Visual Scanning Behaviour during a visual search task: an objective indicator of white matter integrity in patients with post-concussion syndrome

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***Abstract*—Post-concussion syndrome (PCS) is associated with incomplete recovery following a mild traumatic brain injury (mTBI). Currently, there is no biomarker to diagnose post-concussion syndrome. Although microstructural damage to white matter tracts is postulated and reported in some studies, there is no diagnostic biomarker available. In this paper, we present preliminary results of a novel and simple-to-administer eye-tracking paradigm that relates visual scanning behaviour to microstructural integrity of the corpus callosum (CC).**

The novel paradigm is based on the Matching Familiar Figures Test (MFFT). In the MFFT test, a series of slides each containing a familiar standard figure and six variants are presented. Only one of the variants is identical to the standard figure and subjects are instructed to select the matched variant. The normalised number of transitions to the standard figure prior to the first selection (NNTP) is used as an indirect measure of the microstructural integrity of the CC.

Microstructural integrity was evaluated by measuring the fractional anisotropy (FA) of the CC derived from tract based spatial statistics on diffusion tensor imaging (DTI). Fifty-five patients with PCS completed the visual scanning paradigm and magnetic resonance imaging. Significant inverse correlation was found between the NNTP and the FA of the CC (r= -0.463, $p<0.001$). Mediation analysis showed that damage to the CC could affect NNTP directly or through pathways that affect attention, somatic and cognitive symptoms. The results suggest that visual scanning behaviour during the MFFT is a multi-factorial cognitive and behavioural process that can provide a surrogate marker of the structural integrity of the corpus callosum.

***Keywords*-eye tracking, concussion, visual search, visual scanning behaviour, post-concussion syndrome**

I. Introduction

Post-concussion syndrome (PCS) is associated with incomplete recovery after a mild traumatic brain injury (mTBI). PCS affects up to 15% of patients with mTBIs and causes emotional changes, depression, anxiety, difficulties in concentration and reduced scores on working memory and executive function tests [1]–[4]. Studies have shown that microstructural damage to white matter tracts was frequently observed in patients with PCS [5]–[7] and that this damage was correlated with symptoms suffered by the patients [8], [9]. Currently, magnetic resonance imaging (MRI) scans are performed to study PCS. However, the majority of mTBI patients show normal MRI scans (for review please see [10]). As such, it is difficult to predict the development of PCS symptoms after an mTBI [11]. A surrogate marker for microstructural damage in the brain may provide an addition avenue to identify patients who are likely to suffer from PCS during the early phases of the disease.

Recent evidence shows that deficits in visual attention are associated with damage to white matter tracts in patients with mTBI [12]. In the present study, we explored measures of visual scanning behaviour during a visual search task as possible indicators of white matter integrity. The visual search task that was used, the Matching Familiar Figures

Test (MFFT) [13], is a test of impulsivity, attention, working memory and decision making. The MFFT paradigm uses a complex perceptual discrimination and matching task that stresses ambiguity between conjunctions of features in familiar objects and requires the subject to make decisions regarding differences between images that are very similar to each other. In our paradigm, eye movement parameters are used as indicators of subjects' performance on the MFFT. In this study, eye movement parameters were related to measures of integrity of the corpus callosum (CC) derived from diffusion tensor imaging (DTI). Furthermore, the pathways by which the microstructural integrity of the CC affect eye movement parameters during the MFFT were studied by mediation analysis that uses data from neurocognitive tests, clinical questionnaires, DTI and eye-movement indicators.

II. Methods

A. Visual scanning

Visual Attention Scanning Technology (VAST, EL-MAR Inc., Toronto, Ontario) [14], [15] was used to obtain eye gaze positions and to display visual stimuli. The eye tracking system in VAST consists of three infrared (IR) light sources, an IR video camera and a processing unit, that was mounted on a 23-inch monitor. VAST estimates binocular gaze positions 30 times/sec with an accuracy of 0.5° [16]. During the test, subjects sat approximately 65 centimetres away from the monitor. Following a calibration procedure, subjects looked at a series of slides that were presented on the LCD monitor and their eye positions were recorded. The eye positions are segmented into fixations that are linked to the images that were displayed [17].

