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ORIGINAL ARTICLE

Marked Increases in Resting-State MEG Gamma-Band Activity in Combat-Related Mild Traumatic Brain Injury

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Abstract

Combat-related mild traumatic brain injury (mTBI) is a leading cause of sustained impairments in military service members and veterans. Recent animal studies show that GABA-ergic parvalbumin-positive interneurons are susceptible to brain injury, with damage causing abnormal increases in spontaneous gamma-band (30–80 Hz) activity. We investigated spontaneous gamma activity in individuals with mTBI using high-resolution resting-state magnetoencephalography source imaging. Participants included 25 symptomatic individuals with chronic combat-related blast mTBI and 35 healthy controls with similar combat experiences. Compared with controls, gamma activity was markedly elevated in mTBI participants throughout frontal, parietal, temporal, and occipital cortices, whereas gamma activity was reduced in ventromedial prefrontal cortex. Across groups, greater gamma activity correlated with poorer performances on tests of executive functioning and visuospatial processing. Many neurocognitive associations, however, were partly driven by the higher incidence of mTBI participants with both higher gamma activity and poorer cognition, suggesting that expansive upregulation of gamma has negative repercussions for cognition particularly in mTBI. This is the first human study to demonstrate abnormal resting-state gamma activity in mTBI. These novel findings suggest the possibility that abnormal

gamma activities may be a proxy for GABA-ergic interneuron dysfunction and a promising neuroimaging marker of insidious mild head injuries.

Key words: cognition, frontoparietal network, gamma activity, magnetoencephalography, mild traumatic brain injury

Introduction

Combat-related traumatic brain injury (TBI), mainly due to blast exposure to improvised explosive devices, is a leading cause of sustained physical, cognitive, emotional, and behavioral deficits in military service members and veterans. Of TBIs in which blast was the main cause in active-duty military personnel and veterans wounded in combat in Iraq and Afghanistan, the majority (89%) were mild TBIs (mTBIs) (MacGregor et al. 2011). However, the pathophysiology of blast mTBI is not completely understood, and controversy remains over the long-term effects of mTBI. In this regard, a major challenge is identifying and assessing neuropathological, cellular, cognitive, emotional, behavioral, and neurological consequences of blast TBI (DePalma and Hoffman 2018). Although it remains debatable whether blast-related head injuries are a separate subtype of TBI, different from blunt trauma TBI (Fischer et al. 2014; Young et al. 2015b; DePalma and Hoffman 2018), there is consensus that blast TBI has some unique injury mechanisms (Young et al. 2015a). Optimal rehabilitation treatments for blast mTBIs are also unknown, in part due to insufficient information about the loci and mechanisms of the injury. Conventional neuroimaging techniques such as magnetic resonance imaging (MRI) and computed tomography are typically insensitive to physiological alterations caused by mild and some moderate TBIs (Johnston et al. 2001; Bigler and Orrison 2004; Kirkwood et al. 2006), even in individuals with persistent post-concussive symptoms and cognitive deficits. This highlights the need for techniques that are sensitive to the effects of blast exposure on the brain and therapeutic interventions aimed at improving functional capacity.

Diffuse axonal injury plays a major role in mTBI, producing an imbalance in excitatory/inhibitory neural activity. Traditionally, it is assumed that white matter tracts are primarily vulnerable to diffuse axonal injury, which produces cortical network disconnection [see reviews in Hannawi and Stevens (2016) and Asken et al. (2018)]. Yet even sophisticated diffusion-based MRI techniques for detecting white matter abnormalities in mTBI are not sufficiently sensitive for meaningful clinical applications (Douglas et al. 2015; Asken et al. 2018). However, recent animal studies challenge this view by showing that gray matter is also vulnerable to diffuse axonal injury, which damages GABA-ergic inhibitory interneurons, specifically near the soma of the parvalbumin-positive (PV+) interneurons [see references in Vascak et al. (2018)], or degrades the perineuronal net, which is a specialized extracellular structure enwrapping cortical PV+ inhibitory interneurons (Hsieh et al. 2017). Fast-spiking PV+ inhibitory interneurons are the most common type of GABA-ergic cells that express the calcium-binding protein PV+ and receive N-methyl-D-aspartate (NMDA)-dependent excitatory input from pyramidal cells (Jones and Bühl 1993; Carlén et al. 2012). Fast-spiking PV+ interneurons regulate the activity of neural networks through GABA-ergic inhibition of local excitatory neurons and generate gamma oscillations (30–80 Hz) through synchronous activity (Traub et al. 1996; Cardin et al. 2009; Fries 2009; Sohal et al. 2009; Carlén et al. 2012). Animal studies demonstrate that dysfunction or injury to PV+ interneurons causes disinhibition in the neural network by 1) directly eliminating synchronized gamma-band (30–80 Hz) signals that are normally evoked by stimuli during the post-stimulus interval (Carlén et al. 2012; Cho et al. 2015; Kalemaki et al. 2018) and 2) upregulating spontaneous gamma (and maybe beta) activity due to absent inhibition of excitatory neurons (Korotkova et al. 2010; Carlén et al. 2012; Del Pino et al. 2013; Cho et al. 2015; Kalemaki et al. 2018).

Synchronized gamma oscillatory activity occurs throughout the cortex, in support of information processing during cognition (Bartos et al. 2007). In humans with TBI, synchronized gamma signals are abnormal during evoked electroencephalography (EEG) or magnetoencephalography (MEG) recordings. We found that during working memory, evoked gamma-band MEG responses in individuals with mTBI were reduced in posterior dorsolateral prefrontal cortex, a component of the working memory network, but increased in the frontal pole and anterior dorsolateral prefrontal cortex (Huang et al. 2018). During working memory retention, gamma-band functional connectivity of posterior regions was aberrantly increased in individuals with TBI or major depressive disorder following TBI (Bailey et al. 2017). Abnormally delayed gamma-band (40 Hz) EEG latency in TBI patients was also observed during an auditory oddball task (Slewa-Younan et al. 2002). Interestingly, reduced synchronization of gamma-band signals is found in evoked MEG responses to somatosensory stimuli in patients with human immunodeficiency virus (HIV) (Spooner et al. 2018) and in evoked EEG responses to auditory stimuli in schizophrenia (Kwon et al. 1999; Popov et al. 2011). Importantly, both disorders exhibit injury to GABA-ergic interneurons (Carlén et al. 2012; Buzhdygan et al. 2016).

