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"CNR comparison to identify the detectability rate and FA histogram analysis of FLAIR lesions in DTI metrics"

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Background and Motivation

- Neuroimaging methods are extensively used for:
  - Accurate diagnostic purposes of central nervous system disorders .
  - Determine pathophysiology of and injury severity after head trauma.
  - Better assessment and prognosis after injury.
  - Informing acute clinical management post injury and predictive of functional recovery at chronic stages.
- Computed Tomography (CT) and Conventional Magnetic Resonance Imaging (MRI) are proven to be clinically useful diagnostic tests.
- Unlike CT, MRI can produce different image contrasts by adjusting various variables.
- However, there is enough literature suggesting these techniques are insensitive for certain types of pathology and milder forms of head injury.

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Background and Motivation

- Standard MRI sequences include:
  - T1- weighted Imaging
    - Structural imaging to visualize atrophy.
  - T2- weighted Imaging
    - Hemorrhagic contusions and edema.
  - Fluid Attenuated Inversion Recovery (FLAIR) Imaging
    - White matter hyperintensities, cortical surface contusions and periventricular lesions.
  - $T2^{*}$- weighted Gradient Recalled Echo (GRE) Imaging and Susceptibly Weighted Imaging (SWI).
    - Traumatic microhemorrhages, blood break down products and hemosiderin.

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Background and Motivation

- Standard MRI sequences include:
  - Diffusion Weighted Imaging (DWI).
    - Measures water diffusion; detects ischemia from cytotoxic edema causing diffusion restriction.
      - Apparent Diffusion Coefficient (ADC) and Trace.
  - Diffusion Tensor Imaging (DTI).
    - Sensitive to microstructural white matter injury leading to Diffuse axonal Injury (DAI) in both acute and chronic injuries.
      - Fractional Anisotropy (FA), Axial Diffusivity (AD) and Radial Diffusivity (RD).
- Additional Sequences
  - Perfusion Weighted Imaging, Magnetic Resonance Spectroscopy (MRS), Functional Magnetic Resonance Imaging (FMRI) etc.

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Background and Motivation

- *Macroscopic level* abnormalities, localized brain changes in tissue composition and white matter shear injury are manifested as multifocal white matter hyperintensities (WMH's) on FLAIR.
- Unfortunately, it is insensitive, to adequately visualize the more widespread *microstructural component* of DAI.
- DTI is advanced neuroimaging technique that measures the white matter microstructural integrity noninvasively.
- Many labs report DTI sensitivity to DAI using FA as biomarker.
- Various factors like crossing fibers, partial voluming effects, susceptibility artifacts, nonlinear distortions, low signal to noise ratio (SNR) and low resolution causes substantial variability in FA image that hinders the lesion conspicuity.

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Objective

- Though both of them have the capability of detecting white matter injuries, FLAIR lesions are easily detectable whereas DTI lesions are not but requires additional processing to detect the injury.

- The relationship between FLAIR lesions and how well they can be seen corresponding areas on DTI indices like ADC, FA, AD and RD remains unclear.

- Does the size of the lesion help in being visualized on DTI indices remains questionable?

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Objective

- The detectability of lesions on FLAIR and DTI are evaluated based on calculating contrast to noise ratio (CNR) and utilizing Rose criterion (CNR>3-5).

- Further investigated the behavior of FLAIR lesions on DTI indices by performing histogram analysis and voxel based z-score analysis (VBA) to see if the information on FLAIR and DTI indices the same or complementary?

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Materials and Methods

- **Study design:**
  - CNR analysis of FLAIR lesions using Rose criterion.
  - FA histogram analysis of FLAIR lesions and compared against FA values of healthy controls in the same location.
  - Voxel based z-score analysis of FA images and compared against healthy controls FA images.

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Materials and Methods

- **Subjects:**
  - 27 Former National Football League (FNFL) players enrolled in IRB approved TBI study.
    - age range: 32-72
    - Mean age = 51.8 years, SD= 11 years.
    - A total of 92 white matter hyperintensity lesions were analyzed. Only those lesions that are clearly seen on T2 and as well as DTI-b_0 image.
  - 37 Healthy controls (HC).
    - age range: 19-57
    - Mean age = 29 years, SD= 10 years.

		FLAIR			DTI				
	n	TR	TE	Resolution	TR	TE	Resolution	Channel	Scanner
FNFL	92	6000	364	0.5X0.5X1.0	13300	124	1.3x1.3x2	32	Siemens Verio
HC	-	9000	78	1x1x4	13300	124	1.3x1.3x2	32	Siemens Verio

