Network imaging biomarkers: insights and clinical applications in Parkinson's disease

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Parkinson's disease presents several practical challenges: it can be difficult to distinguish from atypical parkinsonian syndromes, clinical ratings can be insensitive as markers of disease progression, and its non-motor manifestations are not readily assessed in animal models. These challenges, along with others, are beginning to be addressed by innovative imaging methods to characterise Parkinson's disease-specific functional networks across the whole brain and measure their expression in each patient. These signatures can help improve differential diagnosis, guide selection of patients for clinical trials, and quantify treatment responses and placebo effects in individual patients. The primary Parkinson's disease-related metabolic pattern has been replicated in multiple patient populations and used as an outcome measure in clinical trials. It can also be used as a predictor of near-term phenoconversion in prodromal syndromes, such as rapid eye movement sleep behaviour disorder. Functional network imaging holds great promise for future clinical use in the management of neurodegenerative disorders.

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Introduction

Parkinson's disease is typically described in focal terms: it is caused by the loss of dopaminergic neurons in the substantia nigra and diagnosed clinically on the basis of the resulting motor triad of resting tremor, bradykinesia, and rigidity. Yet Parkinson's disease is quite complex, manifesting in structural and functional alterations throughout the brain. For example, changes in cognition, affect, behaviour, and personality can appear early in Parkinson's disease, even before motor symptoms, and clearly involve multiple regions and neurotransmitter systems beyond nigrostriatal dopamine projection.[1,2]

The clinical difficulties presented by Parkinson's disease are many. Most notably, several other disorders cause similar motor signs and symptoms.[3] 20–25% of patients diagnosed as having Parkinson's disease actually have atypical forms of parkinsonism (eg, progressive supranuclear palsy, multiple system atrophy, or corticobasal degeneration).[4] The usual approach to differential diagnosis is to treat the patient with levodopa and wait to see if they improve; suboptimal response will prompt further diagnostic work-up, but in some patients, the drug response is transient (eg, multiple system atrophy)[5] or misleading (eg, dopa-responsive dystonia).[6] To further complicate matters, Parkinson's disease is associated with an unusually strong placebo effect, which makes it difficult to discern whether a patient is actually improving because of the treatment being tested.[7,8] From the perspective of both the patient and the neurologist, then, Parkinson's disease poses a more daunting challenge than is usually appreciated.

Modern neuroimaging in conjunction with computational algorithms based on pattern recognition and machine learning are now beginning to address these challenges. Neuroimaging is particularly well suited to the study of neurodegenerative diseases, in which neuronal dysfunction spreads along discrete brain networks in a pattern that is highly replicable from one patient to the other, despite the clinical heterogeneity of disease manifestations.[9] Various analytical approaches can be used to identify and visualise abnormal brain networks,[10–12] but to develop biomarkers that can measure metabolic network expression in individuals (and not just to differentiate between groups of patients), one needs multivariate methods, such as spatial covariance mapping, which provide information about interactions between brain regions.[13] Multivariate approaches have proven adept at analysing functional network abnormalities in patients with Parkinson's disease, Alzheimer's disease, frontotemporal dementia, Huntington's disease, and several parkinsonian disorders, among others (appendix).[14–19] In this Review, we highlight advances in network analysis that have shed light on brain circuit disruptions that underlie Parkinson's disease and have the potential to alter clinical practice and facilitate the development of new therapies.

See Online for appendix

Metabolic network patterns in Parkinson's disease

The most well validated metabolic network pattern in Parkinson's disease is known as the Parkinson's disease-related pattern (PDRP), which is characterised by increased activity in the pallidothalamic and pontine regions and reduced activity in the premotor cortex, supplementary motor area, and parietal association regions (figure 1A).[14] Given that prolonged metabolic derangement causes atrophy, it is not surprising that structural MRI shows a pattern of atrophy in patients with Parkinson's disease that overlaps with the spatial topography of the PDRP.[28]

To identify the PDRP, we applied voxel-wise network analysis to ^{18}F-fluorodeoxyglucose (FDG) PET data from a combined group of 20 healthy participants and 20 patients with Parkinson's disease. Establishing a disease-related covariance pattern requires extensive validation; therefore, only after showing excellent test–retest reproducibility in 20 patients scanned twice over a 2-month interval[14] did we consider the possibility of using PDRP as an objective biomarker of disease progression. Since the initial characterisation, we and other groups[14,20–26] have shown that PDRP expression is consistently elevated in patients

Panel: **Definitions of mathematical concepts**

Network
In mathematics, a set of nodes (the basic network element, usually represented as points or dots) that are connected by edges (lines). Many neural systems can be modelled as networks. Subsets of nodes with high connectivity form modules (subnetworks).

Graph theory
Mathematical approach to studying properties of networks. An array of graph theory metrics captures different topological features of the network.

Average path length (in graph theory)
The approximate number of edges that must be traversed to connect two nodes; reflects the ease with which information can be shared between regions in the network.

Clustering coefficient (in graph theory)
The fraction of a given node's neighbours that are also neighbours of each other; reflects the tendency of nodes to associate with nearby nodes for purposes of subspecialisation.

Small-worldness (in graph theory)
The ratio of the clustering coefficient to the average path length in comparison with that of a random network. Small-worldness balances segregation (local subspecialisation) and integration within a network while minimising energetic costs.

Spatial covariance analysis
An analytical method based on principal component analysis, designed to reduce the complexity of multivariate data. Identifies the principal components (covariance patterns) that explain the largest statistical effects (variances) in multisubject-multiregional datasets.

with Parkinson's disease (figure 1B) regardless of medication state or scanner parameters. In fact, PDRP expression increases with disease severity and begins to rise in at-risk individuals (eg, those with rapid eye movement sleep behavior disorder [RBD]).[29,30] Patients scanned while treated with levodopa (or with deep brain stimulation [DBS] or gene therapy) show PDRP levels that are suppressed relative to their OFF-state but still significantly elevated relative to healthy controls, indicating that symptomatic treatment does not completely correct the underlying network abnormality.[24,26,27]

PDRP expression values consistently correlate with independent motor ratings for bradykinesia and rigidity.[14] Tremor is reflected in a different metabolic network, the so-called Parkinson's disease-related tremor pattern. PDRP correlates strongly with intraoperatively recorded subthalamic nucleus activity[31] and, to a lesser degree, with reduced nigrostriatal dopaminergic input.[22,24]

At present, PDRP is one of only a few functional network imaging biomarkers for neurological disease in general, and the only one for Parkinson's disease specifically, that has been validated in multiple patient populations[14] who were studied on different scanners at different imaging centres (table).[13]

Abnormal network architecture

Newer mathematical tools allow analysis of the organisational structure of disease networks and show that even in the early stages of Parkinson's disease, alterations in brain connectivity are widespread, particularly in the frontolateral cortex and cerebellum.[12] Our group used graph theory[16,46] (panel) to delineate the functional architecture of PDRP in finer detail.[10] We found that the Parkinson's disease network (or PDRP space) in patients with the disease differs from that of healthy controls, in that its core consists of a greater number of dense, bidirectional connections between metabolically active nodes in the putamen, globus pallidus, and thalamus, whereas the periphery contains metabolically less active cortical regions with weak node-to-node interactions (appendix). The Parkinson's disease network also contains a separate module defined by interconnected, metabolically active nodes involving the cerebellum, pons, frontal cortex, and limbic regions.

This increased clustering and reduced average path length between key nodes (panel) is known as small-worldness, which is common in many biological systems that need to process information efficiently at minimal energetic cost.[47] For example, the PDRP space in healthy controls exhibits some small-worldness because these brain regions have high information-processing demands in the normal resting state.[10] Parkinson's disease, however, produces an exaggerated small-worldness that is associated with high metabolic costs and inefficient, noisy information transfer between network regions[10] (Alzheimer's disease, in contrast, involves a loss of small-worldness between network nodes).[48] The Parkinson's disease network's hyperconnectivity is centred in two discrete subnetworks consisting of three nodes each: the putamen, globus pallidus, and thalamus on the one hand, and the pons, cerebellum, and frontal cortex on the other (figure 2). Each of these subnetworks has been associated with spontaneous oscillatory activity, which likely mediates specific clinical features: bradykinesia-rigidity through the basal ganglia subnetwork and tremor through the brainstem and cerebellum subnetwork.[10] The existence of a tremor subnetwork dovetails neatly with repeated observations that tremor arises from dysfunction in regions different from those producing other motor symptoms.[49–52]

The graph theory analysis also sheds light on the beneficial effects of levodopa. The drug partially normalises the average path length between network nodes to improve information transfer within the PDRP space, but does not correct the exaggerated small-worldness in patients with Parkinson's disease.[10] Whether these changes are more responsive to DBS than levodopa is not known.

