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Brain Temperature as an Indicator of Cognitive Function in Traumatic Brain Injury Patients

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Abstract: Whether brain temperature noninvasively extracted by magnetic resonance imaging has a role in identifying brain changes in the later phases of mild to moderate traumatic brain injury (TBI) is not known. This prospective study aimed to evaluate if TBI patients in subacute and chronic phases had altered brain temperature measured by whole-brain magnetic resonance spectroscopic imaging (WB-MRSI) and if the measurable brain temperature had any relationship with cognitive function scores. WB-MRSI was performed on eight TBI patients and fifteen age- and sex-matched control subjects. Brain temperature (T) was extracted from the brain's major metabolites and compared between the two groups. The T of the patients was tested for correlation with cognitive function test scores. The results showed significantly lower brain temperature in the TBI patients ($p < 0.05$). Brain temperature derived from N-acetylaspartate (T_{NAA}) strongly correlated with the 2 s paced auditory serial addition test (PASAT-2s) score ($p < 0.05$). The observation of lower brain temperature in TBI patients may be due to decreased metabolic activity resulting from glucose and oxygen depletion. The correlation of brain temperature with PASAT-2s may imply that noninvasive brain temperature may become a noninvasive index reflecting cognitive performance.

Keywords: traumatic brain injury; echo-planar; magnetic resonance spectroscopic imaging; metabolite; whole-brain; temperature

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1. Introduction

Traumatic brain injury (TBI) is a brain injury caused by an external force, such as falls and vehicle collisions [1]. About 69 million people are globally affected annually [2]. The direct cost of TBI can amount to USD 13.1 billion. The indirect cost of TBI is even more enormous; it is reported that the cost due to loss of productivity amounts to USD 64.7 billion [3]. Often, the burden of total cost is initially underestimated since cognitive impairment in mild TBI is left unnoticed until late. Of mild, moderate, and severe TBI classified based on the level of consciousness or the Glasgow Coma Scale (GCS) at the time of initial hospital admission [4,5], the outcome of severe TBI is often recognized in the early phases of injury. Yet, the burden posed by the consequences of mild and moderate TBI cannot be neglected. According to a previous survey, one-third of mild TBI and two-thirds

of moderate TBI patients remain unemployed three months after injury [6–8]. Impaired memory, attention, processing speed, and executive function have been reported in mild and moderate TBI patients in subacute (8 to 89 days from injury) and chronic (after 90 days) phases [9–11].

Rehabilitation proves to be effective in improving cognitive function after brain injury [12]. To correctly estimate and reduce the socioeconomic burden of TBI, mild to moderate TBI patients must receive appropriate cognitive assessment and rehabilitation as early as possible. However, completing the lengthy cognitive assessment protocols is not always easy when ill patients cannot cooperate. Thus, patients' cognitive status needs to be assessed through alternate means that do not demand patient cooperation.

Computed tomography (CT) and magnetic resonance imaging (MRI) are typically used to diagnose TBI [9,13,14]. MRI is particularly effective in identifying brain injuries such as cerebral contusion and diffuse axonal injury (DAI), owing to its superior tissue contrast [15]. With new quantitative MRI techniques, minute abnormalities at the microstructure level can even be identified [16,17]. These quantitative MRI techniques not only detect structural abnormalities but also aberrations in the brain's metabolism. Proton magnetic resonance spectroscopy (^{1}H-MRS), a quantitative MRI technique, has successfully identified areas with abnormal brain major metabolite ratios, such as N-acetylaspartate (NAA)/creatine (Cr) and choline (Cho)/Cr, in otherwise normal-appearing brain tissue of mild TBI patients [18]. More importantly, a prior study has shown the correlation of these metabolite changes in certain brain regions with the cognitive status of TBI patients [19].

Areas of brain involvement usually differ among TBI patients. While area-wise assessment of the brain can provide estimates of cognitive involvement, a singular quantitative index applicable to all brain regions would allow us to compare severity across patients. Brain temperature, reflective of the brain's energy consumption, can be a good candidate for this. Prior research has reported changes in the brain temperature's circadian rhythm in acute (within 7 days from injury) moderate to severe TBI patients and the magnitude of this alteration as a predictor of survival [20]. Although the conventional way of measuring brain temperature involves inserting a thermistor into the brain parenchyma, less invasive alternatives have also been introduced. Brain temperature measurement by ^{1}H-MRS is among these alternatives. This technique calculates the brain temperature from the frequency or amplitude of major brain metabolites [21,22]. The accuracy of the measurement has also been documented through phantom and animal experiments [23,24]. Its clinical utility has been reported in several pathological states, including myalgic encephalomyelitis/chronic fatigue syndrome [25].

