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Thalamic gamma oscillations correlate with reaction time in a Go/noGo task in patients with essential tremor

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ABSTRACT

Intracerebral recordings of neuronal activity in patients undergoing deep brain stimulation have revealed characteristic movement-related desynchronization at frequencies <30 Hz and increased activity in the gamma band (~30–100 Hz) in the basal ganglia and thalamus. Thalamic gamma activity is also found during arousal. Here, we explore oscillatory gamma band activity recorded from the ventralis intermedius nucleus of the thalamus during motor performance in a Go/noGo task in 10 patients with essential tremor after implantation of deep brain stimulation electrodes. We show that movement-related gamma activity is lateralized to the nucleus contralateral to the moved side similar to previous findings in the globus pallidus internus and the subthalamic nucleus. The onset of contralateral gamma band synchronization following imperative Go cues is positively correlated with reaction time. Remarkably, *baseline* levels of gamma activity shortly before the Go cue correlated with the reaction times. Here, faster responses occurred in patients with higher levels of pre-cue gamma activity. Our findings support the role of gamma activity as a physiological prokinetic activity in the motor system. Moreover, we suggest that subtle fluctuations in pre-cue gamma band activity may have an impact on task performance and may index arousal-related states.

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Introduction

Oscillatory local field potential activity has been used as a surrogate measure of the pattern of underlying neuronal synchronization in the basal ganglia in patients undergoing deep brain stimulation for severe movement disorders. Up to now, most interest in oscillatory activity in the basal ganglia has been focussed on the beta (13–35 Hz) band that is pathologically enhanced in patients with Parkinson's disease (Brown, 2003). This activity shows characteristic patterns of modulation preceding and following movement (Kempf et al., 2007; Kühn et al., 2004; Levy et al., 2002). Oscillatory activity in the gamma frequency range (30–100 Hz) is found in various cortical areas and has been related to visual object binding, cognitive processing, memory retrieval and motor processing (Bauer et al., 2006; Engel et al., 2001; Jensen et al., 2007; Schoffelen et al., 2005; for an overview see Buzsáki, 2006). More recently, gamma band activity has been described in different recordings from the thalamus, globus pallidus internus (GPi) and subthalamic nucleus (STN) irrespective of the underlying disease in patients undergoing deep brain stimulation. In patients with Parkinson's disease gamma synchronization occurs at rest during levodopa treatment (Brown et al., 2001; Cassidy et al., 2002; Pogosyan et al., 2006; Trottenberg et al., 2006; Williams et al., 2002) and has been associated with levodopa induced dyskinesia (Alegre et al., 2005; Alonso-Frech et al., 2006; Fogelson et al., 2006). Gamma synchronization occurs with self-paced (Androulidakis et al., 2007) as well as externally paced movements (Kempf et al., 2007; Liu et al., 2008) and is more prominent contralateral to the moved side (Brücke et al., 2008), similar to synchronized gamma activity over motor cortical areas (Ball et al., 2008; Cheyne et al., 2008; Crone et al., 1998; Pfurtscheller et al., 2003). The degree of motor cortical gamma synchrony has been related to motor parameters such as movement amplitude or speed (Muthukumaraswamy, 2010). Similarly, the event-related gamma synchronization around movement onset recorded in the pallidum in patients with dystonia has been correlated with the scaling of movement and has been associated with response vigor (Brücke et al., 2012). Taken together these findings suggest that motor related gamma activity in the cortex –

Abbreviations: BP, button press; DBS, deep brain stimulation; ERS, event related synchronization; ERD, event related desynchronization; FDR, false discovery rate; GPi, globus pallidus internus; LFP, local field potential; STN, subthalamic nucleus; VAS, visual analogue scale; VIM, ventralis intermedius nucleus of the thalamus.

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basal ganglia circuit is not pathological but primarily physiological in nature.

Interestingly, finely tuned gamma activity has been observed in thalamic recordings during wakefulness and REM sleep and is increased with the startle reaction (Kempf et al., 2009) possibly reflecting shifts in arousal levels (Jenkinson et al., in press). If baseline thalamic gamma activity indeed depends on a critical level of arousal related to state modulation of the reticular activating system (Kempf et al., 2009), these activity changes should be predictive of changes in behavioral performance, especially in reaction time tasks. One opportunity to explore this hypothesis is to record neuronal activity from patients undergoing deep brain stimulation in the ventralis intermedius nucleus of the thalamus (VIM) to treat severe essential tremor (Limousin et al., 1999; Schuurman et al., 2000). The human VIM nucleus is considered homologous to the cerebellum-recipient nuclei of the monkey (Sommer, 2003) and thalamic recordings in monkeys have revealed movement-related activity during visually triggered voluntary arm movements (van Donkelaar et al., 1999), whereas interruption of thalamic activity during infusion of lidocaine leads to an alteration of visually triggered movements with increased reaction time (van Donkelaar et al., 2000). Human single unit recordings from the VIM have confirmed movement-related increases in firing rate within the nucleus with a somatotopic distribution of the movement responsive neurons (Crowell et al., 1968; Hua and Lenz, 2005; Lenz et al., 1988, 1990). Here, we used direct thalamic local field potential recordings in 10 patients with essential tremor to explore the impact of fluctuations in baseline gamma band activity on reaction time and its relation to movement-related changes in thalamic gamma activity during the performance of a visually triggered Go/noGo task.

Methods

Patients and surgery

10 patients (3 males, mean age 62.50 ± 18.85 years) undergoing deep brain stimulation for severe essential tremor (ET; for clinical details see Table 1) were included in this study. All patients were diagnosed with essential tremor according to the diagnostic criteria (Deuschl et al., 1998) and none had clinical signs hinting at the presence of Parkinson's disease or dystonia, none had a history of hyperthyroidism or concurrent use of tremor-inducing medications. Intracerebral lesions were excluded in all patients on pre-operative MRI. The study was approved by the local ethics committees of the Charité, University Medicine Berlin (Germany) and the Medical School Hannover (Germany) according to the Declaration of Helsinki and all patients gave informed consent. Patients underwent simultaneous bilateral implantation of deep brain stimulation (DBS) electrodes in the ventral intermediate nucleus (VIM) of the thalamus. The operative procedure has been described before (Kempf et al., 2009; Krauss et al., 2001). Target points were calculated on individual stereotactic MRI and intraoperatively adjusted according to microelectrode recordings, and the clinical effects of macrostimulation in all patients. The permanent quadripolar macroelectrode used was model 3387 (Medtronic Neurologic Division, Minneapolis, MN, USA) featuring 4 platinum–iridium cylindrical surfaces. Its contacts were numbered 0, 1, 2, and 3 with 0 being the most caudal and contact 3 being the most cranial. The intended coordinates at the tip of the electrode contact 0 were about 13–15 mm lateral from the midline and 5–7 mm behind the midcommissural point and 1 mm below the anterior commissure–posterior commissure line. Electrode localisation was confirmed on post-operative T2 weighted MR imaging (except for the patient from Hannover, case 1, where a postoperative CT scan was performed and correct placement of electrodes was verified by measuring the stereotactic coordinates of the electrode contacts relative to the anterior commissure–posterior commissure line) and correct placement of electrodes was verified in all patients (see Table 1). In order to assess the relation of electrode contacts with respect to thalamic nuclei, individual postoperative MRI data were transformed onto the standard stereotaxic space of the Montreal Neurological Institute (MNI; Schönecker et al., 2009). Localizations of the geometrical centre of electrode contacts were derived from the centre of the corresponding hypointense susceptibility artefact of contacts (Pollo et al., 2004). Finally, localization of contacts were superimposed to the boundaries of thalamic nuclei as specified by the mean three-dimensional Morel–Atlas based on multiple stereotactic anatomical data (Krauth et al., 2010). Post-operative assessment of the clinical outcome at least 3 months after implantation of electrodes further supported correct placement of electrodes with a mean subjective improvement in tremor of 73.5 ± 19.4% (mean ± SD; self rating on visual analogue scale, VAS) and an improvement of 72.2 ± 35.4% (mean ± SD) using an index of tremor-related general disability for activities of daily living (ADL, Index of general disability and measured by the Tremor-ADL Disability questionnaire, Bain et al., 1993). Both scores are self-rating scores. The ADL score was shown to correlate well with the evaluation of tremor severity (Bain et al., 1993).

