Follow-up evaluation of oculomotor performance with fMRI in the subacute phase of concussion

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ABSTRACT

Objective: To expand on our previous study by performing a follow-up testing session in the subacute phase of injury for participants recently diagnosed with a concussion.

Methods: A battery of oculomotor tests were administered to participants 30 days postconcussion while simultaneous fMRI was performed.

Results: Three of the 7 oculomotor tasks (antisaccade, self-paced saccade, and memory-guided saccade) administered showed significant differences between the recently concussed group compared with normal volunteers. However, performance in these 3 tasks did show improvement from the acute phase of injury. The fMRI analysis revealed significant differences in brain activation patterns compared with normal volunteers, with the concussed group still demonstrating increased and larger areas of activation. Similar to the oculomotor performance, the fMRI analysis showed that at 30 days postinjury, the concussed group more closely mirrored that of the normal volunteer group compared with at 7 days following insult.

Conclusions: Even at 30 days postinjury, and despite being clinically asymptomatic, advanced techniques are able to detect subtle lingering alterations in the concussed brain. Therefore, progressive neuroimaging techniques such as fMRI in conjunction with assessment of oculomotor performance may be beneficial in clinical management of concussion. *Neurology*® 2015;85:1163-1166

GLOSSARY

NV = normal volunteer.

Concussion initiates complex sequelae that produce disturbances in brain function and numerous somatic and cognitive symptoms.¹ The majority of sports-related concussions demonstrate spontaneous recovery and resolution of clinical symptoms within 10 days postinjury.² However, more advanced technologies have highlighted subtle changes and nuances in brain morphology, physiology, and function following concussion even though participants have returned to baseline on clinical measures. The direct relationship between the functional integrity of the brain and corresponding eye movements makes testing of oculomotor behavior a potential tool to allow for objective measures and inferences on brain integrity postconcussion.³ Given that concussion can disrupt multiple brain functional networks, including the oculomotor control networks, our previous study focused on the acute effects of concussion by having participants perform a battery of oculomotor tests while simultaneously undergoing fMRI. Behavioral results revealed that concussed participants performed worse in all oculomotor tasks and had increased fMRI recruitment and larger areas of activation.

Here, we performed a follow-up to this study in the subacute phase of concussive injury. Based on our previous findings, we hypothesized that the more complex oculomotor tasks would demonstrate significant behavioral differences that coincide with increased activation areas and patterns. We also expected to still see impaired oculomotor performance, albeit less pronounced than in the acute phase of injury.

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METHODS **Standard protocol approvals, registrations, and patient consents.** This study was approved by the institutional review board of the Pennsylvania State University, and all participants signed informed consent.

For the original study, 9 recently concussed participants were scanned within 7 days of injury along with 9 age-matched normal volunteers (NVs) who were physically active. Unfortunately, because of attrition, only 7 of these participants (4 men, 3 women, aged 18–21 years) completed follow-up testing at 30 days postinjury. All participants were clinically asymptomatic at the time of follow-up testing.

The battery of oculomotor tasks included eye fixation, reflexive saccades, antisaccades, memory-guided saccades, self-paced saccades, and circular and sinusoidal smooth pursuit (see Johnson et al.⁴ and Heitger et al.⁵ for details). All saccades were performed in the horizontal plane. Visual stimuli were presented via MRI-compatible goggles (Resonance Technology, Inc.) with a resolution of 800 × 600 and integrated eye tracking system with a sampling rate of 60 Hz. Eye position of the left eye was recorded with the ViewPoint EyeTracker (Arrington Research, Inc., Scottsdale, AZ); following a 16-point fine calibration, raw pupil locations are mathematically mapped from the video-display space to visual-stimulus space to track the participant's eye position. Functional and anatomical images were acquired on a 3.0-tesla S Trio using a 12-channel head coil. Whole brain T1 anatomical images and 2-dimensional BOLD (blood oxygen level–dependent) echo planar fMRIs (2 × 2 × 3 mm, echo time = 25 milliseconds (ms), repetition time = 2,500 ms, 44 slices, number of signal averages = 1) were acquired.

