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# Quantitative proton MRS predicts outcome after traumatic brain injury

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**Article abstract**—*Objective:* To determine whether proton MRS ( $^1\text{H-MRS}$ ) neurochemical measurements predict neuropsychological outcome of patients with traumatic brain injury (TBI). *Background:* Although clinical indices and conventional imaging techniques provide critical information for TBI patient triage and acute care, none accurately predicts individual patient outcome. *Methods:* The authors studied 14 patients with TBI soon after injury ( $45 \pm 21$  days postinjury) and again at 6 months ( $172 \pm 43$  days) and 14 age-, sex-, and education-matched control subjects. *N-acetylaspartate* (NAA), creatine, and choline were measured in normal-appearing occipitoparietal white and gray matter using quantitative  $^1\text{H-MRS}$ . Outcome was assessed with the Glasgow Outcome Scale (GOS) and a battery of neuropsychological tests. A composite measure of neuropsychological function was calculated from individual test *z*-scores probing the major functional domains commonly impaired after head trauma. *Results:* Early NAA concentrations in gray matter predicted overall neuropsychological performance ( $r = 0.74, p = 0.01$ ) and GOS ( $F = 11.93, p = 0.007$ ). Other metabolite measures were not related to behavioral function at outcome. *Conclusion:*  $^1\text{H-MRS}$  provides a rapid, noninvasive tool to assess the extent of diffuse injury after head trauma, a component of injury that may be the most critical factor in evaluating resultant neuropsychological dysfunction.  $^1\text{H-MRS}$  can be added to conventional MR examinations with minimal additional time, and may prove useful in assessing injury severity, guiding patient care, and predicting patient outcome.

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Traumatic brain injury (TBI) is a leading cause of neuropsychological dysfunction and persistent disability. In the United States each year, 500,000 patients with head trauma are hospitalized, 70,000 incur long-term disability, and 2,000 remain in a persistent vegetative state.<sup>1</sup> The annual cost of treatment and rehabilitation of TBI is estimated to approach \$25 billion.

Despite advances in acute patient care and rehabilitation, it remains difficult to predict function and outcome after injury. The Glasgow Coma Scale (GCS)<sup>2</sup> obtained on admission to the emergency room remains the standard for predicting gross outcome (i.e., dead, persistent vegetative state, disabled, good outcome).<sup>3</sup> Complex combinations of injury severity variables (e.g., GCS, intracranial pressure, pupillary reactivity, age, sex) improve prognostication, and can

predict gross social and occupational outcome levels.<sup>3–5</sup> Although prediction of gross outcome level is clinically important, neuropsychological outcome is a better predictor of long-term social and occupational status.<sup>4</sup> A study of 436 adults with TBI found that initial GCS was only weakly related to overall neuropsychological functioning at 1 year postinjury.<sup>6</sup>

Neuroimaging with conventional radiologic interpretation provides essential information for guiding clinical management, especially in the acute stage of injury.<sup>7,8</sup> However, cellular injury, which is likely associated with cognitive dysfunction, cannot be visualized with conventional imaging techniques.<sup>9–12</sup> As with other clinical predictors, quantitative evaluation of lesions and atrophy seen on MRI and CT provides some prediction of outcome, but is less satisfactory for neuropsychological function.<sup>13–16</sup>

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Proton MRS ( $^1\text{H-MRS}$ ) provides a noninvasive measurement of the brain metabolites *N*-acetylaspartate (NAA), creatine (Cre), and choline (Cho) to assess metabolic derangement after brain injury.<sup>17</sup> In stroke and neurodegenerative and inflammatory disease, NAA is depressed and Cho is elevated, indicating neuronal injury and inflammation or demyelination.<sup>17-21</sup> Evidence of partial recovery of NAA suggests that it may be a metabolic marker of mitochondrial function.<sup>19,22</sup>