Recordings

Local field potentials (LFP) were captured via the DBS electrode leads that were externalized during the time interval (2–6 days) between electrode implantation and connection to a subcutaneous pulse generator. Patients were taking their usual medication. Adjacent bipolar contact pairs of each electrode (01, 12, and 23) were used to record bipolarly from the VIM. Signals were band-pass filtered between 1 and 250 Hz and amplified (×50,000) either using a custom-made, 9 V battery-operated high-impedance amplifier (INA128 instrumentation amplifier, Texas Instruments, Inc., Dallas, TX, USA) ($n = 4$), a D360 amplifier (Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK) ($n = 5$), or a portable amplifier (Biopotential Analyzer Diana, St. Petersburg, Russia) ($n = 1$). Signals were sampled at 1000 Hz (1250 Hz using the Diana amplifier) and recorded through a 1401 A/D converter (Cambridge Electronic Design, Cambridge, UK) onto a computer using Spike2 software (Cambridge Electronic Design) and monitored online. In patients 3, 4, 5, and 6 electromyographic (EMG) activity was recorded bilaterally (except for case 6) from the first dorsal interosseus muscles, which allowed us to define movement onset in a subgroup of patients. EMG signals were band pass-filtered (10 Hz–3 kHz), amplified (×5000) and recorded through a 1401 A/D converter (EMG recordings were not possible with the other amplifiers with fixed hardware settings).

Paradigm

While sitting comfortably in a chair, patients were asked to look at a portable PC screen and performed a precued Go/noGo reaction time task, which has been described previously (Brücke et al., 2008; Kühn et al., 2004). The paradigm starts with a fixation cross and consists of a 500 ms duration warning signal (a pair of arrows either side of the cross indicating the laterality of a subsequent imperative cue) followed with a fixed time interval of 2.5 s either by a Go signal (presented by a "0") or a noGo signal (presented by an "S") shown for another 500 ms. Patients were instructed to press the button of a clicker in their left or right hand, respectively, when seeing the Go signal (80%), and to withhold the prepared button press when a noGo signal (20%) appeared. The inter-trial duration was pseudorandomized and varied between 6, 6.5, and 7 s with each category presented equally frequently.

Data analysis

Data files were opened in Spike2 and down sampled to 625 Hz using nearest neighbour interpolation. VIM electrode channels were inspected visually and trials containing mains noise or movement

Table 1
Patient's clinical details.

Age (years)/sex	Disease duration (years)/family history	Medication	Tremor score pre/post OP[b] (out of 75) and change VAS [%]	Electrode contact pair used for gamma band analysis	Contacts in VIM according to post-operative MRI	Mean reaction time during motor task (ms.)[d]	Stimulation parameters
Case 1[a]	8/	None	36/8[b]	R: 01	CT scan performed	R: 490	R: 4.5 V, 120 μs, 140 Hz, 0−, 1−,2+
51/M	n.a.		80%	L: 23		L: 533	L: 4.0 V, 120 μs, 140 Hz, 0−, 1−, 2+
Case 2	>20	Gabapentin 2400 mg/d	45/4	R: 12	R: 12	**R: 450**	R: 4.5 V, 60 μs, 130 Hz, 1−, 2+
69/M	Positive	Propranolol 160 mg/d		L: 12	L: 23	L: 493	L: 3.0 V, 60 μs, 130 Hz, 0−
			80%				
Case 3	>45	Propranolol 120 mg/d	46/n.a.	R: 01	R: 123	**R: 696**	R: 2.5 V, 60 μs, 150 Hz, 1−
80/F	Negative			L: 23	L: 123	L: 725	L: 2.5 V, 60 μs, 150 Hz, 1−
			80%				
Case 4	20	Propranolol 20 mg/d	27/26	R: 01	R: 123	**R: 468**	R: 1.5 V, 60 μs, 240 Hz, 2−
66/F	Negative	Primidone 125 mg/d		L: 23	L: 123	L: 459	L: 2.0 V, 60 μs, 240 Hz, 1+
			20%[c]				
Case 5	9	Lisinopril 10 mg/d	80%	R: 23	R: 123	**R: 466**	R: OFF, only mild tremor
48/F	Negative	Hydrochlorothiazide 25 mg/d	n.a.	L: 12	L: 12	L: 444	L: 1.0 V, 60 μs, 130 Hz, 0−
Case 6	49	none	33/3	R: 01	R: 12	**R: 375**	R: 2.9 V, 60 μs, 130 Hz, 1−, 2+
63/F	Positive			L: 12	L: 12	L: 414	L: 2.5 V, 60 μs, 130 Hz, 0−
			90%				
Case 7	>25	Venlafaxine 150 mg/d	27/13	R: 23	R: 12	**R: 646**	R: 3.0 V, 60 μs, 130 Hz, 0+, 1−
59/F	Positive	Primidone 500 mg/d	80%	L: 23	L: 123	L: 679	L: 2.0 V, 60 μs, 130 Hz, 1−
		L-Thyroxine 50 μg/d					
		Allopurinol 50 μg/d					
		Esomeprazole 20 mg/d					
Case 8	>50	Propranolol 120 mg/d	35/1	R: 01	R: 12	**R: 539**	R: 2.8 V, 60 μs, 210 Hz, 1−
72/F	Positive	Primidone 500 mg/d		L: 01	L: 012	L: 662	L: 2.0 V, 60 μs, 210 Hz, 1−, 2−
		Ramipril 2.5 mg/d	80%				
Case 9	23	Valsartan 80 mg/d	31/1	R: 01	R12	**R: 455**	R: 1.5 V, 60 μs, 90 Hz, 2−, 3−
48/F	Positive	Popranolol 240 mg/d		L: 01	L 12	L: 515	L: 2.7 V, 60 μs, 90 Hz, 2−, 3+
			75%				
Case 10	20	Doxazosin 4 mg/d	41/n.a.	R: 23	R23	**R: 571**	R: 3.7 V, 60 μs, 130 Hz, 1−
69/M	Positive	Amlodipine 5 mg/d		L: 01	L12	L: 569	L: 2.7 V, 60 μs, 130 Hz, 1−
		Enalapril 5 mg/d	70%				
		Pregabaline 600 mg/d					

