NeuroImage: Clinical 4 (2014) 283–294

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Neuroimaging after mild traumatic brain injury: Review and meta-analysis ☆

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ARTICLE INFO

Article history:
Received 4 September 2013
Received in revised form 2 December 2013
Accepted 22 December 2013
Available online 4 January 2014

Keywords:
Mild traumatic brain injury
DTI
fMRI
Meta-analysis
Neuropsychological assessments
Post concussion syndrome

ABSTRACT

This paper broadly reviews the study of mild traumatic brain injury (mTBI), across the spectrum of neuroimaging modalities. Among the range of imaging methods, however, magnetic resonance imaging (MRI) is unique in its applicability to studying both structure and function. Thus we additionally performed meta-analyses of MRI results to examine 1) the issue of anatomical variability and consistency for functional MRI (fMRI) findings, 2) the analogous issue of anatomical consistency for white-matter findings, and 3) the importance of accounting for the time post injury in diffusion weighted imaging reports. As we discuss, the human neuroimaging literature consists of both small and large studies spanning acute to chronic time points that have examined both structural and functional changes with mTBI, using virtually every available medical imaging modality. Two key commonalities have been used across the majority of imaging studies. The first is the comparison between mTBI and control populations. The second is the attempt to link imaging results with neuropsychological assessments. Our fMRI meta-analysis demonstrates a frontal vulnerability to mTBI, demonstrated by decreased signal in prefrontal cortex compared to controls. This vulnerability is further highlighted by examining the frequency of reported mTBI white matter anisotropy, in which we show a strong anterior-to-posterior gradient (with anterior regions being more frequently reported in mTBI). Our final DTI meta-analysis examines a debated topic arising from inconsistent anisotropy findings across studies. Our results support the hypothesis that acute mTBI is associated with elevated anisotropy values and chronic mTBI complaints are correlated with depressed anisotropy. Thus, this review and set of meta-analyses demonstrate several important points about the ongoing use of neuroimaging to understand the functional and structural changes that occur throughout the time course of mTBI recovery. Based on the complexity of mTBI, however, much more work in this area is required to characterize injury mechanisms and recovery factors and to achieve clinically-relevant capabilities for diagnosis.

1. Introduction

Two important points about today's neuroimaging clinical standard of care of mTBI may be surprising. First, even though MRI is a premier modality for imaging the brain, when used in conventional clinical modes (e.g. T2- and T1-weighted structural scans) it adds little to clinical diagnoses beyond what is provided by CT (computed tomography). Thus CTs, which are faster and more cost-effective (Holmes et al., 2012; Stein et al., 2006), are routinely used by the emergency department, while MRIs, which do not pose a health risk from repeated ionizing radiation exposure, are virtually never utilized for mTBIs. Second, imaging is not used to diagnose mTBI itself, but to test for hematomas as well as to rule out head injury complications from more severe trauma. Various guidelines for diagnosing mTBI exist, most of which rely on the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) and details of the injury (such as self and witness reported descriptions of the accident, loss of consciousness, and evaluation of sustained trauma) (Ruff et al., 2009). The GCS assesses motor, verbal and eye responses; while there is some variability in the categories, a GCS

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http://dx.doi.org/10.1016/j.nicl.2013.12.009

from 13 to 15 is often designated as mild TBI, 8 or below is considered severe, and 9 to 12 is considered a moderate TBI (Jennett, 1998; Parikh et al., 2007). Ultimately, the diagnosis of TBI and its severity is made by a clinician. Approximately 1.4 million Americans receive TBI (Langlois et al., 2004), with most of these categorized as mTBIs (Cassidy et al., 2004).

Although mTBI has long been considered a noncritical injury, serious short and long term effects have been documented. Additionally, there is broad acceptance that multiple mTBIs can have serious long-term consequences (Guskiewicz et al., 2003). There are two common conjectures regarding the etiology of mTBI. The first is that the frontal and anterior cortices are vulnerable to neural contusion (Adams et al., 1980; Beaumont and Gennarelli, 2006; Brandstack et al., 2006; Levin et al., 1992). The second is that linear and rotational forces act on axon bundles, leading to axonal injury (Buki and Povlishock, 2006; Gennarelli et al., 1982; Meythaler et al., 2001; Povlishock et al., 1992). After initial injury, secondary mechanisms elicit biochemical, metabolic, and cellular changes in the time frame of minutes, days and months (Giza and Hovda, 2001; Loane and Faden, 2010; Xiong et al., 1997). Within the first fifteen minute post-injury, there is an extreme dip in neuropsychological performance (McCrea et al., 2002) and deficits can often linger for a week or longer (McCrea et al., 2003). The definition of the acute time frame varies across publications and some studies report acute periods of up to 1 month post-injury (Landre et al., 2006). Our study uses the term acute mTBI up to two weeks post-injury. Using the term acute or "semi-acute" for time periods up to 2 weeks post-injury is common in the literature (Gasparovic et al., 2009; Mac Donald et al., 2011; Mayer et al., 2010; Messe et al., 2011). Most mTBI patients recover, but a substantial minority have persistent disabling problems (Alexander, 1995; Kushner, 1998), known as post-concussion syndrome (PCS). Although criteria have been established by the Diagnostic and Statistical Manual of Mental Disorders IV (American Psychiatric Association, 2000) and International Statistical Classification of Diseases and Related Health Problems (ICD-10), PCS is difficult to diagnose and its symptoms are nonspecific. PCS also manifests symptoms similar to other disorders such as major depression (Iverson, 2006; Iverson and Lange, 2003), chronic pain (Smith-Seemiller et al., 2003) and other diseases such as somatization disorder. Indeed, neuropsychological testing in chronic stages of mTBI (even on the time scale of months) has been criticized as non-specific and insensitive (Iverson, 2005; McCrea and American Academy of Clinical Neuropsychology, 2008), and several studies have questioned the ecological validity of these assessments (Satz et al., 1999; Silver, 2000) and proposed improved approaches for detecting persisting cognitive deficits and linking these to neuroimaging results (Geary et al., 2010).

Heterogeneity of injury and current limitations in the sensitivity of imaging are challenges to developing diagnostic tools as well as predictors of recovery. Some of the major complicating factors include: 1) the fact that mTBI is a heterogeneous injury, with complicated dependencies on the mechanism of injury (e.g. an automobile accident vs. a military blast exposure) and the directional and temporal profiles of the forces impacting the skull and body; 2) mTBI lesions are diffuse and microscopic; and 3) the expected outcome of most patients is an eventual recovery. Thus, the physical size and heterogeneous distribution of injury in the brain make detection in an individual challenging and further make reliance on group averages problematic. In addition, since the time course of the injury leads to lingering post-concussive symptoms in a small number or injuries (Alexander, 1995; Kushner, 1998), it is a statistically challenging goal to try to predict which individuals will not recover fully. Finally, longitudinally, the presence or absence of CT findings does not correlate with long-term outcomes such as PCS (Hanlon et al., 1999; Huynh et al., 2006; Kurca et al., 2006; Lee et al., 2008; McCullagh et al., 2001; Tellier et al., 2009). To summarize, imaging is challenging at both acute and chronic stages of mTBI, and attempting to characterize the full time course compounds the level of complexity.

Despite the challenges, there has been a growing research effort to characterize structural and functional effects of mTBI. As shown in this paper, the full range of neuroimaging technologies have been brought to bear on this issue, including CT, positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetoencephalography (MEG), electroencencephalography (EEG), and 12 subtypes of MRI, such as diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), arterial spin labeling (ASL) and functional magnetic resonance imaging (fMRI). Moreover, collectively, these studies have examined mTBI at both acute and chronic stages of the injury. In reviewing the literature, it is important to note that the time post-injury of a study can affect its participant exclusion criterion, leading to prospective and symptomatic mTBI groups (Dikmen et al., 1992). In prospective mTBI studies, the exclusion criteria are independent from mTBI (e.g. specific age ranges or drug dependences). Symptomatic mTBI studies recruit chronic participants. Based on estimated recovery rates, this corresponds to effectively excluding the majority of those who sustain mTBIs. In other words, studies of symptomatic groups enroll participants because they have lingering complaints caused (presumably) by their head injury, whereas prospective studies recruit based on mTBI records at the time of concussion (before any chronic mTBI is known).

