Longitudinal magnetic resonance spectroscopy and cognitive impairment in Parkinson's disease

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1 Parkinson's disease (PD) at a glance

PD: A neurodegenerative movement disease.
Prevalence: Affects up to 2% of individuals over 60.
Risk factors: Age.
Diagnosis: Clinical & neuropsychological assessment
Symptoms: Motor: tremor, slow movement, rigidity;
Cognitive: impairments in multiple domains, including attention, executive, function, and memory;
Others: sleep disturbance and swallowing difficulties.
Treatment: Medications & Surgical (motor symptoms only).

2 The problem

As the disease progresses, cognitive impairments become more manifest in many patients, ultimately leading to dementia in the majority. However, there is considerable variation (range 2-20 years) between onset of the initial motor disorder and the emergence of dementia.[1] Importantly, this delay provides a window for potential therapeutic intervention.

Detecting cognitive impairment at its earliest stages would facilitate the most appropriate and timely intervention aimed at slowing the progression to dementia.

However, the assessment of neuroprotective and disease-modifying therapies in PD has been hampered by a lack of clinically useful, reliable neurobiomarkers.

3 The proposed solution

Magnetic Resonance Spectroscopy (MRS) provides an attractive option to identify a neurobiomarker of cognition in PD.[2]

4 Aim

To examine whether MRS of posterior cingulate cortex (PCC) can track the metabolic changes associated with cognitive impairment in Parkinson's disease.

5 Methods

- All subjects completed a neuropsychological battery and were classified as healthy controls (HC), PD with normal cognition (PDN), PD with mild cognitive impairment (PDMCI), or PD with dementia (PDD) (**Table 1**).
- At baseline, 179 subjects underwent MR spectroscopy examinations.
- The follow-up stage involved re-imaging 173 controls and non-demented subjects for up to 4 years after their initial assessment.
- 2 × 2 × 3cm^3 MRS voxel was placed on the posterior cingulate cortex of the brain (**Figure 1**).
- We quantified 4 metabolites and their ratios (**Table 2**).

6 Results

- Cognition performance scores significantly varied at baseline and over time among the groups.
- MRS markers showed no significant group difference at baseline.
- At follow-up, neither a significant change in MRS markers nor a relationship between the MRS markers and the change in the cognitive status were identified (**Table 3**).

7 Conclusion

- With a large sample size and comprehensive neuropsychological assessment, we were unable to identify any significant change in MRS parameters relating to cognitive status at baseline or over time.
- Our findings suggest that MRS, of the PCC at least, is not a clinically useful biomarker of longitudinal change in cognitive impairment in Parkinson's disease.

Table 1. Demographic and neuropsychological data by group at baseline

	Controls	PDN	PDMCI	PDD
n	49	77	33	20
Sex (M/F)	33/16	51/26	21/12	17/3
Age (years)	68(8)	64(8)*	70(5)	73(7)*
Education (years)	13(2)	13(2)	13(3)	12(2)
Disease duration(years)	NA	2(3)	5(5)	10(8)
LED (mg/day)	NA	221(333)	403(428)	736(400)
Cognitive Z score	0.63(0.37)	0.26(0.43)**	-0.72(0.39)**	-1.71(0.58)**
MoCA	27(1.9)	26(2.2)**	27(2.4)**	17(3.8)**

Values are mean (sd). *p<0.05 & **p<0.001 between control and PD groups at baseline. LED = Levodopa Equivalent Dose. MoCA = Montreal Cognitive Assessment. Z score = represents the global cognition.

Table 2. The brain metabolites and their physiological significance.

Metabolite	Physiological Significance	Interpretation
N-Acetylaspartate (NAA)	Neuronal integrity marker	Reduced NAA indicates compromised neuronal integrity
Choline (Cho)	Cell membrane breakdown marker	Increased Cho indicates higher cell membrane breakdown
Creatine (Cr)	Represents energy storage	Relatively stable in most diseases
myo-Inositol (mI)	Glial cell marker	Increased mI indicates an ongoing gliosis

