

## Cortical structural involvement and cognitive dysfunction in early Parkinson's disease

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Cortical dysintegrity in early Parkinson's disease

**Abbreviations**

DWI diffusion-weighted imaging

ICA independent component analysis

GLM general linear model

MD mean diffusivity

PD Parkinson's Disease

SN substantia nigra

## Abstract summary

### Introduction

MRI studies in early Parkinson's disease (PD) have shown promise in the detection of disease-related brain changes in the white and deep grey matter. We set out to establish if intrinsic cortical involvement in early PD can be detected with quantitative MRI.

### Methods

We collected a rich, multi-modal dataset including diffusion MRI, T1 relaxometry, and cortical morphometry in 20 early PD patients (disease duration  $1.9 \pm 0.97$  years, Hoehn & Yahr 1-2), and 19 matched controls. Cortex was reconstructed using FreeSurfer. Data analysis employed linked independent component analysis (ICA), a novel data-driven technique that allows for data fusion and extraction of multi-modal components before further analysis. For comparison, we performed standard unimodal analysis with a general linear model (GLM).

### Results

Linked ICA detected multi-modal cortical changes in early PD ( $p=0.015$ ). These comprise fractional anisotropy reduction in dorsolateral prefrontal, cingulate, premotor cortex and the superior parietal lobule; mean diffusivity increase in the mesolimbic, somatosensory and superior parietal cortex, sparse diffusivity decrease in lateral parietal and right prefrontal cortex; and sparse changes to cortex area. In PD, the amount of cortical dysintegrity correlated to diminished cognitive performance. Importantly, unimodal analysis detected no significant group difference on any imaging modality.

### Conclusions

We detected microstructural cortical pathology in early PD using a data-driven, multi-modal approach. This pathology is correlated with diminished cognitive performance. Our results indicate that early degenerative processes leave an MRI signature in the cortex of patients with early PD. The cortical imaging findings are behaviorally meaningful, and provide a link between cognitive status and microstructural cortical pathology in early PD patients.

## Introduction

In recent years, a number of MRI studies in early Parkinson's disease (PD) have shown promise in the detection of PD-related pathology. While, naturally, studies into midbrain or striate pathology dominate research in early PD, there is also evidence suggestive of cortical involvement even in the early stages of the disease. PET ligand studies in early PD have provided evidence for cortical dopaminergic dysfunction, even in the absence of cognitive defects<sup>1</sup>. Analysis of the PPMI dataset has demonstrated morphological changes in the dopaminergic pathways in early PD, including some involvement of frontal regions<sup>2</sup>. Furthermore, mild cognitive changes in early PD including executive function, working memory, and attention<sup>3</sup> point to changes in the cortex beyond mere dopaminergic depletion. Impairments in phonemic and semantic fluency have been demonstrated in both cognitively impaired and non-demented patients with PD, and fluency deficits are thought to arise separate to the impairment of cognitive processing speed or effortful retrieval<sup>4</sup>, suggesting that the process driving fluency deficits in PD is not simply driven by dopamine dysfunction of the basal ganglia.

Recently, the ICICLE-PD study demonstrated an increased rate of cortex thinning even in non-demented early PD over a period of 18 months, crucially in absence of cortical atrophy at baseline<sup>5</sup>. There are reports of microstructural involvement of white matter underlying frontal or parietal association areas in particular<sup>6-8</sup>. One voxel-based study has reported microstructural changes in the frontal lobe that may include some cortical grey matter<sup>9</sup>. However, such measurements focused on cortical grey are lacking so far.

The question arises whether early changes in the cortex can be quantified with MR imaging, given its wide availability and low cost compared to nuclear methods.

The most frequently used MR measures to investigate PD-related pathology are derived from diffusion-weighted imaging (DWI), assessing the directionality and restriction of the movement of free water protons in brain tissue<sup>10</sup>.

