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Neuroimaging in Blast-Related Mild Traumatic Brain Injury

Weiya Mu, BA; Eva Catenaccio, BA; Michael L. Lipton, MD, PhD

Objective: To summarize imaging findings in blast-related mild traumatic brain injury. **Design:** Our structured review of the literature yielded 5 structural magnetic resonance imaging (sMRI), 18 diffusion tensor imaging, 9 functional magnetic resonance imaging (fMRI), 3 positron emission tomography, 4 magnetoencephalography, 2 electroencephalography, and 1 single-positron emission computerized tomography studies. **Results:** Four of the 5 sMRI studies reported decreased cortical thickness and decreased thalamus and amygdala volume. Diffusion tensor imaging studies showed abnormal diffusion within white matter tracts commonly associated with traumatic brain injury, including the corpus callosum (8 of the 18) and superior longitudinal fasciculus (8 of the 18). Resting-state fMRI studies reported a variety of functional network differences. Other functional imaging studies showed diffuse changes in activity, especially in the frontal, parietal, temporal, and cingulate regions. **Conclusion:** Vast variation in the sample, design, and measurement features across studies precludes salient conclusions regarding the effectiveness of neuroimaging to assess outcomes and elucidate pathomechanisms. The inherent spatial heterogeneity of mild traumatic brain injury pathology presents a major challenge to meaningful convergence across and generalizable inferences. Approaches to standardize methodology and facilitate access to data and integration across studies hold promise for enhancing our understanding of this complex brain disorder, but can only bear fruit if they are actually consistently implemented. **Key words:** *blast*, *imaging*, *mild traumatic brain injury*, *veterans*

BLAST-RELATED TRAUMATIC BRAIN INJURY (TBI) is very common among veterans of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF).[1] Traumatic brain injury occurs when force is transmitted to the brain with consequent disruption of brain functioning because of cellular or subcellular injury.[2,3] Many diagnostic criteria have been proposed for the diagnosis of mild traumatic brain injury (mTBI) including loss or alteration of consciousness (LOC or AOC) for less than 20 to 30 minutes, posttraumatic amnesia lasting less than 24 hours, and/or a Glasgow Coma Scale score of 13 to 15.[4] In combat settings, the Military Acute Concussion Evaluation is often used to assess acutely injured warriors; poor performance on the Military Acute Concussion Evaluation is correlated with greater injury severity and longer postinjury recovery time.[5] However, because of the nature of the combat setting, records of time-of-injury assessments may be incomplete. Lack of standardized assessment of initial injury severity is a major, and at present perhaps insurmountable, weakness of studies that investigate blast-related mTBI. Even when records of the acute period are made, they may not be accessible to subjects or researchers.

The mechanisms of blast-related mTBI may differ from those of impact or blunt mTBI. In addition to the whiplash or head rotation commonly implicated in blunt TBI,[6] the blast pressure wave passes through the skull[6] and is also transmitted to the brain through large cervical blood vessels after compression of the thorax.[7] These mechanisms of primary blast injury are not mutually exclusive. Furthermore, they are typically complicated by secondary injury when the head is struck by flying debris, and/or tertiary injury when the body is thrown and the head strikes the ground or other structures/objects. Although experimental studies have characterized the isolated effects of blast on animals, mechanisms underlying primary blast mTBI cannot be differentiated from secondary or tertiary injury in humans, and are unlikely to actually occur in isolation. Blast-related mTBI outcome is also complicated by its occurrence in the setting of combat stress; there is considerable overlap between postconcussive symptoms (PCS) and those of posttraumatic stress disorder (PTSD) and major depressive disorder (MDD), among other combat-related neurobehavioral disorders. Symptom overlap also impedes appropriate diagnosis and treatment, which itself motivates the use of

Author Affiliations: *Albert Einstein College of Medicine, Bronx, New York (Mss Mu and Catenaccio and Dr Lipton); Montefiore Medical Center, Bronx, New York (Dr Lipton).*

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Corresponding Author: *Michael L. Lipton, MD, PhD, Albert Einstein College of Medicine, 1300 Morris Park Ave, Bronx, NY 10461 (michael.lipton@einstein.yu.edu).*

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neuroimaging to characterize combat-related mTBI. Despite diagnostic challenges, blast-related mTBI in veterans of OEF/OIF is widely recognized as a pressing public health issue.

Clinical neuroradiologic assessments of conventional computed tomography (CT) and magnetic resonance imaging (MRI) are characteristically unrevealing in mTBI. Advanced and quantitative neuroimaging techniques, however, offer a unique opportunity to quantify structural and functional changes. Noninvasive imaging techniques reveal the evolution of mTBI over time and can be correlated with PCS, cognitive function, PTSD, MDD, and other sequelae. This systematic review of the literature on neuroimaging of blast-related mTBI includes structural MRI and diffusion tensor imaging, and functional neuroimaging techniques of functional magnetic resonance imaging, positron emission tomography, magnetoencephalography, electroencephalography, and single-photon emission computed tomography. After describing and assessing the studies' findings, we provide an assessment of the salient conclusions that can and cannot be drawn from this literature and offer suggestions for moving the field forward toward meaningful and generalizable inferences that can improve recognition and treatment of blast-related mTBI.

METHODS

In consultation with 2 research librarians, we searched PubMed for articles published before August 2014 using search terms listed in Table 1. A total of 325 articles were identified. Exclusion criteria included language other than English, focus on moderate or severe TBI, focus on disease processes other than TBI, nonclinical studies (eg, animal studies and computational models), reviews, case reports, and abstracts. When a relevant article was found, the "Related Citations in PubMed" feature was used to look for additional articles. Because of the very limited literature on blast-related mTBI before OEF/OIF, and differences in the nature of warfare and injuries sustained during earlier military engagements, we did not include the latter articles in the current analysis.[8,9] A total of 34 articles met criteria for inclusion and are included in this review.

Definition of mTBI

A summary of criteria used to define mTBI is shown in Table 2. The most commonly used criteria include AOC, LOC less than 30 minutes, and posttraumatic amnesia less than 24 hours. Four articles used the American Congress of Rehabilitation criteria,[10] 9 studies used the Department of Defense criteria,[11] and the rest used study-specific definitions of mTBI. Although there is variation in how authors defined mTBI, these differences likely did not contribute to the differences in outcomes, as each patient must only fulfill one criterion to be diagnosed with mTBI.

