



Persistent differences in patterns of brain activation after sports-related concussion: A longitudinal fMRI study

A. Dettwiler¹, M. Murugavel¹, M. Putukian², R. Echemendia³, V. Cubon⁴, J. Furtado², D. Osherson⁵

¹Princeton Neuroscience Institute, Princeton University, NJ; ²University Health Services, Princeton University, NJ

³Psychological and Neurobehavioral Associates Inc., State College, PA; ⁴Kent State University, Kent, OH

⁵Department of Psychology, Princeton University, NJ

Introduction

Avoiding recurrent injury in sports related concussion (SRC) requires understanding the neural mechanisms involved in recovery. Prior studies have reported functional differences of brain activation in athletes with SRC. fMRI studies using working memory tasks suggest altered patterns of activation in the dorsolateral prefrontal cortex. Chen et al. (2004) reported fewer task-related activations and significantly decreased BOLD signal changes in the DLPFC in athletes with persistent symptoms compared to normal controls. Differences in brain activation in response to varying degrees of working memory processing load (N-back: 0, 1, 2 and 3 back) were identified by McAllister et al. (1999) in subjects with mTBI (Glasgow score 13-15) within one month after injury. The primary purpose of this study was to define neural correlates of SRC during the 2 month following injury, using a working memory task and fMRI.

Methods

Participants:

15 right-handed, varsity level contact sport athletes who suffered a SRC were scanned doing an N-back memory task (N = 1 to 3) within 72 hours, 2 weeks and 2 months post injury. 15 age and sex matched control subjects (non-contact varsity level athletes) were scanned at baseline and 2 weeks. All athletes were evaluated prospectively (prior to injury) using a hybrid NP testing battery consisting of a (SCAT2), Paper/Pencil testing battery and *ImpACT* test. All athletes who subsequently sustained a SRC were evaluated again on SCAT2 and the same hybrid NP testing battery as used for the baseline test within 72 hours, 2 weeks and 2 months post injury.

Concussed					Controls			
Subject	Sex	Age	Sport	NP normal	Return to Play	Sex	Age	Sport
1	F	19	Field Hockey	13 days	no return to play	F	19	Volley Ball
2	M	19	Foot Ball	2 mo*	18 days	M	19	Crew Heavyweight
3	M	19	Water Polo	6 days	24 days	M	19	Volley Ball
4	M	20	Foot Ball	24 days**	31 days	M	21	Crew Lightweight
5	F	21	Basket Ball	9 days	9 days	F	21	Volley Ball
6	F	18	Rugby	17 days	no return to play	F	18	Swimming
7	M	21	Ice Hockey	3 days	12 days	M	21	Volley Ball
8	M	20	Foot Ball	6 days	15 days	M	18	Swimming
9	M	20	Basket Ball	9 days	12 days	M	18	Squash
10	M	19	Foot Ball	18 days***	18 days	M	18	Crew Heavyweight
11	M	21	Ice Hockey	15 days	82 days	M	22	Cross country
12	M	20	Lacrosse	17 days	23 days	M	22	Track
13	M	20	Wrestling	11 days	18 days	M	22	Track
14	M	19	Ice Hockey	2 days	23 days	M	18	Crew Heavyweight
15	M	21	Sprint Foot Ball	13 days	16 days	M	22	Track

Table 1 : Subject demographics of concussed athletes and matched controls. * not normal 2 weeks, not repeated until 2 mo since season over. ** 1st injury. *** NP not repeated till 2 weeks for study; season over.

Imaging Parameters:

Images were acquired on a 3T Siemens Skyra scanner (EPI PACE, FoV read 192 mm, FoV phase 100 %, slice thickness 3 mm, base resolution 64, phase resolution 100 %, TR 2020 msec, TE 30 msec, Flip angle 76 degrees, 284 volumes, 0.9 mm isotropic whole brain MPRAGE for registration). Each imaging session consisted of 30 randomized blocks of N-back tasks with 15 sec rest intervals. N-back task behavioral responses were collected using a Psychtoolbox program (Brainard, 1997).

