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Gender-specific effect of uric acid on resting-state functional networks in de novo Parkinson's disease

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ABSTRACT

Introduction: The pattern of resting-state networks is influenced by several factors besides the underlying pathological changes of Parkinson's disease (PD). Uric acid (UA), as an antioxidant, has a neuroprotective property against PD-related microenvironment; however, this effect would be gender-specific. We aimed to evaluate a gender-sensitive resting-state networks (RSN) according to the UA level in drug naïve de novo patients with PD to elucidate the role of antioxidant in cortical functional networks of PD.
Methods: This study enrolled 135 de novo patients with PD underwent functional magnetic resonance imaging (MRI). Based on the distribution, the serum UA level was stratified into tertiles in the PD patients by gender. With a seed-based approach, we investigated the pattern of RSN within the dorsal attention network (DAN), executive control network (ECN), and default mode network (DMN).
Results: Interaction analysis showed a significant interaction between the lowest (PD-L-UA) and the highest UA level (PD-H-UA) groups according to gender within the DAN, ECN, and DMN. Compared to the control subjects, male patients with PD-H-UA had higher cortical functional connectivity (FC), while female patients had lower cortical FC regardless of UA level within all seeds. In a direct comparison, male patients with PD-H-UA had increased FC than did those with PD-L-UA. However, there was no significant difference in FC between PD-L-UA and PD-H-UA in female PD patients.
Conclusions: These data suggest that RSN might be closely and gender-specifically associated with the status of serum UA in de novo PD patients.

1. Introduction

Resting-state networks (RSN) reflect the spontaneous neural activities of the blood oxygenation level-dependent signals between temporally correlated brain regions. They also provide indirect information regarding the status of functional systems within the brain, without externally goal-directed cognitive performance [1]. In neurodegenerative diseases, the RSN pattern seems to differ depending on the underlying pathologies causing cognitive impairment [2]. In addition, the RSN pattern might differ according to the cognitive status, including mild cognitive impairment and dementia [3]. We previously reported that the RSN in patients with Parkinson's disease (PD) exhibit specific functional network maps that correspond to a neurochemical and neuropathological basis even in the same disease condition [4]. Therefore, as an indicator of synchronous neural activity, the RSN pattern is influenced by several factors besides the underlying pathological changes of PD [5].

Oxidative stress is one of the primary contributors to PD pathogenesis, particularly through the insoluble modification of α-synuclein [6]. Uric acid (UA), a main end product of purine metabolism, has an antioxidant effect that protects cells from oxidative damage by reactive nitrogen and oxygen species [7]. Epidemiological studies have demonstrated that UA concentration is inversely correlated to the risk and progression of PD [8]. However,

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the antioxidant effect of UA appears to differ according to gender. Higher UA is associated with reduced rates and PD progression in men, while it shows the opposite trend in women [9,10]. In the present study, we hypothesized that UA may play a role in regulating the PD-related microenvironment. RSN provides human brain activity by measuring localized, intrinsic signal changes that are directly driven by changes in transient neuronal activity such as medication including antioxidant effect or substance use [11]. Therefore, its level would influence the pattern of functional connectivity (FC) in patients with PD according to gender. We performed a gender-sensitive RSN analysis according to UA level in 135 drug naïve de novo PD patients to further elucidate its antioxidant role in corticl-cortical functional networks of PD. We chose the default mode network (DMN), executive control network (ECN), and dorsal attention network (DAN), which are highly correlated with cognitive function in PD patients [2,13].

