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Whole-brain Proton MR Spectroscopic Imaging in Parkinson's Disease

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Abstract

Objective—To examine the distributions of proton magnetic resonance spectroscopy (MRS) observed metabolites in Parkinson's Disease (PD) throughout the brain.

Methods—Twelve well-characterized PD patients and 18 age-matched controls were studied using MRI and volumetric MR Spectroscopic Imaging. Average values of signal normalized metabolite values for N-acetyl-aspartate, total-creatine, and total-choline (NAA, Cre, Cho, respectively) and their ratios were calculated for grey- (GM) and white-matter (WM) in each lobar brain region. PD participants also underwent comprehensive neuropsychological testing.

Results—Analyses revealed altered metabolite values in PD subjects relative to controls within the GM of the temporal lobe (Right: elevated Cre, $p=.027$; decreased NAA/Cre, $p=.019$; decreased Cho/Cre, $p=.001$ and Left: decreased NAA/Cre, $p=.001$, decreased Cho/Cre, $p=.007$); the right occipital lobe (decreased NAA, $p=.032$ and NAA/Cre, $p=.016$); and the total cerebrum GM (decreased NAA/Cre, $p=.029$). No meaningful correlations were obtained between abnormal metabolite values and the neuropsychological measures.

Conclusions—This study indicates that PD is associated with widespread alterations of brain metabolite concentrations, with a primary finding of increased creatine. It is hypothesized that higher creatine values in our PD sample may reflect greater neuronal energy expenditure early in the disease process that are compensatory. This is the first MRS study of PD that has examined metabolite changes across a large fraction of the brain volume, including the cortical mantle. Further work is needed to define the changes that take place in brain metabolites as PD progresses and their relationship to cognition and motor function.

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Disclosures:

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Search Terms

[30] Parkinson's disease with dementia; [38] Assessment of cognitive disorders/dementia; [120] MRI; [125] MRS; [165] Parkinson's disease/Parkinsonism

Introduction

In vivo proton magnetic resonance spectroscopy (MRS) is a noninvasive technique that enables measurement of several low molecular weight metabolites in the brain. It offers an opportunity to examine changes in chemical markers that cannot be detected by conventional MRI. Previous MRS studies in Parkinson's disease (PD) have examined brain regions known to be affected by dopamine depletion in the striatum, with limited assessment of the cortex. In this study, a volumetric MR Spectroscopic Imaging (MRSI) approach was used that permits evaluation of a large fraction of the brain, including cortical surface regions. The aim of this study was to evaluate metabolite changes across a large volume of the brain in a sample of PD patients who also underwent neuropsychological testing.

Methods

Participants

Twelve PD participants (nine male) and 18 age-matched controls (seven male) provided written informed consent for an IRB-approved protocol and took part in the imaging study. Each PD participant underwent neurologic evaluation and met U.K. PD Brain Bank criteria. Exclusion criteria included a history of substance abuse, major psychiatric or medical illness, non-PD neurological illness, neurosurgical intervention, or MRI contraindications. Sample characteristics are shown in Table 1. PD participants were between the age of 40 and 79, had a minimum 8th grade education, and were on optimal medical management for at least six weeks. All PD participants underwent a 3-hour neuropsychological evaluation using the measures listed in Table 2.¹

Procedures

Magnetic Resonance and Spectroscopy—MR data were atscquired at 3 Tesla (Siemens, Tim-Trio) using an eight-channel phased-array coil. Structural MRI included T1-weighted (MPRAGE), proton-density, T2-weighted, FLAIR, and gradient-echo acquisitions.