Magnetic resonance spectroscopy has shown altered neurochemistry associated with poor outcome after TBI.<sup>23-26</sup> Our group found strong correlations between concurrent neuropsychological function and NAA in gray matter (GM) and Cre measured in normal-appearing GM and white matter (WM) of the occipital lobe.<sup>27</sup> These observations support the hypothesis that diffuse cellular injury is an important contributor to brain dysfunction after TBI. However, the value of early neurochemical assessment for predicting detailed neuropsychological outcome has yet to be determined. The current study sought to determine whether quantitative neurochemical measurements performed soon after injury would predict the extent of neuropsychological dysfunction at approximately 6 months postinjury. Most spontaneous recovery occurs within this time frame, and although additional gains may be observed, it is a commonly used time point to assess outcome.<sup>28</sup>

**Methods.** *Subjects and study design.* Fourteen patients (13 men, mean age  $33.8 \pm 13.7$  years) who had moderate to severe head trauma were recruited from local rehabilitation facilities. Our aim was to study patients using MRS and MRI as soon as possible after injury and then again at 6 months postinjury. Contraindications to early initial scanning included coma, implanted metal, limb fixation, or unstable medical condition. Patients with TBI were compared with 14 control subjects (13 men, mean age  $33.9 \pm 11.7$  years) matched for age, sex, and education. All studies were approved by the Institutional Review Board. Before study, informed written consent was obtained from patients, or a legal guardian if patients were unable to provide consent.

Paired neuropsychological testing and MRI/MRS examination was performed within 24 hours for all subjects. If neuropsychological testing and imaging were performed on the same day, neuropsychological testing was conducted first to minimize the potential effect of fatigue on performance. Neuropsychological tests were administered by a trained neuropsychological technician blinded to spectroscopic findings.

The GCS on admission was obtained from chart review. A revised GCS was calculated (number of points obtained/possible, with the language portion of the scale removed for those patients who were intubated) to obtain a more accurate assessment of injury.<sup>29</sup> At the second time point, patients were also evaluated using the Glasgow Outcome Scale (GOS).

*Neuropsychological testing.* The neuropsychological test battery was designed to probe a wide range of brain functions commonly impaired after TBI. These measures

typically have minimal practice effects over repeated administrations, and multiple test forms were used when possible.<sup>15,28,30</sup> Cognitive functions assessed included attention and information processing speed—Paced Auditory Serial Addition Task (PASAT); verbal memory—California Verbal Learning Test (CVLT); visual memory—Benton Visual Retention Task (BVRT); sensorimotor function—Grooved Pegboard; Symbol Digit Modalities Test (SDMT); language—verbal fluency (FAS); frontal or “executive” functioning—Wisconsin Card Sorting Task (WCST), Trail Making Tests A and B; estimated premorbid intelligence—New Adult Reading Task (NART); estimated Full-Scale IQ (FSIQ); and orientation—Galveston Orientation and Amnesia Test (GOAT).<sup>30</sup>

Because a range of neuropsychological deficits are expected after TBI,<sup>28</sup> and our hypotheses were not specific to a given cognitive domain, a composite measure of neuropsychological performance was used to quantify brain function at each time point. This composite was determined by selecting a representative variable for each test, and converting this variable to a *z*-score using relevant norms from control populations: PASAT (number correct on trial four); 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 performance (percent perseverative errors); and Trails A and B (time). These individual *z*-scores were then averaged and the result provided a quantitative measure of overall brain function.

*Magnetic resonance spectroscopy/imaging.* All MR acquisitions were carried out with a 1.5-Tesla clinical MR scanner using standard software (GE Medical Systems, Waukesha, WI). We used a highly reproducible protocol for spectroscopic acquisition and analysis.<sup>31</sup> On the first scan, the position of the head was carefully noted using the angle of the interpupillary line compared with the transverse landmark light on the scanner. The angle of head flexion–extension was determined by moving the subject so that the tragus was aligned with the axial landmark light, and the position of the intersection with longitudinal light along the midline (typically on the nose) recorded. The imaging sequence included a T1-weighted sagittal localizer (echo time [TE] = 16 msec, repetition time [TR] = 500 msec,  $256 \times 128$  matrix, and 5-mm thick slices with a 2.5-mm gap), a T1-weighted volume axial series (fast-SPGR, TE = 6.9 msec, TR = 17.7 msec, flip angle = 25 degrees,  $256 \times 192$  matrix, 3-mm contiguous slices), and a conventional T2-weighted series (TE = 30/100 msec, TR = 2,800 msec, 4-mm slices with a 1-mm gap). Spectroscopic voxel locations were selected from T1- and T2-weighted images.

