	VIM bilaterally	R: 60 Hz L: 58 Hz
4	37/M	Segmental dystonia (secondary)	Mannheim	None	Rest awake	VIM bilaterally	R: 78 Hz L: –
5	34/F	Segmental dystonia (secondary)	Mannheim	None	Rest awake	Right VIM	R: 90 Hz
6	43/M	Segmental dystonia	Mannheim	Flupirtine, tolperisone, lorazepam, venlafaxine,	Rest awake	VIM bilaterally	R: 65 Hz L: 60 Hz
7	54/M	Dystonia	Hannover	None	Rest awake, startle, movement	VIM bilaterally	R: 75 Hz L: –
8	16/F	Generalized dystonia	Hannover	None	Rest awake, startle	VIM bilaterally	R: – L: 67 Hz
9	33/M	Myoclonic epilepsy	Freiburg	Levetiracetam, clobazam	Rest awake, startle, sleep, movement	VIM bilaterally	R: – L: 63 Hz
10	44/M	Essential tremor	Berlin	None	Rest awake, movement	VIM bilaterally	R: – L: 68 Hz
11	55/M	PD	Rome	Levodopa, cabergoline, apomorphine	Rest awake (on and off levodopa)	Left centromedian -parafascicularis	L: 72 Hz
12	47/F	PD	Rome	Levodopa, amantadine, cabergoline	Rest awake (on and off levodopa), movement	Centromedian -parafascicularis, bilaterally	R: 75 Hz L: –
13	55/M	PD	Rome	Levodopa pergolide	Rest awake (on and off levodopa), startle, movement	Left centromedian -parafascicularis	L: 65 Hz

Case 11 had a prominent akinetic-rigid syndrome with severe dyskinesias (motor UPDRS scores on and off medication were 46 and 74), case 12 had marked left-sided tremor and dyskinesias (motor UPDRS scores on and off medication were 15 and 55) and case 13 had marked right-sided tremor together with his akinetic rigid syndrome (motor UPDRS scores on and off medication were 29 and 38). PD, Parkinson's disease; VIM, ventral intermediate nucleus.

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essential tremor (case 10), and the centromedian nucleus (CM)–parafascicularis complex in patients with Parkinson's disease (PD; cases 11–13). The basal ganglia were also surgically targeted in the majority of these patients. These were the globus pallidus (cases 1–8 and 11–13) and the border zone between the STN and the substantia nigra pars reticulata (case 9).

Sixteen patients (mean age 56 years, range 29–75 years, 11 females and five males) did not show discrete gamma frequency band peaks in spectra of thalamic LFPs recorded postoperatively. The thalamic target was the VIM nucleus bilaterally in all these cases. Two had myoclonic dystonia (operated in Berlin), three had dystonia (Mannheim 2, Berlin 1), three had myoclonic epilepsy (Freiburg 2, Dusseldorf 1) and eight essential tremor (Berlin 6, Hannover 2).

Details about the choice of target and surgical techniques involved have been previously published (Trottenberg *et al.*, 2001; Garonzik *et al.*, 2002; Krauss *et al.*, 2002; Starr, 2002; Mazzone *et al.*, 2006; Vesper *et al.*, 2007). Thalamic localization was confirmed by comparison of preoperative magnetic resonance imaging (MRI) with postoperative stereotactic MRI (T2-weighted images) or image fusion of postoperative stereotactic computed tomography (cases 4–6).

Postoperative recordings

Recordings were made 1–6 days postoperatively during the period of externalization of deep brain stimulation electrodes prior to their connection to the stimulator device. The electrode used was model 3389 (Medtronic, Minneapolis, MN, USA) with four platinum-iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length and 0.5 mm gaps between contacts), except in cases 1, 2, 9 and 10 where model 3387 with 1.5-mm gaps between contacts was used. Signals were recorded bipolarly from the four adjacent electrode contacts in cases 3–6 and 11–13. Signals were recorded monopolarly in the remaining cases, referenced against linked mastoids, linked ears or a frontal ground electrode (case 9), and bipolar derivations computed offline. LFPs were recorded or derived from all three bipolar recording sites of a given thalamic electrode, except in cases 3 and 4, where LFPs were recorded from contacts 01 and 23 on each side. In cases 11 and 13 LFPs were recorded from one hemisphere only (Table 1). In total, LFPs were sampled from 65 bipolar recording sites in 23 hemispheres. Signals were filtered with a minimum pass band of 1–97 Hz (range of upper cut-off frequency 97–300 Hz), amplified using different recording systems (ISO-1064CE EEG AMPLIFIER, Braintronics, Almere, the Netherlands; Biopotential Analyzer Diana, Institute for Evolutionary Physiology and Biochemistry, St Petersburg, Russia; and a custom-made, 9 V battery-operated portable high-impedance amplifier with at its front-end input stage the INA 128 instrumentation amplifier; TX Instruments, Dallas, TX, USA), and recorded at sampling frequencies ranging from 256 to 1500 Hz.

Paradigms and settings

In all cases LFPs were recorded at rest for a minimum period of 180 s, while patients were awake with their eyes open but not speaking or moving, as determined by visual inspection. Additionally, four different tests were performed in individual cases to assess the reactivity of thalamic LFPs. First, startling acoustic stimuli were applied (Table 1). To this end, hand claps performed by the investigator or balloon bursts were made while subjects were at rest or in light sleep (case 9). The response to the stimuli included movement apparent on visual inspection and confirmed by surface electromyography (EMG) in all but case 8 in whom this was not recorded. Second, in two patients (cases 1 and 9) LFPs were recorded during sleep at night, together with electroencephalogram (EEG; including F3, F4, Fz, Cz, O1, O2, A1 or T1, and A2 or T2 according to the 10–20 system), EMG from masseter, deltoid and quadriceps muscles in case 9, and an electrooculogram (EOG) allowing for the assessment of sleep stages. Sleep stages were scored based on the criteria of Rechtschaffen & Kales (1968) by one of the investigators experienced with sleep stage assessment (F.S.) who was blinded to thalamic LFP activity. Third, LFPs at rest were recorded in three patients with PD (cases 11–13) after overnight withdrawal as well as after reinstitution of treatment with the dopamine precursor levodopa (200 mg). Finally, reactivity of LFPs to self-paced movement was assessed (Table 1). To this end, subjects performed rapid forward and back movements of a joystick with either hand in turn (cases 1 and 4) or with their dominant hand (cases 6, 8, 9 and 10). Movements were performed at variable intertrial intervals of 8–15 s, but the joystick handle was grasped throughout. Surface EMG was also recorded from the forearm flexors during joystick movements in all but cases 12 and 13.

Analysis of LFP recordings

Rest recordings sampled at > 256 Hz were down-sampled to 256 Hz as the common sampling frequency for all datasets after first low-pass filtering where necessary to avoid aliasing. Average and time-evolving power spectra were estimated using the discrete Fourier transform as outlined in Halliday *et al.* (1995) and Grosse *et al.* (2002). Rest records were divided into a number of blocks of 256 data points, affording a resolution of 1 Hz and 1 s. Peaks in spectra of average power in the gamma band (58–90 Hz) were considered significant when mean power per Hz in the peak (1-Hz bin width, average of three bins) differed (Wilcoxon signed-rank test $P < 0.05$) from the mean power at bordering frequencies [mean of bins (over +4 to +8 Hz) + (over −4 to −8 Hz from the gamma peak)]. For time-evolving power spectra, blocks were shifted by 100 ms until the whole record length had been analysed using a script in Spike2 (CED, Cambridge, UK). The resulting matrices of time-evolving power were smoothed using a sliding average of 3–15 overlapping blocks, with the greater smoothing being performed when long time periods (e.g. 1 h) were to be visualized.