To our knowledge, no brain temperature documentation about TBI in the late phases exists. We hypothesized that the brain temperature measured by ^{1}H-MRS would be altered in these patients, which can indirectly reflect cognitive function. This prospective study aimed to evaluate if TBI patients in subacute and chronic phases had altered brain temperature measured by ^{1}H-MRS and if the brain temperature measured by ^{1}H-MRS had any relationship with cognitive function scores.

2. Materials and Methods

2.1. Participants

The institutional review board of Hokkaido University Hospital, Sapporo, Japan, approved this prospective study (015-0271). Written informed consent was obtained from all participants. TBI patients in subacute to chronic phase who consulted at the Department of Rehabilitation, Hokkaido University Hospital, and consented to participate in this study were recruited over 25 months (November 2015–December 2017). The inclusion criteria were (1) male sex, (2) 20 years of age or older, and (3) diagnosed to have neurological sequelae of brain injury. The exclusion criteria were (1) absolute contraindications to MRI, (2) lack of MRI including short echo time (TE) whole-brain magnetic resonance spectroscopic imaging (WB-MRSI), (3) image artifacts that limit interpretation, (4) lack of cognitive function test results, and (5) concurrent central nervous system (CNS) pathologies

either reported or detected on conventional MRI sequences. Eleven patients consented to this study. Of them, three were excluded for lacking short TE WB-MRSI. Eight patients (mean age ± standard deviation (SD) = 44.00 ± 13.34 years; age range = 20–68 years) were thus eligible for the study. The demographic details of the patients are provided in Table 1. Five of them were diagnosed with mild TBI, and three with moderate to severe TBI. The average interval ± SD between the injury and MRI was 73.63 ± 136.91 months (range = 2–432 months).

Table 1. Demographic details about patients.

Patient	Age (Years)	Time from Injury (Months)	Severity of TBI	Medical and Drug History
1	20	11	Mild	Taking Lamotrigine
2	43	16	Mild	-
3	47	2	Mild	Taking traditional medicine with potential nervous system effects
4	48	68	Mild	Controlled diabetes mellitus Taking Metformin
5	68	11	Mild	-
6	33	38	Moderate to severe	-
7	39	11	Moderate to severe	Taking antihistamines
8	54	432	Moderate to severe	-

As the control group, 15 age-matched males (age range = 22–68 years) were selected from a WB-MRSI database of 21 male and 17 female healthy adults [26]. The inclusion criteria for the normal database were (1) male sex and (2) age 20 years or older. The exclusion criteria were (1) contraindications to MRI, (2) history of diseases that affect the integrity of the CNS, and (3) visible motion artifacts.

A radiologist with 22 years of experience in neuroimaging reviewed the images of conventional MRI sequences of the patients to exclude any gross abnormalities and image artifacts.

2.2. MRI

All examinations were conducted using a 3T scanner (MAGNETOM Prisma, Siemens Healthcare, Erlangen, Germany) and a 64-channel head/neck coil.

In all participants, WB-MRSI was performed using an echo-planar sequence and the following scan parameters: repetition time (TR)/TE/inversion time (TI) = 1710/17.6/198 ms, flip angle (FA) = 73°, sampling of 50 × 50 × 18 k-space points over 280 × 280 × 180 mm^3, and acquisition time (TA) = 16:49 min. To obtain a water reference signal (i.e., water MRSI) with WB-MRSI, an additional dataset was obtained in an interleaved manner without water suppression and 10° excitation and gradient-echo observation (TE = 3.8 ms). A sagittal T1-weighted 3D magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence (TR/TE/TI = 1900/2.85/900 ms, TA = 1:51 min), an axial fluid-attenuated inversion recovery (FLAIR) imaging sequence (TR/TE/TI = 12,000/115/2800 ms, TA = 1:52 min), an axial proton density-weighted imaging (PDWI) sequence (TR/TE = 4000/12 ms, TA = 1:52 min), and an axial diffusion imaging sequence (TR/TE = 4000/83.2 ms, maximum b-value = 8000 s/mm^2, TA = 17:52 min) were also acquired to obtain structural images and to check for other abnormalities. TBI patients also received an axial 3D gradient-echo susceptibility-weighted imaging (SWI) (TR/TE = 24/3.9 ms, FA = 73°, TA = 2:21 min) to identify subtle hemorrhagic lesions such as DAI.

2.3. Cognitive Function Tests

The TBI patients underwent a set of cognitive function tests, which included the Wechsler Adult Intelligence Scale (WAIS) [27], 1 s (PASAT-1s) and 2 s (PASAT-2s) paced auditory serial addition tests [28], and the trail making tests (TMT) [29]. All test results were corrected for age.

2.4. Processing of WB-MRSI

2.4.1. Reconstruction of Metabolite Ratio and Temperature Maps

WB-MRSI was processed using Metabolic Imaging and Data Analysis System (MIDAS) software version 2.35 (University of Miami, Miami, FL, USA) running on IDL version 8.4.1 (Exelis Visual Information Solutions, Boulder, CO, USA) [30]. The same procedures were applied to all participants (i.e., TBI patients and control subjects [26]). The workflow and processing steps are summarized in Figure 1.

