Progressive changes in a recognition memory network in Parkinson’s disease

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ABSTRACT

Background In a previous functional MRI (fMRI) study, we found that patients with Parkinson’s disease (PD) presented with dysfunctions in the recruitment of recognition memory networks. We aimed to investigate the changes in these networks over time.

Methods We studied 17 PD patients and 13 age and sex matched healthy subjects. In both groups fMRI (recognition memory paradigm) and neuropsychological assessments were obtained at baseline and at follow-up. To analyse changes over time in functional networks, model free (independent component analysis) analyses of the fMRI data were carried out. Then, a cross correlation approach was used to assess the changes in the strength of functional connectivity.

Results At follow-up, patients showed reduced recruitment of one network, including decreased activation in the orbitofrontal cortices, middle frontal gyrus, frontal poles, anterior paracingulate cortex, superior parietal lobes and left middle temporal gyrus, as well as decreased deactivation in the anterior paracingulate gyrus and precuneus. Cross correlation analyses over time showed a decrease in the strength of functional connectivity between the middle frontal gyrus and the superior parietal lobe in PD patients.

Conclusions Model free fMRI and cross correlation connectivity analyses were able to detect progressive changes in functional networks involved in recognition memory in PD patients at early disease stages and without overt clinical deterioration. Functional connectivity analyses could be useful to monitor changes in brain networks underlying neuropsychological deficits in PD.

INTRODUCTION

Cognitive dysfunction occurs at the early stages of Parkinson’s disease (PD) and most frequently involves impairment of memory, executive and visuo-spatial functions. Regarding memory dysfunction, learning and delayed recall are known to be impaired in early disease stages. Recognition memory is not usually impaired at these stages, although it is in patients who fulfil the diagnostic criteria for dementia. In addition, recognition memory dysfunction has been related to the level of difficulty of the task.

Functional connectivity refers to temporal correlations (concurrent activity) of spatially remote neuropsychological events. Functional MRI (fMRI) data can be analysed using model free fMRI approaches in order to obtain whole brain patterns of functional connectivity, as well as with cross correlation methods to quantify connectivity strength between two predefined brain regions, called seeds. While the first approach can be used as an exploratory method without a priori knowledge of the functional pattern, the second needs prior hypotheses regarding the brain regions that are considered to be connected.

Tensorial probabilistic independent component analysis is a model free approach to analyse fMRI data. This method identifies patterns of coherent blood oxygen level dependent signal fluctuations across all voxels in the brain and groups such patterns into components in the spatial, temporal and subject domains. Distinct functional networks made up of different brain areas can be characterised as distinct components using this technique. Studies using model free analyses have helped detect subtle progressive changes in brain function in other degenerative diseases, such as Alzheimer’s disease.

In a previous study, we used tensorial probabilistic independent component analysis to detect alterations in the functional cerebral network involved in recognition memory. Compared with controls, PD patients showed a decreased task related activation in areas involved in this network. We also observed decreased task related deactivations in the default mode network (DMN), a group of spatially segregated brain structures which are more active during tasks that direct attention away from external stimuli or during the resting state, with functions related either to internal mentation or to the exploratory monitoring of the external environment when focused attention is reduced. These results indicated that functional brain changes related to memory processes can occur prior to overt recognition memory deficits in PD patients.

In PD, different connectivity analysis methods have demonstrated abnormal patterns of interaction within brain networks involved in motor performance, cognitive tasks such as attention to action and card sorting tasks, or in the resting state, but deterioration over time of these connectivity patterns has not been investigated.

A longitudinal (18F)-fluorodeoxyglucose–positron emission tomography (FDG-PET) study reported a progressive decline in metabolic activity in the medial prefrontal and parietal associative regions.
which sustain cognitive functions that are impaired in PD.\(^{19}\) However, to the best of our knowledge, specific recognition memory network deterioration and loss of functional connectivity strength between its specific areas has not been studied.

The two main aims of this study were: (1) to investigate how deterioration in recognition memory network activation patterns progresses using a model free approach and (2) to study the possible loss of functional connectivity strength between the main regions of this network over time.

**METHODS**

**Participants**

Patients were recruited from an outpatient Movement Disorders Clinical Neurology Service, Hospital Clinic i Provincial de Barcelona, in collaboration with the Department of Psychiatry and Clinical Psychobiology (University of Barcelona). Healthy controls were volunteers matched by age, gender and years of education with the patients. All subjects were right handed. The study subjects were part of a previously studied sample,\(^{20}\) and were subsequently invited by telephone to participate in a follow-up evaluation (average period of 35.50 months, SD=1.85, range=51–40 months). At baseline, 24 early PD patients and 24 healthy controls participated in the study. In the follow-up assessment, 17 PD patients and 15 healthy controls agreed to participate (table 1).

