Evidence for cortical dysfunction in clinically non-demented patients with Parkinson's disease: a proton MR spectroscopy study

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Abstract

***Objectives*—To investigate whether proton magnetic resonance spectroscopy (^{1}H MRS) can detect cortical dysfunction in non-demented patients with Parkinson's disease, and to correlate changes with cognitive function on formal neuropsychological testing.**

***Methods*—Multivoxel ^{1}H MRS was performed in 17 patients with levodopa treated idiopathic Parkinson's disease without clinical dementia, and 10 age matched control subjects. Measurements of N-acetylaspartate (NAA)/choline (Cho), NAA/creatine+phosphocreatine (Cr), and Cho/Cr were obtained from right and left temporoparietal cortex and occipital cortex. Fourteen patients with Parkinson's disease underwent a full battery of neuropsychological testing including performance and verbal subtests of the WAIS-R, Boston naming test, FAS test, and California verbal learning test.**

***Results*—There were significant temporoparietal cortex reductions in NAA/Cr ratios in right and left averaged spectra of the patients with Parkinson's disease (p=0.012 after Bonferroni correction) and in spectra contralateral to the worst clinically affected limbs of the patients with Parkinson's disease compared with controls (p = 0.003 after Bonferroni correction). There was a significant correlation between reduction in NAA/Cr ratios and measures of global cognitive decline, occurring independently of motor impairment (p=0.019).**

***Conclusions*—This study suggests that ^{1}H MRS can detect temporoparietal cortical dysfunction in non-demented patients with Parkinson's disease. Further longitudinal studies are needed to investigate whether these ^{1}H MRS changes are predictive of future cognitive impairment in the subset of patients with Parkinson's disease who go on to develop dementia, or occur as part of the normal Parkinson's disease process.**

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Estimates of the prevalence of dementia in Parkinson's disease are variable and range from 10% to 40%, the frequency increasing with age.[1–3] Mild cognitive slowing without overt dementia is a common feature of Parkinson's disease even in patients with early untreated disease.[4 5] Formal neuropsychological tests show additional deficits in visuospatial capacity, memory, and frontal lobe function,[4–6] although assessment can be complicated by motor dysfunction. Pathological processes contributing to cognitive impairment in the Parkinson's disease patient group may include striatal and extrastriatal dopamine deficiency, ascending noradrenergic, cholinergic, and serotonergic cortical deficits, and the presence of coexistent Alzheimer's pathology or cortical Lewy bodies.[4–6] However, not all patients with Parkinson's disease and cognitive impairment go on to develop dementia. Independent variables predictive of development of subsequent dementia in patients with Parkinson's disease may include an older age of onset of disease, poor verbal fluency, and poor scoring on the picture completion subtest of the Wechsler adult intelligence scale (WAIS).[7]

Proton magnetic resonance spectroscopy (^{1}H MRS) allows the in vivo, non-invasive study of brain metabolism and has been widely applied to the study of disease mechanisms in the CNS.[8–10] Principal metabolite signals detected by ^{1}H MRS include N-acetylaspartate (NAA; an amino acid contained almost exclusively within neurons and their processes within adult brain[11–13]), choline (Cho; metabolites involved in phospholipid membrane synthesis and breakdown including mainly glycerophosphocholine and phosphocholine[12–14]), and creatine and phosphocreatine (Cr; a cellular energy buffering system[12 13]). ^{1}H MRS has been extensively used to investigate Alzheimer's disease and vascular dementia showing significant reductions in NAA/Cr and NAA/Cho ratios in frontal, temporal, and parietal cortex consistent with a regional pattern of neuronal damage to the associative cortices.[15–17] Studies in patients with the AIDS dementia complex have shown significant NAA/Cho and NAA/Cr reductions in parietooccipital cortex compared with controls.[18] In Parkinson's disease and the parkinsonian syndromes, ^{1}H MRS has been largely used to study striatal metabolism,[19–23] and few if any studies have specifically examined cortical function in patients with Parkinson's disease without overt dementia.[9 24] Preliminary studies from our unit have suggested the presence of temporoparietal cortex NAA/Cr reductions in patients with Parkinson's disease.[25] Based on these initial

Table 1 Clinical details of the 17 patients with idiopathic Parkinson's disease studied

