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ABSTRACT

Background: Traumatic brain injury is believed to be a public health disorder with some complications. Post Traumatic Neurocognitive Disorders (PTND) received much attention among these complications because of the high prevalence of mild traumatic brain injuries. On the other hand, advanced neuroimaging is increasingly becoming an exciting modality in the field of traumatic brain injury. Magnetic resonance spectroscopy (MRS) provides a new window to understand the detailed biochemistry alterations following traumatic brain injury. Therefore, some researchers have addressed the relations between MRS data and PTND.

Objectives: The research aimed to achieve the biochemistry alterations following TBI and find the relations between these alterations and PTND based on published literature in this field.

Materials & Methods: With this mind, a systematic search in MEDLINE and EMBASE databases performed to identify relevant published articles without date limitation. The systematic search keyword-targeted all MRS data relevant to the post traumatic neurocognitive disorders.

Results: Of the search results, a total of 22 journal articles were reported relations between MRS data and neurocognitive disorders. Most studies focused on N-acetyl aspartate (NAA), Choline (Cho), Creatine (Cr), Myo-inositol (MI), and their ratios. As MRI scanners are becoming stranger detecting extra-metabolites such as glutamate, glutamine and glutathione are more reliable. In this regard a few studies reported significant relations between alterations in these metabolites and PTND.

Conclusion: MRS is a powerful tool that can provide important data to detect long-term neurocognitive disorders following TBI.

Keywords: Magnetic resonance spectroscopy; Brain injuries; Brain concussion; Neurocognitive disorders
Introduction

Traumatic Brain Injury (TBI) is a major area of interest within the field of Magnetic Resonance Spectroscopy (MRS). Neurocognitive disorders have been an essential concept in the study of brain trauma [1]. Because TBI is prevalent, Post-Traumatic Neurocognitive Disorders (PTND) are becoming increasingly important [2].

Detecting these pathological changes before affecting patients’ life can be essential for a wide range of solutions. Specifically, having a reliable tool can play a vital role in monitoring the therapeutic interventions [1-5].

Several studies showed the involvement of different brain structures in the pathogenesis of traumatic brain injuries [6]. On the other hand, the concepts of probable underlying biochemical etiology of neurocognitive disorders after brain trauma raising the importance of neurochemistry evaluations in this area [1, 4]. Trauma is a well-known condition that has a considerable impact on metabolite alterations [7]. Determining the role of metabolite alterations in PTNDs is vital for expanding the frontiers of neurocognitive disorders [2, 4].

Advanced neuroimaging provides non-invasive techniques to reach a more helpful concept of concussion [2, 4]. One of the most potent modalities is MRS. In the last few decades, there has been a surge of interest in the importance of MRS as a modality for detecting metabolite alterations after TBI [1]. Magnetic resonance spectroscopy is a non-invasive neuroimaging technique that measures metabolic levels based on chemical alterations, i.e., frequency deviations from a standard reference in selected regions of interest in a tissue. As it is a quantitative technique, it can be used as a diagnostic and predictor modality in various diseases [8, 9]. MRS can be applied in single-voxel or multi-voxel settings. Multi-voxel MRS is also referred to as Magnetic Resonance Spectroscopy Imaging (MRSI) or Chemical Shift Imaging (CSI) [10].

Various known nuclei are available to use in medical and pharmacological research, such as proton (1H), fluorine (19F), phosphate (31P), carbon (13C), and sodium (23Na). As water molecules are abundant molecules in the human body, H-MRS (proton magnetic resonance spectroscopy). Thus, in routine MRI scanners available in clinical studies (1.5 T and 3 T), H-MRS is most commonly used [8].

The number of detected metabolites depends on the magnetic field strength of the MRI scanner and acquisition sequence [11]. N-acetyl aspartate (NAA), creatine (Cr), choline (Cho), and Myo-inositol (MI) are the most important metabolites of the brain that are commonly detected in MRS studies. The peak of each metabolite arises from several compositions. Stronger scanners can detect extra-metabolites such as glutamate, glutamine, glutathione, gamma-aminobutyric acid (GABA), and lactate [12-14]. Some studies are pointing to the neglected relationship between neuro-metabolites alterations and PTND. This paper aims to assess these relationships.

