2013

Detection of Brain Abnormalities in Football Players Through Diffusion Weighted Imaging

Allan Emilio Diaz Gaez
Purdue University

Graduate School ETD Form 9
(Revised 12/07)

PURDUE UNIVERSITY
GRADUATE SCHOOL
Thesis/Dissertation Acceptance

This is to certify that the thesis/dissertation prepared

By Allan Diaz Gaez

Entitled
Detection of Brain Abnormalities in Football Players through Diffusion Weighted Imaging

For the degree of Master of Science in Electrical and Computer Engineering

Is approved by the final examining committee:

THOMAS M. TALAVAGE
Chair

ERIC A. NAUMAN

MICHAEL D. ZOLTOWSKI

To the best of my knowledge and as understood by the student in the *Research Integrity and Copyright Disclaimer (Graduate School Form 20)*, this thesis/dissertation adheres to the provisions of Purdue University's "Policy on Integrity in Research" and the use of copyrighted material.

Approved by Major Professor(s): THOMAS M. TALAVAGE

Approved by: M. R. Melloch 11-19-2013
Head of the Graduate Program Date

DETECTION OF BRAIN ABNORMALITIES IN FOOTBALL PLAYERS THROUGH DIFFUSION WEIGHTED IMAGING

A Thesis

Submitted to the Faculty

of

Purdue University

by

Allan E. Diaz Gaez

In Partial Fulfillment of the

Requirements for the Degree

of

Master of Science in Electrical and Computer Engineering

December 2013

Purdue University

West Lafayette, Indiana

I dedicate this thesis to my parents, Alonso Diaz and Dolores Gaez de Diaz. They have taught me the most important lesson: “Confia en Dios y siempre mantenen un equilibrio entre la familia y el trabajo”.

ACKNOWLEDGEMENTS

Special thanks to Prof. Thomas Talavage for his support, guidance and encouragement over the years we have worked together. I would also like to thank the members of my advisory committee Eric Nauman and Michael Zoltowski for taking the time to revise my work. Finally, I give my immense gratitude to Il Yong Chun (Bobby) for his advisory support and patience throughout our collaboration.

TABLE OF CONTENTS

LIST OF FIGURES

ABSTRACT

Diaz Gaez, Allan E. M.S.E.C.E., Purdue University, December 2013. Detection of Brain Abnormalities in Football Players through Diffusion Weighted Imaging. Major Professor: Thomas M Talavage.

Depression and cognitive impairment are commonly found in retired football players. Although they receive high magnitude hits to the head, the majority of the hits are sub-concussive, resulting in no clinical symptoms. Recent work using functional magnetic resonance (fMRI) and neurocognitive testing confirms that blows, causing changes in brain function, might not necessarily result in clinical diagnosis of concussion. Furthermore, cognitive deficiency in football players may be attributed to repetitive sub-concussive blows to the head. Diffusion weighted imaging (DWI) has previously been utilized to detect white matter (WM) abnormalities in mild traumatic brain injury (mTBI) patients, including those who have previous concussions from sports. DWI has been proposed as a means to effectively identify pre-clinical deficiencies in individuals exposed to repeated blows to the head, with a goal of prevention and treatment for subsequent neurodegenerative disease. This work demonstrates the potential of DWI as a tool for detection of changes in white matter of high school athletes involved in high-collision sports.

1. INTRODUCTION

American football is the most famous sport played in the United States of America. Players usually start practicing at the age of 5-9 years old. It is truly concerning the amount of blows to the head that these players have accumulated by the time they graduate from high school. Furthermore, studies have shown that problems with memory, naming, word finding and depression are correlated with white matter abnormalities in aging former NFL players [1].

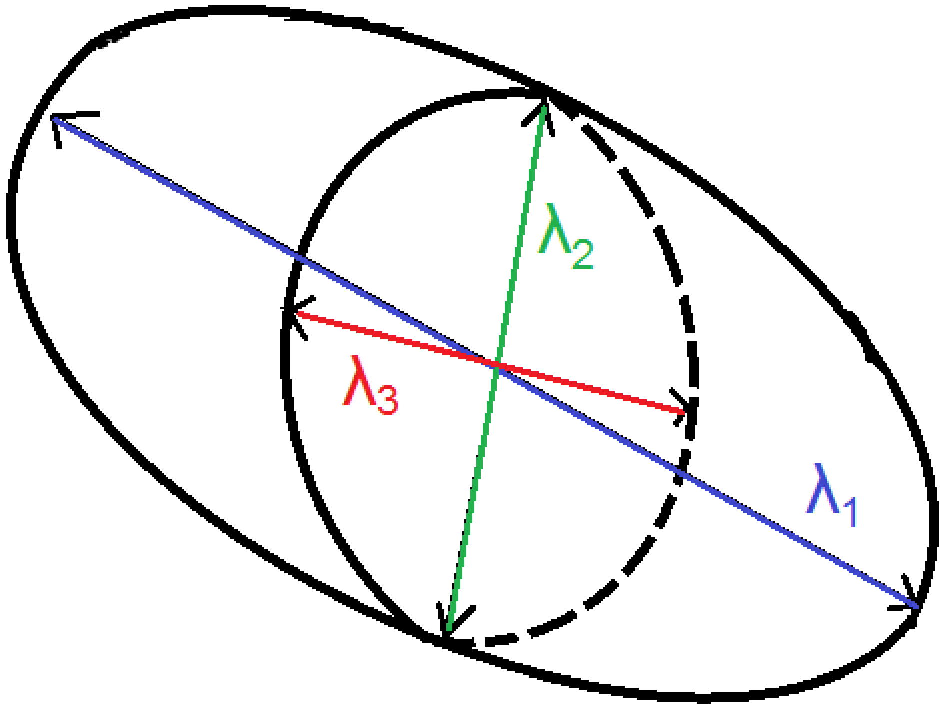
Nowadays, football teams do not track the magnitude or the total number of hits received to the head. Players are only taken out of the field if they are diagnosed with a concussion. However, it has been shown that cognitive deficiency may not result in clinical diagnosis of concussion [3, 4, 5]. Consequently, there is an obvious sub-concussive damage due to multiple hits exposure.

Although the most established clinical application of diffusion weighted imaging is the evaluation of ischemic brain injury and neurological disorders, white matter abnormalities in mTBI patients have been detected using diffusion weighted imaging (DWI). Moreover, the combination of DWI along with powerful statistical analysis can be utilized to effectively measure pre-clinical significant deviations in the brains of football players

2. BACKGROUND

Diffusion weighted imaging is a magnetic resonance imaging method that measures the diffusion of water in the brain. Two magnetic field gradients are applied to cause and undo a signal dephasing. As a result, only the dephase of moving molecules such as water will not be undone and a signal loss on the diffusion weighted image is obtained. Hence, a series of diffusion weighting gradients in different directions is applied to obtain the diffusion information in all directions.

