Imaging chronic traumatic brain injury as a risk factor for neurodegeneration[☆]

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Abstract

Population-based studies have supported the hypothesis that a positive history of traumatic brain injury (TBI) is associated with an increased incidence of neurological disease and psychiatric comorbidities, including chronic traumatic encephalopathy, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. These epidemiologic studies, however, do not offer a clear definition of that risk, and leave unanswered the bounding criteria for greater lifetime risk of neurodegeneration. Key factors that likely mediate the degree of risk of neurodegeneration include genetic factors, significant premorbid and comorbid medical history (e.g. depression, multiple head injuries and repetitive subconcussive impact to the brain, occupational risk, age at injury, and severity of brain injury). However, given the often-described concerns in self-report accuracy as it relates to history of multiple TBIs, low frequency of patient presentation to a physician in the case of mild brain injuries, and challenges with creating clear distinctions between injury severities, disentangling the true risk for neurodegeneration based solely on population-based studies will likely remain elusive. Given this reality, multiple modalities and approaches must be combined to characterize who are at risk so that appropriate interventions to alter progression of neurodegeneration can be evaluated. This article presents data from a study that highlights uses of neuroimaging and areas of needed research in the link between TBI and neurodegenerative disease.
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1. Introduction

Neuroimaging can and should have a significant role in defining the bounding criteria and risk prediction model to identify those at increased risk of neurodegeneration in acute and chronic traumatic brain injury (TBI). It is one of the few methods that allows in vivo, noninvasive assessments of neurobiology. The challenge with defining the role is that we do not have a single imaging modality that meets all the following criteria: (1) accessible and safe for use in acute injury in those with altered consciousness. (2) equally sensitive to all injury severities, (3) equally sensitive to the acute through chronic time course, and (4) appropriate for the identification of the earliest of pathological changes in the transition to neurodegenerative disease. Practically, this

means that instead of assessment of the injury as a continuum (or continuous variable), we triage and segregate our imaging tools in a large part by injury severity (to be treated as categorical). This is a challenge in terms of identifying factors that predict who will be at greater risk for neurodegeneration, and the precipitating cause for increased concern because these factors likely can be found in all stages of injury (e.g. less than full recovery in mild without acute imaging, delayed recovery in repeated TBI, and magnetic resonance imaging in the chronic stage only, with less than full recovery). Also complicating this challenge is that there is an understandable disconnect between the clinical need and motivation for imaging and the lack of sensitivity of that imaging across our continuum.

Neuroimaging does provide some degree of diagnostic value in TBI (e.g. identification by computed tomographic scan of blood product or swelling after moderate to severe injury), characterization of acute reaction to injury (e.g. positron emission tomographic ligands for inflammation), quantification of injury severity (e.g. quantification of degree of white matter damage assessed via diffusion tensor imaging), assessment of degree of alteration of functional networks (e.g. resting state functional magnetic resonance imaging), and chronic progressive alterations (e.g. changes in cortical thickness, atrophy, alterations in biochemistry of high-risk brain regions). These tools, taken together with changes in screening and management of brain injury, and ongoing studies in high-risk populations can inform risk for neurodegeneration.

To provide an initial foundation for future work in identifying neuroimaging-based markers of risk for neurodegeneration, we set out to characterize the effects of single and multiple concussion in a chronic, largely recovered (having returned to work or school after injury and not seeking clinical care for symptoms related to the TBI), civilian population. Neuropsychological testing was also conducted in part to characterize the population, and in part to allow correlation with tissue volume.

2. Methods

This study was approved by the human subjects committee of the University of Illinois–Chicago and is consistent with all local and federal requirements for human subjects research. All participants provided written informed consent before participation. A total of 80 participants were recruited at the University of Illinois Medical Center via advertisements in the community seeking individuals who had ever sustained a closed head injury, concussion, brain injury, or TBI.

We used a minimum definition for TBI consistent with the memorandum issued by the Assistant Secretary for Defense [1]. A TBI is defined as "a traumatically induced structural injury and/or physical disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event: any period of loss of or

decreased level of consciousness; any loss of memory for events immediately before or after the injury; neurologic deficits; intracranial lesion" [1].

