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Procedural Learning Impairments Identified via Predictive Saccades in Chronic Traumatic Brain Injury

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Abstract

Objective—To characterize integrity of fronto-striatal circuitry in chronic traumatic brain injury (TBI).

Background—Due to both direct and indirect effects, TBI is hypothesized to affect frontal and striatal function. On the basis of elegant animal, lesion, and neuroimaging literatures, oculomotor testing can provide a useful tool for in vivo assessments of neurophysiologic function. The predictive saccade paradigm in oculomotor function is well established to provide assessment of this fronto-striatal circuit.

Methods—Sixty patients with a history of chronic TBI completed 2 specific tests of oculomotor function, including a test of reflexive visually guided saccades to assess basic oculomotor function and a predictive saccade test to assess procedural learning.

Results—TBI (mild and moderate/severe) was associated with a decrease in rates of procedural learning, with degree of impairment increasing with injury severity. This was observed as a decrease in the proportion of anticipatory saccades (primary measure of learning).

Conclusions—This abnormal oculomotor performance supports the hypothesis that TBI results in chronic impairment of frontal-striatal functions proportionally to injury severity and demonstrate that oculomotor testing is sensitive to all severities of closed-head injury.

Keywords

traumatic brain injury; oculomotor function; predictive saccades; reflexive guided saccades

Although traumatic brain injury (TBI) has a civilian incidence of 100 per 100,000^{1,2} and is the “signature” injury among military personnel serving in Iraq and Afghanistan,³ there is much that is still not understood about the specific relationships between injury, resultant neuropathology, and chronic neurobehavioral disability. Trauma can result in contusions

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(typically in the frontal lobes, temporal horn, and occipital pole^{4,5}) and diffuse axonal injury.⁶ Diffuse axonal injury has been hypothesized to underlie neurobehavioral dysfunction secondary to disruption of cortical-subcortical pathways.⁷⁻⁹ In milder cases, diffuse axonal injury may be the only significant pathology raising concern that standard clinical neuroimaging may not be sensitive to persistent impairment in brain function.

Oculomotor testing provides a noninvasive method to assess the integrity of many neural circuits that are of interest in TBI, including the frontal-striatal circuit. One basic oculomotor task is the visually guided saccade (VGS) paradigm, which requires subjects to complete a reflexive saccade to targets that appear unpredictably in the visual field. The VGS task depends upon the frontal and parietal eye fields, striatum, thalamus, superior colliculus, and cerebellar vermis.¹⁰ Previous work in our laboratory demonstrated abnormalities in VGS performance in chronic, moderate-to-severe TBI (msTBI), especially in circumstances where the target appeared with the central fixation target still present (overlap condition). This condition requires subjects to first disengage attention from the central cue to generating a saccade to the peripheral target. Increased latencies in this condition indicates difficulty disengaging from the fixation point, suggesting frontal lobe dysfunction, even in mild TBI (miTBI).¹¹ This finding of frontal dysfunction was further characterized with a second oculomotor task (the anti-saccade paradigm). This is more specifically dependent on the integrity of the frontal lobes, as it requires subjects to inhibit a reflexive saccade to peripheral targets and then generate a saccade to the hemifield opposite of the presented peripheral target. Patients with TBI made more prosaccade errors (initiation of saccades to the target rather than the opposite hemifield), which more specifically indicates frontal dysfunction.¹¹

In addition to frontal lobe dysfunction in TBI, there is also evidence of damage to striatal systems (upon which certain frontal circuitry is dependent). The predictive saccade (PRED) test provides a measure of procedural learning that is known to rely upon frontal striatal circuitry.¹² As such, the goal of the present study was to examine the effects of TBI on this circuitry using specific tests of oculomotor function that assess saccade responses to unpredictable and predictable targets.

The PRED task typically involves a sequential presentation of 2 targets, each at a fixed location. This serial reaction time task rapidly induces procedural learning because, within 5 to 10 responses, subjects learn to “predict” target appearance and initiate saccades close to, if not anticipating, target appearance. This task has been shown in human neuroimaging studies to rely on regions within the dorsolateral prefrontal cortex, pre-supplementary motor area, anterior cingulate, hippocampus, mediodorsal thalamus, and striatum.¹³

The PRED task previously has been used in TBI, and there is preliminary evidence that it is, in fact, sensitive to the neuropathology of mild trauma.¹⁴ In a small sample of mixed chronic and subacute miTBI, Suh et al¹⁴ demonstrated significant effects of TBI on accuracy of PREDs and variability of response timing. Although based on the small sample and period of recovery during testing conclusions about the fronto-striatal deficits cannot be clearly delineated, the study provides evidence of the usefulness and validity of PRED in TBI. The present study was designed to characterize performance on PRED and VGS tasks in 60 patients with a history of chronic TBI (patients were at least 1 y from injury, and therefore stable in recovery) across a range of trauma severities. These patients and methods were selected to determine whether there is persistent evidence of frontal-striatal circuitry dysfunction after chronic TBI of varying severity.

