Journal of the Neurological Sciences 366 (2016) 27–32

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

# Prediction of individual clinical scores in patients with Parkinson's disease using resting-state functional magnetic resonance imaging

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ARTICLE INFO

*Article history:*
Received 24 January 2016
Received in revised form 27 March 2016
Accepted 16 April 2016
Available online 19 April 2016

*Keywords:*
Parkinson's disease
Relevance vector regression
Resting-state functional magnetic resonance imaging
Prediction

ABSTRACT

Neuroimaging holds the promise that it may one day aid the clinical assessment. However, the vast majority of studies using resting-state functional magnetic resonance imaging (fMRI) have reported average differences between Parkinson's disease (PD) patients and healthy controls, which do not permit inferences at the level of individuals. This study was to develop a model for the prediction of PD illness severity ratings from individual fMRI brain scan. The resting-state fMRI scans were obtained from 84 patients with PD and the Unified Parkinson's Disease Rating Scale-III (UPDRS-III) scores were obtained before scanning. The RVR method was used to predict clinical scores (UPDRS-III) from fMRI scans. The application of RVR to whole-brain resting-state fMRI data allowed prediction of UPDRS-III scores with statistically significant accuracy (correlation = 0.35, P-value = 0.001; mean sum of squares = 222.17, P-value = 0.002). This prediction was informed strongly by negative weight areas including prefrontal lobe and medial occipital lobe, and positive weight areas including medial parietal lobe. It was suggested that fMRI scans contained sufficient information about neurobiological change in patients with PD to permit accurate prediction about illness severity, on an individual subject basis. Our results provided preliminary evidence, as proof-of-concept, to support that fMRI might be possible to be a clinically useful quantitative assessment aid in PD at individual level. This may enable clinicians to target those uncooperative patients and machines to replace human for a more efficient use of health care resources.



## 1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disease, and the number of PD patients over age 50 will be between 8.7 and 9.3 million by 2030 [1]. As PD is characterized by cardinal motor symptoms and various non-motor symptoms (NMS) [2], the accurate clinical evaluation relying on patients' cooperation and movement disorder specialists' experience could be difficult sometimes. However, studying these symptoms offers a window into the stages of illness and may inform the individual intervention aimed at delaying disease progression.

Neuroimaging offers a promising translational tool to characterize brain abnormalities in individuals [3] and a new non-invasive method for assessing regional and neural circuitry function at rest, known as resting-state functional magnetic resonance imaging (fMRI). This method requires minimal patient compliance, avoids potential performance confounders associated with cognitive activation paradigms in task-design fMRI research, and is relatively easy to implement in clinical studies. In addition, the spontaneous low-frequency (0.01 Hz–0.08 Hz) fluctuations of blood oxygen level dependent (BOLD) signal observed by fMRI during resting state are considered to be physiologically meaningful and related to spontaneous neural activity [4]. The amplitude of low frequency fluctuation (ALFF), calculating the sum of amplitudes within a specific low-frequency range, such as 0.01 Hz–0.08 Hz, shed light upon changes BOLD signal. This approach avoids specifying seed locations and can be applied to conduct the whole-brain voxel-wise analysis of cerebral function during resting state. It has been reported that alterations of ALFF detected in PD could be a potential biomarker [5,6].

Previous studies using resting-state fMRI reported altered functional activity in PD patients [7–14], which in many cases have been observed to correlated with clinical scores [9–13]. However, they were based on average estimates at a group level and not at the level of individual patient, which are of little use in clinical practice where doctors need to make decisions about individuals. At present, it remains unclear whether neuroimaging could be used to inform clinical assessment of individual patient. Under the limited translational applicability of

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http://dx.doi.org/10.1016/j.jns.2016.04.030
0022-510X/

**Table 1**
Demographic and clinical characteristics of PD patients.

| Characteristic | PD patients ($N = 84$) | | |
|---|---|---|---|
| | Min | Max | |
| Male: female | – | – | 40:44 |
| Age (years) | 28 | 78 | 53.38 ± 10.61 |
| Disease duration (years) | 0.17 | 10.59 | 2.91 ± 2.46 |
| UPDRS-I | 0 | 11 | 2.46 ± 2.35 |
| UPDRS-II | 0 | 41 | 10.21 ± 6.61 |
| UPDRS-III | 4 | 81 | 29.07 ± 15.84 |
| UPDRS-IV | 0 | 0 | 0 |
| H&Y staging | 1.0 | 5.0 | 2.0(1.0) |
| NMS scores | 0 | 167 | 34.63 ± 33.25 |
| MMSE score | 17 | 30 | 27.17 ± 2.85 |
| Education (years) | 0 | 16 | 9.03 ± 4.11 |
| LEED (mg/day) | 50 | 950 | 358.33 ± 280.89 |

Key: PD: Parkinson's disease; UPDRS: Unified Parkinson's Disease Rating Scale; H&Y staging: Hoehn and Yahr staging; LEDD: levodopa equivalent daily dose.

standard mass-univariate analytical methods that are typically used in neuroimaging, a great hope is given to the multivariate machine learning technique.

