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The Clinical Utility of Magnetic Resonance Spectroscopy in Traumatic Brain Injury: Recommendations from the ENIGMA MRS Working Group

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Abstract

Proton magnetic resonance spectroscopy provides a non-invasive and quantitative measure of brain metabolites. Traumatic brain injury impacts cerebral metabolism and a number of research groups have successfully used this technique as a biomarker of injury and/or outcome in both pediatric and adult TBI populations. However, this technique is underutilized, with studies being performed primarily at centers with access to MR research support. In this paper we present a technical introduction to the acquisition and analysis of *in vivo* magnetic resonance spectroscopy and review magnetic resonance spectroscopy findings in different injury populations. In addition, we propose a basic data acquisition scheme that can be added to any imaging protocol, regardless of clinical magnetic resonance platform. We outline a number of considerations for study design as a way of encouraging the use of magnetic resonance spectroscopy in the study of traumatic brain injury, as well as recommendations to improve data harmonization across groups already using this technique.

Keywords: magnetic resonance spectroscopy, trauma, brain injury, concussion

Introduction

In vivo ^1H magnetic resonance spectroscopy (MRS) provides a non-invasive method to measure brain metabolites. Since abnormal metabolism is part of the pathophysiologic cascade following traumatic brain injury (TBI), MRS has been utilized to identify metabolite changes in regions of injury, to define the extent of pathology, and as a biomarker of outcome. The extent of metabolite change differs depending on the mechanism of injury, injury severity, the region studied, and the specific acquisition technique used. However inconsistent findings, especially with milder injuries, are likely magnified due to the limited number of studies, small sample sizes, duration between injury and MRS study (72 hours – several years), as well as the underlying heterogeneity of the condition and premorbid influences. To facilitate the expanded use of MRS in TBI and to improve data harmonization, the ENIGMA Brain Injury MRS subgroup has collaborated to define and to encourage the use of standardized data acquisition and analysis protocols that can be used on all clinical MR platforms.

This paper is divided into three sections. First, we introduce the neurometabolites quantified by proton MRS, current acquisition methods, and the basics of spectral analysis. In the second section, the reader is given an overview of the current state of MRS as applied to TBI including the potential of MRS as a biomarker of injury and its role in outcome prediction. Lastly, we present a number of important considerations for MRS study design, recommendations and opportunities for data harmonization; we also propose a basic data acquisition scheme for TBI studies.

An introduction to the MR spectra

In contrast to MR images, an MR spectrum consists of peaks or resonances that represent the signal intensity (amplitude) received from protons in a given metabolite as a function of their frequency (i.e., position on the chemical shift axis). Each functional group of a metabolite resonates at a frequency dependent on its chemical structure. The difference in frequency between a metabolite and a known reference standard is its chemical shift and is typically expressed as parts per million (ppm), which is a magnetic field-independent frequency scale. Each peak is proportional to the concentration of that metabolite in a specified volume of

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4 interest. *In vivo* MRS focuses on protons in the 1-5 ppm chemical shift range (Figure 1) that are
5 present at high enough concentrations (>0.5 mmol/L). Several brain metabolites can be
6 measured using either short (20-40 ms), intermediate and long (135-270 ms) echo times (TE).
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10 The most commonly measured brain metabolites in proton MRS and their chemical shift
11 values can be seen in Figure 1, taken from a single voxel (8 cm³) region in the frontal white
12 matter. *N*-acetylaspartate (2.01 ppm) is often reported as total or tNAA, representing NAA and
13 *N*-acetylaspartylglutamate (NAAG; 2.04 ppm) as it is challenging to separate NAA and NAAG
14 signals completely. NAA is an amino acid synthesized in neuronal mitochondria - an indicator of
15 neuronal energy metabolism - and is considered a marker of neuronal health as it decreases
16 with neuronal loss or dysfunction (Moffett, Ross, Arun, Madhavarao, & Namboodiri, 2007). NAA
17 is also considered a marker of neuronal density due to its high concentration in healthy
18 neurons, although this interpretation is overly simplified as NAA is also an osmolyte and may be
19 a water pump that extracts water from neurons. Additionally, NAA is a source of acetate for
20 myelin lipogenesis and is thought to act as a reservoir for glutamate synthesis in the Krebs cycle
21 (Clark et al., 2006). NAA levels increase dramatically from birth and plateau at 2-3 years of age
22 (Kreis et al., 2002). During development NAA reflects active myelination and is observed early in
23 the thalamus and later in parieto-occipital and periventricular white matter (Cady et al., 1996;
24 Huppi & Inder, 2001).
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28 Total creatine (Cr; 3.03 ppm), comprised of phosphocreatine and its precursor free Cr are
29 markers for intact brain energy metabolism. The Cr signal has been commonly used as an
30 internal standard for proton MRS based on the assumption that the Cr-phosphocreatine (PCr)
31 equilibrium provides a stable concentration of Cr. However, Cr concentrations change with age
32 (increasing from birth until 2-3 years of age; (Pouwels et al., 1999) as well as with pathologic
33 conditions including TBI (Gasparovic et al., 2009). The total choline peak (Cho, 3.20 ppm)
34 consists primarily of phosphoryl and glycerophosphoryl choline and is considered a marker for
35 membrane synthesis or repair, inflammation or demyelination. Cho levels are elevated at birth
36 and decrease rapidly with maturation (Barker, Bizzi, De Stefano, Gullapalli, & Lin, 2010).
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40 Metabolites with multiple associated (multiplet) resonances are optimally detected using
41 short TE MRS acquisitions. This includes Glutamate (Glu), an excitatory neurotransmitter, which
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can be released into the extracellular space after brain injury and plays a major role in excitotoxic neuronal death (Alessandri et al., 1999; Bullock et al., 1998). Its resonance overlaps with the amino acid glutamine (Gln) and the two are therefore often reported together as Glx (2.05-2.5 ppm and 3.7 ppm). At higher field strengths (≥ 3 T) the two metabolites are better resolved and may be measured separately, though at 3T Glx is still often reported. Myo-inositol (mIns; 3.56 ppm) is an organic osmolyte located in astrocytes that increases as a result of glial proliferation (Brand, Richter-Landsberg, & Leibfritz, 1993). Myo-inositol levels are high at birth and decrease rapidly with brain maturation leveling off by approximately 2-3 years of age (Pouwels et al., 1999). Lactate (Lac; 1.31 ppm) accumulates as a result of glycolysis in conditions of decreased oxidative metabolism and is often poorly resolved in normal brain short TE MRS as the threshold for detection is within the 0.5-1 mmol range (Barker et al., 2010). While the presence of Lac in a MR spectrum has historically been considered pathological, resulting from an increase in anaerobic glycolysis, signal to noise ratio (SNR) improvements with higher field strengths have resulted in the routine appearance of small Lac peaks in otherwise normal MRS (Tomiya et al., 2016).

Metabolite levels also vary by region and tissue type (Baker et al., 2008; Frahm et al., 1989) and change rapidly as the brain develops (Kreis et al., 2002). In general, metabolite changes associated with brain maturation (increasing NAA and lower Cho and mIns levels) occur rapidly in the first year of life (Holshouser et al., 1997) and continue to a lesser degree through adolescence and early adulthood (Horská et al., 2002; McLean, Woermann, Barker, & Duncan, 2000), before declining with normal aging (Eylers et al., 2016). As a result of differences in metabolites across the brain and lifespan, the proper interpretation of spectroscopy data typically requires comparison to “control” data sets acquired from the same brain region, using the same parameters, in age-matched control subjects. If normative data from the literature is used, care must be taken to appreciate the effects of technical differences such as acquisition methods and pulse profiles, scanner field strength, and tissue composition. Other possible considerations include data processing methods, error corrections, and artifacts.

