Published in final edited form as:
J Pediatr Rehabil Med. 2009 ; 2(4): 249–253. doi:10.3233/PRM-2009-0099.

The promise of evolving neuroimaging techniques for pediatric Traumatic Brain Injury

Stacy J. Suskauer*
Kennedy Krieger Institute, Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, Baltimore, MD, USA

1. Neuroimaging in TBI – current and future contributions to care

The use of neuroimaging, namely computed tomography (CT), has played an important role in the clinical management of children with traumatic brain injury (TBI) for decades and today continues to be a critical tool for directing acute medical and surgical management of TBI. While CT plays a critical role in rapid detection of blood collections and evaluation of edema, mass effect, and ventricular size, it is poor for identifying diffuse axonal injury (DAI), now understood to be of critical importance for consciousness and long term outcomes after TBI. Furthermore, the radiation exposure associated with CT limits its desirability for use in research studies.

The introduction of magnetic resonance imaging (MRI) in the 1980's improved the detection of DAI and provided a mechanism for neuroimaging without radiation exposure. Using sequences such as T1, T2, fluid attenuated inversion recovery (FLAIR), and gradient echo sequence (GRE), the literature comes together to support that increased volume of injury and greater depth of lesions, as identified with neuroimaging, are associated with worse outcomes. Beyond that, there has been little reproducibility in studies to suggest that, at this time, neuroimaging findings can be reliably associated with specific outcomes. As we have now come to understand that these clinical MRI sequences identify only a minority of DAI lesions, emerging neuroimaging techniques with greater sensitivity for DAI hold promise for changing the role of neuroimaging in pediatric TBI.

Improved detection of traumatic brain injury could impact research and care in multiple ways. Currently, TBI is often referred to as a "messy" disease process, largely due to the heterogeneity in injuries across individuals and the difficulty which currently exists in identifying all regions of injury. Currently, for clinical and research purposes, individuals with TBI are grouped by clinical severity measures, such as initial Glasgow Coma Scale score or time to follow commands, and the patterns of injury may vary significantly among individuals within one severity group. Improved detection of injury will allow categorization of individuals based on location and extent of injury, thereby reducing some of the variability that comes from only categorizing subjects based on global severity of TBI.

More accurate identification of presence, location, and extent of injury will facilitate identification of key brain-behaviorrelationships, facilitating improvements in prognostication shortly after injury for chronic outcome. This may allow targeting of rehabilitation therapies, improving the efficiency of the delivery of rehabilitation care. Furthermore, differential response to varying therapies may be identified for sequelae of TBI

*Address for correspondence: Stacy Suskauer, M.D., Kennedy Krieger Institute, Pediatric Rehabilitation, 707 North Broadway, Baltimore, MD 21205, USA. Tel.: +1 443 923 9440; Fax: +1 443 923 9445; suskauer@kennedykrieger.org.

resulting from differing patterns of injury; for example, disinhibition resulting from focal frontal lobe injury versus disruption of white matter tracts connecting frontal and parietal regions may respond differentially to the use of stimulants or cognitive-behavioral interventions.

There is promise that ongoing advances in neuroimaging will impact care across the entire spectrum of TBI, from patients with mild TBI to those with disorders of consciousness resulting from severe TBI. On the mild end of the spectrum, more advanced neuroimaging has demonstrated detection of abnormalities in adolescents without evidence of injury on standard clinical imaging [6], and functional imaging is demonstrating that altered recruitment of brain structures underlies the production of what behaviorally appears to be “normal” or “baseline” function (for examples, see the work by Kramer et al. in this issue and [2]). In the future, neuroimaging may be used to more precisely define severity of “mild” injuries and to aid in answering challenging clinical questions, such as when an adolescent athlete can safely return to sport.

For severely injured individuals, functional imaging holds the promise for expanding the armamentarium for evaluating consciousness and responsiveness. Imaging measures of consciousness may have wide-ranging impact, including implications for payers, and could significantly impact the type and intensity of services that a child receives. Furthermore, structural and functional imaging findings together may point to the etiology of an individual’s disorder of consciousness and may thereby facilitate differentiation of the most likely therapeutic intervention to improve that patient’s function. For example, an individual whose thalamic injuries contribute most significantly to alterations in consciousness may respond differently to pharmacologic intervention in comparison to an individual whose brain stem injury is the major contributor to impaired consciousness.

In addition, neuroimaging techniques with sensitivity for identifying areas of injury also hold promise for identifying the neural basis of recovery after TBI. Important information stands to be gained, including whether/how white matter tracks re-organize after TBI, how neurometabolite concentrations change in association with recovery, and what functional neural activation patterns after TBI are associated with better functional performance. Such information is likely to spur further research into facilitation of recovery with traditional therapeutic techniques and through pharmacological intervention and transcranial stimulation. Additionally, brain measures of recovery may become important intermediate outcomes for research projects.