In contrast, we are not aware of any resting-state EEG or MEG (rs-MEG) studies that have observed abnormal spontaneous gamma-band activity in individuals with mTBI. Likewise, potential associations between abnormal spontaneous gamma-band activity and cognitive functioning have not been investigated. This is an important gap because mild brain injuries can produce enduring cognitive symptoms that frequently go undiagnosed or untreated, despite their adverse effect on quality of life. While post-concussive symptoms resolve within days post-injury in the majority of individuals with mTBI (Bigler 2008), symptoms can last more than 3 months post-injury, indicating chronic sequelae (McInnes et al. 2017). Estimates of the prevalence of persistent symptoms vary widely in veterans with mTBI, with between 7.5% and 40% of patients reporting at least 3 enduring symptoms (Schneiderman et al. 2008; Terrio et al. 2009; Morissette et al. 2011; Cooper et al. 2015). Moreover, in individuals with blast mTBI, the majority of persistent post-concussive symptoms are in the cognitive domain (e.g., executive function, attention, working memory) (McInnes et al. 2017).

The present study investigated spontaneous gamma-band activity during rs-MEG recordings in individuals with chronic combat-related blast mTBI and persistent post-concussive symptoms. MEG directly measures neuronal activity from populations of neurons in gray matter (Hamalainen et al. 1993) with high spatial resolution (2–3 mm in cortex) and excellent temporal resolution (<1 ms), which permits separation of different

oscillatory frequencies of neuronal populations (Leahy et al. 1998). Study participants included active-duty service members or veterans with combat-related mTBI and healthy controls with similar combat experiences. Our group has employed MEG preprocessing and high-resolution source imaging approaches that demonstrate gamma-band spontaneous signals (Huang et al. 2014a). Based on animal studies (Korotkova et al. 2010; Carlén et al. 2012; Del Pino et al. 2013; Cho et al. 2015; Kalemaki et al. 2018), we predicted abnormal increases (i.e., hyperactivity) in gamma-band signals in the prefrontal cortex of mTBI patients, owing to the vulnerability of this region to blast and the functional roles that it plays in enduring cognitive symptoms, especially those associated with executive functioning. We also predicted abnormal gamma-band hyperactivity in posterior parietal regions, which are also vulnerable to brain injury (Diwakar et al. 2015) and support cognitive symptoms in mTBI. To determine the cognitive relevance of individual differences in spontaneous gamma-band activity, measures of executive functioning and visuospatial processing/psychomotor speed were correlated with rs-MEG gamma-band activity.

Materials and Methods

The study protocol was approved by institutional review boards of the VA San Diego Healthcare System and Naval Health Research Center at San Diego. All participants gave written informed consent prior to study procedures. The informed consent followed the ethical guidelines of the Declarations of Helsinki (sixth revision, 2008).

Research Subjects

All study participants were males and US active-duty military service members or Operation Enduring Freedom/Operation Iraqi Freedom veterans. Twenty-five participants had a chronic combat-related blast mTBI and with persistent post-concussive symptoms for an average of 19.5 months post-injury [standard deviation (SD) = 17.6; range = 4–84 months]. Combat-related mTBI was corroborated from medical records. Healthy controls included 35 individuals with combat experience, but without a significant history of concussion based on self-report. There were no group differences in age or education (Table 1A). Exclusion criteria for study participation are detailed in the Supplementary Materials.

All mTBI participants were evaluated in a clinical interview to assess the nature of their injuries. The diagnosis of mTBI was based in part on standard Veterans Affairs and Department of Defense diagnostic criteria (The Management of Concussion/mTBI Working Group 2009): 1) loss of consciousness <30 min or transient confusion, disorientation, or impaired consciousness immediately after the combat-related trauma; 2) post-traumatic amnesia <24 h; and 3) an initial Glasgow Coma Scale (Teasdale and Jennett 1974) between 13 and 15 if available.

Table 1A Demographic characteristics in the control and blast mTBI groups

	Control ($n = 35$)		mTBI ($n = 25$)		*t*-test
	Mean	SD	Mean	SD	*P* value
Age	29.00	5.00	28.00	7.52	0.307
Years of education	14.00	1.48	13.00	1.89	0.126

Since the Glasgow Coma assessment was not accessible for most individuals who received their injury in theater, volunteers missing an assessment, but who met other inclusion criteria, were also enrolled. As for loss of consciousness, 28% of mTBI participants reported that they were altered/dazed and the remaining patients reported loss of consciousness for 1 min or less (40%), 2–15 min (24%), and 15–30 min (8%). Regarding post-traumatic amnesia duration, 48% of mTBI participants reported 0–15 min, 44% reported 16–30 min, and 8% reported 31 min–24 h. The majority of participants experienced 1 mTBI (76%), with 16% reporting 2–3 mTBIs, and 8% reporting 4–5 mTBIs.

The clinical interview also assessed 21 enduring post-concussive symptoms (Table 1B), modified slightly from the Head Injury Symptom Checklist (McLean et al. 1984). Only mTBI participants with at least 3 persistent symptoms were enrolled into the study. The number of symptoms endorsed ranged from 4 to 14 (mean = 6.88; SD = 1.61). Table 1B lists the percentages of the mTBI and control participants that endorsed each symptom. Though controls were asked about these symptoms, they did not sustain a TBI and thus, symptoms were unrelated to brain injury.

Neuropsychological Exams

The neuropsychological assessment focused on tests of executive functions from the Delis–Kaplan Executive Function System (D–KEFS) (Delis et al. 2001) and visuospatial processing and psychomotor speed from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler 1997, 2008), which are sensitive to cognitive decline in mTBI [see cited references in Robb Swan et al. (2015)]. The neurocognitive correlation analyses presented herein focused on the following subset of measures from a larger battery that was administered (see Supplementary Table S1), namely those showing significant or nonsignificant trends for performance differences between the mTBI and control groups (Table 2). The D–KEFS Number–Letter Switching subtest of the Trail Making Test measures cognitive flexibility. This test requires participants to connect circles as quickly as possible in numerical, alphabetical, and alternating numerical/alphabetical orders. Subtests of the D–KEFS Verbal Fluency Test require participants to generate, as quickly as possible, words beginning with specific letters (Letter Fluency subtest) and words in specific semantic categories while shifting between categories (Category Switching subtest). Letter Fluency tests phonemic processing, which is sensitive to language difficulties, whereas Category Switching tests cognitive flexibility during semantic processing. The WAIS Digit Symbol-Coding subtest utilizes a number of cognitive processes and is primarily used as a measure of visuospatial processing and psychomotor speed. The test requires participants to fill in, as quickly as possible, boxes below digits with symbols that are paired with them in a key at the top of the page. The WAIS-III was administered to most participants, although a subset of participants completed the fourth edition (WAIS-IV) (Wechsler 2008). Sensitivity analyses were performed removing the WAIS-IV scores and the tests for group differences were unchanged.