Materials and Methods

Search Strategy

This study comprehensively reviews the data to trace the relationship between neuro-metabolite alterations and PTND. We followed preferred reporting items for systematic review and meta-analysis (PRISMA) (www.prisma-statement.org) [15] (Figure 1). The systematic

Highlights

- Alterations in N-acetyl aspartate in acute stages and choline/creatine ratio in the acute stages of traumatic brain injury are associated with post-traumatic neurocognitive disorders.
- Increased myo-inositol levels in subacute phases suggest significant neuronal damages, following traumatic brain injury. The detection of lactate levels presents poorer outcomes.
- As more powerful magnetic resonance imaging scanners are available, the interest in extrametabolites, such as glutamate, glutamine, and glutathione is on the rise; some studies reported significant associations between these metabolites and PTND.
search was performed in Medline and Embase databases. Unpublished articles were not included. Notably, the search was performed from the first edition of electronic databases until March 21, 2021.

**Keywords**

The combinations of the following keywords were used in the search strategy: (magnetic resonance spectroscopy (title/abstract) AND ((head trauma) OR (head injury) OR (head injuries) OR (Traumatic Brain Injury) OR (traumatic brain injuries) OR (concussion) (title/abstract).

**Exclusion and inclusion criteria**

When the search was completed, citation titles and abstracts were reviewed. Non-English articles, unrelated articles, topic/narrative/systematic reviews, and irrelevant studies were excluded. Also, MRS studies without data for PTND were excluded. We included all articles that report any relation (association, correlation, or regression model) between MRS data and PTND.

**Quality assessment**

Quality assessment performed using a modified version of the ROBINS-I (risk of bias in non-randomised studies of interventions) tool to classify studies as low, high, or unclear risk judgments based on evaluation of confounding, selection, classification of intervention(s), missing data, and the measure of outcome(s) [16, 17].

**Data extraction**

After removing duplicates, all articles were screened independently in a blinded standardized manner. We collected groups involved in studies, duration between injury and imaging, MRS settings, regions and metabolites of interest, and bold findings of each study.

**Results**

The literature search yielded 22 relevant articles (Figure 1). The studies are summarized in Table 1. Although some studies are designed due to the availability of MRS scanners, both MRS and MRSI have advantages and disadvantages. Some expertise preferred to use both voxels in different pathologies.

While MRSI can be performed in 2D or 3D and detects a broader area of the brain, single voxel spectroscopy (SVS) provides higher quality spectra. Furthermore, to apply SVS, a region of interest needs to be defined. Hence, when the researchers want to detect a selective structural region, SVS is preferable [8, 11, 18].

According the results, Anterior Cingulate Cortex (ACC) [19, 20], posterior cingulate cortex [20, 21], frontal [22] and parietal white matter [20, 21, 23], prefrontal cortex [24] doralateral prefrontal cortex (DLPFC) [25-27], corpus callosum [28, 29], occipital gray matter [23, 30, 31], parieto-occipital white matter [31], basal ganglia [32], and mid-temporal cortex [32] contribute significantly in neurocognitive functions. We believe that the ACC and prefrontal cortex are important structural parts of the brain with a significant effect on neuro-cognitive pathways such as Papez and emotion circuits [33].

MRSI studies are more focused on the supraventricular area to cover corpus callosum level [34-38], thalamus, centrum semiovale [2], ant-post commissure axis, ACC [29], frontal gyri, and superior longitudinal fasciculus.

Interested metabolites were N-acetylaspartate, choline (Cho), creatine (Cr), and MI in the majority of studies. Increasing interest for extra-metabolites such as glutamine, glutamate, and glutathione was seen over time.

**Neurocognitive Disorders and Evaluation Tools**

Several tests are used to evaluate neurocognitive function after TBI. Diagnostic and Statistical Manual of Mental Disorders criteria can be assessed in the discussed patient diagnosis of post-concussion syndrome. To quantify Post-Concussion Syndrome (PCS) grading, Rivermead Post-Concussion Syndrome Questionnaire (RPQ) is a valid questionnaire. The RPQ asks participants to rate a series of common symptoms following TBI on a 5-point Likert-type scale from 0 to 4 (King et al., 1995) [35]. Sours et al. reported that the Cho/Cr ratio in the thalamus of mTBI (mild Traumatic Brain Injury) patients who self-reported sensory symptoms on the RPQ is significantly higher compared to mTBI patients who did not report sensory symptoms at the acute time point (after controlling the age influence) [35].

Mini-mental state examination and military acute concussion evaluation are other questionnaires available to assess general mental functions [35].

