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Filling in the gaps: Anticipatory control of eye movements in chronic mild traumatic brain injury

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ABSTRACT

A barrier in the diagnosis of mild traumatic brain injury (mTBI) stems from the lack of measures that are adequately sensitive in detecting mild head injuries. MRI and CT are typically negative in mTBI patients with persistent symptoms of post-concussive syndrome (PCS), and characteristic difficulties in sustaining attention often go undetected on neuropsychological testing, which can be insensitive to momentary lapses in concentration. Conversely, visual tracking strongly depends on sustained attention over time and is impaired in chronic mTBI patients, especially when tracking an occluded target. This finding suggests deficient internal anticipatory control in mTBI, the neural underpinnings of which are poorly understood. The present study investigated the neuronal bases for deficient anticipatory control during visual tracking in 25 chronic mTBI patients with persistent PCS symptoms and 25 healthy control subjects. The task was performed while undergoing magnetoencephalography (MEG), which allowed us to examine whether neural dysfunction associated with anticipatory control deficits was due to altered alpha, beta, and/or gamma activity. Neuropsychological examinations characterized cognition in both groups. During MEG recordings, subjects tracked a predictably moving target that was either continuously visible or randomly occluded (gap condition). MEG source-imaging analyses tested for group differences in alpha, beta, and gamma frequency bands. The results showed executive functioning, information processing speed, and verbal memory deficits in the mTBI group. Visual tracking was impaired in the mTBI group only in the gap condition. Patients showed greater error than controls before and during target occlusion, and were slower to resynchronize with the target when it reappeared. Impaired tracking concurred with abnormal beta activity, which was suppressed in the parietal cortex, especially the right hemisphere, and enhanced in left caudate and frontal–temporal areas. Regional beta-amplitude demonstrated high classification accuracy (92%) compared to eye-tracking (65%) and neuropsychological variables (80%). These findings show that deficient internal anticipatory control in mTBI is associated with altered beta activity, which is remarkably sensitive given the heterogeneity of injuries.

1. Introduction

Traumatic brain injury (TBI) is the leading cause of disability and death in people under the age of 45 in the United States (Bruns, Jr. and Hauser, 2003), with approximately 5.3 million Americans living with TBI-related disabilities (Thurman et al., 1999; Langlois et al., 2006). Individuals with mild TBI (mTBI) report a host of somatic (e.g., headache, visual disturbances, dizziness), emotional (irritability, anxiety, depression), and cognitive (memory, attention, processing speed) symptoms that can persist years after injury, leading to long-term disability (Shenton et al., 2012). A major barrier in the diagnosis of TBI stems from the lack of measures that are adequately sensitive in detecting mild head injuries. Between 84% and 96% of mTBI patients with a Glasgow Coma Scale (GCS) of 14 or 15 at time of injury have no abnormal findings on MRI or CT (Culotta et al., 1996). MRI and CT are also typically negative in mTBI patients with persistent symptoms

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of post-concussive syndrome (PCS) (Rugg-Gunn et al., 2001; Arfanakis et al., 2002; Schrader et al., 2009; Konrad et al., 2011). Insidious changes in cognition can also go undetected on clinical neuropsychological testing (Belanger et al., 2005; Dikmen et al., 2009; Ivins et al., 2009; Bigler, 2013).

Patients with mTBI frequently experience difficulties in focusing and sustaining attention (Stuss et al., 1989; Binder et al., 1997), yet neuropsychological measures can be insensitive to momentary lapses in concentration because they test attention to discrete events (Belanger et al., 2005; Ivins et al., 2009). Conversely, visual tracking strongly depends on sustained attention over time and can be impaired in chronic mTBI patients (Heitger et al., 2009; Maruta et al., 2010b), independent of general oculomotor deficits. Visual tracking is supported by retinal and extraretinal processing networks, which also subserve attention (Corbetta et al., 1998), including the frontal eye fields, the prefrontal cortex, the parietal cortex, the cerebellum and the basal ganglia (O'Driscoll et al., 2000; Burke and Barnes, 2008; Nagel et al., 2008). Hence, visual tracking may be particularly sensitive to disconnection among distributed brain networks from diffuse axonal injury (DAI) in mTBI (Povlishock and Coburn, 1989; Shenton et al., 2012), which disrupts communication in cortico-cortical and cortical–subcortical networks that regulate attention (Kraus et al., 2007). Importantly, deficits in TBI patients are accentuated when tracking a target that is occluded for varying periods of time (Suh et al., 2006), owing to the greater emphasis on internal (extraretinal) predictive or anticipatory mechanisms (Lencer et al., 2004; Nagel et al., 2006; Barnes, 2008; Lencer and Trillenberg, 2008). Hence, visual tracking when a target is periodically occluded may be particularly sensitive to deficient anticipatory control, secondary to fluctuations in attention (Maruta et al., 2010a). Likewise, tracking under this condition may be an effective probe for neuronal sources of deficient anticipatory control in chronic mTBI, which are poorly understood.

In the present study, we investigated the neuronal bases for deficient anticipatory control during visual tracking in chronic mTBI patients with persistent PCS symptoms and healthy control subjects as they tracked a predictably moving target that was either continuously visible or occluded at random locations for varying periods of time (gap condition). The task was performed while undergoing magnetoencephalography (MEG), which measures the magnetic signal generated by neuronal activity. Emerging research suggests that functional neuroimaging measures such as MEG may aid in the diagnosis of mTBI and elucidate mechanisms of the disease process (Huang et al., 2012; Huang et al., 2014b). MEG localizes sources of activity with high spatial (2–3 mm) and high temporal resolution (<1 ms), thereby enabling measurement of brain activity at specific frequency bands to better characterize the nature of neuronal dysfunction (Huang et al., 2009; Huang et al., 2012). This approach allowed us to examine whether neural dysfunction associated with anticipatory control deficits was due to altered alpha, beta, and/or gamma activity. We were also able to isolate brain activity that was associated with predictive control before, during and immediately after target occlusion. We hypothesized that deficits in mTBI would be more prominent in the gap condition, especially in frontoparietal regions, which are vulnerable to disconnection from DAI (Bendlin et al., 2008) and are more engaged during maintenance of visual tracking when a target is occluded (Kawawaki et al., 2006; Nagel et al., 2006; Nagel et al., 2008; Ding et al., 2009). We also evaluated the classification accuracy of abnormal MEG frequency band activity, visual tracking, and neuropsychological measures.

2. Methods

Study procedures were approved by the University of California San Diego (UCSD) Human Research Protections Program and performed in accordance with ethical guidelines in the Declaration of Helsinki (sixth revision, 2008).

2.1. Subjects

Participants included 25 chronic mTBI patients with persistent PCS symptoms and 25 healthy controls of a similar age, educational level, gender, and estimated premorbid IQ (Wechsler Test of Adult Reading) (Table 1). Most mTBI participants were recruited from TBI clinics at UCSD, referrals from neurologists, and other mTBI studies conducted at UCSD. Some patients were recruited from community advertisements. Healthy adult controls were recruited from other studies conducted at UCSD and from community advertisements. Subjects were right handed, with the exception of two control subjects who were left handed. Scores on the Edinburgh Handedness Inventory did not differ between the groups (Table 1). Inclusion criteria for mTBI patients were: 1) a single TBI with or without loss of consciousness within 3 months to 5.5 years prior to testing, 2) any persistent PCS symptoms, 3) a normal CT or MRI for patients who went to the emergency room, and 4) a Glasgow Coma Scale (GCS) of 13–15 at time of injury, if

Table 1
Demographic characteristics, behavioral symptoms, and neuropsychological test performance in the control and mTBI groups.

	Control group		mTBI group			
	Mean	SD	Mean	SD	*p*-Value	Partial *eta*^{2}
Age	31.8	10.6	32.7	11.2	0.79	.002
Years of education	15.2	1.5	14.7	1.4	0.25	.032
WTAR premorbid IQ	113.9	4.9	110.8	6.9	0.08	.063
CAARS-S:S (ADHD)	19.0	11.1	20.3	11.4	0.69	.003
CESD (depression)[a]	6.7	6.5	9.2	8.4	0.26	.027
PCL-C (stress)	21.9	7.0	26.8	9.1	0.037	.087
Gender (% males)	68%		84%		0.32	
Attention (ANT)[b]						
Alerting	34.2	20.6	29.4	23.5	0.44	.013
Orienting	35.4	17.1	39.4	23.4	0.49	.010
Conflict	130.2	31.7	130.3	41.2	0.99	.000
Overall reaction time	549.1	57.8	596.9	67.3	0.01	.131
Executive function (COWAT)[c]						
Letter Fluency (FAS)	12.0	2.4	10.6	2.5	0.045	.081
Animal Fluency	12.3	1.9	11.0	2.3	0.03	.094
Verbal memory (CVLT-II)[d]						
Immediate Recall	58.3	8.3	52.0	7.2	0.006	.149
Short Delay Recall	0.56	1.0	−0.26	1.1	0.008	.138
Short Delay Cued Recall	0.46	0.9	−0.40	1.1	0.013	.164
Long Delay Recall	0.48	0.9	−0.52	1.1	0.001	.214
Long Delay Cued Recall	0.38	0.9	−0.54	1.0	0.002	.185
Spatial working memory[e]						
Forward Span	10.16	2.7	9.24	3.0	0.26	.027
Backward Span	9.60	2.3	8.76	2.5	0.22	.032
Information processing speed[f]						
SDMT	13.0	2.7	10.92	2.5	0.008	.147
Psychomotor speed[g]						
Finger Tapping	51.2	11.8	48.5	13.3	0.46	.011

Group differences on the measures reported in the table were tested using independent *t*-tests, except for gender (chi-square test). WTAR = Wechsler Test of Adult Reading; CAARS = Conners' Adult ADHD Rating Scale; CESD = Center for Epidemiologic Studies Depression scale (total score); PCL-C = Post-traumatic checklist (civilian version; total raw score).

