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This information is current as of December 12, 2024.

AJNR Am J Neuroradiol 1998, 19 (10) 1879-1885
<http://www.ajnr.org/content/19/10/1879>

Proton MR Spectroscopic Findings Correspond to Neuropsychological Function in Traumatic Brain Injury

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BACKGROUND AND PURPOSE: Traumatic brain injury (TBI) causes substantial irreversible damage to neurons. Our aim was to investigate whether proton MR spectroscopic measures of diffuse cellular integrity were related to neuropsychological dysfunction after TBI.

METHODS: Twelve patients with TBI (mean, 53 ± 23 days postinjury) and 14 control subjects were included in the study using paired MR spectroscopy and neuropsychological assessment. *N*-acetylaspartate (NAA), creatine, and choline were measured in normal-appearing occipitoparietal white and occipital gray matter using short-echo quantitative spectroscopy. A composite measure of neuropsychological function was calculated from *z*-scored individual tests probing the major functional domains commonly impaired after head trauma.

RESULTS: Patients with TBI displayed reduced NAA in white matter and elevated choline in gray matter, suggestive of neuronal injury and inflammation, respectively. NAA and creatine in white and gray matter were significantly associated with composite neuropsychological function and many individual neuropsychological tests. Gray matter choline, although abnormal, was not related to neuropsychological function.

CONCLUSION: The concordance between neurometabolic levels and behavioral function supports the hypothesis that diffuse axonal injury is an important contributor to brain dysfunction after TBI.

Traumatic brain injury (TBI) affects approximately 2 million people in the United States each year, and many of these individuals sustain subsequent long-term disability. Although CT and MR imaging provide anatomic information relevant for clinical management, quantitative measurements of lesion severity from these imaging techniques are only weakly related to neuropsychological dysfunction or gross outcome (1–3). This difficulty likely stems from the fact that structural imaging techniques do not resolve the widespread cellular injury found in autopsy studies (4, 5).

Findings of histologic studies have shown extensive diffuse axonal damage after TBI (4–8). After TBI, reactive cytoskeletal disorganization causes axonal swelling that may lead to disconnection and ultimately

cell death (4). Indeed, recent staining studies suggest that axonal swelling may be a near-universal consequence of fatal brain trauma (7). Moreover, although focal white matter abnormalities related to shearing injury are commonly seen in the subcortical white matter, corpus callosum, and midbrain on MR images, selective antibody staining for the 68-kd cytoskeleton subunit shows widespread axonal insults throughout the white matter, within the gray-white interface, and within subcortical gray matter structures (5). Specific areas in which axons change anatomic course, travel around blood vessels, or enter tissue of differing densities (ie, gray/white interface) appear especially vulnerable (4, 5). Reactive axonal changes are seen in the majority of tissue samples and in areas distant from focal findings (i.e., occipital gray matter) (5).

Diffuse axonal injury after TBI, as seen in histologic findings, is influenced by injury severity and may be the major injury component relating to behavioral impairment. For example, Gennarelli et al (8) reported that the number of damaged axons and their distribution predicted morbidity in primates. In humans, relationships have been found between morbidity and number of injured axons, head velocity on impact, and Glasgow Coma Scale score, a commonly used assessment tool for rating injury severity (9, 10).

Received April 1, 1998; accepted after revision August 6.

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In general, the extent of axonal damage after fatal TBI appears to be related to severity of injury and may well determine the extent of behavioral dysfunction in patients who survive.

Proton MR spectroscopy provides a sensitive, non-invasive assessment of *N*-acetylaspartate (NAA), a marker of neuronal integrity, total creatine (Cre), and total choline (Cho) (11–14). NAA falls rapidly and irreversibly with neuronal death (eg, in cerebral infarct) but may partially increase after the acute phase of multiple sclerosis, suggesting partial recovery from injury (11, 15). In previous studies of TBI, decreased NAA/Cre has been shown in the frontal lobes of patients with poor outcomes (16, 17), and decreased NAA has been shown within the brain stem (18), subcortical white matter (18, 19), and gray matter regions (19). Although gross measures (ie, Glasgow Outcome Scale [20]) are commonly used for assessing behavioral function, neuropsychological testing provides enhanced behavioral specificity. For example, characteristic deficits of attention, processing speed, and sensorimotor integration, impairments that resolve at different rates after injury, are shown after TBI (2, 21).

