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Activation of dominant hemisphere association cortex during naming as a function of cognitive performance in mild traumatic brain injury: Insights into mechanisms of lexical access

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ABSTRACT

Patients with a history of mild traumatic brain injury (mTBI) and objective cognitive deficits frequently experience word finding difficulties in normal conversation. We sought to improve our understanding of this phenomenon by determining if the scores on standardized cognitive testing are correlated with measures of brain activity evoked in a word retrieval task (confrontational picture naming). The study participants (n = 57) were military service members with a history of mTBI. The General Memory Index (GMI) determined after administration of the Rivermead Behavioral Memory Test, Third Edition, was used to assign subjects to three groups: low cognitive performance (Group 1: GMI ≤ 87, n = 18), intermediate cognitive performance (Group 2: 88 ≤ GMI ≤ 99, n = 18), and high cognitive performance (Group 3: GMI ≥ 100, n = 21). Magnetoencephalography data were recorded while participants named eighty pictures of common objects. Group differences in evoked cortical activity were observed relatively early (within 200 ms from picture onset) over a distributed network of left hemisphere cortical regions including the *fusiform gyrus*, the *entorhinal* and *parahippocampal cortex*, the *supramarginal gyrus* and posterior part of the *superior temporal gyrus*, and the *inferior frontal* and *rostral middle frontal gyri*. Differences were also present in bilateral *cingulate cortex* and *paracentral lobule*, and in the *right fusiform gyrus*. All differences reflected a lower amplitude of the evoked responses for Group 1 relative to Groups 2 and 3. These findings may indicate weak afferent inputs *to* and *within* an extended cortical network including association cortex of the dominant hemisphere in patients with low cognitive performance. The association between word finding difficulties and low cognitive performance may therefore be the result of a diffuse pathophysiological process affecting distributed neuronal networks serving a wide range of cognitive processes. These findings also provide support for a parallel processing model of lexical access.

1. Introduction

Models of language processing have been significantly advanced by psycholinguistic and neurolinguistic studies in patients with acquired cognitive deficits, including aphasic syndromes due to stroke and other brain injuries (Poeppel and Hickok, 2004). Approximately 15% of the patients with a history of mild traumatic brain injury (mTBI) report persistent physical, cognitive and psychological symptoms (Jagoda et al., 2008; Marshall et al., 2015). For some of these patients the cognitive complaints include word finding difficulties, which are described in a variety of terms indicating a spectrum of speech difficulties (Rohrer et al., 2008), such as problems *finding words* (example reproduced from the reports of the participants in our study: “I know what I want to say but can't find the word in casual conversations”), problems *getting words out* (“Sometime the words won't come out right”) or *using jumbled words* (“I know what I want to say but jumble up the words”), complaints of a *reduced vocabulary* (“My vocabulary is not as large or as easily accessible as before”), frequent experiencing of the *tip-of-the-tongue* phenomenon (“I forget words and I feel like they are on the tip of my tongue”), or overlapping difficulties with word finding and planning of the message in normal conversations (“At times, I pause in inordinate amount of time while thinking of a word”; “I get stuck and I can't think”). These subjective reports could be indicative of a general deficit of *accessing* stored lexical representations.

Psycholinguistic multi-stage models of lexical retrieval have been useful in explaining difficulties in retrieval from lexical memory.

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Several potential mechanisms have emerged from observations of speech errors or of tip-of-the-tongue phenomenon, which occur in all healthy individuals and increase in frequency with age (Finley and Sharp, 1989; Burke et al., 1991; Brown and Nix, 1996; Rastle and Burke, 1996). Early in the process of lexical retrieval, a neuronal representation of a word is activated that is comprised of a unique combination of all semantic and syntactic features of the word, but devoid of phonological features, an entity known as a *lemma* (Levelt, 1989). Selection of the correct lemma involves initial activation of multiple lexical representations corresponding to the target and *competitor* words, until one lemma attains a level of activation exceeding all others with similar semantic features by some particular threshold. Other representations are then deactivated by inhibitory mechanisms in a "winner-takes-all" fashion. Subsequently, the phonological features of the lemma are encoded prior to phonetic coding if the word is to be articulated. Differences of opinion exist as to whether some of these processes occur serially or in parallel (a review of the theories of spoken word production is available in Rapp and Goldrick, 2000). Levelt has championed the view that these processes remain strictly serial (feedforward) in nature, such that phonological retrieval takes place only for the lemma that was selected at the previous processing stage. Connectionist architectures (Dell, 1986; Dell et al., 1999) have modeled a mechanism of parallel processing in lexical access involving cascading activations and feedback. In this model, multiple neuronal representations at the semantic level send activations to the phonological processing level, such that feedback from the latter stage helps constrain the appropriate lemma selection and feedforward input from the lemma processing level influences phonological encoding even prior to final lemma selection. In this conceptualization, disruption of neuronal signaling both within and between cortical processing modules could adversely affect word retrieval simultaneously at multiple stages.

Neuronal signaling can be disrupted following TBI due to axonal injury (Hulkower et al., 2013) or to alterations of neurotransmitter systems. Mechanisms underlying an inefficient inhibition of competing neuronal representations could contribute for example to word selection difficulties manifested sometimes by retrieval of different (intrusive) words (Brown, 1991; Schwartz, 1999). This can be due to a loss of inhibitory interneurons or impaired GABAergic signaling, which has been observed after TBI (Cantu et al., 2015; Almeida-Suhett et al., 2014) or in anxiety disorders that are frequently comorbid in patients with a history of TBI. An excitation-inhibition imbalance may also result from alterations in long range cortico-cortical connections that can bias the local competition between neuronal representations of target and competitor words, influencing cortical attractor dynamics (this perspective will be addressed in more details in the Discussion section). Such connections may originate in other language processing areas or in higher order regions involved in top-down control (see Desimone and Duncan, 1995; Bar, 2003 for discussions on influential models of biased competition). These higher order regions may play an executive role in accessing items from memory or directing selective attention, as well as detecting and correcting errors prior to or during articulation. Difficulties with the access/selection of (target) memory representations, manifested at different stages of the word retrieval, may lead to the spectrum of symptoms reported by many patients with a history of mTBI, from problems finding words to increased frequency of *word substitutions* (the target word gets substituted by an intrusive word in an unfolding utterance) or *words blends* (when two lemmas activated at a similar level get selected and encoded as one word form).

The subjective complaint of mild anomia in patients with persistent post-concussive symptoms generally defies quantification by standard aphasia batteries or language evaluations using insensitive analysis approaches due to its subtle nature. This underlines the nature of the subjectively reported deficits, which manifest irregularly and as *transitory* unavailability of the stored lexical representations. In addition, it may reflect the fact that an increased effort or attention in the specific context of speech-language examination may successfully overcome the difficulties encountered in casual conversation. Furthermore, despite common complaints of word finding difficulties during conversational speech, these patients do not demonstrate evidence of impairment on confrontational naming tasks even when stimuli are presented along with auditory distractors (Barrow et al., 2006). Extensive confrontational naming data from our institute corroborate these results (unpublished data). A likely explanation is that propositional speech production poses a greater demand on executive/attentional resources involving planning and monitoring of the message and speech structure in parallel with the word retrieval processes. For example, evidence suggests than in verbal sentence production, multiple lemmas (the word specific semantic and syntactic information) for the individual words of a clause can be activated before the phonological encoding of any of the lemmas is completed and phonological encoding takes place for all words concurrently (Dell, 1986). This presents a greater likelihood for the elicitation of errors than the process of single word production. Furthermore, there is a direct connection proposed from the representation of visual objects to the phonological representation of whole words, bypassing the steps of activation of semantic concepts and lemma selection required for the activation of phonological word forms during the production of propositional speech. The presence of this pathway is demonstrated by the phenomenon of nonoptic aphasia, in which patients with degenerative brain processes may name visually presented objects relatively well, even in the absence of semantic knowledge of those words and in the absence of the ability to produce any words spontaneously or to definition (Shuren et al., 1993; Bennen, 1996; Roth et al., 2006).