2. Imaging techniques

The biological processes associated with TBI provide multiple targets for neuroimaging identification of areas of injury. Acutely, axons are disrupted physically, changing not only brain architecture, but also the neurochemical environment, with the latter potentially resulting in additional cell injury. Additionally, just as the neuronal structures are sheared, so is the nearby brain vasculature, resulting in extravasation of blood products. With time, many of these acute changes appear to persist, such that architectural disruption, neurochemical changes, and extravascular blood products are observed chronically after TBI. In addition, over time, Wallerian degeneration results in atrophy of brain structures. Finally, physiologically patterns of brain activation can be examined through the use of functional neuroimaging. A brief introduction to several imaging techniques is presented below, with key points summarized in Table 1. The interested reader is referred to a recently published review [4] for additional information regarding these techniques and their application to pediatric TBI.

Susceptibility weighted imaging (SWI) relies on post-processing techniques to highlight deoxygenated blood including extravasated blood products. As such, SWI identifies areas of disruption of vasculature, assumed to co-occur with axonal shearing injury. Thus, SWI facilitates identification of location and extent of injuries.

Diffusion-based MRI techniques permit evaluation of brain properties based on the diffusion of water molecules. Diffusion weighted imaging (DWI) permits identification of edema associated with DAI; this may result in identification of a much greater extent of brain involvement beyond a focal lesion identified by classical anatomic imaging. Diffusion tensor imaging (DTI) is an extension of DWI which provides information about the directionality of water diffusion. In TBI, DTI is believed to provide information about axonal integrity, as water molecules within axons are more likely to diffuse parallel to, as opposed to perpendicular to, the axonal walls. In contrast, in the absence of intact cellular structure, water will diffuse in all directions more equally. In TBI, thus far the most commonly reported DTI measure is fractional anisotropy (FA), which ranges from 0 (perfectly isotropic diffusion, or equal diffusion in all directions) to 1 (perfectly anisotropic diffusion, or diffusion along only one axis). In white matter, higher FA represents greater axonal integrity, and after TBI, FA is often decreased, representing axonal injury. FA can be measured across large portions of the brain (i.e. entire brain, frontal lobe, etc.) as well as within specific white matter tracts. One DTI technique, tractography, permits isolation of white matter tracts based on FA and turning angle in adjacent image voxels. Tractography can facilitate identification of focal areas of injury along white matter tracts and also permits evaluation of the volume and FA within an isolated tract.

Morphometric analyses permit evaluation of the shape and size of brain regions as well as cortical thickness. In the past, size of brain regions was typically evaluated by two-dimensional hand-tracing of brain structures. Now, sophisticated programs, such as FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), provide automated analyses of white and gray matter volumes and cortical thickness at the level of the hemisphere or individual white and gray matter structures. In TBI, these techniques are likely to be most useful for evaluating atrophy that follows injury and, compared to hand-tracing techniques, are likely to allow for more detailed analyses regarding location and degree of atrophy. Even more sophisticated are analyses, such as those performed using Large Deformation Diffeomorphic Metric Mapping (LDDMM, http://www.cis.jhu.edu/software/lddmm/about.html), examining shape of brain structures. As an example, this type of analysis has the power to identify specific changes to the shape of a brain region that are associated with particular outcomes. For example, LDDMM may be useful in helping to clarify the role of atrophy of the centromedian nucleus of the thalamus in chronic disorders of consciousness.

Proton magnetic resonance spectroscopy (^{1}H-MRS) suppresses the signals from the water molecules of the brain, allowing evaluation of other neurochemicals. Because these other neurometabolites are present in far smaller quantities than water, MRS is not able to yield the spatial information obtained in other forms of MRI imaging, and instead a spectra is produced summarizing the quantity of each neurochemical within an imaging voxel. Three neurometabolites are most often evaluated in studies of TBI. N-acetyl-aspartate (NAA) is a marker for neuronal integrity and decreases in the presence of neuronal injury. Creatine is a marker of neuronal inflammation and repair and typically increases after TBI. Choline is a cell membrane marker and may also increase after TBI. Additional neurometabolites which can be evaluated using MRS and which may have importance in TBI include lactate, glutamate, Gamma-Aminobutyric acid (GABA), and N-acetylaspartylglutamate (NAAG). As often MRS is performed within very small brain regions, it will be important to determine, in individuals with TBI, which brain regions are best studied. There are data to suggest that neurometabolite levels in normal-appearing brain are related to outcome after

TBI in children and adults [1], but additional work is required to tease apart the implications of neurochemical profiles within focal lesions versus that in otherwise normal-appearing brain. Magnetic resonance spectroscopy imaging (MR-SI) is a technique which allows examination of multiple brain regions simultaneously with higher spatial resolution and may be well-suited for use in evaluation of regional neurometabolite profiles and their relationship to outcomes in TBI.