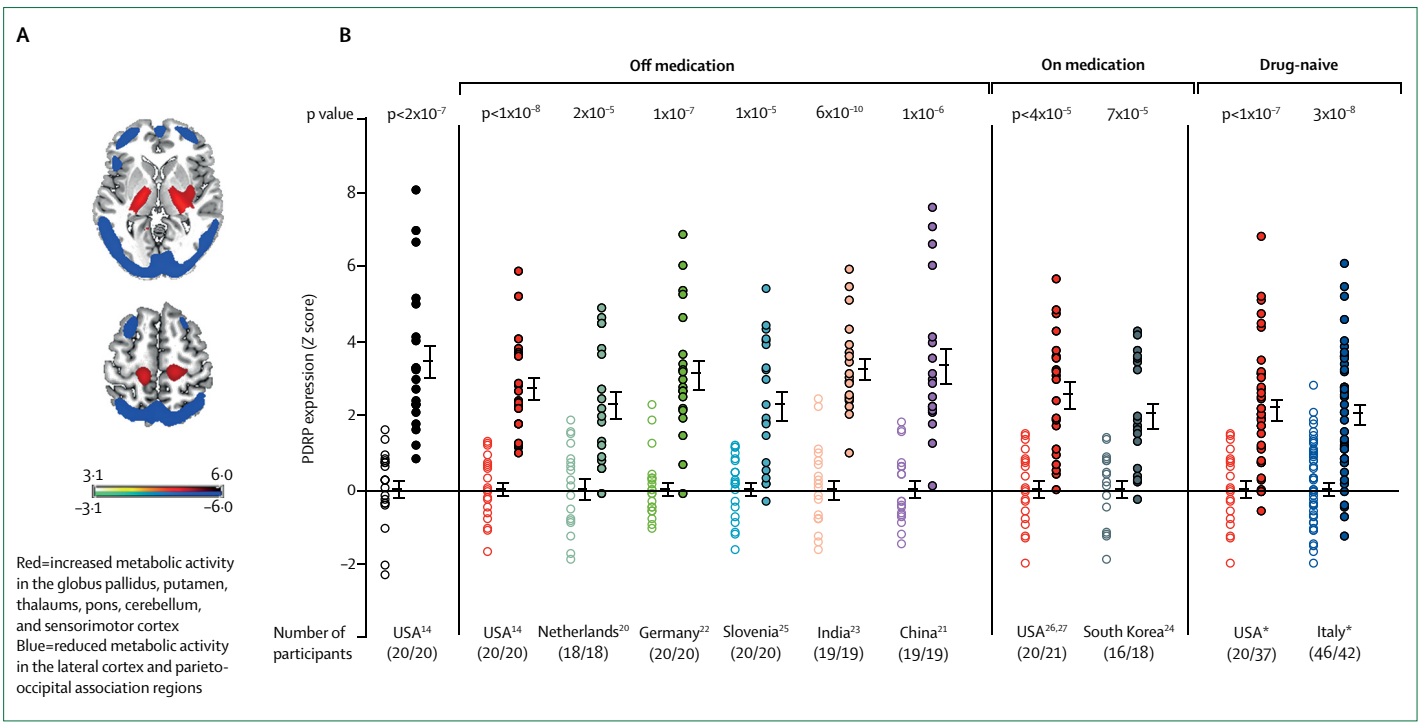

Figure 1: **Discovery and validation of the Parkinson's disease-related pattern**
(A) The Parkinson's disease-related pattern (PDRP) displayed as voxel weights (ie, regional loadings) thresholded at Z=3·1 (p<0·001), and overlaid on T1-weighted MRI template. (B) Data are Z scored with respect to healthy control values; means (SE) are presented to the right of the individual data. PDRP expression was increased in patients with Parkinson's disease (closed circles) relative to healthy controls (open circles) in the North Shore University Hospital derivation cohort ($p<2\times10^{-7}$),[14] and it was consistently elevated across six independent testing samples when scanned in a medication-free (OFF) state.[20–25] Significant PDRP elevations were also observed in Parkinson's disease cohorts who were scanned in a medicated (ON) state (USA,[26,27] South Korea)[24] and in two cohorts of newly diagnosed patients who had not yet begun drug therapy (denoted by *: USA, courtesy of Chris C Tang, The Feinstein Institute for Medical Research, Manhasset, NY, USA; Italy, courtesy of Flavio M Nobili, University of Genoa, Genoa, Italy). These results show that the underlying pathogenic changes are quantifiable regardless of the patients' disease stage or treatment state. Slight differences in mean PDRP expression scores across the different cohorts are due to group differences in disease duration and severity.

Cognitive dysfunction and other non-motor symptoms of Parkinson's disease

Cognitive dysfunction and affective or behavioural changes can appear early in Parkinson's disease but tend to progress more slowly than the motor symptoms.[53] With time, however, most patients will develop multidomain mild cognitive impairment or dementia.[53] Why cognitive deficits in Parkinson's disease evolve into dementia is not entirely clear, but the dual syndrome hypothesis posits that this evolution marks the transition from early executive dysfunction due to frontostriatal dopaminergic loss to a later posterior cortical syndrome due to cholinergic loss.[54] One of the difficulties in unravelling the biology of cognitive dysfunction in Parkinson's disease is that the neuropathology—including Lewy bodies, neurofibrillary tangles, and microvascular disease—does not correspond well to non-motor symptoms. Numerous genetic and cellular factors also make the pathology difficult to unravel by traditional molecular techniques.[55–59] In this context, network approaches have proven particularly useful.[60]

Spatial covariance analysis has revealed a distinct metabolic network underlying cognitive loss. The Parkinson's disease-related cognitive pattern (PDCP) is characterised by prominent metabolic reductions in medial frontal and parietal activity. Originally identified in a small cohort of 15 non-demented patients with Parkinson's disease, PDCP expression has since been found to rise along with increasing degrees of cognitive dysfunction, reaching the highest levels in those with Parkinson's disease dementia and dementia with Lewy bodies (figure 3).[24,40,41,62] PDCP expression consistently correlates with neuropsychological indices of executive dysfunction and deficits in verbal learning, memory, visuospatial ability, and perceptual motor speed, but not motor disability.[14,63,41] In line with the dual syndrome hypothesis, the PDCP topography involves dopaminergic and cholinergic afferents to the cerebral cortex: dysfunction of dopaminergic projections to the medial frontal cortex (represented by the anterior hypometabolic hubs of the PDCP) emerges before loss of cholinergic input to the temporal and parietal cortex (represented by the posterior hypometabolic hubs of the network).[22,41,42] Note that PDCP levels in patients with dementia with Lewy bodies and in patients with Parkinson's disease dementia are elevated to a similar degree.[24,64] Given the relative sparing of medial temporal metabolic changes in these disorders compared with Alzheimer's disease, it is not surprising

