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 assist 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

Parkinson’s 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).
phMRI in nonhuman primate 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 bradykininess 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-tetrahydropyridine (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 bradykininess, 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 R2*, i.e. ΔR2* which represents the phMRI activation response to drug, was determined as the difference between the mean R2* across 20 images post drug administration during the period of peak response (5–15 min) and the mean R2* within the 40 baseline images. A reduction (“negative” change) in R2* 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