### Title

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# Emerging approaches to neurocircuits in PTSD and TBI: Imaging the interplay of neural and emotional trauma

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## Abstract

Posttraumatic Stress Disorder (PTSD) and Traumatic Brain Injury (TBI) commonly co-occur in general and military populations and have a number of overlapping symptoms. While research suggests that TBI is risk factor for PTSD and that PTSD may mediate TBI-related outcomes, the mechanisms of these relationships are not well understood. Neuroimaging may help elucidate patterns of neurocircuity both specific and common to PTSD and TBI, and thus help define the nature of their interaction, refine diagnostic classification, and may potentially yield opportunities for targeted treatments. In this review, we provide a summary of some of the most common and the most innovative neuroimaging approaches used to characterize the neural circuits associated with PTSD, TBI, and their comorbidity. We summarize the state of the science for each disorder, and describe the few studies that have explicitly attempted to characterize the neural substrates of their shared and dissociable influence. While some promising targets in the medial frontal lobes exist, there is not currently a comprehensive understanding of the neurocircuitry mediating the interaction of PTSD and TBI. Future studies should exploit innovative neuroimaging approaches and longitudinal designs to specifically target the neural mechanisms driving PTSD-TBI related outcomes.

## Introduction

Posttraumatic Stress Disorder (PTSD) and Traumatic Brain Injury (TBI) are highly overlapping disorders (Stein and McAllister, 2009). Based on a sample of 1,965 OEF/OIF/OND veterans, an estimated near two thirds of those with PTSD and nearly one third had comorbid TBI (Tanielian and Jaycox, 2008). Given their prevalence, TBI and

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PTSD have been termed the “signature wounds” of veterans returning from recent conflicts (Tanielian and Jaycox, 2008). Moreover, TBI is thought to be an important risk factor for the development of PTSD. A recent study on 4,645 American veterans deployed to Afghanistan showed that those who experienced a TBI had 1.81 increased odds of having PTSD within three months and 1.48 at 9 months (Stein et al., 2015; Yurgil et al., 2014). Research also indicates that PTSD may mediate the impact of TBI-related symptoms. A survey of 2,525 post-deployment Army soldiers indicated that while TBI was associated with more physical health problems, PTSD and depressive symptoms mediated this relationship(Hoge et al., 2008). However, the mechanisms for these relationships are as yet, not fully understood, and few imaging studies have focused on this comorbidity (Table 1). Thus, there is a high demand for more advanced and powerful methodology that may shed light on the relationship between TBI and PTSD for the purposes of (1) clarifying the psychiatric nosology specific to each disorder and their overlap, and (2) providing opportunities for improved psychological and pharmacologic treatments. In this manuscript, we will review the methodologies and the findings from these modalities and discuss how these could potentially be applied to further our understanding of these commonly coupled disorders.

## Neurocircuits in PTSD and TBI:

There is a large and heterogeneous set of findings noted in a broad array of imaging studies with divergence both in structural and functional modalities describing PTSD and TBI. In addition, many functional imaging findings do not find results that are unique to these specific disorders. Indeed, meta-analyses consistently show substantial overlap across *numerous* psychiatric disorders. For example, studies in both anxiety and depression report increased activation in the amygdala, anterior insula, and anterior cingulate. There have been numerous meta-analyses specific to PTSD (O’Doherty et al., 2015; Patel et al., 2012; Simmons and Matthews, 2012) and TBI (Eierud et al., 2014). Together these findings suggest that much of the brain imaging work may be tied to similar key functions and networks that regulate brain behavior, potentially with the insula, amygdala and cingulate as important hubs (Menon, 2011). While clinically and symptomatically PTSD and TBI show substantial overlap, the constructs point to a potential dissociable etiology. However, there is no currently accepted way to apportion such etiologies beyond clinical judgment. In an effort to understand the scope and the nature of this overlap, much of the early work on PTSD and TBI has focused on different aspects, approaches and methodologies.

In this article, we will focus primarily on providing some familiarity in the range of imaging methodologies that are utilized for the inspection and dissociation of PTSD and TBI diagnoses, with special emphasis on novel methodologies or approaches that may gain greater prominence in the coming years. A brief introduction to numerous methods is given in the section Measurement of Neural Circuits, and is followed by a Summary of Current Findings. Each section is divided into major imaging methodologies including magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), positron emission tomography (PET), magnetoencephalography (MEG), and other. In the summary section, we suggest future directions or analyses that may yield areas for growth in future work, with the goal of clarifying existing diagnostic criteria for TBI

as separable from PTSD, and ultimately elucidating mechanistic processes that may lead to efficacious treatments.

## Measurement of Neural Circuits

### MRI:

Magnetic Resonance Imaging (MRI) was initially utilized for medical use in 1977. Since then, the application of this technology, and its ability to provide non-invasive imaging of internal structures, has seen particular growth and utilization for understanding the neural correlates of mental health diagnoses. By placing the brain within a standing magnetic field the absorption and release of radiofrequency waves can be predicted and measured to determine structure and location of specific substances (Haacke et al., 1999). This highly prevalent technology is broadly available in a hospitals and clinics and has allowed for numerous studies focused on finding structural differences in PTSD and TBI. The most often weighting of structural images is T1 weighted (short radiofrequency echo times, bright white matter, and dark cerebral spinal fluids (CSF)), although T2 weighted (longer radiofrequency echo times, dark white matter, and bright CSF) can be helpful for TBI or when taken in combination with T1.

As applied to psychiatric research, two major analysis paths have been employed to quantify brain structure either looking at the quantity or thickness of gray matter. Voxel-Based Morphometry (VBM) uses signal intensities in MRI to estimate the probable density of gray matter in a region of the brain and the probable size of known cortical areas (Ashburner and Friston, 2000). Conversely, these gray matter maps can be seen as two meshes, one on the inner surface and one on the external surface; from the distance between these two meshes a cortical thickness can be derived (Dale et al., 1999; Fischl et al., 1999).

An additional recent advancement is in methodology is macromolecular proton fraction (MPF) mapping, which provides information on the relative quantity of immobile macromolecular protons involved in the magnetization exchange with mobile water protons, and is characterized by marked distinctions between white matter and gray matter (Naumova et al., 2017). Recent work in humans has used MPF mapping for quantitative assessment of microscopic demyelination in both white and gray matter brain tissues (Yarnykh et al., 2015). The application of MPF in gray matter, in particular, may provide an additional sensitive clinical index of TBI and or PTSD burden.

### fMRI:

Functional MRI utilizes the methods of MRI, but by interpretation of distortion of the signal due to blood flow it allows for inference of hemodynamic change (Ogawa et al., 1990). While the core of this technology has stayed relatively static in the last 20 years, there have been a few advancements in the collection capacity and substantial advancement in the statistical decomposition of the signal.

A notable technological advancement has been in the utilization of multiband sequences in the collection of MRI data, an advance that benefits primarily fMRI and DTI approaches. Principally, the number of coils used to emit and collect the radio frequencies for the

measurement of change in blood flow has increased. A new approach has been to split these coils to run independently to allow for simultaneous data acquisition. This, in addition to other streamlining advances, such as multi echo sequences and increased strength of the static field, has allowed for a profound increase in the speed and resolution of the acquired scans.