The diffusion patterns of these molecules can be anisotropic or isotropic within voxels in the brain. Many measurements can be derived from DWI such as fractional anisotropy (FA). FA maps of the brain are computed utilizing the eigenvalues, λ_1, λ_2 and λ_3, from the DWI information and a mathematical ellipsoid model, shown in figure 2.1, to describe the diffusion effects at a voxel level. FA is a scalar with range from zero to one that quantifies the degree of diffusion in a given voxel. If the diffusion is unrestricted and flows in many directions, the FA value will be zero. On the other hand, an FA value of one means that the diffusion is anisotropic.



$$\mathrm{FA} = \sqrt{\frac{1}{2}}\frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

Figure 2.1 Fractional Anisotropy Representation for a Given Voxel

The white matter consists of the communication pathways between different brain regions. Although, grey matter is associated with cognition, abnormalities in white matter can also alter the cognitive performance. Moreover, the integrity of the white matter can be evaluated by observing changes in FA.

3. METHODS

3.1 Participants

A total of 68 high school football players (age: 14-18 years) participated in our study. Over three seasons, the players were recruited from two local high school football teams. For each football season, the players were scanned before, during and after the season to evaluate their progress. Some players were studied more than once during the season, depending on availability. Along with the DWI scans, an ImPACT test [14] was given to assess their cognitive performance. Subjects who participated in more the one season were treated independently, resulting in 264 total scans.

An additional 21 healthy non-contact sport high school athletes were brought for the control group. There were 13 males and 8 females. Also, 9 of the 21 controls were scanned a second time, approximately one month after their first scan.

Three additional symptomatic subjects, I1, I2 and I3, with diagnosed concussions were included in the study in order to have a reference for symptomatic injuries.I1 and I3 are 19 and 21 years old females, respectively. I2 is a 47 year old male. The injured patient I3 was scanned 5 times over the year following her injury, to evaluate her progress.

3.2 Magnetic Resonance Imaging

All imaging was performed using a GE 3T Signa HDx and a Nova Medical Inc. 16-channel brain array. Subjects participated in pre-season, in-season, and post-season sessions for each of the three seasons (see [5]). DWI data (b=1000 s/mm^2) were acquired over the period of the study using two sets of diffusion angles: (1) 25 angles for Season 2 and Controls; (2) 30 angles for Season 3, 4 and Symptomatic Subjects. Note that In1 and In2 refer to in-season scans performed in first and second halves of a season, respectively.

3.3 Image Processing

All the Digital Imaging and Communications in Medicine (DICOM) standard images were converted to Neuroimaging Informatics Technology Initiative (NIfTI) format using the software converter, DCM2NII [15]. The eddy current and movement correction, brain extraction and registration are processed using the FMRIB Software Library (FSL) v5.0 [6, 7, 8].

3.3.1 Movement and Eddy Current Correction

The eddy correct tool from FSL is utilized to correct for eddy current-induced distortion and subject movements by using affine registration to the b0 image [6]. It is assumed that the signal from two acquisitions acquired with diffusion weighting along two vectors with a small angle between them is more similar than for two acquisitions a large angle between them. Also, the signals from two acquisitions along vectors v and –v are assumed to be identical.

3.3.2 Brain Extraction Tool

The Brain Extraction Tool (BET) removes non-brain tissue from the image collected for each subject [6, 9]. It calculates the minimum and maximum intensities by ignoring the lower 2% and the higher 98% of the cumulative histogram of the whole intensity image. Then, a center of gravity is computed along with a radius of the brain based only the voxels with intensity higher than t, which is set to lie 10% of the way between the $t_{2\%}$ and $t_{98\%}$. Afterwards, the surface of the brain consists of a sphere of connected triangles making a tessellated surface centered in the center of gravity and with half the radius obtained before. The program iterates to expand the surface until only the brain is extracted.

3.3.3 Diffusion Tensor Fitting

The DTIFIT tool estimates the diffusion tensor at each voxel of the brain. It generates multiple images such as the fractional anisotropy (FA) maps, tensor vectors and eigenvalues [6].

3.3.4 Non-Linear Registration

The FA images were co-registered to the FMRIB58 FA template using the non-linear registration toolbox FNIRT from FSL [10, 11]. Also, the datasets were aligned into the 1x1x1 mm MNI152 standard space by affine transformation, which uses a b-spline representation of the registration warp field [12].

3.3.5 White Matter Segmentation

The main focus was to evaluate the changes in white matter. Hence, a white matter (WM) mask was applied to every FA map. The WM mask was obtained by computing a mean FA map of all datasets including controls, players and symptomatic patients and considering only FA values above 0.3 [13].

3.3.6 Isotropic Smoothing

A full width half maximum Gaussian 3mm filter was applied to all the data sets in order to ameliorate registration problems.

3.4 Angle Transformation

The FA values are expected to be inversely proportional to the number of angles by which the data is collected. Therefore, an event was organized where 17 volunteers, with no history of concussions, were scanned to evaluate the differences in the FA distribution. All of them were scanned twice, once with 25 angles and once with 30 angles immediately after. As expected, the FA distributions of the data collected with 30 angles were shifted left compared to the data collected with 25 angles. The FA distributions were treated as probability density functions. Two mean FA distributions were computed, one for the 25 angles and one for the 30 angles datasets. Then, scaling and shifting parameters were globally estimated from the mean distributions. Finally, a non-linear transformation, using equation 3.4 shown below, was applied to the 25 angles FA distributions to match the FA distributions of the 30 angles data.

$$y=[x^2 \quad x \quad 1]\begin{bmatrix}a\\b\\c\end{bmatrix}=X\,\theta \tag{3.1}$$

$$\theta^*=(X^TX)^{-1}X^Ty \tag{3.2}$$

$$E\left[\theta^*-\theta\right]=0 \tag{3.3}$$

where y is the 30 angles mean distribution and x is the 25 angles mean FA distribution.

3.5 Statistical Analysis

A voxel-wise bootstrapped z-score (z_{BS}) was proposed to detect significant changes in the white matter for each subject. The z_{BS} values are computed using equation 3.4. The bootstrapping resampling method is included to better characterize the controls due to our limited population. $\bar{x}_b$ is the mean of each set of uniformly sampled data with placement for b = 1,..,B, where B is the number of bootstrapped samples. Then, a mean and standard deviation of $\bar{x}$ is calculated as shown in figure 3.3. It is assumed that each voxel is independent and identically distributed. Two different approaches were taken to identify the abnormalities in the subjects: comparison of z_{BS} distributions by groups and outliers plot of percent of voxels outside the 99.9% confidence interval of each individual.

