Neurobiology of Aging 35 (2014) 2592–2602

Contents lists available at ScienceDirect

Neurobiology of Aging

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

Cortico-striatal-thalamic network functional connectivity in hemiparkinsonism

Federica Agosta [a], Francesca Caso [a], Iva Stankovic [b], Alberto Inuggi [a], Igor Petrovic [b], Marina Svetel [b], Vladimir S. Kostic [b], Massimo Filippi [a,*]

[a] Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy
[b] Clinic of Neurology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

ARTICLE INFO

Article history:
Received 2 December 2013
Received in revised form 24 April 2014
Accepted 8 May 2014
Available online 11 June 2014

Keywords:
Hemiparkinsonism
Parkinson's disease (PD)
Cortico-striatal-thalamic network
Resting state functional MRI (RS fMRI)

ABSTRACT

Cortico-striatal-thalamic network functional connectivity (FC) and its relationship with levodopa (L-dopa) were investigated in 69 patients with hemiparkinsonism (25 drug-naïve [n-PD] and 44 under stable/optimized dopaminergic treatment [t-PD]) and 27 controls. Relative to controls, n-PD patients showed an increased FC between the left and the right basal ganglia, and a decreased connectivity of the affected caudate nucleus and thalamus with the ipsilateral frontal and insular cortices. Compared with both controls and n-PD patients, t-PD patients showed a decreased FC among the striatal and thalamic regions, and an increased FC between the striatum and temporal cortex, and between the thalamus and several sensorimotor, parietal, temporal, and occipital regions. In both n-PD and t-PD, patients with more severe motor disability had an increased striatal and/or thalamic FC with temporal, parietal, occipital, and cerebellar regions. Cortico-striatal-thalamic functional abnormalities occur in patients with hemiparkinsonism, antecede the onset of the motor symptoms on the opposite body side and are modulated by L-dopa. In patients with hemiparkinsonism, L-dopa is likely to facilitate a compensation of functional abnormalities possibly through an increased thalamic FC.

1. Introduction

In Parkinson's disease (PD), dopamine deficiency in the striatum induces imbalance of the direct and indirect pathways, and ultimately leads to insufficient thalamo-cortical facilitation (Lees et al., 2009). A neurophysiological hallmark of PD is a spontaneous neural oscillations change across the cortico-striatal-thalamic network (Gatev et al., 2006). Resting-state (RS) functional MRI (fMRI) allows the characterization of low-frequency, spontaneous fluctuations of blood oxygenation level-dependent signals across the brain (Biswal et al., 1995). RS fMRI has several advantages for clinical applications compared with traditional, task-based approach, such as a broader sampling of patients populations, circumventing task-related confounds, the possibility to study multiple cortical systems using the same fMRI data set, and a better signal to noise ratio (Fox and Greicius, 2010). To date, only a few studies assessed the RS fMRI pattern of the cortico-striatal-thalamic-cortical circuits in mild to moderate patients with PD, most of which report reduced functional connectivity (FC) in some regions and decreased FC in others relative to healthy controls (Hacker et al., 2012; Helmich et al., 2010; Kwak et al., 2010, 2012; Wu et al., 2009a, 2009b; Yang et al., 2013; Yu et al., 2013). A levodopa (L-dopa)-induced spatial remapping of the cortico-striatal connectivity has also been detected in chronically treated PD patients (Kwak et al., 2010, 2012; Wu et al., 2009a, 2009b), suggesting that the clinical improvement associated with dopaminergic treatment could be related to the dopaminergic modulation of RS FC. Only 2 recent studies have suggested that dopaminergic-related changes in FC occur also in drug-naïve (n-PD) cases (Choe et al., 2013; Esposito et al., 2013).