Structural magnetic resonance imaging

In uncomplicated mTBI, by definition, acute conventional CT and MRI are unremarkable. The identification of abnormalities on clinical images by visual inspection in patients who otherwise exhibit symptoms in the mTBI range confers a classification of "complicated mTBI." Even when these images *appear* normal, however, quantitative morphometry may reveal significant loss of brain volume.

Five cross-sectional studies used structural magnetic resonance imaging (sMRI) for quantitative volumetric assessment, examining a total of 136 veterans (see Table 3).[12–16] All mTBI examined were combat-related,

TABLE 1 *PubMed search terms*[a]

OR		OR		OR
Blast	**AND**	Mild traumatic brain injury	**AND**	Imaging
Combat		mTBI		Neuroimaging
Veteran		Concussion		MRI
Explosive				DTI
				fMRI
				PET
				MEG
				EEG
				CT
				SPECT

Abbreviations: CT, computed tomography; DTI, diffusion tensor imaging; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; MRI, magnetic resonance imaging; mTBI, mild traumatic brain injury; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

[a]Key words from the same column were combined with the Boolean operator "OR," and the 3 columns were combined with the operator "AND."

TABLE 2 *Definitions of mTBI*

Criteria	*n* (article)
AOC	22[12–16,21,23–26,28,31,34,36,38,41,56,57,62–65]
<20 min	3[27,33,37]
<30 min	2[29,30]
LOC	3[24,25,65]
<15 min	1[35]
<20 min	3[27,33,37]
<30 min	23[12–16,23,26,28–31,34,36,38,40,41,43,45,56,57,62–64]
PTA	2[25,65]
<24 h	22[12,14,15,23,24,26,28–31,34–36,38,41,43,45,56,57,62–64]
PCS	9[21,23–25,35,38,45,62,63]
Focal neurologic symptoms	4[28,34,36,56]
Normal MRI/CT	12[12,15,26,29–31,40,41,43,45,57,64]
None stated	4[32,42,44,66]

Abbreviations: AOC, alteration of consciousness; CT, computed tomography; LOC, loss of consciousness; MRI, magnetic resonance imaging; PCS, postconcussive symptoms; PTA, posttraumatic amnesia.

though only one study specifically targeted blast mTBI.[12] All studies used high-resolution T1-weighted MRI with automated quantitative whole-brain analysis completed using atlas-based parcellation (eg, Freesurfer) or voxel-based morphometry (VBM; eg, FSL). Two studies also used region of interest (ROI) analyses in addition to whole-brain VBM.[13,14]

Regions found to have decreased cortical thickness included the frontal[12,14] and temporal lobes,[12] and decreased volumes were identified in the amygdala (associated with impulsivity)[15] and thalamus (associated with suicidal ideation)[13] (see Table 4). One study, however, did not find any volumetric differences between combat mTBI patients and healthy controls.[16] Depue et al[15] quantified injury severity on the basis of the length of LOC and number of symptoms related to the most recent mTBI. However, these data were not included in their analysis of imaging data. Another study specified time since mTBI (mean = 103 days), and examined the relationship between time since blast and volumetric findings, though no association with volumetric measures was found.[12]

The widespread reduction in cortical thickness reported across studies is consistent with the diffuse nature of blast-related mTBI including the component of brain injury that may arise from increased intravascular pressure because of thoracic compression by the blast pressure wave. Given the small number of studies reporting significant findings, minimal overlap between studies in abnormal brain regions, and lack of focus specifically on blast in at least some studies, it is difficult to disambiguate the component of variance because of these factors from the variable manifestations of blast-related mTBI itself in sMRI. Methodological consistency in future studies and comparison of blast-related mTBI and non-blast-related mTBI could address the specific and potentially unique additive role of blast in mTBI.

Diffusion tensor imaging

Structural MRI identifies loss of brain volume, which may be a late effect of direct gray matter trauma such as cortical contusion, but may also represent a late effect of microscopic traumatic axonal injury (TAI), a pathology that is not directly detectable using macrostructural sMRI. Diffusion tensor imaging (DTI), however, indexes white matter microstructure, as a function of the directional coherence of water diffusion.[17] The ability of DTI to detect TAI in mTBI, even in the absence of abnormalities on conventional neuroimaging, is well-established and of great research and clinical interest.[18,19] Most DTI studies report fractional anisotropy (FA), a summary measure of directional coherence of water diffusion, which decreases in the presence of TAI.[18,20] Although other DTI metrics, such as relative anisotropy, axial diffusivity, radial diffusivity, and mean diffusivity, may provide more granular insight into underlying mechanisms of TAI, too little data have been reported to date to allow an appreciation of their added contribution.

We identified 18 studies that applied DTI to a total of 489 veterans with mTBI.[13,16,21–36] All studies focused on mTBI, though 2 studies also compared mTBI with moderate/severe TBI in separate analyses,[24,31] and one study included patients with TBI of all severities.[16] Table 3 shows demographic, blast, and chronicity characteristics of these samples, as well as exclusion criteria applied in the studies. Because blast-related mTBI occurs in the setting of active combat, and because many warriors experiencing mTBI continue on duty and/or do not leave the combat theater for treatment, it is highly exceptional