$$z_{BS}=\frac{\text{data-mean}(\bar{x})}{\text{std}(\bar{x})} \tag{3.4}$$

$$\bar{x} \in R^{Bx1}$$

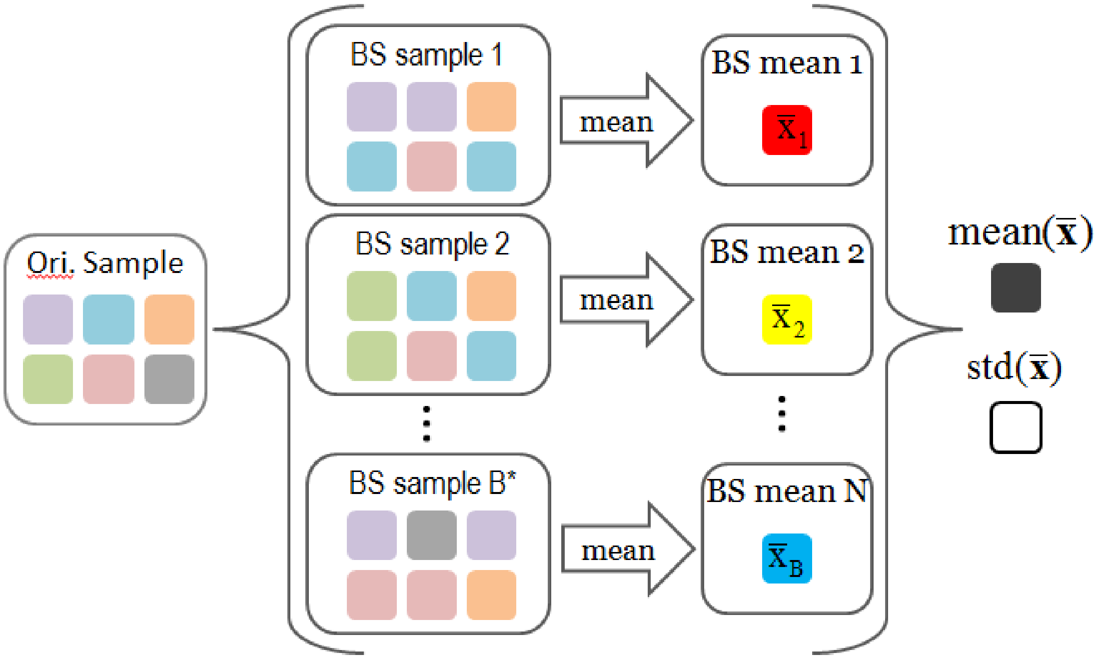


Figure 3.1 Graphical Representation of Bootstrap Method. B^* is 500.

4. RESULTS

4.1 Angle Transformation

The non-linear transformation applied to the 25 angle data allows the data collected with different angles to be compared. The transformed training data from 25 to 30 angles successfully matches data collected with 30 angles. It is worth noting that the transformed data of those controls collected with 25 angles do not completely overlap the data collected with 30 angles because they are not derived from the same people.

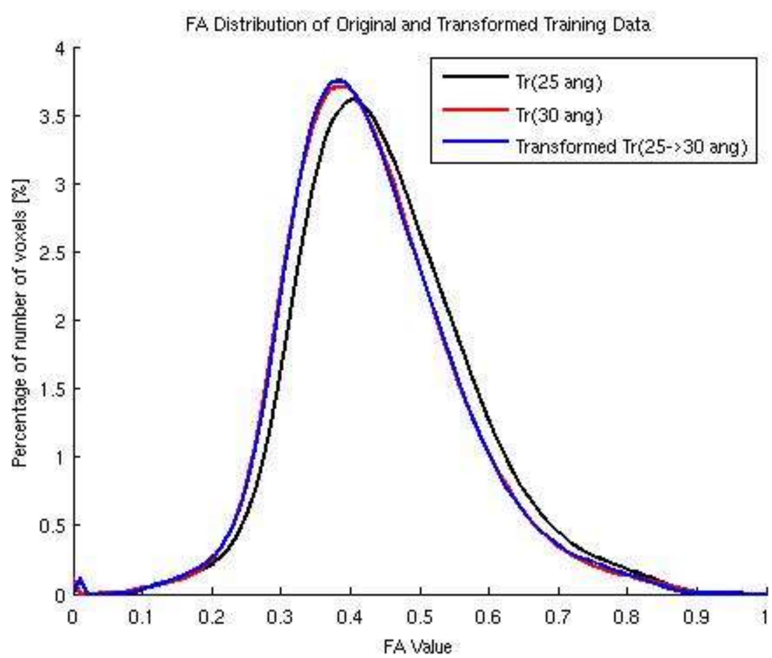


Figure 4.1 Probability Density Function Image Transformation from $FA_{25angle}$ to $FA_{30angle}$.

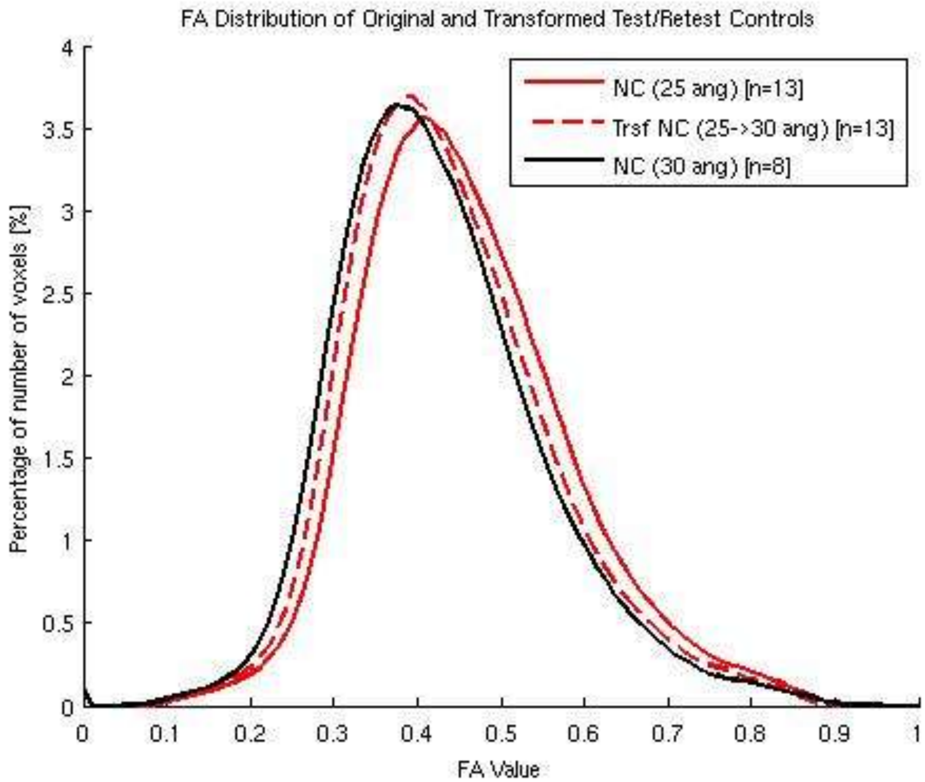


Figure 4.2 Probability Density Function Matching for Non-Contact Controls (NC) Test and Re-Test.

4.2 z_{BS} Distribution Comparison

Probable changes in white matter are reflected in the bootstrapped zscore distributions. The symptomatic injured patients showed a left shift compared to the control population. The football players exhibit differences that are dependent on the team, a right- or a left-biased shift. The z_{BS} distributions results are shown in the following figures.