MATERIALS AND METHODS

Subjects

Sixty subjects with a history of a single TBI, closed head type, participated (Table 1). Thirty subjects (18 females and 12 males) had a history of miTBI, and 30 (14 females, 16 males) had msTBI. All were at least 1 year out from injury, with an average of 80 months for miTBI and 125 months for msTBI. Subjects were recruited from the University of Illinois Medical Center through advertisements. Thirty demographically matched healthy controls (22 females, 8 males) were recruited from the community. Experimental procedures complied with the code of ethics of the World Medical Association and the standards of the University of Illinois Institutional Review Board. All subjects provided written informed consent consistent with the Declaration of Helsinki.

As both nicotine and caffeine have been reported to affect eye movements, we collected information from the participants on the usage of both. Only 1 control reported light use (1–10 cigarettes/d), and 2 miTBIs reported moderate use (11–20 cigarettes/d). In the msTBI group, 3 of the 30 participants reported light use, and 3 reported moderate use. The gross majority of all participants reported average daily caffeine consumption to be less than 2 cups daily (26 controls, 24 miTBI, 23 msTBI). Both nicotine and caffeine use were recoded, such that participants were grouped in either no to light use or moderate use categories, with 10 cigarettes per day being the cutoff for nicotine use, and 2 cups of coffee (or the equivalent in tea or other beverages) the cutoff for caffeine. Each analysis reported below was run with caffeine and nicotine use as independent variables. The main effect of nicotine and caffeine use was not significant in any of the analyses. As such, all the conducted analyses were collapsed across nicotine and caffeine use.

Exclusion criteria were: any history of major psychiatric disorder, including major affective or psychotic disorder such as schizophrenia, substance abuse, pending litigation, or any neurologic/medical condition (other than TBI for the TBI patients) that could result in cognitive changes (eg, hypertension, diabetes, stroke, seizure). None of the participants reported a family history of major psychiatric disorder in first-degree relatives. Subjects were not receiving any treatments for cognitive deficits at the time of the study. The criteria used for defining miTBI were set forth by the American Congress of Rehabilitation Medicine.¹⁵ Subjects were categorized as mild severity (miTBI) if the length of loss of consciousness was less than 30 minutes and duration of posttraumatic amnesia was less than 24 hours. Patients were classified as msTBI if the length of loss of consciousness was >30 minutes, posttraumatic amnesia was >24 hours, and/or the Glasgow Coma Scale was >13. The average reported loss of consciousness was 0.1 hours (range, 0–0.50 h) for miTBI and 380 hours (range, 0.50–2880 h) for msTBI. Injury mechanisms were motor vehicle accidents (67%), pedestrian versus motor vehicle accidents (10%), sports injuries (10%), and a small percentage of other causes. The healthy controls were not different from the TBI groups in age or education. The controls and miTBI groups were not significantly different in estimates of premorbid IQ (Table 1). The premorbid IQ estimate for msTBI was significantly lower than in controls ($P=0.02$).

Neuropsychologic Assessment

The neuropsychologic battery used to characterize the population assessed executive function, attention, and memory, although it was heavily weighted toward executive function. Tests included Tower of London,¹⁶ Stroop Color-Word Test,¹⁷ Paced Auditory Serial Addition Test,¹⁸ Trail Making Test,¹⁹ Conners' Continuous Performance Test – II (CPT),²⁰ Controlled Oral Word Association Test,²¹ Ruff Figural Fluency Test,²² Wechsler Test of Adult Reading,²³ California Verbal Learning Test (2nd Edition),²⁴ Brief Visual

Spatial Memory Test (Revised),²⁵ Digit Span and Spatial Span (3rd Edition),²⁶ and Grooved Pegboard.²⁷ All subjects passed the tests for malingering and effort (Test of Memory Malingering).²⁸

