SAMPLE REPORT

THE CONCUSSION GROUP

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Results of Quantitative Volumetric and Diffusion Tensor Imaging Analyses

Client Name:	[redacted]
Date of Birth:	[redacted]
Gender:	**Male**
Date of Data Collection:	**09/25/2020**
Date of Report:	**10/05/2020**

Background

The patient is a 41 year old male who self-reports that he was in an industrial accident 6 months prior to this test. He states that he has developed worsening headaches, fatigue, memory difficulties and personality changes. He indicates that he “does not feel right.” His doctor wanted him to have this test.

Technical Details

Magnetic resonance imaging was performed on 09/25/2020 at the MRI facility. Data were collected on an MRI machine using multiple imaging protocols including a 3D thin-slice T1-weighted sequence and a Diffusion Tensor Imaging (DTI) sequence with 30+ directions.

Images from the T1-weighted acquisition were used for quantitative volumetric analyses. The *Quantify Volumetric* process uses a standardized, objective, and automated SPM12-based processing pipeline to calculate regional brain volumes from 107 brain areas pre-selected from TDBrodmann and AAL Atlases. These volumetric measures were scaled by total brain volume to correct for brain size. As part of the *Quantify Volumetric* quality-assurance process, a senior neuroscientist evaluated the T1 data with respect to template alignment, motion, and artifacts that might substantially compromise the validity of results. The T1 data for the client were determined to be of acceptable quality for volumetric analyses.

Data from the Diffusion Tensor Imaging sequence were used for quantitative evaluation of white matter integrity, with regional average Fractional Anisotropy (FA) as the core metric. The *Quantify DTI* process uses a standardized, objective, and automated FSL-based processing pipeline to calculate FA values from 48 fiber tract regions pre-selected from the Johns Hopkins University white matter atlas. This pipeline includes automated motion and Eddy current corrections. As part of the *Quantify DTI* quality-assurance process, a senior neuroscientist evaluated the DTI data with respect to template alignment, motion, and other artifacts that might substantially compromise the validity of results. The DTI data for the client were determined to be of acceptable quality for analyses of FA values.

The volumetric and FA metrics for the client were statistically evaluated with respect to average volumetric and FA metrics derived from all gender and age-range (+/- 10 years) matched control subjects within a large database of >1000 neuro-typical subjects that is maintained by the MINDSET Integrated in Albuquerque, New Mexico. For this statistical evaluation, a total of 106 matched MINDSET control datasets were identified for volumetric evaluation, with 104 datasets identified for FA evaluation. Each MINDSET database control subject was without any reported history of (1) traumatic brain injury, (2) neurological or psychiatric disease or injury, (3) substance use disorder, or (4) learning or developmental disability.

The MINDSET control data has been collected on an MRI system that belongs to the MIND Research Network (MRN) in Albuquerque. MRN and the MRI faciality data acquisition parameters were identical. To account for any systematic differences between the scanners employed, several procedures were implemented. First, data acquisition parameters for the client were set to be comparable to those used in the collection of the MINDSET control datasets. Second, the data analysis procedures used to assess the data from the client were the same as those used in generation of the MINDSET control database. Third, prior to statistical analyses, data metrics for the client were scaled using brain-region specific, across-site matching factors derived from a traveling human phantom previously evaluated on both the MINDSET and MRI facility scanners. This scaling procedure provides for harmonization of datasets across the two scanners and allows the client's DI data to be validly evaluated with respect to the MINDSET normative database.

See the document Appendix-I-MR-2020 for additional information of basic neuroscience and methodological details.

Volumetric Findings

As shown in Figure 1, volumetric analyses conducted individually on 107 brain regions showed 13 of the 107 evaluated regions to have an atypical volume ($p<0.05$; 3 low; 10 high). Figure 2 provides demonstrative information on the spatial location of each evaluated brain region that showed an atypical volume on isolated individual testing.

Given the number of multiple regional brain volume comparisons (N=107), there is the possibility that even a subject without any history of neurological/psychiatric disease or injury may show a few brain regions with 'false positive' identification as statistically abnormal. To address this issue of false positives during multiple comparisons, a Benjamini-Hochberg correction was applied with a False Discovery Rate of 25%.

Following statistical correction for multiple comparisons, 6 of the brain regions with an atypical volume on isolated individual evaluation was still found to be abnormal from a statistical perspective (2 low; 4 high).

DTI Findings

As shown in Figure 3, DTI analyses conducted individually on 48 fiber tract regions showed 10 of the 48 evaluated tract regions to have an atypical FA value ($p<0.05$; 0 low; 10 high). Figure 4 provides demonstrative information on each of the evaluated fiber tract regions with an atypical FA value on isolated individual testing.

Given the number of multiple fiber tract FA comparisons (N=48), there is the possibility that even a subject without any history of neurological/psychiatric disease or injury may show a few fiber tract

regions with 'false positive' identification as statistically abnormal. To address this issue of false positives during multiple comparisons, a Benjamini-Hochberg correction was applied with a False Discovery Rate of 25%.

Following statistical correction for multiple comparisons, all 10 of the fiber tract regions with an atypical FA value on isolated individual evaluation was still found to be abnormal from a statistical perspective (0 low; 10 high).

Summary

The volumetric data for Mr. [redacted] were abnormal from a statistical perspective, with 6 brain regions (2 low and 4 high) showing deviant volumes on both isolated individual testing and after correction for multiple comparisons.

Low volumes may reflect perturbation of early developmental processes, malnutrition, toxic stress, toxic exposures, or more commonly neurological-psychiatric disease and/or brain injury. High volumes may reflect a perturbation of early developmental processes; baseline skill enhancement; or injury/disease related edema, astrogliosis, chronic inflammation, or reactive compensatory mechanisms triggered by damage to other brain regions.

The DTI data for Mr. [redacted] were abnormal from a statistical perspective, with 10 fiber tract regions (0 low and 10 high) showing deviant FA values on both isolated individual testing and after correction for multiple comparisons.

Possible causes for high FA include a developmental failure of axonal pruning, disease/injury related intracellular cytogenic edema, compaction of neurofilament, neuro-inflammation with microglial activation, astrogliosis, loss of crossing fibers, and/or compensatory mechanisms.

In summary, both the volumetric and DTI data for Mr. [redacted] were objectively abnormal from a statistical perspective.

