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Neural correlates of anxiety symptoms in mild Parkinson's disease: A prospective longitudinal voxel-based morphometry study

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ABSTRACT

Background: Anxiety is prevalent in patients with Parkinson's disease (PD) and may affect patients' quality of life. Yet, little is known about the neural basis of anxiety in PD, and none have used a longitudinal design.
Methods: 73 patients with mild PD were recruited and followed up for 18 months. A whole-brain analysis was first used to identify brain regions associated with anxiety symptoms, followed by a regional analysis focusing on a priori hypothesised regions at baseline. A multivariate generalized estimating equations analysis was then conducted to determine the longitudinal association between grey matter (GM) volumetric changes of these significant regions and changes of anxiety symptoms.
Results: At baseline, anxiety symptom severity was associated with decreased GM volumes in the bilateral precuneus and anterior cingulate cortex (ACC). Over 18 months, increased severity of anxiety symptoms was associated with decreased GM volume in the left precuneus and ACC, independent of age, gender, education, depressive symptom severity or use of psychiatric medication.
Conclusions: These results mainly implicate the precuneus and ACC in the pathogenesis of anxiety in PD. We speculate that these structural changes could reflect the disrupted default mode network due to PD pathology, contributing to spontaneous anxiety-related self-focused thoughts.

1. Introduction

Anxiety is increasingly recognised as one of the most common psychiatric symptoms in Parkinson's disease (PD), with an estimated prevalence of up to 40% [1]. Despite this high prevalence, anxiety is relatively understudied in PD. [2] Though often overlooked, these symptoms have a significant impact on quality of life and are associated with negative health outcomes and increased mortality [3].

Neuroimaging investigations of anxiety in healthy individuals and patients with anxiety disorders consistently reveal both structural and functional changes in a "fear network" comprising the amygdala, the insula, anterior cingulate cortex and precuneus [4,5]. Neurotransmitter abnormalities have also been implicated in the pathogenesis of anxiety. For instance, individuals with anxiety disorders appear to have reduced levels of dopamine uptake in the striatum [6]. In contrast with the general population, very few studies have examined the neural basis of anxiety in PD. In patients with PD, anxiety symptoms were associated with a specific loss of dopaminergic and noradrenergic innervation in the limbic system [7], as well as functional polymorphisms in the serotonin transporter gene [8].

Despite increasing evidence for a role of functional brain impairment in the genesis of anxiety, the relationship between structural brain changes and anxiety symptoms in PD remain poorly studied. To date, only three morphological studies have reported the neural structural basis of anxiety in the PD brain [9–11]. Anxiety symptom severity was linked with smaller left amygdala volumes, but this association was no longer significant after adjustment for depressive symptoms. Furthermore, what is critically lacking in the field is longitudinal data, which would provide empirical support for causal interpretations.

Thus, the present study employed a prospective longitudinal design to assess the relation between regional grey matter (GM) tissue volume and severity of self-reported anxiety symptoms in a large group of PD patients over 18 months. We hypothesised that anxiety would be negatively associated with GM volumes in the amygdala, insula, anterior cingulate cortex (ACC), and precuneus. Unlike the previous morphological study, we first performed an exploratory whole-brain analysis to identify regions of interest. We also adjusted the model for the severity of depressive symptoms and use of psychiatric medications, in order to remove their confounding influences.

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2. Methods

2.1. Participants

This is a prospective longitudinal study of participants consecutively recruited from outpatient movement disorders clinics at a tertiary neurology centre between August 2011 and March 2012. Patients with a diagnosis of probable idiopathic PD meeting the National Institute of Neurological Disorders and Stroke (NINDS) criteria, [12] with mild PD (Hoehn and Yahr stage of 1–2.5) and without severe cognitive impairment were recruited. All patients' cognitive status was confirmed by a cognitive screening test, Montreal Cognitive Assessment (MOCA), as well as full psychometric assessment to exclude those who fulfilled Movement Disorder Society criteria for PD dementia. Motor severity was determined with the motor subscale of the Unified PD Rating Scale (UPDRS-III). [13] Patients were taking their normal medication and in the levodopa "ON" state during the entire study period. Levodopa equivalent dose (LEDD) was calculated according to the formula provided in a prior work [14]. The study was approved by the Centralized Institutional Review Board of the Singapore Health Services and voluntary informed consent was obtained from all participants.

2.2. Mood assessment

The Hospital Anxiety and Depression Scale (HADS 'A' [15]; 7 items with a four-level scale, cutoff score ≥ 8) and the Geriatric Depression Scale (GDS [16,17]; 15 items with a binary response, cutoff score ≥ 4) were employed at baseline and at 18-month follow-up.