Z-scores were calculated for all subjects, with the mean and standard deviation of data from healthy subjects used to define unity for all subject groups. Negative scores indicated performance below the mean of healthy subjects. Domain scores for measures of executive function, attention, and memory were defined based on convention as well as a review of the relevant literature. The references indicated below represent a literature that uses these tests to assess functions similar to the current manuscript. The executive function domain score included the total moves in the Tower of London,²⁹ the age-corrected Stroop Color-Word,^{30,31} the total score of the Paced Auditory Serial Addition Test,³² Form B of the Trail Making Test,³³ the number of errors of commission of the CPT,³⁴ the total score on the Controlled Oral Word Association Test,³⁵ the number of unique designs as part of the Ruff Figural Fluency Test,³⁵ and the scaled scores in the Digit Span and Spatial Span backward.³⁶ The attention domain was calculated using the scales' scores in the Digit Span³⁷ and Spatial Span forward,³⁸ the time required to complete Form A of the Trail Making test,³⁵ and the number of errors of omission in the CPT.³⁴ Finally, the memory domain was calculated based on the California Verbal Learning Test³⁷ (total trials 1 to 5 and long-free recall) and the Brief Visual Spatial Memory Test (trials 1 to 3 and delay recall). The final domain scores were generated by averaging the standardized data from tests assessing these cognitive domains as presented in the Appendix 3.

Oculomotor Tasks: Procedure and Apparatus

Subjects were tested in a darkened black room without extraneous visual stimuli. Subjects were positioned in a chin and forehead rest to minimize head movement. Visual targets were presented in the horizontal plane at eye level via rear projection onto a screen. Electrodes were placed at the lateral and nasal canthi of each eye to obtain direct current electro-oculography recordings (Grass Neurodata 12 Acquisition System). Eye blinks were monitored using electrodes placed above and below the left eye. Before processing, data were smoothed with a finite impulse response filter. Performance on each trial was reviewed to identify blink artifacts and occasional failures of the software to identify primary saccades. Quantitative assessment of eye movement data was performed without knowledge of subject group or other characteristics.

VGS Task—Subjects were required to fixate on a central target for 1.5 to 2.5 seconds before looking toward peripheral targets presented unpredictably at 10, 20, or 30 degrees of visual angle to the right or left of central fixation. A total of 72 trials were presented across three 24-trial blocks, with a rest between each block. Peripheral targets were presented randomly either 200 milliseconds after the central fixation point was extinguished (gap condition) or 200 milliseconds before the central fixation point was extinguished (overlap condition). Latency, peak velocity, and gain of primary saccades were measured. Saccade gain (percent of distance moved to the target location) is a measure of accuracy, indicating the extent the saccade overshoot or undershot the target.

PRED Task—Subjects were required to fixate on a central target for 5 seconds, then follow the target as it moved back and forth to the left and right of center (+6 and -6 degrees) every 750 milliseconds for 40 target displacements. Latency, peak velocity, and gain of primary saccades were obtained.

Statistical Analyses

For the descriptive data and neuropsychologic testing, a 1-way between subjects analysis of variance (ANOVA) with group membership (controls, miTBI, and msTBI) as the between-subjects factor was performed. Bonferroni corrections were applied and post hoc testing carried out using a corrected P value of 0.05 as the threshold for significance. For the VGS task, the primary analyses were 2-way mixed design ANOVAs with group membership (controls, miTBI, and msTBI) as the between-subjects factor and condition (gap and overlap) as the within-subjects factor. Comparisons between measures within subject groups were carried out using paired-samples T tests. TBI was not related to any laterality difference in eye movements, nor were there any differential effects of target displacement amplitude for any variables of interest. Therefore, data were collapsed across both direction of saccade and size of target displacement in the primary analysis.

To determine whether TBI affected procedural learning, the primary analyses evaluated systematic changes in response to latency across the 40 trial tasks. Best-fit lines using a nonlinear inverse second order regression were applied to the latency data for each group. Two-way, mixed design ANOVAs were used to examine differences in the slope (rate of learning) for each group. Additionally, learning was examined by classifying the proportion of saccades, which could be classified as regular saccades (latencies >140 ms in duration), anticipatory saccades (latencies <90 ms), and an intermediate group of speeded saccades (latencies falling between 90 and 140 ms). The relative proportions of each type of saccade were then quantified in blocks of 5 trials. Additional 2-way mixed design ANOVAs were carried out on the total number of saccades within each type as well as overall saccade gain.