This paper broadly reviews mTBI neuroimaging studies of structure and function to highlight the tremendous effort that has taken place to investigate the spectrum of acute to chronic time scales. We additionally provide meta-analyses to examine the current utility of MRI for studying both structure and function. In terms of structure, some reports claim that MRI is more sensitive to detect complicated mTBI than CT (Mittl et al., 1994). Similar to other authors, we use complicated mTBI to include the broad range of abnormalities that lead to non-negative imaging results (Arciniegas et al., 2005; Iverson, 2005; Williams et al., 1990). It should be pointed out that definitions of 'mild' vary widely among both clinicians and researchers. Thus while many studies exclude participants with imaging findings, this is not universally the case. Among the other neuroimaging methods, it is also unique in that it can be used to study both structure and function. Many physical parameters provide MRI with a wide range of contrast mechanisms, enabling "traditional" T1- and T2-weighted structural scans, neural correlates of brain function using fMRI, white-matter microstructure by diffusion MRI, and biochemistry through MR spectroscopy. Thus our meta-analyses focus on three areas of MRI study. The first meta-analysis is motivated by the heterogeneity of fMRI findings and focuses on the question of anatomical consistency for fMRI. Similarly, the second analysis examines the issue of white matter vulnerability to mTBI. Looking at anatomically localized findings, previous neuroimaging data suggest that anterior regions of the brain are more vulnerable to abnormalities (Hashimoto and Abo, 2009; Lipton et al., 2009; McAllister et al., 1999; Niogi et al., 2008a). However, published reports are highly heterogeneous in their findings of regional white matter changes. Thus we examined whether anatomical consistency in mTBI lesions exists in the literature.

Our third meta-analysis examines the apparent inconsistency in diffusion-based anisotropy findings across studies that has led to debates about whether or not anisotropy values increase, decrease, or even change at all after mTBI (Lange et al., 2012) as well as whether anisotropy levels positively or negatively correlate with performance levels in neuropsychological assessments (FitzGerald and Crosson, 2011). Recent reports suggest that it is important to consider the time post injury in diffusion weighted imaging (Mayer et al., 2011; Niogi and Mukherjee, 2010). For example, Niogi and Mukherjee (2010) suggest that anisotropy is increased in the acute phase and decreased in the chronic phase in symptomatic TBI patients. Similarly Mayer et al. (2011) note that anisotropy values can be either reduced or increased in semi-acute time points, but tend to be decreased in later, chronic stages of symptomatic mTBI. Based on these considerations, we tested the hypotheses that anisotropy is increased in the acute phase and

decreased in the chronic phase. Specifically, we performed a meta-analysis that considered the time post-injury of each study's mTBI cohort. Our results support the hypothesis that acute mTBI is associated with elevated anisotropy values and chronic mTBI complaints are correlated with depressed anisotropy.

2. Methods

2.1. Data collection

We queried PubMed (http://www.ncbi.nlm.nih.gov/pubmed) for articles on imaging-based mTBI studies. The authors extracted key information from these articles and entered items into a LimeSurvey database (http://www.limesurvey.org) that we developed for this study. LimeSurvey is an open source web-based survey application that features an unlimited number of participants in a survey (in our case, each paper constituted a survey participant) and flexible export functions to multiple text and software formats. The LimeSurvey web interface enabled the authors to collaborate from different locations. Data from the articles were manually entered into LimeSurvey and these data were examined and summarized using custom-built Python parsing scripts. See Supplementary Materials for the actual survey we used for each paper.

We examined publications spanning 21 years from 1990 to 2011 using a query focused on mTBI and neuroimaging:

> (mTBI or "mild traumatic brain injury" or "post concussive syndrome" or "post concussion syndrome" or "postconcussion syndrome" or "postconcussive syndrome") and (neuroimaging or "magnetic resonance imaging" or MRI or "positron emission tomography" or PET or magnetoencephalography or MEG or electroencephalography or EEG or "functional magnetic resonance imaging" or fMRI or "diffusion tensor imaging" or DTI or T2 or "diffusion spectrum imaging" or DSI or "diffusion weighted imaging" or DWI or SWI or "susceptibility weighted imaging" or "T2*" or "CT" or "computed tomography" or FLAIR or "diffusion kurtosis imaging" or "diffusional kurtosis imaging" or DKI or "single photon emission computed tomography" or SPECT or NIRS or "near-infrared spectroscopy" or fNIRS or "functional near-infrared spectroscopy" or "resting state" or "functional connectivity" or "default mode network") and ("1990" [Publication Date]: "2011" [Publication Date]).

Our search date was November 11, 2011. This query resulted in 298 publications from which we excluded 176, using seven exclusion criteria. Specifically, we excluded 85 review articles, 47 non-imaging articles (most of which mentioned CT in relation to subjects' TBI status, but without any association to a statistical variable), 13 case studies, 12 animal studies, 9 articles that mixed mTBI with moderate/severe TBI or PTSD, 7 articles that were not in English, and 3 others (a video article, a fatigue article, and a mold exposure article). See Table S1 for a full listing of the 122 publications that we included

We extracted the following into the LimeSurvey database: 1) Time after concussion (the median/mean time between injury and neuroimaging). If studies were longitudinal or had multiple groups of subjects, multiple time points were reported. 2) Range of time after concussion (the minimum and maximum time between injury and neuroimaging). In publications where only standard deviations were provided, we approximated the range as the median $\pm$ 1.6 standard deviations. Note that this is analogous to the 90% confidence interval. 3) Number of subjects (sum of mTBI and control groups). Note that some publications (such as longitudinal studies) included multiple separated time points. 4) Imaging modality (CT, 12 subtypes of MRI including DTI and fMRI, PET, SPECT, MEG, EEG and near infrared spectrometry). 5) Hypothesized effect of mTBI motivating the imaging study, which we termed the "theme." For example, several studies hypothesized that mTBI would lead to white matter abnormalities, and thus to characterize this they measured anisotropy. In contrast, studies that hypothesized that connectivity would be affected, could address this research "theme" not only by using diverse measures including fMRI but also diffusion imaging-based tractography. 6) Other imaging results (anatomical coordinates, ROIs with significant anisotropy, and other parameters).

2.2. Statistical analysis

The fMRI meta-analysis used Ginger ALE (Eickhoff et al., 2009, 2012; Turkeltaub et al., 2012). All fMRI coordinates were converted into Talairach space. We used the default Ginger ALE parameters (Eickhoff et al., 2009), and additionally added the number of subjects per experiment. We chose a false discovery rate threshold level of 0.05. We used all available fMRI publications of mTBI, most of which used working memory tasks, but the tasks also included resting state fMRI, an auditory odd-ball task, and a spatial navigation task (Chen et al., 2007; Krivitzky et al., 2011; Mayer et al., 2009, 2011; McAllister et al., 2001, 2011; Slobounov et al., 2010; Witt et al., 2010). Only coordinates from contrast images using two-sample test (mTBI and control) were included. AFNI (Cox, 1996) was used to present fMRI meta-analysis images in Talairach space.

For the DTI meta-analyses, each reported region of interest (ROI) was coded using the ICBM-81 atlas (Mori et al., 2008). ROIs that were outside of this atlas were only used in the analyses involving time post-injury and omitted for the spatial DTI analysis. Most publications reported FA values, however we also included studies that reported relative anisotropy (RA). Publications found anisotropy differences in two predominant ways — either categorically (by examining anisotropy means between mTBI and control groups), or parametrically (through regression analyses correlating anisotropy values with neuropsychological performance). AFNI (Cox, 1996) was used to present DTI meta-analysis results in Montreal Neurological Institute (MNI-152) space.