	Salient regional changes in functional activity*	Current level of validation by modality†	Research or clinical applications	Remaining needs or questions
Biomarkers for differential diagnosis and staging				
Parkinson's disease-related pattern[14,21,24,25,29,30,32,33]	Increase in the globus pallidus, putamen, thalamus, pons, cerebellum, and sensorimotor cortex; decrease in the lateral premotor cortex parieto-occipital association regions	FDG PET: generalisation; ASL, SPECT: development; rs-fMRI: prospective validation	Measure disease progression; assess therapy outcome; identify patients for clinical studies before randomisation; explore effects of new therapies	Large-scale validation at population level; measure rate of progression in prodromal states and develop algorithms to accurately predict time of phenoconversion
Progressive supranuclear palsy-related pattern (PSPRP); multiple system atrophy-related pattern (MSARP); corticobasal degeneration-related pattern (CBDRP)[23,24,34-39]	PSPRP: decrease in the upper brainstem, medial frontal cortex, and medial thalamus; MSARP: decrease in the putamen and cerebellum; CBDRP: decrease in the asymmetric frontal and parietal lobes, caudate, and basal ganglia	FDG PET: prospective validation	Classify individual patients with parkinsonism and uncertain clinical diagnosis (eg, before invasive therapy), differentiate Parkinson's disease from progressive supranuclear palsy, multiple-system atrophy, and corticobasal ganglionic degeneration; classify individual patients or trial participants before randomisation; track network progression in natural history studies	Additional cross-sectional validation in large independent samples; validate network progression through longitudinal studies
Network markers for cognitive assessment				
Parkinson's disease-related cognitive pattern[24,33,40-42]	Increase in the pre-supplementary motor area, precuneus, posterior parietal, prefrontal regions; decrease in the cerebellum and dentate nucleus	FDG PET: prospective validation; rs-fMRI: development, standardisation across scanners and protocols	Assess rates of cognitive decline at the systems level; assess treatment response at the network level; explore effects of new therapies	Additional longitudinal studies to confirm rates of network progression
Intervention-related assessment				
Parkinson's disease-related tremor pattern[14]	Increase in the anterior cerebellum, dentate nucleus, dorsal pons, primary sensorimotor cortex, and caudate or putamen	FDG PET: development	Assess treatment response at the network level; assess the effects of novel interventions on tremor	Validation across multiple scanners or laboratories; compare network topographies in Parkinson's disease tremor *vs* essential tremor
Sham surgery-related pattern[43]	Increase in the cingulate gyrus and cortex, inferior temporal cortex, hippocampus, amygdala, and cerebellar vermis	FDG PET: development	Assess brain network response to placebo or sham surgery; identify patients predisposed to developing placebo responses prior to their participation in clinical trials	Test whether specific to motor effects and sham surgery, or generalisable to cognitive responses and placebo drugs
DBS functional connectivity profile[44,45]	Increase in the supplementary motor area, anterior cingulate, and medial prefrontal cortex; decrease in the primary motor cortex	PET and rs-fMRI: development	Predict clinical outcome of DBS in individual patients with Parkinson's disease; assess non-motor DBS responses in individual patients	Prospective validation; assess contribution of anatomical connectivity to outcome prediction

Network biomarkers can be applied prospectively to new patients and datasets to generate predictions about clinical status, symptoms, and future outcomes. DBS=deep brain stimulation. FDG=^{18}F-fluorodeoxyglucose. ASL=arterial spin labelling. rs-fMRI=resting-state functional MRI. *Brain regions that drive each metabolic network are indicated or, in the case of DBS, the changes in connectivity that correlate with outcome. †We follow Woo et al[13] in classifying the stages of validation these various biomarkers have achieved—development, prospective validation (replication in a new sample), generalisation (replication across multiple scanners and laboratories), or population-level (large-scale, diverse population).

Table: **Applications of functional network patterns in patients with parkinsonism to define clinical status and predict future outcomes**

that the PDCP is topographically distinct from the independently characterised Alzheimer's disease-related metabolic brain pattern.[40,65]

Graph theory approaches have also been used in conjunction with resting-state functional MRI (rs-fMRI) to delineate network abnormalities underlying cognitive decline in Parkinson's disease. Patients with mild cognitive impairment have attenuated long-range connections but increased local connectivity (clustering and small-worldness) in the cognitive network, which parallels our observations with the motor-associated networks.[66] Combining graph theory analysis with rs-fMRI, dopaminergic imaging, and neuropsychological testing showed that executive dysfunction is associated with increased frontostriatal connectivity and disinhibition of subcortical processing, both of which are linked to nigrostriatal loss.[67] Drawing an analogy with Mink's hypothesis that the basal ganglia enable initiation and termination of motor activity,[68] it has been proposed[67] that nigrostriatal dopamine facilitates transitions between inhibition and facilitation of frontosubcortical circuits.

Network imaging also helps explain why dopaminergic treatment is often associated with behavioural side-effects, such as impulse control disorders.[69,70] Affecting up to 20% of patients with Parkinson's disease who are taking dopamine agonists, impulse control disorders have been linked to functional abnormalities in the reward network of frontal and mesolimbic circuits, such that the patient has difficulty inhibiting a dysfunctional behaviour even when they anticipate a negative outcome.[71] Tessitore and colleagues[72] followed 85 patients with Parkinson's disease

for 36 months after they began dopaminergic therapy and found that those (15 [17%]) who developed impulse control disorders showed hyperconnectivity in the salience network and reduced connectivity in the central executive and default mode networks (DMN), which could have increased their susceptibility to dopaminergic side-effects. Further studies with larger sample sizes, studying cohorts across time, or measuring network activity while engaging patients in cognitive tasks, should provide more insight into cognitive dysfunction in Parkinson's disease.

Importantly, although the metabolic network patterns correlate with certain clinical measures, PDRP and PDCP do not reflect symptoms: rather, they reflect the underlying pathology that gives rise to symptoms. The unbiased, data-driven approach employed for metabolic network pattern discovery[61,73] identifies the patterns with the greatest effect size, corresponding to the major sources of variability in the data. These topographies are generally linked to the dominant clinical manifestations of a given disorder, which in the case of Parkinson's disease are motor disability and cognitive dysfunction. Therefore, although PDRP and PDCP expression values in individual patients show reproducible correlations with motor ratings and specific cognitive tests, these patterns also reflect other clinical features not measured by the Unified Parkinson's Disease Rating Scale (UPDRS) or neuropsychological testing. Abnormal elevations in PDRP expression are detectable even before motor symptoms appear.[29,30] Measures of network progression and clinical disability thus serve as complementary, non-redundant descriptors of the underlying disease process. Other non-motor symptoms of Parkinson's disease, such as pain, depression, and apathy, are likely to be represented by smaller effects in the data, and extracting valid network descriptors of these symptoms will probably require large patient samples.

Network analysis in the clinical setting

Early detection and prediction of symptom onset

There is considerable interest in identifying markers for prodromal disease stages, which would allow novel disease-modifying therapies to be started earlier.[74] Given that roughly 50% of individuals with RBD phenoconvert to Parkinson's disease within 5 years,[75] we used network quantification to assess the likelihood of phenoconversion in at-risk individuals.[76] PDRP expression levels have been measured in four independent, cross-sectional cohorts with RBD. In each group, PDRP expression was significantly elevated relative to corresponding age-matched healthy controls.[29,30,32] On average, the various RBD groups showed levels of PDRP expression that were intermediate between values for healthy controls and patients with early-stage Parkinson's disease with unilateral symptoms (hemi-Parkinson's disease).[29,30] Long-term clinical follow-up data[29] suggest that the patients with RBD most likely to phenoconvert to Parkinson's disease or dementia with Lewy bodies already have network-level functional abnormalities at baseline. Unexpectedly, the same study[29] found that abnormally low PDRP values with negative subject

