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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.