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Visual Tracking Synchronization as a Metric for Concussion Screening

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Our goal was to determine whether performance variability during predictive visual tracking can provide a screening measure for mild traumatic brain injury (mTBI). Seventeen subjects with chronic postconcussive syndrome and 9 healthy control subjects were included in this study. Eye movements were recorded with video-oculography as the subject visually tracked a target that moved through a circular trajectory. We compared the variability of gaze positional errors relative to the target with the microstructural integrity of white matter tracts as measured by the fractional anisotropy (FA) parameter of diffusion tensor imaging. Gaze error variability was significantly correlated with the mean FA values of the right anterior corona radiata (ACR) and the left superior cerebellar peduncle, tracts that support spatial processing and sustenance of attention, and the genu of the corpus callosum. Because the ACR and the genu are among the most frequently damaged white matter tracts in mTBI, the correlations imply that gaze error variability during visual tracking may provide a useful screening tool for mTBI. Gaze error variability was also significantly correlated with attention and working memory measures in neurocognitive testing; thus, measurement of visual tracking performance is promising as a fast and practical screening tool for mTBI.
Keywords: *Attention Network Test (ANT)*, *California Verbal Learning Test, 2nd edition (CVLT-II)*, *diffuse axonal injury (DAI)*, *hemispheric specialization*, *head injury*, *neuroimaging*, *neuropsychology*, *prefrontal cortex*, *smooth pursuit*, *traumatic axonal injury*

TRAUMATIC BRAIN INJURY (TBI), often simply referred to as head injury, occurs when an external force causes damage to the brain. A common pathological feature of TBI includes distributed injury in the subcortical white matter, or diffuse axonal injury (DAI), that may occur with or without focal injury.[1–5] Concussion, a mild form of TBI (mild TBI or mTBI), may involve DAI.[6] Although DAI is difficult to detect by traditional computed tomography and magnetic resonance imaging (MRI) scans,[7–11] histological and imaging methods have demonstrated that DAI is prevalent in the frontal lobes.[1,2] The outcome of DAI is frequently strikingly similar to that after a focal damage to the frontal lobe,[12] and the cognitive symptoms of both types of injury include deficits associated with concentration, attention, memory, and high-level executive functions such as planning and decision making.[12–14] These symptoms are consistent with postconcussive syndrome, subtle cognitive deficits that can lead to chronic disability.[15–19] Because the probability and the degree of injury are considered to be proportional to the shear strain and the frontal lobes are highly susceptible to deformation,[20,21] the functional deficits associated with mTBI may involve microstructural changes in the frontal white matter.

Results of magnetic resonance diffusion tensor imaging (DTI), a powerful new tool for detecting microstructural changes in white matter[8,9] and its severity,[22–24] corroborate the prevalence of DAI in mTBI in the frontal lobes[25–28] although more widely distributed microstructural changes may take place. Of the several quantitative parameters that can be derived from DTI,[29] fractional anisotropy (FA) is considered to be a robust indicator of white matter microstructural integrity.[8,9,22–28,30–35] In a parallel fiber arrangement of a white matter tract, the diffusion of water molecules is directionally constrained, which results in a high FA value. The theoretical range of FA values is from 0 (isotropic) to 1 (completely anisotropic); the larger the value of the index, the greater the white matter structural alignment. Because FA is a continuous measure, the spectrum of TBI-induced white matter changes[24] can be evaluated along the extension of the same FA axis that characterizes the normal population. In this comparison, a tract with a large deviation in the FA value can be interpreted as damaged. In particular,

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Niogi et al[27] found that, among the population of 34 mTBI subjects with chronic postconcussive syndrome, including the 17 with eye movement data comprising the present report, the most frequently damaged white matter tracts were the anterior corona radiata (ACR), the uncinate fasciculus, the genu of the corpus callosum, and the cingulum bundle.

Important insights into postinjury cognitive functions may be provided by neuropsychological tests. However, these measures require lengthy testing sessions and may be best suited for moderate to severe forms of TBI.[14,36–38] In addition, although a characteristic of TBI is frequent lapses of attention,[39,40] traditional measures that use discrete responses would not detect momentary lapses in attention. Because attention varies over time, relatively continuous measures of performance should be used to gauge moment-to-moment fluctuations in attention within individuals.[41]

A supplement to conventional neuropsychological testing in mTBI subjects may be found in the examination of visual tracking performance.[42] With videooculography, eye movement can be monitored easily, precisely, and continuously. Visual tracking of a moving target, which involves both smooth and saccadic elements to match the eye and target motions, requires integration of multiple sensory inputs as well as one's own motor efforts.[43] Visual tracking also requires cognitive processes such as selection of the target, sustenance of attention, spatiotemporal memory, and expectation.[44–46] Because these complex requirements involve a broadly distributed neural system, impaired visual tracking behavior by itself may not implicate injury to a unique location in the brain. However, in the presence of structural changes in the white matter, the associated cognitive dysfunctions are expected to manifest themselves as deficits in the individual's performance. Given the suspected vulnerability of frontal white matter in mTBI, examination of visual tracking performance may provide a valuable and sensitive tool for assessment of functional as well as structural impairments in mTBI.

The use of a circular target trajectory is exceptionally suited for assessing visual tracking performance.[47,48] With a target traveling at a constant velocity with a fixed radius from the center, the motion can be described with only 2 constants. That is, the target movement is highly predictable. This periodic movement can continue indefinitely within the orbital range of the eye, which makes the stimulus particularly suitable for studying the processes required to maintain predictive visual tracking.