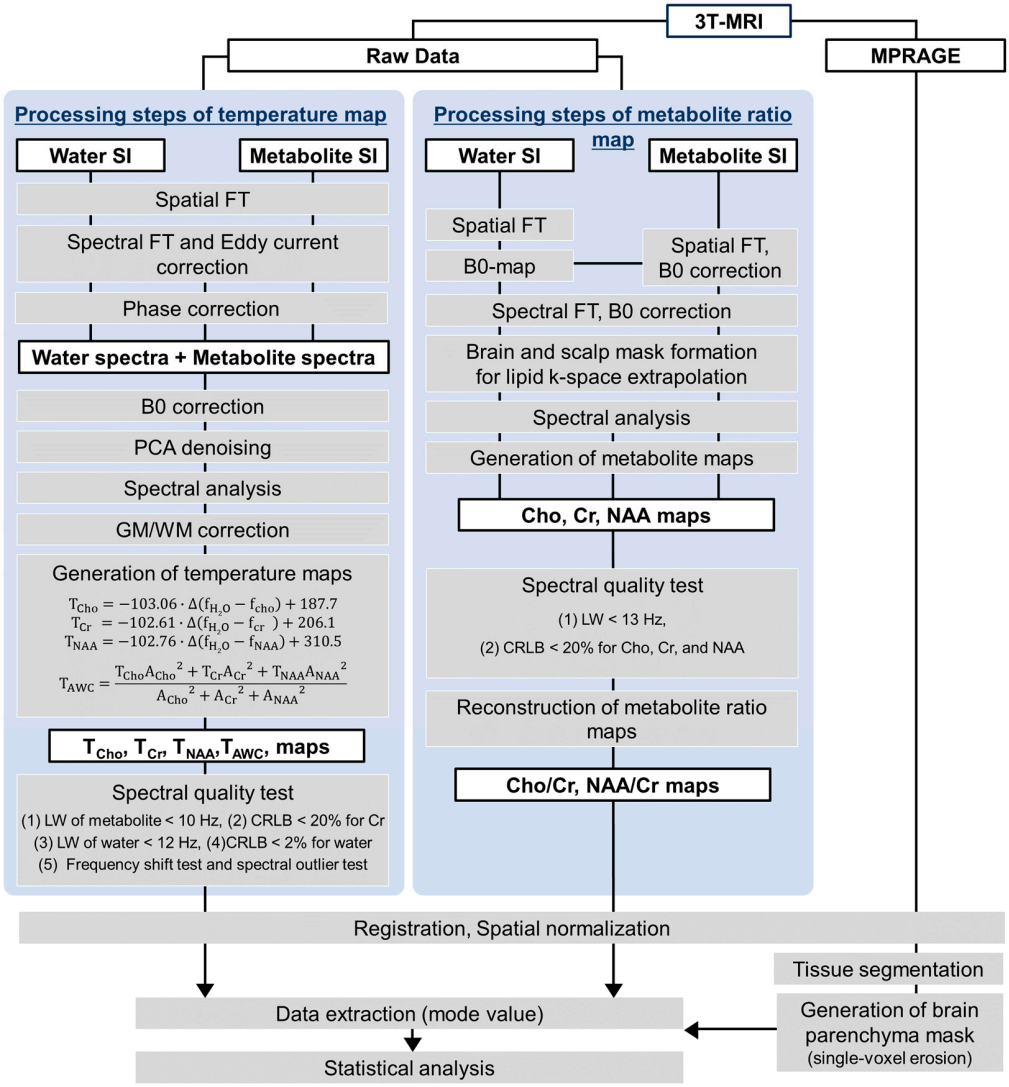

Figure 1. The workflow and processing steps of whole-brain magnetic resonance spectroscopic imaging (WB-MRSI). Abbreviations: SI = signal intensity; FT = Fourier transform; PCA = principal component analysis; WM = white matter; GM = gray matter; T_{Cho} = temperature derived from choline; T_{Cr} = temperature derived from creatine; T_{NAA} = temperature derived from N-acetyl aspartate; f = frequency of the respective metabolite; A = the peak amplitude for each metabolite.

Since brain temperature by WB-MRSI is estimated from the frequency and amplitude of the brain's major metabolites, this study also reconstructed the maps of major metabolite concentrations. The calculation of these concentrations (i.e., NAA, Cho, and Cr) followed the processing steps and parameters for the normal database. The steps included data resampling, spatial reconstruction, B0 correction, spatial registration, brain and scalp mask formation for lipid k-space extrapolation, spectral fitting, and signal normalization. For all metabolites, only those voxels with (1) linewidth (LW) less than 13 Hz and (2) Cramer–Rao lower bound (CRLB) less than 20% were extracted. From these metabolite concentrations, two brain metabolite ratio maps commonly used metrics in clinics, i.e., NAA/Cr and Cho/Cr, were reconstructed using ImageJ software version 1.51 (National Institutes of Health, Bethesda, MD, USA) [31].