Movement-related power was estimated with blocks of 128 data points, affording a resolution of 2 Hz and 0.5 s over trial durations of 8 s. Trials with EMG evidence of spontaneous movements not related to the task and trials containing epileptic discharges were discarded. Fourteen to 35 trials were analysed per subject. Blocks were shifted by 100 ms and the resulting spectra smoothed using a sliding average of three overlapping blocks.

Data were normalized so that maximum intensities in the gamma frequency range were set to 1 and all other bins displayed as corresponding fractions of this. Another normalization procedure was used in order to compare LFPs recorded before and after pharmacological treatment in patients with PD or for the display of movement-related changes of the LFPs. In this case, for each point in time, total power over 5–90 Hz (excluding 45–55 Hz to avoid artefact due to mains noise) was set to 100, allowing the display of 'percentage' power with respect to total power over 5–90 Hz. Finally, coherence and phase between pallidum and thalamus was analysed using the Matlab command 'mscohere' (The Mathworks, Natick, MA, USA). This estimates the magnitude squared coherence with input pallidal LFP activity and output thalamic LFP activity using Welch's averaged

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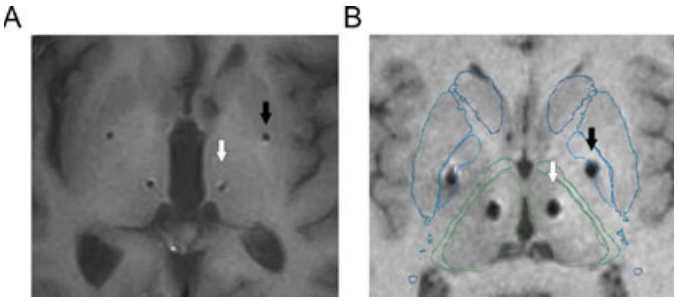

FIG. 1. Postoperative MRI scans with axial views of thalamic (white arrows) and pallidal (black) electrodes in (A) the CM/parafascicularis area in subject 11, and (B) the VIM area in subject 4. (B) The atlas of the human basal ganglia by Yelnik *et al.* (2007) is superimposed, confirming electrode localization in the nucleus VIM/MD (contacts 2 and 3) and CM (contacts 0 and 1) on both sides. MD, medial dorsal nucleus.

periodogram method. Coherence is a function of frequency with values between 0 and 1 that indicates how well the input corresponds to the output at each frequency. Peaks of coherence in the gamma band were considered significant when they met two criteria: (1) coherence exceeded the 95% confidence limits defined using the method of Halliday *et al.* (1995); and (2) any peak in coherence overlapped in frequency with the peak in the corresponding autospectrum of thalamic LFP power. Analyses were performed in Spike2 and Matlab.

Results

The 13 patients with discrete and significant gamma frequency band peaks in spectra of postoperatively recorded thalamic LFPs were studied 1–6 days after surgical implantation of macroelectrodes in the thalamus, in the period between implantation and subsequent subcutaneous connection of electrodes to an internal stimulator. Surgical targets were the VIM nucleus in cases 1–10 and the CM nucleus in cases 11–13. The ipsilateral globus pallidus was also targeted in 11 of the patients (cases 1–8 and 11–13). Representative postoperative MRI scans are shown in Fig. 1.

Thalamic LFPs at rest

Figure 2 shows examples of thalamic LFP power during rest and its variation over time as recorded in PD (Fig. 2A, case 11), segmental dystonia (Fig. 2B, case 4), generalized dystonia (Fig. 2C, case 8) and myoclonic epilepsy (Fig. 2D, case 9). Activity at ~70 Hz (range 58–90 Hz) was observed in 16 out of the 23 implanted hemispheres. The mean half-peak width in individual spectra was 3.6 ± 0.2 Hz (± SEM), with the relative power of peaks amounting to 17.1 ± 3.1% of total power over 6–100 Hz. The peaks were distinct relative to the mean background activity in neighbouring bins (mean power in peak compared with that in five bins below and five bins above, as described in Materials and methods; Wilcoxon signed-rank test, $P < 0.001$).

Peaks in gamma activity were relatively focal. There was a mean drop of 57.4 ± 5.7% (SEM) in peak power when the two remaining contact pairs were compared with the contact pair with the maximal gamma power ($P < 0.001$, paired *t*-test). In addition, gamma activity underwent polarity reversal across bipolar contacts in eight out of 13 subjects (cases 1–3, 5, 6, 8, 11–12), and in cases 9 and 10 was only present in one contact pair.

Modulation of activity in response to startling stimuli

Reactivity of the gamma bands to startling stimuli was assessed in five patients (Table 1). To this end, unexpected high-intensity acoustic stimuli were delivered while subjects were awake or drowsy. Figure 3 shows the corresponding LFP recordings in a patient with PD (Fig. 3A, case 13) and a patient with dystonia (Fig. 3B, case 7). The five patients showed at least a 50% increase in gamma activity within 1 s of the startling stimulus, as marked by a manual key press during the recording. The temporal imprecision of the event timing, however, precluded averaging across subjects. The startle-evoked power increase lasted for up to 20 s, in other words for longer than visible startle-elicited movements.

Thalamic LFPs during sleep

In two patients (cases 1 and 9) LFPs were also recorded during sleep at night. In both cases non-REM sleep stages 1–4 as well as REM sleep were found, although in case 9 recordings included interspersed epileptic activity. Examples of sleep recordings and summary spectral data are illustrated in Fig. 4. Stretches of 1 h of sleep from cases 9 and 1 are shown in Fig. 4A and B, respectively. In both subjects, the continuous gamma activity seen in the awake state was largely absent during non-REM sleep. Activity in the ~70-Hz band re-emerged during REM sleep. The pattern of this, however, was different from that seen in the awake state. In contrast to waking, during REM sleep the activity was less continuous, with 3- to 15-s-long periods of high activity separated by 10- to 40-s-long periods of low activity (Fig. 4C). The peak frequency of activity was nearly identical for REM sleep and the awake state, although half-peak widths of spectral activities were 50–100% wider during REM sleep. Periods with increased ~70 Hz activity could precede or outlast periods of polysomnographically defined REM sleep by tens of seconds, extending into non-REM sleep stages 1 and 2, or REM sleep could be interleaved with short periods of non-REM sleep while the ~70 Hz activity persisted (Fig. 4A and B). On the other hand, the occurrence of rapid eye movements during REM sleep was associated with periods of increased activity at ~70 Hz (Fig. 4D). Individual high-activity periods consisted of a series of 10–30 bursts, with single bursts being ~200 ms long and separated from one another by 200–500 ms (Fig. 4E). Still, eye movements could precede or outlast periods of ~70 Hz activity by up to 5 s, and bursts of eye movements could occur without increases of ~70 Hz activity so that the association between gamma activity and eye movements was not exclusive. In both subjects, the gamma activity was significantly stronger during the awake state compared with all sleep stages (Fig. 4F and G), and significantly stronger during REM sleep compared with non-REM sleep stages ($P < 0.001$, Mann–Whitney *U*-test), except non-REM1 in case 9.

Effect of dopaminergic treatment on thalamic LFPs in PD

In the three patients with PD, in whom the surgical target was the CM, LFPs were recorded after overnight withdrawal of levodopa treatment as well as after the reintroduction of levodopa. Figure 5 shows that gamma activity was absent when patients were off treatment (Fig. 5A, C and E), and almost continuous ~70 Hz activity was seen on treatment (Fig. 5B, D and F), in parallel with clinical improvement of parkinsonism. One subject (case 11) had mild dyskinesias on treatment. The ~70 Hz peak on treatment amounted to 8–15% of total spectral power over 6–100 Hz.

