IMAGING IN NEURAL REGENERATION

The metabolic brain network in patients with Parkinson's disease based on ^{18}F-FDG PET imaging: evaluation of neuronal injury and regeneration

Over the past two decades, the development of functional imaging methods has greatly promoted our understanding on the changes of neurons following neurodegenerative disorders, such as Parkinson's disease (PD). The application of a spatial covariance analysis on ^{18}F-FDG PET imaging has led to the identification of a distinctive disease-related metabolic pattern. This pattern has proven to be useful in clinical diagnosis, disease progression monitoring as well as assessment of the neuronal changes before and after clinical treatment. It may potentially serve as an objective biomarker on disease progression monitoring, assessment, histological and functional evaluation of related diseases.

PD is one of the most common neurodegenerative disorders in the elderly. It is characterized by progressive loss of dopamine neurons in the substantia nigra pars compacta. Throughout the course of disease, the most obvious symptoms are movement-related, such as resting tremor, muscle rigidity, hypokinesia and postural instability (Worth, 2013). Currently, a definite diagnosis of PD is made by clinical evaluation with at least 2 years of follow-up (Hughes et al., 2002; Bhidayasiri and Reichmann, 2013), due to the overlap of motor symptoms between early PD and atypical parkinsonism including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). However, this classic diagnostic criterion does not benefit the early diagnosis of disease. The prognostic outcome and treatment option are substantially different between PD and atypical parkinsonism. Thus it is critical to develop biomarkers for earlier and more accurate diagnosis of PD.

Generally, appropriate diagnostic biomarker for PD ought to cover several key characteristics: (i) minimal invasiveness to detect the biomarker in easily accessible body tissue or fluids, (ii) excellent sensitivity to explore the patients with PD, (iii) high specificity to prevent false-positive results in PD-free individuals, and (iv) robustness against potential affecting factors. A PD-related spatial covariance pattern (PDRP) with quantifiable expression on ^{18}F-FDG PET imaging has been gradually detected using a spatial covariance method during the last two decades and it has been demonstrated to be the right diagnostic biomarker for PD (Eidelberg et al., 1994). PDRP has proven not only to be effective in early discrimination of PD from atypical parkinsonian disorders, but also to be able to assess the disease progression and treatment response. Thus it is considered as a multifunctional biomarker. In this review, we aim to provide an overview of the development in pattern-based biomarker for PD.

The development of PDRP

PDRP was initially recognized in 1994 by Eidelberg on ^{18}F-FDG PET imaging using a spatial covariance technique (Eidelberg et al., 1994). This method is based on Principal Component Analysis (PCA) and known as Scaled Subprofile Model (SSM). The major feature of this spatial covariance pattern was characterized by relative increases in pallidothalamic, pontine, and cerebellar metabolism, and concurrent metabolic decreases in the premotor and posterior parietal-occipital areas (Eidelberg et al., 1994). Before the SSM/PCA was employed to map metabolic alterations in local neural activity associated with PD, there already existed some cerebral functional imaging analysis method such as statistical parametric mapping (SPM) (Eckert et al., 2005). However, these univariate strategies were designed to localize significant differences between patients and controls by whole brain voxel-to-voxel searches. They are not able to capture disease-related alterations arising at the system level. Therefore, the development of the SSM/PCA, a multivariate strategy for system level analysis can overcome such a kind of limitation of univariate strategies (Niethammer and Eidelberg, 2012). Moreover, the SSM/PCA has the advantage to be able to calculate the metabolic network activity in individual patient (Eidelberg et al., 1994). The expression of PDRP has demonstrated substantial evidences relating to the evaluation of motor dysfunction based on Unified Parkinson's Disease Rating Scale (UPDRS) part 3 composite scores (Eidelberg et al., 1994). The measurability of PDRP makes it an objective tool in assessing abnormalities of cerebral metabolic changes. To date, similar PDRP has been reproduced in independent patient populations using a variety of resting state imaging techniques (Poston and Eidelberg, 2010). Our recent work conducted in a Chinese patient cohort has also confirmed the high reproducibility of this network in the identification of PD, as well as the association with UPDRS rating (**Figure1**) (Wu et al., 2013).

