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^{1}H MRS in stroke patients with and without cognitive impairment

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Abstract

The pathophysiological basis of cognitive impairment in patients with cerebrovascular disease (CVD) is not well understood, particularly in relation to the role of non-infarction ischemic change and associated Alzheimer-type pathology. We used single voxel ^{1}H MRS to determine the differences in brain neurometabolites in non-infarcted frontal white matter and occipito-parietal gray matter of 48 stroke patients with or without cognitive impairment and 60 elderly controls. The results showed that there were no significant neurometabolite differences between the stroke cohort and healthy elderly controls, but there was a difference in NAA/H_2O between the stroke patients that had cognitive impairment (vascular dementia (VaD) and vascular cognitive impairment (VCI)) compared with those patients with no impairment. This was significant in the occipito-parietal gray matter, but not in the frontal white matter, although the results were in the same direction for the latter. This suggests that cognitive impairment in stroke patients may be related to cortical neuronal dysfunction rather than purely subcortical change. Moreover, cortical regions not obviously infarcted may have dysfunctional neurons, the pathophysiological basis for which needs further study.

Keywords: Magnetic resonance spectroscopy; Cognition; Vascular dementia; Vascular cognitive impairment; *N*-Acetylaspartate; Stroke; Cerebrovascular disease

1. Introduction

It is well recognised that vascular cognitive impairment (VCI) and vascular dementia (VaD) are common consequences of stroke [58,59]. The prevalence of VaD in this group is quite variable, however, with reported rates at 3 months post-stroke being between 13% and 32% [8,43]. This wide variation is explained on the basis not only of methodological differences in the studies, but also the discrepancies between diagnostic criteria for VaD and the overlap with Alzheimer disease (AD) [41]. Furthermore, dementia after stroke is heterogeneous and may occur due to large vascular lesions, strategic lesions, multiple lacunar infarcts in subcortical regions, non-infarction ischaemic change and/or intracranial hemorrhage [34], which may account for the variance.

Neuroimaging has thus far played a major role in the understanding of VaD. Structural neuroimaging studies indicate that the occurrence of dementia after stroke is related to the number and location of infarcts, the extent of atrophy [21], and the severity of white matter hyperintensities (WMHs) on T2-weighted magnetic resonance imaging (MRI) [55], but these studies alone do not adequately indicate the extent of neuronal involvement after stroke. In addition to MRI-visible pathology, brain dysfunction due to cerebrovascular disease could occur due to incomplete infarction, chronic ischaemia, diaschisis and other such mechanisms. Since these phenomena cannot be detected by structural imaging, better markers of cognitive dysfunction after stroke may be provided by functional neuroimaging measures. In the study, we examine the applica-

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tion of proton magnetic resonance spectroscopy (^{1}H MRS) to VCI.

^{1}H MRS allows the non-invasive in vivo analysis of certain neurometabolites that indicate biochemical changes in the brain. The major metabolites detected by this technique are *N*-acetylaspartate (NAA), choline-related compounds (Cho), creatine + phosphocreatine (Cr) and *myo*-inositol (mI). While the functional roles of these metabolites are not fully known, in simple terms NAA may be considered to be a marker of neuronal viability, Cr is involved in energy metabolism, Cho is associated with membrane turnover and mI is a putative glial cell marker [2].

^{1}H MRS studies of patients with cerebrovascular disease (CVD) indicate decreases in NAA/Cr or NAA/Cho in the cortical areas overlying subcortical infarct sites [9,29], and in one study these changes were related to cortical symptoms such as aphasia [9], indicating their functional relevance.

Additionally, a relationship between NAA and WMHs has been reported in several studies. In patients with VaD, a reduction in NAA has been observed to be greater in WMHs than in normal appearing white matter (NAWM) [10,51], with one study observing a correlation between frontal white matter NAA and the extent of WMHs [57].

^{1}H MRS has been used to differentiate patients with VaD from healthy elderly control subjects. Previous studies indicate that patients with VaD have reduced NAA/Cr and NAA/Cho, and increased Cho/Cr compared with normal controls in various regions of the brain [7,38], but no study has compared VaD patients to a stroke control group with no cognitive impairment (NCI) using ^{1}H MRS.

We studied a stroke cohort at 3 months post-stroke to determine the differences in brain neurometabolites in non-infarcted frontal white matter and occipito-parietal gray matter of patients with and without cognitive impairment. We hypothesized that the patients with VCI and VaD would exhibit a decrease in NAA/H_2O and an increase in Cho/H_2O compared to the cognitively normal group, particularly in the frontal white matter, which would be consistent with disruption of frontal-subcortical circuits as a possible basis of cognitive impairment.