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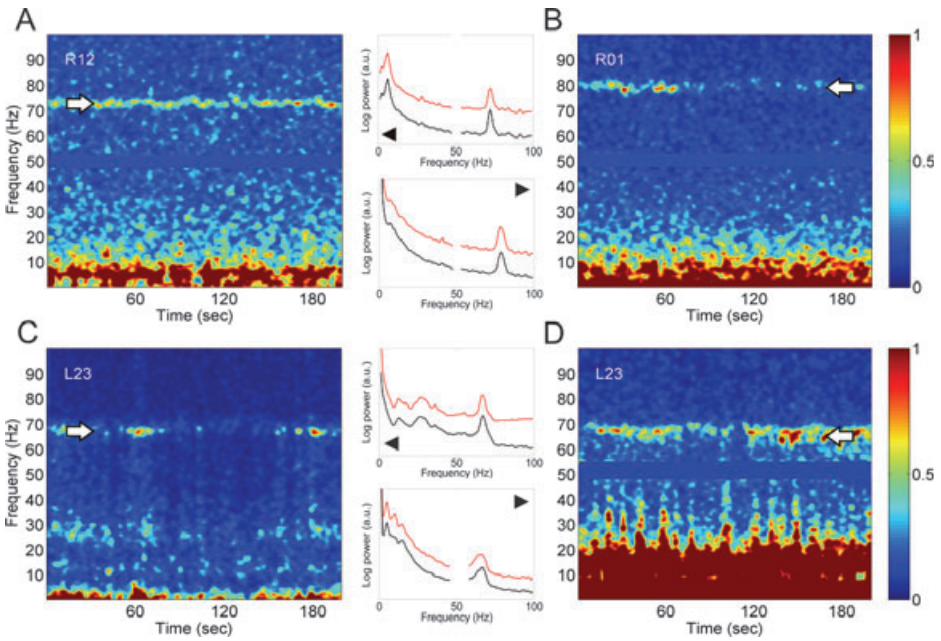

FIG. 2. Sharply tuned oscillatory activities in the gamma frequency range in thalamic LFPs during rest in four different patients. (A) PD on dopaminergic treatment (case 11, right hemisphere, contact 12); (B) segmental dystonia (case 4, right hemisphere, contact 01); (C) generalized dystonia (case 8, left hemisphere, contact 23); (D) myoclonic epilepsy (case 9, left hemisphere, contact 23). Both time-evolving power (large panels) and time-averaged power spectra (small panels) are illustrated in each case, with the average power spectrum (black trace in small panels) being accompanied by its 95% confidence limit (red trace). Note that gamma oscillations were seen across disease entities. In this, and Figs 3 and 4, colour scales have been normalized so that maximal gamma power in each time-evolving spectrum equals 1. Note the artefact at 50 Hz due to power line noise has been digitally suppressed in (A), (B) and (D). a.u., arbitrary units.

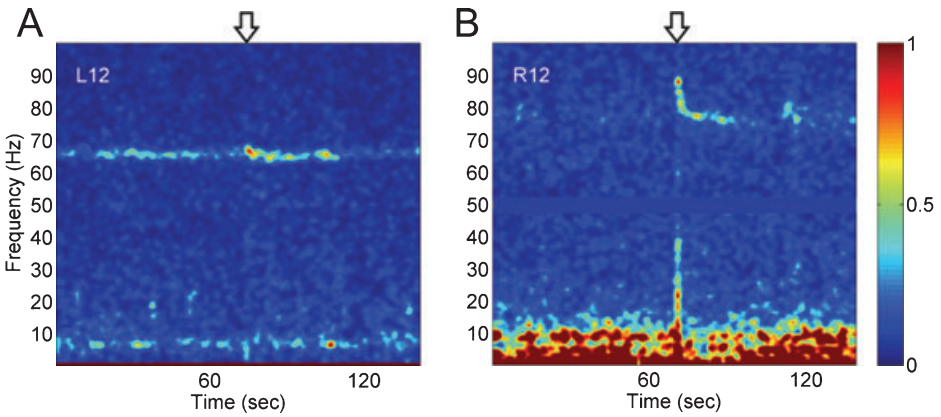

FIG. 3. Increase of activity in the 70-Hz band in response to startling stimuli delivered at the arrow in: (A) a patient with PD (case 13); and (B) a patient with dystonia (case 7).

Reactivity to movement

There was a power increase of the ~70 Hz activity during movement (Fig. 6B–E). The mean power increase over the period from movement onset to joystick maximum was 75.7 ± 24.8% (SEM) of baseline (from 4 to 1 s before movement), and that over the period from movement onset to 90% decay of joystick amplitude was 71.1 ± 24.3% ($P = 0.018$ and $P = 0.022$, respectively, paired t-tests). The activity transiently increased in frequency during movement in the two patients with dystonia (Fig. 6A–D).

Coherence between thalamic and pallidal LFPs

The globus pallidus was also surgically targeted in 11 patients (cases 1–8 and 11–13), allowing us to perform simultaneous recordings from ipsilateral thalamus and globus pallidus. These showed a peak in coherence between nuclei at ~70 Hz at rest in eight cases (cases 1 and 2, 4–6, 8, 11 and 13). Figure 7 illustrates the spectra in case 1, in whom pallido-thalamic coherence was strongest. In this patient phase spectra derived with a block size of 256 data points suggested that pallidal gamma activity preceded that in thalamus (e.g. negative phase gradient at frequencies corresponding to the peak in gamma band coherence in the lower panel of Fig. 7). However, this relationship was lost when spectra were calculated with blocks of 512 data points and there was no linear relationship between phase and frequency in the remaining seven cases with an unambiguous gamma peak in coherence between nuclei. In case 12 there was a peak in coherence at 83 Hz, which met our criteria for significance except that it did not match the frequency of the gamma peak in the corresponding power spectrum of thalamic activity (peak centred on 75 Hz). The thalamus and the

