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Advances in neuroimaging of traumatic brain injury and posttraumatic stress disorder

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Abstract—Improved diagnosis and treatment of traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) are needed for our military and veterans, their families, and society at large. Advances in brain imaging offer important biomarkers of structural, functional, and metabolic information concerning the brain. This article reviews the application of various imaging techniques to the clinical problems of TBI and PTSD. For TBI, we focus on findings and advances in neuroimaging that hold promise for better detection, characterization, and monitoring of objective brain changes in symptomatic patients with combat-related, closed-head brain injuries not readily apparent by standard computed tomography or conventional magnetic resonance imaging techniques.

Key words: diagnosis, diffusion tensor imaging, fMRI, neuroimaging, OIF/OEF, posttraumatic stress disorder, PTSD, TBI, traumatic brain injury, veterans.

Abbreviations: Aβ = amyloid-β; ACC = anterior cingulate cortex; ACR = anterior corona radiata; AD = Alzheimer disease; ADC = Apparent Diffusion Coefficient; ADNI = Alzheimer's Disease Neuroimaging Initiative; ANT = Attention Network Task; ASL = arterial spin labeling; BOLD = blood oxygen dependent level; CA = cornu ammonis; CAPS = Clinician-Administered PTSD Scale; CBF = cerebral blood flow; CBT = cognitive-behavior therapy; Cho = choline; CNS = central nervous system; Cr = creatine; CT = computed tomography; DG = dentate gyrus; D-MRI = diffusion magnetic resonance imaging; DTI = diffusion tensor imaging; EPI = echo-planar imaging; FA = fractional anisotropy; FDG = fluorodeoxyglucose; fMRI = functional magnetic resonance imaging; LDFR = long-delay free recall; mI = myo-inositol; MR = magnetic resonance; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; MRSI = magnetic resonance spectroscopic imaging; NAA = N-acetylaspartate; OIF/OEF = Operation Iraqi Freedom/Operation Enduring Freedom; PCS = postconcussion syndrome;

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Abbreviations (continued): PET = positron emission tomography; PIB = Pittsburgh Compound B; PTSD = posttraumatic stress disorder; PW-MRI = perfusion-weighted magnetic resonance imaging; QA = quality assurance; rCBV = regional cerebral blood volume; ROI = region of interest; RT = reaction time; SNR = signal-to-noise ratio; SPECT = single photon emission computed tomography; SWI = susceptibility-weighted imaging; TBI = traumatic brain injury; UCSF = University of California, San Francisco; UF = uncinate fasciculus.

TRAUMATIC BRAIN INJURY AND POSTTRAUMATIC STRESS DISORDER: "INVISIBLE WOUNDS"

Improved diagnosis and treatment of traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) are needed for our military and veterans, their families, and society at large. According to a RAND Corporation study based on screening questionnaire data, nearly one out of five Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) servicemembers (300,000) are estimated to experience symptoms of PTSD or depression and more than 320,000 OIF/OEF servicemembers have sustained a TBI [1]. Similarly, 23 percent (907/3,973) of a returning brigade combat team were clinician-identified to have a history of TBI [2].

The majority of cases of TBI in civilian and combat-related settings are categorized as "mild," a category based primarily on the characteristics of the acute sequelae following the injury. The criteria for the classification of mild can vary, but the Department of Defense/Department of Veterans Affairs March 2009 Clinical Practice Guideline has adopted the following criteria: (1) brief loss of consciousness (30 minutes or less), (2) brief alteration of consciousness (up to 24 hours), (3) posttraumatic amnesia for 0 to 1 days, or (4) Glasgow Coma Score (best score within the first 24 hours) of 13 to 15 (15 = normal), and (5) a normal-appearing brain on computed tomography (CT) scan [344].

In contrast to civilian TBIs due to falls, sports, etc., nearly 70 percent of combated-related TBIs are a result of blast "plus" injuries, i.e., the effects of blast plus another modality [3]. In mild TBI, the underlying pathology is not well understood and the lesion(s) may be subtle, scattered, varied, and, as indicated above, not detected on conventional brain CT studies. Further diagnostic challenges are posed by virtue of the varied and nonspecific postconcussion symptoms (e.g., concentration problems, irritability, headaches) that are also found in PTSD, depression, sleep disorders, or in otherwise healthy persons. However, improving the sensitivity of neuroimaging to subtle brain perturbations and combining these objective measures with careful clinical characterization of patients may facilitate better understanding of the neural bases and treatment of the signs and symptoms of mild TBI.

For combat-related PTSD, the clinical manifestations include not only intrusive recurrent memories and hypervigilance but also nonspecific symptoms, including insomnia, concentration difficulties, irritability, impaired decision-making abilities, and memory problems. Moreover, overlap of symptoms and the comorbidities of PTSD, TBI, depression, and their sequelae (e.g., sleep deprivation, drug or alcohol abuse) make assessment, diagnosis, and management of these patients very difficult. As in the case of TBI, objective and specific biological or anatomical markers would be invaluable in the diagnosis of PTSD. Neuroimaging assays could also aid in the monitoring and evaluation of treatment approaches. In addition, these data may also provide information on brain vulnerability to subsequent injury and help establish guidelines for safe return to duty.

Brain imaging offers an important class of biomarkers because of its ability to obtain structural, functional, and metabolic information concerning the brain with various X-ray CT, magnetic resonance (MR) imaging (MRI), and positron emission tomography (PET) scanning techniques. CT remains an extremely valuable and the most commonly utilized imaging modality. It is very sensitive to fractures of the skull and facial bones and can rapidly assess the possible need for urgent neurosurgical interventions, such as evacuation of hematomas [4]. MRI has exquisite soft-tissue contrast and also can measure function and metabolism. Various PET scanning techniques can measure brain function and amyloid deposition.

This article reviews the application of various imaging techniques to the clinical problems of TBI and PTSD. For TBI, we focus on findings and advances in neuroimaging that hold promise for better detection, characterization, and monitoring of objective brain changes in symptomatic patients with combat-related, closed-head brain injuries not readily apparent by standard CT or conventional MRI techniques.

OVERVIEW: NEUROIMAGING IN TRAUMATIC BRAIN INJURY

Advanced neuroimaging techniques are finding increased use in the study of TBI. Whereas CT and standard

MRI structural images can readily demonstrate large focal contusions or bleeds, diffuse axonal injury may be detected indirectly by brain volume loss (volumetric analysis) or diffusion tensor imaging (DTI). DTI studies have shown reductions in fractional anisotropy (FA) at sites of traumatic axonal shearing injury, corresponding to a loss of microstructural fiber integrity, resulting in the reduced directionality of microscopic water motion [5–6]. More recently, an increasing number of DTI studies in TBI have been emerging [5–33], a few of which also indicate correlations between DTI findings and neurocognition [10,32,34]. Several studies have confirmed the potential of single-voxel proton MR spectroscopy (^{1}H-MRS or MRS) for the detection of neuronal injury following TBI [35–44]. One common finding includes altered metabolite concentrations in regions that appear normal on structural MR images, suggesting widespread and diffuse tissue damage. In particular, studies using single-voxel techniques have shown a significant correlation between unfavorable clinical outcome and reduced N-acetylaspartate (NAA), a marker of neuronal integrity [40,45–47], and increased choline (Cho) [45,47–48]. Proton MR spectroscopic imaging (MRSI) is a technique similar to MRS, except instead of acquiring data from a single region or voxel, spectroscopic information is collected from multiple voxels during the same imaging acquisition. MRSI, like MRS, has been found useful in the detection of metabolic abnormalities that predict outcome [36]. In addition, a few investigators have studied relationships between metabolic and neurocognitive effects with the use of MRS [49–50] and MRSI [42]. Susceptibility-weighted imaging (SWI) has been applied on a clinical 1.5 T MRI scanner in several studies of pediatric TBI [41,51–53]. These studies demonstrated that SWI allows detection of hemorrhagic lesions in children with TBI with significantly higher sensitivity than conventional gradient-echo MRI [52]. The number and volume of hemorrhagic lesions correlated with the Glasgow Coma Scale score [54] as well as with other clinical measures of TBI severity and with outcome at 6 to 12 months postinjury [53]. Significant differences were detected between children with normal outcome or mild disability and children with moderate or severe disability when regional injury was compared with clinical variables [53]. In addition, negative correlations between lesion number and volume with measures of neuropsychological functioning at 1 to 4 years postinjury were demonstrated [41]. Studies using functional MRI (fMRI) in patients with TBI show abnormal patterns of brain activation in patients compared with healthy control subjects [55–73]. While dynamic contrast-enhanced perfusion-weighted MRI (PW-MRI) has shown that regions of both normal-appearing and contused brain may have an abnormal regional cerebral blood volume (rCBV) and that alterations in rCBV may play a role in determining the clinical outcome of patients [74], to our knowledge, no studies using arterial spin labeling PW-MRI in TBI have been published to date. PET studies in TBI demonstrate that early reductions in cerebral perfusion can result in cerebral ischemia that is associated with poor outcome [75–82]. Finally, a potential new avenue of research in TBI involves imaging amyloid plaque depositions in TBI, particularly using Pittsburgh Compound B (PIB). Currently, no published studies have employed imaging with PIB in combat-related TBI.

OVERVIEW: NEUROIMAGING IN POSTTRAUMATIC STRESS DISORDER

Brain imaging studies in PTSD have implicated a circuit of brain regions, including the hippocampus, prefrontal cortex (including anterior cingulate), and amygdala, in the symptoms of PTSD.

Numerous studies used structural MRI to show smaller volume of the hippocampus and/or used MRS to show reduced NAA in the hippocampus, a brain area that mediates verbal declarative memory [83–100]. However, some studies of adults did not show smaller hippocampal volume to be specific to PTSD [101–103] and studies in children have not found smaller hippocampal volume to be associated with PTSD [104–106]. Results are mixed regarding whether new onset or recent PTSD is associated with smaller hippocampal volumes [107–109]. Two meta-analyses pooled data from all the published studies and found smaller hippocampal volume for both the left and right sides equally in adult men and women with chronic PTSD and no change in children [110–111]. Interestingly, paroxetine, a selective serotonin reuptake inhibitor, appears to effectively improve short-term memory deficits and possibly reverse hippocampal atrophy [112]. These data suggest that PTSD is associated with deficits in verbal declarative memory and with smaller hippocampal volume.

Multiple studies have shown smaller volume of the anterior cingulate in PTSD [113–118]. A recent twin study of combat-related PTSD suggests that atrophic changes in the pregenual anterior cingulate cortex (ACC) and both insula may represent (or at least be contributed to by) an acquired stress-induced loss rather than a preexisting condition [115]. In contrast, the authors concluded that the

reduced hippocampal volume found in these subjects represented a pretrauma vulnerability factor and was not related to stress-induced losses [90].