MRS pulse sequences and analysis methods

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4 A number of localization techniques can be used to acquire proton MRS and the selection of
5 sequence and parameters are key factors in determining the outcome of the study. Following
6 TBI both single voxel spectroscopy (SVS) and multivoxel MR spectroscopic imaging (MRSI)
7 techniques have been used. The following sections discuss these localization techniques, their
8 specific advantages, disadvantages, and analysis.
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15 16 Single Voxel Spectroscopy

17 The two conventional localization schemes for SVS available on all commercial scanners are
18 Point RESolved Single voxel (PRESS) and Stimulated Echo Acquisition Mode (STEAM). The most
19 widely used localization scheme is PRESS (Bottomley, 1987). While both sequences apply
20 orthogonal gradients with selective pulses for the voxel localization, a PRESS acquisition results
21 in approximately twice the SNR compared to STEAM, although this is at the expense of having
22 to use a slightly longer TE. Both methods are known to exhibit localization inaccuracies known
23 as the chemical shift displacement (CSD) error, which is worse for PRESS acquisitions
24 particularly at high field strengths. As a result, modifications of the PRESS technique such as
25 semi-LASER (Scheenen, Klomp, Wijnen, & Heerschap, 2008) to reduce the CSD error and
26 shorten the TE, have been validated at 3T (Bednařík et al., 2015; Deelchand, Kantarci, & Öz,
27 2018; Terpstra et al., 2016; Wijnen et al., 2010) and are now available on some clinical systems.
28 For a detailed review of the PRESS sequence and its modifications, readers are directed to the
29 review by (Yahya & Gino Fallone, 2007).
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43 Single voxel localization methods such as PRESS and STEAM can readily quantify NAA, Cr,
44 Cho, mIns, Lac and Glx. However, other metabolites of interest to study after TBI, such as
45 gamma-aminobutyric acid (GABA) and glutathione, are more challenging to reliably quantify
46 due to lower concentrations and/or overlapping resonances. The use of spectral editing
47 methods, such as J-difference editing, MEGA (Mescher, Merkle, Kirsch, Garwood, & Gruetter,
48 1998) or BASING (Star-Lack, Nelson, Kurhanewicz, Huang, & Vigneron, 1997) - which separates
49 the molecules of interest from stronger, overlying signals of more concentrated metabolites -
50 have been developed and used at specialized imaging centers. A comprehensive review of
51 editing approaches for brain metabolites may be found in (Harris, Saleh, & Edden, 2017)).
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The disadvantage to using SVS is the relatively large voxel size (typically 8 cm³) needed to obtain enough signal from the metabolites of interest. The result is that the voxel generally contains cerebrospinal fluid (CSF), which contains no observable metabolites, as well as a mixture of white matter and gray matter (see Figure 1). The CSF fraction can be accounted for with tissue-voxel composition correction by segmenting the voxel into its white and gray matter and CSF, and scaling the metabolite level based on the volume fraction of CSF (fCSF) using the formula $C_{\text{corr}} = C_{\text{meas}}/(1-f\text{CSF})$, where C_{meas} is the measured metabolite level and C_{corr} is the corrected metabolite level. We recommend more comprehensive tissue corrections that additionally correct for differences in water and metabolite signal relaxations (Gasparovic et al 2006 and 2018, discussed below). An additional challenge is accounting for differences in metabolite concentration between white matter and gray matter. On average, NAA and Cr concentrations are higher in gray matter compared to white matter while Cho concentrations are lower in gray matter (Wang & Li, 1998). While this too can be included in the tissue-volume correction (Harris, Puts, & Edden, 2015), an alternative is to include the tissue fractions as a covariate in the statistical analysis (i.e., a factor in an ANOVA model) although at the expense of statistical power. As most MRS studies have small sample sizes, mathematical corrections are generally preferred.

MR spectroscopic imaging (MRSI)

As it can provide “images” of metabolite distributions, multi-voxel MRS is also known as MR spectroscopic imaging (MRSI; Figure 2). The metabolic images are typically obtained with spatial resolutions in the range of ~1 cm³ for studies ≤3 T to smaller volumes at higher field strengths (Hangel et al., 2018), and may be acquired over a single (2D MRSI) or multiple (3D MRSI) brain slices. The obvious advantage of the multi-voxel approach is the simultaneous acquisition of data over multiple regions, although local B₀ field susceptibility variations limit the volume over which spectra can be obtained with adequate quality. Volumetric MRSI methods may sample as much as 80% of the brain volume (Sabati et al., 2015), although with considerable variation between subjects and scanners. MRSI is of benefit for the following types of studies: (i) identification of multi-focal injury; (ii) identification of global injury (with 3D MRSI); (iii) exploratory analyses, in which a large number of brain regions are investigated; (iv) testing of

research hypotheses formulated *after* data acquisition, *e.g.*, examining regions implicated by new literature, or those functionally or structurally related to a newly identified injury site. A second, often overlooked, advantage of MRSI is the ability to separate white and gray matter components using post-processing methods. This is often done by linear regression (Hetherington et al., 1996; Tal, Kirov, Grossman, & Gonen, 2012) or spectral decomposition methods (Goryawala, Sheriff, Stoyanova, & Maudsley, 2018), which combine information from multiple voxels with knowledge of the relative tissue content in each voxel. Linear regression can be applied in any number of ($n \geq 2$) voxels to investigate small regions such as the hippocampus (<10 voxels; Meyer et al., 2016), larger areas such as 2D slabs (McLean et al., 2000; Gasparovic et al., 2011), in entire brain lobes (Maudsley et al., 2009), and/or in global brain white matter/gray matter metabolism (100s of voxels; Tal et al., 2012). It is especially useful for studying cortical gray matter, which due to its tortuous shape, always incurs voxel partial volume effects when examined with SVS.

There are caveats to the above MRSI advantages relative to SVS methods. First, the smaller voxel size comes at a cost of lower SNR, which translates to reduced sensitivity to detect changes. Second, MRSI studies generally take longer to acquire (on the order of 12-18 mins). Therefore, there is a higher potential for patient movement, which can affect not only data quality, but also the co-localization of the spectral matrix with the volumetric information. Third, quality control is more challenging compared to SVS as some spectra may display artifacts such as incomplete water suppression and lipid contamination. Finally, because of the effects of limited spatial sampling, each voxel contains signal from adjacent voxels, a phenomenon called “voxel bleed,” which can be remedied by avoiding acquisitions with low resolution spectral matrices, or by increasing the voxel size using a post-processing filter.

In 2D MRSI, a rectangular volume is placed at the desired transverse brain section, covering as much of the brain while avoiding the scalp lipids. 3D MRSI offers improved spatial sampling, with multiple slices allowing for the inclusion of more brain volume and structures. This can enable the study of commonly injured white matter tracts (Mandl et al., 2012) and areas remote from structural MRI-observed injury. PRESS with phase-encoding is generally used for 2D MRSI, and in principle can be extended to 3D. However, scan times become prohibitively

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4 long for full brain coverage and therefore rapid spatial-spectral sampling methods are being
5 increasingly used for this purpose (Vidya Shankar, Chang, Hu, & Kodibagkar, 2019). A difficulty
6 for obtaining full-brain coverage, including sampling of cortical surface regions, is signal
7 contamination from the strong extracranial lipid regions. Multiple approaches can be used to
8 minimize this effect, including frequency-selective saturation, inversion-nulling (Ebel,
9 Govindaraju, & Maudsley, 2003), and the use of higher spatial resolutions (Hangal et al., 2018)
10 and constrained reconstruction methods (Lam, Ma, Clifford, Johnson, & Liang, 2016).
11 Additionally, the high likelihood of sampling regions with inadequate spectral quality places
12 greater demands on robust spectral analysis and quality control. For these reasons, fully whole-
13 brain 3D MRSI methods are not currently supported by the instrument vendors.
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25 MRS Analysis Methods