We have also observed that lexical retrieval difficulties are more likely to be reported by mTBI patients with objective evidence of declarative memory impairment, suggesting that a low cognitive performance in such standardized tests may be a neuropsychological marker of a diffuse alteration in cortical architecture in dominant hemisphere association areas. In this study, we sought to explore the neurophysiological basis of this phenomenon by determining if the scores on cognitive testing of memory are associated with specific patterns of brain responses evoked in a word production task (confrontational picture naming). Furthermore, we sought to use this potential marker of functional alteration of dominant hemisphere association cortex to investigate the time course of regional brain activity during naming that may provide support to some current theories of lexical access, which invoke multiple stages of processing but vary in terms of whether these stages are strictly serial or parallel in nature. We recorded magnetoencephalography (MEG) data using a picture naming paradigm used in different versions by other neuroimaging studies (Salmelin et al., 1994; Levelt et al., 1998; Breier and Papanicolaou, 2008; Liljeström et al., 2009). One assumption of this study was that the spatio-temporal information about the evoked brain activity may help us understand if neuronal processes underlying lexical retrieval are disrupted in patients with lower cognitive performance even when this is not necessarily reflected in impaired behavioral performance during the task. For example, alterations in neuronal signaling leading to low afferent input to cortical neurons (due to *e.g.* trauma-induced axonal injury or to alterations of neurotransmitter systems) within the brain network serving lexical retrieval may be reflected in changes in amplitude or timing of the regional brain activity. Our results demonstrate that performance on cognitive tests is associated with specific patterns of cortical activation during lexical retrieval, with spatio-temporal characteristics indicative of early activity in distributed brain networks, lending support to a parallel processing model of lexical access.

2. Methods

2.1. Participants

Participants (n = 80, 79 males) were military service members with a history of TBI and persistent post-concussive symptoms enrolled in a

4 week interdisciplinary intensive outpatient program at the National Intrepid Center of Excellence, Walter Reed National Military Medical Center. A TBI was defined as being the result of an application of external forces to the brain that resulted in at least one of the following symptoms: any period of loss of consciousness (LOC), any loss of memory for events immediately before or after the event (post-traumatic amnesia, PTA) or any alteration in consciousness (AOC) or mental state (*e.g.* feeling dazed, disoriented or confused). The TBI severity was considered to be mild when the LOC was 30 min or less, and the duration of the PTA or AOC was no longer than 24 h (American Congress of Rehabilitation Medicine, 1993). Injuries with outcomes exceeding these criteria were characterized as moderate/severe. The study was approved by the Walter Reed National Military Medical Center and Naval Medical Research Center Institutional Review Boards in compliance with all applicable Federal regulations governing the protection of human subjects. Informed consent was obtained from each subject before participation in the study.

All participants completed the Rivermead Behavioral Memory Test-Third Edition (RBMT-3, Wilson et al., 2008) as part of the standard speech and language evaluation performed during the assessment phase of an intensive outpatient program. The RBMT-3 is an ecologically valid test that includes 14 subtests assessing aspects of immediate and delayed verbal and non-verbal everyday memory function: *Story Recall* (immediate and delayed recall of a story), *Names* (remembering the first and second names of portrait photos), *Picture Recognition* (delayed recognition of line drawings), *Faces* (delayed recognition of photographs of faces), *Novel Task* (immediate and delayed recall of puzzle pieces laid in a specific order within a template), *Route* (immediate and delayed recall of a short route), *Appointments* (asking a set of questions when prompted 25 min later), *Belongings* (remembering to ask for personal items at the end of the test session), *Message* (immediate and delayed remembering to pick up an envelope and book), *Orientation and Date* (orientation to person, place and time). In some of the subtests, memory is tested immediately following the stimulus presentation, while in other subtests memory is tested after a filled delay. The delayed recall tests are used to assess performance in retrieving previously memorized information after a period of time during which the subject focuses attention on other tasks. The test was administered to the participants by a speech and language pathologist. Raw scores on each subtest were converted into scaled scores with a mean of 10 and a standard deviation of 3. The General Memory Index (GMI) was used as an overall cognitive performance measure derived from scaled scores on all subtests. GMI scores are calculated by summing the scaled scores on the RBMT-3 subtests and then converting this sum to a GMI using an appropriate conversion table (the index is standardized to have a mean of 100 and a standard deviation of 15).

The subjective word-finding difficulties were rated using a three-level ordinal scale, based on self-reported frequency of occurrence and level of concern expressed by the patient: if they were reported to occur frequently and/or they were of significant concern, they were characterized as *significant*; if they were reported to occur occasionally/sometimes and/or the patient description of the symptoms revealed they were of moderate concern, they were quantified as *moderate*; and if the patients reported they have no word finding difficulty or they were of no concern, they were quantified as *minor/none*. These subjective reports were used to assess the relationship between objective cognitive deficits assessed with the RBMT-3 and self-reported word-finding difficulties.

To determine if cognitive performance in our sample of patients is related to physiological processes that may be associated with the presence of co-morbid conditions (which are common in patients with post-concussive symptoms), all participants completed the PTSD Check List-Military version (PCL-M, a 17-item self-report scale used to screen individuals for PTSD symptom severity, total score range from 17 to 85, Kang et al., 2003; Bliese et al., 2008), Patient Health Questionnaire PHQ-9 (9-item depression assessment module, total score range from 0 to 27, Spitzer et al., 1999) and Generalized Anxiety Disorder GAD-7 scale (7-item scale used to assess the severity of various signs of anxiety, total score range from 0 to 21, Spitzer et al., 2006). In addition, sleep related symptoms which are common post-concussive symptoms that can affect performance in cognitive testing were assessed using the Insomnia Severity Index (total score range 0 to 28, Bastien et al., 2001) and Epworth Sleepiness Scale for daytime sleepiness (total score range from 0 to 24, Johns, 1991).

2.2. Assignment of participants to groups

Several participants were excluded from the analysis for the following reasons: two participants did not complete all study sessions; five participants were diagnosed with moderate/severe TBI; one participant was not a native English speaker; one participant had invalid co-registration between MEG and MRI and four others had high artifacts in the MEG data caused by body shrapnel and/or excessive movements during the recording. Furthermore, ten left-handed participants (handedness assessed using the Edinburgh Inventory, Oldfield, 1971) were not included in the analysis to minimize the potential effects due to a different distribution/lateralization of the language processing areas of the brain. All remaining participants ($n = 57$, all native English speakers) had experienced either a single or multiple head injury events, either the result of exposure to blast overpressure from an explosive device or due to blunt head trauma (caused by motor-vehicle accidents, helicopter crashes, hard parachute landings, sports-related concussions) that met the criteria for mTBI.

The General Memory Index from the RBMT-3 test was used to assign subjects into three groups: Group 1 included participants with low GMI (GMI $\leq$ 87, *i.e.* within the lowest 20 percentile of the normative data), Group 2 included participants with intermediate GMI (88 $\leq$ GMI $\leq$ 99, *i.e.* between 21 and 50 percentile of the normative data), and Group 3 included participants with high GMI (GMI $\geq$ 100, higher than 50 percentile of the normative data). According to these criteria, 18 participants (31.6%) were assigned to Group 1, 18 participants (31.6%) were assigned to Group 2, and 21 participants (36.8%) were assigned to Group 3. The majority of these participants had a history of multiple mTBI events. The proportions of participants in each group with respect to several injury characteristics are summarized in Table 1.

2.3. Medication use

No subjects were excluded from this study based on medication use. Five patients in Group 1 were taking antidepressant medication at the time of the MEG recording (Sertraline-three patients and Venlafaxine-two patients) *versus* four patients in Group 2 (Sertraline, Fluoxetine, Bupropion, and Venlafaxine) and four patients in Group 3 (Sertraline,

Table 1
Injury characteristics: number and proportion of subjects in each group for different injury types (blast, non-blast, and injuries with loss of consciousness, LOC) and the results of Fisher's exact test of proportions. Percentages are rounded to integer values.

	Group 1 ($n = 18$)	Group 2 ($n = 18$)	Group3 ($n = 21$)	Fisher's exact test
Multiple mTBI	17	17	18	$p = 0.61$
	94%	94%	86%	
Blast-related mTBI[a]	14	15	14	$p = 0.47$
	78%	83%	67%	
Only non-blast mTBI	4	3	7	
	22%	17%	33%	
mTBI with LOC	11	14	15	$p = 0.5$
	61%	78%	71%	

[a] A subgroup of these patients also have a documented history of non-blast or blunt head injury, often in conjunction with one or more of their blast injuries. Many authorities believe that some degree of blunt head injury accompanies the majority of blast injuries even if the non-blast component is undocumented.

