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Loss of integrity and atrophy in cingulate structural covariance networks in Parkinson's disease

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ABSTRACT

Background: In Parkinson's disease (PD), the relation between cortical brain atrophy on MRI and clinical progression is not straightforward. Determination of changes in structural covariance networks - patterns of covariance in grey matter density - has shown to be a valuable technique to detect subtle grey matter variations. We evaluated how structural network integrity in PD is related to clinical data.

Methods: 3 Tesla MRI was performed in 159 PD patients. We used nine standardized structural covariance networks identified in 370 healthy subjects as a template in the analysis of the PD data. Clinical assessment comprised motor features (Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MDS-UPDRS motor scale) and predominantly non-dopaminergic features (SEverity of Non-dopaminergic Symptoms in Parkinson's Disease; SENS-PD scale: postural instability and gait difficulty, psychotic symptoms, excessive daytime sleepiness, autonomic dysfunction, cognitive impairment and depressive symptoms). Voxel-based analyses were performed within networks significantly associated with PD.

Results: The anterior and posterior cingulate network showed decreased integrity, associated with the SENS-PD score, $p = 0.001$ ($\beta = -0.265$, $\eta_p^2 = 0.070$) and $p = 0.001$ ($\beta = -0.264$, $\eta_p^2 = 0.074$), respectively. Of the components of the SENS-PD score, cognitive impairment and excessive daytime sleepiness were associated with atrophy within both networks.

Conclusions: We identified loss of integrity and atrophy in the anterior and posterior cingulate networks in PD patients. Abnormalities of both networks were associated with predominantly non-dopaminergic features, specifically cognition and excessive daytime sleepiness. Our findings suggest that (components of) the cingulate networks display a specific vulnerability to the pathobiology of PD and may operate as interfaces between networks involved in cognition and alertness.

1. Introduction

Parkinson's disease (PD) is characterized by a broad spectrum of motor and non-motor features. It has been proposed that widespread pathological changes (Lewy bodies and Lewy neurites) in select nuclei of the central and peripheral nervous system underlie the complex clinical presentation of PD (Jellinger, 2012). Increasing evidence points at the existence of a coherent grouping of some of the clinical domains, which largely involve symptoms that do not improve on dopaminergic medication. The grouping of these symptoms is present early in the disease course (Van der Heeden et al., 2016), worsens over time (Van der Heeden et al., 2016), and probably reflects advancing Lewy body pathology in the nervous system (Adler and Beach, 2016).

Previous anatomical magnetic resonance imaging (MRI) studies commonly investigated voxel-wise differences in regional grey matter volume between PD patients and control subjects. These studies revealed reduced grey matter in patients (Pan et al., 2012), which, however, is nonspecific to PD. Further, the findings are inconsistent across studies (Pan et al., 2012), which is likely explained by the clinical heterogeneity of PD and the current insensitivity of imaging

Abbreviations: PD, Parkinson's disease; MRI, magnetic resonance imaging; SCN, structural covariance network; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; SENS-PD, SEverity of Non-dopaminergic Symptoms in Parkinson's Disease; LDE, levodopa dose equivalent; VBM, voxel-based morphometry; FSL, FMRIB's software library; MNI, Montreal Neurological Institute; MMSE, Mini Mental State Examination; DA, dopamine agonists; TFCE, Threshold-Free Cluster Enhancement

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techniques to detect subtle changes in brain structures. New techniques including computational network-based analyses are increasingly important in uncovering in vivo patterns of brain atrophy not readily apparent by regional structural analysis (Alexander-Bloch et al., 2013; Hafkemeijer et al., 2016). Evidence suggests that anatomical structures that are spatially distributed but functionally linked, co-vary in grey matter density (structural covariance networks; SCNs) within individuals across a population (Alexander-Bloch et al., 2013; Andrews et al., 1997).

Factors like age and disease affect SCNs (Hafkemeijer et al., 2014; Möller et al., 2015). Distinct aging effects on the organization of SCNs were demonstrated in healthy elderly (Montembeault et al., 2012; Spreng and Turner, 2013). Also, it was shown that Alzheimer's disease and frontotemporal dementia have specific SCNs of degeneration (Hafkemeijer et al., 2016). These findings support that this methodology may have the potential to identify brain regions within disease specific structural networks that confer a preferential vulnerability to the pathobiology of PD.

In this study, we studied SCN integrity in PD patients. We evaluated whether the integrity of SCNs - constructed from grey matter density in healthy elderly adults, is associated with clinical severity of PD and if the integrity is associated with predominantly dopaminergic or non-dopaminergic symptoms.

2. Materials and methods

2.1. Study design and participants

PD patients were recruited from the outpatient clinic for Movement Disorders of the Department of Neurology of the LUMC (Leiden University Medical Center) and nearby university and regional hospitals. All participants fulfilled the United Kingdom Parkinson's Disease Society Brain Bank criteria for idiopathic PD (Gibb and Lees, 1988). The present study is a cross-sectional cohort study of PD patients and is part of the 'PROfiling PARKinson's disease' (PROPARK) study. Written consent was obtained from all participants. The Medical Ethics Committee of the LUMC approved the study.

