Parkinsonism and Related Disorders 21 (2015) 23–30

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Akinetic-rigid and tremor-dominant Parkinson's disease patients show different patterns of intrinsic brain activity

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ARTICLE INFO

Article history:
Received 17 May 2014
Received in revised form
17 October 2014
Accepted 18 October 2014

Keywords:
Parkinson's disease
Resting-state fMRI
Regional homogeneity
Akinetic-rigid
Tremor-dominant

ABSTRACT

Background: Parkinson's disease (PD) is a surprisingly heterogeneous neurodegenerative disorder. It is well established that different subtypes of PD present with different clinical courses and prognoses. However, the neural mechanism underlying these disparate presentations is uncertain.
Methods: Here we used resting-state fMRI (rs-fMRI) and the regional homogeneity (ReHo) method to determine neural activity patterns in the two main clinical subgroups of PD (akinetic-rigid and tremor-dominant).
Results: Compared with healthy controls, akinetic-rigid (AR) subjects had increased ReHo mainly in right amygdala, left putamen, bilateral angular gyrus, bilateral medial prefrontal cortex (MPFC), and decreased ReHo in left post cingulate gyrus/precuneus (PCC/PCu) and bilateral thalamus. In contrast, tremor-dominant (TD) patients showed higher ReHo mostly in bilateral angular gyrus, left PCC, cerebellum_crus1, and cerebellum_6, while ReHo was decreased in right putamen, primary sensory cortex (S1), vermis_3, and cerebellum_4_5. These results indicate that AR and TD subgroups both represent altered spontaneous neural activity in default-mode regions and striatum, and AR subjects exhibit more changed neural activity in the mesolimbic cortex (amygdala) but TD in the cerebellar regions. Of note, direct comparison of the two subgroups revealed a distinct ReHo pattern primarily located in the striatal-thalamo-cortical (STC) and cerebello-thalamo-cortical (CTC) loops.
Conclusion: Overall, our findings highlight the involvement of default mode network (DMN) and STC circuit both in AR and TD subtypes, but also underscore the importance of integrating mesolimbic-striatal and CTC loops in understanding neural systems of akinesia and rigidity, as well as resting tremor in PD. This study provides improved understanding of the pathophysiological models of different subtypes of PD.

1. Introduction

Parkinson's disease is a surprisingly heterogeneous neurodegenerative disorder. The classical triad of motor symptoms includes resting tremor, akinesia and rigidity [1]. Patients with PD can be classified into the akinetic-rigid (AR) subtype and tremor-dominant (TD) subtype, based on the predominant motor signs. There is clear clinical proof that different subtypes of PD have a different clinical course and prognosis [2,3]. Compared to patients with TD type, AR subjects show a more rapid clinical progression and have an increased risk to develop disability and dementia [3]. The neural basis for these disparate manifestations of PD is not completely understood.

Previous functional neuroimaging studies using positron emission tomography (PET) or single photon emission computed tomography (SPECT) have demonstrated that parkinsonian tremor has a different neurobiological substrate from those of akinesia and rigidity [4,5]. For instance, loss of nigral dopaminergic projections to the putamen correlates consistently with the clinical ratings of akinesia and rigidity but not tremor [4]. Indeed,

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http://dx.doi.org/10.1016/j.parkreldis.2014.10.017
1353-8020/

Table 1
Subject demographic data.

	HC ($n = 26$)	AR ($n = 27$)	TD ($n = 20$)	P value
Age, year (mean ± SD)	59.31 ± 7.15	63.38 ± 9.46	54.55 ± 12.58	>0.005*
Gender, F/M	15/11	11/16	10/10	>0.05**
Disease duration (years)	–	4.17 ± 4.07	5.0 ± 3.21	0.46***
H&Y (off mediation)	–	2.21 ± 0.67	1.88 ± 0.70	0.11***
UPDRS-III (off medication)	–	19.88 ± 6.70	19.35 ± 9.35	0.82***
TD/AR ratio	–	0.40 ± 0.26	1.78 ± 0.77	<0.005***
Handedness	R	R	R	–

Abbreviations: AR, akinetic-rigidity; TD, tremor-dominant; HC, healthy control; R, right.
*Comparison of age for controls and AR subjects $P = 0.086$, controls and TD subjects $P = 0.11$, and for AR and TD subjects $P = 0.009$.
**Comparison of gender for controls and AR subjects $P = 0.27$, controls and TD subjects $P = 0.60$, and for AR and TD subjects $P = 0.60$.
***P value reflects the comparison between AR and TD subjects.