Predictive visual tracking requires both attention and working memory.[46] The prefrontal cortex is considered to be an important substrate for these cognitive functions,[49] and these functions are often compromised in mTBI patients.[15–17,19,50] Because the right prefrontal cortex subserves spatial working memory[51] and sustenance of attention,[49,52] the integrity of the fiber tracts that connect to and from this region, in particular, the right ACR, was suspected to be correlated with the performance of predictive visual tracking.

Although previously not reported as vulnerable to mTBI, the forceps major and the superior cerebellar peduncle (SCP) subserve visuomotor functions. Hence, the integrity of these tracts was also suspected to be correlated with visual tracking performance. The forceps major mediates smooth pursuit eye movements by interconnecting bilateral middle temporal and medial superior temporal areas.[53] The SCP is the cerebellar output of prefrontal cerebellar loops. The crossed cerebrocerebellar connections suggest that the cerebellar counterpart of the prefrontal functions are localized contralaterally.[54,55] Therefore, in connection with the right prefrontal cortical functions, the integrity of the left SCP was suspected to be correlated with the performance of predictive visual tracking.

Our goal was to determine whether performance variability during visual tracking can provide a useful screening measure for mTBI. Because TBI is known to increase intraindividual performance variability in visuomotor tasks,[39,40] we quantified the variability of visual tracking performance. Correlating and combining this cognitive parameter with anatomical quantification of the white matter microstructure in mTBI using DTI would provide a practical method to gauge the severity of mTBI.

METHODS

Participants

Seventeen mTBI subjects (10 males, 7 females) with chronic postconcussive syndrome (PCS), aged 20 to 52 years, with the history of injury between 6 weeks and 5 years (mean 2.7 years) before testing were recruited (Table 1). The conditions for inclusion were blunt, isolated TBI, posttraumatic amnesia, and a Glasgow Coma Scale score of 13 to 15 at time of injury. The conditions for exclusion were pregnancy, a history of neurological or psychiatric diagnosis, seizure (before the injury), or drug or alcohol abuse. The mTBI subjects were recruited through referrals from local concussion clinics. Nine healthy subjects (6 males, 3 females) aged 19 to 31 years, with no prior history of TBI were recruited as controls through advertisements distributed in the community. Potential subjects were screened before enrollment in the study. The experimental protocol was approved by the Internal Review Board of Weill Cornell Medical College, and all subjects provided informed consent before testing.

TABLE 1 *Demographic data for subjects with mTBI and summary of conventional clinical MRI findings*

Subjects	Age (y)	Sex	GCS score	Time since TBI (mo)	Conventional MRI reading
T05	45	M	15	56.0	Mild white matter gliosis
T06	25	M	15	33.1	Unremarkable
T08	29	F	15	44.3	Normal
T09	37	M	15	26.2	Hemorrhagic shear injury
T11	31	F	15	15.3	Focal hemorrhagic contusion; cerebellar atrophy; microhemorrhages
T14	44	M	15	35.0	Foci of white matter ischemic change
T15	52	F	15	55.4	Unremarkable
T16	37	M	15	59.9	Normal
T17	49	F	15	36.2	Normal
T20	42	F	15	39.2	Small focus of shear injury in anterior limb of internal capsule
T21	20	M	15	1.4	Right inferior temporal lobe contusion; microhemorrhage
T23	23	M	15	25.8	Small left frontal chronic cortical hemorrhagic contusion
T24	48	F	15	29.3	Normal
T26	43	M	15	7.3	Ischemic white matter change
T27	47	F	15	16.6	Normal
T29	32	M	15	14.7	Craniotomy/craniectomy; encephalomalacia; hemosiderin deposition
T30	23	M	15	64.6	Normal

Abbreviations: GCS, Glasgow Coma Scale; MRI, magnetic resonance imaging; mTBI, mild traumatic brain injury; TBI, traumatic brain injury.

Measures and procedure

Eye movement recording and analysis

Eye movements were recorded binocularly with a video-oculography device (EyeLink II, SR Research, Osgoode, Ontario, Canada) at 500-Hz sampling frequency. Before testing, an eye chart was used to verify that the subject had normal or corrected-to-normal vision. The visual stimulus was presented on a computer screen 40 cm from the subject, and the subject's head was stabilized with a head- and chin-rest during the experiment (Fig 1a). The subject was instructed to visually track a target presented on the computer screen. Calibration based on 9 fixation points whose boundary encompassed the test stimulus was performed before each trial. The test stimulus consisted of a target, a red circle of 0.2° diameter in visual angle, moving clockwise in a circular trajectory of 8.5° radius at 0.4 Hz for 10 to 12 cycles on a black background.

Analyses of eye movement data were conducted using a custom-made MATLAB program (The MathWorks, Natick, MA). The eye and target positions were expressed in visual angle. Blinks and other events during which the pupil was occluded were detected and excluded from the analysis. The data segments for the first cycle were excluded because they included a transient response to the initial target movement. To compensate for small unwanted camera translation relative to the face during eye movement recording, the offsets were estimated with polynomial fits of horizontal and vertical eye positions and subtracted from the data.