[a] The range of CES-D scores was 0–25 in the control group and 0–42 in the mTBI group. Three subjects in each group had scores ≥16 (control group values: 16, 22, 25; mTBI group: 17, 22, 42).

[b] Values for the Attention Network Task (ANT) are in milliseconds.

[c] Controlled Oral Word Association Task (COWAT) standard scores.

[d] California Verbal Learning Test (CVLT-II) *t*-scores (Immediate Recall) and standard scores (all other subtests).

[e] Wechsler Memory-III Spatial Span scaled scores.

[f] Symbol digit modalities test (SDMT) scaled scores.

[g] Finger Tapping Speed *t*-scores for dominant hand.

available. GCS was not available for most patients and therefore not reported. Patients were excluded if they were hospitalized for their injury, were intubated, had multiple TBIs, had loss of job due to the injury, confirmed use of psychotropic or cognitive enhancing medication, or showed evidence of malingering on the Test of Memory Malingering (i.e., cutoff score below 45 on trial 2) (Teichner and Wagner, 2004). Exclusion criteria for all subjects included neurological diagnosis other than mTBI, history of post-traumatic stress disorder, neurological disorders other than TBI (e.g., seizure disorder), pre-morbid major psychiatric disorders (e.g., major depressive disorder), alcoholism or substance abuse, and attention deficit hyperactivity disorder (ADHD).

The mean number of months post-injury was 31.8 (SD = 18.3, range = 3 to 65). Only 4 patients (20%) were 3–9 months post-injury; 80% of mTBI patients were more than 1 year post-injury. Causes of injuries included motor vehicle accidents ($n = 4$), sport related injuries ($n = 13$), falls ($n = 5$), and blows to the head ($n = 3$). Most mTBI patients (96%) reported post-traumatic amnesia and 64% reported loss of consciousness. Table 2 shows the percent of mTBI patients who endorsed various symptoms on the modified Head Injury Symptom Checklist. The most frequently endorsed symptoms were headaches (88%), memory difficulties (88%), trouble concentrating (80%), fatigue (68%), dizziness (60%) and sleeping problems (60%). On the average, mTBI subjects reported 6.3 (SD = 3.2; range = 1–14) new symptoms post-injury and endorsed 3.2 (SD = 1.9; range = 1–8) PCS symptoms.

2.2. Behavioral and cognitive assessments

All subjects completed the Center for Epidemiologic Studies Depression (CES-D) scale, which assessed the frequency of various symptoms of depression during the last week. The Post-traumatic stress disorder Checklist (Civilian version; PCL-C, National Center for PTSD) assessed how disturbed individuals were in the past month by stressful life experiences. The Conners' Adult ADHD Rating Scale — Self-Report: Short Version (CAARS-S: S, Pearson, San Antonio, TX) assessed symptoms of adult ADHD.

The Wechsler Test of Adult Reading (WTAR) was used to estimate premorbid IQ (Green et al., 2008). A battery of neuropsychological tests was administered to evaluate: 1) attention, including alerting, orienting, and conflict control (Attention Network Test; ANT) (Fan et al., 2002); 2) verbal fluency (Controlled Oral Word Association Task; COWAT) (Loonstra et al., 2001); 3) short- and long-term memory (California Verbal Learning Test (CVLT)) (Delis et al., 1987); 4) information processing speed (Symbol Digit Modalities Test (SDMT) (Smith, 1995); 5) psychomotor speed (Finger Tapping); and 6) nonverbal working memory (Spatial Span) (Wechsler, 1997).

Table 2
Percent of mTBI patients who endorsed various symptoms from the Head Injury Symptom Checklist.

Symptoms	Percent
Headaches[a]	88
Memory	88
Concentration	80
Fatigue[a]	68
Dizziness[a]	60
Sleep[a]	60
Bothered by light	48
Irritability[a]	48
Anxiety[a]	44
Balance	40
Coordination	36
Bothered by noise	32
Blurred vision	24
Apathy[a]	20
Loss of temper	16
Depression[a]	16
Sexual difficulties	16
Personality changes[a]	8
Smell	4
Taste	0

[a] Items used for the calculation of total PCS symptoms.

2.3. Visual tracking task

Eye movement data were collected during MEG recording using the SR Research Eyelink 1000 system (Ontario, Canada). Subjects were seated 126.4 cm (eye to screen distance) from a display projected with a digital light processing projector. The visual tracking task involved tracking a red disk-shaped target (diameter of 0.9 visual angle degrees) that moved clockwise in a circle (radius of 10 visual angle degrees at 0.4 Hz) on a black background (Fig. 1). Time-stamped eye position was recorded monocularly for three blocks, each consisting of three tracking conditions (continuous, gap, and distractor). Each condition consisted of 10 trials (2.5 s per trial, 25 s total) or revolutions of the target. In the continuous tracking condition, the target was visible throughout the period of tracking. In the gap condition, the target was visible for a random interval of 1250–3250 ms and then disappeared for 30° (208 ms), 45° (312 ms), or 60° (416 ms) before reappearing. The order of the gap periods was random. Subjects were instructed to continue tracking by predicting the target movement. Each subject completed a single practice block prior to the test blocks. The results from the distractor condition were not analyzed in this study and will not be reported in this paper. Subjects were informed of the tracking condition prior to recording. The order of the tracking conditions was counterbalanced across subjects and blocks.

2.4. Analysis of visual tracking data

Eye movement data were initially preprocessed to detect blinks and saccades. Blinks were identified by the Eyelink camera. Saccades were identified during post-processing as eye movements surpassing velocity and acceleration thresholds of 100°/s and 1500°/s^2. Saccades and blinks were removed prior to computing averaged measures, but not removed for analyses of dynamics. The data were also adjusted for the combined video display lag of the display computer, video card, and projector, which was a constant delay of 35 ms. Data associated with the first and last revolutions of the target per trial were also discarded before processing. Several time-averaged metrics of eye position variability during the continuous and gap conditions were computed to compare the two groups. For the continuous condition, average radius of the gaze trajectory, average phase error, variability of tangential error, variability of radial error, and saccade frequency (Maruta et al., 2010b) were computed and averaged over all three blocks. Average radius was expressed in units of degrees of visual angle. Average phase was defined as the angle subtended by the subject's gaze and the target's position per time point averaged over time, and expressed in units of degrees of phase angle. Variability of tangential error was computed as the standard deviation over time of the instantaneous gaze position error in the direction tangential to the target trajectory in units of degrees of visual angle. Variability of radial error was computed as the standard deviation over time of the instantaneous gaze positional error in the direction perpendicular to the target trajectory in units of degrees of visual angle. Saccade frequency was computed by dividing the total time of saccades by the trial duration. For the gap condition, the same five measures were computed during the following time windows: 1) target visible, 2) 208 ms prior to target disappearance (pre-gap), 3) the first 208 ms of target disappearance (within gap), 4) the first 208 ms after target reappearance (post-gap 1), and 5) the first 400 ms after target reappearance (post-gap 2).

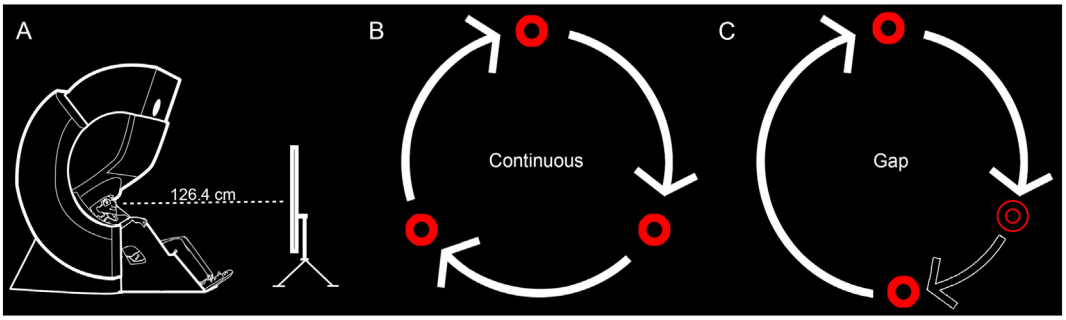


Fig. 1. Illustration of the visual tracking task. Panel A illustrates the subject and screen positioning for viewing the visual tracking task. Panel B illustrates the target trajectory during the continuous tracking condition, where the target was visible throughout the period of tracking. Panel C illustrates an example of the target disappearing (outlined arrow and target) and then reappearing during the gap tracking condition.

