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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.

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