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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

images of all PD patients, using multivariate exploratory linear optimized decomposition into independent components (Beckmann et al., 2005). The independent component analysis was restricted to nine components, the same amount as in the study of Hafkemeijer et al. (2014). Significance of individual voxels within a spatial map was derived using a mixture model, with a standard threshold level of 0.5 (Smith et al., 2004), which indicates an equal loss is placed on false positives and false negatives.

2.7. Voxel-based morphometry

To investigate group differences in grey matter volume, a voxel-wise general linear model in FSL was used. Grey matter region-of-interest masks were obtained by identifying anatomical structures that were present in the SCNs (Hafkemeijer et al., 2014). A design matrix was constructed for estimating the relationship between grey matter volume (in each region-of-interest) and clinical measures. Gender, age and disease duration were used as covariates to correct for confounding effects. The voxel-wise general linear model was applied on the previously derived four-dimensional data set. 'Randomise', FSL's tool for nonparametric permutation inference on neuroimaging data, was used with 5000 permutations to perform non-parametric statistics (Winkler et al., 2014). We used the TFCE (Threshold-Free Cluster Enhancement) technique to correct for multiple comparisons (Smith and Nichols, 2009).

Brain structures were identified using the Harvard-Oxford atlas integrated in FSL.

2.8. Statistical analysis

Differences in age and gender between patients and control subjects in which the template was defined, were analyzed with an independent-sample *t*-test (age) and a chi-square test (gender). The relationship between SCN integrity and clinical measures was investigated using general linear modeling within the PD group, adjusted for gender, age and disease duration. Associations were studied between SCN integrity scores (dependent variable) and the MDS-UPDRS motor score, and between SCN integrity scores and the SENS-PD score. Bonferroni correction was applied to account for multiple comparisons (p-value: 0.05/18 = 0.003). If the integrity score of a network showed a statistically significant association with the MDS-UPDRS motor score or the SENS-PD score, we examined associations between the SCN integrity score and the domains scores of the concerning clinical scale. A Bonferroni correction was applied across the different networks (p-value = 0.05/amount of items of the concerning clinical score, i.e. six domains of the SENS-PD and four of the MDS-UPDRS motor score). To investigate whether dosage of dopaminergic medication could affect structural networks, we examined associations between the SCN integrity scores and LDE scores within the PD group who used dopaminergic medication. To study group differences between de novo patients and patients who used dopaminergic medication, we performed additional general linear modeling analyses in which network integrities were treated as dependent variables and the group (de novo patients or patients who used dopaminergic medication) as an independent, fixed, variable, while adjusting for age and gender. SPSS version 23.0 was used for all analyses (IBM SPSS Statistics for Mac, Version 23.0. Armonk, NY: IBM Corp.).

3. Results

3.1. Demographic characteristics

159 patients were included in the analysis. Demographic and clinical data of all participants are shown in Table 1.

Table 1
Participant characteristics.

	Patients	Controls	
N	159	370	p-Value
Men/women (% men)	101/58 (63.5)	178/192 (48.1)	0.001
Age, year, mean (SD)	64.9 (7.1)	65.7 (6.7)	0.234
Disease duration, year, mean (SD)	9.1 (4.8)		
MDS-UPDRS motor score, mean (SD) (0 – 132)	34.3 (15.7)		
SENS-PD, mean (SD), n = 153 (0–54)	13.0 (6.1)		
MMSE, mean (SD), n = 156 (0 – 30)	28.4 (1.8)		
Total LDE, mg/day, n = 129	1010.2 (561.2)		
Dopaminergic drug-naïve patients, n = 2	–		
De novo patients[a], n = 22	–		
LDE-Dopa, mg/day	735.1 (507.5)		
LDE-DA dose, mg/day	198.0 (216.7)		

For all measurement instruments, the score range is presented in parentheses. SD: standard deviation; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; SENS-PD: SEverity of Non-dopaminergic Symptoms in Parkinson's Disease; MMSE: Mini Mental State Examination; LDE: Levodopa dosage equivalent; DA: dopamine agonists.

[a] De novo patients were defined as dopaminergic drug-naïve patients with a disease duration shorter than five years.