For spectroscopic acquisition, a STEAM pulse sequence, including water suppression,<sup>32</sup> was used to sample a voxel of  $25 \times 35 \times 21$  mm (TE = 30 msec, TR = 2,000 msec, 128 averages) within normal-appearing left occipitoparietal WM. A short TE sequence was used to reduce the effects of alterations to metabolite spin–spin relaxation times, and a moderately long TR was used to reduce the effects of saturation through alterations of spin–lattice relaxation times. Voxels were centered on the first axial image slice of the T1-weighted series, which was superior to the lateral ventricles. Voxel boundaries were located to maximize the WM

**Table 1** Patient descriptive data

Patient	Age, y/sex	Injury	GCS	MRI findings	Test date*		NAA concentration, mM	z-Score at outcome
					Initial	Outcome		
1	29/M	Blunt trauma	8T	Atr, SI (cc)	60	182	11.91	-2.11
2	46/M	Blunt trauma	N/A	Focal lesion (r pons)	36	210	12.35	-1.73
3	37/M	MVA	6	C (rl ft); Atr	53	216	12.18	-0.52
4	18/F	MVA	9	C (rl t)	50	112	12.17	-1.49
5	32/M	MVA	14	Normal	25	123	12.94	-0.65
6	23/M	MVA	3T	Normal	13	185	12.74	-0.54
7	26/M	Blunt trauma	13	C (l ft, r f), SDH (l t)	14	212	12.79	0.52
8	20/M	MVA	15	C, H (r f); SI (pons); skull fx (depressed)	36	181	13.44	0.32
9	24/M	MVA	N/A	Normal	46	183	13.39	1.17
10	45/M	MVA	6T	C (l t); SDH (l t)	80	168	—	-2.28
11	19/M	MVA	13	C (lr f), SI (r f)	77	—	13.15	—
12	49/M	MVA	7	C (l f)	66	232	11.61	-1.20
13	65/M	MVA	7T	SDH (l); SI (l f, scwm); H (r bg)	41	93	13.71	-0.27
14	40/M	MVA	5T	SDH (r); H (l cso); C (r p); SI (cc)	31	150	—	-3.07
Mean	30.7	—	9.4	—	45	172	12.70	-0.91

\* In days postinjury.

GCS = Glasgow Coma Scale; NAA = *N*-acetylaspartate; N/A = not available; MVA = motor vehicle accident; Atr = atrophy-diffuse cerebral; C = contusion (blood, encephalomalacia, or gliosis); SI = axonal shearing injury-hemorrhagic or nonhemorrhagic; SDH = subdural hematoma; H = hemorrhage; cc = corpus callosum; bg = basal ganglia; cso = centrum semiovale; scwm = subcortical white matter; f = frontal; l = left; o = occipital; p = parietal; r = right; t = temporal; T = patient was intubated when GCS was measured.

contribution by aligning the medial margin of the voxel with the interhemispheric fissure GM-WM boundary. Next, a voxel of 25 × 35 × 21 mm (TE = 30 msec, TR = 2,000 msec) was placed along the longitudinal fissure to probe the integrity of normal-appearing GM tissue. The voxel was specifically placed to avoid inclusion of the sagittal sinus and corpus callosum on inferior slices. The precise location of the spectroscopic voxels was chosen to sample only normal-appearing tissue, that is, tissue unaffected by obvious focal hemorrhage, edema, demyelination, or gliosis. In addition, each examination was subsequently reviewed by an experienced neuroradiologist for such abnormalities. In no subject was focal hemorrhage, edema, demyelination, or gliosis seen in any location corresponding to either the GM or WM voxels.

