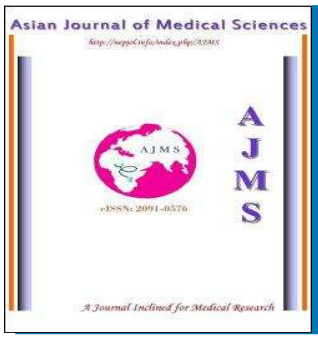


MAGNETIC RESONANCE SPECTROSCOPY IMAGING OF MEDULLA OBLONGATA AND SUBSTANTIA NIGRA IN IDOPATHIC PARKINSON'S DISEASE

ORIGINAL ARTICLE, Vol-4 No.3

Asian Journal of Medical Science, Volume-4(2013) http://nepjol.info/index.php/AJMS

[1]Netra Rana,[2]Ma Shaohui [3]Guo Chenguang,[4] Li Min,[5]Zhang Ming.[1,2,3,4,5]First Affiliated Hospital of Xi'an Jiaotong University, Department of Medical Imaging, 277-West Yanta Road, Xi'an-710061, Shaanxi, PR China.

CORRESPONDENCE:

Prof Zhang Ming, MD, PhD
First Affiliated Hospital of Xi'an Jiaotong University,
Department of Medical Imaging
277-West Yanta Road, Xi'an-710061, Shaanxi, PR China.
Phone numbers:
+86-13519133887
Facsimile numbers:
+86-2985323428
E-mail address:
profzmmri@gmail.com

"Parkinson's disease (PD) is a common neurodegenerative disorder of the elderly. Magnetic Resonance Spectroscopy (MRS) is a non-invasive technique that allows direct observation of cerebral metabolites and provides insight into the underlying metabolic abnormalities"

ABSTRACT

Objective: To use 1.5T 1H-MRS as a research tool in vivo and demonstrate the feasibility of obtaining long-echo 1H MR spectra in small volumes like substantia nigra (SN) and medulla oblongata (MO) in healthy volunteers and patients with Parkinson's disease (PD) and observe the clinical correlations.

Subjects and Methods: Twenty patients of the idiopathic Parkinson's disease (IPD) were recruited from the Out Patient Department of Neurology. Additionally, 14 age-matched healthy subjects were taken as controls group. After baseline evaluation, the patients satisfying inclusion and exclusion criteria underwent 1H-MRS study. All MR examinations were performed on a 1.5 T system (Philips Gyroscan Intera, Netherlands) using a standard quadrature head coil.

Results: We succeeded to achieve 74.19% and 77.42% of spectra from MO and SN of both PD and control groups. MO showed slightly weak negative result to total UPDRS and UPDRS- II, but no significant correlation was found between metabolites and clinical indexes in MO. The result also showed no significant correlations between H&Y scale and metabolites in MO and SN of PD patients. But there was a significant correlation between H&Y, NAA/Cr and Cho/Cr in SN.

Conclusions: MRS ratios from MO and SN does not play any significant role to differentiate PD from the normal subjects, but metabolites ratios from SN of PD patient can help to understand the progression and severity of the disease. Therefore, it is not practical to employ MRS as a diagnostic tool for PD.

Key-words: Substantia nigra; Medulla Oblongata; Neurodegenerative; Parkinson's disease; Magnetic resonance spectroscopy.

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder of the elderly characterized by tremor, rigidity and slowness of movements comprising non-motor symptoms like depression, sleep disorders, hyposmia, constipation, cognitive dysfunction, dementia and body mass index (BMI) abnormalities;[1-3] though the relationship between BMI and PD is controversial. The low body weight was more pronounced in patients with greater disease severity where the disease duration was not associated with BMI.[2,3] However, the mean BMI values were not statistically significant in the absence of comorbid depressive symptoms compared with age-matched controls. PD results from the progressive death of dopaminergic neurons in the substantia nigra (SN) pars compacta, where neuronal loss is most severe compared to the ventral tegmental area and the central grey matter. The continuing evolution of new techniques for imaging the central nervous system has produced significant advances in understanding the changes in brain structure and function associated with neurodegenerative disease. Magnetic Resonance Spectroscopy (MRS) has provided insights into some of the underlying metabolic abnormalities, thereby helping to elucidate the underlying pathophysiology of these disorders. It has been extensively utilized in various clinical conditions, including tumor, stroke, inflammatory diseases, AIDS and HIV related disorders and degenerative diseases, like Huntington's disease and Alzheimer's disease.[4-7] In vivo ^{1}H MRS is a non-invasive technique that allows direct observation of cerebral metabolites, including include N-acetyl aspartate (NAA), choline (Cho), and creatine (Cr).

