Function MRI Studies of the Effects of MPTP-Lesions on the Nigrostriatal System of Awake Rhesus Monkeys

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Introduction
Parkinson’s disease (PD) is characterized neuropathologically by a progressive degeneration of mesencephalic dopamine neurons, resulting in a severe depletion of dopamine in the basal ganglia. The possibility of using the functional MRI (fMRI) to investigate the phenomenon is attractive, largely because the technique of fMRI is noninvasive and does not require any radioactive agent involved, as PET does. Our group has demonstrated that fMRI can be used for mapping apomorphine-induced activation of the nigrostriatal system in normal awake and anesthetized parkinsonian rhesus monkeys (3,5). In present study, we hypothesized that fMRI can detect functional changes of dopaminergic circuits in the basal ganglia after unilateral MPTP lesion and fMRI signal correlates with behavior. fMRI can be utilized to noninvasively follow functional changes in the nigrostriatal dopamine system in animals showing behavioral recovery from various drug therapies.

Methods
Animals: Eight female rhesus monkeys (Macaca mulatta), age between 13-15 years old were used in the study. Under general anesthetic condition, MPTP (0.4 mg/kg) was administrated through right carotid artery with a 27-gauge butterfly needle at the rate of 2 ml/min. Behavioral changes after MPTP were evaluated by using the standard videotaped test (4). For the L-dopa testing, Sinemet 500mg (10:1 levodopa/carbidopa) was given by oral gavage with lightly sedated with ketamine. 

fMRI Procedures: The animals were adapted to a MRI compatible chair, constructed from non-ferromagnetic materials and designed to comfortably position an adult rhesus monkey within the magnet bore. The head holder was modified from that previously described (5). Under local anesthetia (1% lidocine 2.5 ml on each side), two MRI compatible pins were inserted through the overlying skin and fascia to contact the boy cranium. The advantage of the modified hold is compatible pins were inserted through the overlying skin and fascia to contact the boy cranium. There was no surgical procedure involved for the current study. The scans were conducted on a Siemens VISION (VB33A) 1.5 T MRI scanners using the body coil to transmit radio frequency and an 8 cm surface coil placed above the monkey’s head for RF signal reception. The functional MR images were acquired continuously using a Flash 2D Navigaion sequence. The Flash 2D acquisition parameters were: TR=250 ms, TE=67.2 and 13.39 ms, image matrix size = 112x128, field of view =128 mm, slice thickness = 3 mm, flip angle = 40°, bandwidth = 156 Hz/pixel.

The anatomic structures of interest were visualized using a 3D FLASH sequence with isotropic resolution (TR/TE=21/6 ms, flip angle = 30°, image matrix size = 128x128x90, field of view = 128). For each animal, 20 minutes of baseline imaging data was acquired, after which 0.1mg/kg apomorphine was injected subcutaneously, data collection was resumed for another 20 minutes.

Data Analysis: ROIs were selected manually for three structures (caudate nucleus, putamen and substantia nigra) in each of the left and right hemispheres. The ROIs were 3x3x3 mm each, representing a 27-mm3 volume. Calculation of R2* values was carried out on a pixel-by-pixel basis by fitting the gradient echo signal decay to a first-order model (R2* = ln(S0) - ln(S) / R2*TE). Prior to administration of any drug, a total of 40 time frames were collected over 20 min for the baseline state. Following injection of apomorphine or amphetamine, an additional 40 images were collected to track the dynamic response.

Principal component analysis (PCA) was used as a filter to identify and subsequently remove confounds in the time-series data such as periodic signal components due to aliased biorythms and respiration (12). Information in the navigator echo data from all three echo data was used to detect and subsequently discard image time frames where motion had occurred during the acquisition. From the filtered data, the change DR2* representing the fMRI activation response to apomorphine was determined as the difference between the mean R2* value across 20 images post drug during the peak response and the mean value within the 40 images acquired as baseline prior to injection.

Discussion
The present study was consistent with our previous study (Zhang et al., 2000), dopaminergic neuronal activity in the normal and MPTP-lesioned rhesus monkeys could be directly visualized after APO administration. Prior to MPTP-lesions, activations were seen in all three structures (caudate nucleus, putamen and substantia nigra) evaluated in this study, however, there was no hemisphere effect was seen in those animals. Post MPTP-lesions, activations were only seen in the lesioned side of striatum, while responses in the other direction were seen in the intact side. There was a strong hemisphere effect. The results of the present study are consistent with receptor supersensitivity being an important factor in the modulation of striatal fMRI responsiveness to APO. Different responses to APO in the intact side may reflect the changing regulation of dopamine release and reuptake at the dopamine terminals to compensate for the low dopamine levels in the contralateral basal ganglia.

References