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Objective Documentation of Traumatic Brain Injury Subsequent to Mild Head Trauma: Multimodal Brain Imaging With MEG, SPECT, and MRI

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Objective: To determine to what extent magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and magnetoencephalography (MEG) can provide objective evidence of brain injury in adult patients with persistent (>1 year) postconcussive symptoms following mild blunt head trauma. **Design:** A retrospective and blind review of imaging data with respect to the presence of specific somatic, psychiatric, and cognitive complaints. **Setting/Participants**: Thirty complete data sets (with MRI, SPECT, MEG, and neuropsychological testing results) were collected between 1994 and 2000 from the MEG programs at the Albuquerque VAMC and the University of Utah. **Main Outcome Measures:** MRI data were evaluated for focal and diffuse structural abnormalities, SPECT data for regions of hypoperfusion, and resting MEG data for abnormal dipolar slow wave activity (DSWA) and epileptiform transients. **Results:** Structural MRI was abnormal for 4 patients. SPECT showed regions of hypoperfusion in 12 patients, while MEG showed abnormal activity in 19 patients. None of the imaging methods produced findings statistically associated with postconcussive psychiatric symptoms. A significant association was found between basal ganglia hypoperfusion and postconcussive headaches. For patients with cognitive complaints, abnormalities were more likely to be detected by MEG (86%) than either SPECT (40%) or MRI (18%) ($P < .01$). MEG also revealed significant ($P < .01$) associations between temporal lobe DSWA and memory problems, parietal DSWA and attention problems, and frontal DSWA and problems in executive function. **Conclusions:** Functional brain imaging data collected in a resting state can provide objective evidence of brain injury in mild blunt head trauma patients with persistent postconcussive somatic and/or cognitive symptoms. MEG proved to be particularly informative for patients with cognitive symptoms. **Keywords:** *head trauma*, *magnetoencephalography*, *MEG*, *MRI*, *postconcussive syndromes*, *SPECT*, *traumatic brain injury*

IN the United States alone, it is estimated that emergency departments treat more than 2 million cases of head trauma each year. When blunt trauma is severe, many patients will show a wide range of persistent posttraumatic problems that may include headache, fatigue, impaired memory, reduced concentration and attention, reduced information-processing capacity, poor impulse control, personality changes, depression, irritability, sleep disturbances, and sexual dysfunction.[1,2] Similar symptoms may be reported initially after mild head trauma (mild HT), but in most cases, all symptoms subside within a few weeks. However, 15% to 30% of patients who suffer minor trauma report postconcussive symptoms that persist for many years after the traumatic incident.[3–6] Given that more than 80% of all head traumas are of the mild type, this translates into 200,000 to 400,000 new patients in the United States each year with a persistent postconcussive syndrome resulting from mild HT. Available data suggest that many of these patients will experience vocational and interpersonal distress that place a significant economic and

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social burden on our society, with many cases giving rise to litigation.[3–6]

In considering both treatment and legal ramifications of head trauma, objective documentation of traumatic brain injury (TBI) subsequent to mild HT would be of utility, especially in view of the common assertion that cognitive symptoms following mild HT reflect "compensation neurosis" rather than brain damage.[7] In cases of moderate-severe head trauma, there is a very high likelihood of TBI, with structural brain imaging via computed tomography (CT) or magnetic resonance imaging (MRI) often demonstrating chronic abnormalities including focal encephalomalacia, diffuse axonal injury, ventricular dilation, and cortical atrophy.[8,9] Consequently, many researchers and clinicians use the term *TBI* interchangeably with the term *head trauma*. Unfortunately, this can lead to confusion when considering mild HT because clinical CT and MRI are typically negative for mild HT patients, especially several months after the traumatic event.[9] Thus, objective evidence of actual TBI subsequent to mild HT is often lacking. TBI is a potential consequence of head trauma, but it is not a necessary one. Throughout this article, special care is therefore taken to distinguish mild HT from mild-TBI, with a major goal of the study being to provide objective documentation of actual mild-TBI in cases of observed mild HT.

Because routine clinical MRI rarely reveals gross structural abnormalities following mild HT (even in cases with significant and persistent postconcussive complaints), many research teams are exploring the possibility that functional brain imaging methods will be more sensitive to subtle TBI. Methods of particular interest include hemodynamic techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), and electrophysiological methods such as electroencephalography (EEG) and magnetoencephalography (MEG).

In cases of moderate and severe head trauma with clear structural lesions on MRI, resting-baseline PET and SPECT data generally demonstrate concordant perfusion and metabolic deficits. These perfusion deficits may extend into normal appearing tissue, and in some cases, very diffuse hemodynamic abnormalities consistent with the concept of diaschisis have been reported.[10,11] Some resting PET studies reveal a high sensitivity to mild HT,[10,12,13] but this is not always the case.[14] SPECT studies in mild trauma often show focal regions of hypoperfusion consistent with expectations based on neuropsychological testing,[15,16] but not all groups have reported a strong correlation between specific regional SPECT findings and specific cognitive test results.[2,17,18] Overall, resting PET and SPECT demonstrate abnormalities in 25% to 80% of head trauma survivors–the likelihood of a positive finding being dependent on the severity of initial trauma, the presence of MRI findings, the severity of postconcussive compromise, and the time lag between imaging and the traumatic event.[2,10–18] When scanning is performed several months after mild trauma, most studies report resting hemodynamic abnormalities in fewer than 50% of subjects, even when considering only patients who report persistent postconcussive problems. Another limitation of the resting hemodynamic approach to mild HT is a general lack of specificity for the methods. Although normal comparison participants rarely show hemodynamic anomalies, hypoperfusions can be seen in almost all neurologic and psychiatric diseases, including stoke, epilepsy, depression, schizophrenia, attention-deficit disorder, and dementia.

Most hemodynamic imaging studies in head trauma have focused on resting hemodynamic profiles, but there is a growing trend in functional brain imaging to examine activity profiles during performance of specific cognitive tasks. Recently, several investigators have used PET, SPECT, and/or functional MRI (fMRI) to examine hemodynamic responses in patients with mild HT performing working memory tasks.[14,19,20] These studies indicate that mild HT can lead to activation deficits, but most deficits are subtle and apparent only in group data, with critical observations failing to be sufficiently robust for diagnostic use on a case-by-case basis.

Turning toward electrophysiological methods (EEG and MEG), there are also 2 general types of studies–those that use evoked response paradigms to assess specific cognitive processes and those that examine "resting" activity patterns. In general, simple sensory and motor evoked responses (potentials and fields) are within normal limits following mild HT,[21] although some recent pilot data indicate that somatosensory evoked magnetic responses show depressed M30 responses following head trauma (J.D. Lewine, J.T. Davis, E. Bigler, et al, unpublished data, 2006). Some data indicate that evoked responses related to mnemonic processing (eg, N2 and P3) are abnormal following mild HT,[21] but these are very nonspecific findings common to many disease conditions. Also, there is a general lack of diagnostic utility and validity on a case-by-case basis.

Considering "resting-state" studies, routine clinical EEG is very unlikely to reveal abnormalities (and thereby support the existence of TBI) subsequent to mild HT.[22] In contrast, quantitative EEG (qEEG) often reveals abnormalities subsequent to mild HT. For example, Thatcher and colleagues[23,24] have developed qEEG discriminant functions that allow for the identification of individual patients with a history of mild HT with better than 90% accuracy. However, it has been difficult to place specific qEEG discriminant factors (eg, changes in coherence in a narrow frequency band) in a functional neuroscience framework that allows for an

understanding of the relations between regional brain dysfunction and specific symptoms following head trauma.