26 All clinical scanners provide spectral processing packages that can be used for visual
27 interpretation and a basic quantification of metabolite integrals (area under the peak). In
28 addition, there are offline post processing tools which are commercially available (LCmodel;
29 (Provencher, 1993)) or freely available as research packages such as jMRUI (Jabłoński,
30 Starčuková, & Starčuk, 2017; Naressi, Couturier, Castang, de Beer, & Graveron-Demilly, 2001),
31 TARQUIN (Wilson, Reynolds, Kauppinen, Arvanitis, & Peet, 2011), VeSPA (scion.duhs.duke.edu),
32 and FID-A ([https://www.opensourceimaging.org/project/fid-a-advanced-processing-and-](https://www.opensourceimaging.org/project/fid-a-advanced-processing-and-simulation-of-mr-spectroscopy/)
33 [simulation-of-mr-spectroscopy/](https://www.opensourceimaging.org/project/fid-a-advanced-processing-and-simulation-of-mr-spectroscopy/)). Many of these tools use sets of simulated or empirically
34 measured spectra of known metabolites, macromolecules and lipid signals, known as a basis
35 set, that are then parametrically fit to the data with modeling of the baseline and line shape
36 variations. Basis sets may be acquired experimentally using phantoms of known concentrations
37 or simulated from known parameters (Young, Govindaraju, Soher, & Maudsley, 1998) with the
38 addition of macromolecules and lipid signals to the basis set improving the quantification of
39 short TE data sets (Seeger, Klose, Mader, Grodd, & Nägele, 2003). These tools not only provide
40 quantitative metabolite levels and ratios but also provide a numerical estimate of the model fit.
41 For example, Cramer-Rao lower bounds (CRLBs) are widely used in the literature and reflect the
42 estimate of the error of the concentration measurement as influenced by SNR, linewidth, and
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4 signal overlap. In most publications, a CRLB <20% is often used as the cut off for a reliable
5 measurement, although this is an arbitrary guideline and should be used with caution -
6 particularly in TBI studies where spectra with low SNR due to injury could be arbitrarily
7 eliminated (Kreis 2016).
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11 When reporting spectral findings, the integral of all measured resonances for each
12 metabolite peak is normalized by the number of protons contributing to the signal and scaled
13 using a reference signal. The use of metabolite ratios, typically to Cr, has been widely used.
14 However, more recently this approach has been discouraged, as Cr levels are not static, as
15 noted above. Alternatively, semi-quantitative MRS can be obtained by scaling using the
16 unsuppressed water signal from the same volume of interest (VOI), typically acquired in a
17 separate acquisition commonly called a “reference” scan. The results are presented in
18 institutional units, which can be used for comparisons to data obtained with the identical
19 measurement parameters in identical VOIs with similar tissue concentrations. To report values
20 that are closer to an absolute (molar or molal) concentration, the ratio of each metabolite to
21 the water signal acquired from the same volume of interest is used and the different water and
22 metabolite relaxation times (T1 and T2) effects and water visibility are taken into account
23 during the quantification procedures (Gasparovic et al., 2006; Gasparovic, Chen, & Mullins,
24 2018; Poole et al., 2014). Another method, called “phantom replacement”, quantifies absolute
25 amounts using as reference the metabolite signals from a separate scan of a phantom with
26 known concentrations (Jansen, Backes, Nicolay, & Kooi, 2006). In this case, the relaxation values
27 of the metabolites in the phantom should be known. In single voxel studies, the T1 and T2
28 effects can be minimized using longer repetition times (TR) and short echo times (TE). However,
29 this is at the expense of a more complicated baseline due to the presence of short T2-
30 macromolecular signals and longer scan durations with increasing TR. For larger multivoxel MR
31 spectroscopic imaging data sets, normalization or scaling to the internal water signal represents
32 a practical alternative to absolute concentrations.
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36 The data analysis methods used in most SVS and MRSI TBI studies have been based on
37 sampling preselected brain regions known to be susceptible to injury, with comparison to
38 results from the same region in normal control subjects. For MRSI studies, multiple individual
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voxel results can be averaged over a region of interest (ROI) to improve SNR (Davitz et al., 2019; Johnson, Gay, et al., 2012; Kirov et al., 2007; Sours, George, Zhuo, Roys, & Gullapalli, 2015), and ROI analysis methods can be automated using spatial normalization that matches each metabolite image to a brain atlas (Maudsley et al., 2009; Spurny et al., 2019). Also widely used in TBI studies are global MRSI approaches, which obtain average concentrations over large 2D or 3D volumes (Cohen et al., 2007; Gasparovic et al., 2009; Govind et al., 2010; Kirov et al., 2013; Mayer et al., 2015; Yeo et al., 2006). Since it is well-known that TBI injury is multi-focal (Biasca & Maxwell, 2007; Bigler, 2013; Browne, Chen, Meaney, & Smith, 2011; Johnson, Stewart, & Smith, 2013), averaging over a large area of diffuse injury would be expected to yield better sensitivity to injury compared to examining a smaller region (due to the higher SNR in a larger volume). Indeed, it was recently shown that when studying NAA decreases in white matter, global linear regression had better sensitivity for discriminating patients from controls when compared with regional voxel averaging (Davitz et al., 2019). Such global approaches also eliminate bias in choosing what particular (smaller) region(s) should be interrogated.

Analysis of MRSI data may also be carried out using voxel-based analysis (VBA) methods to create maps of abnormal metabolism (Maudsley et al., 2015). For analysis of individual subject data, a comparison can be made with the mean and standard deviation of a group of normal control subjects, for example to create a z-score map, and differences between groups can similarly be made using standard statistical tests (Figure 3). VBA methods are best implemented following spatial normalization, so that comparisons are made for the same brain region and should account for the relative gray- and white-matter content in each voxel, as well as for individual metabolite maps, and for CSF volume fraction. VBA maps have the advantage that normal spatial and tissue variations are accounted for, and the result directly highlights abnormal tissue regions. Nonetheless, this approach remains difficult to integrate into clinical protocols due to the requirement for strict standardization. Prior to performing any of the above analyses, spectral quality tests must be applied and voxels not meeting these requirements should be excluded.

Machine learning (ML) or artificial intelligence approaches for analysis of MRS data are still very much in their nascent stages but show great promise in potentially extracting novel factors

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4 within MRS data that go beyond the traditional analytical approaches. For example, the
5 conventional fitting of MRS data as described earlier could potentially be improved, particularly
6 in situations where SNR is low or the spectra contain artifacts (Das, Coello, Schulte, & Menze,
7 2017). Alternatively, ML methods may be effective in removing artifacts (Kyathanahally, Döring,
8 & Kreis, 2018). Another potential application of ML methods in MRS of TBI may be to identify
9 patterns in differences in brain metabolites. For example, in military-related TBI one such
10 confound can be the comorbidity of post-traumatic stress disorder (PTSD). Pattern classification
11 algorithms can be applied in different cohorts of soldiers with mTBI, PTSD, co-morbid mTBI and
12 PTSD, and controls to identify potential biomarkers that can classify these groups (Mariano et
13 al., 2017). Alternatively, the metabolite concentrations themselves can be used as the model
14 input as applied in distinguishing between chronic repetitive sports-related TBI and controls
15 (Louis et al., 2017). Thus far, the application of ML methods in MRS of TBI is preliminary, as
16 robust classification can only be achieved using large datasets and most MRS studies have used
17 relatively small cohort sizes. With uniformity in MRS methods, multisite studies that allow for
18 combined datasets will facilitate the magnitude of data necessary for ML algorithms to be
19 effective. Endeavors such as the ENIGMA groups or data repositories such as FITBIR will be
20 necessary to achieve this goal.
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39 **MRS findings following TBI**