Previous MRS studies in PD patients have yielded mixed results. Some studies reported decreased ratios between NAA and other metabolites in the SN and lentiform nucleus and striatum.[8,9] In the resent study, Levin and colleagues,[10] described reduced in NAA/Cr and Cho/Cr in bilateral temporal gray matter (GM) relative to controls, as well as increased Cr in right temporal GM. This result was supported by earlier findings.[11] Additionally, Ellis and colleagues,[12] reported no metabolite differences between controls and PD patients receiving treatment but found a significant reduction in NAA/Cr ratio among the untreated PD patients. In contrast, some studies have reported no differences between PD and control subjects in either metabolite ratios or concentrations of NAA, Cr, and Cho.[13-15] Majority of studies were concentrated on the metabolites visible with proton ^{1}H MRS and were measured in specified tissue volumes in the brain. The few published MRS studies of the SN in PD utilized larger volumes encompassing the SN, and have overlooked the medulla oblongata (MO) in their studies due to previous understanding of caudo-rostral disease progression.[16] In addition, it has several challenges to measure MR spectra because of its small size. However, increased sensitivity potentially can be achieved by utilizing a high magnetic field and an efficient volume coil. In this study, we choose MO (much overlooked) and SN(the most affected brain region in PD) as a region of interest (ROI). The purpose of this study was to use 1.5T ^{1}H-MRS as a research tool in vivo, and demonstrate the feasibility of obtaining long-echo ^{1}H MR spectra in small volumes and investigate the metabolic changes in MO and SN to determine whether the proton spectra obtained from patients with PD differ from those obtained from healthy control.

SUBJECTS AND METHODS

Subjects Selection and Clinical Assessment

20 patients with various stages of the IPD, (UPDRS scores 12 to 105, mean score 47.29 SD± 27.80; UPDRS-II scores 7 to 69, mean score 31.59 SD ± 17.47; H&Y stages, ranges from 1-4, mean stage

1.88 SD ± 0.82; disease duration after diagnosis, 0.5-20 years, mean duration 4.56 SD ± 5.08 years; 15-men, 2-women; mean age, 61.29 SD ± 5.55 years) were recruited from the Out Patient Department of Neurology. Fifteen of the 20 patients satisfied the inclusion criteria for the study and entered final statistical analysis. Five patients were excluded due to incompetent data and MRS spectra caused by head movement. Disease severity was scored in accordance with the UPDRS and the H&Y scale. All patients satisfied the UK Brain Bank criteria for the diagnosis of idiopathic Parkinson's disease. All subjects were evaluated by a neurologist and a neuropsychologist to determine their neurological and cognitive status. All patients were taking their usual anti-parkinsonian medications at the time of the imaging and were clinically determined to be within the effective therapeutic range of medications. Signs of autonomic failure, Mini Mental Examination scores (MMSE) ≥24/30, and significant medical conditions (i.e., cardiac, hepatic or renal dysfunctions) were considered as exclusion criteria. Additional exclusion criteria for all subjects included the following: history of stroke, cerebral tumor, traumatic brain injury, claustrophobia, epilepsy, or psychiatric illness other than depression. After baseline evaluation, the patients satisfying inclusion and exclusion criteria underwent ^{1}H-MRS study. All patients were kept off their antiparkinsonian medications for at least 12 hours prior to the MR scan. Additionally, 14 age-matched healthy subjects were taken as control group (13-men, 1-women; mean age, 58.07 SD ± 4.81 years). All patients and healthy controls gave their informed consent to participate to the study in accordance with the guidelines of our Institutional Review Board. A total of 62 spectra were acquired in 31 subjects to calculate the metabolite ratios. Forty-seven of 62 computable spectra were included in this experiment. Twenty-three spectra were obtained in the MO and 24 in SN of both PD and control groups (TE=136 msec).