Paroxetine, Bupropion, and Venlafaxine). Some of these medications were prescribed for headache prophylaxis as opposed to psychiatric symptoms. Additionally, three patients in Group 1 and two patients in Group 2 were taking anticonvulsant medications for headache prophylaxis (Gabapentin or Zonisamide). Two patients in Group 1 *versus* three patients in each of the Groups 2 and 3 were taking Prazosin as a treatment for nightmares. One patient in each of Groups 1 and 3 were taking Methylphenidate Hydrochloride. Some patients in each group were taking multiple medications from the categories described above; the total number of medicated patients was seven (Group1), six (Group 2), and five (Group3).

2.4. Radiologic evaluation

T1-weighted, T2-weighted and susceptibility-weighted MR images were acquired with a 3 T 750 MRI scanner (General Electric, Milwaukee, WI) and were reviewed by a neuroradiologist to assess for the presence of brain parenchymal abnormalities, such as white matter signal changes and microhemorrhages that may be sequelae of the traumatic brain injury, and to rule out other incidental findings, such as mass lesions, that would be unrelated to the TBI but which could potentially confound the neurophysiological findings of this study.

2.5. MEG data acquisition and pre-processing

MEG recordings were performed inside a magnetically shielded room using the Elekta VectorView™ whole-head MEG system (Elekta-Neuromag, Helsinki, Finland) with 102 triplet-sensors made of one magnetometer and two orthogonal planar gradiometers. The head position relative to the sensor array was determined at the beginning of the recording using four localization coils attached to the participant's head. The locations of three fiduciary points (nasion, and left and right auricular points) defining the head-frame coordinate system, together with the location of the four localization coils and of a set of head surface points were digitized using a 3D Fastrak digitizer (Polhemus, Colchester, VT, USA) to allow co-registration of the MEG and MRI data.

Data were acquired with 1 kHz sampling rate while 80 color drawings of common objects spanning different categories (*e.g.* animals, fruits/vegetables, tools, instruments, *etc.*) were presented on a screen for 2 s each using the Neuroscan Stim2 software (Compumedics Neuroscan, El Paso, TX, USA). All latencies reported herein were corrected for a delay of 18 ms (measured using a photodiode) introduced by the stimulus presentation system. Participants were instructed to silently name the object as soon as a picture is shown on the screen and say the name out loud after the picture was off the screen, during a 4 s inter-stimulus interval measured from the offset of one picture to the onset of the next picture. This strategy was chosen to avoid the contamination of the MEG data on the temporal interval of interest by strong interference from muscle activity associated with speech as it would have been the case if participants were asked to say the words out loud as soon as possible after the presentation of each image. The subject responses were recorded on a score sheet and were used to determine the number of correct object naming trials; alternative or incorrect naming was also recorded manually on the score sheet. Responses were considered to be correct for alterations of the target name consisting in variations that shared a key portion of the word without changing its meaning (*e.g.* “bike” for “bicycle”, “tie” for “necktie”). Responses were considered to be incorrect for names from the same semantic category which did not define accurately the object depicted (*e.g.* “cantaloupe” instead of “watermelon”). Responses were also considered incorrect for names defining a semantic category rather than the object depicted (*e.g.* “fruit” instead of “apple”, “tool” instead of “wrench”). Participants were instructed to fixate their gaze in the screen center and to minimize eye movements. The total recording duration was of approximately 8 min.

Data were filtered off-line between 1 Hz and 40 Hz and then processed using the Independent Component Analysis (ICA) Infomax algorithm (EEGLAB, Delorme and Makeig, 2004). ICA was used to segregate the activity of the underlying electrophysiological generators on separate independent components (ICs). ICs corresponding to cardiac and eye movement interferences, as well as other sources of external artifacts (if any) were removed. The reconstructed data were divided into epochs from − 500 ms to 3500 ms relative to the onset of the images. Epochs with incorrect responses were discarded. The remaining epochs with correct responses were averaged and corrected with a DC offset estimated from a 250 ms temporal window preceding the stimulus. These averaged datasets were subsequently used to estimate the brain generators of the evoked responses.

2.6. Source reconstruction

Each participant's cortical surface was determined using the *FreeSurfer* image analysis software (http://surfer.nmr.mgh.harvard.edu) from T1-weighted MR volumetric images. The source reconstruction was done using the *Brainstorm* software (Tadel et al., 2011). The cortical sources were estimated at 10,000 locations using a minimum-norm estimator (Hämäläinen and Ilmoniemi, 1994) and a multiple-sphere model of the volume conductor. The inverse projection operator incorporated the noise-covariance matrix derived from the baseline pre-stimulus segments. Cortical currents with unconstrained orientation were estimated using a depth weighting parameter of 0.5 and were subsequently projected on the averaged *FreeSurfer* template brain. The signal power at each source-space point was normalized with the mean signal power on a 250 ms temporal segment preceding the stimulus. The normalized power values were subsequently integrated in each of the 84 cortical regions of a modified *Desikan-Killiany* anatomical atlas (Desikan et al., 2006). The original *Desikan-Killiany* atlas with 68 regions was modified to refine (divide) several regions with an extended area into smaller, functionally more specific sub-regions. Examples include lateral and ventral temporal regions (superior, middle and inferior temporal gyri and the fusiform gyrus), which were each divided into two sub-regions of approximately equal area along the anterior-posterior direction, or the superior frontal gyrus that was similarly divided along the anterior-posterior direction into three sub-regions with approximately equal area.

2.7. Statistical analysis

Group differences for demographic and neuropsychological data were tested for statistical significance using ANOVA or Kruskal-Wallis tests. The bivariate correlation between the subjective word finding difficulty and the RBMT-3 general memory index was tested for statistical significance using the Kendall rank correlation test.

To investigate the relationship between brain activity and GMI, the normalized power of the evoked responses was first integrated over four temporal intervals, which were selected based on reports from previous MEG studies and our own observations regarding the latencies of the evoked response components: the first temporal interval, defined from 60 ms to 130 ms following stimulus onset, was selected to characterize the response components mainly reflecting early visual processing and object recognition; two middle temporal intervals defined from 100 ms to 200 ms and 200 to 300 ms, respectively, were selected to characterize the response components that presumably correspond to accessing the lexical concept and lemma selection (Levelt et al., 1998); the last temporal interval defined from 300 ms to 550 ms allows to characterize the response components corresponding to later stages of lexical retrieval including phonological encoding and phonetic processing. The first two intervals were selected to be partially overlapping in order to characterize the early response component from posterior visual cortex (on the interval between 60 ms–130 ms) as well as the components from other brain regions (on the interval 100 ms–200 ms) that emerge around 100 ms, before the end of the early visual

Table 2
Demographic and neuropsychological data: descriptive statistics and results of statistical tests for significance of group differences (ANOVA or Kruskal-Wallis tests were used as appropriate). Neuropsychological data include the General Memory Index (GMI) and scores from the Generalized Anxiety Disorder (GAD-7), Patient Health Questionnaire PHQ-9 (which assesses the severity of the major depressive disorder symptoms) and PTSD Check List-Military version (PCL-M) scales.

	Group 1 (n = 18)	Group 2 (n = 18)	Group 3 (n = 21)	Test statistics	p
GMI	79.3 ± 6.9	95.1 ± 3.3	110.4 ± 7.1		
Age (years)	37.0 ± 6.5	41.0 ± 5.2	39.3 ± 5.7	$F = 2.14$[a]	$p = 0.13$
Education (years)	14.1 ± 2.1	14.8 ± 2.3	14.1 ± 1.9	$F = 0.7$[a]	$p = 0.48$
GAD	15.7 ± 5.6	15.0 ± 5.1	13.2 ± 5.2	$H = 2.4$[b]	$p = 0.3$
PHQ-9	8.1 ± 5.3	7.2 ± 4.7	6.7 ± 5.3	$H = 0.9$[b]	$p = 0.64$
PCL-M	52.2 ± 13.3	52.1 ± 15.0	44.0 ± 15.2	$H = 4.3$[b]	$p = 0.12$
Insomnia severity*	10.9 ± 5.9	13.8 ± 5.8	11.5 ± 6.8	$H = 1.8$[b]	$p = 0.42$
Daytime sleepiness**	8.6 ± 4.8	11.4 ± 4.2	9.0 ± 4.5	$H = 3.5$[b]	$p = 0.17$
Time elapsed since last mTBI (months)	58.3 ± 39.9	66.2 ± 38.2	64.3 ± 45.8	$F = 0.18$[a]	$p = 0.84$

* Insomnia severity scores were not available for 2 participants in Group 1 and one participant in Group 3
** Daytime sleepiness score was not available for one participant in Group 2
[a] ANOVA test of group differences
[b] Kruskal-Wallis test of group differences

component.

