IMAGING IN SEVERE TBI

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1) Summary

Advances in structural and functional neuroimaging are occurring at a rapid pace. Novel techniques for measuring white matter connectivity and neural network activity have the potential to improve the accuracy of diagnosis and prognosis for patients with severe traumatic brain injury (TBI), while also providing biomarkers to guide the development of new therapies. This syllabus summarizes recent advances in structural and functional neuroimaging methods and the potential applications of these techniques to the clinical care of patients with severe TBI. The pitfalls and confounders that should be considered when interpreting data from each technique are also discussed. Recommendations of the NIH Common Data Elements workgroup pertaining to each imaging technique are also presented.[1, 2]

2) Computed Tomography (CT) and Conventional Magnetic Resonance Imaging (MRI)

Head CT continues to be the preferred technique for acute neuroimaging of patients with severe TBI because of its accessibility, speed of acquisition, and its ability to detect skull fractures and large intracranial hemorrhages that require urgent neurosurgical intervention. CT grading systems such as the Marshall CT classification[3] and Rotterdam CT score[4] continue to be used in clinical practice, and elements of both grading systems have been incorporated into commonly used prognostic models, such as the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT)[5, 6] and the Medical Research Council (MRC) CRASH[7] models. Recent studies suggest that sophisticated multivariate models using CT parameters may further improve outcome prediction.[8, 9]

Conventional MRI may not be feasible during acute stage of severe TBI because of lack of access, prolonged data acquisition time, or clinical factors that preclude MRI (i.e. raised intracranial pressure or metallic implants). Nevertheless, conventional MRI utilizing T2-FLAIR, GRE, DWI and derived apparent diffusion coefficient (ADC) maps provides better detection of traumatic axonal injury (TAI) than does CT.[10-13] Accordingly, conventional MRI has been shown to be a more useful prognostic tool than CT.[10, 14, 15] White matter ADC is particularly useful for predicting outcomes, with one recent study demonstrating that ADC values in the whole-brain white matter and in the corpus callosum correlate with functional outcome in severe TBI patients at the time of hospital discharge.[16]

In addition, conventional MRI studies, particularly those utilizing DWI, ADC and GRE, have yielded important insights about TAI pathophysiology. For example, restricted diffusion of water, as indicated by DWI hyperintensity and ADC hypointensity, develops over a highly variable timeline in TAI, likely due to the variable pathophysiological changes that occur in the intracellular compartment depending on the severity of shear-strain forces. Unlike in ischemic stroke, in which the DWI and ADC signal changes associated with diffusion restriction appear within minutes and follow a stereotyped time course with pseudonormalization of the ADC signal by seven to ten days,[17] TAI-related diffusion restriction may occur in a delayed fashion and has been reported to persist up to 18 days post-TBI.[18] Furthermore, whereas diffusion restriction is typically associated with irreversible, cytotoxic edema in ischemic stroke, there are rare reports of neurological recovery in TBI patients despite evidence of extensive TAI-related diffusion restriction.[19, 20] These observations are consistent with animal studies showing that TAI may be reversible when shear-strain forces do not cause acute, primary axotomy.[21] Consequently, the terms “cytotoxic edema” and “neurotoxic edema” should be used with caution when describing TAI-related diffusion restriction, since these lesions are not invariably associated with secondary axotomy or neuronal death. Moreover, the dynamic nature and potential reversibility of TAI-related signal abnormalities on DWI/ADC suggest a longer window for therapeutic intervention as compared to ischemic stroke.

Just as the DWI/ADC sequence has helped to elucidate the complex and heterogeneous pathophysiology of non-hemorrhagic TAI, the GRE sequence has yielded important insights about hemorrhagic TAI. From a pathophysiological standpoint, it has long been recognized that the shear-strain forces that disrupt and/or sever axons in TAI also cause disruption of the brain’s microvasculature, resulting in extravasation of blood.[22] Whereas CT studies in the 1990s found that microhemorrhages, or traumatic microbleeds (TMBs), are associated with

approximately 20% of radiologically apparent TAI lesions,[23] GRE studies subsequently demonstrated that up to 80% of DAI lesions may be associated with TMBs.[13, 24] While a TMB is not incontrovertible evidence of concurrent axonal injury, the biomechanical and pathophysiological links between vessel disruption and axonal disruption suggest that the presence of axonal injury can be reasonably inferred when a TMB is present in the same neuroanatomic region.

Even if radiologic evidence of axonal pathology (i.e. signal change on T2 FLAIR or DWI) is not identified, the presence of a TMB is considered in clinical practice, research studies, and in the Common Data Element guidelines, as evidence of hemorrhagic TAI.[1] Supporting this assumption are studies showing that the total number of TMBs correlates with admission GCS score,[24-26] duration of post-traumatic unconsciousness,[25, 27] and degree of neurological recovery.[25, 27] Furthermore, individual TMBs have been shown to account for focal neurological deficits at 1 month post-TBI.[27] Yet, while TMBs identified by GRE have been correlated with acute TBI severity and short-term outcomes, prior studies have failed to consistently demonstrate GRE's utility as a tool for predicting long-term outcomes.[13, 24, 27-29] These results highlight the need for advanced imaging techniques that are more sensitive for TMB detection and thus potentially more useful for prognosis.