(Ω μA N τ i fγ)

Quantify analyses provide an objective assessment of the structural integrity of the brain. They may reveal neurobiological insults that can be caused by head trauma, toxic exposures, or other conditions. However, quantitative volumetric and DTI analyses in isolation do not identify specific causes of brain compromise as multiple conditions can give rise to volumetric and FA abnormalities. The results should be interpreted by qualified experts with an understanding of the volumetric, DTI, and statistical methods used and knowledge of the foundational research and peer-reviewed literature linking imaging findings to neurobiological factors.

Determination of the most likely etiology of volumetric and DTI findings requires a comprehensive assessment of an individual's history and current status and use of the scientific method for differential evaluation of possible contributions from premorbid and co-morbid factors. Such a process is needed to elucidate the relationships between specific past events and present imaging findings and neurobiological status.

To request a free 15-minute consultation phone call to go over present results, please email info@quantifymri.com. Include your name and contact information and available dates and times for a call within the next week. You will then receive additional information on scheduling the call.

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THE CONCUSSION GROUP
in collaboration with MINDSET

PATIENT

Patient: [redacted]
Date of Birth: [redacted]
Gender: Male
Date of Data Collection: 09/25/2020
Date of Report: 10/05/2020

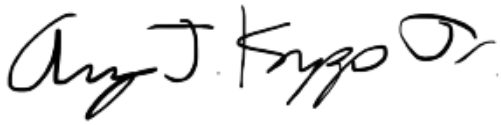
Review and Comment:

I have supervised the DTI DiCOM data acquisition process performed onsite at Doctors Imaging and reviewed the Mindset Volumetric/DTI analysis; and confirm that the MRI protocols as well as the applied analytic tools were methodically utilized as designed. I accept the final DTI and Volumetric Z-Scores as statistically appropriate.

Edward L. Soll. M.D.
Radiologist and Medical Director
Certified American Board of Radiology, 1973
The Concussion Group

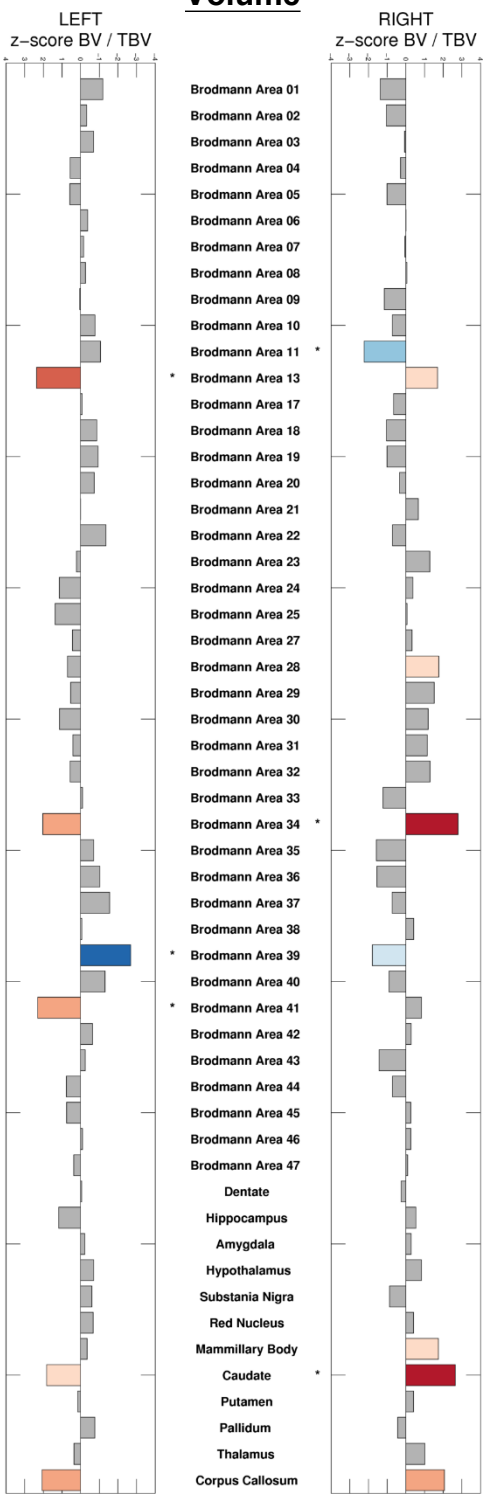
Review and Comment:

I have reviewed the Mindset Volumetric/DTI analysis and accept the final DTI and Volumetric Z-Scores as statistically appropriate.



Avery Knapp. M.D.
Radiologist
Certified American Board of Radiology, 2008
The Concussion Group

Figure 1: Mr. [redacted] Z-scores for Regional Brain Volume Scaled by Total Brain Volume



The corpus callosum is a midline structure.
Identical values are indicated in left and right columns.

Region-of-interest volumetric analyses

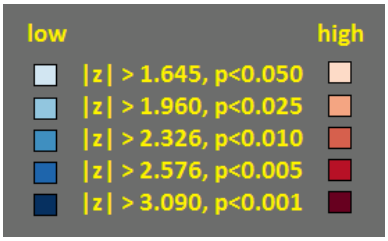
Data are shown as Z-score deviates based on comparison of client data with average data from a gender and age-range (+/- 10 years) matched group of **106** neuro-typical subjects.

At the level of individual isolated analyses

Gray bars show regions with volumes within normal limits.

Red bars show regions with atypically high volume (p<0.05).

Blue bars show regions with atypically low volumes (p<0.05).