3.2. Structural covariance network integrity

Of the nine SCNs, the integrity of the posterior and anterior cingulate network (SCN c and d) both showed a negative association with the SENS-PD score (p = 0.001 and p = 0.001, respectively; Table 2). The integrity of the anterior cingulate network showed a negative association with the MDS-UPDRS motor score (p = 0.032). After correction for multiple comparisons, the associations between the posterior and anterior cingulate network and the SENS-PD score remained significant (Table 2).

As the associations between the posterior and anterior cingulate network and the total SENS-PD score were significant, the associations between SCN integrity of the cingulate networks and the domain scores of the SENS-PD scale (postural instability and gait difficulty, cognitive impairment, depressive symptoms, psychotic symptoms, excessive daytime sleepiness and autonomic symptoms) were subsequently tested. The SCN integrity scores of the posterior and anterior cingulate network were negatively associated with cognitive impairment (posterior cingulate network: $\beta = -0.309$, $p < 0.001$, $\eta_p^2 = 0.097$; anterior cingulate network: $\beta = -0.162$, $p = 0.049$, $\eta_p^2 = 0.026$) and excessive daytime sleepiness (posterior cingulate network: $\beta = -0.172$, $p = 0.021$, $\eta_p^2 = 0.034$; anterior cingulate network: $\beta = -0.213$, $p = 0.005$, $\eta_p^2 = 0.051$). After correction for multiple comparisons, the association between the posterior cingulate network and cognitive impairment remained significant. The association between the anterior cingulate network and EDS remained significant as well. No significant associations were found between the SCN integrity and the domain scores of postural instability and gait difficulty, depressive symptoms, psychotic symptoms and autonomic symptoms. The associations between SCN integrity and the different domain scores of the MDS-UPDRS motor scale (i.e., tremor, rigidity, bradykinesia and postural instability and gait difficulty) were not tested because no significant associations were found between SCN integrity scores and the total MDS-UPDRS motor score after correction for multiple comparisons. We found that LDE score was not associated with SCN integrity scores. For none of the nine SCNs, a significant group difference in SCN integrity score was shown between de novo patients and patients who used dopaminergic medication.

Table 2
Associations between the SCN integrity scores and the composite clinical measures (MDS-UPDRS motor scale; SENS-PD scale).

	Predominant brain region in SCN	MDS-UPDRS motor score		SENS-PD score	
		Beta	p-Value (η_p^2)	Beta	p-Value (η_p^2)
SCN a	Thalamus	− 0.052	0.511 (0.003)	0.040	0.617 (0.002)
SCN b	Lateral occipital cortex	− 0.075	0.348 (0.006)	− 0.052	0.520 (0.003)
SCN c	Posterior cingulate cortex	− 0.155	0.052 (0.024)	− 0.264	0.001 (0.074)*
SCN d	Anterior cingulate cortex	− 0.172	0.032 (0.030)	− 0.265	0.001 (0.070)*
SCN e	Temporal pole	− 0.071	0.418 (0.004)	− 0.025	0.785 (0.001)
SCN f	Putamen	0.012	0.879 (0.000)	0.024	0.769 (0.001)
SCN g	Cerebellum	0.094	0.260 (0.008)	0.087	0.311 (0.007)
SCN h	Cerebellum	0.119	0.156 (0.013)	0.014	0.868 (0.000)
SCN i	Cerebellum	0.012	0.891 (0.000)	0.037	0.677 (0.001)

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.
Beta: standardized β; η_p^2: partial eta squared.
* p-Value remained significant after correction for multiple comparisons. All analyses were adjusted for age, gender and disease duration.