3) Advanced Structural Imaging Techniques

Susceptibility-weighted Imaging (SWI)

The development of a 3-dimensional high-resolution susceptibility-weighted imaging (SWI) technique by Haacke and colleagues in 2004[30, 31] significantly enhanced the detection of TMBs that are associated with hemorrhagic TAI. The increased sensitivity for TMB detection that SWI provides over standard 2-dimensional GRE images is due to advances in both data acquisition and data post-processing. Unlike the conventional GRE sequence, which relies solely upon T2*-weighted magnitude images to identify the susceptibility effects of extravasated blood, SWI combines both magnitude and phase data to produce an image with enhanced susceptibility contrast. SWI thereby increases the conspicuity between blood products and the surrounding brain parenchyma. As a result of these methodological advances, SWI has been shown to detect more microbleeds than GRE does in patients with TAI.[25, 26, 32] Furthermore, the total number and volume of TMBs detected by SWI correlate with functional outcomes after TBI,[25] whereas earlier studies that used GRE to detect TMBs failed to consistently demonstrate such a correlation.[13, 24, 28, 29] Tong and colleagues demonstrated that SWI is especially sensitive at detecting TMBs in the brainstem,[25, 32] a region in which unilateral and bilateral lesions are associated with odds ratios of 8 and 182, respectively, for poor outcome on the Glasgow Outcome Scale-Extended (GOSE).[14] It is therefore possible that SWI improves outcome prediction by identifying TMBs in neuroanatomic regions where lesions have a particularly high prognostic significance.

In interpreting SWI data in patients with TBI, there are several important methodological factors that should be considered. The first and most important is the magnetic field strength at which the SWI data are acquired. Just as cerebral microbleeds (CMBs) caused by hypertension or cerebral amyloid angiopathy are more readily detected at higher field strength,[33, 34] TMBs are easier to detect at 3 Tesla as compared to 1.5 Tesla[35] due to increased sensitivity to susceptibility effects at higher field strengths. Second, the in-plane spatial resolution and the distance between adjacent slices (i.e. interslice gap) may significantly affect the number of TMBs that are detected, since higher spatial resolution decreases volume averaging.[36] Thus, SWI data obtained from different patients or longitudinally in a single patient can only be reliably compared when magnetic field strength and imaging acquisition parameters are held constant.

Diffusion Tensor Imaging (DTI)

The development of DTI by Pierpaoli and Basser in the late 1990s revolutionized neuroimaging of white matter in the human brain and led to significant new insights about TAI pathophysiology.[37, 38] The principle upon which DTI is based is that the self-diffusion (i.e Brownian motion) of water molecules in the brain is directionally dependent. Water molecules within and around myelinated axons tend to diffuse in a directional (anisotropic) manner along the axis of the axon, whereas water molecules in grey matter or CSF tend to diffuse in a less directional (isotropic) manner. Assuming that the diffusion of water molecules in the brain is directionally dependent, it can be characterized by a tensor with six degrees of freedom.[39] From a methodological standpoint, measuring the diffusion tensor requires the application of directional diffusion gradients in at least six non-collinear directions, as well as the acquisition of at least one non-diffusion-weighted (i.e. $b = 0$ sec/mm^2) measurement. From the diffusion tensor, several scalar quantitative metrics of water diffusion can be calculated.[40] One of the most commonly used is fractional anisotropy (FA). In a unitless scale ranging from 0 to 1, completely non-directional or isotropic diffusion is defined as FA=0, and completely directional or anisotropic diffusion is defined as FA=1.

The feature of DTI-derived scalar metrics that is of particular relevance to TBI is their ability to detect structural changes in the white matter axons that are the pathophysiologic substrate of TAI. Low FA in the white matter has been correlated with histopathological evidence of TAI in experimental animal models.[41, 42] In addition, low FA in multiple white matter regions has been associated with neurological deficits and long-term functional outcomes in patients with severe TBI.[43-50] Moreover, low FA in specific white matter bundles correlates with abnormal cognitive functions that are known to be associated with those bundles. For example, memory dysfunction has been correlated with low FA in the uncinate fasciculus, superior longitudinal fasciculus, and fornix,[49, 51] poor attention with low FA in the anterior corona radiata,[51] and poor executive function with low FA in the dorsolateral prefrontal region.[52] Given the growing body of evidence that FA provides a functionally relevant assessment of white matter integrity, DTI is currently listed in Tier 2 of recommended protocols in the Common Data Elements guidelines.[1]

From a DTI data acquisition standpoint, an important methodological consideration is that of reproducibility of the quantitative anisotropy and diffusivity values. Both hardware (i.e. the MRI scanner) and software (i.e. the pulse sequence) may affect the characterization of the diffusion tensor. With regard to hardware, potential effects of the MRI scanner on the diffusion measurements include inconsistent shimming, gradient miscalibration, and gradient non-linearity, each of which may lead to signal attenuation and/or inconsistent measurements.[40] Even if standardized hardware and software are ultimately used in DTI analyses, white matter anisotropy may still vary with gender[53] and age,[54] and therefore normalization according to these demographic characteristics may be necessary. Furthermore, it remains unknown when the optimal timing of DTI data acquisition is for diagnosing TAI and/or prognosticating outcome. A recent retrospective analysis found that DTI data acquired after post-trauma day 7 may provide more reliable prognostic information than DTI data acquired within the first week of injury.[55]