The calculation of brain temperature maps followed the processing steps detailed in a previous report by Maudsley et al. [32]. The steps included spatial and spectral reconstruction, eddy current correction, phase correction, B0 correction, denoising, gray (GM) and white matter (WM) fraction correction, and temperature calculation. To avoid the inclusion of noise in the results, only those voxels with (1) LW of each metabolite less than 10 Hz, (2) CRLB of Cr less than 20%, (3) LW and CRLB of water less than 12 Hz and 2%, respectively, (4) frequency shift less than 20 Hz, and (5) voxels with values falling within mean ± 3 SD were further processed [32]. Brain temperature can be calculated from the frequencies of each major metabolite (i.e., NAA, Cho, and Cr) as well as their combination (amplitude-weighted combination) [22]. This study employed both calculations since variable performance has been reported among the methods. The brain temperature (T) derivation from the frequency (f) of each metabolite is given by the following:

$$T_{Cho} = -103.06 \cdot \Delta(f_{H2O} - f_{Cho}) + 187.7\ [^{\circ}C] \quad (1)$$

$$T_{Cr} = -102.61 \cdot \Delta(f_{H2O} - f_{Cre}) + 206.1\ [^{\circ}C] \quad (2)$$

$$T_{NAA} = -102.76 \cdot \Delta(f_{H2O} - f_{NAA}) + 310.5\ [^{\circ}C] \quad (3)$$

where T_{Cho}, T_{Cr}, and T_{NAA} are the temperatures derived from each metabolite concentration, f_{H2O} is the frequency of water, and f_{Cho}, f_{Cr}, and f_{NAA} are the frequencies of the respective metabolites. As for the brain temperature derived by amplitude-weighted combination, the temperature (T_{AWC}) is given as follows:

$$T_{AWC} = \left(T_{Cho}{A_{Cho}}^2 + T_{Cre}{A_{Cre}}^2 + T_{NAA}{A_{NAA}}^2\right) / \left({A_{Cho}}^2 + {A_{Cr}}^2 + {A_{NAA}}^2\right)\ [^{\circ}C] \quad (4)$$

where A_{Cho}, A_{Cr}, and A_{NAA} are the peak amplitudes for each metabolite.

2.4.2. Extraction of Brain Temperature and Metabolite Ratios

The temperature and metabolite ratio maps and the corresponding MPRAGE images were then spatially normalized to the standard Montreal Neurological Institute (MNI) space using the default parameters of Statistical Parametric Mapping 12 (SPM12) software (Wellcome Trust Centre for Neuroimaging, London, UK) running in MATLAB version 7.9.0 R2009b (The MathWorks, Natick, MA, USA). Voxels other than the brain tissue were removed by applying a brain parenchyma mask, which was formed by segmenting the brain parenchyma (GM and WM) voxels from the corresponding spatially normalized MPRAGE images (SPM12) and eroding a single voxel to limit partial volume errors (ImageJ). Finally, the mask was applied to the brain temperature and metabolite ratio maps, and the mode of the brain parenchyma histogram was extracted for each map.

2.5. Statistical Analysis

Differences in brain temperature between TBI and control groups were compared using students' *t*-tests or Mann–Whitney U-tests. The choice of statistical test was based on the normality of data distribution.

The relationship between the MRI measure (i.e., mode of brain temperature or metabolite ratios) and cognitive function test scores was evaluated using partial correlation analysis in the TBI group. Our previous study on the normal database showed a variation in brain metabolite concentration with aging [26]. In addition, a considerable variation in the time lapsed from trauma was observed in the patients. Thus, correlation analysis was adjusted for age and time interval from trauma through linear regression.

A false discovery rate (FDR)-corrected $p < 0.05$ was considered statistically significant. Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) software version 26 (IBM, New York, NY, USA).

3. Results

3.1. Conventional MRI

Six of eight patients had brain contusion or DAI on conventional MRI sequences. Representative images of a patient are given in Figure 2.