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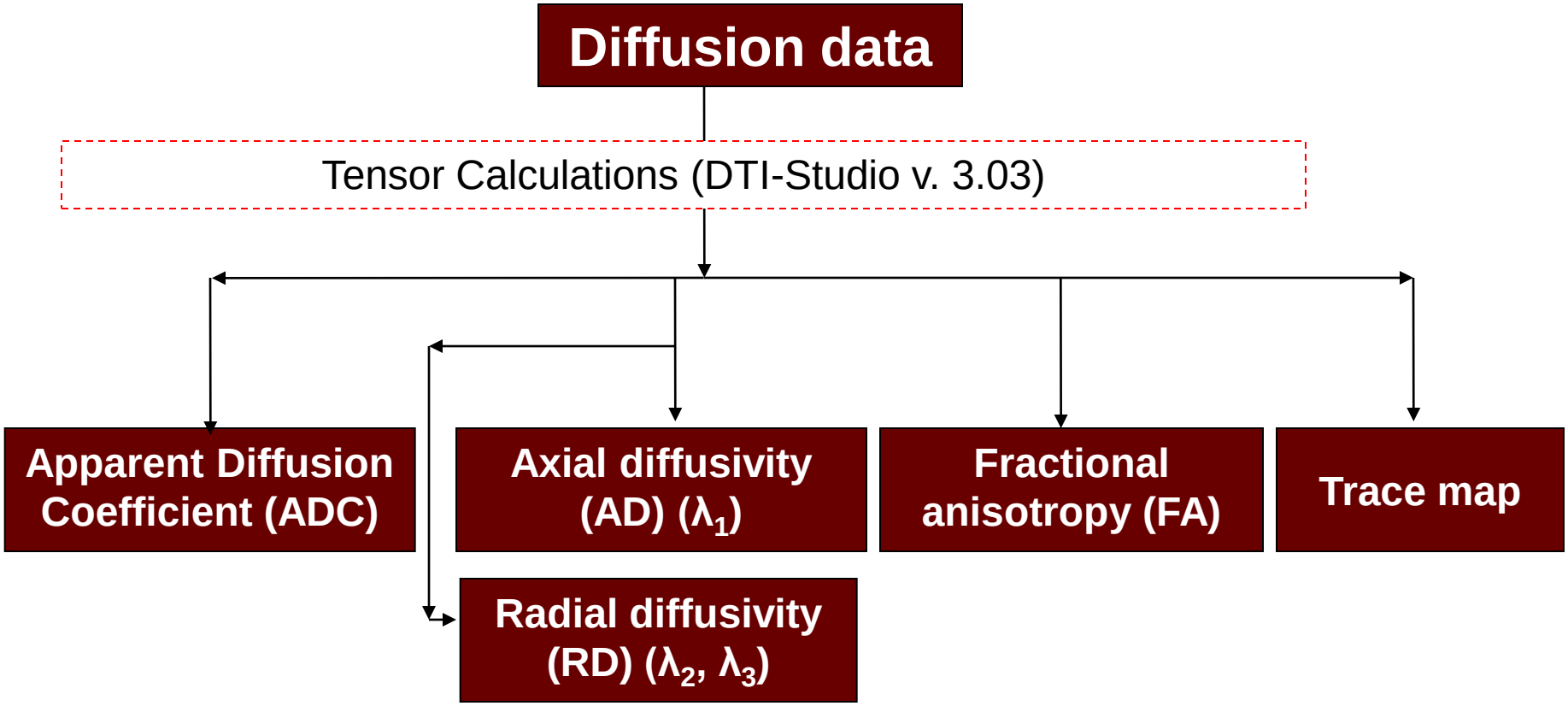
Processing Methods

Creating DTI Maps:



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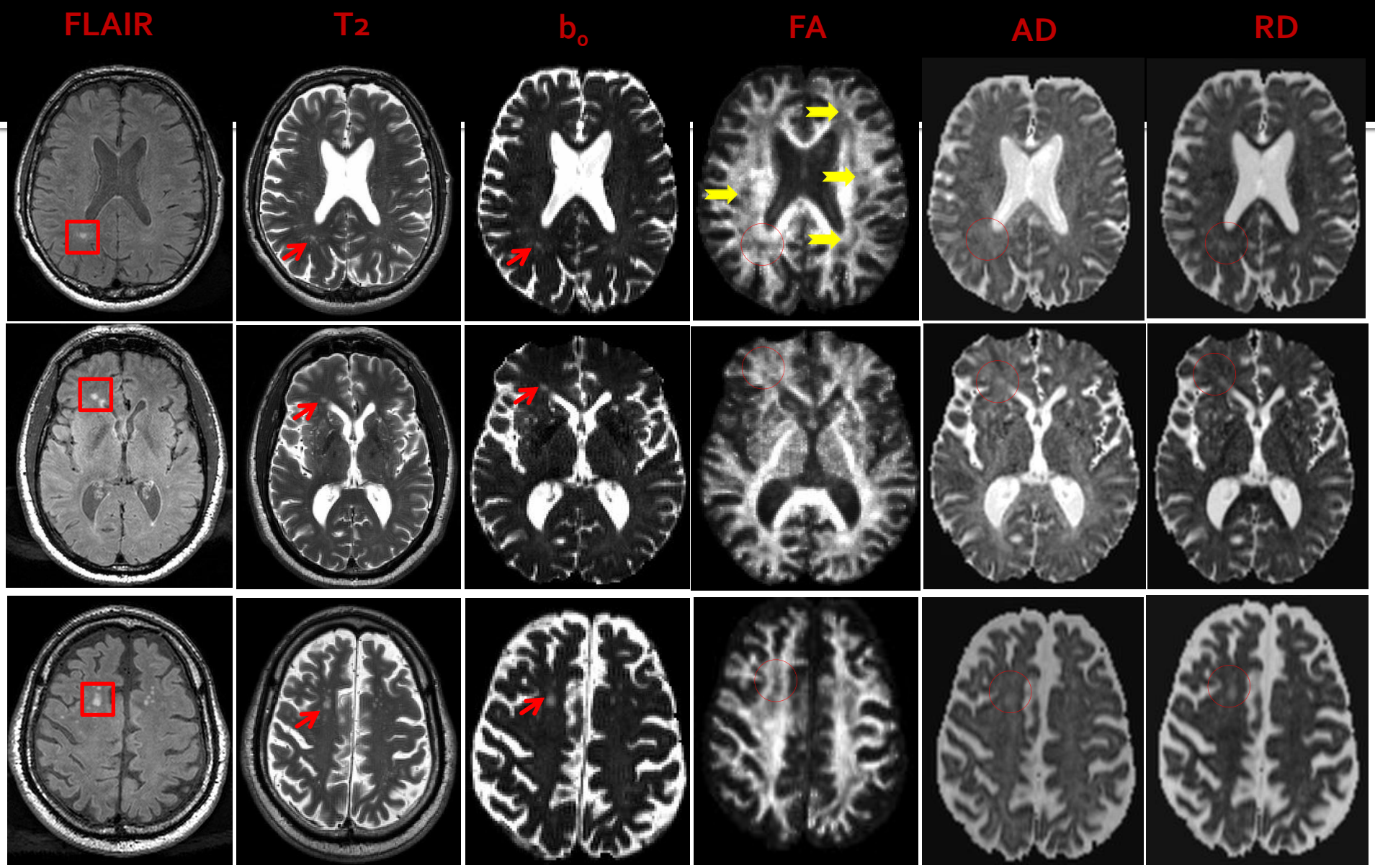
Lesion Detection :