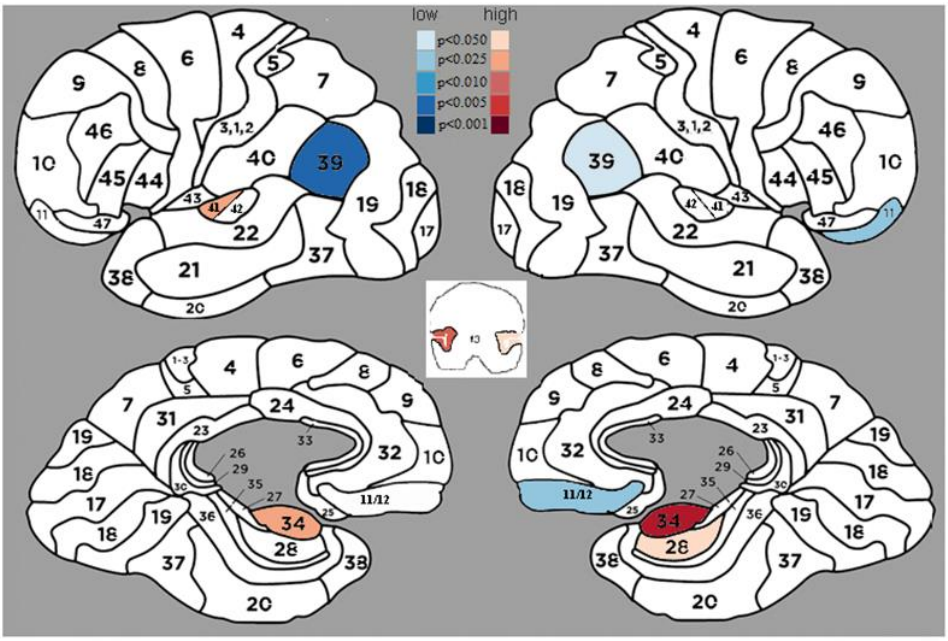
For Mr. [redacted], isolated evaluation of individual brain regions revealed 13 of 107 brain regions to show atypical volumes: (p<0.05; 3 low; 10 high).

However, only those observations marked with an * survive additional correction for multiple comparisons (FDR=0.25). After correction for multiple comparisons, 6 of the brain regions with an abnormal volume on individual testing were still considered to be abnormal from a statistical perspective: (2 low, 4 high).

Overall, 6 of the 107 evaluated brain regions showed statistically abnormal volumes (2 low; 4 high) on both isolated individual testing (p<0.05) and following correction for multiple comparisons (FDR=0.25).

Figure 2: Mr. [redacted]
Shaded Brain Regions Show Atypical Volumes on Isolated Individual Testing

Following correction for multiple comparisons, **6** of the brain regions with atypical volumes on isolated individual evaluation were still considered to be abnormal from a statistical perspective.



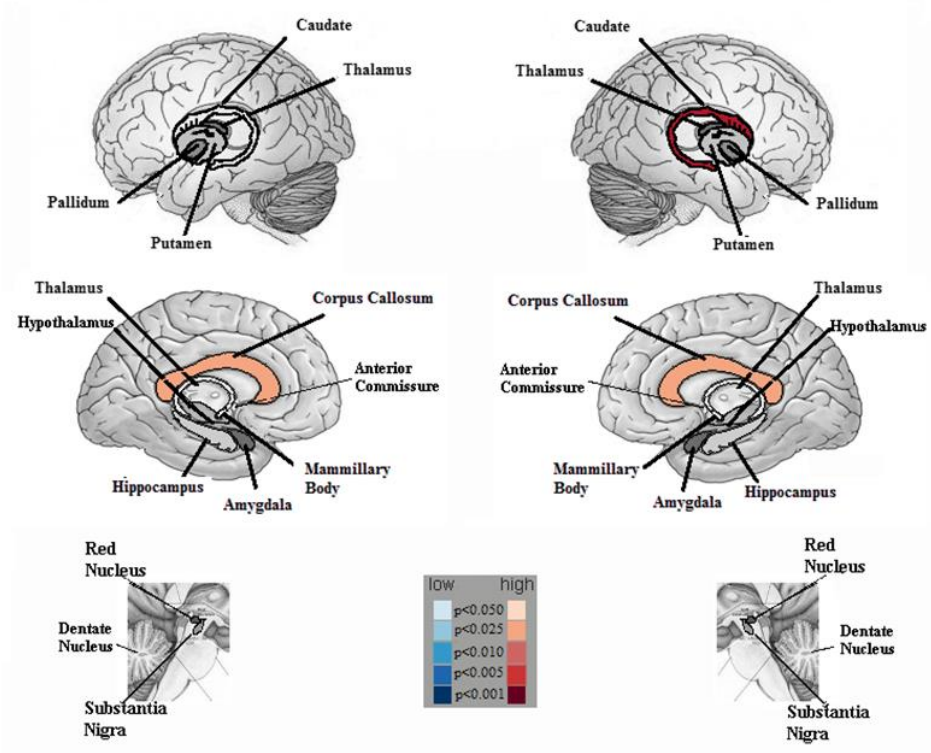


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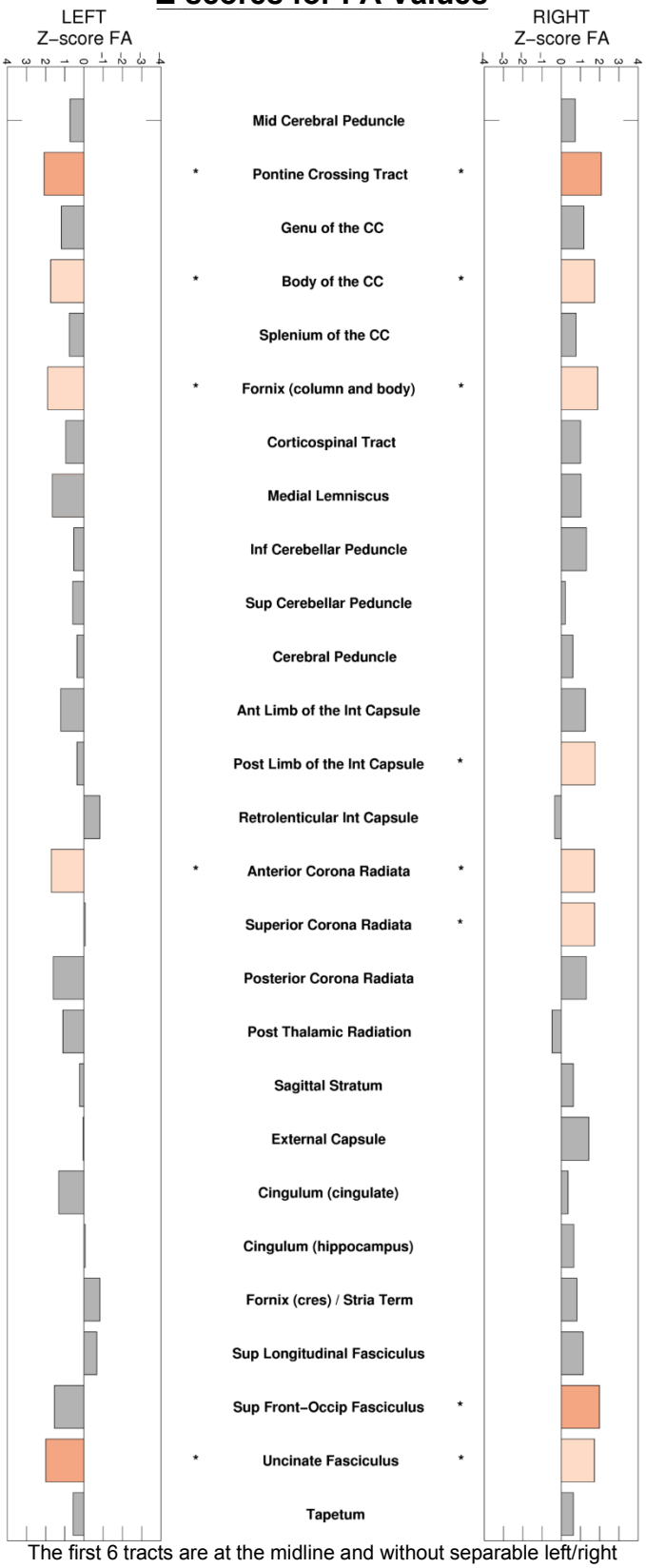
Figure 3: Mr. [redacted]
Z-scores for FA Values