Data Processing and Statistical Assessment:

Neuroimaging data were processed using standard block design processing routines in FSL-FEAT (Smith et. al., 2004; version 4.1.9). 'First Level' analyses GLM model employed a Double-Gamma HRF to model the three original N-back task conditions (1 to 3 Back; with respect to the 15 second rest intervals). A 'Second Level' analysis via a 'Fixed Effects' model was used to collapse the three discrete runs in each session, resulting in beta volumes for the 2-1 and 3-1 contrasts. Post hoc analyses were run on the derived contrasts in the AFNI (Cox, 1996) environment, chiefly employing 3dANOVA3. AFNI subroutines 3DFWHMx and 3dClustSim were used to compute cluster size thresholds to address the issue of multiple comparisons correction.

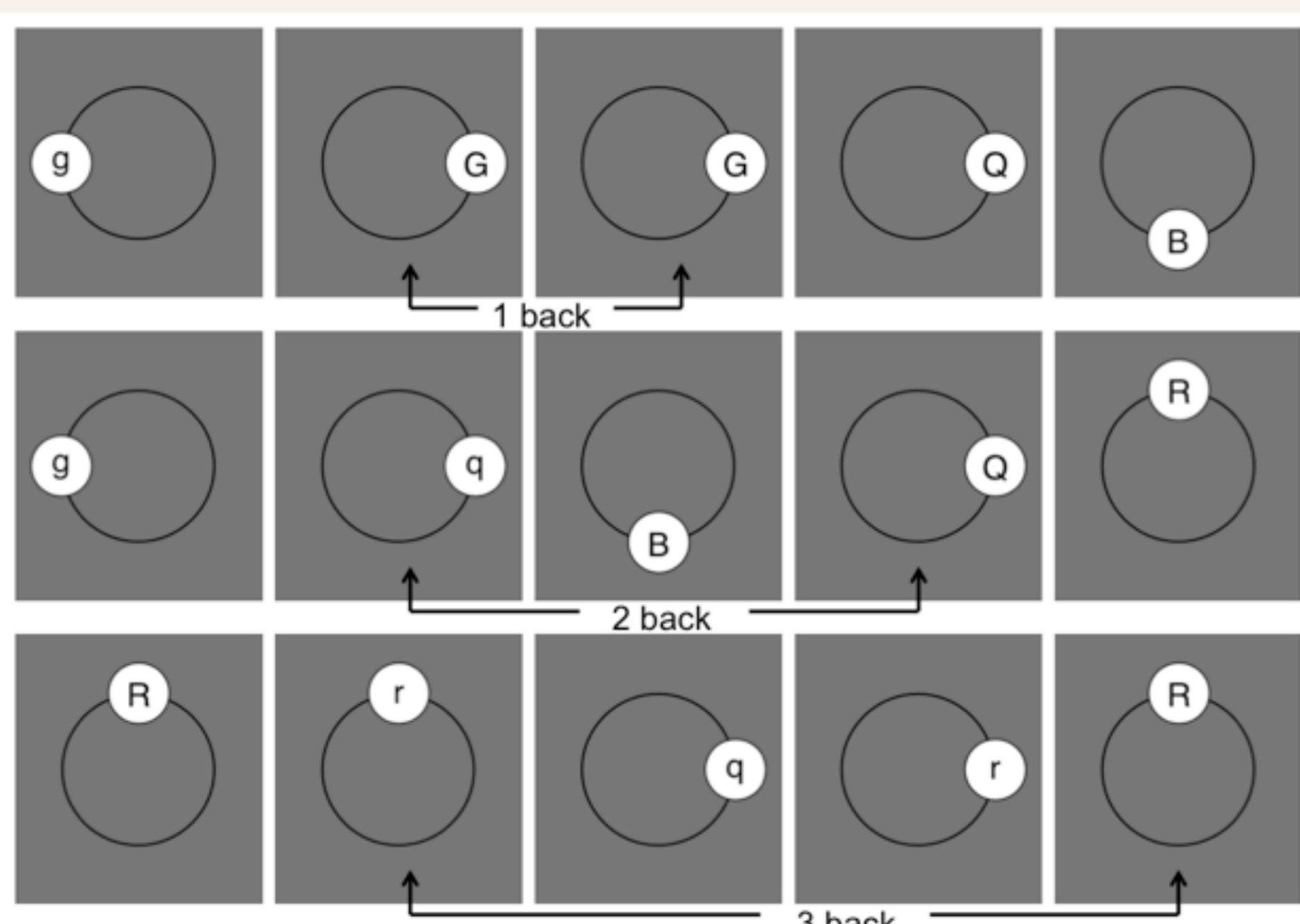