2. Methods

2.1. Subjects

The study sample was drawn from 252 subjects who were recruited as part of an ongoing longitudinal Sydney Stroke Study from consecutive admissions to the Neurology and Geriatric services of the Prince of Wales/Prince Henry and St. George Hospitals in Sydney. Inclusion criteria included diagnosis of acute ischaemic stroke, and meeting the criteria for cerebral infarction based on the NINDS Stroke Data bank [18] or transient ischaemic attack (TIA) [23] (hereafter referred to as stroke subjects), age between 50 and 87 years, good knowledge of English for neuropsychological testing, absence of severe aphasia (<3 on the Aphasia Severity Rating Scale of the Boston Diagnostic Aphasia Examination), availability of an informant who had known the subject on a regular basis for a minimum of 5 years, and ability to give informed consent. Exclusion criteria included hemorrhagic stroke, persistent impairment of consciousness (>7 days) following stroke, concomitant CNS disease known to affect cognition, concomitant medical disease that is judged to possibly limit life expectancy or affect cognition secondarily, mental retardation (DSM-IV diagnosis), alcohol dependence, contraindications to MRI (pacemaker, metallic foreign bodies, severe claustrophobia), or involvement in an independent research project investigating stroke treatment.

The control group comprised volunteers from the same neighbourhood, recruited from community organizations, and matched group-wise for age and sex with the stroke patients. They were screened for absence of stroke, cognitive impairment and psychiatric disorder on history and examination, with the same exclusion criteria as the stroke patients.

MR imaging was performed in 112 patients and 87 controls were recruited for the study, of which 103 and 86 agreed to participate in the MRS study, respectively. ^{1}H MRS was performed in the left frontal white matter and the midline occipito-parietal gray matter. Usable spectra in either of the voxels were available for 48 patients and 60 controls. Reasons for not being able to use spectra included the use of a different acquisition protocol in the first 14 months of the study (which data are not included), presence of infarction in the region of interest, inability of the subject to complete the MR imaging session, movement during acquisition and poor quality spectra. There were no significant differences between those subjects who had ^{1}H MRS and those who did not for age, MMSE or sex in each group, or for diagnosis or percentage of patients with TIA in the patient group (data not shown), indicating that there was unlikely to be a selection bias within the ^{1}H MRS sample.

Subjects also received a medical, neurological and psychiatric assessment by a physician and a detailed neuropsychological assessment by a clinical psychologist. A diagnosis of VaD, VCI or no cognitive impairment (NCI) was made by consensus, based on the medical, neurological, psychiatric and neuropsychological assessments at a conference attended by two psychiatrists, a neurologist and two or more research psychologists.

The neuropsychological battery comprised the following tests pertaining to various cognitive domains: verbal memory (Logical memory I & II from WMS-R [67]; visual memory (Visual Reproduction I & II from WMS-R [67]); working memory (Digit Span backwards, Arithmetic from Wechsler Adult Intelligence Scale Revised (WAIS-R) [66]; attention/concentration (Digit Span forwards (WAIS-R) [66], Mental Control (WMS-R) [67]); language (15 item Boston Naming Test [36]); information processing speed (Trail Making Test Part A [46] and Symbol Digit Modalities Test [54]); visuoconstruction (Block Design (WAIS-R) [66] and copying simple figures); praxis-gnosis (Western Aphasia Battery

(WAB) ideomotor apraxia subtest items [31], finger gnosis and stereognosis [6,56]; abstract reasoning (Similarities, Picture Completion (WAIS-R) [66]); mental flexibility (Colour Form Sorting Test [68] and Trail Making Test Part B [46]); verbal fluency (phonemic [FAS] [5] and semantic (animals) [40]).

The medical and psychiatric assessment included a functional assessment: Social and Occupational Functioning Scale (SOFAS), Activities of Daily Living (ADL) [30] and Instrumental ADL (IADL) [33]; a standard neurological examination; European Stroke Scale (ESS) [24]; detailed psychiatric assessment: past psychiatric history, Structured Clinical Interview for DSM-IV (SCID) [16], 28 item General Health Questionnaire (GHQ-28) [20], 15 item Geriatric Depression Scale (GDS) [52], Hamilton Depression Rating Scale (HAM-D) [22], and Neuropsychiatric Inventory (NPI) [13].

Patients with VaD had a definitive impairment (<5th percentile for age-matched controls) in at least two cognitive domains as well as functional (social or occupational) deficit. Patients with VCI had definitive impairment in one domain or marginal impairment (between 5th and 10th percentile for age-matched controls) in two or more domains. An adaptation of the IQCODE [28] was used to determine cognitive change over the past 5 years, in order to screen for the presence of cognitive deterioration prior to the stroke according to a knowledgeable informant. Those with scores > 3 on the IQCODE were excluded.

In the stroke group, six NCI patients, three VCI patients and no VaD patients were taking sedatives. One NCI patients was taking anti-depressants. Four patients had incomplete records of medication. In the control group, seven subjects were taking sedatives; two subjects were taking antidepressants, with one of these subjects also taking sedatives; and one subject was taking anti-convulsants.