nigrostriatal dopaminergic loss appears to be necessary but not sufficient for the development of PD tremor [6]. From the circuit standpoint, the circuit changes that mediate parkinsonian tremor differ from those underlying akinesia and rigidity. The nigrostriatal dopaminergic loss with the consequent dysfunction of striatal-thalamo-cortical (STC) loop is a hallmark of PD, which explains akinesia and rigidity, but not resting tremor [7]. Instead, resting tremor is linked to altered activity in not one, but two distinct circuits: the STC pathway, which is primarily affected by dopamine depletion in PD, and the cerebello-thalamo-cortical (CTC) circuit, which is also involved in many of the other types of tremors [8,9]. Several recent MRI studies provide further evidence for the necessity of incorporating CTC circuitry into any discussion of parkinsonian tremor. For example, a voxel-based morphometry study showed that TD patients had reduced grey matter volume in the cerebellum [10]. In addition, an event-related fMRI study found that activation patterns in the STC and CTC pathways were different for AR and TD subjects [11]. Taken together, it would necessitate exploration of the subtype to uncover the neural underpinnings of PD.

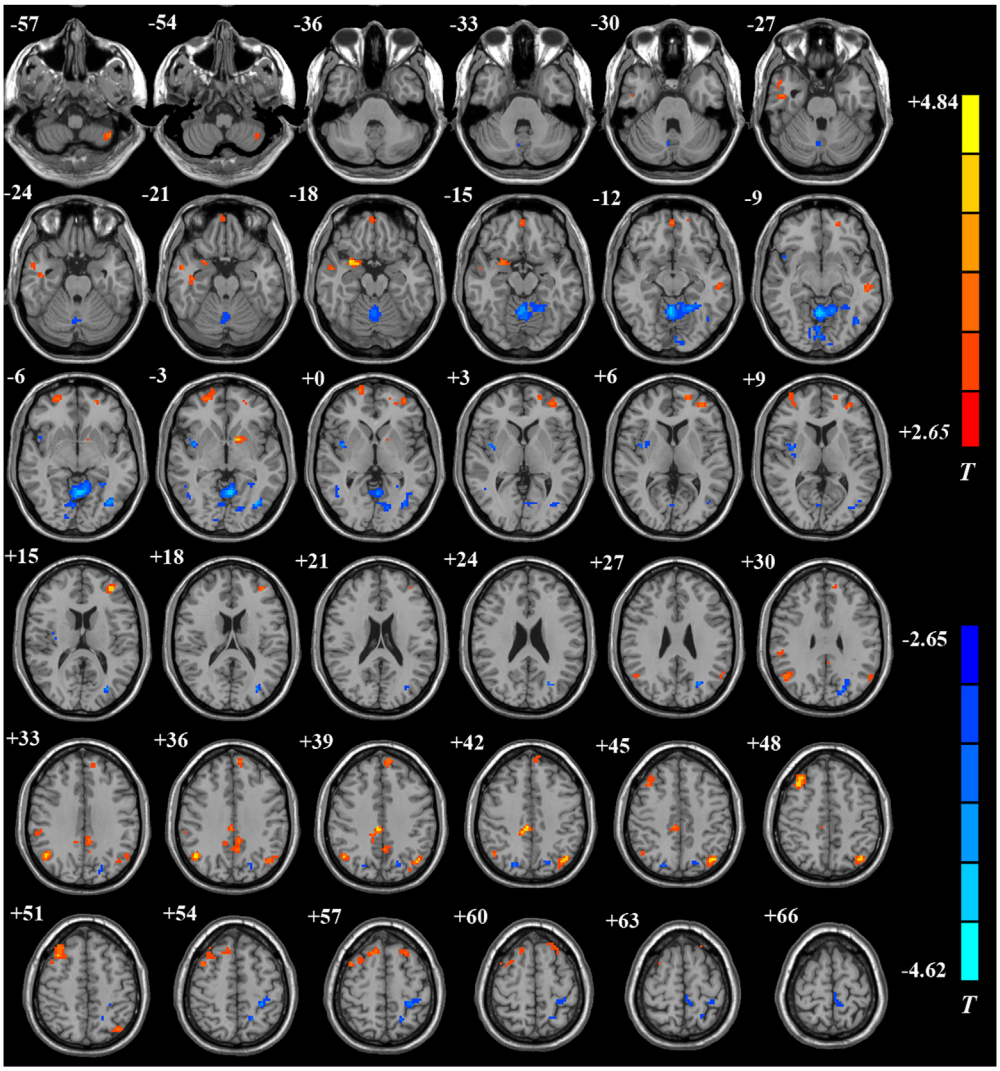

Fig. 1. Brain regions with abnormal ReHo values in PD patients compared to controls. The results were corrected by AlphaSim ($P < 0.05$, combined height threshold of $P < 0.005$ and a minimum cluster size of 12 voxels). More details of these regions are described in Table 2.