Functional MRI data have traditionally been collected in 3 dimensional matrices of the brain (i.e., a set of voxels) repeatedly, over a duration of interest. This provides a 4 dimensional matrix (i.e., 3 spatial and time), where the individual voxels show fluctuations over time. These fluctuations in signal are associated with either an external stimulus (using a correlation approach) (Friston and Penny, 2003; Josephs et al., 1997; Penny and Friston, 2003), or an internal stimulus (using a connectivity approach) (Friston et al., 1996). The seed-based connectivity approach takes the activation in a region of interest and observes other areas of the brain that show related activation. Another approach that can be taken is to decompose this signal into core components using independent component analysis (Beckmann et al., 2005). These regions can then be linked to known temporal or spatial patterns for further interpretation.

Recently, additional methods of note have emerged, e.g. graph theory has been applied to seed-based connectivity to provide a data driven, whole brain analytic approach that describes how brain networks interact together instead of simply within or between segregated regions (Bullmore and Sporns, 2009). Such interactions may provide important information in distinguishing how these pathologies interact and diverge. This has led to the notion that areas acting in conjunction have local hubs and nodes.

Another interesting methodological advancement is multi-voxel pattern analysis (Norman et al., 2006) and multivariate Bayesian decoding (Friston et al., 2008) which provide a way to integrate multiple voxels in predicting or classifying brain state.

**DTI:**

Diffusion weighted imaging is a variant of MRI that characterizes water movements, or Brownian motion, within tissues. First introduced in the mid 1980’s and early 90’s (Le Bihan et al., 1986), it has undergone significant refinement over the past 3 decades to accommodate improved description of white matter neural microstructure. Diffusion tensor imaging (DTI) was the first application of this technology, providing indirect information regarding the structural orientation of white matter fiber tracts, and is the most common method used to characterize the “integrity” or directional coherence of white matter (i.e., fractional anisotropy). Voxelwise calculations of fractional anisotropy (FA) and mean diffusivity (MD) are the primary measures of white matter integrity, and indicate the degree of restriction allowing for greater water diffusion along the length of an axon, versus perpendicular to it. While these are the primary measures that have been used for assessment of TBI, other diffusivity measures, such as axial (AD), and radial (RD) diffusivity, may be helpful in measurement of TBI (Mohammadian et al., 2017). Healthy tissue is generally associated with high FA and low MD values (Beaulieu, 2002). Other qualitative metrics such as regional tract count (i.e., number of efferent and afferent tracts), and visualization of white matter tracts can also be obtained. Two common DTI analysis pathways include tract-

based spatial statistics(TBSS)) which allows for the creation of structural FA maps (Smith et al., 2006), and tractography which allows for the visualization of diffusion directional preference applied to map the white matter fiber pathways between specific regions (Basser et al., 2000)). Recently, tractography has been utilized to perform graph theory analysis (Bullmore and Sporns, 2009). These traditional measures of DTI are limited to conveying a single fiber orientation in each voxel. In regions of complex fiber geometries, this may result in ambiguous orientation estimates and subsequent failure of tractography. High Angular Resolution Diffusion Imaging (HARDI) (and similar e.g., "Q-ball imaging") which was developed to better handle situations where multiple crossing white matter fibers/tensors mimicking free water. HARDI and the Orientation Distribution Function (ODF) (Tuch, 2004) does not constrain the shape of diffusion (i.e., not necessarily elliptical), and thus allows for a measure of generalized fractional anisotropy (GFA) that summarizes integrity across multiple directions within an MRI voxel (Assemlal et al., 2007). This approach may be superior for the assessment of crossing fibers or areas in which axons converge or diverge.

**PET:**

The first positron emission tomography (PET) device used for large-scale cerebral scanning was developed in the 1950s for the detection of brain tumors (Portnow et al., 2013). Modern era PET provides mapping of functional utilization of specific compounds by putting a radioactive tracer on a compound and measuring the release of positrons as the compound is metabolized in the body (Worsley et al., 1992). While traditionally sugar molecules are used as a tracer, such that energy utilization can be quantified, a plethora of markers have been developed to look at the transmission of serotonin (Drevets et al., 1999), dopamine (Elsinga et al., 2006) and other transmitters that have been relevant to psychiatric conditions.

**MEG:**

Magnetoencephalography (MEG) is a non-invasive functional imaging technique that directly measures the magnetic signal due to neuronal activation in gray matter with high temporal resolution (< 1 ms) and spatial localization accuracy (2–3 mm at cortical level) (Leahy et al., 1998). Although first introduced over 40 year ago (Cohen, 1968), innovations over the past decade have dramatically improved its implementation. MEG measures neuronal activity from gray matter with a population about 100,000 neurons (Hamalainen et al., 1993). Recent development of high-resolution MEG source imaging techniques such as the VESTAL (Vector-based Spatio-temporal Analysis of L1 minimum norm) algorithm (Huang et al., 2016a; Huang et al., 2006; Huang et al., 2014a) allow the application of MEG to many psychiatric and neurological disorders such as PTSD and TBI.

**Summary:**

Each imaging modality has a unique set of strengths and weaknesses important to acknowledge in the attempt to describe the interplay of PTSD and TBI. Inherent limitations of spatial and temporal resolution (Figure 1) as well as cost, storage, and design (Table 2) support a multimodal approach with the goal of adequately describing the overlap of these two commonly comorbid disorders.

## Summary of Current Findings

### PTSD:

**MRI:** Hippocampal atrophy has been consistently related to PTSD (Karl et al., 2006; Kitayama et al., 2005; Nelson and Tumpap, 2017; Smith, 2005). Notably reductions occur in the absence of treatment (Sheline et al., 2003), but volume loss is mitigated when treatment is provided (Vermetten et al., 2003; Videbech and Ravnkilde, 2015). The hippocampus is critical for fear processing (Gewirtz et al., 2000; Kuhn and Gallinat, 2013; Liberzon et al., 1999a; Rauch et al., 2006), in particular contextual information that modifies responses based on environmental cues (Phillips and LeDoux, 1992).

**fMRI:** A growing body of functional MRI literature supports the prevailing theory that PTSD is associated with a prefrontal–limbic imbalance wherein structures responsible for assigning salience to environmental cues are over active (i.e., amygdala, insula, dorsal anterior cingulate) and insufficiently modulated by prefrontal structures (e.g., ventrolateral and ventromedial prefrontal cortex) (Etkin and Wager, 2007; Hayes et al., 2012; Patel et al., 2012; Sartory et al., 2013; Simmons and Matthews, 2012). The hippocampus may also figure prominently into this model, as it is thought to provide additional modulation to the amygdala by providing access to contextual information allowing for the classification of environmental stimuli as safe or unsafe. However, there have been few direct investigations of the contribution of this structure to the presentation of PTSD despite consistent findings of decreased volumes in trauma exposed individuals.

The amygdala is central to the emotional processing and regulation of fear, including fear conditioning, generalization, and extinction learning (Phelps and LeDoux, 2005). Individuals with PTSD tend to exhibit hyper-reactivity of the amygdala to trauma-related stimuli (Hayes et al., 2012; Liberzon et al., 1999b), and greater amygdala functional connectivity with other regions of the salience network (i.e., insula) (Rabinak et al., 2011; Sripada et al., 2012a). Amygdala activity as measured by fMRI is predictive of symptom severity in PTSD patients (e.g., (Liberzon et al., 1999b)). It has also been hypothesized that exaggerated amygdala activity may partially account for the observed decrease in activity in the prefrontal cortex (PFC) by way of an increased feedback inhibition (Kelmendi et al., 2017). Exaggerated amygdala activity may also explain some of the core behavioral patterns in PTSD, such as hypervigilance and a failure to extinguish maladaptive fear response (Shin et al., 2006).