We hypothesized that changes in NAA measured in normal-appearing tissue remote from primary injury sites would reflect diffuse axonal injury after TBI, and that the extent of neurochemical changes would be closely related to global neuropsychological dysfunction.

Because a wide range of neuropsychological deficits are expected with diffuse injury (21–23), we chose our primary analysis to represent neuropsychological function by standardizing and aggregating individual test scores into a composite.

Methods

Patient Population

Twelve patients (11 men and one woman, aged 34 ± 12 years [range, 18 to 49 years]; education, 13.8 ± 2.4 years) with moderate to severe head trauma (21) were recruited from local rehabilitation facilities (see Table 1 for clinical description). Fourteen control subjects matched for age and years of education (13 men and one woman, aged 31 ± 11 years [range, 19 to 52 years]; education, 13.4 ± 2.1 years) were also included in the study. All subjects were approved by the Human Research Review Committee. Informed consent from patients or a legal guardian was obtained before inclusion in the study. Neuropsychological testing and MR imaging or spectroscopic examinations were performed within 24 hours of each other. If both neuropsychological testing and imaging were conducted on the same day, neuropsychological testing was conducted first to minimize the potential effects of scanning or fatigue on performance.

Neuropsychological Testing

The neuropsychological test battery was designed to probe a wide range of cognitive functions commonly impaired by TBI (22–24): attention and information processing speed, Paced Auditory Serial Addition Task (PASAT); verbal memory, Cal-

TABLE 1: Subject descriptive data

Patient	Age (y)/ Sex	Injury	GCS*	Exam Date† (days)	White Matter (mmol/L)			Gray Matter (mmol/L)			MR Findings
					Cho	Cre	NAA	Cho	Cre	NAA	
1	29/M	Blunt trauma	8T	60	2.21	5.42	9.77	1.52	7.39	11.31	Atr, SI (CC)
2	46/M	Blunt trauma	N/A	36	2.18	7.70	10.82	1.57	8.35	11.50	Focal lesion (R pons)
3	37/M	MVA	6	53	1.94	7.95	13.32	1.69	8.27	11.57	C (R and L frontotemporal); Atr
4	18/F	MVA	9	50	2.15	8.58	12.40	1.52	8.79	11.84	C (R and L temporal)
5	32/M	MVA	14	25	1.77	7.56	12.25	1.27	8.40	12.28	Normal
6	23/M	MVA	3T	91	1.41	8.07	12.19	1.88	7.34	12.12	Normal
7	26/M	Blunt trauma	13	14	1.79	8.24	11.75	1.48	8.93	12.51	C (L frontotemporal, R frontal), SDH (L temporal)
8	20/M	MVA	15	36	1.54	7.46	11.09	1.71	7.91	13.22	C, SDH (R frontal); SI (pons); skull fx (depressed)
9	24/M	MVA	N/A	46	2.22	7.29	11.47	1.49	9.21	13.08	Normal
10	45/M	MVA	6T	80	1.18	6.26	10.70	C (L temporal); SDH (L temporal)
11	19/M	MVA	13	77	2.27	7.47	11.66	1.70	9.17	12.73	C (L and R frontal), SI (R frontal)
12	49/M	MVA	7	66	2.08	7.70	11.43	1.62	8.22	10.78	C (L frontal)
Mean	30.7	...	9.4	52.7	1.8	7.5	11.6	1.3	8.4	12.4	...

Note.—MVA indicates motor vehicle accident; Atr, diffuse cerebral atrophy; C, contusion (blood, encephalomalacia, and/or gliosis); SI, axonal shearing injury (hemorrhagic or nonhemorrhagic); SDH, subdural hematoma; CC, corpus callosum; GCS, Glasgow Coma Scale; Cho, choline; Cre, creatine; NAA, *N*-acetylaspartate; fx, fracture.