Fourteen PD patients at baseline and all 17 patients at follow-up were taking antiparkinsonian drugs, consisting of different combinations of levodopa, levodopa with catechol-O-methyl transferase inhibitors, monoamine oxidase inhibitors, dopamine agonists and amantadine. All assessments were made while patients were in the on state. Levodopa equivalent daily doses (LEDD) were calculated as proposed by Tomlinson et al.\(^{21}\) Six PD patients at baseline and four patients at follow-up were taking antidepressant drugs (see supplementary materials 1, available online only).

From the initial sample, two patients died, two moved to another province and three patients declined to participate. In the healthy control group, two subjects died, another province and three patients declined to participate. In total, 24 PD patients at baseline and 24 healthy controls were included in the longitudinal assessment (average period of 40 months). At baseline, 24 early PD patients and 24 healthy controls participated in the study. In the follow-up assessment, 17 PD patients and 15 healthy controls agreed to participate (table 1).

**Statistical analyses** of the neuropsychological and clinical variables were performed using the statistical package PASW-18 (SPSS, Inc, 2009, Chicago, Illinois, USA, http://www.spss.com). A general linear mixed model (GLM) for repeated measures was used to test whether variables changed in each group across time.

### Table 1: Sociodemographic and clinical data for the participants at baseline

|                | PD (n=17) | Controls (n=13) | Test Stat | p Value |
|----------------|-----------|-----------------|-----------|---------|
| Age (years)    | 59.59±8.29| 57.15±10.57     | 0.17*     | 0.87    |
| Sex (M/F)      | 13/4      | 10/3            | 0.001†    | 0.98    |
| Education (years) | 10.82±4.76 | 12.31±3.35     | 0.96*     | 0.35    |
| Age at onset (years) | 53.68±8.50 | –               | –         | –       |
| Disease duration (years) | 2.91±1.04 | –               | –         | –       |

Values are mean±SD.

Test stats: *Student’s t test or \(t^2\) test statistics.

†Duration of motor symptoms.

PD, Parkinson’s disease.

The inclusion criteria for participating in the study at baseline were: (i) fulfilment of the UK PD Society Brain Bank diagnostic criteria for PD,\(^{22}\) (ii) Hoehn and Yahr stage ≤II; and (iii) disease duration ≤5 years. Exclusion criteria for all subjects were: (i) presence of dementia, as diagnosed by a neurologist according to the Movement Disorder Society diagnostic criteria for PD dementia,\(^{23}\) (ii) presence of other neurological or psychiatric disorders, such as depression, which was evaluated by means of BDI,\(^{24}\) and (iii) presence of visual hallucinations, assessed by the NPI questionnaire.\(^{25}\)

The study was approved by the institutional ethics committee and all enrolled subjects gave written informed consent prior to taking part in the study.

**Neuropsychological assessment**

All participants underwent a comprehensive neuropsychological examination performed by a trained neuropsychologist (NI-B). The neuropsychologist in charge of the assessment was the same at the baseline and follow-up examinations. Verbal memory assessment was made using Rey’s Auditory Verbal Learning Test (RAVLT).\(^{26}\) The RAVLT variables computed were total learning, delayed memory recall after 20 min and recognition.

Additionally, other neuropsychological domains known to be impaired early in the course of PD were assessed using the forward digit span and backward digit span from the Wechsler Adults Intelligence Scale-III to measure working memory, and verbal fluency tests, including assessment of phonemic (total number of words starting with ‘p’ in 1 min) and semantic fluencies (number of animals in 1 min). Details of the neuropsychological battery used are described elsewhere.\(^{8}\)

**fMRI acquisition**

Data were acquired with a 3 T Magnetom Tim Trio scanner (Siemens, Germany), using a multislice gradient echo, echo planar imaging functional sequence with the following parameters: repetition time (TR)=2000 ms; echo time (TE)=35 ms; 36×3 mm axial slices providing whole brain coverage. A T1 weighted structural image was also acquired for each subject with an MPRIAGE 3D protocol (TR=2500 ms; TE=2.98 ms; inversion time=900 ms; FOV: 256×256 mm; 1 mm isotropic voxel).