Regarding functional neuroimaging data of PTSD, exposure to traumatic reminders in the form of traumatic slides and/or sounds or traumatic scripts is associated with increased PTSD symptoms and decreased blood flow and/or failure of activation in the medial prefrontal cortex/anterior cingulate, including Brodmann (area 25) or the subcallosal gyrus (areas 32 and 24), as measured with PET or fMRI [93,119–126]. Other findings in studies of traumatic-reminder exposure include decreased function in the hippocampus [119], visual association cortex [119,125], parietal cortex, and inferior frontal gyrus [119,124–125,127] and increased function in the amygdala [127–128], posterior cingulate [119,121–122,125], and parahippocampal gyrus [119,121,123]. Several studies have shown that PTSD patients have deficits in hippocampal activation while performing a verbal declarative memory task [88,93] or a virtual water-maze task [129]. Other studies found increased posterior cingulate and parahippocampal gyrus activation and decreased medial prefrontal and dorsolateral prefrontal activation during an emotional Stroop paradigm [130] and increased amygdala function with exposure to masked fearful faces [131] or during classical fear conditioning, with decreased medial prefrontal function with extinction in PTSD [132]. Retrieval of words with emotional valence [133] or emotional Stroop tasks [134] were associated with decreased medial prefrontal function. The findings point to a network of related regions mediating symptoms of PTSD, including the medial prefrontal cortex, anterior cingulate, hippocampus, and amygdala [135].

Neuroreceptor studies are consistent with prefrontal dysfunction in PTSD. Bremner et al. used single photon emission CT (SPECT) and the benzodiazepine receptor ligand [^{123}I] iomazenil and found decreased prefrontal cortical binding in Vietnam combat veterans with PTSD [136]. Another study by Fujita et al. in First Gulf War veterans with PTSD showed no difference in binding with SPECT [^{123}I] iomazenil from controls [137], although this study did show a significant negative correlation between binding in the right superior temporal gyrus and severity of childhood trauma in PTSD patients. In this study, the subjects also had less severe PTSD than those included in the study by Bremner and colleagues.

In summary, these studies are consistent with dysfunction of the prefrontal cortex, hippocampus, and amygdala in PTSD.

IMAGING MODALITIES

The following sections will discuss applications of advanced neuroimaging modalities to TBI and PTSD. The primary focus will be on advanced MRI techniques (**Table**).

Diffusion Magnetic Resonance Imaging

The ability to visualize anatomical connections between different parts of the brain, noninvasively and on an individual basis, has opened a new era in the field of functional neuroimaging. This major breakthrough for neuroscience and related clinical fields has developed over the past 10 years through the advance of "diffusion magnetic resonance imaging" or D-MRI. D-MRI produces MRI quantitative maps of microscopic, natural displacements of water molecules that occur in brain tissues as part of the physical diffusion process. Water molecules are thus used as a probe that can reveal microscopic details about tissue architecture, either normal or diseased.

Concept of Molecular Diffusion

Molecular diffusion refers to the random translational motion of molecules (also called Brownian motion) that results from the thermal energy carried by these molecules. Molecules travel randomly in space over a distance that is statistically well described by a "diffusion coefficient." This coefficient depends only on the size (mass) of the molecules, the temperature, and the nature (viscosity) of the medium.

D-MRI is, thus, deeply rooted in the concept that during their diffusion-driven displacements, molecules probe tissue structure at a microscopic scale well beyond the usual millimeter image resolution. During typical diffusion times of about 50 to 100 ms, water molecules move in brain tissues on average over distances around 1 to 15 m, bouncing, crossing, or interacting with many tissue components, such as cell membranes, fibers, or macromolecules. Because of the tortuous movement of water molecules around those obstacles, the actual diffusion distance is reduced compared with free water. Hence, the noninvasive observation of the water diffusion-driven displacement distributions in vivo provides unique clues to the fine structural features and geometric organization of neural tissues and to changes in those features with physiological or pathological states.

Table.
Magnetic resonance imaging (MRI) neuroimaging techniques.

Technique	What It Measures	Applications
BOLD fMRI	Indirect measure of blood flow, BOLD signal changes originate in venules. BOLD fMRI takes advantage of susceptibility differences between oxygenated and deoxygenated blood.	Evaluate regional brain activity related to particular cognitive tasks or sensory/motor stimulation. Evaluate brain networks related to cognitive states. Evaluate brain "resting state" or "default" networks.
PW-MRI	Direct measure of blood flow, allows quantification of blood perfusion.	Assess brain perfusion or resting cerebral blood flow. Evaluate brain function in manner similar to fMRI.
DTI	Indirectly measures diffusion of water molecules. Mean diffusion, diffusion direction, and anisotropy white matter tracts.	Use diffusion anisotropy measures as marker of disease. Improved visualization of edema. Evaluate structural "connectivity" between brain regions.
MRS	Proton (^{1}H) MRI spectra typically contain signals from the metabolites N-acetylaspartate, creatine, choline, glutamate/glutamine, and myo-inositol.	Evaluate changes in brain metabolites related to myelination, neuronal density, edema, etc.
SWI	MRI sequences that are especially sensitive to changes in magnetic susceptibility, in particular blood.	Improved detection of hemorrhages. Improved imaging of blood vessels.

BOLD = blood oxygen level dependent, DTI = diffusion tensor imaging, fMRI = functional MRI, MRS = magnetic resonance spectroscopy, PW-MRI = perfusion weighted MRI, SWI = susceptibility-weighted imaging.

Imaging Diffusion with Magnetic Resonance Imaging: Principles

While early water diffusion measurements were made in biological tissues with the use of Nuclear Magnetic Resonance in the 1960s and 1970s, it was not until the mid-1980s that the basic principles of D-MRI were laid out [138–140]; see, for instance, Le Bihan [141] for a review. MRI signals can be made sensitive to diffusion through the use of a pair of sharp magnetic field gradient pulses, the duration and separation of which can be adjusted. The result is a signal (echo) attenuation that is precisely and quantitatively linked to the amplitude of the molecular displacement distribution: fast diffusion results in a large distribution and a large signal attenuation, while slow diffusion results in a small distribution and a small signal attenuation. Of course, the effect also depends on the intensity of the magnetic field gradient pulses.

In practice, any MRI imaging technique can be sensitized to diffusion by the insertion of the adequate magnetic field gradient pulses [142]. By acquiring data with various gradient pulse amplitudes, one gets images with different degrees of diffusion sensitivity (**Figure 1**). Contrast in these images depends not only on diffusion but also on other MRI parameters, such as the water relaxation times. Hence, these images are often numerically combined to determine, with use of a global diffusion model, an estimate of the diffusion coefficient in each image location. The resulting images are maps of the diffusion process and can be visualized with a quantitative scale.

Because the overall signal observed in a "diffusion" MRI image voxel, at a millimetric resolution, results from the statistical integration of all the microscopic displacement distributions of the water molecules present in this voxel, Le Bihan et al. suggested portraying the complex diffusion processes that occur in a biological tissue on a voxel scale by using a global statistical parameter, the Apparent Diffusion Coefficient (ADC) [143]. The ADC concept has been largely used since then in the literature. The ADC now depends not only on the actual diffusion coefficients of the water molecular populations in the voxel but also on experimental technical parameters, such as the voxel size and the diffusion time.

Although the first diffusion images of the brain were obtained in the mid-1980s in normal subjects and in patients [143], D-MRI did not really take off until the mid-1990s. Initially, the specifications of the clinical MRI scanners made obtaining reliable diffusion images difficult because acquisition times were long (10 to 20 minutes) and the large gradient pulses required for diffusion also made the images very sensitive to macroscopic motion artifacts, such as those induced by head motion, breathing, or even cardiac-related brain pulsation [144]. Therefore, although D-MRI was shown to be potentially

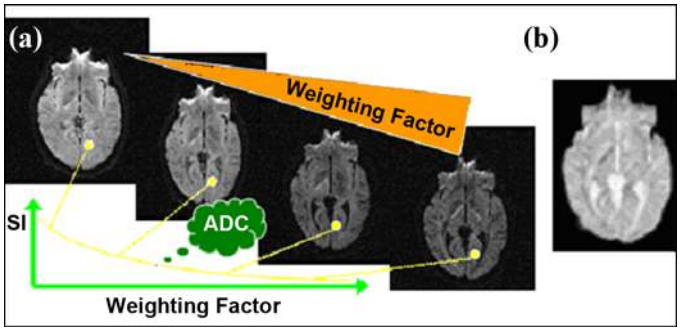

Figure 1.
Diffusion-weighting. In practice, different degrees of diffusion-weighted images can be obtained by varying the weighting factor, which is carried out by varying time and strength of gradient pulses (represented by orange triangle). **(a)** The larger the weighting factor, the more the signal intensity (SI) becomes attenuated in image. This attenuation, though, is modulated by the diffusion coefficient: signal in structures with fast diffusion (e.g., water-filled ventricular cavities) decays very fast with the weighting factor, while signal in tissues with low diffusion (e.g., gray and white matter) decreases more slowly. By fitting signal decay as a function of weighting factor, one obtains the Apparent Diffusion Coefficient (ADC) for each elementary volume (voxel) of image. **(b)** Calculated diffusion images (ADC maps), depending solely on diffusion coefficient, can then be generated and displayed using gray (or color) scale: high diffusion, as in ventricular cavities, appears bright, while low diffusion appears dark.

useful in the clinic, demonstrative clinical studies started only later, when better MRI scanners equipped with echo-planar imaging (EPI) became available. Exploiting gradient hardware EPI makes it possible to collect a whole-brain image in a single "shot" lasting a few tens of milliseconds and images of the whole brain in less than a second, virtually freezing macroscopic motion.

Diffusion Tensor Magnetic Resonance Imaging

Diffusion is truly a three-dimensional process; therefore, water molecular mobility in tissues is not necessarily the same in all directions. This diffusion anisotropy may result from obstacles that limit molecular movement in some directions. It was not until the advent of D-MRI that anisotropy was detected for the first time in vivo, at the end of the 1980s, in spinal cord and brain white matter [145–146]. Diffusion anisotropy in white matter grossly originates from its specific organization in bundles of more or less myelinated axonal fibers running in parallel: diffusion in the direction of the fibers (whatever the species or the fiber type) is about three to six times faster than in the perpendicular direction. However, the relative contributions of the intra-axonal and extracellular spaces, as well as the presence of the myelin sheath, to the ADC and the exact mechanism for the anisotropy are still not completely understood and remain the object of active research (see, for instance, Beaulieu [147] for a review). It quickly became apparent, however, that this anisotropy effect could be exploited to map out the orientation in space of the white matter tracts in the brain, assuming that the direction of the fastest diffusion would indicate the overall orientation of the fibers [148]. The work on diffusion anisotropy really took off with the introduction into the field of D-MRI of the more rigorous formalism of the diffusion tensor by Basser et al. [149–150]. With DTI, diffusion is no longer described by a single diffusion coefficient but by an array of nine coefficients that fully characterize how diffusion in space varies according to direction (see, for instance, Le Bihan and Van Zijl [151] for a review on DTI). Hence, diffusion anisotropy effects can be fully extracted and exploited, providing even more exquisite details on tissue microstructure.