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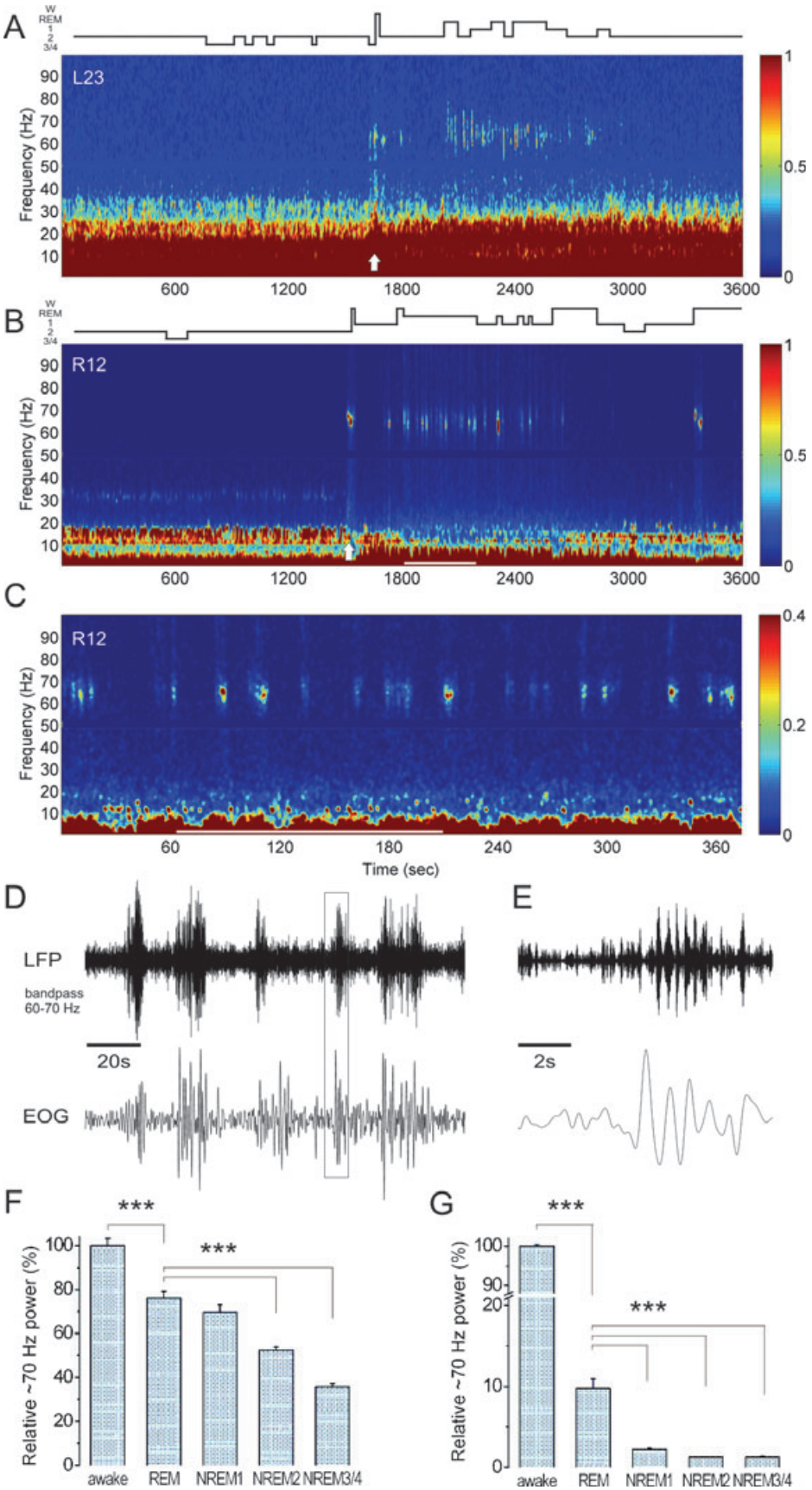

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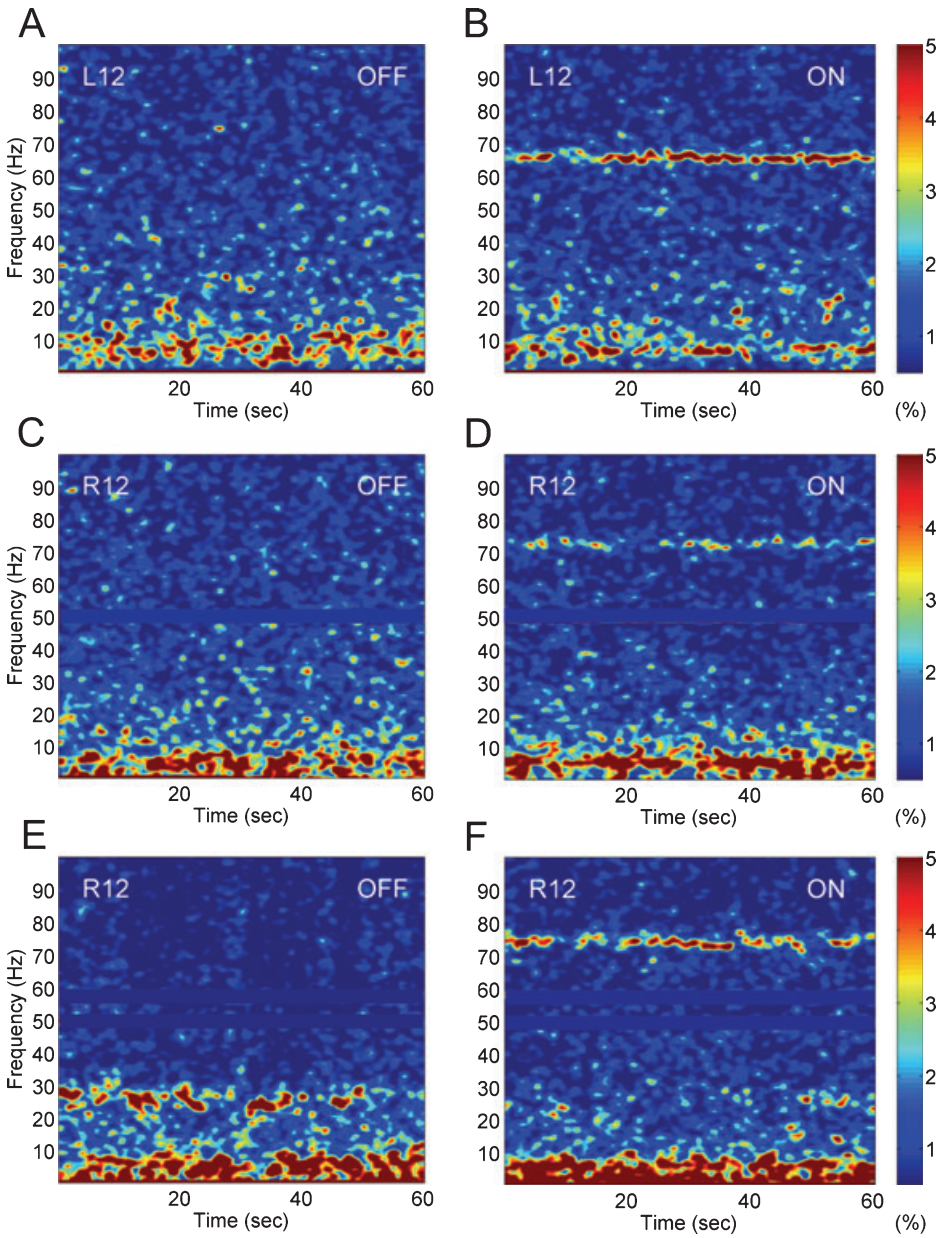

FIG. 5. LFPs recorded at rest in three patients with PD. (A, C and E) Off treatment with levodopa. Gamma oscillations are absent. (B, D and F) On treatment with levodopa. A sharply tuned band at ~70 Hz appears in all cases. Note the artefact has been digitally suppressed at 50 Hz (power line noise) in (C–F), and 58 Hz (noise from the PC monitor screen refresh) in (E) and (F). Colour bars refer to percentage power of total power over 5–90 Hz.

border zone between the STN and the substantia nigra pars reticulata was implanted in one patient (case 9) and again there was a significant peak in coherence between LFPs from these two sites (at 63 Hz). The gamma band peaks were distinct relative to the mean background activity in neighbouring bins (mean power in peak compared with that in five 1-Hz bins below and five 1-Hz bins above; Wilcoxon signed-rank test, $P < 0.002$).