In reference to TBI injury severity, we adopted the standards from the American Congress on Rehabilitation Medicine (ACRM) [2], the American Academy of Neurology Practice Guidelines on concussion grading [3], and the report on definition of TBI and TBI severity from the Assistant Secretary for Defense [1]. It is important to note that although the ACRM includes the Glascow Coma Scale (GCS) as one method for determining severity in the acute stage, the Department of Defense definition does not [1]. In addition, it has been reported that more than 60% of soldiers (in the early years of the War on Terror) with confirmed TBI were never assessed for GCS score. This report also includes a category for defining severity based on duration of altered consciousness and loss of consciousness [1]. Severity is defined by duration and presence of loss of consciousness, alteration in mental status and duration of alteration of consciousness, posttraumatic amnesia for events leading up to or following the injury, and focal neurological defects. For the present study we use both the Department of Defense definition of TBI [1] and the American Academy of Neurology Practice Guidelines for definitions within the mild TBI spectrum [3] (Table 1).

According to the ACRM guidelines, 47 participants were classified as having a history of mild closed head TBI at least 6 months from injury. Of the 43 participants with mild TBI, 14 reported a history of multiple mild TBIs (range, 2–3). Comparisons between mild TBI with a single injury and multiple injuries did not yield any significant differences on any neuropsychological, demographic, or imaging measures. None of the participants were recruited from active clinical practice, but instead responded to advertisements in local papers, flyers, or advertisements on Craig's List. Thirty-seven healthy control subjects were also recruited from the community to match the participants with TBI in terms of age, years of education, years of employment, and estimated premorbid intelligence (Table 2). Participants (control and TBI) were excluded if they had a history of psychiatric disorder before the TBI, substance abuse/dependency, current or past litigation, failure on a formal measure of effort, or any other neurological or medical condition that could

Table 1
TBI severity definitions [1,3]

Severity	LOC	AOC	PTA	GCS, pt
Mild	0–30 min	0.01 min–24 h	<24 h	≥13
Grade I	0 min		<15 min	
Grade II	0 min		>15 min	
Grade III	0.01–30 min			
Moderate	30 min–24 h		>24 hours and <7 days	9–12
Severe	>24 hours		>7 days	<8

Abbreviations: AOC, alteration of consciousness, GCS, Glasgow Coma Scale; LOC, loss of consciousness; PTA, posttraumatic amnesia.

Table 2
Participant, injury, and group characteristics

Sample characteristics	Mild TBI Composite	1 TBI	>1 TBI	Control subjects
Sample size	n = 43	n = 29	n = 14	n = 37
No. of women (%)	20 (47)	14 (49)	6 (43)	21 (57)
Age at MRI, y	34 (20–58)	35 (20–58)	33 (21–51)	33 (19–60)
Age at TBI, y	29 (16–57)	30 (16–57)	28 (16–48)	NA
MMSE score out of 30 pt, pt	29 (26–30)	29 (26–30)	29 (28–30)	29 (25–30)
Estimated IQ	112 (80–123)	112 (80–123)	112 (87–121)	111 (84–123)
No. with LOC (%)	24 (56)	14 (48)	10 (71)	NA
Average time since TBI, y	5.3 (0.5–28)	5.7 (0.5–21)	4.4 (0.5–28)	NA
Average length of LOC, h	0.07 (0–0.5)	0.08 (0–0.5)	0.03 (0–0.5)	NA
Average length of PTA, h	0.47 (0–1)	0.47 (0–1)	0.48 (0–1)	NA
No. with posttraumatic seizure (%)	1 (2)	1 (3)	0 (0)	NA
No. with posttraumatic headache (%)	25 (58)	15 (52)	10 (72)	NA
No. with other significant injuries (%)	15 (35)	12 (41)	3 (22)	NA
No. employed/student at TBI (no. returned to work/school after TBI)	41 (39)	28 (26)	13 (13)	NA

Abbreviations: LOC, loss of consciousness; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NA, not applicable; PTA, posttraumatic amnesia; TBI, traumatic brain injury.