**Recognition memory fMRI paradigm**

We used a recognition memory fMRI paradigm; the experimental design has been described in detail previously.\(^{3}\) In brief, before image acquisition, participants viewed a list of 55 words that they asked to remember. Afterwards, during scanning, subjects were asked to recognise the previously learned words from a list of 70 words. The experiment consisted of a 20 block design, with two conditions: recognition memory or control. In the recognition memory condition, participants had to recognise the previously learned words from a list of 70 words while in the on state. The previous experience of each subject was recorded with an fMRI model (GLM) for repeated measures was used to test whether variables changed in each group across time.
fMRI data analysis

Preprocessing of fMRI data

The following data preprocessing algorithm was carried out on the fMRI data set using FSL tools (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl): motion correction using MCFLIRT\textsuperscript{27} removal of non-brain structures from the echo planar imaging volumes using BET\textsuperscript{28} spatial smoothing using a Gaussian kernel of 5 mm full width at half maximum (FWHM), mean based intensity normalisation of all volumes by the same factor (4D grand mean), high pass temporal filtering (FWHM=100 s) and Gaussian low pass temporal filtering (FWHM=11.2 s). The functional scans were registered to the MNI152 standard space through affine registration with FLIRT\textsuperscript{29}.

Model based analysis

After preprocessing the data, model based fMRI data analysis was carried out using FEAT (FMRI Expert Analysis Tool) V5.98, part of FSL. At the individual level, we obtained an activation map for each subject (recognition task>control task). Higher level analysis was then carried out using FLAME (FMRIB Local Analysis of Mixed Effects)\textsuperscript{30,31} in order to explore between group differences and to obtain global average (one sample t test) activation maps (patients and controls). Z (gaussianised T/F) statistic images were thresholded using Z>2.3 and a corrected cluster significance threshold of p≤0.05 using Gaussian random field theory to define each cluster’s estimated significance level.

Independent component analysis

The preprocessing streamline was the same as that used in the model based analysis. Then, analysis of the task related fMRI images was carried out using tensorial independent component analysis, as implemented in the Multivariate Exploratory Linear Decomposition into Independent Components tool (MELODIC V3.05),\textsuperscript{5} part of FSL. MELODIC allows fMRI data to be decomposed into three-dimensional sets of vectors, also named independent components (IC), which describe signal variations across the temporal domain (time courses), the spatial domain (spatial maps) and the subject domain (subject modes). Spatial maps reflect brain regions of synchronous activations and deactivations, and subject modes reflect the strength of both of these activations and deactivations; higher subject mode values indicate higher activations and higher deactivations of the positive and negative parts of an IC, respectively. The number of IC dimensions was estimated by MELODIC using the Laplace approximation to the Bayesian evidence of the model order.\textsuperscript{32} Spatial maps were thresholding modelling the probability of the noise class to 50% (using gamma densities).

The fMRI data set was decomposed into 18 IC. Afterwards, a selection of biologically relevant components was made, excluding the components that, according to the subject mode analysis, appeared to be driven by outliers, as well as artefactual components produced by motion, high frequency noise or vascular pulsations.\textsuperscript{5} Five IC were finally selected, two associated with the task>control and three to the control>task contrast. Subsequently, we identified the main task related components by computing spatial correlations between the average activation maps obtained with FEAT and the selected IC. Z (gaussianised T/F) statistic images were thresholded using clusters determined by Z≥3. ICI was the task related component that showed the greatest spatial correlation with the task pattern identified in the model based analysis (r=0.56). Specific information about the other selected components is included in the supplementary materials (supplementary materials 2, available online only).

Cross correlation connectivity analysis

To investigate connectivity between the main activated regions of the recognition memory component, we created eight spherical 8 mm regions of interest (ROI) centred on the peak voxels of the most relevant clusters from the main task component obtained from the model free analysis (recognition memory network IC1).

From preprocessed fMRI data sets, the mean time course was extracted from each of these ROIs. Pearson’s correlation coefficients were then computed between the time courses from each pair of ROIs and normalised using Fisher’s r to Z transformation for each subject. A repeated measures GLM was used to test whether variables changed in each group across time. PASW-18 software was used to perform the statistical analyses.

The fMRI analysis pipeline is summarised in figure 1.

RESULTS

Clinical variables and neuropsychological performance

In the patient group, there were no statistically significant differences between baseline and follow-up LEDD or Hoehn and Yahr and Unified Parkinson’s Disease Rating Scale motor section scores. Moreover, GLM analysis showed a significant time effect on MMSE and group effect on BDI. No significant group by time interaction was found for these variables. NPI did not show significant between group differences or over time changes (table 2).

Verbal memory performance, assessed by RAVIT, did not show any statistically significant effects for any of the variables analysed (table 2).

Supplementary materials 3 (available online only) show the results of the other neuropsychological tests used. Significant group differences were observed for semantic fluency and backward digit span. A significant group by time interaction was observed for forward digit span, resulting from a slight worsening in controls and a slight improvement in PD patients in performances over time.