* GCS score at admission; T indicates that patient was intubated when GCS was measured.

† Time between injury and spectroscopic examination/neuropsychological testing.

ifornia Verbal Learning Test (CVLT); visual memory, Benton Visual Retention Task (BVRT); perceptual-motor function, Grooved Pegboard and Symbol Digit Modalities Test (SDMT); frontal "executive" functioning, verbal fluency (FAS), Wisconsin Card Sorting Task (WCST), and Trail Making Tests A and B; premorbid intelligence, New Adult Reading Task (NART); and orientation, Galveston Orientation and Amnesia Test (GOAT) (20).

A composite measure of neuropsychological function was calculated by averaging *z* scores (determined with norms from control populations) as follows. A representative variable was selected from each test to maximize the assessment of functional impairment: PASAT (number correct on trial 4); CVLT (total words recalled over five trials); BVRT (total errors); Grooved Pegboard (speed for both left [GP-L] and right [GP-R] hands); SDMT (total correct); FAS (total production over three trials); WCST function (percentage of perseverative errors); and Trails A and B (time). Representative variable *z* scores were calculated by comparison with normative samples. Composite *z* scores were then determined for each subject by summing representative *z* scores and dividing by the number of measures.

MR Imaging and Spectroscopy

All MR acquisitions were performed on a 1.5-T clinical MR scanner. Localizing imaging sequences included a T1-weighted fast spoiled gradient-recalled scan with imaging parameters of 17.7/6.9 (TR/TE), a flip angle of 25°, and 3-mm-thick sections, and a conventional T2-weighted series with imaging parameters of 2800/30,100 and 4-mm-thick sections. A stimulated-echo acquisition mode pulse sequence, including water suppression, was used to sample a voxel of $25 \times 35 \times 21 \text{ mm}^3$ (2000/30, 128 averages) within normal-appearing left-sided occipitoparietal white matter. The first voxel was carefully positioned to maximize white matter, minimizing gray matter and ventricular contribution (Fig 1). Voxels were prescribed from the first axial image section of the T1-weighted series that was superior to the lateral ventricles and located to maximize the white matter contribution by aligning the medial margin of the voxel with the interhemispheric fissure gray-white matter boundary using graphic prescription. In compliant patients, a second, long-echo time spectrum (2000/272) to probe for lactate was ac-

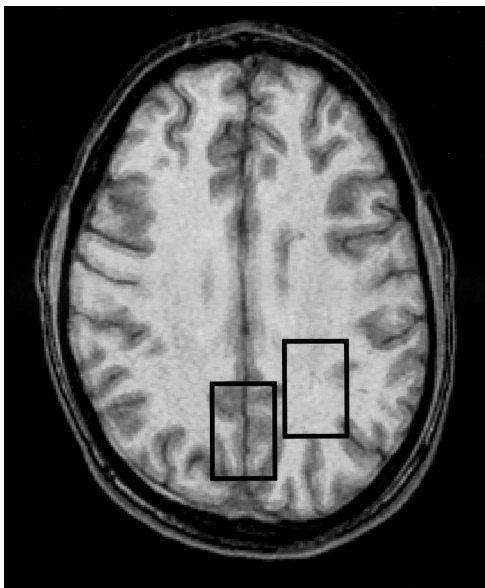


Fig 1. Axial T1-weighted MR image shows the locations in the occipital lobe of the gray matter (midline) and white matter spectroscopic voxels used in this study.

quired. Next, a voxel of $25 \times 35 \times 21 \text{ mm}^3$ (2000/30) was placed along the occipital longitudinal fissure to probe the integrity of gray matter tissue. The gray matter voxel was specifically placed to avoid inclusion of the sagittal sinus and corpus callosum on inferior sections (Fig 1). The local magnetic field homogeneity, transmitter pulse power, and water suppression for each voxel were optimized by automated procedures.