Magnetic Resonance Protocol and spectra processing

All examinations were performed on a 1.5 T system (Philips Gyroscan Intera, Netherlands) using a standard quadrature head coil. The MRI protocol consisted of sagittal T1 weighted fast field echo sequences (TR=73 msec, TE=2 msec, 1 NSA, FOV=250mm, flip angle=80°), axial/transverse T2 FLAIR (TR=6000 msec, TE=110 msec, NSA=1, IR=2000msec, TSE factor=25, FOV=256mm,) and coronal T2 weighted turbo spin echo sequences (TR =1213 msec TE =120 msec, 1= NSA, TSE factors =21, FOV= 250, flip angle= 90°). Slice thickness were 5.0 mm with 0.0 mm gap for all three sequences and the matrix of 256×256 for sagittal T1-FFE and coronal T2-TSE but 256×512 for axial/transverse T2-FLAIR. The voxel was a cube of 10mm×10mm×20mm (2 mL) for the MO. The VOI was positioned using as anatomic landmarks sagittal T1, coronal and axial T2 images. The mid-slice of sagittal view was chosen to decide the exact location of VOI in MO. The lower border/edge of pons was defined as an upper border for the VOI in MO (caudo-rostral view). Transverse and coronal slices were then used to adjust the lateral borders and make sure of exact location for VOI, and avoid inclusion of the surrounding tissues as well as less CSF (Figure 1). Similarly, a cube of 10mm×15mm×15mm was chosen for the SN (Figure 2). Special care was given to avoid inclusion of CSF spaces within the volume of interest.

After automatic shimming, water suppression was obtained with an adiabatic RF pulse centered on the water peak with a spectral width of 60 Hz, followed by dephasing crusher gradients. The performance of water signal suppression was optimized by fine tuning the flip angle of the water suppression RF pulse slightly in excess of 90°. A

point-resolved proton spectroscopy sequence (PRESS) technique was used for acquisition of the proton spectrum with TR 2000 msec, and 128 measurements. With 512 spectral points and 128 averages, the single spectrum acquisition time was of 4minutes and 56 seconds.

Data Analysis

All spectra were preliminarily evaluated for overall quality and the criteria for scoring spectrum included signal to noise ratio, peak shape (wide peaks reflect poor shimming or patient motion), and separation of cho and cr peaks. Post-processing of the proton spectra involved the following steps: data selection and handling, selection of spectrum from chemical shift (0 to 4 ppm), frequency domain signal correction, base line correction, analysis and quantification, single peak analysis, and at last we selected the peak of interest chemical shift (i.e., NAA, Cho and Cr). Resonances were assigned as follows: NAA at 2.0 ppm, Cr at 3.0 ppm and Cho at 3.2 ppm in the real part of the spectrum and were computed interactively on the MR system console using the software provided by the manufacturer. The ratios of NAA/Cr and Cho/Cr were then calculated. It is difficult to measure absolute values with our technique; therefore, results were obtained in terms of ratios of metabolite signals. Ratios between areas underlying metabolite spectral peaks have therefore been used. Cr has been used as denominator because it is expected to remain unchanged by neurodegenerative disease processes.

Statistical analysis

The Mann-Whitney *U* test was used to perform the comparative study of age and MRS ratio between PD and healthy subjects. The results were expressed as ratio with 95% confidence intervals (CI). To investigate the correlation between PD, clinical indexes and metabolic ratios, stepwise regression analysis was performed with the following dependent variables in turn: (1) age, (2) disease duration, (3) total UPDRS score and, (4) motor experiences of daily living (UPDRS-Part II). A variable was kept in the model if the *P* value was less than 0.05. A *P* value of 0.1 or less was used to add variables to the multivariable model, whereas *P* value of 0.05 or less was used to retain variables in the model. Statistical significance was assigned for $P < 0.05$. If variable shows the significant difference with metabolites ratios, we used Stepwise regression method to show the correlation. We also used the Nonparametric Correlations test and performed Spearman Correlation to show the correlation between H&Y stage and MRS ratios.

Statistical analysis was performed using a commercial statistical package (SPSS version 16.0; SPSS Inc; Chicago, IL).