Performance in the fMRI recognition memory task

In the fMRI recognition memory task performance, we found several significant time effects. Both patients and controls performed worse in the correct–reject responses at follow-up, but worsening was similar in both groups (group effect and group by time interaction were not significant). The main differences between groups were observed for false positive responses. For this variable, a significant group effect was seen—the performance of patients was worse than controls, and both groups presented a significant over time decline. In addition, the group by time interaction showed a trend to significance, indicating that the decline in this ability was more marked in patients (table 3).
calculating spatial correlations. Intergroup comparisons revealed no significant results.

**Model free analysis**
From the five task related components identified (see supplementary materials 1, available online only), IC1 was the only one to show decreased activity over time in PD patients (p<0.04). This independent component had a left hemisphere predominance and was characterised by activation in the bilateral orbitofrontal regions, bilateral middle frontal gyri, bilateral frontal poles, anterior paracingulate regions, bilateral superior parietal lobes and the posterior region of the left middle temporal gyrus. In the left frontal lobe, a single cluster of activation, with a peak in the left orbitofrontal area, included all of the above mentioned frontal regions. IC1 also involved deactivation in DMN areas, including the anterior part of the paracingulate gyrus and the precuneus (figure 3; see also supplementary materials 5, available online only).

**Correlation analyses between IC1 activation and performance in the recognition task**
A correlation analysis was performed between IC1 and individual activations–deactivations (subject modes) and recognition task results. In PD patients, there was a significant correlation between false positive errors and IC1 subject modes (r=−0.403, p=0.027), as well as with its complementary measure, the correct rejects (r=0.403, p=0.027). In the control group we did not observe any significant correlation.

**Cross correlation connectivity analysis**
The main spherical ROIs of 8 mm radius included the right middle frontal gyrus (RMFG), right superior parietal lobe, right frontal pole (RFP), right orbitofrontal cortex, anterior paracingulate cortex, left superior parietal lobe, left orbitofrontal cortex (LOFC) and left middle temporal gyrus. Longitudinal analyses of correlation coefficients between ROIs showed some significant effects, indicating deterioration of functional connectivity between specific regions of IC1 in PD patients. In this group, there was a decrease in functional connectivity (weaker positive correlation) between RMFG and bilateral superior parietal lobes, whereas the opposite effect was found in controls. Moreover, whereas in controls connectivity between RMFG and RFP decreased at follow-up, in PD patients it remained stable (table 4 and figure 4).

**Correlation strength between the RFP and the left orbitofrontal cortex was significantly lower in PD patients than in**

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**Table 2**  
Clinical data and memory performance at baseline and at follow-up, and time effect, group effect and group by time interaction

|                          | PD (n=17) | Controls (n=13) | F (G×T) | F (G) | F (T) |
|--------------------------|-----------|-----------------|---------|-------|-------|
|                          | Baseline  | Follow-up       | Baseline| Follow-up |       |       |
| MMSE                     | 29.53 (0.51) | 27.88 (2.55) | 29.92 (0.28) | 28.85 (0.69) | 0.72 | 2.79 | 16.49* |
| BDI                      | 7.53 (5.31)  | 5.65 (4.81)    | 3.31 (2.39)  | 2.62 (2.63)   | 0.59 | 7.50* | 2.75 |
| NPI                      | 3.12 (5.38)  | 2.00 (1.90)    | 1.08 (1.44)  | 1.46 (1.66)   | 1.36 | 1.68 | 0.32 |
| UPDRS                    | 15.24 (3.68) | 15.06 (4.41)  | –          | –          | –   | 0.25 |
| Hoehn and Yahr           | 1.77 (0.38)  | 1.85 (0.42)    | –          | –          | –   | 0.68 |
| LEDD                     | 277.65 (308.51) | 430.59 (350.78) | –          | –          | –   | 3.10 |
| RAVLT learning           | 44.29 (12.20) | 43.12 (10.69) | 50.62 (9.09) | 48.92 (10.10) | 0.03 | 2.79 | 0.85 |
| RAVLT delayed recall     | 8.59 (3.50)  | 9.41 (3.30)    | 10.39 (2.29) | 9.92 (2.75)   | 2.03 | 1.25 | 0.16 |
| RAVLT recognition        | 27.59 (2.24) | 28.29 (2.34)  | 28.39 (1.9)  | 28.46 (1.94)  | 0.88 | 0.45 | 1.37 |

Values are mean (SD).
*Significant at p<0.05.
The F values refer to those obtained with the repeated measures general linear model. $F (G \times T)$, group by time interaction; $F (G)$, group effect; $F (T)$, time effect.