Another important consideration in the data acquisition stage of DTI is the number of directional diffusion gradients that are used to measure FA. Jones demonstrated that at least 20 directional measurements may be needed to generate reproducible measurements of FA.[56] At the present time, the Common Data Element guidelines recommend 30 diffusion directions for DTI scans performed on 1.5 Tesla MRI scanners. Alternatively, either 64 diffusion directions or 12 diffusion directions with 5 averages are recommended for DTI scans on 3 Tesla MRI scanners.[1] Reduction of DTI data acquisition time is currently an active area of investigation[57, 58] that will help facilitate clinical implementation. Notably, the recent development of simultaneous-multislice image acquisition has the potential to cut DTI data acquisition time in half.[59] Other data acquisition considerations include the degree of diffusion-weighting that is used (i.e. b-value) and the spatial resolution (i.e. voxel size).

Methodological factors during the statistical analysis stage of evaluating DTI metrics may also impact the validity of the FA measurements. Mean FA within a white matter bundle can be measured using a variety of methods, including manual tracing of a region of interest (ROI), automated segmentation of an ROI, voxel-based analysis, and tract-based spatial statistics.[60] Template-based approaches may not be possible in patients with severe TBI due to acute tissue shifts and chronic atrophy, which may preclude automatic segmentation of white matter tracts.

Diffusion Tensor Tractography

The development of diffusion tensor tractography by Mori,[61] Jones,[62] Basser,[63] and others in the late 1990s provided the opportunity for *in vivo* 3-dimensional analysis of white matter connectivity in the human brain. The principle upon which tractography is based is that as long as the primary diffusion directions of the tensors in adjacent voxels are directionally coherent, these tensors can be modeled as being part of a single fiber tract. A fiber tract can therefore be conceptualized as a “streamline” of connected vectors along a single deterministic path, hence the term “deterministic streamline tractography.” Fiber tracts are typically generated by manually tracing or automatically segmenting a white matter ROI, such as the corpus callosum, and then using this ROI as a seed for the generation of 3-dimensional fiber tracts passing through it. It is important to emphasize that tractography is an inferential technique in which white matter tracts are reconstructed on the basis of water diffusion measurements. The number of axons that corresponds to a single fiber tract is unknown and is affected by data acquisition parameters, particularly the spatial resolution (i.e. voxel size). Although studies have begun to validate tractography with “gold-standard” histopathology results in human spinal cord and brain specimens,[64, 65] tractography results should be interpreted with caution given the inherent limitations of the technique.[66]

The application of diffusion tensor tractography to the study of TAI is based on the ability of tractography to identify alterations in white matter connectivity, as well as changes in the mean FA, number of fiber tracts, average tract length, and total volume of a white matter bundle. Wang and colleagues found that early diffusion

tensor tractography (mean day 7) identified fiber tract damage in the corpus callosum, fornix, and cerebral peduncle projections, as measured by lower mean FA, fiber volume, and/or fiber number, in 12 patients with severe TBI as compared to age- and gender-matched controls.[67] Furthermore, mean FA, fiber number and fiber length in the corpus callosum correlated with TBI patients' functional outcome scores on the GOSE at a mean follow-up of 8 months. A longitudinal study by the same laboratory involving 28 patients with TBI demonstrated that diffusion tensor tractography identifies changes in structural connectivity between the acute (day 0-9) and chronic (6-14 month) periods, and that DTI measurements of structural connectivity in both the acute and chronic periods predicted patient performance on a variety of neurocognitive tests.[68] In another diffusion tensor tractography study performed at 8 months post-TBI, grey matter atrophy correlated with the presence of damage in associated white matter tracts (i.e. hippocampal volume correlated with mean FA in the fornix).[69] These correlations between the spatial extent of grey matter injury and the degree of damage to associated white matter bundles are consistent with recent histopathological analyses linking cortical atrophy to TAI-related damage in underlying white matter.[70]

Newcombe and colleagues provided additional support for the utility of diffusion tensor tractography as a diagnostic and prognostic tool in TBI by showing that patients in post-traumatic vegetative state (VS) have a different pattern of white matter injury than patients in post-anoxic VS.[71] Specifically, tractography demonstrated preferential damage of brainstem fiber tracts, a finding that is consistent with histopathological and biomechanical studies showing that the brainstem is susceptible to rotational shear-strain forces in severe TBI.[72-75] Similarly, tractography studies of moderate and severe TBI patients indicate that the corpus callosum, which is also known to be susceptible to shear-strain forces in TAI,[72] undergoes volume loss, shortening of fiber tracts, a decrease in mean FA and a decline in total tract number in the subacute and chronic stages of injury.[45, 76, 77] Finally, a recent study of 52 patients with disorders of consciousness (32 with severe TBI) by Fernandez-Espejo and colleagues demonstrated that tractography-based measurements of connectivity within the default mode network (DMN), a brain network believed to be involved in self-awareness, correlated with patients' levels of consciousness on behavioral testing[78] (see resting-state fMRI section below for additional DMN studies in severe TBI). This tractography analysis suggests that structural connectivity data may provide critical information about the brain's potential for conscious awareness in patients with traumatic disorders of consciousness.