40 *MRS as a biomarker of injury*

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43 Standard clinical neuroimaging methods such as computed tomography (CT) and
44 conventional MRI are the primary clinical neuroimaging methods for lesion detection after TBI
45 and continue to provide diagnostic and prognostic information, particularly for patients with
46 more severe TBI (Jeter et al., 2013; Mayer et al., 2018). Additionally, advanced MRI techniques
47 such as volumetric MRI analysis, susceptibility-weighted imaging (microhemorrhages), diffusion
48 tensor imaging (DTI) and tractography (white matter injury), functional MRI (network
49 connectivity), and perfusion imaging (blood flow or volume) have produced sets of imaging
50 biomarkers used to predict neurological and/or neuropsychological outcome across all
51 severities of brain injury (Hunter, Wilde, Tong, & Holshouser, 2012; Kou et al., 2010). However,
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4 the exquisite sensitivity of MRS to noninvasively measure key neurometabolites provides a
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6 unique window into the brain's response to injury above and beyond clinical symptoms, as well
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8 as beyond structural and functional changes observed on more conventional imaging.
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10 Combining MRS in multimodal imaging studies can also be valuable as each modality
11 provides information that can be complementary. For example, combining MRS with diffusion
12 MRI can provide additional insight into alterations in white matter health and can lead to more
13 accurate outcome prediction (Dennis et al., 2018). Moreover, MRS biomarkers (i.e., metabolite
14 levels or ratios) often show abnormalities in the injured brain even when conventional
15 neuroimaging appears normal (Garnett, Blamire, Rajagopalan, Styles, & Cadoux-Hudson, 2000;
16 Holshouser, Tong, & Ashwal, 2005; Kirov et al., 2013). Following TBI, decreases in brain NAA,
17 whether regional or whole-brain, have consistently been associated with outcomes following
18 moderate to severe TBI (Friedman, Brooks, Jung, Hart, & Yeo, 1998; Garnett et al., 2000;
19 Holshouser et al., 2005; Kirov et al., 2013; Maudsley et al., 2017). Longitudinal studies have
20 shown that NAA levels are dynamic after injury - NAA remains low in patients with poor
21 recovery suggesting neuronal loss, and recovering in patients with good outcomes suggesting
22 recovery of mitochondrial function and/or neuronal repair (Garnett et al., 2000; Holshouser et
23 al., 2019; Signoretti et al., 2002). Several studies have correlated reduced NAA levels after
24 injury to long-term memory or attention deficits (Babikian et al., 2006; Holshouser et al., 2019)
25 and combined neuropsychological function measures (Friedman et al., 1998; Govind et al.,
26 2010; Maudsley et al., 2015; Babikian et al., 2018; Dennis et al., 2018). Increasing levels of Cho
27 (Maudsley et al., 2017), mIns (Ashwal et al., 2004), and Glx (Ashwal et al., 2004; Garnett et al.,
28 2001; Gasparovic et al., 2009; Shutter, Tong, & Holshouser, 2004) have also been associated
29 with poor neurological outcome. The presence of Lac and lipids after severe TBI has been
30 reported in patients with the worst outcomes (Ashwal et al., 1997; Panigrahy, Nelson, & Blüml,
31 2010). All told, there is mounting evidence that MRS provides unique biomarkers of injury,
32 which improves injury detection and prognosis and may be more sensitive following milder
33 injury than imaging alone as detailed below under the heading of sports-related TBI.
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56 The following factors complicate generalizations about MRS findings following TBI: the use
57 of metabolite ratios and differences in (i) regions of interest (ROI); (ii) sensitivity of the
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1 measurement (i.e., SNR, partial volume); (iii) age of the studied population; (iv) injury severity
2 and type of TBI within the patient pool; and (v) duration of time between injury and MRS study.
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4 Given the heterogeneity of injury and variability in acquisition methods and sampled locations
5 it is perhaps not surprising that findings across studies are not always consistent even when
6 patients are examined at similar post-TBI periods, e.g., George et al. (George et al., 2014)
7 reported reduced Cho/Cr in the thalamus, whereas increased (Govind et al., 2010) and normal
8 (Yeo et al., 2011) white matter Cho have been reported in subacute TBI. Nevertheless, the
9 consensus is that NAA declines, both in acute and post-acute patients, with a secondary finding
10 of increased Cho (Gardner, Iverson, & Stanwell, 2014; Kirov, Whitlow, & Zamora, 2018; Lin et
11 al., 2012). These abnormalities seem to increase with injury severity as assessed by the Glasgow
12 Coma Scale (GCS), post-traumatic amnesia (PTA) and MRI findings (Garnett et al., 2000; Govind
13 et al., 2010), and in general, white matter may be more affected than gray (Govind et al., 2010;
14 Yeo et al., 2011). In studies including mild injuries, the interpretation of cross-sectional studies
15 may also be hampered by a recruitment bias and prior injury in acute versus post-acute studies.
16 The latter studies are likely to enroll patients from a physician's office, thereby biasing their
17 sample towards patients with worse outcome; while the former would tend to recruit all
18 patients sustaining TBI, most of whom will recover. Indeed, serial studies in the acute stage of
19 mild TBI show normalizations of abnormalities (Vagnozzi et al., 2010, 2013, 2008; Yeo et al.,
20 2011), including the recovery of NAA/Cr (Vagnozzi et al., 2010, 2008). In contrast, NAA/Cr
21 declines over time in cohorts of moderate and severe TBI (Garnett et al., 2000), where fewer
22 people will proceed to good recovery. Another aspect to consider in relation to outcome is that
23 Cr and Cho abnormalities likely represent different processes in acute and post-acute TBI stages
24 (Lin et al., 2012). This is important, because initial findings may reflect reversible processes,
25 while later measurements may reflect a longer term mechanism responsible for clinical
26 impairment.

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28 TBI in the pediatric population also defies generalization as there are several distinct types
29 of injury that are associated with different ages within this population: non-accidental trauma
30 (NAT; usually 2 years of age and under), auto versus pedestrian accidents (school age), and
31 concussions/sports injuries and motor vehicle accidents (adolescence). In addition,
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4 neuropsychological testing becomes problematic when trying to include a large age span in a
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6 pediatric cohort since testing varies by age and cannot always be directly compared. In research
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8 studies, many of these challenges are mitigated by recruiting age-matched controls, an issue
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10 discussed below and in the companion piece in this special issue focused on pediatric
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12 moderate/severe TBI (Dennis et al., 2019).
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15 16 *MRS in outcome prediction*

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18 MRS is not only a tool to assess the presence and extent of an injury (as in acute studies),
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20 but it can also be used as an early predictor of future outcomes. When applied post-acutely, it
21
22 can identify ongoing metabolic abnormalities that underlie persistent functional deficits. MRS
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24 studies have been used for clinical outcome prediction in both pediatric and adult populations,
25
26 reviewed below separately for mild versus more severe injuries.
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28 In children with moderate/severe TBI, acute MRS studies have shown reductions in NAA
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30 and elevations in Cho. These abnormalities correlate with later neurologic and
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32 neuropsychological outcome (Ashwal et al., 2000; Babikian et al., 2006), with reduced NAA in
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34 subcortical regions strongly predicting poor long-term cognitive outcomes (Babikian et al.,
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36 2006). Post-acute or chronic evaluations have shown similar neurometabolic alterations (Yeo et
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38 al., 2006), with correlations observed with neuropsychological and behavioral functioning
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40 (Babikian et al., 2010; Parry et al., 2004; Walz, Cecil, Wade, & Michaud, 2008), and continued
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42 abnormalities in subgroups of patients correlate with poorer trajectories of outcome (Babikian
43
44 et al., 2018). Similar to children with msTBI, adult patients with TBI of varying injury severities
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46 have shown widespread alterations in whole brain Cho and/or NAA that are correlated with
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48 injury severity, symptomatology or neuropsychological functioning (Govindaraju et al., 2004;
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50 Govind et al., 2010; Kirov et al., 2013; Maudsley et al., 2015) as well as with gross neurologic
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52 outcomes (Glasgow Outcome Scale; GOS) at 3 months post injury (Marino et al., 2007). Post-
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54 acute or longer measurements of decreased NAA/Cho in the basal ganglia have also correlated
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56 with neuropsychological measures of psychomotor speed, motor scanning and attention (Ariza
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58 et al., 2004).
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60 The prognostic utility of MRS in milder injuries (including concussions) has been primarily
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4 focused on youth and sports related injuries. In two studies of MRS in pediatric populations,
5 serial spectra were collected at multiple time points (72 hours or less, 14 days, and after
6 symptom recovery), and no metabolic abnormalities were observed, with symptom resolution
7 and cognitive functioning normalizing by day 14 (Maugans, Farley, Altaye, Leach, & Cecil, 2012).
8 On the other hand, in post-acute measurements of a persistently symptomatic group,
9 reductions in NAA/Cr and NAA/Cho were observed (Bartnik-Olson et al., 2014). In adult
10 athletes, decreased NAA/Cr ratios observed through 30 days post injury, with a modest
11 recovery by day 15, were reported, although self-report of symptoms resolved by day 3
12 (Vagnozzi et al., 2008). In another study, reduced Cr in the right dorsolateral prefrontal cortex
13 was correlated with structural and functional imaging markers that seemingly underlie
14 persistent post-concussive symptoms (Dean, Sato, Vieira, McNamara, & Sterr, 2015). Further,
15 higher levels of white matter Cr in the early subacute period (<1 month) were predictive of
16 executive function difficulties and emotional distress (Gasparovic et al., 2009). A later sub-acute
17 (> 1 month) and chronic (> 6 months) assessment identified decreases in Cho/Cr in the
18 thalamus and *centrum semiovale*, which correlated with cognitive measures of recognition and
19 memory (George et al., 2014). Taken together, in both pediatric and adult studies, and across
20 all severity ranges, when there are MRS abnormalities observed on acute studies, these
21 abnormalities have predictive utility for not only gross neurologic outcomes but also deficits in
22 neurocognitive functions. MRS examinations beyond the acute period have also shown utility in
23 explaining the pathobiology of persistent cognitive and other behavioral deficits (Bartnik-Olson
24 et al., 2014). Optimally, models to assess TBI will incorporate biomarkers from multiple sources
25 including several neuroimaging modalities, MRS, and blood biomarkers (Kawata, Tierney, &
26 Langford, 2018), all provided at the optimal time point after injury to enhance prognostic
27 information, treatment decisions, and patient outcome (Manivannan, Makwana, Ahmed, &
28 Zaben, 2018). For example, blood biomarkers, CT and conventional MR are useful early after
29 injury, whereas metabolite levels from MRS or other advanced imaging techniques such as DTI
30 may provide better prognostic information measured subacutely.
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59 *Distinct injury mechanisms*

