Dopamine-dependent functional connectivity in Parkinson disease

A resting-state diagnosis?

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Resting-state fMRI (RS-fMRI) is a noninvasive imaging technique that identifies brain regions exhibiting correlated patterns of spontaneously occurring, slow changes in brain activity that are present at rest.[1] This resting brain activity is observed with MRI through changes in blood flow referred to as a blood oxygen level–dependent (BOLD) signal. RS-fMRI research has revealed a number of networks consistently present in healthy persons and representing specific patterns of synchronous activity.[2] One such resting-state network, labeled the basal ganglia network (BGN), is identified in the basal ganglia and thalamus, including the pallidum, putamen, subthalamic nucleus, and substantia nigra, with a projection also to the supplementary motor area.[3] The characterization of the BGN opens a potential means to investigate motor-related neuropathologies, in particular Parkinson disease (PD).

In this issue of *Neurology*®, Szewczyk-Krolikowski et al.[4] present findings on group discriminatory findings of MRI functional connectivity of the BGN in a sample of PD and control participants. The authors utilized a BGN template derived from 80 elderly healthy controls; they compared network maps between 19 patients with PD "on" and "off" dopaminergic medication and 19 age- and sex-matched control participants. Their objective was to identify a connectivity threshold for optimal group separation. Patients with PD in the medication "off" state showed reduced functional connectivity within the BGN across different clusters: putamen and caudate, midbrain, superior temporal gyrus, dorsolateral prefrontal cortex bilaterally, medial prefrontal cortex, and precuneus. Administration of dopaminergic medication improved BGN connectivity. Average BGN connectivity differentiated PD participants from controls with 100% sensitivity and 89.5% specificity. The connectivity threshold was then applied to 13 patients with PD in a validation cohort group to establish independent reproducibility of findings and achieved 85% accuracy. The authors conclude that functional connectivity is reproducibly reduced in the BGN in patients with PD and increases in response to dopaminergic medication.

A potential pitfall when using RS-fMRI to determine functional network integrity is contamination of the BOLD signal by physiologic noise.[5] The authors applied independent component analysis (ICA) of the RS-fMRI data, which is a data-driven approach that separates a signal into nonoverlapping spatial and time components and allows for better removal of noisy components of the BOLD signal.[5] The authors applied additional steps to reduce possible confounding effects of noise both in terms of image processing (ICA-based de-noising approach) and the deliberate selection of patients without prominent tremor.

The authors discuss their findings in light of previous RS-fMRI studies in PD. There are, however, methodologic differences from these studies, as most were not analyzed by ICA but were seed-based, using a region of interest method of analysis. With this method, signal arising from only a certain voxel or cluster of voxels (the "seed") is used to calculate correlations with other voxels of the brain based on a simple averaging of time series from the region of choice. In contrast, with the ICA approach only variance specific to the signal connectivity component of interest is taken into account.[6] Therefore, comparison of seed-based studies with ICA-based analyses needs to be done with caution and may account for some of the discrepant findings among studies.

Strict clinical criteria allow a highly accurate diagnosis of idiopathic PD based solely on motor manifestations and responsiveness to dopaminergic therapy, which is comparable to or even higher than found in this study.[7] Furthermore, the diagnostic accuracy of about 85% in the present study is derived from highly selected patient and control participant samples. Patients had a relatively short duration of disease (diagnosis within the preceding 3 years), no substantial cognitive impairment, and no relevant structural MRI abnormalities. Specific exclusion criteria included physician-rated certainty of diagnosis <90% and presence of moderate or severe tremor (excluded for methodologic, not diagnostic, reasons). Further studies are needed to investigate the robustness and specificity of BGN connectivity in a more

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real-world patient population that also includes patients with atypical parkinsonism, such as progressive supranuclear palsy or multiple system atrophy. The currently approved indication for dopamine transporter radioligand imaging is the differential diagnosis between patients with mixed or atypical tremor, a situation that may result in artifactual changes with the RS-fMRI technique.

Administration of dopaminergic medication clearly improved connectivity, as shown in the medication "off" and "on" comparison. Although this finding suggests a functional process related to PD-specific dopamine-dependent processes, the authors were unable to find correlations between BGN connectivity and clinical motor and disease features. This may indicate that BGN connectivity, similar to substantia nigra hyperechogenicity as identified by transcranial sonography,[8] is a trait and not a state biomarker of disease. Although the validation cohort was slightly older with lower cognitive scores than the healthy control group, the mean connectivity estimates were higher in the validation patient group, i.e., closer to the normal range, rather than lower, arguing against a statistical floor effect where gradation of severity is lost.

Clinical utility of a diagnostic biomarker may be enhanced when it is able to identify at-risk subjects with prodromal PD.[9] It is possible that BGN connectivity may fulfill such a future role. However, reduced nigrostriatal dopaminergic activity is not only seen with prodromal PD but also with normal aging.[10] Despite the wide range of BGN connectivity estimates in the control group, no specific relationship was found with age in the control participants.

Although clinical translation of RS-fMRI to real-world neurology practice will need to clear many more hurdles, this proof-of-concept study offers great promise for the future. It demonstrates the potential for a functional and dopaminergic medication-responsive MRI technique to characterize disease-specific brain networks that can be quantitatively expressed and provide a reader-independent diagnosis.

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