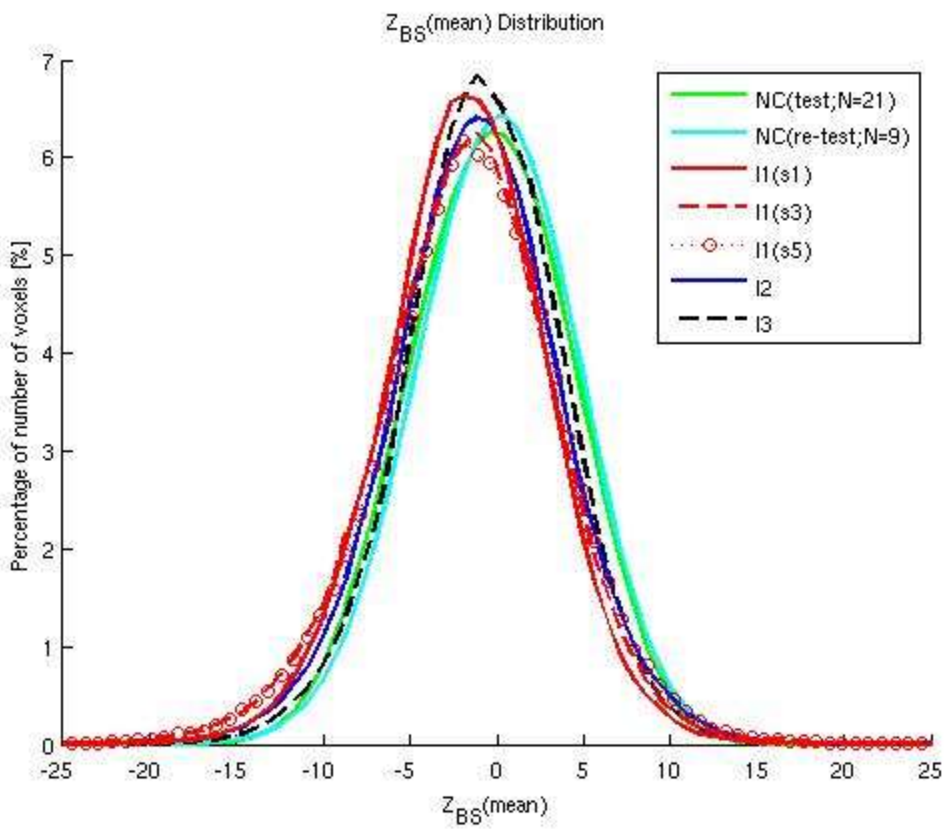


Figure 4.3 z_{BS} Distribution for Controls and Symptomatic Patients. The Injured patients I1, I2 and I3 show a significant left shift, meaning that FA values are lower, an observation typical in the case of TBI [16].

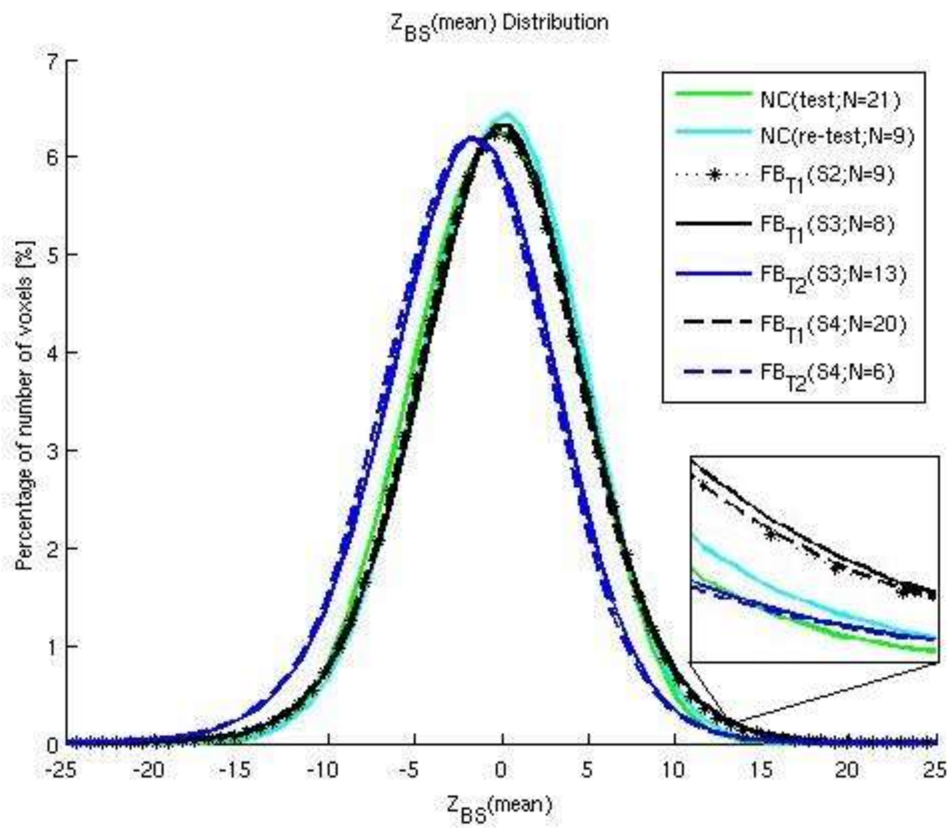


Figure 4.4 z_{BS} Distribution for Controls and Football Players. T1 shows a left shift while T2 have an increased right bias compared to the controls.

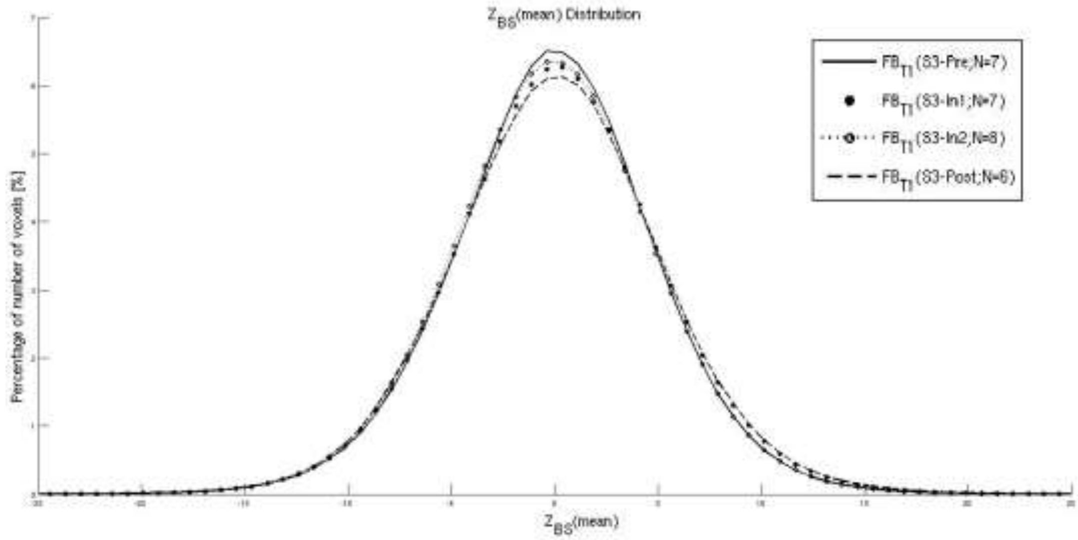


Figure 4.5 z_{BS} Distribution for Controls and Season 3 of Team 1. It can be seen that there is a right bias in the Post Season and In-Season 1.