The eye position data were differentiated to obtain eye velocity, which was then smoothed with a 10-point moving average filter. The eye velocity data were differentiated to obtain eye acceleration, which was further smoothed with a 5-point moving average filter. Saccades were detected with velocity and acceleration thresholds of 100°/s and 1500°/s^2, respectively, and the saccade segments in the velocity data were replaced with straight lines connecting the remaining segments. Gain is defined as the ratio between the eye and target velocities. To obtain the smooth pursuit gain, sine curves with the frequency of the circular movement of the target were fit to the horizontal and vertical eye velocities using fast Fourier transformation, and the ratios between the eye and target velocities in the horizontal and vertical directions were computed. When a subject was tested with multiple trials, the gain values were averaged.

To visualize the variability of gaze positional errors relative to the target, the target position was expressed in polar coordinates, and the gaze positions were recomputed in a reference frame in which the target was

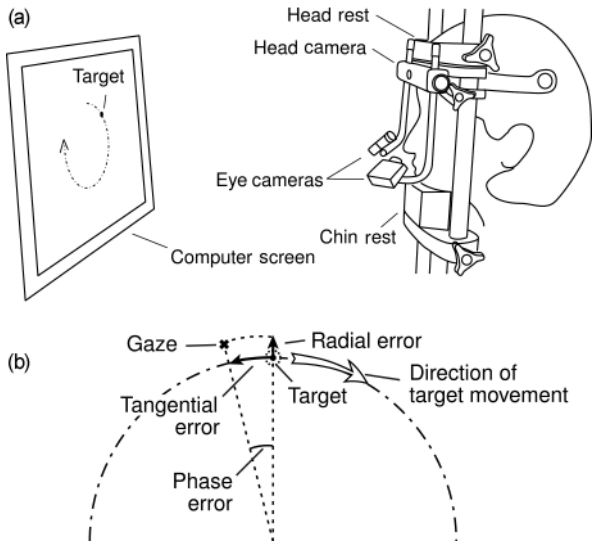

Figure 1. (a) Experimental setup. (b) Schematic definition of parameters. The target, moving clockwise along a circular trajectory (dot-dashed curve), is at the 12 o'clock position. The difference between the gaze and the target positions (gaze error) are indicated by the phase difference and the vectoral components in the radial and tangential directions.

fixed at the 12 o'clock direction (Fig 1b). In this reference frame, the distance between the origin and the gaze represented the instantaneous radius of the gaze trajectory, and the angle formed by the vertical axis and the gaze vector represented the phase difference between the target and the gaze (phase error). The positive phase error was defined as the gaze leading the target (ie, the gaze being ahead of the target along the target's path).

Performance variability in the visual tracking behavior was characterized by the standard deviation (SD) of gaze positional errors relative to the target. The variability in the radial direction was defined as the SD of gaze errors perpendicular to the target trajectory, whereas the variability in the tangential direction was defined as the SD of gaze errors along the target trajectory. To facilitate comparison, the error variability measures are expressed in visual angle for both the radial and tangential directions. The radial error corresponds to the deviation in the radius from the circular trajectory, and the tangential error is proportional to the phase error.

Neurocognitive tests

The Attention Network Test[56] (ANT) is a language independent measure of the efficiency of the neurocognitive networks involved in alerting, orienting, and executive attention based on changes in the reaction times resulting from different types of prompts. The California Verbal Learning Test, 2nd edition (CVLT-II, Pearson, San Antonio, TX) is a verbal learning and memory test, in which examinees are read a list of words and asked to recall them across a series of trials. Seven normal and 12 mTBI subjects took the ANT, and 7 normal and 13 mTBI subjects took the CVLT-II. In total, 5 normal and 10 mTBI subjects completed the ANT, the CVLT-II, and the visual tracking test. The reasons for the incompleteness were technical problems or voluntary withdrawals by the subjects.

The results of the ANT and visual tracking performances were compared for the subset of subjects who took both tests (7 normal, 12 mTBI). Based on the assumption that cognitive deficits exist on a spectrum, and because the ANT scores are continuous measures for different attentional components, the data for the normal and mTBI subjects were analyzed together ($n = 19$).

Similarly, the results of the CVLT-II and visual tracking performances were compared for the subset of subjects who took both tests (7 normal, 13 mTBI). Jacobs and Donders[36] reported that the total recall discriminability and recognition discriminability indices of the CVLT-II varied meaningfully with the degree of severity of TBI; thus, we used these indices for the comparisons. Because these indices are continuous measures of verbal memory, the data for the normal and mTBI subjects were analyzed together ($n = 20$).

Magnetic resonance imaging/diffusion tensor imaging

All subjects underwent MRI and DTI with a 3 Tesla GE Signa EXCITE scanner (GE Healthcare, Waukesha, WI) equipped with 8-channel phased-array head coils. The methodological details and the results of the scans were included in previous publications.[27,35] Briefly, whole-brain DTI was performed with a multisection single-shot spin-echo echo-planar pulse sequence (echo time = 63 ms, repetition time = 14 seconds) using 55 diffusion-encoding directions, isotropically distributed over the surface of a sphere with electrostatic repulsion, acquisition at $b = 1000$ s/mm^2, 1 at $b = 0$ s/mm^2, 72 interleaved slices of 1.8-mm thickness with no gap between slices, a 128×128 matrix zero-filled to 256×256 during reconstruction, and a field of view of 230 mm. Images were postprocessed offline using DTIstudio to calculate the diffusion tensor and FA maps.[57] The results of conventional MRI were interpreted by board certified neuroradiologists. As described previously, the FA parameter of DTI was obtained for specific structures throughout the brain selected a priori as regions of interest (ROI). The FA values from the voxels within each ROI were averaged to obtain our index.

