

Supplementary Appendix 6: Tractography Methods for the EBDS Neonate DTI Atlas

Introduction

White matter fasciculi were derived from an atlas-based tractography approach using predefined regions of interest to “seed” or initialize the tracing of trajectories for each major fiber bundle. These seeding regions of interest, called “Label Maps,” were hand drawn using previously established protocols—however—with great considerations made to accommodate the unique anatomical features and patterns of myelination found only in the neonatal human brain. All fiber bundles were reconstructed bilaterally with the exception of the Corpus Callosum. Four fiber bundles were separated into “tract segments” based on trajectories to predefined cortical surface targets that correspond to putative functionally related regions. The Arcuate, however, was separated into tract segments that correspond to the direct and indirect pathways that constitute the three components of the AF (1). In all, a total of 47 “tract segments” were obtained from the neonatal atlas for further analysis. The protocol used to generate each bundle and identify each segment is detailed below:

Note: this document details the methods for delineating the fiber bundles using language specific to the tools and software used throughout development of these protocols. Please see Table of Terminology for reference

Table of Terminology

Term	Description
CorticoFugal	“CorticoFugal” encompasses any and all corticoefferent and corticopetal fiber groups that interconnect the cerebral cortex, corona radiata, internal capsule, cerebral peduncles, pontine nuclei and/or the brainstem. All projections that continue to the cerebellar cortex were excluded. Examples of fiber bundles encompassed in CF bundle include the following groups of fiber bundles: corticopontine, corticospinal, corticobulbar, and corticoreticular fibers.
CorticoThalamic	“CorticoThalamic” fiber bundles correspond to the white matter pathways that radiate from the thalamus to the cerebral cortex, with waypoints in the internal capsule and the corona radiata. Also known as thalamic radiations and/or thalamocortical tracts
Fiber tract	Also known as: white matter tracts; Fiber bundle; fascicular projection; projections of white matter; trajectory of white matter fascicles
Tract segment	A segment of a larger white matter pathway that was extracted from the primary fiber bundle based on cortical target terminations
ROI nodes	3D Slicer tool for interactive application of target regions of interest; target regions represent putative connectional targets based on a priori anatomical knowledge of white matter structures; alternative tool to predefined cortical target mask (2)

OrbitoFrontal Cortical Termination (OFC)	Includes gyrus rectus (BA 11, BA 47) N.B. applies to corpus callosum rostrum segment only
PreFrontal Cortical Termination (PFC)	Includes projections to the hemispheric surface in the prefrontal lobe, including BA 9, BA 10, BA 46, and BA 47. N.B. the corticothalamic PFC tract segments include projections that terminate in the anterior cingulate N.B. the corpus callosum PFC tract does not include the projections to the orbital frontal cortex (see: OFC)
PreMotor Cortical Termination (PMC)	Includes projections to the hemispheric surface in the frontal lobe that are anterior to the precentral sulcus and posterior to the prefrontal cortex (includes premotor cortex and supplementary motor cortex, e.g. segment of BA 6 that is anterior and adjacent to BA 4, BA 8, BA 44, and BA 45) (3)
Motor Cortical Termination (MC)	Region encompassed the cerebral cortex from the precentral sulcus (Pre-CS) until immediately anterior to the central sulcus (CS); includes precentral cortex (BA 4 and the segment of BA 6 that is directly ventral to BA 4)
Parietal Cortical Termination (PC)	Region encompassed the cerebral cortex immediately posterior to central sulcus (CS) until the the parieto-occipital sulcus; includes postcentral gyrus, superior parietal gyrus, posterior parietal lobe/precuneus area
Label Map	Predefined “seed” region for 3D Slicer, hand drawn label volume used as input to tractography seeding module, every voxel is a seed within the ROI, created with the Editor module (2)
Color FA (cFA)	RGB color directional map
+ ROI	“AND” operation, must-pass ROI, target ROI, Annotation box, 3D Slicer interactive “must pass” region, target region of interest; termination in gray matter of the brain; ROI node in cerebral cortex that encompasses trajectories to cortical regions that are targets for fascicles to project to (2)
- ROI	“NOT” operation, do not pass ROI, exclusion ROI, 3D Slicer interactive “do not pass” region of interest (2)

Table of Abbreviations

Abbreviation	Description
AF-fp	Arcuate fasciculus frontoparietal, the segment of the arcuate fasciculus that interconnects the frontal and parietal lobes, aka anterior indirect segment, SLF III (1)
AF-ft	Arcuate fasciculus frontotemporal, the segment of the arcuate fasciculus that interconnects the frontal and temporal lobes, aka direct segment (1)
AF-tp	Arcuate fasciculus temporoparietal, the segment of the arcuate fasciculus that interconnects the parietal and temporal lobes, also known as Catani’s posterior indirect segment, also referred to as the Temporal Parietal Segment (TPS) (1)
AG	Angular gyrus
ALIC	Anterior limb of internal capsule (includes genu of internal capsule)

Supplementary Appendix 6: Tractography Methods for the EBDS Neonate DTI Atlas

Bg	Basal ganglia
CB	Cerebellum
CC	Corpus callosum (e.g. CC--OFC is the segment of the corpus callosum that interconnects the orbital frontal cortices)
CC-TC	Tapetum
CF	Corticofugal
CG-WM	Cingulate gyrus white matter
CGC	Cingulum superior part (originates in anterior cingulum, terminates in parietal cortex)
CGH	Cingulum hippocampal part (originates in posterior cingulum, terminates in hippocampus)
Color FA	RGB map
CP	Cerebral peduncle
CR	Corona radiata
CS	Central sulcus
CT	Corticothalamic
DTI	diffusion MRI, diffusion tensor imaging
EC	External capsule
FL	Frontal lobe
FX	Fornix
FVL	FiberViewerLight (4)
IC	Internal capsule
IFG	Inferior frontal gyrus
IFOF	Inferior frontooccipital fasciculus
ILF	Inferior Longitudinal Fascicles
ITG	Inferior temporal gyrus
MC	Motor cortex
MFG	Middle frontal gyrus
ML	Medial lemniscus
MTG	Middle temporal gyrus
OFC	Orbitofrontal cortex
OL	Occipital lobe
OT	Optic tract
POS	Parieto-occipital sulcus
PC	Parietal cortex
PFC	Prefrontal cortex
PL	Parietal lobe
PLIC	Posterior limb of internal capsule

Supplementary Appendix 6: Tractography Methods for the EBDS Neonate DTI Atlas

PMC	Premotor cortex
Post-CG	Postcentral gyrus
Pre-CG/Pre-CS	Precentral gyrus, precentral sulcus
RLIC	Retrolemniscal limb of internal capsule
SCP	Superior cerebellar peduncle
SFG	Superior frontal gyrus
SLF	Superior longitudinal fasciculus II (corresponds to SLF II) (5)
SLF-WM	Superior longitudinal fasciculus
SMG	Supramarginal gyrus
STG	Superior temporal gyrus
Th	Thalamus
TL	Temporal lobe
UNC	Uncinate fasciculus

Association Pathways: Reconstructing the Arcuate Fasciculus (AF) and Superior Longitudinal Fasciculus (SLF)

To obtain the three individual segments of the AF, we used an approach modeled closely after Catani, Jones, & Ffytche (1). Specifically, we used one single label map to first reconstruct all fibers of the AF and SLF at once and then, using positive ROI nodes in the “Tractography Display” module, we extracted the individual fiber tract segments based on anatomical knowledge.

The AF-ft, AF-fp, and AF-tp segments correspond to the direct pathway, the anterior indirect pathway, and the posterior indirect pathway, respectively (1). Additionally, the AF-ft, the AF-fp, and the AF-tp are also known as the long segment, the SLF III, and the temporal parietal segment, respectively. The AF-fp corresponds to SLF III while the SLF tract segment corresponds to SLF II (5)

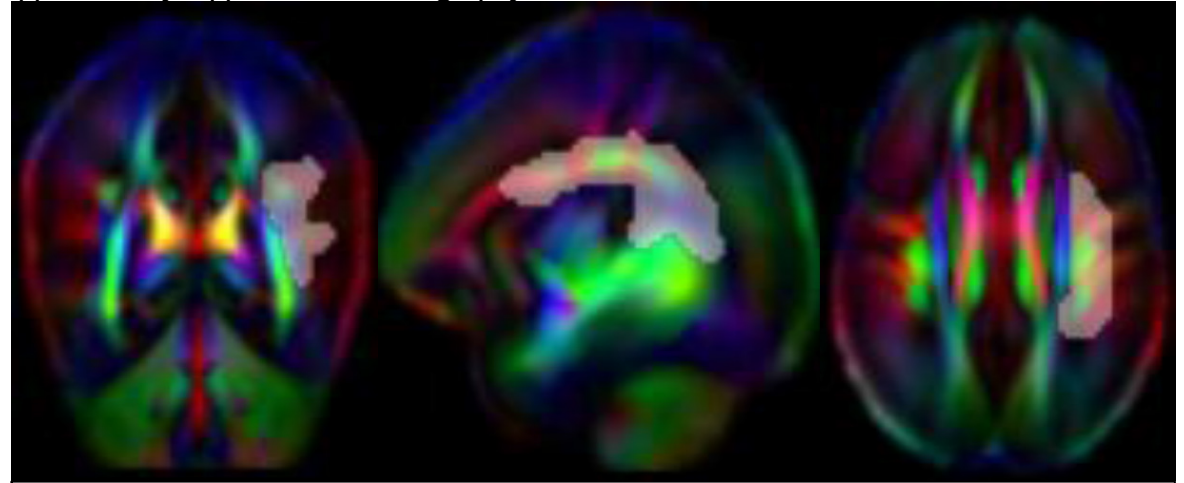


Figure: A single hand drawn label map was used to generate all three segments of the AF as well as the SLF in the axial orientation of the neonatal atlas color FA image (a) the sagittal orientation (b) and the coronal orientation (c)