We used ANOVA on each temporal interval to test the significance of the main effect of group on the log-transformed regional mean power values. Statistical significance was considered at $p < 0.05$ adjusted to control the false discovery rate (FDR), unless otherwise mentioned.

3. Results

3.1. Sample characteristics: demographic and neuropsychological data

No significant group differences were present for *age*, *education* and *time elapsed from last injury* (Table 2). Similarly, no group differences were observed for scores of *general anxiety*, *major depression*, *PTSD*, *insomnia severity* and *daytime sleepiness*. The RBMT-3 subtests with the most important contribution to the group differences in GMI were the *Story Recall* (immediate and delayed), *Picture Recognition* (delayed) and *Face Recognition* (delayed), *Names*, *Novel Task* (delayed) and *Belongings* (Table 3), showing that group differences in GMI are due to differences in both verbal and non-verbal memory performance. Two of the test components, *i.e. Messages* - immediate and delayed, showed ceiling effects for Groups 2 and 3. The self-reported symptoms of word finding difficulties correlated with the RBMT-3 GMI scores across the study participants (Kendall tau-b = −3.9, $p < 0.001$). This shows that patients with mTBI and evidence of cognitive (memory) impairment were more likely to report experiencing word finding difficulties in conversation.

3.2. Radiologic findings

Small foci of T2 hyper-intensities in the white matter were identified in the MRI scans of 12 subjects from Group 1 (67%), 7 subjects from Group 2 (39%), and 9 subjects from Group 3 (43%). Specifically, T2-hyper-intensities were identified in the frontal lobes (Group 1: 56% on the left and 50% on the right; Group 2: 28% on the left and 22% on the right; Group 3: 29% on the left and 29% on the right); temporal lobes (Group 1: 11% on the left and 17% on the right; Group 2: 6% on the right; Group 3: 10% on the left); and parietal lobes (Group 1: 11% on the left and 17% on the right; Group 2: 22% on the left and 11% on the right; Group 3: 19% on the left and 14% on the right). Areas of white matter gliosis were present in 28% of subjects from Group 1, 11% of subjects from Group 2, and 14% of subjects from Group 3. Microhemorrhages were identified in the right frontal lobe for one subject from Group1. Barnard's two-sided tests of proportions showed a trend for increased proportion of patients with brain parenchymal abnormalities localized in the left and right frontal lobes for Group 1 relative to Groups 2 and 3 (p-values between 0.049 and 0.1), and no significant group differences for the proportion of subjects with brain parenchymal abnormalities localized in the temporal and parietal lobes.

3.3. Neuromagnetic evoked responses

Subjects from all three groups named correctly the objects in a high proportion of trials: 99.4% in Group1, 99.2% in Group 2, and 99.6% in Group3 (up to two incorrect responses were noted for every participant).

Table 3
Performance on the RBMT-3 test: descriptive statistics (mean ± SD) for the scaled scores from each subtest and results of Kruskal-Wallis tests for significance of the group differences.

RBMT-3 subtest	Group 1 (n = 18)	Group 2 (n = 18)	Group 3 (n = 21)	Test statistics	p
Names	6.8 ± 2.3	8.9 ± 2.0	9.7 ± 2.1	$H = 13.7$	$p = 0.001$
Belongings	8.3 ± 2.2	9.3 ± 3.0	11.0 ± 1.8	$H = 11.3$	$p = 0.0035$
Appointments	9.2 ± 2.2	9.1 ± 2.4	10.4 ± 1.6	$H = 3.6$	$p = 0.17$
Picture Recognition - delayed	5.4 ± 2.7	9.4 ± 2.3	10.0 ± 2.0	$H = 20.2$	$p < 0.0001$
Story Recall - immediate	6.8 ± 2.5	8.4 ± 2.6	11.1 ± 2.9	$H = 18.5$	$p < 0.0001$
Story Recall - delayed	6.3 ± 2.2	8.4 ± 2.2	11.3 ± 2.4	$H = 25.9$	$p < 0.0001$
Face Recognition - delayed	8.2 ± 3.8	11.5 ± 2.8	12.1 ± 2.0	$H = 12.2$	$p = 0.0022$
Route Recall - immediate	8.4 ± 2.2	8.7 ± 2.2	9.9 ± 1.9	$H = 4.9$	$p = 0.08$
Route Recall - delayed	7.7 ± 2.9	7.8 ± 2.2	9.5 ± 2.0	$H = 6.4$	$p = 0.04$
Messages - immediate	9.2 ± 2.3	11.0 ± 0.0	11.0 ± 0.0	$H = 5.5$	$p = 0.06$
Messages - delayed	9.9 ± 2.1	11.0 ± 0.0	11.0 ± 0.0	$H = 1.8$	$p = 0.41$
Orientation and Date	9.7 ± 2.5	9.9 ± 1.9	10.5 ± 1.6	$H = 1.1$	$p = 0.58$
Novel Task - immediate	7.8 ± 1.7	8.9 ± 2.6	9.6 ± 2.0	$H = 6.9$	$p = 0.03$
Novel Task - delayed	8.6 ± 2.4	10.7 ± 1.8	11.1 ± 0.4	$H = 11.6$	$p = 0.003$