A white matter structure was considered to be damaged if the FA value was less than the mean −2.5 SDs of healthy control subjects analyzed for the previous publication.[27] However, to examine the relationship

between visual tracking performance and the integrity of white matter tracts, the data for the normal and mTBI subjects were analyzed together ($n = 26$).

Statistical analyses

Two-tailed Student's t test and Pearson's correlation coefficient r were used to test for a group difference and dependence between 2 parameters, respectively. All comparisons were considered pairwise. A statistical difference or a correlation was considered to be significant for P less than .05.

RESULTS

General characteristics

Good visual tracking was characterized by smooth sinusoidal modulation of eye positions without large saccades (Fig 2A-a) and high-velocity gains (c, d). The radius of the gaze trajectory was nearly constant over time (b, e) and the corresponding histogram had a sharp peak (f). The fluctuations in the phase errors were also small (g, h). Overall, the gaze positions were tightly clustered around the target (i).

In contrast, poor visual tracking of mTBI subjects was generally characterized by the presence of large saccades (Fig 2B-a) and low-velocity gains (c, d). The radius of the gaze trajectory was uneven (b) and fluctuated over time with both saccadic jumps and smooth changes (e). A directional preponderance of these components was not evident. The corresponding histogram showed a wide spread (f). The phase errors were typically modulated with a sawtooth waveform (g) with the fast components being saccades directed in the direction of the target movement, the majority of which placed the gaze ahead of the target (phase error > 0). The presence of residual velocity with a positive gain indicated that, after landing ahead of the target, the gaze continued to move in the direction of the target movement at a velocity slower than the target instead of completely stopping or reversing the direction to meet it. Corresponding to the amplitude of modulation, the histogram of phase errors also showed a wide spread (h). Overall, the gaze positions relative to the target were widely spread along the circular path (i).

The horizontal and vertical smooth pursuit gains of normal subjects were 0.94 ± 0.055 (mean ± SD) and 0.83 ± 0.16, respectively, whereas those of mTBI subjects were 0.86 ± 0.20 and 0.74 ± 0.24, respectively (Fig 3a, b). Student's t test did not reveal a significant difference between the 2 subject groups. The mean phase error of the normal subjects was 2.3° ± 1.6° and that of the mTBI subjects was 4.9° ± 8.2° (Fig 3c). Student's t test did not reveal a significant difference between the 2 subject groups.

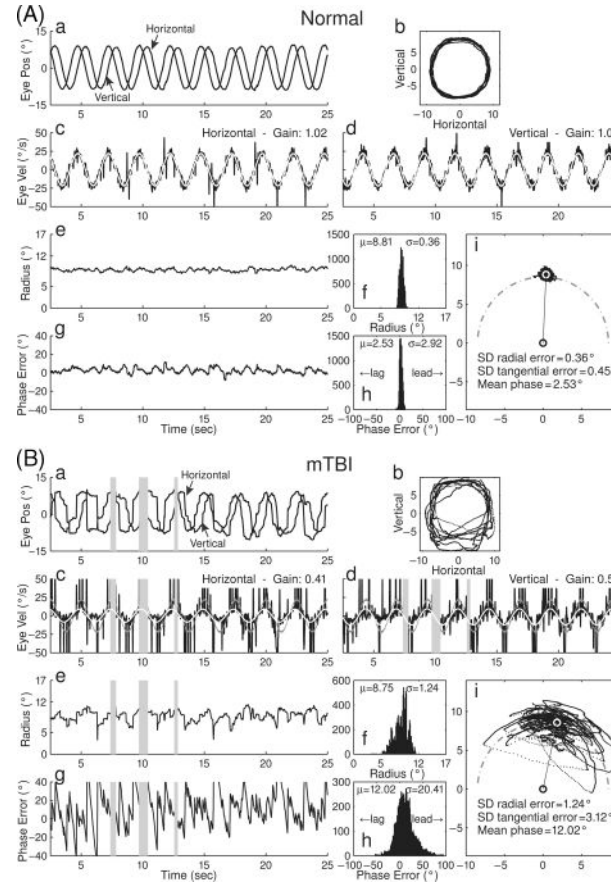

Figure 2. (A) Example of a good performance by a normal subject (N02). (B) Example of a poor performance by a mild traumatic brain injury subject (T17). (A, B) a: Horizontal and vertical eye positions in relation to time. b: Two-dimensional trajectory of the gaze superimposed over the 9 cycles shown in (a). c, d: Horizontal and vertical eye velocities in relation to time. The superimposed white curves indicate sine fits. e: Radius of gaze trajectory in relation to time. f: Histogram of gaze radius distribution. g: Phase error in relation to time. h: Histogram of phase error distribution. i: Scattergram of gaze positions relative to the target fixed at the 12 o'clock position. The white circle indicates the average gaze position. The dot-dashed curve indicates the circular path. In (a, c, d, e, g), the gray vertical strips indicate blinks.