The visual stimuli consisted of 22 slides (the first slide was used for training) with line drawings of familiar figures that are based on the Matching Familiar Figures Tests (MFFT) [13], [18]. Each slide includes a standard figure at the top of the slide and six variants (labelled 1 to 6). Only one of the variants is identical to the standard figure (see Figure 1). The visual angle subtended by each of the images was approximately ($5^\circ \times 5^\circ$).

VAST controls the progression of the test and provides feedback to the subject by interpreting the subjects' gaze patterns on the six buttons that are displayed at the bottom of the slide. The subject indicates a selection by fixating on the button that corresponds to their selection for more than 500 milliseconds. This selction method reduces the amount of time in which the subjects' gaze leaves the screen. If the subjects' selection is correct, the colour of the button changes from blue to green and the next slide is presented. If their selection was incorrect, the colour of the button changes from blue to red and they have to re-try and find a correct match on the current slide before the next slide is presented.

The gaze positions and the decisions made by the subject were analysed and the following parameters were measured:

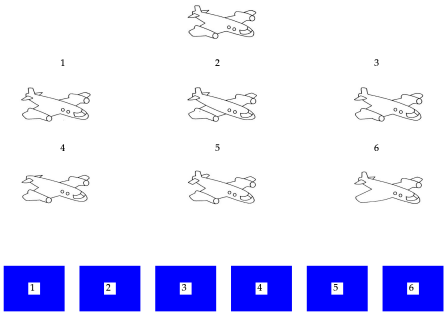

Figure 1. An example of the visual stimuli. The image on the top is the standard familiar figure. The six variant images (labelled 1 to 6) are placed in a 2×3 configuration. The buttons at the bottom of the slide are used to indicate the subject's selection.

1) Percentage of correct first selections
2) Response time (measured by the latency of first selections)
3) Normalised number of transitions into the standard image prior to the first selection (NNTP)

The first two parameters were reported in the standard MFFT protocol. These parameters can be estimated without using an eye-tracking system. The third parameter (NNTP) was calculated by dividing the number of transitions into the standard image before the first selection by the total number of variants viewed. The denominator of the normalised measure was an attempt to compensate for differences in the motivation levels of patients. Subjects who did not view all the variants on the slide before making a decision are likely less motivated to do the task. The mean of each parameter was calculated over the 21 slides (excluding the first slide that was used for training) to characterise the visual scanning behaviour of each subject.

B. Neuropsychological/cognitive assessments

A battery of neuropsychological measurements was carried out to assess the capacity of standard objective cognitive tests to predict the integrity of white matter tracts in the CC. The neurocognitive measurements included results from the sustained attention to response test (SART) and the visual-spatial forward span (VSFS) tests of attention [19]. The SART is a computerised go/no-go task that counts the number of errors on the "go" (SART.G) task and the "no-go" (SART.N) task. High values of the SART measures suggest that the subject has lower sustained attention capabilities. Visual spatial forward span is a test of visual-spatial working memory where higher values represent larger attention capabilities [20]. Clinical evaluations of self-reported symptoms were assessed for concussive symptoms in the following domains: memory, executive function, sensory, and headaches [21]. Clinical evaluation was categorised into cognitive (memory and executive functions) and somatic (sensory and headache) symptoms. Higher values of the

clinical symptoms represent more severe post-concussive symptoms.

C. Diffusion Tensor Imaging (DTI)

High resolution anatomical whole brain scans were acquired using T1-weighted inversion recovery prepped, 3-dimensional fast spoiled gradient echo (IR-FSPGR) sequence with a Signa HDxt 3.0T MRI scanner (General Electric, Milwaukee) and a standard 8-channel head coil. The DTI analysis was conducted using the FMRIB software library (v 5.0, available at https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Motion and eddy current correction, skull stripping and fitting a diffusion tensor model at each voxel were conducted as pre-processing steps. The fractional anisotropy (FA) was derived using tract-based spatial statistics (TBSS). Details of the procedures are provided in [21].

D. Statistical analysis

Pearson correlation was used to explore the relationships between the visual scanning parameters, neuropsychological tests, and DTI measurements while controlling for the subjects' age, gender, and years of education. Correlation models that had an α of less than 0.05 were considered significant.