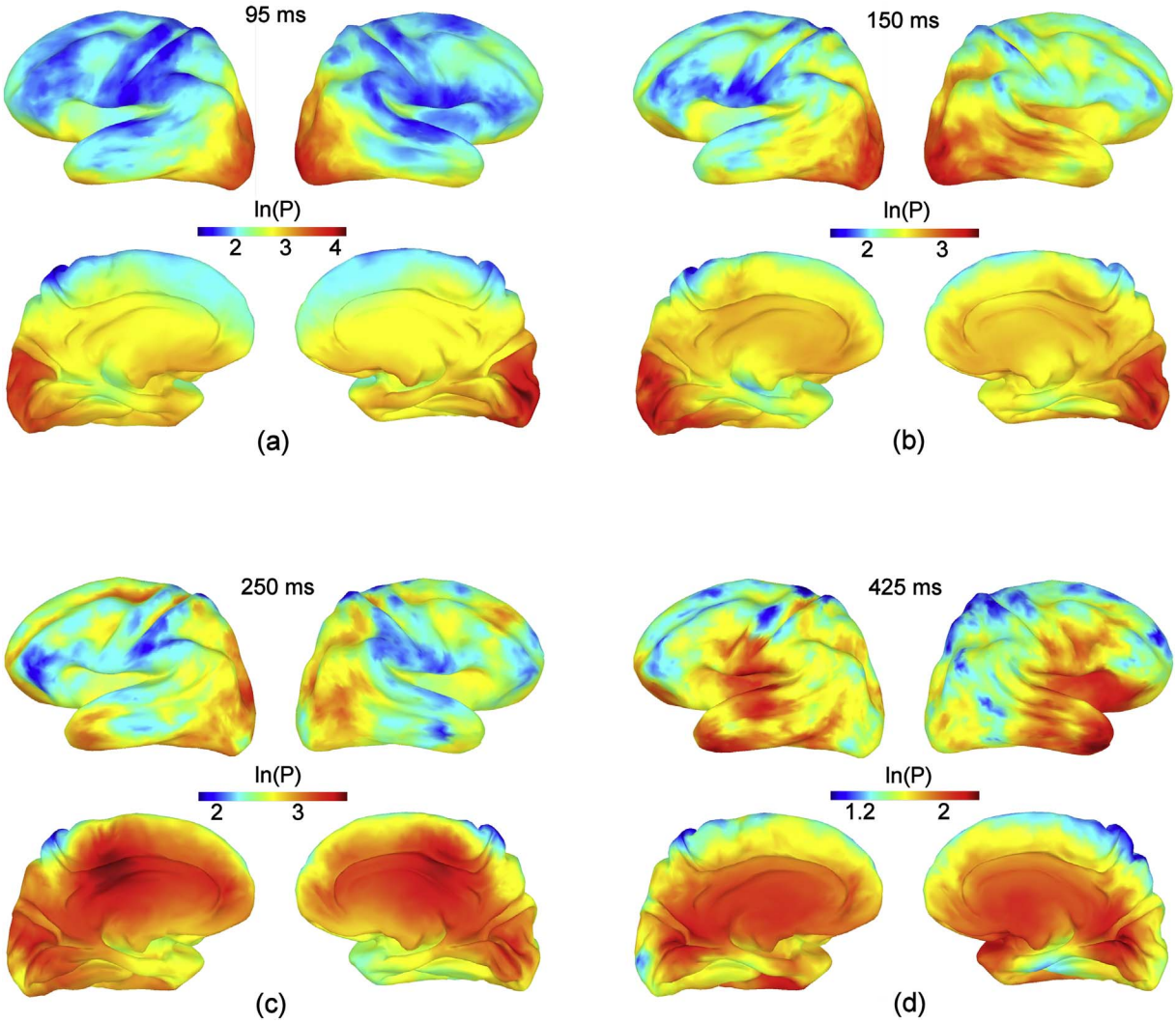

Fig. 1. The normalized power of the reconstructed sources, averaged across all participants, is shown at four latencies (panels a–d) of the evoked response (latencies were selected in the middle of each temporal interval considered for statistical analysis). The log-transformed normalized power is illustrated in lateral (upper row) and medial (lower row) views of the two hemispheres for each latency. Colormaps are scaled to cover the range between the minimum and maximum values across the source space at each latency. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The power of the estimated sources, averaged across participants, is exemplified in Fig. 1 at four latencies selected in the middle of each temporal interval considered for statistical analysis. The maps show a dominant response in bilateral occipital visual areas at early latencies (Fig. 1, a), which progresses with time to bilateral occipitotemporal cortex (Fig. 1, b). The activity in temporal and frontal areas becomes more evident during the middle and late intervals (Fig.1, b, c, and d), when the sources amplitude in occipital areas becomes progressively lower. This leads to a shift of the relative maximum of activity in the posterior-anterior direction with time, which has also been reported by other MEG studies (Liljeström et al., 2009; Miozzo et al., 2015).

3.3.1. Early temporal interval (60 ms to 130 ms)

On the early temporal interval, dominated by activity in bilateral occipital visual areas, no group differences were significant after adjusting *p*-values for multiple comparisons.

3.3.2. First middle temporal interval (100 ms to 200 ms)

On the middle temporal interval, significant group differences at $p < 0.05$ adjusted to control the FDR were observed over an extended network comprising mainly regions of the left hemisphere (Figs. 2 and 3). They include the anterior part of the *left fusiform gyrus* ($F = 5.51$, $p = 0.007$), *left entorhinal cortex* ($F = 6.41$, $p = 0.003$), and *left parahippocampal cortex* ($F = 6.23$, $p = 0.004$); the *left supramarginal gyrus* ($F = 6.94$, $p = 0.002$) and posterior part of the *left superior temporal gyrus* ($F = 6.08$, $p = 0.004$); the *left inferior frontal gyrus*, *i.e. pars opercularis* ($F = 8.04$, $p = 0.0009$) and *pars triangularis* ($F = 5.95$, $p = 0.004$), and the *left rostral middle frontal gyrus* ($F = 7.46$, $p = 0.001$). Differences were also seen in bilateral regions of the *cingulate cortex* (*left isthmus cingulate*: $F = 5.09$, $p = 0.009$, *right isthmus cingulate*: $F = 5.19$, $p = 0.008$; *left posterior cingulate*: $F = 7.49$, $p = 0.001$; *right posterior cingulate*: $F = 6.73$, $p = 0.002$; *left caudal anterior cingulate*: $F = 5.11$, $p = 0.009$), the *paracentral lobule* (*left*: $F = 6.19$, $p = 0.004$, *right*: $F = 5.35$, $p = 0.008$), and in the *right fusiform gyrus* ($F = 6.03$, $p = 0.004$). Figs. 2 and 3 illustrate the activation curves (group averages) for brain areas showing significant group differences over this temporal interval. These activation curves consistently show lower amplitude of the evoked responses for Group 1 compared to Groups 2 and 3 over this temporal interval, with the exemption of the right fusiform area where activations for Groups 1 and 2 are similar but reduced relative to Group 3.

3.3.3. Second middle temporal interval (200 ms to 300 ms)

Group average activation curves (Figs. 2 and 3) showed a robust response component that peaks during the temporal interval between 200 and 300 ms. No group differences in normalized signal power were

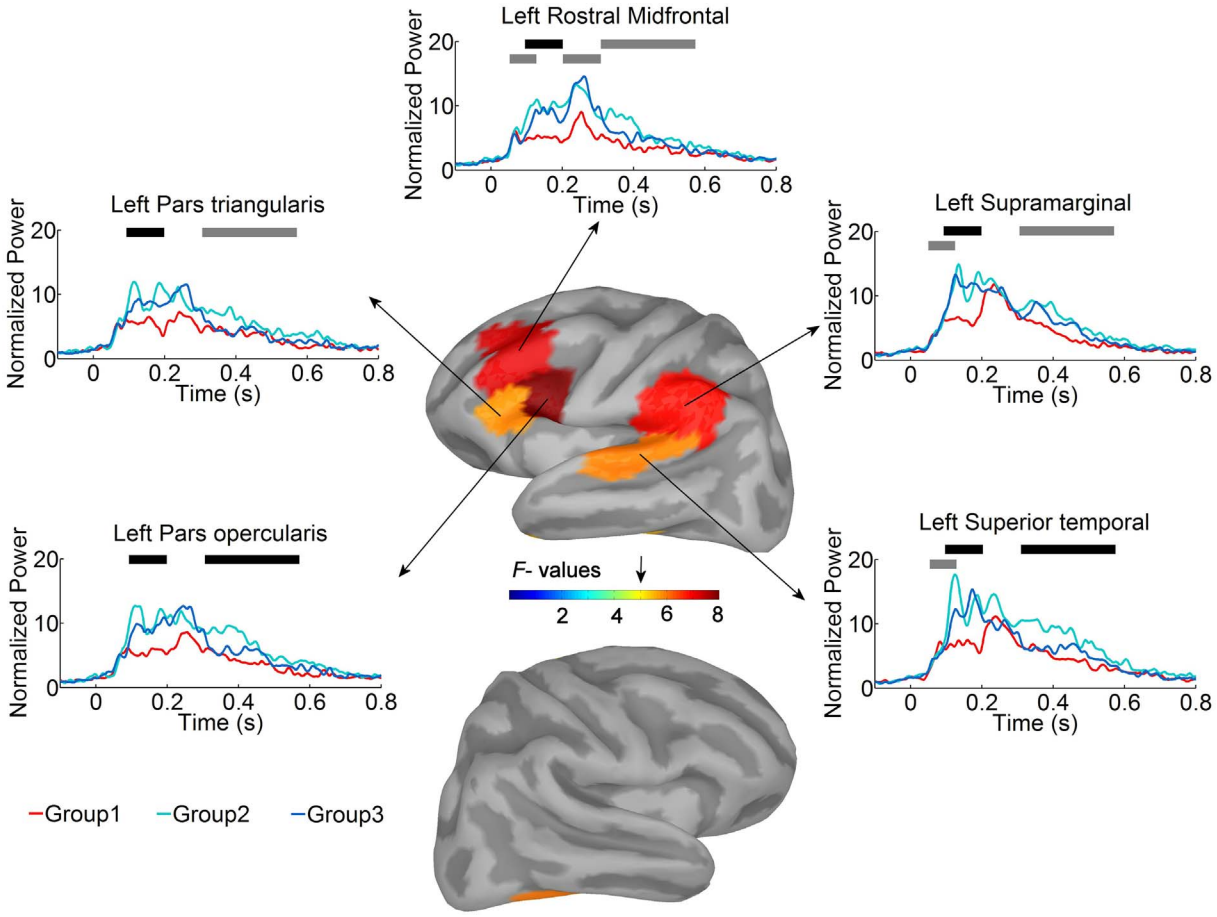

Fig. 2. Lateral brain regions with significant group differences between 100 ms and 200 ms after stimulus onset. Statistical maps (*F*-values) are shown in lateral views of the two hemispheres. The arrow shown with the colorbar marks the threshold *F*-value corresponding to $p = 0.05$ adjusted to control the FDR. In panels showing the group mean activation curves, horizontal bars are used to mark this and other temporal intervals with significant group differences (*black color*: significance at $p < 0.05$ adjusted to control the FDR; *gray color*: significance at $p < 0.05$ uncorrected). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

significant on this temporal interval when *p*-values were adjusted for multiple comparisons.