Figure 1 : Illustrates N-Back task employed in the scanner

Results

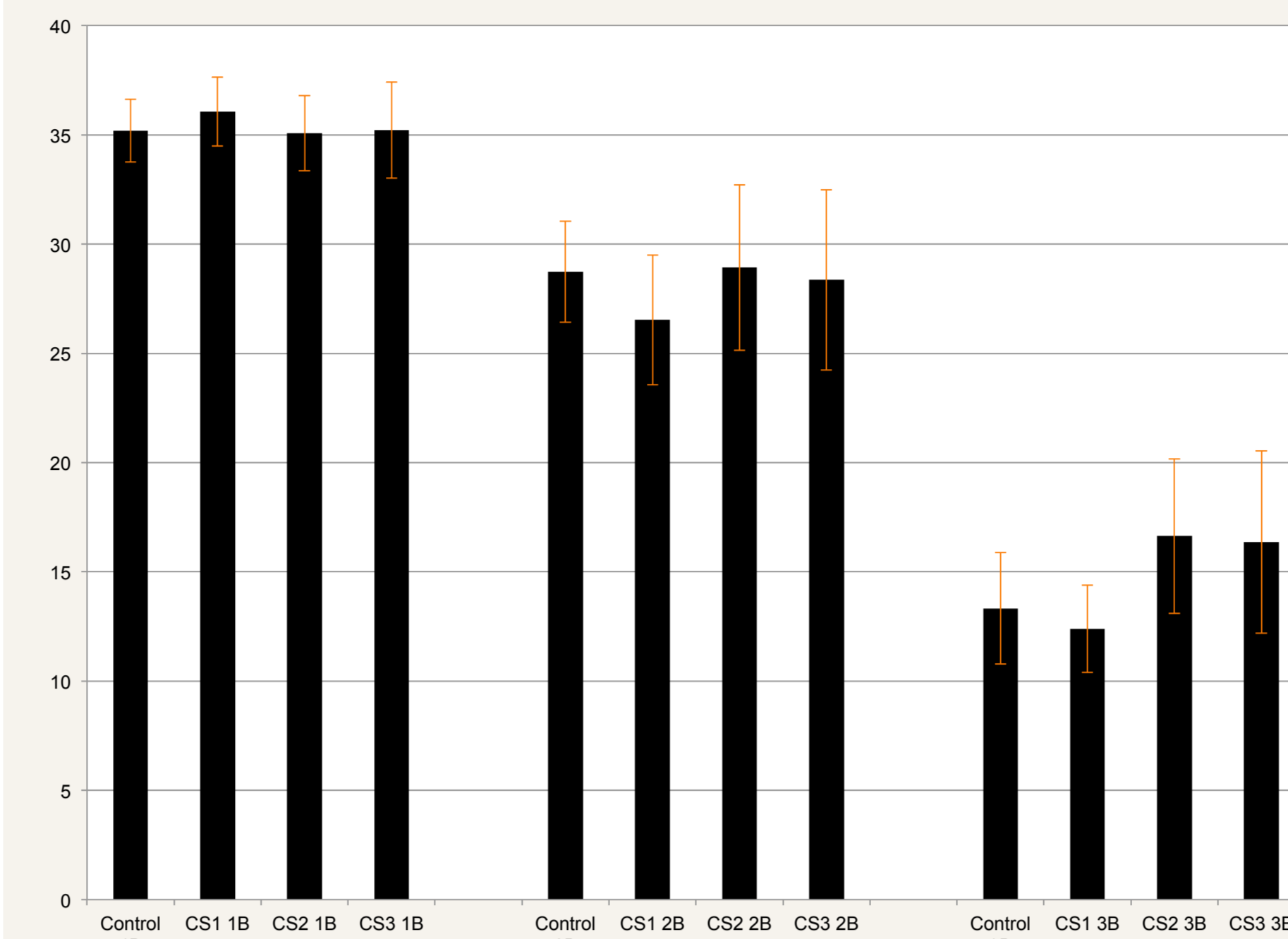


Figure 2 : Pooled T-Test for the between group comparisons (Concussed Vs Control) for subject's True - False positive responses during the 1 Back, 2 Back and 3 Back task condition in the scanner showed no between group differences (P > 0.05)

Results reported in this study pertain to the post hoc analysis of the whole brain 3dANOVA3 (group x task x subjects) for the between group 2-1 contrast (concussed- controls). In all brain areas demonstrating significant between group differences for the 2-1 contrast (FDR corrected, alpha < 0.01) across all three sessions, concussed subjects demonstrated significantly increased activity as compared to their age and sex matched controls.