NOTE. Unless indicated otherwise, data are shown as mean (range). Loss of consciousness data for mild TBI with more than one injury is for greatest severity injury (longest loss of consciousness or longest posttraumatic amnesia). Please note that MMSE data were available only for 26 control subjects and 31 participants with mild TBI. Also, there were no significant differences among groups ($P < .01$) for age at study, highest levels of education or employment, premorbid IQ, or MMSE score.

result in cognitive changes (e.g. hypertension, severe chronic pain). Participants were not receiving any psychiatric medication or medications used for cognitive enhancement at the time of the study. Detailed demographic information is presented in Table 2. Statistical comparisons among groups with regard to age at the time of assessment, educational attainment, Mini-Mental State Examination score, estimated IQ, age at the time of the injury, and other TBI variables identified no significant differences among any of the groups.

The mechanism of injury varied and included motor vehicle accidents (n = 10), pedestrian motor vehicle accidents (n = 3), assault (n = 3), sports related (n = 8), and falls or blows to the head (n = 14).

2.1. Neuropsychological testing

Participants completed a neuropsychological test battery that was assembled to assess executive function, attention, and memory. Because of the prevalence of executive function impairments in TBI, the battery was weighed more heavily on executive measures. Tests included the Stroop [4–6], Trail Making Test [7], Continuous Performance Test [8], Controlled Oral Word Association Test [9,10], Ruff Figural Fluency [11], forward and backward Digit Span [12], Spatial Span [12], California Verbal Learning Test [13], Brief Visual Memory Test [14], Mini-Mental State Examination [15–17], Wechsler Test of Adult Reading [18], Test of Memory Malingering [20,21], and Dot Counting Task [19]. Additional details on these tests, battery, and justification for domain score calculation can be found in work by others [22–24].

2.2. Voxel-based morphometry

Magnetic resonance images were analyzed with SPM5 (Wellcome Department of Neurology, London, UK). SPM5 was run using MATLAB 7.0.1 (Mathworks, Natick, MA). Data for each subject was aligned in the axial, coronal, and sagittal planes. Images were then normalized spatially to the Montreal Neurological Institute T1 template and smoothed using an 8-mm full-width at half maximum Gaussian kernel. The final preprocessing step was segmentation into gray matter, white matter, and cerebrospinal fluid (CSF) at a $1 \times 1 \times 1$-mm voxel size. Primary analyses were conducted among subject groups (control subjects, participants with mild TBI, participants with moderate–severe TBI). Threshold masking was set to 0.01. Correlations were carried out between tissue concentration and key injury variables (loss of consciousness, length of posttraumatic amnesia, time from injury), cognitive status (executive function, memory, attention), and mood. A false discovery rate (FDR) of p(FDR) less than 0.001 was applied to all contrasts among groups.

2.3. Statistical analysis

Neuropsychological test scores were converted to Z-scores (mean, 0; standard deviation, 1) based on the control mean and standard deviation, then averaged to derive composite domain scores. Two different types of analyses were conducted on the neuropsychological data. First, the primary analysis was a two-way repeated-measures analysis of variance (ANOVA), with cognitive domain (executive, attention, memory) as the within-subjects factor and subject group as the between-subjects factor. Second, directed one-way

ANOVAs comparing groups within each domain score were also conducted.

3. Results

3.1. Neuropsychological testing

With regard to neuropsychological domain scores, there was no interaction between cognitive domain and subject group: $F(2,160) = 1.436$, $P = .241$, $\eta^2 = 0.20$. And, although there was a trend for poorer performance from the participants with mild TBI relative to the control subjects, this main effect was not significant: $F(1,80) = 3.637$, $P = .060$, $\eta^2 = 0.048$. However, follow-up comparisons within each cognitive domain and among groups did demonstrate a significant reduction in overall executive function for the participants with mild TBI relative to control subjects: $F(1,80) = 7.000$, $P = .008$. The groups did not differ on either attention or memory domains. Results from one-way ANOVAs on all three domain scores and each individual test are presented in Table 3. These data were then converted to Z-scores relative to the control group mean. Fig. 1 shows how both groups of participants with mild TBIs performed relative to control subjects.

3.2. Whole-brain volumetric analysis

Before voxel-wise comparisons using voxel-based morphometry (VBM), whole-brain volumes were extracted from each subject group to include total intracranial volume (TIV), total intracranial gray matter volume, total intracranial white matter volume, and total CSF volumes. First, there was no effect of participant group on TIV ($F = 0.069$, $P = .933$, $\eta^2 = 0.001$). Second, there was an effect of participant group on TIV gray matter ($F = 34.797$, $P < .001$, $\eta^2 = 0.406$) and white matter ($F = 5.625$, $P = .005$, $\eta^2 = 0.099$), and on TIV CSF ($F = 4.957$, $P = .009$, $\eta^2 = 0.089$).