Factor analysis and mediation analysis were conducted using structural equation modelling (SEM). The neuropsychological and cognitive tests were used as latent factors mediating the relationship between the MFFT and DTI measurements. The Lavaan package [22] was used with maximum likelihood method of estimation. The following measures were used to evaluate the model fit: RMSEA < 0.05 (0.05-0.08 acceptable; lower boundary of RMSEA confidence interval contains zero), CFI > 0.97 (0.95-0.97 acceptable), and SRMR < 0.05 (0.05-0.10 acceptable) [23], [24]. Mediation effect size was computed using (as suggested and used in [23], [25]):

$$Effect \quad size = \frac{(a1 \cdot b1) + (a2 \cdot b2) + (a3 \cdot b3)}{(a1 \cdot b1) + (a2 \cdot b2) + (a3 \cdot b3) + c}$$

All parameters were scaled to $0 - 1$ range and compete cases across different measurements (i.e., data with no missing values) were used. All analyses were conducted using R [26].

III. Results

A. Subjects

Fifty-five patients with PCS and at least two concussions were recruited from the Canadian Concussion Centre (see Table I for demographic details). The research ethics board of the University Health Network, Toronto, ON approved the study. All participants consented to the study procedures.

Table I
DEMOGRAPHY OF THE PARTICIPANTS OF THIS STUDY.

	Patients with PCS (n=55)
Age	34.56 $\pm$ 13.69 (17 - 64) years
Years of Education	14.79 $\pm$ 2.36 (10 - 18) years
Gender	Male=38, female=17
Average number of concussions	3.96 $\pm$ 2.01

B. Correlation analysis

The three measures of the MFFT test: selection latency, percentage of correct first selections and the NNTP were computed. The mean selection latency for the first selection was 25.22 $\pm$ 8.1 seconds and an average of 79.3 $\pm$ 15.14 % of first selections were correct. The mean normalised number of transitions prior to the first selection was 1.77 $\pm$ 0.518.

Significant correlations were found between NNTP and the FA of the CC (r=-0.4365, p$<$0.001) (the correlation was controlled for age, gender, and years of education). The standard MFFT measures: selection latency (r=-0.106, p=0.442) and percentage of correct first selections (r=-0.0485, p=0.723), as well as the results of the cognitive tests (SART and VSF) were not correlated with the FA of the CC.

C. Mediation analysis

To gain insights into possible pathways by which the CC integrity is related to visual scanning behaviour (as measured by NNTP) we explored pathways that affect attention, cognitive symptoms and somatic symptoms (three latent factors). Specifically, mediation analysis was conducted to explain the variance in a three latent factor model. The latent factors included: attention, which was measured by SART and VSF; cognition, which was measured by memory and executive symptoms; and somatic, which was measured by sensory and headache symptoms.

The Baron and Kenny's causal-steps test was conducted to confirm that mediation was possible with the current dataset [27]. The three-factor mediation model fit the data well (χ^2=21.110, p=0.331, RMSEA=0.045 (0.000-0.130), CFI=97.5, SRMR=0.076). The regression coefficients between the FA of the CC and NNTP and the factors are shown in Table II. Furthermore, the path diagram is shown in Figure 2.

From Figure 2 and Table II, we can observe that both the direct and indirect pathways play a role in explaining the correlation between the FA of the CC and NNTP. The direct effect had a factor loading of -0.197, which is consistent with the negative correlation between the two parameters of CC integrity and NNTP. The indirect pathway, which is associated with the somatic factor was the largest ($-0.191 \times 0.363 = -0.0693$) followed by the attention ($0.178 \times -0.378 = -0.0670$) and cognition factors ($0.352 \times -0.101 = -0.035$) factors. The total indirect loading was -0.172 compared to the direct loadings of -

