Brain Stimulation 6 (2013) 147–154

Contents lists available at SciVerse ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Parieto-motor functional connectivity is impaired in Parkinson's disease

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ARTICLE INFO

Article history:
Received 8 December 2011
Received in revised form
20 March 2012
Accepted 23 March 2012
Available online 24 April 2012

Keywords:
Parkinson's disease
Transcranial magnetic stimulation
Dopaminergic treatment
Bradykinesia
Parietal cortex

ABSTRACT

Background: Bradykinesia in Parkinson's disease is associated with a difficulty in selecting and executing motor actions, likely due to alterations in the functional connectivity of cortico-cortical circuits.
Objective/Hypothesis: Our aims were to analyse the functional interplay between the posterior parietal cortex and the ipsilateral primary motor area in Parkinson's disease using bifocal transcranial magnetic stimulation, to evaluate its modulation by dopaminergic treatment and its relationship to a simple choice reaction task.
Methods: We studied 12 Parkinson's disease patients with and without dopaminergic treatment and 12 healthy controls. A paired-pulse transcranial magnetic stimulation protocol was applied over the right posterior parietal cortex and the right primary motor area using different conditioning stimulus intensities and interstimulus intervals. Reaction and movement times were studied by a simple choice reaction task.
Results: In controls, we observed a significant facilitation of motor evoked potential amplitudes at 4 ms interstimulus interval when conditioning stimulus intensity was set to 90% of resting motor threshold. This functional interaction was not observed in Parkinson's disease patients without dopaminergic treatment and was not restored with treatment. Moreover, correlation analyses revealed that Parkinson's disease patients with less impaired parieto-motor interaction were faster in executing reaching movements in a choice reaction time task, suggesting that the functional parieto-motor impairment described here could be related to bradykinesia observed in Parkinson's disease patients.
Conclusions: Parieto-motor functional connectivity is impaired in Parkinson's disease. The reduced efficacy of this connection could be related to presence of bradykinesia previously observed in Parkinson's disease.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder commonly diagnosed as motor triad of symptoms including tremor, rigidity and bradykinesia. The loss of dopaminergic projections caused by the degeneration of the Substantia Nigra pars compacta (SNc) in PD leads to alterations in the function of cortical areas including primary motor cortex (M1) and other non-primary motor areas [1–3], that are probably due to a defective control of the ascending thalamocortical system [4]. The posterior parietal cortex (PPC) has been suggested as a key area involved in selecting and executing motor actions, receiving inputs from sensory association cortices and connecting to motor and premotor areas [5–9]. Positron emission tomography (PET) and functional MRI (fMRI) studies have shown that alterations in PPC neural activity are associated

Francisco J. Palomar, Virginia Conde, Fátima Carrillo and Pablo Mir were supported by grants from the Ministerio de Ciencia e Innovación de España (SAF2007-60700); the Instituto de Salud Carlos III (PI10/01674); the Consejería de Innovación, Ciencia y Empresa de la Junta de Andalucía (CVI-02526); the Consejería de Salud de la Junta de Andalucía (PI-0377/2007, PI-0741/2010), the Sociedad Andaluza de Neurología and the Jacques and Gloria Gossweiler Foundation.

Miguel Fernández-del-Olmo was supported by the Ministerio de Ciencia e Innovación (PSI2008-03175), Spain.

Giacomo Koch was supported by the Jacques and Gloria Gossweiler Foundation and by grants of the Italian Ministry of Health (RF08.18, MR08.7, GR).

The authors have no conflict of interest.

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doi:10.1016/j.brs.2012.03.017

Table 1
Clinical characteristics of Parkinson's disease patients.