RESULTS

All MR spectroscopic data was evaluated by a senior doctor from our department and found it to be competent to include for further analysis. Good quality spectra from MO and SN with stable baseline and distinct peak for NAA, Cho and Cr were considered acceptable. Forty-seven of 62 computable spectra were included, 23 from MO and 24 from SN of PD patients and healthy subjects. We succeeded to achieve 74.19% and 77.42% of spectra from MO and SN of both groups. No significant differences between the age of PD group and healthy subjects were observed, (U=51, *P*=0.383 and U=54, *P*=0.297, respectively). This result shows that, age of all subjects were matched and qualified to join the research.

^{1}H-MRS findings: PD vs. healthy subjects

Each mean was determined from the corrected peak ratios of the individual subjects. No statistically significant difference was observed between the PD and control values for NAA/Cr (U=63; P=0.901) and Cho/Cr (U=62; P=0.852) in MO

and NAA/Cr (U=55; P=0.326) and Cho/Cr (U=57; P=0.386) in SN, respectively. Although NAA/Cr and Cho/Cr mean values for the total Parkinson group were slightly lower than those for healthy control subjects, the difference was not statistically significant.

MRS findings: compared with clinical indexes of PD

Stepwise regression test was done to analyze the metabolite ratios of MO and SN to correlate with PD and its clinical indexes (e.g., age, disease duration, total UPDRS and UPDRS- II).

1) MO: Dependent variable are NAA/Cr and Cho/Cr, both have no variables entered. However, we found negative correlation between Cho/Cr ratio with UPDRS (r=-0.335) and UPDRS-II (r=-0.364). No significant correlation were found between metabolite ratios (NAA/Cr and Cho/Cr) with clinical indexes in MO but there is a slightly larger negative result to total UPDRS and UPDRS- II (See Table 2) which was also not statistically significant.

2) SN: The entered variable for NAA/Cr is UPDRS-II (Model I: F=11.028, P=0.008, R2=0.711); and the entered variables for Cho/Cr are UPDRS and UPDRS-II. (Model I: F=11.028, P=0.008; Model II: F=20.608, P=0.000, R2=0.821). NAA/Cr ratio to UPDRS-II served as unique predictors of PD, this variables explained 52.4% of the variance. Cho/Cr ratio to UPDRS and UPDRS-II served as unique predictors of PD, and together, these variables explained 82.1% of the variance. UPDRS-II uniquely explained 71.1% of the variance. In SN, Pearson correlations between Cho/Cr with UPDRS and UPDRS-II are -0.770 and -0.843, respectively; where the correlation between NAA/Cr with UPDRS-II is -0.724 (Table 2). The result showed that there was correlation of SN's metabolites with UPDRS and UPDRS-II. Although the Pearson correlation between UPDRS with NAA/Cr in SN shows the strong negative correlation, it was not statistically significant.

Results of the stepwise regression analysis with clinical indexes (age, duration of the disease, total UPDRS score and UPDRS-II), and the MRS variables are shown in Table 3.

Correlation between H&Y stage and metabolites ratio of PD

Spearman correlation of nonparametric method was chosen to explore the relationship between H&Y scale and metabolites ratios in MO and SN of PD patients (Table 4). The result in MO did not show any significant correlations (NAA/Cr = -0.394; P=0.182 and Cho/Cr = -0.165; P=0.589). But in SN we found significant correlation between H&Y and NAA/Cr (NAA/Cr = -0.697; P=0.012), Cho/Cr (Cho/Cr=-0.715, P=0.009). The linear curve estimation shows the linear correlation between H&Y scale and metabolites ratios (Figure 3 A and B).

DISCUSSION

We have demonstrated the feasibility of obtaining long-echo 1H MR Spectra at 1.5 T in small volumes encompassing the unilateral SN and of MO in healthy volunteers and patients with PD. Our results did not show any significant difference in MRS findings between the IPD patients and the control subjects. This result is in agreement with the findings of previous reports, though the PD subjects had slightly lower values for each ROI.[12-15,17,18] This must be viewed in the context of some possible sources of error. One issue raised in our study is determining the sample size for the study, which is too small and inadequate to judge the result. A second point is that the volume of interest is again too small; the small size of the VOIs required avoiding partial volume effects with adjacent CNS structures and CSF spaces, implying low signal-to-noise ratio. Other possible sources of poor quality spectra include motion of the brain,

