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Editorial

Imaging Parkinson's disease using functional and diffusion MRI

Resting-state functional MRI (fMRI) and diffusion MRI (dMRI) have been widely exploited in studies of Parkinson's disease (PD) in the attempt to identify early diagnostic biomarkers of PD and to describe neural correlates of both motor and non-motor symptoms of the disease and their progression [1].

With resting-state fMRI (rs-fMRI), study results remain controversial particularly because of the heterogeneity of PD populations studied, the various analytical methods used, and the impact of distinct brain pathology, neurodegeneration, and dopaminergic medication on the resting-state functional connectivity (rs-FC) strength [2,3]. Moreover, the association between PD symptoms and fMRI results is not straightforward but rather complex: the rs-FC changes seem to reflect various mechanisms employed at various disease stages [4]; both rs-FC increases and decreases may co-occur in a cross-sectional study [5]. The rs-FC may decrease due to brain pathology; it may increase in an attempt to compensate for the pathological load and brain (dis)function [6]. Increases of the between-network connectivity may be caused by increases in connections between specific nodes engaged in large-scale brain networks or by decreases in normally occurring negative correlations (so-called anticorrelations) between nodes of task-positive networks and the task-negative network (i.e. the default mode network) [7]. Particularly in the latter case, increases of between-network FC may reflect brain malfunction [8]. Genetic risk factors and cognitive reserve [1] play roles, as do other potential variables, and therefore the resulting patterns of fMRI changes vary. The results are on the whole difficult to generalize and to use as biomarkers in individual subjects.

In the current issue of *Parkinsonism and Related Disorders*, Sreenivasan et al. [9] studied the whole-brain network functional organization using the graph theoretical approach and its relation to clinical measures in a well-characterized cohort of very early-stage, drug-naïve PD patients without tremor-dominant forms of the disease derived from the Parkinson's Progression Markers Initiative database (mean PD duration was 1.03 ± 1.12 years, and mean modified UPDRS-III score was 16.15 ± 7.79 points). The studied groups of PD and healthy controls (HC) were rather small (n = 20 and n = 16, respectively), but the results revealed clearly significant changes in the global and local brain topology of PD patients as compared to HC, including a loss in optimal modular information processing (i.e. an abnormal functional segregation that reflects a decreased ability to form functionally specific clusters) and inefficient overall long-distance information processing (i.e. abnormal functional integration). The normalized clustering coefficient (a calculated ratio of connections between neighbors to all connections: a measure of functional segregation) was significantly associated with disease duration, and the node characteristics within the left supramarginal gyrus and the left middle frontal gyrus were related to the striatal binding ratio, showing an association of the results with basal ganglia dopaminergic denervation. While the functional network-based changes in PD were present both globally and locally, both HC and PD groups still maintained a "small world" brain network organization, i.e. an optimized organization that enables the efficient spread of information in the brain. This result in very early unmedicated PD subjects accords well with the theory of dedifferentiation that is not unique to PD but it also occurs in healthy aging [10] and in other neurodegenerative brain diseases such as early Alzheimer's disease [11]. According to this theory, there is a decrease of functional distinction between specific brain areas (i.e. decreased modularity and local efficiency) in older age (and in disease) that seems to occur on the level of resting-state functional brain networks, particularly within the cingulo-opercular (salience) network, the fronto-parietal control network (FPCN), and the default mode network (DMN). On the other hand, functional networks show increased inter-network connections. This compensatory mechanism, which occurs along with decreased intra-network connections, makes it possible to keep the global efficiency intact [10].

The meta-analysis by Wolters et al. [12] in the current issue was carried out using the anisotropic effect size version of signed differential mapping (AES-SDM) and focused on rs-fMRI in more advanced PD patients with cognitive impairment. The authors aimed to compare groups of cognitively impaired PD patients (PD-CI) with either a sample of healthy controls (HC) or a sample of PD patients with normal cognition (PD-NC). Seventeen studies met the criteria for inclusion and data from altogether 932 participants were analyzed: 353 HC, 289 PD-NC, 222 PD-MCI, and 68 with PD-dementia (PDD). Several interesting results were reported that add to our understanding of neural correlates of cognitive impairment in PD, although several study limitations have to be mentioned. The limitations include heterogeneous groups of PD-CI subjects based on various criteria for CI/MCI, not controlling for brain atrophy, combining studies with patients examined while "ON" and "OFF" dopaminergic medication, and the inclusion of studies with different types of analytical methods (e.g. region of interest versus whole brain, or seed-based versus ICA), which may have introduced a bias in study results towards specific regions of interests.

The direct comparison between PD-CI and PD-NC revealed a lower connectivity in PD-CI patients in the left precuneus, right median cingulate gyrus, left superior frontal gyrus, and right precentral gyrus. In addition, increased functional connectivity of the right cerebellum was identified in the PD-CI group as compared to PD-NC. A spatial correlation analysis of the reported peak coordinates with the intrinsic connectivity network templates showed that the major rs-FC decreases observed in PD-CI were located within the DMN; compensatory increases were present within the cerebellar network. The authors conclude that the DMN may hold promise as a biomarker for CI in PD patients. This result may be true for distinct PD populations; however, it does not accord with the results of some previously published studies

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comparing PD-NC and PD-MCI directly [13,14]. Further research is definitely warranted exploring both intra-network and inter-network rs-FC (see also above) in well-characterized patient subgroups using a multimodal imaging approach and prospective longitudinal study design.

The study by Yang et al. [15] in the current issue describes the use of free water imaging, a novel dMRI technique that uses a bi-tensor model to estimate the fractional volume of free water within a voxel for depicting early microstructural changes in gray matter subcortical structures. The fractional volume of free water is expected to increase in PD over time due to the loss of melanized nigral neurons and increased extracellular fluid space due to substantia nigra dopaminergic perikaryal changes particularly within the posterior substantia nigra (pSN), which reflects changes within the ventrolateral tier of the SN [16,17].

In the study, a total of 129 PD and 75 HC underwent behavioral testing and dMRI. In addition, in vivo [^{11}C] dihydrotetrabenazine (DTBZ) vesicular monoamine transporter type 2 (VMAT2) PET imaging was performed in order to assess the presynaptic dopaminergic terminal integrity, which correlates with striatal dopamine and fiber density. Compared with controls, PD patients had reduced DTBZ binding in the putamen and caudate, and increased free water in the pSN. The authors report an inverse correlation between free water in the pSN and DTBZ binding in the putamen and caudate. Multiple regression revealed that increased free water in the pSN, decreased DTBZ binding in the putamen, and age were predictors of motor impairment, including the posture and gait MDS-UPDRS subscores; increased pSN free water alone was associated with tremor scores. Increased free water in the caudate and pSN, decreased DTBZ binding in the caudate, and education were associated with higher dementia scores. The authors stress that changes in striatal VMAT2 binding probably occur much earlier than pSN microstructural changes identified by free water imaging and that both imaging modalities might serve as independent markers of motor and cognitive decline in PD. To confirm this assumption, longitudinal studies including subjects with prodromal PD are warranted. In addition to free water imaging, other novel dMRI techniques may prove useful in identifying early microstructural changes of gray matter cortical and subcortical structures, such as diffusion metrics describing the restricted non-Gaussian diffusion fraction derived from the restriction spectrum imaging model [18] or the diffusion kurtosis imaging technique (DKI) [19] which also quantifies the non-Gaussian motion of water molecules and describes the degree of heterogeneity of the gray matter tissue.

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