Commonly, the diffusion tensor model is applied to DWI to derive quantitative indices of microstructural tissue properties. Fractional anisotropy (FA), one such measure, quantifies the local directionality of water diffusion, while mean diffusivity (MD) quantifies the overall restriction of water diffusion in the tissue. A number of groups have reported changes of FA or MD in the substantia nigra (SN) in PD<sup>11-14</sup>. However, these studies reported conflicting results for DWI-derived measurements of microstructural integrity in the SN so far, ranging from decreased nigral FA over no change up to increased FA when comparing Parkinsonian subjects to normal controls<sup>15</sup>. Similarly, measurements of MD in the SN have produced variable results<sup>15</sup>, and it is currently not clear whether this heterogeneity in PD is related to methodological issues, such as variable image acquisition protocols, or possibly an expression of phenotypic variation.

Quantitative mapping of relaxivity in the substantia nigra has found a decrease of absolute T1 relaxation time in early PD<sup>16</sup>, providing another imaging indicator of PD-associated neurodegeneration in the midbrain. Attractively, T1 quantitative MRI (qMRI) probes the chemical composition of the tissue under study, providing complementary insight to the parameters on microstructure available with diffusion imaging.

Here, we set out to test if quantitative MR imaging can detect cortical involvement in a cohort of early PD patients. We hypothesized that such cortical involvement would be reflected in changes indicative of a loss of cortical volume or microstructural integrity in the imaging parameters studied. We use a multivariate approach that comprises analysis of gross cortical

structural parameters, mapping of cortical absolute T1 relaxivity, and measurement of cortical FA and MD to assess changes in the microstructural composition of cortical tissue. We employ FMRI's Linked Independent Component Analysis (FLICA) multi-modal fusion analysis in this rich dataset, a novel, data-driven technique designed to explore multiple imaging parameters in a single process<sup>17</sup>. This way, we can assess changes across several imaging contrasts, collecting evidence from different aspects such as tissue composition, its macro- and its microstructure<sup>18</sup>. Linked ICA is an unsupervised learning process oblivious to parameters external to the imaging data, such as age or diagnostic group. ICA component extraction captures cross-modal spatial patterns of covariation, and removes structured confounds and artefacts by extracting them as separate components. This in turn increases statistical power by removing these confounds from the other components of interest<sup>19</sup>. For comparison, we performed standard GLM analysis using the individual imaging contrasts separately.

## Methods

### Participants

This study was approved by the local ethics committee, and complied with national legislation and the 1995 declaration of Helsinki.

Participants were recruited from the Oxford Parkinson's Disease Centre (OPDC) cohort<sup>20</sup>. The OPDC recruits participants from the Thames Valley area, PD patients are recruited within 3 years of diagnosis. Written informed consent was obtained from all participants. We included 20 early PD patients with a clinical diagnosis of idiopathic PD, all of which met the UK PD Society Brain Bank criteria and 20 age- and sex-matched controls. Exclusion criteria for all participants were contraindications to MRI, other neurologic or psychiatric disease, and more than one risk factor for cerebrovascular disease (hypertension, diabetes mellitus, hypercholesterolemia, cardiovascular disease). For the PD group, additional exclusion criteria

were physician-rated certainty of diagnosis <90%, dyskinesia or dystonia to avoid motion artifacts during imaging. Only controls who did not have first- or second-degree relatives with PD were eligible for the study.

One control subject was excluded due to data quality concerns. Therefore, 19 control subjects were included in the final analysis. Participant characteristics are given in Table 1. Levodopa equivalent daily dose (LEDD) was calculated following established guidelines<sup>21</sup>. The groups did not differ in sex, age, or cognitive scores (Mann-Whitney U test).

*Table 1 about here please*

#### Data Acquisition and Preprocessing

All MRI was performed on a 3T Siemens Trio. Details of data acquisition and preprocessing are available in Supplementary Methods 1. In brief, we collected MP-RAGE (192 axial slices, isotropic voxel size 1 mm)<sup>22</sup>, quantitative T1 maps (DESPOT-HiFi, 144 slices, 1.1 mm isotropic)<sup>23</sup> and DWI (SE-EPI, 65 axial slices, isotropic voxel size 2 mm, 60 diffusion gradients,  $b$ -value 1,000 seconds  $\cdot$  mm<sup>-2</sup>) to derive FA and MD.