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Region of interest (roi) CNR calculations and Rose Criterion:

- CNR calculations:
  - S_L - Signal from Lesion.
  - S_N - Signal from Normal appearing tissue.
  - σ_{BG} - Standard deviation from normal appearing tissue.
  - n – lesion size.

$$CNR_L = \left(\frac{S_L - S_N}{\sigma_{BG}}\right) \times \sqrt{n}$$

- Rose criterion:
  - the detectability of an object is possible when the CNR exceeds 3:1 to 5:1.
  - As these lesions cover multiple voxels, a factor of √n needs to be multiplied by the contrast to obtain an effective CNR as seen by the observer.

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Histogram Analysis:

- A manual FA histogram analysis was laboriously intensive hence employed a semi automated method.
- FA images of both groups were spatially normalized to a FA template in standard space.
- Lesions are drawn on b0 image in native space and then the lesions are transformed into standard space by using transformation matrix from the above step.
- Roi in standard space is later transformed onto all the control FA images.
- FA histograms were extracted on all 92 lesions and compared against 37 controls in the corresponding areas .

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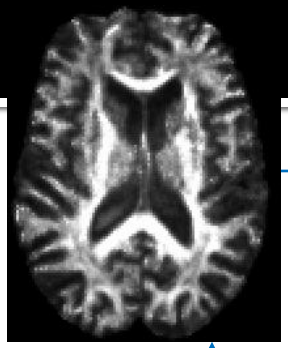
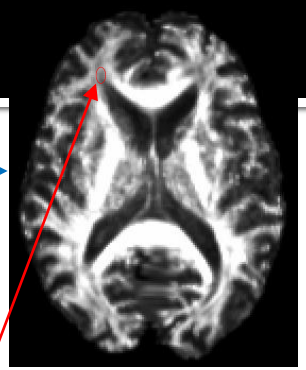
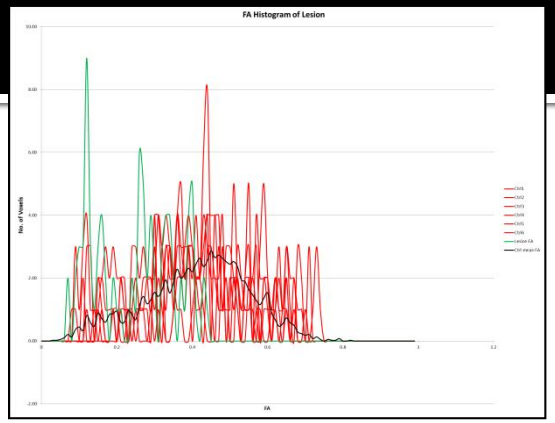
Histogram Analysis:

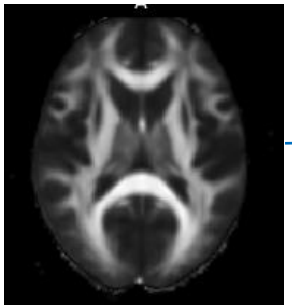
FNFL FA in native space

FNFL normalized FA

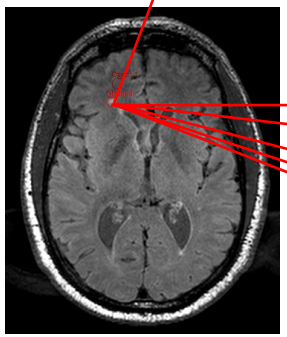




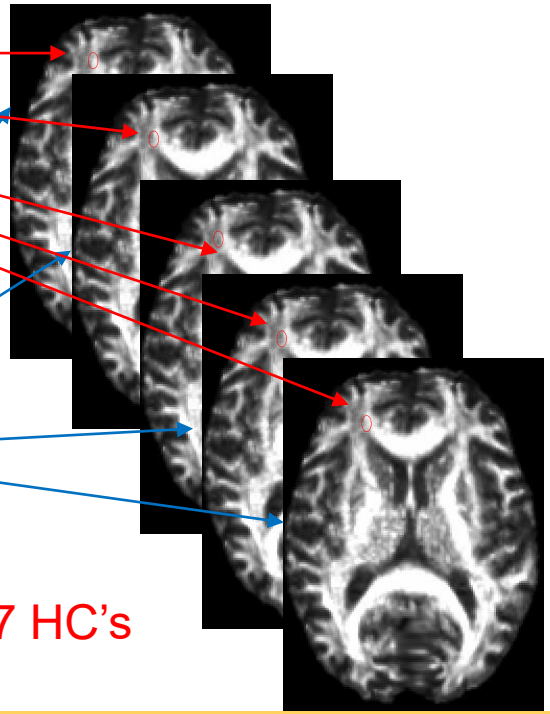




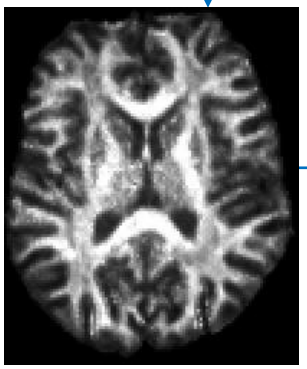
Spatial Normalization

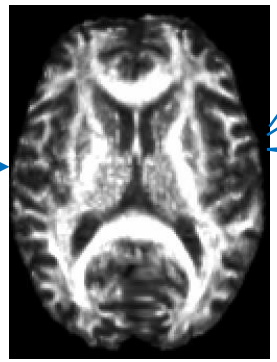


Lesion transformation onto controls



FMRIB58_FA template in Standard space





HC FA in native space

HC normalized FA

37 HC's

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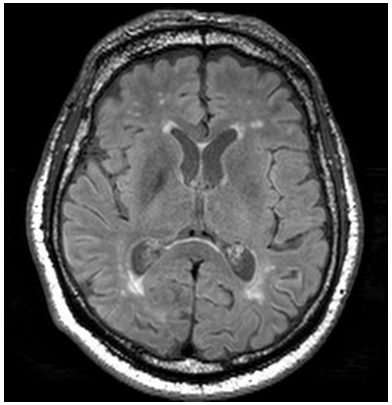
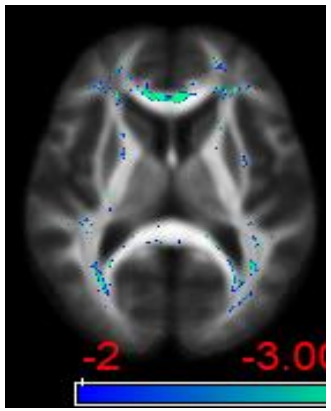
Voxel based Z-score analysis

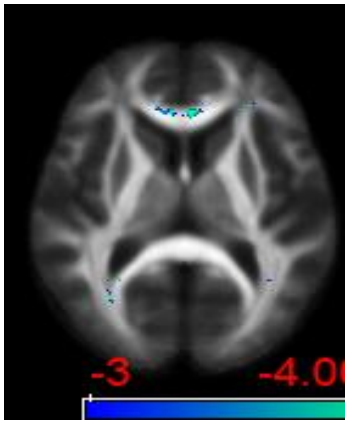
- Subjects FA map is spatially non linearly normalized in spm8.
- Z score map is created by taking the difference between the subjects FA and control groups mean FA (voxel by voxel) and dividing it over control groups Stdev map.
- Z score map is filtered by using a subjects segmented white matter mask .
- The filtered z-score map is transformed back into the native space by using a transformation matrix and is then overlaid back on to the native b_0 or FA map after setting at different thresholds (z=-2,z=-3 etc) (blue overlay) .