However, these questionnaires provide an essential view of the patients’ quality of life; behavioral tests. Full-scale IQ (FSIQ) score, Wechsler abbreviated intelligence scale, California verbal learning test–second edition or its children’s version, Wechsler memory scale–third edition, and children’s memory scale are some tests used to
assess behavioral functions [38]. In addition, there are many computerized tests to assess cognitive situations such as backward, digit span, Stroop test A, and trail making test (TMT)-B time.

In this regard, Sivak et al. reported positive correlations between NAA level and cognitive tests (backward, digit span, Stroop test A, TMT-B time). Also, NAA/Cr was associated with Stoop test A and the total score of digit span [27]. Finally, some studies used the Glasgow Outcome Scale (GOS) to evaluate the outcomes of traumatic patients. While GOS is more accurate for moderate to severe injuries, few studies reported GOS for mTBI.

Govindaraju et al. reported that metabolite ratios were not significantly correlated with GCS score at admission or six months after injury, although they were weakly correlated with GOS score at discharge. There was some evidence of a weak correlation between NAA/Cho and GOS score on discharge approaching statistical significance. However, this GOS does not seem to be an appropriate criterion in mTBI.

Predictive value of MRS and Post-traumatic Neuropsychological Disorders

Few studies have reported on the prognostic value of MRS in TBI using regression models. Holshouster et al. found that neuro-metabolite changes in corpus callosum can predict neurocognitive outcomes with 83% accuracy. The majority of these outcomes are expressed by NAA/Cr and Cho/Cr ratios.

In this regard, Gasparovic et al. introduced a regression model based on Cr in corpus callosum for executive functions outcome. He also reported that this model was significant for emotional disorders [27]. Despite these results, further studies are needed to find the most accurate MRS result for outcomes in TBI models.
### Table 1. Summary of Published Articles Used Magnetic Resonance Spectroscopy (MRS) to Find Relations Between MRS and Post-Traumatic Neurocognitive Disorders (PTND)

