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REVIEW

Significance of the potential role of pharmacological MRI (phMRI) in diagnosis of Parkinson's disease

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Abstract **The initial diagnosis of Parkinson's disease (PD) is currently based on a clinical assessment. Many patients who receive an initial diagnosis of PD have parkinsonian features related to other diseases such as essential tremor, vascular parkinsonism and atypical parkinsonian disorder. It has been challenging to differentiate PD from those disorders, especially in the early disease stages, due to an overlap of clinical signs and symptoms. Therefore, there is a great need for development of noninvasive, highly sensitive, and widely available imaging methods that can potentially be used to assistant physicians to make more accurate diagnosis of the disease; and to longitudinally monitor treatment of PD. Recent advance of pharmacological MRI (phMRI) technology allows non-invasively mapping functional stages for nigrostriatal dopamine (DA) system. This article aims to review research findings primarily from our group in nonhuman primates modeling the neurodegenerative disease on the value of phMRI techniques in the diagnosis of PD.**

Keywords pharmacological MRI (phMRI), Parkinson's disease, phMRI techniques

Introduction

Parkinsons' disease (PD) is a relentlessly progressive disorder causing disability in most individuals that cannot be controlled with available medication; and is the second most prevalent neurodegenerative disease after Alzheimer's disease. It has been challenging to differentiate PD with various atypical parkinsonian disorders (APDs) such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and corticobasal syndrome despite published consensus operational criteria for the diagnosis of PD. In addition, studies have demonstrated that most patients when diagnosed with PD have already lost a significant amount of SNc DA neurons in the range of 50% cell loss. Based on detailed pathological studies, Fearnley and Lees (1991) have proposed the notion that the loss of nigral neurons would occur exponentially, with greater loss occurring within the first decade in the disease process, and reaching over 90% loss at the time of death. To date, so far, no objective measures are available for the diagnosis of PD (Wu et al., 2011) and it is unknown whether a linear relationship exists between a worsening in the Unified Parkinson's Disease Rating Scale (UPDRS), or other clinical scales, and the progressive degeneration of the nigrostriatal system. Clearly there is a need for imaging techniques that do not require any invasive procedures and radioactive isotopes, but ones that would still be sensitive enough to usefully and longitudinally monitor the development, progression, and treatment of PD. MRI appears being the ideal technique which permits high-resolution imaging of brain sites affected by PD processes, can provide valid assessment of the underlying neuroanatomical state, and is safe to allow repeated tests. Based on our own previous studies, and those of others in rodents, nonhuman primates, and humans, pharmacological MRI (phMRI; or functional MRI with specific pharmacological stimulation) would be a good candidate because of its high resolution, sensitivity, reproducibility, wide availability, and low cost (Nguyen et al., 2000; Tracey, 2001; Honey and Bullmore, 2004; Jenkins et al., 2004; Chin et al., 2008; Thiel, 2009; Rasmussen, 2010).

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Significance of pharmacological MRI (phMRI) based imaging studies in PD

phMRI in nonhuman prmiates model of PD

What is phMRI?

Ample studies have shown evidence that blood-oxygenation-level-dependent (BOLD)-phMRI can be used as a non-invasive imaging modality to detect functional changes of the dopamine system in parkinsonian monkeys (Zhang et al., 2001, 2006). More importantly, the studies were conducted in a conventional clinical MRI scanner without the injection of contrast agents. Using this imaging method, a significant correlation was found between the amphetamine-evoked BOLD response and the number of surviving dopamine neurons in the nigra, which was also significantly correlated with bradykinesia scores on the nonhuman primate parkinsonian rating scale (Zhang et al., 2006), suggesting that phMRI may be used as a biomarker to assess dopamine neuronal loss in PD. The BOLD signal has several constituents: (1) the neuronal response to a stimulus or background modulation; (2) the complex relationship between neuronal activity and triggering a hemodynamic response (termed neurovascular coupling); (3) the hemodynamic response itself; and (4) the detection of the response by an MRI scanner (Arthurs and Boniface, 2002). Our nonhuman primate phMRI studies have demonstrated that the BOLD-fMRI response to a specific DA stimulation could serve as a potential biomarker for PD because of its unique features which are different from other neuroimaging technologies as follows: (1) High sensitivity and reproducibility, and relatively high specificity, (2) Minimal invasiveness or patient discomfort ("subject friendly"), (3) Low per-usage cost (this is especially important if widespread screening is contemplated), and (4) Wide availability.

