MEMRI reveals functional changes in Basal Ganglia output nucleus in Parkinson's disease

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Introduction: Parkinson disease (PD) is characterized by neuronal malfunctions originating in the basal ganglia (BG). Understanding the neuronal changes underlying the disease is dependent on combining both anatomical and functional neuronal information. The unique characteristics of manganese-enhanced MRI (MEMRI) were utilized to follow dynamic connectivity changes in the 6-OHDA rat PD model. $MnCl_2$ transfer was followed between the BG input nucleus (the CPu) and it's affiliated subcortical nuclei, mainly the output nucleus - the substantia nigra (SN).

Materials and Methods: Twelve Sprague-Dawley rats (6 controls and 6 unilateral 6-OHDA lesion rats, 225-275g) were used in this study. Both groups received intracranial $MnCl_2$ injections (0.2µl of 0.06M solution) into the CPu (A -0.9; L -4.3; V -6.2 mm from dura). T1-weighted coronal images were acquired with a 4.7T Bruker BioSpec system using a gradient-echo sequence (TR=58ms, TE=3.1ms, matrix=256×192, FOV=3cm, NR=100). Scan schedule: pre-$MnCl_2$ injection (baseline), 3h, 24h, 48h and 72h post injection. Dopaminergic lesions (above 90% cell loss in the CPu) were confirmed by apomorphine-induced rotational tests and tyrosine hydroxylase immunohistochemistry.

For each animal, T1 images were aligned and normalized to baseline. Principal component analysis (PCA) was preformed on the aligned data. For each principal component (PC), ROI was defined as an assembly of voxels having a significant contribution (above 3 standard deviations of that PC contribution at an irrelevant brain location). To maintain similar PC weighting and shape across data sets, PCA was performed only over the brain, excluding non-relevant areas such as major blood vessels, ventricles or the ear artifacts.

Results: Signal enhancement was observed in the injection site as well as in various locations known to be neuronally connected to the BG circuit. PCA identified two temporal patterns that are common to many brain areas; the first is described by an initial plateau followed by a sharp ascending slope and a slow (or none) descent (termed hereafter- PC1. See fig. 1(A) top panel). The second pattern displays a sharp increase followed by a sharp decrease (termed PC2. See fig. 1(A) bottom panel). More than 80% of the temporal variance in our data was described by PC1 and PC2, with the major component being PC1. An exception to this finding was at the injection site, where as expected, most of the voxels behaved according to PC2, having a prompt steep slope. This was used to semi-quantify injection volume assuming a linear relation between PC2 and Mn^{2+} diffusion volumes. No significant differences in injection volume were found between or within groups. In both groups signal increase was observed in BG nuclei (such as globus palidus (GP) and SN), the habenula (Hab) and various thalamic nuclei. Significant differences between the PD and control groups were found only in the SN and Hab. In the Hab, PC1 described mainly the control group whereas PC2 was typical to the PD group. Also, the volume of PC1 in the control group was significantly higher than PC2 in the PD group. The most interesting results were obtained from the *SN*. Both groups were similar in both PC2 weight and volume (shown in Fig. 1(B) bottom panel, group comparison (C) & (D)). They differed in the volume characterized by PC1. Although the averaged weight of PC1 did not change between groups, the number of voxels was significantly lower in the PD group compared to the control group ($p<0.05$, Fig 1(B) top panel, (C) & (D)). The reduction was localized to the ventro-medial SN aspect.

Conclusions: When comparing control and PD groups, changes in BG connectivity were observed in the SN and in the Hab. Regarding the SN, our results suggest that the connections between the CPu and the SN are characterized by at least two independent mechanisms: one described by PC1 and the other by PC2. Although both exist in control and PD groups the disease affects one (PC1) but not the other. Moreover, since only the PC1 volume is affected by the disease and not its weight, we conclude that this difference reflects localized reduction in connectivity between nuclei. Hab changes are currently under investigations.

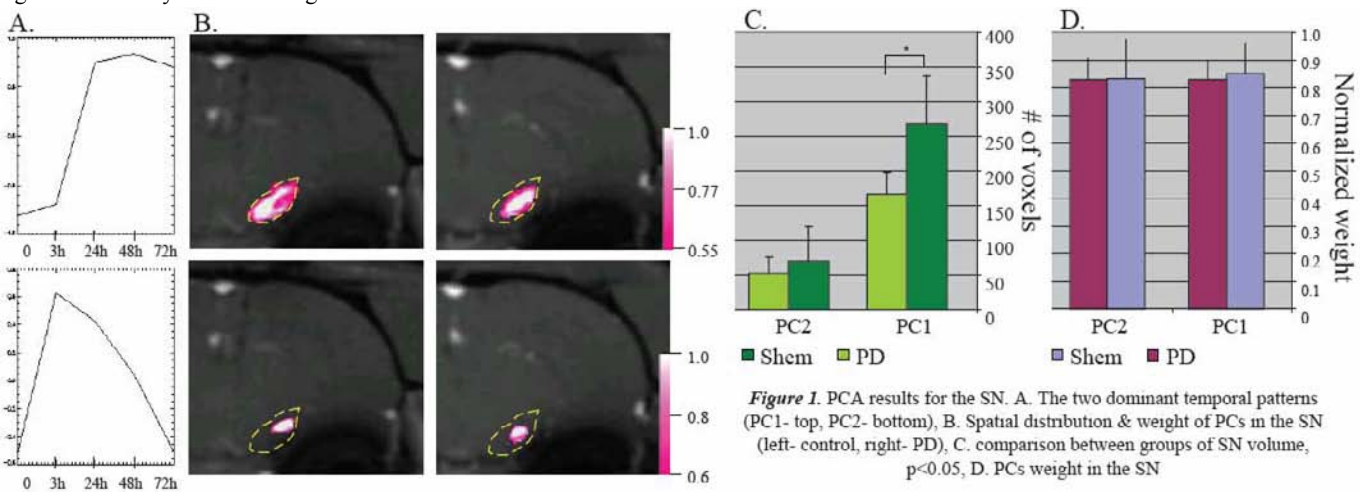

Figure 1. PCA results for the SN. A. The two dominant temporal patterns (PC1- top, PC2- bottom), B. Spatial distribution & weight of PCs in the SN (left- control, right- PD), C. comparison between groups of SN volume, $p<0.05$, D. PCs weight in the SN