

Gender dependent response of dopaminergic administration in Parkinson's disease: a fMRI study

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Introduction: Parkinson's Disease (PD) is a neurodegenerative disorder leading to motor dysfunction. The tremors in PD can be attributed to the striatal dopamine depletion (70-90%) in the substantia nigra and basal ganglia that disrupts the corticostriatal balance leading to increased activity in the indirect circuit and reduced activity in the direct circuit (Whone et al. 2003, Obeso et al.2008). The abnormal activation of primary motor cortex could be normalized to an extent by dopaminergic replacement (Haslinger et al.2001). Using Functional magnetic resonance imaging (fMRI) we wish to determine whether the effectiveness of dopaminergic therapy is gender influenced.

Materials and Methods: Eighteen right handed patients (table 1), and 8 healthy controls were recruited from the movement disorder clinic of our institute. Standard diagnostic and exclusion criteria were followed. Two functional MRI scans were conducted at 1.5T (Magnetom Avanto, Siemens, Erlangen, Germany); one in the practically "off" state (i.e. after 12 hours of last dopa administration) and the other after 2 hours of dopa administration in the "on" state. Single-shot echo planar imaging sequence was used for the BOLD studies with number of slices: 31, slice thickness 4.0 mm; TR: 4000 ms, TE: 44 ms, FOV: 230mm, resolution: 128 x 128. The design was a simple finger tapping exercise (minimum tapping frequency 1 Hz) during the active state, and rest in baseline in four alternating cycles. Pre- and post-processing was carried out on an offline server using SPM2 (Wellcome Department of Cognitive Neurology, London, UK). The Bold activation pattern was overlaid onto the 'mni' template and coordinates were estimated using the Talairach and Tornoux atlas. One way ANOVA (p<0.001, cluster threshold 5) was used for group analysis, while paired t-test was carried out for comparing the results during "on" and "off" states.

Table 1. Demographic profile and clinical evaluation of subjects

Type	Subjects	Subjects detail	Age	Disease Duration	Mean daily dopa intake	Stage of the disease	MMSE	UPDRS III
PD	18	11 M 7 F	59.8 ± 14.3	6.53 ± 3.5	712.5 ± 303.5 mg	H & Y 1.7 ± 0.61	27.2 ± 2.67	20.5 ± 10.8
Controls	8	5M 3F	48.6 ± 5.2	-	-	-	29.0 ± 1.0	-

Results: PD patients did not exhibit any activation of the primary motor cortex and supplementary motor area during the off state, instead activation in the right occipital cuneus (BA 18), and left inferior parietal lobule (BA 40) and superior frontal gyrus (BA 8) were observed. On dopa administration, the primary motor cortex (BA 4) and supplementary motor (BA 6) area were activated. Also, right cerebellar involvement was observed (figure 1).

During gender distinguished analysis, the "off-state" in male subjects showed activation in the left pre- and post-central gyrus (BA 6) apart from the left superior frontal gyrus (BA 8) and left inferior parietal lobule (BA 40) and right superior temporal gyrus (BA 42). During the "on-state" in male patients, maximum activation was observed in the left pre-central gyrus (BA 4) and left middle, medial and superior frontal gyri (BA 6). In female subjects, the cerebellar activation was observed both in the "off" and "on" states. Major activation was observed in bi-hemispheric supplementary motor area (BA 6) and occipital gyri (BA 18, 19), though left primary motor cortex (BA4) was also activated in the off state. The female patients in the 'on-state' showed improved primary motor cortex activation (BA4) and reduced supplementary motor area (BA6) interestingly, right supplementary motor area was suppressed.

Discussion: Basic movement parameters such as rate of tapping are believed to be controlled by sensory motor cortex, while higher order finger tapping movements involves prefrontal cortex (Rao et al.1996). We observed a hyperactivity in primary motor cortex in patients. The male patients had no BA4 activation in 'off state' (table 2). The activation in BA 6 increased in males while it reduced in female subjects. The cerebellar activity was profound in females but present only in 'on state' in males. The PD patients use the lateral premotor cortex to compensate for the hypofunction in the striato-frontal cortex even for a simple task (Haslinger et al. 2001). Dopaminergic administration has restored the motor function in male as well as female patients. The PD patients have been shown to employ cerebellar- thalamic pathway to compensate for the basal ganglia motor loop, more so in females patients (Ivry et al.1996).

References:

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Brain areas		Cluster count			
		Males		females	
		Off	On	Off	On
Primary motor cortex	BA 4	-	246	81	304
Supplementary motor area	BA6	20	143	531	50
Superior posterior gyrus	BA8	63	-	-	-
Inferior parietal lobule	BA 40	46	-	-	33
Cerebellum		-	61	433	450

Fig.1. The brain activation pattern showing difference in activity in the primary motor cortex (PMC) and supplementary motor corte (SMC) in response to dopaminergic administration.

