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Metabolite ratios in the posterior cingulate cortex do not track cognitive decline in Parkinson's disease in a clinical setting

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ABSTRACT

Introduction: Parkinson's Disease (PD) is classified as a motor disorder, but most patients develop cognitive impairment, and eventual dementia (PDD). Predictive neurobiomarkers may be useful in the identification of those patients at imminent risk of PDD. Given the compromised cerebral integrity in PDD, we investigated whether brain metabolites track disease progression over time.
Methods: Proton Magnetic Resonance Spectroscopy (MRS) was used to identify brain metabolic changes associated with cognitive impairment and dementia in PD. Forty-nine healthy participants and 130 PD patients underwent serial single voxel proton MRS and neuropsychological testing. At baseline patients were classified as either having normal cognitive status (PDN, n = 77), mild cognitive impairment (PDMCI, n = 33), or dementia (PDD, n = 20). Posterior cingulate cortex (PCC) was examined to quantify N-acetylaspartate (NAA), choline (Cho), creatine (Cr), and myo-inositol (mI). A hierarchical Bayesian model was used to assess whether cognitive ability and other covariates were related to baseline MRS values and changes in MRS over time.
Results: At baseline, relative to controls, PDD had significantly decreased NAA/Cr and increased Cho/Cr. However, these differences did not remain significant after accounting for age, sex, and MDS-UPDRS III. At follow-up, no significant changes in MRS metabolite ratios were detected, with no relationship found between MRS measures and change in cognitive status.
Conclusions: Unlike Alzheimer's disease, single voxel MR spectroscopy of the PCC failed to show any significant association with cognitive status at baseline or over time. This suggests that MRS of PCC is not a clinically useful biomarker for tracking or predicting cognitive impairment in Parkinson's disease.

1. Introduction

In addition to the classic motor symptoms of rigidity, tremor, and bradykinesia, many Parkinson's disease (PD) patients experience cognitive impairments. These cognitive problems worsen as the disease progresses, ultimately leading to dementia in the majority [1,2]. However, there is considerable variation (range 2–20 years) between onset of PD and the emergence of dementia [3]. This delay provides a window for potential therapeutic intervention [2,4]. Neuroimaging is an attractive option for identifying neurobiomarkers of cognitive status, especially mild cognitive impairment (PDMCI), and the progression to dementia. Suitable biomarkers may facilitate timely interventions to slow cognitive decline.

One candidate is proton Magnetic Resonance Spectroscopy (MRS). This technique allows in vivo measurement of the metabolites N-acetylaspartate (NAA, a neuronal marker), choline (Cho, a cell membrane turnover marker), creatine (Cr, an energy metabolism marker; typically used as an internal control metabolite in MRS analysis), and myo-Inositol (mI, a glial cell marker) [5,6].

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Abnormal metabolic ratios (NAA/Cr, Cho/Cr and mI/Cr) in the posterior cingulate cortex (PCC) have been identified in Alzheimer's disease (AD), as well as other neurodegenerative diseases such as fronto-temporal dementia [7]. A recent meta-analysis of single voxel MR spectroscopy in the PCC of patients with dementia and mild cognitive impairment (MCI) of the Alzheimer's type reported accelerated metabolic changes over time in the PCC of MCI patients relative to controls [8]. Metabolic changes measured by MRS in such degenerative disorders have been linked to neuronal loss, axonal injury and compromised neuronal energy metabolism [9], but the value of MRS as a similar biomarker in PD remains uncertain.

In this study, we used single-voxel proton MRS to investigate the integrity of the PCC in PD over time. The PCC exhibits high resting state metabolism, is a key hub in the fMRI-identified default mode network, and is highly involved in multiple cognitive processes [10–12]. Additionally, it is one of the first areas to be compromised in early Alzheimer's disease [9]. It is also affected in PD, showing compromised metabolism (via positron emission tomography), reduced perfusion (via arterial spin labeling MRI), and cortical thinning (via structural MRI) [13–15]. Furthermore, cross sectional MRS in the PCC has identified reduced NAA/Cr in both PDD and non-demented PD [16–18], therefore suggesting it as a potential biomarker to track Parkinson's progression. However, abnormal MRS in PD cross-sectional studies is not a universal finding and provides no information on whether such a measure reflects progression [19]. We therefore investigated the relationship between single-voxel proton MRS metabolite ratios and PD-related cognitive decline, cross-sectionally and over time, in order to evaluate its utility as an imaging biomarker. In order to make any possible findings immediately applicable in the clinic, we used automated, scanner-quantified MRS ratios [20,21].