Speed and magnitude of learning can be evaluated in 2 distinct but complementary analyses. First, the effects of learning on latency were evaluated by extracting best-fit measures of the rate (slope) of learning. These were then compared across groups. This provides a general assessment of learning. To examine more specifically the effects of TBI, the latency data were reanalyzed across all 40 trials and within subgroups of the 40 trial paradigms. Each saccade was characterized as either regular (latency >140 ms), speeded (latency between 90 and 140 ms), or anticipatory (latency <90ms). The relative proportion of total anticipatory saccades provides an overall measure of learning.

RESULTS

Neuropsychologic Function

There was an overall effect of group membership (controls, miTBI, and msTBI) on all 3 neuropsychologic domains (Fig. 1). Detailed results for each measure included in the domain scores are reported in the Appendix 3. Post hoc testing demonstrated that the miTBI group differed from controls on the executive domain ($P=0.044$), but not in memory or attention. However, the msTBI group performed significantly worse than controls in all domains after correction for multiple comparisons (Bonferroni, executive: $P<0.001$; attention: $P<0.001$; memory: $P<0.001$) and they were more impaired than miTBI as well (executive: $P=0.028$; attention: $P=0.005$; memory: $P<0.001$).

VGS

Latencies—As shown in Figure 2A, all subject groups showed longer latencies in the overlap than gap condition [controls: $T(29)=19.49$, $P<0.001$; miTBI: $T(29)=11.83$, $P<0.001$; msTBI: $T(29)=18.27$, $P<0.001$]. This relative increase in latencies from gap to overlap conditions is found normally, and is defined as the gap effect.³⁹ Figure 2A also illustrates the interaction between the conditions (gap, overlap) and groups (controls, miTBI, msTBI) [$F(2,87)=11.33$, $P<0.001$], with msTBI showing the greatest gap effect, ($M=101.1$

ms, $SEM = 5.54$ ms), followed by the miTBI, ($M = 81.97$ ms, $SEM = 6.93$ ms) and the controls, showing the smallest gap effect ($M = 64.31$ ms, $SEM = 3.03$ ms). The differences between the groups were primarily driven by latency differences in the overlap condition during which both miTBI and msTBI showed longer latencies than controls.

Gain—Although there was no significant interaction between group and gap/overlap condition [$F(2,87) < 1$, $P = 0.943$], there was a main effect of subject group such that the miTBI undershot the target more than controls. This pair-wise comparison reached significance in the overlap condition [$T(58) = 2.041$, $P = 0.046$] and showed a trend for a similar pattern in the gap condition [$T(58) = 1.87$, $P = 0.067$]. Although there was a similar trend for the msTBI relative to controls, this did not reach significance. This effect is depicted in Figure 2B.

Velocity—As with saccade gain, there was no interaction between condition and subject groups on measures of peak saccade velocity, $F(2,87) = 1.288$, $P = 0.281$. There were also no main effects of either group or condition (Fig. 2C).

PREDs

Latency—Response latencies decreased significantly across the 40-trial protocols as subjects learned to anticipate when and where targets would appear, and to entrain a synchronized response sequence.

Serial Position Effects on Latency—Best-fit models using nonlinear inverse first order regression coefficients were applied to the trial-wise latency data for each group of subjects, and are presented in Figure 3 (controls: $r^2 = 0.94$; miTBI: $r^2 = 0.87$; msTBI: $r^2 = 0.92$). Controls showed a more rapid and greater decrease in response latency than the msTBI and miTBI groups. Estimates of each parameter for all 3 groups are included in Table 2. Learning curves of all 3 groups differed significantly from each other [$F(9,120) = 17.15$, $P < 0.001$].

Proportion of Regular, Speeded, and Anticipatory Saccades—The total proportion of anticipatory saccades across all 40 trials for each group of subjects is presented in Figure 4. All the 3 groups showed a robust procedural learning effect, as indicated by a high proportion of anticipatory saccades. However, the magnitude of learning differed across subject groups, $F(2,88) = 3.513$, $P = 0.034$, such that 22 of the 40 trials were classified as anticipatory for the controls, 19 of 40 for the miTBI, and 17 of the 40 trials for msTBI. Posthoc comparisons showed a significant difference only between the controls and msTBI.

Gain—There were no differences between the groups from the aspect of the gain of anticipatory saccades, nor were there differences in gain of anticipatory saccades as a function of serial position, $F(14,609) < 1$.

Velocity—There were no differences between groups or between groups and serial position in the peak velocity of anticipatory saccades, $F(14,609) < 1$.