Table 1 Clinical and MR Spectroscopic data of PD patients from MO and SN

No.	Age	D (y)	H-Y	UPDRS	UPDRS- II	MO		SN	
						NAA/Cr	Cho/Cr	NAA/Cr	Cho/Cr
1	66	20	2	105	69	1.2	0.65	-	-
2	64	4	1.5	58	34	-	-	1.22	1.04
3	60	4	3	42	30	1.49	1.59	-	-
4	64	3	2	32	32	2.75	1.96	-	-
5	60	1	1	15	7	-	-	2.01	1.67
6	67	3	2.5	51	38	1.07	0.61	1.19	0.48
7	59	9	1.5	56	35	2.91	2.28	1.92	1.05
8	66	2	1.5	44	29	1.87	1.77	2.69	0.91
9	54	1	1	27	15	2.95	2.34	2.73	1.29
10	60	12	4	87	56	1.46	1.36	1.36	0.82
11	49	2	1.5	18	16	1.99	0.87	1.81	1.36
12	65	2.5	2	28	17	1.51	0.86	2.31	1.39
13	65	0.5	1	12	10	0.83	1.45	2.45	1.26
14	66	1.5	2.5	82	50	2.46	0.98	1.24	0.77
15	50	2	2.5	66	46	1.28	0.91	1.06	0.74

D (y) =Duration of disease (years), H-Y=Hoehn & Yahr, UPDRS= Unified Parkinson's Disease Rating Scale, NAA= N-acetyl-aspartate; Cr=creatine; Cho= Choline.

Table 2 Pearson correlation

Variable	MO		SN	
	NAA/Cr	Cho/Cr	NAA/Cr	Cho/Cr
Age	-0.221	-0.130	0.062	-0.237
Duration	-0.164	-0.175	-0.312	-0.304
UPDRS	-0.126	-0.335	-0.686	-0.770
UPDRS-II	-0.157	-0.364	-0.724	-0.843

MO: medulla oblongata; SN: substantia nigra; UPDRS: Unified Parkinson's Disease Rating Scale

Table 3 Stepwise regression- SN

	B	*P*	R^2	F	Model p
Cho/Cr					
Model I					
UPDRS- II	-0.843	0.001	0.711	24.594	0.001**
Model II					
UPDRS- II	-2.655	0.008	-	-	-
UPDRS	1.842	0.043	0.821	20.608	0.000**
NAA/Cr					
Model I					
UPDRS- II	-0.724	0.008	0.524	11.028	0.008**

Stepwise Criteria: Probability of F to enter <=0.050, Probability of F to remove >=0.100

** Strong significant

Table 4 Nonparametric Correlations: Spearman Correlations

	MO (N=13)		Substantia Nigra (N=12)	
	NAA/Cr	Cho/Cr	NAA/Cr	Cho/Cr
Correlation	-0.394	0.165	-0.697	-0.715
P	0.182	0.589	0.012*	0.009**

* Significant ** Strong significant

vessels, and avoid CSF inclusion of within the volume of interest, which is unavoidable. Apart from this, we have studied the direct correlation of PD with its clinical indexes and disease severity. The weak correlation between age and metabolites ratios of PD group may be due to subjects we have chosen were very close to each other. We think the metabolites on MO and SN are similar to this age group. Disease duration shows negative correlation with NAA/Cr and Cho/Cr in SN, respectively but did not show statistically significant result. MO did not show any correlation with each metabolite. Our findings showed, the duration prolonged, the NAA and Cho decreased. We think this, because PD is a progressive neuro-

-degenerative disease, where neuron cell deaths and membrane damages take place gradually. But this phenomenon is not well understood in MO. Our result found H&Y have significant correlation with NAA/Cr and Cho/Cr respectively, particularly with Cho/Cr in the SN**.** MO showed no statistically significant correlation, but we found slightly negative and weak correlation between H&Y and Cho/Cr. So we can get the hypothesis that the NAA and Cho may decrease according to the severity of PD in SN. Similar result was found in the recent study.[10,18] The majority of previous MRS studies have applied ^{1}H-MRS method to study PD in the selected brain regions and have primarily targeted NAA, Cr, and Cho levels of brain. Clarke and

Figure 1 Locations of the volume of interest in MO of PD and corresponding 1H MR Spectra. Sagittal T1 (a), coronal T2 (b), axial T2 FLAIR (c) and corresponding 1H MR Spectra (d).

