NeuroImage 90 (2014) 15–23

Contents lists available at ScienceDirect

NeuroImage

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

Levodopa reinstates connectivity from prefrontal to premotor cortex during externally paced movement in Parkinson's disease

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ARTICLE INFO

Article history:
Accepted 14 November 2013
Available online 22 November 2013

Keywords:
Dynamic causal modelling (DCM)
Electroencephalography (EEG)
Oscillatory coupling
Effective connectivity
Motor system

ABSTRACT

Dopamine deficiency affects functional integration of activity in distributed neural regions. It has been suggested that lack of dopamine induces disruption of neural interactions between prefrontal and premotor areas, which might underlie impairment of motor control observed in patients with Parkinson's disease (PD). In this study we recorded cortical activity with high-density electroencephalography in 11 patients with PD as a pathological model of dopamine deficiency, and 13 healthy control subjects. Participants performed repetitive extension–flexion movements of their right index finger, which were externally paced at a rate of 0.5 Hz. This required participants to align their movement velocity to the slow external pace. Patients were studied after at least 12-hour withdrawal of dopaminergic medication (OFF state) and after intake of the dopamine precursor levodopa (ON state) in order to examine oscillatory coupling between prefrontal and premotor areas during respectively low and high levels of dopamine. In 10 patients and 12 control participants multiple source beamformer analysis yielded task-related activation of a contralateral cortical network comprising prefrontal cortex (PFC), lateral premotor cortex (lPM), supplementary motor area (SMA) and primary motor cortex (M1). Dynamic causal modelling was used to characterize task-related oscillatory coupling between prefrontal and premotor cortical areas. Healthy participants showed task-induced coupling from PFC to SMA, which was modulated within the γ-band. In the OFF state, PD patients did not express any frequency-specific coupling between prefrontal and premotor areas. Application of levodopa reinstated task-related coupling from PFC to SMA, which was expressed as high-β–γ coupling. Additionally, strong within-frequency γ-coupling as well as cross-frequency θ–γ coupling was observed from PFC to lPM. Enhancement of this cross-frequency θ–γ coupling after application of levodopa was positively correlated with individual improvement in motor function. The results demonstrate that dopamine deficiency impairs the ability to establish oscillatory coupling between prefrontal and premotor areas during an externally paced motor task. Application of extrinsic dopamine in PD patients reinstates physiological prefrontal–premotor coupling and additionally induces within- and cross-frequency coupling from prefrontal to premotor areas, which is not expressed in healthy participants.

Introduction

Patients with Parkinson's disease (PD) exhibit difficulties in initiating and executing movements (Lang and Lozano, 1998a,b). This has been attributed to a progressive degeneration of dopaminergic midbrain neurons, which impairs action selection and reinforcement via motor loops connecting the cortex and basal ganglia (Alexander et al., 1986; Redgrave et al., 2010). At the cortical level, the functional changes associated with motor impairment in PD go beyond alterations in primary motor and premotor regions, involving the prefrontal cortex (PFC). The PFC plays an important role during motor control, e.g. when selectively attending to an action or online monitoring of movements (Durstewitz et al., 2000; Jueptner et al., 1997; Ullsperger and von Cramon, 2006). In PD, several executive functions that have been assigned to the PFC are impaired (Cools and D'Esposito, 2011) and functional magnetic resonance imaging (fMRI) studies revealed abnormal functional interactions between the PFC and motor areas during movement in PD patients (Jahanshahi et al., 2010; Rowe et al., 2002b, 2010;

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1053-8119
http://dx.doi.org/10.1016/j.neuroimage.2013.11.023

Wu et al., 2010). These abnormal prefrontal–motor connectivity patterns are modified by dopaminergic medication (Jahanshahi et al., 2010; Rowe et al., 2002b, 2010).

Neurophysiologically, PD is characterized by pathological coupling between spatially remote oscillating neural regions (Brown, 2007; Schnitzler and Gross, 2005; Timmermann et al., 2003). So far the oscillatory coupling between PFC and premotor areas in PD has not been studied. Recent advances in deep and transcranial brain stimulation allow adjusting stimulation to ongoing oscillatory activity in a closed-loop fashion (Little et al., 2013; Thut et al., 2011). Thus, improved knowledge of pathological oscillatory activity underlying motor impairment in PD is crucial for the development of novel treatment strategies. In this study, we combined source analysis and dynamic causal modelling of induced responses (Chen et al., 2008) to assess changes in oscillatory coupling within a cortical network comprising the left PFC, left lateral premotor cortex (lPM), supplementary motor area (SMA), and primary motor cortex (M1). We recorded high-density electroencephalography (EEG), whilst PD patients both ON and OFF medication, and healthy control participants performed a motor task that required an attentive closed-loop motor control. The task consisted of externally-paced sinusoidal extension–flexion movements of the right index finger, which has been linked to PFC activation in PD (Cerasa et al., 2006; Gonzalez-Garcia et al., 2011) and induces oscillatory activity in cortical neural populations (Gross et al., 2002; Pollok et al., 2005). Based on the previous fMRI studies, we hypothesized that PD patients express abnormal movement-induced oscillatory coupling from prefrontal to lateral and medial premotor areas, which is strongly modulated by dopaminergic medication.