Neuropsychologic Assessment and Oculomotor Variables—A series of exploratory correlations were conducted between neuropsychologic measures and oculomotor variables. No correlations were found for either the TBI groups or the controls between latencies and any of the cognitive domains (memory, attention, and executive) in an exploratory analysis. Neither the proportion of regular nor the anticipatory saccades correlated with the domain scores. We also conducted exploratory correlations with each individual neuropsychologic measure used to calculate the domain scores with our primary

oculomotor variables. For the proportion of anticipatory saccades generated by the TBI group, there was a negative relationship with the number of commissions on the CPT ($P=0.035$), such that greater commissions were associated with fewer anticipatory saccades. For the gap effect on the VGS, a larger gap effect (greater disengagement cost) was associated with increased reaction time on the CPT ($P=0.044$), and increased total time to complete Trails B ($P=0.045$).

DISCUSSION

The neuropathology of TBI commonly results in the disruption of critical cortical and cortical-subcortical circuitry. Oculomotor testing is well suited to quantify and qualify the neurophysiologic effects of these disruptions *in vivo*. Yet, relatively few prior published studies have used this methodology to study TBI, and fewer yet to study chronic injury (defined here as greater than 1 y postinjury) or to compare deficits across a range of TBI severities.

In the current study, procedural learning was assessed in chronic TBI across severities using a standard PRED task, whose neuroanatomy has been well described to include fronto-striatal systems, which are of interest in TBI. The VGS task was included as a means of assessing basic sensorimotor function in TBI. The primary effect of TBI on VGS performance was noted in the overlap condition, with impairment greatest in the msTBI group. In the overlap condition, the central fixation stimulus overlaps temporally with the onset of appearance of peripheral targets, adding in the additional requirement to actively disengage attention from the central cue before executing the saccade. The data suggest that TBI subjects have difficulty disengaging visual attention, and that this impairment is associated with injury severity. This deficit may affect performance on the PRED task, as the planning and initiation of anticipatory saccades typically occurs while the previous target is still present. The modest difference found in saccade gain found for the miTBI group most likely did not significantly affect the results of the PRED task, as the gain of PREDs was not altered.

The PRED data indicate that both groups of TBI subjects showed slower procedural learning rates compared with the controls, and this impairment was proportional to the severity of injury. Group differences in the proportion of anticipatory saccades paralleled these findings. By the end of the 40 trial experiments, subjects of all the 3 groups showed a similar proportion of anticipatory saccades. So, although TBI slows the rate of procedural learning, with greater severity of injury resulting in slower rates, it does not eliminate it. Importantly, the PRED was able to characterize a specific type of learning deficit in TBI via a neurophysiologic method, and hence adds another important dimension to our understanding of neuropathology in TBI across all severities, including those classified as “mild.”

A series of exploratory correlations were conducted between neuropsychologic measures and oculomotor variables. No correlations were found for either the TBI patients or the controls between oculomotor variables (latencies, proportion of regular or anticipatory saccades) and any of the cognitive domains (memory, attention, and executive) in an exploratory analysis. This may be explained in part by a relative lack of sensitivity of many standard neuropsychologic testing batteries (inclusive of the one used here) for the assessment of procedural learning specifically, and could be a focus of further study.

The results of this oculomotor testing reflect the continuum of TBI neuropathology, and the effect of TBI on fronto-striatal circuitry. Neurophysiologic dysfunction logically follows that continuum, as the current data demonstrate. These findings strengthen the role of oculomotor studies in the assessment of all severities of chronic TBI, and document

persistent deficits in fronto-striatal circuitry well after acute recovery from trauma even with mTBI.