3.3. Voxel-based analyses

Loss of integrity in a SCN is due to grey matter changes in one or more component(s) in the network. To detect which components were specifically atrophied, voxel-based analysis within the posterior and anterior cingulate network was performed. We used the domain score of cognitive impairment to examine decreased grey matter in the posterior cingulate network and excessive daytime sleepiness to examine decreased grey matter in the anterior cingulate network, as is shown in Fig. 1. Large clusters of grey matter volume reductions in the posterior cingulate network related to cognitive impairment were localized in the posterior cingulate cortex ($p = 0.002$, peak cluster MNI coordinates: 0, − 52, 24, voxel size = 509) and the central operculum cortex ($p < 0.001$, peak cluster MNI coordinates: 54, − 2, 4, voxel size = 786). Smaller clusters of decreased grey matter were found in the subcallosal cortex ($p = 0.015$, peak cluster MNI coordinates: 0, 16, − 12, voxel size = 103), the parietal operculum cortex ($p = 0.046$, peak cluster MNI coordinates: 38, − 22, 18, voxel size = 21) and the posterior middle temporal gyrus ($p = 0.020$, peak cluster MNI coordinates: − 58, − 34, − 10, voxel size = 28). In the anterior cingulate network, decreased grey matter related to excessive daytime sleepiness was found in the middle frontal gyrus ($p = 0.014$, peak cluster MNI coordinates: 36, 16, 48, voxel size = 191), the frontal medial cortex ($p = 0.007$, peak cluster MNI coordinates: − 4, 52, − 20, voxel size = 252) and the cuneus ($p = 0.013$, peak cluster MNI coordinates: 2, − 86, 18, voxel size = 178).

3.4. Cingulate networks in patients with PD

To visualize the abnormal architecture of both cingulate SCNs, the networks were also defined in all patients with PD. As is shown in Fig. 2, some components of the cingulate networks identified in healthy control subjects are missing in the networks identified in patients with PD. These missing components do not significantly co-vary in grey matter density with the network. The most prominent changes are seen in the anterior (Fig. 2A and B) and posterior cingulate cortex (Fig. 2A) and the frontal medial cortex (Fig. 2B).

4. Discussion

Within individuals across a population, spatially distributed regions of the brain, which are functionally linked, may show a structural covariance of grey matter volume. Although the neurobiological underpinnings of SCNs and functional covariance network associations are unclear, it has been posited that SCNs reflects shared long-term trophic influences within functionally synchronous systems (Zielinski et al., 2010). Recently, nine SCNs were established in 370 healthy elderly (Hafkemeijer et al., 2014). In four out of nine SCNs (subcortical network, sensorimotor network, posterior cingulate network, anterior cingulate network), grey matter volume decreased with advancing age. Given the important role of age in the development and prognosis of PD, we examined the influence of PD on the topological organization of nine SCNs established in healthy elderly. Our study led to two main findings: (1) only the anterior and posterior cingulate SCN showed a loss of integrity beyond the effects of aging; (2) the reduced integrity of both cingulate SCNs was significantly associated with predominantly non-dopaminergic domains, including cognitive impairment and excessive daytime sleepiness.

To unravel if specific regions that make up the SCNs explained the clinical associations, we studied grey matter changes within both networks in relation to these two predominantly non-dopaminergic domains. The largest clusters of decreased grey matter were found in relation to cognitive impairment in two regions of the posterior cingulate network: central operculum cortex and posterior cingulate cortex. Compared to cognitive impairment, smaller clusters of decreased grey matter, albeit still significant associations, were found for excessive

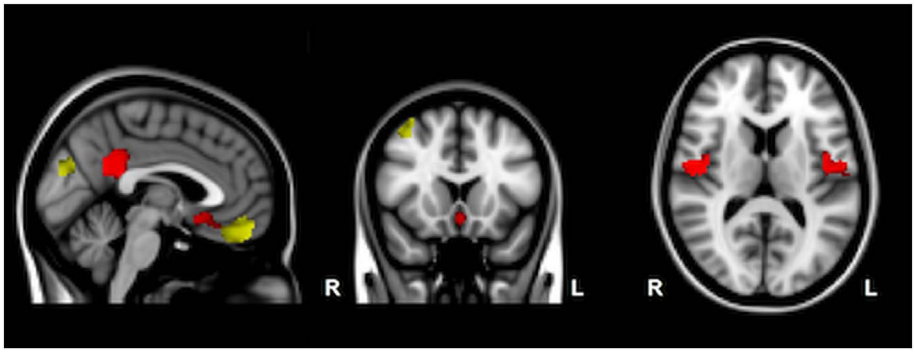

Fig. 1. Regional grey matter changes in PD patients.
Red: Reduced grey matter in the posterior cingulate network related to cognitive impairment. Yellow: Reduced grey matter in the anterior cingulate network related to excessive daytime sleepiness. Images are overlaid on the most informative sagittal, coronal and transversal slices of the MNI (Montreal Neurological Institute) standard anatomical image (MNI coordinates are − 2, 18, 12). Results with a Threshold-free cluster enhancement (TFCE)-Family wise error (FWE) corrected p-value < 0.05 and a voxel size above 30 are shown. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