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4 TBI is the result of a number of different mechanisms. In the sections below the application
5 of MRS in non-accidental trauma (NAT), sports-related concussion, and military TBI are
6 reviewed. While these injury mechanisms share some common pathological features (e.g.,
7 metabolic dysfunction, white matter injury) with other forms of accidental trauma, they have
8 biomechanically distinct features that influence their MRS signature and outcome.
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15 NAT

16 Neurotrauma caused by child abuse is commonly termed NAT (non-accidental trauma). NAT
17 features complex injury mechanisms resulting from multiple types of axonal injury that can
18 occur in the same brain including hypoxic-ischemic injury designated as vascular axonal injury
19 and diffuse traumatic axonal injury resulting from acceleration-deceleration forces (i.e., shaken
20 baby) (Dolinak & Reichard, 2006; Gill et al., 2009). Inflicted trauma to the brain is reported as
21 the leading cause of death in children younger than 2 years of age. However, non-fatal injuries
22 can leave the victim with a lifetime of neurologic deficits (Keenan et al., 2003; Theodore et al.,
23 2005). Skeletal radiographs and CT serve as initial imaging approaches to the suspected victim
24 of abusive trauma, as osseous injuries are second only to skin wounds as signs of child
25 maltreatment (Pfeiffer et al., 2018). A follow-up MRI is often used to evaluate for the presence
26 of suspected bridging vein thrombosis in patients with subdural hematoma, microhemorrhages,
27 ischemic injury, or ligamentous neck injury, and can increase the specificity for the diagnosis of
28 NAT (Colbert et al., 2010; Foerster et al., 2009; Hahnemann et al., 2015; Jacob et al., 2016; Suh,
29 Davis, Hopkins, Fajman, & Mapstone, 2001).
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45 MRS is also useful for evaluating brain injury after NAT and provides insights into brain
46 neurometabolism that differ from accidental TBI. Since victims of abuse are usually younger
47 compared to children who suffer accidental TBI; normal spectral changes associated with brain
48 maturation need to be taken into account. NAT injuries also tend to be repetitive and not
49 isolated events, further complicating the pathobiology if subsequent injuries occur during
50 recovery. An immature brain may explain why the degree of neurological damage suffered in
51 children after NAT is often greater than the apparent severity of trauma (Haseler, Arcinue,
52 Danielsen, Bluml, & Ross, 1997). In addition, infants and young children have less mature
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4 airway protective reflexes thereby placing them at higher risk of respiratory failure as reflected
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6 in the higher rates of intubation after NAT compared to accidental TBI (Ichord et al., 2007). The
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8 presence of Lac in the brain spectrum is often attributed to impaired aerobic glycolysis and is
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10 both a specific and sensitive marker of hypoxic-ischemic injury (HII). In addition, Lac
11
12 accumulation has been related to multiple pathophysiological changes associated with TBI
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14 including: excessive release of glutamate, disordered mitochondrial and oxidative metabolism
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16 and systemic responses to trauma (Hovda, Becker, & Katayama, 1992; Krishnappa, Contant, &
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18 Robertson, 1999; Prasad et al., 1994). Lac is found more often in brain spectra of children after
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20 NAT and in combination with reduced NAA is associated with poor outcome (Figure 4; Aaen et
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22 al., 2010; Ashwal et al., 1997; Haseler et al., 1997; Makoroff, Cecil, Care, & Ball, 2005). As in
23
24 accidental TBI, reduced NAA is a key MRS finding after NAT since it reflects neuronal injury or
25
26 dysfunction resulting from both traumatic and hypoxic-ischemic injury and as a result is more
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28 predictive of long-term outcome than lactate presence alone. As shown in one MRSI study,
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30 reductions in NAA/Cr ratios were more predictive than clinical findings such as retinal
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32 hemorrhages or lactate presence alone for long-term outcome prediction after NAT (Aaen et
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34 al., 2010).

35 36 37 Sports-Related TBI

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39 With over 3.8 million concussions occurring in the United States alone, sports-related head
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41 injury is one of the leading causes of TBI (Langlois, Rutland-Brown, & Wald, 2006). Unlike single
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43 incidences of mild TBI discussed earlier, sports-related TBI are of a more repetitive nature with
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45 multiple head impacts over the course of months and years. For example, an average high
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47 school football player receives 652 hits to the head that exceed 15 G's of force per season
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49 (Broglio et al., 2011). Similarly, longer and repeated deployments have exposed soldiers to
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51 repeated blasts (Eskridge et al., 2012). This is especially concerning as exposure to repetitive
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53 brain impacts can lead to the development of chronic traumatic encephalopathy (CTE), a
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55 neurodegenerative brain disorder that is marked by an accumulation of phosphorylated tau and
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57 leads to cognitive, psychological, memory, and mood problems later in life (McKee et al., 2009).
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59 CTE, a confirmed diagnosis only at post-mortem, has been identified in both athletes and
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4 soldiers, and has been shown to be evident even in repetitive subconcussive impacts (Stern et
5 al., 2013). MRS is well suited for examining the effects of these potential impacts, even at a
6 subconcussive level given its high sensitivity to injury. The recent decade has seen an increased
7 interest in using MRS for the evaluation of sports-related head injury in the acute, subacute,
8 and chronic settings of concussions.
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14 As described earlier, the studies of sports-related injury by Vagnozzi et al. (Vagnozzi et al.,
15 2010, 2013, 2008) were seminal in describing reductions of NAA/Cr ratios post-concussion and
16 subsequent recovery. Similar findings of reductions in NAA/Cr in the motor and dorsolateral
17 prefrontal cortex have also been shown along with changes in Glu with the use of short-echo
18 MRS (Henry, Tremblay, Boulanger, Ellemberg, & Lassonde, 2010; Henry et al., 2011). Using 3D
19 MRSI, another study also found reductions in NAA in the corpus callosum one to three weeks
20 post injury (Johnson, Gay, et al., 2012). In that same time frame, Friedman et al. (2017;
21 Friedman et al., 2017) used MEGAPRESS to examine GABA levels and found increased GABA in
22 the frontal lobe but decreased in the posterior cingulate in children with sports-related
23 concussion. Other studies have also used MEGAPRESS to assess collegiate athletes mid-season
24 but did not find changes in GABA (Tremblay et al., 2014; Lefebvre et al., 2018). Manning et al.
25 (Manning et al., 2017) examined male hockey players within 24-72 hours of injury and 3 months
26 post concussion and found decreased Cho in the prefrontal white matter only at the 3 month
27 time point.
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41 In a pediatric population of athletes, Bartnik-Olson et al. (Bartnik-Olson et al., 2014) used
42 3D MRSI and reported decreases in NAA/Cr and Cho in the corpus callosum and in parietal
43 white matter at 2-12 months post injury. Also at the subacute stage, namely 6 months to one
44 year post-injury, there are also gender differences reported. For example, Henry et al. (Henry et
45 al., 2011) found increased mIns in the motor cortex in male athletes whereas Charmard et al.
46 (Chamard et al., 2013) found decreased amounts of mIns in both the motor cortex and
47 hippocampus.
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54 Other studies focused upon subconcussive injury by utilizing a study design where athletes
55 were scanned prior to the start of the season and then again at the end of the season. In these
56 studies, athletes were not necessarily concussed at this time period, indicating that any exposure
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4 to head injury would likely be at a subconcussive level. Poole et al. (Poole et al., 2014)) studied
5 the dorsolateral prefrontal cortex and primary motor cortex at pre-, mid-, and postseason time
6 points and found that relative to non-contract sports controls, football players exhibited
7 decreased Cr and mIns in the DLPFC and Glx, Cr, Cho in the motor cortex. A follow up study
8 including head impact telemetry measures showed that in the DLPFC, the number of 60 G hits
9 inversely correlated with Cr and mIns concentrations, and hit metrics predicted NAA and Cho
10 changes. In the motor cortex, duration of exposure was the strongest predictor of Glx and that
11 it correlated negatively with number of hits, and Cr positively correlated with total number of
12 hits experienced in the previous week. Chamard et al. (Chamard et al., 2013) also found
13 significant decreases in NAA/Cr in the corpus callosum over the course of a season in female ice
14 hockey players without a history of concussion, but not in male ice hockey players.