As in other publications that account for diverse sets of assessment scores (Bazarian et al., 2007), we normalized neuropsychological results using algebraic negation (multiplying the original score with a negative one) such that better performance corresponds to positive scores. For example, we did not transform results from the California verbal learning test in which scores should be higher for normal performance than for impaired performance, but we did transform (negate) completion time for the Trail making A test (in this case, better raw scores are lower, corresponding to faster completion times). Our motivation for doing this was that it enables us to unambiguously discuss negative and positive correlations between neuropsychological results with changes in imaging measures.

3. Results

3.1. Neuroimaging literature

The number of mTBI publications has dramatically increased over the past two decades. Fig. 1A shows the number of publications with respect to time for the neuroimaging articles we analyzed in the context of mTBI research as a whole. The more general mTBI PubMed search in Fig. 1A excluded our neuroimaging keywords (to include both imaging and non-imaging studies). Specifically, we used (mTBI or "mild traumatic brain injury" or "post concussive syndrome" or "post concussion syndrome" or "postconcussion syndrome" or "postconcussive syndrome") and ("1990"[Publication Date]: "2011"[Publication Date]). The figure shows that the rate of mTBI publications has been increasing over time, with a notable upsurge occurring around 2007. Fig. 1B classifies imaging modalities of the publications we analyzed over time. Most of the imaging modalities are MRI-based. The number of studies relying (at least in part) on CT is relatively large, primarily because it is used ubiquitously (and almost exclusively) in emergency room settings. Thus, CT was used as part of the clinical characterization of the subjects in many studies. The functional modalities (EEG/MEG, fMRI,

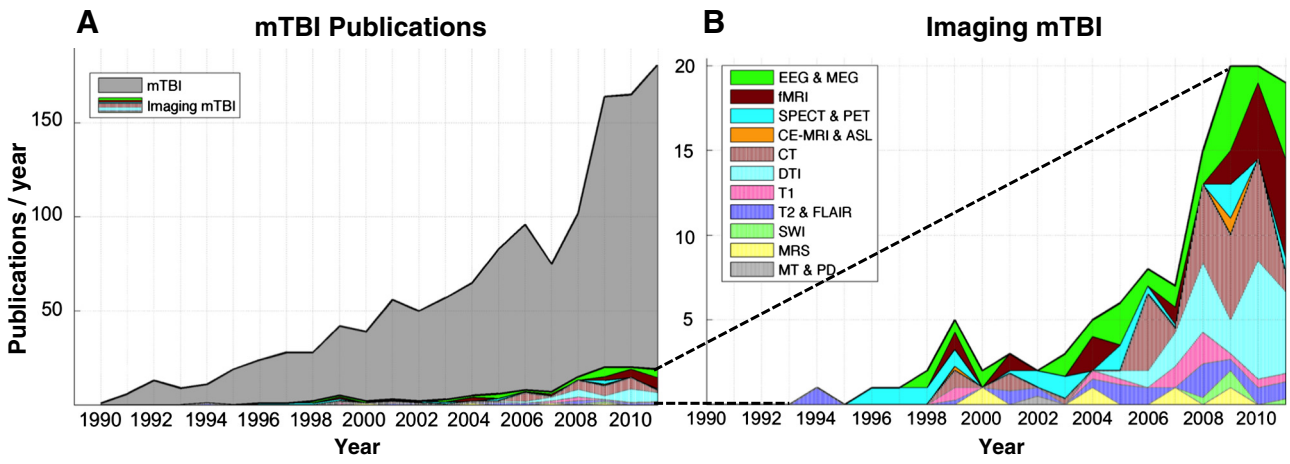

Fig. 1. mTBI publications between 1990 and 2011: The levels of mTBI studies have been increasing over the past two decades and the focus on neuroimaging has increased proportionately with the field as a whole. (A) The histogram shows 1314 mTBI articles published from 1990 to 2011. (B) Focuses on the 122 imaging-based studies, and provides a graphical breakdown of what imaging modalities were used. To date the predominant imaging modalities have been CT and MRI.

SPECT/PET, and ASL) have been steadily used during the time period shown.

Figs. 2 and 3 show that structural and functional neuroimaging studies have examined mTBI across acute to chronic time scales with a wide range of imaging modalities. It is important to note that the number of subjects in these publications represents the total number of mTBI and control participants for each experiment, which could include different participant cohorts. Note too, that many experiments have large variability for subjects' post-injury data collection times. Also, while the number of subjects includes control participants, for obvious reasons these controls did not contribute to the post-injury collection times in these Figs. 2 and 3. Focusing on some observations from each figure,

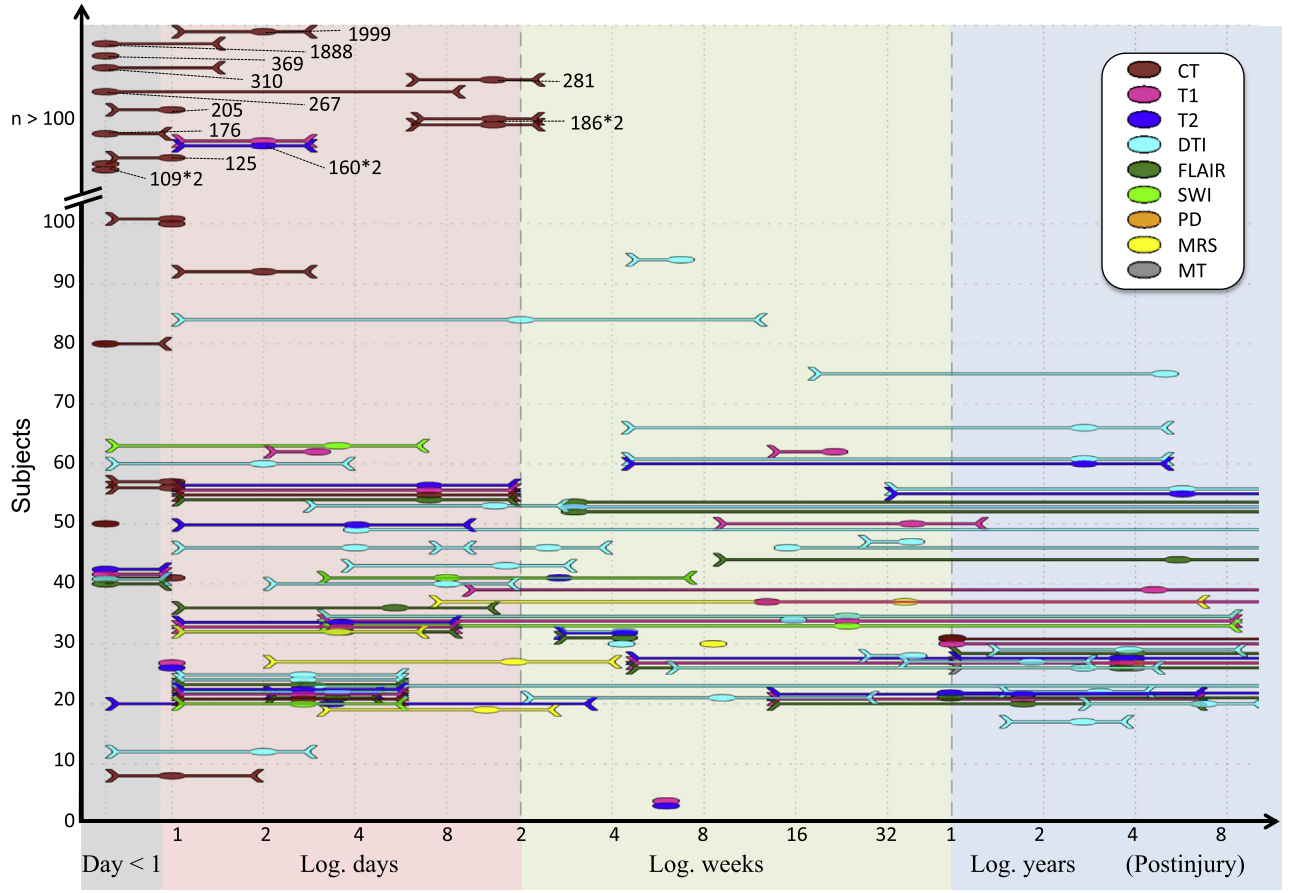

Fig. 2. Structural neuroimaging studies of mTBI vary widely both in terms of the number of subjects studied as well as in the time range from injury. Shown is a graphical depiction of the number of subjects (mTBIs as well as any controls in each experiment) and the time post-injury (for the mTBIs) of data collection for structural imaging studies. The colored backgrounds indicate the time axis scales (days, week, and years). The imaging modality is indicated by color, and each line indicates the study's post-injury scan range (earliest and latest reported times post-injury). The line's ellipse represents the median time after injury. To keep all data "visible," overlapping lines have been shifted up by two subjects.