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Subjects</th>
<th>Control Group</th>
<th>Time after Injury</th>
<th>Magnetic Resonance Spectroscopy setting</th>
<th>Regions of Interest</th>
<th>Brain Metabolites</th>
<th>Goal of Study</th>
<th>Significant results</th>
</tr>
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<tbody>
<tr>
<td>Alosco et al. 2020 [20]</td>
<td>Seventy-seven former NFL players</td>
<td>Twenty-three HC without history of head trauma</td>
<td>-</td>
<td>3 T (SVS)</td>
<td>ACC, PCC, parietal white matter</td>
<td>NAA, Cr, Cho, glutamate, glutathione, MI</td>
<td>Assessing the relationship between neuro-metabolite alterations and neuropsychological tests and self-report measures of neuropsychiatric function</td>
<td>A higher CHII correlated with lower PWM creatine, The ACC was the only region associated with clinical function, including positive correlations between glutamate, glutathione, and MI with behavioral/mood symptoms</td>
</tr>
<tr>
<td>Sheth et al. 2019 [19]</td>
<td>Twenty-seven TE-PTSD 18 TBI</td>
<td>Twenty-eight HC</td>
<td>-</td>
<td>3 T (SVS)</td>
<td>dACC</td>
<td>NAA, Cr, Cho, GABA, Glutamate, Gln</td>
<td>Differences between traumatic groups with and without PTSD and HC group</td>
<td>Negative correlation between Gln/H2O and sleep-related symptoms in TE-PTSD group</td>
</tr>
<tr>
<td>Kim et al. 2019 [24]</td>
<td>Twenty professional boxers</td>
<td>Fourteen HC</td>
<td>-</td>
<td>3 T (SVS)</td>
<td>Prefrontal cortex</td>
<td>GABA/Cho and glutamate/glutamine (Glx)</td>
<td>Correlation between metabolites and cognitive performance</td>
<td>The GABA level correlated with memory performance in the Boxers, but not in attention performance</td>
</tr>
<tr>
<td>MacMaster et al. 2019 [26]</td>
<td>Thirty-five mTBI</td>
<td>Seventeen OI 1.7 y</td>
<td>3 T (SVS)</td>
<td>DLPFC</td>
<td>NAA</td>
<td>Relationship between neuro-metabolite levels and emotional symptoms degree</td>
<td>A significant association between low NAA level and emotional stress degree</td>
<td></td>
</tr>
<tr>
<td>Panchal et al. 2018 [28]</td>
<td>Thirty-three ice-hockey athletes</td>
<td>-</td>
<td>3 T (SVS) 10x20x30 mm³</td>
<td>CC</td>
<td>NAA, Cr, Cho, Glx</td>
<td>Evaluating association between neuro-metabolites and neurocognitive outcomes</td>
<td>A negative correlation was found between change in Glu from preseason to postseason assessments and verbal memory</td>
<td></td>
</tr>
<tr>
<td>Gardner et al. 2017 [21]</td>
<td>Sixteen retired professional rugby league players</td>
<td>Sixteen HC</td>
<td>-</td>
<td>3 T (SVS)</td>
<td>Posterior cingulate gray matter and parietal white matter</td>
<td>NAA, MI, Cho, glutamate, and glutathione</td>
<td>Examining brain neuro-metabolite concentrations and neuropsychological disorders in retired rugby league players who had a history of numerous self-reported concussions</td>
<td>In retired athletes, there were significant positive correlations between DASS and grey matter MI and grey matter glutamate scores, and Glx, Rivermead PCSQ symptoms scores were positively correlated with grey matter glutamate, MI, NAA, and creatine, BESS scores were negatively correlated with grey matter glutathione and white matter glutathione. There was also a positive correlation between AUDIT scores and white matter glutamate.</td>
</tr>
<tr>
<td>Author (ref)</td>
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<tr>
<td>Sours et al. 2015 [35]</td>
<td>Seventy-seven mTBI</td>
<td>Thirty-five HC</td>
<td>6±3 d</td>
<td>3 T MRSI 160×160×106 mm³</td>
<td>At the level of the corpus callosum</td>
<td>NAA/Cr, Cho/Cr</td>
<td>Assessing the relationship between acute neuro-metabolite ratios and persistent neurocognitive disorders</td>
<td>Significantly higher Cho/Cr ratio in the thalamus of mTBI patients who self-reported sensory symptoms on the RPQ compared to mTBI patients who did not report sensory symptoms at the acute time point after controlling for the influence of age</td>
</tr>
<tr>
<td>Dean et al. 2014 [25]</td>
<td>Eight mTBI+ PCS</td>
<td>Nine HC</td>
<td>More than one year from injury</td>
<td>3 T SVS 1.5×1.5×1.5 cm³</td>
<td>DLPFC</td>
<td>NAA</td>
<td>Assessing brain NAA and its correlation with PCS in concussed patients one year after injury</td>
<td>Decreased NAA was associated with PCS</td>
</tr>
<tr>
<td>George et al. 2014 [2]</td>
<td>Forty-three mTBI</td>
<td>Twenty-one HC</td>
<td>4±3.15 d</td>
<td>3T (MRSI) 160×160×160 mm³</td>
<td>Thalamus and centrum semiovale</td>
<td>NAA, Cr, Cho</td>
<td>Assessing predictive effect of neuro-metabolites and neurocognitive outcomes</td>
<td>Positive correlation between NAA/Cr ratio in the thalamus and cognitive tests</td>
</tr>
<tr>
<td>Parry et al. 2004 [22]</td>
<td>Fifteen children with sTBI</td>
<td>Fifteen HC</td>
<td>5.7±4.7 y</td>
<td>1.5 T (SVS)</td>
<td>Right frontal white matter</td>
<td>NAA, Cho</td>
<td>Magnetic resonance spectroscopy (MRS) and its association with neuro-psychological functioning was examined in the chronic injury phase of pediatric traumatic brain injury (TBI).</td>
<td>Lower levels of NAA and Cho displayed reduced performances on neuro-psychological tests.</td>
</tr>
<tr>
<td>Sivak et al. 2014 [27]</td>
<td>Twenty-one mTBI</td>
<td>Twenty-two HC</td>
<td>Within 3 d</td>
<td>1.5 T (SVS)</td>
<td>Upper brain stem and bilateral DLPFC</td>
<td>NAA, Cho, Cr</td>
<td>Assessing neuro-metabolites and cognitive tests</td>
<td>Positive correlation between NAA level and cognitive tests (backward, digit span, Stroop test A, TMT-B time) NAA/Cr was associated with Stroop test A and total score of digit span)</td>
</tr>
<tr>
<td>Kirov et al. 2013 [40]</td>
<td>Fifteen mTBI+ PCS</td>
<td>Thirteen HC</td>
<td>3-55 d</td>
<td>3 T MRSI 10×8×4.5 mm³</td>
<td>CC</td>
<td>NAA, Cr, Cho, MI</td>
<td>Assessing the association between neuro-metabolites and post-concussion syndrome</td>
<td>The lower level of NAA in the PCS+ group</td>
</tr>
</tbody>
</table>