2.2. MRI/^{1}H MRS protocol

MRI and ^{1}H MRS were performed using a 1.5 Tesla Signa scanner (GE Medical Systems, Milwaukee, WI, USA), and included a scout mid-sagittal cut for AC-PC plane alignment (2D, TR 300 ms, TE 14 ms; thickness 5 mm, nex 1), a 1.5 mm thick T1-weighted contiguous coronal sections through whole brain using a FSPGR sequence and 3D acquisition (TR 14.3 ms, TE 5.4 ms), and 4 mm thick T2-weighted FLAIR coronal slices through the whole brain (TR 8900, TE 145, TI 2200, FOV 25, 256X192.). ^{1}H MRS was performed in the left frontal white matter (single voxel 2 cm × 2 cm × 2 cm) and occipito-parietal gray matter (single voxel 2 cm × 2.7 cm × 2 cm). The voxels were localized using the axial plane, with the frontal voxel positioned anterior to the frontal horn of the left lateral ventricle and the occipito-parietal voxel in the posterior midline (Fig. 1). Automated shimming was performed before acquisition using the STEAM sequence with a 30 ms echo time, 1500 ms repetition time, 13.7 ms mixing time (s-probe 1500/30/13.7), pulse bandwidth of 2500 Hz. The number of data acquisitions was 256, averaged across 2048 data points. Typical line-widths for the frontal voxel were 4–10 Hz and from the occipito-parietal voxel were 2.5–6 Hz. Spectra with line-widths greater than 8 Hz were excluded from analysis. The line-width was the full-width of the peak at half height.

2.3. MRI/^{1}H MRS analysis

The spectra from the ^{1}H MRS were analyzed using MRUI-99x software [61] on MATLAB 5.3, with the user blind to subject group. Zero filling of the 2048 acquisition points was performed, with automatic correcting for zero phasing. The residual water peak was removed using time-domain Hankel Lanczos singular value decomposition (SVD) filtering. Time-domain fitting was then carried out for all peaks using Advanced Method for Accurate, Robust and Efficient Spectral (AMARES) fitting to measure the area under the curve, with input of prior knowledge. The area of the water peak was determined separately from the unsuppressed water scan using SVD. Noise was taken from the last 100 data points. Intra-class correlation coefficients for the inter-rater reliability, in 10 randomly selected subjects using this method of analysis were $\alpha = 0.975$, 0.975, 0.972, 0.825 for NAA, Cr, Cho and mI, respectively ($p < 0.001$). For intra-rater reliability the Pearson's correlation coefficients were $\alpha = 0.972$, 0.976, 0.973, 0.967 for NAA, Cr, Cho and mI, respectively ($p < 0.0001$).

Structural MRI data were analyzed with ANALYZE^R software (Biomedical Imaging Resource, Mayo Clinic, Rochester MN, USA), by a rater blind to subject group. To correct for partial volume effects within the voxels, the proportion of cerebrospinal fluid (CSF) was estimated using an automatic segmentation algorithm developed in-house, with manual input of the threshold for brain tissue, determined individually from T1-weighted structural images. The intra-rater reliability for five randomly selected control subjects was $\alpha = 0.995$ in the frontal voxel and $\alpha = 0.996$ in the occipital voxel ($p < 0.0001$). The proportion of CSF was multiplied by the unsuppressed water value for each voxel to provide the corrected water value, and then ratio values for NAA, Cr, Cho and mI were calculated with respect to the corrected water value for each voxel. The proportion of white matter hyperintensities (WMHs) was also estimated for each voxel from the FLAIR images using an automatic segmentation algorithm, with manual input of a threshold value to differentiate between normal tissue and WMH. The intra-rater reliability for five randomly selected control subjects was $\alpha = 0.962$ in the frontal voxel ($p < 0.004$) and $\alpha = 1.000$ in the occipital voxel ($p < 0.0001$).

2.4. Data analysis

Statistical analysis was performed using SPSS 11.0 for Windows (SPSS Inc., 2001). To increase the power of the analysis, the VaD and VCI groups were combined to form a cognitively impaired (VaD + VCI) group. Univariate ANOVA

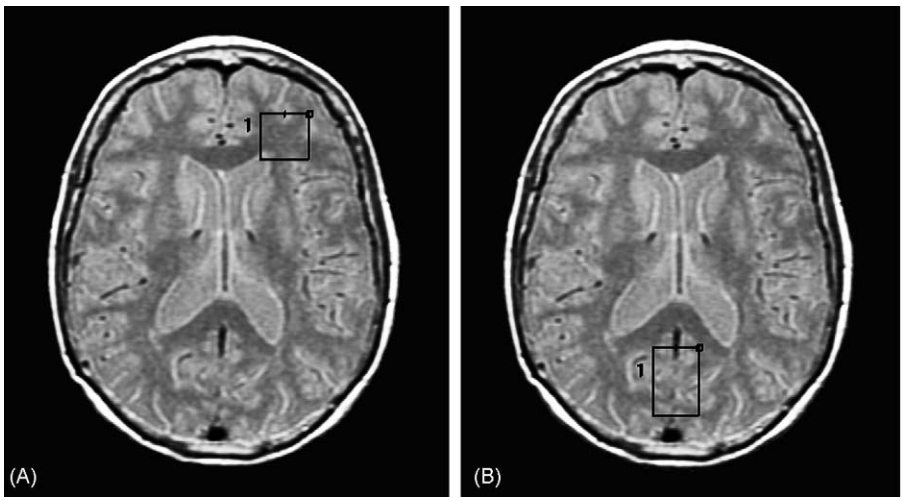

Fig. 1. Voxel placement was performed in (A) the left frontal region to maximize white matter content (2 cm × 2 cm × 2 cm) and (B) the mid-line occipito-parietal gray matter (2 cm × 2 cm × 2.7 cm). Voxels were localized using the axial plane.