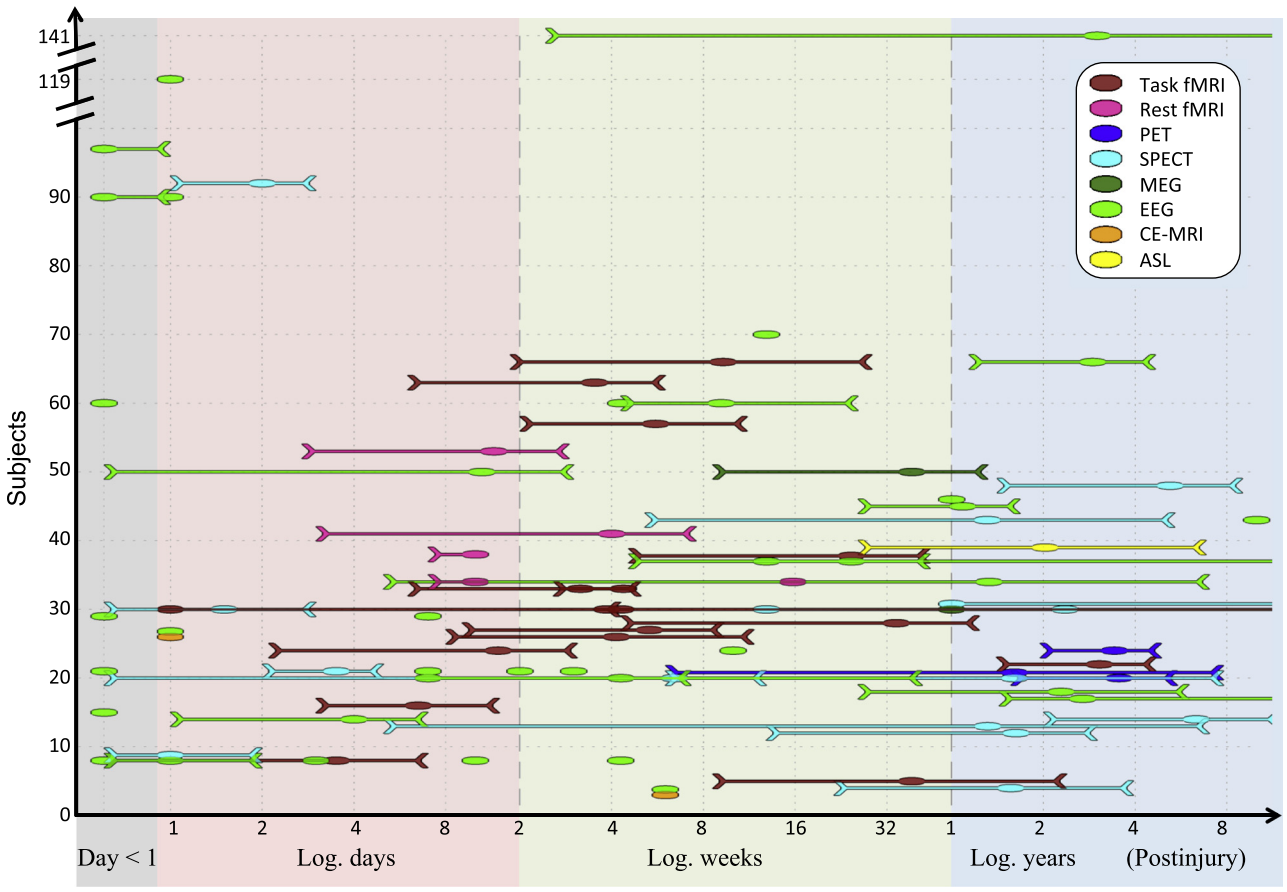

Fig. 3. Functional neuroimaging studies of mTBI also vary widely both in terms of the number of subjects studied as well as the time range after injury. Conventions are the same as in Fig. 2.

Fig. 2 shows that CT studies have been performed on both small and large cohorts, but the majority of these studies occur soon after injury, usually using the subjects' clinical CTs. DTI and the other structural modalities have a much better coverage of the time post-injury. For Fig. 3, one observation is that many EEG studies also occur soon after injury but in contrast to CT, EEG has also been broadly applied to the entire time course post-injury and to a large number of subjects. Fig. 3 also shows that task-based fMRI has been similarly broadly applied, while

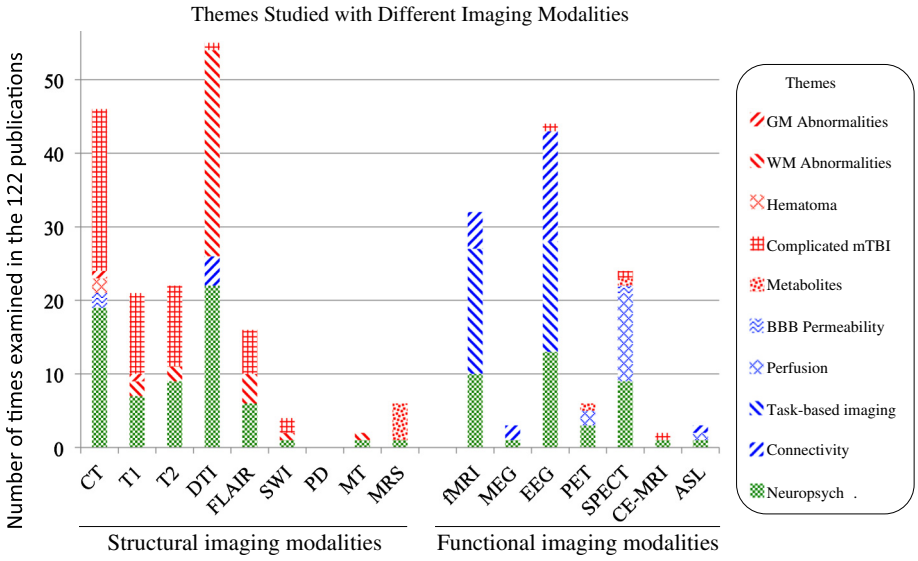

Fig. 4. Two major goals of neuroimaging studies are to find structural and functional markers of mTBI and to establish links between neuropsychological assessments and neuroimaging. Shown is a breakdown of imaging methods and study focus "themes." Themes include gray matter (GM) abnormalities; white matter (WM) abnormalities; intracranial hematomas; complicated mTBI (non-negative imaging results, excluding hematomas and abnormalities localized to GM and WM such as increased blood brain barrier permeability, contusions, intracranial lesions, and micro bleeds); metabolites (changes in magnetic resonance spectroscopic results); blood brain barrier (BBB) permeability; perfusion deficits; task-based imaging; connectivity analysis; and neuropsychological assessments (used in conjunction with a neuroimaging modality).

resting state fMRI studies have predominantly focused on acute and semi-acute time ranges. PET, ASL, CE-MRI and MEG seem to be rarely used. In addition, there is a lack of PET studies of acute mTBI and both PET and MRS publications used groups that were smaller than 40 subjects.