2. Materials and methods

2.1. Subjects

A total of 135 patients with drug-naïve de novo PD and 45 age- and gender-matched controls that underwent functional magnetic resonance imaging (fMRI) were included. Subjects were recruited from Severance Hospital, Korea between September 2011 and March 2015. PD was diagnosed according to the clinical criteria of the United Kingdom PD Society Brain Bank [14]. Brain MRI and routine chemistry including UA levels were routinely performed at the same time within two weeks after the initial visit in consecutive de novo patents with PD as a diagnostic procedure. The enrolled participants completed dopamine transporter (DAT) scan within a month after the initial visit. Parkinsonian motor symptoms were assessed using the Unified PD Rating Scale Part III (UPDRS III). Depressive mood was scored using the Beck Depression Inventory (BDI). All subjects with PD had scores of the Korean version of the Mini-Mental State Examination (K-MMSE) score, or cross-cultural smell identification (CCSI) test. The level of serum UA was determined by an enzymatic colorimetric method using an automatic analyzer (Hitachi 7600; Hitachi, Tokyo, Japan). Because UA level differs substantially between the sexes, results were analyzed separately. Based on the distribution, the UA level was stratified into tertiles in the PD patients by gender: PD with the lowest UA level (PD-L-UA, $n = 20$, UA < 4.5 mg/dL), PD with an intermediate UA level (PD-I-UA, $n = 21$, $4.5 \leq UA \leq 5.6$ mg/dL), and PD with the highest UA level (PD-H-UA, $n = 21$, UA > 5.6 mg/dL) in men and PD-L-UA ($n = 25$, UA < 3.6 mg/dL), PD-I-UA ($n = 24$, $3.6 \leq UA \leq 4.6$ mg/dL), and PD-H-UA ($n = 24$, UA > 4.6 mg/dL) in women. Additionally, the baseline total cholesterol, history of smoking, alcohol, hypertension, diabetes mellitus, and body mass index (BMI) (kg/m^2) were obtained. A history of hypertension was defined as a prior physician diagnosis with or without the use of antihypertensive agents. A history of diabetes was defined by self report or the use of hypoglycemic agents. DAT uptakes in the PD patients were quantitated using SPM2 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London, UK) and MRIcro version 1.37 (Chris Rorden, Columbia, SC, USA). This detailed DAT method was provided as supplementary information. Exclusion criteria included: evidence of focal brain lesions on MRI, atypical parkinsonism, the use of symptomatic therapy for parkinsonism, dementia compatible with the clinical diagnostic criteria for probable PD dementia [15], and treatment with diuretics or UA modifying agents. The study protocol was approved by the Yonsei University Severance Hospital ethical standards committee on human experimentation and was exempt from providing informed consent by the IRB due to the retrospective design.

2.2. MRI analysis

The PD and control participants underwent fMRI scanning with a 3.0 T MRI scanner (Achieva, Philips Medical System, Best, Netherlands) to obtain T2* weighted single shot echo planar imaging sequences. Each 330-sec scan produced 165 fMR images, which is known to be sufficient to evaluate resting de state FC and to obtain low frequency oscillations for resting-state FC. Preprocessing of the resting-state fMRI data was performed using Analysis of Functional Neuro Image (AFNI_16.3.15) software (http://afni.nimh.nih.gov/). With a seed-based approach, we investigated the pattern of resting-state networks within the DMN, ECN, and DAN. To investigate the PD and gender main effects and the interaction effect between PD group and gender, we performed a two-way analysis of variance (ANCOVA) using the group (PD-L-UA, PD-H-UA, and control) and gender (male and female) as between-subject factor with age and education as covariates. Then, post-hoc two-sample t tests were further performed in F-map of significant main effects and interaction effect. The 2×2 interaction *t*-test between the PD group and gender was defined as follows: (PD-L-UA male − PD-H-UA male) − (PD-L-UA female − PD-H-UA female). Detailed fMRI analysis and techniques are described in the supplementary information.

2.3. Statistical analysis

The data are expressed as means ± standard deviations. Demographic characteristics were compared using the chi-squared test for categorical variables. For continuous variables, the Mann-Whitney *U* test or Kruskall Wallis test followed by post hoc Mann-Whitney *U* test was applied. The interaction analysis was performed among gender, UA level and all clinical and demographical variables to control confounding variables, which affect RSN connectivity. Statistical analyses were performed using commercially available software (SPSS, Inc, Chicago, IL, USA, Ver. 21.0). A two tailed $p < 0.05$ was considered significant.

3. Results

3.1. Demographic characteristics

The demographic patient characteristics are shown in Table 1. The women in the PD-H-UA group had a higher mean BMI than those in the PD-L-UA group. There were no significant differences in vascular risk factors and cholesterol level among the PD-L-UA, PD-H-UA and control groups, and no differences were found in disease duration, education duration, UPDRS III score, BDI score, K-MMSE score, CCSI test score, or DAT activity between the PD-L-UA and PD-H-UA groups, regardless of gender.

3.2. PD- and gender-specific effect on resting-state cortical FC

To determine the gender-specific effect of UA, we first analyzed whether there is a difference in FC depending on the group and gender. Compared with the control group, the PD group had decreased FC in bilateral insular, frontal, and temporal areas within DAN, bilateral medial temporal and right insular areas within ECN, and bilateral cingulate, postcentral and lingual gyri within DMN (Supplementary Fig. 1). Then, we analyzed the differences in FC according to gender (F-map in Supplementary Fig. 2A). In the control group, male showed lower FC in bilateral insular, left middle temporal, right postcentral and cingulate gyri within DAN, right frontal area and left inferior parietal lobule within ECN, and bilateral cingulate and right lingual gyri within DMN than did female (Supplementary Fig. 2B). In the PD group, male had increased

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