and the χ^2-test were used to compare demographic variables between the groups. Multivariate ANCOVAs (Wilk's Lambda) (one for each voxel), were used to compare neurometabolite ratios between the stroke and the control groups, and between the VaD + VCI, NCI and control groups, followed by post hoc univariate ANOVA tests to determine the differences between groups. Age, gender were treated as covariates, since they may independently affect neurometabolite ratios. In the frontal voxel, and extent of WMHs was also treated as a covariate. Spearman's *r* was used to test for a relationship between WMHs and neurometabolite ratios.

3. Results

3.1. Description of the sample

The demographic and diagnostic data for the subjects are summarized in Table 1. Of the 48 stroke patients with usable ^{1}H MRS data in either the frontal or occipito-parietal voxel, 20 had no cognitive impairment (NCI), 17 were diagnosed with VCI and nine were diagnosed with VaD. One patient was diagnosed with mixed dementia (VaD and Alzheimer's) dementia and another with possible Alzheimer's disease. These two subjects were not included in the analysis.

Of the CVD patients, 12% had a TIA rather than a stroke, with three in the NCI group and three with VCI. On structural MRI at 3 months post-stroke, the primary infarct type for the CVD patients was lacunar for 31%, and cortical for 36%, with the remaining 33% showing no infarcts on MRI. The primary infarct side was the right hemisphere for 72% of the CVD patients with evidence of an infarct, and the remaining 28% were primarily left.

There were no significant differences in age or education level between the groups. MMSE scores were significantly lower in the VaD + VCI group ($p < 0.001$) compared with the NCI group. A history of hypertension was observed significantly more often in stroke patients overall ($p < 0.0001$), in stroke patients with NCI ($p < 0.0001$) and in the VaD + VCI group ($p < 0.05$), compared with the control subjects. The total brain WMH rating was significantly greater in the stroke

Table 1
Demographic and diagnostic data of stroke patients and control subjects

	Stroke patients			Controls	Stroke vs. control			VaD + VCI vs. NCI	VaD + VCI vs. control	NCI vs. control
	NCI	VaD + VCI	Total		F/χ^2	d.f.	*p*	*p*	*p*	*p*
N	20	26	46	60						
Age, year	70.9 (7.8)	71.3 (10.5)	71.1 (9.2)	71.4 (6.7)	0.210	1	0.886	1.000	1.000	1.000
M/F	14/7	15/11	29/18	32/29	0.894	1	0.345	0.615	0.607	0.299
Education, year	11.1 (3.5)	10.5 (3.2)	10.8 (3.3)	12.0 (3.6)	3.441	1	0.066	1.000	0.218	0.070
MMSE score	29.5 (0.6)	27.9 (2.1)	28.6 (1.8)	28.7 (1.3)	0.058	1	0.811	0.001	0.058	0.845
Stroke/TIA	17/3	23/3	40/6	–		1				
Hypertension (%)	85.7	65.7	74.5	37.5	12.09	1	0.001	0.133	0.030	0.001
Total brain WMH rating[a]	6.0 (2.5)	8.1 (4.6)	7.2 (3.9)	5.6 (2.8)	7.245	1	0.008	0.163	0.003	1.000

Values are mean (S.D.). NCI: no cognitive impairment, VaD: vascular dementia, VCI: vascular cognitive impairment, VaD + VCI: cognitively impaired group, MMSE: mini-mental state examination [17], TIA: transient ischemic attack, WMH: white matter hyperintentisty.

[a] Modified Fazekas et al. [15] rating in different brain regions (range 0–18).

Table 2
Metabolite ratios for Voxels locations in stroke, VaD + VCI, NCI and controls

Voxel location	Stroke patients			Controls
	NCI	VaD + VCI	Total	
Frontal				
WMH (%)	2.90 ± 3.95	10.59 ± 18.88[a]	7.01 ± 14.45	3.18 ± 6.51
NAA/H_2O	1.93 ± 0.53 (1.93)	1.73 ± 0.48 (1.78)	1.83 ± 0.51 (1.86)	1.99 ± 0.48 (1.96)
Cr/H_2O	1.51 ± 0.42 (1.50)	1.42 ± 0.45 (1.45)	1.46 ± 0.43 (1.48)	1.55 ± 0.37 (1.53)
Cho/H_2O	1.26 ± 0.39 (1.24)	1.13 ± 0.37 (1.17)	1.19 ± 0.38 (1.21)	1.32 ± 0.32 (1.31)
mI/H_2O	0.96 ± 0.25 (0.95)	0.89 ± 0.35 (0.92)	0.93 ± 0.30 (0.94)	0.97 ± 0.28 (0.96)
No. subjects	18	17	35	40
O-P				
WMH (%)	0.16 ± 0.38	0.34 ± 0.55[a]	0.26 ± 0.48[b]	0.06 ± 0.11
NAA/H_2O	1.28 ± 0.14 (1.28)	1.19 ± 0.13 (1.19)[c]	1.23 ± 0.14 (1.23)	1.22 ± 0.10 (1.21)
Cr/H_2O	0.98 ± 0.09 (0.98)	0.97 ± 0.13 (0.97)	0.98 ± 0.10 (0.98)	0.95 ± 0.09 (0.94)
Cho/H_2O	0.63 ± 0.11 (0.63)	0.63 ± 0.16 (0.63)	0.63 ± 0.10 (0.63)	0.58 ± 0.10 (0.57)
mI/H_2O	0.58 ± 0.06 (0.58)	0.54 ± 0.13 (0.54)	0.56 ± 0.09 (0.56)	0.54 ± 0.09 (0.54)
No. subjects	16	19	36	54