Resting-State MEG Data Acquisition and Signal Pre-processing to Remove Artifacts

Resting-state MEG data were collected at the UCSD MEG Center using the VectorView™ whole-head MEG system (Elekta-Neuromag) with 306 MEG channels. Participants sat inside a

Table 1B Percentage of subjects showing individual symptoms in mTBI and control groups

Symptoms	mTBI (%)	Control (%)	Symptoms	mTBI (%)	Control (%)
Headaches	84.0	14.3	Lack of spontaneity	4.0	0.0
Dizziness	56.0	11.4	Affective lability	8.0	2.9
Fatigue	48.0	14.3	Depression	28.0	14.3
Memory difficulty	88.0	14.3	Trouble concentrating	16.0	20.0
Irritability	64.0	20.0	Bothered by noise	12.0	2.9
Anxiety	64.0	20.0	Bothered by light	12.0	17.1
Trouble with sleep	60.0	14.3	Coordination/balance problems	20.0	11.4
Hearing difficulties	60.0	14.3	Motor difficulty	0.0	0.0
Blurred vision and other visual difficulties	16.0	2.9	Difficulty with speech	4.0	2.9
Personality changes	20.0	2.9	Numbness/tingling	20.0	11.4
Apathy	4.0	0.0			

Table 2 Neuropsychological test performance in the control and blast mTBI groups

	Control ($N = 35$)		mTBI ($N = 25$)				
	Mean	SD	Mean	SD	*t*-value	*P* value	Cohen's *d*
D–KEFS Trail Making Test							
Number–Letter Switching	11.09	1.98	9.08	2.55	3.30	**0.002***	1.37
D–KEFS Verbal Fluency Test							
Letter Fluency	10.83	3.21	9.08	2.74	2.27	**0.027***	0.59
Category Switching	11.54	2.62	10.16	2.75	1.96	0.056	0.51
WAIS							
Digit Symbol Coding†	10.34	2.82	8.83	2.66	2.09	**0.042***	0.55

In the first column, the name of a neuropsychological exam is in bold font. D-KEFS refers to the Delis-Kaplan Executive Function System and WAIS refers to the Wechsler Adult Intelligence Scale-Third Edition. Group differences on the measures reported in the table were tested using independent *t*-tests.
Neuropsychological measures are scaled scores (mean = 10, SD = 3).
*Statistically significant ($P < 0.05$).
†An outlier in the mTBI group was removed from this assessment (see main text).

multilayer magnetically shielded room (Cohen et al. 2002). MEG recording was divided into 2 5-min blocks with eyes closed, alternating with 2 5-min blocks with eyes open. In the eyes-closed condition, the participant was instructed to keep his/her eyes closed and empty his/her mind. In the eyes-open condition, the participant was instructed to fix his/her eyes on a fixation point and empty his/her mind. The order of blocks was counterbalanced between participants. Data were sampled at 1000 Hz and run through a high-pass filter with a 0.1 Hz cut-off and a low-pass filter with a 330 Hz cut-off. Eye blinks and eye movements were monitored using 2 pairs of bipolar electrodes, and heart signals were monitored with another pair of bipolar electrodes. Since the eyes-open data were contaminated with eye blinks in many participants, only the eyes-closed data were analyzed.

Substantial efforts were taken to help ensure that participants were alert during the MEG recordings. Prior to the MEG session, participants completed a questionnaire about the number of hours they slept the previous night, how rested they felt, and if there was any reason that they might not be attentive and perform to the best of their abilities (e.g., headache, pain). During MEG recording, technicians viewed participants on camera and continuously monitored alpha band oscillations, which are consistently associated with tonic alertness (Oken et al. 2006).

Eyes-closed rs-MEG sensor waveforms were first run through MaxFilter, also known as signal space separation (Taulu et al. 2004a, 2004b; Song et al. 2008), to remove external interferences (e.g., magnetic artifacts due to metal objects, strong cardiac signals, environment noises) and to co-register the MEG data by removing the small head movements across the 2 5-min eyes-closed sessions. Residual artifacts near the sensor array due to micro eye movements and residual cardiac signals were removed via Independent Component Analysis using FastICA (http://research.ics.aalto.fi/ica/fastica/) (Hyvarinen 1999; Hyvarinen and Oja 2000). The waveforms associated with top independent components were examined by an experienced MEG data analyst, along with eye and heart signals. Independent components associated with eye movement, heartbeats, and other artifacts were removed.

Structural MRI, MEG-MRI Registration, and BEM Forward Calculation

Structural MRI of the participant's head was collected using either a General Electric 1.5T Excite MRI scanner or 3T MRI scanner. The acquisition contains a standard high-resolution anatomical volume with a resolution of $0.94 \times 0.94 \times 1.2$ mm^3 using a T1-weighted 3D-IR-FSPGR pulse sequence. Scanner-related nonlinear imaging distortions were corrected using a gradient nonlinearity correction approach (Jovicich et al. 2006). To co-register the MEG with MRI coordinate systems, 3 anatomical landmarks (i.e., left and right pre-auricular points and nasion) were measured for each participant using the Probe Position Identification system (Polhemus). By using MRILAB (Elekta/Neuromag) to identify the same 3 points on the participant's MR images, a transformation matrix involving both rotation and translation between the MEG and MR coordinate systems was generated. To increase the reliability of the MEG-MR co-registration, approximately 120 points on the scalp

were digitized with the Polhemus system, in addition to the 3 landmarks, and those points were co-registered onto the scalp surface of the MR images.

The T1-weighted images were also used to extract the brain volume and innermost skull surface (SEGLAB software by Elekta/Neuromag). The Realistic Boundary Element Method (BEM) head model was used for MEG forward calculation (Mosher et al. 1999; Huang et al. 2007). The BEM mesh was constructed by tessellating the inner skull surface from the T1-weighted MRI into ~6000 triangular elements with ~5 mm size. A cubic source grid with 5 mm size was used for calculating the MEG gain (i.e., lead field) matrix, which leads to a grid with ~10 000 nodes covering the whole brain. Other conventional MRI sequences typical for identifying structural lesions were also performed: 1) Axial T2*-weighted; 2) Axial fast spin-echo T2-weighted; and 3) Axial FLAIR. MRIs were reviewed by a board-certified neuroradiologist (Dr R.R.L.), who determined that no participant had visible lesions on MRI.