In addition to window-based measures, we examined differences in visual tracking dynamics between the groups. For each subject, average time-courses across trials of phase error and radius were constructed for epochs associated with the 30, 45, and 60 degree gap conditions. The average time-courses were then compared between the control and mTBI groups at each time point. To correct for multiple comparisons, we used a nonparametric statistical test (Maris and Oostenveld, 2007) to identify clusters of time points with significant differences between the groups. Clusters were defined as contiguous time points in which the group *t*-statistic computed for a specific metric at each time point within the cluster satisfied a threshold ($p < 0.10$). This threshold was chosen as it provided the most robustly sized clusters for subsequent cluster-level statistical analysis. A cluster-level test statistic was computed as the sum of *t*-statistics in each cluster. A *p*-value for the cluster-level test statistic was then calculated under a permutation distribution. This distribution was constructed by collecting the maximum cluster-level statistic of 2000 random partitions of the set of all of the individual errors from both groups. A cluster with a corrected *p*-value of less than 0.05 under the permutation distribution was considered significant. Thus, the uncorrected time point-by-time point test statistic was used to define and identify clusters, whereas the cluster-level test statistic was used to determine statistical significance. This method effectively controls for type I error rate.

2.5. MEG acquisition and analysis

MEG data were acquired continuously for each tracking condition in a magnetically shielded room (IMEDCO-AG, Switzerland) using an Elekta/NeuromagTM whole-head MEG system (VectorView) equipped with 204 gradiometers and 102 magnetometers. EOG electrodes were used to detect eye movements and blinks. Data were recorded spontaneously at 1000 Hz from all 306 sensors, with no signal averaging. Data were subsequently processed by MaxFilter to remove environment noise (Taulu et al., 2004a; Taulu et al., 2004b; Taulu and Simola, 2006; Song et al., 2008). The realistic boundary element method (BEM) head model was used for MEG forward calculation (Mosher et al., 1999; Huang et al., 2007). A BEM mesh of 5-mm size for the subject was generated from the inner-skull surface using a set of T1-weighted MRI images taken on a 1.5 T MRI scanner. Co-registration of MRI and MEG was performed using data obtained from the Polhemus Isotrak system prior to MEG scanning. MEG data were then band-pass filtered into the alpha (8–13 Hz), beta (15–30 Hz), and gamma (30–100 Hz) bands using frequency-domain filtering with appropriate Hanning windows. Delta (1–4 Hz) and theta (4–7 Hz) bands were not analyzed due to the limited time samples in each recording and contamination from eye movements. Source reconstruction of each condition for each frequency band was performed on all sensors using the Fast-Vestal MEG source imaging approach (Huang et al., 2014a), which is capable of detecting activity from cortical and deep brain structures such as the hippocampus and amygdala (Huang et al., 2014b; Huang et al., 2014c). For analysis of the continuous tracking condition, epochs containing a single target revolution (2500 ms) from all three blocks were combined. Covariance matrices of these epochs were then averaged prior to source reconstruction. For analysis of the gap tracking condition, epochs containing 500 ms of data prior to and 1500 ms of data after target disappearance (for all gap durations) were isolated. This time window was chosen as it reflected brain activity during the pre-gap, within-gap, and post-gap periods. This time window also maximized epoch length and avoided overlap of gaps, allowing construction of stable covariance matrices but only allowing analysis in a single common time-window. Covariance matrices of these epochs were then averaged and subsequently used for source reconstruction. An evenly spaced grid (5 mm spacing) with ample coverage of the brain volume was used to model the source-space. Root-mean-square (RMS) amplitude per grid point was then computed for each reconstruction and saved in a 3-D nifti format file. The RMS reconstructions were then smoothed (Gaussian kernel, 10 mm FWHM, corresponding to a voxel size of 5mm × 5mm × 5mm) and averaged within condition for each subject.

2.6. Group analysis of MEG data

Averaged RMS amplitude reconstructions per condition were transformed to MNI 152 space using FLIRT registration (FSL). A square-root transformation was applied to all data and group differences in the alpha, beta, and gamma bands were then examined for the following conditions: 1) continuous tracking (main effect), 2) gap tracking (main effect), and 3) gap minus continuous tracking (interaction effect). The randomize routine in FSL (2000 iterations) was applied to generate uncorrected *p*-values for group tests using age as a covariate. Age was used as covariate to directly test for group differences in the MEG measures, independent of age, and to conduct separate analyses in the mTBI and control groups that adjusted for normal aging effects on the correlations among various measures. Next, cluster analysis was performed to correct for family-wise error across voxels in which mass clustering at a threshold voxel-wise *t*-statistic of 2.0 was employed to correct for multiple-comparisons. Large clusters surviving multiple comparisons (cluster-level p-value < 0.05) were further subdivided into regions of interest (ROIs) by using the *t*-statistic profile as a guide.

2.7. Classification analyses

To determine the accuracy of the behavioral and neuroimaging measures in classifying subjects into their respective groups, the support vector machine (SVM) learning algorithm (implemented in the Machine Learning MATLAB toolbox) was separately applied to 1) neuropsychological variables that were sensitive to cognitive impairment in the mTBI group; 2) visual-tracking parameters that were sensitive to mTBI deficits and 3) measures from ROI showing abnormal frequency-band amplitude in the mTBI group. SVMs function by building models to

classify samples into two distinct categories in a non-probabilistic geometric fashion. Each sample occupies a specific position in space determined by its set of variables (i.e., neuropsychological, eye tracking, and MEG). The samples are then separated by the best-fitting hyperplane as determined by the SVM. The general SVM analysis procedure for this dataset was as follows: Classifiers were generated to determine group separability for each of the three variable sets described above. A linear kernel function was used with SVM to classify data, owing to its ease of interpretation and its better performance than other kernel functions (e.g., Gaussian, nonlinear) for the current datasets. Leave-one-out cross validation was conducted for each SVM classification. A signed distance score and a classification outcome were assigned to each of the subjects in the cross-validations to compute classification accuracy for each set of variables. In addition, an index of the contribution of a variable was obtained for each analysis.

We took the analysis one step further by performing SVM optimization. After conducting SVM leave-one-out cross validation by including all variables in a dataset and computing classification accuracy, we then removed the least contributing variable one-by-one and computed classification accuracy at each step. This procedure generated a curve for classification accuracy and number of variables used in the SVM. Choosing the highest point on this curve gave the best SVM classification and a list of the most important variables. To examine if any further improvement in the classification could be achieved, a fourth SVM optimization and classification analysis combined the top ranked ROIs and top ranked neuropsychological variables from the above analyses.

2.8. Optimized SVM functions and behavioral measures

Partial correlations (age adjusted) were conducted to examine the association between the optimized SVM function for the ROI amplitude and the visual tracking measures that were impaired in the mTBI group. These analyses were conducted separately for the mTBI and control groups. Owing to our a priori interest in the relationship between these specific abnormal eye movement measures and the expression of the SVM function, partial correlations with uncorrected *p*-values were reported. Partial correlations were also conducted to explore the association of the optimized SVM functions that best distinguished between the two groups with 1) clinical symptoms, 2) months post-injury, and 3) the neuropsychological measures that showed significant impairment in the mTBI group. To adjust for the multiple analyses, uncorrected *p*-values were FDR corrected ($p < .05$, corrected).

3. Results

3.1. Behavioral symptoms and neuropsychological test performance

Table 1 details behavioral symptoms and neuropsychological test performances in the groups. The groups did not differ in the extent to which they endorsed symptoms associated with ADHD (CAARS-S: S) and depression (CES-D). The range of CES-D scores was 0–25 in the control group and 0–42 in the mTBI group. Three subjects in each group had scores ≥16 (control group values = 16, 22, and 25; mTBI group values = 17, 22, 42), possibly signifying a risk for depression. However, there was a significantly higher level of post-traumatic stress in the mTBI group than in the control group (PCL-C). No group differences were found in attentional control (ANT), although the overall reaction time of the mTBI group was slower than the control group. The groups performed comparably on tests of spatial working memory and psychomotor speed. The mTBI group was impaired relative to controls on executive function tests (COWAT Letter Fluency and Animal Fluency), information processing speed (SDMT), and verbal memory (CVLT-II). Months post-injury did not correlate with any of the neuropsychological tests that were impaired in the mTBI group.