Yet despite preliminary evidence that diffusion tensor tractography may be used to detect TAI and predict outcomes in patients with TBI, major obstacles and challenges to clinical implementation remain. The results of any tractography analysis depend upon the data acquisition and post-processing parameters, and therefore tractography results must always be interpreted in the context of the analytic techniques that are being utilized. Several of these methodological factors have been discussed above in the section on DTI, but there are additional considerations that are unique to diffusion tensor tractography. For example, the number and neuroanatomic location of fiber tract disruptions reflect tract termination criteria (e.g. angle threshold between adjacent vectors and FA threshold within individual voxels) that are chosen by the tractographer, since there is not a standardized set of tractography methods accepted in the field. As a result, any tractography analysis may be susceptible to false tract disruptions and non-physiologic tract connections between regions that do not in fact connect with each other.

4) Advanced Functional Imaging Techniques
Resting State Functional MRI (rs-fMRI)
The observation that spontaneous, temporally correlated fluctuations in brain activity occur in functionally related brain regions at rest, and that these regions are deactivated during goal-directed cognitive tasks, has led to the concept of "resting state networks" in the human brain. These resting state networks include the DMN,[79-82] salience network,[83] thalamocortical networks,[84] and the executive control network.[83] Functional connectivity is defined by temporal correlations in low frequency (<0.1 Hz) spontaneous fluctuations of the blood oxygen level-dependent (BOLD) signal.[85-87] Hence, the functional connectivity of the DMN can be investigated by analyzing BOLD fluctuations within the grey matter nodes of the DMN, which include the posterior cingulate/retrosplenial cortex, precuneus, medial prefrontal cortex, inferior parietal lobule, and hippocampal formation.[88, 89] From a methodological standpoint, rs-fMRI network connectivity can be analyzed using a variety of approaches, such as independent component analysis or seed-based (i.e. ROI) techniques.[90-92]

Recent studies have demonstrated that rs-fMRI measurements of DMN connectivity are altered by TBI.[93-101] Moreover, functional connectivity of cortical nodes within the DMN, as measured by rs-fMRI, correlates with structural injury in the white matter pathways connecting these nodes, as measured by DTI.[95, 97, 99, 101] These correlative rs-fMRI/DTI findings suggest that the integration of advanced imaging techniques may enable

individualized assessments of structural white matter disconnections and their corresponding functional alterations in grey matter. Furthermore, Vanhaudenhuyse and colleagues demonstrated that the degree of DMN connectivity determined by rs-fMRI correlates with a patient's level of consciousness during recovery from severe TBI.[102] Although the prognostic utility of early DMN connectivity analysis has yet to be demonstrated in patients with severe TBI, the correlation of DMN connectivity with concurrent states of consciousness provides the basis for future prognostication studies.

There are several important limitations to the rs-fMRI technique that should be considered. First, administration of sedatives in patients with acute severe TBI may confound rs-fMRI connectivity analyses, as demonstrated by Boveroux and colleagues in their analysis of resting state networks in subjects receiving propofol.[103] Second, the BOLD signal that is used as a surrogate for neural activity in rs-fMRI studies is affected by a variety of physiological parameters, including cerebral blood flow (CBF), blood volume and oxygen consumption, and therefore the BOLD signal is not necessarily a direct measure of neuronal activity. Third, the BOLD signal reflects changes in venous blood oxygenation that cannot be quantified in an absolute manner or with physiologic units; rather, changes in the BOLD signal are defined in relative terms or using statistical models. Fourth, there are potential sources of artifact in the rs-fMRI signal that are not related to neuronal activity or cerebrovacular hemodynamics. These include the behavioral state of the patient (i.e. eyes closed, eyes open and inattentive, or eyes open and fixated on a visual target),[104] as well as hardware noise.[105] It is therefore important that data be acquired under similar conditions when comparing results across cohorts. The Common Data Elements guidelines include a discussion of rs-fMRI techniques and their application to TBI, but rs-fMRI is not included in its current protocols.[1]

Stimulus- and Task-Based fMRI

The discovery that BOLD signal changes can be detected in the brain during stimulus- and task-related fMRI experiments has significantly advanced the study of human brain function. Since the discovery of BOLD fMRI by Kwong, Ogawa, and others in 1992,[106, 107] fMRI has rapidly overtaken PET, SPECT, EEG, and MEG as the most commonly used technique for evaluating brain function.[108] Functional MRI has recently been used to identify abnormal brain activation patterns in TBI patients with a variety of neurocognitive and behavioral deficits, including memory impairment[101, 109] and motor dysfunction.[110] Palacios and colleagues demonstrated that BOLD signal changes during an "n-back" memory paradigm correlated with working memory performance in patients in the chronic stage of severe TBI.[101] Newsome and colleagues observed in a cohort of adolescents (age 12 to 19 years) with chronic moderate-to-severe TBI that during a perspective-taking task (i.e. thinking of the self from a third-person perspective), TBI patients experienced BOLD signal changes in regions such as the cuneus and parahippocampal gyrus that are not activated in controls.[111] These fMRI brain activation patterns were present despite the fact that patients exhibited normal performance scores on neurocognitive tests conducted outside the MRI scanner. Functional MRI may therefore have the potential to elucidate the biological mechanisms involved in neuroplasticity, as BOLD activation patterns reveal the neural pathways responsible for recovery of function after TBI.[65, 112]