Magnetic resonance spectroscopy (MRS) and its association with neuro-psychological functioning was examined in the chronic injury phase of pediatric traumatic brain injury (TBI). Lower levels of NAA and Cho displayed reduced performances on neuro-psychological tests.
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<th>Goal of Study</th>
<th>Significant results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babikian et al. 2010 [38]</td>
<td>Ten moderate to severe TBI</td>
<td>-</td>
<td>5 mon</td>
<td>1.5 T MRSI</td>
<td>Anterior and posterior part of CC</td>
<td>NAA, Cho, Cr</td>
<td>To find out correlation between assessed metabolites and neurocognitive outcomes</td>
<td>Positive correlations between posterior CC NAA and several neurocognitive measures, reaching statistical significance for FSIQ, visual memory, and processing speed. Further, generally negative correlations were observed between posterior CC Cho and neurocognitive performance, which reached statistical significance for FSIQ, and approached significance for visual memory.</td>
</tr>
<tr>
<td>Gasparovic 2009 [29]</td>
<td>Ten mTBI</td>
<td>Nine HC</td>
<td>8.1 d (4-19)</td>
<td>3 T MRSI and SVS 1x1x1 cm³</td>
<td>(MRSI) from the superior part of the anterior cingulate gyrus and inferior part of the medial frontal gyrus (SVS) from splenium of CC</td>
<td>NAA, Cr, Cho</td>
<td>Providing a predictor model for executive function and emotional disorders outcomes</td>
<td>Significant model for Cr in CC introduced in this study for both executive function and emotional disorders.</td>
</tr>
<tr>
<td>Yeo et al. 2006 [41]</td>
<td>Thirty-six TBI</td>
<td>Fourteen HC</td>
<td>3.5 wk</td>
<td>1.5 T (MRSI) Supraventricular slice</td>
<td>NAA/Cr, Cho/Cr</td>
<td>Regression analyses were conducted to determine the proportion of variance in composite scores</td>
<td>Association between relative metabolites and neuropsychological performance</td>
<td>Both ratios in the anterior part of the slice and Cho/Cr in the posterior part were significantly associated with several aspects of neuropsychological performance.</td>
</tr>
<tr>
<td>Holshouser et al. 2006 [34]</td>
<td>Forty-two sTBI</td>
<td>Ten HC</td>
<td>7±4 d</td>
<td>1.5 MRSI</td>
<td>Corpus callosum (CC), frontal white matter (FWM), (mid)frontal gray matter (FGM), parietal white matter (PWM), and (mid)occipital gray matter (OGM).</td>
<td>NAA, Cr, Cho</td>
<td>To provide a predictive model for long-term neuropsychological outcomes</td>
<td>Anterior NAA/Cr and Cho/Cr, and posterior Cho/Cr measures. For the overall composite, 38% of the variance was accounted for by these three ratios, as compared to 43% for language and 39% for visuomotor domains,</td>
</tr>
<tr>
<td>Babakian et al. 2006 [38]</td>
<td>Twenty TBI</td>
<td>-</td>
<td>6±4 d</td>
<td>1.5 T MRSI and SVS</td>
<td>CC, FW, FGM, POW, POGM</td>
<td>NAA, Cho, Cr and ratios</td>
<td>Assessment of association between neurometabolites and long-term neuropsychological outcomes</td>
<td>NAA was significantly associated with neuropsychological outcomes so that more than 40% of neuropsychological disorders were justified with a decrease in NAA/Cr level in the regression model.</td>
</tr>
<tr>
<td>Author (ref)</td>
<td>Subjects</td>
<td>Control Group</td>
<td>Time after Injury</td>
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<tr>
<td>Marino et al. 2007 [37]</td>
<td>Ten HC</td>
<td>Ten HC</td>
<td>48-72 h</td>
<td>1.5 T MRSI 100×20×90 mm³</td>
<td>CC and bilateral mesial cortex</td>
<td>NAA, Cho, Cr, Lactate</td>
<td>Assessing the correlation between neuro-metabolites and long-term outcomes</td>
<td>Significant correlation of reduced in NAA level and La presentation with GOS</td>
</tr>
<tr>
<td>Ashwal et al. 2004 [31]</td>
<td>Thirty-eight HC</td>
<td>Ten HC</td>
<td>7 d (1-17)</td>
<td>1.5 T SVS</td>
<td>Occipital gray matter (OGM) and parieto-occipital white matter (PWM)</td>
<td>NAA, Cr, Cho, MI, GLx</td>
<td>Assessing the association between neuro-metabolites and neuropsychological outcomes</td>
<td>An increase in MI level and decrease in NAA/Cr ratio were associated with poorer outcomes.</td>
</tr>
<tr>
<td>Ariza et al. 2004 [32]</td>
<td>Twenty long-term moderate to severe TBI</td>
<td>Twenty HC</td>
<td>-</td>
<td>1.5 T SVS</td>
<td>Left basal ganglia, left mid temporal cortex</td>
<td>NAA, Cho</td>
<td>To investigate the use of proton magnetic resonance spectroscopy in detecting possible gray subcortical neurochemical impairments and their relationship with neuropsychological performance</td>
<td>N-acetyl aspartate–choline-containing compounds ratios were decreased in patients in the basal ganglia (t&gt;3.28, P=0.002) and medial temporal region (t&gt;3.52, P=0.001). The basal ganglia ratio correlated to measures of speed, motor scanning, and attention</td>
</tr>
<tr>
<td>Shutter et al. 2004 [23]</td>
<td>Forty-two HC</td>
<td>-</td>
<td>7 d</td>
<td>1.5 T SVS</td>
<td>Parietal WM occipital gray Matter (OGM)</td>
<td>NAA, Cr, Cho, GLX</td>
<td>Assessment of the predictive effect of brain metabolites on GOS</td>
<td>Increasing in GLx and Cho in OGM and PWM was associated with poorer outcomes. The accuracy of Cho and GLx to predict outcomes were 94%.</td>
</tr>
<tr>
<td>Brenner et al. 2003 [30]</td>
<td>Twenty-two children</td>
<td>-</td>
<td>1-7 y</td>
<td>1.5 T SVS</td>
<td>Occipital gray matter</td>
<td>NAA, Cho, Cr and their ratios</td>
<td>The ability to predict long-term neurologic and neuropsychological outcomes in 22 children, aged 1 week to 14 years at the time of traumatic brain injury, was investigated using proton magnetic resonance spectroscopy.</td>
<td>The presence of lactate is a particularly important prognostic marker of poor long-term intellectual and neuropsychological outcomes</td>
</tr>
</tbody>
</table>