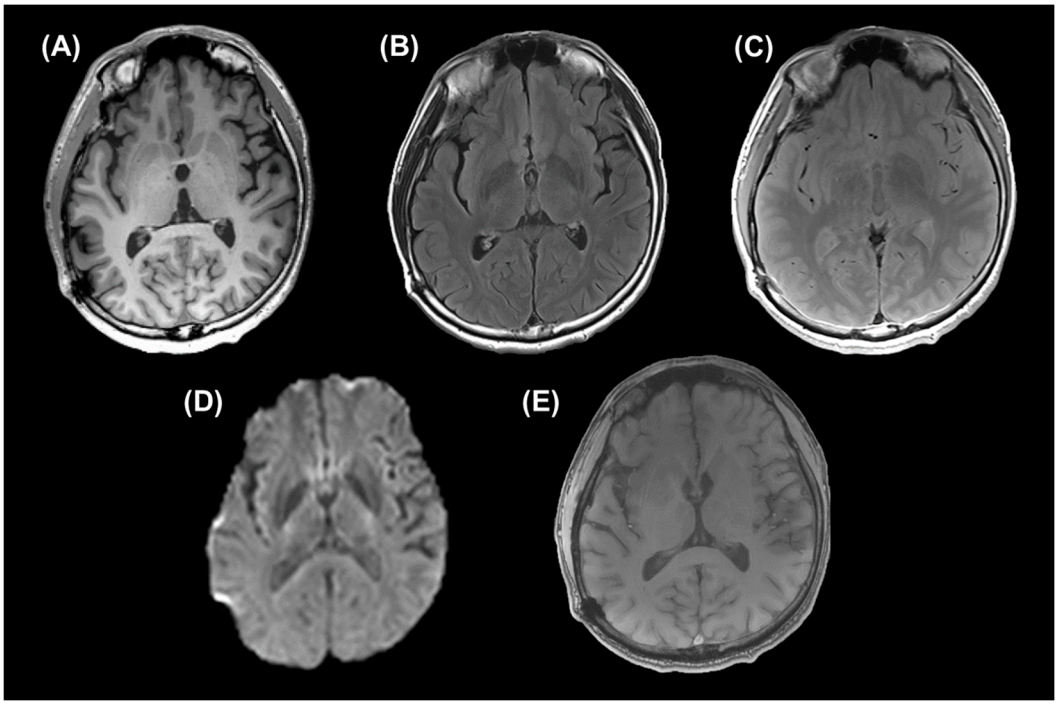

Figure 2. Conventional MRI sequences of a patient {48-year-old male with mild traumatic brain injury (TBI) in chronic phase}. (**A**) An axial reconstructed image of magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence (repetition time (TR)/ echo time (TE)/ inversion time (TI) = 1900/2.85/900 ms), (**B**) an axial fluid-attenuated inversion recovery (FLAIR) image (TR/TE/TI = 12,000/115/2800 ms), (**C**) an axial proton density-weighted image (PDWI) (TR/TE = 4000/12 ms), (**D**) trace of an axial diffusion imaging sequence (TR/TE = 4000/83.2 ms, maximum b-value = 8000 s/mm^2), and (**E**) an axial 3D gradient-echo susceptibility-weighted image (SWI) (TR/TE = 24/3.9 ms, flip angle (FA) = 73°) are given.

3.2. Group Differences in Brain Temperature

The brain temperature measurable by any method (i.e., T_{Cho}, T_{Cr}, T_{NAA}, or T_{AWC}) was significantly lower in the TBI patients than in the control group (FDR-corrected $p < 0.05$). Figure 3 summarizes the results.