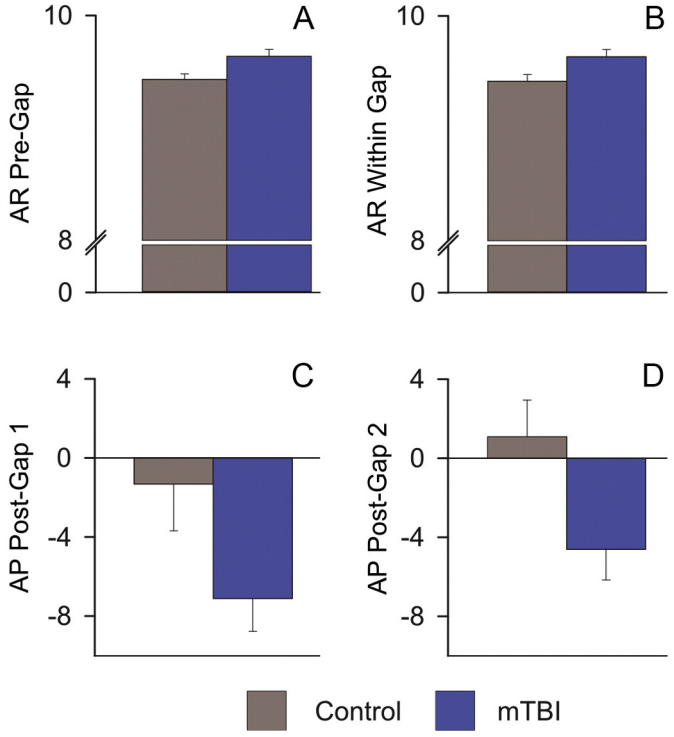


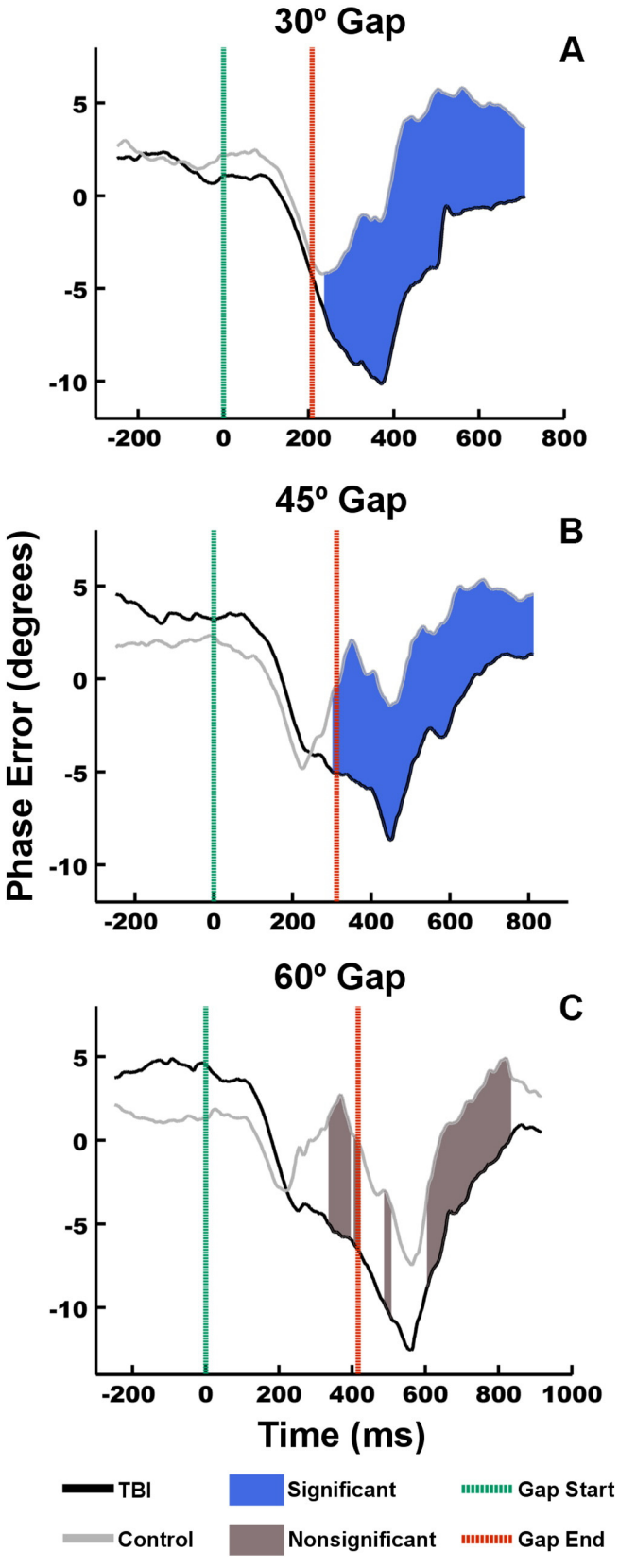
Fig. 2. Group differences in average radius (AR) and average phase (AP) error before, during, and after target occlusion. Graphs A and B display AR for the control and mTBI groups 208 ms before (Pre-Gap) and 208 ms during (within Gap) target occlusion. The mTBI patients showed significantly greater AR than the control group during both periods. Graphs C and D display AP for the control and mTBI groups 208 ms (Post-Gap 1) and 400 ms (Post-Gap 2) after the target reappeared. The mTBI group lagged behind the target during both post-gap periods (i.e., more negative values), whereas the control group tracked more closely to the target.

3.2. Visual-tracking performance

In the continuous tracking condition, the mTBI group performed comparably to the control group on all measures (Supplementary Table 1). In the gap condition, however, significant group differences were found. Fig. 2A and B show that the mTBI group had a larger average radius than the control group during the pre-gap ($p = 0.01$) and the within-gap ($p = 0.02$) time windows. Fig. 2C and D also show that the mTBI group exhibited greater negative average phase during the post-gap 1 ($p = 0.05$) and post-gap 2 ($p = 0.02$) time windows. This finding demonstrates that the gazes of mTBI patients lagged behind the target after its reappearance (i.e., more negative values), whereas the control subjects tracked more closely to the target, anticipating its speed and continuous changes in direction. There were no significant group differences in other tracking measures in the gap condition (Supplementary Table 2). Fewer months post-injury correlated with a larger within-gap average radius ($r_{age} = -0.517$, $p < .05$, FDR corrected), but not with other eye tracking variables that were impaired in the mTBI group.

The group difference in average-phase was consistent with the dynamics of target tracking in the gap condition between the two groups. Fig. 3 shows the average phase error for both groups over a time course extending from 250 ms before target disappearance to 500 ms after the target reappears. In the 30 degree gap condition (Fig. 3A), phase lag is statistically similar for both groups until approximately 100 ms after the disappearance of the target, at which point lag increases for both groups. However, as the target reappeared at 208 ms, the control group showed a marked improvement in phase lag and was able to synchronize with the target and return to baseline tracking. In contrast, the TBI group took much longer to respond to the target reappearance and return to baseline tracking. This difference was verified by the

statistically significant ($p < 0.05$) cluster of time-points beginning at 25 ms after target reappearance. Similar behavior was noted for the 45 degree gap condition (Fig. 3B). Here, control subjects began to return to baseline at approximately 200 ms after the target disappeared, and the cluster of time points that differed significantly from the mTBI group ($p < 0.05$) started before the time of target reappearance at 312 ms. Though similar trends were observed in the 60 degree gap condition (Fig. 3C), none of the clusters survived the cluster-level statistical test, suggesting that the larger gap rendered the task too challenging for many of the control subjects. Cluster analysis of tracking in the radial direction showed no significant group differences, irrespective of the gap degree. Analyses of saccade frequency, which was directly related to the subject's execution of catch-up saccades, showed no statistically significant difference between control and mTBI subjects (see Supplementary Table 2). This suggested that differences in saccade execution did not play a major role in these findings.



3.3. MEG results

No significant differences in brain activity were found between the control and the mTBI groups (i.e., main effect test) for the continuous or gap conditions, irrespective of frequency band (alpha, beta, and gamma). To adjust for individual differences in baseline performance during continuous tracking and examine the interaction of group and tracking condition, we tested for group differences in brain activity for the gap minus continuous tracking conditions (interaction test). Group differences in the alpha and gamma bands were not significant for this contrast. However, significant group differences were found for this interaction in the beta band for ten regions (Table 3; Fig. 4). These regions included the right superior parietal lobe (SPL) (1), left SPL (2), bilateral precuneus (3), right angular gyrus (4), right supramarginal gyrus (SMG) (5), right temporal–parietal junction (TPJ) (6), left caudate nucleus (7), left frontal pole (8), left amygdala (9), and left temporal pole (10). Fig. 5 displays the mean differences in beta amplitude for the gap minus continuous tracking contrast in each of these significant regions. For regions 1 to 6, which were in the parietal cortex, beta amplitude was increased in the gap condition relative to the continuous condition in the control group, and decreased in the mTBI group. For regions 7 to 10, the relationship was reversed. To test for significance of the differences in beta amplitude between the gap and continuous conditions within each group, follow-up paired *t*-tests were conducted. The mTBI group showed lower beta amplitude in the gap condition than the continuous tracking condition for regions 1 to 6, whereas the control group showed greater beta amplitude for regions 1, 2, 5, and 6. The mTBI group showed greater beta amplitude in the gap condition than the continuous tracking condition for regions 9 and 10, whereas the control group showed lower beta amplitude for regions 7 to 10. Months post-injury did not correlate with beta amplitude in these regions, except for the right SMG wherein decreased beta amplitude in the gap condition relative to the continuous condition was greater for patients with fewer months post-injury ($r_{age} = 0.55$, $p = .005$, FDR corrected).

