Development of MRI Template Library for Nucleus Accumbens

by

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Abstract

Segmentation of medical images is one of the most critical steps in many clinical applications. In brain MRI analysis, image segmentation is commonly used for measuring and visualizing the brain's anatomical structures, for analyzing brain changes. In this project a manual template library of Nucleus Accumbens is created by manually segmenting the MRI images. Nucleus Accumbens is situated in the basal ganglia part of brain and is major component of ventral striatum. A protocol is generated in order to recognize the structure and boundaries of Nucleus Accumbens in the MRI images. The FreeSurfer images are used and manually segmented. The FS-LDDMM algorithm is then used for mapping the segmentations over the rest of the subjects. This template library is a heterogeneous combination of healthy and diseased Nucleus Accumbens structures which were used to train FS+LDDMM and therefore, enable FS+LDDMM to identify Nucleus Accumbens over a diverse range of structural variation which would be present for different neurodegenerative diseases. Cross-validations are done in order to compare the efficiency of the FreeSurfer segmented images and the segmentations performed by FS-LDDMM method. The manual template library generated will be used with a multi-atlas segmentation algorithm like FS-LDDMM to segment large number of images acquired from patients with neurodegenerative disorders so as to get better understanding of the diseases.

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CHAPTER 1:

Introduction

1.1. Motivation

Various technological developments have changed the healthcare dramatically. The advancement of technology in medical science has led to prevention and cure of many diseases and thus saving many lives. This advancement has led to development of technology for recognizing brain disorders.

In this project a manual template library of Nucleus Accumbens is created by manually segmenting the MRI images. Nucleus Accumbens is situated in the basal ganglia part of brain and is major component of ventral striatum. A protocol is generated to recognize the structure and boundaries of Nucleus Accumbens in the MRI images. The manual template library generated will be used with a multi- atlas segmentation algorithm like FS-LDDMM to segment large number of images acquired from patients with neurodegenerative disorders to get better understanding of the diseases.

1.2. Introduction to Brain Anatomy

The human brain is the central organ in the human body which is most complex and important. It controls all senses and functions of the human body such as interpreting the information and preparing an appropriate response to the body. The different parts of the brain can be described by looking at different views, which are: axial view, coronal view and sagittal view. Axial view means viewing brain from above, coronal view means viewing brain from front (anterior) or back (posterior) and sagittal view means viewing brain from the side. Figure 1.1 shows how the three planes- axial, coronal and sagittal helps in viewing brain from different views.

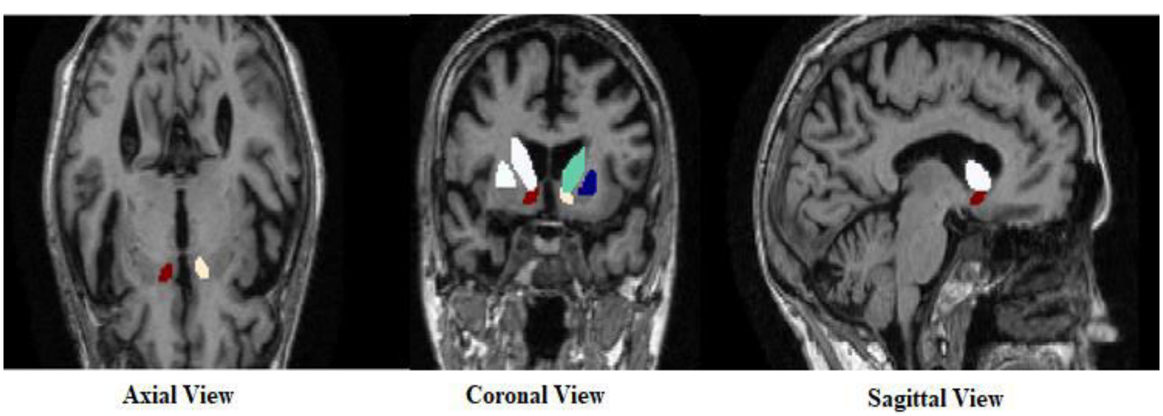


Figure 1.1: Axial, Coronal and Sagittal planes

The brain is protected by skull and consists of three major parts: cerebrum, cerebellum and brainstem. These parts are covered by three membranes called as meninges. The three membranes are: tough dura mater, middle arachnoid mater and delicate pia mater. The deep structures of brain can also be classified as: ventricular system, deep grey nuclei and several white and grey matter structures. The ventricular system consists of brain cavities which are filled with cerebrospinal fluid (CSF). CSF provides cushion to the brain and support the weight of the brain. The ventricles that are filled with CSF are two lateral ventricles, third ventricle and fourth ventricle.

