

Review

The Future of Brain Imaging in Parkinson's Disease

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Abstract. Parkinson's disease (PD) is a progressive neurodegenerative disorder that is associated with distinct abnormalities in brain function and structure. Here we discuss how future developments in functional, structural and nuclear brain imaging may help us to better understand, diagnose, and potentially even treat PD. These new horizons may be reached by developing tracers that specifically bind to alpha synuclein, by looking into different places in the body (such as the gut) or in smaller cerebral nuclei (with improved spatial resolution), and by developing new approaches for quantifying and interpreting altered dynamics in large-scale brain networks.

Keywords: Parkinson's disease, biomarkers, neuroimaging, magnetic resonance imaging, positron emission tomography

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor symptoms such as bradykinesia, rigidity and tremor, and a large variety of non-motor symptoms. The pathological hallmark of the disease is a profound loss of nigro-striatal dopamine cells and an accumulation of intracellular inclusions called Lewy bodies, which are comprised of alpha-synuclein aggregates. In concert with dopaminergic cell loss, several other neurotransmitter systems also degenerate, and in later stages Lewy body pathology also spreads to the cortex. This makes PD a prototypical systems disorder,

which can be fully understood only when investigating molecular, structural and functional abnormalities at the level of brain networks [1, 2]. With the rise of neuroscience in the last few decades, a plethora of new methods and approaches have become available. In this paper, we review and speculate how future developments in functional imaging, structural imaging, and nuclear imaging can help us understand, diagnose or even treat PD.

FUNCTIONAL IMAGING

Imaging of brain activity can be done with functional magnetic resonance imaging (fMRI) or positron emission tomography (PET). These approaches have made significant contributions to our understanding of the pathophysiology of PD. The field has grown from focussing on abnormal,

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task-related activity in isolated brain regions (such as the putamen) to demonstrating abnormal interactions between intrinsic, large-scale networks in patients with PD (such as the cortico-striatal circuit). For example, a recent paper has demonstrated that PD patients spend more time in “brain states” that are characterized by increased interactions between cerebral networks, at the expense of more sparsely connected, segregated brain states [3]. The shift from single brain regions to large-scale networks comes with new difficulties: the data have become multi-dimensional, and this makes it more difficult to extract meaningful patterns. The challenge is to extract biologically relevant parameters that capture (dys)function of an entire network.

An existing approach that has been used for a long time is the Parkinson's Disease Related Pattern (PDRP), i.e., a metabolic covariance pattern (or network) that is specific to PD, and that can be calculated using PET and fMRI data [2]. The validity of this approach has been proven in different centres across the world, although it has not been translated into standard clinical practice. This is probably because it works best with PET, which is not widely available. A second, more recently developed approach to deal with multi-dimensional data is the use of generative models, i.e., computational models that estimate how observed (fMRI) data were generated, given a set of priors and hypotheses regarding the configuration of the network [4]. This approach, which is implemented in dynamic causal modelling (DCM), has the advantage that different competing models of brain function can be compared within a group or between two groups (using Bayesian model selection). In PD, DCM has been used to test how network interactions give rise to tremor and to (abnormal) voluntary actions [5–7]. Inter-individual differences in statistical evidence for a particular model of brain function may be used to define (and clinically validate) imaging-based PD phenotypes, or even to support differential diagnosis through Bayesian model selection [4]. Finally, a third approach is to extract biologically meaningful features from multi-dimensional imaging data. For example, using resting state fMRI data, parameters can be calculated that reflect the gradient of cortico-striatal connectivity across striatal subregions [8]. These parameters (such as the direction and steepness of the gradient) are biologically meaningful, because they reflect the underlying anatomy and distribution of dopamine. Also, they may be sensitive to changes in cortico-striatal connectivity, which are

known to occur in PD [9]. These data could be used to build normative models (analogous to “growth curves”) to determine whether an individual departs from the normal pattern [10]. If clinically validated, such approaches may be helpful for diagnosis and disease monitoring.