DTI data are often summarized in three ways to provide information on tissue microstructure and architecture for each voxel [141,152]: (1) the mean diffusivity or ADC characterizes the overall mean-squared displacement of molecules and the overall presence of obstacles to diffusion, (2) the degree of anisotropy describes how much molecular displacements vary in space and is related to the presence and coherence of oriented structures, and (3) the main direction of diffusivities is linked to the orientation in space of the structures. For instance, in stroke, the average diffusion and the diffusion anisotropy in white matter had different time courses, potentially enhancing the use of D-MRI for the accurate diagnosis and prognosis of stroke [153]. The diffusion along the main direction of diffusion is often termed axial diffusion, whereas radial diffusion is the diffusion along directions perpendicular to the main direction. Early studies with mice have indicated that changes in radial diffusion may be more specific to myelination than are changes in axial diffusion or other measures of anisotropy [154].

Diffusion Anisotropy in White Matter: Toward Brain Connectivity

Studies of neuronal connectivity are important in order to interpret fMRI data and establish the networks underlying cognitive processes. Basic DTI provides a means to determine the overall orientation of white matter bundles in each voxel, assuming that only one direction is present or

predominant in each voxel and that diffusivity is the highest along this direction. Three-dimensional vector field maps representing fiber orientation in each voxel can then be obtained back from the image data through the diagonalization (a mathematical operation that provides orthogonal directions coinciding with the main diffusion directions) of the diffusion tensor determined in each voxel. A second step after this "inverse problem" is solved consists in "connecting" subsequent voxels on the basis of their respective fiber orientation to infer some continuity in the fibers (**Figure 2**). Several algorithms have been proposed (see Mori [155] and van Zijl and Jones [156] for reviews). Line propagation algorithms reconstruct tracts from voxel to voxel from a seed point [157–158]. Another approach is based on regional energy minimization (minimal bending) to select the most likely trajectory among several possible [159]. Finally, a promising approach is probabilistic tracking using Bayesian [160] or bootstrapping [161] methodologies. In any case, one has to keep in mind that at this stage only white matter bundles made of somewhat large numbers of axons are visible (and not intracortical connections). The application of tractography to PTSD and TBI studies is an area for future research. While tractography yields very nice pictures, how this technology will be best applied to research is still unclear. A possibility would be the use of probabilistic tractography to determine whether a reduction or break occurs in the anatomical connectivity between two regions, or nodes, of a functional network. These nodes are normally chosen either a priori or empirically from fMRI results. This is an area in which the combination of DTI and fMRI could be particularly useful in both PTSD and TBI [162–163].

Clinical Applications

In white matter, any change in tissue orientation patterns inside the MRI voxel would probably result in a change in the degree of anisotropy. A growing literature body supports this assumption: many clinical studies of patients with white matter diseases have shown the exquisite sensitivity of DTI to detect abnormalities at an early

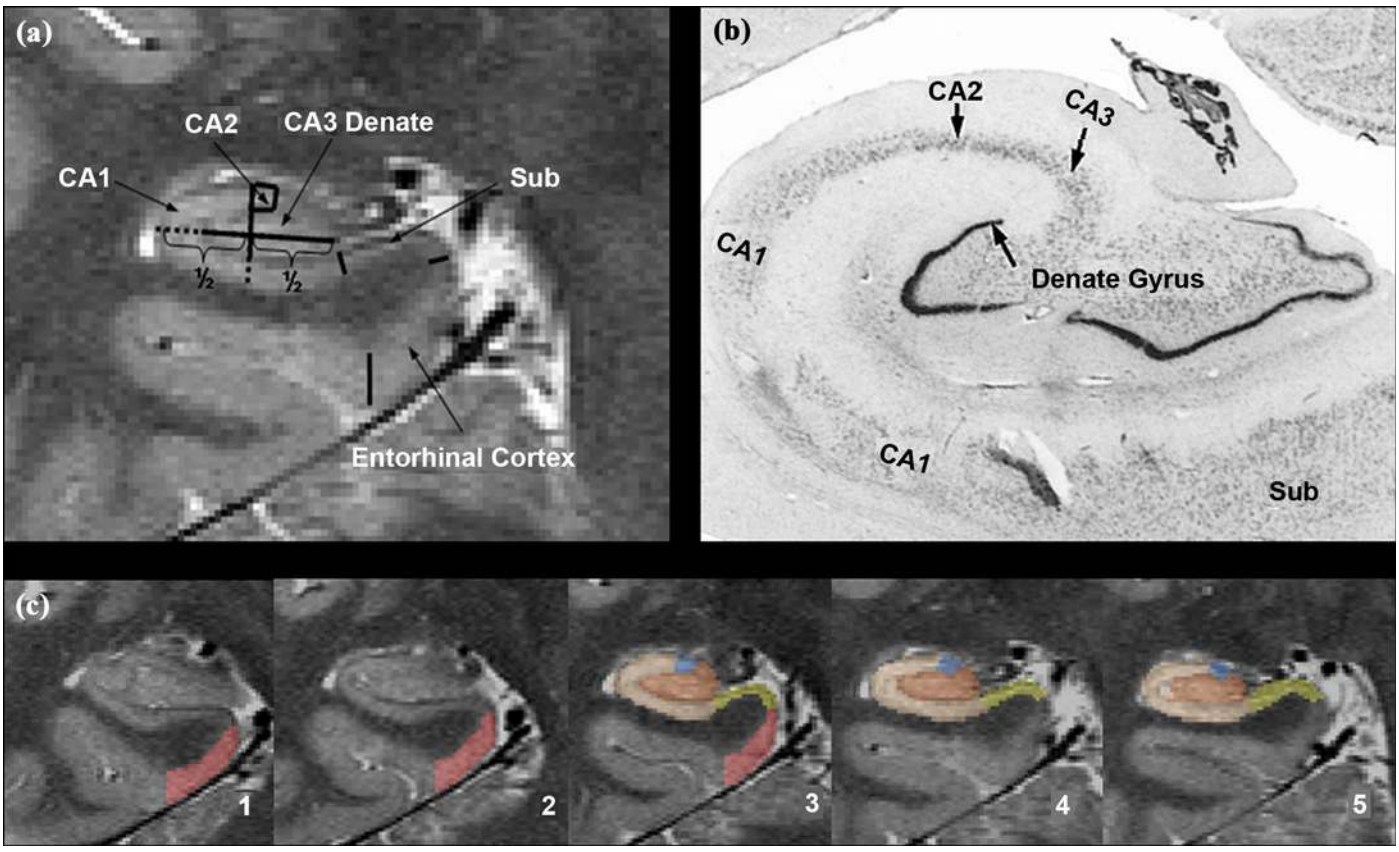

Figure 2.
Imaging the hippocampal subfields. **(a)** High-resolution magnetic resolution imaging. **(b)** Histological section. **(c)** Manual marking. CA = cornu ammonis, Sub = subiculum.

stage or to characterize them in terms of white matter fiber integrity (e.g., multiple sclerosis [164]). Further DTI analysis using other indexes, such as the trace of the diffusion tensor, which reflects overall water content, and anisotropy indexes, which point toward myelin fiber integrity, can be useful. Clinical examples include multiple sclerosis [165–168], leukoencephalopathies [169–170], Wallerian degeneration, HIV-1 (*Human immunodeficiency virus 1*) infection [171], Alzheimer disease (AD) [172–173], or CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) [174] (see Horsfield and Jones [175] for a review).

However, D-MRI could also unravel more subtle functional disorders that do not necessarily translate into macroanatomical anomalies. For instance, anisotropy measurements may highlight subtle anomalies in the microorganization of white matter tracts otherwise not visible with plain anatomical MRI. The potential is enormous for patients with functional symptoms linked to disconnectivity, for instance, in patients with psychiatric disorders (see Lim and Helpern [176] for a review), TBI, or potentially PTSD.

Hence, water diffusion patterns within and between white matter tissue are highly sensitive to microstructural abnormalities/pathologies. However, it is important to emphasize that DTI abnormalities are not specific and may reflect a host of conditions, including demyelination, axonal pathology/loss, gliosis, inflammation, or edema.

Diffusion Tensor Imaging in Mild Traumatic Brain Injury. Several studies have investigated DTI abnormalities in patients with mild TBI [5,20–22,31,33,177–178]. Arfanakis et al. studied five patients within 24 hours of injury, and two of these patients were also studied 1 month later [5]. Five white matter regions of interest (ROIs) were analyzed bilaterally in patients, and comparisons between hemispheres as well as with a control group were performed. Some patients' ROIs had reduced FA values at the anterior corpus callosum and anterior internal capsule (with normal conventional MRI) compared with controls. Further, two subjects had "normalized" FA values in some ROIs 1 month later. However, no clinical correlative data were reported.

Bazarian et al. studied six patients with mild TBI and six orthopedic controls within 72 hours of injury by using both a whole-brain and an ROI approach [177]. In the whole-brain analysis, the first percentile (histogram) showed significantly lower trace values (or ADC) in mild TBI patients. Further, these trace values correlated with symptoms consistent with postconcussion syndrome (PCS) in patients with mild TBI, although the symptoms were not significantly greater than those in the control group. Except for impulse control, psychometric tests (verbal and visual memory, visual motor speed, reaction time) did not significantly differ between the mild TBI group and the controls. However, ROIs showed mild TBI subjects to have significantly lower mean trace in the left anterior internal capsule and higher maximum ROI-specific median FA values in the posterior corpus callosum. These FA values correlated with the 72-hour PCS score and two neurobehavioral tests (visual motor speed and impulse control). The authors speculated that the data represented axonal swelling.

Wilde et al. studied 10 adolescents with mild TBI within 1 week of MRI scanning [178]. They calculated average FA, ADC, and radial diffusivity within the corpus callosum. When compared with that of 10 healthy, age-matched control subjects, the FA for the mild TBI subjects was significantly increased while the ADC and radial diffusivity were significantly decreased. In addition, the FA values correlated with postconcussion symptoms and emotional distress. The authors argued, similar to Bazarian et al., that the increased FA and decreased ADC were likely due to edema that occurs during the acute stage of TBI.

Miles et al. also studied adult patients with mild TBI in the acute stage [33]. These authors compared DTI data from nondisabled control subjects with that of 17 mild TBI patients who were on average 4 days postinjury. They calculated FA and ADC summary values by averaging FA and ADC for voxels over multiple ROIs: centrum semiovale, the genu and splenium of the corpus callosum, and the posterior limb of the internal capsule. This group found significantly higher ADC and lower FA values for the mild TBI group.

More studies are necessary to reconcile the findings of Miles et al. and Arfanakis et al. to those of Wilde et al. and Bazarian et al. Time since injury, age (adolescent vs adult patient), ROI selection, and other factors may influence these discrepancies in the FA/ADC changes in acute mild TBI.