Using MEG, we have previously reported that a moderately high percentage of patients with persistent complaints subsequent to mild HT demonstrate focal dipolar slow wave activity (DSWA).[25] MEG assesses the pattern of magnetic flux associated with intradendritic currents. Mathematical methods for inferring the location of discrete neuronal populations that generate abnormal MEG signals of interest provide data on brain dysfunction within a framework that allows for explicit assessment of the relations between specific post–head trauma symptoms and specific clinical findings.

Presented herein is a retrospective review of integrated MRI, SPECT, and MEG data from patients with persistent psychiatric, somatic, or cognitive complaints subsequent to mild HT. A primary goal of the study was to determine to what extent imaging methods could provide, on a case-by-case basis, objective evidence of brain injury. A secondary goal of the study was to determine the relations between specific patterns of imaging abnormalities and specific postconcussive symptoms. If it can be demonstrated that functional brain imaging methods provide a sensitive and specific measure of brain injury following mild HT, these imaging methods are likely to emerge as critical in the future development of rational and evidence-based therapeutic and medical management plans for patients with persistent postconcussive symptoms.

METHODS

Participants

Between 1994 and 2000 the first author and his colleagues performed whole-head MEG examinations and MRI examinations on 58 adult patients with persistent (>1 year) psychiatric, somatic, and/or cognitive complaints that had developed within the first few weeks following emergency department–documented mild blunt head trauma. This article presents a retrospective review of data from the 30 patients in this group who had detailed neuropsychological testing (completed within 2 months of the neuroimaging procedures) and an additional, clinically ordered SPECT examination. All participants were 18 years or older at the time of MEG evaluation, and none were younger than 14 years at the time of head trauma.

Mild-HT was defined by a Glasgow Coma Scale score of 13 or higher and a loss of consciousness of not more than 20 minutes. In all cases, there was evidence that the head had actually struck (or was struck by) a blunt object. Patients with whiplash injury without evidence of external head trauma were excluded. Most participants (67%) had suffered their trauma in a motor vehicle accident, with 18% being the victims of violent crime and 15% of home or industrial accidents. At the time of referral to the imaging centers, approximately half were taking regular doses of some form of psychoactive medication. Participants were asked to refrain from taking these medications on the days of imaging.

Evaluation of post–head trauma symptoms

Information on post–head trauma symptoms was obtained from several sources, including review of all medical and psychological records and a patient interview and self-report post-concussion symptom checklist completed on the day of MEG examination. (Prior to 1998, this was a 25-item questionnaire designed by our team. After 1998, we switched to the European Brain Injury Questionnaire, which provides for a clear separation of mood, cognitive, and social factors.[26]) All participants also had detailed neuropsychological evaluations performed independent of the imaging studies and completed within 2 months of the imaging. In most cases ($N = 25$), neuropsychological assessment had been completed before the brain imaging, and in fact, mild deficits on cognitive testing were one of the main reasons for referral for imaging. Because referrals were acquired from several different clinical contacts, the exact neuropsychological test protocol that had been used varied somewhat from patient to patient. Nevertheless, all had data available from the following instruments: (1) the Vocabulary and Block Design Subtests of the WAIS-R, (2) the Visual Reproduction and Verbal Paired Associates subtests of the WMS-R, (3) a word fluency test, (4) the Trail Making Test (parts A & B), and (5) the Wisconsin Card Sort Test. All patients also had data from (1) the Beck or Hamilton Depression and Anxiety Inventories, (2) Conner's Continuous Performance Task (CPT) and/or the Test of Visual Attention (TOVA), and (3) the Annett or grooved pegboard.

While blind to neuroimaging results, the investigative team used data from these tests to define for each participant a 3-domain bioclinical profile of symptoms participant: (1) psychiatric, (2) somatic, and (3) cognitive. Psychiatric symptoms were considered present if the patient reported problems in mood and responses on the Beck/Hamilton inventories indicated a mood disorder. Patients were considered to have somatic symptoms if they reported unusually frequent and severe headaches, pain, and/or dizziness. Cognitive impairments were evaluated with respect to 4 subdomains: (1) attention problems (CPT or TOVA), (2) memory problems (WMS-R), (3) executive function problems (WCS and the FAS word generation task), and (4) a generalized reduction in information-processing speed (various time-dependent tasks including the Trails Test [parts A& B], the grooved

or Annett pegboard, and the CPT [when available, $N = 26$]).

Performance in a particular cognitive subdomain was considered impaired if the average performance across relevant tests was more than 1 SD below the mean and the patient (while unaware of test results) had explicitly indicated during the interview that performance in that domain was impaired since the traumatic event. A 1 SD threshold is admittedly quite liberal for defining impairment, but deficits in mild HT are often subtle on formal testing, even when patients report that the traumatic event caused a significant decline relative to their concept of pretrauma abilities.

MEG examination

MEG data were collected using either a 122-channel or a 306-channel biomagnetometer system (both manufactured by Neuromag Ltd, Finland). Studies conducted between January 1994 and January 1997 ($n = 10$) were performed with a 122-channel system located at the Albuquerque Veteran's Affairs Medical Center. Studies conducted between January 1997 and November 1998 ($n = 9$) were performed with a 122-channel system located at the Center for Advanced Medical Technologies of the University of Utah in Salt Lake City. Studies conducted between November 1998 and July 2000 ($n = 11$) were performed with a newly installed 306-channel system at the Center for Advanced Medical Technologies. The 122-channel systems use 61 pairs of orthogonally oriented planar gradiometers to characterize extracranial magnetic field patterns. The 306-channel unit has 102 gradiometer pairs, with an additional magnetometer at each recording location. Because MEG is a somewhat less familiar technology than MRI and SPECT, we provide Figure 1 to illustrate the basic principles of MEG data acquisition and analysis.

For each participant, 10 minutes of data were collected while the participant sat quietly with eyes closed. Data were collected with a bandpass of 0.1 Hz to 100 Hz, at a digitization rate of 300 Hz. Following additional digital filtering (1–70 Hz) and removal of eye blink and cardiac artifacts via a signal space projection method,[27] the 10-minute block of MEG data was inspected visually for epileptiform transients and processed via an automated computer routine for abnormal DSWA.