The research areas of neuroimaging studies tend to follow distinct structural and functional categories as shown in Fig. 4. As mentioned previously, CT was used as part of the clinical characterization of the subjects in many studies. In papers where CT was a research focus, it was used to examine structural abnormalities arising from mTBI. Although the category of "mild" TBI sometimes includes the stipulation of negative findings, CTs can nonetheless be used to detect abnormalities from a wide range of trauma severities that appear as hyper- or hypo-intensities observed in gray matter or white matter regions as well as hematomas, cerebral swelling, and intraventricular hemorrhage. Gray matter is composed largely of neuronal cell bodies, glial cells, and the capillaries. White matter abnormalities are thought to reflect stretched or sheared axon bundles or abnormal cellular microstructures. Abnormalities not clearly falling into the categories of hematomas or white/gray matter findings have been designated as "complicated mTBI" in Fig. 4. Complicated mTBI was examined fifty-six times in our publication sample, mainly using CT and MRI. Gray matter (GM) abnormalities were only reported in one T1 and one CT study. Abnormal blood brain barrier (BBB) permeabilities were reported by three publications using SPECT and CT (CT studies also detected tau/S100b proteins in blood). White matter (WM) abnormalities were examined thirty-eight times (primarily with DTI). Hematomas were only reported in two CT-based studies. Metabolites were analyzed by a PET, a SPECT and five MRS publications. Perfusion was examined by one PET, one ASL and twelve SPECT publications. Task-based imaging was used in seventeen fMRI and fifteen EEG studies, often linking tasks to brain activity. Connectivity analyses were examined twenty-seven times, detecting low frequency activity, connectivity differences between neural regions, EEG pathologies, altered resting state networks (using fMRI), and connectivity maps (using white matter tractography). Neuropsychological assessments were used in seventy-two publications and were the one theme of investigation (despite not relying on any particular imaging modality itself) that spanned all structural and functional modalities.

3.2. fMRI meta-analysis

Figs. 5–7 display results from our MRI meta-analyses (see also downloadable image files in Supplemental data). Fig. 5 shows results from a Ginger ALE analysis of the fMRI publications summarized in Table 1. Table 1 also examines how many independent publications support each ALE peaks. The analysis produced six regions that were consistently more active in mTBI compared to control groups and seven regions with lower activity for mTBI. Spatially, these regions suggest an anterior-to-posterior pattern in which activity is reduced in anterior regions and increased in posterior regions. Of the seven regions with decreased mTBI activity, six were in the frontal lobe or anterior cingulate, with the remaining one being relatively posterior (temporal lobe/BA 39). The regions with increased mTBI activity consisted of two coordinates in the cerebellum, two insula regions, and two foci in the parietal lobe (BA 40). The mean Talairach anterior-to-posterior coordinate for regions with reduced activity was $Y = 15$ mm, compared to $Y = -23$ for increased mTBI activity, and a two-sample *t*-test of Y between the decreased and increased regions was significant ($p = 0.05$, two tailed).

3.3. Anatomical frequency of anisotropy findings

Close examination of the number and anatomical locations of publications reporting white matter abnormalities revealed significant anatomical heterogeneity as shown in Fig. 6. See Table 2 for white matter regions in the ICBM-81 atlas as well as their abbreviations and center-of-mass coordinates. It is important to note that several ICBM-81 regions have not been reported by the publications we examined. These include the pontine crossing tract, medial lemniscus, inferior cerebellar peduncle, cerebral peduncle, posterior thalamic radiation, cingulum to hippocampus, superior fronto-occipital fasciculus, tapetum, and inferior longitudinal fasciculi. These unreported regions were coded in two ways; both leading to statistically significant correlations between

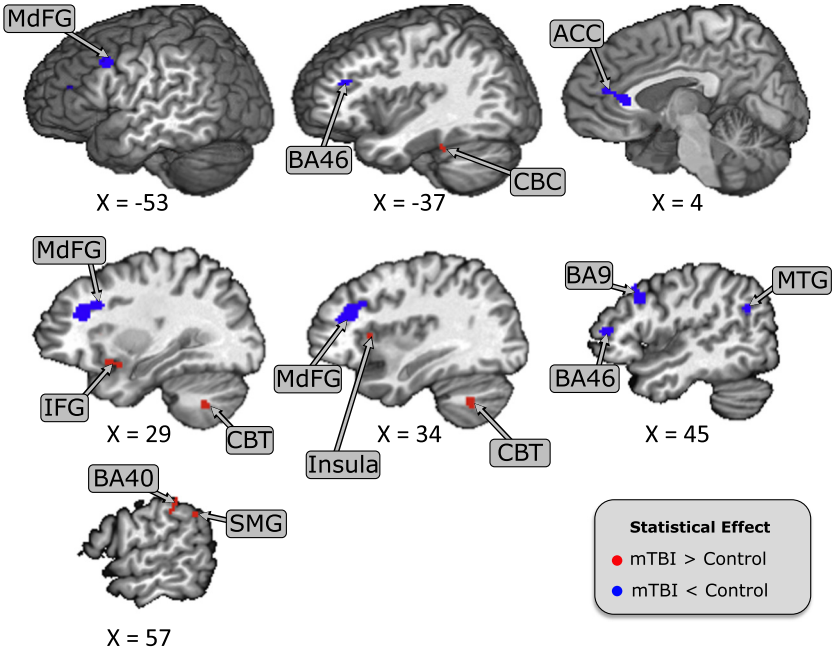

Fig. 5. Activation Likelihood Estimate (ALE) analysis of fMRI mTBI publications shows both increased and decreased BOLD response for mTBI. As shown, mTBI has increased response in cerebellum, insula, and inferior parietal regions (BA 40) compared to controls. Relative to mTBI, control subjects have increased response in several regions in frontal lobe and BA 39. Maps are thresholded at $p < 0.05$ using a false discovery rate (FDR) correction, and a minimal cluster size of 64 μL. Results are displayed on a Talairach brain template.

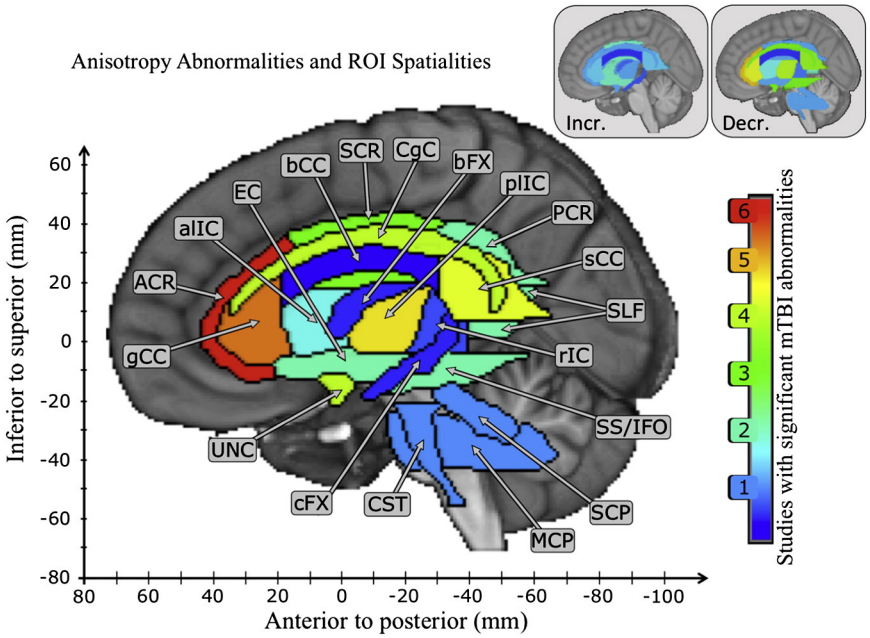

Fig. 6. Shown are the ICBM-81 white matter regions, colored to indicate the number of publications reporting white matter abnormalities (regions with no abnormal findings in the literature are not shown). The Montreal Neurological Institute (MNI-152) template is added for anatomical reference. Using the center-of-mass for each ICBM-81 structure, we determined that a significant anterior-to-posterior relationship exists between frequency in the literature and anatomical location. See Table 2 for full names of the anatomical labels. Note that since more lateral structures are only partially visible, the anatomical labels point to a convenient, visible location and do not necessarily reflect a structure's center of mass. For example, SLF is mostly covered by more medial structures, and is only visible at its most posterior-inferior part. Coordinates are displayed in MNI-152 space.