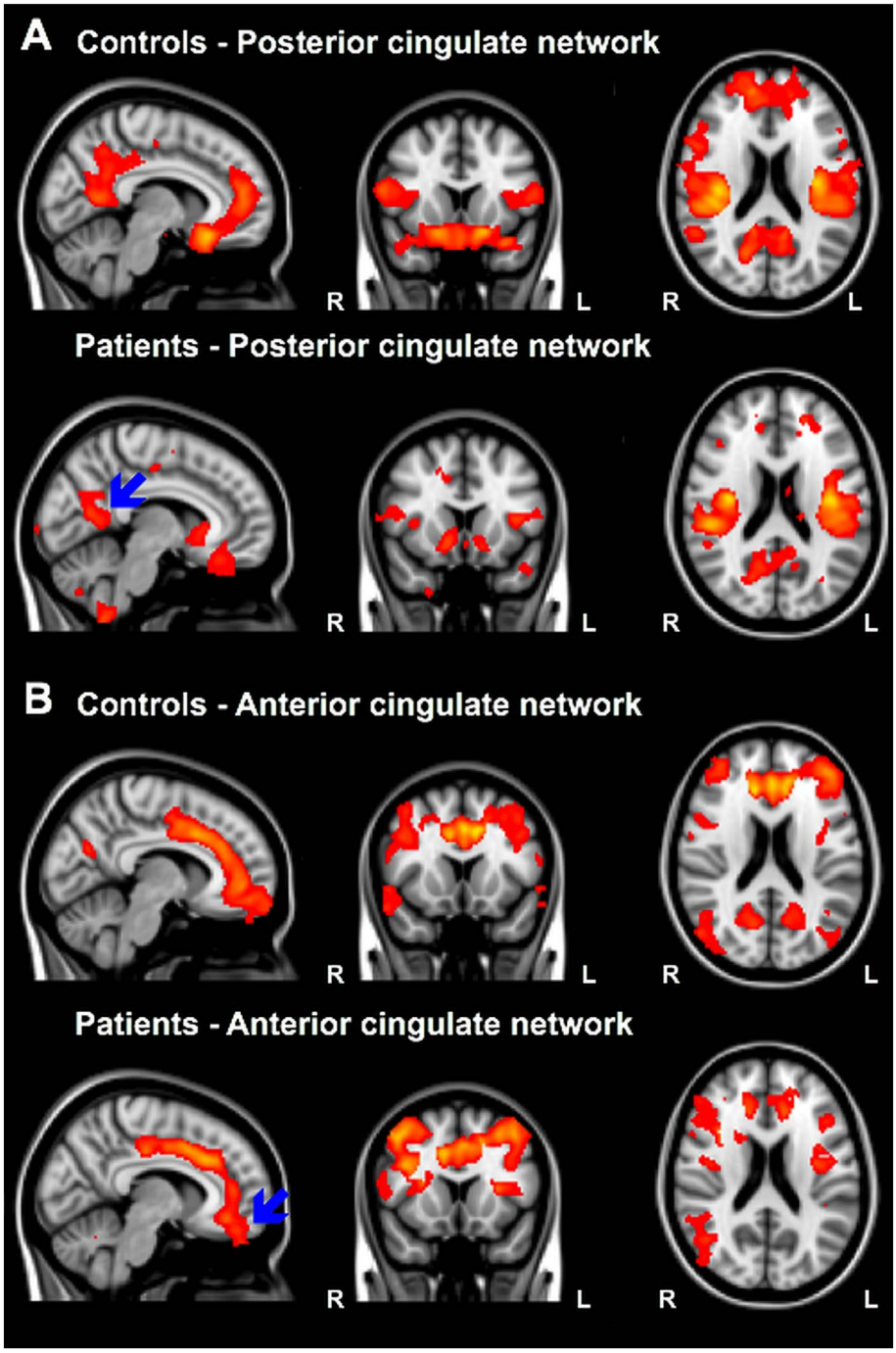

Fig. 2. Cingulate networks defined in healthy control subjects and in patients.
Both cingulate networks defined in healthy control subjects and in patients with Parkinson's disease, overlaid on the most informative sagittal, coronal and transversal slices of the MNI (Montreal Neurological Institute) standard anatomical image (MNI coordinates are 8, −14, 20). A: Posterior cingulate network. B: Anterior cingulate network.