The first 6 tracts are at the midline and without separable left/right components. Identical values are plotted in left and right columns.

FA Values for Fiber Tract Regions

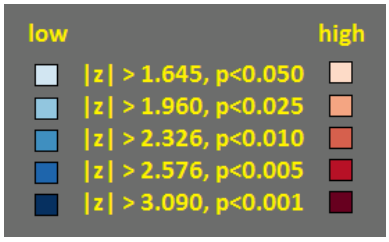
Data are shown as Z-score deviates based on comparison of client data with average data from a gender and age-range (+/- 10 years) matched group of **104** neuro-typical subjects.

At the level of individual isolated analyses

Gray bars show tracts where FA values are within normal limits.

Red bars show tracts with atypically high FA values (p<0.05).

Blue bars show tracts with atypically low FA values (p<0.05).

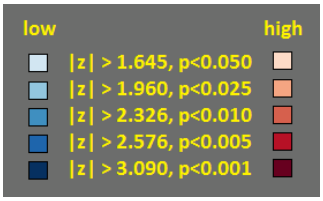


For Mr. [redacted], isolated evaluation of individual fiber tracts revealed 10 of 48 regions to show atypical FA values: (p<0.05; 0 low; 10 high).

However, only those observations marked with an * survive additional correction for multiple comparisons (FDR=0.25). After correction for multiple comparisons all 10 of the fiber tract regions with abnormal FA values on individual testing were still considered to be abnormal from a statistical perspective: (0 low, 10 high).

Overall, 10 of the 48 evaluated fiber tract regions showed statistically abnormal FA values (0 low; 10 high) on both isolated individual testing (p<0.05) and following correction for multiple comparisons (FDR=0.25).

Figure 4: Mr. [redacted]
Shaded Tracts Show Atypical FA Values on Individual Isolated Testing (p<0.05).



Middle Cerebellar Peduncle	Pontine Crossing Tract *	Genu of the Corpus Callosum	Body of the Corpus Callosum *	Splenium of the Corpus Callosum	Fornix *	R Corticospinal Tract	L Corticospinal Tract
R Medial Lemniscus	L Medial Lemniscus	R Inferior Cerebellar Peduncle	L Inferior Cerebellar Peduncle	R Superior Cerebellar Peduncle	L Superior Cerebellar Peduncle	R Cerebral Peduncle	L Cerebral Peduncle
R Anterior Limb of the Internal Capsule	L Anterior Limb of the Internal Capsule	R Posterior Limb of the Internal Capsule *	L Posterior Limb of the Internal Capsule	R Retrolenticular part of the Intern Capsule	L Retrolenticular part of the Intern Capsule	R Anterior Corona Radiata *	L Anterior Corona Radiata *
R Superior Corona Radiata *	L Superior Corona Radiata	R Posterior Corona Radiata	L Posterior Corona Radiata	R Posterior Thalamic Radiation	L Posterior Thalamic Radiation	R Sagittal Stratum	L Sagittal Stratum
R External Capsule	L External Capsule	R Cingulum (cingulate gyrus)	L Cingulum (cingulate gyrus)	R Cingulum (hippocampus)	L Cingulum (hippocampus)	R Fornix (cres) and Stria Terminalis	L Fornix (cres) and Stria Terminalis
R Superior Longitudinal Fasciculus	L Superior Longitudinal Fasciculus	R Superior Frontal-Occipital Fasciculus *	L Superior Frontal-Occipital Fasciculus	R Uncinate Fasciculus *	L Uncinate Fasciculus *	R Tapetum	L Tapetum

Table 1: Mr. [redacted]
Regions-of-Interest with Abnormal Volumes on Individual Evaluation