3.4. Classification analyses

Next, we analyzed the accuracy of the behavioral and neuroimaging measures in classifying subjects into their respective groups. The SVM

Fig. 3. Phase error dynamics for 30° (A), 45° (B), and 60° (C) gap tracking conditions. Clusters of time points in blue survived multiple-comparisons, indicating significant differences in visual tracking between the control and mTBI groups. Clusters of time points in brown were significant uncorrected for multiple comparisons, but were not significant after correction for multiple-comparisons. White regions between the mTBI and control group time-courses failed to cluster and therefore, indicate no statistical difference between the groups. In the 30° and 45° gap conditions, the mTBI group exhibited significantly more phase lag than the control group after re-appearance of the target. Traces for periods between 250 ms before target disappearance and 500 ms after target reappearance are shown.

algorithm was separately applied to four sets of features or variables: 1) the nine neuropsychological variables that showed impairment in the mTBI group (Table 1); 2) the four visual tracking parameters that were impaired in mTBI deficits during gap tracking (average radius for the pre-gap and gap periods; average phase for post-gap periods 1 and 2); 3) the MEG-beta amplitude differences in the ten ROI showing abnormality in the mTBI group (Table 3); and 4) the ROI and neuropsychological measures that were identified by the optimized SVM analyses of these datasets. Table 4 lists the variables that contributed to the classification for each analysis and the relative importance of a variable as measured by the SVM weight. Fig. 6 displays the distance of each subject from the hyperplane that best separated the two groups, which is a measure of the strength of classification. The graphs plot the classification weights (*y* axis) for each subject (*x* axis; subject number 1–25 are controls and 26–50 are mTBI patients). Positively and negatively weighted values respectively designate whether subjects were classified into the control or mTBI group.

3.4.1. MEG beta amplitude in ROIs

Measures from six of the 10 ROIs maximized the classification accuracy of all subjects (Table 4). Measures from the right SPL, bilateral precuneus, and left temporal pole were decisive classification variables, as indicated by their weights. Total classification accuracy was high (92%). The weighted combination of beta amplitude for the 6 ROIs correctly classified 92% of the controls and 92% of the mTBI patients (Fig. 6A), with only two misclassified subjects in each group.

One visual tracking measure that was abnormal in the mTBI group, average phase, correlated with the expression of the SVM ROI function in the control group, but not in the mTBI group (Fig. 7). There was a trend for a partial correlation (age adjusted) between post-gap 1 average phase with the SVM ROI function ($r_{age} = .39$, $p = .06$) and a significant partial correlation between post-gap 2 average phase and the SVM ROI function ($r_{age} = .41$, $p = .047$). In the control group, better anticipation during the post-gap periods (more positive values) was associated with greater separation of a subject from the mTBI group (i.e., higher positive weight), presumably due to better neuronal functioning. Average radius did not correlate with the SVM function for MEG measures in either group. Measures of symptom severity (e.g., PTSD checklist, ADHD, frequency of depression symptoms on the CESD scale), PCS symptom counts, months post-injury, and neuropsychological test performances also did not correlate with the MEG SVM function.

Table 3
Group differences in regional MEG beta-band amplitude for the gap minus continuous condition comparison.

Regions	ml	X	Y	Z
Controls: Gap ≥ continuous tracking [1]				
[1] R superior parietal lobe	4.75	20.9	−55.2	60.2
[2] L superior parietal lobe	1.10	−8.49	−56.1	58.1
[3] Bilateral precuneus[a]	0.34	1.37	−41.9	52.1
[4] R angular gyrus[a]	0.48	41.2	−54.4	42.6
[5] R supramarginal gyrus	0.93	62.7	−43.6	22
[6] R temporal–parietal junction	1.56	55.6	−60.2	13.8
mTBI: Gap ≥ continuous tracking [2]				
[7] L caudate[b]	0.75	−19.3	22.3	4.6
[8] L frontal pole[b]	0.30	−20	38.1	−18.9
[9] L amygdala	3.57	−30	3.5	−24.9
[10] L temporal pole	1.64	−40.2	15.1	−30.8

Talairach coordinates (X, Y, Z) were used to map the location of regions. For each group, follow-up *t*-tests were performed to test for significant differences in beta amplitude between the gap and continuous tracking conditions. L and R = left and right hemisphere.

[1] In the control group, beta amplitude in the gap condition was greater than or equal to (designate by [a]) the continuous condition. In the mTBI group, all 6 regions showed lower beta amplitude in the gap condition than in the continuous condition.

[2] In the mTBI group, beta amplitude in the gap condition was greater than or equal to (designated by [b]) the continuous condition. In the control group, all 4 regions showed lower beta amplitude in the gap condition than in the continuous condition.

Table 4
Results from the optimized SVM analyses of the MEG. ROIs, eye tracking measures and neuropsychological variables.

	SVM weight
MEG regions	
Right superior parietal lobe	5.92
Bilateral precuneus	4.96
Left temporal pole	4.10
R supramarginal gyrus	2.92
Right angular gyrus	1.98
Left caudate	1.12
Visual tracking measures	
Average phase post-gap 2	3.00
Average phase post-gap 1	1.86
Average radius within gap	1.14
Neuropsychological variables	
CVLT-II: Short Delay Free Recall	7.78
CVLT-II: Long Delay Free Recall	6.78
SDMT	6.36
CVLT-II: Short Delay Cued Recall	4.96
CVLT-II: Immediate Free Recall	3.74
ANT RT	3.20
CVLT-II: Long Delay Cued Recall	2.12
COWAT: Animal Fluency	1.60
MEG regions & neuropsychological variables	
Right superior parietal cortex	7.98
Left temporal pole	6.80
Right supramarginal gyrus	6.02
Right angular gyrus	4.70
CVLT-II: Short Delay Cued Recall	4.44
COWAT: Animal Fluency	2.92
Bilateral precuneus	2.06
ANT RT	1.08

3.4.2. Visual tracking measures

Of the four eye movement measures, three maximized total classification accuracy, including within-gap average radius and average phase during the post-gap periods 1 and 2 (Table 4). Average phase during the post-gap period 2 (400 ms after target reappearance) was especially influential in the classification. Still, total classification accuracy was poor (64%). Only 60% of the controls and 68% of the mTBI patients were correctly classified (Fig. 6B), with 10 controls and 7 mTBI patients misclassified. Symptom severity (e.g., PTSD checklist, ADHD, frequency of depression symptoms on the CESD scale), PCS symptom counts, months post-injury, and neuropsychological performances did not correlate with the eye movement SVM function.

3.4.3. Neuropsychological variables

Of the 9 neuropsychological measures, 8 maximized total classification accuracy (Table 4), which was moderate (80%). Letter Fluency was the only measure that did not add to the classification. Decisive variables were CVLT-II measures and the SDMT. The optimized SVM function correctly classified 84% of the controls and 76% of the mTBI patients (Fig. 6C), with 4 controls and 5 mTBI patients misclassified. Symptom severity (e.g., PTSD checklist, ADHD, frequency of depression symptoms on the CESD scale), PCS symptom counts, frequency of depression symptoms on the CESD scale, and months post-injury did not correlate with the neuropsychological SVM function.