Tract Segment	+ ROI 1	+ ROI 2	- ROI
AF-ft	ventrolateral frontal cortex (MFG, PreCG) and posterior IFG (Broca’s territory)	Posterior and middle parts of the STG and MTG (Wernicke’s territory)	OL, CB, brainstem
AF-fp	ventrolateral frontal cortex (MFG, PreCG) and posterior IFG (Broca’s territory)	Inferior PC—SMG, AG (Geschwind’s territory)	OL, CB, brainstem
AF-tp	Posterior and middle parts of the STG and MTG (Wernicke’s territory)	Inferior PC—SMG, AG (Geschwind’s territory)	OL, CB, brainstem
SLF	IFG	Superior PC	OL, CB, brainstem

Fiber Tractography results for the three tract segments of the AF and the SLF tract segment

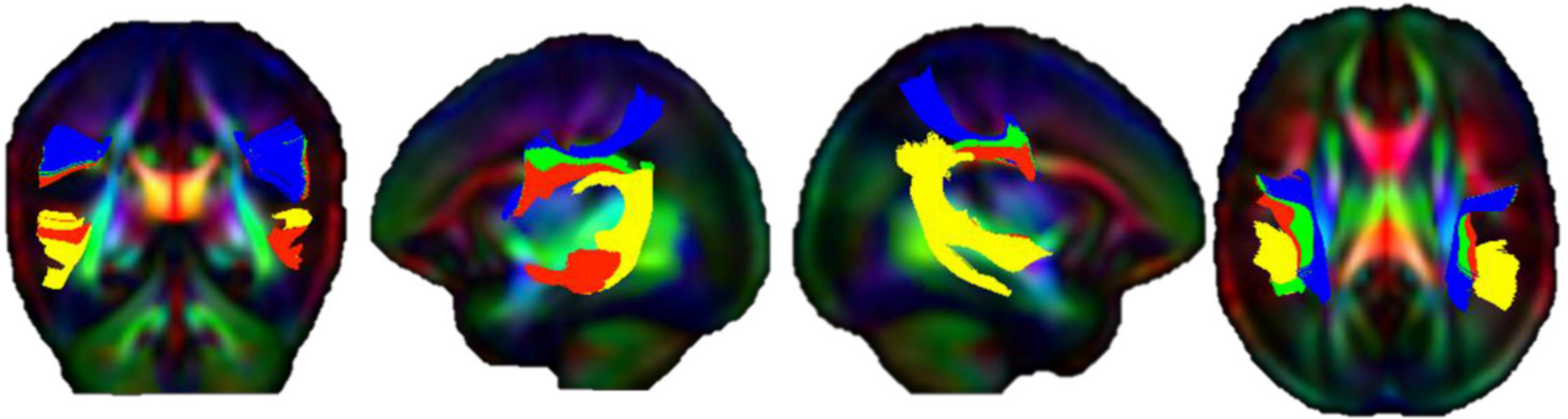


Figure: 3D reconstructions of white matter tract segments from an atlas of neonatal DTI data are displayed with the atlas color FA map. The Left and Right tracts were divided into segments based on cortical target regions for analysis. The tract segment colors are defined as follows: AF-ft (red), AF-fp (green), AF-tp (yellow), and SLF (blue). Note: The AF-fp tract corresponds to SLF III and the SLF tract corresponds to SLF II.

Association Pathways: Reconstructing the Cingulum Cingulate Gyrus (CGC)

To reconstruct the CGC tract segment of the cingulum fiber group, the part of the cingulum in the cingulate gyrus that coursed longitudinally (running anterior to posterior, aka the superior segment) was seeded using the sagittal orientation on the color FA map to include only the *green* regions of the cingulum that tightly wrapped the CC dorsally. The CGC fiber bundle was cleaned with ROI nodes to encompass the course of the cingulum part that runs through the cingulate gyrus with projections to the portion of the cingulate gyrus in the PL (precuneus) (9). The cutter tool in FVL was used to remove the FL u-shaped fibers along the length of the tract so that only the tightly bundled fibers that run dorsal to the CC in the FL were retained for analysis.

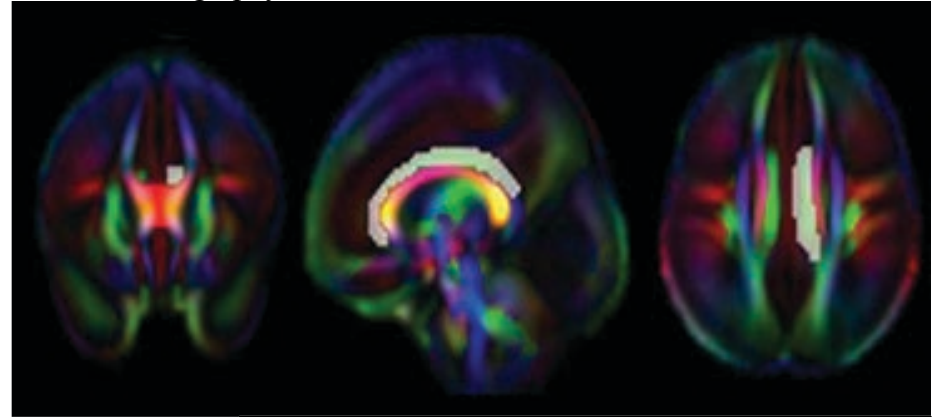


Figure (above): Hand drawn Label Map delineating the left CGC on the neonatal atlas color FA image in the axial (a) the sagittal (b) and the coronal (c) orientations.

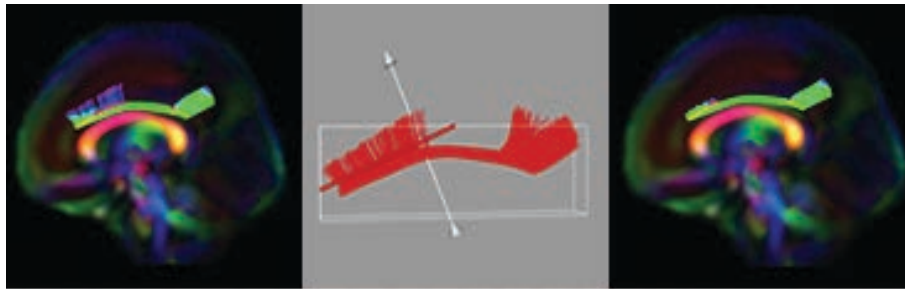
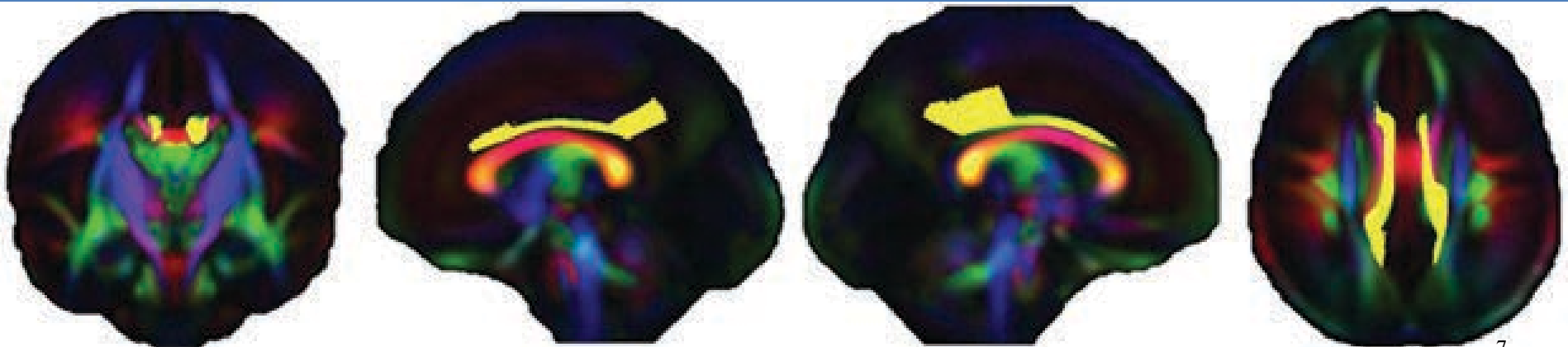


Figure (left): frontal lobe projections colored by mean orientation (a), FVL cutter tool removes short u-shaped fibers to the frontal lobe above the plane in the direction of the arrow (b), the edited CGC bundle with cut frontal projections colored by mean orientation

Tract Segment	+ ROI 1	+ ROI 2	- ROI
CGC	ACC (FL)	Posterior cingulate gyrus just dorsal to isthmus of CC, precuneus	Contralateral cortex, CB, Bg Fx

Fiber Tractography Results for the CGC



Association Pathways: Reconstructing the Cingulum Hippocampal Part (CGH)

The CGH tract segment was reconstructed with a hand drawn label map that surrounded the retrosplenial purple region of the cingulum that wrapped around the CC posteriorly in the sagittal orientation. The label map included the entorhinal area and the parahippocampal gyrus.