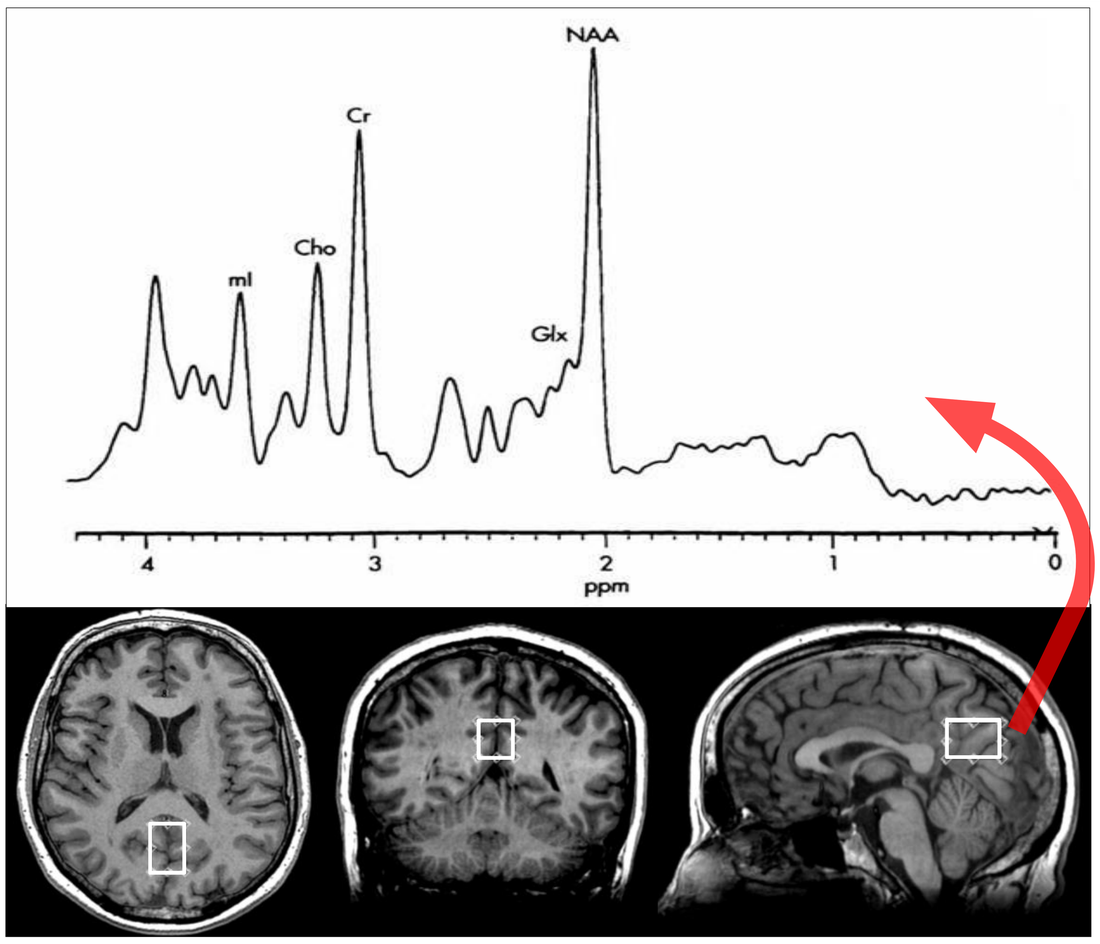

Figure 1. Axial, coronal, and sagittal (left to right) MRI structural images showing the voxel location and an example MR Spectrum.

Table 3. Baseline and follow-up results of cognitive performance and MRS markers

Baseline	HC (95% PI)	PDN – HC (95% PI)	PDMCI – HC (95% PI)	PDD – HC (95% PI)
Cognitive Z score	**0.53** (0.37 — 0.70)	**-0.32*** (-0.48 — -0.16)	**-1.23*** (-1.42 — -1.03)	**-1.53*** (-2.33 — -0.60)
NAA/Cr	**1.64** (1.52 — 1.76)	**0.013** (-0.06 — 0.08)	**0.002** (-0.07 — 0.07)	**-0.248** (-0.53 — 0.01)
Cho/Cr	**0.50** (0.45 — 0.56)	**0.01** (-0.02 — 0.04)	**0.01** (-0.02 — 0.05)	**0.08** (-0.056 — 0.21)
Follow-up change	**HC unit/year (95% PI)**	**PDN unit/year – HC (95% PI)**	**PDMCI unit/year – HC (95% PI)**	
Cognitive Z score	**0.007** (-0.0368 — 0.0510)	**-0.068*** (-0.1278 — -0.0058)	**-0.141*** (-0.2296 — -0.0410)	
NAA/Cr	**-0.013** (-0.0333 — 0.0064)	**-0.008** (-0.0265 — 0.0108)	**-0.003** (-0.0292 — 0.0216)	
Cho/Cr	**0.002** (-0.0059 — 0.0101)	**0.004** (-0.0045 — 0.0122)	**-0.004** (-0.0157— 0.0072)	