When interictal spikes were identified, a multiple-dipole, spatiotemporal source modeling algorithm was used to elucidate the spatial position of the spike initiation zone. Most slow waves (in the 1- to 6-Hz upper delta and lower theta bands) show very complicated magnetic field patterns that cannot be explained by even 5 or 6 dipole sources. While these may still represent significant pathophysiology, for the purposes of this study we focused only on that subset of large amplitude (>200 fT) slow waves whose generation could be reasonably well explained by a single focal dipole source. The basic data analysis strategy used by our group for examining slow waves in patients with head trauma has been described in detail.[25]

Briefly, following artifact removal, data are filtered between 1 and 6 Hz, and large amplitude (>200 fT) slow waves are identified. A 50-millisecond window about the peak of each slow wave is marked and a single equivalent current dipole is fit every 10 milliseconds. The single best fit during within each event window is then retained for further consideration. If the goodness of fit for the dipole model is greater than 0.8 (with all planar sensors included during the fitting procedure), the dipole is considered a viable model, and its spatial parameters are noted. A spatial clustering algorithm is then used to determine for each viable dipole how many neighbor dipoles are seen within a $2 \times 2 \times 2$ cubic centimeter region. If this value exceeds 1 dipole per minute of recording time, then all members of the dipole cluster are retained and plotted on spatially aligned MRI to generate magnetic source localization images. For regional analyses in the present study, the brain was divided into 8 regions (right and left frontal, temporal, parietal, and occipital lobes). A region was coded as demonstrating abnormal function if it contained 10 or more dipolar slow wave sources. MEG is relatively insensitive to subcortical activity with none of the participants in this study showing a substantive number (>10) of slow wave dipole sources localizing to subcortical nuclei. Exploratory data analyses showed no significant right-left differences, so findings were collapsed with respect to right hemisphere versus left hemisphere.

Magnetic resonance imaging

Following MEG, all participants also underwent a structural MRI evaluation on the same or following day. In each case, MRI data were collected using a 1.5-T whole-body imaging system. Acquisition sequences included a T1-weighted 3D volumetric sequence (1.5-mm contiguous sagittal slices, no interslice gap), T2-weighted and FLAIR sequences (5-mm axial slices, no interslice gap), and a gradient recalled echo sequence (5-mm axial slices, no interslice gap). Data were clinically evaluated by a board-certified neuroradiologist, and the report and data were available for review in this study. While blind to all other imaging and clinical observations, data sets were coded as showing evidence of atrophy, diffuse axonal injury, or focal encephalomalacia in right/left frontal, temporal, parietal, occipital, or subcortical regions. In the majority of cases, CT or MRI reports were also available from the time of the traumatic event. These findings were also reviewed and tabulated. Exploratory analyses showed no significant

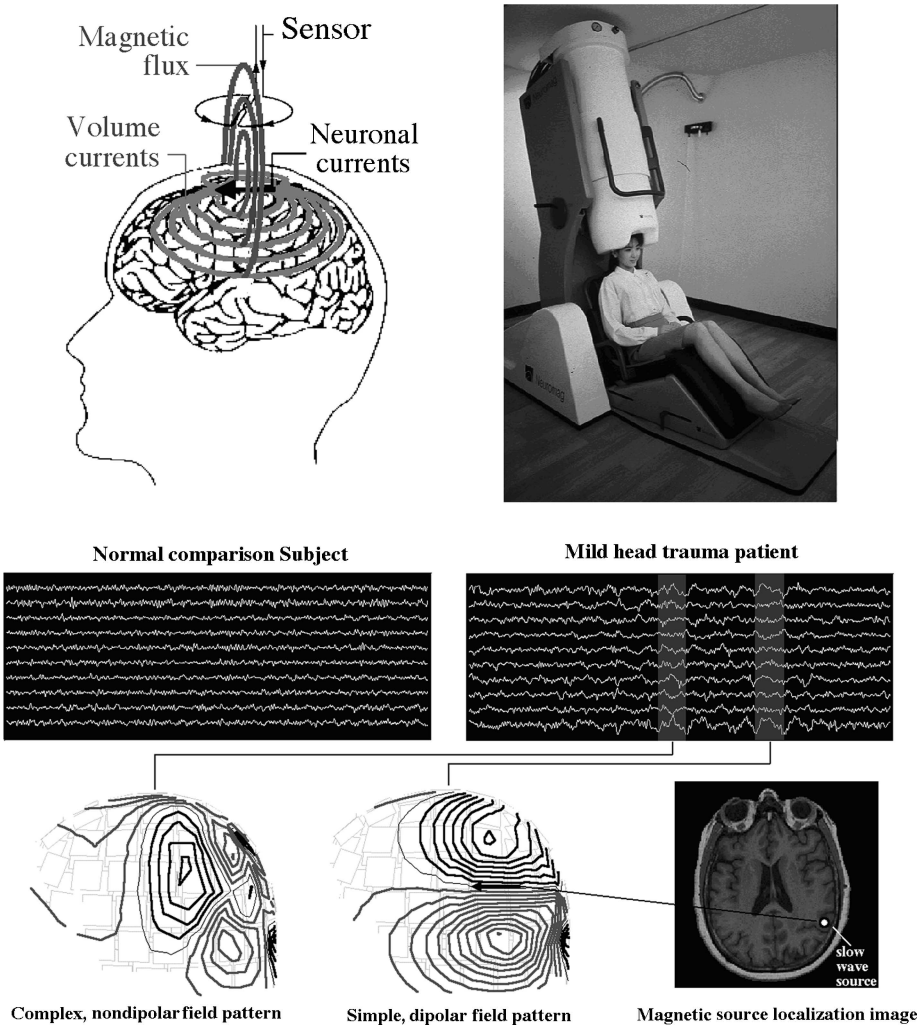

Figure 1. Basic principles of magnetoencephalography: Currents flowing within the apical dendrites of pyramidal cells oriented parallel to the skull surface give rise to a magnetic field that can be measured outside of the head using supercooled sensors connected to SQUIDs (superconducting quantum interference devices). The sensors are arrayed within a head-shaped cryogenic vessel. During testing, the participant sits underneath the sensor unit. A 122-channel unit is pictured. The output of each sensor is a waveform that shows how the local magnetic flux changes in time. Representative data are shown for a normal comparison and mild head trauma patients. A 6.8-second long epoch of data is shown for 10 sensors over the left posterior temporal region. For the control participant, the bulk of activity is of low amplitude and high frequency. In contrast, the patient with head trauma displays prominent, large amplitude slow waves (1–6 Hz, each approximately 800 fT, peak-to-peak). Most slow waves have complicated magnetic field patterns as revealed by iso-field contour maps that show multiple regions of emerging (gray contour lines) and entering flux (black contour lines). In contrast, some slow waves have a dipolar field pattern characterized by single regions of emerging and entering flux. The source location for the neuronal currents that contribute to dipolar slow waves can be inferred using mathematical techniques that identify the position, orientation, and time course for the best-fitting dipole source. This location can be plotted on a spatially aligned magnetic resonance image to generate a composite magnetic source localization image.

right-left differences, so findings were collapsed across the hemispheres.

SPECT imaging

In all cases, SPECT imaging of baseline regional brain perfusion was performed on the same day or the day immediately before or after MEG and MRI. Following 10 minutes of rest, a 30-mCI dose of Tc-99m-HMPAO (Ceretec, used for studies in Albuquerque) or a 25-mCI dose of Tc-99m-ECD (used for studies in Salt Lake City) was administered intravenously. Fifteen minutes later, SPECT imaging was performed using a triple-headed gamma camera equipped with high-resolution fan-beam collimators (Albuquerque–Picker, Odyssey 3000, SLC–Picker, IREX). Data were acquired using a simultaneous

transmission and emission protocol. A total of 120 rotation stops were acquired using a 128 × 128 acquisition matrix. Images were reconstructed using a Butterworth or Weiner filter. Data were reformatted in axial, coronal, and sagittal planes, and evaluated for regions of hypoperfusion by a board-certified radiologist specializing in nuclear medicine. The radiology report and all images were available for review by the investigative team. Raters who were blind to other imaging and behavioral findings coded SPECT data sets as showing evidence of hypoperfusion in right/left frontal, temporal, parietal, occipital, or subcortical basal ganglia nuclei, or in a diffuse pattern consistent with generalized brain atrophy. Exploratory analyses showed no significant right-left differences, so findings were collapsed across the hemispheres.