The CGH tract segment was isolated from the CGC by restricting the fibers, using a + ROI, to those that wrapped around the splenium posteriorly (retrosplenial). The CGH fibers posterior to the splenium projected to the OL and posterior precuneus. Next, we isolated the CGH pathway to the TL using a + ROI around the fibers that reached the most anteriorly in the TL.

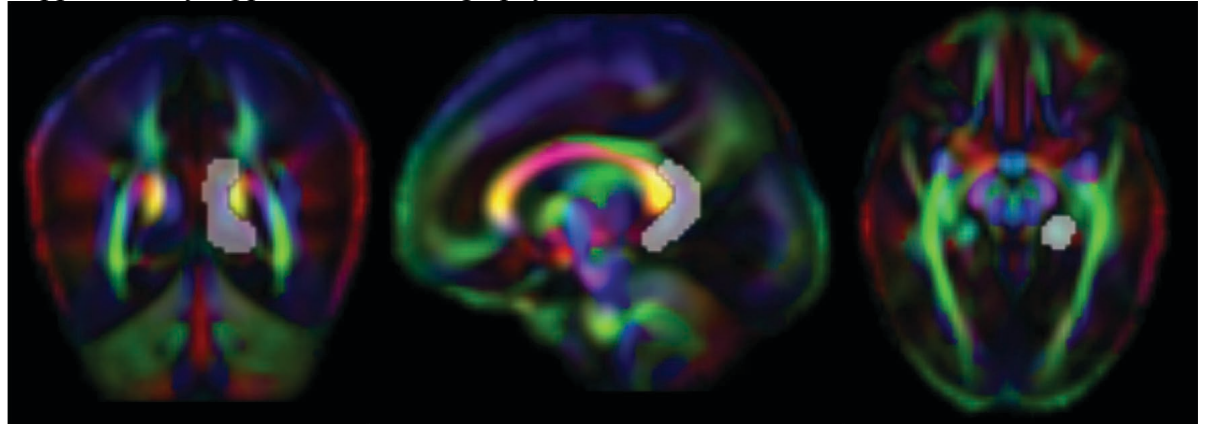
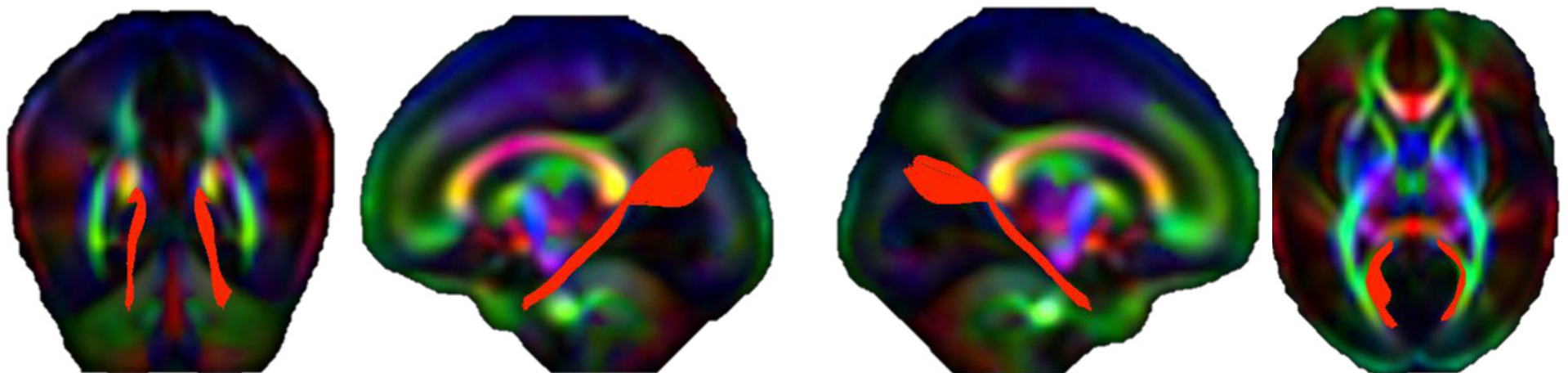


Figure: Hand drawn Label Map delineating the left CGH in the axial orientation of the neonatal atlas color FA image (a) the sagittal orientation (b) and the coronal orientation (c)

Tract Segment	+ ROI 1	+ ROI 2	- ROI
CGH	Posterior cingulate gyrus in OL (retrosplenial)	Parahippocampal regions, Hippocampus (TL)	Contralateral cortex, CB, Bg Fx

Fiber Tractography results for the CGH



Association Pathways: Fornix (Fx)

The label map for seeding the Fx was defined around both the Fornix column and body as well as the fimbriae (6). A + ROI node surrounded streamlines that reached the hippocampus in the temporal lobe used to separate the Left and Right Fornix.

Spurious, artifact streamlines that coursed beyond the hypothalamus through the optic tract were removed using the cutter tool from FVL. The tract was cut with a plane placed at the level of the anterior commissure (8).

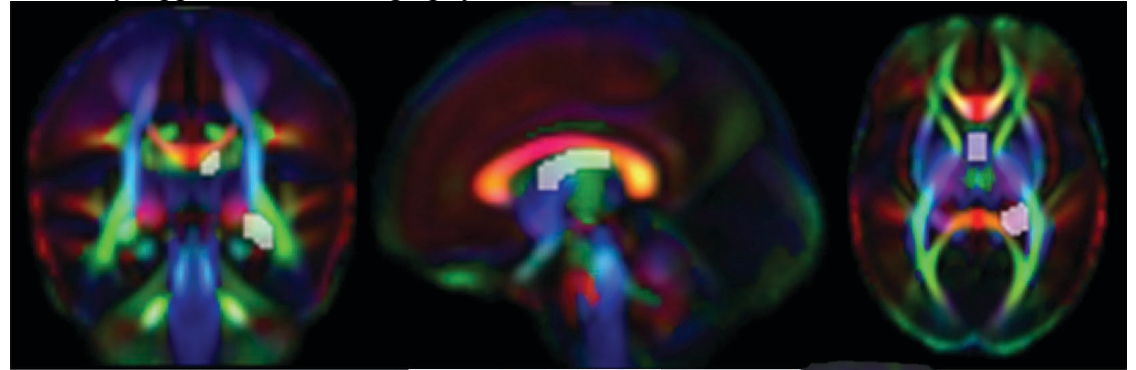
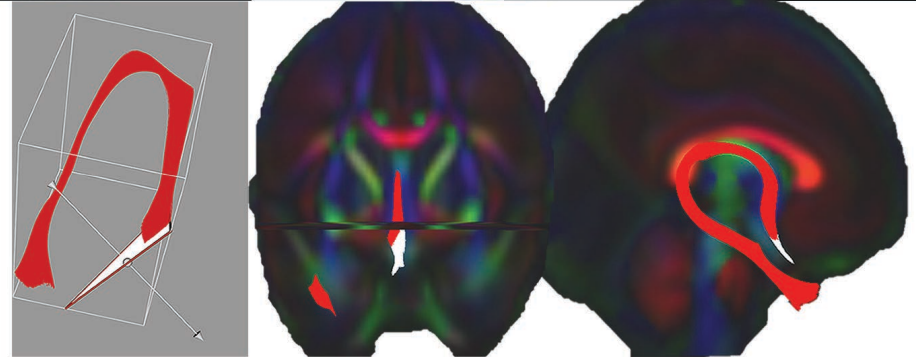


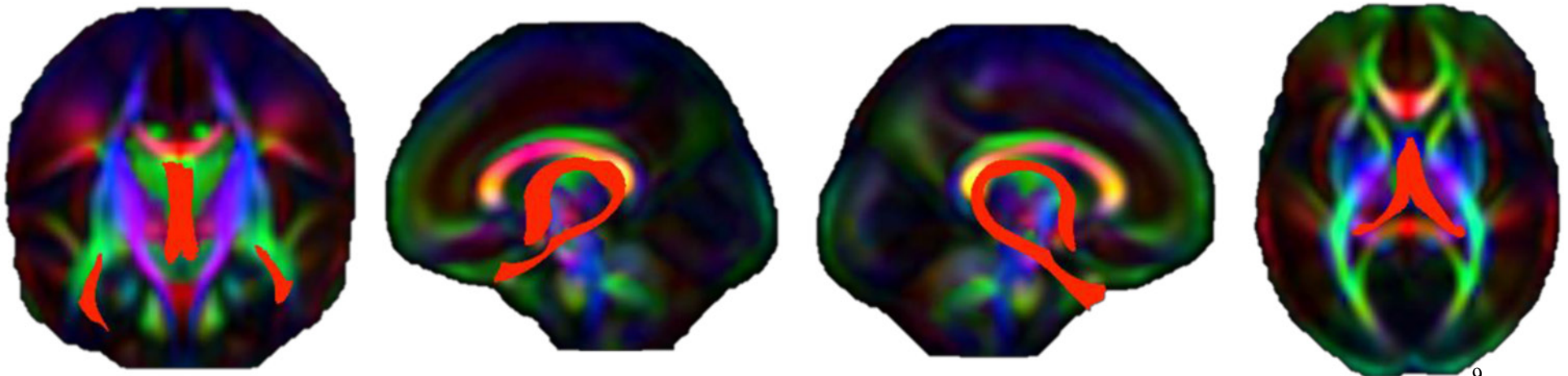
Figure: (top) Hand drawn Label Map delineating the left IFOF in the axial orientation of the neonatal atlas color FA image (a) the sagittal orientation (b) and the coronal orientation (c)