Quantification and Statistical Methods

Spectroscopic data were transferred to a Sun UltraSparcstation (Sun Microsystems, Mountain View, CA) for analysis using the MRUI software package (provided by A. van den Boogaart, Katholieke Universiteit, Leuven, Belgium). All data were run in a single batch and processed blind to group. Residual water resonances were removed using time-domain Hankel Lanczos Singular Value Decomposition (HLSVD) filtering (24). Time-domain fitting of gaussian lineshapes to NAA, Cre, and Cho was performed using VARPRO (25), and the areas corresponding to NAA, Cre, and Cho were recorded. The area from the water peak was determined from the unsuppressed water scan using Singular Value Decomposition (SVD) (24). Data were quantified using the internal water signal as a concentration reference and were corrected for metabolic and water T1 and T2 effects during the pulse sequence by using literature values (26–28).

All scans were read by an experienced neuroradiologist who was blinded to subject group, clinical or neuropsychological score, and neurochemical concentration data. Each scan was assessed for atrophy, contusion, hematoma, and focal shearing injury of white matter by using a simple scale of present or absent.

Spectroscopic findings and neuropsychological testing results were compared by Spearman correlation analyses. Group differences were compared using independent *t*-tests. All statistics were performed in SPSS for Macintosh (Chicago, IL).

Results

Scans were performed when patients were clinically stable enough to be transported to the scanning facility (mean duration after injury = 53 ± 23 days), sufficiently oriented (GOAT score > 75), and able to sustain attention long enough for neuropsychological testing (30–45 minutes). A summary of clinical findings is presented in Table 1. Although abnormalities on MR images were shown in 10 of the 12 patients, none had left parietal or occipital lobe findings. Two patients were assessed as being atrophic, and signs of focal white matter shearing injury were shown in three, although all positive findings were mild. One patient had positive findings by both criteria. Although patients with positive findings on either scale performed more poorly on neuropsychological testing, these differences did not reach statistical significance (atrophy: $t = 1.27$, $P = .40$; shearing injury: $t = .45$, $P = .69$).

No significant differences in age or education were found between control subjects and patients with TBI (Table 2). However, NART Full-Scale IQ estimates were lower in patients with TBI ($t = 1.92$, $P = .07$). Neuropsychological function, assessed by composite *z*-score, was significantly poorer in patients with TBI compared with control subjects ($t = 4.61$, $P < .001$).

All examinations yielded high-quality spectra. White matter short-TE (TE = 30) spectra were obtained for all subjects, and, in eight patients, long-TE

spectra (TE = 272) were also collected. However, one patient was not able to remain in the scanner long enough for us to collect a gray matter spectrum. Representative spectra from patients with TBI and control subjects in both white and gray matter are shown in Figure 2.

Concentrations of NAA, Cre, and Cho for gray and white matter voxels are presented in Table 2. White matter revealed markedly reduced NAA in patients with TBI compared with control subjects ($t = 2.59$, $P = .02$), although no significant differences in Cre or Cho between groups were found. No lactate was observed in any patient at TE = 272. Mean NAA concentration in gray matter was lower in patients with TBI than in control subjects, although this did not reach significance. Cho levels in gray matter were significantly elevated in patients with TBI ($t = -4.80$, $P < .0001$). No differences were found between group Cre levels.

The focus of this study was to determine the relationships between neurochemical markers of neuronal integrity and neuropsychological function. NAA ($r = .75$, $P = .008$) and Cre ($r = .67$, $P = .02$) measured in gray matter were correlated with composite neuropsychological function (Fig 3). Similarly, NAA and Cre in white matter were correlated with composite neuropsychological function ($r = .52$, $P = .08$; $r = .65$, $P = .03$, respectively) (Fig 4). Neither Cho levels nor Glasgow Coma Scale scores were significantly related to neuropsychological function. In control subjects, relationships between neurochemical levels and neuropsychological function were not significant.

Although our primary aim was to determine relationships between neurometabolic measures and overall neuropsychological function, we also found substantial relationships between neurometabolites and individual neuropsychological tests (Table 3). Because of the small sample size of this study, these results need to be interpreted with caution.