Mean Age: 62.5 ± 18.8 years. All patients have been operated at the Charité, University Medicine Berlin if not indicated otherwise.
[a] Patient has been operated in Hannover.
[b] ADL, Index of general disability and measured by the Tremor-ADL Disability questionnaire.
[c] Clear effect on tremor (>50%), but low subjective rating due to concomitant hyperkinetic hemisyndrome of unknown origin that developed during chronic DBS.
[d] Dominant hand in bold letters (Edinburgh Handedness Inventory). VAS = visual analogue scale.

artefacts were excluded from further analysis. Also, trials with erroneous responses (errors of omission or laterality errors in Go trials, errors of commission in noGo trials), premature responses or responses made 1 s or more after the Go cue were excluded. A mean of 53 ± 4 trials were left per side for further analysis. To assess event-related changes in LFP activity, responses were averaged across trials of the same movement laterality and aligned to the Go signal, the noGo signal, and the button press (BP), respectively. Where available, EMG activity was rectified, averaged and aligned to BP. LFP spectra were estimated using the discrete Fourier transform in Spike2. To this end, data were segmented into time windows of 8 s, beginning 6 s before the button press, or 5 s before the Go/noGo signal, respectively. To estimate the spectra in each block, discrete fast Fourier transforms were applied to sections of 256 data points using a Hanning window, resulting in a frequency resolution of 2.4 Hz and an epoch time of 0.41 s. Blocks of this latency were then averaged across trials, and blocks shifted by 99.2 ms and averaged again until the whole record length had been analysed using a custom written script in Spike2 software. Average time–frequency plots of VIM LFPs contra- and ipsilateral to hand responses were then further analysed and displayed using MATLAB (The MathWorks Inc.; custom written scripts). These showed median percentage power changes relative to baseline (6–4 s before movement for data averaged around the response or 5–3 s before the Go or noGo cue for epochs averaged around the imperative cues). Power changes across all patients and electrode contacts were analysed by means of Wilcoxon's signed rank test as the data sets were not normally distributed in all time frequency bins (according to the Kolmogorov–Smirnov test). In each time–frequency bin of the median time–frequency plot we tested whether changes in contra- and ipsilateral VIM LFP power during button press were different from baseline and compared the time–frequency bins between ipsi- and contralateral sides. This provided matrices with each bin represented by its respective *p*-value. To correct for multiple comparisons in the time–frequency analysis the false discovery rate (FDR) procedure was used and the thresholds corresponding to the alpha level of $p < 0.01$ calculated (Benjamini and Hochberg, 1995).

Additionally, data were analysed in three frequency bands that captured the main features during movement. These were empirically defined as: (i) a gamma band (55–80 Hz) synchronization (ERS) seen at −200 to 300 ms around button press, (ii) a low beta band (12–20 Hz) desynchronization (ERD) seen −300 to 300 ms around button press, and (iii) a higher beta (17-30Hz) band ERS seen 500 to 1500 ms after movement. In our initial analyses we averaged power changes across all contact pairs in each electrode, so as to avoid any possible selection bias. However, this ignores evidence of local maxima, which is also important in demonstrating the focality of sources and in determining activity from smaller generators. Thus, for each electrode, the contact pair with the strongest mean reactivity within the low beta, high beta and gamma band over the timings specified above, averaged for ipsi- and contralateral movements, was also selected for subsequent analysis. In all patients at least one contact of the contact pair selected for analysis was located within or at the border of the VIM ($n = 18$; post-operative MR imaging was not available in case 1; Fig. 1).

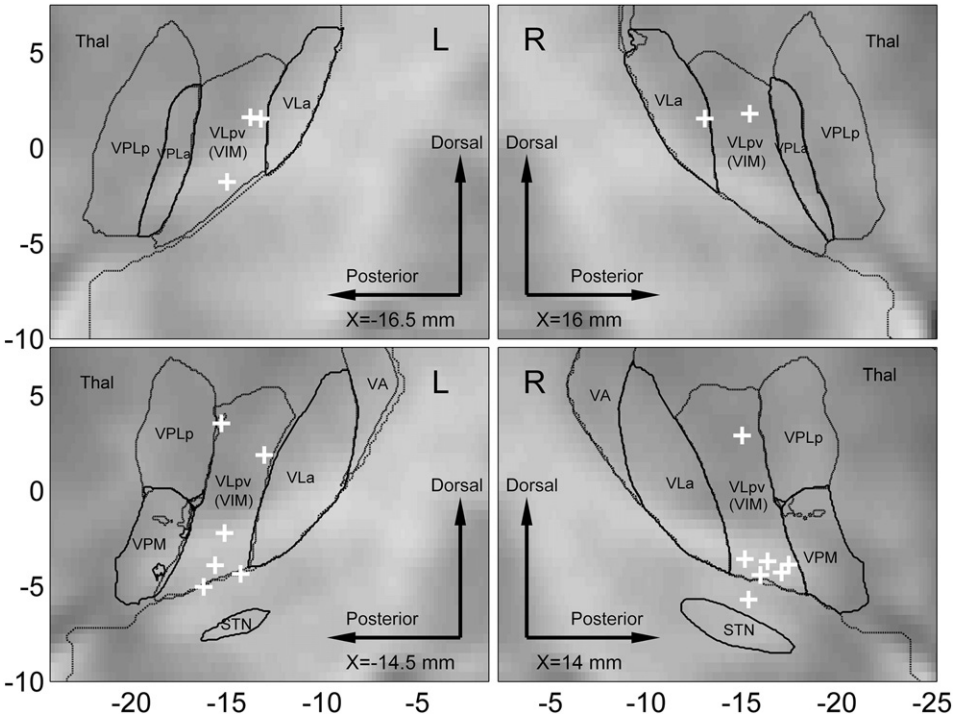

Fig. 1. Localizations of contact pairs of the DBS electrodes in standard MNI stereotactic space coordinates (dimensions in mm: X — mediolateral). Localizations of the centre (+) of the bipolar contact pairs selected for LFP analysis are depicted (white crosses, L left side, R right side) on corresponding sagittal slices of the MNI standard brain template. Mean nuclear boundaries of the thalamus are outlined (black) based on the three-dimensional Morel–Atlas (Krauth et al., 2010). Note that the actual contacts are located up to 2.25 mm more dorsal (proximal contact) and more ventral (distal contact) with respect to the displayed centre of the contact pairs. Note that with respect to the nomenclature of the Morel thalamus atlas in comparison to the terminology of Hassler widely used in neurosurgical targeting, the VIM refers to the dorsal division of the ventral lateral posterior nucleus (VLpv; Hebb and Ojemann, in press).