Discussion

We have shown that focal and sharply tuned oscillatory LFP activity centred around 70 Hz occurs at rest in the human thalamus. Not all patients showed this phenomenon, perhaps because of sampling error (failure to record from relevant regions) within the thalamus or because we did not systematically keep patients fully alert and

FIG. 4. Local field potential (LFP) activities recorded during non-rapid eye movement (NREM) and REM sleep. Periods of 1 h of sleep are shown in (A) for a patient with myoclonic epilepsy (case 9) and (B) a patient with myoclonic dystonia (case 1), with sleep stages indicated by hypnograms on top of figures. There were brief awakenings with gamma bursts some (arrowed) 5 min before onset of REM in both cases. (C) LFPs during REM sleep characterized by bursts of ~70 Hz activity (case 1). (D) Pass band (60–70 Hz)-filtered LFP signal and electrooculogram (EOG) over the period indicated by the horizontal bar at the bottom of (C). Bursts of rapid eye movements are associated with periods of increased ~70 Hz activity. (E) Example of period of increased ~70 Hz activity (indicated by frame in D) showing that this consists of a series of bursts (same patient as C and D). (F and G) Histograms summarizing power levels of ~70 Hz activity during the awake state (defined as 100%) and different sleep stages as fractions of this in cases 9 and 1, respectively. Note that the ~70 Hz activity was significantly stronger in the awake state and REM sleep compared with slow-wave sleep in both cases. ***$P < 0.001$.

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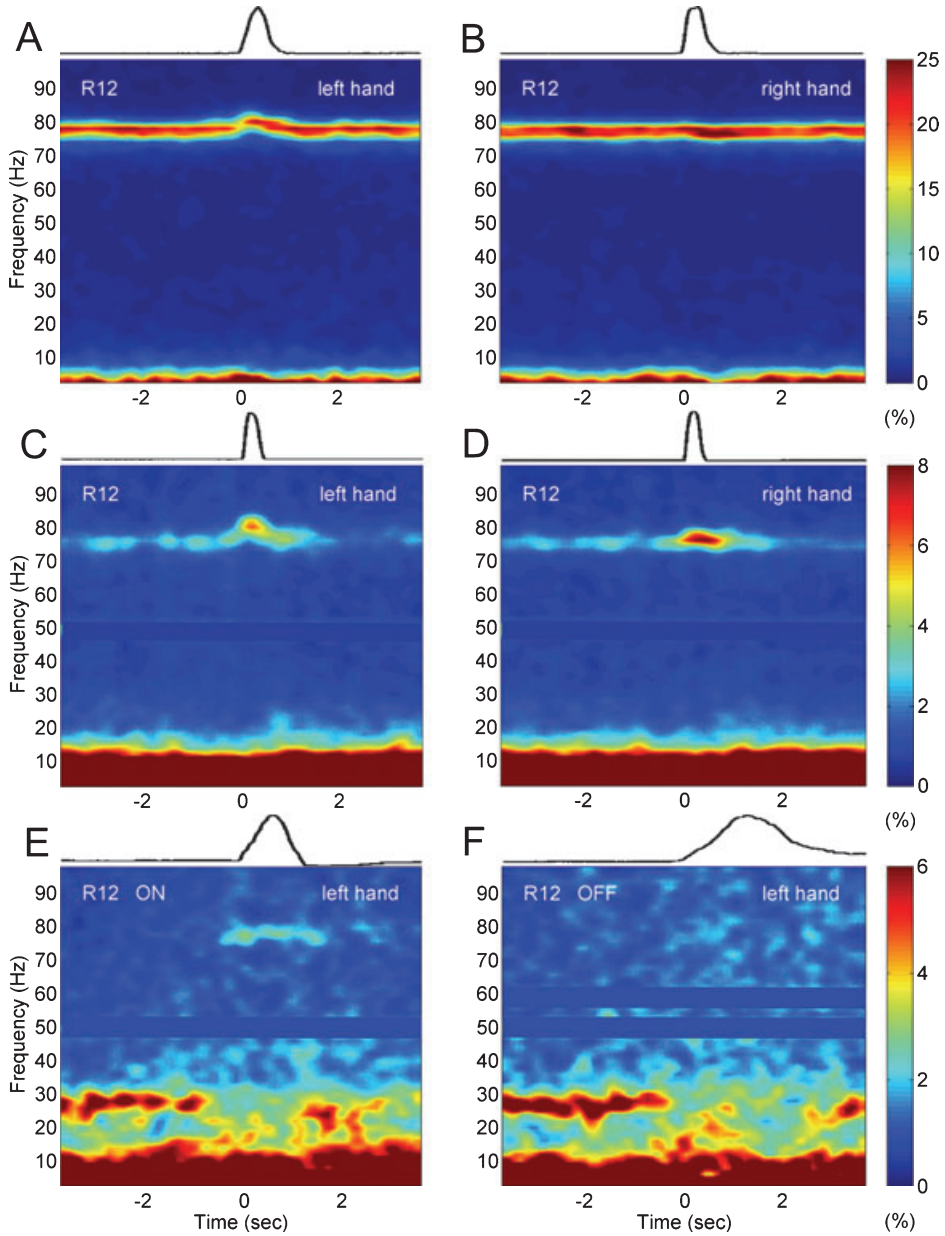

FIG. 6. Movement-related changes in thalamic LFPs. Movement (at time = 0 s, joystick traces on top of figures) of the contralateral (A) and ipsilateral (B) hand in a patient with myoclonic dystonia (case 1). Movement of the contralateral (C) and ipsilateral (D) hand in a patient with dystonia (case 7). (E) Movement of the contralateral hand in a patient with PD (case 12) on treatment with levodopa, and (F) off treatment. Note the tendency for either an increase in frequency and/or power at ~70 Hz at the time of movement except in the case of PD off treatment. Note the artefact has been digitally suppressed at 50 Hz (power line noise) in (C–F), and 58 Hz (noise from the PC monitor screen refresh) in (F). Colour bars refer to percentage power of total power over 5–90 Hz.

engaged during peri-operative recordings. Nor can we comment on the precise distribution of sharply tuned oscillatory gamma activity within the thalamus, which would presuppose comprehensive sampling of the whole thalamus with a finer spatial resolution than possible with our deep brain stimulation electrodes. Nevertheless, the occurrence of sharply tuned oscillatory LFP activity across different thalamic surgical targets and many patients with different pathological conditions suggests that such gamma activity represents a primarily physiological thalamic feature, although we cannot exclude its quantitative exaggeration in certain disease states (Fogelson *et al.*, 2006). The activity was modulated by voluntary movement, often increasing in power and sometimes frequency. Of note, it was recorded in three patients with PD, but only after treatment with the dopamine precursor levodopa. It was also coherent with simultaneously recorded activity in the globus pallidus.

Relationship of ~70 Hz oscillations with arousal and wakefulness

The modulation of the ~70 Hz activity over the course of the sleep–wake cycle and enhancement in response to startling stimuli is in accord with a possible involvement of these waves in, or dependence on, arousal. The ~70 Hz oscillations were much more manifest during waking and the arousal state of REM sleep relative to slow wave sleep, paralleling the pattern in epidural EEG recordings in humans

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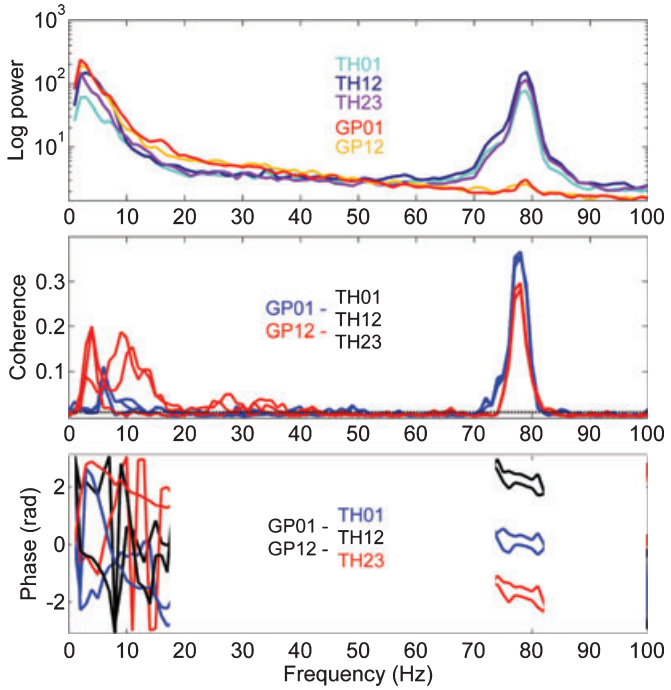

FIG. 7. Coherence and phase between LFP activities recorded in globus pallidus and thalamus in case 1 with DYT-11-positive myoclonic dystonia. There is a large peak in coherence (the highest in all patients) and corresponding phase slope centred at 78 Hz. Coherence and phase have been estimated between every possible internuclear contact pair between pallidal contacts 01 and 12 and thalamic contacts 01, 12 and 23. There were no recordings from pallidal contact 23.