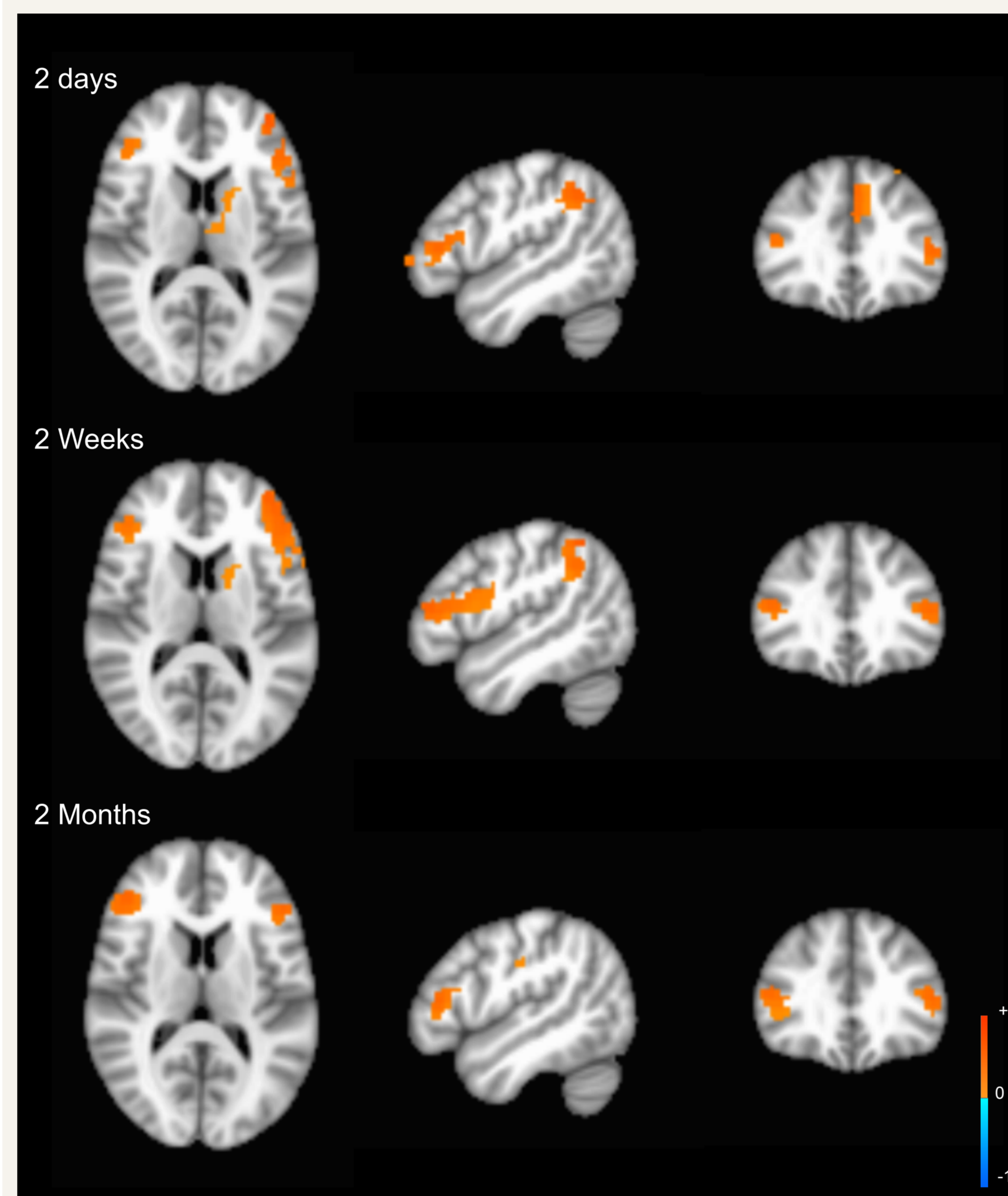


Figure 3 : Whole brain 3dANOVA3 (Group X Task X Subjects) for the between group N-back, 2-1 contrast (Concussed - Controls) demonstrated persistent, significantly increased (alpha < 0.01) activity in bilateral, dorsolateral prefrontal areas throughout all three time points and in left inferior parietal area within 72 hours and at 2 weeks post injury.