For each frequency band of interest, significant movement-related changes from baseline activity were evaluated by comparing mean power values over time to baseline values using a Wilcoxon's signed rank test. A change from baseline was only considered significant, if $p < 0.05$ for at least three consecutive data points. A paired Student's t-test was applied to find significant ($p < 0.05$) power differences between ipsi- and contralateral movements since data was normally distributed (as assessed with one-sample Kolmogorov–Smirnov test). The effect of laterality was assessed by a repeated measures ANOVA on averaged power changes in the beta and gamma band for the time window around button press (see above) from the contra- and ipsilateral VIM.

The onset of gamma synchronization was defined as the point at which power rose by twice the standard deviation derived from the entire record for at least three consecutive data points. This time point was correlated with the mean reaction time of the corresponding side using parametric Pearson's correlation (since all latency data were normally distributed as confirmed by the Kolmogorov–Smirnov test). To evaluate the influence of background pre-stimulus gamma activity on task performance, the mean pre Go cue gamma power (averaged from −250 ms to −130 ms before the Go cue) was correlated with the corresponding reaction time using non-parametric Spearman's test (power data not normally distributed). For both correlation analyses, time resolution for gamma power modulation was increased by reducing the block size to 128 data points. All results are reported as mean ± SEM, unless stated otherwise.

Results

Movement-related changes in thalamic oscillatory activity

The main features that occurred in the time–frequency plots of event related power changes around movement were i) an event-related desynchronization (ERD) starting about 100 ms before movement in the 12–20 Hz range; ii) an increase in synchronized activity (ERS) in the 17–30 Hz band starting around 500 ms after button press in the contralateral VIM, and iii) a movement-related synchronization at 55–80 Hz predominantly in the contralateral VIM starting about 100 ms before movement. Fig. 2 shows the median LFP power change, expressed as percentage change from baseline (6–4 s before button press) averaged to button press, separately for contra- and ipsilateral VIM ($n = 60$, e.g., 3 bipolar recordings ×20 sides ×10 patients; Figs. 2A and B). The most striking difference in spectral power changes between the ipsilateral and contralateral VIM is the gamma band ERS, which is stronger contralateral to the movement. Statistical comparison of power in each time–frequency bin between contralateral and ipsilateral movements showed a significant difference in the gamma ERS from −100 ms to around 500 ms after button press ($p < 0.01$, corrected, Fig. 2C). The post-movement beta synchronization (17–30 Hz, starting at about 500 ms after button press) was also more pronounced on the contralateral side ($p < 0.01$, Wilcoxon's signed rank test, corrected for multiple comparisons, Fig. 2C). Time-evolving mean power changes normalised to baseline activity revealed similar results for the three frequency bands of interest with a larger gamma (55–80 Hz) ERS starting about 250 ms before button press and a larger post-movement beta (17–30 Hz) synchronization contralateral to the moved side (Fig. 3). No significant difference between contra- and ipsilateral activity occurred in the lower beta (12–20 Hz) frequency range (Fig. 3, paired Student's t-test). Fig. 4 shows the time course of EMG and thalamic gamma band activity aligned to button press in a subgroup of patients ($n = 4$). Note that averaged, rectified EMG-activity from the first dorsal interosseus muscles increased around 150 ms before button press, which was preceded by an increase in gamma band activity. Single trial data support an early increase of gamma wave amplitude in parallel with higher EMG activity (Fig. 4B).

These laterality effects were confirmed by repeated measures ANOVAs with the factor LATERALITY (two levels: ipsilateral and

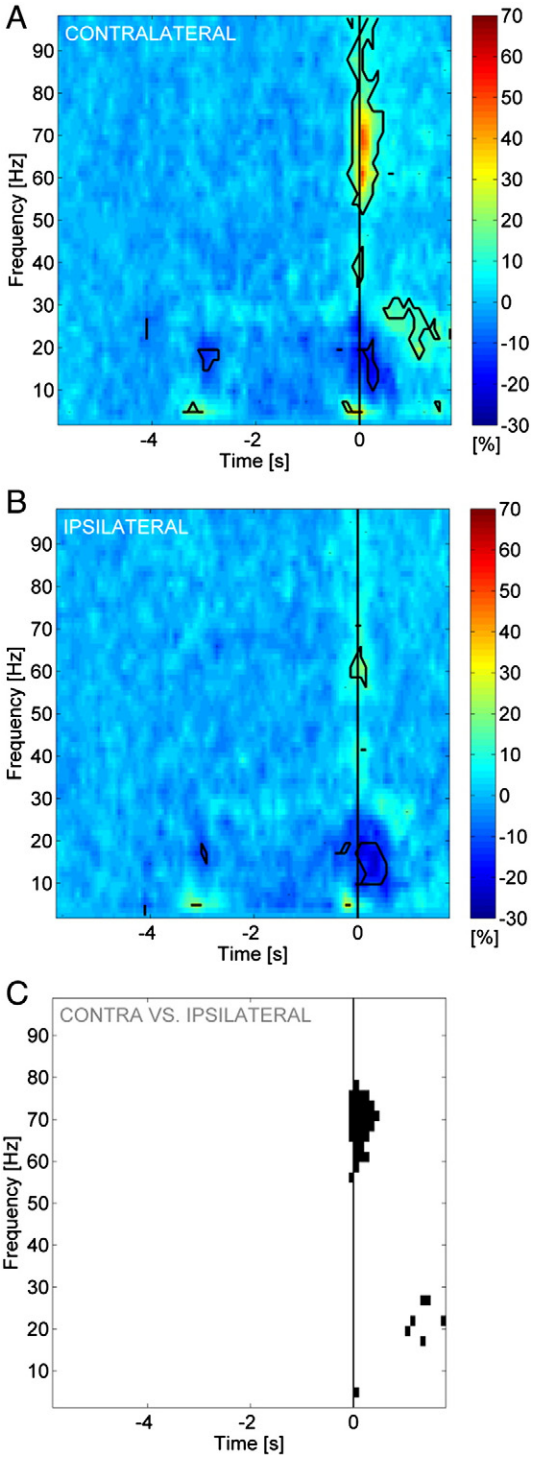

Fig. 2. (A + B) Time–frequency plots representing median oscillatory power changes in the LFP of the VIM ipsi- and contralateral to voluntary movement in 10 patients. Activity is re-aligned to button press and has been averaged over three contact pairs ($n = 60$) per electrode and is shown relative to baseline (−6 to −4 s before button press at time point 0). Contour lines indicate statistically significant changes compared to baseline ($p < 0.01$, FDR corrected) (C) Wilcoxon's signed rank test between contra- and ipsilateral movement (statistically significant time–frequency bins in black ($p < 0.01$, FDR corrected).