Intraindividual performance variability

Performance variability was associated with inaccurate visual tracking. The intraindividual gaze positional error variability was examined in 2 orthogonal directions defined relative to the target trajectory. The variability measures for radial errors for the normal and mTBI subjects were 0.9° ± 0.4° and 1.4° ± 0.5°, respectively (Fig 3d). The variability measures for tangential errors for the normal and mTBI subjects were 1.1° ± 0.6° and 2.4° ± 1.3°, respectively (Fig 3e). Although the distributions of these error variability measures of the 2 subject groups overlapped, Student's t test revealed

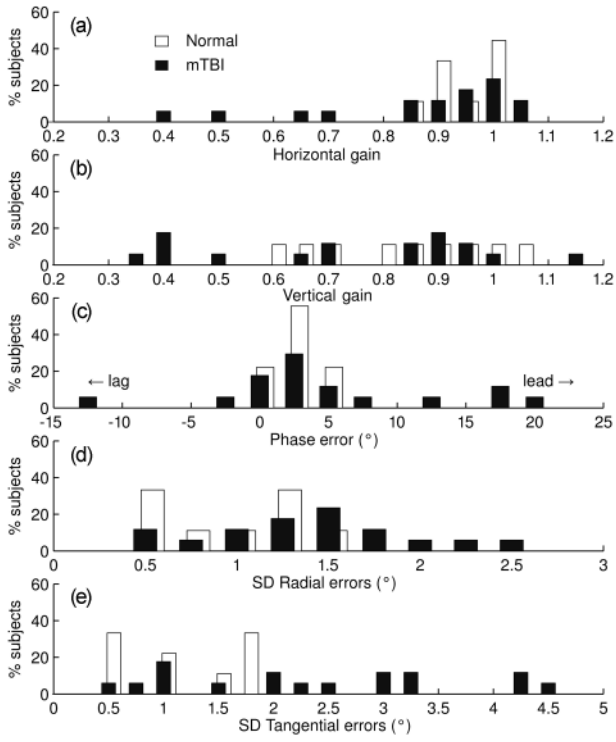

Figure 3. Histogram distribution of visual tracking performance parameters expressed in percentages of the subject populations. (a) Horizontal smooth pursuit velocity gain. (b) Vertical smooth pursuit velocity gain. (c) Mean phase error. (d) Radial error variability. (e) Tangential error variability.

significant group differences (radial: $P = .014$; tangential: $P = .002$). None of the 9 normal subjects exceeded 1.5° in radial error variability, whereas 9 of the 17 mTBI subjects did so, and none of the normal subjects exceeded 1.9° in tangential error variability, whereas 11 of the mTBI subjects did so. The variability measures of radial and tangential errors were closely correlated with each other ($r = 0.90$, $P < 10^{-9}$, $n = 26$, all subjects combined), but the tangential error variability was significantly larger than the radial error variability ($P = .00013$, $n = 26$, paired t test).

Correlations with DTI FA values

Anterior corona radiata

Of the 17 mTBI subjects, 11 sustained damage in the ACR and 10 of these cases involved the right ACR (Table 2). The variability measures for the radial and tangential errors were both significantly correlated with the FA values of the right ACR (Fig 4a, Table 2) with $r = -0.44$ and -0.50 ($P = .024$ and .0094), respectively, larger variability being associated with poorer white matter alignment. The variability measures were not correlated significantly with the FA values of the left ACR (Table 3).

Other cortical tracts vulnerable to mTBI

Of the 17 mTBI subjects, 3 sustained damage in the genu of the corpus callosum (Table 2). The variability measures for the radial and tangential errors were both significantly correlated with the FA values of this structure (Fig 4b, Table 3) with $r = -0.54$ and -0.53 ($P = .0042$ and .0052), respectively.

The variability measures for the radial and tangential errors were correlated with the FA values of the left uncinate fasciculus with $r = -0.42$ and -0.43, respectively ($P = .030$ for both). The variability measures for the radial and tangential errors were correlated with the FA values of the right uncinate fasciculus with $r = -0.45$ and -0.38 ($P = .021$ and .052), respectively. The variability measures were not significantly correlated with the FA values of the cingulum bundle (Table 3).

Forceps major and SCP

Significant correlations were found between the gaze error variability and the integrity of the forceps major of both hemispheres (Table 3). The variability measures for the radial and tangential errors were correlated with the FA values of the left forceps major with $r = -0.42$ and -0.43 ($P = .035$ and .027), respectively. The variability measures for the radial and tangential errors were correlated with the FA values of the right forceps major with $r = -0.52$ and -0.53 ($P = .0069$ and .0054), respectively.

The variability measures for the radial and tangential errors were both significantly correlated with the FA values of the left SCP (Fig 4c, Table 3) with $r = -0.59$ and -0.67 ($P = .0016$ and .00020), respectively. The variability measures were not correlated significantly with the FA values of the right SCP (Table 3).

Centrality measures of visual tracking and FA values

The horizontal and vertical pursuit gains and the mean phase error were significantly correlated with the FA values of the left SCP with $r = 0.52$, 0.57, and -0.49 ($P = .0059$, .0025, and .011), respectively, with lower gains and a larger phase error being associated with poorer white matter alignment. In comparison, neither the pursuit gain nor the mean phase error was significantly correlated with the FA values of the right SCP. Neither the pursuit gain nor the mean phase error was significantly correlated with the FA values of either the right or the left ACR. The horizontal and vertical pursuit gains were correlated with the FA value of the genu of the corpus callosum with $r = 0.47$ and 0.42 ($P = .014$ and .035), respectively. The horizontal pursuit gain was correlated with the FA value of the right uncinate fasciculus with $r = 0.39$ ($P = .05$).

