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Quantitative susceptibility mapping as an indicator of subcortical and limbic iron abnormality in Parkinson's disease with dementia

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ABSTRACT

Late stage Parkinson's disease (PD) patients were commonly observed with other non-motor comorbidities such as dementia and psychosis. While abnormal iron level in the substantia nigra was clinically accepted as a biomarker of PD, it was also suggested that the increased iron deposition could impair other brain regions and induce non-motor symptoms. A new Magnetic Resonance Imaging (MRI) called Quantitative Susceptibility Mapping (QSM) has been found to measure iron concentration in the grey matter reliably. In this study, we investigated iron level of different subcortical and limbic structures of Parkinson's disease (PD) patients with and without dementia by QSM.

QSM and volumetric analysis by MRI were performed in 10 PD dementia (PDD) patients (73 ± 6 years), 31 PD patients (63 ± 8 years) and 27 healthy controls (62 ± 7 years). No significant differences were observed in the L-Dopa equivalent dosage for the two PD groups ($p = 0.125$).

Putative iron content was evaluated in different subcortical and limbic structures of the three groups, as well as its relationship with cognitive performance. One-way ANCOVA with FDR adjustment at level of 0.05, adjusted for age and gender, showed significant group differences for left and right hippocampus ($p = 0.015$ & 0.032, respectively, BH-corrected for multiple ROIs) and right thalamus ($p = 0.032$, BH-corrected). Post-hoc test with Bonferroni's correction suggested higher magnetic susceptibility in PDD patients than healthy controls in the left and right hippocampus ($p = 0.001$ & 0.047, respectively, Bonferroni's corrected), while PD patients had higher magnetic susceptibility than the healthy controls in right hippocampus and right thalamus ($p = 0.006$ & 0.005, respectively, Bonferroni's corrected). PDD patients also had higher susceptibility than the non-demented PD patients in left hippocampus ($p = 0.046$, Bonferroni's corrected). The magnetic susceptibilities of the left and right hippocampus were negatively correlated with the Mini-Mental State Examination score ($r = -0.329$ & -0.386, respectively; $p < 0.05$).

This study provides support for iron accumulation in limbic structures of PDD and PD patients and its correlation with cognitive performance, however, its putative involvement in development of non-motor cognitive dysfunction in PD pathogenesis remains to be elucidated.

1. Introduction

Patients with Parkinson's disease (PD) in advanced stage may develop concomitant non-motor symptoms related to neuropsychiatric or cognitive disturbances (Tolosa et al., 2014), significantly exacerbating their disability. One of the most common non-motor

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manifestations in Parkinson's disease is dementia (PDD), for which the prevalence and annual incidence are estimated at respectively 30–40% (Burn and Yarnall, 2014; Emre et al., 2007; Goetz et al., 2008) and 10% (Goetz et al., 2008) of PD patients. This indicates that such potentially disabling complication of PD should be carefully addressed in clinical management. Patients with PDD generally experience significant cognitive decline, distinct from that due to Alzheimer's disease (AD), including impairment of executive function, attention, visuospatial function, constructional praxis, and memory (Burn and Yarnall, 2014; Goetz et al., 2008). Notably, greater deficits in executive and visuospatial functions and lesser in language functions are observed in PDD than AD (Burn and Yarnall, 2014; Goetz et al., 2008). While some studies propose an association between Apolipoprotein E (APOE) and the dementia symptoms of PDD (Irwin et al., 2012; Monsell et al., 2014), others do not support such claims (Burn and Yarnall, 2014; Mengel et al., 2016), thus rendering the mechanism underlying development of dementia in PD and its relationship with the AD-type dementia to be inconclusive.

Various studies have been performed to identify abnormalities in the brain of PDD patients. Imaging studies such as Magnetic Resonance Imaging (MRI) reported structural change in the hippocampus and amygdala of PDD patients, suggesting that the dementia symptom in PD might be associated with limbic atrophy (Aarsland et al., 2008); one study by Kalaitzakis et al. also suggested the involvement of limbic system in PDD, with the association between dementia and α-synuclein pathology in the limbic structures being observed (Kalaitzakis et al., 2009). These findings suggest plausible association between limbic abnormality and the dementia symptom, and that further investigation of the involvement of limbic structures in PDD is warranted.

Abnormal subcortical iron deposition in PD has been postulated to be the cause of the degeneration of dopaminergic neurons in the substantia nigra pars compacta (Hare et al., 2013; Jenner, 1991; Rouault and Cooperman, 2006). In a hypothesis of PD neurodegeneration, iron is suggested to induce α-synuclein pathology (Hare et al., 2013). α-synuclein is a presynaptic neuronal protein that is abundant in human brain and can be found in different brain regions including neocortex, hippocampus, substantia nigra, thalamus, and cerebellum. Abnormal aggregation of α-synuclein in PD patients, a clinical pathological hallmark of the disease, contributes to the formation of Lewy bodies which the major component is α-synuclein (Marques and Outeiro, 2012; Stefanis, 2012). Such pathological feature rendered PD to be considered as a type of synucleinopathies. Since α-synuclein aggregation has also been observed in limbic structures and is itself associated with the onset of dementia in PDD, we hypothesize that iron accumulation in PD could also be involved in the later overt development of neuropsychiatric symptoms in PD patients.