While the previous studies mentioned here studied patients with mild TBI in the acute stage, Rutgers et al. divided 24 mild TBI subjects into two groups: 12 subjects less than 3 months postinjury and 12 subjects more than 3 months postinjury [22]. The authors calculated the average FA and ADC within three regions of the corpus callosum: genu, body, and splenium. When compared with

10 control subjects, mild TBI subjects who were less than 3 months from injury showed significantly increased ADC and decreased FA within the genu ROI. However, the mild TBI subjects imaged more than 3 months after their injury did not show any significant differences in FA or ADC compared with the control group.

In studies focused more on chronic subjects, Kraus et al. studied 55 patients with chronic TBI (more than 6 months postinjury), 20 of whom had mild TBI (average 92 months postinjury) [31]. The authors acquired DTI data and evaluated 3 estimates of anisotropy (FA, axial and radial diffusivity) from 13 ROIs and also estimated total white matter load (total number of regions with decreased FA). A battery of more than 20 neuropsychological tests was also administered. For the mild TBI group, performance was impaired compared with controls in only the Conner's continuous performance test and did not differ from the controls in the domains of attention, memory, or overall executive function. Decreased FA was found in the corticospinal tract, sagittal stratum, and superior longitudinal fasciculus for the mild TBI group (with no clinical correlate).

Lipton et al. studied DTI data from 17 mild TBI patients with cognitive impairment who were at least 8 months postinjury [20]. The authors used voxelwise morphometry analyses and whole-brain histograms to compare FA and ADC between the mild TBI subjects and 10 healthy control subjects. The histograms showed an overall downward shift in FA for the mild TBI patients, and the voxelwise analyses revealed significantly reduced FA for the mild TBI patients in the corpus callosum and internal capsule (bilaterally). The areas showing decreased FA also showed significantly increased ADC.

Chappell and colleagues reported widespread FA reductions and ADC increases in professional boxers, mainly in white matter, despite negative conventional MRI scans [179]. Abnormalities were seen in the internal capsule, medial temporal lobes, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and midbrain and are interpreted to represent injury from chronic blows to the head. No neuropsychometric testing or report of "major trauma to the head" (undefined) was described.

A recent combined imaging-neuropsychometric study of patients with chronic mild TBI performed jointly between Weill Cornell Medical College and the University of California, San Francisco (UCSF) examined the spatial extent of microstructural white matter injury and its relationship with global cognitive processing speed [9]. All subjects had a Modified Glasgow Coma Scale score of 13 to 15 at the time of original assessment postinjury, a history of loss of consciousness shorter than 30 minutes, and posttraumatic amnesia. All had at least one postconcussion symptom persisting at least 1 month (range 1–65 months) at the time of imaging and cognitive assessment for the study. Subjects were excluded if they had a history of prior TBI, drug/alcohol abuse, or other preexisting neurological or psychiatric conditions. A white matter tract in a TBI patient was considered "damaged" if DTI demonstrated an FA value more than 2.5 standard deviations below the mean FA of that tract in a group of normal volunteers. The measure of cognitive processing speed was reaction time (RT) in the Attention Network Task (ANT) [180], which involves pressing a button to indicate the direction of an arrow flashed on a computer monitor. A robust and statistically significant correlation was found between increasing number of white matter tracts with microstructural injury and poorer RT ($r = 0.49$, $p = 0.012$). In contradistinction, the number of traumatic microhemorrhages detected by T2*-weighted gradient echo imaging at 3 T did not correlate with RT ($r = –0.08$; $p = 0.701$). These results demonstrate that, in chronic mild TBI, increasing spatial extent of regional white matter injury on DTI is associated with slower cognitive processing speed, whereas the number of focal hemorrhagic shearing lesions on conventional 3 T MRI is not.

The two most frequently damaged white matter tracts in this cohort of mild TBI patient were the anterior corona radiata (ACR) and the uncinate fasciculus (UF). This finding was not surprising, since the two most common cognitive symptoms in PCS, in addition to slowed overall processing speed, are impairments in attention and memory [181]. The ACR contains fibers that connect the anterior cingulate with the prefrontal cortex and therefore plays a critical role in attentional processes. The UF connects temporal lobe structures with prefrontal cortex and is vital to working memory.

The relationship of these two tracts to attention and memory was examined for 43 chronic mild TBI patients in a follow-up 3 T DTI study performed jointly at Cornell and UCSF [34]. Attentional performance was gauged with the conflict measure of the ANT [180], which measures the difference in RT between congruent and incongruent trials requiring the subject to determine the direction of an arrow flashed on a computer monitor in the presence of flanking arrows. Verbal memory was assessed with the long-delay free recall (LDFR) subtest of the California Verbal Learning Test, 2nd Edition, which requires the

subject to recall a list of 16 words after a delay of 20 minutes after presentation. FA of the UF in both hemispheres correlated significantly with memory performance on the LDFR in mild TBI subjects. The bilateral average ACR FA correlated significantly with attentional control, as measured by the conflict score on the ANT. A closer examination of the contributions of each hemisphere showed that the left ACR FA was the primary contributor to this relationship. These results show that in mild TBI, lower FA of the UF is related to poorer verbal memory performance and lower FA of the ACR is related to poorer attentional control. These findings form a double dissociation, because FA of the UF did not correlate with attentional control, nor did FA of the ACR correlate with verbal memory. These results show that DTI is sensitive to microstructural white matter injury in chronic mild TBI that correlates with functional disability. The spatial extent of axonal injury is associated with impairments in global cognitive processing, whereas damage to specific white matter tracts can account for deficits in specific cognitive domains, such as memory and attention.

Larger-scale longitudinal investigations are needed to determine whether DTI in the acute phase of TBI can predict long-term functional outcomes, which would represent a first step toward validation of this methodology as a biomarker for TBI for use in applications such as assessment of neuroplasticity during recovery and monitoring of the efficacy of therapeutic interventions and rehabilitation.

Early studies support the notion that DTI combined with behavioral assessments may indeed provide useful prognostic information. Sidaros et al. reported in a longitudinal study of 30 patients with severe TBI studied acutely and after 1 year (n = 23) that FA in the cerebral peduncle correlated with Glasgow Outcome Scale scores at 1 year (r = 0.60, p < 0.001). Moreover, favorable dichotomized outcomes at 1 year were accurately predicted when FA was used in combination with clinical evaluation at the time of the first scan [27] (but see Bendlin et al. [19]).

Hence, it is important to underscore that the underlying processes mediating DTI disturbances may vary in the acute and chronic states, and prognostic information might be gleaned from these data.

Diffusion Tensor Imaging in Posttraumatic Stress Disorder. In recent years, DTI has shown promise in PTSD applications. Two studies used morphometry to compare FA values between PTSD and healthy control subjects on a voxelwise basis [182–183]. Abe et al. compared 25 subjects who were victims of the Tokyo subway sarin attack, 9 of whom were diagnosed with PTSD [182]. These authors found increased FA in the left anterior cingulum with the morphometry analysis and followed this analysis with a post hoc ROI analysis of the FA values in the anterior cingulum. The ROI analysis confirmed the significant increase in FA, providing support that the increase in FA was not an artifact created by misalignment or excessive smoothing in the morphometry procedures. Kim et al. compared 20 survivors of a subway fire who developed PTSD with 20 healthy control subjects [183]. These authors reported a decrease in FA in the left anterior cingulate of the PTSD subjects. Further, a correlation analysis within the PTSD subjects revealed that both lifetime and current-experience scores of the Clinician-Administered PTSD Scale (CAPS) were negatively correlated with FA values in the anterior cingulate white matter.

Jackowski et al. used DTI to investigate possible changes in myelination or white matter coherence in the corpus callosum in maltreated children with PTSD as compared with healthy children [184]. These authors used an ROI analysis and divided the corpus callosum into seven regions: rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus, and splenium. The ROI analysis revealed significant reductions in FA within the anterior and posterior midbody regions of the maltreated PTSD group. However, since the control group was comprised of healthy children as opposed to maltreated children without a PTSD diagnosis, the differences could be attributed to either PTSD or maltreatment. These early DTI studies show promise for the further characterization of PTSD-related brain abnormalities.

BRAIN VOLUMETRICS

By differentiating tissues on their MRI signal intensities, compartment segmentation algorithms in combination with either voxel-based measures or ROI analyses can indirectly measure local volume loss.

Detection and quantification of loss of both white and gray matter have been demonstrated in TBI through MRI volumetric analyses [19,185–191]. Both whole-brain volume and regional volume decreases have been demonstrated and appear to correlate with clinical injury severity (e.g., Levine et al. [185]). However, longitudinal changes may not necessarily correlate with behavioral/cognitive measures [19]. Advances in volumetric methodology in

combination with other modalities will, nonetheless, likely provide new insights into structural-functional relations in both TBI and PTSD (see below).

Many studies have investigated volumetric differences between PTSD and control subjects in whole-brain [192–193], amygdala [194], corpus callosum [192,195], insula [115], anterior cingulate [113–118], and hippocampal [87,92,118,133,194] analyses.

Volumetric Analyses of Hippocampus

The fact that the hippocampus is involved in learning and memory—processes requiring a high degree of neuronal plasticity—and is capable of life-long neurogenesis, renders it particularly vulnerable to all types of insults. As a consequence, hippocampal atrophy is found in different diseases such as AD, epilepsy, schizophrenia, and hypothyroidism, as well as in PTSD and chronic TBI, even in cases in which the primary impact site was remote from the hippocampus. The hippocampus, however, is not a homogeneous structure but consists of several histologically and functionally distinct but tightly interconnected subfields: the subiculum with the subdivisions presubiculum, parasubiculum, and subiculum proper; the four cornu ammonis sectors (CA1–4); and the dentate gyrus (DG) [196]. Animal studies have shown that different disease processes affect these subfields differently; e.g., AD is associated with a prominent neuronal cell loss in CA1, whereas temporal lobe epilepsy is typically characterized by cell loss in the DG. Evidence also exists that TBI and PTSD affect certain subfields more than others. Acute stress is associated with activation of the sympathetic-adrenomedullary system and the hypothalamo-pituitary-adrenal axis, resulting in increased levels of catecholamines and adrenal steroids that are restored to baseline levels by a negative feedback mechanism once the stressor has been removed. Evidence exists that this feedback is pathologically enhanced in PTSD, which results in chronically lowered basal cortisol levels but increased sensitivity of glucocorticoid receptors in target tissues [197]; one of those is the hippocampus. Adrenal steroids play a crucial role in the hippocampus, where they modulate short-term functions (excitability, long-term potentiation, and depression) as well as long-term, delayed effects (neuronal plasticity, neurogenesis) [198–199].

Animal models of chronic stress have shown that adrenal steroids can adversely influence basal synaptic excitability and neuronal plasticity in CA1, cause reversible dendritic atrophy in CA3, and impair neurogenesis in DG. Interestingly, TBI can lead to a similar pattern of neuronal dysfunction/damage in the hippocampus as PTSD. Animal studies have shown that TBI is associated with hippocampal damage in CA3, DG, and, to a lesser degree, CA1 [200] and that although the mechanisms leading to hippocampal damage in TBI are complex, it is partially mediated by posttraumatically increased adrenal steroids and altered adrenocorticosteroid receptor properties in those subfields [201–202]. A review of the broader distribution of injuries in a well-studied animal model of TBI may be found in Thompson et al. [203].