ROI	Cluster size	MNI coordinates, Maximum p value		
		x	y	z
Controls Vs CS1				
Left inferior frontal gyrus, BA10 Extending into BA46/44	253	36	-57	0
Left cingulate gyrus BA 31	212	0	24	42
Left inferior parietal (supramarginal) gyrus BA40	166	36	66	51
Left medial frontal/cingulate gyrus BA6, BA9	140	0	-24	51
Left middle frontal gyrus BA 8	76	33	-18	57
Left thalamus	58	3	6	6
Right inferior parietal (angular) gyrus, BA39	55	-39	69	42
Right postcentral gyrus BA3	35	-24	39	66
Right superior frontal gyrus BA6	34	-27	-12	63
Right superior frontal gyrus BA11	33	-27	-60	-12
Right inferior frontal gyrus BA46	32	-48	-33	18
Controls Vs CS2				
Left inferior frontal gyrus BA10 extending into BA46/44	339	39	-51	15
Left inferior parietal (supramarginal) gyrus BA40	134	42	54	54
Right inferior frontal gyrus BA46	46	-48	-33	18
Left caudate	43	12	-6	12
Right caudate	42	-15	-15	6
Left medial frontal gyrus BA8	41	3	-24	42
Controls Vs CS3				
Left cingulate gyrus BA 31	105	0	24	42
Right inferior frontal gyrus, BA46	96	-45	-39	12
Right precentral BA 4	87	-33	24	63
Left inferior frontal gyrus BA46	60	48	-33	12
Left parahippocampal (Lentiform, putamen)	47	18	3	-18
Left precentral	33	63	21	24

Table 2 : MNI coordinates of the voxel with the maximum p value for each significant cluster (3dANOVA3, 2-1 between group contrast, alpha < 0.01)

Results (cont'd)