Role of PDRP in early diagnosis of disease

"Hemiparkinsonism" is a condition followed by asymmetrical onset of motor manifestation in patients with PD. For PD, the cerebral hemisphere ipsilateral to the initial affected limbs of hemiparkinsonian patients can be considered as "presymptomatic". The investigation emphasizing on hemiparkinsonism may provide information concerning the activity of PDRP in early phase of the disease. Based on this hypothesis, Tang et al (2010) examined 15 hemiparkinsonian patients with ^{18}F-FDG PET for three time points, *i.e.*, baseline, 24 months and 48 months, respectively. With a longitudinal evaluation of network activity, they found constant putamen metabolism ipsilateral to the initially unaffected limbs at all three time points. By contrast, putamen metabolic activity elevated progressively in the initially presymptomatic hemisphere, reaching abnormal levels only at 4 years. Moreover, PDRP scores in the presymptomatic hemisphere were found to be above the normal at the baseline, which is about 2 years before the appearance of motor signs on the opposite body side. Although it is not clear for the reason of increased network activity ahead of symptoms, these findings confirmed that abnormal increase of PDRP scores preceded the appearance of clinical manifestation, and may be useful as a biomarker for early identification of the disease for at least 2 years.

Network distinction and differential diagnosis of parkinsonism

The differential diagnosis of parkinsonism based solely on clinical evaluation is not highly reliable. According to a postmortem study, about one-third of living patients diagnosed as PD according to motor symptoms proved to have other pathologies at autopsy (Hughes et al., 1992). Among these misdiagnosed subjects, the most frequent alternative diagnosis consists of MSA and PSP. A variety of functional methods, including dopaminergic imaging, have been employed as potential aid for accurate diagnosis. However, there has been limited prospective assessment of these approaches on an individual case basis so far (Eckert et al., 2008). Nevertheless, an alternative method jointly using distinctive metabolic patterns associated with PD and atypical parkinsonism has proven feasible in differential diagnosis of the disease (Spetsieris et al., 2009; Holtbernd and Eidelberg, 2012).

Since the initial identification, MSA and PSP-related pattern (*i.e.*, MSARP and PSPRP) in 2008 have been reproduced in dependent patient cohorts (Eckert et al., 2008). In Chinese parkinsonian patients, we found that the metabolic network for MSA was associated with decreases in the putamen and cerebellum (**Figure 2**). In contrast, the features of PSPRP were characterized by metabolic reduction in the medial prefrontal cortex (PFC), ventrolateral prefrontal cortex (VLPFC), caudate nuclei, medial thalamus, and upper brainstem (**Figure 3**). Based on these distinctive metabolic patterns, Tang et al (2010) developed an automated image-based classification procedure to differentiate parkinsonian patients by calculating the probability on an individual case basis. It was reported

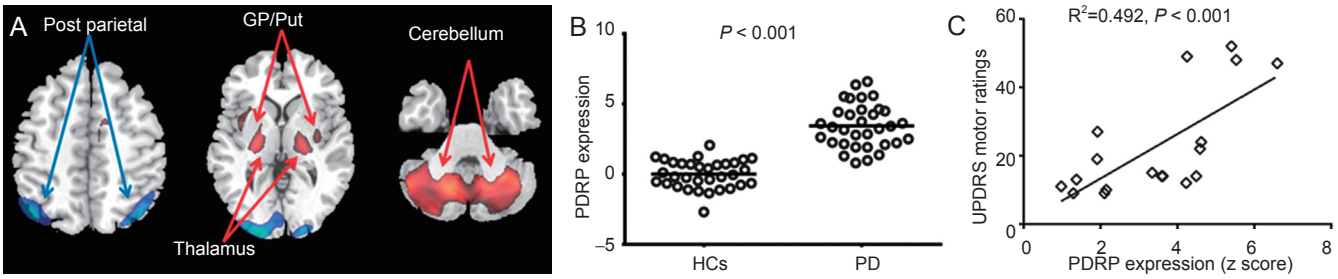

Figure 1 PD-related spatial covariance pattern.
(A) Parkinson's disease (PD)-related pattern (PDRP) identified by network analysis of ^{18}F-FDG PET scans from PD patients and age-matched normal controls. This spatial covariance pattern was characterized by metabolic increases in the pallidum, thalamus, pons, and cerebellum, associated with decreases in the premotor and posteriorparietal-occipital areas. Cerebral regions with metabolic increases are color coded from red to yellow, while those with metabolic decreases are color coded from blue to purple. (B) PDRP expression (subject scores) was increased in patients with PD relative to the normal subjects. P value was assessed by independent two sample t-test and differences in PDRP scores between two groups reached significance ($P < 0.001$). (C) Correlations between PDRP expression and clinical indicators of disease severity in PD. Subject scores in individual patients presented significant correlation with the Unified Parkinson's Disease Rating Scale motor ratings (UPDRS).