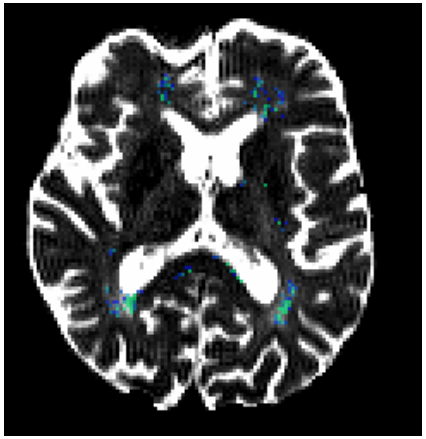
Subjects Flair with WMH's



Controls mean FA map with z-score overlay in standard space at z= -2

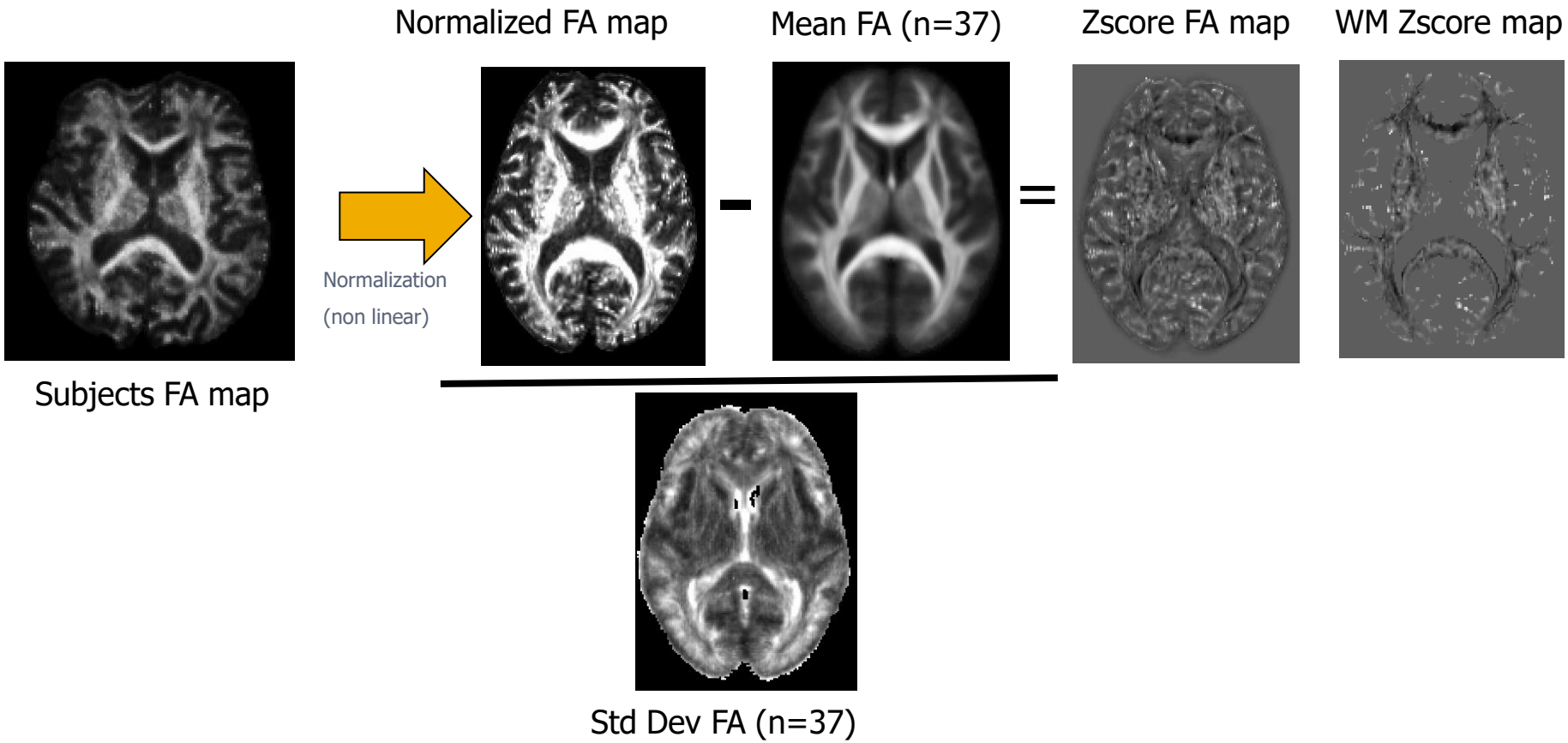


Controls mean FA map with z-score overlay in standard space at z= -3



Subjects $b_0$map with z-score overlay in native space at z= -2

Voxel based Z-score analysis: Flow chart



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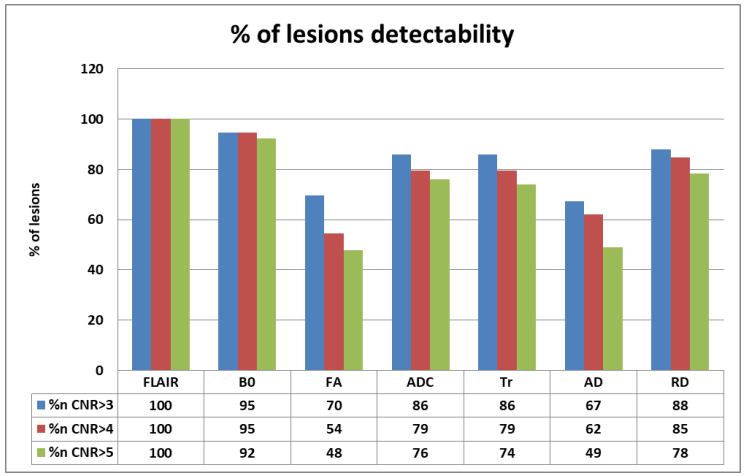
Results: CNR analysis

- Based on Rose criterion (CNR>5), the detectability rate of FLAIR lesions was higher in RD (78%), ADC (76%) and was lower in FA (48%) and AD (49%).
- The detectability rate of FLAIR lesions was strongly associated with lesion detection on b_0, ADC, AD and RD. The detectability of FLAIR lesions on FA was very weak.
- Lesion detection on b_0 showed stronger relationship with ADC, RD followed by AD.
- Lesion detection on RD showed stronger relationship with ADC and B0 followed by FA and was somewhat weak with AD.