daytime sleepiness in three regions of the anterior cingulate network: frontal medial cortex, middle frontal gyrus and cuneus. Collectively, these findings are in line with those of others indicating a role of the cingulate cortex in mediating processes involved in cognition and vigilance in patients with PD (Leech and Sharp, 2014; Menon and Uddin, 2010; Zielinski et al., 2010).

Cognitive impairment is an important non-motor feature of PD, which reflects the variable and interacting dysfunction in a number of diffusely distributed, yet interrelated, neural networks that contribute to distinct cognitive processes (Gratwicke et al., 2015). Compelling evidence shows that structural and functional abnormalities of the posterior cingulate cortex are found in neurological and psychiatric diseases, e.g. Alzheimer's disease, schizophrenia, autism, depression and attention deficit hyperactivity disorder (Leech and Sharp, 2014). Congruent with results of other studies in PD, our study shows that abnormalities of the posterior cingulate cortex are associated with cognitive impairment (Christopher et al., 2015; Leech and Sharp, 2014).

In PD, excessive daytime sleepiness has been found associated with various clinical factors, including cognitive impairment, postural instability and gait difficulty, hallucinations, advanced disease, and dopaminergic medication (Tholfsen et al., 2015; Zhu et al., 2016). The neurological substrates of excessive daytime sleepiness are incompletely understood, but likely involve extended subcortical-cortical networks acting to promote arousal and sleep (Brown et al., 2012). The anterior cingulate network shows spatial overlap with the functional connectivity salience network (Seeley et al., 2007). The salience network is considered to be involved in the integration of internal and external stimuli, supporting the association we found with excessive daytime sleepiness (Seeley et al., 2007). Our findings showing

involvement of multiple regions of the anterior cingulate network, are congruent with those of two other studies showing cortical atrophy of occipital and frontal brain regions in PD patients with excessive daytime sleepiness as compared to PD patients without excessive daytime sleepiness (Gama et al., 2010; Kato et al., 2012).

Our patients had mild to moderate disease severity and a mean disease duration of approximately nine years. In PD, cortical α-synuclein aggregation occurs in advanced stages and except for the cingulate gyrus, neocortical regions have low frequencies of α-synuclein aggregation (Beach et al., 2009; Jellinger, 2012). However, the functional consequences of α-synuclein aggregation in the brain are unclear and Braak stages are not related to clinical severity of PD (Schulz-Schaeffer, 2010). Recent evidence proposes that diverse molecular and cellular pathologies involved in PD can give rise to common patterns of dysfunction at the neural systems level (Gratwicke et al., 2015).

The finding that reduced anterior and posterior cingulate network integrity is associated with two different categories of predominantly non-dopaminergic symptoms, may suggest that (components) of both SCNs act as an integrative hub. Indeed, it is suggested that both the anterior and posterior cingulate cortex may operate as important interfaces between different functional networks involved in cognition and alertness (Leech and Sharp, 2014; Menon and Uddin, 2010). Cognition and alertness are regulated by large-scale functional networks, consisting of numerous interconnected brain areas, which act (dynamically) in concert to perform the circumscribed functions (Leech and Sharp, 2014; Seeley et al., 2007). These large-scale brain networks comprise cortical and subcortical areas and their interconnecting structural or functional connections. Some brain areas perform important integrative roles in networks (hubs) because they display an unusually high degree of intermodular connectivity which is not critical to distinctive functions of the brain (van den Heuvel et al., 2013). Findings from a human brain structural connectivity study using diffusion imaging and tractography suggest that damage to hub regions has a larger disruptive effect on network communication than damage to non-hub regions of a network (van den Heuvel et al., 2013). This finding may explain why damage of two cingulate structural networks is associated with important dysfunctions on the level of cognition and vigilance.