Image integration

After MEG, MRI, and SPECT data were initially evaluated in an independent manner, image fusion was performed to explore the relations between modalities. Image fusion was accomplished by first sending DICOM images from the MR scanner to the MEG workstation. Using proprietary software (Neuromag Ltd), the fiducial points used during MEG to define the head-centered coordinate system were identified on the MR images. The software then aligned MEG and MRI coordinate systems so that MEG source locations could be plotted on the MR images to form magnetic source localization images. These images, with MEG source points now an inherent part of the data set, were then DICOM transferred to the SPECT workstation, which treated the magnetic source localization images as though they were simply MR images. A 9 df volume registration protocol with interactive processing was then used to align SPECT and MRI/MEG coordinate frames. The magnetic source localization images were reformatted in planes centered on the SPECT slices and image blending was performed.

RESULTS

Neuroimaging

Table 1 summarizes demographic, neuroimaging, and clinical observations for each patient. As previously mentioned, there were no significant laterality effects, so a region was coded as being abnormal if an abnormality was observed for either hemisphere. A descriptive summary of findings is provided below.

CT/MRI

Structural imaging performed at the time of accident revealed abnormalities in only 5 of the 30 patients (all with subdural hematomas). MR follow-up at the time of MEG and SPECT (performed, on average, 33.2 months after trauma) revealed chronic MR findings (mild atrophy) in only 2 of these 5 cases. There were also 2 cases with initially normal MR scans that showed mild cortical atrophy and some ventricular dilation at follow-up. Hence, there were 4 cases with evidence of atrophy on MRI at the time of MEG and SPECT imaging. No patient showed focal lesions or clear MR evidence of diffuse axonal injury. Ten patients had history of more than 1 traumatic event, including each of the 4 patients with chronic MR findings.

SPECT

Perfusion imaging using SPECT revealed abnormalities in 12 participants (40%), including each of the 4 with chronic MR findings and 8 others. SPECT was abnormal for 7 of 9 patients with histories of multiple mild traumatic events but only 5 of 21 patients with single traumas ($P < .05$ by the Fisher exact test, odds ratio [OR] = 11.2, 95% confidence interval [CI] = 1.7–100.1). In all cases with abnormal SPECT findings, focal perfusion deficits were seen in regions not explicitly identified as abnormal by MRI.

MEG

Six patients showed intermittent epileptic spikes, even though none had reported clinical seizures. MEG also revealed the presence of abnormal DSWA in 19 patients (63%). All 4 patients with structural findings and 9 of the 12 patients with SPECT findings showed MEG abnormalities. When focal MR or SPECT abnormalities were present, MEG always provided evidence of concordant electrophysiological dysfunction (except with respect to subcortical hypoperfusion). In most of these cases, MEG also revealed a more extensive picture of dysfunction than was shown by either MRI or SPECT.

There were 10 patients with normal MRI and normal SPECT who showed MEG abnormalities. Three patients with abnormal SPECT showed normal MEG and MRI examinations. As was seen for both MRI and SPECT, participants with a history of multiple traumas were more likely to show MEG abnormalities than patients with only a single traumatic event (9/9 vs 10/21, $P < .05$ by the Fisher exact test).

It should be noted that there were no significant differences in the slow wave sensitivity profiles across study sites or for the 122-channel recording system versus 306-channel recording system. Although the 122- and 306-channel sensor units differ significantly in the number of sensors, the actual area of coverage for the 2 units shows only a modest difference, with the increased number of sensors in the 306-channel unit being mostly a reflection of slightly increased packing density and addition of a magnetometer at each recording site. A set of exploratory data analyses failed to provide evidence that

TABLE 1 *Data for individual participants*[*,†]

						SPECT						MEG					Clinical profile					
Age	Sex	No. of trauma	Initial MRI	Time	Current MRI	A	F	T	P	O	B	F	T	P	O	e	P	S	M	A	E	PS
36	M	1	Normal	30	Normal			Normal					Normal				P					
54	M	1	NA	45	Normal			Normal					Normal				P					
43	F	1	Normal	20	Normal			Normal					Normal				P					
34	M	1	NA	22	Normal			Normal					Normal									PS
31	M	1	Normal	34	Normal			Normal					Normal					S				
21	M	1	NA	40	Normal			Normal					Normal				P	S				
19	F	1	Normal	14	Normal			Normal					Normal						M			PS
57	M	1	NA	36	Normal			Normal					Normal						M	A	E	PS
61	F	1	NA	51	Normal						B		Normal					S				
31	F	1	Normal	86	Normal						B		Normal					S				
32	F	1	Normal	76	Normal		F				B		Normal				P	S			E	
26	M	2	Abnormal	20	Normal			Normal				F					P				E	
44	F	1	Normal	22	Normal			Normal					T		O							PS
45	F	1	Normal	31	Normal			Normal					T	P					M			
41	M	1	Abnormal	19	Normal			Normal					T			t			M		E	
37	M	1	Normal	21	Normal			Normal						P						A		
38	M	1	Normal	32	Normal			Normal				F				p				A	E	
40	F	1	Normal	23	Normal			Normal					T						M			
50	F	1	NA	40	Normal			Normal					T						M			PS
29	M	1	Normal	15	Normal			Normal					T	P						A		PS
27	F	2	Normal	32	Normal			Normal				F	T			f			M	A	E	PS
44	F	1	Normal	15	Normal			T			B		T					S				
53	M	2	NA	13	Normal				P					P						A	E	
67	M	2	NA	140	Normal		F					F	T	P		p					E	PS
23	F	1	Normal	21	Normal			T					T	P		t			M	A	E	PS
42	M	2	Abnormal	19	Normal			T		O	B		T	P	O		P		M	A	E	PS
21	F	2	Abnormal	14	Mild atrophy		F					F	T						M		E	
18	F	2	Abnormal	12	Mild atrophy	A	F					F	T	P		f	P				E	PS
36	M	3	Normal	22	Mild atrophy	A		T					T						M			PS
52	M	2	NA	30	Mild atrophy	A	F		P		B	F	T	P			P	S	M	A	E	PS

*MRI indicates magnetic resonance imaging; SPECT, single photon emission computed tomography; and MEG, magnetoencephalography.

†Demographic, clinical, and neuroimaging findings are provided. Reported information includes participant age (in years), total number of head trauma prior to imaging, whether MRI done at the time of trauma was normal, abnormal, or not available (NA) and the time (number of months) between the traumatic event and MRI/SPECT/MEG imaging. Current MRI findings are indicated as normal or showing atrophy (no patients showed focal encephalomalacia). SPECT findings are indicated as normal, or abnormal in the following ways: A indicates evidence of atrophy, ventricular dilation, and/or global depression of cortical perfusion; F, frontal hypoperfusion; T, temporal hypoperfusion; P, parietal hypoperfusion; O, occipital hypoperfusion; and B, basal ganglia subcortical hypoperfusion. MEG findings are indicated as normal or showing abnormal dipolar slow wave activity in the following regions: F indicates frontal; T, temporal; P, parietal; and O, occipital. When epileptiform activity was present, it is indicated in column 'e' with the region indicated as follows: f indicates frontal; t, temporal; p, parietal; and o, occipital. Clinical findings are indicated in each of the following domains: P indicates psychiatric; S, somatic; M, memory problems; A, attention problems; E, problems in executive function; and PS, decreased processing speed.

magnetometers were more sensitive to dipolar slow waves than planar gradiometers. The increased packing density for the 306-channel unit does give this unit a greater degree of spatial resolution than the 122-channel unit, but it does not appear to provide a significant increase in the efficiency of detection of dipolar slow wave events.