25
26 Given the concern with CTE and its impact on retired professional athletes, several studies
27 have focused on the effects of years of repetitive head injury by examining retired athletes and
28 controls. De Beaumont et al. (De Beaumont et al., 2013) showed reduced Glu in the motor
29 cortex in former collegiate athletes. Lin et al. (Lin et al., 2015), however, showed increased Glu
30 but in the posterior cingulate, as well as increases in Cho in a preliminary study of retired
31 professional athletes. This study was then followed up in a larger cohort of retired NFL athletes
32 where the primary finding was a decrease in NAA in the parietal white matter and reductions of
33 Cr (Alosco et al., 2019). In a study of Australian-rules rugby players, the most significant finding
34 was a reduction on glutathione and mIns in the posterior cingulate (Gardner et al., 2014).
35 Chronic exposure to subconcussive injuries has also been explored in a study of retired
36 professional soccer players who never reported a concussion during their career but were
37 exposed to subconcussive impacts to the head through heading of the soccer ball (Koerte et al.,
38 2015). This study found increases in choline and myoinositol in the posterior cingulate in
39 athletes with a history of heading compared to those that did not. The increase in myoinositol
40 also correlated with the self-reported number of headings of the soccer ball.

54
55 MRS studies of sports-related head injury are consistent with other types of brain injury
56 with reductions in NAA, increases in choline and glutamate, and reductions in creatine. The
57 changes observed in studies of subconcussive injury demonstrate the sensitivity of MRS
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measures. In addition, they also provide insight into potential mechanisms of injury such as neuroinflammation. While there appears to be a cumulative effect of repetitive injuries, the patterns observed are not as simple as cumulative changes in brain metabolites. While NAA changes are found, it is not as pronounced as would have been expected. Changes in myoinositol point to other changes that occur in the brain, perhaps to the impact on glial cells in addition to the neuronal injury reflected in NAA reductions. As the literature grows in this area of research, MRS will play an important role in providing insight into the underlying pathophysiological changes of repetitive brain injury.

Military TBI

There has been a surprising paucity of studies of military-related TBI. Hetherington et al. (Hetherington et al., 2014) examined 25 veterans at least 1 year after exposure to 1 or more blasts and compared them to age and gender matched healthy controls with no history of brain injury at 7T. The results of the study showed that veterans had significantly decreased NAA/Cr and NAA/Cho ratios (possible increased Cho) similar to sports-related head injury. One of the interesting findings, particularly for a military cohort, was there was no significant difference between TBI subjects with and without post-traumatic stress, anxiety, depression, or alcohol dependence, which are the major comorbidities in military TBI. This is surprising given that MRS studies in military subjects with PTSD have shown changes in hippocampus such as decreased NAA and changes in Cho (Brown, Freeman, Kimbrell, Cardwell, & Komoroski, 2003; Freeman, Cardwell, Karson, & Komoroski, 1998; Kimbrell, Leulf, Cardwell, Komoroski, & Freeman, 2005; Schuff et al., 2001) that may have shown a compounding effect. Mariano et al (Mariano et al., 2017)), examined several different cohorts of military veterans with and without both mTBI and PTSD and found differences in the regions of the spectrum including Glu, GABA, Cr, and Lac. Classifiers based on these features exhibited correct classification rates of 80% or better in cross-validation demonstrating that MRS has the potential to be used to differentiate between the different conditions.

Considerations for study design, multisite studies, and recommendations

The following sections outline a number of important considerations when incorporating MRS into TBI studies. In addition, opportunities for multisite MRS studies and the role of the ENIGMA consortium are also discussed. Finally, we leave the reader with a recommended MRS protocol that can be incorporated into clinical and research neuroimaging protocols, providing an additional biomarker of injury, repair/recovery, and/or prognosis.

Choice of brain region

A variety of factors determine the choice of investigated region. Chief among them are the hypothesis, level of available technical expertise, investigators' own experience and interpretation of the supporting literature, and the question driving the application of spectroscopy. Below we list the most commonly studied ROIs, by acquisition type, i.e., SVS and MRSI.

The most common SVS voxel placement reflects the fact that preclinical and postmortem studies have identified white matter diffuse axonal injury as the hallmark site of TBI injury (Su & Bell, 2015). Most often, the targeted regions have been frontal/prefrontal white matter (Maugans et al., 2012; Schranz et al., 2018; Sivák et al., 2014; Vagnozzi et al., 2010, 2008; Walz et al., 2008); Dhandapani et al., 2014), splenium (Cecil et al., 1998; Gasparovic et al., 2009; Johnson et al., 2012; Johnson et al., 2012) and genu (Johnson et al., 2012) of the corpus callosum. SVS voxel placement in gray matter is also common, with most studies focusing on the cingulate gyrus (Koerte et al., 2015; Lin et al., 2012; Louis et al., 2017), dorsolateral prefrontal cortex (Dean et al., 2015; Henry et al., 2010; Poole et al., 2014; Bari et al., 2019) and primary motor cortex (Tremblay et al., 2014). Two-dimensional spectral matrices are usually positioned to include prominent white matter regions, often either at the level of the corpus callosum, or slightly superior at the level of the *centrum semiovale* and *corona radiata* tracts (Gasparovic et al., 2009; Yeo et al., 2011; Lawrence et al., 2019; Mamere, Saraiva, Matos, Carneiro, & Santos, 2009; Narayana et al., 2015; Sarmiento et al., 2009); or through the temporal lobe for the study of the hippocampus (Hetherington et al., 2014; Kontos et al., 2017). Three-dimensional volumes are usually centered around the corpus callosum to cover these regions and the deep gray matter (George et al., 2014; Kirov et al., 2007; Kirov et al., 2013;

Holshouser et al., 2019; Sours et al., 2015), while whole-brain coverage techniques by default cover most of the supratentorial brain (Govind et al., 2010; Maudsley et al., 2015; Widerström-Noga, Govind, Adcock, Levin, & Maudsley, 2016; Maudsley et al., 2017; Babikian et al., 2018; Dennis et al., 2018). While there is no literature consensus on which exact brain region(s) to study with either SVS or MRSI, recent evidence suggests that for maximum sensitivity to white matter injury, location is less important than the sensitivity of the method (Davitz et al., 2019). Specifically, it was found that NAA deficits in patients would have been detected in white matter regions, as long as the MRS technique yielded coefficients of variation of less than 8%, a feat achievable with large single-voxels, or global MRSI approaches, such as linear regression over 2D or 3D volumes (Davitz et al., 2019).

Quantitation methods: ratios vs. absolute quantification

As discussed earlier, results can be obtained either as metabolic ratios (e.g., NAA/Cr) or as individual metabolites following normalization in the form of institutional or biochemical units (e.g., millimoles per kilogram of wet weight). A decision between the two requires knowledge of the mean and standard deviation of both the numerator and denominator of the proposed ratio (Hoch, Kirov, & Tal, 2017). This information can be obtained from a previous study, which used absolute quantification (Hoch et al., 2017). Therefore, we suggest that exploratory studies be carried out with absolute quantification (water referencing or phantom replacement), so that these values can be obtained before a decision is made regarding whether to use ratios. When considering literature values in TBI as the basis for this decision, the referenced and the planned study need to be matched in as many technical parameters as possible. In addition, comparisons should take into account patient age, sex, time from injury, studied region, and relative gray- and white matter tissue volume.

