NeuroImage: Clinical 9 (2015) 450–457

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Adaptive grip force is modulated by subthalamic beta activity in Parkinson's disease patients

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ARTICLE INFO

Article history:
Received 30 March 2015
Received in revised form 7 July 2015
Accepted 11 September 2015
Available online 29 September 2015

Keywords:
Subthalamic nucleus
Motor control
EEG
Synchronization
Beta oscillations

ABSTRACT

Introduction: Healthy subjects scale grip force to match the load defined by physical object properties such as weight, or dynamic properties such as inertia. Patients with Parkinson's disease (PD) show an elevated grip force in dynamic object handling, but temporal aspects of anticipatory grip force control are relatively preserved. In PD patients, beta frequency oscillatory activity in the basal ganglia is suppressed prior to externally paced movements. However, the role of the subthalamic nucleus (STN) in anticipatory grip force control is not known.
Methods: After implantation of deep brain stimulation (DBS) electrodes in the STN, PD patients performed adaptive and voluntary grip force tasks, while we recorded subthalamic local field potentials (LFP) and scalp EEG.
Results: During adaptive grip force control (Shake), we found event related desynchronization (ERD) in the beta frequency band, which was time-locked to the grip force. In contrast, during voluntary grip force control (Press) we recorded a biphasic ERD, corresponding to peak grip force and grip force release. Beta synchronization between STN and cortical EEG was reduced during adaptive grip force control.
Conclusion: The time-locked suppression of beta oscillatory activity in the STN is in line with previous reports of beta ERD prior to voluntary movements. Our results show that the STN is involved in anticipatory grip force control in PD patients. The difference in the phasic beta ERD between the two tasks and the reduction of cortico-subthalamic synchronization suggests that qualitatively different neuronal network states are involved in different grip force control tasks.

1. Introduction

Scaling and temporal adjustment of precision grip force is a highly efficient skill in everyday life. While grasping an object, healthy subjects precisely scale the applied grip force to match the load defined by physical object properties, such as weight and shape, as well as dynamic properties such as inertia (Prodoehl et al., 2009).

Neural implementation of precision grip force control is embedded in a complex network involving pre-motor cortical areas, the cerebellum and sub-cortical structures, particularly the basal ganglia (Nowak et al., 2007; Dafotakis et al., 2008; Prodoehl et al., 2009). Neuroimaging studies have shown that basal ganglia are involved in both predictive (dynamic) aspects of grip force control, as well as parameterization of grip force scaling (Vaillancourt et al., 2007; Prodoehl et al., 2008, 2009; Wasson et al., 2010).

In Parkinson's disease (PD) a distinction between dynamic grip force control and grip force scaling is observed: Whereas temporal aspects of dynamic grip force control are relatively preserved (Nowak and Hermsdörfer, 2002; Albert et al., 2010), grip force scaling is pathologically elevated in PD patients (Fellows et al., 1998). Direct evidence for the involvement of the subthalamic nucleus (STN) in grip force scaling has been obtained in PD patients treated by deep brain stimulation (DBS), where pathologically elevated peak grip force could be normalized by chronic DBS (Wenzelburger et al., 2002).

For temporal adaptation of precision grip force, the cerebellum is another key structure: It has been shown that patients with cerebellar disease suffer from impaired grip force control (Rost et al., 2005; Nowak et al., 2007). In this line, grip force adaptation relies on internal

Abbreviations: PD, Parkinson's disease; DBS, deep brain stimulation; STN, subthalamic nucleus; ERD, event related desynchronization; ERP, event related potentials.

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http://dx.doi.org/10.1016/j.nicl.2015.09.010

anticipatory models in the brain, which are mainly based in the cerebellum (Miall et al., 1993; Wolpert and Miall, 1996; Wolpert et al., 1998). The tight functional connections between basal ganglia and cerebellum (Hoshi et al., 2005; Bostan et al., 2010), suggest a dynamic interplay between the cerebellum and the basal ganglia in dynamic grip force control. While data from neuroimaging, anatomy and behavior point to an important role of basal ganglia networks in grip force control, the underlying neuronal activity is still unknown.

Various studies have demonstrated high beta power in the STN of PD patients (Brown et al., 2001) and the amount (Kühn et al., 2004; Pogosyan et al., 2010; Zaidel et al., 2010) and stability (Little et al., 2012) of beta activity in the STN correlates negatively with motor performance. The outstanding role of beta oscillations for bradykinesia has been demonstrated by inducing a frequency-specific impairment in a grip force task upon low-frequency stimulation in the STN of PD patients (Chen et al., 2011). Whereas beta activity in the basal ganglia may simply be an epiphenomenon of enhanced neuronal synchronicity during movement initiation, the suppression of beta activity before movement initiation in event-related tasks (Brown et al., 2001; Kühn et al., 2006; Oswal et al., 2012) provides evidence that dynamic changes in beta oscillations are critical for motor control *per se*. Extending this idea, dissociation of salient cues and actual motor execution supports the hypothesis that beta desynchronization prospectively modulates executive motor processing (Oswal et al., 2012; Gremel and Costa, 2013). To investigate prospective motor control, we examined how STN beta activity is modulated with adaptive grip force control during a shaking movement as compared to a control condition with voluntary grip-force initiation.