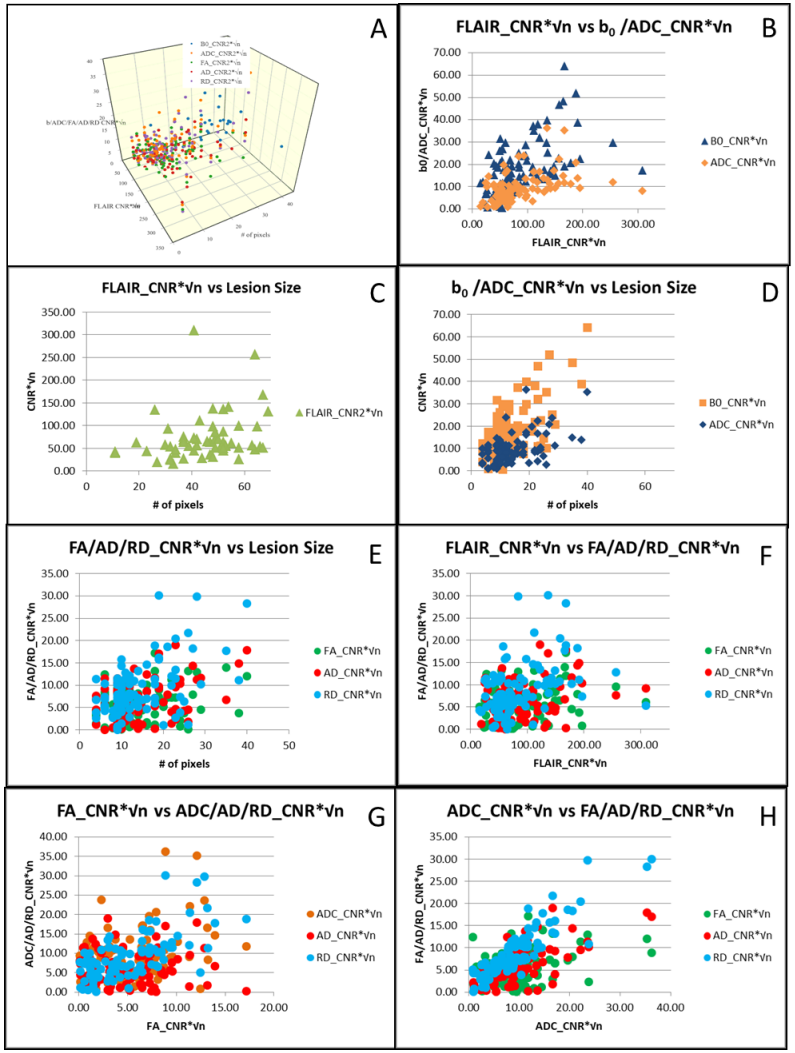


Plot showing the % of lesions detected using Rose criterion.

r-values	FLAIR	B0	FA	ADC	Trace	AD	RD
FLAIR	1						
B0	0.55	1					
FA	0.29	0.38	1				
ADC	0.43	0.72	0.38	1			
Trace	0.43	0.73	0.38	1.00	1		
AD	0.43	0.55	-0.11	0.70	0.70	1	
RD	0.39	0.68	0.66	0.89	0.89	0.47	1

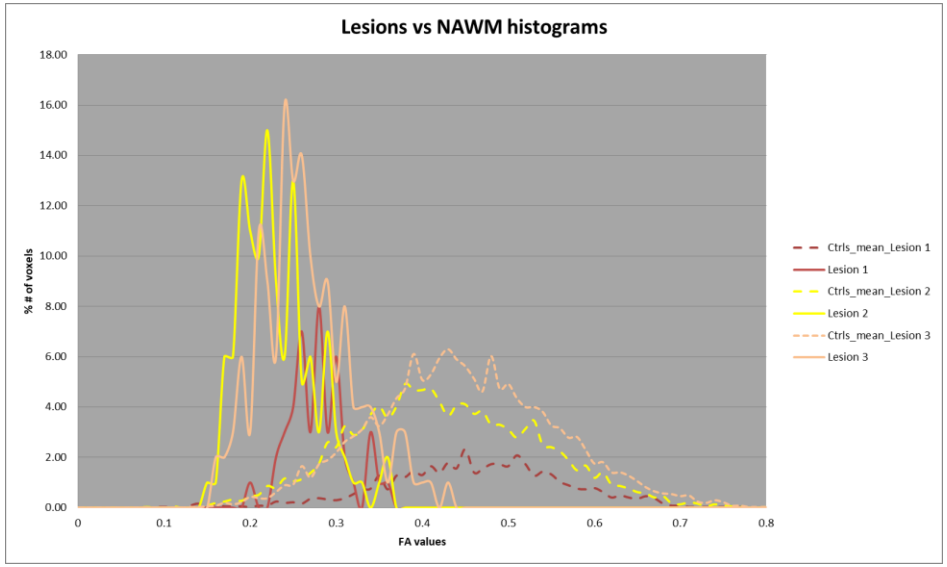
Table showing the association indicated by r-value between FLAIR CNR and DTI indices CNR