The same patterns of results were found when gray matter volume, white matter volume, and CSF were controlled for TIV, representing the relative proportion of gray matter, white matter, and CSF. As would be expected, given the nonsignificant effects of subject group on TIV, the pattern of statistical results is identical to that mentioned earlier. Specifically, there was an effect of participant group on gray matter ($F = 13.370$, $P < .001$, $\eta^2 = 0.208$) and white matter ($F = 7.651$, $P = .001$, $\eta^2 = 0.130$), and on CSF ($F = 3.958$, $P = .022$, $\eta^2 = 0.072$).

3.3. Groupwise VBM results

Comparisons were conducted among control and TBI participants for both cerebral gray and white matter. Areas of significant decrease in intensity in participants with mild TBI relative to control subjects were found in both the gray and white matter. Overall, for those with a single TBI, there were relatively few changes. With regard to white

Table 3
Summary of neuropsychological test results for control subjects and participants with mild TBI organized by domain

	Control		Mild TBI		
	Mean	SEM	Mean	SEM	ANOVA
Executive domain	0.00	0.10	−0.37	0.10	0.008*
CPT hit reaction time, msec	392.87	12.35	366.17	9.85	0.294
Tower of London, total no. of moves	105.61	2.45	99.05	2.61	0.072
Stroop Color–Word, age corrected, seconds	48.53	1.77	44.84	1.62	0.127
PASAT total correct	138.53	7.36	124.32	6.51	0.152
Trails B, sec	52.64	3.69	65.00	5.57	0.071
CPT, number of omissions	10.25	1.08	13.71	1.07	0.025*
COWAT total score	43.83	1.96	41.05	1.81	0.301
RUFF Unique Designs, *t* score	45.77	2.07	44.07	1.44	0.500
Digit Span Backward, items recalled	8.58	0.37	7.32	0.43	0.029*
Spatial Span Backward, items recalled	8.44	0.31	8.13	0.32	0.484
Attention domain	0.00	0.10	−0.14	0.10	0.315
Digit Span Forward, items recalled	11.17	0.42	11.03	0.39	0.807
Spatial Span Forward, items recalled	9.75	0.32	8.92	0.36	0.088
Trail Making Test Part A, sec	23.36	1.94	24.71	1.28	0.559
CPT, number of omissions	2.56	1.01	2.05	0.63	0.673
Memory domain	0.00	0.15	−0.28	0.13	0.151
CVLT trials 1–5, total recalled	57.44	1.62	53.29	1.77	0.088
CVLT Long-Free Recall, total recalled	12.50	0.54	11.53	0.50	0.189
BVMT trials 1–3, total recalled	27.19	0.97	25.53	0.78	0.181
BVMT Delay Recall, total recalled	9.92	0.30	9.74	0.28	0.661

Abbreviations: ANOVA, analysis of variance; BVMT, Brief Visual Memory Test; COWAT, Controlled Oral Word Association Test; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; PASAT, Paced Auditory Serial Addition Test; RUFF, Ruff Figural Fluency Test; SEM, standard error of the mean; TBI, traumatic brain injury.
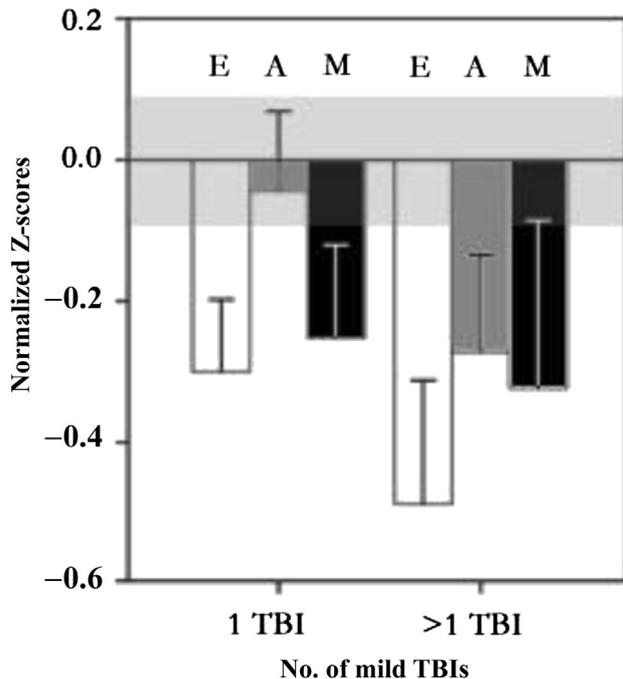
*$P < .05$.

