Investigation of Vigilance and Working Memory Impairment in Sport Related Concussion Patients with functional MRI

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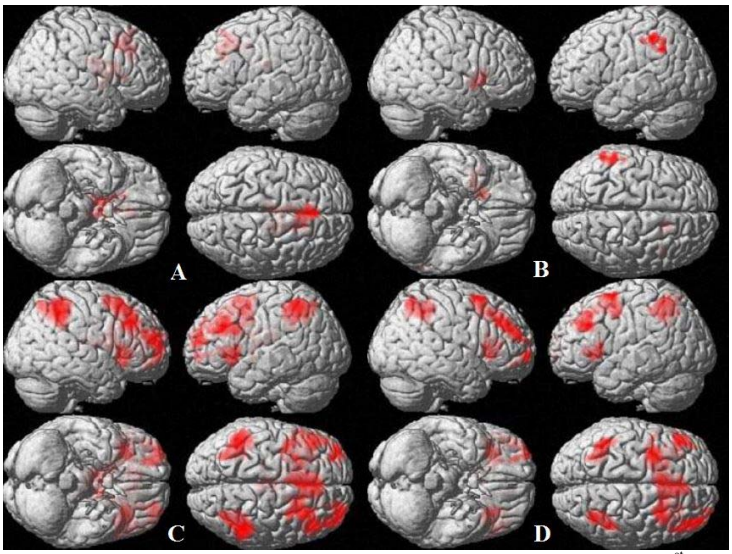
PURPOSE: Sports Related Concussion (SRC) is a mild form of head trauma, which has been shown to primarily affect brain function rather than structure [1]. While neuropsychological testing can be utilized to demonstrate the short-term effects and symptoms of SRC, the neuropathological processes underlying the observed changes in function are still poorly understood. To improve the understanding of these processes, multiple studies have used fMRI to evaluate neuronal impairments and were able to detect altered BOLD activations following concussion. In the current study, we aimed to substantiate previous research by comparing the fMRI results in the acute (< 7 days) and delayed (one month) phases of recovery from SRC with those from matched normal controls. This setup enables us to investigate both the effects of SRC on neuronal responses and effectiveness of recovery following injury.

METHODS: ***Subjects:*** 29 subjects were recruited from the Sports Medicine Department in our hospital. This included 15 right-handed, concussed males and 14 right-handed controls with each control matching to concussed subjects in terms of both the age (14-18y) and football team. The concussed group must have a Glasgow Coma Scale score of 13-15 and have less than 5 minutes loss of consciousness. The controls were all concussion-free for the past year at the time of enrollment. Both groups were scanned twice (21 days apart) with the same imaging sequences. For the concussed group, the first scan was done within 7 days of the concussion. ***Imaging:*** Participants were scanned in a 3 Tesla Siemens Trio scanner. A forehead strap and cushioning around the head were applied to restrict head movement. The MRI session lasted roughly an hour and included anatomical T1 MPRAGE, fMRI, pCASL and DTI scans. Primary imaging parameters for the fMRI scan include: TR=2130ms, TE=30ms, FA=90°, resolution=3x3x3 mm^3. ***fMRI Paradigm (N-Back):*** Participants completed a letter N-Back task (roughly 4 minutes) with stimuli consisting of 15 upper and lowercase letters (5 targets, 10 non-targets). The paradigm was repeated in 3 runs/scans (conditions were pseudo-randomized). For each run, the block-designed paradigm contains a 0-, 1-, 2-, and 3-back task, as well as a cross-hair (CH) block. The participants were instructed to press a button if the condition goal is met (e.g., for 2-back, press the button when the letter being displayed matches the letter shown 2 letters previously). Participants were trained on the task prior to entering the scanner to ensure they understood the task. ***Analysis:*** A three level (run/individual/group) analysis was done for the fMRI data using FSL (version 5.0.6). At the run level, the data was preprocessed in the following order: motion correction, spatial smoothing (FWHM=5mm), and high pass temporal filtering. The preprocessed data was then registered to its corresponding high-resolution T1 images and subsequently to the MNI152 T1 2mm standard brain template using linear boundary based registration. General linear modeling (GLM) was then performed on the process data to generate 8 contrasts: 0-, 1-, 2-, 3-Back vs CH, 0+1 vs CH, 2+3 vs CH, 2+3 vs 0+1, and 0+1 vs 2+3. Difference contrasts were contrast masked to reveal only positive activation. An individual level analysis was then carried out to take care of the repeated measure problem by averaging the contrasts at run level for each participant. Finally, the between and within group statistically analysis was done with a group level GLM to compare the between group and between visit differences for the 8 contrasts specified above.

RESULTS AND DISCUSSION: Two of our control subjects had incidental findings and were excluded from the study. One control and four concussion subjects showed excessive motion (mean displacement>3mm) in at least one of the fMRI datasets and were also excluded from further analysis. As a result, we had totally 11 concussed and 11 normal controls in the fMRI analysis. Qualitatively, the control group exhibited more extensive activations than the concussed group for 7 of the 8 contrasts we inspected (except the 0+1 vs 2+3 contrast) in both visits. Regardless of group and visit, the appearance of the BOLD activation patterns were similar for the same contrast and were consistent with previous research findings [2], however, the differences between the groups were less pronounced for the second visit. In the group difference contrasts, statistically significant reduction of activation in the concussed group was observed for the first visit (i.e., acute concussion period) while nothing passed the statistical test for the second visit. We specifically checked two contrasts: 0-back vs CH and 2-back vs CH contrasts. The 0-back contrast primarily captures vigilance whilst the 2-back contrast reflects working memory contribution. The control > concussed results (1st visit) for these two contrasts are shown in Figure A and B, respectively. It can be seen that the control group exhibits stronger activation in the medial frontal gyrus during the vigilance task, possibly reflecting attention impairment in concussed patients. For the working memory contrast (Fig. B), the control group exhibited stronger activation in right caudate (part of working memory network) and left PPC (possible role in episodic retrieval [3]). It should be noted that when the confidence level in statistical testing was lowered to Z>1.96 the caudate and PPC in both hemispheres showed statistically significant reduction in the concussed group. Within group (i.e., visit 2 vs visit 1) comparisons are more complicated as we noticed that activations during the second visit were generally lower in both groups than those during the 1st visit. This potentially reflects the effect of practicing the tasks. Such practicing effect confounds our evaluation of the neuronal recovery in the concussed patients. None of the contrasts showed statistical significant differences (Z>2.3, cluster correct p<0.05) between visits for both groups. The activations were very comparable between groups for the 2nd visit (e.g., Fig. C and D show the 3-back condition for both groups). This likely demonstrates that the neuronal function rapidly returns to following a SRC.



A. The control >concussed result of the vigilance task (0-back vs CH) for the 1st visit; **B.** The control >concussed result of the working memory task (2-back vs CH) for the 1st visit; **C.** The mean activation of 3-back task on the 2nd visit for the control group; **D.** The mean activation of 3-back task on the 2nd visit for the concussed

CONCLUSION: In conclusion, the current study demonstrates that the acute phase of SRC reduces BOLD activation in both vigilance and working memory tasks. It also suggests that SRC induced impairment may largely recover after a relatively short period of time. However, practice effects confound the interpretation of the results of the delayed phase of the study.

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