Among those multivariate techniques, support vector machines (SVM) technique has been applied to classification of individual subject neuroimaging data with success, and it has also been extended to regression to allow prediction of continuous variables [15]. However, SVM approach has several limitations. First, SVM requires estimation of margin insensitivity parameters for regression, using cross-validation, which is computationally expensive. Second, the prediction is not probabilistic and so estimation of the confidence level of prediction is not straightforward. Third, for regression purpose, SVM uses many basis functions that potentially limit generalizability. In order to overcome these limitations, relevance vector regression (RVR) has been proposed, which is a promising one. The RVR has three main advantages: first, allowing inferences at individual level and therefore provides results that have higher translational applicability in everyday clinical practice; second, being sensitive to subtle differences and differences in spatial distribution by virtue of taking inter-regional correlations into account [16]; third, permitting quantitatively predict variables of interest, such as clinical scores, rather than a discrete categorical decision which point at pattern classification techniques. This method, RVR, has been applied in previous studies on psychosis [3], trauma survivors [16], major depression [15] and Alzheimer's disease [17]. For example, Mwangj et al. has been suggested that T1-weighted MRI scans contain sufficient information about neurobiological change in patients with major depressive disorder to permit accurate predictions about illness severity [15].

However, to date, no study has applied the RVR method to explore the capability of neuroimaging in predicting UPDRS-III scores in individual PD patients. Therefore, the current study aims to explore whether the application of RVR to resting-state fMRI data would allow quantitative prediction of UPDRS-III scores in PD patients.

## 2. Methods

### 2.1. Participant

A total of 84 patients were recruited from the movement disorders outpatient clinic of West China Hospital of Sichuan University from June 2010 to March 2013. Diagnosis of PD was based on the UK PD Society Brain Bank Clinical Diagnostic Criteria [18]. Using standard questionnaires to collect demographic and clinical data during face-to-face interviews by movement disorder specialists. All patients underwent clinical assessments including Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr staging, Non-Motor Symptom Scale (NMSS) and Mini-Mental State Examination (MMSE). On the basis of previous studies [19,20], we used the following cut-off points to define abnormal MMSE in our patients: ≤17 for illiterate subjects, ≤20 for grade-school literate, and ≤23 for junior high school and higher education literate. Patients were excluded if they had (1) secondary Parkinsonism and Parkinson-plus syndrome; (2) moderate-severe head tremor; (3) a history of head injury, stroke, or other neurologic disease; (4) abnormal MMSE scores; (5) any disorder that interfered with the assessment of the manifestation of PD; (6) gross structural brain abnormality that radiological observed. Table 1 summarized demographic and clinical information of all participants. The local research ethics committee approved this study and written informed consent was obtained from all the participants prior to the inclusion in this study.

### 2.2. Data acquisition

Each patient off the medication for at least 12 h was investigated using resting-state fMRI and the time interval of collecting clinical and fMRI data was about 1 h. Two hundreds images were obtained using a 3.0-T magnetic resonance imaging system (Excite; GE, Milwaukee, WI, USA) with a gradient-echo echo-planar imaging (EPI) sequence. Sequence parameters were as follows: repetition time = 2000 millisecond, echo time = 30 ms, flip angle = 90°, 30 axial slice per volume, 5 mm slice thickness (no slice gap), matrix = 64 * 64, field of view = 240 * 240mm$^2$, voxel size = 3.75 * 3.75 * 5mm$^3$. The scanning was performed in darkness, and the participants were instructed to be relaxed, close their eyes, and not fall asleep (confirmed by subjects immediately after the experiment) during the resting-state fMRI acquisition. Earplugs were used to reduce scanner noise, and cushion was used to minimize head motion.

### 2.3. Data analysis

Functional image preprocessing and statistical analysis was carried out using the Statistical Parametric Mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm/), the Resting State fMRI Data Analysis Toolkit [21] (REST; http://www.restfmri.net/forum/) and the Pattern Recognition for Neuroimaging Toolbox (PRoNTo; http://www.mlnl.cs.ucl.ac.uk/pronto/) which implementing RVR to analysis the data. They were all under Matlab (R2009b).

Discarding the first 10 images because of the signal equilibrium and participants' adaptation to scanning noise. The remaining 190 images were then preprocessed as the following steps: slice timing, motion correction, spatial normalization to the standard Montreal Neurological Institute EPI template, resample to 3 * 3 * 3 mm$^3$, and smoothing with a 6 mm full-width half-maximum (FWHM) Gaussian Kernel. According to the record of head motion, all participants had <2.0 mm maximum displacement in the x, y, or z plane and <2.0° of angular rotation about each axis, so 5 patients were excluded. Using the smoothed images, the average amplitude of low frequency fluctuation (ALFF), across the frequency band 0.01 Hz to 0.08 Hz, was calculated within each

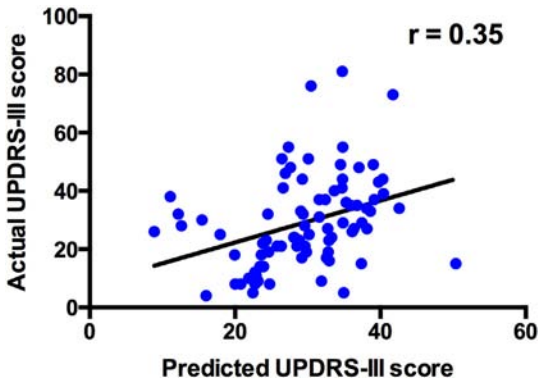


**Fig. 1.** Scatter plot showing the predicted clinical scores for each subject derived from resting-state fMRI data using the RVR analysis, compared with their actual clinical scores.