Figure (bottom) The FVL cutter tool was used to crop the Fx with a plane at the level of the anterior commissure (a); The entire pre-cut tract displayed in the coronal and left sagittal views with the removed portion (white)



Tract Segment	+ ROI 1	+ ROI 2	- ROI
Fx	Hypothalamus and mammillary bodies at a slice just inferior to AC	TL (hippocampus and parahippocampal gyrus), lateral to CP and medial to SS	CC, contralateral cortex, OL, tapetum, CGH

Fiber Tractography results for the Fx



Association Pathways: Inferior Fronto-Occipital Fasciculus (IFOF)

The IFOF label map encompassed regions of the OC and regions of the FL (6). For the OL, the label was drawn to cover a generous amount of OL white matter, including the PTR, SS, and cuneus. For the FL, the label was drawn around the external capsule dorsal to the UNC. The reconstructed IFOF streamline was traced from the OL through the PTR, SS, and RLIC as it curved dorsally through the external capsule to enter the frontal lobe and follow the anterior corona radiate until it began to fan out projections to the IFG and OFC. Using + ROI nodes, only the fibers reaching the most anteriorly to the OFC and only the fibers reaching the most posteriorly to the OC were retained.

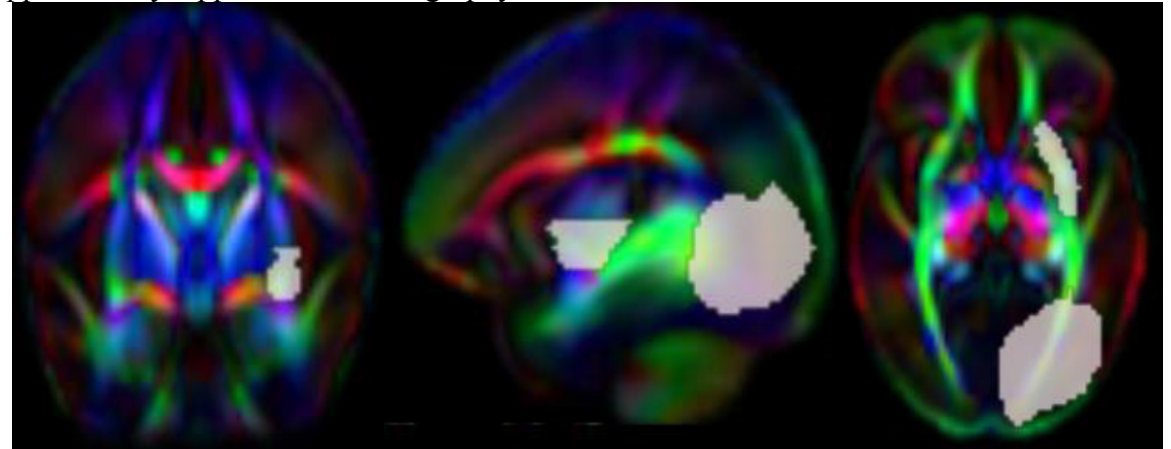
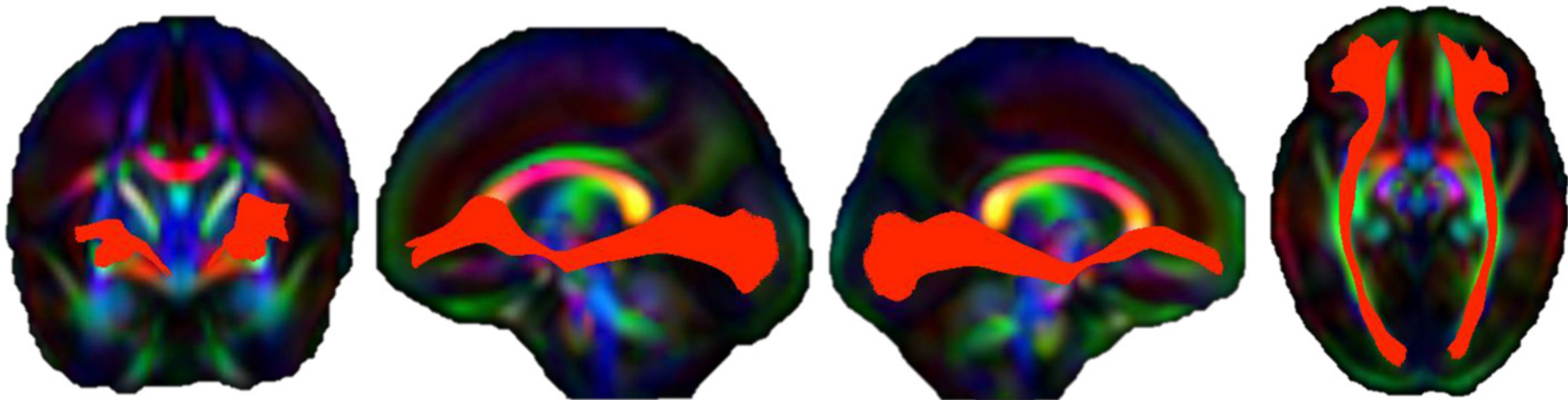


Figure: Hand drawn Label Map delineating the left IFOF in the axial orientation of the neonatal atlas color FA image (a) the sagittal orientation (b) and the coronal orientation (c)

Tract Segment	+ ROI 1	+ ROI 2	- ROI
IFOF	FL (anterior CR, IFG, OFC)	OL, RLIC, posterior CR, SS	Contralateral cortex, CB, Superior PL, precuneus

Fiber Tractography results for the IFOF



Association Pathways: Reconstructing the Inferior Longitudinal Fasciculus (ILF)

The ILF label map encompassed the OL similar to the IFOF label map, the STG, the SS, and included a generous amount of coverage for the TL on a coronal slice anterior to the UNC (6)(7). Using + ROI nodes, only the fibers reaching the most anteriorly to the TL and only the fibers reaching the most posteriorly to the OC were retained.

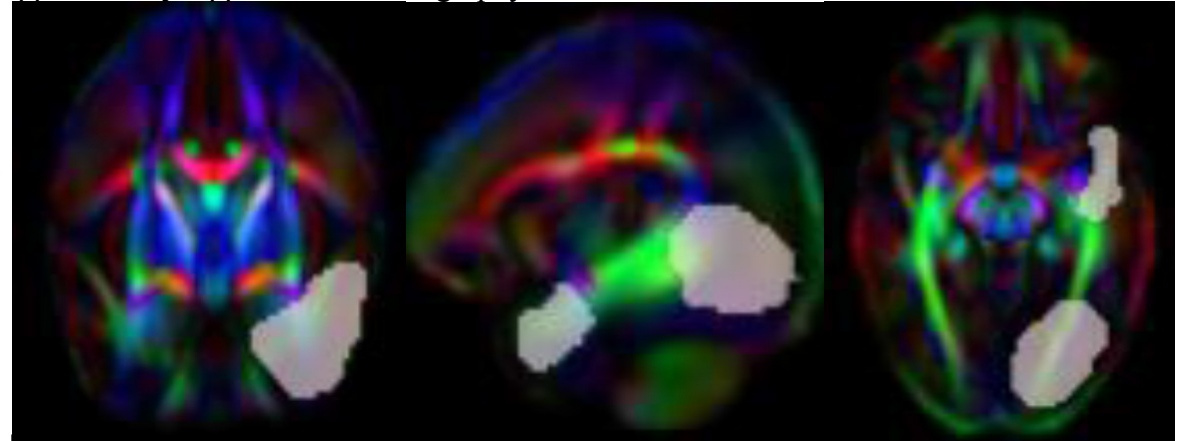
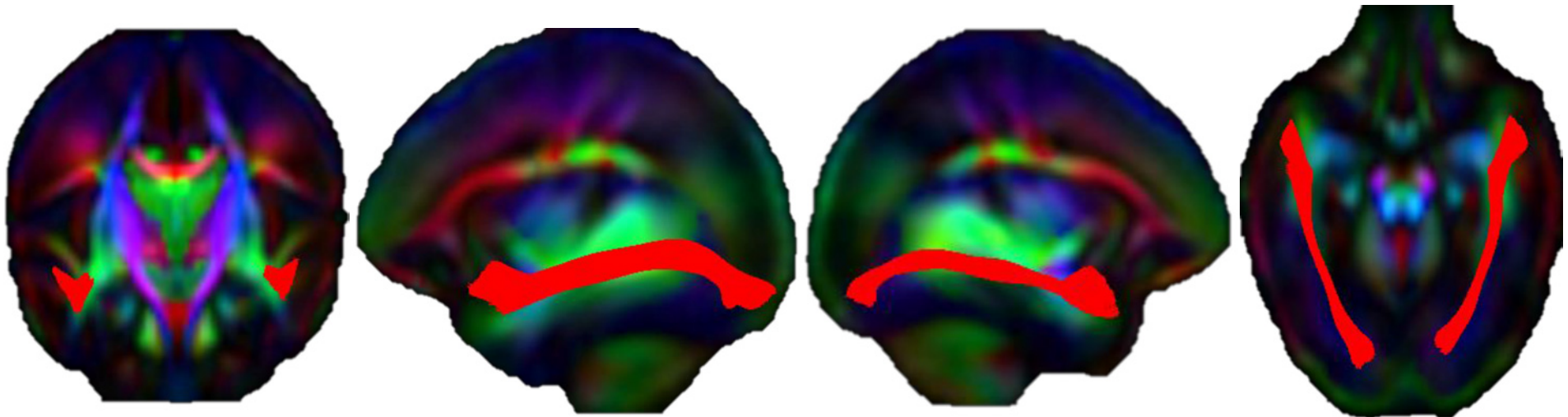


Figure: Hand drawn Label Map delineating the left Internal Capsule (IC) in the axial orientation of the neonatal atlas color FA image (a) the sagittal orientation (b) and the coronal orientation (c)

Tract Segment	+ ROI 1	+ ROI 2	- ROI
ILF	Anterior TL	SS, OL	Contralateral cortex, CB, FL, tapetum

Fiber Tractography results for the ILF



Projection Pathways: Uncinate Fasciculus (UNC)

The UNC label map included the uncinate fasciculus white matter structure, the temporal lobe, the ITG, and the anterior portion of the SS. Using + ROI nodes, only the fibers reaching the medial and lateral fibers running most anteriorly to the OFC and only the fibers reaching the most anteriorly to the TL were retained. The shortest fibers running medially to the OFC were removed as a result.