Patient No	*Age (y)*	*Duration (y)*	*Hoehn and Yahr stage (1–5)*	*Motor UPDRS (0–56)*	*Drugs*
1	69	6	2.0	15	Levodopa, amantadine
2	74	3	2.5	19	Levodopa
3	61	3	2.0	19	Levodopa
4	66	15	4.0	31	Levodopa, pergolide, selegiline
5	50	8	4.0	30	Levodopa, apomorphine,
6	64	2	1.5	15	Levodopa, pergolide
7	61	4	2.0	14	Levodopa
8	66	5	3.0	25	Levodopa
9	57	5	4.0	33	Levodopa, apomorphine
10	76	16	4.0	40	Levodopa, apomorphine, pergolide
11	57	5	2.5	17	Levodopa
12	66	16	2.5	19	Levodopa, benzhexol
13	53	5	1.0	12	Levodopa
14	62	8	2.5	16	Levodopa, cabergoline, benzhexol
15	55	5	1.0	10	Levodopa, entacapone
16	47	4	1.0	9	Levodopa, entacapone
17	59	2	2.0	14	Levodopa

Duration=Symptom duration in year; motor UPDRS=total motor score of the UPDRS scale for worst clinically affected limbs.

findings, we have used a multivoxel technique to investigate whether ^{1}H MRS can detect cortical dysfunction in a larger group of non-demented patients with Parkinson's disease, and whether such dysfunction correlates with the presence of cognitive impairment on formal neuropsychological testing.

Methods

SUBJECTS

Seventeen patients with Parkinson's disease, mean age 61 (SD 8) years (range 47 to 74 years), and 10 age matched healthy volunteers, mean age 58 (SD 8) years (range 48 to 67 years) were studied. Patients with Parkinson's disease were Hoehn and Yahr stage I to IV (mean 2.4 (SD 1.1)), with a mean disease duration of 6.6 (SD 4.6) years (range 2 to 16 years). All patients satisfied the United Kingdom Brain Bank criteria for the diagnosis of idiopathic Parkinson's disease.[26] Further clinical details of the patients are shown in table 1.

CLINICAL ASSESSMENTS

All patients were assessed in the "off" state on the morning of the MRS examinations using the unified Parkinson's disease rating scale (UPDRS) and Hoehn and Yahr rating scale after withdrawal of all antiparkinsonian medication for 12 hours. Patients were screened for atypical parkinsonian features, in particular cardiovascular autonomic dysfunction, ataxia, and cognitive impairment.[26] On the same day as MRS 14 patients underwent an extensive battery of neuropsychological testing (in the "on" state while receiving antiparkinsonian medication) including the Folstein abbreviated mini mental test (AMT),[27] the National adult reading test (NART) to assess premorbid IQ,[28] measures of frontal lobe function including the FAS test[29] and the Boston naming test,[30 31] the California verbal learning test to quantify components of verbal learning and memory,[32 33] performance subtests of the WAIS-R[34] including object assembly and block design, and verbal subtests of the WAIS-R including digit span, comprehension, similarities, and vocabulary. All patients also completed a geriatric depression score[35] and a Beck depression inventory.[36] The remaining patients with Parkinson's disease and controls underwent Folstein AMT testing. Patients with features suggestive of dementia with Lewy bodies, such as visual hallucinations, paranoid delusions or fluctuating confusion[37] were excluded from the study.

MAGNETIC RESONANCE IMAGING

Brain ^{1}H MRS was performed at the magnetic resonance unit of the Hammersmith Hospital using a Picker prototype spectroscopy system, based on a whole body magnet (Oxford Magnet Technology, Oxford, UK), operating at 1.5 Tesla. T1 weighted axial images were acquired to position a 2 cm transverse slice at the level of the basal ganglia (fig 1). A two dimensional chemical shift imaging (2-D CSI) technique was used to obtain spectra from multiple contiguous voxels covering all the brain in the selected slice. Chemical shift imaging spectral acquisition consisted of a 1331–180° spin echo; a 1331 composite pulse for water suppression, with a 90° excitation at the NAA resonance, a slice selective 180°, and phase encoding in the two in lane directions. Spectral acquisition parameters were TR 1500s, TE 130 s, and 32 phase ncoding steps in each direction giving 1024 averages in 26 minutes.[38] Chemical shift imaging resolution was 15 mm×15 mm×20 mm, giving a voxel size of 4.5 cm^3. In addition, a non-selective inversion pulse preceded each data acquisition, T1150 ms, to reduce the fat signal from the surface voxels, and consequent bleeding into neighbouring voxels. Shimming was performed on the water signal from the slice, typically achieving a line width at half height of 5 Hz. Total examination time was about 60 minutes. Patients were scanned in the off phase after overnight withdrawal of medication to reduce movement artefacts with the exception of three patients who were severely disabled and required apomorphine injections, but were clinically off by the time of the scan.

