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Journal Club: Default-mode network connectivity in cognitively unimpaired patients with Parkinson disease

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This Journal Club article looks at a study by Tessitore et al.,[1] who investigated functional connectivity (FC) within the default-mode network (DMN) in cognitively unimpaired patients with Parkinson disease (PD). PD is the second most common neurodegenerative disorder after Alzheimer disease (AD) and is expected to become progressively more prevalent in our aging societies. Thus, its social and economic burden on societies is expected to be even greater in the future.[2] Cognitive impairment is one of the most disabling nonmotor symptoms of PD, further affecting functioning and quality of life as well as increasing caregivers' burden and health-related costs.[3] When an individual is alert but not actively engaged in cognitive tasks, organized neural activity occurs in a set of brain regions called the DMN (figure), which involves the posterior cingulate cortex (PCC), parts of the ventromedial prefrontal cortex, and the precuneus.[4] Interestingly, DMN abnormalities have been linked to cognitive profiles in several neurologic and psychiatric disorders, such as AD, autism, frontotemporal dementia, multiple sclerosis, and vegetative states[5]; however, contradictory results have been reported in PD.[1] This study for the first time cogently demonstrates decreased FC within the DMN in cognitively unimpaired patients with PD.

HYPOTHESIS AND DESIGN Does gray matter (GM) atrophy correlate with cognitive decline, similar to that in other dementing conditions? Is there an association between FC within the DMN and neuropsychological performance? Moreover, do disease duration and daily dopaminergic therapy affect DMN FC? Tessitore et al. tried to address these important questions with a case-control study in an adequate cohort of 16 patients with PD (4 female) and 16 age- and sex-matched healthy controls (HCs) who underwent neuropsychological screening and neuroimaging assessments. These questions are relevant to research and clinical practice, and potentially could lead to novel imaging biomarkers for early disease detection and progression toward cognitive impairment in PD.

METHODS Patients with a diagnosis of PD according to the clinical diagnostic criteria of the UK PD Society Brain Bank were recruited for the study. Other inclusion criteria were at least 45 years of age, disease duration less than 10 years, right-handedness, and 1-month stable and optimized treatment. Dementia symptoms, major depression or other clinically significant conditions, and treatment with antidepressants or neuroleptics were exclusion criteria. Moreover, only those patients with a Hoehn & Yahr scale <2 in an "on" state were included. Mini-Mental State Examination, Frontal Assessment Battery, and a detailed neuropsychological battery to assess global cognitive functions (attention/executive functions, verbal episodic memory, visuospatial and memory abilities) were performed. Cognitive performance was divided into 3 general domains (attention/execution, memory, and visuospatial) and subsequently converted into z scores adjusted for age, education, and sex on the basis of a multiple regression analysis performed in a different control group. A resting-state functional MRI (fMRI) scan was then performed. However, fMRI recorded signal can be obscured by various sources of variability, such as machine artifacts, physiologic pulsation, head motion, and others.[6] To solve this problem, data were processed using single-subject and group-level independent component analyses (ICA). In fact, ICA is a powerful computational method to separate a multivariate signal into its additive subcomponents under some assumptions (i.e., that they are statistically independent of each other and non-Gaussian).[6] Linear correlation analysis was also performed between ICA z scores obtained from DMN clusters and 1) duration of the disease, 2) motor impairment (measured with the Unified Parkinson's Disease Rating Scale [UPDRS] III score), 3) levodopa equivalent daily dose (LEDD), 4) single cognitive tests, and 5) the 3 general domains z score. Voxel-based morphometry (VBM), an analysis technique allowing the study of focal differences in cerebral anatomy that is less time-consuming than traditional morphometry and further able to capture even small differences, was used to test whether between-group differences in resting-state FC were related to structural abnormalities in the GM.

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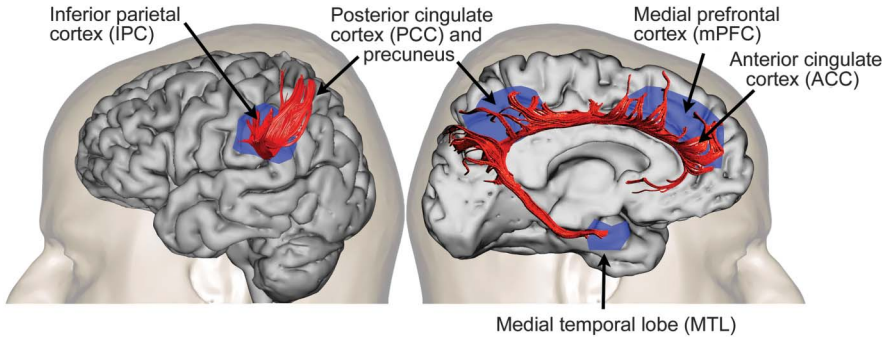
Figure **Lateral and medial view of the default-mode network of the left hemisphere**



The medial regions of the default-mode network are connected through the cingulum, whereas the inferior parietal cortex is connected to the precuneus and posterior cingulate cortex through a short intraparietal tract. The tracts are reconstructed using diffusion tensor imaging tractography.