Careful relocation of spectroscopic voxels for the second examination ensured that the same anatomic tissue was examined. Briefly, voxels were placed by referring to specific sulcal patterns of GM identified from thin-slice T1-weighted images on films from the original scans. These methods are described more fully in Brooks et al.<sup>31</sup>

**Data analysis.** Spectroscopic data were transferred to a Sun UltraSparcstation (Sun Microsystems, Mountain View, CA) for analysis using MRUI software (Leuven, Belgium). For metabolites, a single data batch was processed blindly, requiring only starting values for resonance frequencies and decay constants for spin-spin relaxation. Residual water resonances were removed using time-domain Hankel Lanczos singular value decomposition filtering.<sup>33</sup> Time-domain fitting of gaussian line shapes to NAA, Cre,

and Cho was carried out by variable projection,<sup>34</sup> and peak areas corresponding to NAA, Cre, and Cho recorded. The areas from water peaks were determined, in a second batch, from unsuppressed water scans using singular value decomposition.<sup>33</sup> Metabolite concentrations were calculated using the internal water signal as a concentration reference, correcting for the tissue percentage within the spectroscopic voxel using automated segmentation of the images corresponding to the voxels, and correcting for relaxation effects during the pulse sequence using literature values.<sup>35</sup>

Spectroscopic findings, GCS, GOS, intelligence estimates (NART), and neuropsychological testing results were compared using Pearson correlation analysis, independent *t*-tests, analysis of variance, and paired *t*-tests using SPSS for Macintosh (Chicago, IL).

**Results. Descriptive data.** Patients were studied twice: initially as soon as MRS scanning was possible (45 ± 21 days postinjury) and then at approximately 6 months (172 ± 43 days) postinjury. Clinical data are summarized in table 1. No significant differences in age, years of education, or intelligence estimates were found between control subjects and patients with TBI (table 2). Although abnormalities were seen on MRI in 11 patients at initial examination, none was in the left parietal or occipital lobe. Two patients had a history of TBI approximately 10 years previously.

The initial examination protocol was to obtain spectra from WM and GM. However, we did not acquire a GM

**Table 2** Summary of control and traumatic brain injury sample measures

Measure	Controls, mean (SD)	TBI (initial)		TBI (outcome)	
		Mean (SD)	<i>p</i> Value	Mean (SD)	<i>p</i> Value
Composite <i>z</i> -score	0.07 (0.50)	-1.78 (1.41)	0.0001	-0.91 (1.22)	0.01
Age, y	33.9 (11.7)	33.8 (13.7)	NS	—	—
Education, y	13.4 (2.1)	14.0 (2.5)	NS	—	—
FSIQ, estimated	104.1 (9.3)	99.63 (10.4)	NS	—	—
Gray matter					
NAA, mM	12.90 (0.77)	12.70 (0.66)	NS	12.14 (0.84)	0.02
Cre, mM	8.73 (0.46)	8.77 (0.51)	NS	8.66 (0.96)	NS
Cho, mM	1.34 (0.16)	1.65 (0.16)	0.0001	1.61 (0.36)	0.02
White matter					
NAA, mM	12.72 (0.83)	11.79 (0.92)	0.01	12.18 (1.03)	NS
Cre, mM	7.67 (0.48)	7.37 (0.88)	NS	7.50 (1.04)	NS
Cho, mM	1.81 (0.22)	1.94 (0.33)	NS	1.76 (0.24)	NS

*p* Values reflect comparison with control subjects using *t* tests.

TBI = traumatic brain injury; FSIQ = Full-Scale IQ; NAA = *N*-acetylaspartate; Cre = creatine; Cho = choline.

spectrum from three patients who were less compliant. Three patients were not sufficiently oriented or attentive for neuropsychological testing at the initial examination (as determined by a GOAT score of greater than 75), although MR examinations were completed.<sup>28,30</sup> At the late time point, WM and GM spectra were collected in 12 of the 14 patients. One patient was not scanned because of surgical metal implantation after the initial examination, and one moved out of state and was lost to follow-up.

**Neuropsychological function.** Neuropsychological performance was significantly poorer in patients with TBI than control subjects at both examinations (initial examination,  $t = 4.58$ ,  $p = 0.0001$ ; late examination,  $t = 2.79$ ,  $p = 0.01$ ) (table 2), although neuropsychological function in patients with TBI improved between time points, with the mean *z*-score improving from -1.78 to -0.91 ( $t = -4.36$ ,  $p = 0.002$ ).