Discussion

Returning to the question posed at the beginning of this study, it is now possible to state that magnetic resonance spectroscopy can detect dynamic biomarkers of neuronal dysfunction at an earlier stage of disease progression.

It seems likely that MRS is a useful tool for diagnostic and therapeutic monitoring approaches [42]. It can be used in two ways: Single-Voxel Spectroscopy (SVS) and Magnetic Resonance Spectroscopy Imaging (MRSI) or Chemical Shift Imaging (CSI).

Biochemistry: Background in TBI

N-acetylaspartate (NAA) is an acetyl-amino acid that resonates at 2.01 ppm in the H-MRS. NAA originates from mitochondria and reflects neuronal integrity and viability [43]. Most research supports a diffuse nature of NAA decrease after traumatic brain injuries [26, 27, 31, 34, 37, 44-52]. Nevertheless, despite similar results, some studies did not find any changes in NAA after TBI [53, 54]. We believe that the main reason for these results was the prolonged interval between injury and imaging [55, 56]. These data do not rule out hyperacute metabolite alterations and the value of early metabolite alterations in clinical evaluations [53].

Choline (Cho) or total choline includes free choline, glycerol-phosphocholine, and phosphocholine. It is observed as a prominent singlet at 3.2 ppm in the H-MRS [11, 13]. However, the range of Cho changes is too tiny. Such changes may associate with changes in membrane turnover or brain injuries [13]. Regarding the literature, the increase in Cho level in the TBI group compared with the healthy group is due to tissue breakdown [9, 62, 63]; Recently, Babikian et al. argued that lower lobar Cho levels in the chronic stage of TBI were correlated with declined Interhemispheric Transfer Time (IHTT) in moderate to severe TBI subgroups [69]. Nevertheless, probably Cho levels would be higher in more severe TBI cases, compared to a healthy population; however, the lower level of Cho in patients with more severe neurocognitive outcomes, compared to patients with better outcomes may be attributed to decreased membrane turnover in the setting of permanent cellular damage [28, 55].

Creatine (Cr) is an indirect intermediator of the energy used as a marker for the total stored energy of the cell [57, 58]. Cr peak resonates at 3.03 ppm [13]. A decrease in Cr in the traumatic infarction area supports dropping Cr level when the cell is dead [59]. Yeo et al. found a significant negative correlation between Cr and days after injury, suggesting that damaged cell repair occurs using cell storage energy [53]. Of note, an interval of 3 to 5 months for complete biochemically repairing of the injured cells suggests that this interval may associate with Cr level base as a marker for cellular energy [29].