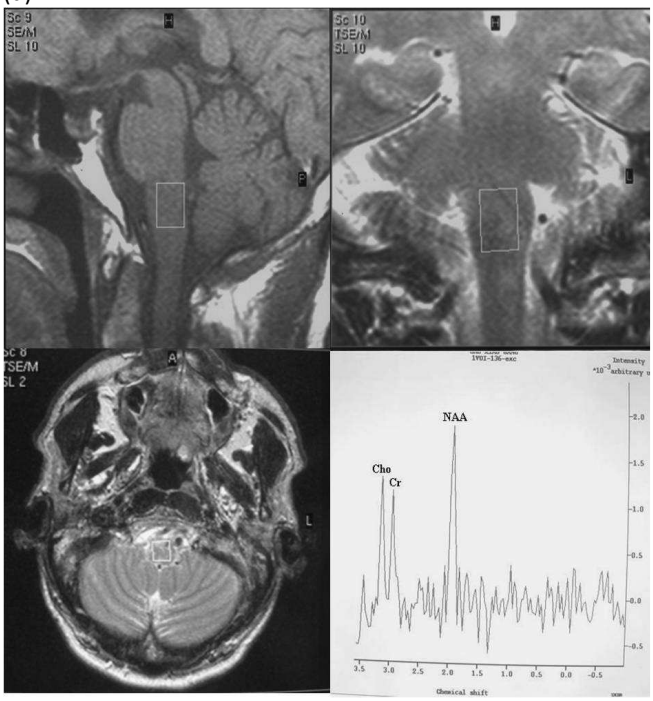


Figure 2 Locations of the volume of interest in SN of PD and corresponding 1H MR Spectra. Sagittal T1 (a), coronal T2 (b), axial T2 FLAIR (c) and corresponding 1H MR Spectra (d).

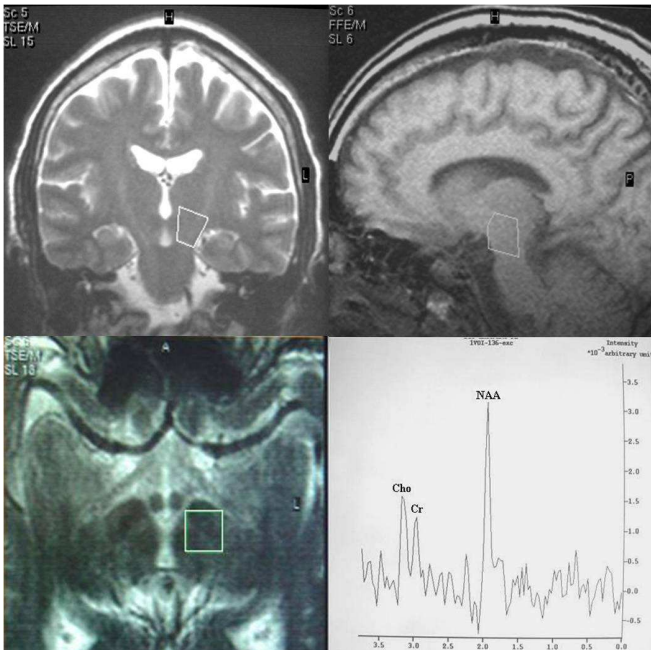
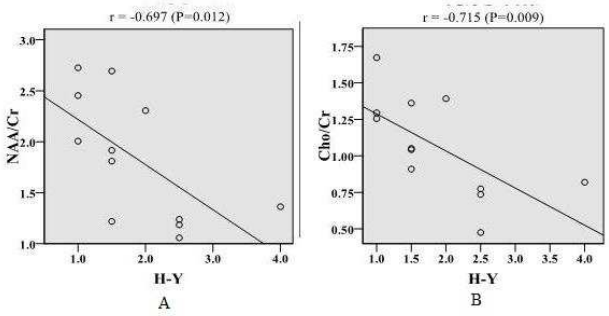


Figure 3 Linear correlations between H&Y scale and metabolites ratios. (A) NAA/Cr vs. H-Y; (B) Cho/Cr vs. H-Y.