The nonhuman primate model of PD and imaging protocol used in phMRI studies

The most commonly used model of PD in nonhuman primate is developed by unilateral administration of neurotoxin 1-methyl-4-phenyl-1,2,3,6-etrahydropyridine (MPTP) through the carotid artery. The neurotoxin can specifically damage dopamine in the substantia nigra (Langston and Ballard, 1983; Nicklas et al., 1987; Richardson et al., 2007). After receiving MPTP administration, animals developed parkinsonian features often seen in idiopathic PD such as bradykinesia, rigidity, postural, and balance instability and these PD features can be partially normalized by levodopa treatment, which is the most efficacious drug to treat PD motor symptoms and is widely considered the "gold standard" treatment for the disease. Pathological results showed massive neuronal loss of dopaminergic neurons in the SNc and dopaminergic fibers in the striatum and remarkable declines in DA and DA metabolites (Ding et al., 2008). phMRI scans were performed after PD features were fully developed, which usually took 3 months. In early studies, the scans were conducted on a Siemens VISION 1.5 T MRI scanner using the body coil to transmit radio frequency and an 8 cm diameter surface coil placed above the monkey's head for RF signal reception. For later studies, images were acquired on a Siemens 3T Trio clinical MRI system using a dedicated receive-only coil for reception, which was designed and developed by our group. The BOLD-effect weighted MR images used to measure the phMRI response were acquired in an anatomically coronal plane. The image planes of the acquisition were arranged to cover the motor cortex and the basal ganglia. A segmented gradient-echo EPI sequence with TE = 28 ms and a turbo factor of 7 was used to reduce echo train length and minimize magnetic susceptibility-related artifacts. The EPI sequence acquisition parameters are FOV = 112 × 98 mm and image matrix 64 × 56 for an in-plane resolution of 1.75 mm. A total of 15 contiguous slices, each 2 mm-thick, were acquired at a rate of 15 s per EPI volume. The overall scan duration was 80 min with 128 volumes acquired prior to apomorphine (APO) administration as a baseline and 192 after APO to track the response. Images were motion corrected and spatially smoothed using a Gaussian kernel of width 3.5 mm. phMRI response was calculated as the fractional signal change in % of the average of the post-APO image data relative to the pre-APO baseline. A co-registered high-resolution (0.67 × 0.67 × 1 mm) T1-weighted anatomical MRI scan was acquired in each session for spatial localization of the activation response. Prior to the administration of d-amphetamine (2.0 mg/kg) or APO (0.1 mg/kg), a total of 40 image frames were collected over 20 min to determine the baseline state. Following injection of d-amphetamine or APO, an additional 40 frames were collected to track the dynamic response (Zhang et al., 2001; Andersen et al., 2002). The change in R_2*, i.e. ΔR_2* which represents the phMRI activation response to drug, was determined as the difference between the mean R_2* across 20 images post drug administration during the period of peak response (5–15 min) and the mean R_2* within the 40 baseline images. A reduction ("negative" change) in R_2* associated with a local decrease of paramagnetic deoxyhemoglobin is an indicator of BOLD-effect activation (Chen et al., 1996).