Fig. 1. Normalized (Z-scored) neuropsychological performance of groups with mild traumatic brain injury (TBI; 1 mild TBI, n = 29; >1 mild TBI, n = 14) relative to control subjects (mean for control subjects, 0.0). Shaded box represents 1 standard deviation around the control mean. A, attention; E, executive function; M, memory.

matter, those with a history of mild TBI showed atrophy in the right internal capsule and right ventrolateral prefrontal white matter (Fig. 2).

There were many different areas of tissue density change observed in the gray matter in participants with mild TBI relative to control subjects, with indicators of significant atrophy in the somatosensory, parietal, temporal, parahippocampal, and cerebellar regions (Fig. 3).

We then examined differences between those with a single TBI vs. those with a history of two to three mild TBIs. Those with a history of multiple mild TBIs showed decreased tissue density in the temporal lobes, parahippocampal gyri, ventrolateral prefrontal regions external capsule, and cerebellum (Fig. 4).

4. Correlations between VBM and cognition (within group)

Voxel-wise bivariate correlations were conducted for the combined white and gray matter VBM maps relative to executive, attention, and memory domain scores for the participants with mild TBI. Interesting, executive function was associated with decreased tissue concentrations in the posterior cingulate and increased concentrations in the internal capsule for participants with mild TBI. With regard to attention, the cingulate, parietal and occipital white matter, and temporal gray matter were associated with improved performance. Within the mild TBI group, memory function was
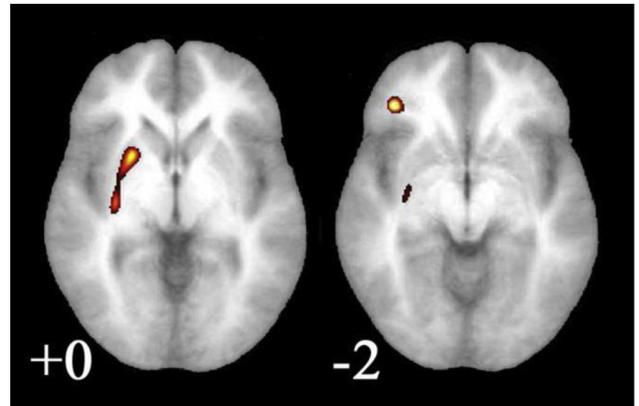

Fig. 2. Areas of significant alteration in tissue density as assessed with voxel-based morphometry. Regions shown indicate lower density for mild traumatic brain injury in the cerebral white matter relative to control subjects.

associated with reductions in tissue concentration in the parahippocampal gyri, anterior temporal lobe, and internal capsule.

In summary, there does appear to be an effect on tissue concentration from even one mild TBI. However, it is unlikely that these data suggest that all participants with a history of mild TBI are at risk for poorer outcomes. In fact, when we normalized the volumetric data relative to control subjects and examined the z-distribution of volumes within participants with mild TBI, only 14 fell below two standard deviations of the control mean. This highlights the need to move from examination of group data into examinations of neuroimaging modalities relative to prognostic value. It is unclear, however, what that end point prognostic indicator should be. Our data do, however, suggest that atrophy, however sensitive to volumetric changes, is likely to be one marker that is worth including in the ultimate risk definition model, if one is created to inform individual patient risk.

5. Discussion

Although the mechanisms that underlie increased risk for onset of neurodegenerative disease in patients with a history of TBI are not currently known, neuroimaging can and will be important in developing methods to identify those at risk, to monitor those individuals in a noninvasive way, to be useful in the prediction of disease progression, and, potentially, to have a significant role in evaluating early intervention effectiveness. Furthermore, neuroimaging can also have a role in helping define the gross acute and chronic differences in those who may be at a differential risk. However, it is critical that "significant" findings between and within groups be interpreted within the context of symptom severity and impairment, and not overreach into prediction of risk based on nonspecific imaging markers.