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References

1. Bazarian J, McClung J, Shah M, et al. Mild traumatic brain injury in the United States, 1998–2000. *Brain Injury*. 2005; 19:85–91. [PubMed: 15841752]
2. Bruns JJ, Hauser AW. The epidemiology of traumatic brain injury: a review. *Epilepsia (Copenhagen)*. 2003; 44(suppl 10):2–10.
3. Taber KH, Warden DL, Hurley RA. Blast-related traumatic brain injury: what is known? *J Neuropsychiatry Clin Neurosci*. 2006; 18:141–145. [PubMed: 16720789]
4. Adams J, Graham D, Scott G, et al. Brain damage in fatal non-missile head injury. *J Clin Pathol*. 1980; 33:1132–1145. [PubMed: 7451661]
5. Levin HS, Williams DH, Eisenberg HM, et al. Serial magnetic resonance imaging and neurobehavioral findings after mild to moderate closed head injury. *J Neurol Neurosurg Psychiatry*. 1992; 55:255–262. [PubMed: 1583509]
6. Graham, D.; Gennarelli, T.; McIntosh, T. Trauma. In: Graham, D.; Lantos, P., editors. *Greenfield's Neuropathology*. 7. Vol. 2. London: Arnold, Hodder Headline Group; 2002.
7. Gennarelli TA, Thibault LE, Adams JH, et al. Diffuse axonal injury and traumatic coma in the primate. *Ann Neurol*. 1982; 12:564–574. [PubMed: 7159060]
8. Kraus MF, Susmaras T, Caughlin BP, et al. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain*. 2007; 130(Pt 10):2508–2519. [PubMed: 17872928]
9. Povlishock JT. Traumatically induced axonal injury: pathogenesis and pathobiological implications. *Brain Pathol*. 1992; 2:1–12. [PubMed: 1341941]
10. McDowell J, Dyckman K, Austin B, et al. Neurophysiology and neuroanatomy of reflexive and volitional saccades: evidence from studies of humans. *Brain Cogn*. 2008; 68:255–270. [PubMed: 18835656]
11. Kraus M, Little D, Donnell A, et al. Oculomotor function in chronic traumatic brain injury. *Cogn Behav Neurol*. 2007; 20:170–178. [PubMed: 17846516]
12. Hubert V, Beaunieux H, Chételat G, et al. The dynamic network subserving the three phases of cognitive procedural learning. *Hum Brain Mapping*. 2007; 28:1415–1429.
13. Simo L, Krisky C, Sweeney J. Functional neuroanatomy of anticipatory behavior: Dissociation between sensory driven and memory-driven systems. *Cerebral Cortex*. 2005; 15:1982–1991. [PubMed: 15758195]
14. Suh M, Kolster R, Sarkar R, et al. Cognitive and neurobiological research consortium. deficits in predictive smooth pursuit after mild traumatic brain injury. *Neurosci Lett*. 2006; 401:108–113. [PubMed: 16554121]
15. ACoR Medicine. Definition of mild traumatic brain injury. *J Head Trauma Rehabil*. 1993; 8:86–87.
16. Culbertson, W.; Zilmer, E. The Tower of London—Drexel University (TOLDX): Technical Manual. North Tonawanda, NY: Multi-Health Systems; 2001.
17. Golden, C.; Freshwater, S. The Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Wood Dale, IL: Stoelting Co; 2002.
18. Gronwall D. Paced auditory serial-addition task: a measure of recovery from concussion. *Percept Mot Skills*. 1977; 44:367–373. [PubMed: 866038]
19. Reitan RM, Wolfson D. Category Test and Trail Making Test as measures of frontal lobe functions. *Clin Neuropsychol*. 1995; 9:50–56.