contralateral) performed separately for the gamma frequency range (55–80 Hz) in the time window −200 ms to 300 ms around button press ($F(1, 19) = 17.4$, $p < 0.001$, Huynh–Feldt corrected) and the high beta frequency band in the time window 500 ms to 1500 ms after button press ($F(1, 19) = 11.38$, $p = 0.003$). Post-hoc Student's t-test confirmed a larger gamma ERS contralateral to the movement ($p < 0.001$; 78.2 ± 19.1% vs. 19.7 ± 7.2%, contra- vs ipsilateral) as well as a larger post-movement high beta ERS ($p = 0.003$; 24.8 ± 6.95% vs. 7.6 ± 4.1%, contra- vs. ipsilateral). No difference between hemispheres was revealed for the low beta ERD (12–20 Hz) for the time periods −300 to 300 ms after button press (contralateral −20.1 ± 5.7% vs. ipsilateral −23.2 ± 5.1%, $F(1, 19) = 0.6$, $p = 0.45$, Huynh–Feldt corrected; data not shown).

Individual data confirmed the predominant contralateral occurrence of the gamma ERS in 19 out of 20 sides. In one single case the movement-related increase in contralateral gamma activity did not exceed twice the standard deviation of mean baseline activity and no difference was found compared to the ipsilateral side. Contralateral post-movement beta-ERS occurred in 15 out of 20 hemispheres. The maximum gamma ERS was randomly distributed along the macroelectrode contacts but showed a clear gradient between adjacent contact pairs. The mean decrease of gamma ERS at the remaining contact pairs was 38.8 ± 5.8%, supporting a focal origin of the activity.

Stimulus-related changes in thalamic oscillatory activity

In order to evaluate the reactivity pattern related to the noGo signal, we also analysed the stimulus-locked data averaged to the imperative cues. Go cue related activity showed the pattern described above with a significant gamma synchronization in the thalamic LFP contralateral to the moved side starting at about 400 ms after the Go cue (Figs. 5A, D) and a bilateral desynchronization in the beta frequency band (12–20 Hz) that occurred shortly after the Go cue during the movement (Figs. 5A, E). Imperative noGo trials were not followed by prominent changes of LFP activity averaged over all contact pairs and electrodes ($n = 60$, Fig. 5B). Subsequent analysis of selected contact pairs (see Methods) did not reveal a significant change in gamma activity after noGo trials (Fig. 5D). The stimulus-locked ERD in the low beta band started around 250 ms both after Go and noGo cues (Fig. 5E). However, in contrast to the Go cue trials where a significant beta desynchronization lasted for around 800 ms, the beta ERD was prematurely reversed during noGo trials 264 ms after the imperative noGo stimulus, which was before the mean reaction time in our patients (Fig. 5E; mean reaction time 532 ms).

Stimulus-locked data further revealed a significant bilateral beta ERD following the warning cue (Figs. 5A, E) similar to previous recordings from the STN (Kühn et al., 2004) and GPi (Brücke et al., 2008), pointing to a general phenomena during motor preparation. This beta ERD was less prominent in noGo trials, which was most likely due to the limited number of trials for analysis. A theta ERS occurred bilaterally after the warning and imperative cue (Fig. 3A) that could reflect the short latency evoked potential described in thalamus (Marzinzik et al., 2008) and STN (Kühn et al., 2004).

Gamma activity correlates with task performance

The mean reaction time was 532 ± 23 ms (SD 102 ms; range 375–725 ms). Patients made 1.4 ± 0.3 (range 0–5) errors of commission in noGo trials. The combined error rate in Go trials was 9.2 ± 3.4%. Overall, errors were too infrequent to enable separate evaluation of the pattern of activity changes in error trials.

In order to evaluate the functional significance of gamma activity for behavioral performance, we correlated the onset and degree of gamma ERS contralateral to the moved hand with reaction time. The onset of the gamma ERS was defined in individual trials as the time point at which gamma power exceeded twice the standard deviation of mean baseline activity. We found a significant positive correlation between the onset of the gamma ERS averaged across trials and the mean reaction time (Spearman's correlation, $r = 0.79$, $p < 0.001$, $n = 19$ hands/hemispheres, Fig. 6A; right hand in case 8 was excluded for correlation

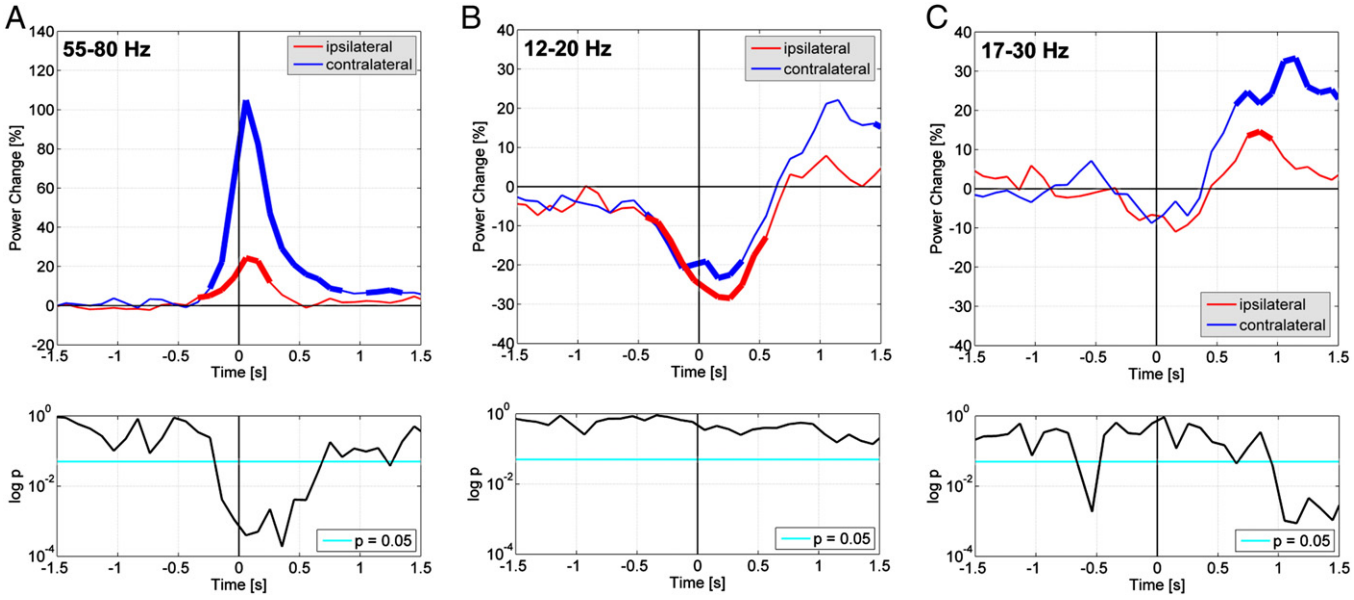

Fig. 3. Mean (A) gamma band (between 55–80 Hz), (B) low beta band (12–20 Hz), and (C) high beta band (17–30 Hz) activity expressed as percentage power changes compared to baseline (−6 to −4 s before button press at time point 0) and re-aligned to button press. Electrode contact pairs were selected for highest reactivity around movement ($n = 20$). Thick lines indicate significant changes from baseline ($p < 0.05$, Wilcoxon's signed rank test). Corresponding p-values of paired Student's t-test between ipsi- and contralateral movements are plotted below. Note the movement-related synchronization of gamma band activity, which is significantly larger contralateral to the moved side (A).