TABLE 3 *Number of studies, subject characteristics, exclusion criteria, and chronicity in each imaging method*

	sMRI	DTI	fMRI	PET	MEG	EEG	SPECT
Total number of studies	5	18	9	3	4	2	1
Blast mTBI subjects	136	489	242	59	78	38	16
Mean age	27.9	32.7	27.5	31.4	27.6	30.5	30
Male, %	95.0% (115/121)	98.4% (311/316)	97.5% (236/242)	100%	100% (78/78)	100% (38/38)	100%
1° blast injury only		33[26,29]		12[57]			
Blast + 2°/3° injury	136[12–16]	456[13,16,21,23–25,27,31,33,35]	242[32,33,37,40–45]	47[34,56]	78[35,62–64]	38[36,65]	16[66]
Include nonblast mTBI	124[13–16]	168[13,16,21,28,31]	51[32,40,44]		3[64]	3[65]	
Include moderate/severe TBI		89[16,24,31]					16[66]
Controls	79	276	167	42	155	8	0
Mean age	33.3	32.8	29.7	38.0	28.9	30.3	
Male, %	92.4% (73/79)	96.0% (265/276)	96.4% (161/167)	85.7% (36/42)	92.3% (143/155)	100% (8/8)	
Military w/o blast/mTBI	56[12,14,15]	165[23,24,26,28–31,38]	73[32,41–44]	18[34]			
Civilian w/o blast/mTBI		10[16]	44[42]	12[56]			
Mixed or unstated	32[13,16]	32[13,16]	50[45]		155[35,62–64]	8[36]	
No unexposed controls[a]		21[21,25,27,33]	0[33,37,40]	12[57]		0[65]	
Exclusion criteria							
None[b]		3[21,31,32]	1[32]				
Neurological disease	5[12–16]	8[16,24,27,28,30,33,38]	7[33,37,40–43,45]	3[34,56,57]	3[35,62,63]	2[36,65]	1[66]
Psychiatric disease	1[12]	10[13,16,23–26,28,29,34,38]	2[41,43]	1[57]	3[35,62,63]	2[36]	
Allowed MDD, PTSD, and/or AUD/SUD	4[13–16]	5[13,16,28,30,34]	6[33,37,40,42,44,45]	2[34,56]	2[35,63]	1[65]	1[66]
Prior TBI		4[25–27,33]	3[41,43,45]				
Chronicity[c]							
<3 mos	1[12]	2[23,25]	1[41]		2[62,63]		
3–12 mos	1[12]	1[25]	1[41]		2[62,63]		
>12 mos		18[13,16,21,24,26–36,38]	5[32,33,37,42,43]	3[34,56,57]	3[35,62,63]	1[36]	1[66]
Unreported[d]	4[13–16]		3[40,44,45]	1[40]		1[65]	

Abbreviations: AUD, alcohol use disorder; DTI, diffusion tensor imaging; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MDD, major depressive disorder; MEG, magnetoencephalography; mTBI, mild traumatic brain injury; PET, position emission tomography; PTSD, posttraumatic stress disorder; sMRI, structural magnetic resonance imaging; SPECT, single-photon emission computed tomography; SUD, substance use disorder; TBI, traumatic brain injury.

[a] No controls used,[21] veterans exposed to blast without clinical symptoms,[21,25,27] veterans with blunt but no blast mTBI.[57]

[b] Except for contraindications to MRI.

[c] All time points of longitudinal studies are included in this table.

[d] Unreported timeframes for injuries are likely chronic, as these patients are recruited from Veterans Affairs care centers and the community.

TABLE 4 *Location of abnormal brain structure or activity for each imaging modality and type of task used*

Brain region	sMRI sMRI	fMRI resting	fMRI emotion	fMRI cognitive	PET resting	MEG resting	EEG resting	SPECT resting
Prefrontal		1[41]	2[33,44]	3[37,40,41]		2[35,62]	2[36,65]	
Frontal	2[12,14]	2[32,41]	1[33]	3[41–43]	1[57]	4[35,62–64]	2[36,65]	1[66]
Parietal		1[41]	1[33]	3[41–43]	2[34,57]	4[35,62–64]	1[65]	1[66]
Temporal	1[12]	1[41,45]	1[33]	2[41,42]	2[56,57]	4[35,62–64]		1[66]
Occipital		1[41]	1[33]	2[42,43]	2[34,56]	3[35,62,63]		1[66]
Temporo-occipital		1[45]						
Insula		1[41]		1[43]				
Cingulate		2[32,41]	1[44]	4[40–43]	1[46]	2[35,63]	1[65]	
Subcallosal gyrus			1[44]					
Fusiform gyrus					1[56]	1[63]		
Operculum						1[63]		
Parahippocampal gyrus					1[34]	1[63]		
Hippocampus						1[62]		1[66]
Thalamus	1[13]		1[33]		1[57]			1[66]
Caudate nucleus					1[46]			
Amygdala	1[15]		2[33,44]	1[42]				
Cerebellum			1[33]	1[43]	1[56]	1[62]		1[66]
No change	1[16]							

Abbreviations: DTI, diffusion tensor imaging; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; PET, position emission tomography; sMRI, structural magnetic resonance imaging; SPECT, single-photon emission computed tomography.

for sophisticated brain imaging to be performed within the early postinjury period. Notably, only 3 of the 18 studies applied no exclusion criteria.[21,31,32] Extensive exclusion criteria used by the other studies may significantly skew the nature of their samples, with important implications for generalizability of results to combat-related mTBI in general.

Seventeen of the 18 studies compared mTBI subjects with a control group; 3 of these studies compared veterans with blast-related mTBI with veterans exposed to blast who did not develop symptoms of mTBI. Only one study performed a within-subject analysis comparing DTI to measures of PTSD, but not employing a separate control group (see Table 3). Regional image analysis techniques included a priori ROI (10 of the 18 studies) and tractography-defined ROI (4 of the 18) analyses. Whole-brain voxel-wise analyses, including tract-based spatial statistics, were used by 11 of the 18 studies. Some studies thus applied more than one analytic approach.[24,31,35]

As is characteristic of DTI studies of TBI in general, 14 of the 18 studies we included compared DTI metrics between mTBI subjects and controls only *at the group level*.[18] Four of the 18 studies, however, individually assessed DTI metrics from individual subjects, comparing the values from each individual with those from the control group, with abnormality defined, for example, by a Z-score threshold. In this manner, Mac Donald et al[25] found that within 90 days of injury, 25 of the 63 (40%) patients with blast mTBI showed no abnormality of FA across 17 ROIs, 20 of the 63 (32%) exhibited decreased relative anisotropy in 1 ROI, and 18 of the 63 (29%) showed a decrease in relative anisotropy in 2 or more ROIs; at their follow-up visits 6 to 12 months later, regions of abnormality persisted in 11 and the 12 subjects with mTBI who initially showed 2 or more areas of abnormality. Mac Donald et al[26] found that 3 of the 4 patients with pure primary blast-related mTBI showed diffusion abnormalities in the cerebellar white matter. Huang et al[35] found that 4 patients with blast mTBI each showed unique regions of decreased FA. The sensitivity of DTI to mTBI pathology in these 3 studies that analyzed DTI at the individual subject level ranged from 60% to 100%. Taber et al[29] found that at the individual level, FA measurement was a predictor of reaction time and spatial working memory. Although few studies of combat-related mTBI have used an individualized approach to DTI, on the basis of the highly variable nature of mTBI and apparent advantages of this approach, not to mention the clinical need for individualized assessments, it is critical that future studies incorporate subject-level assessment of DTI.