The MI is another metabolite that can be detected using short echo time spectroscopy [31]. MI, known as an osmolyte, increases parallel to activation of microgliosis following TBI. Contrary to NAA, Cr, and Cho, which have a trend toward average over time, it is believed that MI level increases [6]. Still, there is no evidence of significant MI changes on the day of brain injury. Since MI is a gliotic marker, an increase in MI is expected in subacute and chronic TBI stages [6]. It has to be mentioned that some extra-metabolites are less common to calculate by MRS due to their very low concentration in the brain. Glutamate, glutamine, glutathione, GABA, and lactate are important extra metabolites that MRS can detect.

Glutamate (Glu) is an excitatory neurotransmitter that converts to glutamine (Gln) within astrocytes. Because most clinical MRI scanners are 1.5 T, Glu and Gln are usually reported in combination due to their overlapping resonances [60]. Elevated Glx and Glu following TBI are supposed to happen due to excitotoxicity [29].

Glutathione is a tripeptide thiol that acts as an oxidation-reduction cofactor in enzyme reactions [61].

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the human cortex. Literature indicates that GABA may play a potential role in cognitive dysfunctions following TBI [62]. A few previous translational studies have suggested that neurotransmitters, including acetylcholine, glutamate, dopamine, serotonin, and GABA, may potentially be biomarkers of cognitive dysfunctions in TBI [40]. Lactate occupies a unique position in energy metabolism. It is believed that the presentation of lactate in MRS suggests a poorer prognosis [63].

Absolute Neuro-Metabolites and Post-Traumatic Neurocognitive Disorders

N-Acetylaspartate (NAA) is the commonest neuro-metabolite assessed by the MRS. The majority of studies found a lower level of NAA in traumatic patients compared with control groups in various parts of the brain [32]. Research supports a strong relationship between decreased NAA level and neurocognitive outcomes [22, 36, 40, 64-66]. According to a study performed by Babikian et al., NAA explains over 40% of the variance.
in long-term outcomes of the cognitive functions [36]. MacMaster et al. found a significant association between decreased NAA in the left dorsolateral prefrontal cortex (DLPFC) and emotional symptoms in youth with a concussion in a recent study. In addition, a significant negative correlation exists between NAA level and emotional stress degree [26]. Previously, Sivak et al. reported a significant correlation between NAA in left DLPFC and computerized cognitive tests (backward digit span, Stroop test A, TMT-B time) [27].

However, most studies did not report a significant correlation between neuro-metabolites and computerized tests. Some authors reported a significant negative correlation between NAA and computerized cognitive tests. Babikian et al. noted a positive correlation between NAA in the posterior part of the corpus callosum and several neurocognitive measures, reaching statistical significance for FSIQ, visual memory, and processing speed [38]. Although longitudinal studies support that increased NAA level towards a normal value after 30 days of injury [36].

Choline (Cho) increase after TBI has been reported by some studies [37]. Some are reported the association between the increase mentioned above with insignificant outcomes [23, 64, 68]. In contrast, Parry et al. found that lower levels of Cho displayed reduced performances on neurocognitive tests [23]. Babikian et al. evaluated the correlation between single-voxel spectroscopy (SVS) data from the anterior and posterior part of the corpus callosum and neurocognitive performance. In this regard, the authors reported a positive correlation in the anterior part for response time, while in the posterior part, they concluded that this metabolite was statistically significant for FSIQ and approached significance for visual memory [38].

In a more recent study, Babikian et al. showed that lower lobar Cho levels in the chronic stage of TBI were correlated with lower interhemispheric transfer time (IHTT) in moderate to severe TBI subgroups [69].

Nevertheless, We believe that probably Cho level would be higher in more severe TBI than in a healthy population; but the lower level of Cho in the patients with more severe neurocognitive outcomes comparing patients with better outcomes may be due to decreased membrane turnover in the setting of permanent cellular damage [28, 55].

Few specialists believe that the creatine (Cr) level is stable in different situations [38], while some studies report that Cr can be changed significantly due to different situations [2, 29]. Gasparovic et al. introduced a significant regression model to predict emotional disorders based on Cr level in the splenium of the CC and white matter of the cingulate gyrus [29]. In addition, George et al. and Babikian et al. found a significant positive correlation between the acute phase of Cr level and neurocognitive outcomes in traumatic brain injuries [2, 38].