In accordance with the findings in animal studies, MR studies in chronic TBI have reported smaller total hippocampal volumes that were inversely associated with memory problems [204–206], although one study found that the memory problems were related more to diffuse brain injury than to hippocampal injury [207]. Similar findings have been reported in PTSD, although not consistently so [208]. Several reasons exist for this inconsistency in PTSD, e.g., presence of comorbidity affecting hippocampal volume, different severity of PTSD, and time since traumatic event. However, measurements of total hippocampal volume may also not be sensitive enough to detect subtle atrophic changes restricted to a relatively circumscribed region of the hippocampus (CA3 and DG) and leaving the majority of the structure otherwise intact. The same might be true for very mild cases of TBI. Therefore, volumetric measurements of hippocampal subfields might provide a better measure of the hippocampal pathology in PTSD and mild TBI than volumetric measurements of the whole hippocampus.

Measurement of Hippocampal Subfields with High Resolution Imaging at High Field

Measurements of hippocampal subfields require that details of the internal structure of the hippocampal formation can be depicted in vivo. Recent advancements with high field MRI (3–4 T), achieving increased gray/white matter contrast because of the increased signal sensitivity at high fields, additional magnetization transfer effects, and T1 weighting, have resulted in excellent in vivo anatomical images at submillimeter resolution that can be acquired within a few minutes [209]. The manual marking scheme depends on anatomical landmarks, particularly on a hypointense line representing the leptomeningeal tissue in the vestigial hippocampal sulcus, which can be reliably visualized on these high-resolution images (cf. **Figure 2**). For a detailed discussion on a marking procedure measuring hippocampal subfields that provides good to excellent inter- and intrarater reliability, refer to Mueller et. al [210].

FUNCTIONAL MAGNETIC RESONANCE IMAGING

Advances in MRI methods make extension from imaging of structure toward inferences about function possible. fMRI studies typically measure signal changes due to changes in blood flow or oxygenation while a person is performing a task, making use of the link between blood oxygenation and neural activity to determine task-related neural activity [211–212]. The signal changes in fMRI related to blood oxygenation is referred to as blood oxygen dependent level (BOLD) contrast. Experimental paradigms for fMRI generally involve comparison of a baseline condition with two or more experimental conditions consisting of specific cognitive tasks or sensory stimulation. These conditions can occur during extended periods of time (e.g., 10–60 s) in "blocked" design experiments or during very brief periods of time (e.g., 1–2 s) in "event-related" design experiments. Blocked-design experimental paradigms allow for the BOLD signal to add up over time because local neuronal firing constantly elevates during the experimental block. The increase in BOLD signal yields a larger effect size and higher detection rates than in event-related designs, allowing for adequate detection rates for shorter scan durations. This is important clinically because limiting scan duration is often necessary for clinical populations. Other methods that emphasize perfusion as opposed to BOLD contrast are also being tested, e.g., Kim et al. [213].

fMRI techniques have been used extensively for investigating mechanisms of brain function in health and may be useful for examining changes in brain function after injury as well as changes that occur over recovery or as a result of treatment interventions. However, the application of fMRI to various clinical populations, such as TBI and PTSD, is more complicated than fMRI experiments using healthy populations, and many variables need to be considered, such as hemodynamic changes due to injury, medications, and increased movement artifacts with patients, when fMRI studies are being designed and analyzed (see Hillary et al., D'Esposito et al., and Bartsch et al. [214–216]).

Thus far, most applications of fMRI to TBI and PTSD patients have emphasized techniques for "mapping" brain activations. These techniques have the advantage of allowing exploratory analyses, such as comparing differences between a patient group and a control group on a voxelwise basis, asking the open-ended question of which regions differ in activity. This inquiry may provide hypothesis-generating information about sources of dysfunction with TBI. Standard statistical parametric mapping approaches are suited to this type of question. However, potential confounders, such as changes in vasculature postinjury in TBI, may affect across-group comparisons.

Longitudinal Studies

fMRI is noninvasive and does not require injection of a radioisotope into the bloodstream; therefore, it is suitable for repeated studies and potentially useful for investigating the nature of longitudinal changes during recovery or with treatment interventions, such as pharmacotherapy [217]. Within-subjects comparisons also make across-group confounders less of an issue.

Functional Magnetic Resonance Imaging Studies of Mild Traumatic Brain Injury

A handful of studies have utilized functional MRI methods to examine functional activation patterns in patients with TBI [57–58,61–62,218–219]. Because cognitive dysfunction is of paramount concern with TBI, these studies have primarily used tasks that challenge working memory with conventional blocked-design fMRI tasks. Results have been mixed. Chrisodoulou et al. found that patients with severe TBI showed more widespread activation as a group on the Paced Auditory Serial Addition Task [57]. McAllister and colleagues found that patients had somewhat greater extent of activation with easier *n*-back tasks but, unlike healthy controls, seemed not to activate larger areas of cortex with increasing task load; this finding was corroborated by Perlstein et al. [58,61–62]. The specific interpretation of these studies is controversial but overall may suggest that patients with even mild TBI require larger areas of cortex to perform a given task, and those with moderate-severe TBI may have difficulty recruiting additional cortical resources when needed for more difficult tasks.

An active area of fMRI research with mild TBI comes from studies of athletes and sports-related concussions (see review by Ptito et al. [219]). Lovell et al. studied 28 athletes with concussions who were evaluated within approximately 1 week of injury and again after clinical recovery [67]. They used an *n*-back (0-, 1-, and 2-back) fMRI task along with a computer-based battery of neurocognitive tests and subjective symptom scales. The authors found that athletes who demonstrated hyperactivation on fMRI scans at the time of their first fMRI scan demonstrated a more prolonged clinical recovery than athletes who did not demonstrate hyperactivation.

Chen et al. used a working memory task (externally ordered task) to study a group of 16 athletes with concussions (15 symptomatic, 1 asymptomatic) and 8 matched healthy control subjects [72]. The authors reported that the activation pattern of the asymptomatic athlete was similar to that of the healthy controls while the activation patterns for the symptomatic athletes were abnormal in one manner or another (differences were not consistent). The authors also longitudinally followed one subject who had multiple concussions and found that as the subject's symptoms improved, the subject's ability to do the task improved and fMRI activation in the dorsolateral prefrontal region increased (i.e., activation pattern became normalized or similar to that of healthy control subjects).

Chen et al. later studied a group of 28 male athletes, 18 with concussion and 10 without [73]. The concussion group was further divided into two subgroups, those with mild concussions (PCS score 6–21) and those with moderate concussions (PCS score >21). The moderate PCS group showed significantly slower response times than the control group on matching and 1-back behavioral tasks, while the mild group did not show any significant behavioral differences. However, both groups showed reduced fMRI task-related activation within the dorsolateral prefrontal regions. Also, the activation patterns for both concussion groups were more dispersed compared with the control group. The authors also reported a negative relationship between the PCS scores for the concussion group and BOLD signal changes within prefrontal regions. Further, the same authors have shown that the differential activation within the dorsolateral prefrontal regions can be affected by depression [220], which underscores the complexity of fMRI research in TBI and PTSD populations, because depression symptoms are often associated with both groups.

Functional Magnetic Resonance Imaging Studies of Posttraumatic Stress Disorder

The majority of fMRI studies of PTSD use traumatic stimuli or emotional pictures. The most common methods for traumatic stimuli involve traumatic scripts [221–222] or traumatic pictures [220–226]. Tasks involving emotional stimuli normally use either fearful or emotional faces [131,221–230]. However, more recently, researchers have been using more cognitive tasks without an emotional component, such as an auditor oddball task [231], visual working memory task [232], Stroop task [233], and Go No-Go task [234–235]. Most of these studies showed differential activation in at least one of the areas most often implicated in PTSD: amygdala, anterior cingulate, and medial temporal lobe.

Functional Magnetic Resonance Imaging Studies of Mild Traumatic Brain Injury Recovery and Rehabilitation

Discovery of the dynamic brain mechanisms of recovery and rehabilitation through neuroimaging is anticipated to advance both the rationale and methods of brain injury treatment in particular and learning and memory in general. Many studies, some of which performed repeated imaging during spontaneous recovery, have described fMRI patterns of activation in patients with mild TBI [67,72,218]. MRI studies of moderate-severe TBI have also been performed [236–239]. However, we are aware of only a few groups that have conducted fMRI neuroimaging investigations during rehabilitation in TBI [71,240–250].

Strangman et al. studied 54 patients with chronic TBI (>1 year postinjury, mean 11 years), 14 of whom had mild TBI, and found that after 12 sessions of rehabilitation focusing on internal strategies of improving memory, severe versus mild baseline injury ($p = 0.049$) or extreme abnormal activation (under- or overactivation) in the left ventral lateral prefrontal cortex at baseline ($p = 0.007$) predicted poorer responses to ~6 weeks of rehabilitative training [241]. No posttraining fMRI acquisitions were obtained to correlate with performance changes.

Kim et al. studied 17 subjects with moderate TBI (Glasgow Coma Scale 9–12) of variable duration (3–57 months, mean 16 months), 10 of whom underwent cognitive training for 4 weeks as well as pre- and post-fMRI imaging [71]. Improved performances in attentional tasks were accompanied by attentional network changes, i.e., decreased frontal lobe activity and increased activity in the anterior cingulate and precuneus areas. Given the heterogeneity in duration since injury (some less than 6 months postinjury), some changes in activation patterns may have reflected spontaneous recovery.

Before and after 4 to 8 months of individualized cognitive therapy, Laatsch et al. studied a case series of five patients with mild TBI and suggested that changes in activation for visual saccade and reading comprehension tasks might be related to, or due to, training [239]. The study suffered from many design and methodological concerns, including that the subjects were dissimilar in age, histories, duration and frequencies of brain injury events, and MRI findings (e.g., frontal lobe atrophy in a

20-year-old male). Further, this study lacked standardized training, duration, and control subjects. Laatsch and colleagues also used this testing paradigm in a case study of severe TBI [239] and in a study of three other patients with severe TBI [240] and reported "diffuse and variable activation patterns" compared with qualitative imaging stability between sessions for controls.

Functional Magnetic Resonance Imaging Studies of Posttraumatic Stress Disorder Rehabilitation

A few functional imaging studies have investigated the effects of cognitive-behavior therapy (CBT) on PTSD. Felmingham et al. studied eight patients with PTSD before and after eight once-weekly sessions of CBT with an fMRI paradigm consisting of neutral and fearful faces [242]. The authors reported an increase in fMRI activation in the rostral anterior cingulate cortex (bilaterally) after therapy. A significant positive correlation was also found between the changes in CAPS scores and the right anterior cingulate activation as well as a negative correlation between the CAPS scores and the amygdala activation. However, although a significant correlation existed between the CAPS scores and BOLD response within the amygdala, there were no significant activations compared with the fMRI baseline control condition within the amygdala during the individual sessions (before or after treatment).