MRSI data were obtained using a volumetric spin-echo EPSI sequence (TR/TE=1710/70-ms, FOV: 280×280×180-mm³, 100(read)×50(phase)×18(slice) spatial samples over a 135-mm slab, and acquisition time of 26-min as previously described.² The MPRAGE and MRSI acquisitions were performed at the same angulation. MRSI data were processed using the MIDAS package,^{2,3} including interpolation to 64×64×32-voxels and spatial smoothing to give a resultant voxel volume of approximately 1-mL. Processing included calculation of the MRSI voxel tissue content based on tissue segmentation of the T1-weighted MRI; signal normalization to institutional units using the brain tissue water reference data; and spatial registration to match a brain atlas that delineated the eight hemispheric lobes.²

Data Analyses and Statistics

Average values of the individual metabolites N-acetyl-aspartate, total-creatine, and total-choline (NAA, Cre, Cho, respectively) and their ratios (NAA/Cre, Cho/Cre, Cho/NAA) were calculated for grey- (GM) and white- (WM) matter in each lobar brain region. Metabolite values were corrected for partial volume signal loss due to CSF contribution at each voxel, and values corresponding to 100% of each tissue type were obtained using a regression of the metabolite parameter against the tissue content for all voxels selected from that region. Results of spectral fitting were selected only from voxels with spectral line widths within 3–12 Hz and with fractional tissue volume within the voxel >80%. Outlying values greater than three times the standard deviation of the corresponding metabolite parameter over all fitted voxels were excluded. Independent sample *t*-tests were employed to compare metabolite values between groups.

Results

Group Differences in Metabolite Measures

Mean values and standard deviations of GM metabolite values and ratios are shown in Table 3. In GM, within the right temporal lobe, Cre was significantly elevated in the PD group ($p=0.027$). Significant decreases relative to controls were also observed, bilaterally, in the temporal lobes for NAA/Cre (Right: $p=0.019$; Left: $p=0.001$) and Cho/Cre (Right: $p=0.001$; Left: $p=0.007$). In the right occipital GM, significant decreases relative to controls were found for NAA ($p=0.032$) and NAA/Cre ($p=0.016$). NAA/Cre for total cerebrum GM (average of all lobar regions) was also significantly lower in the PD group ($p=0.029$). In WM, Cre values were lower within the left temporal ($p=0.029$) and right parietal ($p=0.033$) lobes for the PD group vs. controls.

Neuropsychological Test Scores

Correlational analyses between individual metabolites shown to be altered in our PD sample and neuropsychological performance scores revealed three significant correlations: LT Cho/Cre was correlated with Symbol Digit Modality Task (SDMT) ($p=.017$) and the Beck Depression Inventory (BDI) ($p=.013$) and right occipital NAA/Cre with Auditory Consonant Trigrams (ACT) ($p=.037$). Neuropsychological test performance for the PD group is summarized in Table 2. Z-scores were calculated using age and education-corrected normative values, along with the percent of subjects performing one or more standard deviations below the mean (Table 1). For 7 of the 15 neuropsychological measures, 25% or more patients met the cut-off.

Discussion

Proton MRS studies in patients have produced mixed results. The lack of reproducibility may in part be explained by different imaging technologies, discrepancies in the way metabolites are measured and selection-bias in region of interest (ROI) analyses. A major strength of this study was the use of a volumetric MRS technique that facilitated the evaluation of metabolic alterations across cortical regions, permitting an unbiased analysis.

The main findings of this study were reductions in NAA/Cr and Cho/Cr in bilateral temporal grey matter relative to controls, as well as increased Cr in RT grey matter. These findings support work by Hu et al.⁴ showing bilateral reduction of NAA/Cr in temporoparietal cortex. Our data are also consistent with voxel based morphometry demonstrating regional temporal lobe changes in PD. Martin et al.⁵ found a reduction in right anteromedial temporal lobe subcortical white matter in early untreated PD, Camicioli et al.⁶ reported decreased hippocampal volume in advanced PD. Ramirez–Ruiz et al.⁷ reported reduced gray matter volume in limbic and paralimbic, and neocortical associative temporo-occipital regions among nondemented PD patients. The only other cortical gray matter reduced in our sample was NAA and NAA/Cr in the right occipital region.

Creatine is present in all cells and is considered to be a marker of energy metabolism. While neurodegeneration may be assumed to cause an overall reduction in creatine, we hypothesize that the observed increase in creatine represents greater neuronal energy expenditure as a means of compensation in our sample of early PD. The significant reductions in metabolite ratios may also be due to increased creatine, as opposed to decreases in other metabolites.