2. Methods

2.1. Patients and surgery

We included 6 PD patients who underwent DBS in the subthalamic nucleus (STN). Patients' demographic data and clinical details are summarized in Table 1. Bilateral DBS electrodes (Model 3389, Medtronic Neurological Division, Minneapolis, MN, USA) were implanted after MRI-based direct targeting of the STN (Bejjani et al., 2000). Intraoperatively, accurate implantation of the electrodes within the STN was verified by microelectrode recordings, followed by test stimulation to assess the clinical response, and by CT-imaging to reconstruct the effective electrode position (Schrader and Mehdorn, 2004). The data presented here were recorded on the second post-operative day at preoperative L-dopa levels (ON condition). Local field potentials (LFP) were recorded on temporarily externalized wires before implantation of the DBS impulse-generator. All patients gave informed written consent to participate in the study. The study was approved by the institutional ethics review board (*Kantonale Ethikkommission Zurich* KEK-ZH: 2012-0327).

2.2. Grip force recording

Adaptive grip force control during motor tasks was measured by a customized device. This device determines and records the applied grip force of the patient's fingers with an in-built force sensor and contains linear acceleration sensors for simultaneous registration of movement in three dimensions (Fig. 1A). In the case of oscillatory movements (e.g. shaking), force adaptation relies on an anticipatory internal model. Successful anticipatory grip force control is characterized by a matching of the applied grip force to the loading forces (mass + acceleration) of the device, which were generated by the movement. The device is cuboid ($60 \times 60 \times 40$ mm) and weighs 300 g (Fig. 1B) and emits a TTL pulse for synchronization with other data acquisition systems. To quantify the accuracy of the time-dependent grip-force adaptation, we calculated the correlation coefficient between grip force and loading force (Table 2) as a quantitative measure for the quality of grip force adaptation (Nowak and Hermsdörfer, 2005).

2.3. LFP and EEG recordings

The LFP was recorded from all contacts within both STN of each patient (sampling rate 200 Hz). Simultaneously, we recorded scalp EEG from a 12-channel subset of the 10–20 system at the fronto-polar (Fp1/Fp2), frontal (F3/F4), central (C3/C4), occipital (O1/O2) and midline (Fpz/Fz/Cz/Oz) electrode sites (Fig. 1C). The central midline electrode Cz was used as recording reference for EEG and LFP. As verified by post-operative reconstruction of the electrode position, the second lowest contact (Fig. 1D, Sarnthein et al., 2013) was located in the motor part of the STN in all patients and taken for further analysis. To reduce movement and electrode artifacts, we digitally re-referenced all signals to a Laplacian montage with weighted averages of the surrounding deep brain electrodes (for LFP channels) and surface electrodes (for EEG channels). This montage allowed for a significant reduction of the artifact level, but at the same time ensured the linear independence of cortical and LFP signals for the calculation of cortico-subthalamic synchronization.

2.4. Motor tasks

All experiments were performed in a sitting position. Patients grasped the measurement device with all fingers of one hand, while the other arm was in a resting position. To minimize interference with visual feedback, all experiments were performed with closed eyes.

For the shaking task (Shake), patients were instructed to shake the cube in a predefined manner, i.e. to perform consecutive point-to-point up- and downward movements in front of the trunk with an amplitude of about 20 cm. This shaking movement was self-paced, but patients were instructed to reach a frequency of approximately 2 Hz, if possible, depending on bradykinesia and rigor. After instruction of the patients and test-runs where necessary, we recorded a 90 s-epoch for each hand.

Two control tasks were performed: In a hold condition (Hold), the device was held steadily in one hand without movement to measure the 'resting state' background level of the STN and cortical EEG signal. For a pressing condition (Press), patients pressed rhythmically on the device in the same frequency as the arm was moved during the shaking task, but without moving the device itself. This task was introduced to control for *voluntary* self-paced grip-force initiation (Press), as compared to *anticipatory* grip force control adjusted by somatosensory feedback (Shake). By this experimental design we were able to compare two

Table 1
Demographic and clinical patient characteristics. UPDRS: Unified Parkinson's Disease Rating Scale, ON/OFF values of preoperative L-dopa challenge test; LED: levodopa equivalent dose at the time of recording.

ID	Age [y]	Gender	Parkinson type	Disease duration [y]	Hoehn–Yahr Scale	UPDRS III ON/OFF	LED [mg/d]
1	61	F	Rigid akinetic	9	2	12/24	850
2	63	M	Tremor dominant	12	2	16/55	1000
3	48	M	Young onset	10	2.5	11/53	500
4	47	M	Young onset	12	2	18/46	1000
5	73	M	Tremor dominant	10	2	18/37	1000
6	53	M	Rigid akinetic	14	2.5	28/52	2300