Task-based fMRI studies have also demonstrated that some patients diagnosed with VS or minimally conscious state (MCS) after severe TBI have fMRI activation patterns that are similar to those of healthy control subjects. In the largest such study to date, Monti and colleagues found that 5 of 54 patients with disorders of consciousness (23 in VS and 31 in MCS; 33 with severe TBI) could willfully modulate their brain responses to motor and spatial imagery paradigms (all five patients had TBI as the etiology of their altered consciousness). Furthermore, a single subject in traumatic VS was able to consistently communicate "yes" and "no" responses by performing specific imagery tasks while in the MRI scanner.[241] These findings build upon prior observations by Schiff and colleagues that patients with disorders of consciousness due to severe TBI may possess regions of preserved cerebral metabolism, or "islands" of neural network activity, which persist despite catastrophic brain injury.[212]

5) Future Directions – Multimodal Data Integration and Clinical Implementation

Major methodological hurdles remain and significant additional research is needed before several of the advanced imaging techniques discussed in this syllabus will be incorporated into clinical practice. Nevertheless, just as conventional MRI has been shown to be superior to CT in providing clinically useful diagnostic and prognostic data for patients with severe TBI, there is a growing body of evidence that advanced neuroimaging techniques may surpass conventional MRI in their clinical utility. The challenge that will thus confront clinicians in coming years is how to best incorporate data from these novel techniques into clinical practice. The results of advanced imaging techniques will only be useful if they are organized into readily interpretable, easily visualized data elements. Clinicians will need to play an active role in shaping the manner in which data is visually

represented to them. This effort will be especially important when one considers that no single technique is likely to provide all of the diagnostic and prognostic data that are needed to make well informed clinical decisions. Rather, the data reviewed in this syllabus suggest that a multimodal approach that integrates data from structural and functional imaging techniques may have the best potential to improve care for patients with severe TBI.

References

1. Haacke EM, Duhaime AC, Gean AD, et al. Common data elements in radiologic imaging of traumatic brain injury. J Magn Reson Imaging 2010;32:516-543.
2. Duhaime AC, Gean AD, Haacke EM, et al. Common data elements in radiologic imaging of traumatic brain injury. Arch Phys Med Rehabil 2010;91:1661-1666.
3. Marshall LF, Marshall SB, Klauber MR, et al. A new classification of head injury based on computerized tomography. J Neurosurg 1991;75:S14-S20.
4. Maas AI, Hukkelhoven CW, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. Neurosurgery 2005;57:1173-1182; discussion 1173-1182.
5. Murray GD, Butcher I, McHugh GS, et al. Multivariable prognostic analysis in traumatic brain injury: results from the IMPACT study. J Neurotrauma 2007;24:329-337.
6. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS medicine 2008;5:e165; discussion e165.
7. Perel P, Arango M, Clayton T, et al. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. BMJ 2008;336:425-429.
8. Nelson DW, Nystrom H, MacCallum RM, et al. Extended analysis of early computed tomography scans of traumatic brain injured patients and relations to outcome. J Neurotrauma 2010;27:51-64.
9. Yuh EL, Cooper SR, Ferguson AR, Manley GT. Quantitative CT improves outcome prediction in acute traumatic brain injury. J Neurotrauma 2012;29:735-746.
10. Firsching R, Woischneck D, Diedrich M, et al. Early magnetic resonance imaging of brainstem lesions after severe head injury. J Neurosurg 1998;89:707-712.
11. Paterakis K, Karantanas AH, Komnos A, Volikas Z. Outcome of patients with diffuse axonal injury: the significance and prognostic value of MRI in the acute phase. J Trauma 2000;49:1071-1075.
12. Gentry LR, Godersky JC, Thompson B, Dunn VD. Prospective comparative study of intermediate-field MR and CT in the evaluation of closed head trauma. AJR Am J Roentgenol 1988;150:673-682.
13. Lee H, Wintermark M, Gean AD, Ghajar J, Manley GT, Mukherjee P. Focal lesions in acute mild traumatic brain injury and neurocognitive outcome: CT versus 3T MRI. J Neurotrauma 2008;25:1049-1056.
14. Skandsen T, Kvistad KA, Solheim O, Lydersen S, Strand IH, Vik A. Prognostic value of magnetic resonance imaging in moderate and severe head injury: a prospective study of early MRI findings and one-year outcome. J Neurotrauma 2011;28:691-699.
15. Lagares A, Ramos A, Perez-Nunez A, et al. The role of MR imaging in assessing prognosis after severe and moderate head injury. Acta neurochirurgica 2009;151:341-356.
16. Betz J, Zhuo J, Roy A, Shanmuganathan K, Gullapalli RP. Prognostic value of diffusion tensor imaging parameters in severe traumatic brain injury. J Neurotrauma 2012;29:1292-1305.
17. Schlaug G, Siewert B, Benfield A, Edelman RR, Warach S. Time course of the apparent diffusion coefficient (ADC) abnormality in human stroke. Neurology 1997;49:113-119.
18. Liu AY, Maldjian JA, Bagley LJ, Sinson GP, Grossman RI. Traumatic brain injury: diffusion-weighted MR imaging findings. AJNR Am J Neuroradiol 1999;20:1636-1641.
19. Muccio CF, De Simone M, Esposito G, De Blasio E, Vittori C, Cerase A. Reversible post-traumatic bilateral extensive restricted diffusion of the brain. A case study and review of the literature. Brain Inj 2009;23:466-472.
20. Edlow BL, Giacino JT, Hirschberg RE, Gerrard J, Wu O, Hochberg LR. Unexpected recovery of function after severe traumatic brain injury: the limits of early neuroimaging-based outcome prediction. Neurocritical care 2013;19:364-375.
21. Maxwell WL, Povlishock JT, Graham DL. A mechanistic analysis of nondisruptive axonal injury: a review. J Neurotrauma 1997;14:419-440.
22. Ommaya AK. Head injury mechanisms and the concept of preventive management: a review and critical synthesis. J Neurotrauma 1995;12:527-546.
23. Gentry LR. Imaging of closed head injury. Radiology 1994;191:1-17.