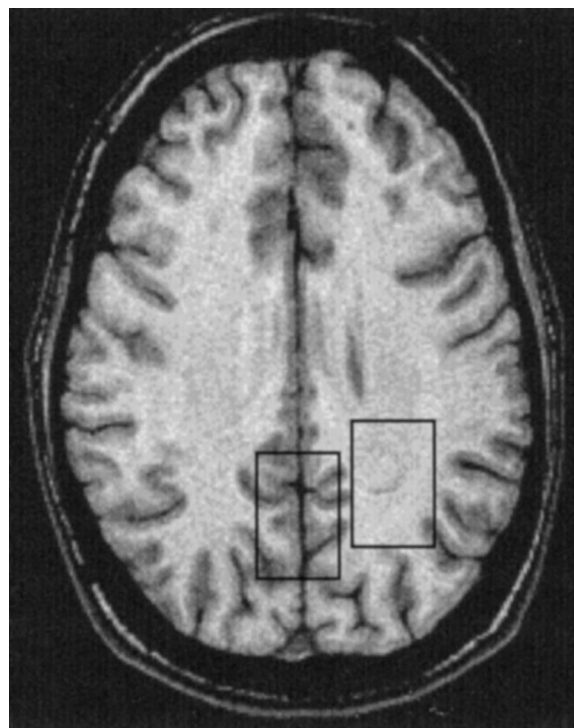
**Neurochemical abnormalities.** Figure 1 shows representative voxel locations and figure 2 the high-quality spectra obtained from all subjects in completed examinations. At the initial examination, NAA measured in WM was lower in patients with TBI than in control subjects ( $t = 2.81$ ,  $p = 0.01$ ), although Cre and Cho concentrations were not significantly different. In GM, mean NAA and Cre concentrations were not significantly different, although Cho was markedly elevated ( $t = -4.80$ ,  $p = 0.0001$ ; see table 2).

At outcome, mean WM NAA, Cre, and Cho in patients with TBI were not significantly different from levels in control subjects. However, Cho in GM remained elevated compared with control subjects ( $t = 2.53$ ,  $p = 0.02$ ). NAA in GM was decreased compared with control subjects ( $t = 2.42$ ,  $p = 0.02$ ). No significant changes in mean Cre at outcome were found.

The concentration of NAA measured in the GM at the early scan was strongly correlated with neuropsychological function at outcome ( $r = 0.74$ ,  $p = 0.01$ ; figure 3 and table 3). Premorbid intellectual functioning and age may influence recovery after TBI.<sup>3,36</sup> Using partial correlations to

control for these factors, we found that the correlation between GM NAA and neuropsychological function was strengthened ( $r = 0.84$ ,  $p = 0.005$ ). Other neurometabolite measures did not predict neuropsychological function at outcome.

Gray matter NAA at the initial scan was also associated with a number of individual neuropsychological test *z*-scores at outcome: CVLT,  $r = 0.73$ ,  $p = 0.01$ ; PASAT,  $r =$



**Figure 1.** The locations in the occipital lobe of the gray matter (midline) and white matter spectroscopic voxels used in this study are shown on an axial T1-weighted image.

