Whole-Brain Metabolic Profiling of Patients with Parkinson's Disease Using High-Resolution MR Spectroscopic Imaging

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Target audience: Those who are interested in the applications of MR spectroscopic imaging (MRSI) to study metabolite alterations in neurodegenerative diseases.

Purpose: To detect regional metabolite alterations in PD at multiple brain structures and to correlate these alterations with the disease severity by using high-resolution whole-brain quantitative MRSI.

Methods: Twelve PD patients and 24 age and gender-matched controls, as summarized in Table 1, were scanned at 3T (Tim/Trio, Siemens) using an 8-channel phased-array head coil. Scan protocol included a 1x1x1 mm^3 T1-weighted (MPRAGE) and an MRSI acquisition obtained using a volumetric spin-echo EPSI sequence (TR/TE=1710/70-ms, FOV=280x280x180 mm^3, 50(read)x50(phase)x18(slice) spatial samples over a 135-mm slab) as previously described.[1,2] MRSI data were processed using the MIDAS package,[3] which included signal normalization to the interleave-acquired brain-tissue water reference MRSI data; and spatial registration to match a brain atlas that delineated 47 hemispheric lobes. Average values (in institutional units) of individual metabolites N-acetylaspartate (NAA), total-creatine (Cre), and total-choline (Cho) and their ratios were calculated for grey- (GM) and white- (WM) matter in each region.[3] Independent sample *t*-tests were employed to compare metabolite values between groups and linear regression analysis ($\alpha = 0.05$) was used to estimate the correlation of the metabolite concentrations at each region to the disease stage (H&Y) and severity (UPDRS).

Table 1: Sample demographics and disease characteristics

	Group Means (SD) PD (*n* = 12)	Control (*n* = 24)
Age at Exam	60.58 (8.52)	59.82 (8.23)
Gender (M/F)	9/3	15/9
Ethnicity (Non-Hispanic/Hispanic)	7/5	17/7
Education (yrs)	16.92 (2.23)	
Language (English/Spanish)	11/1	
Handedness (R/L/A)	11/0/1	
Age at Disease Onset	54.10 (10.52)	
Disease Duration	5.53 (4.66)	
Disease Stage (H&Y) (1,2,3)	2.10 (.66)	
Disease Disability (UPDRS)	39.14 (19.88)	
Side Onset (R/L)	4/6 (unavailable for 2 patients)	

Results: Table 2 shows significant differences ($P<0.01$) between PD and control groups in left GM found at the [Par] lobe of the cerebral cortex for all metabolites, while in basal ganglia NAA and Water_SI reduced in both [Tha] and [Pal] regions. Areas in midbrain, particularly [Cun], [MCG], [LING], and [Hip], showed an increase in Cho/Cre and Cho/NAA ratios but less metabolite alterations were seen in the [A/M/PCG]. Motor cortex area showed increase in Cho and Water_SI with significant alterations in all metabolites and ratios in the [PoCG] region. [ROL] region showed a decrease in NAA and an increase in Water_SI. Furthermore, significant differences in [Par] and [PoCG] bilateral average NAA values were found for subgroups of disease stages 2 and 3 ($P = 0.013$) but not for stage 1. [Par] and [MCG], and [LING] showed significant differences in [Cho/NAA] between the three stages. For the lateralized UPDRS motor score from the clinically most affected side: 1) NAA decreased at contralateral [Pa] ($R=-0.52$) and [PoCG] ($R=-0.28$); 2) Cho increased at [PreCG] ($R=0.29$) and [PoCG] ($R=0.47$), and decreased at [HIP] ($R=-0.28$); 3) Cho/NAA increased at [Cun] ($R=0.33$) and [MCG] ($R=0.47$); and 4) Cre increased at [Par] ($R=0.30$) and [HIP] ($R = 0.29$). Significant differences were seen between metabolites of the left and right hemispheres in [Occ], [Cun], [FFG], [PreCG], [PoCG], [ROL].

Table 2: Differences in metabolite values and ratios in left hemisphere GM between PD patients and normal controls (*: $P<0.05$, **: $P<0.01$).

Brain region / Met. & Ratio	Frontal **[Fro]**	Parietal **[Par]**	Temporal **[Tpo]**	Occipital **[Occ]**	Caudate **[Cau]**	Thalamus **[Tha]**	Pallidus **[Pal]**	Putamen **[Put]**	Cuneus **[Cun]**	Praecuneus **[PCun]**	Paracentralis **[Pcl]**	A. Cingulate **[ACG]**	M.Cingulate **[MCG]**	P. Cingulate **[PCG]**	Lingual Gy. **[LING]**	Hippocampus **[Hip]**	Fusiform **[FFG]**	Precentral **[PreCG]**	Postcentral **[PoCG]**	Rol. Operculum **[ROL]**	Insula **[Ins]**
NAA	*	**				**	**									*			**	**	
Cre		**				*										**			**	*	
Cho		**							*	*		*		*	*	**		**	**	*	
NAA/Cre	*	**														**	*		**	*	
Cho/Cre	*	**		**					**				*		**	**	**		**		
Cho/NAA		**		*					**	*			**		**	**			**		
Water_SI				**	**	**	**		**			**				**		**	**	**	*

Discussion: Thus far, studies of MRS in PD have produced conflicting results showing either no difference in the basal ganglia metabolite or decreases NAA/Cre ratio in PD.[2] The variability of these results is chiefly related to the difficulty of reliably assessing metabolites in the substantia nigra, due to its small size and increased iron content and due to the focus on suspected focal metabolite changes versus possible wider-spread changes. Growing recognition that PD is a degenerative disorder characterized by motor and non-motor symptoms and that the pathology extends beyond the basal ganglia, has led researchers to start examine cortical regions known to be involved in striatal circuitry. By using a high-resolution MRSI technique this study indicates that the PD-related alterations of brain NAA, Cho, and Cre are regional-dependent, with changes occurring in multiple region of the cerebrum, although a larger study with evenly distributed H&Y and UPDRS subgroups is warranted. Together these results show that the severity of PD, as measured by motor score, is correlated with the NAA and Cho/NAA in a number of atlas-defined regions.

References:

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