Effects of Levodopa administration on cerebral functional connectivity

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Purpose

Low-frequency BOLD signal fluctuations are thought to be related to spontaneous neuronal activity in the resting human brain, and appear to be synchronized between functionally related areas (1). The purpose of the present study was to determine whether cerebral functional connectivity is altered in healthy volunteers following administration of Levodopa (L-dopa), a metabolic precursor of dopamine. We hypothesized that L-dopa would modulate connectivity in the dopamine cortico-striato-thalamic system.

Procedure

Sixteen healthy subjects participated (mean age 26.2; SD 3.9, 8 female). Informed consent was gained prior to the start of the study, which was conducted according to ethical requirements. Subjects were randomly assigned either placebo or 100mg L-dopa in session 1 and the remaining treatment in session 2 at least one week later. Subjects were instructed to close their eyes, relax and make no voluntary movements during the scan session. Blood pressure and heart rate measures were obtained at drug intake, prior to and just after the imaging session.

Measures

The MRI scans were collected using a 4T Bruker MedSpec system, with a TEM head coil. A total of 200 brain volumes showing BOLD contrast were acquired with gradient echo EPI (TE 30ms, TR 2100ms). Each volume consisted of 36 slices, 3mm x 0.6 mm gap, and in-plane resolution of 3.6mm. A high-resolution MP-RAGE 3D T1-weighted image was acquired within the same session (TI 700ms, TR 2500ms, TE 3.83ms, resolution 0.9 x 0.9 x 0.9mm).

Image processing was performed using statistical parametric mapping software (2).

• Bilateral areas of the thalamus and striatum were anatomically defined (3) as separate seed regions of interest (ROIs) for use in the analysis.

• The mean time-series extracted from each ROI was used as a covariate in a whole-brain linear regression analysis.

• Contrast images of this regressor were generated for each participant for each condition (placebo and L-dopa).

• Difference images were generated (L-dopa minus placebo), and random effects analysis was performed using iteratively re-weighted least squares fitting (RLLS) (4).

• Voxels with p < 0.001 (Z > 3.09) within a cluster of five or more contiguous voxels were considered significant.

Results

The striatum and thalamus were strongly correlated with a number of regions in both placebo and L-dopa only conditions. The comparison of conditions showed a subset of areas that responded preferentially to L-dopa. With the striatum as seed ROI, increases in signal were seen in the left occipital cortex and right prefrontal cortex (Fig 1, Table 1). With the thalamus ROI, areas included the right inferior parietal and left dorsal prefrontal cortex (Fig 2, Table 2).

Discussion

Although it is not unusual for drug modulated connectivity studies to show changes in areas that are not part of the specific drug pathway under investigation, (5) all areas that showed positive changes in connectivity with L-dopa here are known to contain dopamine receptors (6). Dopamine receptors do exist within the occipital cortex, although they are scarce.

The striatum showed significantly modulated connectivity on L-dopa in the middle occipital gyrus and middle frontal gyrus, which are areas typically associated with vigilance. The foci in the middle frontal gyrus lay within the frontal eye fields (BA 8), a region that has previously been linked with dopamine availability, having shown increased rCBF with amphetamine administration in healthy volunteers, as measured by SPECT (7).

The thalamus showed greater connectivity with the medial dorsal nucleus, right inferior parietal lobe and the premotor cortex (BA 6). Lesions within the medial dorsal nucleus are accompanied by executive dysfunction (8), whereas lesions within the right parietal cortex lead to poor visuo-spatial abilities (9).

Finally, previous PET studies showed no global blood flow changes due to L-dopa(10). Similarly, fMRI studies with dextroamphetamine and methylphenidate indicate that the BOLD neural-hemodynamic coupling is not altered with dopaminergic drugs (11). In the present study, heart rate and blood pressure remained consistent between L-dopa and placebo, which may be interpreted as indicating there were no general blood flow alterations within this study that might account for the results we observed.

Summary

The results are indicative of the striato-cortical and thalamo-cortical connections. Pharmacological modulation with L-dopa seems to enhance connectivity in regions classically associated with attention/vigilance. These results confirm the viability of fMRI as a marker of pharmacological modulation of functional connectivity.

References