DATA ANALYSIS

A knowledge based algorithm[39] was used both for removal of the water peak residuum and for baseline flattening. Peak area ratios of NAA, Cho, and Cr were measured using the NMR1® spectral processing program (New Methods Research, Inc, E Syracuse, NY, USA) on a SUN SPARCstation 10 (Sun Microsystems, Inc, Mountain View, CA, USA). The results for each spectrum were analysed and their positions were checked by a blinded observer (STR). The resolved spectral lines (NAA, Cr, and Cho) were quantified with gaussian curve fitting, as this gave the best results in terms of fit and reproducible metabolite ratios.[38]

Three regions of interest were sampled in patients with Parkinson's disease and controls: right and left temporoparietal (predominantly temporal) cortex and occipital cortex. It was not possible to sample frontal lobe spectra due to inhomogeneity arising from frontal eye fields and sinuses. Because the multivoxel technique did not always permit accurate voxel placement over the lentiform nucleus or putamen, insuffi-

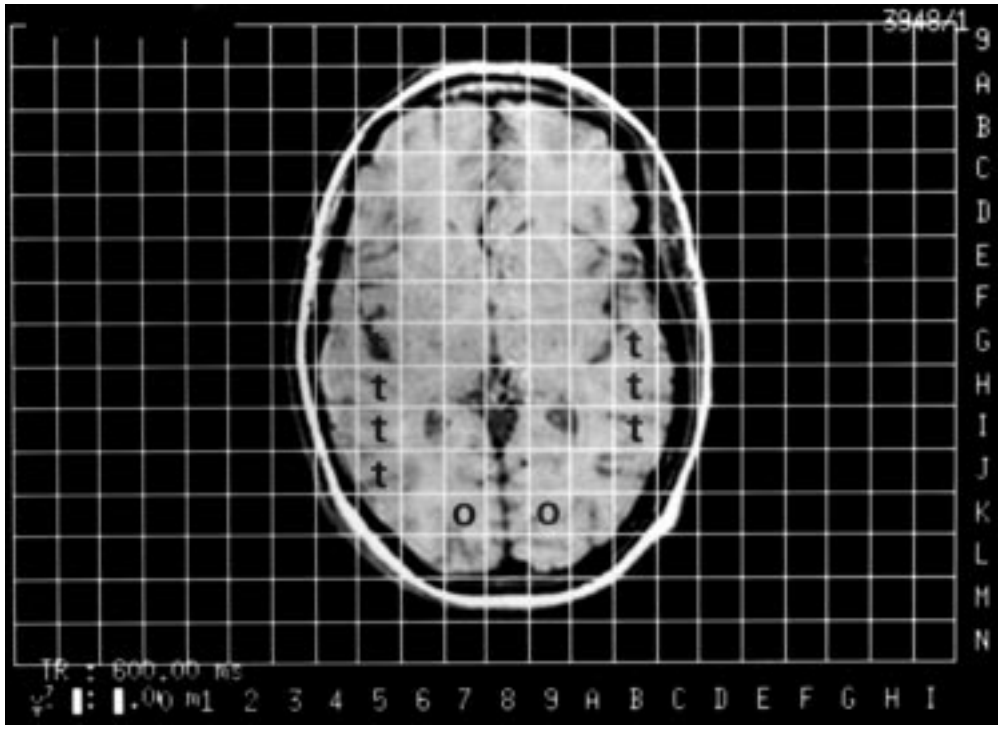

Figure 1 Basal ganglia slice through a brain of a Parkinson's disease patient with ^{1}H 2-D CSI grid applied showing region of interest location. Regions of interest are temporoparietal (predominantly temporal) cortex (t) and occipital cortex (o).

cient basal ganglia spectra were obtained for statistical analysis. To reduce sampling error, an average of 2 to 3 voxels for each cortical region was used in the statistical analysis, with an average of right and left occipital spectra used to give the final occipital values. Care was taken to choose cortical voxels centred as much as possible on grey matter, with minimal CSF content. Thirteen of the 17 patients with Parkinson's disease also underwent T1 weighted volumetric MRI (TR 21 ms, TE 6 ms) on a 1.0 T Picker HPQ scanner, which were visually assessed for degree of cerebral atrophy. The study was approved by the ethics committee of the Hammersmith and King's College Hospitals.