2. Participants and methods

This study was approved by the Upper South Ethics Committee of the New Zealand Ministry of Health. All participants, or significant others where appropriate, provided written informed consent. A convenience sample of 130 PD patients, comprising those with normal cognitive status (PDN, n = 77); mild cognitive impairment (PDMCI, n = 33); or dementia (PDD, n = 20), was recruited from the Movement Disorders Clinic at the New Zealand Brain Research Institute, Christchurch, New Zealand, between May 2007 and August 2013. All satisfied the UK Parkinson's Society criteria for idiopathic PD [22]. Forty-nine healthy adults were recruited to match the PD patients for mean age, years of education and sex ratio. Exclusion criteria included atypical parkinsonian disorder; prior learning disability; history of other neurologic conditions including moderate–severe head injury, stroke, vascular dementia; and major psychiatric or medical illness in the previous six months. Patients diagnosed with dementia (PDD, n = 20) at baseline were not followed further as dementia was considered an endpoint, but data from this group were included for baseline comparisons.

Of the 110 non-dementia PD cases, 64 were re-imaged on at least one other occasion over the subsequent four years for a total of 106 follow-up scans. Of the 49 healthy controls at baseline, 40 individuals were similarly re-imaged, with a total of 59 follow-up scans. These follow-up assessments occurred at approximately two and four years after baseline. Demographic details are presented in Table 1. Fig. 1B depicts the timings of when scanning was performed in each individual.

2.1. Clinical and cognitive assessment

Motor severity was assessed with Hoehn and Yahr (H&Y) [23] staging and part III of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) [24]. Montreal Cognitive Assessment (MoCA) was used as a screening tool for cognitive performance [25]. A comprehensive neuropsychological battery assessed cognitive status consistent with the Movement Disorder Society (MDS) recommended domains [2] (executive function – letter, action and category fluency, category switching, Trails B and Stroop interference; attention, working memory, and processing speed – digits forward and backward, digit ordering, map search, Stroop color and word reading, and Trails A; learning and memory – California Verbal Learning Test-short form short and long delay recall, and the Rey–Osterrieth complex figure short and long delay; visuospatial/visuoperceptual function – judgment of line orientation, fragmented letters and Rey–Osterrieth complex figure copy; and language – Boston naming, DRS-2 similarities subtest, and ADAS-Cog) Standardized scores from the constituent neuropsychological tests were averaged to provide individual cognitive domain scores. Global cognitive ability for each participant was then expressed as an aggregate z score obtained by averaging four domain scores (non-normality of the language scores precluded their inclusion) [26]. Consistent with the MDS task force level II diagnostic criteria, PDMCI patients did not have significantly impaired functional activities of daily living, verified by interview with a significant other, and scored $\geq$1.5 standard deviations (or equivalent) below normative data on at least two measures within at least one of the five cognitive domains [26]. MDS criteria were also used to diagnose dementia (PDD) [1]. Accordingly, patients were classified at baseline as either having normal cognitive status (PDN, n = 77), mild cognitive impairment (PDMCI, n = 33), or dementia (PDD, n = 20) [27]. Table 1 summarizes the neuropsychological assessment results.

2.2. MRS acquisition

Magnetic Resonance spectroscopy (MRS) data were acquired on a 3.0 T General Electric Signa HDxt scanner (GE Medical Systems, Wauwatosa, WI) using an eight channel head coil. The imaging protocol included: (1) a T1-weighted 3D spoiled gradient recalled echo sequence (echo time = 2.8 ms, repetition time = 6.6 ms, inversion time = 400 ms, flip angle = 15°, acquisition matrix = 256 × 256, 170 slices, field of view = 250 mm, slice thickness = 1 mm, voxel size = 0.98 × 0.98 × 1.0 mm^3), and (2) a single voxel Point Resolved Spectroscopy (PRESS) acquisition, echo time = 35 ms, repetition time = 1500 ms, voxel size = 20 × 20 × 30 mm^3, number of averages = 128. At each time point, one of three experienced MR radiographers placed the spectroscopy voxel of interest (VOI) in the midline posterior cingulate cortex (PCC) of the brain (Figure S.1). Pre-scan shimming was performed to achieve full-width half maximum (line width) of $\leq$13 Hz [28]. Table S.1 demonstrates the mean linewidth and water suppression values for the study groups.

Metabolite ratios, with creatine (Cr) as the reference metabolite, were produced using scanner software (PROBE-Q, GE Medical Systems); this included NAA/Cr, Cho/Cr, and mI/Cr. The fully automated PROBE-Q package involves (1) Setting a global frequency fit parameter; (2) performing line-width and line-shape enhancement by appropriate apodisation of the time-domain signal; (3) Fourier transformation of the signal to the appropriate frequency resolution and number of points; (4) calculation of a baseline correction from the frequency-domain signal; (5) and curve fitting the desired regions of the frequency-domain signal. There were two software upgrades over the duration of the study (starting from scanner software v14, through v15 and lastly v16), but acquisition parameters were unchanged.