The cortical sheet was reconstructed from anatomical images using FreeSurfer<sup>24</sup>. To enable unified analysis across all modalities, all these measures (cortical thickness, pial area size, quantitative T1, FA and MD) were projected onto individual cortical reconstructions<sup>25</sup>, and subsequently sampled along the cortical normal, excluding the inner- and outermost 10 percent of the cortex to minimise partial voluming. This process provides a common, individual reference space for all modalities, and constrains the analysis volume to cortex only. A 10 mm FWHM Gaussian filter was applied for smoothing. To satisfy computational constraints, all



measures were resampled to FreeSurfer's fsaverage5 standard space, which possesses a node-to-node distance of about 3 mm along the grey-white interface surface.

### Cognitive testing

All participants received cognitive testing with MoCA<sup>26</sup>, as well as scale measures of phonemic and semantic fluency. Phonemic fluency was studied with a word fluency task using the letters A and S, and semantic fluency was studied with the categories “animal names” and “boys' names”. The duration of each task was one minute. For the phonemic fluency trials, participants were instructed not to use numbers or proper nouns such as names or places. For semantic fluency, participants were instructed not to use variations on previous responses (e.g. different breeds of the same animal, different versions of the same name).

### Linked ICA

All cortical measures were then fed into Linked ICA fusion analysis. The method is introduced and detailed by Groves et al.<sup>17,19</sup>. Linked ICA automatically balances the information content of the different modalities supplied, finding subject loadings that produce statistically independent spatial maps across these modalities<sup>19</sup>. This process supplies component-wise subject-courses, i.e. one vector of subject loadings per component. Each subject-course can be driven by any combination of modalities, or even a singular modality, and the relative contribution of every modality is quantified. We chose a dimensionality of 20 components to avoid over-fitting the data from our 39 subjects. However, linked ICA automatically removes unneeded components using Bayesian model order selection. The impact of artefacts and peculiarities in the data is reduced with subject-wise noise estimation for every modality. This way, the number of components driven by a single outlier scan can be much reduced<sup>19</sup>.

The subject-courses were correlated with age and diagnostic group. Because changes e.g. with age can exhibit strongly non-linear behavior, we also performed a polynomial fit. We defined a threshold of  $p \leq 0.05$  to determine significance, using Bonferroni FWER correction for the number of components and two tails. To examine the effect size of the between-group difference detected by linked ICA, we obtained Cohen's  $d$  by calculating the mean difference between and the pooled variance across study groups from the average weight of the component of interest, sampling the entire cortical surface for each participant. We also calculated the 95% confidence interval for Cohen's  $d$ .

For visualization, the modality-specific spatial maps for each component were converted to pseudo-Z statistics and rendered for display with a threshold of  $|Z|=2$ .

For comparison, we also tested for between diagnostic group differences with standard, unimodal GLM analysis on each individual imaging parameter using FreeSurfer tools, including age as a confound regressor. Vertex-wise, unimodal analysis may suffer from sensitivity issues due to the large number of vertices and therefore tests on the cortical surface. To explore these potential sensitivity issues with the vertex-wise analysis, we also tested for group differences for each individual parameter averaged within an anatomical mask of the frontal lobes. We extracted these values with custom Matlab scripts, and tested for between-group differences (Wilcoxon signed rank test).

#### Post-hoc testing – correlation with cognitive measures

The distribution of cortical changes associated with PD suggested a relationship with frontal function, leading us to exploratory post-hoc correlation analysis. Cognitive data are summarized in Table 1. We explored the relationship between cortical integrity and semantic and phonemic fluency scales, indexing frontal executive function, as well as the MoCA score, indexing overall cognitive functioning in PD patients only. For phonemic and semantic

fluency, words beginning with F, A, and S, and animals and boys' names were generated over 60 seconds<sup>27</sup>.

We tested for a negative correlation between these measures and the weight of the ICA component correcting for age (Spearman rank correlation) a) across all study participants, and b) in each of the diagnostic groups individually. Due to the exploratory nature of these tests, we did not employ correction for multiple comparisons for post-hoc tests.

## Results

### Linked ICA

After Bayesian model order selection, 16 out of the 20 components requested were retained. Among those, one component was related to the diagnostic group, four components showed localised age-related changes, and three were classified as global age-related components<sup>19</sup>.