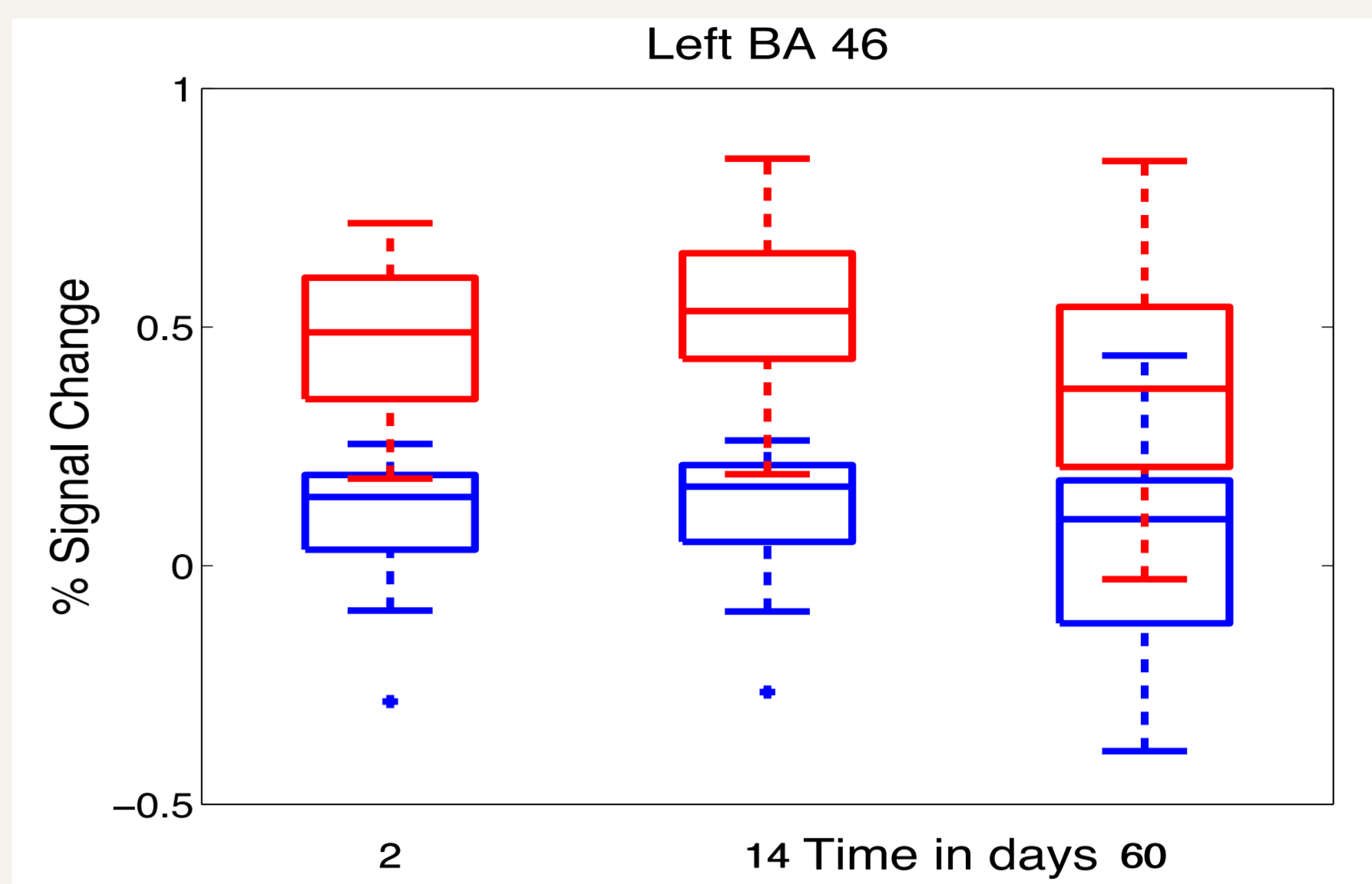


Figure 4 : Boxplot of the average percent signal change derived for each subject across all three sessions for the cluster in left BA for the N-back 2-1 contrast, suggesting a nonlinear pattern of recovery. (Concussed - Red; Controls - Blue)