**BDI**, Beck Depression Inventory-II; **LEDG**, levodopa equivalent daily dose; **MMSE**, Mini-Mental State Examination; **NPI**, Neuropsychiatric Inventory; **PD**, Parkinson’s disease; **RAVLT**, Rey’s Auditory Verbal Learning Test; **UPDRS**, Unified Parkinson’s Disease Rating Scale, motor section.
controls. A significant over time decline in correlation strength between these structures was observed in both groups, with no significant group by time interaction. The strength of correlation between the right and left orbitofrontal cortices also decreased over time in both groups, with no significant group effect or group by time interaction (table 4). No other significant effects in the analyses of correlations between the selected ROIs were detected.

Table 3  Functional MRI performance at baseline and at follow-up, time effect, group effect and group by time interaction

|                     | PD (n=17) Baseline | PD (n=17) Follow-up | Controls (n=13) Baseline | Controls (n=13) Follow-up | F (G×T) | F (G) | F (T) |
|---------------------|--------------------|---------------------|-------------------------|---------------------------|---------|-------|-------|
| Hits                | 54.69 (5.70)       | 54.94 (7.17)        | 54.85 (5.69)            | 56.62 (6.60)              | 0.16    | 0.29  | 0.24  |
| Correct rejects     | 59.57 (9.98)       | 49.71 (20.04)       | 63.23 (9.09)            | 60.15 (6.69)              | 1.56    | 3.01  | 5.68* |
| False positives     | 11.31 (10.20)      | 27.19 (26.53)       | 6.77 (9.09)             | 9.05 (6.69)               | 3.44**  | 7.55* | 5.13* |
| Missing             | 15.31 (7.17)       | 16.06 (8.37)        | 15.15 (5.70)            | 14.39 (6.50)              | 0.16    | 0.24  | 0.01  |
| Reaction time       | 687.54 (152.83)    | 636.37 (134.28)     | 640.05 (83.75)          | 644.01 (70.12)            | 1.70    | 0.24  | 2.32  |

Values are mean (SD).  
*p<0.05, **p=0.07.

The F values refer to those obtained with the repeated measures general linear model. F (G×T), group by time interaction; F (G), group effect; F (T), time effect.

PD, Parkinson’s disease.

Figure 2  Functional MRI model based results. Average activation map (recognition task>control condition) was obtained from all subjects (Parkinson’s disease patients and control group). Results are corrected at p<0.05 for multiple comparisons.
Finally, correlation strength between the right and left orbitofrontal cortices decreased over time in both groups (table 4). No other significant effects between the selected ROIs were detected.

**DISCUSSION**

In this study, we observed that PD patients presented with a progressive loss in the recognition memory network’s pattern of activation and deactivation; moreover, the results revealed deterioration in the strength of connectivity between the main areas involved in this network.

In this study, with an average follow-up of 35.5 months, PD patients remained stable in terms of learning and memory, as assessed by clinical neuropsychological tests. However, we observed a decline in fMRI recognition task performance. The increase in false positive responses at follow-up was

| PD (n=17)          | Controls (n=13)          | F (G×T) | F (G) | F (T) |
|--------------------|--------------------------|---------|-------|-------|
|                    | Baseline | Follow-up | Baseline | Follow-up |       |       |       |
| RMFG-RSPL          | 0.50 (0.26) | 0.33 (0.20) | 0.30 (0.22) | 0.42 (0.29) | 8.38* | 0.52 | 0.31 |
| RMFG-RFP           | 0.26 (0.33) | 0.29 (0.25) | 0.47 (0.14) | 0.29 (0.17) | 4.98* | 1.92 | 2.38 |
| RMFG-LSPL          | 0.45 (0.24) | 0.25 (0.16) | 0.31 (0.18) | 0.42 (0.30) | 8.09* | 0.62 | 0.62 |
| RFP-LOFC           | 0.24 (0.20) | 0.10 (0.22) | 0.32 (0.15) | 0.25 (0.14) | 1.13  | 4.34*| 6.77* |
| ROFC-LOFC          | 0.37 (0.17) | 0.24 (0.25) | 0.51 (0.22) | 0.37 (0.16) | 0.04  | 3.87 | 13.67* |

Values are mean (SD).

*p<0.05.

Mean values are Pearson’s correlation coefficients normalised using Fisher’s r to Z transformation. The F values refer to those obtained with a repeated measures general linear model. F (G×T), group by time interaction; F (G), group effect; F (T), time effect.