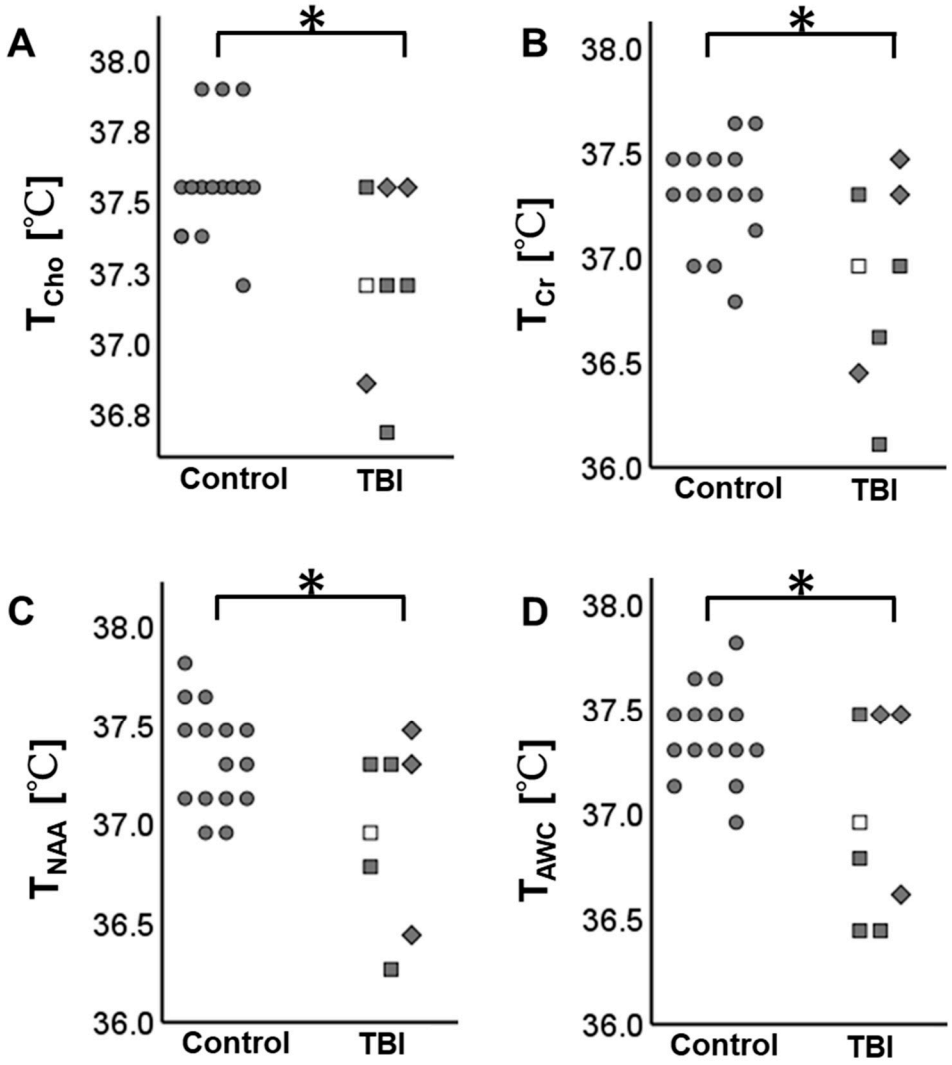

Figure 3. Brain temperature distribution in the participants. The TBI patients have lower brain temperature than the control subjects. (**A**) The brain temperature derived from choline (T_{Cho}), (**B**) the brain temperature derived from creatine (T_{Cr}), (**C**) the brain temperature derived from N-acetylaspartate (T_{NAA}), and (**D**) the brain temperature derived by amplitude-weighted combination (T_{AWC}). * indicates false discovery rate (FDR)-corrected $p < 0.05$. ● Control, □ mild TBI in subacute phase, ■ mild TBI in chronic phase, and ♦ moderate TBI in chronic phase.

3.3. Relationship between Brain Temperature and Cognitive Function Test Scores

Table S1 and Figure 4 summarize significant relationships between T_{NAA} and cognitive function test scores. All variables are adjusted for age and time lapsed from trauma. A strong positive correlation was observed between T_{NAA} and PASAT-2s (r = 0.930, FDR-corrected $p = 0.022$). Brain temperature calculated by other methods (i.e., T_{Cho}, T_{Cr}, and T_{AWC}) and the major metabolite ratios (i.e., Cho/Cr and NAA/Cr) showed no significant correlation with cognitive function test scores.

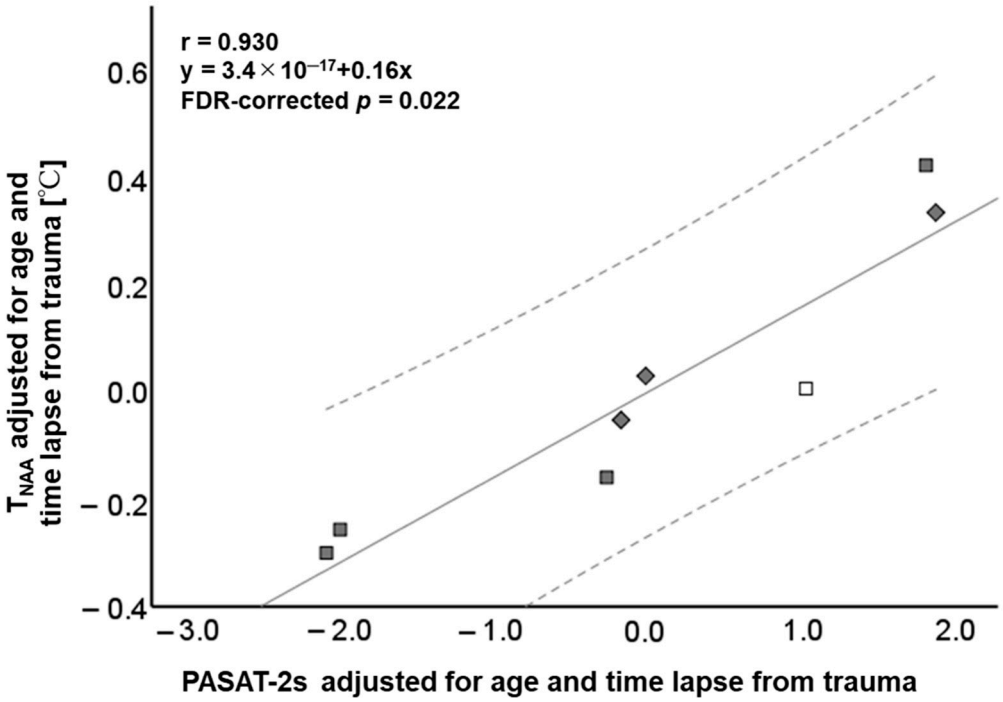

Figure 4. Scatterplots showing the relationship between the brain temperature derived from N-acetyl aspartate (T_{NAA}) and 2 s paced auditory serial addition test (PASAT-2s) (r = 0.930, FDR-corrected p = 0.022). The solid line represents the mean and the dotted lines are the 95% confidence interval. □ Mild TBI in subacute phase, ■ mild TBI in chronic phase, and ♦ moderate TBI in chronic phase.