phMRI data collected from parkinsonian monkeys correlate with PD features

phMRI-responses correlate with severity of MPTP-induced parkinsonism

Six out of six animals responded positively to APO treatment represented by 44% improvements in parkinsonian symptoms. The same dose of APO also evoked phMRI responses by increasing the phMRI signal intensity. The typical phMRI (BOLD effect) responses to APO were gradually increased after APO administration only in the structure on the

ipsilateral side receiving MPTP administration. Interestingly, but not surprising, APO-induced behavioral changes (PD features) were significantly correlated with APO-induced phMRI responses in the putamen, premotor cortex, and cingulate gyrus. When compared with standard but objective measures, there was a significant negative correlation between the phMRI responses in the putamen and distance traveled and movement speed. Similar relationships were also seen between phMRI responses in the motor cortex and daytime home-cage activity and between phMRI responses in the caudate nucleus and movement speed.

phMRI-response correlate with histopathology

Apomorphine administration strongly activated the MPTP-denervated putamen (Figs. 1A and 2C) and substantia nigra (Fig. 2D). An opposite response (a positive ΔR_2* value) was evident in the contralateral putamen (Fig. 2G) and substantia nigra (Fig. 2H). The differences between the intact and lesioned substantia nigra and between the intact and lesioned putamen were highly significant, $P < 0.01$(*t*-test), in both cases. In contrast, ΔR_2* responses in the caudate nucleus and in the corpus callosum were not significant, nor were there significant hemispheric differences in activation or deactivation with the contralateral caudate or with a comparable region in the contralateral callosum (Figs. 2A and 2E).

The phMRI responses to amphetamine treatment in the putamen (Figs. 1B and 2G) and substantia nigra (Fig. 2H) were the inverse of those seen with apomorphine. Amphetamine-induced decreases (positive ΔR2* values) in the lesioned putamen and substantia nigra suggested diminished neuronal activity in both sites. In contrast, amphetamine induced the opposite ΔR2* response in the intact left side, tending to increase activation in the putamen and substantia nigra. The responses in the intact putamen and intact substantia nigra were significantly different from their lesioned counterparts. Again, the corpus callosum and the caudate nucleus displayed only small, insignificant changes in response to amphetamine stimulation (Figs. 2E and 2F).

In a later study, post-mortem histopathological evaluation revealed that the unilateral MPTP administration (received 5 years before the analysis) produced a massive (85%) loss of the rate-limiting enzyme for DA formation, tyrosine hydroxylase, (TH^+) cells in the midbrain on the ipsilateral side receiving the infusion of the neurotoxin. TH^+ cell numbers were significantly reduced on the un-lesioned side compared to the MPTP-lesioned side. More importantly, the number of TH^+ cells was strongly correlated with the phMRI responses in the caudate nucleus and in the cingulate gyrus. When comparing d-amphetamine-induced DA release in the putamen and DA neuron counts in the SNc, a significant correlation was also seen. In an earlier study (Zhang et al., 2006), amphetamine administration evoked a BOLD response in the SN that correlated with the number of TH^+ dopamine neurons in the same structure. These data support that there is a strong relationship between BOLD-responses to dopaminergic challenge and the number of dopaminergic neuron in the midbrain.

Similar to the effect on dopaminergic neurons, the MPTP administration also produced a remarkable reduction of TH^+ fibers on the ipsilateral side of the lesion. A comparison of the fiber density in the putamen on the MPTP-lesioned side with other elements of the cortico-basal ganglia-cortical circuit (Braak and Del Tredici, 2008) such as ipsilateral phMRI responses in the motor cortex (Fig. 3A) and caudate nucleus (Fig. 3B) showed strong correlations. In addition, the fiber density in the MPTP-lesioned caudate nucleus was strongly correlated with phMRI responses in the premotor cortex, caudate nucleus, and cingulate gyrus. Those changes in TH^+ fiber density were also correlated with behavior and DA levels in the striatum and with the number of DA neurons in the SNc.

phMRI-responses correlate with dopamine deficiency

The microdialysis experiments were conducted months after the parkinsonian symptoms had been fully developed and stabilized. First, the single administration of MPTP produced