24. Scheid R, Preul C, Gruber O, Wiggins C, von Cramon DY. Diffuse axonal injury associated with chronic traumatic brain injury: evidence from T2*-weighted gradient-echo imaging at 3 T. AJNR Am J Neuroradiol 2003;24:1049-1056.
25. Tong KA, Ashwal S, Holshouser BA, et al. Diffuse axonal injury in children: clinical correlation with hemorrhagic lesions. Ann Neurol 2004;56:36-50.
26. Geurts BH, Andriessen TM, Goraj BM, Vos PE. The reliability of magnetic resonance imaging in traumatic brain injury lesion detection. Brain Inj 2012.
27. Yanagawa Y, Tsushima Y, Tokumaru A, et al. A quantitative analysis of head injury using T2*-weighted gradient-echo imaging. J Trauma 2000;49:272-277.
28. Scheid R, Walther K, Guthke T, Preul C, von Cramon DY. Cognitive sequelae of diffuse axonal injury. Arch Neurol 2006;63:418-424.
29. Niogi SN, Mukherjee P, Ghajar J, et al. Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. AJNR Am J Neuroradiol 2008;29:967-973.
30. Reichenbach JR, Venkatesan R, Schillinger DJ, Kido DK, Haacke EM. Small vessels in the human brain: MR venography with deoxyhemoglobin as an intrinsic contrast agent. Radiology 1997;204:272-277.
31. Haacke EM, Xu Y, Cheng YC, Reichenbach JR. Susceptibility weighted imaging (SWI). Magn Reson Med 2004;52:612-618.
32. Tong KA, Ashwal S, Holshouser BA, et al. Hemorrhagic shearing lesions in children and adolescents with posttraumatic diffuse axonal injury: improved detection and initial results. Radiology 2003;227:332-339.
33. Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol 2009;8:165-174.
34. Cordonnier C, Al-Shahi Salman R, Wardlaw J. Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting. Brain 2007;130:1988-2003.
35. Scheid R, Ott DV, Roth H, Schroeter ML, von Cramon DY. Comparative magnetic resonance imaging at 1.5 and 3 Tesla for the evaluation of traumatic microbleeds. J Neurotrauma 2007;24:1811-1816.
36. Nandigam RN, Viswanathan A, Delgado P, et al. MR imaging detection of cerebral microbleeds: effect of susceptibility-weighted imaging, section thickness, and field strength. AJNR Am J Neuroradiol 2009;30:338-343.
37. Pierpaoli C, Basser PJ. Toward a quantitative assessment of diffusion anisotropy. Magn Reson Med 1996;36:893-906.
38. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B 1996;111:209-219.
39. Basser PJ, Mattiello J, Le Bihan D. Estimation of the Effective Self-Diffusion Tensor from the NMR Spin Echo. J Magn Reson B 1994;103:247-254.
40. Basser PJ, Jones DK. Diffusion-tensor MRI: theory, experimental design and data analysis - a technical review. NMR Biomed 2002;15:456-467.
41. Mac Donald CL, Dikranian K, Song SK, Bayly PV, Holtzman DM, Brody DL. Detection of traumatic axonal injury with diffusion tensor imaging in a mouse model of traumatic brain injury. Exp Neurol 2007;205:116-131.
42. Li J, Li XY, Feng DF, Gu L. Quantitative evaluation of microscopic injury with diffusion tensor imaging in a rat model of diffuse axonal injury. Eur J Neurosci 2011;33:933-945.
43. Huisman TA, Schwamm LH, Schaefer PW, et al. Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. AJNR Am J Neuroradiol 2004;25:370-376.
44. Newcombe V, Chatfield D, Outtrim J, et al. Mapping traumatic axonal injury using diffusion tensor imaging: correlations with functional outcome. PLoS One 2011;6:e19214.
45. Xu J, Rasmussen IA, Lagopoulos J, Haberg A. Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. J Neurotrauma 2007;24:753-765.
46. Sidaros A, Engberg AW, Sidaros K, et al. Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. Brain 2008;131:559-572.
47. Tollard E, Galanaud D, Perlbarg V, et al. Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: Preliminary results. Crit Care Med 2009;37:1448-1455.
48. Perlbarg V, Puybasset L, Tollard E, Lehericy S, Benali H, Galanaud D. Relation between brain lesion location and clinical outcome in patients with severe traumatic brain injury: a diffusion tensor imaging study using voxel-based approaches. Hum Brain Mapp 2009;30:3924-3933.
49. Palacios EM, Fernandez-Espejo D, Junque C, et al. Diffusion tensor imaging differences relate to memory deficits in diffuse traumatic brain injury. BMC neurology 2011;11:24.
50. Galanaud D, Perlbarg V, Gupta R, et al. Assessment of white matter injury and outcome in severe brain trauma: a prospective multicenter cohort. Anesthesiology 2012;117:1300-1310.