3.3.4. Late temporal interval (300 ms to 550 ms)

Significant group differences re-emerged on the late temporal interval in the posterior part of the *left superior temporal gyrus* ($F = 7.87$, $p = 0.001$), *left transverse temporal area* ($F = 8.50$, $p = 0.0006$), *left parsopercularis* ($F = 6.97$, $p = 0.002$) and the posterior part of the *left superior frontal gyrus* ($F = 6.92$, $p = 0.002$).

3.4. Follow-up analyses

Although no significant group differences were observed for PCL-M, PHQ-9 and GAD scores, the trend of decreased mean group scores from Group 1 to Group 2 and 3 prompted a follow-up correlation analysis that showed a significant correlation between GMI and PCL-M scores (Kendall *tau-b* $= -0.2$, $p = 0.028$), but no significant correlations between GMI and PHQ-9 (Kendall *tau-b* $= -0.9$, $p = 0.37$) or GAD-7 scores (Kendall *tau-b* $= -0.14$, $p = 0.15$). Furthermore, no significant correlations were found between any of these scores and the regional brain activity on any temporal interval. Thus, although a moderate correlation was present between PTSD and cognitive performance scores, the level of regional brain activity evoked in a word production task was not associated with the PTSD symptoms severity.

Similarly, no correlations were found between insomnia severity and daytime sleepiness scores and cognitive performance scores from RBMT-3 or regional brain activity levels.

Picture naming involves both visual and language processing and the brain regions showing significant group effects may in principle be involved in either one or both of these processing domains. In a second follow-up analysis, we sought to investigate the correlation between the neuromagnetic measures and two composite scores derived from RBMT-3 subtests that assess primarily visual and verbal processing, respectively. The first composite score was derived as the sum of the two scores obtained in the *Picture Recognition* and *Face Recognition* tests and used to characterize visual processing ability, whereas the second composite score characterizing verbal processing ability was determined as the sum of the scores obtained in the two *Story Recall* tests (immediate and delayed recall of a story). The correlation between these two composite scores was not significant (Pearson $r = 0.21$, $p = 0.121$). The Pearson correlation was computed to determine if a higher signal power in the brain regions showing significant group effects was associated with better behavioral performance in visual or verbal processing domains, as characterized by each of these two composite scores. The correlation analysis was conducted for each temporal interval using a significance threshold adjusted to control the FDR (adjusted $p < 0.05$, one tailed). On the temporal interval between 100 and 200 ms, *all* regions showing significant group differences on this interval showed significant positive correlations with the composite score characterizing *verbal* processing. On the same temporal interval, the signal power in the *left entorhinal* ($r = 0.33$, $p = 0.007$) and *left fusiform* ($r = 0.31$, $p = 0.009$) regions showed moderate correlations with the composite score characterizing *visual* processing, but these were not significant after adjusting for multiple comparisons. No significant correlations were observed on any other temporal interval.

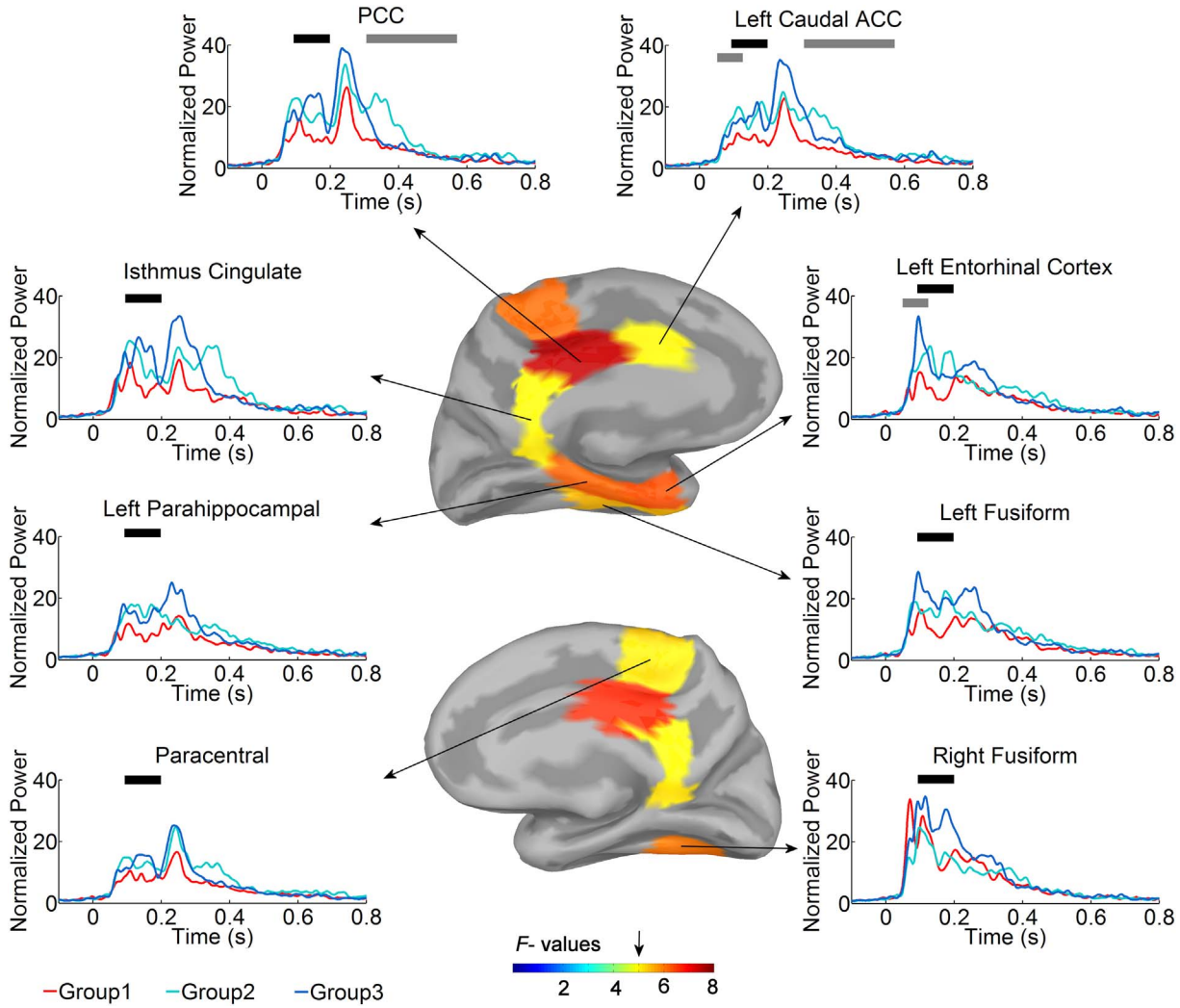

Fig. 3. Medial and inferior temporal brain regions showing group differences between 100 ms and 200 ms after stimulus onset. Statistical maps are shown in medial views of the two hemispheres. The arrow shown with the colorbar marks the threshold *F*-value corresponding to $p = 0.05$ adjusted to control the FDR. Mean activation curves from two regions of the cingulate gyrus (*posterior cingulate* and *cingulate isthmus*) and from the *paracentral lobule* were averaged between analogous areas of the two hemispheres and shown in one panel each (due to the similarity of the signals estimated in proximal medial areas of the two hemispheres). For each panel, horizontal bars are used to mark this and other temporal intervals with significant group differences (*black color*: significance at $p < 0.05$ adjusted to control the FDR; *gray color*: significance at $p < 0.05$ uncorrected). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

4. Discussion

Our study demonstrates a widespread reduction in the amplitude of the event-related activation of dominant hemisphere association areas during a confrontational naming task in mTBI patients with lower measures of cognitive performance. This reduced activity was prominent in brain regions known to support lexical retrieval and may be indicative of an increased predisposition to experience word finding difficulties when engaged in conversation, as indicated by the subjective reports of these patients. Our findings also indicate that confrontational naming results in *early* activation of *distributed* brain networks involved in visual and linguistic processing. To the degree that the lower cognitive performance is due to the sustained mTBI(s), as indicated by the subjective reports of the patients, we regard these findings as an index of a diffuse pathophysiological process, which may impact a wide array of cognitive processes. In patients with a history of mTBI, several mechanisms may contribute to these outcomes, including alterations in white matter integrity and/or disruptions of the neurotransmitter systems, which are due to head trauma and affect the neurotransmission within these distributed networks. The alteration we demonstrated in early cortical activation in patients with lower cognitive performance may also reflect the effects of developmental and genetic mechanisms that influence cognitive function, which may or may not be exacerbated by head trauma.