4.1. Strengths and limitations

The strength of this study lies in detecting grey matter changes with a novel network-based technique in a large group of clinically well-characterized PD patients with simultaneous acquired MR images. Limitations of our study are related to the cross-sectional design. A longitudinal design is preferable to assess the relationship between network integrity and disease progression. Further, our population is characterized by patients with mild to moderate disease severity, limiting the generalizability of the results to the PD population at large. Nonetheless, it is notable that even in these patients SCN analysis was able to detect distinct regions of grey matter atrophy, which were related to severity of predominantly non-dopaminergic symptoms in two domains. Patients were tested while on dopaminergic medication. In addition, the depression scale (the Hospital Anxiety and Depression Scale) (Zigmond and Snaith, 1983), from which items for the depression domain of the SENS-PD were taken, inquires after symptoms in the last week and was completed in the week before the MRI was made, when patients took their regular medication. We cannot rule out that this may have resulted in a decrease of symptom scores that show some sensitivity to dopaminergic influences and possibly have attenuated the examined associations. This likely played a less prominent role with regard to the total SENS-PD scale, which includes symptoms that mainly do not improve with dopaminergic medication, although there are potentially some positive effects on depression (Chaudhuri and Schapira, 2009).

4.2. Conclusions

In conclusion, SCN analysis in mild to moderate PD revealed a loss of integrity of the anterior and posterior cingulate SCN, which in turn was explained by grey matter loss in specific brain regions within the networks. The identified structural changes were associated with cognitive impairment and excessive daytime sleepiness, suggesting that components of both cingulate SCNs may operate as important interfaces between different functional networks involved in cognition and alertness.

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References

Adler, C.H., Beach, T.G., 2016. Neuropathological basis of nonmotor manifestations of Parkinson's disease. Mov. Disord. http://dx.doi.org/10.1002/mds.26605.

Alexander-Bloch, A., Raznahan, A., Bullmore, E., Giedd, J., 2013. The convergence of maturational change and structural covariance in human cortical networks. J. Neurosci. 33, 2889–2899. http://dx.doi.org/10.1523/JNEUROSCI.3554-12.2013.

Andersson, J.L.R., Jenkinson, M., Smith, S., 2007. Non-linear registration aka spatial normalisation FMRIB technial report TR07JA2. In Pract. 22.

Andrews, T.J., Halpern, S.D., Purves, D., 1997. Correlated size variations in human visual cortex, lateral geniculate nucleus, and optic tract. J. Neurosci. 17, 2859–2868.

Beach, T.G., Adler, C.H., Lue, L., Sue, L.I., Bachalakuri, J., Henry-Watson, J., Sasse, J., Boyer, S., Shirohi, S., Brooks, R., Eschbacher, J., White, C.L., Akiyama, H., Caviness, J., Shill, H.A., Connor, D.J., Sabbagh, M.N., Walker, D.G., Consortium, the A.P.D, 2009. Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. Acta Neuropathol. 117, 613–634. http://dx.doi.org/10.1007/s00401-009-0538-8.

Beckmann, C.F., DeLuca, M., Devlin, J.T., Smith, S.M., 2005. Investigations into resting-state connectivity using independent component analysis. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 360, 1001–1013. http://dx.doi.org/10.1098/rstb.2005.1634.

Brown, R.E., Basheer, R., McKenna, J.T., Strecker, R.E., McCarley, R.W., 2012. Control of sleep and wakefulness. Physiol. Rev. 92, 1087–1187. http://dx.doi.org/10.1152/physrev.00032.2011.

Chaudhuri, K.R., Schapira, A.H.V., 2009. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol. 8, 464–474. http://dx.doi.org/10.1016/S1474-4422(09)70068-7.

Christopher, L., Duff-Canning, S., Koshimori, Y., Segura, B., Boileau, I., Chen, R., Lang, A.E., Houle, S., Rusjan, P., Strafella, A.P., 2015. Salience network and parahippocampal dopamine dysfunction in memory-impaired Parkinson disease. Ann. Neurol. 77, 269–280. http://dx.doi.org/10.1002/ana.24323.

Douaud, G., Smith, S., Jenkinson, M., Behrens, T., Johansen-Berg, H., Vickers, J., James, S., Voets, N., Watkins, K., Matthews, P.M., James, A., 2007. Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. Brain 130, 2375–2386. http://dx.doi.org/10.1093/brain/awm184.