The same authors performed a similar study in which they compared fMRI activation before and after eight once-weekly sessions of CBT in 14 subjects with PTSD (8 with comorbid depression) [243]. In this study, the authors altered the fMRI paradigm to increase the amygdala activation. In their previous study, each stimulus (blocks of fearful or neutral faces) was presented for 500 ms with an interstimulus interval of 768 ms [242]. In the latter study, the stimuli were presented for 16.7 ms with an interstimulus interval of 163.3 ms [243]. This rapid presentation of stimuli had been shown previously to activate the amygdala in PTSD patients [131,228]. The short duration of the stimulus was just long enough for unconscious processing of the stimulus but precluded conscious awareness. With this paradigm, not only was activation detected within the amygdala region, but the amygdala activation was also much greater than that for a group of healthy, nontrauma-exposed control subjects. In addition, PTSD subjects who did not significantly improve with therapy had significantly greater activation in the bilateral amygdala and right ventral anterior cingulate regions before therapy than did those subjects who did significantly improve with therapy (defined as at least a 50% reduction in pretreatment scores). Also, a significant positive correlation was found between posttreatment CAPS scores and both amygdala (bilateral) and ventral anterior cingulate activation. This study shows the potential for using fMRI to help predict the efficacy of certain therapies.

Functional Connectivity

Although most fMRI studies have focused on detection of regional brain activations, many cognitive functions affected by TBI are understood to require interactions across brain regions via the very white matter tracts that are vulnerable to injury. Multivariate statistical methods [244–246] or independent component analyses [247–249] may be used to assess injury-related changes in the functional connections across brain regions. Better characterization and understanding of the effects of TBI (and/or PTSD) on the coherence of these functional networks in both task and resting states may also provide insights into recovery and rehabilitation (see reviews by He et al. and Fox and Raichle [250–251]).

MAGNETIC RESONANCE SPECTROSCOPIC IMAGING

MRSI methods represent a fusion of MRI and MRS. While changes in contrast on clinical MRI images may indicate a structural abnormality, signal alterations in the MRS spectrum can give additional information about its nature. In certain cases, such alterations can even appear in regions that look normal on MRI images. Furthermore, as a combination of MRI and MRS, MRSI holds great potential for providing such additional information for a larger volume than is possible with MRS alone [252–253]. Most MRSI applications employ a two-dimensional approach, providing spectra from within one or multiple sections through the structure of interest. Three-dimensional MRSI methods allow coverage of larger volumes or an entire organ [254–256]. Typically, spectra are obtained from a regular array of subvolumes, which allows generation of images from individual peaks. Besides TBI and PTSD applications, other clinical applications of MRSI include the study of tumors [257–259], neurodegenerative disorders [260–262], neuropsychiatric diseases [263–265], epilepsy [266–268], and substance use disorders [269–271].

Magnetic Resonance Spectroscopy in Traumatic Brain Injury

Several metabolites are of interest as markers of injury. NAA is believed to reflect neuronal and axonal integrity [272]. Cho peaks reflect Cho-containing phospholipid constituents of cell membranes, including myelin. A heightened Cho peak may represent increased levels of free Cho, which can be expected in membrane disruption or turnover, as in inflammation, demyelination, and remyelination [273]. Pig models of TBI indicate that NAA/creatine (Cr) is diminished by at least 20 percent in regions of histologically confirmed axonal pathology in the face of negative findings from conventional MRI [274–275]. These findings suggest that MRS may be highly sensitive to microscopic pathology following diffuse brain injury.

Although MRS findings in moderate to severe TBI suggest a correlation with neuropsychological and functional outcomes (e.g., Brooks et al. [50]), such correlations have not been reported for mild TBI. Garnett et al. found that, compared with controls, Cho/Cr ratios of patients with mild TBI ($n = 6$ or 8, depending on classification) were elevated in frontal lobe white matter free of T1 or T2 lesions but NAA levels were not significantly different from normal [276]. All patients were scanned within 18 days of injury and no neuropsychometric testing was reported. Three of these patients had a repeat study about 4 months later [40], but no individual behavioral data or Cho/Cr data points were specified. Son et al. reported that NAA levels were reduced and lactate/Cr ratios were elevated at pericontusional white matter about 1 month after injury (no report of clinical correlate) and that these values improved after 2 months [277]. Cecil et al. reported decreased NAA in a single-voxel analysis in 35 patients with TBI (26 with mild TBI) in the splenium of the corpus callosum and lobar white matter, but clinical correlation was not established [48]. The subjects were scanned 9 days to 4.5 years (mean 1 year) postinjury, and the authors did not separate the mild TBI patients from the more severe TBI patients and do a separate analysis. Studies using MRS to account for cognitive deficits in mild TBI are sparse. In a group of 14 patients within 1 month of sustaining a mild TBI (many of whom had positive CT findings), NAA levels were lower in the parietal white matter bilaterally and Cho/Cr ratios were higher within two separate regions of the occipital gray matter [39]. No significant correlation was found in this small sample for Glasgow Outcome Scale at discharge or at 6 months after injury. In summary, MRS abnormalities have been described in mild TBI, but structural, functional, and clinical relevance need to be established.

Magnetic Resonance Spectroscopy in Posttraumatic Stress Disorder

Researchers have focused primarily on the medial temporal lobe/hippocampus and the anterior cingulate cortex (ACC) for MRS studies in PTSD. Many of these studies used single-voxel techniques and were thus limited to examining one large region at a time. For example, Ham et al. acquired spectroscopic data of a $15 \times 15 \times 15$ mm^3 volume in the ACC and bilaterally in the medial temporal lobe (each volume acquired separately) [278]. The authors found significant NAA decreases within all three volumes when comparing the metabolite levels of 26 survivors of a subway train fire who were diagnosed with PTSD with those of 25 healthy control subjects. Moreover, the NAA levels for the PTSD subjects were correlated with symptom severity. While the authors looked at NAA, Cho, and Cr levels, they only found significant differences in NAA levels. Other studies have found similar results in the ACC [97,279–280] and medial temporal lobe [91,97,280]. However, not all studies have found these differences. Seedat et al. compared NAA/Cr, Cho/Cr, and myo-inositol (mI)/Cr ratios from the ACC in female domestic violence victims (seven with PTSD, nine control subjects) [279]. In this small study, the authors did not find significant differences in NAA/Cr, but they did find a significant increase in Ch/Cr and mI/Cr ratios for the women with PTSD. Also, Freeman et al. examined 20 prisoners of war (10 with PTSD) and 6 controls and did not find any significant group differences in NAA/Cr or Cho/Cr ratios [281].

The most comprehensive spectroscopy study to date used spectroscopic and volumetric data to compare the association of PTSD and alcohol abuse with metabolite ratios and hippocampal volumes [280]. The authors used MRI, MRS (hippocampus), and MRSI (frontal/parietal region) to acquire data from 55 patients with PTSD (28 tested positive for alcohol abuse) and 49 control subjects (23 tested positive for alcohol abuse). The authors found that PTSD was associated with reduced NAA/Cr within both the hippocampus and ACC. Despite finding NAA reductions, the authors did not find any significant volume reductions. Also, the decrease in NAA/Cr associated with the PTSD patients could not be attributed to alcohol abuse.

ARTERIAL SPIN LABELING

Perfusion refers to the delivery of blood to a tissue or organ. Brain perfusion is also termed cerebral blood flow (CBF) and is expressed in units of milliliters/gram/minute,

reflecting the volume of flow per gram of brain tissue per unit time. Primary alterations in CBF occur in a number of central nervous system (CNS) disorders, most notably cerebrovascular disease, but because CBF changes are also coupled to neural activity, regional CBF measurements can be used to indirectly monitor neural activity both at rest and during task or pharmacological manipulations.

For MRI, the two most common methods for imaging perfusion are the dynamic susceptibility contrast approach, which detects the first passage of an intravascular contrast agent such as Gd-DTPA, and arterial spin labeling (ASL), which utilizes magnetically labeled arterial blood water as a diffusible flow tracer. Absolute quantification of tissue perfusion requires a tracer that can diffuse from the vasculature into tissue.

ASL techniques are completely noninvasive (and thus avoid the use of exogenous contrast agents) and can provide quantitative CBF images in standard physiological units of milliliters/gram/minute. ASL perfusion MRI should be particularly useful for multisite or longitudinal studies of brain function in which absolute quantification is critical. Absolute quantification also allows the resting state to be characterized, in contrast to BOLD fMRI, which primarily detects differences between two or more experimentally manipulated conditions. Thus, resting ASL perfusion MRI is useful for characterizing behavioral [213,282] or pharmacological [283] "states" and genetic "traits" [284] and complements BOLD fMRI studies of stimulus-evoked activity. For studies of task activation, ASL also provides sensitivity at extremely low task frequencies where BOLD fMRI becomes insensitive using standard parametric statistics because of low frequency noise [285]. Continual technical advances have dramatically improved the sensitivity of ASL perfusion MRI [282,286–291], and its use is likely to increase in the coming years.

In ASL techniques, arterial blood water is magnetically "labeled" using radio-frequency pulses. It is highly analogous to PET CBF measurements, which use water labeled with radioactive ^{15}O, except that the magnetically labeled arterial water "decays" with T1 relaxation rather than a radioactive decay. Depending on field strength, the T1 relaxation rate for water in blood or tissue is 1 to 2 seconds, which is much more rapid than the ~2 minute decay rate for ^{15}O. As a result, only small amounts of arterial spin-labeled water accumulate in the brain, though the temporal resolution is much faster than with $H_2{}^{15}O$-PET. A postlabeling delay allows labeled arterial spins to exchange with brain microvasculature and tissue [292]. The effects of ASL on brain image intensity are measured by comparison with a control image in which arterial blood is not labeled. Quantification of CBF requires a model that accounts for a variety of parameters, including T1 rates for blood and tissue, arterial transit times, and labeling efficiency [292–294]. Good correlations between ASL and ^{15}O-PET have been demonstrated both for resting CBF [295] and CBF during task activation [296].

ASL perfusion MRI has been used to study rat models of TBI [297–302], and more recently, it has begun to be applied to studies of TBI in humans. A wide variety of potential applications of ASL to TBI exist, including characterization of regional brain function in severe TBI for which task-evoked responses may be difficult to obtain, correlations of changes in regional CBF with attentional and other cognitive deficits to try to identify potential targets for pharmacological or transcranial magnetic stimulation therapy, and use as a biomarker of regional brain function for pharmaceutical trials (**Figure 3**).