Few studies have examined the relationship between cognition and MRS-observed metabolites in PD. In this study, three significant correlations emerged; however, interpretation is limited by the lack of a meaningful pattern and the small sample size. From a descriptive viewpoint, 25% or more of PD patients performed below expectancy on naming, semantic fluency, visuospatial judgment, sustained attention and card sorting and there is research showing activation of temporal lobe structures, the region with altered metabolites in our study, while performing many of these tasks.^{8–10} An unexpected finding was the lack of impairment in verbal learning and memory performance, given the well described role of the temporal lobes in memory. The fact that our memory testing was limited to free recall, subjects were not demented and relatively early in their disease may explain the unimpaired memory performance.

To our knowledge, this is the first MRS study of PD to examine metabolite changes across a wide volume of the brain, including the cortical mantle. Future work is needed to replicate our findings and better define the relationship between regional alterations of individual MRS-observed metabolites and the cognitive and motor changes that characterize PD.

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Figure 1.

Table 1

Sample demographics and disease characteristics.

	Group Means (SD)		<i>p</i>
	PD (<i>n</i> = 12)	Control (<i>n</i> = 18)	
Age at Exam	60.58 (8.52)	59.11 (8.23)	.728
Gender (M/F)	9/3	7/11	.052
Ethnicity (Non-Hispanic/Hispanic)	7/5	16/2	.053
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)	2.10 (.66)		
Disease Disability (UPDRS)	39.14 (19.88)		
Side Onset (R/L)	4/6		
Predom. Symptom (Trem./Non-Trem.)	7/3		

Note. Categorical variables Gender and Ethnicity are Chi-Square analyses; values are frequencies. M/F = Male/Female; R/L/A = Right/Left/Ambidextrous.

Table 2

Neuropsychological test performance.

	PD Group		% Abnormal $z < -1.0$
	Mean (SD)	Range	
Mini Mental State Examination	28.08 (1.51)	26.00–30.00	0.00
Boston Naming Test	52.64 (5.66)	38.00–59.00	37.5 [†]
WAIS-III-Similarities	26.10 (2.92)	22.00–32.00	0.00
WAIS-III-Digit Span-LSB	4.83 (1.40)	3.00–7.00	16.70
Auditory Consonant Trigrams	42.40 (4.69)	36.00–52.00	50.00 [†]
COWAT-FAS total words	40.18 (10.66)	21.00–55.00	27.30 [†]
COWAT-Animals total words	18.09 (5.13)	11.00–29.00	16.70
Proverbs Interpretation	18.33 (1.73)	15.00–20.00	11.10
Wisconsin Card Sort- categories complete	4.90 (1.60)	1.00–6.00	30.00 [†]
CVLT-II-total words (trials 1–5)	51.00 (8.15)	38.00–65.00	9.10
CVLT-II-short delay free recall	10.55 (2.50)	6.00–15.00	0.00
CVLT-II-long delay free recall	11.09 (2.81)	7.00–16.00	0.00
Symbol Digit Modalities Test	41.45 (8.89)	23.00–54.00	30.00 [†]
Judgment of Line Orientation	10.67 (3.06)	6.00–14.00	33.30 [†]
Hooper Visual Orientation Test	22.33 (4.05)	12.50–26.00	18.20
Beck Depression Inventory	8.25 (8.57)	0.00–29.00	25.00 [†]

Note. WAIS-III = Wechsler Adult Intelligence Test, Third Edition; WAIS-III Digit Span- LSB = Longest Span Backward; COWAT = Controlled Oral Word Association Test; CVLT-II = California Verbal Learning Test, Second Edition.

% Abnormal corresponds to the percentage of individuals outside the normal range of performance ($z < -1.0$, Beck Depression Inventory >9).

[†] Impaired performance in at least one quarter of sample. These areas of cognitive impairment are consistent with cognitive decline observed in Parkinson's disease.

Table 3

Gray matter proton metabolite values and ratios from patients with Parkinson's disease and controls.