Quantitative Susceptibility Mapping (QSM) is a novel technique which allows the determination of tissue's bulk magnetic susceptibility distribution from gradient echo magnetic resonance phase images. A previous study by Langkammer et al. reported a strong linear correlation between chemically determined iron concentration and bulk magnetic susceptibility in grey matter structures (Langkammer et al., 2012). The objective of this study is to identify the role of abnormal iron metabolism in PD-type dementia by comparing the in vivo putative iron content measured with QSM, of different subcortical and limbic brain structures amongst healthy subjects and PD patients with or without dementia. In addition, any association between iron and the expression of dementia and psychotic symptomatology in PD is addressed. MR volumetric analysis of the subcortical and limbic brain structures is also performed.

2. Materials and methods

2.1. Participants

This study was approved by the local Institutional Review Board. The recruited participants were divided into three groups based on clinical diagnosis and result of neuropsychiatric assessments. A total of 68 participants were recruited with referral from experienced physicians. All participants or their caregivers were carefully explained for the study by the responsible medical officers before full written informed consent was obtained. The study cohort comprised of 10 PDD patients (8 males, mean age ± S.D. = 73 ± 6 years, mean illness duration ± S.D. = 13 ± 8 years), 31 non-demented PD patients (17 males, mean age ± S.D. = 63 ± 8 years, mean illness duration ± S.D. = 8 ± 5 years) and 27 healthy controls (14 males, mean age ± S.D. = 62 ± 7 years). PD was diagnosed using the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (Hughes et al., 1992). PD patients were classified as PDD when they fulfilled the level one diagnostic criteria proposed by the Movement Disorder Society (MDS) (Dubois et al., 2007; Holden et al., 2016; Vasconcellos and Pereira, 2015). Patients with other known neurodegenerative disorders were excluded. Severity of motor deficit was assessed with both Section III of Unified Parkinson's Disease Rating Scale (UPDRS-III) and Hoehn & Yahr staging (Hoehn and Yahr, 1967). The cumulative L-Dopa Equivalence (mg) of the PD patients were also obtained for the evaluation of the differences between the study cohorts.

2.2. Neuropsychiatric assessments

Neuropsychiatric status of all subjects were assessed with the following tests: Mini-mental State Examination (MMSE) to assess cognitive impairment (Folstein et al., 1975); Parkinson Psychosis Rating Scale (PPRS) and Positive and Negative Syndrome Scale (PANSS) to examine the severity of psychosis (Friedberg et al., 1998); Self-assessment of Montgomery-Åsberg Depression Rating Scale (MADRS-S) to measure the severity of depression symptom (Kay et al., 1987; Montgomery and Asberg, 1979), and Yale-Brown Obsessive Compulsive Scale (Y-BOCS) to measure obsessive-compulsive symptoms (Goodman et al., 1989). The complete demographics and the clinical neuropsychiatric profile of all subjects are listed in Table 1.

Table 1
Demographics and results of neuropsychiatric assessment of healthy controls, non-demented PD and PDD patients.

	Healthy	PD	PDD	p-value
N	27	31	10	–
Age (years)	62.0 ± 7.0	63.1 ± 8.3	72.6 ± 5.8	0.001*
Gender (M:F)	14:13	17:14	8:2	0.29
Duration of illness (years)	n/a	7.6 ± 4.6	12.8 ± 8.1	0.08
Hoehn & Yahr Stage	n/a	2.7 ± 0.8	2.7 ± 1.2	0.90
UPDRS-III	n/a	17.4 ± 9.8	33.7 ± 15.7	< 0.001**
MMSE	28.8 ± 1.0	28.3 ± 1.7	19.3 ± 5.0	< 0.001**
PPRS	6.1 ± 0.3	6.6 ± 0.9	9.8 ± 2.9	< 0.001**
PANSS	30.9 ± 3.3	38.2 ± 8.3	52.9 ± 15.6	< 0.001**
MADRS-S	0.4 ± 1.1	2.4 ± 2.8	3.9 ± 3.0	< 0.001**
Y-BOCS	0.0 ± 0.2	0.9 ± 2.4	3.2 ± 6.3	0.016*
L-Dopa Equivalence (mg)	n/a	663.2 ± 416.8	1174.4 ± 935.6	0.125

Note: Values on the table are displayed as mean ± S.D. UPDRS-III: Section III (motor examination) of the Unified Parkinson's Disease Rating Scale. MMSE: Mini-Mental State Examination; PPRS: Parkinson's Psychosis Rating Scale; PANSS: Positive and Negative Syndrome Scale; MADRS-S: Self-assessment of the Montgomery-Åsberg Depression Rating Scale; Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

* $p < 0.05$

** $p < 0.001$.