High-speed helical CT scanners have facilitated the advent of CT perfusion studies to provide data such as CBF, blood volume, and mean transit times after intravenous administration of iodinated contrast material, which is an approach that is analogous to perfusion MRI based on dynamic susceptibility tracking. Although the need for exogenous contrast and exposure to ionizing radiation

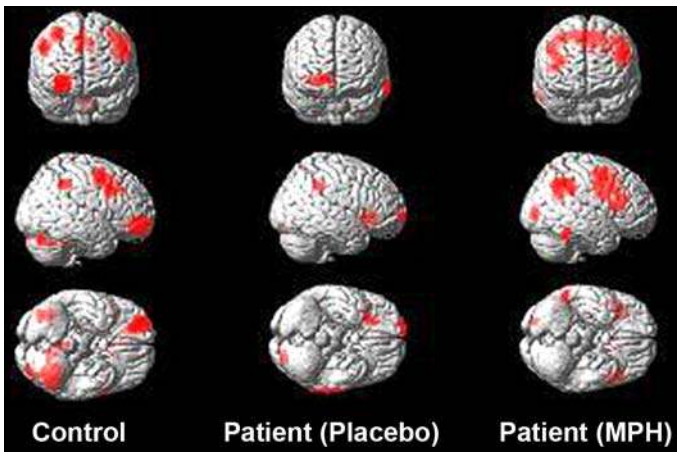

Figure 3.
Arterial spin labeling perfusion. Magnetic resonance imaging perfusion-based group activation maps obtained during letter 2-back working-memory task from control subjects (left) and patients with traumatic brain injury studied following either placebo (middle) or methylphenidate (MPH) (right). Frontal activation in patients is reduced on placebo when compared with activation in controls, but normal-appearing activation is restored after MPH administration. *Source*: Unpublished data courtesy of Junghoon Kim and John Whyte, Moss Rehabilitation Institute.

limits the number of measurements that can be made, CT perfusion imaging is emerging as a powerful and cost-effective tool that avoids logistical problems posed by monitoring equipment or surgical hardware required for MR studies [303].

SUSCEPTIBILITY-WEIGHTED IMAGING

The last of the MRI techniques that we will discuss in this review is SWI and its ability to recognize damage to the brain caused by bleeding, shearing, and loss of oxygen saturation [304–306]. SWI is an imaging technique that is exquisitely sensitive to microhemorrhaging and the presence of hemosiderin and deoxyhemoglobin. Data are usually collected with a resolution of 1.0 mm^3 at 1.5 T and 0.5 mm^3 at 3 T. The entire brain can be covered in less than 5 minutes with the use of parallel imaging with an excellent signal-to-noise ratio (SNR). Special processing incorporates the phase information into the magnitude information to enhance the contrast. Studies have shown that SWI is more sensitive to hemorrhagic lesions than are traditional MRI scans [41,51]. **Figure 4** shows an example of a conventional T2 scan, followed by three different images emanating from the SWI scan. In this case, multiple small lesions can be seen in the frontal lobe and another smaller microhemorrhage in the right side of the brain. SWI has been shown to have three to six times more sensitivity to microhemorrhages than conventional gradient echo imaging or any other imaging in MRI. To date, it has been used predominantly to study patients with severe head trauma, including coma patients [306]. It has also been used to image children [36,52,307].

MULTISITE STUDIES USING MAGNETIC RESONANCE IMAGING

Medical imaging for patient care invokes considerations at the levels of the individual patient and the individual imaging site. However, medical imaging in clinical research studies is often performed at multiple sites. This is true for large observational studies and is particularly true for therapeutic trials, which are nearly always conducted at multiple sites. The reasons for the this are fairly obvious. If one wishes to capture the relevant variation present across an entire population for a natural history study, then subjects must be recruited from multiple sites. The same considerations hold for therapeutic trials in which therapeutic efficacy across a representative range of the population must be demonstrated. In addition, recruiting the number of

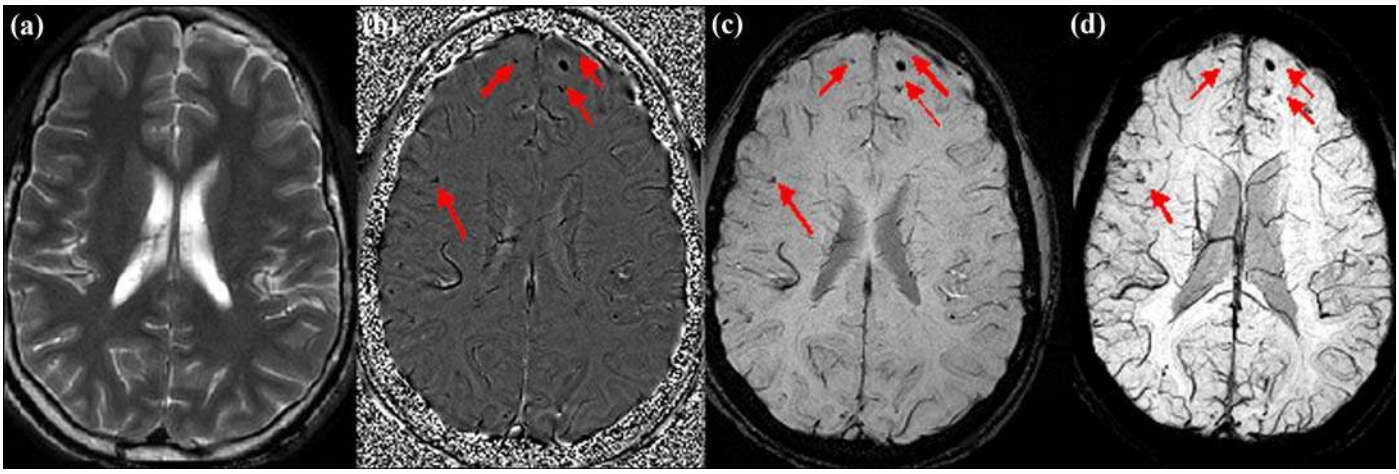

Figure 4.
Susceptibility-weighted image (SWI) example. Comparison of **(a)** T2-weighted, **(b)** SWI filtered phase, **(c)** processed magnitude, and **(d)** maximum intensity projection images on patient with traumatic brain injury, acquired on 3 T TRIO Siemens system. SWI has the following acquisition parameters: echo time/repetition time (TR/TE): 29/20 ms, flip angle: 15°, bandwidth: 120 Hz/pixel, 8-channel phased array coil with a parallel imaging factor of two, field of view (FOV): 256 × 256 mm^2, slice thickness: 2 mm, acquisition matrix: 512 × 416 × 64, spatial resolution: 0.5 × 0.5 × 2 mm^3. T2-weighted image acquired with T2 fast spin echo with TR/TE: 5000/113 ms, FOV: 256 × 256 mm^2, slice thickness: 2 mm, acquisition matrix: 320 × 320. Red arrows label multiple possible microhemorrhages invisible on both T1- and T2-weighted images (some not labeled). In this case, SWI data clearly demonstrate multiple possible microhemorrhages in brain.

subjects needed to power a study is often impossible at a single site.

Like other imaging modalities, MRI captures morphometric or functional data that provide useful information about pathological processes of relevance. That is, imaging measures serve as in vivo surrogates of relevant pathologies. Because of its flexible nature, MRI can provide information about a variety of anatomical and physiological brain processes. These processes include brain morphology, changes in relaxation properties, perfusion, diffusion, and metabolite concentration.

Variability in imaging data collected across different subjects or across individual subjects over time can be considered in three categories. First is the data variability due to the effect of the pathology one seeks to measure. For example, variability in brain volume may be due to presence and severity of AD or due to TBI. Second is data variability due to biology that is irrelevant to the pathology of interest. For example, brain volume may vary with hydration or nutritional status. Third is data variability due to technical or engineering-related factors. In any study, whether single site or multisite, the objective is to maximize the impact of biologically relevant data variability and minimize the impact of other sources of variability. The reason for this objective is self-evident; the more variability in a data set that is directly due to the pathology of interest, the more useful the imaging will be in probing the biologically relevant relationships. Conversely, irrelevant biological variability and engineering-related variability will only obscure the relationships between imaging and the pathology of interest. In designing multisite trials, unwanted data variability due to the irrelevant biology can be minimized to some extent by rigorous inclusion and exclusion criteria. But the source of undesirable data variability that is under greatest control is that due to technical or engineering-related factors.

A variety of specific items should be considered in the design of multisite trials. However, an overarching principle is that unwanted data variability due to technical factors can be minimized by standardization. And the principle of standardization applies in two dimensions: (1) across sites/scanners and (2) across time. MRI has been employed in numerous different multisite observational and therapeutic CNS studies, including studies on AD [308–311], mild cognitive impairment [312], cerebral vascular disease [308–314], and schizophrenia [315]. The remainder of this section will focus on specific features of the design of multisite CNS studies that were gleaned from the experience of the Alzheimer's Disease Neuroimaging Initiative (ADNI) [316]. In multisite studies, enrollment sites are selected on the basis of their ability to recruit and retain subjects meeting specific clinical criteria. Sites are typically not selected on the basis of access to advanced MRI equipment or expertise. Consequently, multisite studies must be performed across a broad array of hardware/software platforms and across sites with variable levels of expertise. State-of-the-art applications may not be available on all systems.

Some basic principles in the design and conduct of multisite CNS MRI studies follow. The main confound to address when different scanners at different sites are used is ensuring that equivalent sequences are being run with equivalent parameters on each scanner to ensure the same contrasts, artifacts, noise, etc. Further, each scanner used in the study should be qualified at baseline before subject enrollment and requalified after any hardware or software upgrades. "Qualified" means using a specific quality assurance (QA) protocol [317] with a specific phantom to ensure that the scanner is performing adequately. Each site should use the same type of phantom and QA protocol. Ideally, a single scanner should be used at each site for the entire study.

Tesla strength of MRI scanners at different sites may vary. If so, the sequences and specific parameters will need to be adjusted to maintain equivalent T1 and T2 weighting for all scanners across sites. Also, in the case of functional imaging, differences in SNR fluctuations between scanners need to be accounted for in postprocessing before activation across scanners/sites is compared [318].

Before start-up of the study, it might be highly useful to conduct a small pilot study of the proposed acquisition protocol on a representative group of systems. Such a pilot study will avoid the unfortunate situation in which incompatibilities between the study protocol and certain platforms are discovered after enrollment has begun. Electronically distributing system-specific protocols to each scanner used in the study is also helpful. Electronic distribution avoids the situation in which protocols are built manually from paper protocols on individual scanners, which dramatically increases the likelihood of protocol errors at individual sites. Imaging sequences in the protocol should be easy to prescribe and use by MRI technologists with a wide range of experience.

Ideally, the study protocol should avoid nonproduct imaging sequences to minimize administrative and regulatory overhead. A central quality control center is recommended. All protocol scans should be checked for protocol compliance, image quality, and medically significant

abnormalities. Identification of medically significant abnormalities by the MRI center should be used for subject inclusion and exclusion purposes. However, clinical interpretations of study scans should be the responsibility of the local enrollment site—i.e., medicolegal responsibility should reside locally, not with the research study.