STATISTICAL ANALYSIS

Metabolite differences between patients with Parkinson's disease and control subjects were examined for each region of interest and for each metabolite ratio (NAA/Cho, NAA/Cr, and Cho/Cr) using Student's independent samples *t* test (SPSS Software Inc, Chicago, IL, USA). Bonferroni correction for multiple regions was applied. Correlations between metabolite ratios and clinical measures were assessed using linear regression analysis.

Results

^{1}H MRS AND MR IMAGING

Results of the NAA/Cr ratios are summarised in table 2. There was a significant reduction in NAA/Cr ratios in right and left averaged temporoparietal cortex spectra of patients with Parkinson's disease compared with control subjects (p=0.012, Bonferroni correction). Comparison of right and left temporoparietal cortex spectra (fig 2) of the patients with Parkinson's disease with those of normal subjects showed a significant reduction in left temporoparietal cortex spectra of patients (p=0.039 corrected), with a non-significant reduction in right temporoparietal cortex spectra of the patients (p=0.135 corrected). Separate comparison of temporoparietal cortex spectra contralateral and ipsilateral to the worst clinically affected limbs of the patients with Parkinson's disease (as determined on motor UPDRS scores when off) with those of normal subjects showed significant reductions in contralateral temporoparietal cortex NAA/Cr (p=0.003 corrected) but not ipsilateral cortex. No significant correlations were found between regional NAA/Cr ratios and motor disability or disease duration. There were no significant differences in NAA/Cho and Cho/Cr ratios between patients with Parkinson's disease and control subjects for any of the regions. Volumetric MRI performed on 14 of the 17 patients with Parkinson's disease showed that three patients had mild cerebral atrophy but no cerebellar or brainstem atrophy.

COGNITIVE TESTING

The results of the psychiatric and neuropsychological testing are summarised in table 3. With the exception of one patient who was being treated for depression, none of the patients with Parkinson's disease were clinically depressed according to Beck depression inventory and geriatric depression scales. All the patients with Parkinson's disease scored 24 or more on the Folstein AMT (mean (SD) 28.3 (1.6)),[40] and all individual neuropsychological test scores fell within a mean ± 2 SD when compared with an age matched control population. None of the patients fitted clinical crite-

Table 2 ^{1}H MRS findings in patients with Parkinson's disease and control subjects

Region	*Parkinson's disease*	*Control subjects*
NAA/Cr		
Right and left TP averaged	1.78 (0.30)*	2.20 (0.38)
Contralateral TP	1.61 (0.30)**	
Ipsilateral TP	1.95 (0.53)	
Right TP (contralateral hemisphere in 7 patients)	1.81 (0.48)	2.24 (0.56)
Left TP (contralateral hemisphere in 10 patients)	1.75 (0.44)*	2.17 (0.34)
Occipital	2.38 (1.10)	2.54 (1.07)
NAA/Cho		
Right and left TP averaged	3.03 (0.65)	2.74 (0.56)
Contralateral TP	3.08 (1.40)	
Ipsilateral TP	2.89 (0.80)	
Right TP	3.08 (0.84)	2.93 (0.64)
Left TP	2.89 (1.38)	2.56 (0.64)
Occipital	4.81 (2.44)	3.79 (1.12)
Cho/Cr		
Right and left TP averaged	0.69 (0.20)	0.82 (0.22)
Contralateral TP	0.63 (0.25)	
Ipsilateral TP	0.76 (0.32)	
Right TP	0.66 (0.24)	0.76 (0.22)
Left TP	0.74 (0.35)	0.83 (0.21)
Occipital	0.64 (0.44)	0.73 (0.45)

Results are given as mean (SD). TP=Temporoparietal; contralateral=contralateral to worst clinically affected limbs in patients with Parkinson's disease; ipsilateral=ipsilateral to worst clinically affected limbs in patients. All right, left, contralateral, and ipsilateral TP values for the patients were compared with the average of right and left TP values for the controls.
*p<0.05; **p<0.01 (Bonferroni correction) between controls and patients.