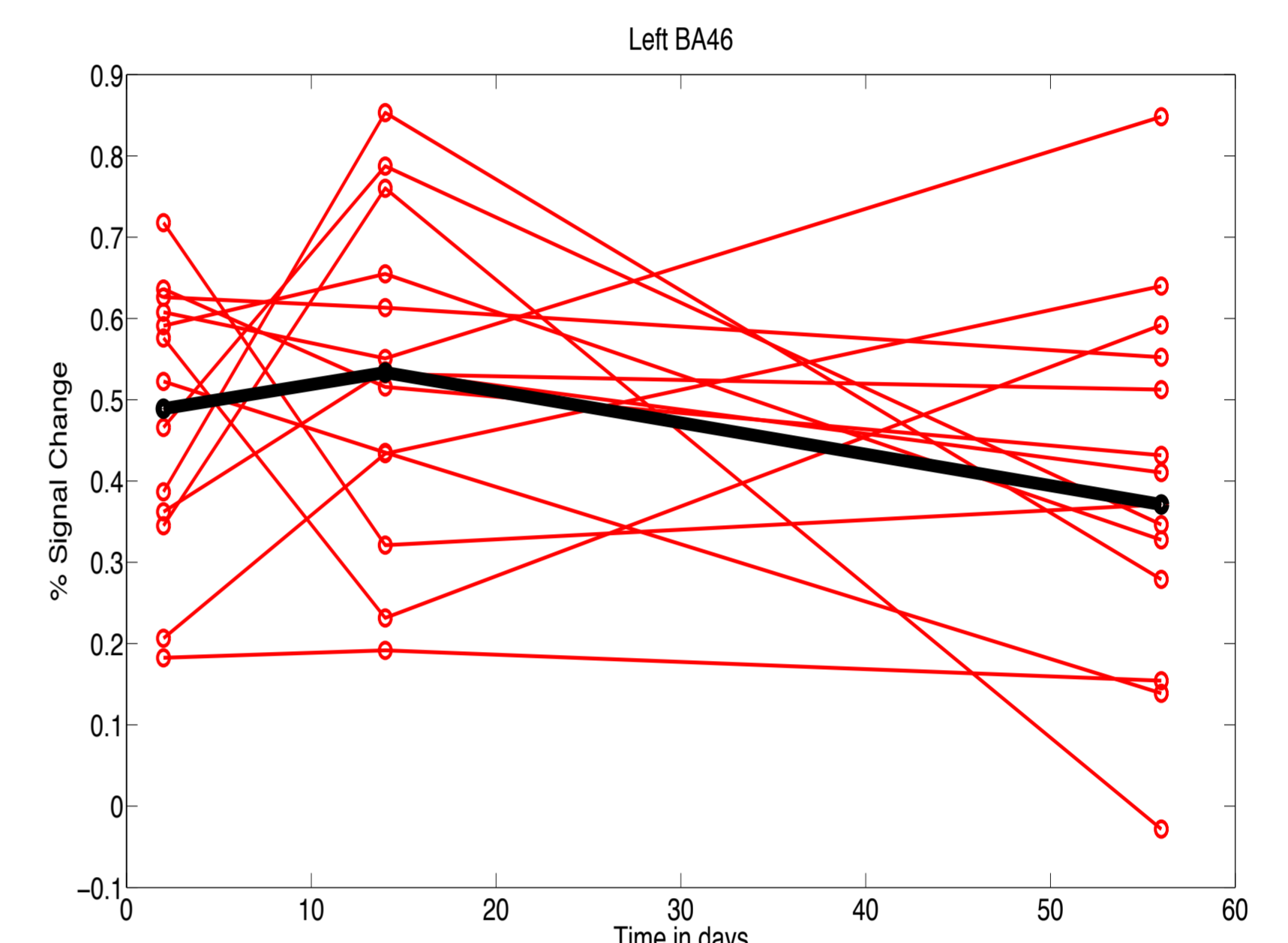


Figure 5 : Individual trajectories of the concussed subjects in left BA 46 with the median overlaid

As shown in Table 2, concussed subjects demonstrated significantly higher activation in 11 clusters in session 1 (within 72 hours after injury) as compared to only 6 clusters in session 2 (2 weeks post injury) and session 3 (2 months post injury).

Significant between group differences were consistently observed in all three sessions, in left and right prefrontal areas (BA 46) and in session one and two, significant between group differences were observed in the left inferior parietal (supramarginal) gyrus (BA40) as well (Figure 3). Average percent signal change was derived for each subject across all three sessions in the cluster in BA 46 identified in the 3dANOVA3 for the 2-1 contrast exhibiting a significant between group difference between the concussed and control group (alpha < 0.01).

Interestingly, percent signal change in this cluster was for most concussed subjects highest in the second time point and subsequently decreased in the 3rd time point. Despite the fact that no significant within group difference was found between the three sessions, the change of mean percent signal change in bilateral BA 46 across the 3 sessions suggests a nonlinear pattern of recovery in the prefrontal areas.

Conclusion

These data suggest that differences of allocation of resources and functional brain activation patterns persist at 8 weeks after injury in concussed athletes, despite the fact that their performance on a standard working memory task is comparable to normal controls and normalization of clinical/hybrid NP tests. These results might indicate a delay between neural and behaviorally-assessed recovery.

References

- Chen, J.K., Johnston, K.M., Frey, S., Petrides, M., Worsley K., & Plito, A. (2004). Functional abnormalities in symptomatic concussed athletes: An fMRI study. *Neuroimage*, 22, 68-82.
- McAllister, T.W., Saykin, A. J., Flashman, L. A., Sparling, M. B., Johnson, S. C., Guerin, S. J., et al. (1999). Brain activation during working memory 1 month after mild traumatic brain injury: A functional MRI study. *Neurology*, 53, 1300-1308.
- Brainard, D. H. (1997) The Psychophysics Toolbox, *Spatial Vision* 10 : 433-436.
- S.M. Smith, et al. Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, 23(S1):208-219, 2004
- RW Cox. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*, 29:162-173, 1996.

Acknowledgements

- New Jersey Commission for Brain Injury Research Grant No. 10-3217-BIR-E-0
- Goldstein family fund
- Peter and Cynthia Kellogg foundation