anatomical location, along anterior-to-posterior gradient, and the number of abnormalities. Specifically, we calculated a Spearman correlation 1) omitting these regions from the statistical test (using only regions that had reported abnormal findings in the literature) resulting in a $\rho^2 = 0.26$ ($p < 0.026$); and 2) including the unreported regions (coding their frequency as zero) resulting in a $\rho^2 = 0.32$ ($p < 0.0025$). We did not find significant correlations in the inferior-to-superior or left-to-right directions. Laterality of the regions was also not significant.

3.4. Anisotropy changes depend on imaging time post-injury

Based on observations by Niogi and Mukherjee (2010) as well as Mayer et al. (2011), we wanted to examine the hypothesis that anisotropy would be elevated at acute time points and depressed post acutely. Fig. 7 demonstrates the critical importance of accounting for the time post-injury in diffusion weighted imaging reports. Shown are the time-resolved anisotropy results for each study. In Fig. 7A, studies compared mTBI groups to control groups. In Fig. 7B, studies correlated mTBI anisotropy values with neuropsychological performance. Note that some publications report experimental results at two different chronological points (Grossman et al., 2012; Inglese et al., 2005; Mac Donald et al., 2011; Mayer et al., 2011; Messe et al., 2011) and thus are represented by two bars. Another complication with the literature is that some research groups seem to have used overlapping mTBI cohorts across publications (see potential overlap in boxed bars in Fig. 7). Thus counting each bar in Fig. 7 as an independent measure likely leads to inflated estimates of significance. To account for this, we report the most conservative statistical estimate by using each boxed group as a single experiment. As shown, elevated anisotropy values are more frequently reported for studies of acute mTBI (<2 weeks), while depressed anisotropy findings are reported more frequently for post-acute mTBI (>2 weeks). In Fig. 7A, a two-sample *t*-test confirms that anisotropy is greater in the acute phase (one-tailed, 14 DOF, $p = 0.02$). In Fig. 7B, acute phase anisotropy was also significantly anti-correlated with neuropsychological performance compared to a predominant positive correlation in the post acute phase (one-tailed, 7 DOF, $p < 0.006$). Finally, to put these results into the context of the literature, it is important to note that the participant populations were recruited using different criteria in the acute and chronic periods. Specifically, all of the acute studies recruited prospective mTBI subjects, the majority of whom would be expected to recover from their injuries. Conversely, many of the post-acute mTBI studies of anisotropy selected for symptomatic subjects.

4. Discussion

An obvious key limitation of this paper (and any review that attempts to report a snapshot of a vibrant field) is that components of it are immediately outdated. Although we believe that the conclusions we draw here will be qualitative accurate for the next few years, the literature we sampled just barely supported any meaningful fMRI meta-analyses, and the issue of the anisotropy values' dependence on time post-injury is far from conclusive. Part of what we have hoped to accomplish here is an assessment of the modalities, questions, and times post-injury that recent publications have examined. Based on this we hope that research teams can use this to strategically bolster areas of this field that would most benefit from additional effort. We are optimistic that we and/or others will improve our literature analysis approaches in the future to continue what has the potential to become an ongoing, reflective process.

Our review of the mTBI literature highlights the fact that currently about 1/10th of published studies have a human neuroimaging component and that several small and large studies spanning acute to chronic time points have been conducted. These studies have examined both structural and functional changes with mTBI, using virtually every available medical imaging modality. Two key commonalities have been used across the majority of imaging studies. The first is the comparison between mTBI and control populations. The second is the attempt to link imaging results with neuropsychological assessments. Indeed, in addition to highlighting the fact that research topics have largely (but not exclusively) fallen into either structural or functional categories and providing a sense of the proportion of work that has been devoted to the two, Fig. 4 strikingly shows that neuropsychology appears to be the predominant commonality across the imaging literature. This