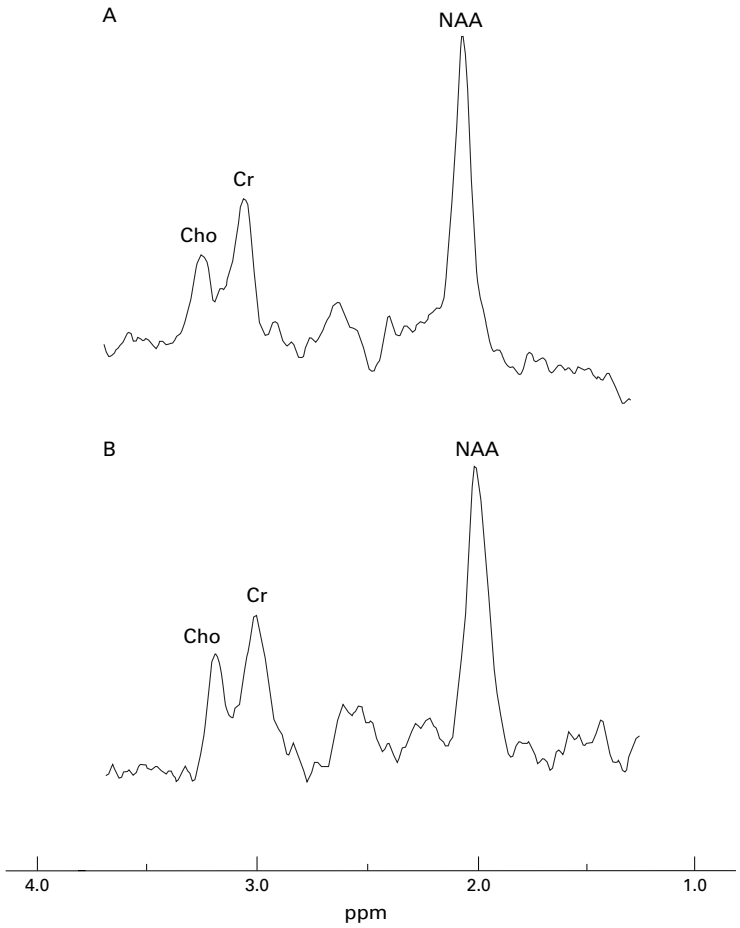

Figure 2 Representative 2-D CSI spectra from (A) temporoparietal cortex and (B) occipital cortex in a patient with Parkinson's disease. Cho=choline (3.22 ppm); Cr=creatine (3.02 ppm); NAA=N-acetylaspartate (2.02 ppm).

ria for a dementing illness. Overall, the mean verbal IQ of the patients was in the high average range and the mean performance and full scale IQ was in the average range. Performance on subtests of the WAIS-R measuring visuospatial performance, such as block design and object assembly, was selectively impaired in the patients with Parkinson's disease unlike performance on verbal subtests. Tests of executive function, such as the FAS test and digit span of the WAIS-R, were also performed poorly as were memory tests such as the CVLT. Naming ability, tested using the Boston naming test was also mildly impaired in the patients. When the reductions in verbal, performance and full scale IQ were calculated by subtracting calculated IQ values from premorbid estimates using the NART, performance IQ was impaired more than full scale IQ, whereas the verbal IQ actually showed a higher level compared with premorbid estimates possibly due to the NART underestimating intelligence in more able patients.

Table 3 Neuropsychology results of the patients with Parkinson's disease studied compared with age matched control data

Neuropsychological test	*Parkinson's disease*	*Control data*
WAIS-R		
Digit span	9.6 (2.3)	10.0 (3.0)
Vocabulary	11.1 (3.0)	10.0 (3.0)
Comprehensions	14.6 (2.9)	10.0 (3.0)
Similarities	13.1 (3.2)	10.0 (3.0)
Block design	9.9 (1.7)	10.0 (3.0)
Object assembly	7.9 (3.0)	10.0 (3.0)
Folstein AMT	28.3 (1.6)	29.2 (1.3)
Boston naming test	54.9 (5.1)	56.7 (3.0)
FAS	28.4 (1.7)	37.6 (10.9)
CVLT	35.4 (11.7)	47.9 (10.0)
Verbal IQ	114.8 (18.5)	100 (15)
Performance IQ	93.5 (10.8)	100 (15)
Fullscale IQ	106.1 (14.0)	100 (15)
NART verbal IQ	108.6 (11.6)	100 (15)
NART performance IQ	109.7 (11.3)	100 (15)
NART full scale IQ	110.4 (12.7)	100 (15)
Difference verbal IQ	−6.8 (12.1)	
Difference performance IQ	16.2 (11.3)	
Difference full scale IQ	4.3 (9.4)*	
Beck depression inventory	9.2 (8.2)	
Geriatric depression scale	3.5 (2.8)	