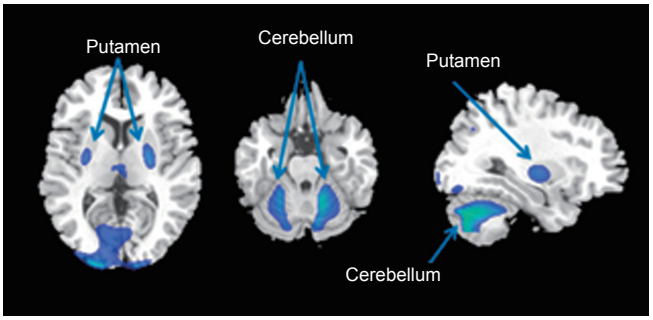

Figure 2 MSA-related spatial covariance pattern.
Multiple system atrophy (MSA)-related pattern (MSARP) identified by network analysis of ^{18}F-FDG PET scans from MSA patients and age-matched normal controls. This pattern was characterized by metabolic decreases in the putamen and the cerebellum. Cerebral regions with metabolic metabolic decreases are color coded from blue to purple.

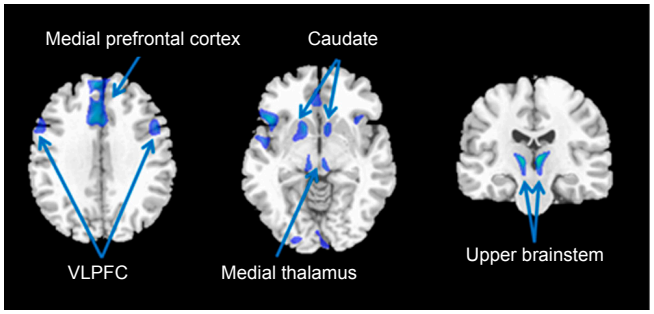

Figure 3 PSP-related spatial covariance pattern.
Progressive supranuclear palsy (PSP)-related pattern (PSPRP) identified by network analysis of ^{18}F-FDG PET scans from PSP patients and age-matched normal controls. This pattern was characterized by metabolic decreases in the medial prefrontal cortex, ventro lateral prefrontal cortex (VLPFC), caudate nuclei, medial thalamus and the upper brainstem putamen. Cerebral regions with metabolic metabolic decreases are color coded from blue to purple.

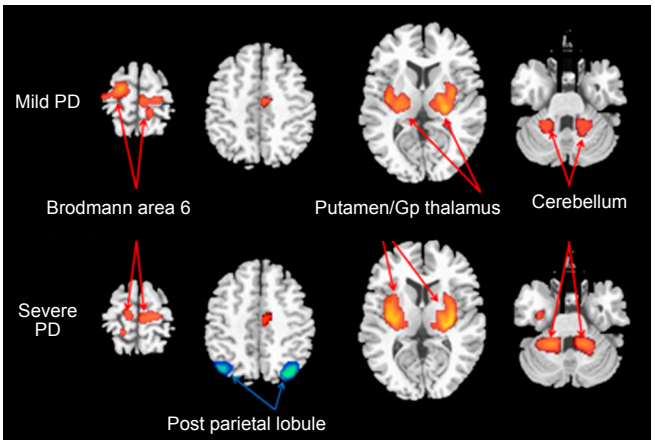

Figure 4 Comparison of abnormal cerebral metabolic regions in patients with mild and severe Parkinson's disease (PD).
In patients with early PD, cerebral hypermetabolism was detected in the thalamus, lentiform nucleus and cerebellum, while hypometaboIism was not observed in any subregions. In those with advanced PD, the hypermetabolism was also found in the thalamus, lentiformnucleus and cerebellum, with a higher magnitude in glucose metabolism rate. Meanwhile, hypometabolism was observed in bilateral parietal lobules. Cerebral regions with metabolic increases are color coded from red to yellow, while those with metabolic decreases are color coded from blue to purple.

that this image-based classification for PD for PD had 97% specificity, 84% sensitivity, 98% positive predictive value (PPV), and 82% negative predictive value (NPV). Meanwhile, the imaging-based classifications were also accurate for MSA (96% specificity, 85% sensitivity, 97% PPV, and 83% NPV) and PSP (94% specificity, 88% sensitivity, 91% PPV, and 92% NPV). These results indicated that the pattern-based differential diagnostic method has distinct values in the discrimination of parkinsonian diseases, and provides the potential help in the therapeutic decision for early-stage patients and the predicting of treatment outcome.