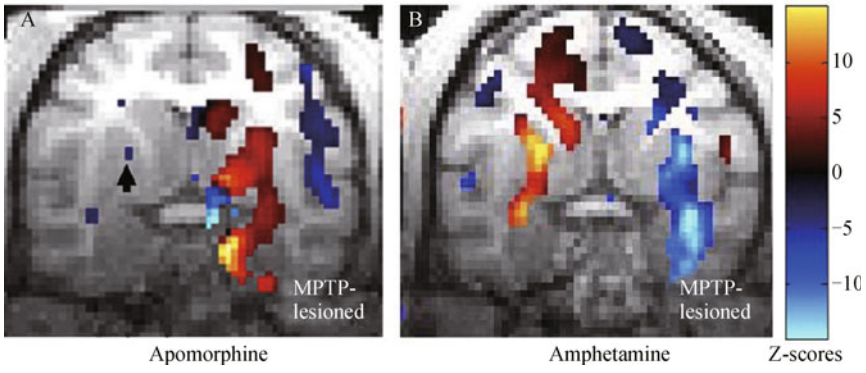

Figure 1 phMRI reveals nigrostriatal system responsiveness to dopamine stimulation. Coronal MRI scans depicting areas of activation and deactivation (represented by the pseudocolor) in the brain after an APO or amphetamine challenge in unitalteral MPTP-lesioned nonhuman primates (Zhang et al., 2006).

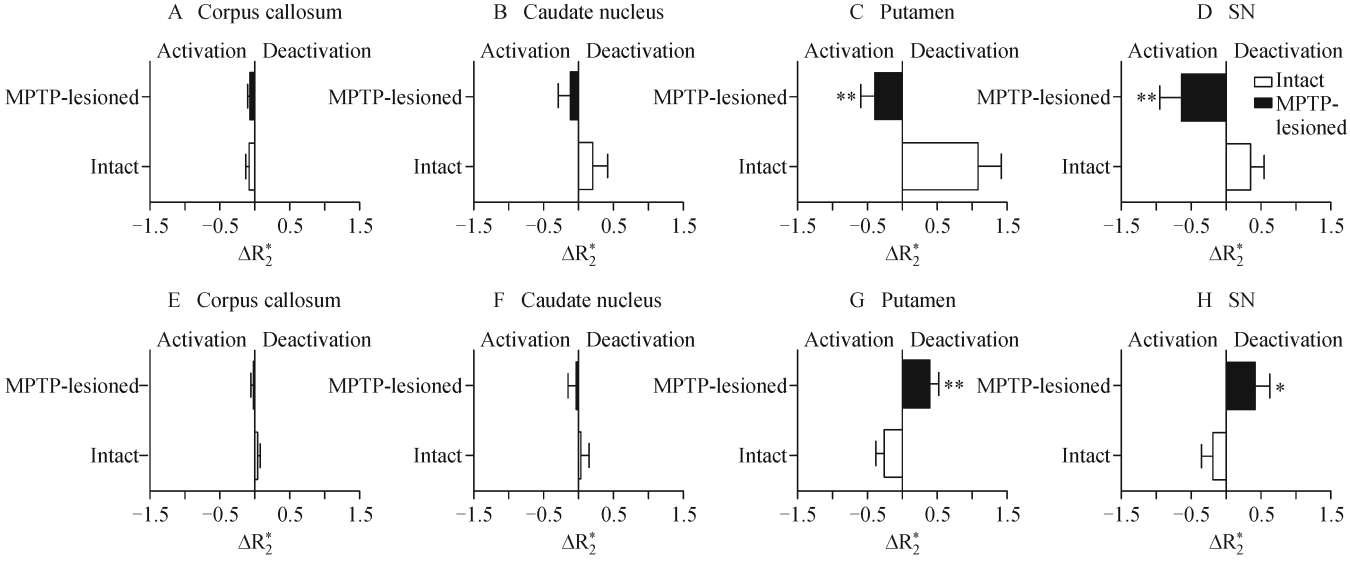

Figure 2 phMRI responses in the nigrostriatal system. Depending on the means of stimulation, phMRI reveals a differential activations and deactivations in the nigrostriatal system. After APO stimulation (A–D) or d-amphetamine stimulation (E–H). **: $P < 0.01$; *: $P < 0.05$; unpaired *t*-test (Zhang et al., 2006).