Case	Gender	Age (y)	Age at onset (y)	Handedness	UPDRS (section III) ON/OFF	H&Y ON/OFF	UPDRS (section I–IV) ON/OFF	Treatment dose/ day, mg
1	M	73	67	R	25/44	1/2	37/64	Ropirinole 16 L-Dopa 450
2	F	70	66	R	16/28	1/2	18/35	Rasagiline 1 L-Dopa 400
3	F	49	46	R	15/35	1/2	25/51	Rasagiline 1 L-Dopa 300 Ropirinole 15
4	M	66	58	R	19/35	1/2	24/47	Pramipexole 2.8 L-Dopa 600
5	F	57	52	R	9/18	1/1	10/22	Pramipexole 2.8
6	M	47	44	R	20/36	1/2	31/52	Rasagiline 1 L-Dopa 300 Pramipexole 2.8
7	F	43	30	R	26/47	1/2	36/69	Pramipexole 2.1 Trihexyphenidyl 9 L-Dopa 700
8	M	77	73	R	21/36	1/1.5	26/47	L-Dopa 400 Pramipexole 2.1 Selegiline 10
9	M	50	46	R	11/18	1/1	15/26	Pramipexole 2.1
10	F	58	55	R	17/35	1/2	23/50	L-Dopa 450 Pramipexole 2.1 Rasagiline 1
11	M	46	40	R	24/41	1/2	30/52	L-Dopa 300 Pramipexole 4.2 Selegiline 10
12	M	67	59	R	32/51	1.5/2	42/72	Ropirinole 24 L-Dopa 300 Rasagiline 1

H&Y, Hoehn & Yahr stage; M, male; F, female; R, right.

with movement preparation or movement execution in PD, suggesting a relationship between these PPC alterations and akinesia or bradykinesia [10,11]. In addition, abnormalities in other different non-primary motor areas have also been identified in PD, which were partially restored with dopaminergic therapy [1,12].

Transcranial magnetic stimulation (TMS) is a non-invasive technique widely used to explore the central nervous system pathways in humans, and with two stimulating coils provides the unique opportunity to study causal functional connections between distinct cortical areas. A conditioning stimulus (CS) is first used to activate putative pathways that originate from the stimulation site, whereas a second test stimulus (TS), delivered over the M1 a few milliseconds (ms) later, is used to explore changes in excitability produced by the input [9,13–19]. TMS of M1 evokes a small motor evoked potential (MEP) on contralateral hand muscles, which is measurable with surface electromyography (EMG). In young healthy subjects at rest, this response is enhanced by a previous ipsilateral PPC stimulation delivered with a short interval in the range of few milliseconds, which suggests the activation of a short-latency cortico-corticol pathway originating from PPC [20]. Notably, there are no significant differences between these parieto-motor connections in the two hemispheres [20,21]. Indeed, this PPC to M1 connection is selectively activated during early phases of the preparation and planning of reaching and grasping movements towards contralateral visual target [22,23].

Hypothesis

Our aim was to study in PD patients right hemisphere PPC–M1 connectivity at rest using this paired-pulse TMS protocol. We also aimed to investigate its possible modulation by dopaminergic treatment and the relationship with reaction and movement times in a simple choice reaction time task. We hypothesize that the right PPC–M1 connection could be impaired in PD patients and that this impairment could be directly related to a predictable slowness in movement time (bradykinesia) in a simple choice reaction time task.

Methods

Subjects

Twelve patients (7 males and 5 females) with defined diagnosis of PD, according to the criteria of the United Kingdom PD Society Brain Bank, were recruited from the Movement Disorders Outpatient Clinic at the Hospital Universitario Virgen del Rocío in Seville. Mean age of PD patients was 58.4 ± 3.4 years. We used section III of the UPDRS for the motor evaluation. Hoehn & Yahr and Schwab & England scales were also used for global clinical evaluation of PD patients. These patients were studied both with (ON) and without (OFF) dopaminergic treatment. We separated two studies by a week and counterbalanced the treatment situation in the first study between PD patients. All studies were performed in the afternoon. In the ON condition, patients were studied after the intake of their usual medication and under the maximum treatment effect. We ensure that this effect was kept constant during the whole study. In the OFF condition, patients remained at least 18 h without dopaminergic medication before the experiment. Clinical data of all PD patients are summarized in Table 1. Twelve healthy subjects with a similar age (mean: 63.2 ± 1.9 years) were used as a control group. All subjects were right-handed as measured by the Edinburgh Handedness Inventory, and they gave written informed consent for the study. The experimental procedures used were approved by the local Ethics Committee and were carried out in accordance with the Declaration of Helsinki.