Behavioral data were analyzed with the ViewPoint EyeTracker (version 2.8.6.21) software in conjunction with a specific MATLAB code written to assess latency, number of self-paced saccades,

percentage of directional errors, and accuracy. The fMRIs were processed using Statistical Parametric Mapping version 8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) toolbox, and standard pre-processing, first-level, and second-level analyses were performed. Data went through factorial analysis of variance design to evaluate group differences (NV vs subacute phase of injury) and within-group analysis (acute vs subacute).

RESULTS As in the acute phase of injury, antisaccade, self-paced saccades, and memory-guided saccades tasks were significantly different in the concussed group at 30 days postinjury, although oculomotor performance did improve (table). In the antisaccade task, the concussion cohort exhibited an approximately 15-ms-longer latency compared with the NV group but this was a significant improvement from their previous lag of 40 ms in the acute phase. Directional and position errors were still significantly higher than that of NVs but were reduced significantly from the acute phase to the subacute phase. This trend was also mirrored by primary and final eye gain. The mean number of self-paced saccades increased significantly from 65 to 80 for the concussed participants despite still being lower than the 106 reported in the NVs. Memory-guided saccades showed marked improvement during follow-up testing with nearly a 3.5- and 1.5-fold reduction in directional and position errors, respectively, but were still significantly more prominent than those seen in NVs.

Table	Oculomotor performance				
	NV (n = 9)	Acute (n = 9)	Subacute (n = 7)	Group p value	Session p value
Latency, ms					
Antisaccades	235 (±36.59)	275 (±45.93)	254 (±32.9)	0.15	0.04 ^a
No. of saccades					
Self-paced saccades	106 (±9.15)	68 (±15.56)	80 (±10.19)	0.01 ^a	0.03 ^a
Directional error, %					
Antisaccades	2.6 (±0.33)	15.0 (±4.0)	10 (±2.79)	0.001 ^a	0.03 ^a
Memory-guided saccades	1.5 (±0.65)	7.1 (±2.44)	2.1 (±0.51)	0.03 ^a	0.002 ^a
Primary saccade gain					
Antisaccades	1.23 (±0.2)	1.50 (±0.33)	1.39 (±0.21)	0.01 ^a	0.05 ^a
Memory-guided saccades	1.01 (±0.18)	1.25 (±0.39)	1.19 (±0.19)	0.04 ^a	0.10
Gain of final eye position					
Antisaccades	1.12 (±0.17)	1.35 (±0.3)	1.26 (±0.19)	0.05 ^a	0.20
Memory-guided saccades	1.1 (±0.2)	1.20 (±0.39)	1.16 (±0.23)	0.14	0.42
Self-paced saccades	1.0 (±0.04)	1.05 (±0.05)	1.02 (0.05)	0.17	0.22
Position error, %					
Antisaccades	27.4 (±11.96)	46.4 (±19.04)	37.2 (±7.33)	0.02 ^a	0.03 ^a
Memory-guided saccades	25.6 (±14.18)	52.7 (±22.59)	37.1 (±13.19)	0.03 ^a	0.02 ^a
Self-paced saccades	7.8 (±4.05)	9.3 (±6.37)	8.9 (±5.56)	0.11	0.15

Oculomotor tests and resultant behavioral data, normal volunteer (NV), and concussed group values at 7 days (acute) and 30 days (subacute) postinjury. Group p value refers to differences between NV and subacute data, while session p value denotes changes from acute to subacute phase of injury for the concussed group only. The 95% confidence interval is in parentheses.

^aSignificant.

No significant differences were seen for the other 4 tasks tested.