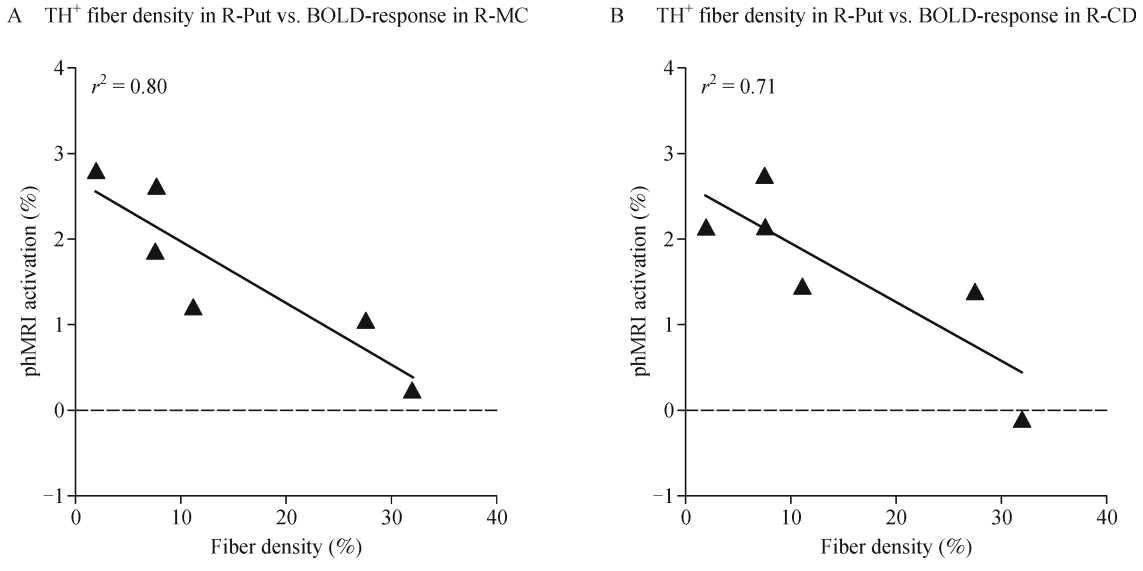

Figure 3 Lower TH^+ fiber density in the ipsilesional putamen corresponds with higher phMRI activation. TH^+ fiber density in the right putamen (R-Put) is inversely correlated with phMRI activation in the right motor cortex (R-MC) (A) and the right caudate nucleus (R-CD) (B).

significant reduction in both potassium- and d-amphetamine-evoked overflow of DA in the putamen (Fig. 4A) and SNc (Fig. 4B) on the ipsilateral side of the lesion. Second, there were several important correlations between DA levels in the putamen and SNc and the phMRI responses. For example, both potassium- and d-amphetamine-evoked overflow of DA in the putamen (each measured for a single time point, 30 min after stimulus administration) had significant correlations with phMRI responses in the putamen. DA levels in the putamen were also significantly correlated with phMRI responses in the premotor cortex and cingulate gyrus, as well as in the caudate nucleus. Finally, d-amphetamine-evoked DA release in the SNc was found to have a significant, but negatively correlated relationship with the motor cortex (Fig. 5).