LOFC, left orbitofrontal cortex; LSPL, left superior parietal lobe; PD, Parkinson’s disease; RFP, right frontal pole; RMFG, right middle frontal gyrus; ROFC, right orbitofrontal cortex; RSPL, right superior parietal lobe.
significantlly more marked in PD patients than in controls. This finding is in agreement with Whittington et al, who demonstrated that the recognition impairment in non-demented PD is seen in tasks of high demand (increased number of items). While in the RAVLT recognition part the number of stimuli is only 30, in the fMRI task there were 70 stimuli; this may have allowed the detection of subtle neuropsychological deficits not identified through standard clinical testing.

The regions that we found to be activated during the recognition memory task, involving both patients and controls, included several cortical areas (occipital lobes, bilateral orbitofrontal cortices and anterior paracingulate) and also subcortical structures involving bilaterally the basal ganglia and the left thalamus. However, the longitudinal data analyses showed that PD patients had decreased task related activity over time in cortical regions (IC1), but not in subcortical ones; specifically, the middle frontal gyrus, frontal pole, orbitofrontal cortex, anterior paracingulate gyrus, superior parietal lobe and the posterior portion of the middle temporal gyrus. All of these areas have been previously related to the recognition memory network, suggesting that appropriate recruitment of the recognition memory network entails a better performance. In line with these results, Van Eimeren et al found a positive correlation between errors in the fMRI task and blood oxygen level dependent signal change in specific regions of the DMN, such as the precuneus and posterior cingulate cortex, meaning that the more deactivated those areas were, the better the performance.

The cross correlation analysis approach allowed us to evaluate variations in connectivity within the recognition memory network between baseline and follow-up. Previous PD cross sectional studies showed abnormal connectivity patterns during cognitive tasks. Van Eimeren et al found cortical deactivation during an executive functions task as well as functional connectivity among the main areas of interest. Their results suggest functional frontostriatal disconnection in PD patients.

In the present study, connectivity analysis between the main regions of interest revealed that PD patients showed a progressive decrease in frontoparietal connectivity whereas connectivity between the frontal areas remained stable. Functional disconnection in PD may result from the primary synucleinopathy and the synaptic dysfunction associated with it or it may be due to white matter microstructural damage, described in PD patients using diffusion tensor imaging techniques. Decreased frontoparietal connectivity could be mediated by degeneration of tracts that connect these regions, such as the superior longitudinal fasciculus or the inferior fronto-occipital fasciculus, which have been described as being affected in non-demented PD patients.

mean \( z_{PD} = 0.502 \) (SD = 0.263); mean \( z_{HC} = 0.327 \) (SD = 0.199)
mean \( z_{PD} = 0.302 \) (SD = 0.221); mean \( z_{HC} = 0.420 \) (SD = 0.294)
mean \( z_{PD} = 0.450 \) (SD = 0.242); mean \( z_{HC} = 0.246 \) (SD = 0.158)
mean \( z_{PD} = 0.365 \) (SD = 0.181); mean \( z_{HC} = 0.421 \) (SD = 0.304)
mean \( z_{PD} = 0.261 \) (SD = 0.330); mean \( z_{HC} = 0.289 \) (SD = 0.249)
mean \( z_{PD} = 0.473 \) (SD = 0.140); mean \( z_{HC} = 0.288 \) (SD = 0.174)
The fact that in PD patients connectivity between the right fronto-parietal regions remained stable, whereas in controls it declined, could be linked to loss of connectivity between the frontal and parietal regions observed in the former. We can speculate that affectation of long range connections could result in an increase in more local circuits as a functional compensation mechanism. Further studies are necessary to evaluate this hypothesis.

Frontoparietal connectivity may play an important role in PD related cognitive deficits, as previous work has found a cognitively relevant network in PD involving these areas. In a cross sectional study, Huang et al.19 identified a cognition related metabolic pattern in the network analysis of FDG-PET scans from 15 non-demented PD patients with mild to moderate motor symptoms. This pattern was characterised by relative hypometabolism of the dorsolateral prefrontal cortex, rostral supplementary motor area and superior parietal regions, associated with relative cerebellar/dentate nucleus metabolic increases. This network expression correlated significantly with indices of memory and executive functioning. The same authors performed a longitudinal FDG-PET study of PD patients without evident cognitive impairment. In accordance with our results, they found that disease progression was associated with declining metabolism in the prefrontal and parietal regions. Similarly, Carbon et al.43 found longitudinal changes in sequence learning performance and associated task related cerebral blood flow (H2 15O PET) in non-demented PD patients. After a 2 year follow-up period, significant declines in learning related activation were detected in parietal and temporo-occipital association areas and in the right dorsolateral prefrontal cortex.