Evidence from functional neuroimaging studies suggests that dysfunction of the ventromedial PFC (vmPFC) –amygdala circuit may be an underlying mechanism driving PTSD symtomotology (e.g., (Rauch et al., 2006)). That is, in healthy individuals, volitional suppression of negative emotion as well as fear extinction are associated with increases in vmPFC activity and decreases in amygdala activity (e.g., (Delgado et al., 2008; Milad et al., 2009)). Therefore, the finding that ventral portions of medial prefrontal cortex (vmPFC) tend to be hyporesponsive (Etkin and Wager, 2007; Felmingham et al., 2010; Milad et al., 2009), coupled with extensive evidence for exaggerated amygdala responsivity argue for dysfunction of this circuitry.

The insula has figured more prominently in neural models of PTSD over the last several years. The anterior insula, which monitors internal homeostasis and the integration of homeostatic assessment (Craig, 2009), has been posited as a key component in understanding PTSD (Paulus and Stein, 2006). The right anterior insula responds primarily to interoceptive information, tying together cognitions, emotions, and internal body state (Craig, 2003) and is a vital part of the salience network (Menon, 2011).The anterior insula has been shown to encode affective distress that is associated with PTSD (Chen et al., 2009; Fonzo et al., 2010; King et al., 2009; Simmons et al., 2009; Simmons et al., 2008; Strigo et al., 2010) and may even predict treatment response in this psychiatric samples (Dickie et al., 2011; Peres et al., 2011). Individuals with PTSD show increased activation in the insula during anticipation of an aversive image (Simmons et al., 2008), while this activation is reduced those with marked resiliency traits (i.e., special forces operatives) (Simmons et al., 2012). New models tying the physiological and affective distress in PTSD to dysregulation in the insula have been proposed(Paulus and Stein, 2006).

The exact contribution of amygdala, insula and vmPFC to the chronology of PTSD and its clinical course has yet to be adaquately studied. Recent meta-analysis suggests that PTSD may represent an excitation of the saliency network (SN) (i.e., amygdala, insula, and dorsal cingulate) and a suppression of the central executive network (CEN) (i.e., dorsal lateral prefrontal and posterior cingulate) (Patel et al., 2012). This network conceptualization of the disrupted networks overlaps and incorporates prior models of PTSD (Liberzon and Sripada, 2008) and provides further evidence that relationships between these core networks may be at the heart of PTSD symptom presentation.

**DTI:** Previous DTI studies examining the relationship between PTSD and white matter integrity in military (Schuff et al., 2011) and adult onset PTSD civilian samples have mixed results, reporting reduced white matter integrity (lower FA) in the corpus callosum (Kitayama et al., 2007; Villarreal et al., 2004), prefrontal cortex (PFC) (Schuff et al., 2011), anterior cingulum (Kim et al., 2005; Schuff et al., 2011; Zhang et al., 2011) and posterior cingulum (Fani et al., 2012), and higher fractional anisotropy in the cingulum (Abe et al., 2006; Zhang et al., 2012) and superior longitudinal fasciculus (Zhang et al., 2012; Zhang et al., 2011). In a recent study that compared adult-onset PTSD to controls, both exposed to a single, specific major trauma (8.0 earthquake), Li and colleagues (2016) found significantly increased FA in the PTSD group in two regions of left dorsolateral prefrontal cortex (DLPFC) and in the left forceps major of the corpus callosum. Furthermore, the region of significantly decreased FA in the middle frontal gyrus was positively correlated with CAPS scores in those with PTSD (Li et al., 2016a). Results of this study are particularly interesting regarding the specific effects of PTSD on white matter, given that participants in both groups shared the traumatic event, were free of past or present psychiatric disorder, unmedicated, and had a relatively short duration of illness (mean = 11 months). Questions remain regarding whether increased FA in DLPFC reflects a predisposition for the development of posttraumatic symptomology rather than a consequence of the disorder, or if decreased FA in the stressed control group may be associated with resilience. Differences from previous studies may also reflect sample characteristics such as chronicity, medication, psychiatric comorbidity, number of traumas, and variable methods to account for a history of TBI.

**MEG:** MEG studies contrasting PTSD patients with healthy volunteers found hyperactivity from amygdala, hippocampus, posterolateral orbitofrontal cortex (OFC), dorsomedial prefrontal cortex, and insular cortex in high-frequency (i.e., beta, gamma, and high-gamma) bands hypoactivity from vmPFC, Frontal Pole, and dlPFC in high-frequency bands in those with PTSD. In individuals with PTSD, MEG activity in the left amygdala and posterolateral OFC correlated positively with PTSD symptom scores, whereas MEG activity in vmPFC and precuneus correlated negatively with symptom scores(Huang et al., 2014c).

MEG has also been used to delineate PTSD and health control subjects with >90% overall accuracy (Georgopoulos et al., 2010). Specifically, those with PTSD had differential communication between temporal and parietal and/or parieto-occipital right hemispheric areas with other brain areas (Engdahl et al., 2010).

**PET:** Studies of post-traumatic stress disorder have shown increased amygdala activation, although this was not confirmed in resting FDG-PET studies (Molina et al., 2010).

**TBI:**

**MRI:** Brain changes in TBI emerge from an abrupt external physical force. These can result in clear regions of injury, such as in the case of an open head injury. In moderate or severe cases of TBI, even in closed head injuries, the brain often has a clear region of damage relating to the site of impact or the contralateral side of the brain. In these cases, the brain can often receive damage from the spiny ridge in the occipital bone. However, in case of mild TBI, the location of this damage cannot be detected by traditional scanning procedures. Some initial evidence suggests that hippocampal and temporoparietal damage may be related to blast injury (Wang and Huang, 2013).

In a comparison of Iraq and/or Afghanistan veterans with a history of blast and blunt mTBI and without a history of mTBI, mean whole brain MPF values were lower in mTBI versus veterans without (Petrie et al., 2014). Results showed decreased values in multiple brain regions including the corpus callosum, cortical/subcortical white matter tracts, and gray matter/white matter border regions. Veterans with greater than 20 blast exposures had the lowest MPF values (Petrie et al., 2014). These findings suggest that axonal injury may be a primary marker of blast-related mTBI.

**fMRI:** Recent meta-analyses of fMRI suggest a widely distributed network of structures that may be affected by mTBI (Eierud et al., 2014; Simmons and Matthews, 2012). This is not surprising, given the heterogeneity of the impacts and sequelae that relate to mTBI. Work by Bonnelle et al. suggests that disruption in SN leads to increases in default mode network, notably the subgenual ACC (Bonnelle et al., 2012). These divergent findings may be highly dependent on the nature of impact, and confounding emotional effects in this highly heterogeneous condition. Similarly, individuals who develop MDD after blast-related mTBI show maladaptive hyperactivity in emotion processing structures such as the amygdala and hypoactivity in emotional control structures such as the dorsolateral prefrontal cortex during performance of an emotional face matching task, irrespective of PTSD diagnosis (Matthews et al., 2011).

