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Deficits in predictive smooth pursuit after mild traumatic brain injury

Minah Suh [a,*], Rachel Kolster [b,c], Ranjeeta Sarkar [b], Bruce McCandliss [c], Jamshid Ghajar [a,b], the Cognitive and Neurobiological Research Consortium

[a] *Department of Neurological Surgery, Weill-Cornell Medical College, New York, NY 10021, USA*
[b] *Brain Trauma Foundation, Weill-Cornell Medical College, New York, NY 10021, USA*
[c] *Sackler Institute, Department of Psychiatry, Weill-Cornell Medical College, New York, NY 10021, USA*

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Abstract

Given that even mild traumatic brain injury (TBI) may produce extensive diffuse axonal injury (DAI), we hypothesized that mild TBI patients would show deficits in predictive smooth pursuit eye movements (SPEM), associated with impaired cognitive functions, as these processes are dependent on common white matter connectivity between multiple cerebral and cerebellar regions. The ability to predict target trajectories during SPEM was investigated in 21 mild TBI patients using a periodic sinusoidal paradigm. Compared to 26 control subjects, TBI patients demonstrated decreased target prediction. TBI patients also showed increased eye position error and variability of eye position, which correlated with decreased target prediction. In all subjects, average target prediction, eye position error and eye position variability correlated with scores related to attention and executive function on the California Verbal Learning Test (CVLT-II). However, there were no differences between TBI and control groups in average eye gain or intra-individual eye gain variability, or in performance on the Wechsler Abbreviated Scale of Intelligence (WASI), suggesting that the observed deficits did not result from general oculomotor impairment or reduced IQ. The correlation between SPEM performance and CVLT-II scores suggests that predictive SPEM may be a sensitive assay of cognitive functioning, including attention and executive function. This is the first report to our knowledge that TBI patients show impaired predictive SPEM and eye position variability, and that these impairments correlate with cognitive deficits.

Keywords: Mild TBI; Smooth pursuit eye movement; Shearing injury; Attention; Executive function; Variability; Diffuse axonal injury (DAI)

Traumatic brain injury (TBI) is the leading cause of death and disability in young people in the US. Of the 1.5 million brain injuries occurring annually, 85% are classified as "mild" [3]. Even mild TBI can produce extensive diffuse axonal injury (DAI) [1,32], leading to cognitive deficits [31,35]. Several studies have indicated that TBI patients are impaired in attentional and executive functions, including learning, working memory and executive control [4,5,28,40]. In addition, studies have demonstrated increased performance variability after TBI [17,42], which is potentially indicative of attentional deficits associated with cerebellar dysfunction [7,13]. However, conventional neuroimaging and neuropsychological measurements have thus far been unreliable in detecting structural abnormalities and cognitive deficits after mild TBI [35,36]. Therefore, patients who sustain a head injury classified as mild TBI may have varying degrees of brain injury severity and symptoms.

Smooth pursuit eye movements (SPEM) are controlled by neural circuitry [11,24,33,39] overlapping with neural pathways involved in attention, anticipation and executive function [13,20,26,29,37], suggesting an association between SPEM and cognitive processes. During tracking of a predictable target, the cerebellum programs SPEM based on both retinal and extra-retinal signals, including cortical input [11,30,33,39,41], enabling the production of predictive SPEM. This compensates for delays (~100 ms) in the processing of visual feedback [21,25]. Behavioral [2,19,22,23,27,39] and fMRI [39] studies show that predictive SPEM is modulated by higher cortical functions such as attention, anticipation and learning. Due to extensive white matter connectivity between cerebral and cerebellar regions, the overlapping pathways involved in predictive

* Corresponding author.
E-mail address: minah@med.cornell.edu (M. Suh).

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SPEM and cognitive functions may be particularly susceptible to damage from DAI [1,18,36,38].

We hypothesized that predictive SPEM would be impaired in TBI patients, and that impairments would correlate with deficits in attention, anticipation and executive function. Correlations between these measures would suggest that predictive SPEM may be a sensitive metric of cognitive functioning. While several studies have demonstrated oculomotor deficits in TBI patients [15,16,47], to our knowledge no studies have shown specific deficits in predictive SPEM after mild TBI.

To explore this issue, a predictable sinusoidal stimulus, circular target tracking, was used to investigate deficits in predictive SPEM in mild TBI patients. Performance was monitored over a 50 s period. However, the tracking period was subdivided into epochs of 12.5 s to provide a thorough analysis of changes in performance over time. Performance on the California Verbal Learning Test (CVLT-II) [9] was studied to investigate whether there is an association between deficits in predictive smooth pursuit and cognitive functioning. To determine whether potential differences in CVLT-II performance between TBI patients and controls may be accounted for by IQ differences, the Wechsler Abbreviated Scale of Intelligence (WASI) [45] was also administered.