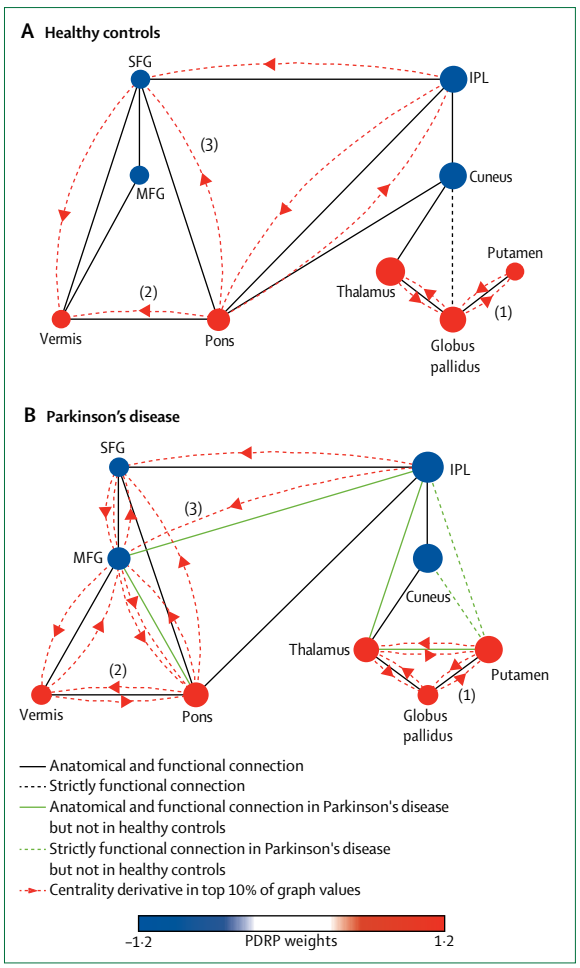

Figure 2: **Abnormal network-level clustering in Parkinson's disease**
Graph theory can identify regions within the network space in which clustering (defined by the number of triangles or closed triples formed when a node's nearest neighbours are connected) is increased in one group of patients relative to another.[10] The radius of each node is proportional to its influence on the network—ie, its centrality. For each network node, corresponding PDRP region weights were colour-coded such that metabolically active regions (PDRP weights ≥1·0) are depicted in red while relatively underactive regions (PDRP weights ≤−1·0) are depicted in blue. (A) In a group of healthy controls, three discrete sets of interconnected nodes (open triples) were seen in (1) the putamen, globus pallidus, and the thalamus; (2) the pons, cerebellar vermis, and frontal cortex; and (3) superior and middle frontal gyri, and inferior parietal lobule. (B) In the Parkinson's disease group (age-matched to the healthy controls), additional interactions (ie, edges) were detected, sealing off each of the triples as a discrete triangle (green lines). These edges denote specific node-to-node functional interactions present in patients with Parkinson's disease, but not in healthy controls. Notably, the closed triples (triangles) in areas (1) and (2) were located within the core zones identified in the structural analysis of the Parkinson's disease network.[10] These triples were formed by abnormal functional connections linking the nearest neighbours of core nodes through bidirectional, mutually facilitating interactions (red arrows). Adapted from Ko, et al.[10] by permission of Oxford University Press. IPL=inferior parietal lobule. MFG=middle frontal gyrus. PDRP=Parkinson's disease-related pattern. SFG=superior frontal gyrus.

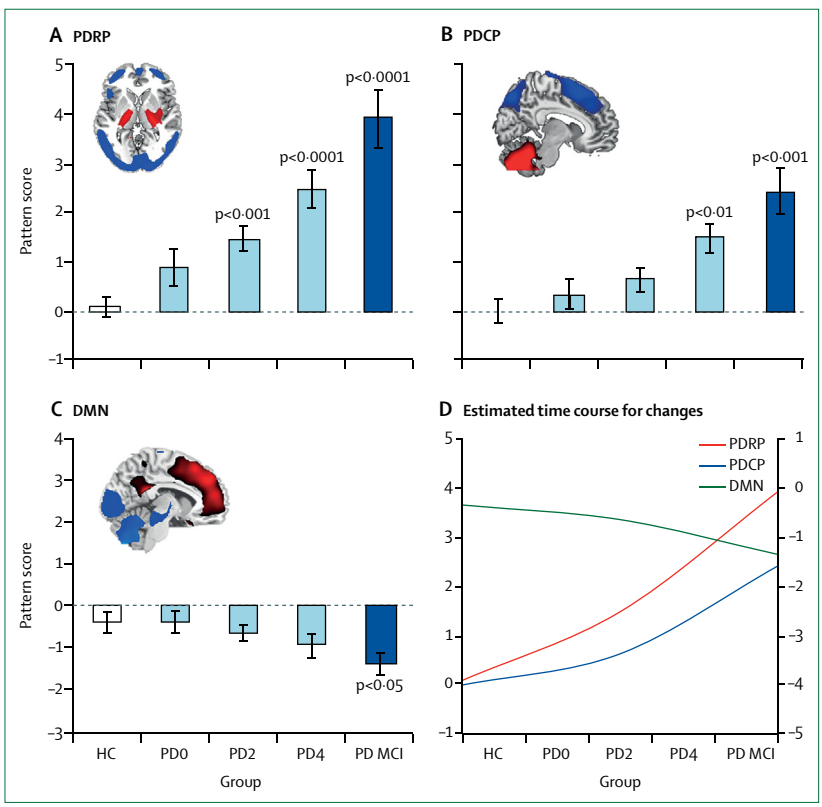

Figure 3: **Longitudinal changes in network activity in patients with Parkinson's disease**
Network expression values were measured on the Z scale for three groups of participants: healthy controls (HC, n=33), patients with advanced disease and cognitive impairment (PD MCI, n=15), and a group (n=15) of early-stage patients scanned at baseline, then 2 years and 4 years later (PD0, PD2, PD4). The mean duration of disease in this group was 2, 4, and 6 years at these three scanning timepoints.[61] Representative brain slices for each of the networks were overlaid on the corresponding T1-weighted MRI template. The y-axes denote network expression as labelled in each panel; note that in panel D the axis to the left marks PDRP or PDCP expression, whereas the axis on the right marks DMN expression. Error bars depict SE. (A, B) PDRP and PDCP expression increased over time in the longitudinal cohort (PD0, 2, 4), without concurrent changes in DMN expression. (C) DMN expression was reduced in the PD MCI group. Adapted from Spetsieris, et al.[61] (D) Estimated time course for changes in PDRP, PDCP, and the metabolic DMN in patients with Parkinson's disease with increasing symptom duration and severity (PD0, 2, 4, PD MCI) compared with age-matched HCs. PDRP and PDCP expression increased over time in patients with Parkinson's disease (main effect of time: PDRP, p<0·0005; PDCP, p<0·001; one-way repeated measures ANOVA). PDRP and PDCP showed different time courses in patients with early-stage Parkinson's disease (PD0, 2, 4), with PDCP increasing at a slower rate than PDRP (p<0·04). Reductions in expression of the DMN were not significant (p>0·11) for PD0, 2, 4, but were significant for patients with PD MCI (p<0·01). The PDCP topography contains some overlap with DMN, such that an increase in the former involves loss of the latter in advanced disease. DMN=default mode network. PDCP=Parkinson's disease-related cognitive pattern. PDRP=Parkinson's disease-related pattern.

scores herald conversion instead to multiple system atrophy, another synucleinopathy associated with RBD.

Separate RDB-related metabolic patterns (RBDRPs) have been described in two groups of patients with RBD and healthy controls.[30,77] Although RBDRP expression levels were elevated in patients with RBD, they did not differ between groups of patients with Parkinson's disease with RBD and those without it. This result suggests that the RBDRP topography is associated more with evolving synucleinopathy than with RBD per se.[77] The topographic similarity of RBDRP with PDRP, and the highly correlated expression levels observed for the two patterns, underscores the close relationship between RBD and the underlying metabolic pathology of Parkinson's disease. Longitudinal data are being analysed to assess the rate of network progression in patients with RBD phenoconverting to Lewy-body disorders.

Though network biomarkers have not yet been clinically validated for diagnosing prodromal conditions, their potential benefits are underscored by the difficulty of assessing prodromal Parkinson's disease by ordinary clinical means.[78] The criteria include risk based on age, non-motor factors (eg, RBD, olfactory dysfunction, daytime somnolence, and constipation), and clinical factors (eg, dopamine transporter imaging).[78] This approach has been validated in a prospective cohort study[79] on 121 individuals with RBD. In the study, the prodromal criteria had about 81% sensitivity and 68% specificity for conversion at 4 year follow-up. A network biomarker, alone or in combination with these variables, would provide earlier notice of phenoconversion, with less uncertainty.

Disease progression

Longitudinal studies[14,43] of early-stage and more advanced Parkinson's disease, performed in the OFF-state to avoid confounding treatment effects, have shown that PDRP expression increases continuously over time. The rate of PDRP progression is similar for different cohorts, consistent with an overall linear process (figure 3).[14,43] PDCP expression increases over time as well, but it lags behind PDRP throughout the course of disease.[40] Interestingly, metabolic expression of the DMN remains at normal levels until roughly the time that cognitive dysfunction becomes evident, along with concomitant increases in PDCP expression (figure 3).[61]

The fact that PDRP expression consistently rises before PDCP in patients with Parkinson's disease indicates that the disease process affects neural activity in the PDRP space before the PDCP space.[14] What is not clear, however, is whether PDCP progresses more slowly than PDRP, or whether PDCP simply gets a later start and the two networks progress at a similar rate. From a practical perspective, however, what is important is that both networks can be quantified in individual patients to monitor disease progression and treatment responses.[40]

Differential diagnosis

A meta-analysis[80] found that both observer-dependent and observer-independent methods using metabolic imaging were very accurate (>90%) in distinguishing Parkinson's disease from atypical parkinsonian syndromes—as long as the observers were highly experienced. Observer-independent approaches that rely entirely upon automated image-based classification are most useful when such expertise is scarce.[13] Given that the clinical diagnosis of Parkinson's disease is inaccurate in as many as 20–25% of cases,[4] the need for observer-independent approaches is clear.