Additional methodological heterogeneity across studies pertains at the level of instrumentation. Either 1.5-T (5 of the 18) or 3.0-T (13 of the 18) MRI was used to perform DTI in each study, with 15 of the 18 studies

employing a single b-value and 3 studies using a multishell method.[27,28,32] In addition to this variation in field strength, a range of imaging parameter choices was employed across studies. The number of gradient directions ranged from 23 to 64, voxel size ranged from 8 to 15.6 mm^3, and the b-value employed ranged from 700 to 1750 s/mm^2.

Fractional anisotropy is the most commonly reported diffusion metric (see Table 5). When studies examined more than one diffusion metric, at least partial overlap of regions of abnormality was always found across metrics. There were also, however, areas of discordance where abnormalities were detected with one metric but not with another. For example, Bazarian et al[21] found FA changes associated with mTBI in the inferior cerebellar peduncle, but there were no changes in mean diffusivity in this region. Because few studies examined measures other than FA (see Table 5), the relative efficacy and implications of each measure cannot yet be ascertained. Standardized comprehensive reporting of all DTI metrics in publications can facilitate comparison of the different diffusion metrics because, by definition, all metrics are available whenever a DTI study is performed; these values could easily be reported even were they not the focus of a given study. In addition, initiatives that archive DTI datasets at the image level, such as the Federal Interagency TBI Repository, permit post hoc analysis of these additional DTI metrics even when they are not reported in the initial study publication.

The number of studies reporting diffusion abnormalities in specific brain regions is summarized in Table 5. The superior longitudinal fasciculus (SLF), corpus callosum (CC), thalamic radiations, and internal capsule were the regions most commonly identified as abnormal. Voxel-wise methods, including tract-based spatial statistics, and studies employing 3.0-T instruments seem more likely to show abnormalities in the SLF than ROI methods; similar patterns of sensitivity were not evident regarding the other most commonly abnormal regions (see Table 5). The prominence of involvement of the CC and SLF is unsurprising given their biomechanical susceptibility to rotational forces and their established vulnerability to TBI. The relative sensitivity of voxel-based analyses to abnormality in these regions highlights the constrained nature of ROI analyses, which limit potential for detection to a predefined menu of locations and suffer more seriously from partial volume effects. On the other hand, only the ROI methods found abnormalities in the cerebellar peduncles, supporting the concept that sensitivity and specificity may vary by the analytical method, and perhaps by the subject sample.

Interestingly and perhaps unsurprisingly, 5 studies reported no significant DTI findings. Two of these combined military and civilian controls, which may have affected results. This latter discrepancy underscores the incompletely understood role of control group selection in the outcome of DTI studies. If findings in combat-related mTBI were simply due to baseline group characteristics, why would multiple studies *not detect* abnormalities (see Discussion)? Regardless, wide variation in data acquisition parameters and analysis methods makes comparison across studies difficult at best.

The nature of blast exposure is notoriously difficult to assess, given the complete absence of contemporaneous validated or even systematic means for characterizing severity. Nonetheless, studies have attempted to characterize exposure severity as number of blast exposures,[13,16,21,23,28,33–35,37] history of single versus multiple blasts,[30,38] and primary blast versus non-blast or mixed injury.[16,21,26,28,30] Petrie et al[34] found that when blast mTBI veterans were grouped by number of blasts (1–5, 6–19, and 20–100), the locations of lower macromolecular proton fraction identified using DTI were different for each exposure level when compared with controls. Davenport et al,[38] however, found no significant changes related to number of blasts. Morey et al[28] found that f1 (partial volume fraction) was associated with duration of LOC in similar regions as those identified when mTBI subjects were compared with controls, but did not demonstrate any association of DTI with the number of mTBI. Although these findings are of interest and support the basic relation of blast exposure to mTBI, validated quantitative measures of exposure severity, a tall if not unachievable order, are necessary to characterize parametric relations of exposure and imaging abnormalities.

Studies generally focused on the identification of brain abnormality in subjects with mTBI, which is similar to DTI studies of TBI in general. However, the clinical significance of imaging abnormalities must be established to advance clinical care. Six of the 18 studies incorporated functional outcome data into the imaging data analyses (see Table 6). The only consistent finding among these studies was an association of diffusion measures in the splenium of the CC, with performance on tasks of short-term memory in 2 studies. This limited convergence of findings across studies must not be taken as an indication that DTI does not index functionally meaningful alterations. The absence of evidence can simply arise from the fact that studies vary in many important ways in the context of a highly heterogeneous disorder.

Functional magnetic resonance imaging

In contrast to sMRI and DTI, which detect macro- and microstructural consequences of mTBI, respectively, functional magnetic resonance imaging (fMRI) reveals the functional state of gray matter in response to a task or at rest.[39] Functional MRI measures neuronal function

TABLE 5 *Brain regions demonstrating abnormal diffusion on diffusion tensor imaging by total number of studies, analytical technique, and diffusion parameter*