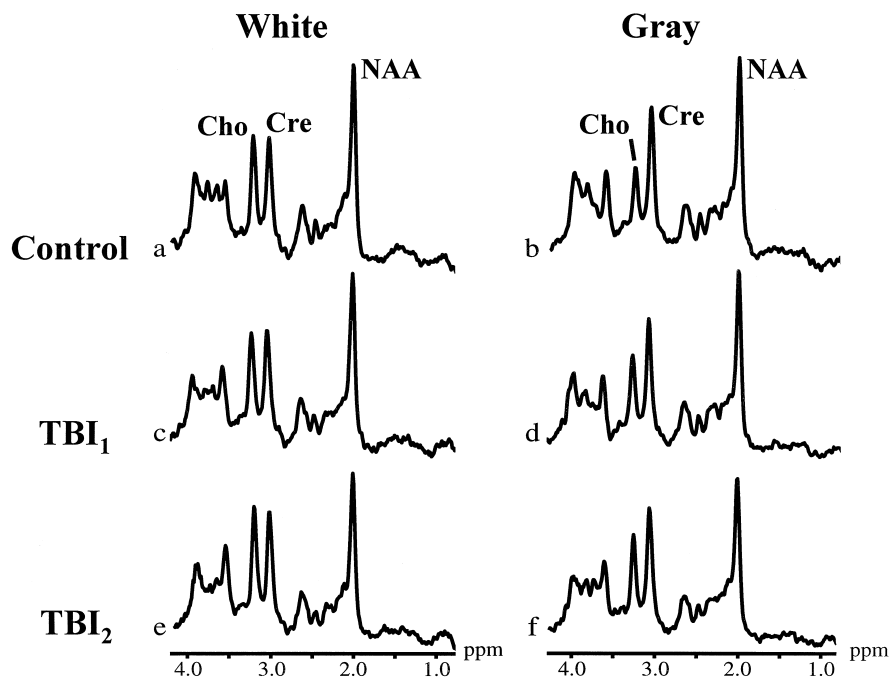


Figure 2. The top panel shows spectra from normal-appearing white (a) and gray matter (b) in control subjects. The middle panel displays spectra from a patient with traumatic brain injury (TBI) with mild neuropsychological deficits at outcome, demonstrating mild N-acetylaspartate (NAA) reduction in white matter (c) and gray matter (d), as well as choline (Cho) elevation in gray matter at initial examination. In contrast, the lower panel displays spectra from a patient with TBI with persistent neuropsychological abnormalities. Note marked NAA depletion in both tissues (e and f), suggestive of neuronal/axonal injury, and Cho elevation in gray matter (f), suggestive of inflammatory processes at initial examination. Cre = creatine.

0.64,  $p = 0.03$ ; Trails A,  $r = 0.76$ ,  $p = 0.007$ ; and Trails B,  $r = 0.68$ ,  $p = 0.02$ .

Gray matter NAA was strongly related to gross outcome assessed by GOS ( $F = 11.93$ ,  $p = 0.007$ ), with little overlap between good outcomes and moderate disability (see table 3; figure 4). However, metabolite concentrations in WM at the initial scan were not significantly related to GOS. Neither GCS nor revised GCS was significantly associated with functional assessment at either time point.

**Discussion.** Predicting outcome from TBI is an integral part of clinical care, facilitating therapeutic decision making and providing family members with much-needed guidance for long-term care.<sup>5</sup> Although conventional neuroimaging can provide important information for acute clinical management, its prognostic value is limited, particularly at early stages of injury resolution. Commonly used outcome assessment scales, such as the GOS, the Functional Independence Measure, and the Disability Rating Scale, provide a measure of gross outcome, but are not sensitive to subtle impairments commonly found after

TBI. Indeed, consistent with the findings of Conzen et al.,<sup>37</sup> the current patient cohort demonstrated only two GOS levels, moderate disability and good recovery, despite a broad range of functional brain impairment measured by neuropsychological testing. Accordingly, the primary objective of the current study was to investigate the ability of early MRS measures of neurochemical markers of injury to predict neuropsychological function at outcome.

We have shown previously that NAA and Cre concentrations, measured in normal-appearing tissue soon after injury, are correlated with neuropsychological functioning in TBI.<sup>27</sup> Our current results demonstrate that these neurochemical measurements may also provide valuable information regarding the long-term functional outcome of traumatically injured patients. In particular, GM NAA concentrations were strongly correlated with general neuropsychological performance at 6 months after injury, a commonly used measure of occupational and psychosocial outcome.<sup>5</sup> In our prior study,<sup>27</sup> over-