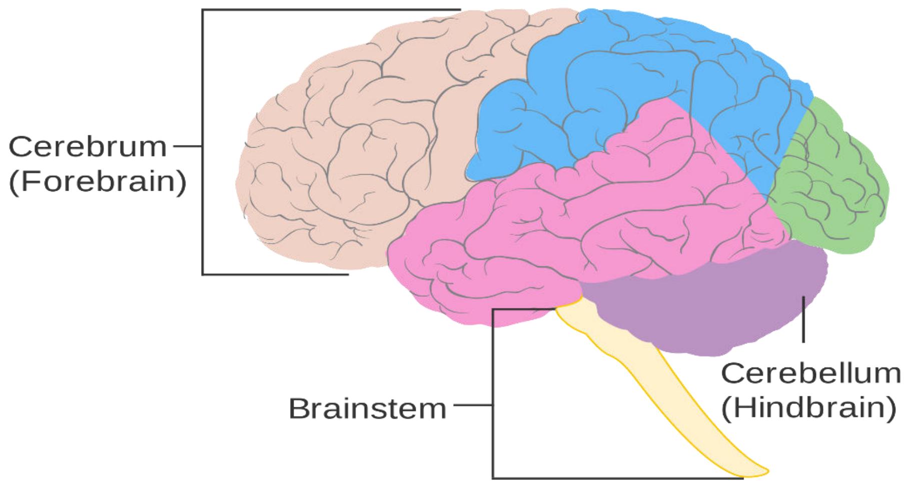


Figure 1.2: Major parts of the brain

Cerebellum:

Cerebellum is a small region in the lower part of the brain. The cerebellum regulates motor movements by receiving sensory information from spinal cord and other parts of the brain. It coordinates movements such as posture, balance, coordination and speech. Any damage to cerebellum causes lack of balance, slower movements and tremors. Cerebellum is divided into two hemispheres and contains a narrow midline zone called as vermis. Cerebellum is separated from cerebrum by a layer of dura mater. Cerebellum can be divided into three lobes based on the surface appearance and divide the cerebellum from rostral to caudal: the anterior lobe, the posterior lobe and flocculonodular lobe.

Brainstem:

Brainstem is the most inferior part of the brain, which connects brain to the spinal cord. Brainstem controls reflexes and basic life functions such as heart rate, breathing and blood pressure. It consists of medulla oblongata, pons and midbrain. Medulla oblongata is mostly made of white matter and connects the higher level of the brain to the spinal cord. It is responsible for autonomous functions such as breathing, heart rate and blood pressure. Pons acts as a bridge between the nerve signals and thus connects superior regions of the brain, medulla oblongata and spinal cord. It is responsible for sensory roles, such as hearing, taste, and facial sensations like touch and pain. The midbrain is the most superior region of the brainstem. It is responsible for vision, hearing, motor control and temperature regulation.

Cerebrum:

Cerebrum is the largest part of the brain, accounting for 85 percent of the brain's weight. The cerebrum controls functions such as language, logic, reasoning and creativity. The outer surface of the cerebrum which is deeply wrinkled and consists of gray matter is the cerebral cortex and beneath cortex is the white matter of the brain. The longitudinal fissure divides the cerebrum in two hemispheres, left hemisphere and right hemisphere. Each hemisphere is further divided into four lobes: frontal lobe, parietal lobe, occipital lobe and temporal lobe. The frontal lobes are situated behind the forehead are responsible for speech, thought learning, emotion, and movement. The parietal lobes are behind the frontal lobes and are responsible for processing sensory information such as touch, temperature and pain. The occipital lobes are at rear part of the brain and are responsible for dealing with vision. The temporal lobes are situated near the temples and responsible for hearing and memory.