In spite of previous evidence, progression of functional brain changes in PD patients remains controversial. In fact, after a longer follow-up period (4 years), Huang et al.18 found an inverse result—that is, an increase in cognition related metabolic pattern similar to motor related metabolic pattern progression. The authors related this result to incipient cognitive impairment. In contrast, Bohnen et al.44 found a decrease in metabolic activity (FDG-PET) in a small sample of patients who converted to PD with dementia after 2 years of follow-up. The metabolic reduction pattern included the thalamus and posterior cingulate, occipital, parietal and frontal areas, with mild reduction in the temporal lobe. The most prominent metabolic reduction in PD with dementia was seen in the cuneus and precuneus and in the mesiofrontal areas. In the future, progression of connectivity patterns between frontoparietal regions should be studied after longer follow-up periods.

Subjects in our study did not present with clinically significant cognitive impairments; however PD patients frequently present with cognitive deficits, specifically, visuospatial/visuo-perceptual deficits, which, in severe cases, could interfere with the performance of tasks such as the recognition memory paradigm used in this study. Hence, this issue should ideally be controlled for in future studies. We also have to point out that all PD patients included in the sample were assessed under their usual antiparkinsonian medication. In order to consider potentially confounding effects of dopaminergic medications, future studies should address the same question in drug abstinent or naïve patients to elucidate the influence of dopaminergic medications on activation of the cerebral areas related to recognition memory. Although the PD patients in our sample presented with normal average BDI scores, these were higher than in controls; future studies should try to pair groups by severity of depressive symptoms, taking into account the effect of anti-depressant medication. Finally, we also have to consider dropout of subjects from the initial sample to follow-up, a common limitation in longitudinal studies. However, comparisons between the initial sample and the one included in the longitudinal assessment, for controls and PD patients, showed no significant differences in demographic or clinical characteristics. Despite that in the future, our study should be replicated with a larger sample.

In conclusion, our results showed a decrease in the recognition memory network activation pattern over time and an abnormal connectivity pattern between the main regions involved in this memory network in PD patients. To the best of our knowledge, this is the first longitudinal study to reveal a progressive decrease in functional connectivity between areas involved in a cognitive network in PD patients.