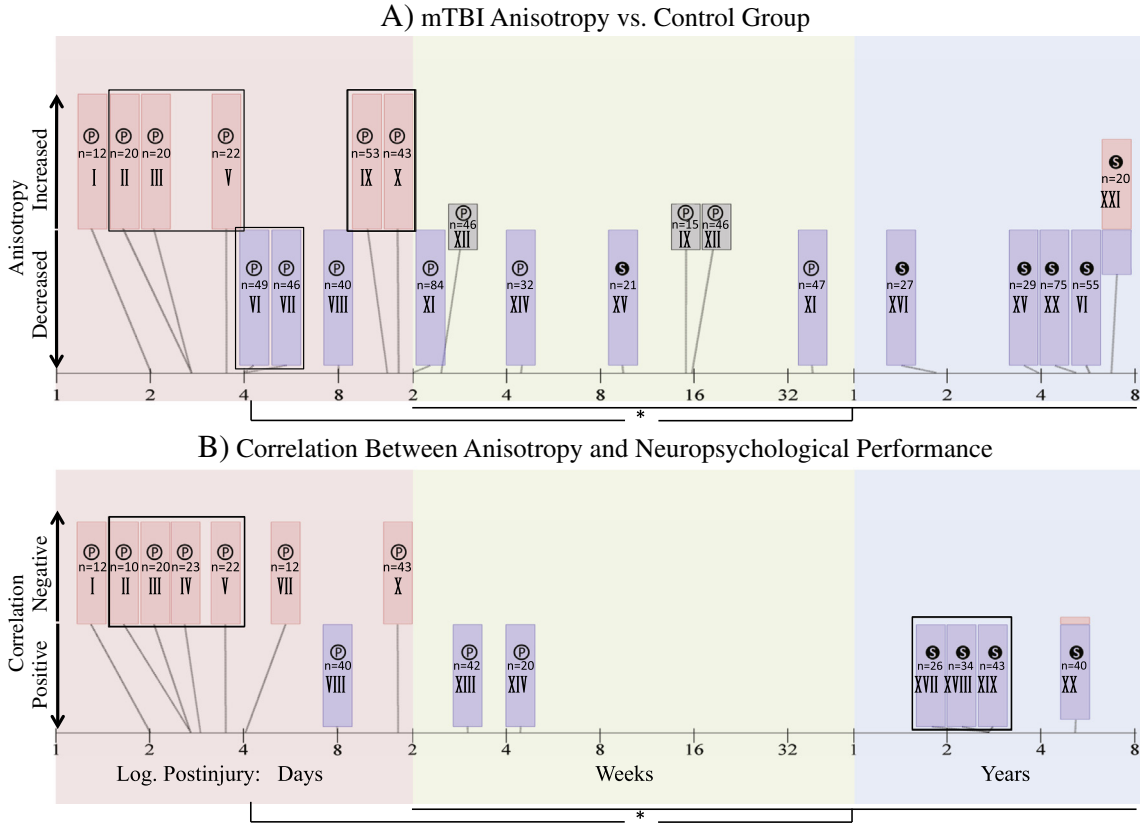

Fig. 7. (A) Elevated anisotropy, for mTBI, is more frequently reported for studies of acute mTBI, while depressed anisotropy is reported more frequently for studies after the acute phase. Each bar represents the ratio of increased (red) to decreased (blue) regions in mTBI vs. a control group for each publication. The gray boxes represent experiments with insignificant FA difference between mTBI and control groups. The lines connecting the bars to the time axis mark the study's median time post-injury. Also indicated is the number of subjects per experiment and whether the mTBI subjects were prospective (P) or selected (S). Boxed bars indicate potentially overlapping subject cohorts. The colored backgrounds indicate the time axis scales (days, weeks, and years). For statistical tests, we have defined post-injury times less than 14 days as an acute mTBI, and post-acute times as 2 weeks and greater. Based on a one-sided, two-sample *t*-test, the acute anisotropy was significantly greater than the anisotropy after the acute phase ($p = 0.02$). (B) Shows the analogous information for studies that reported significant relationships between anisotropy measures and neuropsychological performance. Using a *t*-test analogous to that in 7A, we show that the acute phase anisotropy was significantly anti-correlated with neuropsychological performance compared to a predominant positive correlation after the acute phase ($p < 0.006$). Statistical significance was designated as * for $p < 0.05$. Publications are I) Bazarian et al. (2007); II) Chu et al. (2010); III) Wilde et al. (2008); IV) Wu et al. (2010); V) Yallampalli et al. (2010); VI) Inglese et al. (2005); VII) Miles et al. (2008); VIII) Lipton et al. (2009); IX) Mayer et al. (2011); X) Mayer et al. (2010); XI) Messe et al. (2011); XII) Mac Donald et al. (2011); XIII) Holli et al. (2010); XIV) Smits et al. (2011); XV) Grossman et al. (2012); XVI) Lipton et al. (2008); XVII) Maruta et al. (2010); XVIII) Niogi et al. (2008a); XIX) Niogi et al. (2008b); XX) Geary et al. (2010); XXI) Lo et al. (2009).

underscores the fact that mTBI neuroimaging efforts have prioritized attempting to link brain measurements with neuropsychological assessments. Despite the large efforts to date, neuroimaging methods still lack the individual patient-level sensitivity and specificity to serve as a diagnostic tool for mTBI. Similar to other reviews in this area (Belanger et al., 2007; Hunter et al., 2012; Niogi and Mukherjee, 2010; Prabhu, 2011; Pulsipher et al., 2011), we believe that ultimate motivations for further neuroimaging work are to provide data to predict an

Table 1
mTBI vs. control cluster centroids with FDR ($p < 0.05$) using ALE.

ROI abbrev.	Vol. (μL)	ALE cluster coordinate (X, Y, Z)[a]			ROI name	Supporting publications (ALE coord. within 20 mm)[b]
mTBI > Control						
CBT	304	33	−53	−39	R. cerebellar tonsil	Wi2010, Sl2010, Kr2011
BA40	152	58	−32	39	R. inf. par. lobule/BA 40	Wi2010
CBC	144	−33	−34	−26	L. culmen	Wi2010, Mc2011
IFG	144	29	9	−12	R. inf. front. gyrus	Wi2010, Ma2011
Insula	64	33	17	7	R. insula	Wi2010, Ma2011
SMG	64	57	−47	33	R. supramarg. gyrus	Wi2010, Ma2011
Control > mTBI						
MdFG	1296	32	28	24	R. mid. frontal gyrus	Wi2010, Ma2011, Mc2011, Ch2007
ACC	856	3	30	10	R. ant. cingulate	Wi2010, Ma2011
MTG	616	51	−59	23	R. mid. temp. gyrus/BA 39	Wi2010, Ma2011, Mc2011
BA9	496	45	17	34	R. precentral gyrus/BA 9	Wi2010, Mc2011, Ch2007
MdFG	304	−50	14	35	L. mid. frontal gyrus	Mc2011
BA46	184	46	40	10	R. DLPFC/BA 46	Ma2011, Mc2001, Mc2011
BA46	184	−39	36	19	L. DLPFC/BA 46	Ma2011, Mc2011, Ch2007

[a] ALE cluster coordinate is the center of mass of cluster calculated by ALE algorithm.
[b] Publication codes Wi2010, Sl2010, Kr2011, Mc2001, Mc2011, Ma2011, Ch2007 represent Witt et al. (2010); Slobounov et al. (2010); Krivitzky et al. (2011); McAllister et al. (2001,2011); Mayer et al. (2011); Chen et al. (2007) respectively. Supporting publications have coordinates at least within 20 mm of ALE coordinate.

Table 2
Center of mass of white matter structures in the ICBM-81 atlas.

ROI acronym	X(L)[a]	Y(P)[b] Coordinates	Z(I)[c]	Abnormalities	ROI Name
ACR	22	28	10	6	Anterior corona radiata
alIC	18	8	8	2	Anterior limb of internal capsule
bCC	1	−5	27	1	Body of corpus callosum
bFX	1	−6	13	1	Body of fornix
cFX	28	−24	−6	1	Fornix crus
CgC	8	−11	30	4	Cingulate cortex
CgH	21	−31	−13	0	Hippocampal part of cingulum
CP	12	−18	−12	0	Cerebral peduncle
CST	6	−25	−33	1	Corticospinal tract
EC	30	0	1	2	External capsule
gCC	0	26	7	6	Genu of corpus callosum
ICP	8	−44	−37	0	Inferior cerebellar peduncle
MCP	1	−40	−35	1	Middle cerebellar peduncle
ML	6	−37	−33	0	Medial lemniscus
PCR	24	−38	28	2	Posterior corona radiata
PCT	1	−29	−31	0	Pontine crossing tract
plIC	20	−13	8	5	Posterior limb of internal capsule
PTR	34	−55	7	0	Posterior thalamic radiation
rIC	31	−29	6	1	Retrolenticular part of internal capsule
sCC	1	−42	18	5	Splenium of corpus callosum
SCP	6	−42	−25	1	Superior cerebellar peduncle
SCR	24	−8	30	3	Superior corona radiata
SFO	20	2	21	0	Superior fronto-occipital fasciculus
SLF	36	−26	26	2	Superior longitudinal fasciculi
SS, IFO, ILF	40	−32	−9	2	Sagittal stratum, inf. fronto-occipital fasc., inf. longitudinal fasc.
TAP	28	−46	14	0	Tapetum
UNC	34	0	−16	4	Uncinate fasciculi

All coordinates are in MNI-152 space. Reported anisotropy-abnormalities indicate the number of publications that reported an anisotropy abnormality in ROI.
[a] X coordinate assumes symmetry between left and right hemispheres (mean absolute value of centroid reported here).
[b] Y coordinate increases with anterior direction.
[c] Z coordinate increases with superiority.

individual's recovery, measure her/his transient and persistent cognitive deficits at a level that compliments or exceeds the sensitivity of neuropsychiatric testing, and quantifies the success of cognitive and drug-based interventions (McAllister et al., 2011). In the meantime, the field needs further effort to provide stronger correlative understanding of the relationships between neuroimaging and neuropsychiatry, and simultaneously both types of measures also need improvement.