TABLE 2 *Frequency distribution of damaged tracts in subjects with mTBI*

	Tracts vulnerable to mTBI							Tracts not known to be vulnerable to mTBI			
	ACR		Genu of corpus callosum	Uncinate fasciculus		Cingulum bundle		Forceps major		SCP	
Subjects	**Left**	**Right**		**Left**	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
T05											
T06	X	X	X	X	X						
T08		X									
T09		X									
T11						X			X		
T14		X									
T15	X	X									
T16	X		X	X							
T17		X									
T20		X	X								X
T21	X	X									
T23											
T24		X									
T26											X
T27											
T29		X				X					
T30											
Count	4	10	3	2	1	2	0	0	1	0	2
Mean FA (controls)	0.53	0.53	0.81	0.57	0.57	0.70	0.65	0.72	0.71	0.73	0.75
2.5 SD threshold	0.44	0.45	0.71	0.45	0.44	0.58	0.48	0.37	0.53	0.55	0.57

Abbreviations: ACR, anterior corona radiata; FA, fractional anisotropy; mTBI, mild traumatic brain injury; SCP, superior cerebellar peduncle.

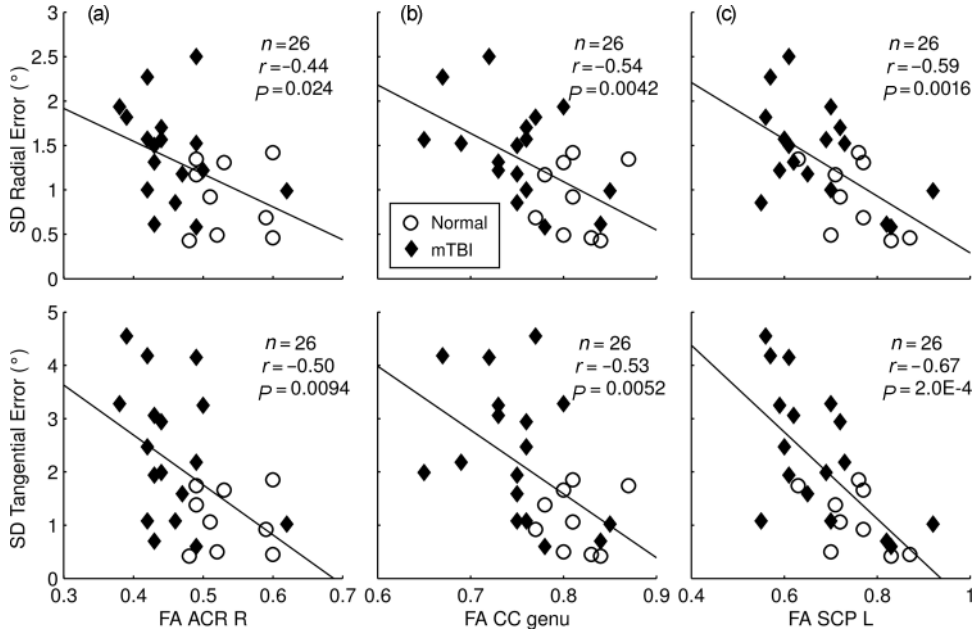

Figure 4. Relationships between fractional anisotropy (FA) values and visual tracking performance variability. (a) Right anterior corona radiata (ACR). (b) Genu of the corpus callosum (CC). (c) Left superior cerebellar peduncle (SCP). Top panels: radial error variability. Bottom panels: tangential error variability. The regression lines were determined from the combined subject population.

TABLE 3 *Correlations between FA values and visual tracking performance variability*

ROI		Radial error variability		Tangential error variability	
		r	*P*	*r*	*P*
Tracts vulnerable to mTBI					
ACR	Left	−0.21	NS	−0.14	NS
	Right	−0.44	<.05	−0.50	<.01
Genu of corpus callosum		−0.54	<.01	−0.53	<.01
Uncinate fasciculus	Left	−0.42	<.05	−0.43	<.05
	Right	−0.45	<.05	−0.38	NS
Cingulum bundle	Left	−0.28	NS	−0.27	NS
	Right	0.03	NS	−0.02	NS
Tracts not known to be vulnerable to mTBI					
Forceps major	Left	−0.42	<.05	−0.43	<.05
	Right	−0.52	<.01	−0.53	<.01
SCP	Left	−0.59	<.01	−0.67	<.001
	Right	−0.14	NS	−0.25	NS

Abbreviations: ACR, anterior corona radiata; FA, fractional anisotropy; mTBI, mild traumatic brain injury; ROI, region of interest; SCP, superior cerebellar peduncle.

Correlations with neurocognitive tests

Attention Network Test

The overall mean reaction time in the ANT was significantly correlated with the variability measures for both the radial and tangential visual tracking errors (Fig 5a) with $r = 0.60$ and 0.54 ($P = .0061$ and .016), respectively, with longer reaction times being associated with larger visual tracking variability. The orienting effect in the ANT was significantly correlated with the variability measures for both the radial and tangential visual tracking errors (Fig 5b) with $r = -0.49$ and -0.46 ($P = .033$ and .040), respectively, with smaller reduction in the reaction time being associated with larger visual tracking variability.