Filippini, N., MacIntosh, B.J., Hough, M.G., Goodwin, G.M., Frisoni, G.B., Smith, S.M., Matthews, P.M., Beckmann, C.F., Mackay, C.E., 2009. Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. Proc. Natl. Acad. Sci. U. S. A. 106, 7209–7214. http://dx.doi.org/10.1073/pnas.0811879106.

Gama, R.L., Távora, D.G., Bomfim, R.C., Silva, C.E., de Bruin, V.M., de Bruin, P.F.C., 2010. Sleep disturbances and brain MRI morphometry in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy - a comparative study. Parkinsonism Relat. Disord. 16, 275–279. http://dx.doi.org/10.1016/j.parkreldis.2010.01.002.

Gibb, W.R., Lees, A.J., 1988. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 51, 745–752.

Goetz, C.G., Tilley, B.C., Shaftman, S.R., Stebbins, G.T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M.B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A.E., Lees, A., Leurgans, S., LeWitt, P.A., Nyenhuis, D., Olanow, C.W., Rascol, O., Schrag, A., Teresi, J.A., van Hilten, J.J., LaPelle, N., 2008. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov. Disord. 23, 2129–2170. http://dx.doi.org/10.1002/mds.22340.

Good, C., Johnsrude, I., Ashburner, J., Henson, R., Friston, K., Frackowiak, R., 2001. A voxel-based morphometric study of ageing in 465 normal adult human brains. NeuroImage 14, 21–36. http://dx.doi.org/10.1006/nimg.2001.0786.

Gratwicke, J., Jahanshahi, M., Foltynie, T., 2015. Parkinson's disease dementia: a neural networks perspective. Brain 138, 1454–1476. http://dx.doi.org/10.1093/brain/awv104.

Hafkemeijer, A., Altmann-Schneider, I., de Craen, A.J., Slagboom, P.E., van der Grond, J., Rombouts, S.A., 2014. Associations between age and gray matter volume in anatomical brain networks in middle-aged to older adults. Aging Cell 13, 1068–1074. http://dx.doi.org/10.1111/acel.12271.

Hafkemeijer, A., Möller, C., Dopper, E.G.P., Jiskoot, L.C., van den Berg-Huysmans, A.A., van Swieten, J.C., van der Flier, W.M., Vrenken, H., Pijnenburg, Y.A.L., Barkhof, F., Scheltens, P., van der Grond, J., Rombouts, S.A.R.B., 2016. Differences in structural covariance brain networks between behavioral variant frontotemporal dementia and Alzheimer's disease. Hum. Brain Mapp. 37, 978–988. http://dx.doi.org/10.1002/hbm.23081.

Jellinger, K.A., 2012. Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. Mov. Disord. 27, 8–30. http://dx.doi.org/10.1002/mds.23795.

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved methods for the registration and motion correction of brain images. NeuroImage 17, 825–841. http://dx.doi.org/10.1016/S1053-8119(02)91132-8.

Kato, S., Watanabe, H., Senda, J., Hirayama, M., Ito, M., Atsuta, N., Kaga, T., Katsuno, M., Naganawa, S., Sobue, G., 2012. Widespread cortical and subcortical brain atrophy in Parkinson's disease with excessive daytime sleepiness. J. Neurol. 259, 318–326. http://dx.doi.org/10.1007/s00415-011-6187-6.

Leech, R., Sharp, D.J., 2014. The role of the posterior cingulate cortex in cognition and disease. Brain 137, 12–32. http://dx.doi.org/10.1093/brain/awt162.

Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. 214, 655–667. http://dx.doi.org/10.1007/s00429-010-0262-0.

Möller, C., Hafkemeijer, A., Pijnenburg, Y.A.L., Rombouts, S.A.R.B., van der Grond, J., Dopper, E., van Swieten, J., Versteeg, A., Steenwijk, M.D., Barkhof, F., Scheltens, P., Vrenken, H., van der Flier, W.M., 2015. Different patterns of cortical gray matter loss over time in behavioral variant FTD and AD. Neurobiol. Aging 38, 21–31. http://dx.doi.org/10.1016/j.neurobiolaging.2015.10.020.