The picture naming task elicits cortical activity in areas of the ventral visual processing stream, which include regions of the fusiform gyri that play a role in the lead-in process of object recognition. The timing of the regional group differences indicates that activity rapidly spreads (before 200 ms) to regions of the left medial temporal lobe, to the posterior part of the left superior temporal gyrus and supramarginal gyrus, as well as to the left prefrontal regions. The early response components in these areas of the dominant hemisphere do not appear to arise from spatial leakage of the early activity in occipital visual cortex (possibly resulting from limitations of the source reconstruction methodology), since group differences are observed only over the left hemisphere, whereas the early visual response is distributed across analog regions of the two hemispheres. Thus, we consider that the early activity in these areas, particularly in regions of the inferior frontal gyrus that have been traditionally associated with processing of late (phonological-articulatory) stages of spoken word production, may be indicative of a *fast spreading activity* within a distributed frontal-temporal-parietal network of the left hemisphere. This finding supports and extends the observations from another recent MEG study using picture naming, which showed that multiple processes (semantic and lexical-

phonological) appear to be carried out in parallel in distributed brain networks (the *simultaneous ignition* hypothesis, Miozzo et al., 2015) within 200 ms after stimulus onset (before completion of lemma selection), providing support to connectionist models of lexical access. Together with the observations of that study, our findings may help refine the more traditional serial models discussed in earlier MEG studies (Salmelin et al., 1994; Levelt et al., 1998; Indefrey, 2011), which were based on observations of a progression of the relative maximum of activity from posterior temporal and inferior parietal regions to frontal regions. Within this framework of an early distributed activation, the low signal amplitude in patients with low cognitive scores may be a signature of weak afferent input due to alterations in distant connectivity or local recurrent collateral connectivity across areas of this extended network.

The group with lower cognitive performance demonstrates a relatively low activation level within the first 200 ms after stimulus onset, at which point there is an abrupt increase in activation, lasting approximately 100 ms, which is more prominent in the left superior temporal and supramarginal gyri, and in regions of the cingulate cortex. According to previous studies, this temporal interval corresponds to the completion of lemma selection (Levelt et al., 1998). An interesting explanation of this finding could be that this group experiences a relative breakdown in the parallel processing, with regions involved primarily in lemma selection activated discretely in the time course of lexical access compared to those patients with better cognitive performance. The activation level at 200–300 ms, producing a distinct response component in this group, may be indicative of preserved lemma selection, whereas a subsequent decrease in activation after 300 ms may reflect a relative deficiency in phonological and articulatory encoding which only manifests occasionally during spontaneous conversational speech as a subjective impairment in lexical access. Our current study in mTBI patients likely facilitated the finding of a significant difference in activation level among the three groups and the presence of a discrete response component between 200 and 300 ms in the lower performing group, as our sample of patients displayed a leftward shift from the normal distribution of memory scores, *i.e.* toward the below-average range, which is likely a result of some alterations in cognitive function due to the TBI. Such a relationship between low cognitive performance and a low MEG activation may be present in healthy individuals as well, and may be due to individual genetic and developmental differences in cortical architecture or neuromodulatory influence on neuronal signaling. This may in part account for individual differences in ability of lexical processing.

Despite considerable past research, uncertainty still exists about mechanisms and brain areas involved in carrying out the different stages of lexical retrieval. The decomposition of the lexical retrieval process into stages as proposed by some psycholinguistic models (Levelt et al., 1998; Levelt et al., 1999) does not necessarily imply that each stage is fully executed before the initiation of the next stage or that each stage is exclusively carried out in a discrete area of the brain. In general, fast inputs representing partial information from one processing stage may begin to feed into other areas that are mainly responsible to carry out later stages of processing before the previous stage is complete. This enables a feedback from those areas to the ones responsible for carrying out earlier stages, as proposed by some models of visual information processing (Desimone and Duncan, 1995). It is possible that the simultaneously ignited local (regional) competition between neuronal representations at some levels of lexical retrieval (*e.g.* semantic, phonological) is most often resolved in a sequential manner across regions of this distributed network. Once competition is resolved in one region, it may help further constrain local competition that corresponds to subsequent stages primarily carried out in other brain regions. Such a refined model of coupled dynamical systems involving interactions (concurrent activations) within spatially extended brain networks may offer not only a plausible alternative to the more traditional view of serial local processing, but also a basis for reconciliation between the proposed serial nature of the psycholinguistic multi-stage models and the parallel processing proposed by connectionist models. They have received support, for example, from studies using intracranial recordings (Sahin et al., 2009), which showed that Broca's area is active during linguistic processes prior to the articulatory stage, possibly influencing the encoding of morphological and phonological features of lexical items that takes place primarily in posterior cortices. Prefrontal regions could receive early inputs from both visual (Bar, 2003) and language processing areas and influence processing in those areas during the initial stages of confrontational naming, including the extraction of semantic features from visual objects as the visual percept is being continuously refined. The group effect seen in fusiform areas may indicate a weaker interaction between the prefrontal cortex and high order visual areas during object recognition/semantic processing in patients with cognitive deficits. Since chromatic objects were used as stimuli, it is also possible that a low response in fusiform areas may indicate a deficit in processing color. However, the service members in our study did not have documented color vision deficiencies.

Some regions showing group differences in our study are also known for playing a role in memory processes including encoding, consolidation and retrieval. Among them are the fusiform gyrus, left inferior frontal gyrus, and parahippocampal gyrus (Weis et al., 2004), the entorhinal cortex (Higuchi and Miyashita, 1996), and the anterior cingulate cortex (Frankland et al., 2004; Einarsson and Nader, 2012). Stimulation using subdural electrodes during object naming in patients with temporal lobe epilepsy (Mikuni et al., 2006) has demonstrated that two of these regions, *i.e.* the fusiform and parahippocampal gyri of the dominant hemisphere, belong to a *basal temporal language area*, which plays a role in both object naming and verbal memory. Also, lesions of the posterior cingulate gyrus were shown to be associated with visual and verbal memory deficits (Yasuda et al., 1997; Kim et al., 2007). Thus, injuries affecting the function of these regions may be reflected in the lower evoked activation observed during cued lexical retrieval in patients with residual cognitive deficits and may explain the relationship between the lower performance in standardized tests of declarative memory and the increased predisposition to experience word finding difficulties in normal conversation.

A set of regions showing significant effects in our study (*i.e.* the fusiform and parahippocampal gyri, IFG, dorsomedial prefrontal cortex, posterior inferior parietal lobe and the posterior cingulate) are also known for playing a role in semantic and conceptual processing, which involves accessing neuronal representations of acquired knowledge and using it in reasoning, planning or problem solving (Binder et al., 2009). It is conceivable that physiological dysfunction within this network may contribute to difficulties with planning the message in conversation, which are sometimes reported by patients as an integral part of their word finding difficulties. Areas of the cingulate cortex have also been shown to play a role in self-monitoring of speech (Christoffels et al., 2007; Möller et al., 2007). The activity in some of these brain regions has not been reported by previous MEG studies using picture naming paradigms. It is possible that the existing relationship between brain activity and variables characterizing the participants' cognitive performance enabled us to observe the early recruitment of a higher number of brain regions than those reported in other MEG studies using picture naming tasks; however, it remains unclear if they all play an *essential* role in the task.