Conclusions and perspectives

Since a diagnosis of PD still solely depends on the judgment

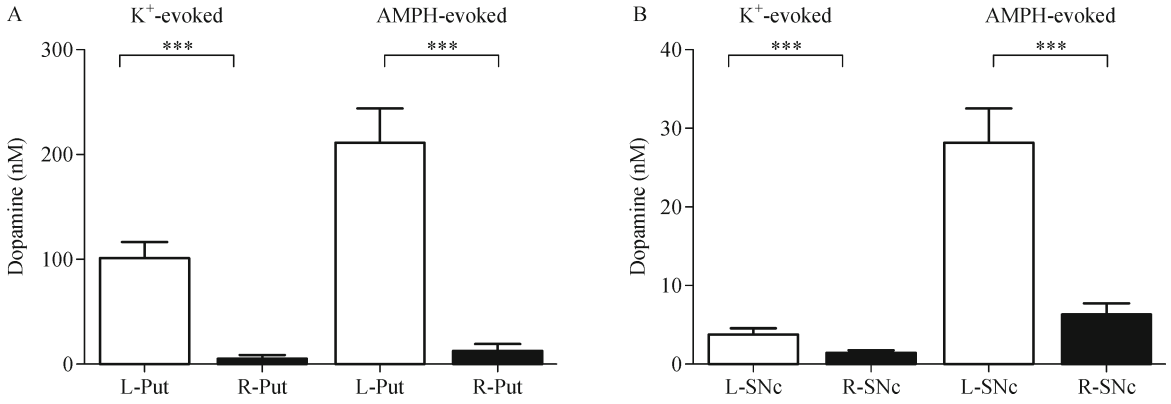

Figure 4 Hemiparkinsonian nonhuman primates have markedly diminished dopaminergic function. K^+ (100 mM)- and amphetamine (250 μM)-evoked DA release was significantly attenuated in the ipsilesional (A) putamen (Put) and (B) SNc; ***: $P < 0.0001$ (paired *t*-test).

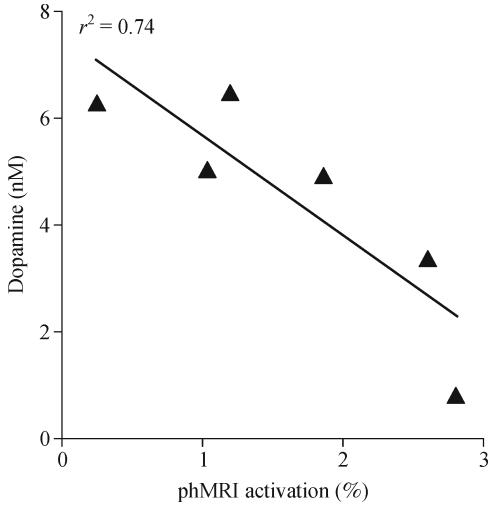

Figure 5 DA levels in the right SNc correlate with the BOLD responses in the right motor cortex. In animals with lower DA levels in the right SNc, less activation was observed in the right motor cortex

of the clinician, there is an urgent demand for the development of reliable and applicable test systems or biomarkers to provide a level of certainty to the diagnosis. Objective biomarkers of PD are pivotal to tracking the disease progression and confirm the therapeutic effects. Non- or minimally-invasive imaging techniques provide a unique, real-time opportunity to assess the changes that occur with neurodegenerative diseases. In addition, with the rapidly expanding use of fMRI to provide a dramatically greater understanding of brain function, imaging techniques such as phMRI are only bound to benefit from this new wealth of knowledge. The advantage of MRI is that MRIs are far more widely available than other imaging modalities and are most commonly used in clinical practice to differentiate idiopathic PD from secondary cause of parkinsonism (Pavese and Brooks, 2009). Recent advancement in high field MRI technology offer even better opportunities for noninvasively, longitudinally, and objectively assessing brain alterations in PD. For example functional and pharmacological MRI has been increasingly employed for preclinical and clinical research of the disease. Ample evidence supports that MRI signals have the potential to be developed as a noninvasive state biomarker in PD. For example, several MRI methodologies such as structural MRI, imaging of brain iron, DTI, functional MRI and pharmacological MRI have provided meaningful insight of brain alteration in PD. That said, we note that while we have gained greater understanding of the changes that occur in disorders of dopaminergic dysfunction with the use of phMRI in the rhesus model of PD, nevertheless the studies are work in progress and ones that still require cautious interpretation because conditions in patients with PD are more complex than in the animal model used in these studies.

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