2.2. Clinical assessments

All patients underwent standardized assessments, including an evaluation of demographic and clinical characteristics. Participants were tested while on-medication, except for 24 patients (22 de novo patients, defined as dopaminergic drug-naïve patients with a disease duration shorter than five years; two other dopaminergic drug-naïve patients). The MDS-UPDRS motor scale (part III) was used to quantify the severity of motor symptoms (Goetz et al., 2008). The SENS-PD (SEverity of Non-dopaminergic Symptoms in Parkinson's Disease) scale is a composite score comprising three items with four response options (0–3) from each of the following six predominantly non-dopaminergic domains: postural instability and gait difficulty, psychotic symptoms, excessive daytime sleepiness, autonomic dysfunction, cognitive impairment and depressive symptoms (total range: 0–54) (van der Heeden et al., 2014; Van der Heeden et al., 2016). These six domains represent a coherent complex of symptoms that is already present in the early disease stages and increases in severity when the disease advances. The SENS-PD is a recently developed short, reliable and valid scale that includes symptoms that do not improve with dopaminergic medication and its score may therefore more accurately reflect severity and progression of the underlying disease than currently used dopamine-sensitive measures. Higher scores on both scales reflect more severe impairment. Trained research associates administered the MDS-UPDRS motor scale and the 'postural instability and gait difficulty', 'psychotic symptoms' and 'cognitive impairment' items of the SENS-PD scale. The 'excessive daytime sleepiness', 'autonomic dysfunction' and 'depressive symptoms' items were self-completed by patients. A levodopa dose equivalent (LDE) of daily levodopa and dopamine agonists dose was calculated for each patient. The total LDE is the sum of levodopa dosage equivalent (LDE-Dopa) and the dopamine agonist dosage equivalent (LDE-DA) (Tomlinson et al., 2010).

2.3. MRI acquisition

Three-dimensional T1-weighted anatomical images were acquired on a 3 Tesla MRI scanner (Philips Achieva, Best, the Netherlands) using a standard 32-channel whole-head coil. Acquisition parameters were: repetition time = 9.8 ms, echo time = 4.6 ms, flip angle = 8°, field of view 220 × 174 × 156 mm, 130 slices with a slice thickness of 1.2 mm with no gap between slices, resulting in a voxel size of 1.15 mm × 1.15 mm × 1.20 mm.

2.4. Data analysis

Before analysis, all MRI scans were visually checked to ensure that no major artifacts or abnormalities were present in the data. All analyses were done using the software provided by FSL (FMRIB's software library, version 5.0.8, Oxford, United Kingdom) (Smith et al., 2004).

2.5. Pre-processing

The 3DT1 images were pre-processed using the pre-processing steps used for voxel-based morphometric analysis (Douaud et al., 2007; Good et al., 2001; Smith et al., 2004). Each step was visually checked. The T1-weighted images were brain-extracted and tissue-type segmentation was performed, resulting in probability maps of a given tissue type (i.e. grey matter, white matter or cerebrospinal fluid). The grey matter images were non-linearly registered to the 2 mm Montreal Neurological Institute (MNI) 152 standard space (Montreal Neurological Institute, Montreal QC, Canada) (Andersson et al., 2007; Jenkinson et al., 2002). The resulting images were averaged to create a study-specific grey matter template. All native grey matter images were subsequently non-linearly re-registered to the study-specific grey matter template and 'modulated' to correct for local expansions or contractions due to the non-linear component of the spatial transformation. The images were smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. The modulated grey matter images in MNI space were concatenated into a four-dimensional data set, which was used for the network and voxel-based morphometry (VBM) analyses.

2.6. Structural covariance networks

We used nine bilateral standardized SCNs, identified in 370 healthy elderly with an age range of 45–85 years, which is the same as the age range in our PD population. For detailed information on the networks see Hafkemeijer et al. (2014). The networks were derived using an independent component analysis, a statistical technique that defines spatial component maps of maximal statistical independence. It is commonly used to study functional network integrity, but it can also be used to study if brain structures of a population co-vary in grey matter volume (Hafkemeijer et al., 2014; Segall et al., 2012). The four-dimensional data set of grey matter images derived from our PD population was used in a spatial regression against the nine SCN probability maps (a general linear model approach integrated in FSL) (Filippini et al., 2009). This way individual SCN integrity scores were calculated. The integrity score is the beta coefficient of the regression analysis. It can be a negative or a positive score, reflecting the strength of the individual expression in each network, with high scores indicating strong individual expression of the network. To allow comparisons of the SCNs of the template and patients with PD, identification of the nine SCNs in patients with PD was conducted using the same approach as Hafkemeijer et al. (2014). An independent component analysis was applied on the four-dimensional data set of modulated grey matter