Area		General Location	Supported Functions
Brodmann 1,2,3 combined	L/R	Primary somatosensory cortex	Tactile sensation
Brodmann 4	L/R	Primary motor cortex	Motor control
Brodmann 5	L/R	Somatosensory association cortex	Tactile object recognition
Brodmann 6	L/R	Premotor and Supplementary motor cortex	Control of proximal and trunk muscles; Motor sequencing
Brodmann 7	L/R	Somatosensory association cortex	Visuo-spatial processing; Praxic abilities
Brodmann 8	L/R	Frontal eye fields	Planning of complex movements, control of eye movements
Brodmann 9	L/R	Dorsolateral Prefrontal Cortex	Executive Function, Working Memory
Brodmann 10	L/R	Anterior Prefrontal Cortex	Strategic Planning, Cognitive Branching
Brodmann 11	R*	Orbital Frontal Cortex	Behavioral/Emotional Regulation, Behavioral Inhibition
Brodmann 13	L*/R	Insula	Social emotions, multimodal sensory processing, salience
Brodmann 17	L/R	Primary Visual Cortex	Basic Vision
Brodmann 18	L/R	Secondary Visual Cortex	Shape recognition, visual attention
Brodmann 19	L/R	Association Visual Cortex	Visual-spatial processing, motion, face/ word processing (L/R)
Brodmann 20	L/R	Inferior Temporal Gyrus	High-level visual information processing and recognition memory
Brodmann 21	L/R	Middle Temporal Gyrus	Complex auditory processing and language
Brodmann 22	L/R	Superior Temporal Gyrus	Auditory processing, Receptive Language (Wernicke's area)
Brodmann 23	L/R	Posterior Cingulate Cortex	Emotion and Memory, Intrinsic Control
Brodmann 24	L/R	Anterior Cingulate Cortex	Behavioral Control, Decision Making, Social Evaluation
Brodmann 25	L/R	Subgenual Ventromedial Prefrontal Cortex	Decision making, emotional processing, social behavior
Brodmann 27	L/R	Periform Cortex	Olfaction
Brodmann 28	L/R	Ventral Entorhinal Cortex	Short-term memory
Brodmann 29	R	Retrosplenial Cingulate Cortex	Episodic memory, navigation, imagination, and future planning
Brodmann 30	L/R	Part of Cingulate Cortex	Episodic memory, navigation, imagination and future planning
Brodmann 31	L/R	Dorsal Posterior Cingulate Cortex	Emotion and Memory, Intrinsic Control
Brodmann 32	L/R	Dorsal Anterior Cingulate Cortex	Behavioral Control, Decision Making, Social Evaluation
Brodmann 33	L/R	Part of the Anterior Cingulate Cortex	Behavioral Control, Decision Making, Social Evaluation
Brodmann 34	L/R*	Dorsal Entorhinal Cortex/Parahippocampal Gyrus	Olfaction, Short-term memory
Brodmann 35	L/R	Perirhinal Cortex	Memory, Emotion,
Brodmann 36	L/R	Ectorhinal Area	Short-term memory
Brodmann 37	L/R	Fusiform Gyrus	Word recognition (L) / Face Processing (R)
Brodmann 38	L/R	Temporopolar Regions	Memory, Language
Brodmann 39	L*/R	Angular Gyrus	Language, reading, mathematics, attention
Brodmann 40	L/R	Supramarginal Gyrus	Spatial perception, phonological choices
Brodmann 41	L*	Primary Auditory Cortex	Basic Hearing
Brodmann 42	L/R	Auditory Cortex	Auditory processing
Brodmann 43	L/R	Gustatory Cortex	Taste
Brodmann 44	L/R	Pars opercularis, part of Broca's area	Expressive Language
Brodmann 45	L/R	Pars triangularis, part of Broca's area	Expressive Language
Brodmann 46	L/R	Dorsolateral Prefrontal Cortex	Executive Function, Working Memory
Brodmann 47	L/R	Pars orbitalis, inferior frontal gyrus	Syntax
Dentate Nucleus	L/R	Cerebellum	Planning and initiation of voluntary movements
Hippocampus	L/R	Medial Temporal Lobe	Short-term Memory
Amygdala	L/R	Medial Temporal Lobe	Emotion
Hypothalamus	L/R	Just left/right of Midline	Regulates autonomic functions, pituitary, hunger, sleep
Substantia Nigra	L/R	Brainstem	Dopaminergic motor control
Red Nucleus	L/R	Brainstem	Motor Coordination
Mammillary Body	R	Just left/right of Midline	Memory
Caudate	L/R*	Part of the Basal Ganglia	Regulates movement, cognition
Putamen	L/R	Part of the Basal Ganglia	Regulates movement
Pallidum	L/R	Part of the Basal Ganglia	Regulates movement
Thalamus	L/R	Just left/right of Midline	Sensory, Motor, Emotional and Cognitive Functioning
Corpus Callosum	midline	Midline	Interconnects L/R hemisphere

Client volume abnormally high, p<0.05 (isolated, individual testing)

High regional brain volumes may reflect perturbation of early developmental pruning, enhanced skill development, or brain injury related edema, astrogliosis, inflammation, and/or compensatory mechanisms.

Client volume abnormally low, p<0.05 (isolated, individual testing).

Low regional brain volumes may reflect perturbation of early developmental processes, malnutrition, toxic stress, toxic exposures, or more commonly neurological/psychiatric disease and/or brain injury.

* indicates survival of correction for multiple comparisons

Table 2: Mr. [redacted]
Fiber Tract Regions of Interest with Abnormal FA Values on Individual Isolated Evaluation

Following correction for multiple comparisons**, ALL 10** fiber tract regions with atypical FA values on isolated individual evaluation are still considered to be abnormal from a statistical perspective.