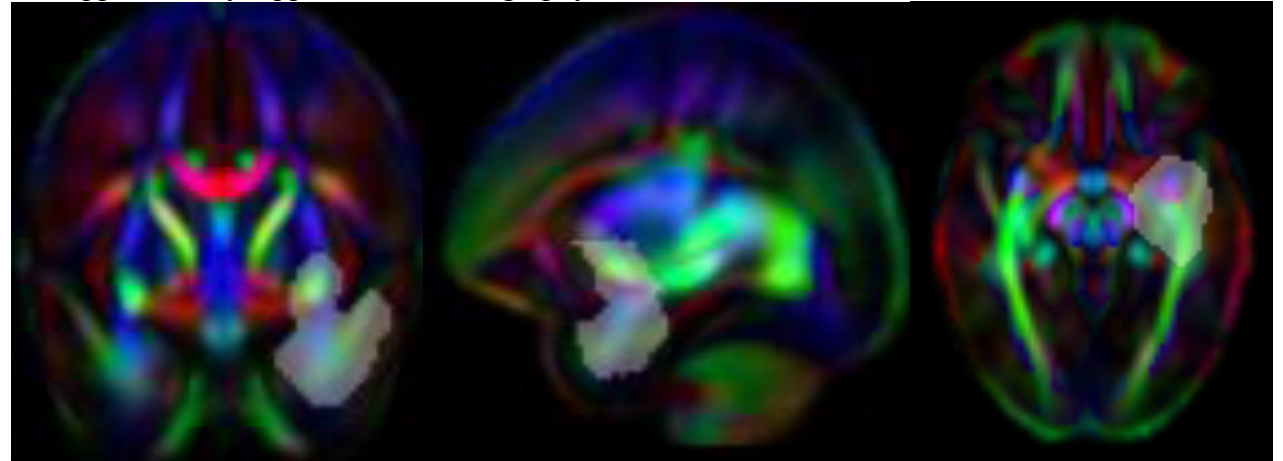
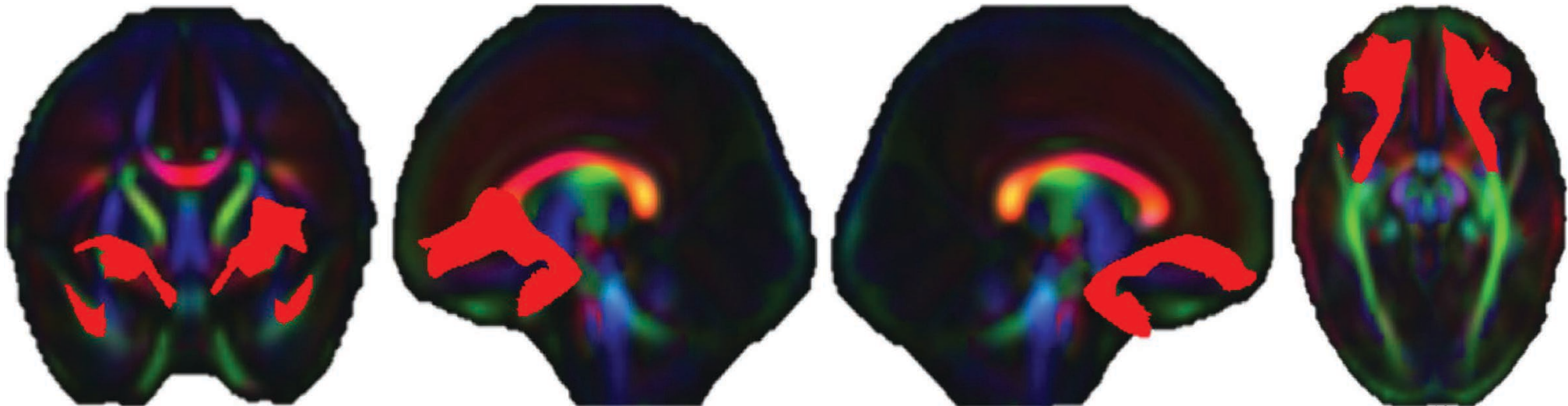


Figure: Hand drawn Label Map delineating the left UNC in the axial orientation of the neonatal atlas color FA image (a) the sagittal orientation (b) and the coronal orientation (c)

Tract Segment	+ ROI 1	+ ROI 2	- ROI
UNC	Anterior TL	OFC (longest medial and lateral fibers retained for analysis, short fibers running medially removed)	Contralateral cortex, CB, FL, tapetum, PHG, PLIC. posterior CR

Fiber Tractography results for the UNC



Association Pathways

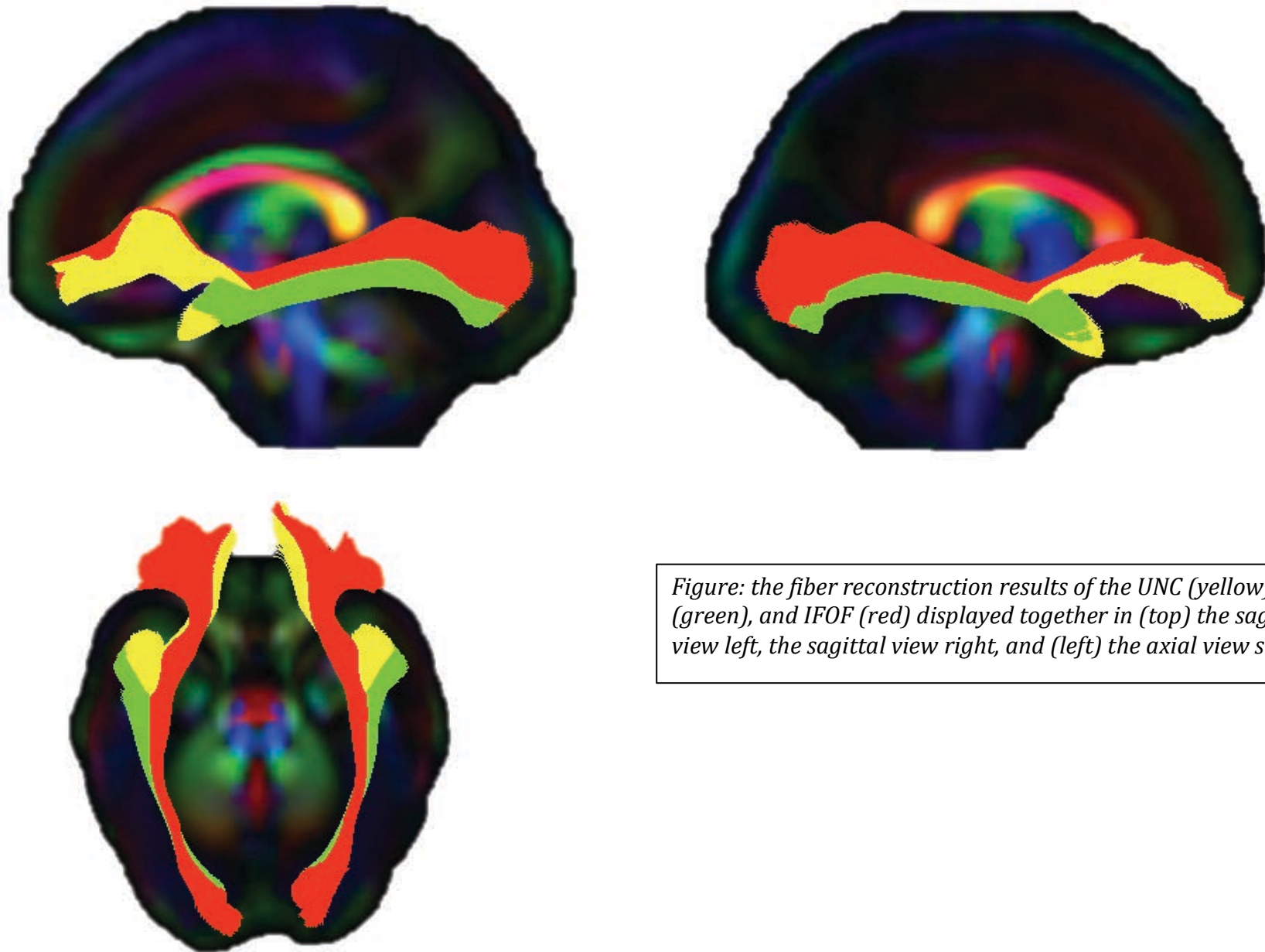


Figure: the fiber reconstruction results of the UNC (yellow), ILF (green), and IFOF (red) displayed together in (top) the sagittal view left, the sagittal view right, and (left) the axial view superior