Imaging summary

Overall, 73% of the patients showed abnormalities on 1 or more imaging tests, with only 4 subjects (13%) showing abnormalities on all 3 imaging tests. Figure 2 illustrates integrated MRI, SPECT, and MEG data from a patient with normal MRI but abnormal SPECT and MEG. Of the 3 imaging methods, MEG provided objective evidence of brain injury for the greatest number of patients (19/30). This "hit" rate was significantly superior to that for MRI (4/30, $P < .01$ by McNemar Test of Proportions), but only marginally better than that seen for SPECT (12/30, $P = .09$ by McNemar test of proportions). However, as discussed in more detail below, MEG and SPECT did not provide merely redundant

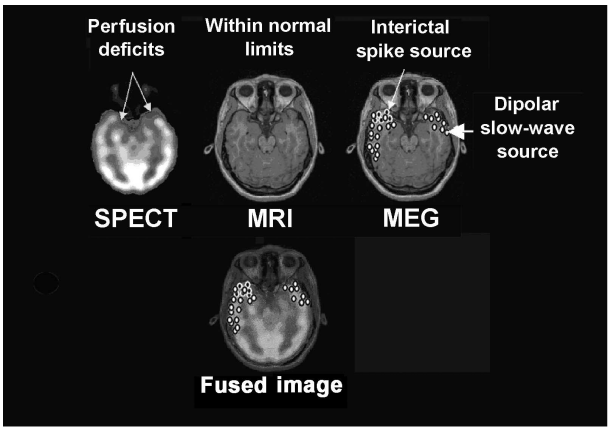

Figure 2. Integrated single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), and magnetoencephalography (MEG) in mild head trauma: Data are shown for a 23-year-old female participant who suffered a mild head trauma in a motor vehicle accident. She reported only a brief less than 1-minute loss of consciousness and her Glasgow Coma Scale was 15 at the time of hospital admission. MRI performed at the time of admission was interpreted to be within normal limits. Nevertheless, she reported a chronic postconcussive syndrome characterized by documented memory and attention problems and some general cognitive decline. Follow-up MRI, 21 months posttrauma, was within normal limits. SPECT revealed bitemporal hypoperfusion. MEG revealed right and left temporal focal slow waves and additional left parietal slowing. MEG also showed rare left temporal epileptiform spikes even though the participant had never been reported to show a clinical seizure. Subsequent to these studies, the patient was placed on valproic acid (Depakote). Follow-up neuropsychological testing conducted 6 months after initiation of Depakote revealed a significant improvement in memory function, although attentional skills and general processing speed did not improve.

information, especially when specific clinical profiles are taken into account.

Imaging in relationship to clinical profiles

Table 2 provides the odds ratio (OR) that brain imaging was abnormal, given the presence of persistent symptoms in psychiatric, somatic, and cognitive domains.

As can be seen, there were no significant general brain imaging correlates of persistent postconcussive psychiatric or somatic complaints, although there was a trend for SPECT to be abnormal in patients with somatic problems ($.05 < P < .10$, by the Fisher exact test). When considering the overall cognitive domain, only MEG findings were significant ($P < .001$). Given that cognitive problems were present, MEG was abnormal for 18 of 22 patients (86%), while only 1 of 9 patients without cognitive problems had an abnormal MEG.

One of the goals of this study was to examine the relations between specific clinical symptoms and specific regional patterns of brain imaging abnormality. Table 3 provides OR on these relations.

TABLE 2 *Odds ratios for finding imaging abnormalities given that postconcussive symptoms were present*[*,†]

	Psychiatric	Somatic	Cognitive
MRI	2.7	1.1	∼ [‡]
SPECT	2.3	5.7	1.5
MEG	0.3	0.1	**48.0**[§]

*Odds ratios are shown for finding imaging abnormalities in patients with post-concussive psychiatric, somatic, or cognitive symptoms. Significant relationships are in bold.
†MRI indicates magnetic resonance imaging; SPECT, single photon emission computed tomography; and MEG, magnetoencephalography.
‡The symbol (∼) indicates infinite odds ratio because one of the cells in the calculation was 0.
§$P < .001$ by the Fisher exact test. All other observations are nonsignificant.

There were no significant imaging correlates of postconcussive psychiatric symptoms. As stated previously, when considering the presence of any abnormality on MRI, SPECT, or MEG, there was also a lack of significant imaging correlates of postconcussive somatic symptoms. However, when imaging profiles are analyzed with respect to a more detailed regional perspective, it becomes clear that there is an imaging correlate of postconcussive headaches. Specifically, there is a significant ($P < .001$) relation with basal ganglia hypoperfusion on SPECT. Seven of the patients in this study reported persistent severe headaches subsequent to mild HT, with 5 of these showing hypoperfusion of the basal ganglia. Of the 6 patients with basal ganglia hypoperfusion, only one did not show headaches.

The relations between cognitive problems and imaging profiles were complex. Each of the 4 patients with mild atrophy on MRI had some degree of cognitive dysfunction, but cognitive problems were also found for many patients without MRI findings. There were no significant relations between MR findings and specific cognitive symptoms.

Although SPECT revealed some hypoperfusion for 40% of the patients with any type of cognitive problem, associations between regional SPECT findings and specific cognitive symptoms were mostly weak. The only significant relation was between problems in executive function and hypoperfusion of the frontal lobes. Each of the 5 patients with frontal hypoperfusion showed problems in executive function. There were 8 patients with executive problems who did not show frontal hypoperfusion, but the overall relation was nevertheless significant ($P < .01$ by the Fisher exact test).

TABLE 3 *Odds ratios for finding specific imaging abnormalities given that a specific postconcussive symptom was present*[*,†]

		Psychiatric all	Somatic all	Cognitive			
				Memory	Attention	Executive	Speed
MRI	Atrophy	2.7	1.1	5.7	0.7	4.8	4.8
SPECT	Atrophy	2.7	1.7	3.4	1.2	2.9	∼
SPECT	Frontal	4.7	2.7	1.0	0.5	**∼**[‡]	0.8
SPECT	Temporal	0.8	1.1	5.7	2.7	1.4	4.8
SPECT	Parietal	2.5	0.8	1.5	∼	∼	∼
SPECT	Occipital	∼	0.0	∼	∼	∼	∼
SPECT	sub-cortical	3.0	**55.0**[§]	0.7	1.2	1.4	0.6
MEG	Frontal	2.1	0.5	1.2	0.9	**∼**[§]	2.1
MEG	Temporal	0.4	0.3	**13.0**[‖]	1.4	2.3	**8.0**[¶]
MEG	Parietal	1.3	0.3	1.0	**12.0**[‡]	4.0	4.0
MEG	Occipital	2.5	0.0	0.4	2.5	1.3	∼

*Odds ratios are shown for relationships between specific imaging observations and specific post-concussive symptoms. Significant relationships are in bold.