Current studies showed more interest in detecting MI in the sub-acute and chronic phases after traumatic brain injuries [20, 21, 31]. In this context, Ashwal et al. found a significant association between higher MI levels in occipital gray matter and poorer outcomes 6-12 months after injury [31]. Recently Alosco et al. published a positive correlation between MI from anterior cingulate cortex and behavioral/mood symptoms in patients with repetitive impact injury history comparing non-exposed control groups [20]. A study performed by Gardner et al. showed that in retired athletes, significant positive correlations between DASS (depression anxiety stress scale) and grey matter MI suggest that increasing MI levels are associated with worse anxiety symptoms in the posterior cingulate cortex [21]. In addition, the authors also reported a significant correlation between RPQ score and MI level in this area [21].

There are some neuro-metabolites which MRS does not usually detect. A few studies reported significant associations between GLx from occipital gray matter and parietal white matter [23]. Shutter et al. indicate that Cho and GLx have 94% accuracy in predicting long-term traumatic brain injuries [23]. Recently, Sheth et al. reported a lower glutamine level in the dorsal anterior cingulate cortex [19]. Besides, few studies have demonstrated a positive correlation between glutamate, glutathione, and behavioral/mood symptoms [20, 69]. Gardner et al. designed a study to examine if brain neuro-metabolite concentrations are associated with neurocognitive disorders in retired rugby league players who had a history of numerous self-reported concussions. The authors performed MRS in the posterior cingulate cortex and parietal white matter using 3 T single-voxel spectroscopy. The results showed that DASS anxiety scores were positively correlated with grey matter glutamate and Glx. Also, Rivermead post-concussion syndrome scores were positively correlated with grey matter glutamate. In addition, BESS scores were negatively correlated with grey matter glutathione and white matter glutathione [21].

Another interested extra-metabolite is GABA. Some studies support the role of GABA in post-traumatic stress...
disorders [19]. In a recent study, Kim et al. showed that the GABA level in the prefrontal cortex was correlated with memory performance in the Boxers but not in attention performance [24]. Lastly, some studies report that the presence of high lactate in patients with traumatic brain injuries had weaker association outcomes [30, 37].

Relative Neuro-Metabolites and Post-Traumatic Neurocognitive Disorders

Some experts believe that the relative value of metabolites is more reliable than the absolute value of metabolites [58]. Although there are some controversies, some authors believe that the Cr level remains stable in pathologic situations. Thus, most studies have used Cr as a base for relative measures [2, 27, 35, 41].

Sivak et al. found significant correlations between NAA/Cr in the right DLPFC and neurocognitive tests (total digit span and Stroop test) [27]. George et al. showed that NAA/Cr ratio in the thalamus is significantly associated with cognitive tests [2]. Likewise, many studies reported an association between reductions in NAA/Cr and poor long-term neurocognitive performance [30, 41]. NAA/Cho is another ratio that has been reported as a valuable relationship with poor long-term neurological outcomes [30, 32].

Cho/Cr is another essential ratio in the setting of TBI. An increasing trend of Cho/Cr in DLPFC in patients with PCS is reported by Dean et al. [25]. Another study by Dean et al. showed an increase in Cho/Cr ratio is correlated with the Rivermead Post-Concussion Syndrome Questionnaire Score (RPQS) [71]. Nevertheless, some studies report that Cho/Cr ratio is higher in traumatic groups with poorer outcomes [30].

A chemical shift imaging study performed by Yeo et al. on Cho/Cr ratios from the frontal lobe to the posterior parietal lobes and sampling from both white and gray matter [41]. Thus, the relationship was confirmed in other parts of the brain, such as the thalamus [35].

Conclusion

We found that MRS data can provide essential data for clinicians to predict neurocognitive outcomes following traumatic brain injuries. Neuro-metabolite ratios provide a broader information to evaluate cellular integrity in brain tissue. Further studies are needed to prepare predictive models based on MRS data for post-traumatic neurocognitive disorders.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were done in compliance with the ethical guidelines of the 2013 version of the Declaration of Helsinki.

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Authors' contributions

Conceptualization and Supervision: Mohammad Haghani Doghae; Methodology: Mohammad Haghani Doghae and Alireza Feizkhah; Investigation: Mohammad Haghani Doghae, Alireza Feizkhah, and Sara Sedighi; Writing the original draft, review, and editing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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