RESULTS DMN regions that survived the random effects at the whole-brain level (thresholded at $p = 0.05$ and Bonferroni-corrected, a statistical method used to avoid making false discoveries when multiple comparisons are tested) in the resting-state analysis included the PCC, precuneus, medial prefrontal cortex, anterior cingulate cortex, bilateral inferior parietal cortex (IPC), and medial temporal lobe (MTL). Compared to HCs, patients with PD showed decreased FC in the bilateral IPC and the right MTL (between-group differences). Interestingly, although patients with PD were cognitively unimpaired, the decreased FC in the DMN correlated significantly ($p < 0.001$) with other cognitive parameters such as 1) average visuospatial z scores (right IPC, $r = 0.86$; left IPC, $r = 0.81$), Corsi block span scores (right IPC, $r = 0.57$; left IPC, $r = 0.71$), clock-drawing test scores (right IPC, $r = 0.69$; left IPC, $r = 0.72$), and bilateral IPC ICA z scores ($p < 0.001$); and 2) average memory z scores ($r = 0.65$), immediate ($r = 0.61$) and delayed ($r = 0.64$) recall of word list scores, and right MTL ICA z scores ($p < 0.001$). In addition, the decreased FC in the DMN was not associated with disease duration, UPDRS III score, or LEDD. The lack of correlation with duration and clinical severity suggests that FC measurements of the DMN are not stage-specific, but rather reflect modifications that occur early in the disease and do not modify throughout its course. The authors also found no between-group differences for the global, regional, or region of interest–based analysis, or GM, white matter, and CSF volumes.

INTERPRETATION In their article, Tessitore et al. report resting-state FC abnormalities in the DMN of cognitively unimpaired patients with PD. In particular, they revealed a decreased FC of the right MTL and bilateral IPC, and a correlation between FC and neuropsychological performance.

Strengths of the study include the following:

- VBM morphometry of the GM to rule out the presence of structural lesions and to offset artifact created by altered cortical thicknesses in degenerated regions that could alter the FC analysis.
- Both single-subject and group-level ICA were performed to describe results at different but convergent levels.
- To further expand the first finding, parallel analyses of structural cortical anatomy and FC of the DMN suggest that functional disruption occurs before anatomical differences in cortical thickness become evident.
- Correlations between FC of the DMN and cognitive tests (i.e., with 1) MTL FC and memory z scores and declarative memory test scores and 2) between IPC FC and visuospatial z scores and visuospatial function tests) suggest that functional changes preceding structural abnormalities to the cortex and deep nuclei may be used as an early marker of cognitive decline.
- In line with previous evidence,[7] the study confirmed that significant GM loss within the DMN does not occur in PD without a comorbid cognitive impairment, thus highlighting the reproducibility of this solid scientific finding often observed by clinician researchers.
- As discussed by the authors, this study, by linking PD and the DMN, addresses conflicting results reported in the previous literature due to different methodologic approaches.[1]

The study also has the following limitations:

- The presence of clinically significant depression was excluded according to *DSM-IV* criteria, but there is no mention of the use of standard screening or clinical questionnaires. This information could have been collected using the Geriatric

Depression Scale–30, which has been suggested to be particularly suitable for patients with PD owing to its brevity and favorable psychometric properties.[8] Mood disturbances are highly prevalent in PD, with up to 35% of patients reporting depressive symptoms even in the absence of a clinical diagnosis.[8] Considering that DMN activity can be affected by mood symptoms,[9] it would have been important to exclude this potential confounding variable from the study.

- The cohort selected in the study excluded patients with moderate to severe PD who are at higher risk of cognitive decline. It would have been important to include this group at higher risk of cognitive impairment in order to assess the specificity of the correlation, even if including this group would have resulted in increased movement artifacts.
- The neuropsychological assessment lacks measurements of language. Cognitive impairment in PD involves speech in a significant number of patients.[10] Considering that many areas of the DMN overlap with the language networks, this aspect should have been considered in the study design.
- The study is cross-sectional, and although the results could have remarkable implications for understanding cognitive impairment in PD, only a longitudinal design would have allowed determination of the validity of the DMN as a possible biomarker predictive of cognitive impairment.
- Postmortem studies demonstrated the presence of pathologic lesions in the cortex of patients with PD even in subjects without cognitive impairment. These changes may be present but not detectable with current MRI methods.

This study, if replicated in a larger population of patients with PD, may lead to the first clinical application of fMRI in PD. This method of investigation is noninvasive and could offer many advantages compared to other neuroimaging methods for the study of the dopamine metabolism. The latter remains an important tool in the clinical workup of patients with PD as it has been recently demonstrated that lower striatal binding at baseline is independently associated with higher risk of motor severity (e.g., motor-related disability, falling, and postural instability), cognitive impairment, psychosis, and clinically important depression symptoms at 22 months follow-up.[11] These results are valuable information for the clinical management of patients with PD at high risk of nonmotor complications.

FC analysis of fMRI is a novel approach and its validation as a clinical tool rests on the following:

- Replication of findings in a larger sample more representative of the real constitution of the PD population
- Comprehensive assessment of neuropsychiatric comorbidity (e.g., depression) and language assessments on subjects with standardized tests
- Extending resting-state fMRI analyses to a more heterogeneous population including patients with mild cognitive impairment and dementia
- Performing longitudinal studies aimed at evaluating the validity of fMRI analysis as a biomarker of cognitive decline

The DMN is one of the most important contributions of neuroimaging to our understanding of the human brain. We hope that methods to measure FC of the DMN will not remain only research tools but will be demonstrated to have a clinical relevance for the treatment and management of neurologic patients.[12]

AUTHOR CONTRIBUTIONS

Stefano Sandrone: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Marco Catani: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision.

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