MEG Gamma-Band Source Magnitude Imaging using Fast-VESTAL

The voxel-wise MEG source magnitude images were obtained using our high-resolution Fast-VESTAL MEG source imaging method (Huang et al. 2014a). This approach requires the sensor-waveform covariance matrix. The artifact-free, eyes-closed, resting-state MEG sensor-waveform data sets were divided into 2.5 s epochs. The data in each epoch were first direct current-corrected and then run through band-pass filters for the gamma band (30–80 Hz). Notch filter at 60 Hz was applied to remove the power line signals. Frequency-domain band-pass filter with zero phase shift via discrete Fourier transform was used. At each end of the band-pass filter, the transition of the Hanning window in the filter was selected to be at 10% of the associated cut-off frequency.

Waveforms from all 306 sensors including 204 planar gradiometers and 102 magnetometers were used in the analysis. Sensor-waveform covariance matrices were calculated for individual epochs after the band-pass filtering. Then the final sensor-waveform covariance matrix was obtained by averaging the covariance matrices across individual epochs for the 10-min resting-state data. From the covariance matrix, whole-brain MEG source magnitude images for the gamma frequency band were obtained for each participant using the Fast-VESTAL procedure (Huang et al. 2014a, 2016).

Statistical Tests of Group Differences in Gamma Activity

In all participants, voxel-wise whole brain MEG source magnitude images obtained from Fast-VESTAL were first spatially co-registered to the MNI-152 (Grabner et al. 2006) brain atlas template using a linear affine transformation program, FLIRT, from FSL software (www.fmrib.ox.ac.uk/fsl/) (Smith et al. 2004; Woolrich et al. 2009). Once in MNI-152 space, the MEG source magnitude images were spatially smoothed using a Gaussian kernel with 5 mm full width half maximum, followed by a logarithmic transformation using FSL.

A voxel-wise, 2-tailed *t*-test was then performed to test for differences between the mTBI and control groups. Family-wise errors across voxels were controlled by using a standard cluster analysis for the t-value maps. In this approach, the uncorrected threshold for voxel-wise *t*-test maps was set at $P < 0.01$, and the cluster size was determined by "3dFWHMx" and "3dClustSim" functions from AFNI software (http://afni.nimh.nih.gov). A mask that contained the statistically significant clusters was created, and then applied to the t-value maps to create the corrected group statistical maps ($P < 0.01$) for the MEG source magnitude images.

Correlations Between Gamma Activity and Neuropsychological Measures

Voxel-wise correlation analyses were performed to examine the association between gamma-band activity and scaled scores on tests of executive functioning (Number–Letter Switching, Letter Fluency, Category Switching) and visuospatial processing/psychomotor speed (Digit Symbol Coding), which showed significant or nonsignificant trends for differences between the mTBI and control groups (Table 2) (Robb Swan et al. 2015; Huang et al. 2017, 2018). To increase statistical power, all subjects from both mTBI and control groups were combined together for the correlation analyses. The rs-MEG source images in the MNI-152 space (following spatial smoothing and logarithm transformation) were formed into 4-dimensional data sets (i.e., first 3 dimensions represent the x-, y-, and z-coordinates; fourth dimension represents all subjects). Next, along the fourth dimension, voxel-wise correlation analyses were performed between gamma-band rs-MEG source images and each of the 4 neuropsychological test scores. The correlation analyses created r-value maps using an uncorrected threshold of $P < 0.01$. A cluster analysis was then used to control for family-wise errors at the corrected threshold for voxel-wise r-value maps ($P < 0.01$).

Although the analyses separately correlated gamma-band activity with 4 neuropsychological test scores, family-wise corrected *P* values were not further adjusted for multiple analyses, partly because we first adopted a conservative uncorrected threshold ($P < 0.01$). Moreover, the family-wise corrected *P* values from the statistical analyses were highly robust (see Results; Table 3), such that all *P* values would have remained significant even if the conservative Bonferroni correction had been applied (i.e., $P < 0.01 \times 4$ comparisons is still <0.05).

Results

Gamma-Band Hyper- and Hypoactivity in mTBI

Figure 1 displays the main findings from the tests for group differences in rs-MEG gamma-band activity. Compared with the controls, mTBI participants demonstrated striking gamma-band hyperactivity, mainly in 1) prefrontal areas including bilateral lateral-frontal pole (Brodmann Area or BA 10) and right pars opercularis (BA 44)/pars triangularis (BA 45) of the inferior frontal gyrus; 2) bilateral supplementary motor area (medial BA 6) and right premotor cortex; 3) posterior parietal areas including bilateral superior parietal lobule (BA 7), right supramarginal gurus (BA 40), and right angular gyrus (BA 39); 4) bilateral superior temporal gyri; 5) bilateral occipital areas including cuneus, superior lateral occipital cortex (BA 19), and calcarine fissure (BA 17); and 6) right cerebellum (anterior lobe). Compared with the controls, mTBI participants also showed hypoactivity in ventromedial prefrontal cortex, midline anterior cingulate cortex, and the midbrain.

Table 3 Significant correlations between gamma activity and performances on the neuropsychological tests

Regions of interest	Letter Fluency	Letter–Number Switching	Category Switching	Digit Symbol Coding
Pattern 1				
Frontal pole		$r = -0.42$; $P < 0.001$	$r = -0.49$; $P < 0.0001$	$r = -0.47$; $P < 0.001$
Supplementary motor area		$r = -0.45$; $P < 0.001$	$r = -0.45$; $P < 0.001$	
Superior parietal lobule	$r = -0.46$; $P < 0.001$	$r = -0.47$; $P < 0.001$	$r = -0.49$; $P < 0.0001$	$r = -0.41$; $P < 0.01$
Supramarginal gyrus	$r = -0.41$; $P < 0.01$	$r = -0.43$; $P < 0.001$	$r = -0.52$; $P < 0.0001$	
Angular gyrus		$r = -0.41$; $P < 0.01$	$r = -0.51$; $P < 0.0001$	$r = -0.47$; $P < 0.001$
Superior temporal gyrus		$r = -0.40$; $P < 0.01$	$r = -0.52$; $P < 0.0001$	$r = -0.57$; $P < 0.00001$
Superior occipital	$r = -0.40$; $P < 0.01$		$r = -0.44$; $P < 0.001$	$r = -0.43$; $P < 0.001$
Pattern 2				
Ventromedial prefrontal cortex	$r = 0.38$; $P < 0.01$		$r = 0.42$; $P < 0.001$	$r = 0.42$; $P < 0.001$
Pattern 3				
Superior frontal	$r = -0.41$; $P < 0.01$		$r = -0.55$; $P < 0.00001$	
Bilateral posterior cingulate cortex		$r = 0.54$; $P < 0.00001$		
Right parahippocampus		$r = 0.42$; $P < 0.001$		
Basal ganglia			$r = 0.43$; $P < 0.001$	

The analyses combined the mTBI and control groups. A cluster analysis was used to control for family-wise errors at the corrected threshold for voxel-wise r-value maps ($P < 0.01$).