1.3. Introduction to Nucleus Accumbens:

Nucleus accumbens is a small part of brain having 1-2 cm3 of cross-sectional area relative to the whole brain (1100 cm3). Nucleus accumbens (NAc) belongs to basal ganglia part of brain and is a major component of the ventral striatum, which also consists of the immediately adjacent parts of caudate nucleus and putamen. Both the cerebral hemispheres have its own nucleus accumbens. Nucleus Accumbens can further be divided into two substructures: Nucleus Accumbens core and Nucleus Accumbens shell. These substructures have overlapping connections but may have different functions. Nucleus accumbens was initially understood as an extension of caudate nucleus.

Nucleus Accumbens has a topographic relationship with septum which makes it distinguishable from rest of the striatum. Also, it is a region of continuity between putamen and caudate nucleus. Various neurological and psychiatric disorders involved NAc. These disorders include depression, obsessive- compulsive disorder, Parkinson's disease, bipolar disorder, anxiety disorder, Alzheimer's disease, obesity, and in drug abuse and addiction.

Role of Nucleus Accumbens:

NAc is generally referred to as pleasure center of the brain and plays an important role in the pleasure and reward. It has a significant role in the motivation, cognitive processing of aversion and response to drugs of abuse. NAc plays important part in the reward circuit in the brain. This is because it has two essential neurotransmitters: dopamine and serotonin. Dopamine is the major transmitter for NAc, which makes it a critical center for experience of reward and pleasure. Nucleus Accumbens is considered as the pleasure center of the brain.

Nucleus Accumbens: Dopamine and its function:

The most important function of Nucleus Accumbens is in reward-circuit. Nucleus Accumbens gets activated through natural behavioral enhancers like motivation, pleasant food intake, money, etc. This leads to activation of NAc neurons along with Dopamine neurons in the ventral tegmental area. An immediate pleasure effect is felt due to increase in dopamine levels. This pleasure also occurs with repeated drug use.

Studies have found that Nucleus Accumbens is not only related to pleasure experience but is related to both reinforcing and aversive stimuli. The dopamine levels increase with reinforcing stimuli and decreases with aversive stimuli. The information related to the positive or negative stimuli can be stored, which can be called upon in future so that we can realize the pleasurable experiences again and can avoid the aversive ones.

Role of Nucleus Accumbens in addiction:

Nucleus Accumbens plays an important role in addiction. Drug or substance abuse causes large amount of dopamine to be released causing the individual to feel immense pleasure. A connection is created between the substance and the feel good and thus the consumption of drugs is continued to feel pleasure.

Part of the medial forebrain bundle (MFB), Nucleus Accumbens is the last target of the reward and pleasure pathway. If an individual think that he needs drugs and crave for drugs, the nucleus accumbens will light up with a surge of electrochemical activity. Key neurochemical events are triggered due to drugs and alcohol which are central to our feelings of both reward and disappointment.

1.4. Software Tools Used:

MRI

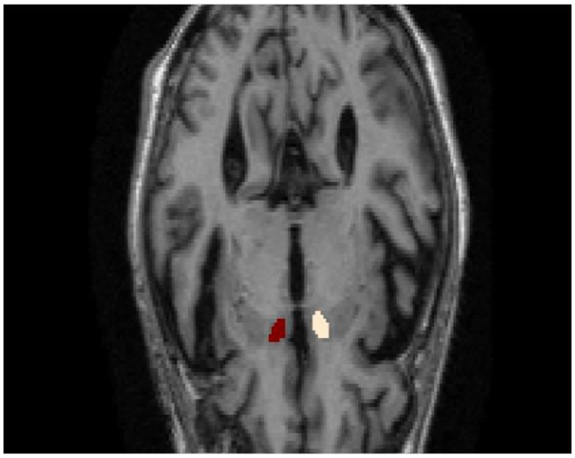
Magnetic Resonance Imaging is an imaging technique which generates the images of the anatomy of organs of the body using magnetic field, field gradients and radio waves. It provides the exquisite details of the brain in all three planes: axial, coronal and sagittal planes. MRI generates images of the parts of the body which can't be seen well with X-rays or CT scans.

MRI is generated with the help of hydrogen atoms which occur in human body in abundance in water and fat. Hydrogen atoms generate radio frequency waves when placed in the magnetic field. The body to be examined is placed in the MRI scanner. The area of concern is surrounded by the magnetic field. The hydrogen atoms present in that area gets excited by absorbing the energy of the magnetic field. When the magnetic field is turned off, the protons come back to the normal state emitting radio signals. These signals are measured and converted into an image. The rate at which the atoms return to the normal state measures the contrast between different tissues. Different type of images will be created by varying the sequence of radio frequency pulses applied and collected. This process uses two parameters: repetition time (TR) and time to echo (TE). Repetition time is the time between two successive pulse sequences and time to echo is the time taken between the delivery of the pulse and receiving of the echo.