Additional insight into the relationship between the reduced activation during naming and deficits in lexical access comes from the field of dynamical neuroscience, in which activated neuronal representations such as the lemma or phonological word form are conceived as attractor states (Hopfield, 1982; McKenna et al., 1994; Wennekers et al., 2006). In neurophysiological terms, the attractor state corresponds to a depolarization of the resting membrane potential in a subpopulation of neurons and an increased rate of action potential firing (Cossart et al., 2003). This increased activity facilitates the initiation of a burst of oscillations in the beta-gamma frequency range forming a synchronous

pattern that persists for a series of cycles, *i.e.* as long as the attractor state is stable (Freeman and Rogers, 2002; Freeman, 2004; Lundqvist et al., 2016). External or internally generated cues can lead cortical activity to settle into appropriate attractor states that are the neural instantiations of words or memories. If the cortical activity settles into a particular attractor from a large region of state space, that attractor has a large basin of attraction, such as in the case of a word we use habitually. The stability of an attractor depends on the level of synchrony and determines the resistance to perturbation out of the oscillatory state by other inputs/cues. A particular density of recurrent collateral connections among cortical networks appears essential for the facilitation of entry into new attractor states and the transition from one attractor to the next during normal cognition, by allowing the network to exceed a threshold level of background activity necessary for the expression of computationally powerful properties (Eeckman and Freeman, 1991; Goudar and Buonomano, 2014). A decrease in recurrent connectivity due to a TBI and/or pre-existing genetic/developmental causes may be responsible for the observed reduction in MEG activity during naming in patients with low cognitive function, and may be akin to a decrease in the energy available to allow the cortical activity to "escape" from a stable attractor. For example, during lexical retrieval an individual may become "stuck" on a related, more frequent but incorrect word with a large basin of attraction, rendering him unable to access the desired word. Without an appropriate level of activation during cognition, the cortical network may not be able to easily exit an inappropriate but stable attractor. Similarly, a high level of cortical activation may be necessary to follow a rapid trajectory among neuronal representations of words to be used in a single clause or sentence. Hence, a loss of recurrent collateral connectivity could lead to slower attractor transitions and to difficulties with word retrieval during sentence production. A reduced rate of transitions among attractor states has been suggested as a characteristic of brain dysfunction in TBI (Hellyer et al., 2015). Reductions in cortical activity may be observed in resting state or during task performance, may be broadband or manifested in specific frequency ranges, and may predispose to other common post-concussive symptoms in mTBI (Popescu et al., 2016).

A related issue concerns the phenomenon of homeostatic plasticity. White matter pathology (axonal injury) leads to a decrease in overall afferent excitatory synaptic strength to cortical pyramidal neurons. Due to inherent mechanisms of homeostatic plasticity, which maintains a stable level of excitatory afference to neurons at multiple time scales, an upscaling of remaining excitatory synapses may occur in TBI in an attempt to reinstate an overall level of excitatory synaptic strength to a premorbid level (Frohlich et al., 2008; Butz et al., 2014). This happens in a generalized, nonspecific manner, thereby undermining the acquired (learned) pattern of connectivity within cortical networks and jeopardizing the fidelity of activation of lexical-semantic representations. Such plasticity will result in an alteration in the attractor itself (the point or trajectory in state space), the size of the basin of attraction for individual attractors (making them potentially less accessible), or perhaps even the elimination of some attractors from the landscape entirely. In very mild injury, homeostatic plasticity is likely an effective compensatory mechanism and can restore normal levels of neural activity. In severe injury, it often results in pathological hypersynchrony leading to epileptiform activity with little or no restoration of normal function (Frohlich et al., 2008). In cases between these extremes, a derangement of stored representations may be a necessary cost in order to return a percentage of cortical neurons to a functional range of excitatory input, though overall activation levels may remain low, as we have observed in this study.

The function of recurrent cortical networks in generating appropriate intrinsic patterns of activity can be influenced by ascending neurotransmitter systems. For example, presynaptic effects of acetylcholine (Ach) on cortical neurons comprising attractor cell assemblies may strengthen or weaken the tendency of the cortical networks to enter, remain stabilized in and exit specific attractor states due to an attentional effect on local cortical function (Kanamaru et al., 2013). The findings of a pair of *in vitro* and *in silico* studies indicate that top-down control enhances the expression of stimulus generated transient local gamma frequency activity (attractor states) in supragranular layers, but only in the presence of cholinergic modulation, increasing neuronal activation (Roopun et al., 2010; Lee et al., 2015). Additionally, Ach exhibits direct effects on the amplitude of evoked/event related responses, generally facilitating an increase in amplitude at physiological levels, especially when baseline amplitudes are relatively low (Wang et al., 1999; Knot et al., 2014; Foster and Deadwyler, 1992). Cholinergic systems can be damaged as a result of TBI (Shin and Dixon, 2015) and the premorbid/developmental or post-concussive status of Ach system function could have a substantial impact on the overall magnitude of early task-related activation of neocortex as well as on the appropriate activation and suppression of specific linguistic representations during lexical access. In support of such a mechanism, cholinergic therapy has proven efficacious for the treatment of naming and other higher level language processing deficits in patients with focal lesions of the dominant hemisphere which may have mildly altered the structure of the attractor landscape (Tanaka et al., 1997; Hughes et al., 2000; Berthier et al., 2011). The case described in Hughes et al. of a patient with a small lacunar infarct involving the left thalamus may be particularly informative as such a lesion was hypothesized to result in a modest decrease in dominant hemisphere activation during language production, similar to what we have observed in our mTBI patients with reduced cognitive performance, leading to mild aphasic symptoms amenable to restoration of function with cholinergic therapy.

In summary, the lower level of activity during naming observed in mTBI patients with lower cognitive performance may reflect a reduced effectiveness of neuronal signaling, which may be due to a combination of the pathological effects of the TBI itself and preexisting conditions including genetic influences. This may undermine parallel processing during lexical access, rendering it less efficient and more prone to errors. Alterations affecting language processing networks may place a relatively greater demand on prefrontal or other higher-order association cortices that provide top-down control which could compensate for a deficit in a more automatic lexical access process. However, injuries involving the frontal lobe may result in a reduction in effectiveness of such top-down executive function necessary to assist the lexical access process and to allow for rapid error correction. In our study, this receives some support from the higher proportion of patients in Group 1 with brain parenchymal abnormalities localized in the frontal lobes. The loss of recurrent collateral connectivity may also increase the risk for the neuronal activity to get "stuck" in inappropriate attractors or representations of lemmas or phonologically encoded words, especially during propositional language production, and produce a subjective state of dysnomia. It is possible that the reduced activation seen in the group with lower cognitive performance could also be present in populations other than the mTBI population as long as the underlying pathology reduces the effectiveness of recurrent collateral connectivity necessary for optimal network function. Healthy individuals may exhibit a level of activation in cortical networks that is within a desirable range of dynamic function such that there is a safety margin to withstand some incidental loss of recurrent connectivity. The level of activation for most patients with mTBI may remain above a minimum threshold that ensures normal function. Despite the low activation during naming in language association cortex, even the patients with low cognitive performance were likely functioning at or above such a threshold and therefore only manifest occasional subjective problems with lexical access in conversation based on fluctuations in the activation level. Future studies can investigate if findings of low early activation during naming generalize to other cognitive domains, and if a reduced activation is present and more profound in patients with moderate and severe TBI, such that this threshold is frequently not met during every day cognition. If this is the case, then the magnitude of such a reduction could serve as a quantitative marker of the underlying

pathophysiology of cognitive impairment and may represent an important physiological tool to assess the efficacy of future therapies designed to increase recurrent connectivity. In terms of the specific symptom of anomia, successful treatment has recently been correlated with measures of recurrent cortical connectivity within and between relevant brain regions engaged in linguistic processing (Bonilha et al., 2016).

One limitation of the study arises from its cross-sectional design. Although the effects we observed can be indicative of abnormal brain activity due to mTBI-related alterations in the function of an extended left hemisphere network, we cannot rule out the possible contribution of other pre-existing conditions unrelated to the TBI. Future studies can investigate the possible association between the low cognitive performance and the signal amplitude recorded during confrontational naming in healthy individuals without a history of TBI. This will help to elucidate the extent to which the observed alteration in physiological signals is due to the traumatic brain injury. Like other functional neuroimaging studies, our study cannot determine which of the regions that were identified as being activated by the picture naming task are *essential* for performing the task. As observed in previous studies (*e.g.* Binder et al., 2009), all goal directed cognitive tasks require a minimum set of domain-general processes that include *e.g.* the maintenance of the task goal and procedures in working memory, maintenance of (selective) attention, or error monitoring. It is therefore possible that the weaker evoked activity observed for participants with cognitive deficits in some brain regions may also be a signature of impairment related to such domain-general processes.

Disclaimers

The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or U.S. Government.

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The study protocol was approved by the Walter Reed National Military Medical Center and Naval Medical Research Center Institutional Review Boards in compliance with all applicable Federal regulations governing the protection of human subjects.

Dr. John D. Hughes is a military service member. This work was prepared as part of his official duties. Title 17 U.S.C.

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