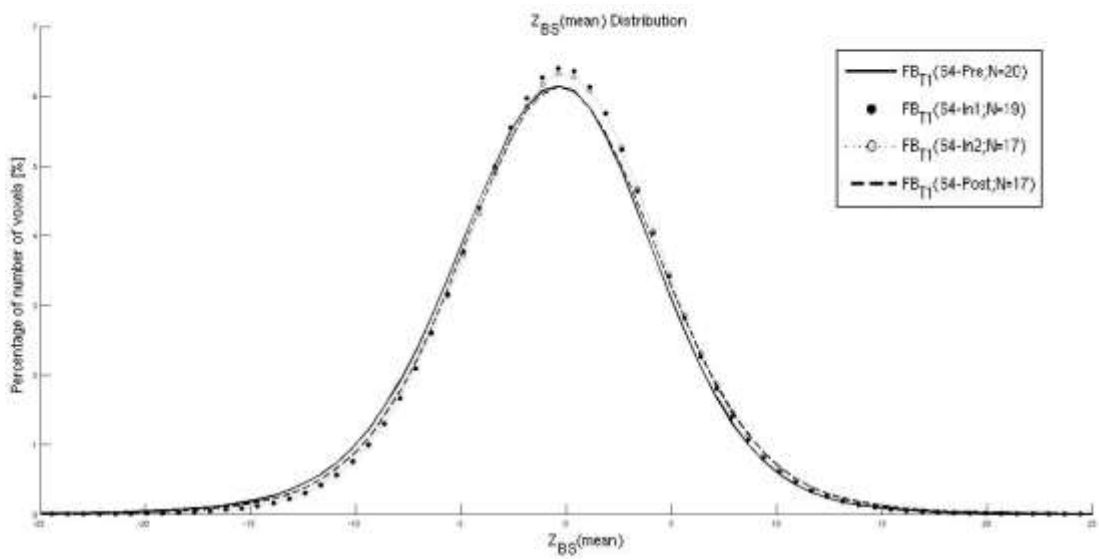


Figure 4.6 z_{BS} Distribution for Controls and Season 4 of Team 1.The In-Season distributions show a right shift compared to the Pre-Season. Also, the Post-Season distribution exhibits a right shift but less than the In-Season distributions, suggesting that the Post-Season exhibited some measure of “recovery” relative to the In-Season measurements.

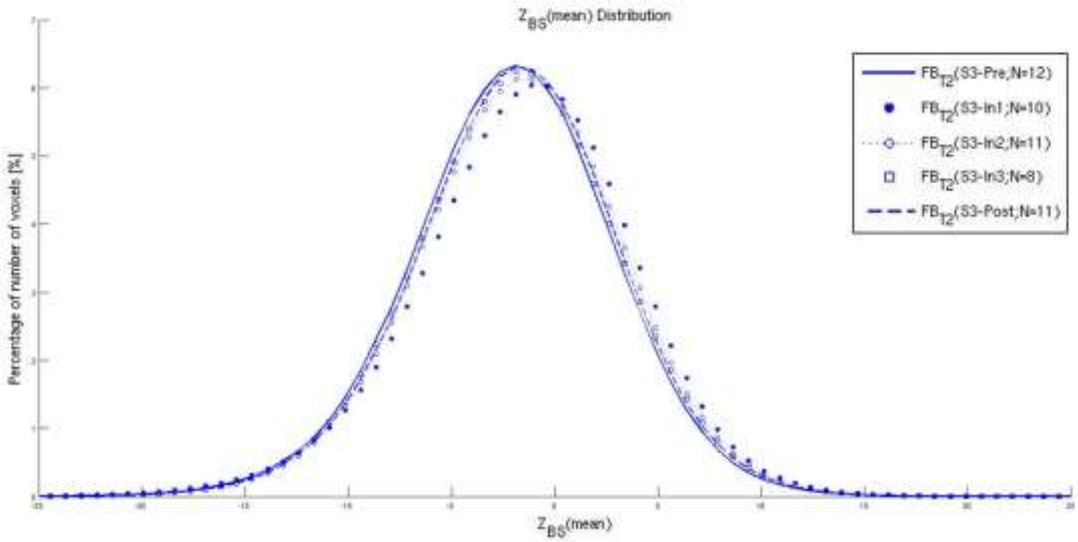


Figure 4.7 z_{BS} Distribution for Controls and Season 3 of Team 2. The most right shifted distribution belongs to In-Season 1. Then, it can be observed that the following sessions progressively shift left, toward the Pre-Season distribution. Possibly indicative of short-term recovery or adaptation.

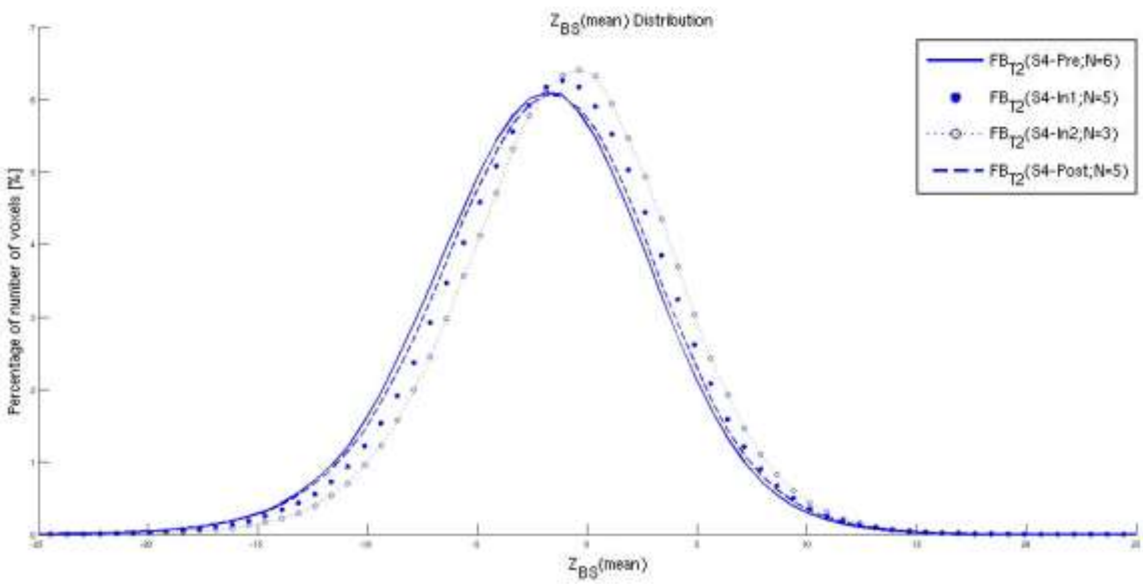


Figure 4.8 z_{BS} Distribution for Controls and Season 4 of Team 2. The behavior is same as shown in fig. 4.7, where the In-Season measures are right-shifted relative to both the Pre- and Post-Season Distributions.