JHU White Matter Atlas Fiber Tract Regions		Connections	Supported Functions
Middle Cerebral Peduncle	Midline	Interconnects Cerebellum and Pons	Initiation and Timing of Volitional Movement
Pontine Crossing Tracts	Midline*	Interconnects Pons and Contralateral Cerebellum	Coordination of Movement
Genu of the Corpus Callosum	Midline	Interconnects Right and Left Anterior Frontal Lobes	Interhemispheric Integration of Executive Functions
Body of the Corpus Callosum	Midline*	Interconnects Right and Left Posterior Frontal Lobes Interconnects Right and Left Parietal Lobes	Interhemispheric integration of Motor and Somatosensory Functions
Splenium of the Corpus Callosum	Midline	Interconnects Right and Left Occipital Lobes	Interhemispheric Integration of Visual Functions
Fornix	Midline*	Interconnects the Hippocampus and Mammillary Bodies	Short-Term Memory
Corticospinal Tracts	L/R	Connects Primary Motor Cortex with Contralateral Spinal Motor Neurons	Motor Control of the Contralateral Side of the Body
Medial Lemniscus	L/R	Connects Dorsal Column Nuclei with the Contralateral Thalamus (VPL)	Somatosensory Perception of the Contralateral Side of the Body
Inferior Cerebellar Peduncles	L/R	Connects Spinal Cord and the Medulla to the Cerebellum	Posture, Balance, and Coordination
Superior Cerebellar Peduncles	L/R	Interconnects Cerebellum to Pons and Midbrain	Motor Coordination and Balance
Cerebral Peduncles	L/R	Interconnects Cerebellum with the Thalamus and Motor Cortex	Motor Control
Anterior Limb of the Internal Capsule	L/R	Contains Fibers Interconnecting the Thalamus and Frontal Lobe; Lentiform and Caudate Nuclei; Cortex and Corpus Striatum	Motor Control; Higher Cognitive Function
Posterior Limb of the Internal Capsule	R*	Contains Fibers Interconnecting Motor Areas with the Brainstem; Midbrain and the Thalamus, Occipital Lobes, and Temporal Lobes	Visual-Spatial Processing, Visual Motion, Face and Word Processing (L/R)
Retrolenticular Part of the Internal Capsule	L/R	Interconnects Thalamus and Occipital Cortex	Visual Processing
Anterior Corona Radiata	L*/R*	Contains Descending and Ascending Fibers Related to Cortex – especially for the Frontal Lobes	Executive Function, Emotional Control
Superior Corona Radiata	R*	Contains Descending and Ascending Fibers Related to Cortex – especially for the Motor Cortex	Motor Control
Posterior Corona Radiata	L/R	Contains Descending and Ascending Fibers Related to Cortex – especially for the Parietal Lobes	Attentional Control, Somatosensory Function
Posterior Thalamic Radiation	L/R	Interconnects Thalamus and Cortex	Visual and Auditory Function
Sagittal Stratum	L/R	Interconnects Thalamus with Occipital, Parietal, Temporal and Cingulate Cortices	Visual, Auditory, and Cognitive Function
External Capsule	L/R	Contains Cortico-Cortical Association Fibers for Occipital, Temporal, Parietal, and Cingulate Cortices	Cognitive Processing
Cingulum (cingulate cortex)	L/R	Interconnects Cingulate and Pre-Frontal Cortices	Cognitive Processing and Decision Making
Cingulum (hippocampus)	L/R	Interconnects Cingulate and Entorhinal Cortices	Memory, Emotional Processing
Fornix (cres) and Stria Terminalis	L/R	Interconnects Hippocampus and Mammillary Bodies; Amygdala with the Septal Region and Hypothalamus	Memory, Emotional Processing, Fear Response
Superior Longitudinal Fasciculus	L/R	Interconnects the Front and Back of the Cerebrum, Including Frontal, Parietal, Occipital, and Cingulate Areas	Higher Cortical Functions including Language, Attention, Motor Control, and Spatial Processing.
Superior Fronto-Occipital Fasciculus	R*	Interconnects the Frontal Lobe with the Occipital and Parietal Lobes	Spatial Awareness
Uncinate Fasciculus	L*/R*	Interconnects Hippocampus and Amygdala with Orbital Frontal Cortex	Memory, Emotional Processing, Language
Tapetum	L/R	Contains Commissural Fibers Interconnecting Right and Left Temporal Lobes	Interhemispheric Integration for Auditory Processing

Client FA value abnormally high, p<0.05 (isolated, individual testing).

High FA values may reflect a developmental failure of axonal pruning, disease/injury related intracellular edema, compaction of neurofilament, neuro-inflammation with micro-glial activation, astrogliosis, loss of crossing fibers, and/or compensatory mechanisms.

Client FA value abnormally low, p<0.05 (isolated, individual testing)

Low FA values may reflect perturbed developmemt or more commonly, disease/injury related extracellular edema, demylination, and/or loss of axonal fibers.

* indicates survival of correction for multiple comparisons

Appendix-I-MRI-2020

Basic Concepts in Brain Organization, Magnetic Resonance Imaging, and Quantitative Assessment of Regional Brain Volumes and Diffusion Tensor Imaging Data.

BASIC CONCEPTS IN BRAIN ORGANIZATION, MAGNETIC RESONANCE IMAGING AND TRAUMATIC BRAIN INJURY

Brain Organization:

The human brain is composed of more than 100 billion cells, including neurons and supporting glial cells. Electrochemical signals are used to encode and transmit information within brain cells, with neurotransmitters used to transfer information from one neuron to another across synapses. Neurons have three key parts: (1) the dendrites, which bring information into the cell, (2) the cell body, which integrates the information, and (3) the axon, which takes information to the next cell. Within the brain, cell bodies often cluster together in what is known as gray matter. The outermost gray matter region of the brain is known as the cerebral cortex. Axons often travel together in tracts, in what is known as the white matter, where they connect different parts of the brain. Cells may be arranged differently in different parts of the cortex. This, along with the specific local and distant interconnections between cells gives rise to cortical specialization and networks – that is, the brain is partly organized into functional modules that are interconnected to support different calculations and behavioral abilities.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a non-invasive technique for evaluating structure and function. By examining how the hydrogen protons of water molecules behave when placed within a steady magnetic field and bombarded by pulses of radio-wave energy, the MRI system can reconstruct a picture of the brain's anatomy. By altering the parameters and sequence of radio-wave pulses, it is also possible to explore the white matter interconnections between brain regions, brain biochemistry, metabolism, and hemodynamics.

Imaging evaluations in patients with brain injury often include T1-weighted, T2-weighted, FLAIR, SWI and DTI sequences. T1-weighted imaging provides exceptional gray-white matter differentiation and a detailed picture of brain anatomy. T2 and FLAIR imaging are especially useful for identifying edema and lesions in the white matter. SWI – susceptibility weighted imaging – is very sensitive to iron deposition associated with bleeding caused by stroke or small hemorrhages that may be caused by traumatic brain injury and other conditions. DTI – Diffusion Tensor Imaging -- examines the diffusion properties of water within the brain. DTI provides insight into the integrity of axonal tracts (which normally restrict the direction of water diffusion to be along [rather than across] the direction of the tracts).

Clinical, visual inspection of MR data can often reveal major pathologies like tumors, multiple sclerosis, and severe head trauma. Milder injuries, however, such as those associated with a concussion, rarely produce MR changes that can be seen on routine visual inspection. Quantitative analyses of regional brain volume (that is, the measurement of the size of various brain regions as visualized on T1-weighted images), and a quantitative assessment of the integrity of white matter pathways (as indexed by Fractional Anisotropy (FA) on DTI), offer more sensitive, objective evaluation of brain compromise.

Volumetric Analyses

The brain is a 3-Dimensional structure that can be divided into small cubes, known as voxels. For MRI images, an automated computer algorithm can, in each voxel, measure the amounts of gray matter, white matter, and cerebrospinal fluid (CSF). The computer can also divide the brain into regions-of- interest, based on known structural-functional relationships. For example, the computer can determine which voxels comprise brain regions like the hippocampus or primary motor cortex and thereby calculate the total amount of brain tissue in these regions for each individual client. These methods provide quantitative measures of the actual volume of brain structures for each client, and they allow for a statistical comparison of the client's data with respect to data from a large group of neuro-typical subjects.