Difference in verbal, performance and fullscale IQ calculated as NART premorbid estimate of IQ minus actual IQ as calculated from the WAIS-R. Control reference ranges quoted as means for men and women, for 60-64 year age group, with education <12 years where applicable.[25 26 28 30 31] *p<0.05; reductions in NAA/Cr ratios of right and left temporoparietal cortex combined and neuropsychometric test.

COGNITIVE TESTING AND METABOLITE RATIOS

There was a significant inverse correlation between the right and left averaged temporoparietal cortex NAA/Cr ratio of the patients with Parkinson's disease and calculated reductions in full scale IQ obtained from estimated premorbid levels (Pearson correlation coefficient r=−0.55, p= 0.043). Additionally, estimated reductions in full scale IQ significantly correlated with motor UPDRS scores (r=0.741, p=0.001). One explanation for the correlation between levels of temporoparietal NAA/Cr and estimated reductions in full scale IQ in Parkinson's disease is that the latter was occurring secondary to motor impairment. To test this possibility, motor impairment as rated by motor UPDRS scores was partialled out in the correlational analysis between NAA/Cr and full scale IQ reduction. The correlation increased in significance (p=0.019) suggesting that the correlation between reduction in full scale IQ and NAA/Cr ratios was actually confounded by motor impairment in the Parkinson's disease group. There were no other

significant correlations between NAA/Cr ratios and neuropsychological tests including subtests of the WAIS-R, and no correlation between NAA/Cr ratios and disease duration or motor UPDRS scores.

Discussion

The most striking finding of this study was the presence of significant global reductions in temporoparietal cortex NAA/Cr ratios in non-demented patients with Parkinson's disease. These reductions show laterality in that they are most marked in the temporoparietal cortex contralateral to the worst clinically affected limbs of the patients with Parkinson's disease. They also correlate significantly with neuropsychological measures of global cognitive decline and individual neuropsychological tests assessing language, executive, and visuospatial function. Reductions in the NAA resonance may be attributed to either reductions in neuronal density or in the mitochondrial synthesis of NAA,[41] reflecting neuronal viability. Reductions in NAA/Cr have been reported in conditions with neuronal or axonal loss[15 42] and NAA concentrations have also been shown to be linearly correlated with morphometrically measured neuronal counts in an animal model of spongiform encephalopathy.[43] Reversible reductions in NAA/Cr shown in acute multiple sclerosis lesions suggest that other mechanisms besides neuronal loss, such as transient neuronal dysfunction leading to reductions in NAA/Cr, may also be contributory.[10] The results of our study indicate that ^{1}H MRS is sensitive enough to detect neuronal loss or dysfunction in the temporoparietal cortex of patients with Parkinson's disease before the onset of overt dementia.

Our findings are consistent with ^{18}FDG PET findings reported in patients with Parkinson's disease which have shown absolute reductions in regional glucose metabolism in the parietal cortex of non-demented patients with Parkinson's disease.[44] Further PET studies using oxygen-15 inhalation have shown regional impairment of oxidative metabolism, predominantly in the parietal cortex of the affected hemispheres of patients with Parkinson's disease.[45] Patients with Parkinson's disease and overt clinical dementia showed more extensive reductions in glucose metabolism throughout frontal, temporal, parietal, and occipital cortices in a pattern similar to that seen in Alzheimer's dementia.[44 46]

Few ^{1}H MRS studies have assessed cortical function in patients with Parkinson's disease. Tedeschi *et al*[9] found no significant cortical changes in NAA/Cho and NAA/Cr ratios in non-demented patients, but significant brainstem and frontal cortex reductions in NAA/Cr ratios in patients with progressive supranuclear palsy and significant NAA/Cho ratio reductions in parietal cortex of patients with corticobasal degeneration compared with controls. There are several reasons to account for the normal cortical ^{1}H MRS findings reported in Parkinson's disease in their study. Firstly, only a single voxel was used for each region of interest (ROI) obtained for cortical and subcortical regions, whereas we took an average value of 2 to 3 voxels for each cortical region to minimise sampling error. Secondly, statistical analysis comparing differences between ROIs contralateral and ipsilateral to the worst clinically affected limbs was not performed for the patients with Parkinson's disease in the study of Tedeschi *et al*.[9] This was, however, performed in the patients with corticobasal degeneration and significant reductions in parietal NAA/Cho were found contralateral to the most affected limbs. Lastly, our study had more patients with Parkinson's disease, increasing the power to obtain a statistically significant result. Our results are in agreement with a previous study which found no differences in NAA/Cho and NAA/Cr ratios in the occipital cortex of patients with Parkinson's disease compared with controls,[24] although we did not detect any lactate peaks in any of the spectra from the patients studied.