**DTI:** Diffuse axonal injury (DAI) is caused by rapid acceleration-deceleration of the brain and has been identified as one of the most important causes of morbidity and mortality in patients with TBI (Frasure-Smith et al., 1995; Gean and Gean, 1994). Such injury to white matter integrity is thought to drive observable clinical and behavioral symptoms associated with mild TBI (Arfanakis et al., 2002), although studies that test these specific relationships are sparse. Neuropathology and imaging studies of TBI have emphasized damage to white matter (Wilde et al., 2006; Wilde et al., 2005), which is characterized by axonal stretching, disruption, and eventual separation of nerve fibers (Adams, 1982). TBI alters brain tissue microstructure via widening of extracellular space secondary to glial cell shrinkage (Goetz et al., 2004), small hemorrhages within the white matter, and Wallerian degeneration (Cernak et al., 2001). These neuropathological changes lead to axonal collapse, breakdown of myelin, and possible disconnection effects (Povlishock and Katz, 2005). Despite this evidence, little is known about the fundamental changes that occur in the brain of individuals who have sustained TBI from blast. Blast injuries may differ from mechanical force related injury (e.g., motor vehicle accidents) because of different mechanisms of brain dysfunction. The mechanism of brain injury from blast results not only from DAI, but also from focal injury from stroke due to air emboli that can form in blood vessels and travel to the brain (Okie, 2005), and from trauma to other internal organs (i.e. lungs or kidneys), which can affect brain function. Although results from animal studies indicate that DAI occurs even after relatively mild head injury (Frasure-Smith et al., 1995; Povlishock and Coburn, 1989), diagnosis and detection of DAI is particularly challenging given that traditional neuroimaging (CT and MRI) is often insensitive to this type of white matter damage (Scheid et al., 2003). Consequently, TBI is frequently undetected or misdiagnosed, leading to inadequate treatment (Gentry et al., 1988).

Diffusion tensor analysis has revealed abnormalities in cerebellar white matter (Mac Donald et al., 2013; Mac Donald et al., 2011), orbitofrontal cortex (Mac Donald et al., 2011), temporal regions and callosal white matter (Petrie et al., 2014) among individuals with a history of blast injury. More generally speaking, mild TBI is associated with widespread white matter abnormalities such as lower FA and higher MD after injury (Aoki et al., 2012; Hulkower et al., 2013; Morey et al., 2013; Niogi and Mukherjee, 2010), and in studies of military cohorts generally echo this result. While some analyses failed to find a consistent relationship between military mTBI and specific hypothesized regions of white matter (Davenport et al., 2012; Levin et al., 2010; Mac Donald et al., 2011; Sponheim et al., 2011), whole brain voxelwise comparisons and overall measures of white matter integrity have since detected lower measures of FA associated with military mTBI (Davenport et al., 2012; Jorge et al., 2012; Morey et al., 2013; Yeh et al., 2014).

Yeh and colleagues (2014) employed a novel DTI “asymmetry analysis” to compare the effects of blunt-only vs blast + blunt TBI. Their results suggested that the mechanism of injury was related to the distribution of low FA clusters, as military personnel with blast + blunt TBI showed lowest FA in central superior-inferior oriented tracts near subcortical regions (e.g., projection fibers interconnecting cortico-subcortical regions such as the superior corona radiata), while blunt trauma-only TBI subjects showed lowest FA in anterior-posterior oriented tracts (e.g., anterior limbs of internal capsules) (Yeh et al., 2014).

These results point to the potential utility of characterizing mTBI by mechanism of injury and could suggest altered sequelae with additional blast force neurotrauma.

**MEG:** Resting-state MEG appears highly sensitive to abnormal neuronal signals resulting from brain injuries. Slow-waves, if present during wakefulness, are a sign of brain dysfunction (Kandel, 2013). Neurophysiological studies in animals have established a solid connection between pathological delta-wave (1–4 Hz) generation in grey matter and injuries in white matter. Polymorphic delta-band slow-waves produced by white matter axonal lesions in cats were localized to the grey matter of cortex overlying the lesion (Ball et al., 1977; Gloor et al., 1977). Abnormal delta-waves can also be induced by the administration of atropine in the white matter (Schaul et al., 1978). It is known that atropine is a competitive antagonist of acetylcholine (ACh) receptors and can block and/or limit ACh. These animal experiments concluded that cortical deafferentation was a key factor in abnormal delta-wave production, owing to white matter lesions (i.e., axonal injury) and/or blockages/limitations in the cholinergic pathway. They also demonstrated that abnormal delta-waves can directly result from axonal and/or cholinergic blockage/limitation.

Human studies in wakefulness suggest that the brains of mTBI patients generate abnormal low-frequency magnetic waves that can be measured and localized by resting state MEG (Huang et al., 2014b; Huang et al., 2012; Huang et al., 2009; Lewine et al., 2007a; Robb Swan et al., 2015). MEG may be more sensitive than conventional MRI or EEG in detecting abnormalities in mTBI patients (Lewine et al., 2007a, b). Unlike normal resting state MEG data, which is dominated by neuronal activity with frequencies above 8 Hz, injured neuronal tissues in many chronic neurological disorders (e.g., head trauma, brain tumors, stroke, epilepsy, Alzheimer's disease, and certain chronic neurovascular diseases) generate abnormal focal or multi-focal low-frequency neuronal magnetic signals (delta-band 1–4 Hz, extending to theta-band 5–7 Hz) that can be directly measured and localized using MEG (Huang et al., 2014b). While TBI is not the only neurological disorder that generates abnormal slow-waves, in practice, brain tumor and stroke can be easily ruled out based on structural imaging (i.e., CT and MRI), whereas epilepsy, Alzheimer's disease, and other chronic neurovascular diseases (e.g., hypertension and diabetes) can be ruled out based on medical history. Using voxel-wise and ROI approaches, MEG slow-wave source imaging has been shown to detect abnormal slow-waves with ~85% sensitivity in patients with persistent post concussive symptoms in chronic and sub-acute phases of mTBI (Huang et al., 2014b; Huang et al., 2012).

In addition, MEG source images were found to be correlated with neuropsychological exams (Robb Swan et al., 2015) and with abnormal eye-movement (Diwakar et al., 2015) in individuals with mTBI. Recently, abnormal resting state MEG functional connectivity in different frequency bands was also found in mTBI population (Engdahl et al., 2010; Huang et al., 2016b).

**PET:** Studies have shown that patients with a history of TBI show diminished activation across wide areas of the brain as detected by PET (Kato et al., 2007; Levine et al., 2002; Nakayama et al., 2006; Shin et al., 2006; Stamatakis et al., 2002; Zhang et al., 2009) both during performance of a task and at rest. Another approach that has been successful in

the differentiation of TBI from controls using PET has been the definition of clusters of contiguous voxels of outliers of FDG-PET. Notably, TBI patients showed larger clusters of deactivation that were located closer to the gray/white junction than in a healthy comparison group (Zhang et al., 2009). In an FDG-PET study of patients with TBI alone, or with PTSD + TBI compared to individuals without history of either condition, Buchsbaum and colleagues (2015) found that both TBI groups had larger clusters of larger, low activity, and more irregular in shape than combat controls (Buchsbaum et al., 2015).