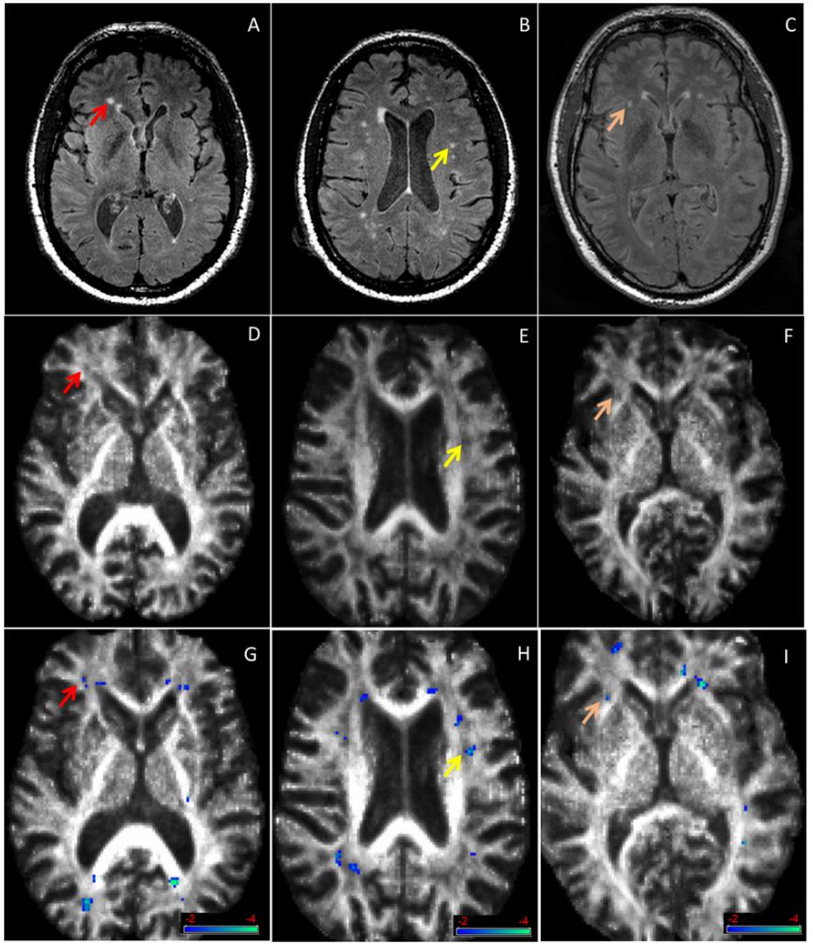
Results: CNR analysis (FLAIR CNR vs DTI CNR vs lesion size



- Plot B: b_0 CNR and ADC CNR are the only CNR's comparable to that of FLAIR. Where as the CNR's of FA, AD and RD are less than 35% of FLAIR CNR.
- The detectability rate of lesions on b_0 images tend to increase linearly as the FLAIR CNR increases. Where as the detectability rate of lesions on ADC tend to level off after a certain value (FLAIR CNR ~50.0).
- Plot C: There is no linear relationship between lesion size and the detectability of lesions on FLAIR.
- Plot D: But the detectability rate of lesions on b_0 and ADC tend to show linear relationship with the lesion size.
- Plot E: The detectability rate of lesions on FA, AD and RD is non linear irrespective of the lesion size.
- Plot F: The detectability rate of FLAIR lesions on FA/AD and RD is nonlinear. But the scattered spread might suggest different lesions might be providing different information about the severity of the injury.
- Plot G: There is no relationship observed between FA lesions CNR and AD CNR but there seems to be a strong association between FA CNR and ADC as well as RD CNR. There is enough literature suggest lower FA driven by higher RD. This association should be taken into account and RD evaluation should be considered during lesion analysis.
- Plot H: ADC CNR tend to show a very strong association with b_0, RD followed by AD and FA CNR.

Results: Histogram analysis





- Lesion FA histograms are having narrow peaks and skewed to the left (solid curves) indicating very low FA suggesting DAI.
- FA histograms in the same corresponding location on control group have higher FA values and widely spread indicating variance (dashed curves).

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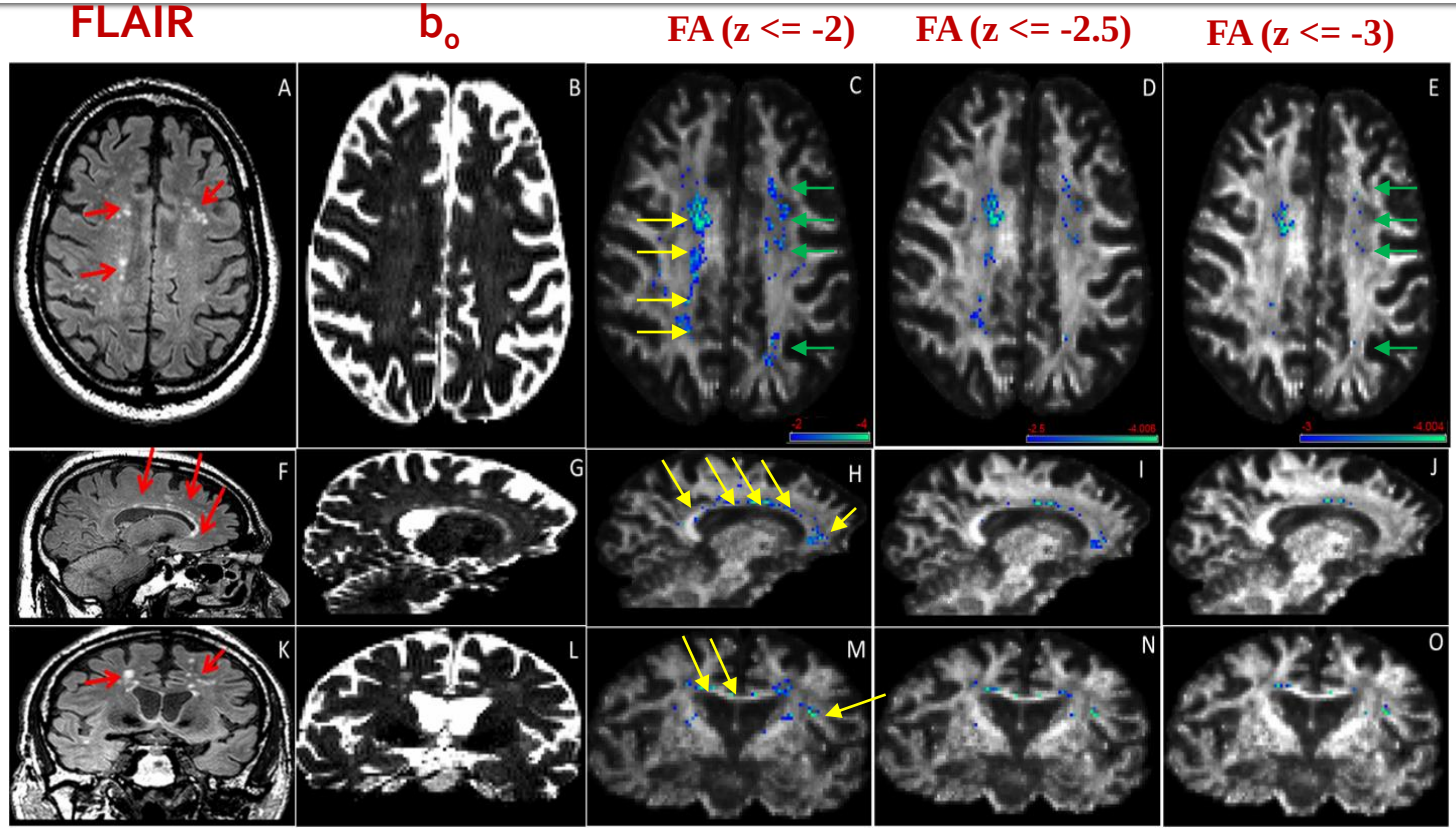
Results: Voxel based analysis