Brain Region		Group Means (SD)			% Difference from Control
		PD (n = 12)	Control (n = 18)		
Frontal	<i>Left</i>				
	NAA	2191(154)	2259(132)		-3.0
	Cre	1669(121)	1736(113)		-3.9
	Cho	370(37)	372(52)		-0.7
	NAA/Cre	1.32(.096)	1.30(.070)		1.2
	Cho/Cre	0.22(.025)	0.21(.025)		4.6
<i>Right</i>	Cho/NAA	0.17(.023)	0.17(.021)		2.9
	NAA	2179(164)	2254(167)		-3.3
	Cre	1737(125)	1773(156)		-2.0
	Cho	369(32)	381(55)		-3.2
	NAA/Cre	1.25(.092)	1.27(.076)		-1.1
	Cho/Cre	0.21(.016)	0.21(.025)		-1.2
Parietal	Cho/NAA	0.17(.016)	0.17(.019)		-0.0
	NAA	2283(163)	2353(199)		-3.0
	Cre	1781(128)	1797(146)		-0.9
	Cho	285(38)	277(38)		2.9
	NAA/Cre	1.27(.105)	1.30(.068)		-2.2
	Cho/Cre	0.15(.022)	0.15(.017)		5.0
<i>Right</i>	Cho/NAA	0.13(.014)	0.12(.013)		7.0
	NAA	2420(180)	2492(192)		-2.9
	Cre	1914(188)	1881(164)		1.8
	Cho	281(45)	289(42)		-2.9
	NAA/Cre	1.25(.130)	1.33(.075)		-6.0
	Cho/Cre	0.13(.029)	0.15(.018)		-8.2
Temporal	Cho/NAA	0.12(.014)	0.12(.014)		1.0
	NAA	2374(201)	2450(233)		-3.1
	Cre	1974(212)	1896(206)		4.1
	Cho	338(54)	358(63)		-5.6

Brain Region		Group Means (SD)		% Difference from Control
		PD (<i>n</i> = 12)	Control (<i>n</i> = 18)	
Occipital	NAA/Cre	1.13(.131)**	1.27(.090)	-11.6
	Cho/Cre	0.14(.028)**	0.18(.032)	-18.9
	Cho/NAA	0.14(.022)	0.15(.027)	-3.7
	NAA	2746(213)	2662(274)	3.2
	Cre	2243(361)*	1995(225)	12.4
	Cho	361(67)	377(71)	-4.2
	NAA/Cre	1.17(.213)*	1.32(.121)	-11.5
	Cho/Cre	0.13(.036)**	0.18(.034)	-27.7
	Cho/NAA	0.13(.032)	0.14(.028)	-9.0
	NAA	2223(266)	2358(228)	-5.7
Left	Cre	1874(276)	1868(171)	0.3
	Cho	274(69)	277(51)	-1.1
	NAA/Cre	1.16(.156)	1.25(.087)	-7.3
	Cho/Cre	0.13(.025)	0.14(.022)	-4.5
	Cho/NAA	0.12(.021)	0.12(.018)	3.3
	NAA	2192(307)*	2421(169)	-9.5
	Cre	1891(248)	1852(115)	2.1
	Cho	259(71)	255(43)	1.8
	NAA/Cre	1.14(.194)*	1.30(.111)	-12.8
	Cho/Cre	0.13(.029)	0.13(.022)	-3.6
Right	Cho/NAA	0.12(.029)	0.11(.019)	10.5
	NAA	2325(133)	2406(151)	-3.3
	Cre	1885(144)	1850(122)	1.9
	Cho	317(31)	323(38)	-1.9
	NAA/Cre	1.21(.110)*	1.29(.054)	-6.4
	Cho/Cre	0.16(.015)	0.17(.016)	-6.8
	Cho/NAA	0.14(.012)	0.14(.014)	1.0
Total Cerebrum				

Note. Metabolite values are in institutional units. Significant differences in metabolites levels between groups for white matter regions are provided in the *Results* section. % Difference = ((PD-Control)/Control)*100.

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