A second development could lie in improved functional MRI sequences, enabling brain imaging at a high temporal and/or spatial resolution. Although fMRI is thought to be too slow to measure brain oscillations, given that it depends on slow changes in blood flow, recent studies have used ultra-rapid fMRI scanning at 7 Tesla to measure visual cortex BOLD oscillations at 0.75 Hz following high-frequency visual stimulation [11]. A further study showed resting state connectivity at frequencies up to 2.5 Hz [12]. Although it remains to be seen whether these signals carry information that is different from the slower BOLD fluctuations, it is possible that future developments will allow us to measure pathological oscillations (e.g., tremor) with fMRI. Furthermore, imaging at both high spatial and temporal resolution makes it possible to detect abnormal fluctuations in small brain stem nuclei while adequately correcting for rapid non-neuronal noise (e.g., cardiac and respiratory fluctuations around the brain stem). Given that the pathophysiological hallmark of PD is a degeneration of several neurotransmitter systems in the brain stem, these new techniques make it possible to test for altered activity and functional connectivity of these nuclei.

STRUCTURAL IMAGING

Structural imaging in PD has made important advances over the past decade [13], and as we look to the future several important themes emerge. The first theme is high-field imaging and improved spatial resolution having a significant impact on visualizing and quantifying features of the basal ganglia and other regions going forward. We are beginning to see progress in this area already in that 7 Tesla structural imaging has enabled automated segmentation of the substantia nigra, subthalamic nucleus, and red nucleus, which is not available at 3 Tesla [14]. Using a multimodal protocol, *in vivo* mapping of the basal ganglia and thalamic connections was achieved at submillimetre resolution and included susceptibility weighted imaging, diffusion imaging, and T1 and T2 weighted imaging [15]. These advances in submillimetre structural imaging have not yet made their

way to routine patient studies but have the potential to enhance clinical practices such as diagnosing PD and DBS surgery.

The second theme is in linking diffusion imaging as a biomarker of differential diagnosis, progression of PD, and relation to pathology. Recent evidence has linked diffusion imaging as a predictor of both cognitive function and motor symptoms in PD [16, 17]. From a methodological perspective, the classic diffusion tensor imaging model is proving to be less important when compared with more advanced computational models for modelling diffusion in the intracellular and extracellular compartments [18]. The bi-tensor model that can be performed on single-shell diffusion scans yielding the free-water metric has shown considerable promise as a biomarker of progression in early stage PD [19]. There is also some evidence that examination of free-water in multiple nodes in the cerebellum and basal ganglia offer key insights into the degenerative patterns that may distinguish PD from other forms of Parkinsonism [20]. In addition, other models of diffusion that leverage multiple shells and more complex mathematics may also provide new paths to better understanding the tissue-specific changes in regions that include the substantia nigra but also nucleus basalis of Meynert, cerebellum, frontal cortex, brainstem, and many other structures [21]. Finally, although there is a major push to develop ligands for PET that will allow neuroimaging to directly assay alpha-synuclein, there is also a case to be made for developing diffusion or other structural imaging markers that may reflect alpha-synuclein pathology. This is because there could be considerable structural events (i.e., inflammation, neurodegeneration, gliosis) that occur prior to and after the clinical diagnosis of PD that are linked to alpha-synuclein pathology, and a multi-modal approach will prove important in the future.

The final theme is in the area of clinical trials. At present, phase 1, 2, and 3 clinical trials are not consistently using structural imaging read-outs for evaluation. It is the case though that many of the therapies under consideration are not directly affecting dopamine, and thus having non-invasive structural imaging assays ready for clinical trial use will prove important going forward [17].

NUCLEAR IMAGING

A major unsolved problem is the lack of a specific imaging marker for the pathological hallmark of

PD, alpha synuclein aggregates. There are a number of reasons for this. First, while many small aromatic molecules are known to bind to alpha-synuclein fibrils, they all invariably bind with high affinity to beta amyloid which can also be present in elderly PD cases [22, 23]. Second, alpha-synuclein exists mainly in multiple oligomeric forms only some of which are toxic [24]. Small molecule ligands tend to bind weakly to these oligomers [25]. Third, alpha-synuclein is subject to multiple post translational modifications. While high throughput screening will no doubt continue to identify potential small molecule PET/SPECT ligands, an alternative way forward is to develop specific antibodies and peptides to alpha-synuclein oligomers and fibrils. This research is already in train, although a major problem is the transport of these ligands across the blood-brain barrier (BBB). Peptides and vesicles can be tagged with moieties that bind to BBB transporters, such as transferrin [26]. However, extraction of these peptides is still slow relative to the short-lived PET and SPECT isotopes which have half-lives of minutes to hours. Other potential approaches may be to: (a) Design lipophilic cage compounds to passively transport peptide ligands [27]; (b) Use aptamers, which are circular loops of RNA that can be tailored to bind specific peptides and transport them across the BBB [28].