Twenty-one patients with mild TBI (Glasgow Coma Scale scores 13–15 at time of injury) between ages 15 and 60 were recruited for this study; 6 patients were tested within 10 days after injury (acute group, mean testing time after injury = 8.8 days), and 15 patients were tested within 5 years after injury (chronic group, mean testing time after injury = 2.3 years). Conditions for study inclusion were blunt, isolated TBI, post-traumatic amnesia, and non-intoxication at the time of testing. Patients were excluded on the basis of prior TBI with loss of consciousness, pregnancy, drug or alcohol abuse, neurological or psychiatric diagnosis, seizures or general anesthesia within two weeks of testing. All patients had significant symptoms of TBI, scoring ≥ 2 on the Head Injury Symptom Checklist [14]. The control group ($n = 26$) consisted of subjects without a history of TBI between ages 15 and 60 and with the same inclusion criteria used for the TBI group. Mean ages and mean years of education for the TBI and control groups were matched (TBI: age 35.7 ± 11.8, education 13.2 ± 3.4 years; Normal: age 28.4 ± 13.2, education 14.1 ± 2.8 years; Mann–Whitney (MW) test, $p = 0.24$ (age), $p = 0.34$ (education)). Before each testing session, an eyechart was used to verify that all subjects had normal or corrected-to-normal vision.

Eye movements were recorded by a human infrared video-based eye-tracking system (Eyelink II) with 500 Hz temporal resolution. The target stimulus, a red circle of 0.2° diameter, was presented on a black computer screen. Subjects were seated in a darkened room 40 cm from the computer monitor, with heads stabilized via a bite bar system. Calibration based on nine central and peripheral locations was performed before each session, and also ensured that all subjects had a full range of oculomotor movement. The task consisted of two blocks of 20 (for TBI subjects) or four blocks of 20 (for control subjects) continuous cycles, in which the stimulus moved in a clockwise circular trajectory of 7.0° radius at a rate of 0.4 Hz. A larger number of blocks was tested for the control group to evaluate test-retest reliability. If subjects expressed signs of fatigue or discomfort, they were encouraged to take a break. Standardized instructions were followed for the administration of the CVLT-II and WASI.

The signals representing eye and target movements were low-pass filtered at 50 Hz and stored on a computer for further analysis. Eye and target velocities were obtained by a two-point digital differentiation. Saccades were detected based on a velocity threshold criteria (100°/s), counted and removed. A linear interpolation technique was used to bridge the gaps produced by removal of saccades. An index for target prediction was obtained by identifying the maximum τ from a cross-correlation analysis between the response and the stimulus velocity. Positive τ indicates phase lead, while negative τ indicates phase lag. Eye position error was defined as the summation of the horizontal and vertical distance between eye and target position, and was averaged across the entire cycle. Intra-individual variability of eye position was defined as the standard deviation of eye position error. Eye gain was defined as the ratio between eye and target velocity. Intra-individual variability of eye gain was defined as the standard deviation of eye gain.

The TBI group showed decreased target prediction (increased phase lag) compared to the control group during the first five cycles (approximately 12.5 s duration) of each block; TBI: $-8.8 \text{ ms} \pm 13.5 \text{ ms}$ versus controls: $+4.4 \text{ ms} \pm 5.7 \text{ ms}$ (MW, $p < 0.001$). No differences in target prediction (ANOVA; $p > 0.05$) were found between blocks in either the TBI or control group, which allowed the averaging of target prediction (τ) across blocks (Fig. 1). Although both TBI and control groups exhibited some degree of target prediction, indicated by maximum τ greater than -100 ms, the standard SPEM latency [21,25], 43% of TBI patients showed deficits in target prediction relative to control subjects during the first five cycles, indicated by a mean τ 2.5 standard deviations below the mean τ of controls. There were no differences between acute and chronic TBI patients on any measures (MW, $p > 0.05$). Therefore, the groups were combined for all analyses.

The lack of differences in target prediction (τ) between the TBI and control group after the first five cycles (TBI: $-9.7 \text{ ms} \pm 12.4 \text{ ms}$ versus controls: $-6.3 \text{ ms} \pm 4.2 \text{ ms}$; MW, $p > 0.05$) suggests that control subjects were unable to sustain the generation of predictive SPEM, decreasing their later performance to the level of TBI patients. Control subjects showed a significant decrease in target prediction over the course of each block (ANOVA; $p < 0.01$), while TBI patients showed no change in performance within each block (ANOVA; $p > 0.05$). It is possible that the control subjects began each block with a higher level of attention and subsequently experienced a decrease in prediction due to a loss of attention. In contrast, the TBI patients may have been consistently inattentive throughout the block. Therefore, only the initial five cycles of each block were used for comparison analyses, as averaging over all cycles would have eliminated differences between the TBI and control group. We will explore this possibility in future dual-task studies investigating the allocation of attention over the course of the experiment.

Compared to the control group, the TBI group showed greater eye position error, TBI: $1.7° \pm 1.1°$ versus controls: $0.8° \pm 0.2°$,