		Analysis				Parameters				
Region	***n* (studies)**	**ROI**	**Tractography**	**Voxel**	**TBSS**	**FA**	**MD**	**AD**	**RD**	**Other**
Brainstem	3			1[31]	3[27,28,31]	3[27,28,31]				
Cerebellar peduncle										
Superior	1	1[26]				1[26]				
Middle	3	3[25,26,31]				2[26,31]				2[25,26]
Cerebral peduncle	1				1[31]	1[31]				
Cerebellar WM	1				1[31]	1[31]				
CC (unspecified)	4	1[25]	1[31]	1[33]	1[28]	3[28,31,33]				2[25,28]
Splenium	2	1[30]			1[28]	2[28,30]				1[28]
Body	3	1[30]			2[27,28]	3[27,28,30]				1[28]
Genu	4	2[16,30]		1[34]	1[28]	4[16,28,30,34]				1[28]
Tapetum	2				2[28,35]	2[28,35]				1[28]
Corona radiata	4	1[31]	1[31]	2[31,33]	3[27,28,31]	4[27,28,31,33]				1[28]
Forceps major	4	2[36,38]			2[28,29]	4[28,29,36,38]				1[28]
Forceps minor	3	2[36,38]			1[28]	3[28,36,38]				1[28]
Cingulum	5	4[16,25,30,31]		1[32]	1[31]	4[16,30–32]			1[30]	1[25]
Fornix	1			1[31]		1[31]				
Uncinate fasciculus	2	1[25]		1[31]		1[31]				1[25]
FOF	4	2[31,38]		1[31]	2[27,29]	4[27,29,31,38]				
SLF	8	1[38]		3[31,33,34]	4[27–29,35]	7[27–29,31,33,35,38]				2[28,34]
ILF	4	2[31,38]		1[31]	2[27,29]	4[27,29,31,38]				
Localized WM										
Frontal	4	3[25,30,31]		1[34]		3[25,30,31]				2[25,34]
Parietal	2			1[34]	1[31]	1[31]				1[34]
Temporal	1	1[31]				1[31]				
Occipital	1	1[31]				1[31]				
Cingulate	2			1[34]	1[27]	1[27]				1[34]
Parietal-temporal	1				1[35]	1[35]				
Temporal-occipital	3		1[31]	1[34]	1[35]	2[31,35]				1[34]
Thalamic radiations	6	3[31,36,38]			3[27–29]	6[27–29,31,36,38]				1[28]
Internal capsule	6	2[25,30]	1[31]	2[31,34]	3[27,28,31]	3[27,28,31]		1[30]		3[25,28,34]
Corticospinal tract	3	1[38]		1[31]	1[29]	3[29,31,38]				
External capsule	2			2[31,34]		1[31]				1[34]
Deep gray matter	1	1[31]		1[31]		1[31]				
No change[a]	5	3[13,16,21,24]	1[24]		2[23,29]	3[13,23,24]	2[16,23]	1[29]	1[29]	1[24]

AD, axial diffusivity; CC, corpus callosum; FA, fractional anisotropy; FOF, fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; MD, mean diffusivity; RD, radial diffusivity; ROI, region of interest; SLF, superior longitudinal fasciculus; TBSS, tract-based spatial statistics; voxel, whole-brain voxel-wise analysis; WM, white matter.

[a]No specific regions identified, but some numbers of voxels or clusters were found to be changed from controls.[21,23,29]

TABLE 6 *Brain regions demonstrating associations between diffusion abnormality and clinical outcomes*

Region	PCS	PTSD	MDD	Memory	Executive function	Suicidal ideation	Impulsivity
Pons				1[31]			
Cerebral peduncle					1[31]		
Cerebellar peduncle							
Superior		1[31]					
Middle				1[31]			
Cerebellar WM				1[31]	1[31]		
Corpus callosum	1[24]	1[24]			1[23]		
Splenium				2[24,31]			
Body			1[27]	1[31]	1[31]		
Genu					1[31]		1[16]
Corona radiata				1[31]	1[31]		
Cingulum		1[31]	1[16]		1[31]	1[16]	1[16]
Fornix					1[31]		
IFOF					1[24]		
Uncinate fasciculus					1[24]		
Cingulate gyrus			1[27]				
Parietal WM					1[31]		
Occipital WM					1[31]		
Thalamic radiation			1[13]				1[13]
Internal capsule		1[31]		1[24]	1[24]		
Deep gray matter		1[31]			1[31]		

Abbreviations: IFOF, inferior fronto-occipital fasciculus; MDD, major depressive disorder; PCS, postconcussive symptoms; PTSD, posttraumatic stress disorder; WM, white matter.

indirectly, through the hemodynamic response to metabolic demand driven by synaptic activity, and allows high-resolution noninvasive assessment of brain function in blast mTBI.

We identified 9 fMRI studies, which reported on a total of 242 veterans with blast-related mTBI (see Table 3).[27,32,33,37,40–44] Six studies employed task-based fMRI; 2 of these studies used emotional processing tasks[33,44] and 4 used tests of executive function.[37,40,42,43] The remaining 3 studies performed resting-state fMRI.[32,41,45] All studies performed T2-weighted blood oxygenation level-dependent fMRI at 1.5 T[41] or 3 T,[32,33,37,40,42,43,45] with one study not reporting field strength.[44] Echo time ranged between 27 and 50 ms. Voxel size used ranged from 16.0 to 52.7 mm^3; an interslice gap of 0.5 to 1.4 mm was employed across the 5 studies that reported this parameter.[32,33,37,40,43] Analysis programs included are Analysis of Functional Neuroimages,[46] Statistical Parametric Mapping,[47] Group Independent Component Analysis fMRI Toolbox,[48] and Brain Connectivity Toolbox.[49] Voxelwise[33,37,40–45] and ROI methods[32,33,41,42,44] were used for analysis, and effects of interest included magnitude of signal change[33,37,42–45] and correlation coefficient.[32,41] Some authors characterized blast exposure severity by direction of blast,[45] number of exposures,[33,37,43,45] single versus multiple blasts,[42] and blast versus blunt or mixed injury.[40,42,43,45] Remarkably, however, none of these studies incorporated the exposure severity estimates in the analyses of fMRI data. A summary of brain regions where significant fMRI effects were reported is shown in Table 4.

Task-based fMRI assessing emotional processing was focused on subgroups of subjects with mTBI with psychiatric disorders. One task-based fMRI study compared patients with blast mTBI with and without MDD.[33] Subjects performed an emotional face-matching task, matching a face displaying happiness, anger, or fear, or a random shape with 1 of 2 probe images. In an ROI analysis focused on the amygdala, patients with MDD showed greater activation bilaterally than those without MDD when processing fearful faces. Roy et al[44] used an affective Stroop task employing emotional pictorial cues and neutral cues (numbers) and also found that veterans with PTSD and/or mTBI had increased activation in the amygdala. Other results of these studies are summarized in Table 4.