Neuroimaging methods incorporating network algorithms offer the most promise for improving

differential diagnosis in patients with parkinsonism (appendix).[80–82] In parkinsonian patients with uncertain initial clinical diagnosis (n=167; final diagnosis: 96 with Parkinson's disease, 41 with multiple systems atrophy (MSA), and 30 with progressive supranuclear palsy [PSP]), accurate network-based categorisation can be achieved 3–4 years before a final diagnosis is determined by an expert clinician masked to the imaging findings.[34] These results were replicated[23] in an independent cohort from New Delhi, India (n=129; 81 with Parkinson's disease, 20 with MSA, and 28 with PSP; final diagnosis after 2·2 years); the positive predictive value (PPV) for discriminating Parkinson's disease from atypical parkinsonism was 97%, and 91% for differentiating MSA from PSP. Most (77 [60%]) of this cohort had short symptom duration (<2 years), yet both PPV and diagnostic specificity remained high (≥95%) when assessed in this group of patients. Preliminary data[35] suggest that a similar logistical categorisation approach can be used to distinguish individuals with corticobasal degeneration from their clinically similar counterparts with PSP. Since post-mortem neuropathology is seldom available to confirm diagnosis, these studies rely primarily on final clinical diagnosis after at least 2 years of follow-up by a movement disorders specialist, which shows a very high concordance with post-mortem findings and 99% PPV.[4] By this measure, network analysis is even more robust in differentiating Parkinson's disease from other parkinsonian disorders than ordinary metabolic imaging, which is already known for its sensitivity and specificity.[80,83]

Although other observer-independent classification algorithms for PET images have been examined, whether these approaches offer substantial improvement over the logistic discrimination method is unclear.[84,85] Automated structural MRI analysis methods have proven able to discriminate among Parkinson's disease, MSA, and PSP, but these studies[86–88] used small or highly selected samples and require further validation. To establish a large open-source database would be extremely useful so that the various classification algorithms could be rigorously compared.[13]

Network analysis in clinical trial design

Among the many challenges that beset clinical trials, three can now be addressed with network analysis. The first is diagnostic uncertainty: some conditions are clinically indistinguishable from Parkinson's disease but pathologically distinct, and they could confound assessment of Parkinson's disease treatments. Clearly, algorithms that improve differential diagnosis, such as those described previously, would be extremely useful in guiding selection of participants for clinical trials. In fact, the network-based classification algorithm has already been used to screen participants in a phase 2 trial of subthalamic nucleus gene therapy for advanced Parkinson's disease[36,89] and to assess patients referred for more routine antiparkinsonian interventions, such as subthalamic nucleus DBS (figure 4).[37]

A second challenge is being able to measure treatment responses with enough sensitivity and reliability to show changes over the course of the trial. Clinical indices (UPDRS motor ratings) are the primary outcome measures, but the placebo response is curiously strong in Parkinson's disease, so motor improvement alone (especially over a period of mere months) is an unreliable indicator of treatment efficacy. PDRP, however, is suppressed by clinically effective levodopa treatment in patients with Parkinson's disease[27] and in macaques receiving putaminal implants of retinal pigment epithelial cells that produce levodopa;[90] PDRP expression is also reduced by both high-frequency DBS and therapeutic ablation of the subthalamic nucleus.[14] In each of these interventions, motor outcome correlated with the degree of therapeutic PDRP modulation that was observed (even though PDRP remains elevated relative to controls). PDRP can thus be useful as an objective secondary descriptor of the treatment effect.

The importance of objective measures becomes clearer when we consider that patients with Parkinson's disease have a tendency to develop strong placebo responses, which pose a third major challenge for clinical trials. The mean placebo response can be as high as 59%, and in one review of 11 randomised placebo-controlled trials, 16% of patients with Parkinson's disease randomly assigned to be given placebo showed an improvement in UPDRS motor ratings of more than 50%, which persisted in the masked conditions of the trial for up to 35 weeks.[7,89] A study[91] turned up yet another placebo-related problem for clinical trials: previous drug therapy actually increases the bradykinetic placebo response in Parkinson's disease. Thus, clinical trials in which participants with Parkinson's disease have taken antiparkinsonian drugs will involve greater placebo responses than those with drug-naive participants. The placebo effect is probably responsible for so many treatments failing to show efficacy, but the discovery of a specific network underlying the placebo response now opens up the possibility of eliminating participants likely to respond to placebo from clinical trials.

A distinct network for placebo responses

In the process of studying treatment effects, we identified and validated a novel metabolic brain network associated with the placebo response in patients with Parkinson's disease who had participated in a double-blind sham surgery-controlled clinical trial.[43] The metabolic topography of the sham surgery-related pattern (SSRP) involves anatomical–functional pathways linking the posterior cerebellar vermis to the limbic cortex via the ventral anterior thalamus, amygdala, and caudate nucleus (appendix).[43] Baseline SSRP expression, measured before randomisation, correlates with the motor sham response that was subsequently observed under masked trial conditions (appendix). The network changes after sham treatment do not appear with experimental subthalamic nucleus gene therapy or

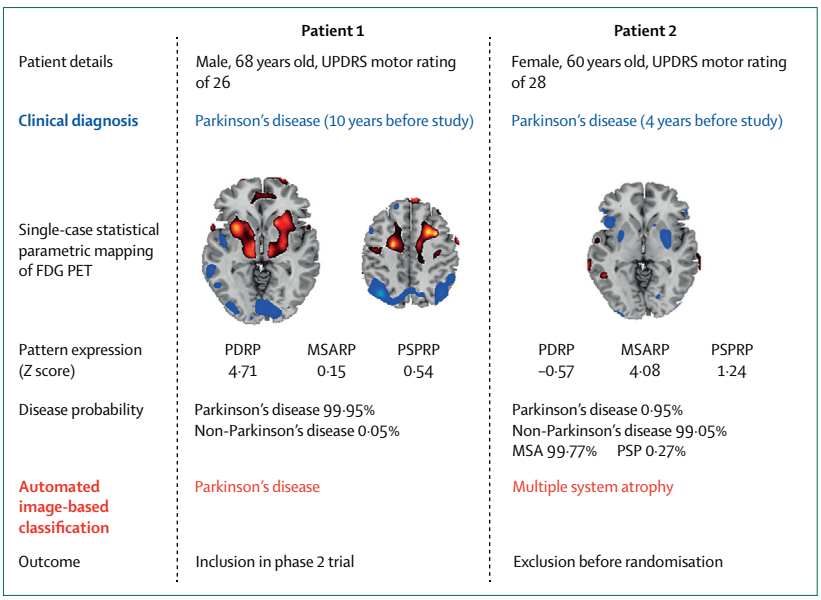

Figure 4: **Differential diagnosis in patients with parkinsonism before randomisation for a clinical trial**
An automated image-based algorithm was used to screen participants for a randomised, double-blind, sham-controlled phase 2 study for gene therapy in advanced Parkinson's disease (with glutamic acid decarboxylase, or AAV2-GAD).[89] Of the 56 participants screened, 45 were confirmed to have Parkinson's disease and enrolled in the study; automated network analysis of FDG PET images indicated that 11 (20%) patients did not actually have Parkinson's disease. Patient 1: automated image-based classification confirmed the clinical diagnosis of Parkinson's disease with a likelihood of 99·95%, revealing typical increases in metabolic activity in pallidothalamic areas. Patient 2: single-case statistical parametric mapping analysis revealed bilateral metabolic reductions in the putamen, which is not typical for Parkinson's disease. The automated image-based classification yielded a 99% likelihood of non-Parkinson's disease and a 99·77% likelihood of MSA at the second-level analysis. Based on these findings, patient 1 was enrolled in the study and patient 2 was excluded before randomisation. Metabolic increases (red) and metabolic decreases (blue) are displayed at p<0·05 (uncorrected) and overlaid on a structural MRI template. FDG=^{18}F-fluorodeoxyglucose. MSA=multiple system atrophy. MSARP=MSA-related pattern. PDRP=Parkinson's disease-related pattern. PSP=progressive supranuclear palsy. PSPRP=PSP-related pattern. UPDRS=Unified Parkinson's Disease Rating Scale.

levodopa treatment, and they are reversed by unmasking. These results strongly suggest that a resting-state metabolic brain network underlies the placebo response in Parkinson's disease.