### PTSD TBI Interaction:

**MRI:** Despite the common clinical overlap (Stein and McAllister, 2009), and evidence that TBI may increase the incidence and severity of PTSD (e.g., (Vasterling et al., 2009)), only a small number of MR studies have attempted to describe the interplay of TBI occurring in conjunction with PTSD. Examination of TBI in the presence of PTSD compared to TBI- and PTSD-only may provide some information regarding risk and resilience for this common dual diagnosis. For example, in a sample of veterans with PTSD-only (n=4), TBI-only (n=32; all severities), or PTSD+TBI (n=20), Brenner and colleagues (2009) employed a standard clinical imaging approach using T2 gradient echo to evaluate TBI based upon the presence of encephalomalacia or hemosiderin deposits. TBl-only was significantly more often associated with MRI physical trauma-related findings than TBl+PTSD. There was no evidence of encephalomalacia or hemosiderin deposits in those individuals with PTSD-only (Brenner et al., 2009). One significant limitation of this study was that the TBI-only group had a higher number of participants with severe TBI (n=17/27) than the TBI + PTSD group (n=4/32). Negative findings signal a need for more sensitive measures of PTSD and TBI burden.

Lindemer and colleagues 2013 examined the interactive effects of PTSD and TBI on regional cortical thickness using T1-weighted high resolution scans. Greater reductions in cortical thickness in bilateral superior frontal regions were found in veterans with higher cumulative lifetime burden of PTSD and mTBI compared to the PTSD-only group (Lindemer et al., 2013). Depue and colleagues 2014, compared comorbid PTSD + mTBI relative to PTSD-only or TBI-only groups using voxel-based and surface-based morphometry. They observed volumetric reductions in the bilateral anterior amygdala in comorbid PTSD + mTBI individuals compared to a OEF/OIF Veterans without mTBI and/or PTSD (Depue et al., 2014). These observed structural alterations in frontal and limbic regions in dually diagnosed individuals point to additive effects in the central executive network and amygdala and may contribute to the putative role these structures play in the symptomology of PTSD (Patel et al., 2012).

**fMRI:** There have been few explicit attempts to delineate the shared and/or unique variance of PTSD and TBI using functional magnetic resonance imaging. One meta-analysis used activation likelihood estimation (ALE) to compare PTSD-only and TBI-only to control patterns of brain activation across 36 PTSD primary studies and 7 primary TBI studies. Results showed that the primary area of overlap, wherein both TBI and PTSD groups differed from control participants was in the middle frontal gyrus (Simmons and Matthews, 2012). More specifically, more activation was observed in those with PTSD and less

activation in those with mTBI relative to controls in this region. Varying study and task design may have significantly contributed to the difference in direction (Simmons and Matthews, 2012), rather than differences in the neural mechanisms of each disorder. Due to the small number of TBI studies available at the time, an updated analysis of this kind may illuminate additional areas of overlap.

Newsome and colleagues 2015 used fMRI to assess differences in brain activation during verbal working memory in Iraq/Afghanistan veterans (n=25) with mild- moderate blast TBI, veterans without history of TBI (n=25), civilians with a history of blunt force mild-moderate TBI (n=25), and civilians with no history of TBI (n=25) (Newsome et al., 2015). In regions that demonstrated a significant load effect during the encoding portion of the task (correct trials only), the military blast TBI group did not show the same monotonic increase in brain activation to increased set size (1 v 3 v 5) in the right head/body/tail of the caudate as did the 3 other groups, even after controlling for differences in age, education, PTSD, depression, fatigue, and pain symptoms. Of importance, military blast TBI group showed a significant and nearly significant negative relationship between caudate activations and re-experiencing and avoidance PTSD symptoms, respectively, suggesting a potential relationship between disrupted caudate response to increasing set size and these symptoms. However, as the military groups were not matched on levels of combat exposure or PTSD, and given the cross-sectional sample, this finding cannot be specifically linked to PTSD.

Interrogation of functional connectivity has been the other principal approach in evaluating the shared and dissociative contributions of TBI and PTSD to brain function. Whereas task related connectivity describes the interaction of brain regions in the context of an external stimulus, resting state connectivity derives from intrinsic patterns of neural synchrony. Work by Newsome and colleagues 2016 employed functional connectivity analyses to describe the intrinsic connectivity of subcortical gray matter structures (caudate, putamen, globus pallidus) and cortical gray matter (DLPFC) during resting state in veterans who had sustained a TBI from one or more blast exposures (n=17; 15 mild, 1 moderate, 1 severe TBI) as compared to veterans who had been deployed but denied blast exposures or history of blunt TBI (n=15) (Newsome et al., 2016). Notably, self-reported PTSD, neurobehavioral, and depression symptoms were significantly greater in the TBI group than combat controls. Results of functional connectivity without controlling for these group differences in PTSD and depression suggested (1) greater positive connectivity in the TBI than the control group between the right putamen and the right angular gyrus and right lateral occipital cortex, (2) reduced connectivity in the TBI between the right DLPFC and bilateral superior parietal lobule, supramarginal gyrus, and post-central gyrus (i.e., the control group demonstrated positive connectivity while the control group demonstrated an anti-correlation between regions. Previous work citing aberrant putamen connectivity in individuals with PTSD (e.g., (Lei et al., 2015; Linnman et al., 2011)) may suggest a specific vulnerability to the comorbid influence of TBI and PTSD in this region.

Spielberg and colleagues 2015 used graph theory to examine the interactive impact of PTSD and mTBI on default network connectivity in veterans with trauma exposure (n=208) and mixed histories of current/past PTSD, and exposures to blast and/or blunt mTBI (e.g., 96% with lifetime history of PTSD; 63% with mTBI) (Spielberg et al., 2015).

Authors discovered a network including the caudate/putamen (basal ganglia) and the PFC wherein re-experiencing symptoms were related to decoupling of these regions, but only in veterans with mTBI. Given previous work suggesting that the basal ganglia and PFC work interactively to provide the mechanism by which contextual information modifies working memory and distracting information (Badre and Frank, 2012), authors theorized that weaker connections in this network may be associated with greater trauma related intrusions in safe contexts (Spielberg et al., 2015). Worse caudate local efficiency, or ability to exchange information within a network, was also related to greater self-reported functional disability, underscoring the potential clinical utility of this finding (Spielberg et al., 2015). Furthermore, re-experiencing symptoms also predicted reduced insula participation, or decoupling, in the mTBI group. Given the well-established role of the insula in assessing the salience of an emotional stimulus (Simmons et al., 2013; Sripada et al., 2012b), disruption of this circuit may relate to increased errors in processing trauma-related versus safe stimuli. These findings propose specific neural mechanisms underlying a particular vulnerability to intrusive memories in the context of a mTBI. Tasks that assess these circuits in direct relation to trauma processing in the context of mild TBI are necessary to explore the potential specificity in the functional pathology associated with PTSD symptoms (Spielberg et al., 2015).