Values are in arbitrary units as mean ± S.D. (estimate of mean adjusted for covariates). NCI: no cognitive impairment, VaD: vascular dementia, VCI: vascular cognitive impairment, VaD + VCI: cognitively impaired group; NAA, *N*-acetyl-aspartate, H_2O: water, Cr: creatine-phosphocreatine, Cho: choline, mI: *myo*-Inositol, O-P: occipito-parietal. Ratios are multiplied by 10^3.

[a] $p < 0.05$ compared with control group.

[b] $p < 0.005$ compared with control group.

[c] $p < 0.05$ compared with NCI.

group than the control group ($p < 0.05$), with this being significant for VaD + VCI, but not the NCI group.

3.2. WMHs within the voxels

The percentage of WMHs within each voxel is shown in Table 2. In the frontal voxel, WMHs did not differ significantly between stroke and control groups, but the VaD + VCI group had significantly more WMHs than the control group ($\chi^2 = 7.608$, $p = 0.006$). In the occipito-parietal voxel, the percentage of WMHs was very small overall, because this voxel is mainly gray matter. There was no significant difference between the stroke and control groups, but the VaD + VCI group again had significantly more WMHs in this voxel than the control group ($\chi^2 = 6.911$, $p = 0.009$).

3.3. Neurometabolite ratios in stroke patients compared to control subjects

There were no significant differences in neurometabolites in stroke patients compared with controls in the frontal white matter ($F = 0.744$, d.f. = 4.68, $p = 0.566$) or the occipito-parietal gray matter ($F = 1.512$, d.f. = 4.85, $p = 0.206$) (Table 2).

3.4. Neurometabolite ratios in stroke patients with and without cognitive impairment

In the frontal white matter voxel, the overall multivariate statistic is non-significant when comparing the VaD + VCI, NCI and control groups ($F = 0.944$, d.f. = 8.130, $p = 0.482$). However, patients with cognitive impairment have lower levels of NAA/H_2O compared to control subjects by about 13%, the difference of which was not significant after adjustment for multiple comparisons. For the number of subjects tested in this study, the power to detect a difference for a medium effect size observed was 43%, due to the large variance in this voxel.

In the occipito-parietal voxel, there was an overall significant effect for group ($F = 1.996$, d.f. = 8.168, $p < 0.05$). The multivariate effects for age and gender were non-significant ($F = 0.973$, d.f. = 4.84, $p = 0.427$, and $F = 1.204$, d.f. = 4.84, $p = 0.315$, respectively). Post hoc tests indicated that NAA/H_2O was significantly lower in stroke patients with VaD + VCI than with NCI ($p < 0.05$). This relationship was also observed when excluding the 13 subjects with WMHs within the voxel and removing the percentage WMHs as a covariate ($p < 0.05$), with significantly lower NAA/H_2O in VaD + VCI compared to the NCI group. There were no significant differences in Cho/H_2O between the three groups. The observed power was 81% for the medium effect size observed in the occipito-parietal voxel for this study.

3.5. WMHs and neurometabolites

There were no significant correlations between the neurometabolite ratios and percentage of WMHs in the frontal white matter in either subject groups. However, there was a significant relationship between the percentage of WMHs in the frontal voxel and frontal NAA/H_2O in all subjects with less than 2% WMHs in the frontal lobe ($r = -0.348$, $p = 0.02$, $n = 45$) (Fig. 2).

Similarly, in the occipital voxel, NAA/H_2O was correlated with the percentage of WMHs within the voxel in the 13 subjects (11 stroke, 2 control) that had a small amount of WMHs present in this voxel ($r = -0.575$, $p = 0.04$, $n = 13$)

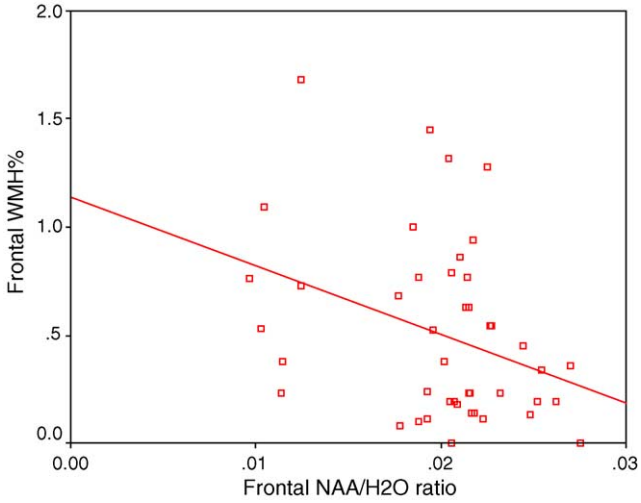

Fig. 2. Correlation between NAA/water and T2-weighted white matter hyperintensity (WMH) proportion in the frontal white matter in subjects with less than 2% WMH in this voxel ($r = -0.348$, $p = 0.02$, $n = 45$).