Another group using fMRI also showed that the placebo response in Parkinson's disease involves a complex network of regions beyond the striatum.[92] In this clever study,[92] an expensive placebo produces a stronger response than a cheap placebo in patients with Parkinson's disease, deactivating the left putamen, sensorimotor cortices, and premotor cortex, whereas the cheap placebo activates the bilateral anterior and posterior cingulate cortices, left lateral sensorimotor cortex, and right parietal cortex, among other regions.

Beyond the intrinsic fascination of finding that the placebo response has a physiological basis, a practical benefit is that the expression of placebo-related topographies could be used in randomised phase 2 studies to identify individuals predisposed to developing placebo responses under masked trial conditions. To assess a treatment's efficacy in a clinical trial, the response to treatment must be distinguished from placebo responses as clearly as possible. Simulations based on published data suggest that the use of baseline SSRP to identify and exclude such patients before randomisation in early proof-of-concept studies could reduce the sample size needed for a pivotal trial by at least 50% (appendix).[43] Once a treatment is in clinical use, the placebo effect should be harnessed in the clinic to improve treatment outcomes.[93] Further research is needed to determine whether the SSRP network reflects only motor placebo effects or also underlies cognitive responses, whether it is activated only by sham surgery or also by oral placebos, and whether it is relevant to individuals who are healthy or who have conditions other than Parkinson's disease.

Development of rs-fMRI-based disease patterns

For the most part, the Parkinson's disease-related covariance patterns described in the previous section were characterised based on metabolic imaging with FDG PET. This technology, although generally available in tertiary hospital settings in Europe, North America, and increasingly in parts of Asia, continues to depend on the administration of short-lived radiotracers in the clinical setting, which limits the scalability of the metabolic network approach. Although spatial covariance mapping has been applied to cerebral perfusion imaging with the use of either single-photon emission CT or arterial spin labelling MRI,[14,29,94] these methods are somewhat less sensitive than FDG PET and might require larger samples for reliable pattern identification. The quantification of PDRP activity in perfusion scans has an additional limitation in that expression values can increase substantially in the levodopa-treated condition. Indeed, these haemodynamic effects are especially pronounced in Parkinson's disease patients with levodopa-induced dyskinesias.[27,95] A 12-h medication washout might be a more practical means of addressing this issue than an explicit correction for drug-related changes in perfusion scans.

Non-invasive rs-fMRI techniques offer a more promising approach to identifying and measuring the activity of disease-related networks.[33] An rs-fMRI-based version of PDRP (fPDRP) has been identified by use of independent component analysis and bootstrap resampling. The topography of fPDRP resembles PDRP, though some differences exist, most notably in the absence of hypometabolic regions (figure 5A). Nevertheless, pattern expression scores in those with Parkinson's disease who have undergone both types of imaging are quite similar, and fPDRP expression values reliably discriminate patients with Parkinson's disease from healthy controls in derivation and validation cohorts (figure 5B, C). As with the PET-based PDRP, fPDRP scores correlate with independent clinical ratings for akinesia rigidity, but not tremor, and fPDRP expression is reduced by levodopa treatment.[33]

Network analysis has also revealed a cognition-related topography in rs-fMRI data from patients with

Parkinson's disease (fPDCP), which resembles its metabolic counterpart in being characterised by alterations in the parietal, frontal, and temporal cortical regions, as well as the cerebellum (figure 5D).[33] Similar to PDCP, fPDCP expression values correlate with individual differences in executive function and verbal learning in non-demented patients with Parkinson's disease.[33] Further validation in independent imaging platforms and optimisation of the method (standardised duration of the scan, uniform scanning protocols, reduction of motion artifacts, etc) will be necessary before fPDRP and fPDCP can become part of routine clinical assessment.

Conclusions and future directions

Network imaging has revealed that Parkinson's disease and related neurodegenerative disorders exhibit characteristic alterations in functional connectivity that are widely distributed throughout the brain. These widespread changes help explain why the clinical manifestations of these diseases are so complex and difficult to treat. As much as they deepen our understanding of neurodegeneration, however, these network biomarkers also hold potential to improve the diagnosis and management of individual patients (table; appendix). In the case of Parkinson's disease, PDRP is now a quantifiable network biomarker that, in combination with other disease-related patterns for syndromes with similar signs, such as PSP, MSA, and corticobasal ganglionic degeneration, can improve differential diagnosis. PDCP is also an objective measure of cognitive dysfunction at the systems level. The ability to quantify the expression of these patterns in individuals enables clinicians to track disease progression and monitor responses to treatment. Nevertheless, larger longitudinal studies are needed with long-term clinical follow-up and more work on prodromal, preclinical disease (ie, RBD).

In practice, the application of network analysis will depend on extrascientific considerations, such as the availability and perceived cost:benefit ratio of functional imaging procedures. Neurologists have sometimes been reluctant to integrate PET into clinical decision making, not wanting to expose patients to radiation. Technical advances in PET instrumentation—eg, the commercial availability of high-sensitivity three-dimensional PET cameras that minimise radiation exposure, less invasive scanning protocols, and shorter imaging acquisition—have largely obviated these concerns, and this increasingly standardised procedure is beginning to be more widely available in Asia, Europe, and North America. Functional network imaging with the use of PET has thus become a realistic option for trials of new therapies for Parkinson's disease and related disorders—and possibly, in the future, for differential diagnosis and customised patient management. Network imaging has already been used to monitor treatment response in some early phase clinical trials.[36] Nevertheless, before this approach is broadly approved by regulatory bodies, more masked diagnostic studies and cost comparisons are needed.

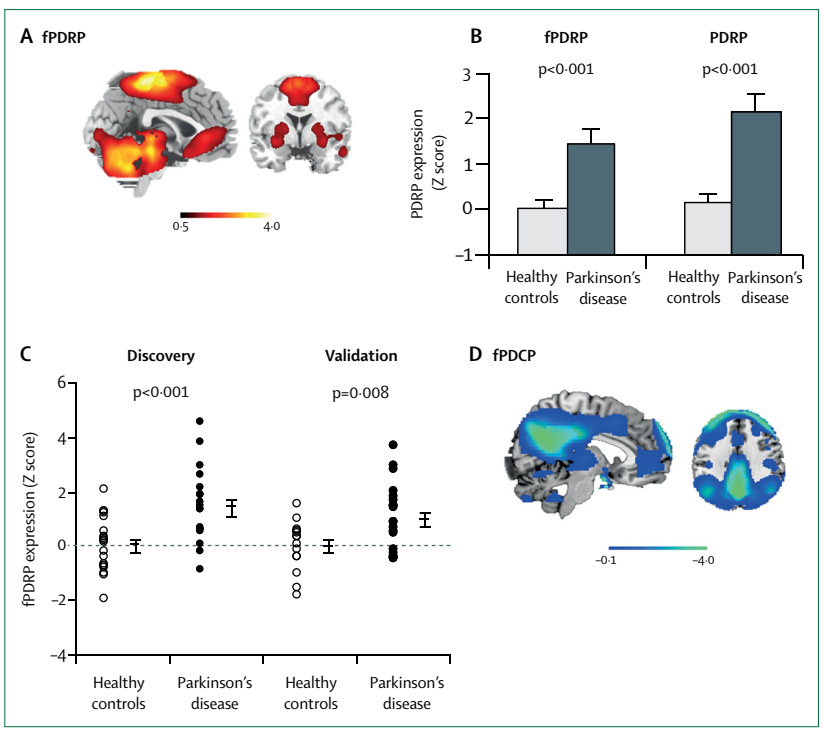

Figure 5: **Parkinson's disease-related pattern identified with rs-fMRI**
(A) fPDRP is characterised by increased activity in the basal ganglia, thalamus, cerebellum, pons, anterior cingulate cortex, and supplementary motor area (derived from 20 healthy controls and 20 patients with Parkinson's disease).[33] Activity increases (red) overlaid on T1-weighted MRI template. *Z* values thresholded at plus or minus 0·5. (B) Data are mean (SE) expression values (subject scores), which were computed for the rs-fMRI-based and PET-based network topographies in individuals scanned with both imaging techniques. Subject scores for both patterns were elevated in patients with Parkinson's disease relative to healthy controls (p<0·001). Error bars represent SE of the means. (C) Data are *Z* scored with respect to healthy control values; means (SE) are presented to the right of individual data. fPDRP expression increased in patients with Parkinson's disease relative to healthy controls in the discovery sample (p<0·001) and in the validation sample (p=0·008). (D) fPDCP is characterised by a negative correlation between pattern expression and performance on the California Verbal Learning Test (derived from 19 patients with Parkinson's disease). Negative correlations (blue) overlaid on T1-weighted MRI template. *Z* values thresholded at plus or minus 0·5. Adapted from Vo et al[33] by permission of John Wiley and Sons. fPDCP=rs-fMRI-based PDCP. fPDRP=rs-fMRI-based PDRP. PDCP=Parkinson's disease-related cognitive pattern. PDRP=Parkinson's disease-related pattern. rs-fMRI=resting-state functional MRI.