colleagues,[19] have reported a significant decrease in the NAA/Cho ratio in PD owing to increase in the absolute concentration of Cho not associated with a change in NAA concentration. Abnormal metabolite levels have been demonstrated in motor cortex,[20] presupplementary motor area,[21] temporoparietal cortex,[22] occipital lobe, and lentiform nucleus and striatum.[8,12,15,21,23] Some changes have taken place in association with medications administered for treatment of PD that resulted in increased motor cortex Cho/Cr ratios.[12, 24] Griffith and colleagues,[25] have demonstrated lower NAA/Cr ratios in the posterior cingulate gyrus of demented versus non demented subjects with PD. Furthermore, same team have demonstrated no changes in NAA/Cr or Cho/Cr of the posterior cingulate gyrus.[26] Other investigators, however, have not detected such changes in NAA, Cr, and Cho measurements, [13,14,27] and the reasons for these different findings need to be resolved. The results of the present pilot study, combined with the conflicting findings from previous work, suggest that further, much larger, studies are required to evaluate the diagnostic capability of proton MRS. In addition to its small size; other challenges of measuring MR spectra, the SN include its location in the midbrain and its

high iron content. Broader lines relative to other brain regions are expected in the SN, even with the use of automated shimming routines. However, increased sensitivity potentially can be achieved in the SN by utilizing a high magnetic field and an efficient volume coil.

Conclusion: Long TE single-voxel spectroscopy of the MO and unilateral human SN are feasible in both healthy volunteers and patients with PD, and can continue for future exercise. MRS ratios from MO and SN cannot differentiate PD from control group, but metabolites ratios from SN of PD patient can help to understand the progression and severity of the disease. It is not practical to employ MRS as a diagnostic tool for PD and not complied with predicted caudo-rostal pattern. This must be viewed in the context of some possible sources of limitation, further evaluation is needed.

REFERENCES

1. Meireles J, Massano J. Cognitive impairment and dementia in Parkinson's disease: clinical features, diagnosis, and management. Frontiers in neurology. 2012;3:88.
2. Pilhatsch M, Kroemer NB, Schneider C, Ebersbach G, Jost WH, Fuchs G, et al. Reduced body mass index in Parkinson's disease: contribution of comorbid depression. The Journal of nervous and mental disease. 2013;201:76-9.
3. van der Marck MA, Dicke HC, Uc EY, Kentin ZH, Borm GF, Bloem BR, et al. Body mass index in Parkinson's disease: a meta-analysis. Parkinsonism & related disorders. 2012;18:263-7.
4. Craciunas SC, Brooks WM, Nudo RJ, Popescu EA, Choi IY, Lee P, et al. Motor and premotor cortices in subcortical stroke: proton magnetic resonance spectroscopy measures and arm motor impairment. Neurorehabilitation and neural repair. 2013;27:411-20.
5. Chang L, Munsaka SM, Kraft-Terry S, Ernst T. Magnetic Resonance Spectroscopy to Assess NeuroInflammation and Neuropathic Pain. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology. 2013;8:576-93.
6.. Cysique LA, Moffat K, Moore DM, Lane TA, Davies NW, Carr A, et al. HIV, Vascular and Aging Injuries in the Brain of Clinically Stable HIV-Infected Adults: A (1)H MRS Study. PloS one. 2013;8:e61738.
7. Graff-Radford J, Kantarci K. Magnetic resonance spectroscopy in Alzheimer's disease. Neuropsychiatric disease and treatment. 2013;9:687-96.
8. Choe BY, Park JW, Lee KS, Son BC, Kim MC, Kim BS, et al. Neuronal laterality in Parkinson's disease with unilateral symptom by in vivo 1H magnetic resonance spectroscopy. Investigative radiology. 1998;33:450-5.
9. Taylor-Robinson SD, Turjanski N, Bhattacharya S, Seery JP, Sargentoni J, Brooks DJ, et al. A proton magnetic resonance spectroscopy study of the striatum and cerebral cortex in Parkinson's disease. Metabolic brain disease. 1999;14:45-55.
10. Levin BE, Katzen HL, Maudsley A, Post J, Myerson C, Govind V, et al. Whole-Brain Proton MR Spectroscopic Imaging in Parkinson's Disease. Journal of neuroimaging : official journal of the American Society of Neuroimaging. 2012 Dec 10.
11. Hu MT, Taylor-Robinson SD, Chaudhuri KR, Bell JD, Morris RG, Clough C, et al. Evidence for cortical dysfunction in clinically non-demented patients with Parkinson's disease: a proton MR spectroscopy study. Journal of neurology, neurosurgery, and psychiatry. 1999;67:20-6.
12. Ellis CM, Lemmens G, Williams SC, Simmons A, Dawson J, Leigh PN, et al. Changes in putamen N-acetylaspartate and choline ratios in untreated and levodopa-treated Parkinson's disease: a proton magnetic resonance spectroscopy study. Neurology. 1997;49:438-44.
13. Tedeschi G, Litvan I, Bonavita S, Bertolino A, Lundbom N, Patronas NJ, et al. Proton magnetic resonance spectroscopic imaging in progressive supranuclear palsy, Parkinson's disease and corticobasal degeneration. Brain: a journal of neurology. 1997;120:1541-52.
14. Cruz CJ, Aminoff MJ, Meyerhoff DJ, Graham SH, Weiner MW. Proton MR spectroscopic imaging of the striatum in Parkinson's disease. Magnetic resonance imaging. 1997;15:619-24.
15. Clarke CE, Lowry M. Basal ganglia metabolite concentrations in idiopathic Parkinson's disease and multiple system atrophy measured by proton magnetic resonance spectroscopy. European journal of neurology: the official journal of the European Federation of Neurological Societies. 2000;7:661-5.
16. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiology of aging. 2003;24:197-211.
17. Bowen BC, Block RE, Sanchez-Ramos J, Pattany PM, Lampman DA, Murdoch JB, et al. Proton MR spectroscopy of the brain in 14 patients with Parkinson disease. AJNR American journal of neuroradiology. 1995;16:61-8.
18. Metarugcheep P, Hanchaiphiboolkul S, Viriyavejakul A, Chanyawattiwongs S. The usage of proton magnetic resonance spectroscopy in Parkinson's disease. Journal of the Medical Association of Thailand = Chotmaihet