Montembeault, M., Joubert, S., Doyon, J., Carrier, J., Gagnon, J.F., Monchi, O., Lungu, O., Belleville, S., Brambati, S.M., 2012. The impact of aging on gray matter structural covariance networks. NeuroImage 63, 754–759. http://dx.doi.org/10.1016/j.neuroimage.2012.06.052.

Pan, P.L., Song, W., Shang, H.F., 2012. Voxel-wise meta-analysis of gray matter abnormalities in idiopathic Parkinson's disease. Eur. J. Neurol. 19, 199–206. http://dx.doi.org/10.1111/j.1468-1331.2011.03474.x.

Schulz-Schaeffer, W.J., 2010. The synaptic pathology of α-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. Acta Neuropathol. 120, 131–143. http://dx.doi.org/10.1007/s00401-010-0711-0.

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349–2356. http://dx.doi.org/10.1523/JNEUROSCI.5587-06.2007.

Segall, J.M., Allen, E.A., Jung, R.E., Erhardt, E.B., Arja, S.K., Kiehl, K.A., Calhoun, V.D., 2012. Correspondence between structure and function in the human brain at rest. Front. Neuroinform. 6, 10. http://dx.doi.org/10.3389/fninf.2012.00010.

Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. NeuroImage 44, 83–98. http://dx.doi.org/10.1016/j.neuroimage.2008.03.061.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 23, 208–219. http://dx.doi.org/10.1016/j.neuroimage.2004.07.051.

Spreng, R.N., Turner, G.R., 2013. Structural covariance of the default network in healthy and pathological aging. J. Neurosci. 33, 15226–15234. http://dx.doi.org/10.1523/JNEUROSCI.2261-13.2013.

Tholfsen, L.K., Larsen, J.P., Schulz, J., Tysnes, O.-B., Gjerstad, M.D., 2015. Development of excessive daytime sleepiness in early Parkinson disease. Neurology 85, 162–168. http://dx.doi.org/10.1212/WNL.0000000000001737.

Tomlinson, C.L., Stowe, R., Patel, S., Rick, C., Gray, R., Clarke, C.E., 2010. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov. Disord. 25, 2649–2653. http://dx.doi.org/10.1002/mds.23429.

Van den Heuvel, M.P., Sporns, O., Collin, G., Scheewe, T., Mandl, R.C.W., Cahn, W., Goñi, J., Hulshoff Pol, H.E., Kahn, R.S., 2013. Abnormal rich club organization and functional brain dynamics in schizophrenia. JAMA Psychiat. 70, 783–792. http://dx.doi.org/10.1001/jamapsychiatry.2013.1328.

Van der Heeden, J.F., Marinus, J., Martinez-Martin, P., van Hilten, J.J., 2014. Importance of nondopaminergic features in evaluating disease severity of Parkinson disease. Neurology 82, 412–418. http://dx.doi.org/10.1212/WNL.0000000000000087.

Van der Heeden, J.F., Marinus, J., Martinez-Martin, P., van Hilten, J.J., 2016. Evaluation of severity of predominantly nondopaminergic symptoms in PD. Parkinsonism Relat. Disord. 25, 39–44. http://dx.doi.org/10.1016/j.parkreldis.2016.

Winkler, A.M., Ridgway, G.R., Webster, M.A., Smith, S.M., Nichols, T.E., 2014. Permutation inference for the general linear model. NeuroImage 92, 381–397. http://dx.doi.org/10.1016/j.neuroimage.2014.01.060.

Zhu, K., van Hilten, J.J., Marinus, J., 2016. Course and risk factors for excessive daytime sleepiness in Parkinson's disease. Parkinsonism Relat. Disord. 24, 34–40. http://dx.doi.org/10.1016/j.parkreldis.2016.01.020.

Zielinski, B.A., Gennatas, E.D., Zhou, J., Seeley, W.W., 2010. Network-level structural covariance in the developing brain. Proc. Natl. Acad. Sci. U. S. A. 107, 18191–18196. http://dx.doi.org/10.1073/pnas.1003109107.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67, 361–370. http://dx.doi.org/10.1111/j.1600-0447.1983.tb09716.x.