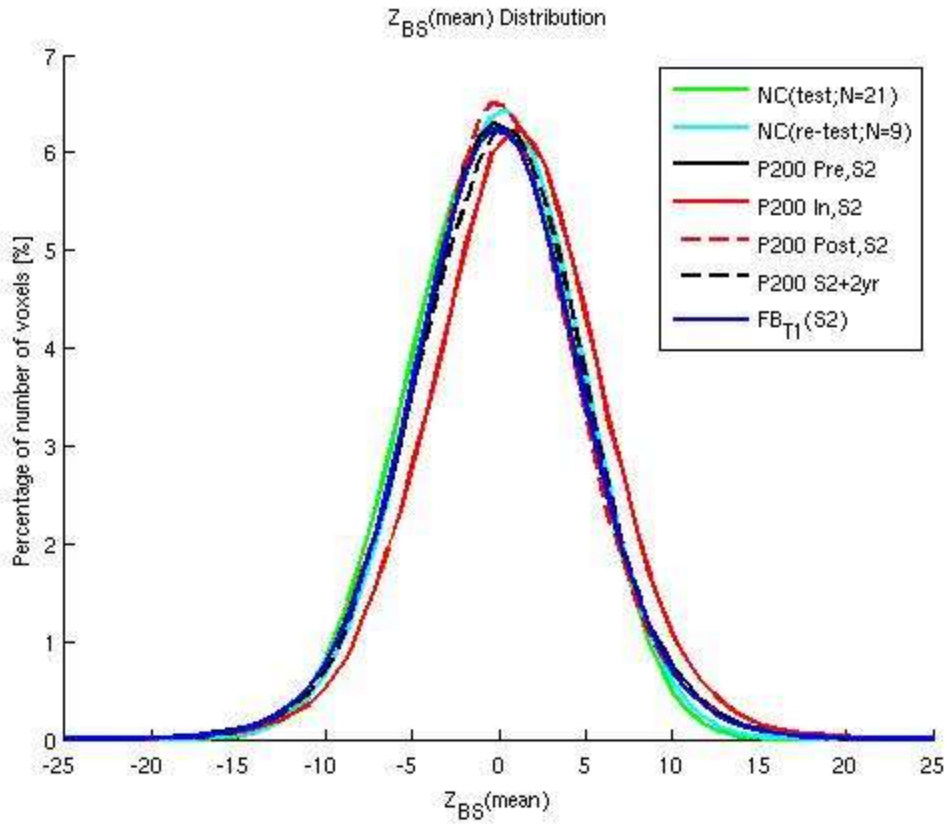


Figure 4.9 z_{BS} Distribution for the Progress of P200.It can be observed that there is a right shift for the In-Season. After two years of recovery, P200 did not apparently recovery back to the distribution of the controls, suggesting persistent changes in white matter health.

4.3 Outlier Plots

The outlier representation provides better insight to investigate individual datasets. The graphs present the percentage of voxels that are outside the 99.9% confidence interval for both the positive and negative sides (expected to be 0.05% for both directions). The players with index less than 1000 correspond to team 1. Players with index greater than 1000 belong to team 2.

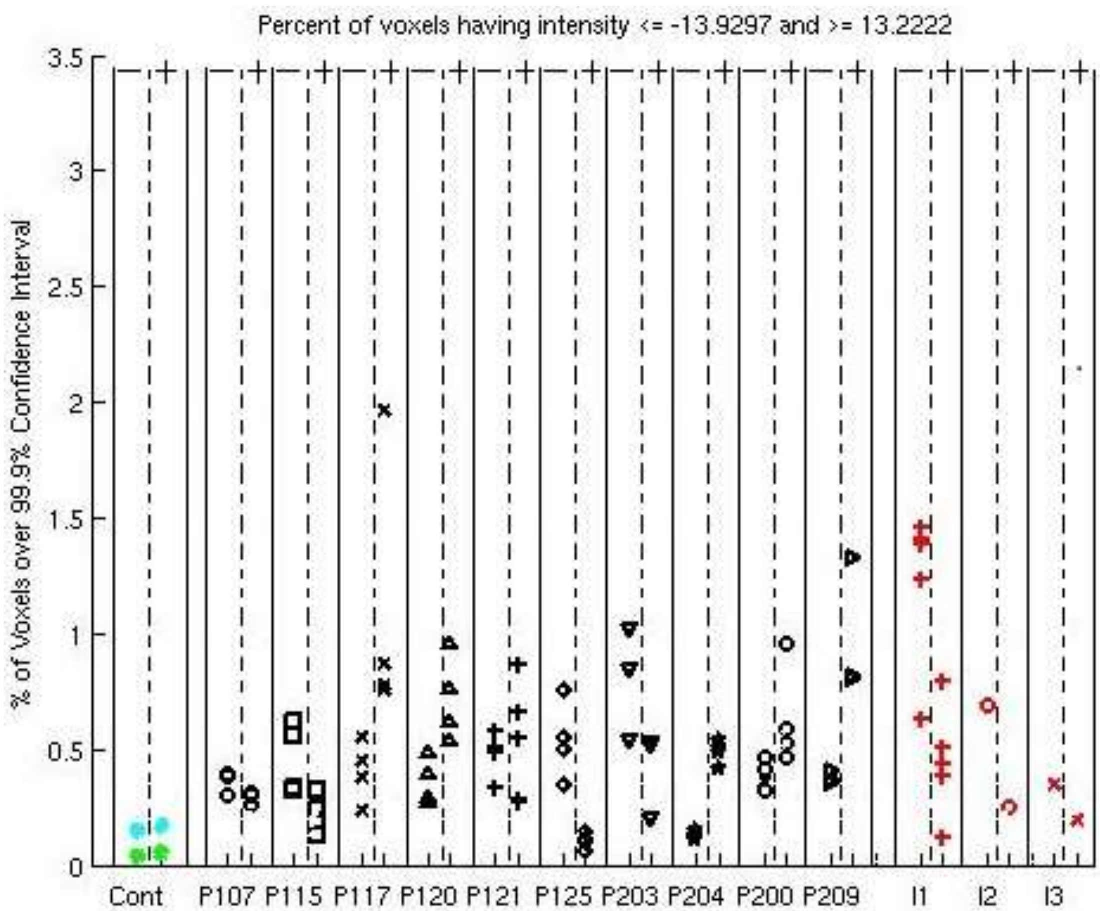


Figure 4.10 Outlier Plot for Symptomatic Patients (I1-I3) and Season 2 Players for Team 1. Symptomatic patients are left-shifted. 6 out of 10 players from season 2 show a right bias, while only three are left-biased.

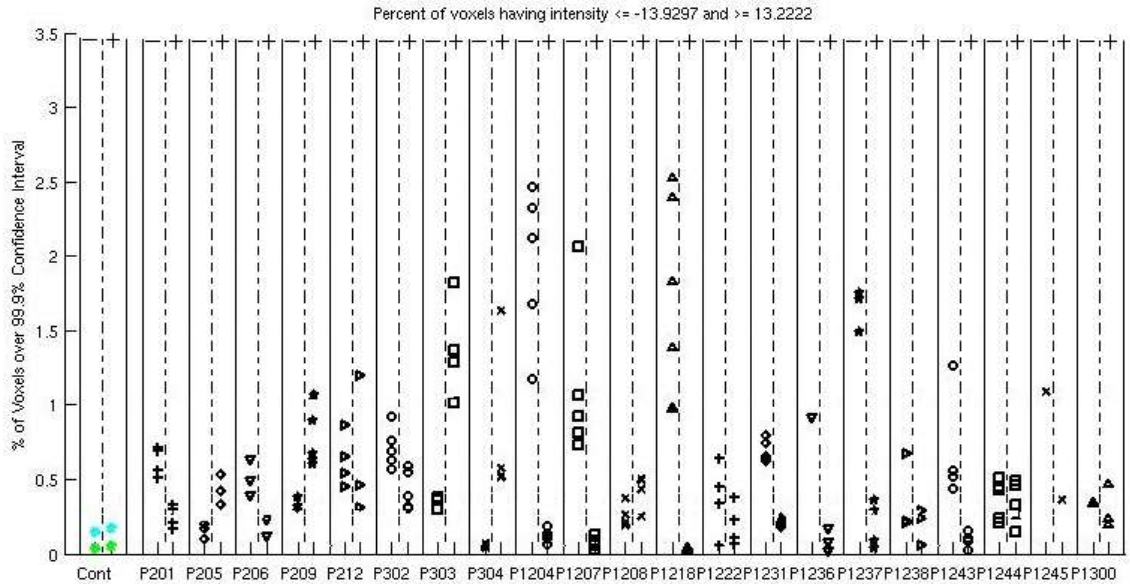


Figure 4.11 Outlier Plot for Season 3 Players from both Team 1 (Pxxx) and Team 2 (Pxxxx). The right bias can be observed in four players which all belong to Team 1. Only P1208 from Team 2 exhibited a slight right bias.