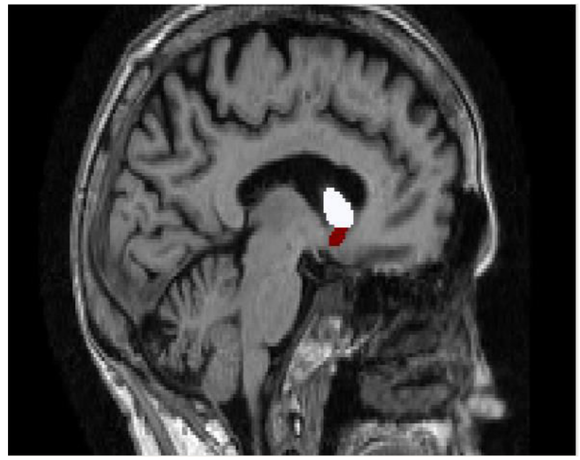
Two most common MRI sequences are: T1-weighted and T2-weighted, where T1 and T2 are two different relaxation times. T1-weighted images are generated by shorter TE and TR times whereas T2-weighted images are produced by longer TE and TR times. The major difference between these images are in cerebrospinal fluid (CSF). The CSF is dark in T1-weighted images and bright in T2-weighted images.

ITK SNAP:

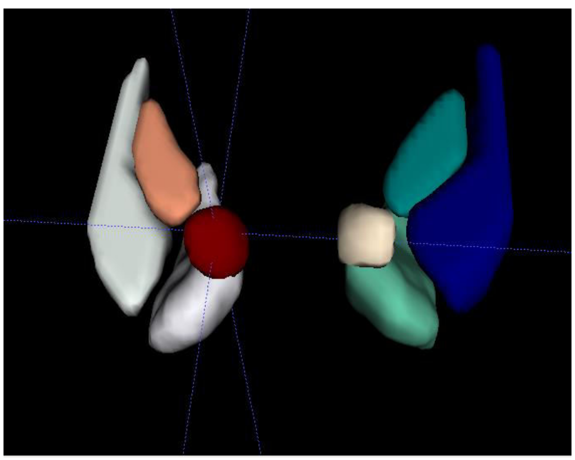
ITK Snap is an interactive software application which is used for segmenting the anatomical structures in medical images. It provides navigation to three-dimensional images and delineating the anatomical regions of interest. This software application is generally used with MRI images and CT scan data sets. The main features of ITK Snap consists of image navigation, manual segmentation and automatic segmentation. The image navigation is done by providing three cut planes which are linked by a common cursor. In case of brain MRI, the three cut planes provided for segmentation are: axial, coronal and sagittal planes. Manual segmentation in the ITKSnap is done by segmenting the anatomical structures using the three planes with the help of labels provided. The segmented structures can be viewed in a three-dimensional view to ensure the reasonable shape. ITKSnap also provides the automatic segmentation functionality using level set method. This functionality helps in segmenting structures which are somewhat homogeneous in medical images.



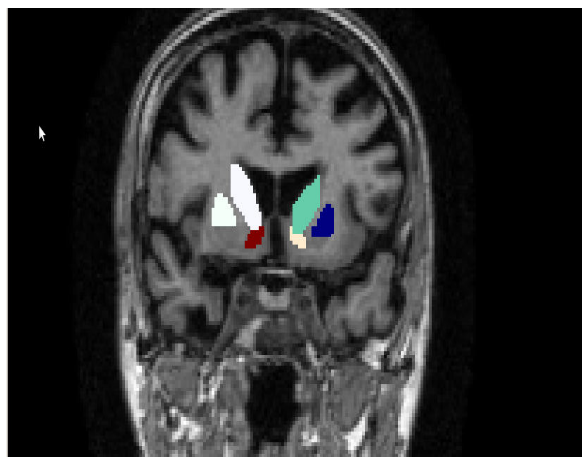
Axial View



Sagittal View



3D View



Coronal View

Figure 1.3: ITK Snap

1.5. FS-LDDMM Algorithm:

FreeSurfer is software tool that helps in analyzing and visualizing the brain anatomy from MRI images which are T1 weighted. FreeSurfer can provide labelling of 37 subcortical brain structures by using its probabilistic approach for voxel classification. This is a fully-automated process, but the segmentation provided by the FreeSurfer is not smooth.