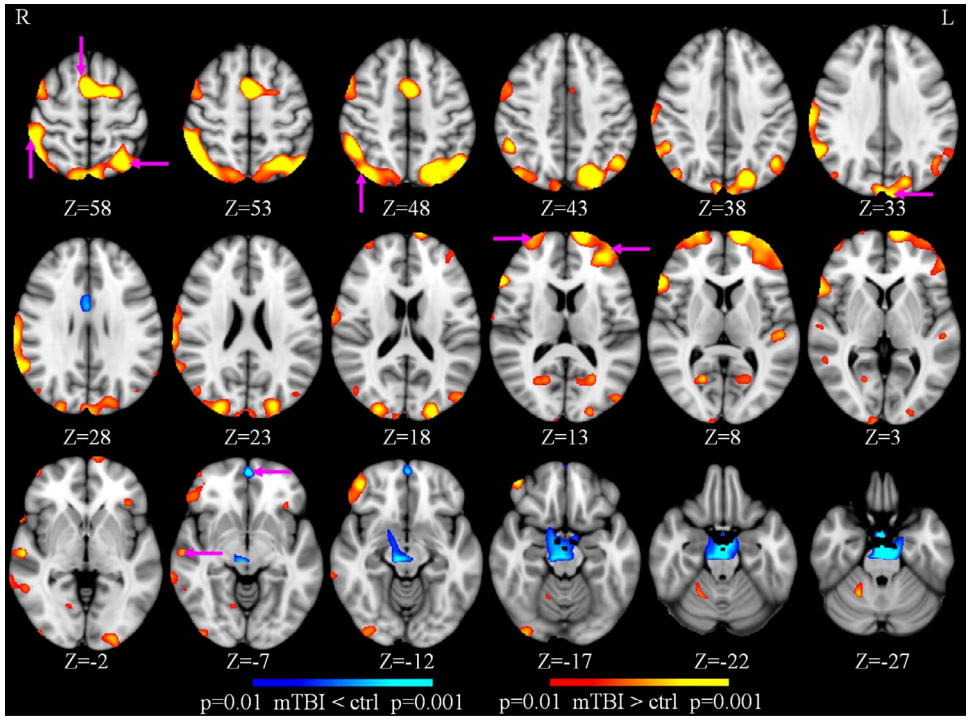

Figure 1. Group differences in gamma-band resting-state MEG activity. Hyperactivity (red-yellow color) and hypoactivity (blue-cyan color) in gamma-band resting-state MEG source imaging in individuals with mTBI, compared with healthy controls. The Z coordinates in MNI-152 standard space are displayed for the images +58 to −27 with 5 mm gaps. The 9 magenta arrows indicate representative areas in which gamma activity was significantly correlated with neuropsychological test scores; see Figures 2 and 3. Images are displayed in radiological view.

Neuropsychological Test Performance

Table 2 shows the mean performance for each group on 4 subsets of the D–KEFS and WAIS representing 3 cognitive domains. The mTBI group performed significantly worse than the control group on the Number–Letter Switching and Letter Fluency subtests. The mTBI group also performed significantly worse than controls on the Digit Symbol-Coding subtest, after removing one outlier in the mTBI group (3 SD above the group mean). There was a nonsignificant trend for scores on Category Switching to be lower in the mTBI than the control group. No other subsets showed significant group difference in performance (see Supplementary Table S1).

Correlation Between Gamma Activity and Neuropsychological Test Performances

Figure 2 and Table 3 present the results from voxel-wise analyses that examined the correlates of gamma-band rs-MEG

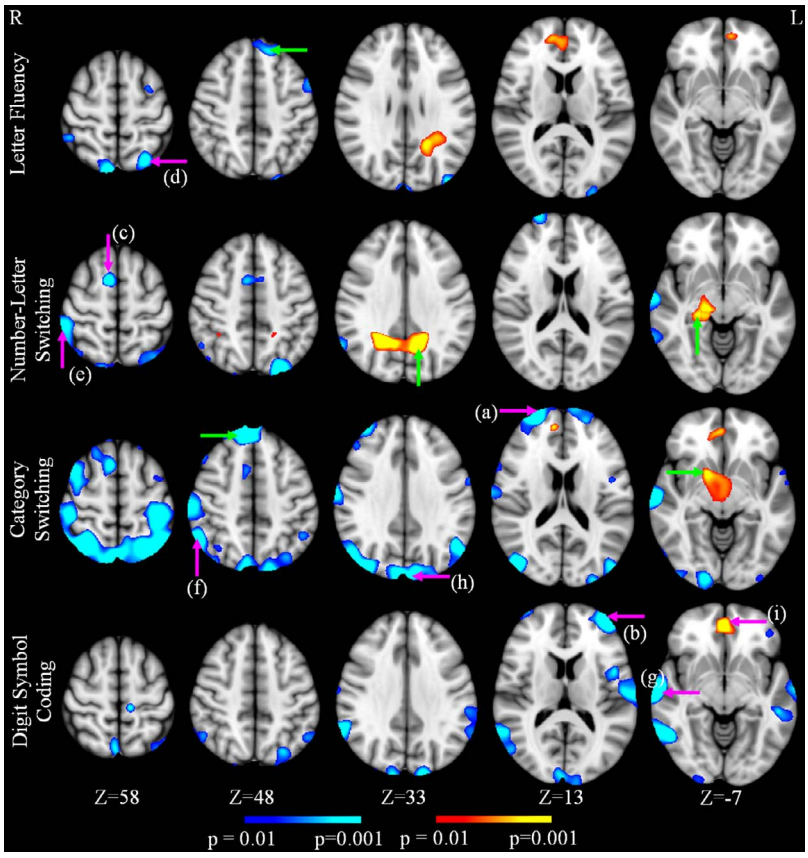

Figure 2. Correlations between gamma-band activity and cognitive functioning. Negative (blue-cyan color) and positive (red-yellow color) correlations between gamma-band rs-MEG activity and 4 neuropsychological scores (larger values signify better performances) in a combined pool of mTBI and healthy control subjects. The Z coordinates in MNI-152 standard space for each column of the images are +58, +48, +33, +13, and −7, respectively. The magenta arrows indicate 9 representative brain areas with group differences in gamma activity that also show significant correlations between gamma activity and neuropsychological scores (scatter plots are shown in Fig. 3). Green arrows indicate areas with significant correlations between gamma activity and neuropsychological scores, but without significant group differences in gamma activity. The corresponding scatter plots of the regions with green arrows are shown in Supplementary Figure S1. Images are displayed in radiological view.

source images with scores on 4 neuropsychological tests in the combined mTBI and control sample. Figure 3 displays scatter plots from representative regions wherein gamma-band activity was significantly correlated with individual differences in cognitive performances. The anatomical areas associated with representative neurocognitive correlations are highlighted by magenta arrows in Figures 1 and 2. These plots demonstrate that neurocognitive correlations with rs-MEG gamma-band activity were not driven by outliers in either group. The significant correlations were characterized by the following 3 patterns.