Volumetric assessments of acute, chronic, and progressive changes in cerebral tissue will inform one part of the
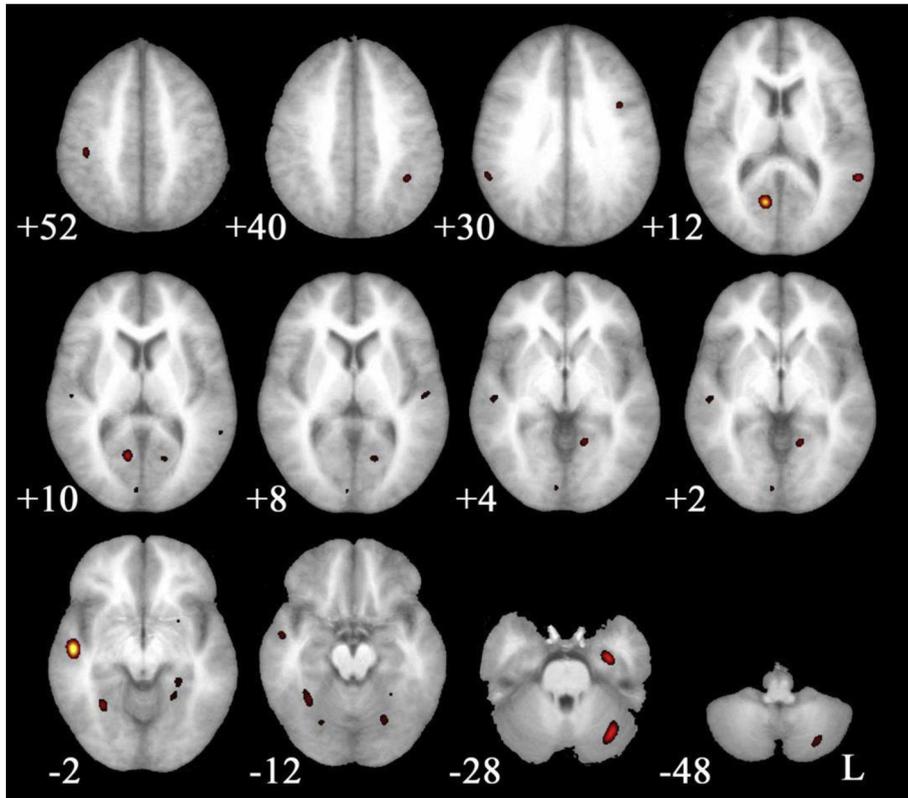
Fig. 3. Areas of significant alteration in tissue density as assessed with voxel-based morphometry. Regions shown indicate lower density for mild traumatic brain injury in the cerebral gray matter relative to control subjects.

equation for identification of those who are at risk for poorer outcomes. As our data demonstrate, for the first time, there are chronic alterations in a recovered mild TBI population, and these alterations do reflect cognitive function even in those who have returned to work or school successfully after their injuries. These data raise two important mechanistic questions in how we begin to address neurodegenerative

risk in this population. One mechanistic question, which cannot be answered using neuroimaging alone, is: What acute or chronic factors lead to alterations in tissue volume, and what role does injury severity play in increased or decreased risk? The second mechanistic question is: Which, if any, of these alterations are clinically relevant and, if so, at what threshold? The population recruited in the current study
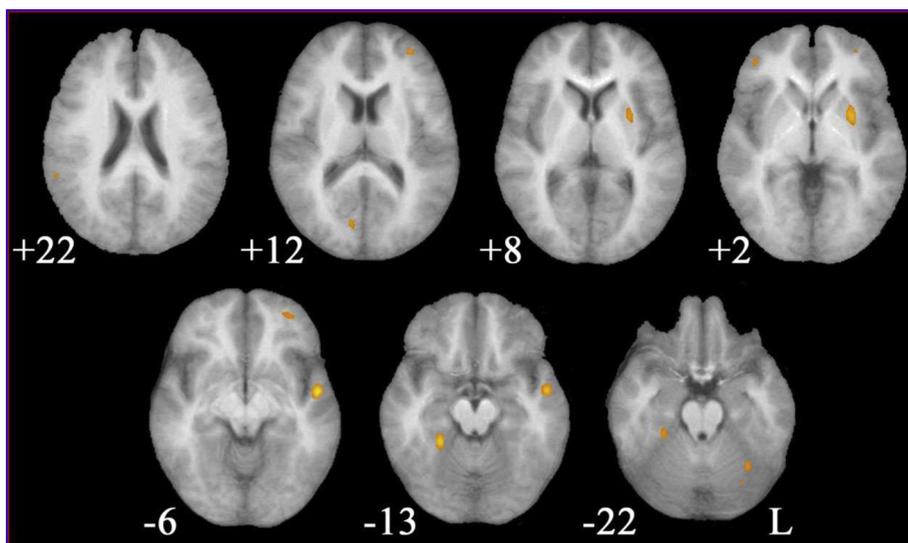