At clinical presentation, the motor manifestations of PD are typically restricted to one side of the body, a condition known as hemiparkinsonism (Hughes et al., 1992; Lees et al., 2009). Even in initial phase, however, a bilateral putaminal dopamine uptake reduction occurs (Seibyl et al., 1995). Therefore, in hemiparkinsonian patients, the cerebral hemisphere ipsilateral to the initially affected limbs can be considered "presymptomatic" as for motor disturbances. In this study, we used RS fMRI to investigate the FC of the cortico-striatal-thalamic networks in patients with hemiparkinsonism and its

* Corresponding author at: Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy. Tel.: +39 02 26433033; fax: +39 02 26433031.
E-mail address: m.filippi@hsr.it (M. Filippi).

0197-4580/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2014.05.032

association with motor disability. We hypothesized that patients with hemiparkinsonism would exhibit an altered FC of the cortico-striatal networks in comparison to healthy controls, and that RS fMRI abnormalities would occur in the affected brain hemisphere as well as in the presymptomatic one, that is, at and before motor symptom onset. We also hypothesized that RS fMRI would be sensitive to functional abnormalities preceding structural brain damage. For this reason, investigations of gray matter (GM) atrophy and white matter (WM) microstructural damage using structural MRI and diffusion tensor (DT) MRI were included.

To assess L-dopa effects on the brain networks at the earliest stage of PD, we included both n-PD patients and patients under stable/optimized dopaminergic treatment (t-PD). Although dopaminergic agents elicit a well established immediate and dramatic response consisting of improved mobility (short-duration response) (Fahn et al., 2004), it is well known that the motor response to dopamine therapy involves also a more gradual improvement in motor function (long-duration response) (Zhuang et al., 2013). The long-duration response has been hypothesized to contribute to the response to therapy that develops over days to weeks of chronic use of dopaminergic medications and continues to gradually accumulate over a few months (Cotzias et al., 1969). Just as the long-duration response builds up slowly after initiation of dopamine replacement therapy, it also dissipates slowly in the absence of dopaminergic therapy or with inadequate therapy (Zappia et al., 1999). Indeed, the duration of long-duration response has been estimated to be several days to weeks after discontinuation of either L-dopa or dopamine agonists. Thus, comparing n-PD patients with t-PD patients under stable/optimized dopaminergic treatment is likely to be the best approach to explore both the short-duration response and long-duration response to treatment in this condition.

2. Methods

2.1. Subjects

PD patients were enrolled consecutively from the outpatient population attending the Centre for Neurodegenerative Diseases, University of Belgrade, Serbia. Clinical assessments were performed by an experienced neurologist blinded to MRI. Hoehn and Yahr, Unified Parkinson's Disease Rating Scale III (UPDRS III), Mini-Mental State Examination (MMSE), and Hamilton Depression Rating Scale (HDRS) scores were obtained during ON time (i.e., period when the dopaminergic medication is working and symptoms are well controlled). Inclusion criteria were: a clinical diagnosis of PD (Hughes et al., 1992); hemiparkinsonism defined as Hoehn and Yahr score = 1; drug-naïve status (n-PD) or stable/optimized L-dopa treatment (t-PD) in the last 3 months; right handedness; MMSE $\geq$26. Patients were excluded if they had: moderate-severe limb and/or head rest tremor; parkin, leucine-rich repeat kinase 2, and glucocerebrosidase gene mutations; ongoing treatments with anticholinergic or other psychotropic drugs; dementia (Dubois et al., 2007); major depression according to the Diagnostic and Statistical Manual of Mental Disorders IV, and an HDRS score $\geq$17 (i.e., moderate to severe depression); cerebrovascular disorders, traumatic brain injury history, or intracranial mass; other major medical illnesses. Sixty-nine PD patients fulfilled the inclusion/exclusion criteria. Twenty-seven healthy subjects with no history of neurologic and psychiatric disorders were recruited from spouses of patients and by word of mouth.

Local ethical standards committee on human experimentation approved the study protocol, and all subjects provided written informed consent before study participation.