Control subjects

The definition of control subjects must also be considered. While controls are defined as unaffected individuals, prior exposure to trauma more generally may impact outcomes. Similarly, consequences of injury such as not being able to participate in normal daily activities can

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4 impact outcomes. Therefore, some studies have opted to use an orthopedic injury (OI) cohort
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6 as the control group, as it shares traumatic event exposure and the associated recovery, can be
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8 recruited using a similar recruitment pathway (i.e., presentation in emergency rooms), as well
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10 as other factors that are non-specific to brain injury but mediate recovery (Yeates et al., 2017,
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12 2009). However, this practice has been called into question as some studies have shown no
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14 clear advantage over community controls (Beauchamp, Landry-Roy, Gravel, Beaudoin, &
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16 Bernier, 2017; Mathias, Dennington, Bowden, & Bigler, 2013). Additional considerations should
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18 be taken into account when acquiring MRS in children and adolescents after TBI. One of the
19
20 more important considerations is the necessity to compare metabolite levels or ratios to
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22 normal age-matched control data as metabolite concentrations differ with developmental age
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24 (see above). In addition, control studies are not as easy to obtain in a pediatric population,
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26 particularly in younger children who may require sedation. As a result, some MRS studies use
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28 normative data acquired from children undergoing MRI for medical but non-neurological
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30 reasons or when the MRI study was interpreted as normal by a Radiologist.
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32 33 *Time after injury and injury severity* 34

35 Early MRS studies have combined TBI patients of all severities with widely variable time post
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37 injury intervals (from hours to years) into single analyses. We now appreciate that there are
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39 dynamic changes in the acute and sub-acute periods following potentially all severity ranges,
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41 and potentially ongoing changes at later time points with more severe injuries. Thus controlling
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43 for some of the variation in evolving brain chemistry over time by grouping patients into
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45 defined time-post injury intervals is critical to avoid additional noise to a study population that
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47 is already quite heterogeneous to begin with. Similar to the above reasons, separating
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49 uncomplicated mild injuries from more severe injuries will also assist to further reduce
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51 confounds in the data, as the nature and/or the time course of biochemical changes sensitive to
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53 MRS may be variable in these two groups.
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55 56 *Choice of outcome measures* 57 58 59 60 61 62 63 64 65

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4 MRS can be useful as both a diagnostic tool as well as a prognostic measure of long-term
5 real-world outcomes. It is important to consider and to incorporate the NIH Common Data
6 Elements (CDE) recommendation in MRS studies that are designed to address its utility as a
7 prognostic tool (Duhaime, Holshouser, Hunter, & Tong, 2012; Haacke et al., 2010). While the
8 Glasgow Outcome Scale Extended (GOSE) is the only CDE core outcome measure for TBI, our
9 recommendation is to stay away from using only gross outcome measures, unless the
10 population studied is severely injured. Rather, focusing on the following outcome categories
11 will provide a broad clinical and real-world perspective on functional outcomes for all age
12 groups, injury types, and most injury severity categories: 1) overall intellectual skills (shortened
13 screening tools included), 2) some composite measure of cognitive efficiency from standardized
14 measures, for example from the NIH Toolbox (e.g., processing speed, attention/concentration,
15 executive functioning) and memory (e.g., encoding), 3) measure of quality of life (NIH Toolbox
16 or other), 4) day-to-day adaptive skills, 5) psychiatric morbidity (e.g., depression, anxiety), and
17 6) return to previous activities. Additional areas of interest may be considered depending on
18 the targeted focus of the study, such as sleep, ADHD, academic functioning, and vocational
19 functioning. In all of the above cognitive, academic, and psychiatric outcome assessments,
20 premorbid functional levels are critical to establish via records, interviews, or formal
21 questionnaires.

22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 *Multisite studies and ENIGMA*

42 While concussion is a highly prevalent condition, recruitment is often challenging. In
43 addition to typical difficulties of recruiting research participation and study compliance, the
44 heterogeneity of concussion and study populations means that researchers are forced to decide
45 between either accepting a high degree of heterogeneity in the sample (i.e., large age range,
46 including prior history of head injury, various presentations times after injury, etc.) or risking a
47 very small sample size when limiting population variance. While these challenges still exist,
48 including multiple sites can be a solution to increasing the sample size while maintaining some
49 degree of homogeneity in participant demographics.

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4 Multisite MRS studies, however, have their own challenges. In addition to different analysis
5 approaches, each of the three main vendors have made different decisions regarding the trade-
6 offs in developing pulse sequences. Even with the well-established PRESS sequence, each of the
7 vendors has chosen different parameters that impact the quality and localization of the PRESS
8 signal. The result is that quantified metabolite levels are not directly comparable between
9 different scanner vendors. There has been some effort to develop universal sequences that
10 have the exact same excitation and refocusing pulses across all vendors, for example with the
11 MRSI sequence (Sabati et al., 2015), and a recent consensus report recommends a semi-LASER
12 acquisition for SVS measurements (Wilson et al., 2019). However, these are currently not
13 provided by the instrument manufacturers and they require access to research pulse-
14 sequences.

15
16 Additional challenges to maintaining uniformity of data acquisition include training of
17 technicians, data quality control, and maintenance of instrumentation performance. A simple
18 voxel replacement study shows the challenges in voxel placement replication without the
19 additional challenges of different technicians and visualization software packages (Bai et al.,
20 2017). One approach is to limit possible variance by not allowing rotations beyond placement
21 on an AC-PC aligned T1-weighted image, although this limits the localization of information.
22 However, an additional advantage of studying white matter, as in TBI, is that misregistration
23 errors are less costly as partial volume errors would be limited to different white matter
24 regions, and not to different tissue type or CSF.

25
26 When developing multisite studies, one option is to use human phantoms and scan the
27 same individuals at all sites to at least be able to quantify and understand the differences in
28 metabolite quantification. This approach was recently used in a 5-site child and adolescent
29 concussion study (Yeates et al., 2017). Nonetheless, at the present time, MRS findings from
30 multisite studies have been limited (Vagnozzi et al., 2010), although a number of ongoing
31 studies are acquiring MRS. One such study is the Diagnostics, Imaging, and Genetics Network
32 for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy (DIAGNOSE-CTE)
33 funded by the National Institutes of Health. This study is currently enrolling former NFL and
34 collegiate football players and healthy controls across four sites (Boston University/Harvard
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4 Medical School, New York University, Mayo Clinic, and Cleveland Clinic) and it includes not only
5 MRS but also neurological and psychological evaluation, structural and functional MRI, blood
6 and CSF samples, and PET scans with the goal of identifying multimodal biomarkers of CTE that
7 will allow for in-life diagnosis and treatment monitoring. Of further note, the Veteran's
8 Administration has the TRACTS study (Translational Research Center for TBI and Stress
9 Disorders), which focuses on military veterans where MRS data is also being collected. The
10 Chronic Effects of Neurotrauma Consortium, funded by the Department of Defense, has also
11 collected some MRS data in several of their sites, but findings have yet to be published.
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21 *ENIGMA*

23 The ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) Brain Injury group
24 was formed in the fall of 2016 with the overarching goal of creating a collaborative framework
25 to address TBI-related questions and objectives. At present there are six subgroups
26 representing specific clinical conditions (pediatric moderate/severe TBI, military TBI and
27 concussion, sports-related head injury, adult moderate/severe TBI, acute emergency
28 department mild TBI, and intimate partner violence) and two subgroups focusing on emerging
29 imaging methodologies (MRS and arterial spin labeling). The immediate goals of the ENIGMA
30 Brain Injury working groups are to conduct analyses on multisite datasets to look for robust
31 effects across samples in addition to raising new hypotheses. Specific details about the goals
32 and approach of the ENIGMA consortium and the individual subgroups can be found in
33 companion articles in this issue.
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47 **Consensus/recommendations and an ENIGMA approach**

48 The foregoing discussion illustrates that MRS is sensitive to brain metabolic changes that
49 occur in some specific TBI contexts in some specific brain regions. However the discussion also
50 illustrates that TBI is clinically heterogeneous and that existing research studies involving MRS
51 have included small numbers of human subjects and only a few specific subtypes of the TBI.
52 Using an ENIGMA approach could potentially enhance knowledge by extending studies to larger
53 numbers of TBI patients having a wide variety of different TBI subtypes at a variety of times
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4 following TBI. In addition, an ENIGMA design could provide normative MRS data over a range of
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6 subject ages, gender, race, etc. which would be helpful in definitively defining the level of
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8 metabolic abnormality that is exhibited in TBI.
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10 The foregoing discussion also illustrates that MRS technology is continuing to evolve.
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12 Frequently the goal of many studies that use MRS to evaluate a specific brain condition is to
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14 demonstrate that some new form of MRS technology is sensitive to the brain condition. While
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16 this is useful for propelling technology development forward, use of such new technologies is
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18 not necessarily optimal for an ENIGMA design that is to be deployed across many centers
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20 because not all centers have access to new MRS technology or the expertise to implement it.
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22 For this reason it seems prudent to propose an ENIGMA design that focuses on a simple, easy,
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24 fast, low cost MRS technology that could be used in a very large number of subjects including
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26 subjects who are patients and are having their TBI evaluated for routine clinical purposes by
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28 MRI. The simplest, fastest, most widely available form of MRS technology is single voxel MRS. It
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30 is available as a product on all commercial MRI scanners and is frequently used in routine
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32 clinical contexts such as brain cancer, epilepsy, developmental disorders and TBI (in some
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34 centers). If single voxel MRS is considered as a candidate for an ENIGMA-inspired MRS study of
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36 TBI, it is important to consider that not all brain regions can be evaluated and there should be
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38 consistency regarding which brain region is sampled. Here it is noteworthy that many studies
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40 that have used endpoints derived from imaging, neuropsychology and electrophysiology have
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42 suggested that although the initial physical impact experienced by the brain can be
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44 heterogeneous in terms of magnitude and direction of the impact vector, a central feature of
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46 TBI seems to be white matter abnormality. Perhaps the best example of this is the fact that a
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48 variety of different TBI situations lead to diffuse axonal injury in the large white matter tracts of
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50 the brain. For this reason we recommend that MRS studies use a single frontal matter white
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52 matter region across subjects for an initial ENIGMA study.