†MRI indicates magnetic resonance imaging; SPECT, single photon emission computed tomography; MEG, magnetoencephalography; ∼, infinite odds ratio because one of the cells in the calculation was 0.

‡$P < .010$ by the Fisher exact test.

§$P < .001$ by the Fisher exact test.

‖$P < .005$ by the Fisher exact test.

¶$P < .050$ by the Fisher exact test.

In general, MEG slow wave abnormalities were significantly associated with cognitive problems. As indicated in Table 3, there were several significant relations between specific regional findings and specific cognitive symptoms. Of the 12 patients with memory problems, temporal slow waves were seen for 10. Given a finding of temporal slowing (15 patients), only 4 were without memory problems. The relation between memory problems and temporal slowing is significant at $P < .005$. Memory problems were not associated with frontal, parietal, or occipital lobe slow waves ($P > .1$).

Of the 9 patients with attention problems, parietal slowing was seen for 6. When parietal slowing was present ($N = 9$), attention problems were seen for 67%. This relation is significant at $P < .01$. Attention problems were not significantly associated with frontal, temporal, or occipital slowing ($P > .1$).

Problems in executive function were significantly coupled to frontal slow waves ($P < .001$). Although 6 of 13 patients with executive problems did not show frontal slowing, in all 7 cases where frontal slowing was present, deficits in executive function were seen. Deficits in executive function were not significantly correlated with temporal, parietal, or occipital slowing. Interestingly, all 6 patients with epileptiform activity (independent of region) showed executive deficits, but only 4 of these also had frontal slowing. This suggests that general epileptiform activity can compromise the complex neural network that supports executive skills.

Decreased processing speed was seen for 10 of 15 patients with temporal lobe slowing, but only 3 of 15 patients without temporal lobe findings, indicating a significant association between temporal lobe findings and decreased processing speed ($P < .05$). Deficits in processing speed were not significantly associated with frontal, parietal, or occipital abnormalities.

DISCUSSION

Brain imaging, head trauma, and postconcussive symptoms

The present data confirm and extend several prior observations on the relations among head trauma, traumatic brain injury, postconcussive symptoms, and structural and functional neuroimaging data. In the acute evaluation of patients with even mild HT, structural methods such as CT and MRI can play an important role in ruling out life-threatening brain injuries (eg, depressive skull fractures, subdural hematomas). The value of MRI in the evaluation of patients with persistent postconcussive symptoms several months after the traumatic event is less clear, although structural MRI is presently one of the most commonly employed imaging tools for these patients. The present data indicate that MRI findings (at least as applied here in a clinically routine manner) are significantly less likely to be abnormal in these patients than findings from functional methods.

In our patients, SPECT was more likely than MRI to be abnormal ($P < .01$ by McNemar test of proportions), with some hypoperfusion seen for 12 of the 30 patients. Prior attempts to examine the relation between SPECT findings and specific postconcussive symptoms have yielded mixed and inconsistent results.[13,17,18,28–30] Critical factors may include the time between injury and imaging, the neuropsychological tests used, and sample size limitations. The present study had one of the largest reported study populations, yet, with the exception of a moderately significant ($P < .01$) relation between frontal hypoperfusion and deficits in executive function, and a highly significant ($P < .001$) relation between persistent postconcussive somatic symptoms (headaches) and subcortical basal ganglia hypoperfusion, no significant relations were seen between specific SPECT findings and other specific symptoms. The relation between frontal lobe abnormalities and problems on tests of executive function is well documented, but at present, we lack understanding of the physiological processes by which basal ganglia hypoperfusion and posttraumatic headache might be coupled. Also, it should be noted that, whereas this observation attained statistical significance, there were only 5 patients with both basal ganglia hypoperfusion and persistent headaches.

Although MEG findings were not strongly associated with psychiatric or somatic symptoms, there were highly significant relations between regional MEG abnormalities and specific cognitive problems. At significance levels of $P < .01$, temporal lobe MEG abnormalities were associated with memory deficits, parietal abnormalities were associated with attention problems, and frontal abnormalities were associated with problems in executive function. These patterns of MEG abnormalities are consistent with the organization of known cortical systems supporting mnemonic, attention, and executive abilities,[31] and they strongly suggest that MEG observations truly reflect traumatic brain injury to the implicated processing systems.

It was also observed that reduced processing speed was associated with temporal lobe slow waves. At present, the full significance of this relation is uncertain, but, like that between temporal lobe slow waves and mnemonic dysfunction, it may partly reflect underlying damage to limbic structures (see the discussion of slow waves, below).

Although no patients showed clear posttraumatic seizures, MEG identified epileptiform abnormalities in 6 cases, as a result of which physicians placed 3 patients on anticonvulsant medications (Depakote or Tegretol). In 2 cases (each with temporal lobe activity), this led to significant clinical improvements, especially in mnemonic function. These observations suggest that, even in the absence of clinical seizures, epileptiform activity can have a negative impact on cognitive functioning that may warrant pharmacologic management.

In considering the utility of multimodal imaging in mild HT, MRI data were fully redundant with data from SPECT and MEG in the sense that each patient with an MRI finding also had abnormalities on functional imaging. In contrast, SPECT and MEG provided some differential data. There were 3 patients with SPECT abnormalities without MEG findings, and 10 patients with MEG findings in the absence of SPECT abnormalities.

Whenever SPECT identified focal cortical abnormalities, MEG identified concordant slow waves. However, MEG failed to reveal a slow wave correlate for hypoperfusion of the basal ganglia. The strength of the MEG signal recorded outside of the head depends on many factors including the number of brain cells that are synchronously active, the geometric configuration of the dendritic trees of these cells, and the distance to the MEG sensors.[32] Through the application of special signal processing techniques (eg, signal-space projection strategies[33]), MEG can, in some circumstances, provide direct evidence for dysfunction of subcortical structures. However, for the most part, MEG is relatively insensitive to subcortical dysfunction, except through indirect observation of the impact of subcortical dysfunction on cortical activities. In the case of basal ganglia hypoperfusion, there seems to be little electrophysiological impact on cortex, at least with respect to generation of focal slow waves.

MEG, executive function, and frontal lobe vulnerability in head trauma

Several lines of data converge to suggest that the frontal lobes are especially vulnerable to head trauma. It is therefore somewhat surprising that MEG (the most sensitive of the employed imaging methods to problems in executive function) revealed frontal abnormalities in only 7 of the 30 trauma patients. Encouragingly, each of the patients with frontal findings showed evidence of deficits in executive functions, but there were 6 additional patients with clear problems in executive function where MEG failed to show any frontal abnormalities.

There are several possible explanations for the rarity of frontal MEG abnormalities. One possibility relates to an inherent limitation of MEG—a lack of sensitivity to intradendritic currents oriented perpendicular to the skull. The frontal lobes, in particular, have large regions where cortical pyramidal cells are oriented in a mostly radial direction, so MEG may be relatively blind to abnormal signals from certain large patches of frontal cortex. A partial solution to this problem that will be employed in future studies is inclusion of simultaneous quantitative EEG recordings. EEG shows a complementary

sensitivity profile to MEG, with relatively greater sensitivity to radial versus tangential currents.

Another possible reason is that frontal dysfunction following mild HT is not well characterized by dipolar slow waves. Examination of nondipolar events, or abnormalities in higher frequency bands (eg, theta, alpha, and beta), might provide a better assessment of frontal dysfunction (see the discussion of slow waves, below).