TABLE 2: Summary means, SD, and significance levels of control and traumatic brain injury sample measures

Measure	Control Subjects (Mean \pm SD)	Patients with TBI (Mean \pm SD)	P Value*
Neuropsychological function (z score)	.07 \pm 0.50	-1.7 \pm 1.4	.0001
Age (yr)	33.9 \pm 11.7	30.7 \pm 10.9	NS
Education (yr)	13.4 \pm 2.1	13.8 \pm 2.4	NS
FSIQ estimate (NART)	104.1 \pm 9.3	96.7 \pm 10.2	.07
NAA ^w (mmol/L)	12.5 \pm 0.9	11.6 \pm 0.9	.02
NAA ^g (mmol/L)	12.4 \pm 0.7	12.1 \pm 0.8	NS
Cre ^w (mmol/L)	7.5 \pm 0.5	7.5 \pm 0.9	NS
Cre ^g (mmol/L)	8.4 \pm 0.4	8.4 \pm 0.6	NS
Cho ^w (mmol/L)	1.8 \pm 0.2	1.9 \pm 0.4	NS
Cho ^g (mmol/L)	1.3 \pm 0.15	1.6 \pm 0.2	.0001

Note.—FSIQ indicates Full-Scale IQ; NART, New Adult Reading Task; NAA, N-acetylaspartate; Cre, creatine; Cho, choline; NS, not significant; TBI, traumatic brain injury; ^w, white matter; ^g, gray matter.

* Independent *t*-tests.

Discussion

Objective methods to assess injury severity and predict the clinical course of TBI are in great demand. Current tools for injury assessment include the Glasgow Coma Scale, measurements of intracranial pressure and cerebral blood flow, and imaging techniques such as CT and MR imaging (22, 29). Composite variables (ie, age, sex, pupillary reactivity, intracranial pressure, motor score) have also been used to predict gross outcome, providing accurate classification in approximately 80% of patients (22, 29). Duration of supported ventilation, extent of posttraumatic amnesia, number of days in intensive care, and length of hospital stay have weak relationships with neuropsychological function (3, 30). Total number of acute lesions and ventricle/brain ratio, measured with MR imaging, correspond to the severity of the Glasgow Coma Scale score, but not with neuropsychological function (1, 31, 32).

In contrast, atrophy is associated with neuropsychological function, suggesting that the extent of diffuse cellular injury is important (1, 31, 32). In the current study, each scan was assessed for the presence of atrophy or focal white matter shearing injury by an experienced neuroradiologist. Although not reaching statistical significance, positive signs for each assessment were associated with lower neuropsychological function, although few patients in this group had positive findings. Moreover, scans acquired later in the course of injury may show more atrophy (1, 32).

NAA measured by proton MR spectroscopy is widely regarded as a marker of neuronal integrity that is reduced in such pathologic states as stroke, systemic lupus erythematosus, vascular dementia, multiple sclerosis, AIDS, and schizophrenia (11). Our observation of reduced NAA in normal-appearing white matter anatomically remote from the overt site of injury is consistent with previous results found in patients after TBI (16–19) and suggests that the diffuse axonal injury present in fatal TBI cases is also present in vivo (5). Furthermore, although gray matter NAA levels were not reduced significantly in patients with TBI, in four patients the NAA levels fell more than 1 SD below the control mean NAA value, suggesting that greater statistical power may reveal group differences.

Although correlations between spectroscopic measures and fine-grained neuropsychological dysfunction have recently been reported in AIDS and neuropsychiatric lupus (33, 34), studies of closed head injury have focused only on gross functioning, with decreased NAA/Cre or NAA related to poor outcome and persistent vegetative state (16, 17, 19). In a study of shaken baby syndrome, those with low NAA after injury remained in a persistent vegetative state, whereas one patient with normal NAA recovered normal neurologic status (35).

In the current study, our main aim was to determine the relationship between quantitative neurochemical concentrations that reflect generalized derangements and overall neuropsychological function.