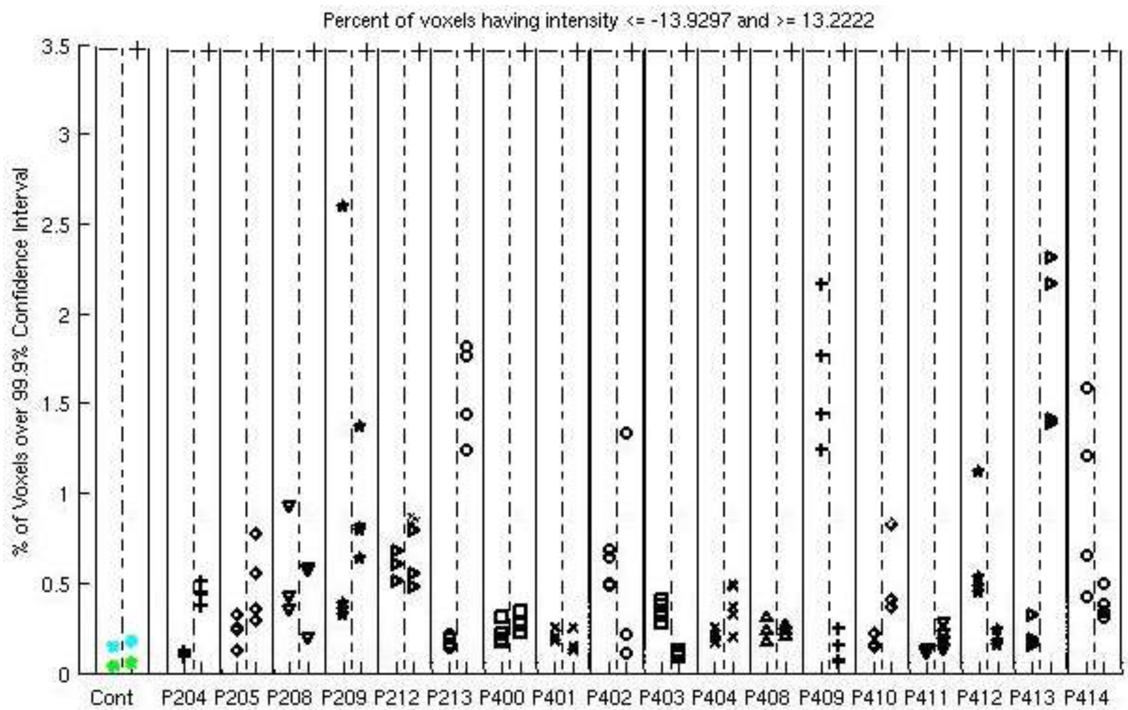


Figure 4.12 Outlier Plot for Season 4 Players from Team 1. For Season 4, the majority of the players from Team 1 continue to have a dominant right bias. Only 3 of 18 players (16.7%) show a left bias.

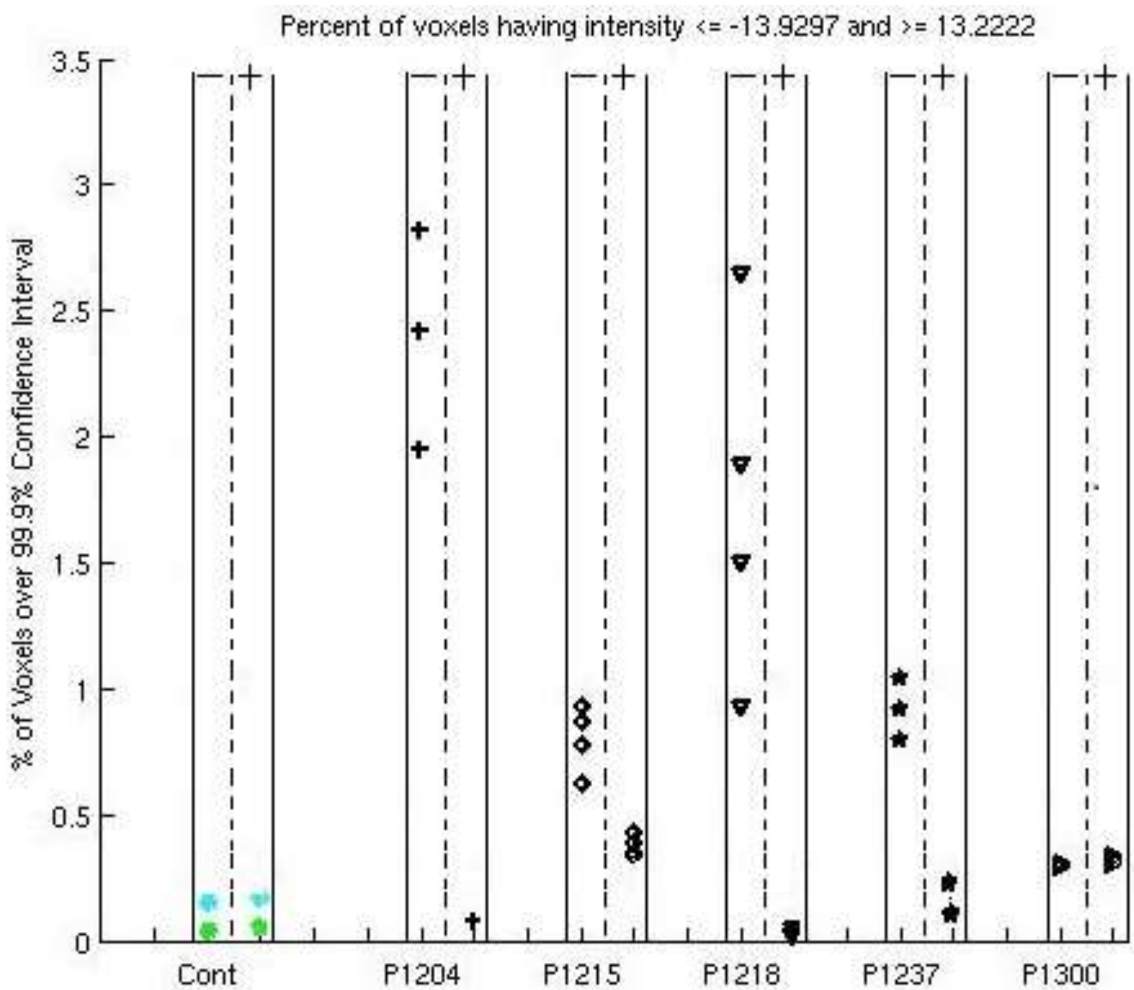


Figure 4.13 Outlier Plot for Season 4 Players from Team 2. Consistent with the observations from Season 3, the players exhibit a left bias.