On the other hand, SPECT also failed to reveal frontal problems in the majority of our patients. This suggests that we may have had a slightly atypical group of trauma patients, or that the selective vulnerability of the frontal lobes to damage by mild trauma is less than suspected. Many of the data supporting the susceptibility of the frontal lobes in mild trauma are inferentially based on the frequent presence of problems in executive function. Whereas it is well established that patients with frontal lobe lesions show deficits in executive function, the converse statement that deficits in executive function are an exclusive reflection of frontal damage is not well established. In our study, 100% of the patients with clear frontal abnormalities on either SPECT or MEG showed problems in executive function, but several patients with executive problems did not show frontal abnormalities. These data combined with those from other functional imaging studies indicate that brain regions beyond the frontal cortex contribute to performance on "executive" tasks.[34]

On the nature and value of slow waves

As previously described, the MEG slow wave analyses performed in this study focused only on those events with a dipolar field pattern. Although single dipole modeling is generally found to be unsatisfactory for modeling the true complexities of spontaneous data,[25] the present results support prior observations that this strategy can be effective in the identification of focal pathology in a wide range of conditions.[25,35–42] The fundamental rationale for the dipole strategy is that abnormal signals from dysfunctional regions are occasionally so large that they dominate the recorded magnetic signals, with the simple dipole model being only minimally perturbed by lower amplitude activity from normal tissue. With respect to nondipolar slow waves, the present study ignored these because we have found it difficult to reliably model such slow waves using even a multiple dipole approach. Nevertheless, complex slow waves may still represent important signs of pathology that merit attention. Fehr and coworkers[43] have used minimum-norm current reconstruction strategies to examine complex slow waves in schizophrenia. Future studies in head trauma should explore the utility of this approach.

An additional analysis strategy that may prove fruitful involves spectral assessment of absolute and relative power and coherence in various frequency bands.[25,43] The advantages of spectral methods are their computational simplicity, objectivity, and model independence. However, these methods can miss clinically significant pathophysiology that has a rare paroxysmal (burst-like) character. A short-duration burst of focal slowing may be of clinical significance, but one or a few bursts of slow waves against an otherwise normal background may not cause significant perturbation of power spectra derived over an extended time period.[25]

The multimodal integration approach employed in this study helps provide information on the neurobiological basis of MEG-identified slow waves. In prior studies of patients with focal encephalomalacia from stroke or moderate-severe head trauma, MEG frequently identified focal slowing only at the margins of the lesions.[35,38] This indicates cell loss and disruption of local interconnections as one likely cause of slow waves. The present study reveals that slowing is also seen in cortical regions that appear structurally intact but with decreased blood flow on SPECT. Additional evidence that a perfusion deficit alone can give rise to slow waves comes from observations in patients with transient ischemic attacks where we and others have found focal slowing.[35,39] Although the present study suggests that decreased perfusion of the basal ganglia does not appear to give rise to cortical slow waves, prior animal and human studies show that disruption of thalamocortical projections can cause focal slow waves in the relevant cortical projection zones. So, some subcortical disruptions do produce cortical slow waves, whereas others do not.[44]

Interestingly, and perhaps importantly, slow wave patterns in the MEG appear to vary according to the nature of the generating condition. Based on the MEG data presented here and in other studies,[25,35,38,39] slowing associated with encephalomalcia and/or perfusion deficits tends to be of a rather continuous nature, whereas that associated with disruption of thalamocortical connections is more burst-like.[25,44] In the present study, MEG slow waves were seen in several patients without MRI or SPECT findings. In most of these cases, a burst-like pattern was observed, suggesting a disruption of thalamocortical connections that was not identified by conventional imaging. Both animal and human literature support the view that mild HT can cause a disruption of axonal connections that is not detectable using conventional MR imaging.[45–47] In future studies, application of newer MR scanning sequences such as magnetization transfer and diffusion imaging may help clarify the situation as these methods are believed to be more sensitive to white matter damage than the traditional sequences used here.[48,49]

Whereas disruption of thalamic input to the cortex can lead to focal slow waves, based on data from patients with stroke, tumors, and multiple sclerosis, it does

not appear to be the case that loss of transcortical input to a region per se causes focal slow waves (although there may be a local increase in coherence). An exception here concerns the hippocampus. Data from epileptic patients with hippocampal atrophy and sclerosis,[41] and also data from Alzheimer's patients with hippocampal atrophy,[42] converge to indicate that hippocampal damage often gives rise to focal slow waves in the temporal neocortex, especially anterior temporal projection zones. In this study, many patients with memory problems showed temporal slow waves. To some extent, this may reflect primary pathophysiology of the temporal neocortex, but in most cases, it probably reflects underlying damage to the hippocampus, as has been noted in several other studies showing disruption of hippocampal integrity following mild HT.[12,20]

Validity and specificity of findings

It must be remembered that there is presently no "gold standard" for the identification of traumatic brain injury in cases of mild HT. All that is certain is that each of our patients experienced a witnessed mild HT, and each reported some persistent problem.

A noteworthy observation from this study is that structural (MRI), hemodynamic (SPECT), and electrophysiological (MEG) methods all failed to provide results that correlated significantly with the presence of postconcussive psychiatric symptoms. This suggests that such symptoms may not directly reflect TBI, but rather may be secondary psychological reactions to other posttraumatic factors. Some of these other factors may directly reflect TBI (eg, changes in cognitive status as discussed below), while others do not (eg, social and economic consequences).

Considering somatic symptoms, there was a statistically significant relation between basal ganglia hypoperfusion and persistent headaches. Admittedly, the number of participants who showed both basal ganglia hypoperfusion and headaches was small ($N = 5$), but the statistical tests used take into account the data from all 30 participants and consider all combinations of being positive versus negative for basal ganglia findings and positive versus negative for headaches. While the present study did not have a normal comparison group, a review of the literature suggests that the false positive rate for identifying SPECT abnormalities in normal participants is less than 5%. It is also noteworthy that SPECT failed to demonstrate basal ganglia abnormalities in patients with mild HT reporting cognitive or psychiatric symptoms without headache (but, see reference 17, for contrary data). This suggests that there is specificity for the basal ganglia observation, although the extent to which subcortical hypoperfusion is seen in patients with headaches without head trauma is not known at present.

Although not especially sensitive to psychiatric or somatic complaints, MEG was highly likely to be abnormal when cognition was disturbed. For the 22 patients with cognitive complaints, MEG was abnormal for 18. Assuming that none of the patients in this study were malingering (all had passed malingering tests during neuropsychological evaluation), this observation, coupled with the significant relations between specific cognitive findings and region-specific MEG findings, suggests that MEG may serve as a neuroimaging gold standard for identifying TBI in patients with persistent postconcussive complaints subsequent to mild HT.

However, with respect to the relations between MEG findings and cognitive problems, the study is limited by a lack of baseline (pretrauma) cognitive data for the subjects. This issue is further compounded by the fact that neuropsychological deficits following mild HT are often subtle. For this study, we considered a domain to be abnormal if performance on relevant tests was at least 1 SD below the mean and the participant indicated he or she was impaired in that domain, the latter criterion being an attempt to gauge the perceived impact of subtle deficits. Supporting the validity of this strategy is the observation that, whenever neuropsychological testing revealed a deficit greater than 1.5 SD below the mean, participants always self-reported a deficit in that domain. Across all participants, there were 5 data points of neuropsychological test performance 1.0–1.5 SD below the mean, but participants did not report problems in the implicated domain. In the main analyses, these data points were coded as within normal limits. A follow-up analysis with these points coded as abnormal (based solely on the neuropsychological testing criteria) did not alter the significance levels for any of the relations reported herein.