Fig. 4. Areas of significant alteration in tissue density as assessed with voxel-based morphometry for mild traumatic brain injury (TBI) with a history of more than one TBI relative to those participants with mild TBI with a history of one TBI.

likely represents those at least risk for poorer outcomes, with a focus on mild TBI, recruitment of those without loss of consciousness, and lack of recruitment of those seeking or in clinical care for symptoms after TBI. Yet, there are findings of chronic alterations in tissue density and, taken together with previous reports, it is likely these changes are progressive and not present until a chronic stage [25]. However, when viewed relative to the epidemiologic literature and grossly normal neuropsychological assessments, it seems unlikely that these markers of volumetric tissue loss are clinically relevant indicators of risk at this specific stage of injury chronicity. We propose that, until the mechanisms that lead to tissue loss are identified, such neuroimaging markers—in a nonsymptomatic patient group—be considered a marker not of neurodegenerative risk itself, but instead a marker of potential biological vulnerability.

This suggestion leads to the most significant challenge in the application of neuroimaging for assessment of neurodegenerative risk: the lack of causative biochemical and biological alterations that drive group differences in derived neuroimaging markers. In other words, neuroimaging provides a nonspecific indication of biological alteration and lacks specificity for the mechanism of impairment and risk for neurodegeneration. Furthermore, the relatively weak correlations between calculated and derived neuroimaging measures and those that assess clinical outcome complicate the interpretation of the meaningfulness of these measures further. In vivo animal imaging combined with ex vivo assays can help disentangle what these measures mean more specifically, and can move neuroimaging further away from being simply descriptive. Neuroimaging can provide the foundation for baseline assessment of brain structure and function, identify factors that correlate with acute and chronic injury, and characterize the progression to dementia in those who follow that risk path. Better animal models and imaging of these models are needed.

In addition, there must be a significant move toward the integration of coherent data analytical plans that allow movement beyond voxel-wise comparisons between groups, to a structure that integrates clinical and neuroimaging markers. One example of such an approach is the application of machine learning models that allow assessments of networks, rather than voxels, relative to meaningful clinical data.

The biggest concern, however, is identifying the significant differences between control subjects, patients with mild TBI, and those with multiple mild injuries. From the data presented, one can find differences among groups even in those with a single mild injury. It is likely that a small proportion of these patients will have poorer outcomes, but the gross majority will recover and be at no additional risk. Adaptation of more traditional clinical evaluation methods and application of these methods to neuroimaging data and results reporting will be beneficial.

Although there are primary studies that link TBI to long-term neurodegeneration, there is still a need for the detection

small injuries at their earliest signs of development. The increased emphasis on the comorbidity of TBI with a wide spectrum of neurological disorders beyond Alzheimer's disease (AD), such as chronic traumatic encephalopathy, and Parkinson's disease should place additional development of TBI neuroimaging as a high priority for research.

AD neuroimaging shares several parallels with TBI neuroimaging research. Both have robust strategies for stratifying patient populations, but clinical presentation still remains divorced from diagnostic testing. It is hoped that research in both spaces will converge so that the interrelationship between TBI and neurodegenerative disease can be better understood. Imaging represents a unique nexus by which this could be accomplished, which could lead to new diagnostic criteria for TBI/AD and a better understating of the longitudinal effects of TBI. This could, subsequently, power studies on the efficacy of cognitive behavioral therapies or even pharmacological interventions.

Acknowledgments

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