**DTI:** Recent work reflects the growing need to examine the conjoint influence of TBI and PTSD on white matter. Jorge and colleagues 2012 used DTI to investigate white matter microstructure in n=72 OEF/OIF veterans with blast-only mTBI and compared to 21 deployed veterans without mTBI (Jorge et al., 2012). Conventional voxelwise tensor analysis revealed no between group differences. However, a greater number of spatially heterogeneous areas of abnormally low fractional anisotropy, or “potholes,” were identified in veterans with a history of mild TBI that were not related to age, time since trauma, presence of PTSD, mood disturbance, or alcohol misuse. A civilian comparison group with blunt-force trauma absent of psychopathogy showed the greatest number of “potholes,” suggesting specificity for mTBI. Across all TBI groups, the number of regions with reduced FA was also significantly associated with greater duration of post-traumatic amnesia, loss of consciousness, and poorer performance on measures of executive functioning (Jorge et al., 2012). In this sample, the presence of PTSD was not significantly related to white matter microstructure in veterans with mTBI.

Morey and colleagues 2013 employed voxelwise analysis of diffusion metrics using HARDI which allowed for the quantification of primary and partial volume fractions of crossing fibers in (1) Iraq/Afghanistan veterans with mTBI with comorbid PTSD and depression (n=30) and (2) non-TBI veterans without PTSD from primary control (n=42) and confirmatory control (n=28) groups. After controlling for age, PTSD, number of TBI events, duration of LOC, and presence of feeling dazed or confused, mTBI relative to control groups was associated with an extensive number of regions with lower white matter integrity including the corpus callosum, forceps minor and major, superior and posterior corona radiata, internal capsule, superior longitudinal fasciculus, among others (Morey et al., 2013). Interestingly, PTSD, in the context of TBI, was not associated with white matter integrity.

Bazarian and colleagues (2013) used conventional T1/T2-weighted MRI and voxel wise and ROI analysis of diffusion values (FA, MD) to investigate the relationship between measures of PTSD and mTBI acquired during deployment (Bazarian et al., 2013). In 52 OEF/OIF veterans with mixed diagnoses (i.e., PTSD and mTBI (n=9), PTSD only (n=6), mTBI only (n=21) and neither PTSD nor mTBI (n=16)), approximately 4 years post duty, self-reported PTSD severity was significantly predicted by whole brain MD values that fell into the 1st percentile of the sample distribution, as well as severity of exposure to combat events, age, time since last tour, and abnormal T1/T2-weighted MRI. Of note, a clinical self-report measure of mTBI was not predictive of PTSD severity. They also found that blast exposure was significantly associated with 1st percentile FA, abnormal T1/T2-weighted imaging, and severity of exposure to traumatic events. This small but well-controlled study may suggest that self-reported mTBI may not relate to neural changes obtained via brain injury, and that biomechanical forces experienced during combat exposure may increase vulnerability for PTSD (Bazarian et al., 2013).

Yeh and colleagues 2014 used voxelwise analysis of diffusion metrics, tract specific analysis, asymmetrical analysis, and fiber tracking to characterize white matter microstructure in active military personnel with a history of TBI (i.e., blast+blunt and blunt-only related concussion) and non-deployed military controls. DTI findings were examined in relation to post-concussive neuropsychological, neurobehavioral and post-traumatic stress symptoms. Compared to military control subjects (n=14), deployed individuals with a history of mild (n=29), moderate (n=7), and severe (n=1) TBI had significantly lower FA and higher trace, or the magnitude of diffusion in a voxel, in a number of white matter tracts located principally in the frontostriatal and fronto-limbic circuits, as well as in the midbrain and brainstem regions (Yeh et al., 2014). These regions of lower FA were related to higher self-reported PTSD and neurobehavioral symptoms.

Petrie and colleagues also attempted to tease apart the influence of PTSD and TBI on white matter in Iraq and Afghanistan deployed veterans. They failed to find significant differences on measures of white matter anisotropy (FA) between blast-mTBI veterans (n=34) with and without PTSD (Petrie et al., 2014). Importantly, there were no significant associations between PTSD symptoms and number of reported concussive events.

Davenport and colleagues (2015) utilized HARDI and the Orientation Distribution Function (ODF) to study white matter in 133 OEF/OIF veterans with PTSD and/or mTBI, as compared to combat controls absent of both conditions(Davenport et al., 2015). Results indicated that PTSD was associated with high GFA in anterior thalamic radiations, corticospinal tract, inferior fronto-occipital fasciculus, and inferior and superior longitudinal fasciculus. PTSD was also associated with lower MD in the corticospinal tract. Traditional tensor measures of FA, MD, and AD proved much less sensitive to PTSD than GFA, and there were no main effects for TBI or TBI+PTSD on GFA, FA, or MD suggesting that measures that account for multiple fiber orientations may be especially sensitive to the relationship of PTSD to white matter microstructure. Authors speculated that relative elevations in FA in association with PTSD may represent preexisting vulnerabilities, or symptom related overuse in association with anxiety regulation. Lopez and colleagues 2017 examined individuals with mTBI (n=27) or mTBI+PTSD (n=12) using a DTI tensor model,

volumetric imaging, and neuropsychological testing (Lopez et al., 2017). The mTBI+PTSD was found to have significantly reduced axial diffusivity (diffusion along the axon) in the right cingulum bundle, significantly *larger* volume in the right entorhinal cortex, and lower scores on tests of mental flexibility, processing speed, encoding and retrieval. These findings indicate the addition of PTSD to mTBI may be associated with decreased white matter integrity, larger medial temporal volumes, and poorer neuropsychological performance.

In a sample of OEF/OIF veterans with a mild or moderate TBI (n = 38) (blunt and/or blast) and n=17 veteran controls, Sorg and colleagues 2016 examined white matter correlates of neurocognition and PTSD symptoms (Sorg et al., 2016). After controlling for PTSD symptoms, a history of TBI significantly predicted lower FA in the genu of the corpus callosum and left cingulum bundle, and higher radial diffusivity in bilateral cingulum bundle and genu of the corpus callosum. PTSD symptoms, however, were not predictive of diffusivity values with or without controlling for mTBI. Similarly, Sorg et al. found that while TBI history was significantly associated with poorer performance on tests of memory and psychomotor speed, PTSD symptoms did not account for significant variance in test scores.

Using DTI, Dretsch and colleagues (Dretsch et al., 2017) assessed white matter integrity associated with posttraumatic symptomology and mTBI in n=74 active-duty U.S. soldiers with posttraumatic symptoms (PTS) (n = 16), PTS with a co-morbid history of mTBI (PTS/mTBI; n = 28), and a military control group (n = 30). They did not find significant between group differences in the number of abnormal DTI values (i.e., >2 SDs from the mean of the control group) for FA and MD or differences in mean FA or MD across ROIs in commissure, association, and projection tracts. While the comorbid PTS/mTBI group had significantly greater traumatic stress, depression, anxiety, and post-concussive symptoms, and performed worse on neurocognitive testing compared to those with PTS and controls, more severe clinical presentation in the comorbid group did not appear to be moderated by pathological changes in white matter induced by mTBI (Dretsch et al., 2017).