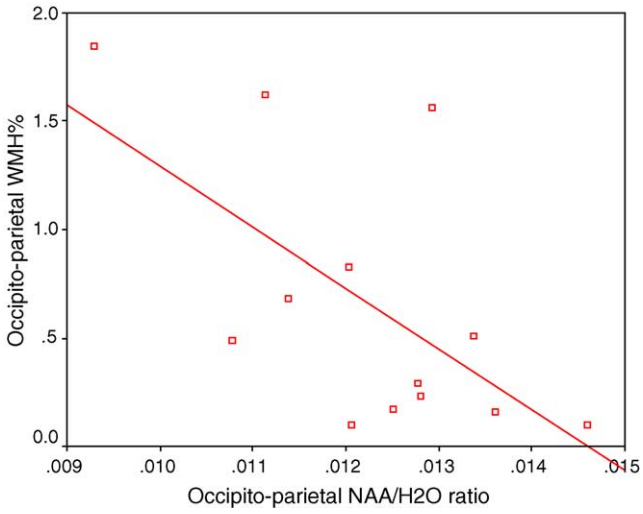

Fig. 3. Correlation between NAA/water and T2-weighted white matter hyperintensity (WMH) proportion in the occipito-parietal gray matter in subjects with WMH in this voxel ($r = -0.575$, $p = 0.04$, $n = 13$).

(Fig. 3). Occipito-parietal NAA/H_2O also correlated with the total amount of severely graded WMHs in the brain in all subjects ($r = -0.244$, $p = 0.021$, $n = 89$) (Fig. 4).

4. Discussion

The major findings from this study were that there were no significant neurometabolite differences between a stroke cohort and healthy elderly controls, but there was a difference in NAA/H_2O between the stroke patients that had cognitive impairment (VaD and VCI) compared with those patients with no impairment. This was significant in the occipito-parietal gray matter, but not the frontal white matter.

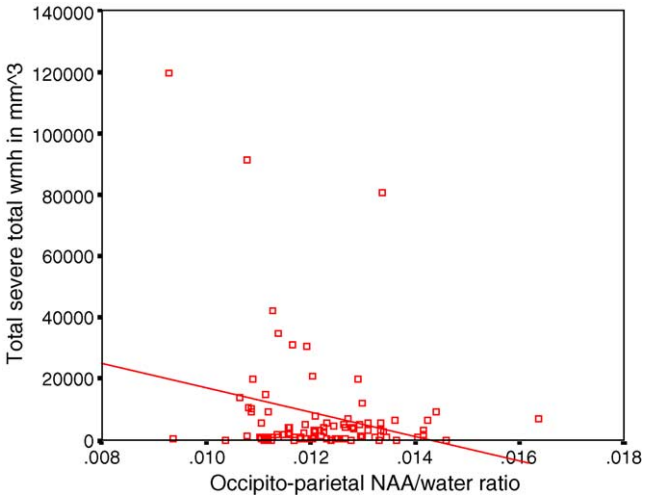

Fig. 4. Correlation between the total amount of severely graded T2-weighted white matter hyperintensity (WMH) and NAA/water in the occipito-parietal gray matter in all subject ($r = -0.244$, $p = 0.021$, $n = 89$).

Previous studies that have investigated differences in neurometabolites in stroke patients and controls have found that NAA/Cho or NAA/Cr are reduced in non-infarcted tissue in the hemisphere ipsilateral to the infarction or arterial occlusion [29,49,62,63], and this has been associated with symptoms of cortical dysfunction, such as aphasia [29,48]. It must be pointed out that NAA values in the tissue contralateral to the side of infarction were not significantly different in the above studies [63]. NAA/Cho and NAA/Cr were also reduced in the parietal white matter of patients with CVD compared to healthy controls, and associated with attentional, but not memory impairment [27]. In patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a hereditary disorder that results in repeated strokes, NAA ratios were reduced in white matter hyperintensities (WMHs) and in normal appearing white matter (NAWM) in a mixed group of both demented and non-demented patients compared to controls [1].

Our study was methodologically different from the above studies. We examined stroke and TIA patients admitted to hospital, and did not select subjects or voxel position on the basis of the type and site of infarction if it did not affect the voxels under investigation. The conclusion we draw from our study is that ^{1}H MRS is unable to distinguish between stroke patients and healthy controls using non-infarcted white matter and gray matter voxels. However, MRS of the occipito-parietal gray matter, which was normal on structural MRI, was able to distinguish those stroke patients who had cognitive impairment from those who were cognitively normal.