At the time of writing this Review, only the PET-derived PDRP and PDCP are suitable for use in the clinic and as secondary outcome measures in clinical trials, but MR-based counterparts of these networks are likely to become applicable in the next 5–10 years. For this to happen, more work is needed to optimise acquisition parameters for the identification of disease-related patterns, including those for atypical parkinsonian syndromes and other neurodegenerative disorders.

Several large studies are underway to assess the accuracy of automated differential diagnosis and to validate disease-related network biomarkers in independent patient cohorts. Studies are also being done to examine the influence of genetic risk factors such as *GBA* or *LRKK2* on network progression rate. Combining network quantification with genotyping might prove useful in the study of new disease-modifying therapies.

Search strategy and selection criteria

We searched PubMed for publications in English from Jan 1, 2012, to March 19, 2018, with the terms "Parkinson's disease", "PET", "brain metabolism", "metabolic networks", "functional networks", "functional brain imaging", "biomarkers", and "functional connectivity". Articles were also identified in the references cited by such articles. Abstracts and reports from meetings were included in the review only if they were peer-reviewed and presented information not otherwise available. The final list reflects papers relevant to the topics covered in the review.

Network biomarkers are likely to play an important part in the precision medicine of the future. By providing quantitative measurements in individual subjects, network imaging provides the basis for a more comprehensive, customised approach to the clinical management of neurodegenerative disorders. As drugs or other therapies are developed to slow or alter the disease course, the need to diagnose patients earlier and track their responses will become more pressing. Functional network biomarkers are well suited to meet this need.

Contributors

KAS and DE did the literature search, created the figures, and wrote the paper.

Declaration of interests

DE serves on the scientific advisory board and has received honoraria from The Michael J Fox Foundation for Parkinson's Research; is listed as coinventor of patents for markers for use in screening patients for nervous system dysfunction as well as a method and apparatus for using same, without financial gain. KAS declares no competing interests.

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Appendix

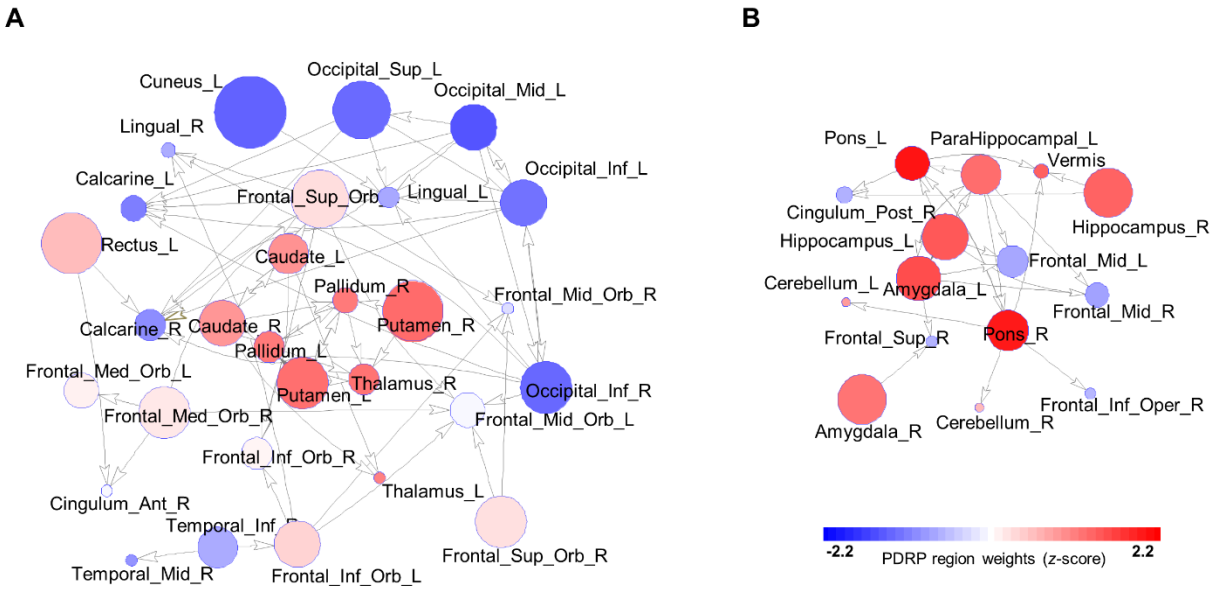
Appendix Table

Appendix Table 1. Multivariate imaging models in neurodegenerative and neurodevelopmental disorders that can be applied to individual subjects to confirm diagnosis or measure disease progression

Disease entity	Pattern and purpose	Imaging modality	References
Functional multivariate models: diagnostic			
Alzheimer's disease	ADRP (AD-related pattern)	FDG PET	1-3
Frontotemporal lobar degeneration (FTLD)	Metabolic connectivity pattern	FDG PET	4
Obsessive-compulsive disorder	OCDRP (OCD-related pattern)	FDG PET	5
Tourette syndrome	TSRP (TS-related pattern)	FDG PET	5
Functional multivariate models: pre-clinical/sub-clinical			
Huntington's disease (preclinical)	HDPP (HD progression pattern); progression in preclinical carriers	FDG PET	6
REM sleep behavior disorder	RBDRP (RBD-related pattern)	FDG PET	7, 8
Torsion dystonia	TDRP (non-manifesting DYT1 carriers)	FDG PET	5
Structural multivariate models			
Alzheimer's disease	SPARE-AD (early detection; Spatial pattern of abnormality for recognition of early Alzheimer's disease)	Structural MRI	9-11
Alzheimer's disease	ORCHID (progression; Ordinal regression characteristic index of dementia)	Structural MRI	12
Alzheimer's disease, FTLD	Dementia pattern (differential diagnosis, prediction)	Structural MRI	13
Alzheimer' disease	sMRI-BAS (amyloid beta; Structural MRI-based brain amyloidosis score)	Structural MRI	14
Huntington's disease	HD volume loss pattern (atrophy)	Structural MRI	6