The first most common pattern of neurocognitive associations involved regions that showed aberrant gamma hyperactivity in the mTBI group (Figs 1–3; Table 3). Significant negative correlations were found for "frontal pole" with cognitive flexibility (Number–Letter Switching, Category Switching (Fig. 3*a*) and visuospatial processing/psychomotor speed (Digit Symbol-Coding subtests (Fig. 3*b*); "supplementary motor area" with cognitive flexibility (Number–Letter Switching (Fig. 3*c*) and Category Switching); "superior parietal lobule" with all 4 subtests (Fig. 3*d*); "supramarginal gyrus" with executive functioning (Number–Letter Switching (Fig. 3*e*), Letter Fluency, and Category Switching); "angular gyrus" with cognitive flexibility (Number–Letter Switching, Category Switching (Fig. 3*f*), and visuospatial processing/psychomotor speed (Digit Symbol Coding); "superior temporal gyrus" with cognitive flexibility (Number–Letter Switching, Category Switching) and visuospatial processing/psychomotor speed (Digit Symbol Coding (Fig. 3*g*); and "superior occipital" (BA 19) with executive functioning (Letter Fluency, Category Switching (Fig. 3*h*) and visuospatial processing/psychomotor speed (Digit Symbol Coding). Increased gamma-band in all areas predicted poorer test performance in both mTBI and healthy control participants. However, the scatter plots suggest that some neurocognitive relationships were partly driven by the preponderance of both higher gamma activity and lower performance on tests of executive functioning (Number–Letter Switching, Category Switching, and Letter Fluency) in many individuals with mTBI.

The second pattern of correlations involved areas showing hypoactivity of gamma in the mTBI group (Figs 1–3; Table 3). Here, gamma activity in midline "ventromedial prefrontal" cortex was positively correlated with executive functioning (Letter Fluency, Category Switching) and visuospatial processing/psychomotor speed (Digit Symbol Coding) (Fig. 3*i*). Thus, decreased gamma activity in this region was associated with poorer test performances in both groups.

The third pattern involved areas for which gamma activity was normal in the mTBI group (Figs 1 and 2; Table 3). For these regions, gamma activity was correlated with executive functions in all subjects (see Supplementary Fig. S1).

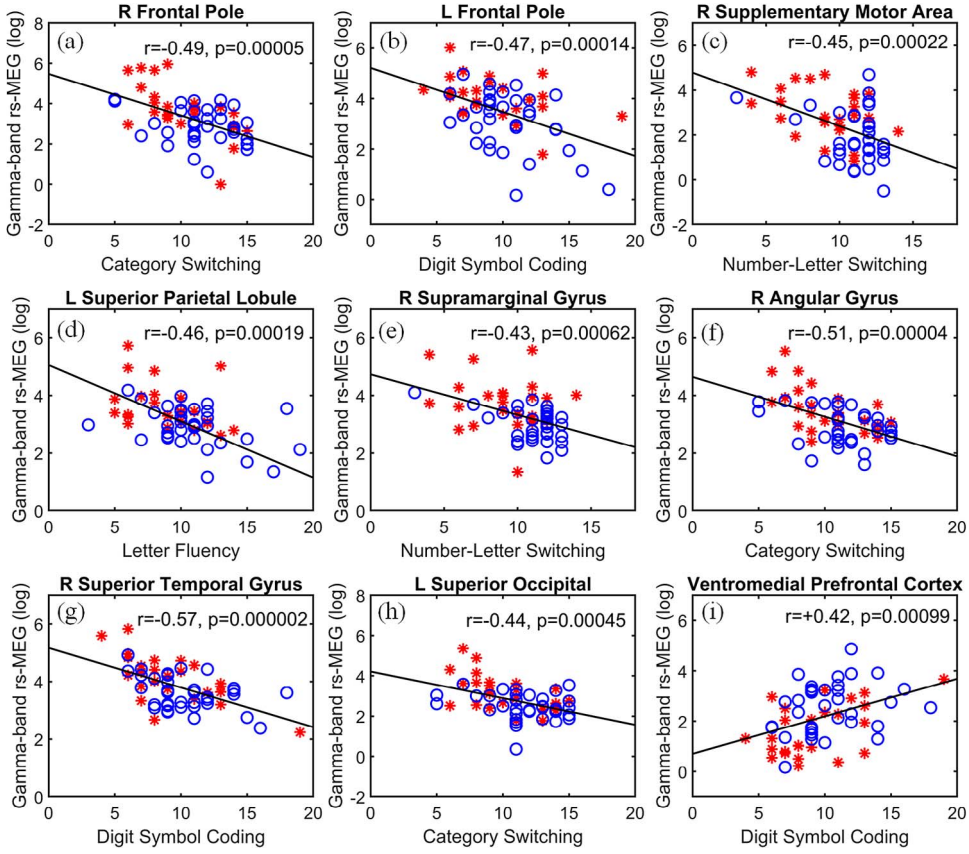

Figure 3. Nine representative scatter plots showing significant correlations between gamma-band rs-MEG activity and neuropsychological test scores for mTBI (red stars) and healthy control subjects (blue circles). The plots are for 9 representative neurocognitive correlations (a)–(i) in which the locations for brain regions are indicated by magenta arrows in the Figures 1 and 2. The mTBI group also showed significantly increased gamma-band rs-MEG activity in all cases, except (i) where decreased gamma activity was found. L and R, left and right hemisphere.

Discussion

To our knowledge this is the first study in humans to demonstrate that mild combat-related head injuries predominantly result in abnormally increased spontaneous gamma-band activity in individuals with chronic mTBI. Upregulation of gamma-band activity was striking throughout the brain in frontal, posterior parietal, superior temporal, and superior occipital cortices. These findings contrasted with the less extensive downregulation of gamma activity in the medial prefrontal cortex, anterior cingulate, and midbrain. Importantly, both upregulation and downregulation of regional gamma were typically cognitively relevant, correlating in a meaningful manner with executive functioning and visuospatial processing/psychomotor speed performances across the entire sample. Collectively, our findings indicate that rs-MEG measures of abnormal gamma-band activity are highly vulnerable to combat-related mTBI in distributed cortical regions that modulate information processing during cognition. Our main findings comport with recent reports that brain injury in animal models causes abnormal increases in spontaneous gamma-band activity (Korotkova et al. 2010; Carlén et al. 2012; Del Pino et al. 2013; Cho et al. 2015). However, the present study uncovered a more complex, regionally specific effect of blast injury on both upregulation and downregulation of gamma activity, the latter of which may be indicative of more severe injury to gray matter. We now discuss the implications of our findings with respect to potential physiological mechanisms and their clinical relevance.