Projection Pathways: Reconstructing the CorticoThalamic (CT) and CorticoFugal (CF) Tracts

The CF and CT fiber groups were reconstructed together from a single fiber bundle. The label map encompassed the internal capsule drawn in the axial orientation. The IC seed region label included all of the following components of the IC: ALIC, GLIC, PLIC, and RLIC (9). To extract the CT fiber tract from the larger bundle of IC projections pathways, a negative ROI node was placed at the level of the CP just inferior to the LGN. This restricted the CT fibers to those that terminate dorsal to the CP and therefore isolated the CT fiber group from the IC fiber group to be cleaned with more precision. To extract the CF fiber tract from the larger bundle of IC projection pathways, the same ROI node placed at the level of the CP was used—however it was set to positive rather than negative. Therefore, only those streamlines that course through the IC and CP and continue towards the level of the pons fibers were retained and all fibers that terminate dorsal to the CP were removed. Both the CT and CF tracts were separated into four segments based on connections to different cortical regions of interest.

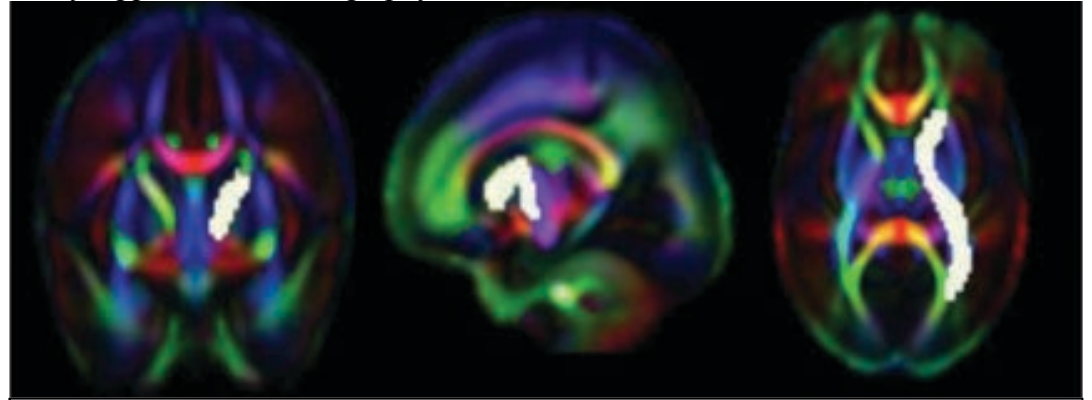


Figure: Hand drawn Label Map delineating the left Internal Capsule (IC) in the axial orientation of the neonatal atlas color FA image (a) the sagittal orientation (b) and the coronal orientation (c)

Tract Segment	+ ROI 1	+ ROI 2	- ROI
PFC	Includes all anterior and superior projections that terminated/originated in the PFC and the ACC, respectively. This pathway coursed through the ALIC, GLIC, anterior 1/3 of the PLIC, and the CR to/from + ROI 2.	Th (for CT), CP (for CF)	Contralateral cortex, CB, Bg Fx
PMC	Includes all superior projections that terminated/originated in the PMC. This pathway coursed through the PLIC and SCR en route to/from + ROI 2. The anterior boundary for the PMC segment was determined based on the natural break in superior frontal projection pathway trajectories created by the abrupt termination of the PFC tract segment in the ACC. The posterior boundary for the PMC tract segments was at the cortex, and located immediately anterior to the Pre-CS.	Th (for CT), CP (for CF)	Contralateral cortex, CB, Bg Fx
MC	Includes all superior projections that terminated/originated in the cortical white matter of the Pre-CG. The cortical target region was defined as the Pre-CS anteriorly and the CS posteriorly.	Th (for CT), CP (for CF) t)	Contralateral cortex, CB, Bg, Fx
PC	Includes all superior and posterior projections that originated/terminated in the PC (posterior to the CS and anterior to the POS)	Th (for CT), CP (for CF)	Contralateral cortex, CB, Bg, Fx

Fiber Tractography results for four tract segments of the CF and CT

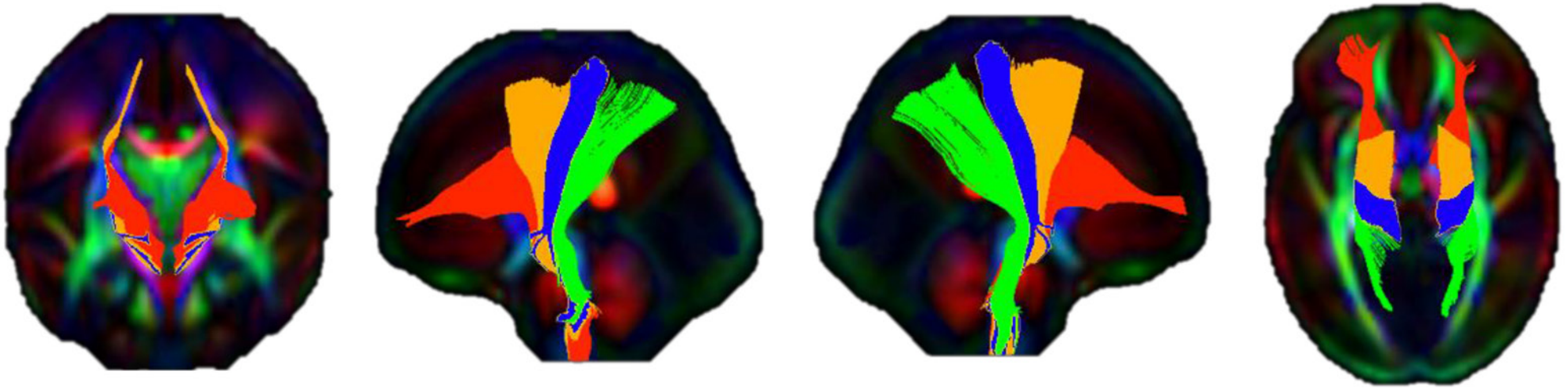
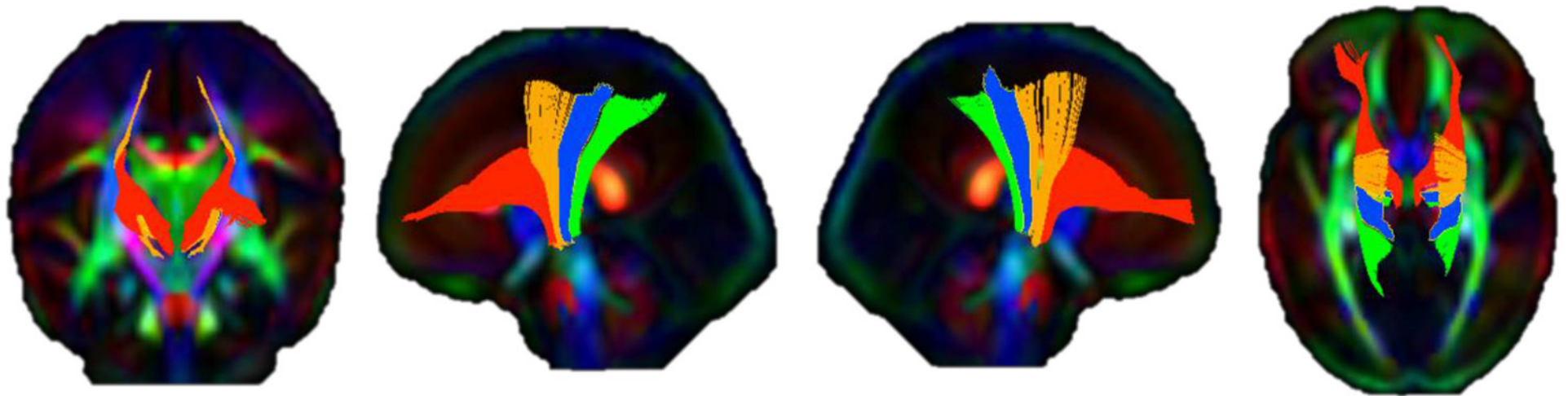


Figure: Fiber Tractography results for the four tract segments of the CorticoFugal (top) and CorticoThalamic (bottom) projection pathways. 3D reconstructions of white matter tract segments from an atlas of neonatal DTI data are displayed with the atlas color FA map. The Left and Right tracts were divided into segments based on cortical target regions for analysis. The tract segment colors are defined as follows: Prefrontal (red), Premotor (orange), Motor (blue), and Parietal (green)



Brain Stem: Reconstructing the Medial Lemniscus (ML)

The ML tract segment ascends from its location in the medulla, which is posterior to CST and courses through the pons until reaching the level of the Th at a location identifiable as posterior to the CP (10). A – ROI node was placed around the fibers belonging to the SCP projecting to the cerebellar cortex

The tract segment runs ipsilaterally so does not include the fibers coursing ventral to the decussation. The trajectory courses through the substantia nigra prior to reaching the Th.