The pathology of PD leads to mitochondrial, lysosomal, and proteasomal dysfunction. Small molecule ligands such as enzyme inhibitors are now becoming available that could act as imaging biomarkers of these processes. BCPP-FE binds selectively to complex I in mitochondria and, in pharmacological doses acts to reduce mitochondrial membrane potential [29]. ^{18}F -BCPP-FE has been shown to be a suitable agent for PET imaging in monkeys and is currently undergoing human trials. Agents that bind selectively to lysosomal and proteasomal components are also being screened as potential imaging markers given the association between glucocerebrosidase A deficiency and PD. One possible candidate could be the GBA inhibitor conduritol- β -epoxide (CBE).

Other fields of development in nuclear imaging include: (1) Surface receptor ligands which are sensitive to synaptic levels of transmitters. These already exist for dopamine (^{11}C -raclopride, ^{11}C -FLB), serotonin (^{11}C -AZ10419369), noradrenaline (^{11}C -yohimbine), and acetylcholine (^{18}F -FP-TZTP) but are inhibitors which are relatively insensitive to changes in transmitter fluxes. More sensitive, possibly agonist markers are required. Specific markers of

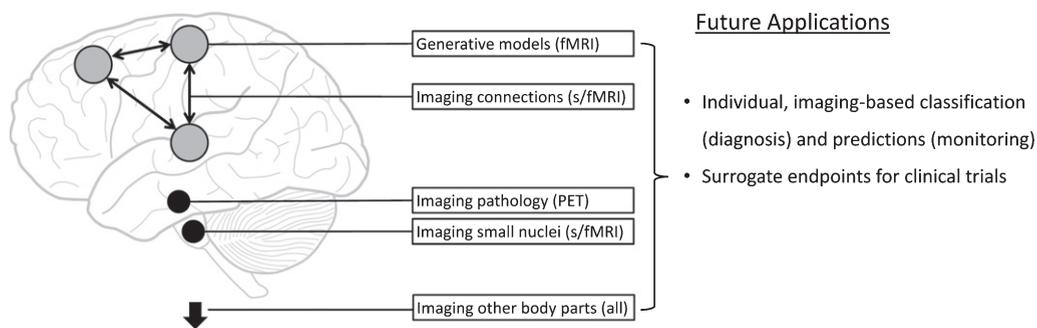


Fig. 1. Potential new imaging methods in Parkinson's disease. This figure schematically represents new approaches for functional magnetic resonance imaging (fMRI), structural MRI, and positron emission tomography (PET) imaging.

synaptic function, such as SV2A transporter ligands, are also under development [30]. ^{11}C -UCB-J is currently being trialled in PD cases with and without cognitive deficits. Finally, imaging peripheral systemic changes in PD has become of interest – it is known alpha-synuclein can be detected in skin and bowel and that sympathetic and parasympathetic activity can also be imaged. If a suitable alpha-synuclein tracer emerges, then peripheral imaging may help to throw light on the proposal that transmission of alpha-synuclein aggregates starts peripherally and proceeds centrally.

CONCLUSION

Parkinson's disease is a brain disorder with distinct molecular, functional and structural features. These characteristics make it a prototypical neurological disorder where new neuroimaging techniques, especially the combination of multiple techniques in single patients [31], have the potential to make significant contributions to clinical practice (Fig. 1).

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CONFLICT OF INTEREST

David Brooks is Consultant for GE Healthcare and Biogen. David Vaillancourt is co-founder and manager of Neuroimaging Solutions, LLC. Rick Helmich does not report conflicts of interest.

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