Executive function, a cognitive domain strongly associated with mTBI, was explored in the largest number of task-based fMRI studies. Scheibel et al[43] used a stimulus-response compatibility task. No significant task-related activation was elicited from healthy controls, but there was widespread task-related activation in patients with blast mTBI (see Table 4). The remaining 3 task-based fMRI studies used a stop signal task to probe response inhibition, also finding widespread

task-related activation in patients with blast-related mTBI compared with unexposed controls (Table 4).[37,40,42] Fischer et al[42] uniquely employed 4 subject groups in their fMRI study: military mTBI, military control, civilian mTBI, and civilian control. In addition to abnormal activation when compared with control groups, patients with military-related mTBI had greater activation in the temporal lobe, caudate, and cerebellum than those endorsing civilian mTBI. It is important to consider that the neuropsychological tests on which fMRI tasks are based were primarily developed to index localized cortical function.[50] mTBI, however, is primarily a white matter injury.[18] Damage to the white matter network connecting cortical regions may lead to the diffuse cortical dysfunction found in these studies. The findings across task-based fMRI studies are consistent with accepted notions of mTBI dysfunction and its brain substrates. However, the number of studies, number of subjects, and great variety of tasks employed, not to mention differences in image acquisition and analysis, effectively preclude meaningful integration of these findings.

The 3 resting-state fMRI studies each used different methods of analysis. Costanzo et al[32] used a seed-based correlation analysis and found a correlation between default mode network connectivity and white matter integrity as determined by DTI. Vakhtin et al[45] used Group Independent Component Analysis and found the blast mTBI group had greater signal amplitude than did civilian controls in the default mode, sensorimotor, attentional, and frontal networks. Han et al[41] used a graph theoretical analysis applied, uniquely, in a longitudinal study design. At the initial visit (<90 days of injury; median 14 days), patients in the mTBI group showed more trivial modules in the lateral prefrontal and anterior cingulate cortex than controls. At the individual level, 14 of the 47 patients demonstrated elevated modularity and 2 had abnormally low modularity compared with controls. This difference was not detectable at the follow-up visit 6 to 12 months later, a solitary though tantalizing finding that might portend a measurable recovery mechanism in mTBI. Although elevated resting activity (correlation, blood oxygenation level dependent amplitude, or modularity), which has been suggested as a manifestation of network dysfunction, seems to be a salient feature across resting fMRI studies, the dramatic differences in analytic technique essentially preclude any coherent integration across these studies.

Given the large variation in methods, design, and analysis across these few fMRI studies, any convergence is quite unexpected and either indicates the possibility of underlying salient functional activation patterns that index alteration of brain function in blast mTBI, or a chance observation. Once again, more data, acquired and analyzed in a consistent manner, will be needed to clarify the functional manifestations of mTBI.

Fluorodeoxyglucose positron emission tomography

Fluorodeoxyglucose positron emission tomography (FDG-PET) permits measurement of cortical and subcortical predominantly grey matter glucose metabolism, which is reduced in civilian TBI and other neurological and psychiatric disorders.[51–55] We identified 3 studies that applied resting FDG-PET to blast-related mTBI, encompassing a total of 59 patients (Table 3). Methods of exposure severity estimation include number of blasts[34,56,57] and distance to blast,[57] though only number of blasts was considered in any data analysis.[34]

Brain regions exhibiting abnormal metabolism are summarized in Table 4. Peskind et al[56] found hypometabolism of glucose in blast mTBI unrelated to PTSD. Mendez et al[57] compared veterans with primary blast-related mTBI with those who experienced blunt mTBI and found that the 2 groups showed many similar areas of hypometabolism relative to healthy controls. Petrie et al[34] found diffuse cortical hypometabolism in blast mTBI; veterans who reported more than 20 blast exposures also exhibited hypometabolism in a single location in the parahippocampal gyrus (laterality not specified).

Multifocal reduction of glucose metabolism seems to be a common feature, but varies widely across even these few studies which are limited by small sample size. Integration of FDG-PET findings with other imaging measures, particularly sMRI and DTI, may facilitate understanding the biological basis of metabolic change (ie, direct injury, volume loss, loss of white matter connections, or systemic effects).

Neurophysiology

Neurophysiological recordings offer a different view of brain function, as these methods directly sample synaptic electrical activity at a temporal resolution on the order of microseconds. Electroencephalography (EEG) and magnetoencephalography (MEG) do not reveal structural brain features, and thus may not be considered imaging methods in the strictest sense. Electroencephalography and especially MEG recordings, however, can be mapped to a 3D surface and even onto sMRI images for localization of neuronal activity. Electroencephalography and MEG can thus be related to other imaging findings including sMRI, DTI, fMRI, and PET. Magnetoencephalography slow-wave activity indicates neuronal dysfunction and occurs in TBI, stroke, and other disorders.[58–60] Electroencephalography is commonly used to diagnose neurological disorders such as epilepsy, and has detected changes in acute nonblast mTBI that resolve over months to years.[61] Portable or even wearable ambulatory EEG monitoring presents an interesting potential means to capture

information near the time of injury, but has not yet been employed routinely in a combat setting.

Four studies have reported resting MEG, comprising a total of 84 patients with blast mTBI (Table 3), with 3 examining slow-wave activity[35,62,63] and 1 examining system complexity. All studies showed abnormal MEG activity in the frontal, parietal, and temporal regions, with other regions summarized in Table 4. Sensitivity of individual subject analyses ranged from 84.5% to 100%.[35,62,63] Although number of blasts[63] and time since injury[35,63,64] were reported as means to estimate blast exposure severity, these estimates were not employed in any analysis of imaging data. MEG slow-wave activity and decreased signal complexity are associated with affective regulation, personality change, and concentration in blast mTBI, suggesting functional significance beyond simple detection of mTBI-related abnormal brain function.[62,64]

Two studies applied EEG to blast-related mTBI in a total of 38 patients (see Table 3);[36,65] one acquired EEG at rest and the other was an event-related potential design employing the Reading the Mind in the Eyes Test. The event-related potential study found that higher-amplitude event-related potentials during the Reading the Mind in the Eyes Test correlated with PTSD in the patients with mTBI.[65] Comparison of results from these 2 studies, however, is precluded by their dramatic differences in measurement paradigm and study design. Although the 2 studies similarly estimated exposure severity on the basis of number of blasts, exposure was not incorporated into analysis of EEG in either study.

