Structural and Functional Network Dysfunction in Parkinson Disease[1]

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https://doi.org/10.1148/radiol.247172401

Content code: NR

Radiology 2017; 285:725–727

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Conflicts of interest are listed at the end of this article.

See also the articles by Arrigo et al, Hepp et al, and Suo et al in this issue.

Parkinson disease (PD) is a neurodegenerative disorder characterized by early involvement of the brainstem, with early prominent neuronal loss in the dopaminergic substantia nigra pars compacta, as well as loss in serotonergic and cholinergic brainstem and basal forebrain nuclei (1). The early disruption of brainstem neuromodulatory structures contributes to more widespread changes in brain function, even before neuropathologic disease has substantially involved the cortex and subcortical nuclei. Beyond the well-recognized motor symptoms of PD–tremor, bradykinesia, rigidity, and postural instability–PD is also commonly associated with a variety of nonmotor symptoms, including cognitive impairment, autonomic dysfunction, sleep disorders, depression, anxiety, and visual hallucinations (2).

Advances in magnetic resonance (MR) imaging have provided new windows into human brain networks. Statistical approaches to structural MR imaging, including voxel-based morphometry, allow quantification of structural variation across subject groups. Diffusion-tensor imaging utilizes anisotropic diffusion of water molecules constrained by white matter to assess the structural integrity of major white matter tracts. Resting-state functional MR imaging utilizes spontaneous fluctuations in blood oxygen level–dependent signal to identify correlated, and presumably functionally integrated, networks. In the current issue of *Radiology*, three articles utilize these methodologies to identify abnormalities of functional and structural networks in PD.

Network Dysfunction in PD

Suo et al (3) measured whole-brain functional connectivity of 153 patients with PD and 81 healthy control subjects matched for age, sex, and handedness. Using graph theory to quantify network properties (4), they report decreased global functional connectivity in PD patients with reduced local connectivity (decreased clustering coefficient, indicating local nodes were less densely interconnected) and reduced global integration (increased path length, indicating more nodes must be traversed to connect disparate nodes in the network). In addition, they report regional decreases in nodal centrality (a measure of the degree to which a node acts as a hub in the overall network) in sensorimotor cortex, the default mode network, and temporal-occipital networks. Decreases in nodal centrality in a subset of these regions–the right precentral gyrus, left postcentral gyrus, and left superior temporal gyrus–were correlated with PD severity as rated by using Hoehn and Yahr stage and Unified Parkinson's Disease Rating Scale III motor scores. Detailed cognitive testing was not available for this patient cohort, so it was not possible for the authors to assess whether changes in these or other networks correlated with cognitive performance in PD.

Decreased functional connectivity of the left (5) or bilateral (6) temporal cortex, as identified by Suo et al (3), have been previously described as early findings of PD that correlate with disease progression, as well as with impaired visual processing and hallucinations (7). Patients with PD commonly have a range of visual symptoms, such as loss of visual acuity, reduced color perception, reduced contrast discrimination, and impaired orientation and motion discrimination (8). Hepp et al (9) compared whole-brain resting-state functional connectivity in 15 PD patients with visual hallucinations, 40 PD patients without visual hallucinations,

and 15 healthy control subjects. They report that PD patients exhibited decreased functional connectivity in paracentral and occipital cortices compared with healthy control subjects, but not specifically in the temporal lobe. However, a distributed set of regions in the frontal, temporal, occipital, and striatal gray matter showed decreased functional connectivity in patients with visual hallucinations compared with control subjects. Functional connectivity in these same regions was associated with cognitive deficits. The authors conclude that this finding supports the hypothesis that visual hallucinations arise out of dysfunction in a distributed network. However, given the correlation between visual hallucinations and cognitive dysfunction and overall disease severity, and the small sample size of the study, it was not possible to fully disentangle each of these factors.

Arrigo et al (10) studied structure and structural connectivity of the visual system in detail in 40 newly diagnosed drug-naive PD patients without visual symptoms. Using DTI and white matter voxel-based morphometry, they report that PD patients exhibited decreased optic chiasm and visual cortical volumes, as well as increased diffusivity in the optic radiations with decreased connectivity between lateral geniculate nucleus (LGN) and V2, with a trend toward decreased connectivity to V1 and V3. Conversely, they report increased LGN to V5 connectivity in PD patients, which they argue may be a compensatory change due to disrupted connectivity to lower visual areas. These results suggest that structural alterations of the visual system may be present even as motor symptoms are just emerging.