51. Niogi SN, Mukherjee P, Ghajar J, et al. Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury. Brain 2008;131:3209-3221.
52. Lipton ML, Gulko E, Zimmerman ME, et al. Diffusion-Tensor Imaging Implicates Prefrontal Axonal Injury in Executive Function Impairment Following Very Mild Traumatic Brain Injury. Radiology 2009;252:816-824.
53. Salat D, Ward A, Kaye JA, Janowsky JS. Sex differences in the corpus callosum with aging. Neurobiology of aging 1997;18:191-197.
54. Salat DH, Tuch DS, Greve DN, et al. Age-related alterations in white matter microstructure measured by diffusion tensor imaging. Neurobiology of aging 2005;26:1215-1227.
55. Edlow BL, Copen WA, Izzy S, et al. Diffusion tensor imaging in acute-to-subacute traumatic brain injury: a longitudinal analysis. BMC neurology 2016;16:2.
56. Jones DK. The effect of gradient sampling schemes on measures derived from diffusion tensor MRI: a Monte Carlo study. Magn Reson Med 2004;51:807-815.
57. Reese TG, Benner T, Wang R, Feinberg DA, Wedeen VJ. Halving imaging time of whole brain diffusion spectrum imaging and diffusion tractography using simultaneous image refocusing in EPI. J Magn Reson Imaging 2009;29:517-522.
58. Setsompop K, Gagoski BA, Polimeni JR, Witzel T, Wedeen VJ, Wald LL. Blipped-controlled aliasing in parallel imaging for simultaneous multislice echo planar imaging with reduced g-factor penalty. Magn Reson Med 2012;67:1210-1224.
59. Setsompop K, Cohen-Adad J, Gagoski BA, et al. Improving diffusion MRI using simultaneous multi-slice echo planar imaging. Neuroimage 2012;63:569-580.
60. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006;31:1487-1505.
61. Mori S, Crain BJ, Chacko VP, van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol 1999;45:265-269.
62. Jones DK, Simmons A, Williams SC, Horsfield MA. Non-invasive assessment of axonal fiber connectivity in the human brain via diffusion tensor MRI. Magn Reson Med 1999;42:37-41.
63. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. Magn Reson Med 2000;44:625-632.
64. Hansen B, Flint JJ, Heon-Lee C, et al. Diffusion tensor microscopy in human nervous tissue with quantitative correlation based on direct histological comparison. Neuroimage 2011;57:1458-1465.
65. Laureys S, Schiff ND. Coma and consciousness: paradigms (re)framed by neuroimaging. Neuroimage 2012;61:478-491.
66. Thomas C, Ye FQ, Irfanoglu MO, et al. Anatomical accuracy of brain connections derived from diffusion MRI tractography is inherently limited. Proc Natl Acad Sci U S A 2014;111:16574-16579.
67. Wang JY, Bakhadirov K, Devous MD, Sr., et al. Diffusion tensor tractography of traumatic diffuse axonal injury. Arch Neurol 2008;65:619-626.
68. Wang JY, Bakhadirov K, Abdi H, et al. Longitudinal changes of structural connectivity in traumatic axonal injury. Neurology 2011;77:818-826.
69. Warner MA, Marquez de la Plata C, Spence J, et al. Assessing spatial relationships between axonal integrity, regional brain volumes, and neuropsychological outcomes after traumatic axonal injury. J Neurotrauma 2010;27:2121-2130.
70. Maxwell WL, MacKinnon MA, Stewart JE, Graham DI. Stereology of cerebral cortex after traumatic brain injury matched to the Glasgow outcome score. Brain 2010;133:139-160.
71. Newcombe VF, Williams GB, Scoffings D, et al. Aetiological differences in neuroanatomy of the vegetative state: insights from diffusion tensor imaging and functional implications. J Neurol Neurosurg Psychiatry 2010;81:552-561.
72. Adams JH, Doyle D, Ford I, Gennarelli TA, Graham DI, McLellan DR. Diffuse axonal injury in head injury: definition, diagnosis and grading. Histopathology 1989;15:49-59.
73. Ommaya AK, Gennarelli TA. Cerebral concussion and traumatic unconsciousness. Correlation of experimental and clinical observations of blunt head injuries. Brain 1974;97:633-654.
74. Gennarelli TA, Thibault LE, Adams JH, Graham DI, Thompson CJ, Marcincin RP. Diffuse axonal injury and traumatic coma in the primate. Ann Neurol 1982;12:564-574.
75. Smith DH, Nonaka M, Miller R, et al. Immediate coma following inertial brain injury dependent on axonal damage in the brainstem. J Neurosurg 2000;93:315-322.
76. Rutgers DR, Fillard P, Paradot G, Tadie M, Lasjaunias P, Ducreux D. Diffusion tensor imaging characteristics of the corpus callosum in mild, moderate, and severe traumatic brain injury. AJNR Am J Neuroradiol 2008;29:1730-1735.