LDDMM (Large Deformation Diffeomorphic Metric Mapping) is based on segmentation using label propagation. This algorithm performs a high-dimensional transformation and does diffeomorphic mapping for smoothing and preserving the topology.

FS-LDDMM combines the probabilistic-based FreeSurfer method with the label propagation based LDDMM method and provides fully-automated subcortical brain segmentation protocol. The segmentations generated by FS-LDDMM method are smooth and require very few or no manual corrections.

The image shown in Figure 1.4 displays the segmentation of Nucleus Accumbens done using FreeSurfer and FS-LDDMM algorithm. It can be seen clearly that the segmentation done by the FreeSurfer is not accurate and have various potholes in the structure which is not possible. The segmentation performed by FS-LDDMM method after providing it with manual segmentations for training is a lot smoother and consistent.

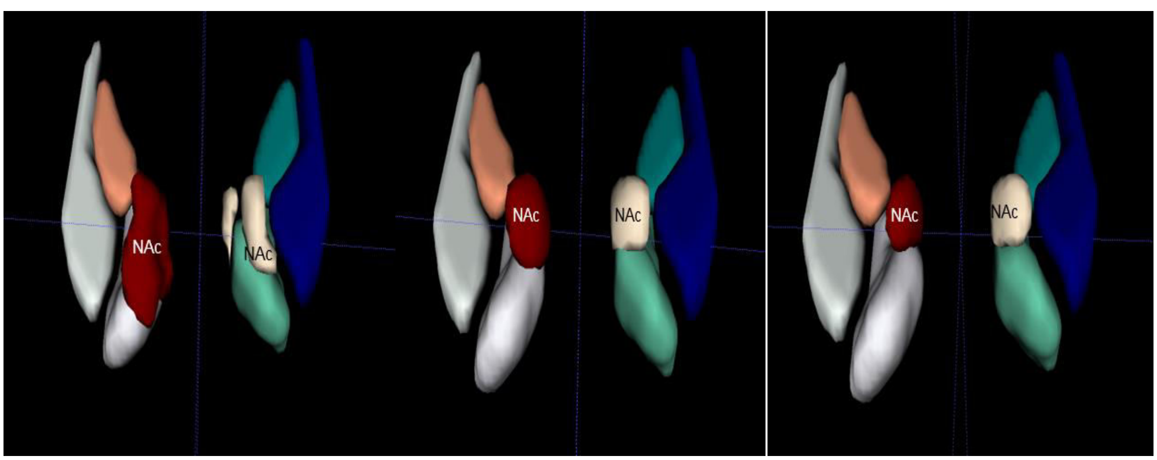


Figure 1.4: (a). Uncorrected NAc; (b). Manually corrected NAc (c). FSLDDMM corrected NAc

CHAPTER 2:

Segmentation of Nucleus Accumbens

2.1. Segmentation Method:

FreeSurfer was initially used for segmenting the Nucleus Accumbens MRI images. FreeSurfer provided the Nucleus Accumbens segmentation library and provided different label to right and left Nucleus Accumbens for differentiation. Further, FS-LDDMM method was applied over all 74 segmentations to make them smooth. However, since the segmentations provided by the FreeSurfer was not efficient, the FS-LDDMM method was not able to generate segmentations that were efficient. The segmentations generated from the above process were further processed to get efficient segmentations.