Some means of monitoring scanner performance for site qualification purposes and throughout the study is useful. In the ADNI, a phantom scan is acquired along with each patient study. Measurements from these phantom scans allow identification of scanning errors that elude detection because the relevant information is not recorded electronically with the imaging data. Measurements from phantom scans can be applied retrospectively to correct drifts or discontinuities in the coupled human images, provided certain assumptions are met. Finally, despite detailed attention to standardization of acquisition and quality control, correcting residual abnormalities in the image data after the fact remains important. The types of corrections that may be useful are corrections for gradient nonlinearity, intensity nonuniformity, and drift or discontinuities in scanner calibration.

The preceding comments are largely recommendations derived from the experience of the ADNI. However, these considerations are relevant for any multisite study. To the extent that technical variation is reduced in a data set, the data set becomes a more useful and powerful tool for achieving the ultimate objective, which is the use of imaging as an in vivo surrogate of specific pathologies of interest. The large patient-population capabilities of multisite studies could be invaluable to combat-related TBI and PTSD research. For more information regarding multisite studies, see the ADNI (www.loni.ucla.edu/ADNI) or the Biomedical Informatics Research Network (www.nbirn.net) Web sites.

POSITRON EMISSION TOMOGRAPHY

PET imaging with the tracer [^{18}F] fluorodeoxyglucose (FDG) has been used for 3 decades to provide information about glucose metabolism in the human brain. Beginning with early studies that carefully validated tracer kinetic models [319] and extending through applications that involved studies of both normal cognition [320] and many disease states, the technique has become a robust approach to human clinical neuroscience. While studies of brain activation and cognition have largely been supplanted by fMRI, which has wider availability, higher spatial and temporal resolution, and no ionizing radiation, FDG-PET has continued to be applied to the study of human disease. This application is largely based on findings that show reductions in metabolism that are often regionally specific in numerous diseases. In addition, a host of basic studies strongly suggest that FDG-PET is a measure that parallels synaptic function [321], providing a good basis for interpretation of image findings.

One example is AD, in which reductions in posterior parietal, temporal, and posterior cingulate/precuneus cortex predominate [322–323]. These metabolic reductions are related to the neuropathological accumulation of amyloid plaques and neurofibrillary tangles, as has been revealed by several studies correlating the pattern of glucose hypometabolism with postmortem pathological evaluation [324–326]. While the recent introduction of techniques to image the accumulation of beta-amyloid offer the promise of a far more specific molecular approach to diagnosis of dementia [327–329], FDG-PET remains a popular technique for brain imaging because of its wide availability and large accumulated experience. Applications to a variety of diseases, including Huntington's [330], epilepsy [331], and brain tumors [332], have been published on extensively over decades.

A limited number of studies have been performed with FDG-PET to investigate TBI. Metabolic rates in the striatum and thalamus are lower in patients soon after episodes of TBI, and in subjects in coma, the thalamus, brainstem, and cerebellum are particularly affected and related to level of consciousness [333]. Dynamic PET studies suggest that these metabolic reductions are related to alterations in hexokinase activity and not to changes in glucose transport [334]. In chronic TBI patients with diffuse axonal injury, metabolic decreases are pronounced in the frontal cortex, temporal cortex, thalamus, and cerebellum and the severity of frontal lobe hypometabolism is related to cognitive function [335]. In particular, abnormalities of glucose metabolism in the cingulate gyrus may be related to neuropsychological function after TBI [336]. FDG-PET studies of patients with mild TBI have not revealed a consistent pattern of disturbances (see review in Belanger et al. [236]). However, with the advent of novel radioligands, new imaging techniques have emerged that may provide new insights into TBI and PTSD. For example, preliminary data suggest that amyloid-β (Aβ) plaques may be useful biomarkers of TBI.

IMAGING AMYLOID IN TRAUMATIC BRAIN INJURY

Head trauma has been identified as a potent risk factor for subsequent development of AD [337], and the connection between TBI and AD neuropathology has been reviewed recently [338]. In particular, cortical Aβ deposits have been observed in about one-third of biopsied temporal cortexes in patients with severe TBI as soon as 2 hours after injury, while tau-positive neurofibrillary tangles have been observed less frequently [339]. Recent advances in the development of imaging agents capable of quantifying regional Aβ plaque densities in living human brain by using PET or SPECT have made Aβ imaging studies in TBI subjects feasible.

The Aβ plaque deposition in TBI subjects and its relationship to long-term cognitive sequelae remain to be fully elucidated. Noninvasive longitudinal imaging studies capable of assessing Aβ plaque changes in TBI could play an important role in this regard.

The most utilized human Aβ imaging agents to date are the PET radioligands [^{18}F] FDDNP (fluoroethyl (methyl)amino]-2-naphthyl} ethylidene) malononitrile) and [^{11}C] PIB [326,338–342]. This area of research is active, and several other radioligands have been reported in human studies, including ^{123}I-labeled and other ^{18}F-labeled agents. Example of PET images from a study using [^{11}C] PIB to assess Aβ plaque pathology in AD is shown in **Figure 5** [342].

Future prospective investigations of long-term cognitive declines or AD development in subjects with TBI may be done in parallel with studies of amyloid (Aβ) deposition to see whether the latter can account for the former. Similar longitudinal studies are underway to determine whether amyloid-burden (Aβ) increases over time correlate with cognitive consequences in elderly patients at risk of AD. An example of a 2-year follow-up study using [^{11}C] PIB to assess Aβ plaque pathology in an elderly control subject is shown in **Figure 6** (University of Pittsburgh, unpublished data).

CONCLUSIONS

Detection and objective characterization of subtle but clinically significant abnormalities in mild TBI and PTSD are important objectives of modern neuroimaging. Several MRI methods have excellent potential to help visualize metabolic (via MRSI), microstructural (via DTI or, more specifically, FA), and functional network changes related to resting and cognitive states (fMRI, MR perfusion). In addition, new MRI methods (SWI) allow for better detection of

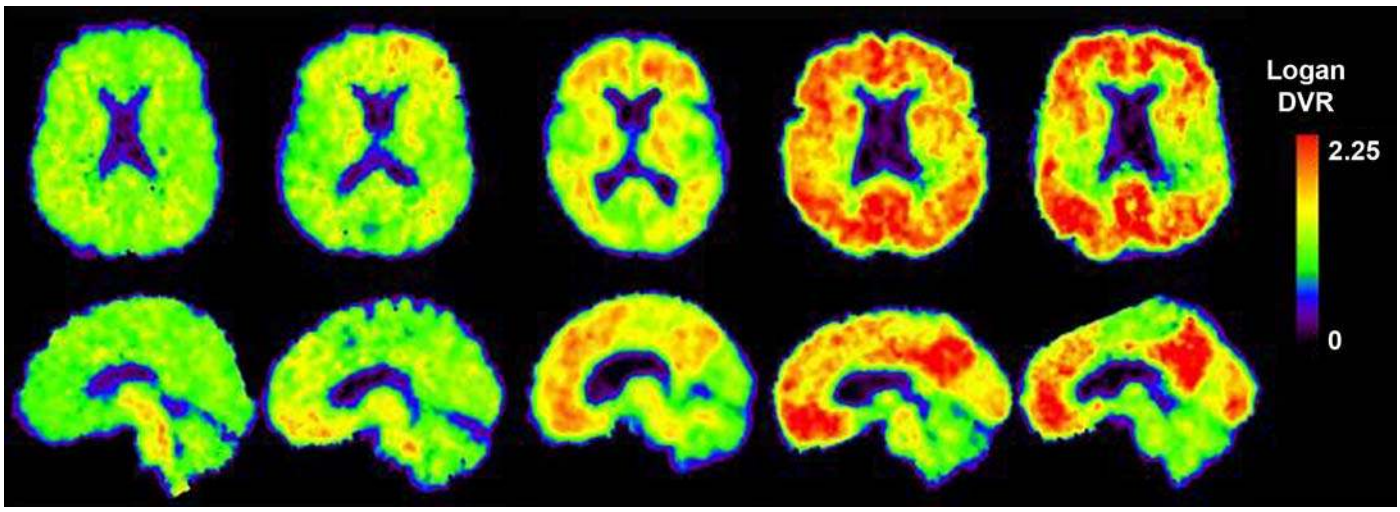

Figure 5.
Positron emission tomography (PET) example. PET images obtained with the amyloid-imaging agent Pittsburgh Compound B ([^{11}C] PIB) in normal control (far left), three different patients with mild cognitive impairment (MCI) (three center images), and patient with mild Alzheimer disease (AD) (far right). Some MCI patients have control-like levels of amyloid, some have AD-like levels, and some have intermediate levels. DVR = distribution volume ratio.

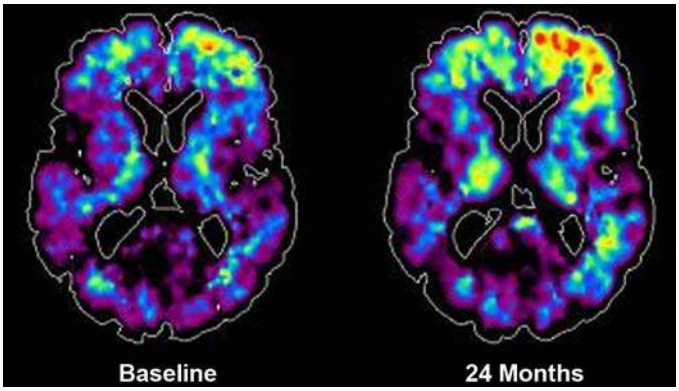

Figure 6.
Positron emission tomography (PET) amyloid-β (Aβ) plaque example. Increased retention of tracer in right frontal cortical area is seen over 2 years during which 74-year-old subject remained cognitively normal. Similar longitudinal PET imaging studies in traumatic brain injury subjects may help assess role and dynamics of Aβ deposition. *Source*: Unpublished data courtesy of University of Pittsburgh.

microhemorrhaging and could be particularly useful in the screening of servicemembers and veterans for lesions related to head trauma. The development of high-resolution imaging of hippocampal subfields may contribute to improved understanding of memory mechanisms in cerebral trauma or PTSD. PET methods may also provide insights into the metabolic and/or degenerative changes that may accompany these disorders.

Multimodal techniques may emerge as helpful orthogonal approaches to enhance the yield of detection and characterization of abnormalities. These methods may provide complementary information about the neural, glial, vascular, and network conditions that subserve cognitive and behavioral states. The development of multivariable models combining structural, neurochemical, physiological, and psychophysical or neurobehavioral findings can be anticipated to be an active area of future research. Future imaging studies of prospective, controlled clinical trials with parallel neuropsychological testing and rehabilitation also hold promise for elucidating mechanisms of learning or relearning. Potential information about predilection, distinguishing neural signatures, objective assays for monitoring recovery and response to treatment, and prognosis for patients may all come to fruition as a result of the continued advances in neuroimaging. Thus, neuroimaging may provide information that contributes substantially to the development of improved, rational approaches to the management of patients with TBI and PTSD.

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