Convergent Findings

Hepp et al and Suo et al both found decreased functional connectivity in the paracentral sensorimotor cortex in patients with PD, which may reflect broader corticostriatal dysfunction (11). In contrast to Suo et al, Hepp et al did not find a correlation between paracentral functional connectivity and motor impairment, though the study may have been underpowered to detect this relationship. Hepp et al did report a correlation between postcentral gyrus functional connectivity and cognitive performance, which was not explored in the larger Suo et al cohort. There is overlap with networks previously identified by using fluorine18 fluorodeoxyglucose positron emission tomographic (PET) imaging in PD. Eidelberg et al (12) found patients with PD had reduced metabolic activity in the paracentral cortex, as well as in lateral frontal, paracentral, inferior parietal and parieto-occipital regions. Reduced metabolic activity of the presupplementary motor area and posterior cingulate cortex correlated with cognitive decline (13). The posterior cingulate gyrus, as well as paracentral cortex, was found by Suo et al and Hepp et al to have decreased functional connectivity.

In addition to decreased functional connectivity of the paracentral sensorimotor cortices, both Suo et al and Hepp et al observed decreased functional connectivity in the superior temporal gyrus and superior frontal gyrus that was associated with motor or cognitive symptom burden. Given the correlation between motor and cognitive symptom burden in PD, larger cohorts with detailed motor and cognitive testing will be required to confidently distinguish network dysfunction uniquely associated with cognitive or motor function. However, the overlap of cognitive and motor networks across these studies also points to the important interaction between cognitive and motor function in PD. Proper motor function in a dynamic and unpredictable world is cognitively demanding. For example, poor performance on the intra-extra dimensional set shift test task used by Hebb et al (14) has been shown to predict freezing of gait in patients with PD.

Suo et al report that even newly diagnosed, drug-naive PD patients already exhibit decreased functional connectivity relative to healthy control subjects. Similarly, Arrigo et al show decreased structural connectivity in the visual system of de novo PD patients. These findings highlight that at the time of diagnosis based on overt motor dysfunction, patients with PD have already experienced measurable changes in a topographically extensive network. Indeed, many nonmotor symptoms including REM sleep behavior disorder, anxiety, depression and autonomic dysfunction may predate PD motor symptoms by a decade or more (15).

Limitations and Open Questions

Each of these studies imaged patients in a single medication state, either on or off levodopa. By using resting-state functional MR imaging, levodopa and dopamine antagonists have been reported to modulate functional connectivity in complex ways in healthy patients with monotonic and nonlinear (inverted U-shaped) effects in different networks (16). A study investigating individual seed regions of the striatum and thalamus found increasing striatal and prefrontal cortex functional connectivity and decreasing ventral striatum and caudate connectivity with levodopa administration (17). Additionally, levodopa has been reported to reduce the amplitude of low-frequency fluctuations in blood oxygen level–dependent signal activity in the primary and secondary motor areas and middle and medial prefrontal cortices (18). These findings argue that some identified functional connectivity networks may be specific to levodopa state. Study participants in Suo et al were drug naive or off levodopa 12 hours prior to the study. Whereas, in Hepp et al study participants were studied while taking levodopa. This, could account for the lack of correlation between functional connectivity and motor dysfunction in Hepp et al study if levodopa obscured both PD-related motor network dysfunction and motor symptoms. Future studies would benefit from data collection in both the on- and off-medication states.

Subject head movement can both degrade and introduce spurious correlations into structural and functional imaging (19,20). This is especially problematic when comparisons are made between healthy individuals and those with movement disorders, as subject movement is likely to have been greater in the patient cohort and may reasonably be expected to correlate with disease

severity. To date, no single standard exists for quantifying motion artifact nor for correcting it. Direct motion tracking, combined with cardiac and respiratory monitoring, may offer the ability to at least track these potential confounds, though at the expense of a more complicated experimental setup (19).

Toward Network Therapeutics

The identification of network-level dysfunction in PD invites a network-targeted therapeutic intervention. Noninvasive stimulation with repetitive transcranial magnetic stimulation (rTMS) can modulate functional connectivity as measured by functional MR imaging and PET activity (21). Manipulations of rTMS pulse sequences such as excitatory or inhibitory quadripulse TMS can decrease or increase functional connectivity of the stimulated site (22). Clinically, in its current form, rTMS to paracentral cortex has modest effects on motor dysfunction in PD (23,24). Deep brain stimulation has more profound effects on motor function in PD. Although deep brain stimulation is targeted to subcortical nuclei, the clinical benefit likely arises due to modulation of network-level dysfunction (25). Horn et al (26) recently reported functional and structural connectivity maps of effective subthalamic nucleus stimulation based on population connectome data. Using these connectivity maps, they were able to predict some of the variance in deep brain stimulation efficacy across patients. In the future, it may be possible to use measurements of network dysfunction, perhaps ultimately derived from individual patients, to target personalized, invasive, or noninvasive network-level therapy.

Disclosures of Conflicts of Interest: T.M.H. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: received consultancy fees from Kernel. Other relationships: disclosed no relevant relationships. **J.B.** disclosed no relevant relationships. **E.E.** disclosed no relevant relationships.

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