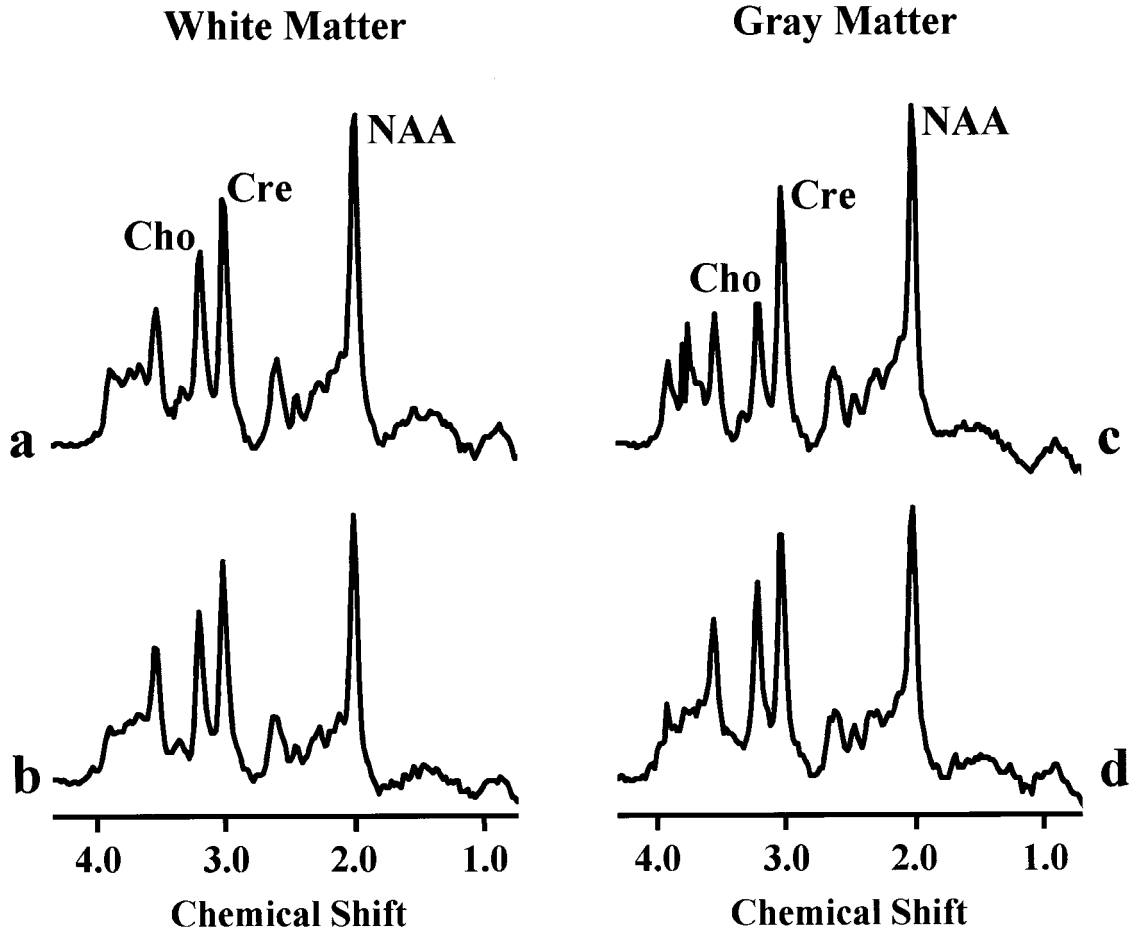


FIG 2. The *left panel* shows spectra from white matter in a control subject (a) and a patient with TBI (b), acquired from normal-appearing tissue. The patient with TBI has reduced NAA, suggestive of neuronal/axonal injury. The *right panel* shows spectra from a central gray matter region in a control subject (c) and a patient with TBI (d). In contrast to the normal levels of NAA, Cre, and Cho found in the control subject, the patient with TBI has reduced NAA, suggestive of neuronal/axonal injury, and elevated Cho, suggesting inflammation and/or membrane breakdown.