Longitudinal work may help clarify conflicting findings and link them mechanistically to PTSD, TBI and their clinical course. For example, using conventional DTI, Li and colleagues 2016 measured FA and MD at acute (3 days), subacute (10–20 days) and chronic stages (1–6 months) following blunt mTBI and examined whether these values prospectively related to the development of PTSD in community participants recruited from the hospital emergency departments (Li et al., 2016b). Relative to healthy controls, mTBI was equally associated with significantly higher FA in the acute phase, regardless of eventual diagnosis. However, compared to both healthy controls as well as individuals who did not develop PTSD, those with onset of PTSD within 6 months also showed increased MD in subacute phase, and decreased FA and increased MD in the chronic phase in several regions including the corpus callosum, inferior fronto-occipital fasciculus, uncinate fasciculus, superior longitudinal fasciculus, inferior longitudinal fasciculus, anterior thalamic radiation, and corticospinal tract. A Bayesian discriminant analysis suggested predictive classification overall accuracy of 76% using subacute MD values, while FA failed to show discriminative significance. Findings are consistent with previous reports of elevated FA within days of mTBI injury (Eierud et al., 2014), but, additionally suggest that measurements of cerebral

edema within weeks of the injury may help to identify blunt injury - mTBI patients with an increased risk of PTSD (Li et al., 2016b).

**MEG:** MEG has been used to study individuals with comorbid mTBI and PTSD (Huang et al., 2016c). Abnormal MEG slow-wave generation was found in vmPFC and bilateral dlPFC areas, indicating potential injuries due to mTBI. The slow-wave generation suggests mTBI in these PFC areas. In addition, similar to the result from an earlier cohort of PTSD-only subjects (Huang et al., 2014c) these comorbid patients also showed MEG hypoactivity from vmPFC and dlPFC in high frequency bands when compared with the HCs. In this comorbid group, the co-existence of an abnormal MEG slow-wave (mTBI component) and hypoactivity of vmPFC and dlPFC in high frequency bands (PTSD component) suggests the mTBI injuries in PFC may result in a lack of inhibition from PFC to other areas of the PTSD neurocircuitry. These data, thus, provide evidence of abnormal slow-wave generation in these PFC areas due to mTBI and the resulting potentiation of PTSD.

**PET:** PET has also been applied to help delineate the separate influence of TBI and PTSD on brain functioning. In an FDG-PET study of combat veterans with TBI alone, with PTSD + TBI, compared to individuals without history of either condition (n=15 combat controls), Buchsbaum et al., 2015 found that comparisons between TBI and TBI+PTSD were not significant, which could be in part due to the fact that the TBI group had elevated scores on a measure of PTSD. Also, there was no PTSD comparison group, which may have provided more clarity (Buchsbaum et al., 2015). Petrie and colleagues 2014 also did not find significant differences in TBI vs TBI+PTSD groups on FDG-PET, which may suggest that this approach lacks in sensitivity for detecting TBI vs TBI+PTSD differences (Petrie et al., 2014).

## Summary

In this paper, we reviewed a number of core and emerging methodologies and the findings from these modalities. In summary, we discussed how these could potentially be applied to further our understanding of the coupled disorders of PTSD and TBI. Functional imaging techniques may hold promise for detecting subtle differences in neuropathology, as these approaches (fMRI, MEG) have shown some evidence of specific variance due to PTSD and TBI in concert, while and volumetric and microstructural studies have shown potentially sensitivity to the contribution of PTSD in the context of TBI.

Functional MRI provides preliminary evidence for aberrant connectivity of the basal ganglia and insula in dually diagnosed individuals (Newsome et al., 2015, 2016, Spielberg et al. 2015). Caudate/putamen and insula connectivity were related to re-experiencing symptoms in individuals with mTBI (Spielberg et al., 2015), a finding that begins to elucidate mechanistic processes driving the increased rate of PTSD in those with mTBI. Authors of a meta-analysis, agnostic for design or approach, found that the middle frontal gyrus was an overlapping area of potential vulnerability (Simmons & Matthews, 2012). Results of these studies point to the continued investigation of frontal and limbic regions, and their interplay, in the increased incidence of PTSD in those with TBI. Graph theory may provide an especially powerful tool to examine the mechanistic basis of dual diagnosis that is less

dependent on nodal differences. PET has yet to provide evidence of its efficacy to describe the interplay of PTSD and TBI neural correlates, however work that has looked at the shape rather than location of divergent findings in TBI may be more sensitive.

Results of MEG work in comorbid individuals also provide some additional evidence of separable contributions of TBI and PTSD to the mechanism of increased vulnerability to PTSD in those with TBI. Specifically, the confluence of slow-wave activity in ventromedial and bilateral dorsolateral frontal regions, consistent with TBI, and hypoactivity in high frequency bands in these same regions, consistent with PTSD, suggests that mTBI injuries to the PFC may aid in the potentiation of PTSD symptoms. These findings are consistent with the hypothesis that mTBI may serve as a catalyst for the onset of PTSD (Bazarian et al., 2013).

Interrogation of macrostructural and microstructural characteristics have provided mixed results. Measurements of volume/thickness suggest structural alterations in superior frontal and amygdalar regions of dually diagnosed individuals (Depue et al., 2014; Lindemer et al., 2013) and are consistent with working models of symptomology of both disorders, in which limbic activity is thought to be either exaggerated and thus difficult to regulate effectively, or wherein limbic function is poorly regulated due to compromised frontal function. Sorg (2016), Jorge (2012), Morey (2013), and Petrie (2014) show evidence for TBI-related reductions in white matter integrity in in dually diagnosed individuals relative to non-TBI controls(Jorge et al., 2012; Morey et al., 2013; Petrie et al., 2014; Sorg et al., 2016). However, the additive effect of PTSD remains unclear, as these studies failed to demonstrate a significant relationship between PTSD and white matter microstructure in the context of TBI. Furthermore, Dretsch (2017) did not find significant differences in white matter across groups with posttraumatic symptomology, mixed posttraumatic symptomology and mTBI, and controls despite a greater preponderance of clinical symptoms in the mixed group. However, Bazarian, Davenport, Li, Lopez and Yeh all found evidence that white matter microstructure was related to PTSD symptomology in the context of TBI (Bazarian et al., 2013; Davenport et al., 2015; Li et al., 2016b; Lopez et al., 2017; Yeh et al., 2014). These findings may be dependent upon time of assay (e.g., (Li et al., 2016b)) or measurement (e.g., (Davenport et al., 2015)). Ultimately, multi-modal approaches in which functional and microstructural relationships are dually specified, ideally in a longitudinal manner, may provide the most insight as to the nature of the observed interactions.

### Limitations:

Mixed etiology within group such as mechanism of injury (blast+blunt), time since event, and premorbid trauma exposure presents a major challenge in the delineation of neurobiological changes in response to these injuries and their comorbidities. Samples of generous size that allow for the examination of symptoms in the context of one another in continuous models may provide essential information regarding the neural underpinnings of these oft-shared disorders and their heterogeneous presentations. Multivariate continuous approaches may also be advantageous as categorically defined groups are difficult to match on exposures (e.g., TBI+PTSD tends to have greater trauma exposure than TBI-only or PTSD-only groups; TBI-only may have greater severity of TBI than TBI+PTSD groups).

Additionally, full factorial designs are costly to image with adequate sample size. Indeed, collaborative data-sharing approaches maybe the most effective way to achieve adequate sample sizes to address these concerns (Thompson et al., 2014).