thangphaet. 2012;95:949-52.
19. Clarke CE, Lowry M. Basal ganglia metabolite concentrations in idiopathic Parkinson's disease and multiple system atrophy measured by proton magnetic resonance spectroscopy. European journal of neurology: the official journal of the European Federation of Neurological Societies. 2000;7:661-5.
20. Lucetti C, Del Dotto P, Gambaccini G, Bernardini S, Bianchi MC, Tosetti M, et al. Proton magnetic resonance spectroscopy (1H-MRS) of motor cortex and basal ganglia in de novo Parkinson's disease patients. Neurological sciences: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2001;22:69-70.
21. Camicioli RM, Hanstock CC, Bouchard TP, Gee M, Fisher NJ, Martin WR. Magnetic resonance spectroscopic evidence for presupplementary motor area neuronal dysfunction in Parkinson's disease. Movement disorders: official journal of the Movement Disorder Society. 2007;22:382-6.
22. Hu MT, Taylor-Robinson SD, Chaudhuri KR, Bell JD, Morris RG, Clough C, et al. Evidence for cortical dysfunction in clinically non-demented patients with Parkinson's disease: a proton MR spectroscopy study. Journal of neurology, neurosurgery, and psychiatry. 1999;67:20-6.
23. Zheng XN, Zhu XC, Ruan LX, Zhang LJ, Yuan M, Shang DS, et al. MRS study on lentiform nucleus in idiopathic Parkinson's disease with unilateral symptoms. Journal of Zhejiang University Science. 2004;5:246-50.
24. Rudkin TM, Arnold DL. Proton magnetic resonance spectroscopy for the diagnosis and management of cerebral disorders. Archives of neurology. 1999;56:919-26.
25. Griffith HR, den Hollander JA, Okonkwo OC, O'Brien T, Watts RL, Marson DC. Brain metabolism differs in Alzheimer's disease and Parkinson's disease dementia. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2008;4:421-7.
26. Griffith HR, Okonkwo OC, O'Brien T, Hollander JA. Reduced brain glutamate in patients with Parkinson's disease. NMR in biomedicine. 2008;21:381-7.
27. Summerfield C, Gomez-Anson B, Tolosa E, Mercader JM, Marti MJ, Pastor P, et al. Dementia in Parkinson disease: a proton magnetic resonance spectroscopy study. Archives of neurology. 2002;59:1415-20.