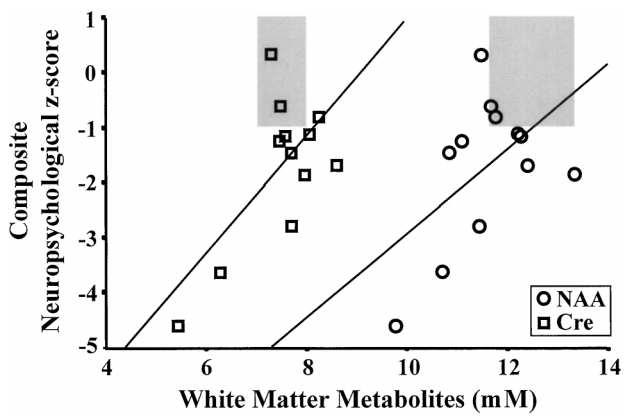


FIG 3. This plot of NAA and Cre in normal-appearing occipitoparietal white matter versus composite neuropsychological z score shows that those subjects with decreased metabolite concentrations have significantly poorer cognitive function. The *shaded boxes* represent the range of control subjects' neuropsychological performance and metabolite concentrations (mean [center] ± 1 SD [edges of box]).

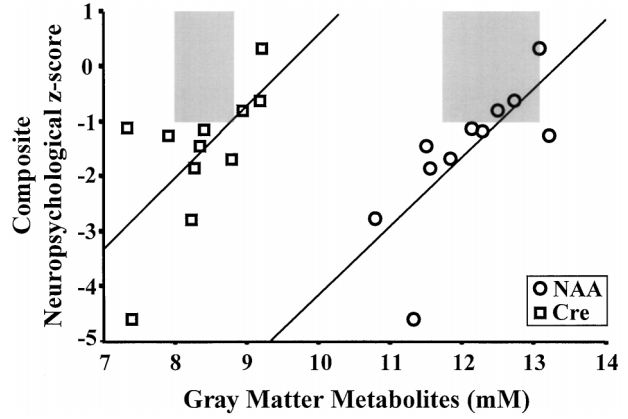


FIG 4. This plot of NAA and Cre in normal-appearing gray matter versus composite neuropsychological z score shows that those subjects with decreased metabolite concentrations have significantly poorer cognitive function. The *shaded boxes* represent the range of control subjects' neuropsychological performance and metabolite concentrations (mean [center] ± 1 SD [edges of box]).

TABLE 3: Correlation between individual neuropsychological measures and neurometabolite concentration (*r* values)

Metabolite	BVRT	CVLT	FAS	GP-L	GP-R	PASAT	SDMT	Tr-A	Tr-B	WCST
NAA ^w	.40	.25	.44	.21	.56	.45	.49	.50	.58*	.18
NAA ^g	.64*	.75†	.59	.38	.58	.59*	.54	.44	.67*	.57
Cre ^w	.55	.49	.65*	.32	.58*	.32	.56	.71†	.69*	.34
Cre ^g	.12	.33	.60	.67*	.70*	.43	.65*	.65*	.74†	-.02
Cho ^w	.27	.19	.16	-.25	-.31	.03	-.14	-.22	-.09	.45
Cho ^g	.19	-.16	.24	.12	.24	-.18	.13	-.23	.29	.03

Note.—NAA indicates *N*-acetylaspartate; Cre, creatine; Cho, choline; ^w, white matter; ^g, gray matter; BVRT, Benton Visual Retention Task; CVLT, California Verbal Learning Test; FAS, verbal fluency; GP-L/R - Grooved Pegboard with left/right hands; PASAT, Paced Serial Addition Test; SDMT, Symbol Digit Modalities Test; Tr-A/B, Trails A and B; and WCST, Wisconsin Card Sorting Task.

* $P < .05$.

† $P < .01$.

We did this by acquiring spectra from brain regions, well separated from the initial site of injury, with no visible abnormality, and by using a composite neuropsychological testing score based on cognitive domains commonly impaired by TBI. Our finding of strong correlations between neurochemical concentrations in gray and white matter and composite neuropsychological functioning supports the hypothesis that diffuse axonal injury is an important contributor to brain dysfunction after TBI.