### PD vs. controls

Linked ICA detected one component that separated the group with Parkinson's disease from the control group ( $p=0.015$ , Cohen's  $d=0.77$  [95% confidence interval 0.15 – 1.36]). This component was dominated by reduced FA in PD (Figure 1) in dorsolateral prefrontal cortex, the cingulum, premotor cortex and the superior parietal lobule. In addition, this component detected increase of MD in mesolimbic cortex, somatosensory cortex and superior parietal cortex. There was sparse evidence of MD decrease in lateral parietal and right prefrontal cortex. This component also included sparse evidence of changes to pial area size.

*Figure 1 about here please*

### Impact on cognitive measures

Correlation analysis in the whole study group identified a significant correlation between the component weight and total MoCA ( $\rho=0.332$ ,  $p=0.021$ , Supplementary Figure 1), and a trend for correlation between the component weight and semantic fluency ( $\rho=0.360$ ,  $p=0.059$ ). When studying the PD group only, there was a trend for correlation between MoCA and the component weight ( $\rho=0.363$ ,  $p=0.06$ ). When studying controls only, we observed no significant correlation between the component weight and the behavioral measures.

### Age-related components

We found several components spanning large parts of the cortex, reproducing findings in the seminal FLICA paper<sup>19</sup>. Out of these, two exhibited significant correlation with age (Figure 2). Fig. 2a presents the first such component, showing a linear correlation of cortical MD with age ( $p<0.001$ ). In a separate component (Figure 2b), age-related change of global MD was detected together with focal changes in FA and cortical thickness ( $p<0.001$ ). The latter component appeared to be driven by age-related changes primarily occurring in elderly subjects. These components were expressed irrespective of diagnostic group.

*Figure 2 about here please*

Localised age-related changes were detected in four separate components, the details of which are available in Supplementary Figure 2.

### Structured noise

Although the linked ICA implementation used here suppresses most noise, some structured noise components remain. These components related to areas of highly variable magnetic

susceptibility (e.g. basal orbital cortex), found in the diffusion imaging modalities due to EPI read-out, and areas of multi-modal signal degradation at the upper and lower edge of the scanner field of view (data not shown).

### Unimodal analysis

Unimodal analysis for each individual parameter did not detect significant differences between PD and controls on both vertex-wise analysis, and when averaging over the frontal cortex.

### Discussion

In this study, we explore quantitative MR parameters that have shown promise in detecting subcortical pathology in PD as potential tools to assess cortical involvement in early PD. To this end, we fed all imaging modalities into a single multi-modal, model-free analysis stream using linked ICA. Linked ICA assesses concomitant changes across modalities and the cortical imaging space, and increases robustness to imaging artefacts<sup>19</sup>. The motivation for exploring cortical pathology in early PD with MRI comes from observations of reduced cortical dopaminergic innervation even in early PD<sup>1,28</sup>, changes in cognitive function<sup>3,29</sup>, and longitudinal studies showing decline of cortical thickness in early PD<sup>5</sup>.

In our study, PD-related cortical changes were predominantly found in diffusivity-derived parameters, suggestive of microstructural dysintegrity. These changes are most prominent in reduced FA of in dorsolateral prefrontal cortex, the cingulum, premotor cortex and the superior parietal lobule. Moreover, MD was increased in mesolimbic cortex, somatosensory cortex and superior parietal cortex, indicating an overall loss of tissue integrity or cellularity<sup>10</sup>.

To investigate the functional significance of these changes, we performed exploratory correlation analyses between these imaging results and cognitive measures in our participants. These demonstrated a correlation between cortical dysintegrity and impaired performance on

the MoCA cognitive assessment in the study group, while there was a trend for reduced semantic fluency. When testing the diagnostic groups individually, the association of cortical dysintegrity with MoCA scores was present in PD patients only at trend level ( $p=0.06$ ), with a similar rho to the study group as a whole. While questions regarding sensitivity in this relatively small sample remain, these results seem to suggest that, in addition to distinguishing between PD and control cohorts, the changes identified by linked ICA are a biologically meaningful index of cortical functioning. Previously, MoCA scores and cortical thickness were shown to be related in a sample comprising both PD-MCI and cognitively intact PD in the PD-ICICLE study<sup>5</sup>. Taken together, these findings suggest that microstructural dysintegrity is present even in the absence of MCI.