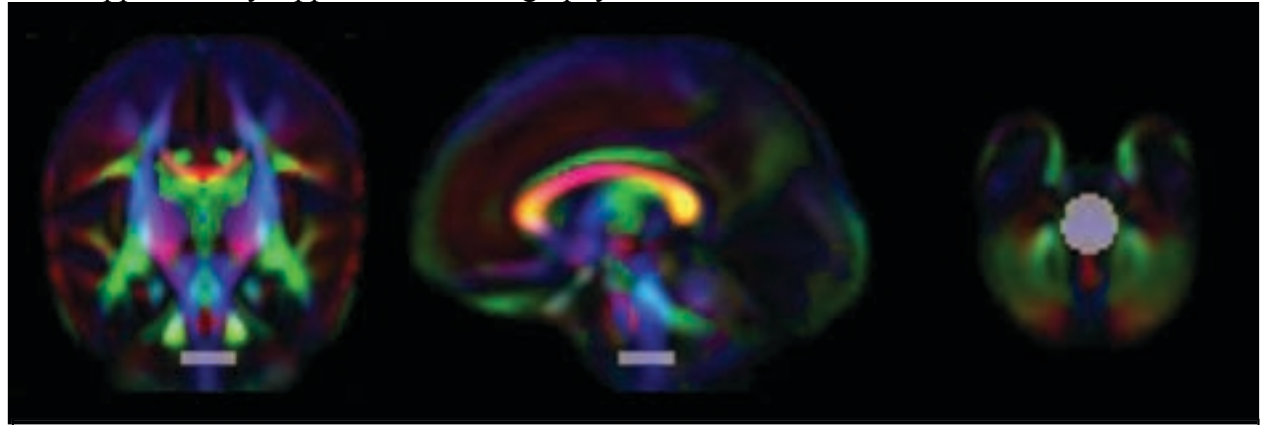
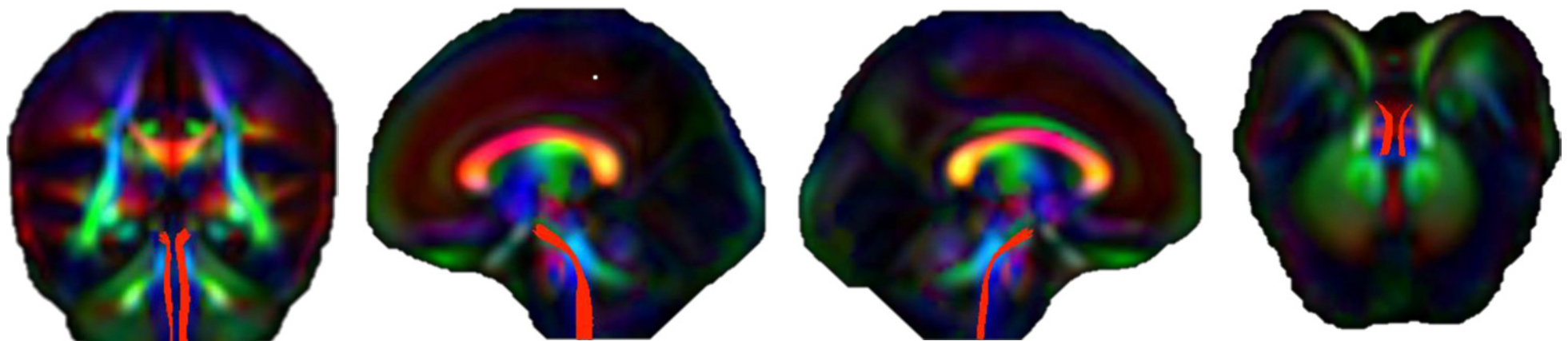


Figure: Hand drawn Label Map delineating the left ML in the axial orientation of the neonatal atlas color FA image (a) the sagittal orientation (b) and the coronal orientation (c)

Tract Segment	+ ROI 1	+ ROI 2	- ROI
ML	ML, Posterior to transpontine or pontine cross tract	Th	CB, SCP

Fiber Tractography results for the ML



Reconstructing the Optic Tract (OT)

The optic tract path could be traced from the LGN of the thalamus to the optic chiasm where artifact streamlines continued ipsilaterally and bilaterally to continue outside of the cerebral cortex potentially as a path resembling that of the optic nerve. This portion of the optic fiber bundle contained artifactual fiber crossings and was unable to resolve so we cropped the streamline to isolate the optic tract using the FVL cut plane tool at the level of the optic chiasm (4). All streams running from the optic chiasm on a dorsal path to the LGN were retained for analysis and served as the "optic tract."

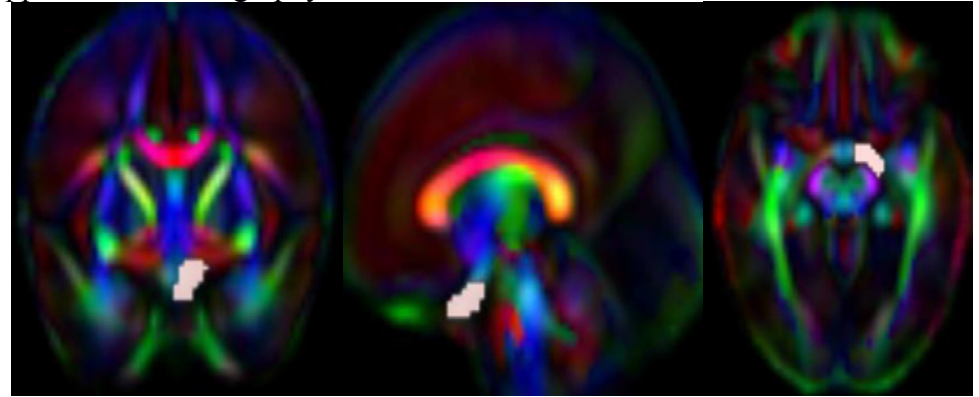
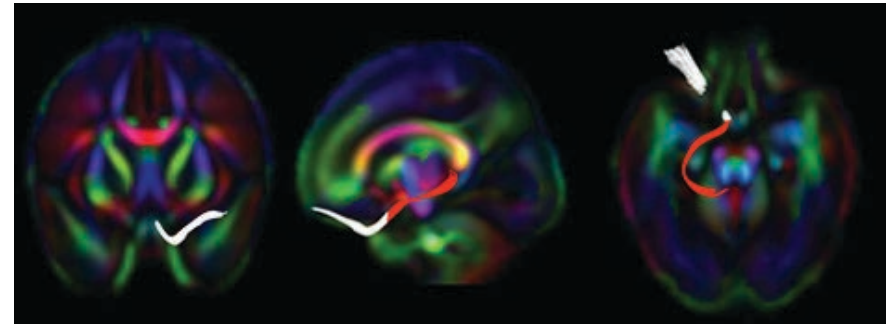


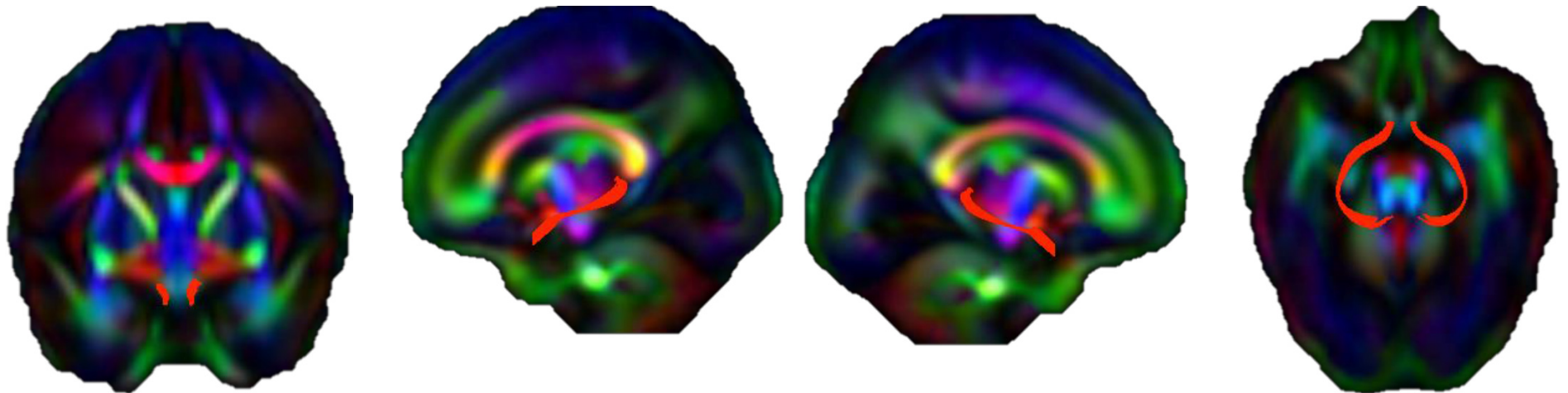
Figure (Top Right): Hand drawn Label Map delineating the left OT in the axial orientation of the neonatal atlas color FA image (a) the sagittal orientation (b) and the coronal orientation (c)

Figure (Bottom Right): Pre-cut Optic Tract with streamlines to optic nerve



Tract Segment	+ ROI 1	+ ROI 2	- ROI
OT	LGN	Optic Tract	

Fiber Tractography Results for the OT



Commissural Pathways: Reconstructing the Corpus Callosum (CC) Tract Segments

For the CC fiber tract segments, a single label map was hand drawn around a series of mid-sagittal slices where the corpus callosum white matter is most red in color. After seeding the raw tract, the entire CC bundle was visualized according to “mean fiber orientation” using a display tool within the **3D slicer** module, Tractography Display (2). This naturally separated the CC into cortical target regions that correspond to the CF and CT divisions for the PFC through PC targets.