(Gross & Gotman, 1999) and rats (Maloney *et al.*, 1997). The ~70 Hz activity during REM sleep was not exclusively associated with periods of eye movements and could not therefore only be ascribed to motor-related phenomena.

Modulation of such EEG activities over different states of vigilance occurs through ascending projections from the brainstem and basal forebrain. One important source of these afferents is the mesencephalic reticular formation (Munk *et al.*, 1996). Another important source is the cholinergic neurons in the PPN and laterodorsal tegmental (LDT) nuclei (Steriade *et al.*, 1990, 1991). These reach the thalamic relay nuclei (Hallanger *et al.*, 1987; Steriade *et al.*, 1988), the intralaminar complex (Paré *et al.*, 1988) and thalamic reticular nucleus (Hallanger *et al.*, 1987; Paré *et al.*, 1988). Accordingly, electrical stimulation of PPN/LDT in animals leads to blockage of delta and spindle oscillations as well as potentiation of high-frequency activity in the thalamocortical system (Hu *et al.*, 1989; Steriade *et al.*, 1991). Other inputs implicated in waking and high-frequency oscillations come from cholinergic and γ-aminobutyric acid (GABA) ergic neurons in the basal forebrain, which preferentially target the thalamic reticular nucleus (Hallanger *et al.*, 1987; Asanuma & Porter, 1990).

The association of bursts of increased gamma during REM sleep with bursts of eye movements provides further circumstantial evidence that the ~70 Hz activity in the thalamus is linked to the ascending reticular activating system, as both rapid eye movements and REM sleep itself are heavily modulated by the PPN area (Scarnati & Florio, 1997; Vanni-Mercier & Debilly, 1998). It is also noteworthy that increased metabolic activation in attention-related cortical systems correlates with the number of eye movements (Hong *et al.*, 1995). Indeed, available physiological evidence indicates global EEG similarities between REM sleep and the awake state in forebrain areas (Llinas & Pare, 1991; Wehrle *et al.*, 2007), particularly 'desynchronized' low-amplitude, high-frequency EEG activity in the neocortex (Siegel, 2005). Furthermore, brain reactivity to external stimuli during REM sleep is more similar to waking responsiveness than that observed during slow-wave sleep (Bastuji & Garcia-Larrea, 1999; Wehrle *et al.*, 2007).

The dependence of the activity at ~70 Hz upon the reticular activating system is also supported by the modulation of these oscillations in the thalamus in response to startle-eliciting stimuli, although it is important to note that startling stimuli also induced movement that may have contributed to the initial part of the gamma increase. The motor response in the human auditory startle is organized in the reticular nuclei of the caudal brain stem (Brown *et al.*, 1991). While the efferent limb mediating the startle reflex is probably provided by the bulbobulbar and reticulospinal pathways originating in this area, ascending projections appear to be preferentially relayed through the intralaminar thalamic nuclei (Robertson & Feiner, 1982).

Although our findings may point to an involvement of the sharply tuned gamma activity in arousal-related processes, they do not exclude the possibility that oscillatory activity over a broader gamma band may be more specifically related to the coding of movement-related parameters (Brown, 2003; Brown & Williams, 2005). In this regard it is interesting to note that the ~70 Hz activity is evident in records made at rest and during movement (Brown *et al.*, 2001; Alonso-Frech *et al.*, 2006), whereas broad gamma band changes are only really evident as spectral features in averages time-locked to movement (Androulidakis *et al.*, 2007; Kempf *et al.*, 2007; Brücke *et al.*, 2008). The possible distinction between finely tuned gamma activity and broad band gamma event-related synchronization requires further investigation.

Dependency of ~70 Hz oscillations on dopaminergic treatment in patients with PD

The frequency and narrow band nature of the ~70 Hz oscillations, together with their increase with movement and dependence on dopaminergic input suggests that they may be functionally linked to those previously recorded in the basal ganglia (see Introduction). In particular, the levodopa dependency of the ~70 Hz oscillations in the thalamus of the three patients with PD is in accord with the pharmacological modulation of comparable activity recorded from the basal ganglia in other patients with PD (Brown *et al.*, 2001; Cassidy *et al.*, 2002; Williams *et al.*, 2002; Alegre *et al.*, 2005; Fogelson *et al.*, 2005; Alonso-Frech *et al.*, 2006; Devos *et al.*, 2006), in whom this activity appears following dopaminergic treatment, in parallel with clinical improvement. Similar high-frequency activity occurring in the subthalamic area of the healthy alert rat is also increased by the dopamine receptor agonist quinpirole (Brown *et al.*, 2002), in line with dopaminergic modulation of physiological activity over this frequency range.

The dopaminergic dependency of the ~70 Hz oscillations in the thalamus is an interesting finding as it suggests either a role for the dopaminergic innervation of the thalamus (Sanchez-Gonzalez *et al.*, 2005; Garcia-Cabezas *et al.*, 2007) or, alternatively, that the reticular activating system's influence on the fast thalamic oscillations may not be exclusively exerted by direct projections to the thalamus, but may, in part, be achieved through brainstem input to the basal ganglia and thence to the thalamus. In particular, the PPN appears to influence striatal dopamine activity through stimulation of dopaminergic cells of

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the substantia nigra pars compacta (Lokwan *et al.*, 1999; Forster & Blaha, 2003). The basal ganglia output nuclei, in turn, have extensive projections to the thalamus, including the centromedian-parafascicular complex (Sidibé *et al.*, 2002).

A possible relationship between gamma activities in the thalamus and basal ganglia is further supported by our finding of coherence between these activities in several patients. Coherence can be interpreted as a measure of functional coupling or connectivity (Magill *et al.*, 2006). However, our findings do not permit an unequivocal statement as to whether thalamus or pallidum provided the predominant drive in the gamma band. This aspect requires further investigation and analysis using additional measures of information flow.

In sum, the above observations raise the possibility that the sharply tuned oscillatory activity at ~70 Hz, previously identified in the basal ganglia and here demonstrated in the thalamus, may partly subserve an arousal mechanism, mediating some of the effects of the reticular activating system. The increase in sharply tuned gamma activity upon voluntary movement, and its identification in and coupling between thalamus and pallidum, suggests that it may help explain how arousal-related processes impact on the extrapyramidal motor system, an interesting notion given the recent evidence linking the basal ganglia with movement vigour and motivation (Mazzoni *et al.*, 2007).

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Abbreviations

CM, centromedian nucleus; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; LDT, laterodorsal tegmental; LFP, local field potential; MRI, magnetic resonance imaging; PD, Parkinson's disease; PPN, pedunculopontine; REM, rapid eye movement; STN, subthalamic nucleus; VIM, ventral intermediate nucleus.