- Voxel based z-score analysis reveal wide spread extent of DAI beyond the lesion location at lower thresholds (yellow arrows) but its absence (green arrows) at higher thresholds might suggest difference in their severity or totally different pathology .

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Discussion :

- Rose criterion makes a connection between the CNR value of a lesion and the probability of observing the lesion.
- Smaller lesions are harder to see with DTI because the SNR is lower and the resolution is not as good as that in FLAIR. Increasing the resolution in DTI would further lower the SNR and would take too long to acquire the data.
- Currently, there are very few papers discussing the relationship between FLAIR lesions and studying DTI abnormalities that are commonly expressed as lower FA in WM.

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Discussion :

- First, DTI measures different physiologic parameter based on diffusion of water molecules rather than change in total tissue water.
- Although DTI does not appear to have the sensitivity of FLAIR, it does show dark regions in the same location where there are major FLAIR lesions and, generally, it doesn't show noticeable darker areas where there are no FLAIR lesions.
- Our study indicates that ADC, AD and RD also tend to detect these FLAIR lesions and by combining the association between these two modalities might provide better insight in determining the severity of underlying pathology or injury in these lesion sites.

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Discussion :

- The limitations of our study are only the lesions detectable on T2 and b_0 were analyzed. Histogram analysis and VBA was not performed on other DTI indices except FA.
- Results from our analysis and qualitative visualization of different diffusion metric images suggest that these lesion sites are suppressed by the bright signal coming from the CSF.
- The possibility of using CSF suppression in DTI will certainly enhance the detectability of lesions and might provide information about the pathology and microstructural damage that extend beyond the lesion sites.

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Conclusions:

- Our CNR calculations have shown that WMHs on FLAIR images have better sensitivity than the DTI metrics.
- The detectability of lesions in the FLAIR image seems to have a stronger association with detectability of the same lesions in the b_o, ADC and RD images than any other DTI metrics.
- Larger lesions are picked up with FA as they have a higher CNR. Despite DTI being less sensitive than FLAIR, the lesions appear to be detectable in the b_o (95%) , ADC (86%) and RD maps (88%).

Conclusions:

- Diagnosis of DAI is very difficult in chronic stage patients with moderate and severe TBI. DTI has an advantage of showing regions with lower FA using histogram analysis and advanced techniques like VBA or tract based spatial statistics (TBSS).
- Our study suggests that the detectability of lesions without any additional techniques can be best visualized using the b_0 , ADC or RD images.
- Employing further additional VBA, fiber tracking or CSF suppression techniques to better visualize these FLAIR lesions in DTI indices might provide better insight about the extent of injury diffused beyond these lesion sites.

Summary:

- In summary, based on our CNR analysis, only bo, ADC and RD measures can compare to the sensitivity of FLAIR.
- Although FLAIR finds more small lesions, once a lesion is found, whether with FLAIR or DTI, the full use of all DTI measures can still be taken advantage better understand the etiology of TBI lesions.
- Our analysis of visibility of FLAIR lesions on RD maps and their high correlations with ADC suggest there is high importance of looking at these maps while assessing white matter injury in TBI or in any other neurological disorders

Future Directions

- Longitudinal study of the same lesions to investigate if there is gradual increase or decrease in the severity of the injury.
- Combine FLAIR with various DTI indices for multivariable MR method to further improve injury description.
- To perform tractography with these lesion sites as the seed points and investigate if there is any altered disruptions in the white matter connectivity across different regions in the brain.

Thank You