Changes in network activity with disease progression

The progression of PD has proven to be associated with the regional metabolic alterations in key nodes of PDRP. In our previous study, a group of PD patients (19 with early PD and 14 with advanced PD) were enrolled and scanned with ^{18}F-FDG PET. Using a transverse comparison method, we found that the presence of hypermetabolism in the bilateral thalamus, lentiform nucleus and cerebellum in the patients with early disease. In contrast, increase of glucose metabolism with a wider range and a higher magnitude were consistently observed in the similar cerebral regions in those with advanced PD. Moreover, additional hypometabolism was observed in the parietal lobule (**Figure 4**).

Longitudinal studies have been reported to investigate the changes of network activities as the disease evolved. Fifteen early stage PD patients were studied with ^{18}F-FDG and ^{18}F-FPCIT PET respectively at baseline, 2 years and 4 years (Huang et al., 2007).

The patients were also assessed by clinical motor rating scales at each time point. The study revealed that disease progression was characterized by increasing metabolism in the internal globuspallidus (GPi) and subthalamic nucleus (STN), as well as in the dorsal pons and primary motor cortex. Disease advancement was also associated with decreasing metabolism in the prefrontal and inferior parietal areas. Moreover, higher PDRP scores were observed for PD patients at baseline compared with healthy controls and the PDRP scores increased consistently over time. Changes in PDRP activity correlated with concurrent reduction in striatal DAT binding and elevation in UPDRS rating scale. These results confirmed that the pattern-related measures mentioned above varied consistently with disease progression, and therefore may be useful to monitor disease development.

Modulation of network activity by medical intervention

In addition to the assistance of the clinical diagnosis and progression monitoring, an ideal biomarker for PD is expected to reflect modulations associated with disease treatment, in particular on an individual basis. Such biomarkers will be extremely helpful for the optimization of therapeutic management, and therefore prevent unnecessary medical waste. To date, a variety of studies have confirmed distinct effects of PD treatments on network activities. These medical interventions covered almost all of the recognized treatments for PD including dopaminergic therapy (Feigin et al., 2001), subthalamic nucleus (STN) lesioning (Trost et al., 2006), as well as deep brain stimulation (DBS) (Trost et al., 2006) and gene therapy (Feigin et al., 2007). Our follow-up study on five advanced PD patients who undertook bilateral DBS of STN also reported suppression of network activity after effective intervention (Wang et al., 2010). Parallel to significant improvement of clinical manifestations in these patients, bilateral STN DBS resulted in a significant decrease in the PDRP values on an individual patient basis between OFF and ON conditions. Additionally, the treatment reduced cerebral metabolism in the right lentiformnucleus, cerebellum, bilateral precuneusand ventral thalamus, but increased metabolism in the left pons and midbrain. These results were generally consistent with the knowledge that the medically-induced metabolic reductions in cortical regions are more likely to be those relative hypermetabolic areas in PDRP, while elevations are more likely to be those regions with hypometabolism (Ma et al., 2009). The degree of network modulation by medical interventions did not differ significantly for DBS and L-dopa therapy (Asanuma et al., 2006), supporting that these effective symptomatic treatments for PD may share a common mechanism. These findings indicated that PDRP could be used as an objective measurement in the assessment of clinical treatments for diseases with motor abnormalities.

Summary

The spatial covariance metabolic pattern for PD is a relative new but generally accepted biomarker for the related disease. The preliminary studies have already proven its wide application in the diagnosis of parkinsonian patients, the assessment of clinical progression and the evaluation of clinical treatments. However, the following questions initiated from these studies remain for further investigation: (1) Whether disease-related networks for MSA and PSP can be similarly served as effective tools in the quantification of clinical progression and treatment modulation for corresponding diseases? (2) Whether the comprehensive application of SSM/PCA method can be transferred to cheaper and potentially more wildly available functional imaging modalities (*i.e.*, functional magnetic resonance imaging [fMRI]) as a replacement of expensive ^{18}F-FDG PET. (3) Novel treatments for PD, including mesenchymal stem cell therapy (Glavaski-Joksimovic and Bohn, 2013) and fetal midbrain dopamine progenitors transplantation (Thompson and Parish, 2013), have come to the forefront of the PD research field as promising neural regenerative therapies. Whether the metabolic brain network can be useful in evaluating these new forms of treatment deserves further investigation. Future researches emphasizing on these questions, will undoubtedly enhance the development of spatial covariance metabolic patterns in clinical application.

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