In terms of course, due to the timing of injury and trauma exposure, there may be some inherent limitations to the conclusions we can draw about the interplay of TBI and PTSD. For example, the fact that PTSD tends to follow TBI in those deployed to combat zones (e.g., (Hoge et al., 2008)) is of questionable utility, as many veterans (irrespective of TBI) report first noticing their PTSD symptoms when they have returned from deployments, wherein symptoms such as hypervigilance are no longer adaptive. Additionally, when there are multiple, similar, traumatic experiences, there may not be a specific event, or even a finite number of events, that are the singular cause of the onset of trauma related symptomology. Therefore, a TBI that occurred at any point throughout these exposures may appear to precede or follow a trauma (e.g., for example, the reported worst trauma). Therefore, a purported temporal precedence may be misleading, as the post traumatic symptomology may be linked more strongly to the overall burden of stress than a singular event, and a reported TBI may not therefore occur as a clear risk factor for PTSD. Likewise, susceptibility to TBI sequelae following traumatic exposures may be similarly misleading. Relationships between TBI effects and trauma exposures might be more clearly delineated in a sample wherein the insults are not temporally overlapping. For example, groups of individuals with separable causal events for TBI (e.g., post-training, pre-deployment breachers) and criterion A trauma (e.g., post-training, post-deployment breachers with combat trauma exposure) and measurement at multiple time points may be helpful in further defining the mechanisms of vulnerability and resilience. The use of objective measurements of TBI presence, in advance of PTSD (or ideally trauma exposure), may be of greater utility in discerning a mechanistic contribution of TBI to the onset of PTSD. Bazarian and colleagues' finding that MR and DTI metrics predicted PTSD severity, but not clinical diagnosis of mTBI, underscores this notion (Hoge et al., 2008).

Finally, cohorts were also mostly cross-sectional, small in size, and many participants were taking medications (e.g., sedatives) at the time of participation. At this time, the literature on the comorbidity of TBI and PTSD is more or less at an exploratory stage. With improved utilization of resources, such as cross sharing of cohorts, or data sharing, the design of such studies could be greatly improved. Conventional measures in parallel with novel measures help to both validate previous results but also push the field forward include GFA, ODF, asymmetry analyses, and MPF. Additional measures of potential interest are genetic measures to assess markers of vulnerability and resilience in conjunction with neuroimaging markers and neuropsychological assessments to help understand whether neurobiological substrates may correlate with cognitive deficits that inhibit recovery from mTBI + PTSD.

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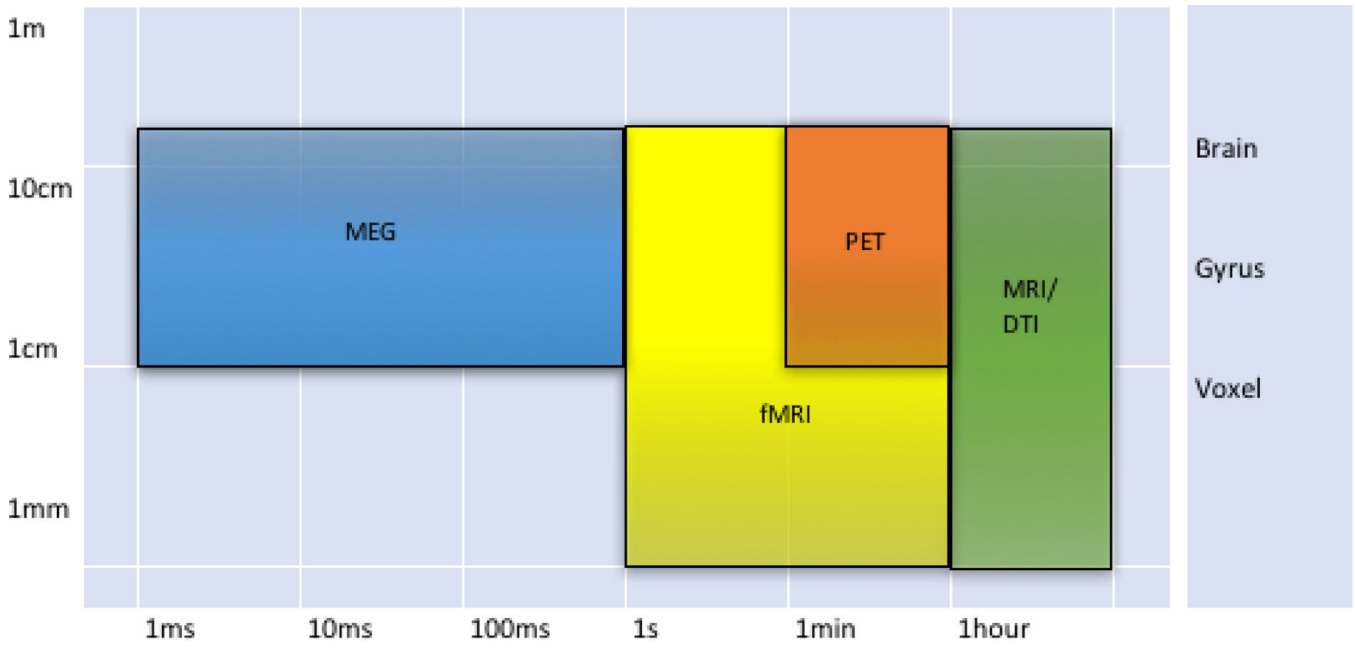


**Figure 1.**
Spatial vs Temporal Resolution of Reviewed Imaging Methods. Adapted from Huettel et al., 2004 (Huettel et al., 2004).

**Table 1.**

Percentage of all published works per imaging method that examine each disorder and their comorbidity. These data suggest that only very small percentage of work addresses the crossover of PTSD and TBI. Data accessed as of 9/25/2017 at 5pm EST.

| Method | TBI/method | PTSD/method | PTSD+TBI/method |
|---|---|---|---|
| **MRI** | 0.23% | 0.17% | 0.01% |
| **DTI** | 2.61% | 0.60% | 0.15% |
| **fMRI** | 0.22% | 0.18% | 0.01% |
| **MEG** | 0.30% | 0.45% | 0.04% |
| **PET** | 0.15% | 0.11% | 0.01% |

**Table 2.**

Advantages and Challenges Associated with Reviewed Imaging Modalities. Storage demands vary due to storage (raw P-files versus dicom files), scan parameters (multi-band, repetitions), and processing. Due to this variance a single file can range from less than 10MB to over 10GB.

| Imaging modality | Cost/hr | Storage | Design | PTSD† | TBI† | Advantages | Challenges |
|---|---|---|---|---|---|---|---|
| **MRI** | ~$500–1000 | Low | Static | + | − | Availability; standardization | Sensitivity to treatment change |
| **Diffusion Imaging** | ~$500–1000 | Moderate-to-high | Static | − | + | Standardization; measurement of microstructure | Sensitivity to treatment change |
| **fMRI** | ~$500–1000 | Moderate-to-high | Dynamic | ++ | + | Spatial resolution | Moderate temporal resolution |
| **MEG** | ~$500–1000 | Moderate-to-high | Dynamic | + | ++ | Excellent temporal resolution; measurement of microstructure | Availability; moderate deep brain signal |
| **PET** | ~$2000–4000 | Low-to-moderate | Mostly static | + | + | Targets specific neurotransmitters | Exposure to radioactive materials; low temporal resolution |

†=potential utility in current literature. Ranking is subjective and anticipated to change with the issuance of further research and methodologies.