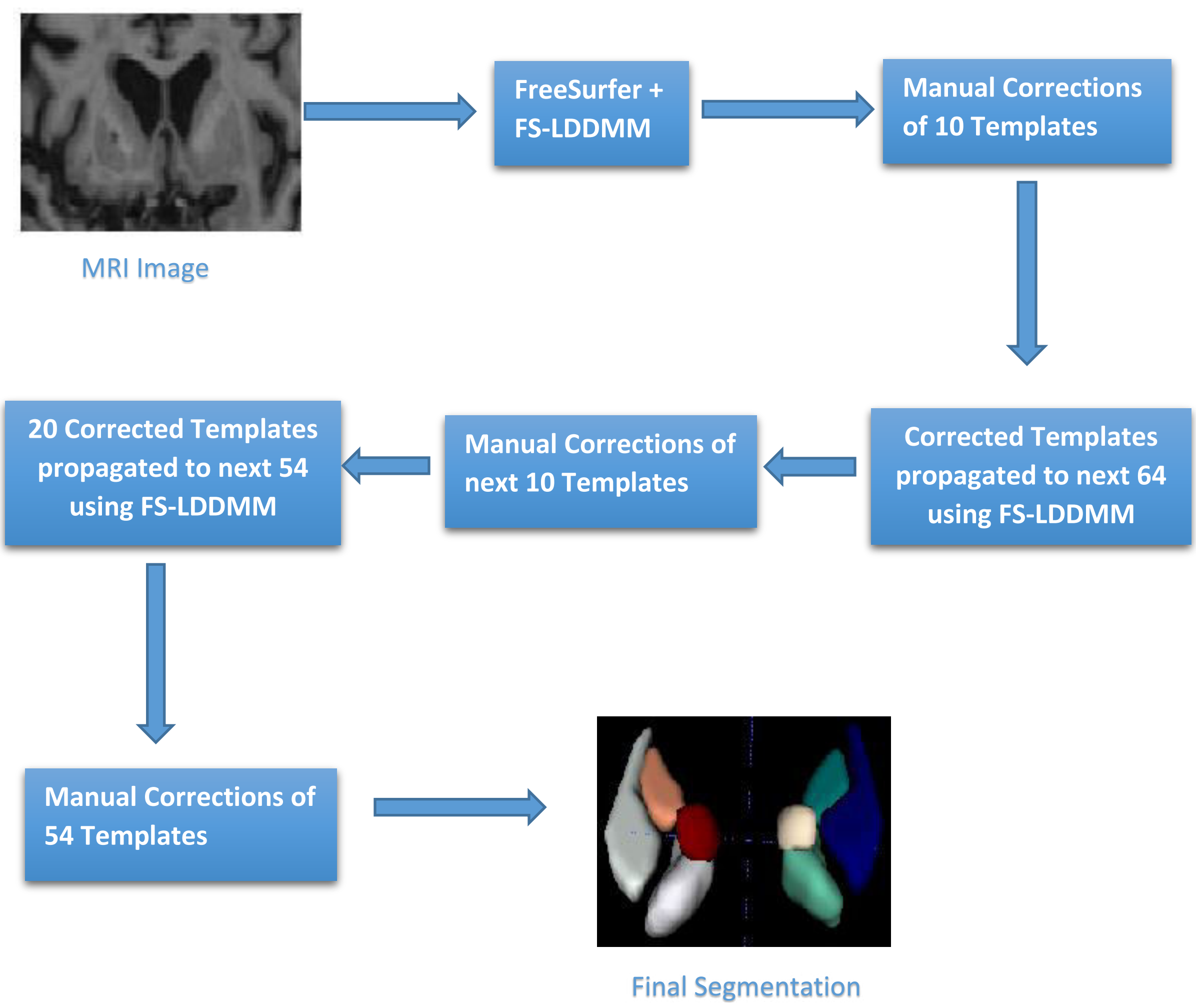


Figure 2.1: Segmentation Pipeline

First 10 segmentations were manually corrected using ITK SNAP and following a segmentation protocol. These corrected segmentations were propagated through the rest of the segmentations using FS-LDDMM. Then, next 10 segmentations were manually segmented and propagated the 20 corrected segmentation though the rest of the 54 segmentations. After this process, majority of the Nucleus Accumbens gets corrected. Only some of the corrections were left which was done manually. This process helped in reducing the amount of correction done, generating smooth segmentations and making the structure more consistent.

2.2. Segmentation protocol followed:

The accumbens is gray matter nucleus located in the basal ganglia, adjacent to caudate and putamen. For differentiating NAc, it is labelled with two labels, different from the ones used for other parts of the brain. The right NAc is labelled with ITK SNAP label 26 (beige color) and left NAc is labelled with ITK SNAP label 58 (Crimson color-shade of red). Nucleus Accumbens is generally traced in the coronal plane. Axial and sagittal planes are used in aiding the segmentation of Nucleus Accumbens. The average number of slices that cover Nucleus accumbens are generally from 7-12.