References

Alegre, M., Alonso-Frech, F., Rodríguez-Oroz, M.C., Guridi, J., Zamarbide, I., Valencia, M., Manrique, M., Obeso, J.A. & Artieda, J. (2005) Movement-related changes in oscillatory activity in the human subthalamic nucleus: ipsilateral vs. contralateral movements. *Eur. J. Neurosci.*, **22**, 2315–2324.

Alonso-Frech, F., Zamarbide, I., Alegre, M., Rodríguez-Oroz, M.C., Guridi, J., Manrique, M., Valencia, M., Artieda, J. & Obeso, J.A. (2006) Slow oscillatory activity and levodopa-induced dyskinesias in Parkinson's disease. *Brain*, **129**, 1748–1757.

Androulidakis, A.G., Kühn, A.A., Chen, C.C., Blomstedt, P., Kempf, F., Kupsch, A., Schneider, G.H., Doyle, L., Dowsey-Limousin, P., Hariz, M.I. & Brown, P. (2007) Dopaminergic therapy promotes lateralized motor activity in the subthalamic area in Parkinson's disease. *Brain*, **130**, 457–468.

Asanuma, C. & Porter, L.L. (1990) Light and electron microscopic evidence for a GABAergic projection from the caudal basal forebrain to the thalamic reticular nucleus in rats. *J. Comp. Neurol.*, **302**, 159–172.

Ball, T., Demandt, E., Mutschler, I., Neitzel, E., Mehring, C., Vogt, K., Aertsen, A. & Schulze-Bonhage, A. (2008) Movement related activity in the high gamma range of the human EEG. *Neuroimage*, **41**, 302–310.

Bastuji, H. & Garcia-Larrea, L. (1999) Evoked potentials as a tool for the investigation of human sleep. *Sleep. Med. Rev.*, **3**, 23–45.

Brown, P. (2003) Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. *Mov. Disord.*, **18**, 357–363 (Review).

Brown, P. & Marsden, C.D. (1998) What do the basal ganglia do? *Lancet*, **351**, 1801–1804 (Review).

Brown, P. & Williams, D. (2005) Basal ganglia local field potential activity: character and functional significance in the human. *Clin. Neurophysiol.*, **116**, 2510–2519 (Review).

Brown, P., Rothwell, J.C., Thompson, P.D., Britton, T.C., Day, B.L. & Marsden, C.D. (1991) New observations on the normal auditory startle reflex in man. *Brain*, **114**, 1891–1902.

Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P. & Di Lazzaro, V. (2001) Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J. Neurosci.*, **21**, 1033–1038.

Brown, P., Kupsch, A., Magill, P.J., Sharott, A., Harnack, D. & Meissner, W. (2002) Oscillatory local field potentials recorded from the subthalamic nucleus of the alert rat. *Exp. Neurol.*, **177**, 581–585.

Brücke, C., Kempf, F., Kupsch, A., Schneider, G.H., Krauss, J.K., Aziz, T., Yarrow, K., Pogosyan, A., Brown, P. & Kühn, A.A. (2008) Movement-related synchronisation of gamma activity is lateralized in patients with dystonia. *Eur. J. Neurosci.*, **27**, 2322–2329.

Buzsáki, G. & Draguhn, A. (2004) Neuronal oscillations in cortical networks. *Science*, **304**, 1926–1929 (Review).

Cassidy, M., Mazzone, P., Oliviero, A., Insola, A., Tonali, P., Di Lazzaro, V. & Brown, P. (2002) Movement-related changes in synchronization in the human basal ganglia. *Brain*, **125**, 1235–1246.

Cheyne, D., Bells, S., Ferrari, P., Gaetz, W. & Bostan, A.C. (2008) Self-paced movements induce high-frequency gamma oscillations in primary motor cortex. *Neuroimage*, **42**, 332–342.

Crone, N.E., Miglioretti, D.L., Gordon, B. & Lesser, R.P. (1998) Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. Event-related synchronization in the gamma band. *Brain*, **121**, 2301–2315.

Devos, D., Szurhaj, W., Reyns, N., Labyt, E., Houdayer, E., Bourriez, J.L., Cassim, F., Krystkowiak, P., Blond, S., Destée, A., Derambure, P. & Defebvre, L. (2006) Predominance of the contralateral movement-related activity in the subthalamo-cortical loop. *Clin. Neurophysiol.*, **117**, 2315–2327.

Fogelson, N., Pogosyan, A., Kühn, A.A., Kupsch, A., van Bruggen, G., Speelman, H., Tijssen, M., Quartarone, A., Insola, A., Mazzone, P., Di Lazzaro, V., Limousin, P. & Brown, P. (2005) Reciprocal interactions between oscillatory activities of different frequencies in the subthalamic region of patients with Parkinson's disease. *Eur. J. Neurosci.*, **22**, 257–266.

Fogelson, N., Williams, D., Tijssen, M., van Bruggen, G., Speelman, H. & Brown, P. (2006) Different functional loops between cerebral cortex and the subthalamic area in Parkinson's disease. *Cereb. Cortex*, **16**, 64–75.

Forster, G.L. & Blaha, C.D. (2003) Pedunculopontine tegmental stimulation evokes striatal dopamine efflux by activation of acetylcholine and glutamate receptors in the midbrain and pons of the rat. *Eur. J. Neurosci.*, **17**, 751–762.

Fries, P., Reynolds, J.H., Rorie, A.E. & Desimone, R. (2001) Modulation of oscillatory neuronal synchronization by selective visual attention. *Science*, **291**, 1560–1563.

Fries, P., Womelsdorf, T., Oostenveld, R. & Desimone, R. (2008) The effects of visual stimulation and selective visual attention on rhythmic neuronal synchronization in macaque area V4. *J. Neurosci.*, **28**, 4823–4835.

Garcia-Cabezas, M.A., Rico, B., Sanchez-Gonzalez, M. & Cavada, C. (2007) Distribution of the dopamine innervation in the macaque and human thalamus. *NeuroImage*, **34**, 965–984.

Garonzik, I.M., Hua, S.E., Ohara, S. & Lenz, F.A. (2002) Intraoperative microelectrode and semi-microelectrode recording during the physiological localization of the thalamic nucleus ventral intermediate. *Mov. Disord.*, **17**(Suppl. 3), 135–144 (Review).

Gross, D.W. & Gotman, J. (1999) Correlation of high-frequency oscillations with the sleep-wake cycle and cognitive activity in humans. *Neuroscience*, **94**, 1005–1018.

Grosse, P., Cassidy, M. & Brown, P. (2002) EEG-EMG, MEG-EMG and EMG-EMG frequency analysis: physiological principles and clinical applications. *Clin. Neurophysiol.*, **113**, 1523–1531.

Hallanger, A.E., Levey, A.I., Lee, H.J., Rye, D.B. & Wainer, B.H. (1987) The origins of cholinergic and other subcortical afferents to the thalamus in the rat. *J. Comp. Neurol.*, **262**, 105–124.

Halliday, D.M., Rosenberg, J.R., Amjad, A.M., Breeze, P., Conway, B.A. & Farmer, S.F. (1995) A framework for the analysis of mixed time series/point process data – theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. *Prog. Biophys. Mol. Biol.*, **64**, 237–278.

Hassler, R. (1978) Interaction of reticular activating system for vigilance and the truncothalamic and pallidal systems for directing awareness and attention under striatal control. In Buser, P.A. & Rougeul-Buser, A. (Eds), *Cerebral Correlates of Conscious Experience*. Elsevier-North Holland, Amsterdam, pp. 110–129.