California Verbal Learning Test

The variability measure for the radial visual tracking errors was significantly correlated with both the total

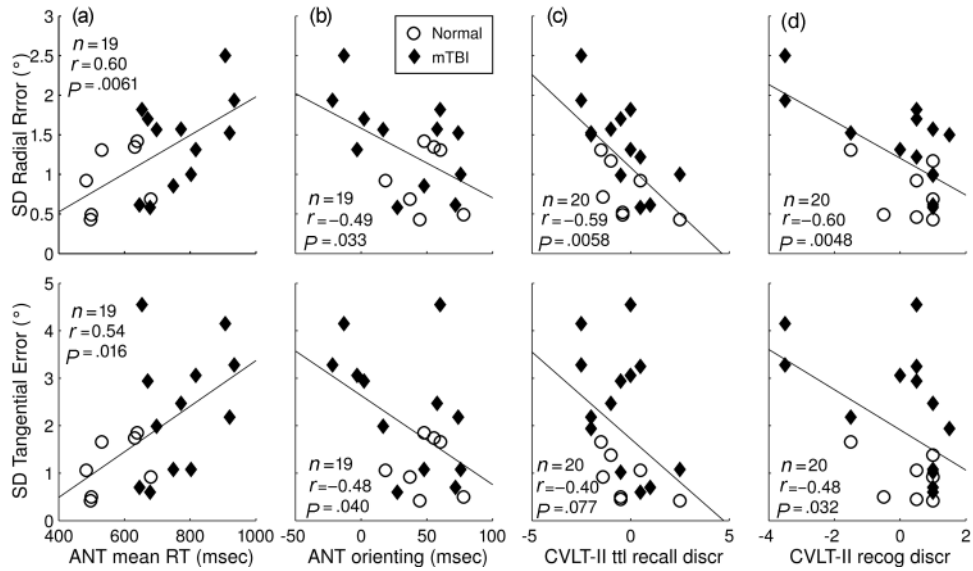

Figure 5. Associations between neurocognitive tests and visual tracking performance variability. (a) Attention Network Test (ANT) mean reaction time. (b) ANT orienting effect. (c) California Verbal Learning Test, 2nd edition (CVLT-II) total recall discriminability. (d) CVLT-II recognition discriminability. Top panels: radial error variability. Bottom panels: tangential error variability. The regression lines were determined from the combined subject population.

recall discriminability (Fig 5c, top) and recognition discriminability (Fig 5d, top) indices of CVLT-II with $r = -0.59$ and -0.60 ($P = .0058$ and $.0048$), respectively, with poorer verbal memory performance being associated with larger visual tracking variability. The variability measure for the tangential visual tracking errors was also significantly correlated with the recognition discriminability index (Fig 5d, bottom) with $r = -0.48$ ($P = .03$). The correlation between the tangential error variability and the total recall discriminability was not significant (Fig 5c, bottom).

Neurocognitive tests and DTI

The overall mean reaction time of the ANT was significantly correlated with the FA value of the genu of the corpus callosum with $r = -0.56$ ($P = .013$), with longer reaction times being associated with poorer white matter alignment. The recognition discriminability index of the CVLT-II was correlated with the FA value of the left uncinate fasciculus with $r = 0.48$ ($P = .034$), with poorer verbal memory performance being associated with poorer white matter alignment.

DISCUSSION

Visual tracking performance as an indicator for mTBI

We used a visual tracking paradigm with a target moving in a circular trajectory. The geometrical simplicity and continuity of such a target trajectory staged predictability. Predictability provides a means to circumvent the constraint of the visuomotor processing delay. That is, if one was to simply react to the target, processing in the visuomotor system would cause as much as 100 ms of delay in response,[43] which would correspond to a 14.4° phase lag of the gaze position relative to the target in the circular paradigm. We observed that none of the subjects had the mean phase lag exceeding this value. Thus, mTBI did not bar the subjects from engaging in predictive behavior during the maintenance of visual tracking.

However, more than 50% of the mTBI-PCS subjects produced above-normal range inaccuracy in visual tracking as measured by the variability of gaze positional errors relative to the target. Our variability parameters, the SDs of gaze positional errors, quantified internal variability of errors and were different from the mathematically similar root-mean-square error,[58,59] which quantifies the overall difference between the target and gaze trajectories. Although the distributions of our variability measures overlapped between the normal and mTBI-PCS subject groups, a finding that is consistent with the notion that TBI-induced changes exist on a spectrum,[15,19,24,37] the group differences were significant. Thus, our variability measures were more sensitive to mTBI than the measures of centrality using the pursuit velocity gains and the mean phase error. The close correlations between the variability measures and the DTI FA values of white matter tracts vulnerable to mTBI indicate that the levels of visual tracking performance can be quantified to match the spectrum of severity of mTBI determined by DTI.

Functional validity

We have demonstrated the association between visual tracking performance variability and the anatomical network connectivity with identified cognitive functions (ie, the right ACR and the left SCP for spatial working memory and attention), wherein the ACR was the most frequently damaged white matter tract among the mTBI-PCS subjects. Visual tracking variability was also associated with the integrity of the genu of the corpus callosum, which has been proposed to be an important interhemispheric transmission conduit in attentional tasks[60,61] and a structure vulnerable to mTBI.[27] In addition, visual tracking variability was associated with the integrity of the bilateral forceps major, a structure that has a specific relation to the visual domain.

Some of these associations suggest that the visual tracking variability measures could provide a method to quantify cognitive functioning. It has been suggested that the stability of performance in even a simple automatic behavioral task may reflect the temporal stability of neural activity that influence the performance of more general cognitive operations.[62] This possibility was addressed by comparing the visual tracking variability measures with those of attention and working memory taken from accepted neurocognitive tests, namely the ANT and the CVLT-II. We also showed that the correlations between the measures of visual tracking variability and cognitive functions were associated with the integrity of shared white matter tracts vulnerable to mTBI.

The correlations between the ANT overall mean reaction time and the measures of visual tracking variability may suggest that the abilities to efficiently process information during the ANT task and hold the gaze on the target during the visual tracking task are related. Furthermore, these abilities may be at least partially subserved by the genu of the corpus callosum because its integrity was correlated with both the ANT overall mean reaction time and the visual tracking variability measures.