2.2. MRI acquisition

Using a 1.5 T Philips Achieva, T2*-weighted single-shot echo planar images for RS fMRI (repetition time [TR]/echo time [TE] = 3000/35 ms, echo train length = 51, flip angle = 90°, 200 sets of 30, 4 mm-thick slices, matrix size = 128 × 128, field of view (FOV) = 240 × 240 mm, in-plane resolution 1.875 × 1.875 mm, acquisition time = 10 minutes) were acquired. Subjects were scanned between 10 and 11 AM, that is, t-PD patients were 90–120 minutes after their regular morning dopaminergic therapy administration (ON state). In addition to RS fMRI, the following MRI sequences were obtained from all participants: (1) dual-echo turbo spin-echo (TR = 3125 ms, TEs = 20/100 ms, echo train length = 6, 44 axial slices, thickness = 3.0 mm, matrix size = 256 × 247, FOV = 240 × 195 mm, SENSE Parallel Reduction Factor In-Plane = 1.5); (2) 3-dimensional T1-Transient Field Echo (phase direction = anterior-posterior; TR = 7.34 ms, TE = 3.40 ms, inversion time = 1000 ms, flip angle = 8°, matrix size = 256 × 256 × 180, FOV = 256 × 256 × 180 mm, SENSE Parallel Reduction Factor out-of-Plane = 1.5, sagittal orientation); (3) pulsed gradient spin-echo single shot echo-planar (TR = 6713 ms, TE = 86 ms, flip angle = 90°, matrix size = 112 × 112, FOV = 224 × 224 mm; 50 contiguous, 2.6-mm thick, axial slices SENSE Parallel Reduction Factor In-Plane = 2), with diffusion-encoding gradients applied in 65 noncollinear directions (b factor = 1000 s/mm^2) and 7 averages of the b = 0 acquisition.

2.3. MRI analysis

MRI analysis was performed at the Neuroimaging Research Unit, Scientific Institute San Raffaele, Milan, Italy by a single experienced observer, blinded to subject identity. White matter hyperintensities (WMH), if any, were identified on the dual-echo scans. WMH load was measured using the Jim software package (Version 5.0, Xinapse Systems, Northants, UK; http://www.xinapse.com/).

2.3.1. RS fMRI preprocessing

RS fMRI data processing was carried out using the FMRIB software library (FSLv4.1.7). First, T1-weighted images were skull-stripped using the Brain Extraction Tool and segmented in GM, WM, and cerebrospinal fluid (CSF) maps using the FMRIB's Automated Segmentation Tool. Resulting images were registered to the RS fMRI native space of each subject through a 7 degree-of-freedom (DOF) linear affine transformation using FMRIB's Linear Image Registration Tool (Jenkinson et al., 2002). The first 4 volumes of the RS fMRI data were removed to reach complete magnet signal stabilization. Then, individual RS fMRI images were processed using MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components; version 3.10; http://www.fmrib.ox.ac.uk/fsl/melodic/) (Beckmann et al., 2005). The following FSL-standard preprocessing pipeline was applied: (1) motion correction using MCFLIRT; (2) high-pass temporal filtering (lower frequency: 0.01 Hz); (3) spatial smoothing (Gaussian Kernel of FWHM 6 mm); (4) single-session independent component analysis (ICA). The group averages of root mean square motion estimates computed by MCFLIRT (Jenkinson et al., 2002) were as follows: (1) relative motion of 0.08 mm for controls and 0.06 mm for both n-PD and t-PD groups (p = 0.53); and (2) absolute motion of 0.36 mm for controls, 0.35 mm for n-PD patients and 0.38 mm for t-PD patients (p = 0.25). Resulting independent components (ICs) were inspected visually by analyzing their spatial patterns and temporal characteristics (Beckmann et al., 2005), and those ICs that could be attributed to subject head movement, physiological noise, or CSF fluctuations were removed from the original set using the "fslregfilt" tool.