NAA is thought to be found only in neurons in the adult CNS [53], with a production rate that parallels oxygen consumption and ATP production in the mitochondria [3]. NAA is therefore thought to be a marker of neuronal viability and metabolic efficiency. Our finding suggests that cognitively impaired stroke patients have reduced number of viable cortical neurons in the occipito-parietal region. Whether this re-

flects a generalized reduction of neuronal viability cannot be determined, but remains a possibility.

Since frontal-executive dysfunction is a salient cognitive disturbance in VaD [35], and the neuroanatomical basis of this is dysfunction in the frontal-subcortical circuits, we had predicted an abnormality in the frontal white matter. While some reduction in NAA was seen in the frontal white matter, it did not reach significance. The greater variance and the small number of subjects with measurements in the frontal voxel meant that the power to detect a difference in this study was reduced. A recent MRS study that observed an 18% reduction in the frontal gray matter, and a 27% reduction in the parietal gray matter, also observed no neurometabolite abnormalities in white matter [51]. The authors reported that a minimum detectable difference of 13% reduction in NAA was required in the white matter, with 80% power. In our study, we observed a 13% reduction in NAA in the frontal white matter in cognitively impaired subjects compared to controls, but we had reduced power. In a study of subcortical VaD [38], reductions of NAA/Cr were observed most prominently in the frontal white matter, but were most likely due to differences in Cr rather than NAA.

The finding of reduced gray matter NAA in cognitively impaired individuals is not surprising. Cognitive impairment in our group was defined as performance below the 5th percentile of age-matched controls on neuropsychological tests in any of the major cognitive domains. It was not restricted to frontal-executive function, and patients with VaD had definitive impairment on two or more domains. One previous study [7] has reported lower NAA/Cr and NAA/Cho ratios in the occipital lobe in demented subjects with diffuse WMHs, compared with non-demented subjects also with diffuse WMHs and healthy elderly controls. Another study did not observe any differences between VaD patients and controls in an occipital gray matter voxel [65], although the control group comprised only five subjects. Reductions in NAA/Cr and NAA have been observed in frontal and parietal gray matter [25,51] and the posterior mesial gray matter [38] in patients with subcortical VaD compared to controls. Although many of these studies are consistent with our results, our study was methodologically different. Since we examined stroke and TIA patients admitted to hospital, rather than comparing clinically diagnosed VaD patients with control subjects, our sample is more likely to be representative of the general stroke patient seen in hospital. It is noteworthy that the NAA levels in the NCI group were non-significantly higher than the controls. This is unexpected as we had hypothesized that the NCI would lie between the VCI and controls in their NAA values. It is possible that the classification of stroke subjects into two groups leads to a selection bias in the NCI group, selecting a 'more healthy' group. In the control group, there may be subjects with early stages of cognitive impairment, who may have NAA levels at the lower end, whereas in the stroke group, these subjects may have been selected out, if brain injury accelerated the development of cognitive impairment. This pattern is also evident in the MMSE scores of each group: MMSE scores in the VaD + VCI group are significantly different to the NCI group, but not the control group, and the MMSE scores of the NCI were non-significantly higher. We cannot however rule out the possibility that the finding represents a type I error, with the NCI group not being representative. The number of subjects in this group is small, but there are no obvious outliers in the group. Independent replication of this finding is therefore warranted.

We did not observe a difference in Cho between our clinical groups. Only two studies have observed an increase in Cho in patients with VaD [11,26], while others have observed no significant changes [4,37,51,69]. The Cho peak includes soluble membrane phospholipids including phosphorylcholine (PCho), glycerophosphocholine (GPCho) and a relatively negligible amount of free choline [39]. Changes in Cho indicate changes in membrane synthesis, and can often indicate gliosis, myelination or inflammation [14,19,47]. Studies that have observed an increase have suggested that this may arise from myelin degradation [25]. The extent of this may not be sufficient in our sample, which included subjects with milder cognitive deficits than in previous studies.

Importantly, we accounted for the presence of WMHs in the voxels. This is an important distinction from other studies, as the presence of WMHs may itself influence the MRS values [10], resulting in abnormal values for the voxel even if the normal-appearing tissue is spectroscopically normal. This would therefore yield information additional to what is already available from structural imaging. We found that the difference in NAA/H_2O between the VaD + VCI and NCI groups was significant even after removing the subjects with WMHs in the occipital lobe. This suggests that the relationship between NAA/H_2O and cognitive impairment is independent of the effects of WMHs in the occipital gray matter, not a surprising finding since there is no significant difference in extent of WMHs between the NCI and VaD + VCI groups in this region. MacKay et al. [37] observed a decrease in NAA/Cr in the frontal white matter, but addition of percentage WMH, white matter and gray matter as covariates, gave a non-significant result between subcortical VaD patients and healthy controls, although with only percentage gray matter, the result was still significant.