Before beginning with the segmentation, each image's contrast was adjusted so that the borders between the gray and white matter are clear and consistent. While segmenting any voxel, all three views (axial, sagittal and coronal) were considered. The image contrast is adjusted in the ITK Snap's Image layer inspector, where the contrast adjustment is done to automatic adjustment.

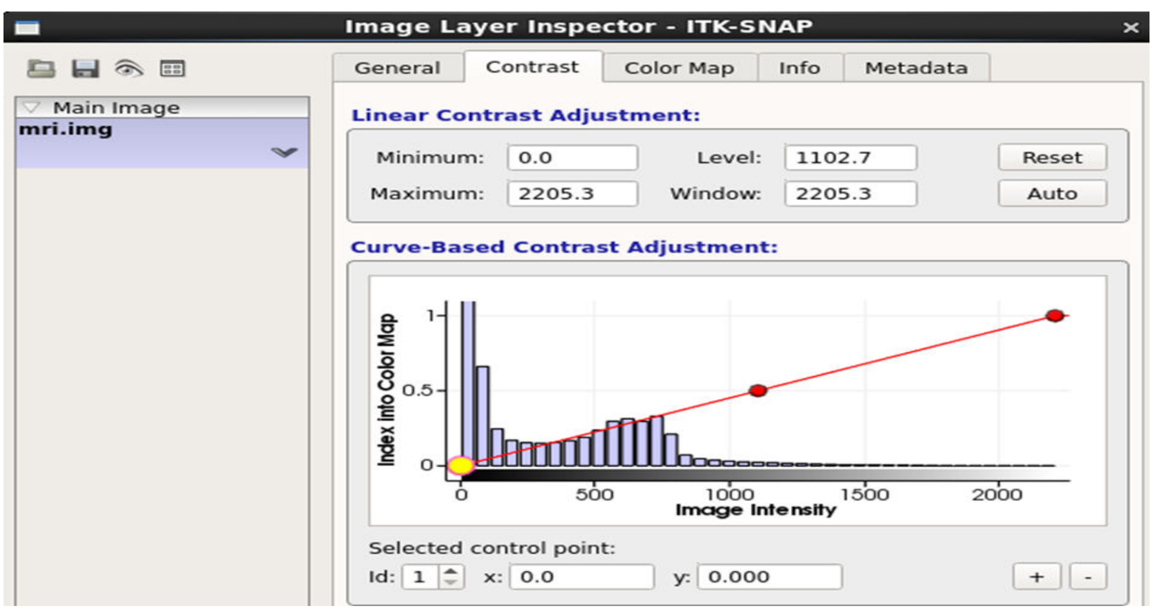


Figure 2.2: Figure showing the basic contrast in Image Layer Inspector

In automatic contrast adjustment, the maximum intensity is brought down from the intensity value where only one or two indexes exist for that value to the intensity value where certain number of the indexes exist to hold that value. Further, the intensity level is set to the half of the maximum intensity adjusted. This intensity adjustment allows better view of the MRI image, such that the boundaries between gray and white matter are clearer