2.3. MRI acquisition and image processing

All MRI scans were acquired using a 3 Tesla whole body MRI system (Achieva 3.0, Philips Medical Systems, Best, The Netherlands). High-resolution volumetric T1-weighted MPRAGE sequence (axial acquisition, TR 7.1 ms, TE 3.3 ms, TI 850 ms, FOV 240 × 240 mm^2, matrix 256 × 256, slice thickness 1 mm, total 180 slices, scan time 5:13) was acquired for all patients. T1-weighted images were preprocessed using the VBM toolbox (http://dbm.neuro.uni-jena.de/vbm/) running on MATLAB R2012a (Mathworks). The default longitudinal pre-processing approach in the VBM8 toolbox was used with the following standardized steps: (1) registering the follow-up image to the baseline image for each subject; (2) calculating the mean image from the realigned images for each subject and using it as a reference image for subsequent spatial realignment; (3) correcting the realigned images for signal inhomogeneities with regard to the reference mean image; (4) performing tissue segmentation in the bias-corrected mean reference image and the bias-corrected realigned images; (5) estimating DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) spatial normalization parameters with the tissue segments of the bias-corrected mean reference image; (6) modulating GM images to preserve relative regional volumes and correct for individual differences in brain size; (7) applying the normalization parameters to the tissue segments of the bias-corrected realigned images; (8) smoothing the resulting normalized tissue segments for each time point of each subject with an 8 mm full-width-half-maximum (FWHM) Gaussian kernel.

2.4. Statistical analyses

Demographic and clinical data at baseline and at follow-up were compared using paired t-tests or Wilcoxon tests when the assumptions of paired t-teste (e.g., normality) were not met.

The correlation between baseline whole-brain GM volume and baseline HADS 'A' scores was conducted using multiple regression in SPM 8, in which age, sex, education (in years), and the severity of depressive symptoms were included as nuisance covariates. We first explored the whole brain to identify regions associated with anxiety, followed by a regional analysis only focusing on few a priori hypothesised brain regions using small volume correction [18]. A binary mask was created using the Automated Anatomical Labelling toolbox (ALL) [19] to include a priori hypothesised brain regions (i.e., bilateral amygdala, insula, ACC and precuneus) before the analysis. Small volume correction was performed to only examine voxels within the mask. Statistical significance was set at $p < 0.05$ at the voxel level (family-wise error [FWE] corrected) for both analyses.

GM volumes of the significant brain regions were subsequently extracted for longitudinal association analysis with anxiety scores. To investigate the structural brain changes associated with severity of anxiety symptoms, we analysed the relationship between these specific regional ROI volumes and HADS 'A' scores in a multivariate generalized estimating equation (GEE) model [20]. We chose this approach to capture both cross-sectional correlations between variables at two different time points and within-subject changes in these relationships over time within a single statistical model. The GEE analysis was adjusted for depression (as measured by GDS scores) and use of anxiolytic and/or antidepressant medication, as these variables have a possible confounding influence on anxiety scores. All longitudinal statistical analyses were performed using geepack package in R version 3.1.2. All analyses were two-sided and results were considered statistically significant if p value < 0.05.

In addition, we also examined the association of whole-brain GM volumetric changes defined by subtracting follow-up GM segments from baseline GM segments and changes of anxiety symptoms defined by subtracting follow-up anxiety scores from baseline anxiety scores between the two timepoints using multiple regression in SPM 8, controlling for the aforementioned covariates of no interest. A prior hypothesised regional analysis examining the association of GM volumetric changes within the eight pre-selected regions (4 per hemisphere) with changes of anxiety symptoms were performed using small volume correction. p values < 0.05 (FWE corrected) were deemed to be significant for both analyses.

3. Results

3.1. Demographic and clinical characteristics

73 patients participated in this study. At study entry, patients were aged 65.19 years on average (SD = 7.99), had mild PD, with a Hoehn and Yahr stage of 1–2.5 and were mildly affected on motor performance (mean UPDRS-III score = 18.42, SD 8.20, Table 1). 19.2% and 8.2% of patients had significant anxiety at baseline and at follow-up, respectively. Out of the 73 patients, 36 showed a decrease in the severity of anxiety symptoms, 20 remained the same, while the remaining patients showed an increase in anxiety severity at follow-up. Overall, anxiety scores were mild at baseline and decreased by 1.14 points (5.43% of the maximum score) over the 18-month period ($t_{(71)} = 3.51$, $p < 0.001$). In addition, 19.2% and 26.0% of patients had significant depression at baseline and at follow-up, respectively. Compared with baseline, there was a slightly decrease in the number of patients with significant anxiety at follow-up ($\chi^2_{(1)} = 3.71$, $p = 0.054$), but no significant difference in depression ($\chi^2_{(1)} = 1.90$, $p = 0.38$). Few patients (5.48%) were using anxiolytic and/or antidepressant medication (SSRIs) at the time of assessment.

3.2. Baseline GM regression analyses

With age, sex, education and the severity of depressive symptoms as nuisance covariates, the whole-brain baseline voxel-wise GM regression analysis did not show any significant brain regions correlating with baseline anxiety scores. In contrast, analysis on the a priori hypothesised regions showed that volumes in the bilateral ACC (left: $z = 3.7$, $p = 0.026$; right: $z = 3.36$, $p = 0.036$) and precuneus (left: $z = 3.69$, $p = 0.031$; right: $z = 3.73$, $p = 0.026$) areas were negatively