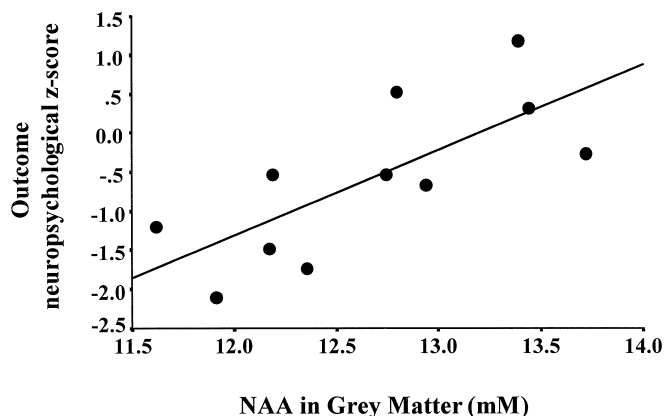
**Table 3** Correlations between neurometabolite measures of brain injury measured at the early scan and neuropsychological function 6 months after traumatic brain injury

	Gray matter		White matter	
	Outcome composite z-score, $r$ ( $p$ value)	GOS, $F$ ( $p$ value)	Outcome composite z-score, $r$ ( $p$ value)	GOS, $F$ ( $p$ value)
NAA*	0.74 (0.01)†	11.92 (0.007)†	-0.03	0.01
Creatine	0.37	0.41	0.34	0.66
Choline	-0.06	0.88	0.01	0.20

\* NAA in gray matter is a strong predictor of both neuropsychological performance and disability (GOS).

† Values in parentheses reflect statistically significant  $p$  values.

GOS = Glasgow Outcome Score; NAA = N-acetylaspartate.



*Figure 3. This plot of the initial examination N-acetylaspartate (NAA) concentration in normal-appearing occipitoparietal gray matter versus composite neuropsychological z-score shows that those subjects with decreased metabolite concentrations have significantly poorer overall cognitive function at outcome.*

all neuropsychological performance was unrelated to GM NAA in control subjects, suggesting that the outcome prediction currently observed reflects the sensitivity of MRS to diffuse brain injury. GM NAA also predicted GOS, which provides information about the patient's ability to live independently and clinical information essential for long-term care. Thus, GM NAA, reflecting neuronal status, may be an important predictor of long-term outcome in TBI.

Although GCS is an essential measure for patient triage and grading injury severity, prediction of fine-grained outcome for individual cases has not been demonstrated.<sup>38</sup> Indeed, although the GCS remains a useful predictor of gross outcome in large patient samples, in the current study we found no significant relationships between GCS and neuropsychological function at outcome.

The current study reveals that outcome can be predicted with MRS at approximately 1.5 months postinjury. If our neurochemical observations are a reliable measure of diffuse axonal injury, the question remains as to how rapidly NAA falls after TBI, and hence what time postinjury is optimal for outcome prediction. Because histologic data show irreversible neuronal damage between 12 and 72 hours postinjury,<sup>10,12</sup> further studies are required to demonstrate how early neurochemistry is altered after TBI, and the optimal time point for predicting outcome.

The current study focused on overall neuropsychological performance after head trauma. However, we also found strong correlations between NAA and individual neuropsychological tests. In particular, tests of function within the cognitive domains of verbal memory, sustained attention, and frontal or "executive" processing were individually sensitive to decrements in neuronal metabolites. However, the issue of whether specific cognitive domains are maximally predicted by GM NAA awaits studies with larger

samples and adequate statistical power to detect significant differences between correlation coefficients.

The finding that overall neuropsychological function was related to neurometabolites from the occipital lobe is important, especially because no patient had radiologic signs of occipital or parietal damage. Also, the neuropsychological tasks used certainly do not specifically probe occipital lobe function more than other cortical regions. Hence, the correlation between occipital GM NAA and neuropsychological function likely reflects that injury in this part of the cortex is strongly related to injury elsewhere. Further studies are required to determine whether similar injury is present elsewhere in the brain, especially in frontal and temporal structures that often sustain acute damage in TBI.

We found that mean WM NAA fell between the injury and initial assessment at 1.5 months and then made a substantial recovery. At the same time, the mean WM Cho became slightly elevated. In contrast, NAA concentration in GM, which was only slightly lower than in control subjects at the initial examination, continued to fall across the total study interval to be significantly lower than in control subjects at 6 months. These results suggest that the processes taking place in the WM and GM may be different. The initial fall and subsequent recovery of NAA in WM suggests a reversible metabolic derangement. This is further supported by the correlation between neuropsychological function and NAA in WM at the early time point,<sup>27</sup> although not at 6 months. Further evidence of WM involvement is that of the four subjects with neuropsychological performance below the normal range, three were one or more SDs below the mean NAA of control subjects, and all had markedly elevated Cho. This suggests a neurochemical pattern associated with TBI that may relate to poor neuropsychological outcome.