4. Discussion

This prospective study evaluated if the brain temperature derived noninvasively by WB-MRSI altered in TBI patients in the later phases of the disease and the potential clinical utility of brain temperature measurement. It was observed that the brain temperature decreased in the TBI patients, although they were already in the subacute or chronic phase. In addition, T_{NAA} was significantly correlated with the PASAT-2s score, which reflects the patient's information processing ability, attention, and concentration to perform a task [28].

Our observation of lower brain temperature in TBI is consistent with a previous study that reports a decrease in lateral ventricular temperature in mild TBI patients in the subacute phase within 20 days of trauma [33]. Our study confirms their results and adds that these patients' brain temperatures remained low until the chronic phase. A drop in the brain temperature may result from decreased metabolic activity due to glucose and oxygen depletion. In a physiological state, the chemical reaction between glucose and oxygen (glucose + $6O_2 \rightarrow 6CO_2 + 6H_2O$) generates most of the energy required for brain metabolic activity. This reaction at 37 °C is associated with a release of ΔH° = 470 kJ of enthalpy per mol of O_2. While some of this energy (33%) immediately dissipates into heat, the rest (67%) produces 38 adenosine triphosphate (ATP) molecules that will further maintain a complex chain of chemical reactions to ensure proper brain functioning. However, because no mechanical work is performed in the brain, the final ATP hydrolysis releases the energy back to the system, and as a result, almost all of this energy ends up as heat [34].

Evidence of glucose and oxygen depletion exists in TBI. According to prior reports, chronic TBI patients with a sports injury have 8–15% lower 18-fluorine fluorodeoxyglucose (^{18}F-FDG) accumulation in the brain than the healthy group [35]. Similar results have been observed in Iraq war veterans with one or more episodes of mild TBI from explosive blasts [36]. In addition, one-week-post-TBI patients have been reported to experience cerebral ischemia and tissue hypoxia [37]. More than half of patients with severe TBI showed decreased cerebral blood flow (CBF) between one and six weeks after injury [38]. Furthermore, the CBF of GM is lower in moderate to severe TBI patients than in controls at

six months and one year post-injury [39]. Additionally, moderate to severe TBI patients with DAI in the chronic phase had lower CBF than controls [40].

This study reports lower brain temperature in TBI patients in subacute to chronic phases. On the contrary, a previous report has shown increased brain temperature in acute TBI [41]. Although the cause of elevated brain temperature after brain injury is not fully understood, sepsis, inflammation, or direct injury to the hypothalamus, the body's thermoregulatory center, might have occurred [42,43]. Alternatively, trauma-led cell membrane disruption might have induced membrane potential changes due to the excessive release of excitatory neurotransmitters [44]. In response, energy, i.e., ATP, is necessary to restore ionic equilibrium to reactivate brain cells [44,45], which further causes an increase in glucose uptake for ATP synthesis. This is consistent with the observation of an increased rate of local brain metabolism of glucose in animal models of acute TBI [46,47].

A significant correlation was observed between WB-MRSI-derived brain temperature and PASAT-2s score, suggesting the potential utility of MRI as an estimate of cognitive function test performance. Generally, cognitive function tests demand patients' cooperation to achieve reliable results, which is not always possible in ill and pediatric patients. On the other hand, WB-MRSI for brain temperature measurement does not require any tasks. The PASAT-2s is the test in which participants answer the correct sum of numbers presented at 2 s intervals before the next number is presented [28]. The results reflect information processing ability, attention, and concentration [28]. These tests have been successfully incorporated to study the effects of TBI on information processing ability [28]. The PASAT score is considered a sensitive measure of cognitive impairment in symptomatic mild TBI patients. Previous studies have shown that approximately 54%, 38%, and 18% of mild TBI patients fall below 1.0 z, 1.5 z, and 2.0 z scores derived from norms [48]. The PASAT tests are also included in "The Minimal Assessment of Cognitive Function in MS", proposed at an international conference for the clinical monitoring of multiple sclerosis (MS), in which many patients exhibit cognitive deficits [49], and its validity has been reported [50]. Several reports have also raised concerns about the influence of brain temperature on cognitive function. For example, a study on healthy volunteers exposed to cold air has shown decreased working memory, choice reaction time, and executive function upon cold air exposure [51]. Another recent study on laboratory animals has reported the exacerbation of glymphatic drainage dysfunction in TBI by hypothermia, leading to an increase in p-tau and beta-amyloid deposition and cognitive impairment [52]. Our observation of the correlation may also imply that TBI patients have difficulties in information processing, attention, and concentration and that rehabilitation targeting these tasks may benefit them. The lack of significant correlation with other cognitive function tests may be due to the small sample size.