Upregulation of Gamma in mTBI and Functional Correlates

Our findings of marked gamma hyperactivity in individuals with blast mTBI are highly consistent with reports that injury to GABA-ergic interneurons in animal models, specifically PV+ interneurons, causes abnormal increases in spontaneous gamma-band activity (Korotkova et al. 2010; Carlén et al. 2012; Del Pino et al. 2013; Cho et al. 2015). Abnormal hyperactivity in spontaneous gamma oscillations also disrupts the NMDA receptor in PV+ inhibitory interneurons (Korotkova et al. 2010; Carlén et al. 2012; Del Pino et al. 2013; Cho et al. 2015), which likely causes an imbalance in the excitatory/inhibitory ratio within neural networks (Buzsáki and Wang 2012). Synaptic inhibition in the brain is primarily mediated by the GABA type-A receptor, and the distribution, properties, and dynamics of these receptors are largely determined by their subunit composition [see Raible et al. (2015)]. Alteration of subunit composition after a TBI may result in abnormally increased synaptic firing and possibly contribute to injury-related pathology (Raible et al. 2015). Since MEG is primarily sensitive to neuronal signals from gray matter, our findings also confirm those from a recent animal study demonstrating

that mTBI impacted local inhibitory networks embedded within neocortical gray matter, where reduced inhibitory transmission occurred in concert with PV+ interneuron perisomatic axonal injury and widespread terminal degeneration (Vascak et al. 2018).

One important question is whether our findings of gamma hyperactivity in mTBI are injury-related or due to compensatory mechanisms. We believe the former explanation is more compelling for 2 reasons. First, aberrant gamma activity was recorded during resting state, in the absence of active tasks that might elicit performance-related compensation. Second, greater gamma hyperactivity throughout the brain was associated with poorer cognition, specifically executive functioning and visuospatial processing/psychomotor speed.

Gamma Hyperactivity in Frontal Pole

Striking gamma hyperactivity in the frontal pole indicates that this is an important feature of combat-related mTBI. This region is involved in higher-order cognitive functions (e.g., organization, planning, executive components of working memory) (Bludau et al. 2014). In particular, the frontal pole is thought to enable cognitive branching; that is, the ability to put a hold on an alternative course of action pending the performance of an action under way [see Koechlin (2011)]. Such a domain-general function supports almost all dynamic behaviors and mental activities, such as reasoning, problem-solving, and multitasking (Koechlin 2011), and comports with its role in governing the coordination of information processing and transfer across supramodal cortex (Owen et al. 2005). The functional significance of the frontal pole is compatible with our findings that gamma hyperactivity in this region in mTBI was related to poorer cognitive flexibility (Number–Letter Switching and Category Switching) and visuospatial processing/psychomotor speed (Digit Symbol Coding) across groups. Notably, however, these neurocognitive associations were partly driven by the preponderance of both higher gamma activity and lower cognitive performance in many individuals with mTBI. Thus, injury to the frontal pole impacted negatively on multiple higher-level cognitive functions. Indeed, we demonstrated the vulnerability of the frontal pole to mTBI in MEG studies of abnormal delta waves (Huang et al. 2012, 2014b), functional connectivity (Huang et al. 2017), predictive control (Diwakar et al. 2015), and working memory (Huang et al. 2018).

Gamma Hyperactivity in Supplementary Motor Area

Although supplementary motor area is not well understood, it is routinely engaged with many cognitive functions including working memory (Harrington et al. 2010), action planning (Elsinger et al. 2006), inhibitory control (Morein-Zamir and Robbins 2015), and temporal processing (Rao et al. 2001). The supplementary motor area is known to have a critical function in diverse cognitive behaviors as it is a central hub in several well-characterized networks such as the corticostriatal–thalamocortical system, the frontostriatal inhibition network, and the default mode network. The default mode network is particularly relevant here as spontaneous activity in this network is aberrant during resting-state functional magnetic resonance imaging (fMRI) in chronic mTBI, partly owing to an upregulation of supplementary motor area connectivity (Nathan et al. 2015). Because default mode network activity is associated with internally focused attention processes, problems suppressing activity in this region during cognitive tasks interferes with performance. This perspective comports with our finding that greater intrinsic gamma activity in supplementary motor area is associated with poorer cognitive flexibility. Thus, one speculation is that aberrantly enhanced connectivity within the default mode network in mTBI, as revealed by resting-state fMRI (Nathan et al. 2015), may arise from elevated gamma in the supplementary motor area, but perhaps also other default mode network hubs, including parietal regions for which intrinsic connectivity is also aberrantly increased in mTBI (Nathan et al. 2015).

Gamma Hyperactivity in Parietal–Occipital Cortices

The parietal association cortex consists of dorsal (superior parietal and occipital) and ventral areas (supramarginal and angular gyri) that govern multisensory integration of information from regions throughout the cortex and thus, are vital for supporting a range of cognitive functions (e.g., attention, semantic processing, visuospatial organization, working memory, numerical decision making, and object use) (Humphreys and Lambon Ralph 2015). Dorsal parietal areas may act as an "executive buffer" (Humphreys and Lambon Ralph 2015) or a multi-domain control system (Duncan 2010; Whitney et al. 2012) that controls goal-directed, attention-demanding behaviors (Corbetta and Shulman 2002; Cabeza et al. 2008). Our finding that greater gamma hyperactivity in superior parietal cortex was associated with poorer cognition on all neuropsychological tests is compatible with this model of attention systems (Corbetta and Shulman 2002). Interestingly, greater gamma activity in the superior occipital cortex, a component of the dorsal visual pathway (Gallivan and Goodale 2018), also correlated with poorer performances on most cognitive tests. However, our tests of executive and visuospatial processing/psychomotor speed engage multiple cognitive functions, including more automatic, stimulus-driven attention, which is supported by ventral parietal areas such as supramarginal gyrus (Humphreys and Lambon Ralph 2015) and processes related to language, number processing, and visuospatial cognition (Humphreys and Lambon Ralph 2015). While all neuropsychological tests in our study likely involved some degree of bottom-up processing, greater gamma activity in the supramarginal gyrus specifically correlated with poorer performances on tests of executive functioning. In contrast, greater gamma activity in the angular gyrus correlated with poorer performances on tests that engage semantic and numerical processing (Number–Letter Switching, Category Switching, Digit Symbol Coding). While these neurocognitive relationships were found in both groups, they were partly driven by individuals with mTBI for whom high gamma in ventral parietal cortices was frequently coupled with poorer cognitive flexibility and visuospatial processing/psychomotor speed.