Appendix Figures

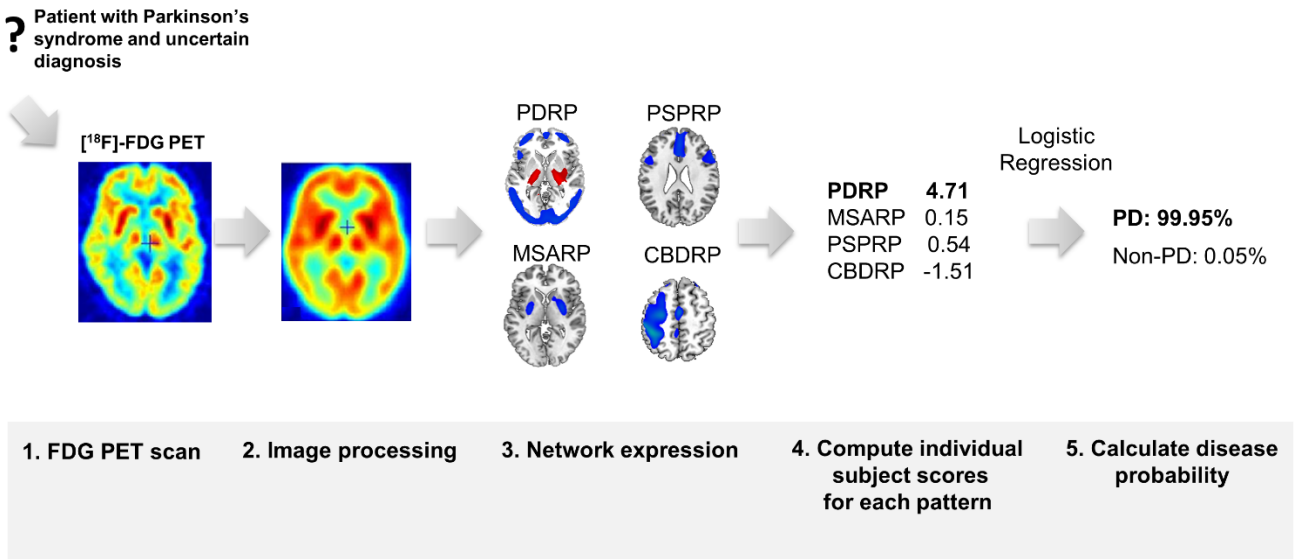
Appendix Figure 1



Appendix Figure 1. Graph theory provides insight into PD pathogenesis. Graph theoretic visualization of the most important nodes of PDRP in a PD cohort (n=33, mild to moderate motor symptoms, scanned in the "off" state).[15] This display shows two distinct nodal clusters: a prominent basal ganglia-thalamocortical subnetwork with a distinct core-periphery structure (*left*), and a smaller discrete subnetwork involving primarily ponto-cerebellar and limbic interconnections (*right*). Both clusters centered around cores defined by high-magnitude, mutually reinforcing node-to-node interactions. Interestingly, the core nodes in this display (those with high centrality or greatest importance within the network and thus positioned close to the center) correspond almost exclusively to metabolically active (*red*) PDRP regions, whereas those with lower centrality tend to be underactive (*blue*) regions. The nodes are connected by unidirectional edges (i.e., a one-way relationship between nodes, indicated by arrows). The radius of each node is proportioned to its influence within the network; the corresponding PDRP region weights are color-coded such that metabolically active regions (PDRP weights ≥1.0) are

red while relatively underactive regions (PDRP weights ≤-1.0) are blue.] [Adapted from Ko JH, Spetsieris PG, Eidelberg D, Network Structure and Function in Parkinson's Disease. *Cereb Cortex*. 2017; Oct 27: 1-15, by permission of Oxford University Press.]

Appendix Figure 2

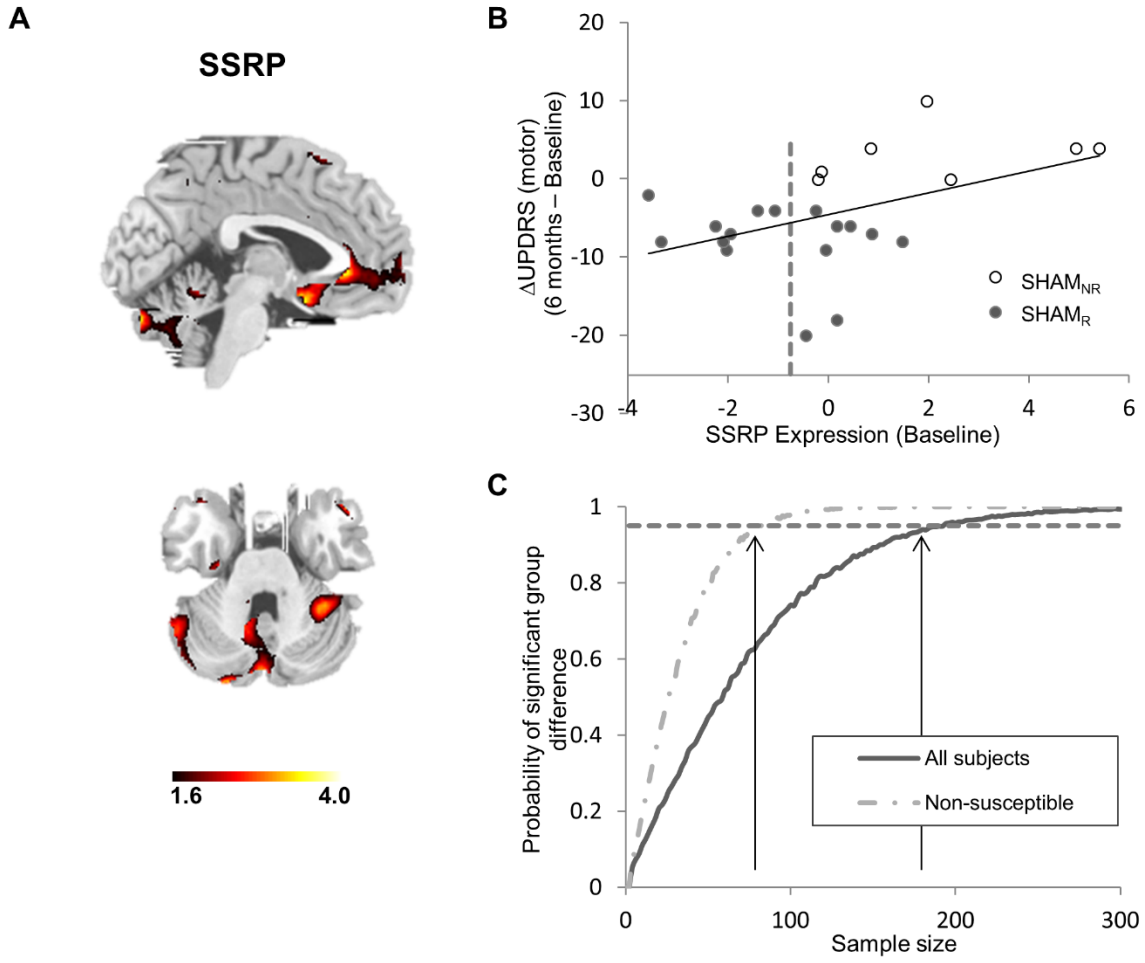


Appendix Figure 2. Metabolic network pattern can assist in differential diagnosis of parkinsonism in clinical practice. *1. FDG PET scan*: Patients with parkinsonism and uncertain clinical diagnosis can undergo [^{18}F]-FDG PET imaging to quantify specific metabolic patterns in the brain. *2. Image processing*: Raw scans are spatially normalized to map voxels (volumetric pixels, the smallest spatial unit within an image) to a common coordinate space. *3. Network expression*: Multivariate analysis enables the user to quantify the expression (activity) of a previously validated disease pattern in an individual patient.[16] Multiple independent studies (see text) have established disease-related patterns for Parkinson's disease and for three "look-alike" syndromes—parasupranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD). *4. Compute individual subject score for each pattern*: The subject score

quantifies the expression of a covariance pattern in a given individual. This measure of pattern expression is computed as the projection of the pattern onto the individual's scan data.

5. Calculate disease probability: Subject scores for the PD pattern and for the MSA-, PSP-, and CBD-related patterns computed for the unknown individual are entered into a logistic regression algorithm to determine the relative likelihoods of each condition.

Appendix Figure 3



Appendix Figure 3. Metabolic network mediating sham effect in PD patients. Network analysis of metabolic images obtained in eight Parkinson's disease (PD) patients scanned at

baseline and again, under the blind, six months after sham surgery.[17] **(A)** The resulting sham surgery-related pattern (SSRP) is characterized by increased metabolic activity in the anterior cingulate cortex, subgenual cingulate gyrus, inferior temporal cortex, hippocampus, amygdala, and posterior cerebellar vermis. The pattern is displayed as a bootstrap reliability map thresholded at Z=|1.64|, p<0.05 (one-tailed); 1,000 iterations and overlaid on T1-weighted MR template image. **(B)** Baseline SSRP expression in the sham surgery subjects (n=23) correlated with motor outcome under the blind at 6 months (r=0.459, p=0.028; Pearson's correlation). *Closed circles* represent sham responders ($SHAM_R$) and *open circles* sham nonresponders ($SHAM_{NR}$). **(C)** Monte Carlo simulations estimate the sample size needed to detect a group difference in motor outcome based upon the data obtained under the blind in a sham surgery controlled clinical trial of subthalamic AAV-GAD gene therapy for advanced PD.[18] The results of 10,000 random trials are depicted for simulations of varying sample sizes for the two groups. The simulations indicate that at least 192 randomized subjects would be needed to detect a significant group difference (p=0.05; two-tailed Student's *t*-test) in 95% of the trials—but the number fell to 84 by *a priori* exclusion of subjects with baseline SSRP expression below the pre-specified criterion. For this analysis, we chose the median baseline SSRP expression in $SHAM_R$ (-0.75; *dashed lines* in **(B)**). Participants with baseline SSRP values below this criterion exhibited more pronounced sham responses. Therefore, excluding all such "sham-susceptible" individuals before randomization lowered the required number of sham surgeries by >50%. [Adapted and republished with permission of Journal of Clinical Investigation, from Ko JH, Feigin A, Mattis PJ, et al. Network modulation following sham surgery in Parkinson's disease. *J Clin Invest*. 2014; 124: 3656-66; permission conveyed through Copyright Clearance Center, Inc.]

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