Of several brain temperature calculation methods, T_{NAA} performed better than the others. Similarly, it outperformed the respective metabolite ratios (i.e., NAA/Cr and Cho/Cr). Thus, T_{NAA} may become a noninvasive alternative for thermistors or an indirect indicator of the patient's CAT performance. As a neuron marker [53], NAA has a relatively high amplitude and can easily be isolated [54]. A group of researchers has suggested that NAA is the easiest to measure accurately, giving the most reliable temperature dependence [21]. On the contrary, determinations of the chemical shifts of Cho and Cr are not so precise because Cho appears to include different components, and Cr has a low signal amplitude and is within ~0.2 ppm of Cho, resulting in peak overlap [21]. Phantom experiments have also shown a good correlation between T_{NAA} and brain temperature measured by implanted thermistor probes [21].

This study employed WB-MRSI as ^{1}H-MRS to receive information about the brain's metabolite concentrations and temperature. WB-MRSI is a recently developed ^{1}H-MRS designed to measure the state of the brain's major metabolites almost throughout the whole brain [30]. An echo-planar spectroscopic imaging (EPSI) sequence and short TE are coupled to enhance the acquisition time and signal-to-noise ratio. There has been another quantitative MRI technique that also permits noninvasive brain temperature measurement.

This technique is diffusion imaging-based magnetic resonance (MR) thermometry and was proposed by Kozak et al. [55]. This technique estimates brain temperature from the cerebrospinal fluid (CSF) in the lateral ventricles since the diffusion coefficient of water changes with temperature. Recently, a more objective analysis method of MR thermometry based on diffusion imaging has been proposed [56,57], which has shown a significant positive correlation with the brain temperature measured by ^{1}H-MRS [58]. Although this method may estimate the temperature in a shorter imaging time than WB-MRSI, it cannot directly estimate brain parenchymal temperature where water diffusion is more restricted than the CSF. Although a strong relationship between the lateral ventricular temperature measured by this method and the temperature of the right centrum semiovale measured by ^{1}H-MRS has been shown, their correlation in conditions with abnormal CSF such as empyema is yet to be studied.

There are several limitations to this study. First, the sample size is small, probably due to the strict inclusion criteria set in this study. This study included only male participants because body and brain temperatures vary with the menstrual cycle in females [59,60]. Brain metabolites are also reported to fluctuate with female hormone levels [61]. Because information about the menstrual cycle could not be obtained from the database, females were excluded from the study. However, it is desired that brain temperature alterations in female TBI patients be also studied. Thus, further studies with larger sample sizes, including female patients, are needed. Also, three of eleven patients did not complete short TE WB-MRSI. Further reduction in acquisition time, achievable by incorporating machine learning technology, may help secure more patients [62]. Because of the small sample size, type II errors could have been introduced, and some important correlations might have been missed. Also, given the sample size limitation, the correlations observed in this study need to be confirmed with a larger sample size. Second, one of the patients had controlled diabetes mellitus. Four patients were on medication. The effect of diabetes mellitus and medication on brain temperature cannot wholly be excluded, although it is believed to be small.

5. Conclusions

Brain temperature decreases in TBI patients despite being in subacute and chronic phases of the disease. Noninvasive measurement of brain temperature in these patients may estimate the depth of brain injury responsible for impaired information processing, attention, and concentration. WB-MRSI-derived T_{NAA} may be suitable for measuring brain temperature in these patients.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/metabo14010017/s1, Table S1: The relationship between MRI indices and cognitive function test scores.

Author Contributions: Conceptualization, K.K.T.; methodology, K.K.T.; software, S.S., A.A.M. and S.A.; formal analysis, M.K., X.L. and K.K.T.; investigation, M.K., K.A., X.L., D.S. and K.K.T.; resources, K.A. and K.K.T.; data curation, M.K. and K.K.T.; writing—original draft preparation, M.K.; writing—review and editing, M.K. and K.K.T.; visualization, M.K.; supervision, K.K.T.; funding acquisition, K.A. and K.K.T. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This prospective study was approved on 2016/4/25 by the Ethical Review Board for Medical Research of Hokkaido University Hospital, protocol number 015-0271.

Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to patient confidentiality or ethical restrictions.

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Conflicts of Interest: Sinyeob Ahn is an employee of Siemens Healthineers. The other authors declare no conflicts of interest.

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