Gamma Hyperactivity in Superior Temporal Gyrus

The superior temporal gyrus consists of primary and secondary auditory cortices, which support multisensory integration and govern auditory processing from simple sound perception to speech recognition (Zevin 2009; Morillon and Schroeder 2015; Nourski 2017; King et al. 2018). Thus, diminishment of GABAergic inhibition in this region may lead to interference in primary (e.g., hearing and tinnitus) and complex auditory (e.g., verbal cognition) processing through possible alterations in plasticity and neural network connectivity (Chen et al. 2017). This is consistent with our mTBI participants' endorsement of markedly

higher percentages of symptoms related to hearing difficulties (60.0% vs. 14.3%) relative to healthy controls (Table 1B). This also is compatible with the neurocognitive associations found across groups between higher gamma in superior temporal cortex and poorer performances on tests that emphasize more complex verbal processing (Letter–Number Switching, Category Switching, Digit Symbol Coding).

Gamma Hypoactivity in mTBI and Physiological Mechanisms

The ventromedial prefrontal cortex was 1 of 3 areas, in addition to the anterior cingulate and midbrain, for which the mTBI group showed gamma hypoactivity. This finding indicates that injury to PV+ interneurons also can lead to confined decreases in gamma spontaneous activity. We believe gamma downregulation signifies more severe injuries than the gamma-band upregulation. This proposal is consistent with a study in mutant mice with NMDAR deficiency (Carlén et al. 2012) demonstrating that only PV+ interneurons exhibited abnormal increases in gamma intrinsic activity under anesthetic or awake conditions, compared with control mice. However, when the NMDAR mutant mice were further challenged by a NMDAR antagonist, causing more severe injury, they exhibited "decreases" in gamma-band intrinsic activity, whereas the control mice challenged by an NMDAR antagonist showed "increases" in gamma-band activity. Thus, it is likely that the gamma hypoactivity we observed was indicative of more severe injuries to these areas than to frontoparietal and temporal–occipital areas, in which gamma was upregulated.

Ventromedial prefrontal cortex controls complex cognitive processes, including decision-making, emotion regulation, and cognitive flexibility (Kim et al. 2011) [see review in Hiser and Koenigs (2018)]. Hypoactivity in this region is also common in individuals who suffer post-traumatic stress disorder (PTSD) (Rauch et al. 1998, 2006; Hughes and Shin 2011; Huang et al. 2014c) and is a key component in an influential neurocircuitry model of PTSD (Rauch et al. 2006; Hughes and Shin 2011). Consistent with its role in high-level cognition, lower gamma-band activity in ventromedial prefrontal cortex correlated with poorer executive functioning, including cognitive flexibility (Category Switching), phonemic fluency (Letter Fluency), and visuospatial processing/psychomotor speed in all subjects. Gamma hypoactivity of the anterior cingulate in mTBI is also consistent with reports of reduced activation in this region during the performance of working memory tasks in fMRI (Cazalis et al. 2006) and MEG studies (Huang et al. 2018). Though prominent theories suggest that the anterior cingulate regulates error detection, conflict monitoring and adjustment, and/or task switching (Botvinick et al. 2004; Kerns et al. 2004; Ullsperger and von Cramon 2004; Carter and van Veen 2007; Hyafil et al. 2009; Cazalis et al. 2011), gamma activity in this region did not correlate with our cognitive measures, possibly because our tests were insufficiently sensitive to key facets of the hypothesized cognitive functions, such as error detection and conflict monitoring.

Conclusion

Our results uncovered abnormal intrinsic gamma activity in individuals with mTBI and long-term behavioral and cognitive symptoms. Compared with the controls, combat-related mTBI participants mainly exhibited gamma hyperactivity throughout frontoparietal and superior temporal–occipital cortices, whereas hypoactivity was confined to the ventromedial prefrontal cortex, anterior cingulate, and midbrain. While aberrant gamma activity was not detected in subcortical areas, this may be due to the limited spatial resolution of MEG for subcortical areas. The more extensive gamma hyperactivity was consistent with animal studies of injury to PV+ interneurons, which causes functional disinhibition. These novel findings suggest the intriguing possibility that abnormal gamma activities may be a proxy for GABA-ergic interneuron dysfunction in chronic blast-related mTBI. In this regard, future studies are needed to directly investigate the hypothesized association between gamma upregulation in mTBI and GABA-ergic interneuron dysfunction (e.g., magnetic resonance spectroscopy and positron emission tomography). Animal models also suggest that the observed gamma hypoactivity in mTBI individuals is indicative of more severe injury to PV+ interneurons, which should be directly examined in future studies of moderate to severe TBI or stroke patients. In addition, it will be of interest to compare gamma activity with the delta/alpha band ratio to assess regional similarities and differences between frequency bands as they concern detection of abnormal neuronal functioning in mTBI individuals. In both mTBI and healthy controls, greater hyperactivity throughout the brain correlated with poorer cognition, whereas greater hypoactivity in ventromedial prefrontal cortex was associated with worse cognition. These findings highlight the cognitive relevance of individual differences in gamma activity. However, we also noted that several significant neurocognitive correlations appeared to be partly driven by a preponderance of both higher gamma activity and lower cognitive performance in many individuals with mTBI, suggesting that the expansive upregulation of gamma activity may have negative repercussions for cognition, particularly in mTBI. Future studies containing larger mTBI and control cohorts are needed to better determine if variations in gamma activity correlate with individual differences in cognitive performance, irrespective of whether participants incurred a brain injury. To more comprehensively assess associations between gamma activity and executive functioning, future studies should also consider expanding the cognitive battery, for example, by including the Attention Network Test (Fan et al. 2002). Altogether, these novel findings suggest the intriguing possibility that abnormal gamma activities may be a promising neuroimaging marker of insidious mild head injuries, which often are overlooked clinically despite chronic behavioral sequelae. Our results may also inform the assessment of other neurological (e.g., epilepsy, stroke, Parkinson's disease, Alzheimer's disease) and psychiatric disorders (e.g., schizophrenia) that have been linked to GABA-ergic interneuron dysfunction.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

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