analysis due to the limited number of trials, which was below the two-fold SD of mean trials across patients). Importantly, the onset of gamma ERS occurred around ~250 ms before the mean reaction time in our patients (note that the time resolution is limited by the chosen parameters for FFT analysis with block size of 128 data points and blocks shifted by 19.2 ms).

EMG activity that was recorded in a subgroup of 4 patients started up to about ~150 ms before button press, but was not assessed in the remaining patients. No correlation was found between reaction time and the degree of contralateral gamma ERS (during the time period of −200 ms to 300 ms after button press; r = 0.32, $p = 0.235$, data not shown).

More remarkably, we found that fluctuations of baseline levels of gamma activity before the imperative Go cue had a significant influence on task performance. The mean bilateral gamma power in the time window from −300 to −130 before Go cue (the end point of −130 ms before Go cue was chosen with respect to the block size of 128 data points) showed a significant negative correlation with the corresponding reaction time (Pearson's correlation, r = −0.53, $p = 0.021$, $n = 19$ hands/hemispheres, Fig. 6B), meaning that increased levels of baseline gamma activity were associated with faster reaction times. Importantly, baseline activity in the beta frequency range did not show any correlation with the reaction time (Pearson's correlation, r = 0.31, $p = 0.25$, data not shown). Thus, the correlation of pre-cue thalamic gamma activity levels with reaction times was frequency-specific.

Discussion

We have demonstrated movement-related increased gamma synchronization in the human thalamus in patients with essential tremor that occurs predominantly contralateral to voluntary movement. Our findings extend previous observations of thalamic gamma activity (Kempf et al., 2009) and are in line with findings of significant contralateral gamma increases observed in pallidal and subthalamic recordings from patients undergoing deep brain stimulation for various movement disorders (Androulidakis et al., 2007; Brücke et al., 2008, 2012; Ray et al., 2012), suggesting that movement-related gamma synchrony is common across different pathologies. Moreover, we could show that the onset of the gamma ERS was highly correlated with reaction time. This lends further support to the idea that movement related lateralized gamma band synchronization is a prokinetic

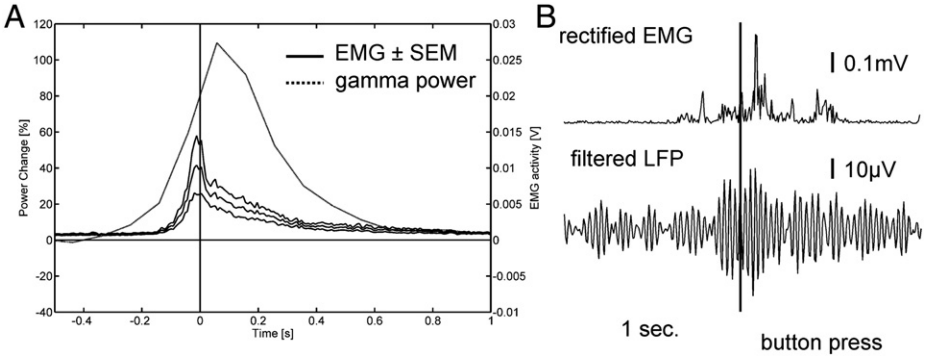

Fig. 4. (A) Averaged rectified EMG activity (continuous lines represent mean and mean ± SEM, respectively) recorded from the first dorsal interosseus muscles in 4 patients. Dashed black line shows averaged gamma activity from the contralateral VIM in these patients. Note the increase of muscle activity around 150 ms before button press (button press at time point 0). (B) Raw rectified EMG and filtered (60–80 Hz) LFP trace of one second length during a single trial in patient 4.