***For baseline:* values are mean difference estimates for PDN, PDMCI and PDD relative to controls.**
***For follow-up:* values are mean difference estimates representing the annual rate of change for PDN and PDMCI relative to controls. Values with negative signs represent the decrease in either the global cognitive score or MRS measures over time. 95% PI = 95% Probability Interval. *Significantly different relative to healthy controls.**

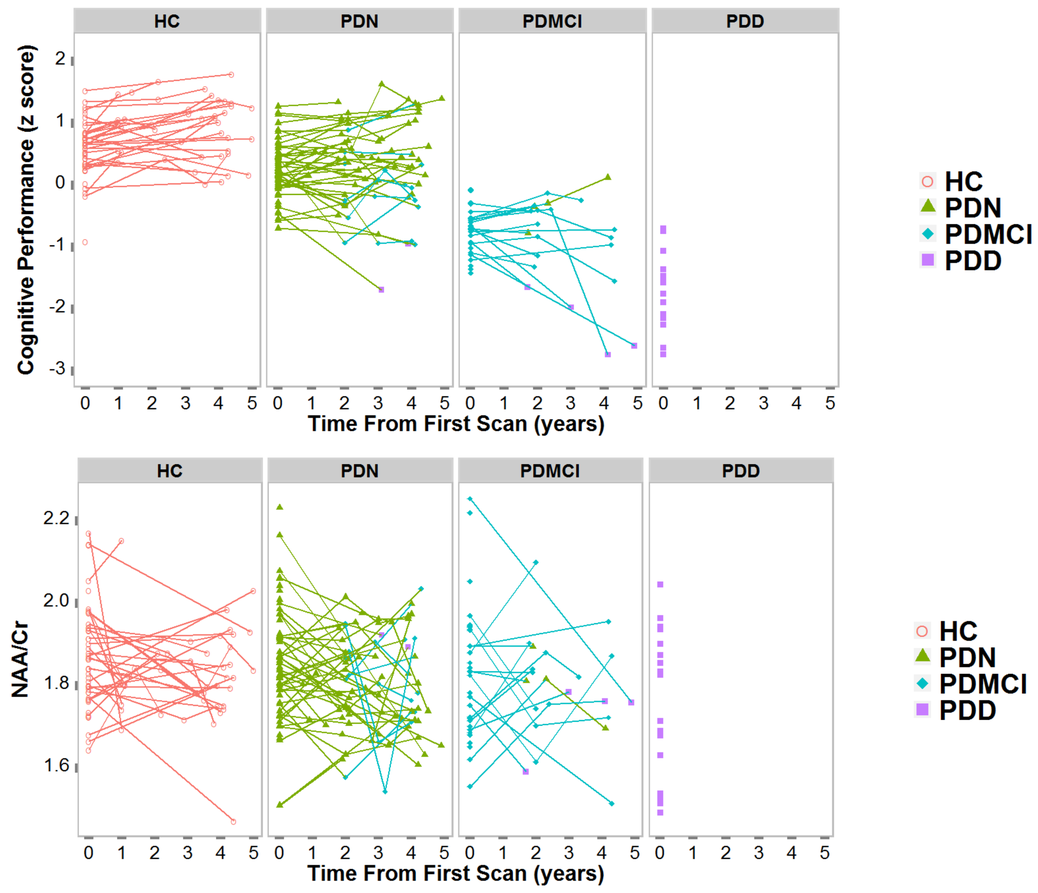

Figure 2. Trajectory of global cognitive Z score over time by cognitive group (top) and NAA/Cr ratio (bottom).

References: [1] Litvan I, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Movement disorders 2012;27:349-356. [2] Griffith, et al. Brain metabolism differs in Alzheimer's disease and Parkinson's disease dementia. Alzheimer's & dementia. 2008;4:421-427.

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