The ANT orienting effect measures the ability to reduce the reaction times in response to the presentation of an orienting cue that indicates where in space the subject should attend. The correlations between the ANT orienting effect and the visual tracking variability measures is consistent with the idea that predictive visual

tracking involves directing attention to the forthcoming location of the target.

Because of the diffuse nature of injury in mTBI, damages are likely to be sustained in areas of the brain that have different functional roles. Therefore, different functional deficits are expected, and the neural bases underlying the correlations among these deficits need to be evaluated carefully. For example, deficits in verbal memory and visual tracking may not originate from a common location in the brain. Therefore, the correlations between the CVLT-II parameters and the visual tracking variability measures may only suggest that deficits in working memory could occur concurrently with deficits in visual tracking of a target. On the other hand, the correlations may suggest that there is a common attentional element for verbal and spatial working memory functions[63] or reflect a common element of temporal stability that influences general cognitive operations.[62]

What causes performance variability in mTBI?

Both saccadic and smooth elements of visual tracking were factors for determining performance variability. In the radial direction, both of these elements bidirectionally contributed to the deviations from the constant radius of a circle. In the tangential direction, saccades would point the gaze in advance of the target, and during the smooth phase of gaze progression the target would catch up with the gaze. This type of coordination is consistent with the notion that there are shared neural pathways for saccades and smooth pursuit.[45,64] Because visual tracking variability typical of mTBI-PCS subjects involved coordination of saccadic and smooth elements, the source of variability is likely to be at high cortical level visuomotor programming.

It has been previously postulated that one function of attention is to reduce performance variability by synchronizing moment-to-moment expectations and the incoming sensory input.[41] In this construct, being in sync would be signified by consistency in visual tracking, which involves correctly matching the predicted target position with the actual target position at specific points in time. On the other hand, being out of sync would be signified by inconsistent tracking. Our results showed that mTBI did not preclude prediction. However, the inability to match the predicted target position and the actual target position created erroneous motor outcome and perpetual need for adjustments, leading to visual tracking performance variability.

One node for the synchronization process may be located in the right prefrontal cortex, at a site of convergence between the partially segregated attentional neural networks. The top-down control of attention involves the frontal eye field and the intraparietal sulcus, whereas the stimulus-driven control of attention involves the temporal-parietal cortex and the inferior frontal cortex.[65] The predictive state in the brain is thought to be maintained with the additional involvement of the cerebellum.[41,66] One cortical site of convergence between the top-down and stimulus-driven attentional neural networks is the right middle frontal gyrus,[67] which appears to correspond to the dorsolateral prefrontal cortex.[68] Thus, damage sustained in the fiber connections to this cortical site would disconnect the top-down and bottom-up control signals. The ROIs defined for both the ACR and the genu[27,35] are likely to include fibers connected to this cortical site,[69] or at the very least, the integrity of the fiber tracts in the ROIs should be similar to the integrity of the tracts connected directly to this cortical site. Our results indicate that the right prefrontal–left cerebellar loop is an important element of the synchronization process. We postulate that visual tracking variability is a consequence of the asynchrony between the top-down and bottom-up signals caused by damage sustained in the right prefrontal cortical white matter.

It is of note that most of the subjects in the mTBI-PCS group sustained damage in the right ACR, but only a few in the left. This difference in the rates is likely to be caused by the hemispherically asymmetrical control of attentional functions.[65,70,71] Because the right hemisphere can compensate for the attentional functions of the left hemisphere,[71] damage on the right side, involving the attentional control, is more likely to produce postconcussive symptoms associated with attention problems. Thus, patients with damage in the right hemisphere, in particular the right ACR, may have had more attention deficits and symptoms causing them to seek assistance in clinics from which they were recruited in this study. Possibly, the presence and extent of damage in the right ACR could serve as a predictor of which acute mTBI patients go on to have chronic symptoms.

A limitation of the present study is the lack of test-retest data of the visual tracking test. Other limitations include the small sample size and the wide range of postinjury periods for the mTBI subjects, which may weaken the relationship of the behavioral test measures and the DTI results to the actual injury. In addition, consideration should be given to the specificity of the visual tracking test to detect mTBI because reduced integrity of white matter structures in the frontal regions is common in many disorders and in aging brains.[72,73] However, the emphasis of this study is the relationship between visual tracking performance variability and the structural integrity of specific white matter tracts vulnerable to TBI. Given the vulnerability of these tracts, there is a high probability that structural changes associated with TBI will increase the variability in the visual tracking performance. Alternatively, there may be premorbid conditions that make particular individuals more susceptible to head injury.[38,74] For example,

individuals with low FA values in the frontal white matter tracts may be more susceptible to head injury because of existing attentional problems, rather than a head injury causing decreases in FA values. Because the progression or stability of white matter changes after the injury can provide an important indication as to whether certain conditions preexisted, a longitudinal study monitoring changes in FA would resolve the question.

SUMMARY

Performance variability during predictive visual tracking is a powerful indicator for decreased integrity in frontal white matter tracts vulnerable to mTBI as well as for altered cognitive functioning. We demonstrated these relationships in the combined data set of normal and mTBI subjects, supporting the concept of a spectrum of white matter changes.

Visual tracking performance can be monitored precisely and continuously, allowing detection and objective quantification of subtle momentary lapses in attention over a matter of seconds, a significantly shorter time than required for administration of traditional neurocognitive testing. Measurement of visual tracking performance is promising as a fast and practical screening tool for mTBI.

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