3.4.4. Optimized MEG ROIs and neuropsychological variables

The 6 MEG beta amplitude ROIs and 8 neuropsychological variables identified by the optimized SVM analyses were combined into another SVM analysis. Of the 14 variables in this analysis, 8 variables (beta

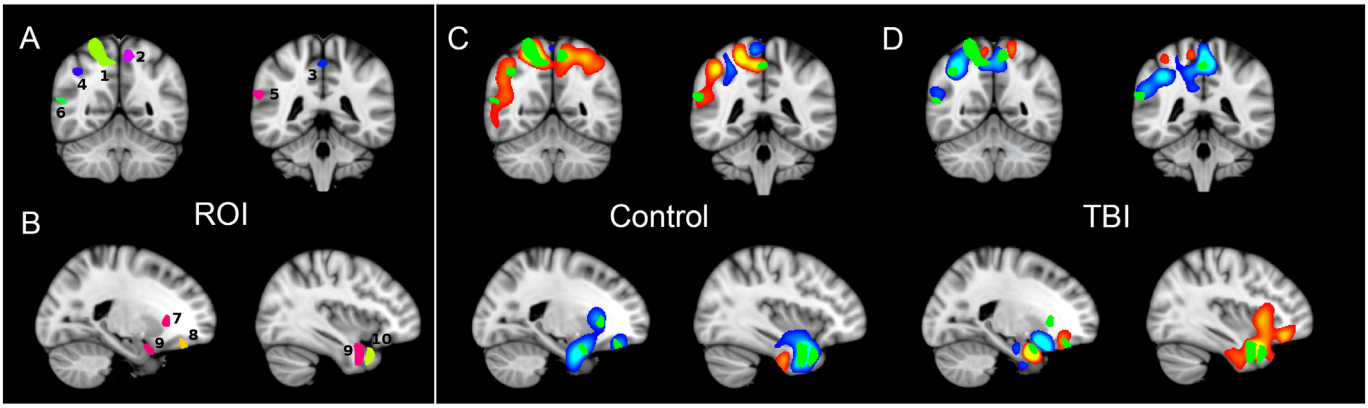


Fig. 4. Regions showing group differences in MEG beta-band amplitude for the gap minus continuous condition comparison. Displayed regions are those that showed a significant group X tracking condition interaction. Numbers correspond to the regions that are detailed in Table 3. Images are display in radiological view. A) For regions 1 to 6, control subjects showed greater beta amplitude in the gap than the continuous condition, whereas the mTBI group showed lower beta amplitude in the gap than the continuous condition. B) For regions 7 to 10, the mTBI group showed greater beta amplitude in the gap than the continuous condition and control subjects showed lower beta amplitude in the gap than the continuous condition. C) Underlying gap minus continuous source activities for control subjects. D) Underlying gap minus continuous source activities for mTBI subjects. For panels C and D, hotter colors (red) indicate regions where gap tracking activity was greater than continuous tracking activity and cooler colors (blue) indicate regions where gap tracking activity was less than continuous tracking. ROIs from A and B are depicted in bright green and are overlaid onto activation in C and D.

amplitude differences in 5 ROIs and 3 neuropsychological measures) maximized classification accuracy (Table 4). The most influential variables were beta amplitude differences in the right SPL, SMG, angular gyrus, and the left temporal pole, and short delay cued recall (CVLT-II). The linear combination of these 8 variables improved total classification accuracy to 94%, owing to the correct classification of one additional control subject, who was misclassified in the ROI SVM analyses. Fig. 6D shows that 96% of the controls and 92% of the mTBI patients were correctly classified, with one control and 2 mTBI patients misclassified.

4. Discussion

In the present study, chronic mTBI patients exhibited striking deficits when tracking a predictably movement target that was occluded from vision at random locations and time periods. Deficits were more pronounced than those found in a study that utilized target occlusion at a fixed location (Suh et al., 2006). Our findings provide the first detailed analysis of the time course of phase error in mTBI patients prior to, during, and immediately after target occlusion. The results suggest that the internal anticipatory control is disrupted in chronic mTBI

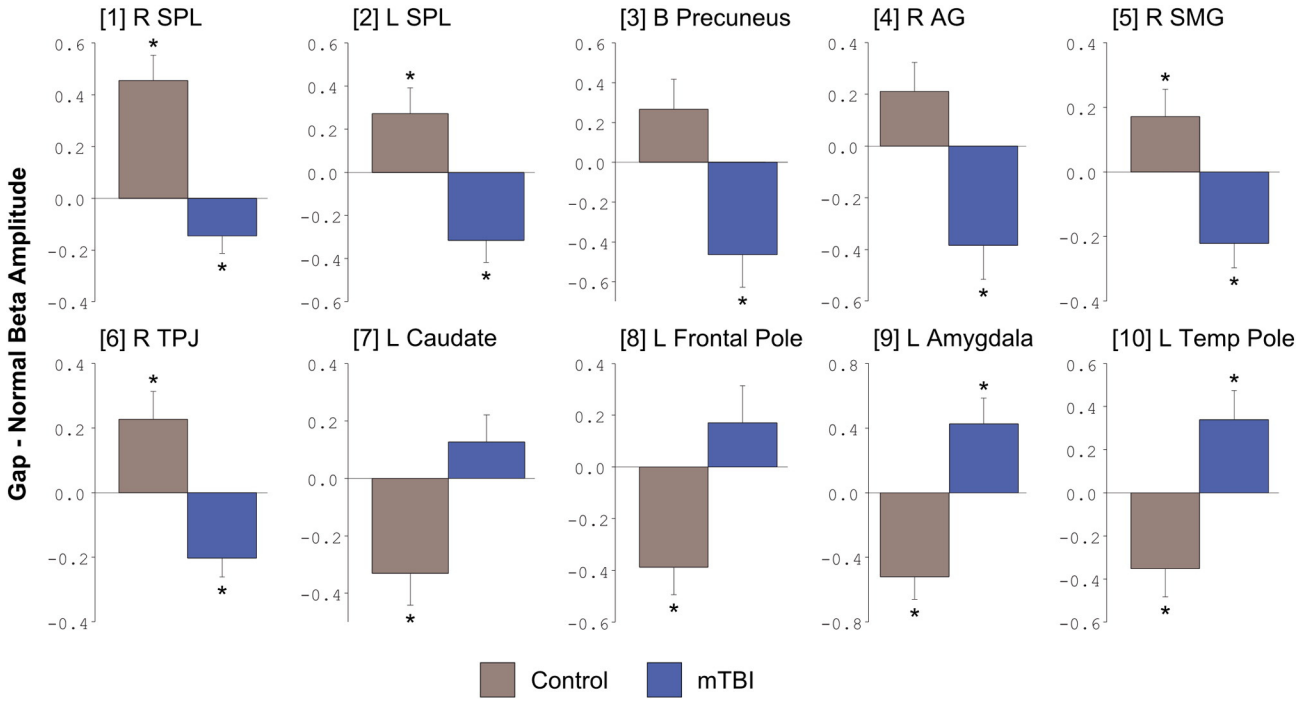


Fig. 5. Regional differences in MEG beta-amplitude between the gap minus continuous condition comparison. Significant differences between the control (brown bars) and mTBI (blue bars) groups were found for the gap minus continuous condition contrast in ten regions (see Table 3 and Fig. 3 for details). *Beta amplitude within a group for the gap minus continuous conditions contrast differed significantly from zero ($p = 0.05$). R and L = right and left hemispheres; B = bilateral; AG = angular gyrus; SMG = supramarginal gyrus; SPL = superior parietal lobule; Temp Pole = temporal pole; TPJ = temporal–parietal junction.

patients with persistent PCS symptoms. Deficits in visual tracking were found only in the gap condition, but even when the target was visible. Thus, the mere expectation of target blanking appeared to gate the output of an internally-generated anticipatory response (Barnes, 2008). Both groups began to lag further behind the target at the onset of the gap, consistent with the normal decay of internal representations of target motion within 100 ms after target disappearance (Orban de Xivry et al., 2008). However, upon the reappearance of the target, patients were slower at re-synchronizing their gaze with the target. This result suggests a degraded ability to maintain an internal model of motion. An alternative explanation is that significant average phase differences were a result of distraction during the gap condition, possibly owing to poor concentration. This explanation, however, cannot account for the average phase data wherein mTBI patients failed to catch up to the 30 and 45 degree targets, yet did not differ from controls in the 60 degree condition, which was specifically designed to push the limits of anticipatory control. Moreover, the absence of group differences in average phase for the pre-gap period further suggests that this measure is more related to anticipation. Though baseline group differences in average radius during the pre-gap and within-gap time windows might signify a more general disruption in concentration, we believe that diminished representation of the expected target location is a more parsimonious interpretation of the mTBI results. It is also possible that deficient reorienting of attention to the reappearance of the target adversely affected tracking in the gap condition. Acute mTBI patients exhibit deficits in orienting attention on the ANT (Halterman et al., 2006) and an auditory task (Mayer et al., 2009), slowed saccadic RTs during a gap saccade task that normally allows for disengagement of attention from a fixation target (Drew et al., 2007), and impaired reorienting on attention tasks (Halterman et al., 2006; Mayer et al., 2009). However, these problems resolve by 1 month post-injury (Halterman et al., 2006; Drew et al., 2007), consistent with our finding of normalized attentional control on the ANT. Thus, the present results support a more fundamental deficit in internal anticipatory control. Although abnormal visual tracking has been reported in chronic mTBI patients when tracking a continuously visible target, discrepant findings may relate to the inclusion of patients with more significant brain injuries (i.e., positive neuroradiological findings) (Maruta et al., 2010b) or more acute injury (within the past 6 months) (Heitger et al., 2009) than in our study.