For volumetric analyses, Quantify uses SPM12 to correct for bias-field inhomogeneities, transform the data into MNI space, segment the data, and extract volume-related metrics. For region of interest volumetric analyses, MATLAB scripts are then used to divide the brain into 107 cortical and subcortical areas derived from TD-Brodmann (Lancaster, 2000) and AAL atlases (Tzourio-Mazoyer, et al., 2002). Figure 6 shows cortical regions from the TD-Brodmann atlas. Additional AAL atlas areas of interest include the basal ganglia and other subcortical motor nuclei, the thalamus, hippocampus, amygdala, and corpus callosum. To correct for variability in overall head/brain size, values are scaled for each individual prior to statistical evaluation.

The Quantify normative database is made up of volumetric and DTI data from more than 1,000 neurotypical subjects collected as control subjects across 36 research studies at the Mind Research Network (MRN) in Albuquerque, NM.

Different physical scanners introduce some variability into volumetric measures, even when they are nominally of the same configuration. Therefore, to compare client data obtained on one scanner with normative control data obtained on a different scanner, there is a need to harmonize data metrics across sites, prior to statistical analyses. Several procedures are implemented to accomplish this. First, data acquisition parameters at the client scanner are set to be comparable to those used in the collection of the Quantify control datasets. Second, data analysis software algorithms, procedures, and processing pipeline used to assess client data and the Quantify control data are the same. Third, prior to statistical analyses, data metrics from the client scanner are harmonized to those of the MRN scanner using a human physical phantom scaling procedure (see Palicios et al., 2017; Venkatraman et al., 2015). Briefly, the same human subject was scanned on both the client and MRN machines. For volumetric scaling, a single multiplicative factor is derived for each ROI. These procedures allow client data to be validly evaluated with respect to the Quantify normative database.

MATLAB scripts are then used to perform statistical analyses Statistical evaluation of client data is based upon comparison of client metrics with sex and age-range matched control subjects drawn from the Quantify database, typically with an age range of +/- 10 years. Standard univariate procedures are used to generate Z-scores for each individual metric.

To account for multiple comparisons, a Benjamini-Hochberg procedure with a false discovery rate of 25% is additionally applied. All procedures are performed in a completely automated and objective manner free of any bias or client information other than gender and age. Table 1, below, provides specific data processing steps:

Table 1:

VOLUMETRIC STEPS	SOFTWARE	COMMAND/ACTIVITY
1. Convert Dicom data to NIFTI	MRICRON	DicomConvert
2. Reorient to AC-PC	SPM12	Reorient-to
3. Grey/White/CSF Segmentation	SPM12	Segmentation-NativeSpace
4. Grey/White/CSF Segmentation	SPM12	Segmentation-StandardSpace
5. Extraction of ROI volumes	MATLAB	AAL and TD-Brodmann Templates
6. Application of scaling factors	MATLAB	Site and region specific factors
7. Database Comparison Statistics	MATLAB	Gender/age-range match, BH correction
8. Plot Generation	MATLAB	Bar plots and scatter plots.
9. Table Generation	MATLAB/Excel	Data tables
10. Quality Control Check	Senior Neuroscientist	Review of data and QC metrics
11. Generation of spatial maps	Senior Neuroscientist	Presently done by hand in GIMP

Figure 1 provides an example of the bar plot outputs which show statistical results (steps 7 and 8).