Our fMRI and DTI meta-analyses show, however, that there is hope for consistent neuroimaging markers of structure and function. The fMRI meta-analysis results in Fig. 5 and Table 1 show a frontal vulnerability in mTBI, demonstrated by decreased signal compared to controls. fMRI studies consistently report decreased activity in mTBI in frontal regions such as right MFG, ACC, and right precentral gyrus. Our finding of bilateral decreases in DLPFC is consistent with three published studies (Chen et al., 2007; Mayer et al., 2011; McAllister et al., 2011). The DLPFC may be related with working memory. Specific localization of working memory intense regions was found in non-human research (Funahashi et al., 1989) and in humans using fMRI (D'Esposito et al., 1995). Even though DLPFC responds to working memory it is a very complex region and serves a multitude of cognitive functions (Kane and Engle, 2002). Interestingly, among the most significant mTBI increases, right cerebellar tonsil and left culmen, were noted in four independent publications (Chen et al., 2007; Mayer et al., 2011; McAllister et al., 2011; Witt et al., 2010). Krivitzky et al. (2011), has noted that the cerebellum has been implicated for regulating behavior, working memory, and other aspects of executive control. In addition, it has long been recognized that cerebellar lesions can lead to postural deficits (Horak and Diener, 1994), which is a prominent issue in mTBI (Guskiewicz et al., 1996, 2007; McCrea et al., 2003). Finally, it is important to note that the well-known fMRI issue of multiple comparisons correction may be a limitation of our Ginger ALE analysis. Most of the publications that we used corrected their findings for multiple comparisons. However, notable exceptions include McAllister et al. (2001) and Witt et al. (2010). Although the predominance of anterior fMRI and DTI findings suggests that frontal areas are more vulnerable to injury, we have not ruled out other possible explanations with this current study (for example, it is possible that there is a sampling bias in the literature, which favors injury mechanisms that lead to more injuries in prefrontal cortex). Another limitation of this fMRI meta-analysis is that, unlike the diffusion-weighted literature, the number of fMRI studies published did not have power enough for an fMRI analysis using time post-injury. We feel that "time-resolving" fMRI studies could be an important area for future investigation.

Structurally, diffusion weighted imaging is currently one of the most promising techniques for characterizing the subtle and heterogeneous changes that occur with mTBI. Note Supplemental Table 2 lists specific details about the studies used to generate Figs. 6 and 7. Fig. 6 demonstrates that differences in the frequency of reported mTBI white matter anisotropy values have an anterior to posterior gradient. Taken independently, each DTI study shows white matter differences that seem to be sporadic. When integrating across all reported findings, though, these frequencies of abnormalities have a systematic spatial distribution corroborating previous suggestions that anterior regions of the brain are more vulnerable to abnormalities (Hashimoto and Abo, 2009; Lipton et al., 2009; McAllister et al., 1999; Niogi et al., 2008a). Anterior regions may also be related with executive/cognitive function disabilities in mTBI (McCrea et al., 2003).

Using the existing literature to time-resolve results, Fig. 7 suggests that white matter anisotropy can serve as an important potential marker of both chronic symptoms as well as of an acute response to secondary injuries. Taken together, the literature demonstrates that elevated anisotropy values (and negative correlations with neuropsychological performance) are more frequently reported for studies of acute mTBI, while depressed anisotropy findings (and positive correlations with neuropsychological performance) are reported more frequently for chronic studies. Our analyses show that elevated anisotropy values are more frequently reported for studies of acute mTBI, while depressed anisotropy findings are reported more frequently for post-acute studies, corroborating conjectures of Mayer et al. (2011) and Niogi and Mukherjee (2010). Thus, Fig. 7 helps to clarify an apparent

inconsistency in the literature about anisotropy changes after mTBI by "time resolving" the results. In addition, Fig. 7B raises important new questions about the interactions of anisotropy, neuropsychological performance, and time post-injury. In particular, the fact that cognitive performance is negatively correlated with anisotropy during acute stages, but positively correlated with anisotropy chronically is puzzling.

At least two issues remain outstanding with the results in Fig. 7. The first is the inconsistency in Fig. 7A of the results for paper XXI (Lo et al., 2009). In discussing their results, Lo et al. (2009) are careful to point out that the small sample size of their study calls for more future work. However, they also suggest potential explanations for their findings, including the possibility that the observed increases in FA could reflect recovery from injury; or that specific degradation mechanisms could target subsets of fibers, leading to enhanced FA; or, finally, that the increases in FA are compensatory for other observed decreases in other brain regions. The second issue relates to the heterogeneity of the neuropsychological testing in the papers used to generate Fig. 7B. Thus a limitation in the literature (and in our results) is the lack of consistency of neuropsychological assessment. As previously mentioned, we have "normalized" the scores such that better performance corresponds to a positive score, regardless of what test was used. We note, however, in light of the literature's "uncontrolled assessment variance", that our results are conservative as well as robust across cognitive domains and testing variability. Undoubtedly, though, more sensitive, standardized assessments that are specifically adapted to mTBI are needed to further reduce the limitations of these types of studies.

The results of Fig. 7 and the outstanding issues that we have raised suggest that more studies focused on mTBI and anisotropy are warranted and necessary. At this point we can only conjecture on possible explanations for our meta-analysis results. One possibility for the increase in FA acutely is that MR diffusion-based measurements are not purely sensitive to white matter microstructure, but additionally are inflated by acute stage secondary injury or compensatory mechanisms (Mayer et al., 2011; Niogi and Mukherjee, 2010). The idea behind this is that inflammation and secondary injury factors (including ischemia, cerebral hypoxia, and cerebral edema) may increase anisotropy in acute phase, but that these factors do not contribute in the chronic phase. Chronically, though, residual damage of white matter could lead to a decreased anisotropy signal. A second possible explanation of Fig. 7B, however, is that there is not a simple causal relationship between anisotropy and cognitive performance. Whatever the mechanism, Fig. 7B indicates that poor neuropsychological performance is associated with high anisotropy scores immediately after injury and with low anisotropy in the chronic phase. From a statistical point of view, Fig. 7A demonstrates a main effect between anisotropy and time post-injury, but Fig. 7B additionally indicates an interaction with cognitive performance. We have previously mentioned that there is controversy surrounding anisotropy changes after TBI. Nonetheless FitzGerald and Crosson (2011) note in their review of the literature a general acceptance that decreases in FA values are expected after TBI induced axonal injury. However, they also point out that mechanisms for increases in FA are also possible (e.g. unequal injury in one fiber in voxels where two or more fibers cross). Furthermore, there are examples in other disorders (such as autism) where widespread differences have been noted in the relationship of FA with cognitive function (Ellmore et al., 2013). Better understanding of the underlying mechanisms of anisotropy changes following TBI will likely need to rely on methods and validation studies in animal models such as those of Budde et al. (2011) and Mac Donald et al. (2011) to relate pathology to diffusion tensor imaging findings. Finally, the majority of the literature focuses on FA, but some publications report radial diffusion (RD), axial diffusion (AD) and mean diffusion (MD) diffusion as well. The four measures are related to each other and usually FA and AD are significant in the same direction while MD and RD tend to be significant in the opposite direction. Results of these measures are found in supplemental Table S2.

To summarize, this review and meta-analysis have demonstrated several important points about the ongoing use of neuroimaging to understand the functional and structural changes that occur throughout the time course of mTBI recovery. A broad range of neuroimaging modalities are being applied to this problem across the range of post-injury time scales and an important component of many studies is the effort to link imaging measurements to neuropsychological assessments of cognitive deficits. Upon closer scrutiny of two MRI-based modalities, we demonstrated the importance of interpreting white-matter measures of anisotropy in the context of time post-injury and for both structure and function we evaluated whether or not consistent findings were available for evaluating anatomical vulnerability to mTBI. The fact that we have been able to produce statistically significant results in this area is encouraging. Based on the complexity of the injury, however, much more work in this area is required. Future publications focused in depth for each image modality would greatly complement this generic analysis and the field of mTBI. Here we have been able to preliminarily examine important factors related to anatomical vulnerability and time post-injury, but these issues need to be refined with future data and many other factors remain to be studied (e.g. injury mechanism differences, number and timing of previous concussions, and psychological comorbidities including major depression and post-traumatic stress) (Iverson and Lange, 2003; Rosenbaum and Lipton, 2012). Ultimately a major driving motivation for continued study is the further efficacy of neuroimaging for clinical diagnosis at both acute and chronic stages and the synergistic improvement with neuropsychological assessments and rehabilitation strategies.

Acknowledgments

We thank Dr. Anders Eklund for comments on the manuscript and data analysis. This work was supported by DoD W81XWH-08-2-0144.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2013.12.009.

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