53 Based on the reasoning given above the minimal technical recommendations for an
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55 ENIGMA MRS study of TBI are as follows:

- 56 a. Field Strength: 3.0 T
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- 58 b. MRI Manufacturer: Any (though needs to be documented)
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- c. Pulse sequence: Although a recent consensus report recommends a semi-LASER acquisition for SVS measurements (Wilson et al., 2019), this sequence is not widely available across all platforms. As such, at this time we recommend a water-suppressed PRESS SVS sequence using manufacturer's commercially available standard pulse sequence software.
- d. TR/TE/number of averages (NAV): 2000/minimum (30-35 ms) /128.
- e. Selected volume size and location: minimum of 6 cm³ placed in the frontal white matter (Figure 6). A number of studies report significant findings in the basal ganglia/thalamus (Holshouser et al., 2019; Kierans et al., 2014) or supraventricular gray matter (anterior or posterior cingulate gyrus; Lin et al., 2012; Yeo et al., 2011), thus an additional voxel may have added benefit depending on the study design.
- f. Other instructions: Perform an identical non-water-suppressed acquisition (matched TR and TE) with at least 8 averages for quantification.
- g. Ancillary MRI measurements: Provide any standard T1w, FLAIR and SWI studies that are done for clinical purposes in the same study as the MRS acquisition.

These recommended parameters will produce sufficient information to determine the water-referenced white matter concentrations of about six brain metabolites in an additional time for MRS of less than 4.0 min. As argued above, if this minimalist procedure could be routinely run on many TBI patients it would be possible to evaluate how sensitive MRS-based white matter neurometabolite assessment is to a variety of different subtypes and instances of TBI. Eventually such measurements could be extended to predicting how MRS-based white matter neurometabolite assessment might be used to predict clinical (neuropsychological and behavioral) outcome, and recovery. As indicated above, obtaining normative MRS data would be important. For this, the present authors suggest that ENIGMA groups who study other brain conditions consider adding the above-described MRS measurement to their studies. The recommended protocols of a short-echo single voxel spectroscopy acquisition in white matter with reference water scan would benefit ENIGMA groups such as sports-related TBI, military TBI, and intimate partner violence studies.

Summary

The goal of this paper was to provide readers with a comprehensive overview of the use of MRS in TBI and how it can be used both clinically and in future research studies. MRS is highly complementary to other MRI modalities by providing biomarkers of tissue injury such as NAA (neuronal health), choline (membrane turnover), creatine (brain energetics), glutamate (excitatory neurotransmission), and lactate (hypoxia). Current MRS methods such as single voxel spectroscopy and chemical shift imaging are clinically available across all MR manufacturers where an additional scan of 5-10 minutes can provide a wealth of information that can assist with diagnosis and prognosis of injury. There still remains the need for large, prospective clinical trials to confirm the clinical utility of MRS in brain injury. The considerations and guidelines provided in this paper are intended to provide clinicians with guidance on how to implement MRS in their own studies and/or clinical practice.

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Author Contributions

Author contributions included conception and drafting the manuscript (BLBO, JA, TB, ADH, BH, IIK, AAM, AL), editing the manuscript, and approval of the final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (All authors).

Conflicts of interest

Dr. Alger is the owner of NeuroSpectroScopics LLC. Dr Lin is the co-founder of BrainSpec and a consultant for Moncton MRI. Dr. Thompson received partial research support from Biogen, Inc. for research unrelated to this manuscript.

Figure 1: Single voxel spectroscopy (SVS PRESS; TR/TE= 3000/30 ms; 3.0T) collected from a 20 x 20 x 20 mm³ voxel the right frontal white matter of a 10 month old showing commonly observed neurometabolites. NAA (N-acetyl aspartate), Glx (overlapping glutamate and glutamine), Cr (creatine), Cho (choline), and mIns (myo-inositol).

Figure 2: Sagittal (a), T1-weighted MRI of a patient's head showing the location and geometry of the 8.0×10.0×4.5 cm³ VOI (white frame) and its 6 spectroscopic slices, 0.75 cm thick each. The yellow arrow indicates the slice presented in b, c, d, e. Presented in gradients from black to red are: each voxel's NAA concentration, overlaid on the T1-weighted image (c); and each voxel's tissue fractions, overlaid on the gray matter (d) and white matter (e) segmentations. The real part of the 8×10 ¹H spectra matrix from the VOI on b, is shown in (f). The four spectra bound by the rectangular box are shown in detail in (g) along with their fitted waveform (gray line) used for quantification. Note that, as reflected in (c), the two outer spectra have no metabolite signal, because they correspond to voxels within the lateral ventricles (b). The two inner spectra originate from the splenium and correspondingly contain no gray matter (d). While they contain equal white matter fraction of about ~100% (e), the NAA signal (g) and concentration (c) are lower in one of the voxels. There are no differences in levels of Cr or Cho. This patient had post-concussive symptoms and was part of a group-level analysis, which found lower global white matter NAA levels in patients compared to controls (Kirov, Tal, Babb, Lui, et al., 2013).

Figure 3: Percent differences of the group mean metabolite measures relative to control values for a group with moderate TBI (mean GCS 12.9, range 6 to 15). Regions with significant differences, for $p < 0.05$, are shown as a color overlay superimposed on the spatial reference magnetic resonance imaging. Results are shown for N-acetylaspartate/creatine (A), creatine (B), and choline (C), with the corresponding color scales indicated for each. Data was acquired at 3T using a volumetric MRSI sequence with spatial sampling of $50 \times 50 \times 18$ points over $280 \times 280 \times 180$ mm³ and TE=70 ms.

Figure 4: A. MRS predictive of severe TBI outcome. Representative spectra acquired in healthy controls (top) and patients with severe traumatic brain injury based on outcome. The second from the top shows spectra with good outcome. Third from the top shows a patient in a persistent vegetative state (PVS) and the bottom spectrum shows a patient who died. Note the decrease in NAA, increase in lactate and glutamate/glutamine with greater severity of outcome. All spectra were acquired at 1.5T using STEAM (TE=30 ms) in the posterior cingulate. B. MRS is sensitive to subconcussive brain trauma. Retired professional soccer players with no history of concussion, with the only exposure to repetitive head impacts due to heading of the soccer ball, and athletes with no exposure to head impacts were scanned using PRESS (TE=30ms) in the posterior cingulate area at 3T. In heavy blue is the averaged spectrum of all controls and in red are the individual soccer players. There was a significant increase in choline and myoinositol found in the soccer players showing spectroscopic changes due to subconcussive impacts.

Figure 5: MRSI volume of interest (VOI) overlaid onto a T2 weighted MR image of a 3 month old NAT patient who presented with an initial GCS score of 3, retinal hemorrhages and diffuse hypoxic-ischemic injury (A). MRSI (PRESS; TR/TE= 3000/144 ms; 1.5T) was acquired 1 day after injury. B). Spectral map shows a diffuse decrease of NAA and large inverted Lac peaks (doublet at 1.33 ppm; B). The Lac peaks are inverted as a result of the intermediate echo time. Spectrum from the right parieto-occipital white matter shows markedly decreased NAA and presence of Lac (C).

Figure 6: Recommended frontal white matter MRS voxel location. In red highlight overlaid on grayscale sections through a T1-weighted 3-dimensional MR volume image is shown the recommended location, angulation and dimensions of a frontal white matter MRS voxel. For convenience displays of the voxel on four representative sagittal, axial and coronal sections of the T1-weighted volume image are provided. The voxel's dimensions are 20 x 25 x 15 mm = 7.5 cm³. Angulation and dimensions, which are expected to depend on subject's anatomy and head position, were adjusted for this particular subject to achieve maximal white matter content and a volume as close to 8.0 cm³ as possible.

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A. Severe Brain Injury

B. Subconcussive Brain Injury