An important limitation of the study presented here remains, as illustrated just above, the small sample size. This is also reflected in the confidence interval of the between-group effect size that we calculated, and further research is needed to evaluate the robustness of our findings. In particular, replication in a larger sample, and including more sensitive tests of fluency and other frontal functions, would be highly desirable.

The detected pattern encompasses and extends the one reported in a previous whole-brain voxel-wise study of FA in PD<sup>9</sup>. Here, the explicit definition of the cortical volume for analysis ensures cortical sampling of the MR parameters, avoiding dilution of the cortical signal through partial voluming of adjacent compartments. This helps disambiguate the cortical FA changes of interest from those in white matter, where frontal FA changes also occur in PD<sup>8,9,30</sup>. Further evidence for early cortical involvement in PD comes from neuropsychological studies: Around the time of first diagnosis, subtle executive dysfunction is found in about a quarter of PD patients, pointing to prefrontal involvement in some of these early patients<sup>31,32</sup>. In this context, it is important that these subtle neuropsychological signs are found in the absence of dementia.

The dysexecutive features of early PD may be related to reduced dopaminergic transmission to the prefrontal cortex. However, a decline in cortical dopaminergic transmission is found even in the absence of neuropsychological deficits<sup>1</sup>, and given the small volume fraction of dopaminergic synapses, the diffusion changes observed here argue for local pathology beyond a mere loss of these synapses.

Unfortunately, it is not possible to directly relate changes in DWI to the underlying histopathology, as the diffusion signal is influenced by various microstructural features including fiber density, cellularity or myelination<sup>10,33</sup>. However, the colocation of cortical microstructural dysintegrity detected here and the loss of dopaminergic transmission reported earlier would suggest a common underlying mechanism: A possible explanation linking these two findings is the established loss of axonal terminals interfacing with cortical neurons, which was accompanied by inflammatory changes in the cortex of PD subjects<sup>34</sup>.

While absolute T1 measurement has shown promise investigating SN pathology in early PD<sup>16</sup>, no such differences were found in the cortex in our early PD study group. The cellularity of brain tissue, or gray-to-white ratio, is a major determinant of T1 relaxivity in the brain. Thus, the discrepancy of results in diffusivity and T1 measurements may be related to the fact that a great number of SN cell bodies are lost before the onset of motor symptoms<sup>35</sup>, while loss of neuronal bodies of a similar magnitude in the neocortex is unlikely at this early stage. In keeping with this hypothesis, we did not detect reduced cortical thickness in these early PD patients, similar to previous evidence that overt cortical thinning occurs in later PD<sup>5,36</sup>. In contrast to these studies, subcortical and cortical atrophy in early PD has been detected in a recent study using ICA decomposition of deformation-based morphometry<sup>2</sup>, which also

showed sparse change in prefrontal cortex suggestive of local pathology even in the earliest stages of the disease.

With regard to the age-related components extracted by linked ICA, there is strong evidence for an age-related increase in cortical MD in our entire study population. Unlike studies targeting white matter<sup>37,38</sup>, we did not detect a decrease in cortical FA with age. These opposing findings could suggest that the mechanisms driving age-related changes of diffusivity are different in the cortex. On the other hand, FA reduction in white matter is usually attributed to age-related demyelination or axonal structure loss<sup>37</sup>. Perhaps these effects are masked by the higher cellularity of cortex, where the contribution of penetrating axons and their myelin sheaths to the overall diffusion signal are considerably smaller than in white matter, and MD might be more sensitive in this case to age-related decline in tissue integrity.