Participants and methods

Participants

Eleven patients with clinical diagnosis of PD according to the British Brain Bank criteria (Hughes et al., 1992) without dementia and 13 healthy individuals participated in the study. Exclusion criteria were as follows: age ≥80 years, neurological disease other than PD, abnormal MRI, and treatment with deep brain stimulation. One PD patient and one control participant were later excluded (see "source analysis"), leaving 10 patients (four females; age 58 ± 9.9 years, mean ± SD) and 12 healthy control participants (six females; age 64 ± 7.2 years). Clinical details are summarized in Table 1. All participants were right-handed as revealed by self-report. In accordance with the declaration of Helsinki all participants gave their written informed consent to the study, which was approved by the local ethics committee of the Faculty of Medicine at the University of Cologne (study-nr: 08 067).

Experimental conditions

Participants were seated in a comfortable chair with their eyes closed. They were asked to perform repetitive slow extension–flexion movements of the right index finger in the metacarpophalangeal (MCP) joint paced at 0.5 Hz by a metronome, while the right hand (ulnar side down) was resting on a desk. They were instructed to perform the movements at constant speed and amplitude, aligning the movement rate to the pace as defined by the metronome. The movement range was approximately 30° in the horizontal plane. Before the EEG recordings, all participants were trained on the task for 5 min.

The main experiment consisted of 20 trials during which participants continuously performed the repetitive extension–flexion movements with their eyes closed. Each trial lasted for 10 s followed by a short break (5–10 s) to avoid fatigue. We also included a baseline condition without movement, where subjects had to keep still with their eyes closed (rest condition) for ~5 min. Two examiners monitored the task performance during the motor task and ensured that participants did not fall asleep during the rest condition. Additionally, all participants performed a second motor task. The second task tested highly automatic fast finger movements, which induced more localized oscillatory activity in core motor and premotor regions, but not the prefrontal cortex, which required a different network model (Herz et al., 2013).

All patients were tested in the morning in the practical OFF state 12 h after withdrawal of their dopaminergic medication. Immediately prior to the experiment, a movement disorders specialist (MTB) assessed the Unified Parkinson's disease rating scale III (UPDRS-III) (Fahn et al., 1987). After completing the testing in the OFF state, patients received 200 mg of fast-released soluble levodopa (Madopar LT®, La Roche, Basel, Switzerland) and motor improvement was assessed consecutively every 15 min until a marked improvement of akinesia and rigidity was observed (at least 15% difference between UPDRS-ON and UPDRS-OFF). We then repeated EEG recordings in the ON state. PD patients did not perform any motor tasks during the break to avoid interference effects. One patient developed severe dyskinesias after application of levodopa and was therefore not tested in the ON state. Healthy participants performed the experiments only once without application of levodopa.

Table 1
Patient clinical details. m = male; f = female; LEDD = levodopa-equivalent daily dose. LEDD were calculated according to (Tomlinson et al., 2010).

Patient	Age/sex	Disease duration (years)	Parkinsonism	UPDRS (OFF/ON)	LEDD
1	47 f	13	left	46/27	1133 mg/d
2	58 f	4	right	24/15	860 mg/d
3	65 f	14	right	35/22	905 mg/d
4	64 f	1	right	17/8	240 mg/d
5	50 m	2	left	11/6	150 mg/d
6	46 m	5	left	31/15	260 mg/d
7	53 m	13	left	22/9	950 mg/d
8	75 m	9	left	34/16	650 mg/d
9	69 m	10	left	30/15	1000 mg/d
10	53 m	7	right	14/12	965 mg/d

Magnetic resonance imaging

Before the EEG experiment, T1-weighted structural magnetic resonance images (MRI) of the whole brain were acquired on a 3-Tesla Trio scanner (Siemens, Erlangen, Germany) using a 3D-MDEFT sequence (Modified Driven Equilibrium Fourier Transform; repetition-time = 1930 ms, echo-time = 5.8 ms, flip-angle = 18°, slice-thickness = 1.25 mm) for the control group and on a 1.5-Tesla Intera scanner (Philips, Amsterdam, the Netherlands) using a 3D-TFE sequence (turbo field echo; repetition-time = 20 ms, echo-time = 4.6 ms, flip-angle = 25°, slice thickness = 2 mm) for patients. In four control subjects and two patients, MR images could not be acquired because of claustrophobia. The MR images were transformed to Talairach-space in Brainvoyager software (Brain Innovation, Maastricht, The Netherlands) and a mesh of the head was generated for electrode co-registration. If no structural MRI was available, we used a standard brain template for electrode co-registration and source analysis.

Electroencephalography

122 electrodes were mounted on the head using an elastic cap in a spherical array (Easy-Cap, Herrsching, Germany). Optimal positioning of EEG electrodes was ensured using an ultrasound localization system (CMS20, Zebris, Isny, Germany) by inspecting position of the most anterior, posterior and lateral electrodes of the cap. EEG-data were recorded with a 122-channel EEG-system (Braintronics, Almere, The Netherlands) after assuring that impedances of all electrodes were ≤10 kΩ. EEG-signals were amplified, band-pass filtered from 0.87 Hz to 344 Hz and digitized at a sampling rate of 1024 Hz. EEG-data preprocessing was carried out on a personal computer using the brain electrical source analysis (BESA) software (BESA, Graefelfing, Germany).