In the subacute phase of injury, we observed fMRI activation that appeared to be recovering to patterns seen in the NV group (figure). Antisaccade hyperactivation from the concussed group in the cerebellum, bilateral secondary visual cortex, and right visual area V5/MT seen on initial scanning was reduced to the left secondary visual cortex ($p = 0.004$) and right visual area V5/MT ($p = 0.006$) at 30 days postinjury. Again, right visual area V5/MT remained significantly hyperactivated ($p = 0.006$) compared with NVs at follow-up testing, although activation dropped between scans in the cerebellum ($p = 0.001$), precuneus ($p = 0.004$), left superior temporal gyrus ($p = 0.001$), and left postcentral gyrus ($p = 0.002$). Increased bilateral hippocampal activity seen at 7 days postinjury was confined to only the left hippocampus ($p = 0.005$) at 30 days postinjury

for the concussed group compared with NVs for encoding of the task over retrieval.

DISCUSSION We performed a follow-up study that acquired simultaneous fMRI with the administration of a battery of oculomotor tasks in the subacute phase of concussion. Oculomotor performance was still significantly impaired for complicated tasks, and fMRI revealed increased activation patterns.

Antisaccade, self-paced saccades, and memory-guided saccades are more challenging tests compared to smooth pursuit or basic saccadic eye movements. Alterations in antisaccade performance have been reported beyond 6 months postconcussion and have been strongly linked to neuropsychological tests of executive function.⁶ The higher degree of difficulty of antisaccades has been documented in the fMRI literature as evidence of hyperactivation in NV studies.⁷ The presence of increased activation at 30 days postinjury in the visual cortices may point to an inefficiency, and hence increased effort, to resolve directional selectivity.⁸ Previous research on mild closed head injury has documented similar deficiencies in oculomotor performance on memory-guided saccades.⁹ Although we saw an improvement in behavior and fMRI results that seemed to be on a trajectory to be restored to normal, there were still significant differences at 30 days postinjury. However, more work is needed to determine whether this gradual recovery ever returns to preinjury levels and whether the brain is using a compensatory strategy or there is a permanent reorganization of cerebral circuits. The NV cohort comprised a representative demographic and fitness level, although a better indicator of recovery would be the ability to compare oculomotor and fMRI results to preseason baseline data. This study is limited by its small sample size and MRI-compatible eye tracking hardware. We also recognize that inclusion of saccade amplitude data would be beneficial and that its absence is another limitation of this study. Unfortunately, a breakdown in proper data backup procedures resulted in the raw oculomotor behavior data being irretrievably lost, and the inability to reanalyze the data to include this metric.

It is worth considering whether these findings are truly asymptomatic. The concussed participants were considered normal, both by themselves and their treating physicians. This likely means that in routine activities, there is no problem. However, in more extreme conditions, such as those that might well be encountered in top-level athletic behavior, there might well be abnormalities. Subtle visual disturbances could lead not only to poor performance but even increased probability of another concussion.

Overall, this report further confirms that current clinical tools lack the ability to detect the subtle

Figure Self-paced saccades

(A) The fMRI activation differences between normal volunteers (NVs) and acute (A.a) and subacute (A.b) phase of injury in concussed participants for the self-paced saccade task. (B) Sample of behavioral data from NVs for the self-paced saccade task with time in seconds on the horizontal axis and vertical axis representing direction of eye movement.

underlying causes of persistent deficits following concussion.¹⁰ The use of progressive neuroimaging techniques in conjunction with oculomotor testing may be beneficial in clinical management of concussion.

AUTHOR CONTRIBUTIONS

As principal investigator, Dr. Slobounov had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Slobounov and Johnson. Acquisition of the data: Johnson. Analysis and interpretation of data: Johnson, Hallett, Slobounov. Drafting of the manuscript: Johnson, Hallett, Slobounov.

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DISCLOSURE

B. Johnson reports no disclosures relevant to the manuscript. M. Hallett is on the editorial board of 20 journals, and received royalties and/or honoraria for publishing from Cambridge University Press, Oxford University Press, John Wiley & Sons, Wolters Kluwer, Springer, and Elsevier. S. Slobounov reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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