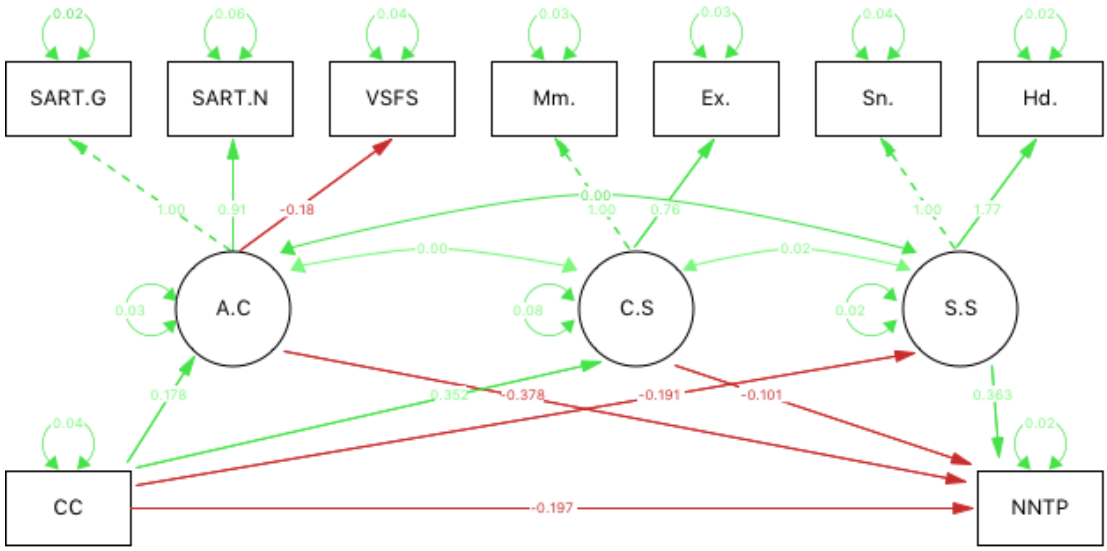

Figure 2. Path diagram of the three-factor mediation model to assess the partial cause of the correlation observed between the NNTP and FA of the CC (CC). The attention (A.C) factor is comprised of the test scores of the SART.GO, SART.NOGO, and VS. The cognitive symptoms (C.S) factor encapsulates scores of the clinical evaluation of memory (Mm.) and executive functions (Ex.). The somatic symptoms (S.S) factor contains scores of the clinical evaluation of sensory (Sn.) and headache symptoms (Hd.).

Table II
REGRESSION COEFFICIENTS OF THE THREE LATENT FACTORS IN THE MEDIATION MODEL TO ASSESS THE PARTIAL CORRELATIONS BETWEEN NNTP AND FA OF THE CC.

Path	Std.est	Std.Err	Z	P
FA of the CC → Latent factors				
CC → Attention	0.178	0.139	1.283	0.200
CC → Somatic symp.	-0.191	0.112	-1.568	0.117
CC → Cognitive symp.	0.352	0.210	1.673	0.094
Latent factors → NNTP				
Attention → NNTP	-0.378	0.231	-1.641	0.101
Somatic symp. → NNTP	0.363	0.207	1.752	0.08
Cognitive symp. → NNTP	-0.101	0.102	-0.990	0.322
Direct effect				
FA of the CC → NNTP	-0.197	0.127	-1.550	0.121

0.197. As such, the total mediation effect size was large (0.467).

IV. DISCUSSION

The results of this study show that loss of corpus callosum integrity (as measured by FA) is correlated with measures of visual scanning behaviour during the matching familiar figures test. The corpus callosum plays a critical role in transferring information between the two hemispheres of the brain and is vital for completing visual scanning tasks [28]. The integrity of the corpus callosum affects visual scanning behaviour through direct and indirect paths. The indirect path is mediated mainly through pathways that affect somatic symptoms. The positive factor loading suggests that individuals with more somatic symptoms perform more transitions/variant before making their first selection. Subjects with more somatic symptoms might have more difficulty reaching decisions which are reflected in their visual scanning parameters. In summary, visual scanning behaviour as measured with the matching familiar figures test may reflect integrity of the corpus callosum in PCS patients.

V. CONCLUSION AND FUTURE DIRECTION

This study shows that VSB parameters during the matching familiar figures test are correlated with both the severity of patients' symptoms and the integrity of the corpus callosum. As such, the study provides insights into mechanisms that link symptoms in PCS patients and visual scanning behavior. The current study is limited by the small number of participants. Future studies should be conducted to reconfirm the findings and to expand the number of VSB parameters that are being tracked (for example, one can track parameters from anti-saccades tests or free scanning procedures). The main objective of the expanded set of parameters should be to improve the correlation between VSB parameters and patients' symptoms. Since VSB parameters can be obtained through simple and non-invasive procedures they can provide clinicians with objective measures that might help in the evaluation of patients with PCS.

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