4.1. Neural mechanisms of impaired tracking

Disturbances in visual tracking performance were accompanied by differences in beta activity in a number of regions. In the mTBI group, beta activity in parietal regions (precuneus, SPL, SMG, angular gyrus, TPJ), especially in the right hemisphere, was suppressed in the gap condition compared to the continuous tracking condition. Conversely, in the control group beta activity in these regions was enhanced or sustained at a similar level in the gap condition as in the continuous tracking condition. These findings comport with EEG and fMRI studies of healthy adults demonstrating that parietal areas (SMG and SPL) regulate the maintenance of eye motion information during target occlusion (Lencer et al., 2004; Nagel et al., 2006; Burke and Barnes, 2008; Makin et al., 2009), possibly by synthesizing relational metrics (Genovesio et al., 2014), such as time, velocity and spatial information (Harrington et al., 1998; Assmus et al., 2003; Merchant et al., 2013), which are critical for predictive control. The TPJ also modulates predictive control, particularly in the face of uncertainty (Jakobs et al., 2009) or when reorienting attention to unexpected stimuli (Corbetta and Shulman, 2002). These factors may come into play during gap tracking, especially when target occlusion and its reappearance are unpredictable. The failure of mTBI patients to modulate parietal cortex activity in accord with the predictive and attentional demands of gap tracking may be associated with damage to white matter tracts that disrupt communication between frontal cognitive-control centers and the parietal cortex (Niogi et al., 2008; Niogi and Mukherjee, 2010).

Although damage to white matter tracts underlying the frontal cortex is common (Niogi et al., 2008), we did not find abnormal beta, gamma, or alpha activities in the mTBI group in frontal centers that modulate visual tracking, namely the frontal eye fields or the dorsolateral prefrontal cortex (Lencer et al., 2004; Ding et al., 2009). Frontal activities may have been maintained through compensation by other areas of the brain. Specifically, in mTBI patients beta amplitude in the caudate, the amygdala, and the temporal and frontal poles of the left hemisphere was enhanced or sustained at the same level in the gap condition as in the continuous tracking condition, whereas in the control group beta was suppressed in these same regions. The basal ganglia normally modulate visual tracking (O'Driscoll et al., 2000; Lencer et al., 2004) and planning (Elsinger et al., 2006; Monchi et al., 2006), and compensatory activity may improve target encoding and prediction via the basal ganglia's dense connectivity with frontal areas. Likewise, compensatory activity in the frontal pole, which facilitates internally maintained attention (Burgess et al., 2007), and the temporal pole, which synthesizes segregated sensory inputs into this region (Pascual et al., 2015), may also assist in anticipatory control during visual tracking.

Importantly, disturbances in neuronal activity were specific to the MEG beta band. It has long been observed that cortical activity exists in distinct frequency bands that have different patterns of activation. Electrophysiological studies of the rat hippocampus show that the beta rhythm allows neuronal synchrony at large time delays, while the gamma band allows such synchrony at short delays. Anatomically, this suggests that beta synchrony is used for communication involving remote structures, whereas gamma synchrony is used for local computations (Singer, 1999; Kopell et al., 2000). Interestingly, investigations into MEG correlates of fMRI resting-state networks demonstrate that power fluctuations in the beta band produce the most robustly similar spatial networks to fMRI resting-state networks (Brookes et al., 2011a; Brookes et al., 2011b). This relationship also suggests that beta-band activity is used for the type of communication required in long-range networks. Since white matter tracts are integral for synchrony of distant cortical regions and white matter changes from DAI are common in mTBI (Miles et al., 2008; Rutgers et al., 2008; Mayer et al., 2010; Niogi and Mukherjee, 2010; Smits et al., 2011; Ling et al., 2012), the present results may suggest that the injuries sustained by our mTBI patients disrupt long-range beta-band communication in networks important for internal predictive control. It is noteworthy, however, that low-frequency brain rhythms, which were not analyzed in the current study (i.e., delta and theta), have also been associated with interregional communication (Mizuki et al., 1980; Mizuki et al., 1992; Takahashi et al., 1997; Niedermeyer and Lopes da Silva, 2005) and are typically increased in neurological disorders including TBI (Lewine and Orrison, Jr., 1995; Vieth et al., 1996; Lewine et al., 1999; Baayen et al., 2003; de et al., 2003; Huang et al., 2009; Huang et al., 2012; Huang et al., 2014b). Thus, potential alterations in delta and theta bands might also be associated with the changes that we observed in long range communications in mTBI.

4.2. Classification accuracy of MEG and behavioral measures

The present study also demonstrated that group differences in regional MEG-beta amplitude associated with target visibility changes showed high accuracy (92%) in classifying mTBI and control subjects, in contrast to visual tracking (64%) and neuropsychological measures (80%), wherein accuracy was poor to moderate. Importantly, in the control group greater expression of the MEG SVM function was associated with better anticipation of the target motion once it reappeared after the target occlusion, thereby validating the behavioral significance of the classification function. This relationship was absent in the mTBI group, who were impaired in recovering gaze-target synchronization

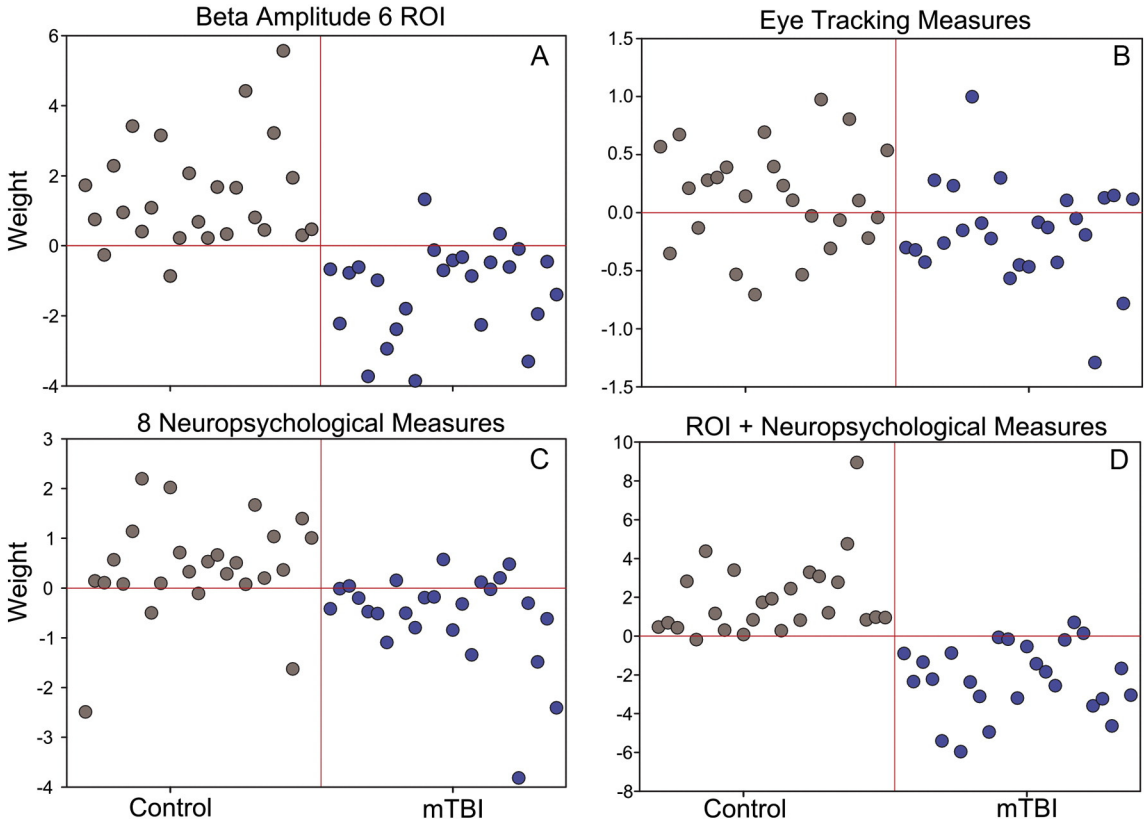


Fig. 6. SVM classification accuracy of regional MEG beta-amplitude, visual tracking and neuropsychological measures. The graphs display the distance of each subject from the hyperplane that that best separated the two groups, which is a measure of the strength of classification. The graphs plot the classification weights (*y* axis) from the optimized SVM analysis for each subject in the control (brown circles) and mTBI groups (blue circles). Positively and negatively weighted values respectively designate whether subjects were classified into the control or mTBI group. The variables that contributed to the optimized SVM classification are listed in Table 4. A: Total classification accuracy using MEG beta-amplitude from 6 ROI was 92%. Two subjects in each group were incorrectly classified. B: Total classification accuracy using 3 visual tracking measures was 64%. Ten controls and 7 mTBI patients were incorrectly classified. C: Total classification accuracy using 8 neuropsychological measures was 80%. Four of the controls and 5 of the mTBI patients were incorrectly classified. D: Total classification accuracy using beta amplitude from 5 ROI and 3 neuropsychological measures was 94%. One control subject and 2 mTBI patients were incorrectly classified.

once the target reappeared. Clinical profiles of the patients were also not associated with abnormal neural functioning, as months post-injury, PCS symptom counts, depression, post-traumatic trauma, and neuropsychological test performances did not correlate with the MEG SVM function. This finding underscores the limitations of clinical measures in characterizing outcomes in chronic mTBI patients (Bigler, 2013). Though MEG is more time and resource intensive to analyze than neuropsychological testing, it greatly improves detection of subtle injuries caused by mTBI, which could aid clinical diagnosis and treatment management.