Neurophysiology has also been studied as a complement to DTI. Huang et al[35] examined the relationship between MEG and DTI in 10 patients with mTBI, 4 of whom had previous blast exposure. Three patients with mTBI showed cortical slow-wave activity at locations consistent with expected white matter projections from areas where low FA was detected using DTI. One of these subjects exhibited many foci of slow-wave generation in cortex, which were linked by the SLF. No correlation, however, was found between MEG abnormalities and number of blasts.[63] Sponheim et al[36] examined the relationship between resting EEG and DTI in patients with blast mTBI. The latter showed lesser phase synchrony across frontal electrodes, which was associated with lower FA in the forceps minor and the left anterior thalamic radiation, locations plausibly affecting tracts connecting the regions of abnormal physiology. Lesser phase synchrony was not, however, associated with PCS, PTSD, or depressive symptoms.

Although neurophysiological measures provide direct access to the state of cortical function, it remains unclear whether neurophysiological changes reflect local cortical pathology or the impact of remote injury within white matter. Findings also suggest that MEG and EEG may be more sensitive than DTI for detection of mTBI. Although EEG is widely available at most hospitals, MEG is only available at a limited number of academic centers, thus limiting clinical utility.

Imaging and treatment

Imaging has the potential to provide noninvasive guidance in the selection, application, and monitoring of therapeutic interventions. Two studies have applied functional neuroimaging, specifically fMRI[44] and single-photon emission computed tomography (SPECT),[66] to monitor patients' response to treatment of PTSD and PCS.

Roy et al[44] used fMRI to study veterans with mTBI ($n = 1$), PTSD ($n = 9$), or both ($n = 15$). After symptom assessments and baseline fMRI employing the affective Stroop task, subjects underwent virtual reality exposure therapy or imaginal exposure therapy. Functional MRI was repeated after completion of therapy. Before treatment, activation of the amygdala, subcallosal gyrus, and prefrontal cortex was higher, and activation of the cingulate cortex was lower than in controls. Treatment reversed these activation patterns in association with behavioral improvement, such as tolerating large public spaces (eg, the subway).

Harch et al[66] used ^{99m}Technetium ethyl cysteinate dimer (ECD) SPECT and neuropsychological testing to monitor response to low-pressure hyperbaric oxygen therapy for chronic blast-related PCS in patients with mild to moderate TBI ($n = 16$) (Table 3). Single-photon emission computed tomography was done before treatment, after 1 week of treatment, and after 40 weeks of treatment. After 1 week of treatment, increased blood flow to regions of the frontal, temporal, and occipital lobes, as well as the thalamus and hippocampus, was detected. The follow-up scan at 40 weeks showed a persistent similar pattern but also revealed increased flow to parietal regions and cerebellum. Twelve of the 15 subjects who completed treatment reported improvement in the majority of their symptoms; they also improved on measures of working memory and executive function. The authors did not report whether patients with no symptomatic or cognitive improvement had changes on SPECT, and the study employed no controls.

These few preliminary studies offer the suggestion that functional imaging might detect modulation of brain physiology after treatment in patients with blast-related mTBI with PTSD and persistent PCS. However, the reliability and generalizability of these findings and their application to clinical care requires substantial further study, including investigations that combine structural and functional imaging to assess patients before, during, and after treatment. Most importantly, these studies must incorporate appropriate longitudinal evaluation

of control subjects to verify that the changes seen after mTBI treatment do not represent normal evolution of changes in mTBI or normal variation in general.

DISCUSSION

Combat-related mTBI, which includes the effects of blast, impact, and acceleration-deceleration, each superimposed on a background of combat stress, affects a large number of warriors who suffer life-altering morbidity because of their injuries. Although it is generally accepted that the biological basis for the adverse consequences of mTBI is microstructural pathology that impedes brain network function, in vivo neuroimaging of combat-related mTBI pathophysiology has just begun. It might be premature to expect to identify salience across the limited number of studies published to date; such big picture inferences typically derive from a much larger body of work, as in the pooling of data across multiple large clinical trials by meta-analysis. In the case of neuroimaging studies of combat-related mTBI, the relevant concern is not so much the lack of coalescence of the data today, but whether it can be achieved, given the current approaches to research reporting we have observed and described. A major problem threatening ultimate integration of study data and findings, which otherwise could leverage the massive ongoing allocation of resources to combat-related mTBI research, is the lack of consistency of methods and data reporting across studies.

The combat-related mTBI studies we have reviewed claim a focus on blast-induced mTBI, which has been referred to as the "signature wound" of modern combat. However, what remains unclear is the extent to which blast mTBI can in fact be isolated from secondary and tertiary impact as well as nonblast mTBI because of other mechanisms in combat. The number of subjects that authors characterized as having only experienced primary blast mTBI was 45 out of over 600 subjects. Moreover, most studies recruited unexposed veterans as controls. Although this might seem an ideal control group, and studies without an unexposed control group would be limited in their ability to distinguish the effects of blast, the extent to which "control" veterans who have experienced combat have actually *not* been exposed to blast is unclear. Thus, combat veteran control groups may differ from subjects with mTBI only in degree with regard to exposure.

Most studies attempted to estimate severity and extent of blast exposure, but few actually examined how these blast characteristics relate to imaging or functional outcomes (see Table 7). Estimates of blast exposure were based on self-reporting, which typically occurs long after the event. Given this long delay between occurrence and reporting, the high stress of the combat environment, the likelihood of numerous exposures, and the neurocognitive effects of acute mTBI, it seems rather implausible that greatly delayed self-reporting can accurately index severity of exposure. The Boston Assessment of TBI-Lifetime is a semistructured interview quantifying blast exposure measures and other head injuries, and has been reported to be useful for this purpose.[67] Ultimately, the implementation of real-time monitoring of exposure utilizing wearable sensor devices that require no user activation or intervention could provide meaningful characterization of blast exposure and enhance our understanding of how blast, its magnitude, character, and frequency lead to brain pathology and modulate clinical outcomes.