Importantly, conventional unimodal analysis of the individual parameters, either vertex-wise or when averaging across the frontal cortex, did not yield significant differences between the cohorts. One aspect of Linked ICA relates to its ability to remove structured confounds from the data, capturing them in separate components external to the components of interest<sup>19</sup>. A practical example presents with the bi-modal process affecting MD in the cortex globally during ageing (Fig. 2). One process is associated with linearly increasing MD across all ages studied (Fig. 2a), while the other process affects subjects from a later age only (Fig. 2b). This temporally bi-modal process is invisible to standard linear regression analysis, where a greater regression error term remains, making it more difficult to detect disease-related differences of interest. A key advantage of linked ICA, however, lies in its multivariate nature, which enables the concurrent extraction of multi-modal components, capturing different aspects of age- or disease-related cortical changes simultaneously. Examples in this dataset include the cross-modality age-related cortical changes (Fig. 2a,b), but also the component distinguishing



between diagnostic groups (Fig. 1). Linked ICA also has its limitations. The user must select an appropriate number of components to extract from the data, and estimating this number can be complex when considering subject numbers, noise level, and the inclusion of varying numbers of modalities. Computational limitations also demand that the data are down-sampled from their full resolution, which is problematic when the processes under study are highly focal or scattered. Fortunately, this was not the case with the data presented here.

In conclusion, our data demonstrate early cortical, predominantly microstructural pathology in our group of early PD patients. The changes reported here occur to a varying degree across the PD patient group (Fig. 1), suggesting different levels of cortical involvement in early PD.

While all subjects included here were cognitively intact, reduced cortical microstructural integrity predicted reduced cognitive performance on a standardized test. Further research will be needed to establish whether these early cortical changes in PD might be predictive of clinically overt cortical dysfunction in the future.

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## Figure legends

## Figure 1

Title “Changes in cortex according to diagnostic group”

PD patients exhibited FA reduction in dorsolateral prefrontal cortex, cingulate cortex, premotor cortex, and the superior parietal lobule ( $p=0.015$ ). MD change is seen in mesolimbic cortex, somatosensory cortex, and superior parietal cortex. There is sparse change in cortex arealization. These changes are inversely correlated with cognitive performance in the whole study group (MoCA,  $\rho=0.332$ ,  $p=0.021$ ; trend for semantic fluency,  $\rho=0.360$ ,  $p=0.060$ ).

## Figure 2

Title “Age-related cortical changes”

There is a linear increase of MD observed over all ages in this study (a,  $p<0.001$ ), encompassing almost the entire cortex. A separate component shows non-linear (therefore, no regression line included), global MD increase, together with focal changes in FA and cortical thinning in subjects above 70 years (b,  $p<0.001$ ).

## Supplementary Figure 1

Title “The relationship between MoCA score and component weight in PD”

Scatter plot of MoCA scores and the weight of the component indexing frontal dysintegrity in PD participants.

## Supplementary Figure 2

Title “Localized components associated with ageing”



The first component is driven by concomitant changes of absolute T1, cortical thickness and pial arealization primarily in temporopolar and prefrontal cortex (a,  $p=0.005$ ). In a similar spatial distribution, the second component depicts concomitant changes of FA with pial surface area, and opposing change of absolute T1 in temporal cortex with a focus on the temporal pole (b,  $p=0.001$ ). The third panel shows age-related decline of cortical thickness in mesial pericingulate cortex (c,  $p=0.002$ ). The last panel shows a spatially similar increase of FA with age (d,  $p=0.01$ ).

Table 1 – Characteristics of the Sample

<b>Participant demographics</b>		PD	Controls
Sex		12M, 8F	11M, 8F
Age		60±10.8	61±7.7
Hoehn & Yahr		H&Y I: 4, H&Y II:16	n/a
Disease duration (from diagnosis)		1.9±0.97 years	n/a
MoCA		27.9±1.55	28.6±1.22
Phonemic fluency		49.0±12.7	55.7±12.76
Semantic fluency		42.3±6.81	44.5±8.15
Education (years)		15.1±3.51	16.5±3.98

  

<b>Characteristics of PD patients</b>			N (of 20)
Medications	MAOBI monotherapy		3
	L-Dopa		4
	- also on MAOBI		2
	Agonist		11
	- also on MAOBI		3
	Therapy naïve		2
LEDD [mg] (excludes unmedicated patients)			347±227.2, Range [40-880]
UPDRS-III scores	Total		24.9±9.95
	Rigidity subscore		5.9±2.30
	Tremor subscore		4.0±2.85

Data reported as mean±standard deviation. MAOBI = MAO-B Inhibitors, LEDD = L-Dopa equivalent dose, MoCA = Montréal Cognitive Assessment, UPDRS = Unified Parkinson's Disease Rating Scale