Neurotypical Control Subject **Example Client Dataset**

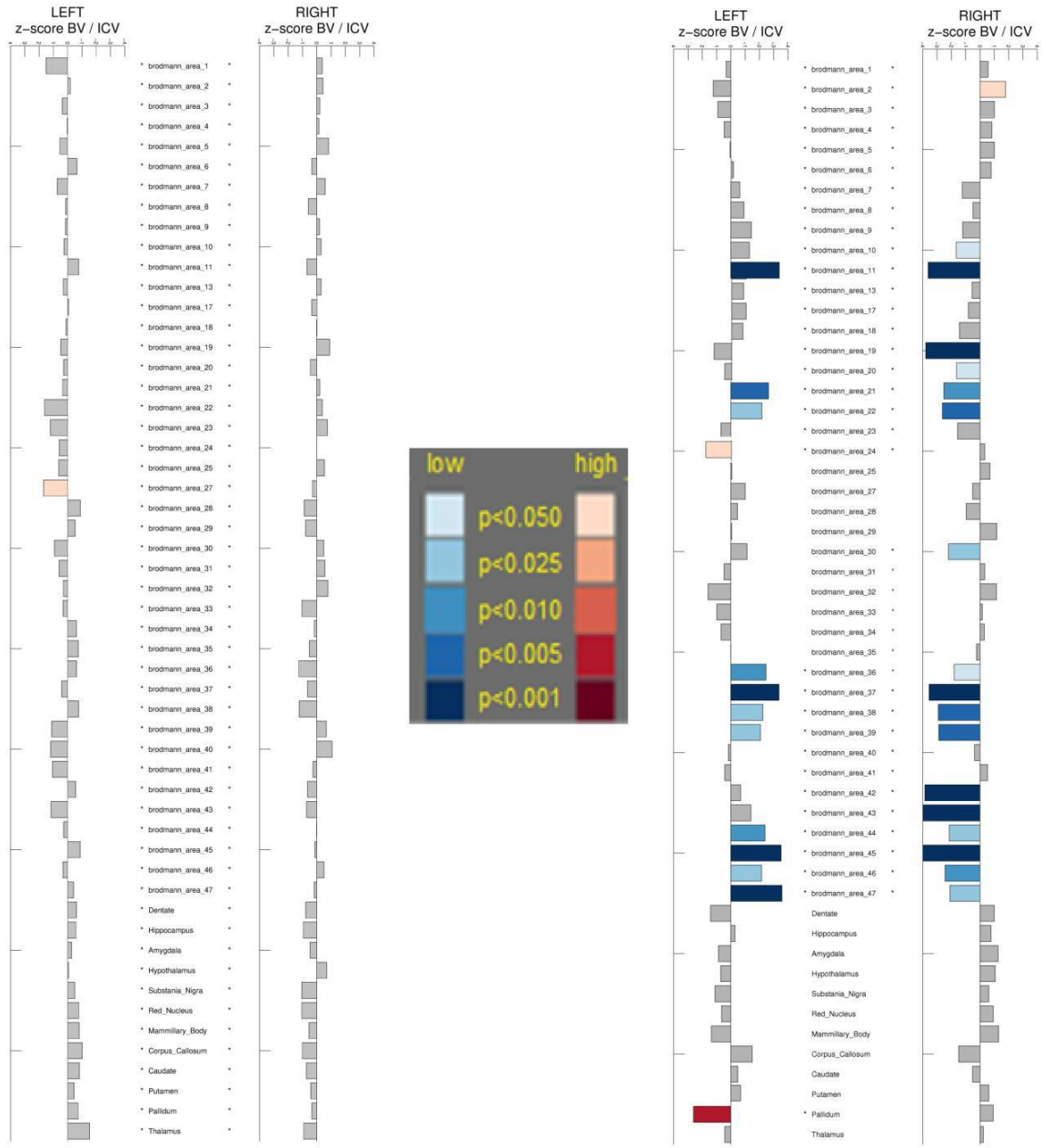


*Figure 1: Main Bar Plot Outputs. Bar plots show z-score deviations from the normative database, in the indicated region. Examples are shown for a neurotypical control subject and an example client dataset. Gray indicates regions that are not statistically significant (-1.645 < z < 1.645; p>0.05). Red indicates that a region has an atypically large volume (z > 1.645; p<0.05). Blue indicates that a region has an atypically low volume (z < -1.645, p<0.05). To correct for multiple comparisons, a Benjamini- Hochberg procedure is used with a False Discovery Rate of 25%. A region is ultimately considered to show a statistically significant deviation from normal if, and only if, it is abnormal on individual, isolated evaluation(p<0.05) and it survives correction for multiple comparisons. Such regions are designated by an *. For the example control subject, left Brodmann area 27 has a z-score of ~ 1.71, which is above of p<0.05 threshold of z = 1.645, so the bar is colored red. However, this observation does not survive correction for multiple comparisons, so it is not ultimately considered to be significant (so no * is indicated). In contrast, the example client has 27 regions of significantly low volumes (blue bars with z-scores < -1.64) and three regions with abnormally high regional volumes. All of the client regions that are significant on individual isolated evaluation survive correction for multiple comparisons. That is, each of these 30 regions (27 low; 3 high) is ultimately considered to show statistically significant deviation from normal (as indicated by the *).*

Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging provides insight into the integrity of white matter tracts by measuring the diffusion properties of water within the brain. For example, if you put a drop of ink in the middle of the ocean, the ink would spread (diffuse) in all directions equally. This is called isotropic diffusion. Now imagine that the ocean was filled with a bunch of pipes running in a common direction. In this case, the ink would spread in a preferred direction along the pipes, since it cannot easily penetrate into/across the pipes. When the ink diffuses in a preferential direction, this is called anisotropic diffusion. The brain is like the ocean filled with pipes – axons running within oriented fiber tracts. So, within the brain, water diffuses in preferred directions based on the local white matter anatomy. Using Diffusion Tensor Imaging the preferred direction of water movement within each voxel can be characterized by Fractional Anisotropy (FA), a value from 0 to 1, where 0 indicates isotropic diffusion and 1 indicates fully restricted diffusion in a single direction.

Typical diffusion tensor images color code the preferred directions of tracts, with color intensity indicating FA values. A process known as tractography can be used to reconstruct tract trajectories based upon FA values.

Just as was described for region-of-interest analyses in volumetric assessments, a computer algorithm can identify white matter tracts within the brain of each client and determine the average FA value for each tract. This client-specific value can then be statistically assessed with respect to a normative dataset.

For DTI, the FNIRT algorithm in combination with the DTIFIT tool in FSL is used to compute FA maps with SPM alignment to the MNI FA template and subsequent extraction of tract-based FA values within the 48 fiber tracts defined by the Johns Hopkins University MRI Atlas of Human White Matter (Mori et al., 2009). Table 2, below, provides the processing steps. For FA harmonization across scanners, a two-step procedure is used. As was the case for volumetric data, human phantoms are evaluated at both client and MRN sites. A global linear scaling factor is then derived by calculating the average FA value across all brain regions-of-interest. Then, a set of additional region-specific multiplicative factors is derived, with both the linear and multiplicative factors applied to the client data to achieve harmonization with the Quantify database. The Quantify analysis outputs include bar graphs and scatter plots similar to those provided for volumetric analyses, plus a demonstrative figure showing which tracts are abnormal.

Table 2:

DTI STEPS	SOFTWARE	COMMAND/ACTIVITY
1. Convert Dicom data to NIFTI	MRICRON	DicomConvert
2. Eddy Current and Motion Correction	FSL	eddy.qc
3. Calculation of Fractional Anisotropy	FSL	dtifit
4. TBSS normalization to standard space	FSL	FSL_reg/FNIRT
5. Extraction of ROI FA average FA	MATLAB	JHU template
6. Application of scaling factors	MATLAB	Site and region specific factors
7. Database Comparison Statistics	MATLAB	Gender/age-range match, BH correction
8. Plot Generation	MATLAB	Bar plots and scatter plots.
9. Table Generation	MATLAB/Excel	Data tables
10. Coloring of abnormal tract ROIs	Custom Code	
11. Quality Control Check	Senior Neuroscientist	Review of data and QC metrics

References

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, Kochunov PV, Nickerson D, Mikiten SA, Fox PT. (2000) Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp 10:120–131.

Mori S, Oishi K, Faria AV. (2009) White matter atlases based on diffusion tensor imaging. Curr Opn Neurol 22(4): 362-339.

Palacios EM, Martin AJ, Boss MA, Ezekiel F, Chang YS, Yuh EL, Vassar MJ, Schnyer DM, MacDonald CL, Crawford KL, Irimia A, Toga AW, Mukherjee, and Track-TBI Investigators. Toward precision and reproducibility of diffusion tensor imaging: A multicenter diffusion phantom and traveling volunteer study. AJNR Am J Neuroradiol 38:537-545.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. (2002) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15(1): 273-289.

Venkatraman VK, Gonzalez CE, Landman B, Goh J, Reiter DA, An Y, Resnick SM. (2015) Region of interest correction factors improve reliability of diffusion imaging measures within and across scanners and field strengths.

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