20. Conners, D.; Staff, M. Conners' Continuous Performance test II (CPT II). North Tonawada, NY: Multi-Health Systems Inc; 2000.
21. Benton, A.; Hamsher, K. Multilingual Aphasia Examination. 2. Iowa City: AJA Associates; 1989.
22. Ruff, R. Ruff Figural Fluency Test (RFFT): Professional. Manual Lutz, FL: Psychological Assessment Resources; 1988.
23. Wechsler, D. Wechsler Test of Adult Reading. Manual San Antonio, TX: The Psychological Corporation; 2001.
24. Delis, D.; Kramer, J.; Kaplan, E., et al. California Verbal Learning Test. Adult version. 2. Manual San Antonio, TX: Psychological Corporation; 2000.
25. Benedict, R. Brief Visuospatial Memory Test—Revised: Professional Manual. Odessa, FL: Psychological Assessment Resources Inc; 1997.
26. Wechsler, D. Wechsler Memory Scale. 3. San Antonio, TX: The Psychological Corporation; 1997.
27. Matthews, C.; Klove, H. Instruction manual for the Adult Neuropsychological Test Battery. Madison: University of Wisconsin Medical School; 1964.
28. Tombaugh, T. Test of Memory Malingering (TOMM). Toronto, Canada: Multi-Health Systems; 1996.
29. Newman S, Carpenter P, Sashank V, et al. Frontal and parietal participation in problem solving in the Tower of London: fMRI and computational modeling of planning and high-level perception. *Neuropsychologia*. 2003; 41:1668–1682. [PubMed: 12887991]
30. Little D, Hartley A. Further evidence that negative priming in the Stroop color-word task is equivalent in older and younger adults. *Psychol Aging*. 2000; 15:9–17. [PubMed: 10755285]
31. Van der Elst W, Van Boxtel M, Van Breukelen G, et al. The stroop color-word test: influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment*. 2006; 13:62–79. [PubMed: 16443719]
32. Jefferson A, Paul R, Ozonoff A, et al. Evaluating elements of executive functioning as predictors of instrumental activities of daily living (IADLs). *Arch Clin Neuropsychol*. 2006; 21:311–320. [PubMed: 16814980]
33. Bearden C, Jawad A, Lynch D, et al. Effects of a Functional COMT Polymorphism on Prefrontal Cognitive Function in Patients With 22q11.2 Deletion Syndrome. *Am J Psychiatry*. 2004; 161:1700–1702. [PubMed: 15337663]
34. Miranda M, Sinnes E, Pompeia S, et al. A comparative study of performance in the Conners' Continuous Performance Test between Brazilian and North American Children. *J Atten Disord*. 2008; 11:588–598. [PubMed: 17495240]
35. Basso M, Bornstein R. Effects of past noninjection drug abuse upon executive function and working memory in HIV infection. *J Clin Exp Neuropsychol*. 2003; 25:893–903. [PubMed: 13680438]
36. Chey J, Lee J, Kim Y, et al. Spatial working memory span, delayed response and executive function in schizophrenia. *Psychiatry Res*. 2002; 110:259–271. [PubMed: 12127476]
37. Bozikas V, Kosmidis M, Kioperlidou K, et al. Relationship between psychopathology and cognitive functioning in schizophrenia. *Compr Psychiatry*. 2004; 45:392–400. [PubMed: 15332203]
38. Snitz B, Macdonald Ar, Carter C. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophrenia Bull*. 2006; 32:179–194.
39. Crevits L, Vandierendonck A. Gap effect in reflexive and intentional prosaccades. *Neuropsychobiology*. 2005; 51:39–44. [PubMed: 15627812]

FIGURE 1.

Mean normalized domain scores for neuropsychologic tests classified as targeting primarily executive, attention, and memory domains. Control means are represented by the line at zero, and 1 standard error around the control mean is identified by the gray box around the control mean. miTBIs are represented by the white bar, msTBI by the black bars. miTBI indicates mild traumatic brain injury; msTBI, moderate-to-severe traumatic brain injury.

FIGURE 2.

Visually guided saccade latencies (left panel, A), gain (middle panel, B) and velocity (peak velocity in degrees/sec divided by the amplitude of the target step eliciting the saccade; right panel, C) for controls (c), mild TBI (mi), and moderate/severe TBI (ms) groups. Error bars represent 1 standard error.

FIGURE 3.

Mean latencies for the controls (triangles), miTBI (squares), and msTBI (circles) across the 40 trials. Overall mean latencies for each group are presented on the right. Best-fit nonlinear regression lines are also presented for each group. Error bars represent 1 standard error. miTBI indicates mild traumatic brain injury; msTBI, moderate-to-severe traumatic brain injury.

FIGURE 4.

Proportion of anticipatory to regular saccades across all trials for the controls, miTBI, and msTBI. Error bars represent 1 standard error. miTBI indicates mild traumatic brain injury; msTBI, moderate-to-severe traumatic brain injury.

TABLE 1

Demographic Information for Traumatic Brain Injury and Control Subjects

	Control			miTBI			msTBI			All Groups	Control vs. miTBI	Control vs. msTBI	miTBI vs. msTBI
	M	SEM		M	SEM		M	SEM					
Age	32.83	2.28		31.83	1.58		34.50	2.08		0.63	0.497	0.805	0.313
Education	16.57	0.36		16.20	0.38		15.03	0.48		0.026*	0.486	0.013*	0.068
WTAR	109.83	1.86		111.80	1.74		103.76	1.82		0.007**	0.444	0.023*	0.002**
Time from injury				78.40	14.98		124.77	22.43		0.09			0.091
Age at time of injury				25.87	1.89		25.33	1.93		0.84			0.844
Length of PTA (h)				0.40	0.14		14202.01	14017.12		0.21			0.205
Length of LOC (h)				0.07	0.04		380.29	128.10		0.018*			0.018*

P values are listed under each contrast and asterisks indicate significant differences between groups (* $P < 0.05$; ** $P < 0.01$).

LOC indicates loss of consciousness; miTBI, mild traumatic brain injury; msTBI, moderate-to-severe traumatic brain injury; PTA, post-traumatic amnesia; SEM, standard error of the mean; WTAR, Wechsler Test of Adult Reading.