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REFERENCES
1. Aarsland D, Bronnick K, Larsen JP et al. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. Neurology 2009;72:1121–6.
2. Elgh E, Dorneloff M, Uinder J, et al. Cognitive function in early Parkinson’s disease: a population-based study. Eur J Neurol 2009;16:1278–84.
3. Higginson CI, Wheelock VL, Carroll KE, et al. Recognition memory in Parkinson’s disease with and without dementia: evidence consistent with the retrieval deficit hypothesis. J Clin Exp Neuropsychol 2005;27:516–28.
4. Whittington CJ, Podd J, Stewat-Williams S. Memory deficits in Parkinson’s disease. J Clin Exp Neuropsychol 2006;28:738–54.
5. Li K, Guo L, Nie J, et al. Review of methods for functional brain connectivity detection using fMRI. Comput Med Imaging Graph 2009;33:131–9.
6. Beckmann CF, Smith SM. Tensorial extensions of independent component analysis for mult-subject fMRI analysis. Neuroimage 2005;25:294–311.
7. Bai F, Shi Y, Yuan Y, et al. Altered self-referential network in resting-state amnestic type mild cognitive impairment. Cortex 2012;48:604–13.
8. Ibarretxe-Bilbao N, Zarei M, Junque C, et al. Dysfunctions of cerebral networks precede recognition memory deficits in early Parkinson’s disease. Neuroimage 2011;57:589–97.
9. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain’s default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008;1124:1–38.
10. Jahanshahi M, Jones CR, Zijlmans J, et al. Dopaminergic modulation of striato-frontal connectivity during motor timing in Parkinson’s disease. Brain 2010;133:727–45.
11. Palmer SJ, Li J, Wang ZL, et al. Joint amplitude and connectivity compensatory mechanisms in Parkinson’s disease. Neuroscience 2010;166:1110–18.
12. Wu T, Chan P, Hallett M. Effective connectivity of neural networks in automatic movements in Parkinson’s disease. Neuroimage 2010;48:2581–7.
13. Wu T, Wang L, Hallett M, et al. Effective connectivity of brain networks during self-initiated movement in Parkinson’s disease. Neuroimage 2011;55:204–15.
14. Rowe J, Stephan KE, Friston K, et al. Attention to action in Parkinson’s disease: impaired effective connectivity among frontal cortical regions. Brain 2002;25:276–89.
15. van Elst P, Chauvenet D, Ballanger B, et al. Dysfunction of the default mode network in Parkinson disease: a functional magnetic resonance imaging study. Arch Neurol 2009;66:877–83.
16. Wu T, Wang L, Chen Y, et al. Changes of functional connectivity of the motor network in the resting state in Parkinson’s disease. Neurosci Lett 2009;460:6–10.
17. Helmich RC, Denkx LC, Bakker M, et al. Spatial remapping of cortico-striatal connectivity in Parkinson’s disease. Cereb Cortex 2010;20:1175–86.
18. Huang C, Tang C, Feigin A, et al. Changes in network activity with the progression of Parkinson’s disease. Brain 2007;130:1834–46.
19. Huang C, Mattis T, Tang C, et al. Metabolic brain networks associated with cognitive function in Parkinson’s disease. Neuroimage 2007;34:714–23.
20. Ibarretxe-Bilbao N, Junque C, Marti MJ, et al. Offactory impairment in Parkinson’s disease and white matter abnormalities in central olfactory areas: A voxel-based diffusion tensor imaging study. Mov Disord 2010;25:1889–94.
21. Tomlinson CL, Stowe R, Patel S, et al. Systematic review of levodopa equivalency reporting in Parkinson’s disease. Mov Disord 2010;25:2649–53.
22. Daniel SE, Lees AJ. Parkinson’s Disease Society Brain Bank, London: overview and research. J Neurotransm Suppl 1993;39:165–72.
23. Dubois B, Burn D, Goetz C, et al. Diagnostic procedures for Parkinson’s disease dementia: recommendations from the movement disorder society task force. Mov Disord 2007;22:2314–24.
24. Beck AT, Steer RA, Brown GK. Manual for the beck depression inventory-II. San Antonio, TX: Psychological Corporation, 1996.
25. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2398–414.
26. Rey A. El Examen Clinico en Psicologia. Editorial Kapelusz. Buenos Aires, Argentina: Editorial Kapelusz, 1962.
27. Jenkinson M, Bannister P, Brady M, et al. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 2002;17:825–41.
28. Smith SM. Fast robust automated brain extraction. Hum Brain Mapp 2002;17:143–55.
29. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. Med Image Anal 2001;5:143–56.
30. Beckmann CF, Jenkinson M, Smith SM. General multilevel linear modeling for group analysis in fMRI. Neuroimage 2003;20:1052–63.
31. Woolrich MW, Behrens TE, Beckmann CF, et al. Multilevel linear modelling for fMRI group analysis using Bayesian inference. Neuroimage 2004;21:1732–47.
32. Beckmann CF, Smith SM. Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE Trans Med Imaging 2004;23:137–52.
33. Cabeza R, Nyberg L. Imaging cognition II: An empirical review of 275 PET and fMRI studies. J Cogn Neurosci 2000;12:1–47.
34. Spaniol J, Davidson PS, Kim AS, et al. Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. Neuropsychologia 2009;47:1785–79.
35. Greicius MD, Krasnow B, Reiss AL, et al. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA 2003;100:253–8.
36. Raichle ME, MacLeod AM, Snyder AZ, et al. A default mode of brain function. Proc Natl Acad Sci USA 2001;98:1064–71.
37. Petrella JR, Sheldón FC, Prince SE, et al. Default mode network connectivity in stable vs progressive mild cognitive impairment. Neurology 2011;76:511–17.
38. Schulz-Schaeffer WJ. The synaptic pathology of α-synuclein aggregation in dementia with Lewy bodies, Parkinson’s disease and Parkinson’s disease dementia. Acta Neuropathol 2010;120:131–43.
39. Koragulle-Kendi AT, Lehericy S, Luciana M, et al. Altered diffusion in the frontal lobe in Parkinson disease. AJNR Am J Neuroradiol 2008;29:501–5.
40. Gattellaro G, Minati L, Grisoli M, et al. White matter involvement in idiopathic Parkinson disease: a diffusion tensor imaging study. AJNR Am J Neuroradiol 2009;30:1222–6.
41. Rye CI, Cem vista MM, Altena E, et al. White matter pathology in Parkinson’s disease: The effect of imaging protocol differences and relevance to executive function. Neuroimage 2012;62:1675–84.
42. Baggio HG, Segura B, Ibarretxe-Bilbao N, et al. Structural correlates of facial emotion recognition deficits in Parkinson’s disease patients. Neuropsychologia 2012;50:2121–8.
43. Carbon M, Reetz K, Ghilardi MF, et al. Early Parkinson’s disease: longitudinal changes in brain activity during sequence learning. Neurobiol Dis 2010;37:455–60.
44. Bohm M, Kupske SA, Minoshima S, et al. Cerebral glucose metabolic features of Parkinson disease and incident dementia: longitudinal study. J Nucl Med 2011;52:848–55.