As shown in Table 3, NAA and Cre had appreciable correlations with individual tests. Nonetheless, these observations are not our major finding, and we made no attempt to correct for multiple analyses in this relatively small cohort. Consequently, these findings need to be interpreted conservatively. Further studies in larger samples will allow us to determine whether certain tests are more closely associated with neurochemistry than others.

Previous spectroscopic studies have reported elevated Cho associated with demyelination, inflammation, or membrane breakdown (13), all of which have been observed after TBI (36). Our finding of elevated Cho in gray matter, in the absence of Cho changes in white matter, is suggestive of cell membrane breakdown and/or inflammation rather than demyelination. Although Cho was substantially elevated in gray matter relative to that in control subjects, Cho changes were not related to neuropsychological function. Cho measurements may provide insight into the active phase of injury resolution; however, further investigation is necessary to determine the significance of Cho changes after TBI.

Cre was also strongly associated with neuropsychological testing results, especially in gray matter. Decreased Cre may reflect neuronal damage seen by NAA directly, or may reflect other mechanisms that give rise to reduced availability of energy metabolites.

Ischemia has been implicated as a confounding factor associated with cellular damage after TBI, as patients with lower cerebral blood flow measurements have poorer prognosis (29). Similarly, brain injury reports of children studied with MR spectroscopy have linked elevated lactate with poor outcomes (35, 37–39). While ischemia may be responsible for widespread cytotoxic damage after TBI (40), no evidence of lactate in white matter was found in the

current adult cohort, suggesting that a persistent ischemic process was not present. Future investigations to assess the presence of elevated lactate within hours of head trauma and to establish primary injury locations may provide useful data for evaluating the role of ischemia in acute neuronal injury.

Clinical imaging tools such as CT and MR imaging are helpful in the acute setting to identify surgical conditions such as extraaxial hematomas and parenchymal lesions. Although axonal shearing injury is known to be associated with a poorer long-term prognosis than other lesions, such as epidural hematomas and contusions, CT and MR imaging are known to be relatively insensitive to axonal injury. It is estimated that CT of acute closed head injury reveals abnormalities in only 20% to 50% of patients with axonal shearing injury. MR imaging is more sensitive, but is still limited in its capacity to identify diffuse injury (41, 42). The presence of more diffuse axonal injury is inferred on later scans when atrophy ensues. MR spectroscopy adds the potential for more objective and earlier evaluation of diffuse axonal injury. Furthermore, the current study establishes that MR spectroscopy may provide additional information regarding neuropsychological functioning.

Conclusion

Brain dysfunction after TBI may be attributable to a complex combination of reversible cellular injury, irreversible cell death, and host factors that affect injury. The MR spectroscopic finding that abnormalities occur in normal-appearing tissue without evidence of focal abnormality indicates the sensitivity of MR spectroscopy in detecting cellular brain injury. Furthermore, the strong correlation between brain neurochemistry and global neuropsychological function suggests that spectroscopic measurements reflect the behavioral manifestations of neuronal dysfunction. MR spectroscopy may be added to routine clinical MR imaging protocols widely available at most clinical centers that care for patients with TBI. In the acute stage after TBI, MR spectroscopy may provide unique neurometabolic data of axonal injury and may add valuable information to the selection of cytoprotective and rehabilitation therapies. However, further studies to evaluate the role of this promising tech-

nique in assessing interventional strategies are required. Although the current results suggest that early assessment by proton MR spectroscopy may prove valuable in predicting recovery, longitudinal studies are needed to confirm its promise in predicting long-term outcome. Finally, proton MR spectroscopy may prove especially useful in examining patients with milder brain injuries, for whom structural studies are often negative.

Acknowledgments

The MRUI software package, which is funded by the European Community project Human Capital and Mobility/Networks, was kindly provided by A. van den Boogaart, Katholieke Universiteit, Leuven, Belgium. We also wish to thank Andrea Halliday, Steven J. Chiulli, John Henry Sloan, Valerie Jack, Marcie Amendologine, Jan Thompson, John O'Malley, and Richard Radecki for their assistance with patient enrollment, and Benito Montoya for patient care during scanning.

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