Our conclusions are also constrained by the fact that performance in a domain was typically assessed by only 1 or 2 specific tests, and in some cases, a given test may tap multiple domains of processing. This was especially true with respect to tests included in the evaluation of processing speed (Trails B and the grooved pegboard task). However, a reassessment of processing speed considering just data from Trails A (or the data from Trails A and the CPT) still revealed a significant relation between processing speed and MEG slow waves from the temporal lobes. Also, cognitive constructs beyond processing speed that are thought to be tapped by Trails B and the pegboard task are not ones that would bias the data toward finding a correlation with the temporal lobes.

The number of comparisons between regional imaging findings and specific symptoms raises some concern about type I errors. The relations between specific imaging findings and deficits in memory, attention, and executive function were each consistent with prior data in the SPECT and MEG literature, and were all significant

at $P < .01$, so it is unlikely that they reflect a type I error. The relation between basal ganglia hypoperfusion and headache has not been reported previously and the number of cases with both findings is small, but the significance level was quite high ($P < .001$, OR = 55), so this, too, is unlikely to be a type I error. The relation between processing speed and temporal lobe slow waves is a bit more suspect since there are no supporting observations in the literature and the significance level was low ($P < .05$). However, even using a sequential rejection procedure to correct for multiple comparisons, the finding remains significant.

Given the above factors, the observed relations between specific MEG findings and specific symptoms are likely to be valid. There are, however, important considerations on the specificity of MEG observations of focal slowing in relation to head trauma. The specificity depends, of course, on the nature of the comparison group. In previously published and unpublished studies of more than 70 normal comparison participants, we have found focal slowing in fewer than 10%.[25,35] There is a slightly increased incidence of slowing in patients with mild HT without cognitive symptoms, but even here, focal slowing is seen in only 15%.[25] It is also clear that cognitive compromise (in the absence of head trauma) is not always associated with focal slowing. For example, in both children and adults with attention problems related to attention-deficit disorder, focal slowing is seen for fewer than 15% (J. D. Lewine, J. T. Davis, and M. E. Funke, in preparation). These observations, combined with the significance of the relations between specific MEG patterns and specific cognitive symptoms, support the view that our liberal criteria for postconcussive cognitive compromise (1 SD below the mean) are viable for this population.

Although focal slowing in MEG appears to be a sensitive and specific marker of pathophysiology in distinguishing patients with traumatic brain injury from normal control participants, trauma patients without cognitive compromise, and some patient groups with cognitive compromise in the absence of head trauma, there are several nontrauma populations where the rate of focal slowing is quite high (between 30% and 80%). Specifically, dipolar slow wave activity has been reported for patients with tumors,[36,37] chronic stroke,[38,39] epilepsy,[40,41] dementia,[42] and schizophrenia.[43] Thus, in the absence of preinjury data or solid evidence that none of the above conditions are present at the time of MEG, some caution must be exercised in attributing the presence of slow waves explicitly to a temporally remote head injury.

Resting versus activation studies

There is a growing trend in imaging science to employ activation tasks to explore the impact of disease of brain function. For example, in studies using PET, SPECT, fMRI, EEG, or MEG in the evaluation of patients with dementia, it is common to collect imaging data during performance of a recognition memory task.[50] While the activation approach has proven quite fruitful from a cognitive neuroscience perspective where there is great advantage in having behavior and imaging measures coupled in time, it has not been especially useful in the evaluation of single patients. First, for at least PET and SPECT, there is a significant confound between imaging results and the behavioral ability to perform a task. In many cases it is unclear whether reduced activation is a cause or consequence of behavioral compromise. Also, in general, there is high between-participant variability in activation results, so differences between patient populations and normal controls can often be seen only in group-averaged data. Finally, activation paradigms are generally designed to probe very specific cognitive functions mediated by a restricted set of neuronal structures. So, using an activation approach, it is difficult to probe the full imaging space unless one uses many tasks.

In contrast, studies of baseline resting activity allow one to look for dysfunction throughout the brain, without a priori assumptions about relations between specific tasks and regions of activation. Also, available data suggest that intrasubject variability in resting measures is surprisingly low, so it is relatively easy to identify normal activity versus abnormal activity using either subjective or objective (statistical) approaches. These are critical concerns in evaluation of patients with mild HT, especially because there are significant interindividual differences in symptom profiles. Nevertheless, in future studies, it may be of value to combine activation and resting strategies to give the most comprehensive view possible.

Limitations

In evaluating the present data, several limitations must be kept in mind. First, the study is retrospective rather than prospective in nature. Patients were clinically referred rather than directly recruited from a trauma care center, and only those reporting persistent postconcussive psychiatric, somatic, or cognitive symptoms were included. Thus, the abnormality rates reported above should not be taken to reflect the incidence of MRI, SPECT, or MEG abnormalities in an unselected population of mild HT survivors–most of whom will not show persistent symptoms or imaging abnormalities. It should also be noted that the extent to which functional imaging might reveal abnormalities in symptomatic whiplash patients was not addressed by the current data.

Approximately 50% of our patients were on regular dosages of psychoactive medications, and even though such medications were withheld on the days of functional imaging, given the half-life of most of these medications, they could have affected imaging findings. While this was not formally examined in this study, we

have (at least with respect to MEG) explicitly examined medication effects in patients with major depression, obsessive-compulsive disorder, schizophrenia, and attention-deficit disorder. In no case have we found that the medications used by trauma patients here result in an increase in DSWA, although in schizophrenia, these medications can cause a reduction in slow waves (J. D. Lewine, unpublished observations, 2007).

It must also be remembered that the present study examined only long-term consequences of trauma. While objective evaluation of the long-term structural and functional consequences of head trauma is of mechanistic, clinical, and legal interest, future studies should evaluate patients soon after trauma, with a goal of predicting which patients will have persistent postconcussive syndromes.

Another qualification of the present study is the fact that data were interpreted in a routine clinical manner and not using more sophisticated quantitative and statistical strategies that might produce a higher yield for each imaging modality. For example, Bigler and colleagues have shown that quantitative tools for assessing ventricular dilation subsequent to head trauma lead to the identification of abnormalities in a greater percentage of participants than when MR data are simply visually inspected by a clinician.[51] It must also be noted that a number of additional MR imaging sequences (eg, diffusion weighted imaging,[48] magnetization transfer imaging[49]) and other functional methods (including PET,[10–14] fMRI,[19,20] magnetic resonance spectroscopy,[52] quantitative EEG,[23,24] and evoked potentials[21]) may be useful in the evaluation of mild HT.

Finally, while MEG appears to be a more sensitive than MRI and SPECT to TBI in patients with persistent cognitive symptoms subsequent to mild HT, MEG is not yet widely available, with fewer than 25 whole-head MEG systems in the United States and fewer than 150 systems installed worldwide. On the other hand, it is likely that the next 5 to 10 years will see MEG availability extended to most major metropolitan regions, so the clinical potential for this imaging modality in the evaluation of head trauma patients must not be ignored.

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