It might be argued that the reduction in NAA/Cr ratios seen in the temporoparietal cortex of patients with Parkinson's disease was occurring secondary to cerebral atrophy. However, only three out of the 14 patients who underwent volumetric MRI showed atrophic changes and these were mild, making it unlikely that the reductions seen were due to neuronal loss. Care was also taken to select voxels centred on grey matter for the analysis of both patients with Parkinson's disease and control subjects, as previous quantitative in vivo studies using ^{1}H MRS have found parietal white matter to have about 10% less NAA than cortical grey matter of healthy volunteers.[47] The use of smaller voxel sizes may have allowed us greater accuracy of voxel placement on grey matter; however, smaller VOIs have a lower signal to noise ratio with risk of greater statistical variation in spectral analysis. Because cerebral atrophy was present in three patients, voxels may have contained differing contributions from CSF across the Parkinson's disease group. However, even if some voxels contained a much larger amount of CSF than others, metabolite signals are equally affected by partial volume effects, hence the actual metabolite ratios would be unchanged. We were not able to perform absolute quantification of metabolites in this study. Our results showed that Cho/Cr ratios were unchanged in patients with Parkinson's disease and this provides circumstantial evidence that the NAA/Cr reductions we found reflect reductions in the NAA peak itself rather than an increase in Cr concentrations, although this cannot be totally excluded in the absence of quantification. There were no significant differences in NAA/Cho ratios between patients and normal subjects. This may be partly due to reported cerebral regional variability in quantitative grey matter Cho concentrations[48] whereas the regional distribution of Cr has been reported as constant in both animal fluorometric[49] and some quantitative human ^{1}H MRS studies.[48 50]

The bilateral temporoparietal reductions in NAA/Cr ratios significantly correlated with measures of global cognitive decline using estimates of premorbid IQ, and this correlation

was present independently of the effects of motor impairment. There was no correlation between NAA/Cr ratios and individual measures of cognitive function such as subtests of the WAIS-R assessing visuospatial function, the Boston naming test, and the CVLT, possibly because the variance between different parkinsonian patients on individual subtests was too great. The fact that the temporoparietal reductions show laterality in the patients with Parkinson's disease, being more marked on the side contralateral to the worst clinically affected limb, is similar to previous findings seen in patients with corticobasal degeneration.[9] This is an interesting finding in patients with Parkinson's disease given experimental data showing corticostriatal connections between the parietal and temporal cortex and the ipsilateral caudate nucleus and putamen in monkeys.[51 52] Connections from the rostral superior parietal lobule and intraparietal sulcus to the dorsal putamen may be involved in basic somatomotor functions, and connections between caudal superior parietal lobule to dorsal putamen and the dorsolateral caudate nucleus may have a role in reaching as well as the preparation and kinematic coding of movement.[52] It is therefore possible that some of the motor symptoms of Parkinson's disease may be due to temporoparietal cortical pathology and disruption of corticostriatal connections, rather than purely mediated through the basal ganglia. The mechanism of cortical NAA/Cr reduction is unclear but may be secondary to Alzheimer's or cortical Lewy body pathology or to deficiencies in ascending dopaminergic, cholinergic, or serotonergic projections that occur in Parkinson's disease.[4–6 53]

Although we have not scanned any patients with Parkinson's disease and dementia in this study, ^{1}H MRS has been widely used to study Alzheimer's dementia, vascular dementia, and AIDS related dementia, showing significant NAA/Cr reductions in the associative cortices indicative of neuronal damage and loss.[15–18] Further larger scale, longitudinal studies using ^{1}H MRS to investigate cortical function in Parkinson's disease should consider whether the reductions we have found in non-demented patients with Parkinson's disease presage the onset of dementia given time, or whether these changes are a common finding in Parkinson's disease uncomplicated by dementia.

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