TABLE 2
Factor Coefficients and Values for Best-fit Lines Representing Latencies Across the Predictive Saccade Test

	Control			mTBI			msTBI		
	Coefficient	SEM	P	Coefficient	SEM	P	Coefficient	SEM	P
y0	-102.82	5.51	<0.001	-57.58	5.98	<0.001	-52.68	5.93	<0.001
a	647.73	63.20	<0.001	557.28	68.56	<0.001	668.52	68.00	<0.001
b	-321.89	67.59	<0.001	-257.84	73.31	<0.001	-384.61	72.71	<0.001

mTBI indicates mild traumatic brain injury; msTBI, moderate-to-severe traumatic brain injury; SEM, standard error of the mean.

APPENDIX

Neuropsychologic Test Results and Domain Scores for all Groups

	Control			msTBI			All Groups	Control vs. msTBI		Control vs. msTBI		msTBI vs. msTBI
	M	SEM		M	SEM			M	SEM	M	SEM	
Executive measures												
Executive domain	0.00	0.15	-0.32	0.11	-0.72	0.11	<0.001**	0.044*		0.010**		<0.001**
Tower of London (total moves)	101.60	2.86	98.87	2.99	94.48	3.10	0.024*	0.511		0.313		0.046*
Stroop Color-Word [age-corrected (s)]	106.33	2.64	103.20	2.30	90.48	3.88	0.217	0.340		0.382		0.036*
PASAT total	132.69	8.94	116.20	7.69	108.96	6.94	0.105	0.166		0.491		0.007**
Trails B (s)	56.60	4.17	57.97	3.81	71.03	5.00	0.040*	0.810		0.041*		0.020*
CPT number of errors of commission	8.00	1.03	14.30	1.34	14.55	1.39	<0.001**	<0.001**		0.897		<0.001**
COWAT total	45.70	1.68	39.30	1.96	33.28	2.06	<0.001**	0.016*		0.039*		<0.001**
RUFF unique designs	45.39	2.13	46.89	1.59	40.48	1.71	0.038*	0.573		0.008**		0.010**
Digit Span backward scaled score	8.50	0.38	8.07	0.47	6.21	0.36	<0.001**	0.476		0.003**		<0.001**
Spatial Span backward scaled score	11.40	0.43	10.93	0.54	10.66	0.55	0.594	0.604		0.632		0.374
Attention measures												
Attention domain	0.00	0.15	-0.30	0.22	-1.25	0.27	<0.001**	0.255		0.008**		0.002**
Digit Span forward scaled score	11.20	0.45	11.30	0.40	9.76	0.47	0.026*	0.868		0.015*		0.078
Spatial Span forward scaled score	10.27	0.56	10.93	0.55	9.86	0.53	0.420	0.494		0.174		0.632
Trails A (s)	23.33	1.44	23.13	1.29	32.41	2.55	0.001**	0.918		0.002**		0.004**
CPT number of errors of commission	0.83	0.23	2.60	0.83	4.69	0.97	0.002**	0.044*		0.106		0.030*
Memory measures												
Memory domain	0.00	0.15	-0.04	0.12	-1.14	0.23	<0.001**	0.842		<0.001**		<0.001**
CVLT total trials 1-5	57.97	1.56	54.93	1.78	45.00	2.17	<0.001**	0.205		0.001**		<0.001**
CVLT Long-Free Recall	12.80	0.52	12.17	0.49	9.34	0.85	0.001**	0.376		0.005**		<0.001**
BVMT Trials 1-3	26.93	1.08	27.30	0.77	21.21	1.38	<0.001**	0.783		<0.001**		0.004**
BVMT delay recall	9.83	0.36	10.53	0.29	8.17	0.51	<0.001**	0.131		<0.001**		0.014*
Other measures												
CPT hit reaction time (ms)	406.43	13.66	370.64	10.17	387.30	13.57	0.134	0.040*		0.328		0.409
Grooved Pegboard [dominant hand (s)]	64.13	1.80	63.07	1.91	106.66	33.51	0.189	0.686		0.192		0.227

P values are listed under each contrast, and asterisks indicate significant differences between groups after correction for multiple comparisons (* $P<0.05$, ** $P<0.01$).

BVMT indicates Brief Visual Spatial Memory Test; COWAT, Controlled Oral Word Association Test; CPT, Conners' Continuous Performance Test; CVLT, California Verbal Learning Test; PASAT, Paced Auditory Serial Addition Test; RUFF, Ruff Figural Fluency Test; Trails, Trail Making Test.