Hong, C.C., Gillin, J.C., Dow, B.M., Wu, J. & Buchsbaum, M.S. (1995) Localized and lateralized cerebral glucose metabolism associated with eye

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movements during REM sleep and wakefulness: a positron emission tomography (PET) study. *Sleep*, **18**, 570–580.
Hu, B., Steriade, M. & Deschênes, M. (1989) The effects of brainstem peribrachial stimulation on perigeniculate neurons: the blockage of spindle waves. *Neuroscience*, **31**, 1–12.
Kempf, F., Kühn, A.A., Kupsch, A., Brücke, C., Weise, L., Schneider, G.H. & Brown, P. (2007) Premovement activities in the subthalamic area of patients with Parkinson's disease and their dependence on task. *Eur. J. Neurosci.*, **25**, 3137–3145.
Krauss, J.K., Pohle, T., Weigel, R. & Burgunder, J.M. (2002) Deep brain stimulation of the centre median-parafascicular complex in patients with movement disorders. *J. Neurol. Neurosurg. Psychiatry*, **72**, 546–548.
Llinas, R.R. & Pare, D. (1991) Of dreaming and wakefulness. *Neuroscience*, **44**, 521–535.
Lokwan, S.J., Overton, P.G., Berry, M.S. & Clark, D. (1999) Stimulation of the pedunculopontine tegmental nucleus in the rat produces burst firing in A9 dopaminergic neurons. *Neuroscience*, **92**, 245–254.
Magill, P.J., Pogosyan, A., Sharott, A., Csicsvari, J., Bolam, J.P. & Brown, P. (2006) Changes in functional connectivity within the rat striato-pallidal axis during global brain activation in vivo. *J. Neurosci.*, **26**, 6318–6329.
Maloney, K.J., Cape, E.G., Gotman, J. & Jones, B.E. (1997) High-frequency gamma electroencephalogram activity in association with sleep-wake states and spontaneous behaviors in the rat. *Neuroscience*, **76**, 541–555.
Mazzone, P., Stocchi, F., Galati, S., Insola, A., Altibrandi, M.G., Modugno, N., Tropedi, D., Brusa, L. & Stefani, A. (2006) Bilateral implantation of centromedian-parafascicularis complex and GPi: a new combination of unconventional target for deep brain stimulation in severe Parkinson disease. *Neuromodulation*, **9**, 221–228.
Mazzoni, P., Hristova, A. & Krakauer, J.W. (2007) Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation *J. Neurosci.*, **27**, 7105–7116.
Munk, M.H., Roelfsema, P.R., Konig, P., Engel, A.K. & Singer, W. (1996) Role of reticular activation in the modulation of intracortical synchronization. *Science*, **272**, 271–274.
Paré, D., Smith, Y., Parent, A. & Steriade, M. (1988) Projections of brainstem core cholinergic and non-cholinergic neurons of cat to intralaminar and reticular thalamic nuclei. *Neuroscience*, **25**, 69–86.
Pogosyan, A., Kühn, A.A., Trottenberg, T., Schneider, G.H., Kupsch, A. & Brown, P. (2006) Elevations in local gamma activity are accompanied by changes in the firing rate and information coding capacity of neurons in the region of the subthalamic nucleus in Parkinson's disease. *Exp. Neurol.*, **202**, 271–279.
Rechtschaffen, A. & Kales, A. (1968) *A Manual of Standardized Terminology, Techniques and Scoring System and Sleep Stages of Human Subjects*. University of California Brain Information Service, Los Angeles.
Robertson, R.T. & Feiner, A.R. (1982) Diencephalic projections from the pontine reticular formation: autoradiographic studies in the cat. *Brain Res.*, **239**, 3–16.
Sanchez-Gonzalez, M.A., Garcia-Cabezas, M.A., Rico, B. & Cavada, C. (2005) The primate thalamus is a key target for brain dopamine. *J. Neurosci.*, **25**, 6076–6083.
Scarnati, E. & Florio, T. (1997) The pedunculopontine nucleus and related structures. Functional organization. *Adv. Neurol.*, **74**, 97–110.
Sidibé, M., Paré, J.F. & Smith, Y. (2002) Nigral and pallidal inputs to functionally segregated thalamostriatal neurons in the centromedian/parafascicular intralaminar nuclear complex in monkey. *J. Comp. Neurol.*, **447**, 286–299.
Siegel, J.M. (2005) REM sleep. In Kryger, M.H., Roth, T. & Dement, W.C. (Eds), *Principles and Practice of Sleep Medicine*, 4th Edn. Elsevier/Saunders, Philadelphia, PA, pp. 120–134.
Starr, P.A. (2002) Placement of deep brain stimulators into the subthalamic nucleus or Globus pallidus internus: technical approach. *Stereotact. Funct. Neurosurg.*, **79**, 118–145 (Review).
Steinmetz, P.N., Roy, A., Fitzgerald, P.J., Hsiao, S.S., Johnson, K.O. & Niebur, E. (2000) Attention modulates synchronized neuronal firing in primate somatosensory cortex. *Nature*, **404**, 187–190.
Steriade, M., Paré, D., Parent, A. & Smith, Y. (1988) Projections of cholinergic and non-cholinergic neurons of the brainstem core to relay and associational thalamic nuclei in the cat and macaque monkey. *Neuroscience*, **25**, 47–67.
Steriade, M., Datta, S., Paré, D., Oakson, G. & Curró Dossi, R.C. (1990) Neuronal activities in brain-stem cholinergic nuclei related to tonic activation processes in thalamocortical systems. *J. Neurosci.*, **10**, 2541–2559.
Steriade, M., Dossi, R.C., Paré, D. & Oakson, G. (1991) Fast oscillations (20-40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. *Proc. Natl Acad. Sci. USA*, **88**, 4396–4400.
Trottenberg, T., Meissner, W., Kabus, C., Arnold, G., Funk, T., Einhaupl, K.M. & Kupsch, A. (2001) Neurostimulation of the ventral intermediate thalamic nucleus in inherited myoclonus-dystonia syndrome. *Mov. Dis.*, **16**, 769–771.
Trottenberg, T., Fogelson, N., Kühn, A.A., Kivi, A., Kupsch, A., Schneider, G.H. & Brown, P. (2006) Subthalamic gamma activity in patients with Parkinson's disease. *Exp. Neurol.*, **200**, 56–65.
Vanni-Mercier, G. & Debilly, G. (1998) A key role for the caudoventral pontine tegmentum in the simultaneous generation of eye saccades in bursts and associated ponto-geniculo-occipital waves during paradoxical sleep in the cat. *Neuroscience*, **86**, 571–585.
Vesper, J., Steinhoff, B., Rona, S., Wille, C., Bilic, S., Nikkhah, G. & Ostertag, C. (2007) Chronic high-frequency deep brain stimulation of the STN/SNr for progressive myoclonic epilepsy. *Epilepsia*, **48**, 1984–1989.
Wehrle, R., Kaufmann, C., Wetter, T.C., Holsboer, F., Auer, D.P., Pollmacher, T. & Czisch, M. (2007) Functional microstates within human REM sleep: first evidence from fMRI of a thalamocortical network specific for phasic REM periods. *Eur. J. Neurosci.*, **25**, 863–871.
Williams, D., Tijssen, M., Van Bruggen, G., Bosch, A., Insola, A., Di Lazzaro, V., Mazzone, P., Oliviero, A., Quartarone, A., Speelman, H. & Brown, P. (2002) Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans. *Brain*, **125**, 1558–1569.
Yelnik, J., Bardinet, E., Dormont, D., Malandain, G., Ourselin, S., Tandé, D., Karachi, C., Ayache, N., Cornu, P. & Agid, Y. (2007) A three-dimensional, histological and deformable atlas of the human basal ganglia. I. Atlas construction based on immunohistochemical and MRI data. *Neuroimage*, **34**(2), 618–638.

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