Another process is suggested by consideration of neurochemical changes in GM. Cho was significantly elevated at the initial scan, suggesting an inflammatory response to irreversibly damaged neurons.<sup>39</sup> This elevation in Cho continued through 6 months, possibly reflecting ongoing inflammation as observed in animal models of irreversible neuronal injury.<sup>40</sup> The greater decline in NAA seen at 6 months than at 1.5 months might be a consequence of this ongoing inflammatory process. Longer-term follow-up is required to determine whether there is a reversible component of NAA change in GM and whether inflammation, as indicated by elevated Cho, resolves.

Changes in nuclear magnetic relaxation processes may account for the apparent changes in neurometabolite concentrations. If present, such a finding would indicate a different interpretation of our results. A change in T2 from 350 to 200 msec would account for the changes in NAA signal seen in our studies. However, even a T2 of 1 second would be insufficient to account for the apparent increase in Cho signal. Because of the sensitivity of line width to T2, changes of such magnitude would be obvious in

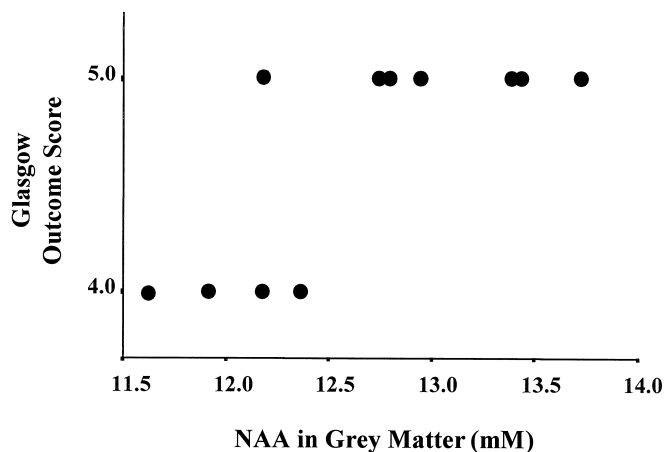


Figure 4. This plot of the initial examination N-acetyl-aspartate (NAA) concentration in gray matter versus the Glasgow Outcome Score demonstrates that those subjects with decreased metabolite concentrations were significantly more likely to have disability at outcome (5 = good outcome, 4 = moderate disability).

the spectra. However, as shown in figure 2, there are no appreciable effects on line width in any spectra. The T1 effect is more complex because of the bimodal relationship between T1 and apparent concentration. For NAA, our results could be accounted for by T1 values of either 275 msec or 1.7 second. An elevation of T1 to 1.7 second is possible, although the physical explanation for this is unclear. However, a T1 of 275 msec is unlikely on line width evidence (see figure 2). The changes in the Cho signal cannot be explained by changes in T1 because the minimum apparent concentration of 1.5 mM was obtained at a T1 of approximately 0.85 second.

Explanations for alterations to relaxation times include fluid changes associated with inflammatory processes, different intracellular milieu associated with proliferation of different cell types such as macrophages, or blood products that may be present after microscopic vascular injury. However, our current data are insufficient to determine whether these mechanisms are implicated.

Proton MRS reveals significant neurochemical changes in normal-appearing WM and GM after TBI that are consistent with histologic findings in this disease. The strong relationship between NAA and neuropsychological performance at outcome suggests that the extent of cellular injury is an important contributor to resultant behavioral dysfunction. Because MRS can be added to conventional MR examinations with minimal additional time ( $\approx 10$  minutes), it may be useful in assessing injury severity and in guiding patient care. The integration of MRS with other injury indices (i.e., GCS, pupillary reactivity) may provide a superior index for outcome prediction after trauma. Moreover, the ability to monitor cellular metabolic changes may prove especially useful in evaluating the efficacy of therapeutic interventions,

both acutely and over the extended time course typical of convalescence associated with TBI.

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