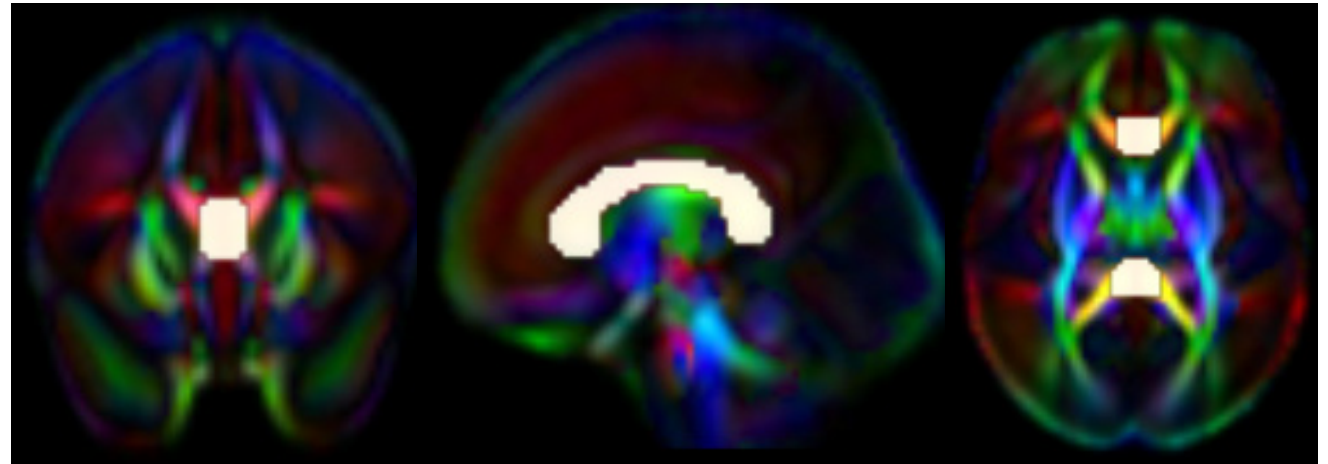


Figure: Hand drawn Label Map delineating the CC in the axial orientation of the neonatal atlas color FA image (a) the sagittal orientation (b) and the coronal orientation (c)

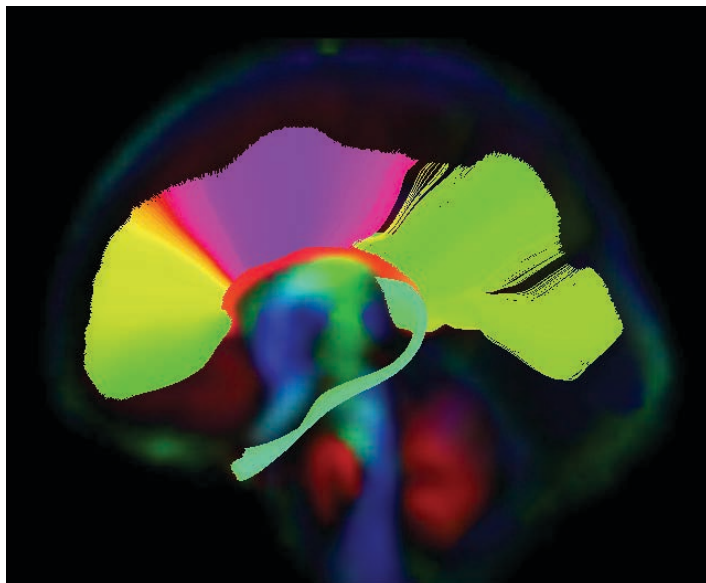


Figure (Top): “Mean Fiber Orientation” color display naturally separates the CC bundle into the cortical divisions for anatomical guidance (2).

Tract Segment	+ ROI 1	+ ROI 2	- ROI
OFC	Rostrum portion of Genu	OFC (Gyrus Rectus)	brainstem, Fx
PFC	Genu	PFC	brainstem, Fx
PMC	Body	PMC	brainstem Fx
MC	Body	MC	brainstem, Fx
PC	Body and Splenium	PC	brainstem, Fx
OC	Splenium	OC	brainstem Fx
TC	Splenium	Tapetum, TL	brainstem, Fx

Fiber Tractography results for the seven tract segments of the CC

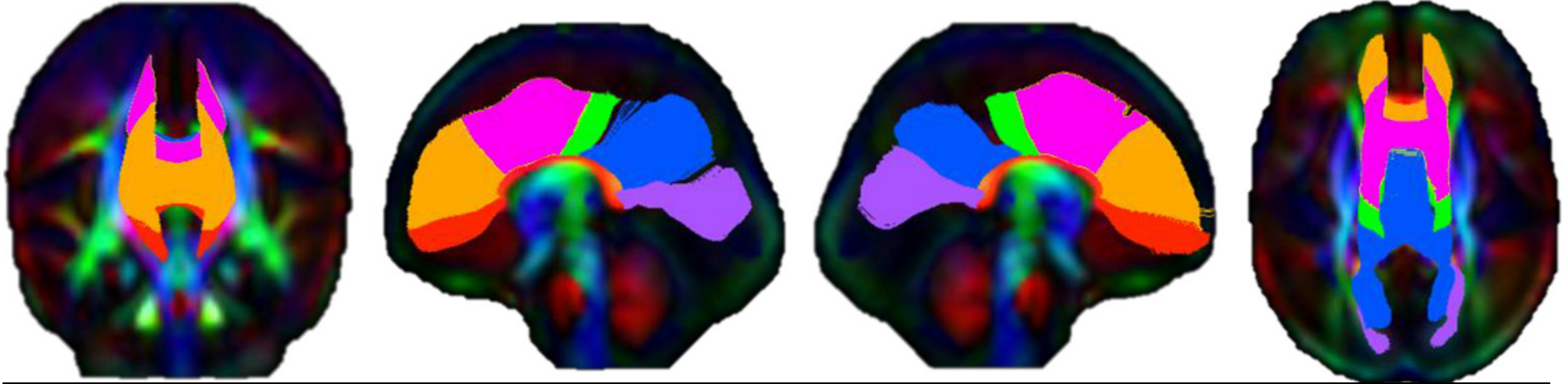
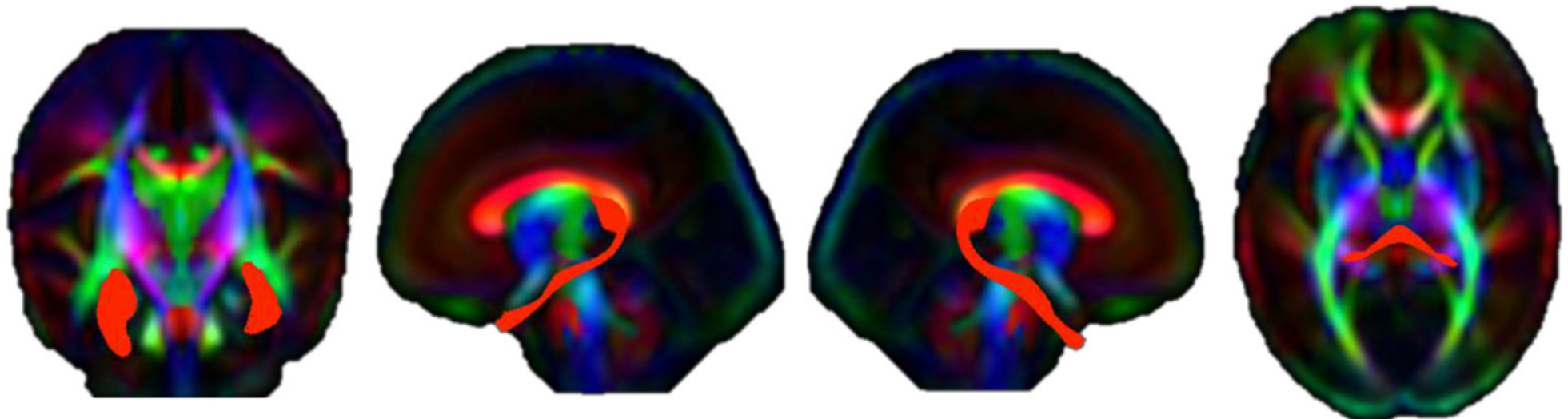


Figure: Fiber Tractography results for six tract segments of the Corpus Callosum (top) and the temporal tract segment (bottom) 3D reconstructions of white matter tract segments from an atlas of neonatal DTI data are displayed with the atlas color FA map. The CC bundle was divided into seven segments based on cortical target regions for analysis. The tract segment colors are defined as follows Orbitofrontal/Rostrum (red), Prefrontal/Genu (orange), Premotor (magenta), Motor (green), Parietal (blue), Occipital/Splenium (purple) and (below) Temporal/Tapetum (red)



Supplementary Appendix 6: Tractography Methods for the EBDS Neonate DTI Atlas
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