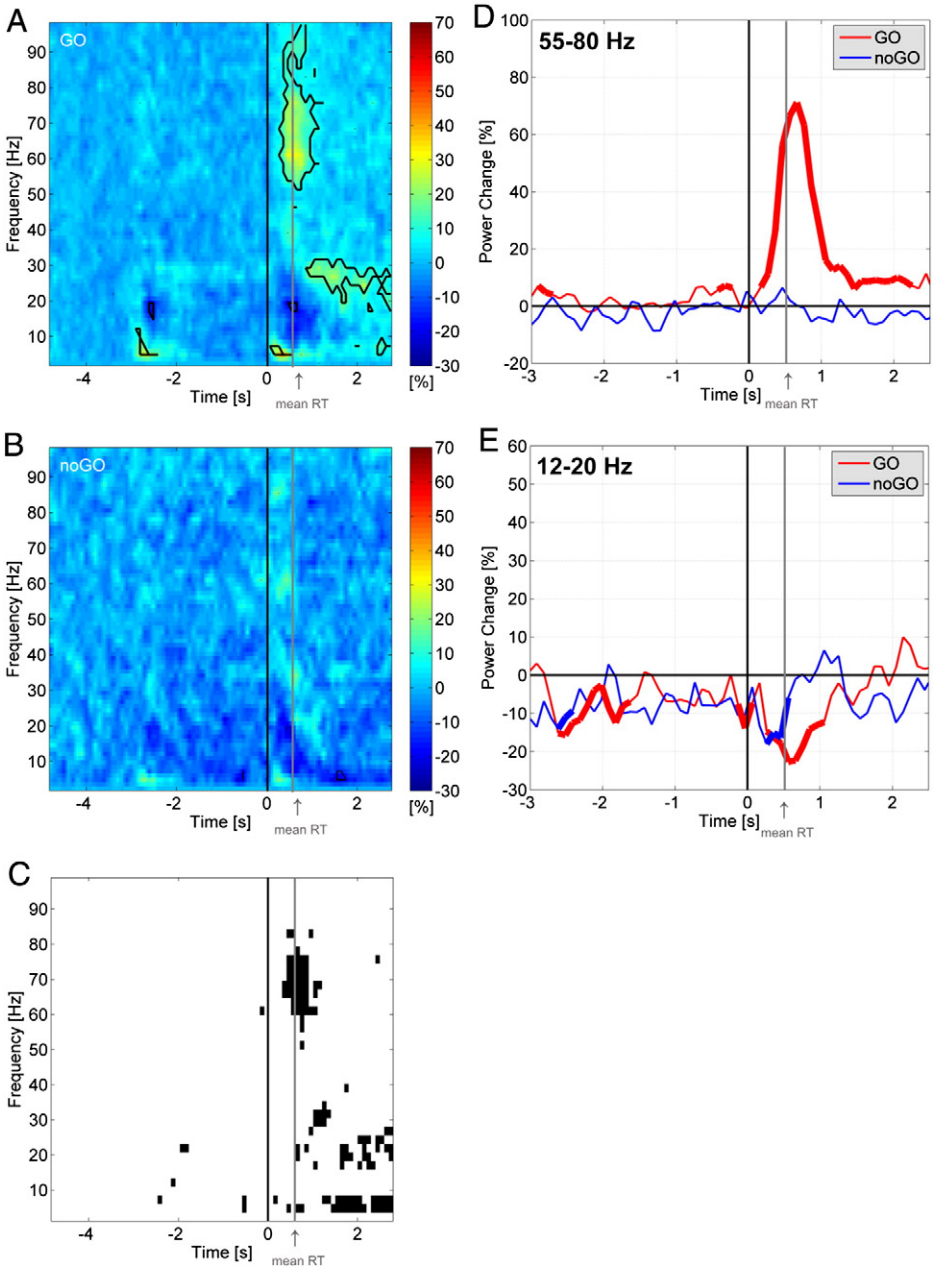

Fig. 5. (A + B) Time–frequency plots representing median oscillatory power changes of the contralateral VIM averaged to the imperative cue. Activity has been averaged over the three contact pairs ($n = 60$) per electrode and compared to baseline −5 to −3 s before the Go (A) or noGo cue (B) at time point 0, denoted by thick vertical line (contour lines indicate statistically significant changes compared to baseline ($p < 0.01$, FDR corrected). Thin line indicates mean reaction time (RT). (C) Wilcoxon's signed rank test between Go cue trials and noGo cue trials (statistically significant time–frequency bins in black ($p < 0.01$, FDR corrected). (D) Averaged spectral gamma activity (55–80 Hz) and (E) beta activity (12–20 Hz) from selected contact pairs ($n = 20$) expressed as percentage power changes. Thick lines indicate significant changes from baseline ($p < 0.05$, Wilcoxon's signed rank test).

activity (Jenkinson et al., in press; Litvak et al., 2012). Importantly, the VIM is embedded in the cerebello-thalamo-cortical circuit, receiving input from cerebellar nuclei (Sommer, 2003), which points to a more general movement-related pattern that may be not restricted to the cortico-basal ganglia-thalamo-cortical loop. Interestingly, variations in pre-cue gamma activity before the imperative cue were correlated with reaction time suggesting that baseline levels of thalamic gamma synchronization may relate to arousal and/or attention.

Limitations and clinical considerations in patients with essential tremor

It is important to bear in mind that our patients had essential tremor and the observed changes in thalamic activity might therefore be influenced by disease-related activity. However, oscillatory activity within a tremor-related network including the basal ganglia and thalamus has been described at frequencies around 4–7 Hz rather than in the gamma band in patients with essential tremor (Kane et al., 2009; Schnitzler et al., 2009). Moreover, our patients did not experience a significant tremor during recordings due to the short-lived postoperative microthalamotomy (stun) effect after electrode insertion leading to improvement in motor symptoms (Kondziolka and Lee, 2004). That said, the stun effect may have compromised our LFP recordings with focal gamma activity being susceptible to lesional effects, which may explain the variability in the degree of gamma synchronization across patients. Another critical point is our electrode localization in VIM which can only be considered presumptive.

However, postoperative MRI confirmed correct placement of macroelectrodes with at least 2 contacts in the thalamus in 9 out of 9

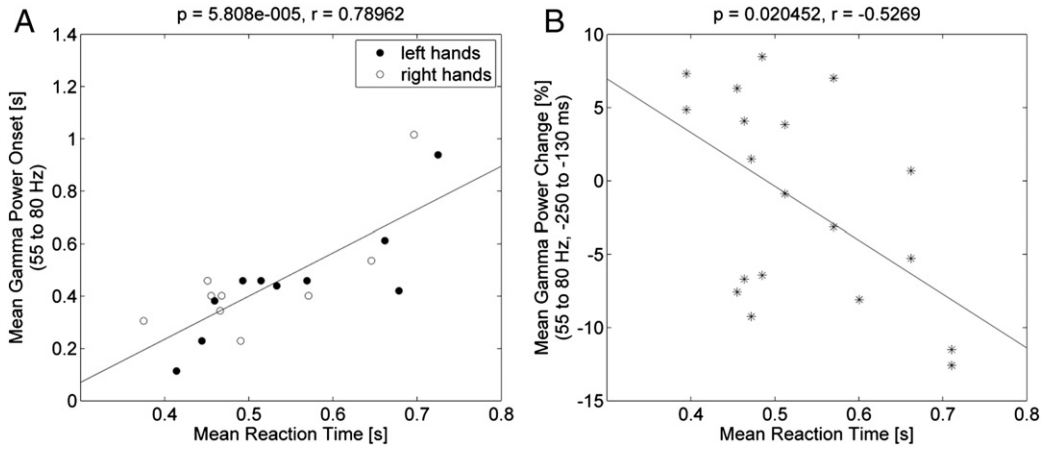

Fig. 6. (A) Scatterplot depicting gamma power onset time and mean reaction time ($n = 19$). The correlation was similar if analysed separately for the right (open circles) and left (filled circles) hand (R: r = 0.78, $p = 0.014$; L: r = 0.83, $p = 0.003$). (B) Scatterplot depicting averaged bilateral gamma power in the −300 ms to −130 ms time-window before GO cue and mean reaction time ($n = 19$). Similar results were obtained for the correlation of reaction time with ipsi- and contralateral pre-cue gamma power, respectively (ipsi: r = −0.517, $p = 0.023$; contra: r = −0.511, $p = 0.025$).

patients (case 1 had post-operative CT scan confirming correct placement of the electrode). Significant clinical improvement of tremor during chronic high frequency stimulation can be considered as further support for correct electrode placement in our patients, although active contacts not necessarily need to be placed within VIM as has been shown by effective high frequency stimulation of fibres in the zona incerta/posterior subthalamic area (Blomstedt et al., 2011).

It has been shown that micro-saccades may induce broad-band gamma synchronization in the EEG over frontal areas (Yuval-Greenberg et al., 2008). The predominant contralateral effect of movement-related gamma synchronization as well as the fact that we used bipolar derivations for thalamic recordings that are not contaminated by volume conduction from cortical areas (Wennberg and Lozano, 2003) makes it highly unlikely that the observed phasic movement-related thalamic gamma synchronization in our patients is contaminated by micro-saccades. Further, we only recorded EMG activity in 4 subjects. Thus, the onset of gamma synchronization prior to onset of EMG activity could only be revealed in a subgroup of patients as presented in Fig. 4. Since EMG recordings were missing in the majority of patients, this observation cannot be ascribed to the entire data set and is a limitation of the present work. Finally, the correlation of gamma band activity and reaction time was restricted to a group level analysis with a fixed chosen frequency band width selected according to the main event-related changes observed at the group level and not performed on a single trial basis with individually adjusted frequency bands. Future studies are needed to explore single trial data and relate the movement-related gamma ERS to onset of EMG activity at this level.