We also observed a relationship between the percentage of WMHs and NAA/H_2O the frontal voxel in subjects with less than 2% WMHs within the voxel, indicating a threshold effect. In the occipito-parietal, there was also a relationship between the percentage WMHs and NAA/H_2O in the 13 subjects that had WMHs present within the voxel, all of these subjects with less than 2% of the voxel white matter so affected. This suggests that some of the variation in NAA/H_2O is mediated by the same mechanism that produces WMHs, particularly with early damage. The extent of whole brain severe WMHs also correlated with NAA/H_2O in the occipito-parietal voxel, indicating an association between subcortical damage and cortical dysfunction. Previous research indicates that NAA is reduced in areas of WMH in subjects with cognitive impairment [7,10,11,42].

In normal subjects, the relationship is an inconsistent finding [7,11,42,50].

It is important to note that the occurrence of WMHs within the voxels is likely to affect the relaxation times of the water peak between subjects, thereby possibly accounting for the difference between groups, and possibly increasing the variance of the water peak more than it would otherwise. A difference was observed in the occipito-parietal voxel when subjects with WMHs were not included, however, the effect of WMHs in the frontal voxel on water relaxation times is likely to be greater, since there is a greater proportion of WMHs in this voxel.

Decreases in NAA are found in many diseases where there is neuronal loss, such as neurodegeneration [60], tumours [14], infarction sites [26] and multiple sclerosis [12], with depletion of NAA not always being irreversible [48]. The reduction of NAA in the occipito-parietal gray matter suggests that there is hypometabolism or neuronal loss occurring in this region in patients with cognitive impairment after stroke. Recent research has shown that neuropathology in patients with strokes is not restricted to the tissue that is obviously infarcted on neuroimaging.

Functional imaging studies have been performed to compare stroke patients with and without cognitive impairment. One positron emission tomography (PET) study found that the overall cortical glucose metabolism was significantly reduced in stroke patients with cognitive deficits compared to both neuropsychologically normal stroke patients and healthy controls [49], but other studies show that there is regional frontal cortical hypometabolism in all stroke patients [32,45,55]. One interpretation of these findings is that there is widespread disturbance of brain metabolism in stroke patients, especially in those with cognitive impairment, consistent with our finding of changes in the occipito-parietal region. A recent neuropathological study [64] lends support to this by reporting reduced hippocampal volumes in VaD patients without hippocampal infarction, possibly related to chronic ischaemia. We considered the possibility that reduced NAA levels in the occipito-parietal cortex were related to coexisting Alzheimer-type pathology in this region. We consider this to be unlikely, as the subjects had been screened for the absence of progressive cognitive decline prior to the stroke. Support for this is offered by the report of Vinters et al. [64] that the reduction in hippocampal volumes in VaD was not because of Alzheimer-type pathology.

In our study, the occurrence of WMHs was minimal in the occipito-parietal voxel. The finding of reduced cortical NAA in this region could be caused by diaschisis and/or neuronal loss by incomplete infarction, which is consistent with the preserved structural integrity in this region. Alternatively, higher NAA/H_2O may have a protective effect against developing cognitive impairment, if NAA/H_2O was greater in the stroke patients with NCI than with VaD or VCI prior to infarction.

There are a number of limitations to our study. Firstly, many of our subjects who underwent structural MRI did not have usable MRS spectra. This was related to technical and patient-related factors, as mentioned above. Even though this exclusion was not systematic, to determine the possibility of bias we compared the subjects included in the study with those excluded, and did not find differences between the two groups on sociodemographic and clinical variables.

Secondly, our control sample was not a random sample, and comprised community-dwelling volunteers from the same neighbourhood. While these subjects were screened for the absence of mild cognitive impairment, it is not unusual for such volunteers to have subtle impairment. We consider this to be unlikely since our subjects underwent detailed neuropsychological assessments on which they performed normally. The demanding nature of the investigations makes recruitment of a truly random sample virtually impossible in such studies.

Thirdly, there are technical difficulties in any MRS investigation. The ratios obtained from the FWM voxel showed much greater variability than the occipito-parietal voxel, thereby reducing the power of the analyses for the FWM voxel. The quality of the data obtained from the FWM voxel was also poorer, as indicated by the subjects with line-widths greater than 8 Hz, due to the proximity of the voxel to the skull, which causes interference by lipids, particularly at the short echo times used in this study [44].

Fourthly, the small number of subjects in each group means that there is a risk of type II errors, due to a lack of power to show the possible real difference between the groups. The power was only sufficient in the frontal voxel to detect large effect sizes, and in the occipito-parietal voxel to detect medium effect sizes.

In conclusion, our study suggests that ^{1}H MRS may be an important imaging modality in providing functional information in stroke patients, and may prove to be an important tool in the investigation of VaD. It also shows that structural imaging must be supplemented with functional imaging to fully appreciate the deficits in stroke patients. Further work in this area is indicated. The newer technique of magnetic resonance spectroscopic imaging (MRSI) may be useful in this regard as larger brain areas can be sampled simultaneously. Imaging of the normal-appearing white matter in the infarction penumbra would be of interest. Longitudinal studies are important to determine if neurometabolite measures predict future cognitive decline.

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