Our results are consistent with reports that eye movement measures alone show poor accuracy (62.5%) in classifying chronic mTBI patients (3 months post-injury) when cross-validation methods are employed in the statistical analyses (Heitger et al., 2008). This study also reported that neuropsychological measures demonstrated poor accuracy (62.5%), which contrasts with our results, wherein we obtained modest levels of classification accuracy. However, MEG beta-band activity in five ROI from the optimized SVM function, combined with three neuropsychological measures (short delay cued recall, verbal fluency, and reaction time), improved classification only slightly (94%) by correctly classifying all but one control subject. This indicates that performance in certain domains of cognition may add independent information that aids in distinguishing healthy individuals from mTBI patients, a prospect that warrants further study in the future. Nonetheless, beta-band activity appears to be a better intermediate marker of residual pathophysiological changes in chronic mTBI than neuropsychological and visual tracking measures. Certainly the relative accuracy of neuropsychological measures over imaging measures may well depend on the activation probes for neural functioning (e.g., task difficulty and reliability) and the analytic methods used to characterize neural activity. For example, our results and those of others (Suh et al., 2006; Maruta et al., 2010a) reliability demonstrate that visual tracking of a periodically occluded target is sensitive to deficient anticipatory control, presumably secondary to momentary lapses in attention. Although our neuropsychological tests did not assess anticipatory control, standardized measures of attentional control (i.e., ANT) and processes that significantly engage attention (i.e., spatial working memory) to discrete events were not impaired in our chronic mTBI group. Thus, visual tracking of an occluded target may be an effective probe for aberrant neuronal functioning because it demands a greater degree of continuous attentional control than classic neuropsychological tests of attention. A caveat is that eye movement and neuropsychological measures may demonstrate greater sensitivity and/or specificity in distinguishing acute mTBI patients with PCS (Heitger et al., 2008), owing to the effects of edema, inflammation, and other physiological processes on the brain. At the same time, MEG and other functional imaging measures may be inherently more sensitive to changes in neuronal functioning than traditional clinical neuropsychological or behavioral assessments (Bigler, 2013).

We are not aware of any studies that have directly compared the relative accuracy of neuroimaging and neuropsychological measures in distinguishing acute or chronic mTBI patients without positive radiological findings from healthy controls. However, in semi-acute mTBI,

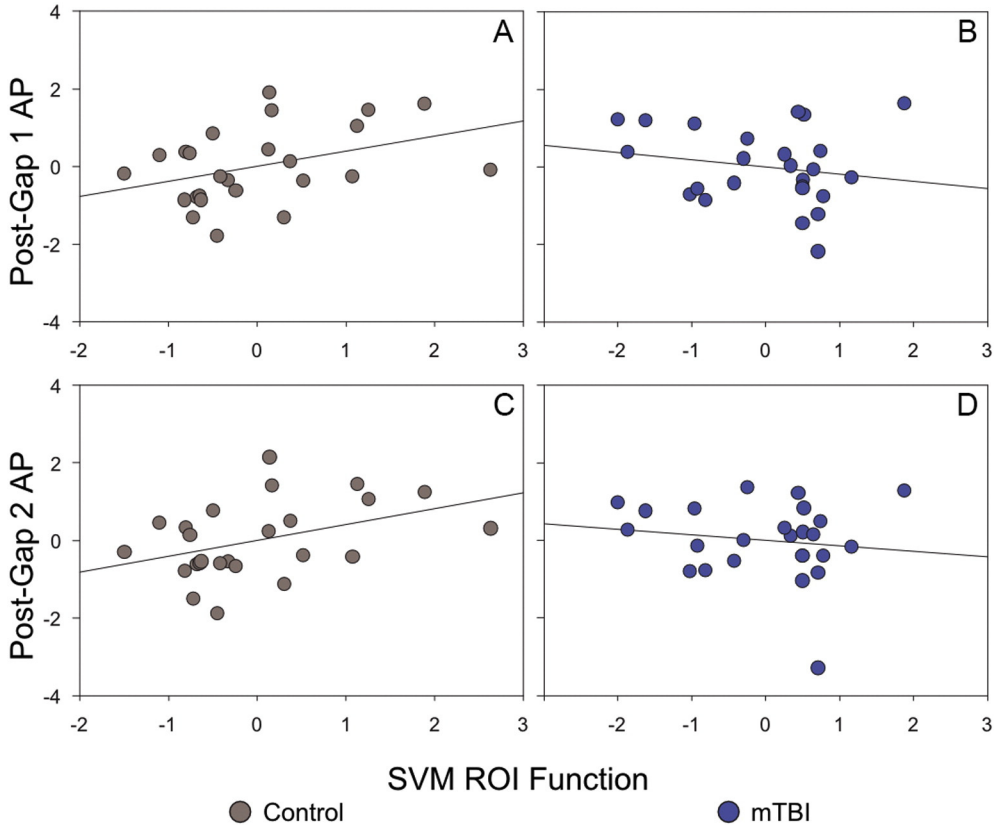


Fig. 7. Scatter plots showing the relationship between average phase (AP) after the target reappeared and the expression of the optimized SVM function for MEG beta-amplitude in 6 ROI. The Post-Gap 1 and Post-Gap 2 periods were defined as 208 and 400 ms after the target reappeared, respectively. Negative and positive AP values (*y* axis) respectively signify lagging behind and tracking ahead of the target. Positively and negatively weighted values respectively designate whether subjects are more likely to classify into the control or mTBI group. Panels A and C: in the control group, more positive AP values during both post-gap periods (better anticipation of the target) were associated with higher SVM values (better neuronal functioning) (Post-Gap 1: $r_{age} = .39$, $p = .06$; Post-Gap 2: $r_{age} = .41$, $p = .047$). Panels B and D: in the mTBI group, no relationship was found between AP and SVM values.

fractional anisotropy in commonly injured white matter tracts (genu of corpus callosum, corona radiata, and superior corona radiata) slightly improved total classification accuracy (71%) beyond estimated premorbid intelligence (65% total accuracy) (Ling et al., 2012). Resting-state functional connectivity measured from BOLD fMRI also improved total classification (84%) of semi-acute mTBI patients beyond estimated premorbid intelligence (65% total accuracy) (Mayer et al., 2011). However, these modest levels of accuracy must be cautiously interpreted as they are likely lower since cross-validation analyses were not reported in either study.

5. Conclusions

Our results show for the first time that MEG beta-band activity associated with a task that required internal anticipatory control is sensitive in identifying abnormal neuronal functioning in chronic mTBI patients. The accuracy of classification was surprisingly high given the heterogeneity of injuries in mTBI (Huang et al., 2009; Huang et al., 2012) and the absence of positive findings on conventional MRI. We believe that the high accuracy is due to MEG's capacity to analyze different frequency bands separately, owing to its high temporal resolution. Another important factor was our MEG source analysis method, Fast-VESTAL, which provides high-resolution source images for complicated signals that contain many sources, without the need for intervention from the data analyst (Huang et al., 2014a). Fast-VESTAL faithfully reconstructs the source time-courses even in data containing highly correlated sources, which many conventional MEG source-analysis methods (e.g., beamformer) have difficulty handling (Van Veen et al., 1997; Gross and Ioannides, 1999; Sekihara et al., 2001). Fast-VESTAL is also robust to high levels of sensor, environment, and brain noise. For example, in our visual tracking task, the number of localized neural sources was large and regional activities were likely highly correlated. Moreover, the signal-to-noise ratio was relatively low, due to the limited number of visual tracking trials. Despite these factors, Fast-VESTAL proved to be a robust method for identifying neural dysfunction in mTBI patients.

Though the current results require further validation in a different and larger sample of mTBI patients and healthy adults, our findings hold promise for identifying neuronal sources of dysfunction in PCS patients, many of whom have subtle, but lingering cognitive problems that affect functioning in daily life and the quality of life. In this regard, it is notable that neuropsychological measures of cognition have been unsatisfactory in gauging recovery from acute mTBI (Carroll et al., 2004; Heitger et al., 2004; Heitger et al., 2006; Heitger et al., 2007; Bigler, 2013). The need for markers of abnormal neuronal functioning has become increasingly important for predicting outcomes in TBI patients and for assessing therapies that may facilitate recovery, even in chronic TBI patients. Longitudinal studies will be needed to ascertain the prognostic value of neuroimaging measures, such as MEG, in predicting outcomes. Any functional imaging marker will likely be used in combination with other markers, since together they may better gauge the degree of neural dysfunction, predict the recovery rate of functions, and unravel individual differences in the evolution of recovery. This includes biomarkers of white-matter integrity, which are related to cognitive functioning in mTBI (Kraus et al., 2007; Miles et al., 2008; Niogi et al., 2008), and blood and cerebrospinal fluid markers (Di Battista et al., 2013; Zetterberg et al., 2013).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2015.04.011.

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