Functional MRI (fMRI) allows evaluation of patterns of brain activation. Unlike other functional imaging methods (i.e., positron emission tomorgraphy (PET) and single photon emission computed tomography (SPECT), radioisotopes are not used. Classically, fMRI has been used to identify patterns of brain activation during a motor or cognitive task (even in those patients without overt responses – see [3]). Recently there has been great interested in resting-state fMRI, or evaluation of brain activation patterns while the participant is simply "resting" in the scanner, not engaged in any specific task. These types of evaluations have resulted in identification of a number of "default mode" networks, and there is tremendous interest currently in examining the relationships between these default mode networks and "task positive" networks in a variety of pathological conditions. Similarly, functional connectivity analyses can be used in task-related analyses to evaluate which regions of the brain activate in association with other regions. Such types of work may provide significant insight into disorders of consciousness (see [5]) as well as common neuropsychological deficits, such as inattention and impulsivity, after TBI. FMRI may also be combined with other techniques to allow investigation into the anatomic features underlying neural activation patterns observed after TBI.

3. Limitations and next steps

To date, many pediatric TBI neuroimaging studies have included very small numbers of patients. While these small studies are very important for demonstrating feasibility and generating preliminary data, they lack the power to reach definitive conclusions. Ultimately, larger studies will be crucial to answer questions regarding brain-behavior relationships after TBI.

A number of issues contribute to the relatively small number of participants in pediatric TBI imaging studies. At a first level, artifacts from cranial or intracranial hardware and orthodontia often render imaging data unusable, often eliminating children with these types of hardware from participation in imaging studies. For those children who can be scanned, movement in the scanner often results in imaging data which is unusable. Movement is likely to be worse in younger children and children with more impulsivity or global impairment, and movement in the scanner may increase in association with active tasks, including typical fMRI paradigms.

Various approaches can be taken to minimizing participant motion. First, participant exposure to the scanning environment, including the physical layout of the scanner and the noises made by scanner, prior to the actual scanning session is important for decreasing participant anxiety. Even with this preliminary exposure, children with TBI may need extra time to settle into the scanning environment; this, and the likely need to repeat one or more acquisitions due to participant movement, should be considered when budgeting time and financial resources for scanning. During structural imaging, motion may be decreased by engaging the child in watching a preferred video during scanning. Lastly, post-processing techniques can also be used, within limits, to help salvage imaging data with motion.

Given the difficulties with obtaining good neuroimaging data in children with TBI, multi-site studies are likely to be needed to generate larger pools of participants. At this time, variability among scanners, especially those from different manufacturers, is a concern

limiting merging of imaging data from different sites. It is anticipated that preliminary studies validating combined use of data from multiple sites will be necessary before larger TBI studies using sensitive neuroimaging techniques can be initiated.

While even small, cross-sectional neuroimaging projects can be challenging at this time, longitudinal studies hold the greatest promise for improving our ability to develop a prognosis after injury, to understand the brain-basis of recovery, and for understanding how injury affects subsequent brain development. Especially for the latter two goals, longitudinal studies will need to include typically developing control participants in addition to children with TBI. It becomes clear that the next generation of pediatric TBI neuroimaging studies will require a great deal of resources for recruiting, retaining, and training of participants, fostering of multi-site collaborations, and technical expertise, in addition to the financial means needed for scanning itself. Only with these investments will the promise of neuroimaging for children with TBI be fulfilled.

Acknowledgments

This work was supported by NICHD 1K23HD061611-01.

References

1. Babikian T, Freier MC, Ashwal S, Riggs ML, Burley T, Holshouser BA. MR spectroscopy: predicting long-term neuropsychological outcome following pediatric TBI. J Magn Reson Imaging 2006;24:801–811. [PubMed: 16941608]
2. Jantzen KJ, Anderson B, Steinberg FL, Kelso JA. A prospective functional MR imaging study of mild traumatic brain injury in college football players. AJNR Am J Neuroradiol 2004;25:738–745. [PubMed: 15140712]
3. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. Science 2006;313:1402. [PubMed: 16959998]
4. Suskauer SJ, Huisman TA. Neuroimaging in pediatric traumatic brain injury: current and future predictors of functional outcome. Dev Disabil Res Rev 2009;15:117–123. [PubMed: 19489082]
5. Voss HU, Schiff ND. MRI of neuronal network structure, function, and plasticity. Prog Brain Res 2009;175:483–496. [PubMed: 19660675]
6. Wilde EA, McCauley SR, Hunter JV, Bigler ED, Chu Z, Wang ZJ, Hanten GR, Troyanskaya M, Yallampalli R, Li X, Chia J, Levin HS. Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. Neurology 2008;70:948–955. [PubMed: 18347317]

Table 1

Summary of advanced MRI techniques and their applicability to Traumatic Brain Injury

Technique name	Detected entity	Outcome variable(s)
Susceptibility Weighted Imaging	Deoxygenated/extravasated blood (proxy for diffuse axonal injury)	Number/volume of lesions
Diffusion Tensor Imaging	Diffusion of water	Fractional anisotropy (FA, integrity of white matter tracts), size of white matter tracts
Morphometric analyses	Size/shape of structures (for evaluating atrophy)	Change in volume and shape of brain structures, cortical thickness
Proton Magnetic Resonance Spectroscopy (^{1}H-MRS)	Neurometabolite levels	Levels of N-acetyl-aspartate, Creatine, Choline, and other neurometabolites
Functional Magnetic Resonance Imaging	Changes in blood oxygenation levels (proxy for cerebral activation)	Cortical activation patterns in response to a task or at rest