5. DISCUSSION

5.1 Changes in the White Matter Integrity

Differences in z_{BS} distributions between the football players, controls and symptomatic injured patients can be observed from figure 4.3 and 4,4. The symptomatic injured players, I1, I2 and I3, are left shifted compared to the controls, which mean a decrease in fractional anisotropy, as expected from a concussed patient [16]. From figure 4.4, the football teams exhibit different changes compared to the controls. For both season 3 and 4, team 1 is left shifted similar to the symptomatic patients. On the other hand, team 2 have an increased right bias for all seasons. When pre-season, in-season and post-season was evaluated separately, the in-season z_{BS} distribution of season 3 for team 1 and season 4 for both teams showed a right shift compared to their pre-season and post-season. These findings suggest there is an increase of fractional anisotropy for the in-season. More importantly, even when changes are observed within pre-, in- and post-season, the changes at the pre- and post- sessions are noticeably when compared to the controls, indicating that their playing history and accumulated hits already had an influence in their white matter integrity.

There are studies showing that increased FA has been found in semi acute stage of mild TBI [17]. Hence, more FA is not necessarily always better. For a given voxel with multiple pathways, the FA will be low as water diffuses in multiple directions. If one of those pathways is broken, the water will diffuse in fewer directions which could ultimately elevate the FA for that voxel. It can be suggested that there might be secondary pathways damage, inducing the increased FA.

5.2 Importance of Coaching and Technique

From both the z_{BS} distributions and the outlier plots, each team shows different behavior. Team 2 exhibits the same leftward shift as the symptomatic injured patients I1, I2 and I3. However, players in team 2 did not reflect any symptoms from the neurocognitive testing. Also, team 1 is closer to the non-contact sport controls than Team2 but has increased right extrema. It was reported that Team1 has taken more hits to the top-front, side and back of the head than team 2 [5]. Also, significant variant in fMRI was present in team 1 [3].

The technique and coaching style influences the amount of hits and their location. The different behaviors suggest two possible types of damages to the brain. The damage related to team 1 could be to secondary pathways to the brain which might not get recovered, shown in figure 4.9. After two years of non-contact sports, P200 from team 1 did not go back to the controls but rather stayed at his pre-season stage. Therefore, increased FA might be considered more dangerous due to correlation with greater changes in fMRI and cognitive testing.

5.3 Are We Observing Short Term Recovery?

Team 2 exhibits an overall left shift compared to the controls as shown in figure 4.4. From results in figure 4.7 and 4.8, the in-season distribution shifted right while the post-season shifted left back, trying to reach their pre-season level. These findings suggest that there is a possible short term healing for such season. However, their pre-season and post-season levels are still left shifted from the controls, which suggest that they were already deviant.

6. CONCLUSION

The differences based by team together with the FA recovery from team 2 strongly suggest that coaching styles and the player's technique can ultimately effect differential changes in white matter integrity. Although a short term recovery was observed after the season exposure, all players appeared to exhibit significant changes, relative to controls, caused by the accumulated hits over previous years reflected by their pre- and post-season deviation. These results confirmed that the proposed z_{BS} distributional analysis effectively detects deviances in FA and the progress of subjects with a history of concussive and sub-concussive hits to the head.

Further studies regarding the meaning of the different shift behavior should be done in depth. Also, it would be beneficial to correlate the changes and progress of each individual with the location, magnitude and amount of hits received. Finally, it is crucial to investigate the location in the brain of the changes seen in our analysis.

LIST OF REFERENCES

LIST OF REFERENCES

[1] Hart, John et al., “Neuroimaging of Cognitive Dysfunction and Depression in Aging Retired National Football League Players”, *Journal of the American Medical Association Neurology*, 2013.

[2] M. Lipton, et al., “Robust detection of traumatic axonal injury in individual mild traumatic brain injury patients: intersubject variation, change over time and bidirectional changes in anisotropy”, *Brain Imaging & Behav.*, 6(2):329-42, 2012.

[3] Breedlove, Evan L. et al., "Biomechanical Correlates of Symptomatic and Asymptomatic Neurophysiological Impairment in High School Football", *Journal of Biomechanics*, 2012.

[4] Poole, Victoria N. et al., “Asymptomatic high school contact sport athletes exhibit metabolic changes that correlate with head collision history”, *Neuroscience*, 2012. . [5] Talavage, Thomas M. et al., "Functionally-Detected Cognitive Impairment in High School Football Players Without Clinically-Diagnosed Concussion", *Journal of Neurotrauma*, 2010.

[6] S.M. Smith, M. Jenkinson, M.W. Woolrich, C.F. Beckmann, T.E.J. Behrens, H. Johansen-Berg, P.R. Bannister, M. De Luca, I. Drobnjak, D.E. Flitney, R. Niazy, J. Saunders, J. Vickers, Y. Zhang, N. De Stefano, J.M. Brady, and P.M. Matthews. “Advances in functional and structural MR image analysis and implementation as FSL”. *NeuroImage*, 23(S1):208-219, 2004.

[7] M. Jenkinson, C.F. Beckmann, T.E. Behrens, M.W. Woolrich, S.M. Smith. “FSL”. *NeuroImage*, 62:782-90, 2012.

[8] M.W. Woolrich, S. Jbabdi, B. Patenaude, M. Chappell, S. Makni, T. Behrens, C. Beckmann, M. Jenkinson, S.M. Smith. “Bayesian analysis of neuroimaging data in FSL”. *NeuroImage*, 45:S173-86, 2009.

[9] S.M. Smith. “Fast robust automated brain extraction”. *Human Brain Mapping*, 17(3):143-155, 2002.

[10] J.L.R. Andersson, M. Jenkinson and S. Smith. Non-linear optimisation. FMRIB technical report TR07JA1 from www.fmrib.ox.ac.uk/analysis/techrep

[11] J.L.R. Andersson, M. Jenkinson and S. Smith. Non-linear registration, aka Spatial normalisation FMRIB technical report TR07JA2 from www.fmrib.ox.ac.uk/analysis/techrep

[12] D. Rueckert, L. I. Sonoda, C. Hayes, D. L. G. Hill, M. O. Leach, and D. J. Hawkes. "Non-rigid registration using free-form deformations: Application to breast MR images". *IEEE Transactions on Medical Imaging*, 18(8):712-721, 1999.

[13] Marco Giannelli.et al., "Dependence of brain DTI mas of fractional anisotropy and mean diffusivity on the number of diffusion weighting directions". *Journal of Applied Clinical Medical Physics, 2010.*

[14] ImPACT Test. ImPACT Applications, Inc., n.d. Web. September 2011. <http://impacttest.com/>.

[15] C. Rorden. DCM2NII. Chris Rorden's MRIcron, n.d. Web September 2011. <http://www.mccauslandcenter.sc.edu/mricro/mricron/dcm2nii.html>.

[16] Kraus, Marilyn F. et al., "White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study", *Brain*, 2007.

[17] Ling, Josef M. et al., "Biomarkers of increased diffusion anisotropy in semi-acute mild traumatic brain injury: a longitudinal perspective", *Brain*, 2012.