77. Singh M, Jeong J, Hwang D, Sungkarat W, Gruen P. Novel diffusion tensor imaging methodology to detect and quantify injured regions and affected brain pathways in traumatic brain injury. Magn Reson Imaging 2010;28:22-40.
78. Fernandez-Espejo D, Soddu A, Cruse D, et al. A role for the default mode network in the bases of disorders of consciousness. Ann Neurol 2012;72:335-343.
79. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A 2001;98:676-682.
80. Raichle ME, Snyder AZ. A default mode of brain function: a brief history of an evolving idea. Neuroimage 2007;37:1083-1090; discussion 1097-1089.
81. Shulman GL, Fiez JA, Corbetta M, et al. Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. J Cogn Neurosci 1997;9:648-663.
82. Binder JR, Frost JA, Hammeke TA, Bellgowan PS, Rao SM, Cox RW. Conceptual processing during the conscious resting state. A functional MRI study. J Cogn Neurosci 1999;11:80-95.
83. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007;27:2349-2356.
84. Tang L, Ge Y, Sodickson DK, et al. Thalamic resting-state functional networks: disruption in patients with mild traumatic brain injury. Radiology 2011;260:831-840.
85. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 2005;102:9673-9678.
86. Vincent JL, Snyder AZ, Fox MD, et al. Coherent spontaneous activity identifies a hippocampal-parietal memory network. Journal of neurophysiology 2006;96:3517-3531.
87. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995;34:537-541.
88. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008;1124:1-38.
89. Fransson P, Marrelec G. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. Neuroimage 2008;42:1178-1184.
90. Fox MD, Greicius M. Clinical applications of resting state functional connectivity. Frontiers in systems neuroscience 2010;4:19.
91. Beckmann CF, Smith SM. Probabilistic independent component analysis for functional magnetic resonance imaging. IEEE Trans Med Imaging 2004;23:137-152.
92. Boly M, Phillips C, Tshibanda L, et al. Intrinsic brain activity in altered states of consciousness: how conscious is the default mode of brain function? Ann N Y Acad Sci 2008;1129:119-129.
93. Johnson B, Zhang K, Gay M, et al. Alteration of brain default network in subacute phase of injury in concussed individuals: resting-state fMRI study. Neuroimage 2012;59:511-518.
94. Zhang K, Johnson B, Gay M, et al. Default mode network in concussed individuals in response to the YMCA physical stress test. J Neurotrauma 2012;29:756-765.
95. Sharp DJ, Beckmann CF, Greenwood R, et al. Default mode network functional and structural connectivity after traumatic brain injury. Brain 2011;134:2233-2247.
96. Hillary FG, Slocomb J, Hills EC, et al. Changes in resting connectivity during recovery from severe traumatic brain injury. International journal of psychophysiology : official journal of the International Organization of Psychophysiology 2011;82:115-123.
97. Bonnelle V, Leech R, Kinnunen KM, et al. Default mode network connectivity predicts sustained attention deficits after traumatic brain injury. J Neurosci 2011;31:13442-13451.
98. Mayer AR, Mannell MV, Ling J, Gasparovic C, Yeo RA. Functional connectivity in mild traumatic brain injury. Hum Brain Mapp 2011;32:1825-1835.
99. Bonnelle V, Ham TE, Leech R, et al. Salience network integrity predicts default mode network function after traumatic brain injury. Proc Natl Acad Sci U S A 2012;109:4690-4695.
100. Stevens MC, Lovejoy D, Kim J, Oakes H, Kureshi I, Witt ST. Multiple resting state network functional connectivity abnormalities in mild traumatic brain injury. Brain imaging and behavior 2012;6:293-318.
101. Palacios EM, Sala-Llonch R, Junque C, et al. White matter integrity related to functional working memory networks in traumatic brain injury. Neurology 2012;78:852-860.
102. Vanhaudenhuyse A, Noirhomme Q, Tshibanda LJ, et al. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Brain 2010;133:161-171.
103. Boveroux P, Vanhaudenhuyse A, Bruno MA, et al. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. Anesthesiology 2010;113:1038-1053.

104. Yan C, Liu D, He Y, et al. Spontaneous brain activity in the default mode network is sensitive to different resting-state conditions with limited cognitive load. PLoS One 2009;4:e5743.
105. Jo HJ, Saad ZS, Simmons WK, Milbury LA, Cox RW. Mapping sources of correlation in resting state FMRI, with artifact detection and removal. Neuroimage 2010;52:571-582.
106. Kwong KK, Belliveau JW, Chesler DA, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci U S A 1992;89:5675-5679.
107. Ogawa S, Tank DW, Menon R, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci U S A 1992;89:5951-5955.
108. Smith K. Brain imaging: fMRI 2.0. Nature 2012;484:24-26.
109. Kasahara M, Menon DK, Salmond CH, et al. Traumatic brain injury alters the functional brain network mediating working memory. Brain Inj 2011;25:1170-1187.
110. Kasahara M, Menon DK, Salmond CH, et al. Altered functional connectivity in the motor network after traumatic brain injury. Neurology 2010;75:168-176.
111. Newsome MR, Scheibel RS, Hanten G, et al. Brain activation while thinking about the self from another person's perspective after traumatic brain injury in adolescents. Neuropsychology 2010;24:139-147.
112. Edlow BL, Giacino JT, Wu O. Functional MRI and outcome in traumatic coma. Current neurology and neuroscience reports 2013;13:375.