Sample heterogeneity, an intrinsic feature of TBI, is a prime challenge for researchers. Ensuring comprehensive characterization of subjects and, most crucially, uniformity of data acquisition has the potential to facilitate characterization of the inherent heterogeneity of TBI pathology. Approaches that attempt to minimize sample heterogeneity, however, may introduce selection bias and diminish the impact and generalizability of study findings. For example, the exclusion of psychiatric disorders may seemingly facilitate isolation of the effects of blast-related mTBI, but will make the study group less representative of the relevant patient population, one which suffers greatly from psychiatric disorders such as

TABLE 7 *Reporting and analysis of blast exposure characteristics criteria*

	Recorded	Analyzed
Number of blast-related TBI	16[13,16,21,23,27,28,33–35,42,43,45,56,62,65,66]	2[28,34]
One vs multiple blasts	2[30,38]	1[38]
Direction of blasts	1[45]	1[45]
Distance to blast	1[57]	0
Time since blast	All[a]	4[12,25,30,31]
Blast vs mixed or blunt injury	15[16,21,26,28,30,35,40,42,43,45,56,57,62,64,65]	5[21,26,35,57,62]
None besides time since blast	6[14,15,24,36,44,63]	N/A

Abbreviation: TBI, traumatic brain injury.

[a]While few papers did not report time since blast related mTBI, chronicity of injury can usually be inferred from recruitment methods.

MDD and PTSD.[68,69] Another sample consideration pertains to the choice of control subjects. Although concern has been expressed that systematic differences in background features between combat veterans and controls might be the basis for imaging abnormalities, rather than mTBI, this remains to be shown in a specific assessment of different control groups.

Due to the relatively low numbers of women serving in combat roles, published studies have included primarily male participants. Women, however, are likely to be a higher risk group for mTBI in combat. Blunt mTBI outcomes are affected by menstrual phase[70]; female athletes are more likely to experience concussion than their male counterparts[71] and may take longer to recover from concussion.[72] Even if salient conclusions regarding combat-related mTBI can be arrived at by improvement and expansion of research studies, results identified in men or highly male-dominated samples may not generalize to women. As women are increasingly entering combat roles, researchers need to specifically focus on female blast mTBI patients to devise sex-appropriate protective, diagnostic, and treatment approaches.

Methodological heterogeneity of studies, particularly pertaining to imaging data acquisition, is a source of concern for the ultimate ability to combine neuroimaging data across studies. Investigators are understandably focused on pushing the technology envelope to develop and utilize newer imaging approaches that promise to be more effective than existing techniques. This well-intentioned march of technology, however, may unintentionally advance the technique of data acquisition faster than actual clinical studies can apply it to sufficiently large, diverse, long-term, and well-designed studies. The studies we encountered are at best designed and powered to demonstrate proof of concept. To counter the premium currently placed on the technological cutting edge, at the seeming expense of generating useful clinical findings, a high-quality standard, which can currently be applied consistently across many centers and subjects, may in fact be the better goal.

The convergence of findings seen across methodologically heterogeneous studies of mTBI in general[20] suggests that a uniform approach to neuroimaging may facilitate pooling of data across studies to leverage large subject samples and thereby better characterize heterogeneity across subjects. FA, for example, has been found reproducible across scanners operating at the same field strength,[73] supporting the notion that multicenter studies are achievable and interpretable. Initiatives such as the Common Data Elements for TBI, provided they are actually adhered to in practice and result in uniform data acquisition, could then facilitate the comparison of DTI data acquired across multiple studies and institutions. It should be recognized that many cutting-edge clinical assays, such as serum peptide biomarkers, are not standardized across assays and institutions, necessitating collection of local normative data. At the present time, most advanced imaging methods operate in this realm, where an approach can be standardized to collect, quantify, and analyze data, but to implement the approach in practice requires that similarly acquired normative data be collected and available. The ultimate, though elusive, entrée to wider data integration is to standardize DTI and fMRI measures as verifiable quantitative metrics validated by phantom-based calibration. Standardized and complete reporting of results is also necessary for the effective integration across studies. For example, new methods for meta-analysis of neuroimaging data have been developed for this purpose.[74] To apply such approaches, however, details regarding study results such as standardized spatial coordinate locations for findings and their effect sizes are required, but these are often not reported in published articles.

Common approaches to the assessment of TBI, such as cognitive assessment or serum biomarker measurement, provide individual measures of the magnitude of one or more parameters (eg, number of errors, reaction time, and protein concentration). Neuroimaging, however, provides an immensely more complex dataset, where measures of parameter magnitude are generated for many thousands of spatial locations in each subject's brain. As discussed above regarding studies of DTI, for any neuroimaging study design that compares mTBI and control subjects at the group level, all findings detected and reported are necessarily limited to those salient across the entire group of mTBI subjects at a specific brain location. A key implicit assumption of these studies is thus that mTBI pathology will affect the same brain regions in the same way across the group of subjects. However, each subject enrolled in the study will have experienced a completely different injury from a biomechanical (eg, proximity, position, and protective equipment) as well as biological (eg, state of stress/arousal, genetics, comorbidity, and substance exposure) perspective. Given the known high degree of spatial variability in mTBI pathology, the group-wise analytic approach will likely be rather insensitive to the presence of pathology at the individual subject level. Moreover, any consistency among areas of abnormality detected using group-level comparisons can provide at best an incomplete, if not outright misleading, representation of the actual extent and consistency of injury location across subjects with mTBI. Although group-wise analytic approaches may be useful in the study of diseases that follow specific spatial patterns of brain pathology, they are simply not suited to the study of heterogeneously distributed pathologic disorders such as TBI. Methods that identify lesions at the subject level are necessary, after which summaries such as lesion load can be

derived for each subject and employed in population-level analyses.

The studies described in this review indicate that human brain imaging is likely to reveal features of combat-related TBI. The true potential of this work, however, will be realized only when salient inferences regarding underlying pathomechanisms of brain injury, recovery, and persistent dysfunction can be made and applied to the diagnosis, management, and ultimately prevention or treatment of brain injury in individual warriors.

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