Functional significance of movement-related gamma synchronization

Go trials

Gamma activity in the basal ganglia is phasically increased by voluntary movements (Alegre et al., 2005; Alonso-Frech et al., 2006; Cassidy et al., 2002; Devos et al., 2006; Fogelson et al., 2006; Williams et al., 2002) and thus has been considered prokinetic (Brown, 2003) and related to motor processing (Engel et al., 2005; Jenkinson et al., in press). More specifically, the degree of gamma ERS may index movement parameters such as speed or movement amplitude possibly related to scaling of movement or motor vigor (Anzak et al., 2012; Brücke et al., 2012; Mazzoni et al., 2007) and the peak latency of the STN gamma ERS was shown to correlate with reaction time in patients with Parkinson's disease (Ray et al., 2012). Movement-related gamma synchrony in the basal ganglia nuclei is considered a feature of physiological activation since it occurs predominantly contralateral to the moved hand and is common across different pathologies (Androulidakis et al., 2007; Brücke et al., 2008) and paralleled by movement-related phasic increases of gamma activity at the cortical level (Crone et al., 1998; Crowell et al., 2012; Muthukumaraswamy, 2010) and increased subcortical-cortical coherence (Litvak et al., 2012). Our data extend these findings to the human thalamus, showing that lateralization of movement-related gamma synchrony occurs in subcortical motor areas irrespective of the underlying disease. Moreover, gamma synchronization occurred about movement onset (onset of EMG activity) as shown in a subgroup of patients (see Fig. 4), which is in further support of the notion that gamma activity may code for the scaling of movement parameters (Brücke et al., 2012). Spectral changes in the thalamus at lower frequency were similar to previous results reporting a movement-related beta ERD during self-paced and externally triggered movements (Klostermann et al., 2007; Paradiso et al., 2004). This movement-related activity pattern is similar to recent observations on LFP-MEG coherence changes between the subthalamic nucleus (STN) and motor and temporal cortical areas in patients with Parkinson's disease (Hirschmann et al., 2013; Litvak et al., 2012; Oswal et al., 2013). These studies ascribe a modulatory role to the increased STN-motor cortex gamma band coherence during movement that may be reciprocally related to a concomitantly observed decrease in STN-temporal cortex alpha band coherence pointing to functionally related systems (Oswal et al., 2013).

The spectral effects noted in the present study were picked up from a relatively circumscribed thalamic area. This area primarily receives cerebellar input. Our findings were, however, similar to those made in nodes of the cortex-BG-thalamo-cortical motor loop, raising the possibility that spectral features like upper band gamma reactivity are characteristics of subcortical motor loops rather than specifically characteristic of cortex-BG-thalamo-cortical motor loops (Fogelson et al., 2006). However, we did not explore the dependency of spectral features across contact pairs and their precise anatomical localisations in each hemisphere, as the goal of the current study was to explore gamma reactivity and its functional correlates.

The bilateral movement-related desynchronization in <35 Hz activity that may start up to several seconds before the movement may be related to more general processes of motor preparation that will allow changes in other frequencies (such as gamma band activity) to occur (Brown, 2007; Jenkinson et al., in press).

noGo trials

In our task noGo trials were less frequent compared to Go trials (20%/80%, respectively) and all imperative cues were preceded by a warning cue with laterality information at a fixed time interval of 3 s, which should have allowed for motor preparation following the warning cue (as supported by the beta ERD). In noGo trials the prepared movement had to be stopped and so a different pattern of oscillatory change was anticipated as compared to the Go trials. No significant change could be revealed in our patients. Previous studies have reported contrasting findings with a decrease in gamma synchronization during stopping in individual subjects in the pallidum (Brücke et al., 2008) but also gamma increase in the STN of Parkinson's disease patients (Ray et al., 2012) possibly related to a variable influence of the stop-signal on go-process activity (Lo et al., 2009; Ray et al., 2012).

The beta ERD observed after noGo cues is most likely related to initial motor preparation of prepotent responses that is reversed early after the imperative noGo cue with a significant relative increase in beta activity. This relative increase in beta activity may support the successful inhibition of the pre-prepared movement at the level of the thalamus. This finding is in line with earlier observations in the STN in Parkinson's disease patients (Kühn et al., 2004) as well as results from EEG studies supporting a role of beta activity in response inhibition (Pastötter et al., 2008; van Wijk et al., 2009).

Pre-cue thalamic gamma activity is correlated to reaction time

An interesting finding in our patients was the significant correlation between pre-cue levels of bilateral gamma activity in the time period immediately before the imperative cue and reaction time, so that higher levels of gamma activity were followed by faster reaction times. The human thalamus is actively involved in motor preparation as supported by an early thalamic slow negative movement-related potential prior to movement onset (Paradiso et al., 2004; Purzner et al., 2007). The thalamic contingent negative variation amplitude before the imperative Go cue correlated with reaction time in patients with essential tremor undergoing deep brain stimulation in the VIM (Nikulin et al., 2008), irrespective of the side of the movement. In our patients pre-cue gamma activity correlated with reaction time. Consistent with this, a role for gamma synchronization in shifting of attention and arousal has been posited (Buzsáki and Draguhn, 2004; Jenkinson et al., in press). Finely tuned thalamic gamma activity is modulated by the sleep-wake cycle and enhanced during startle, pointing to a dependence on the reticular activation system (Kempf et al., 2009). In line with this notion of thalamic gamma activity, we propose that the correlation of fluctuations in pre-cue thalamic gamma activity to motor performance reflects shifts in attention/global arousal levels. Our data suggest that spontaneously increased bilateral thalamic gamma activity is related to higher levels of attention with correspondingly faster reaction times, whereas the gamma synchronization that occurs at movement onset contralateral to the side of the movement may be more specifically related to the processing of motor parameters such as movement vigor or force.

Conclusion

Our results lend further support to the idea that lateralized gamma band synchronization is a physiological feature of movement-related activity within subcortical motor circuits. The onset and degree of gamma synchronization may reflect processing of motor parameters such as force or vigor (Anzak et al., 2012; Mazzoni et al., 2007). In contrast, the observed fluctuations in pre-cue gamma activity that correlate with reaction time may relate to shifts in global arousal and attention. Low frequency activity in the thalamus is symmetrically suppressed during movement pointing to a functional distinction between oscillatory activities of different frequencies that is preserved across motor structures, possibly providing a means of functionally segregating related processing in the motor system (Fogelson et al., 2006; Oswal et al., 2013).

Disclosure

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Conflict of interest

We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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