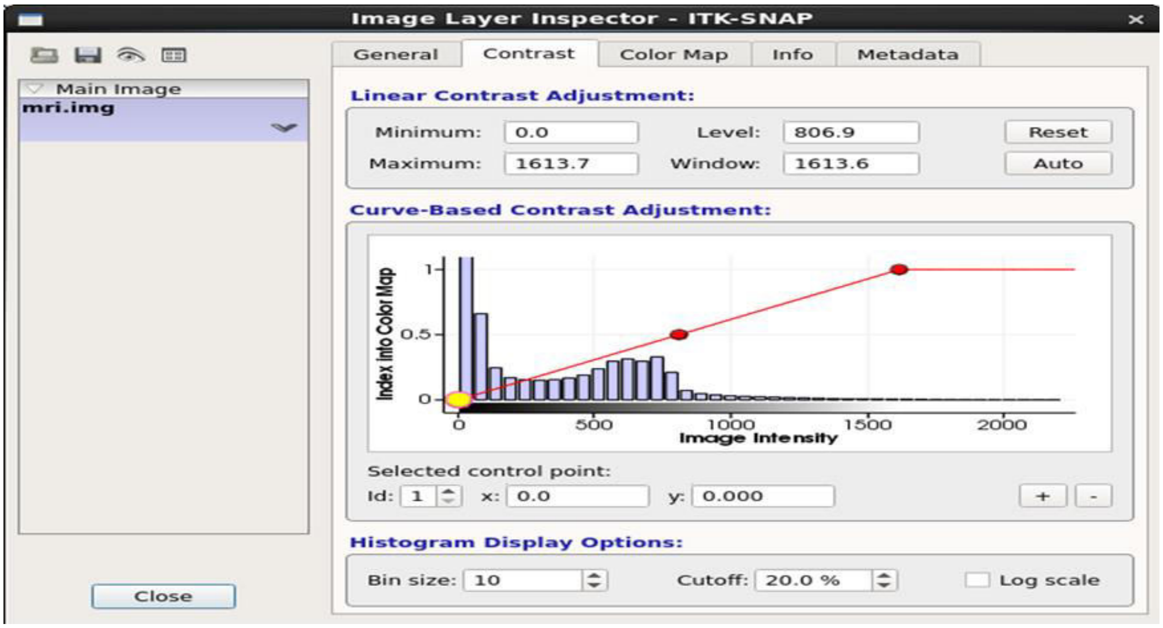


Figure 2.3: Figure showing the Automatic Contrast Adjustment

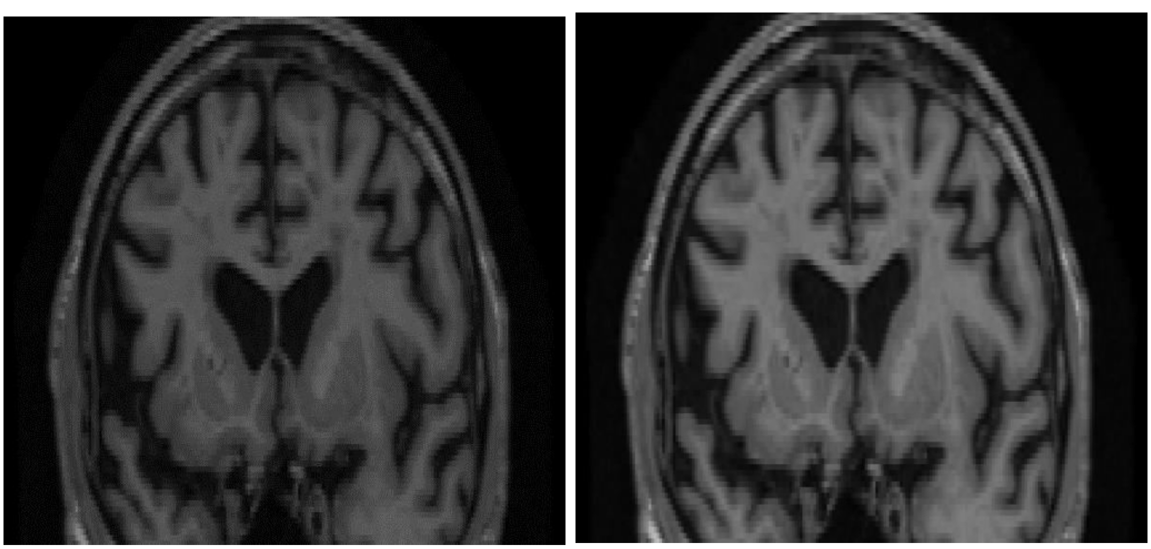


Figure 2.4: (a) Image with basic contrast (b) Image after automatic contrast adjustment

The contrast adjustment helps in better visualization of the boundaries between the gray and white matter. From image 2.4, it is slightly visible that the contrast of the image has changed after adjusting it in the ITKsnap.

Further, Nucleus Accumbens is closely related to caudate and putamen, such that there is no clear distinction between the boundaries of these structures. This is the reason a convention is required to segment it. The caudate and putamen are separated from each other by internal capsule, since internal capsule is having higher intensity and is thus very light in color than caudate and putamen. The Nucleus Accumbens is distinguished slightly from caudate in terms of intensity. This is because Nucleus Accumbens is slightly darker grey than the lighter grey intensity of caudate. The separation of Nucleus Accumbens from caudate can be done by drawing a line with some angle, connecting the most inferior point of lateral ventricles to the most inferior point of the internal capsule. While segmentation, this line is considered as an approximation and not as an exact straight line.

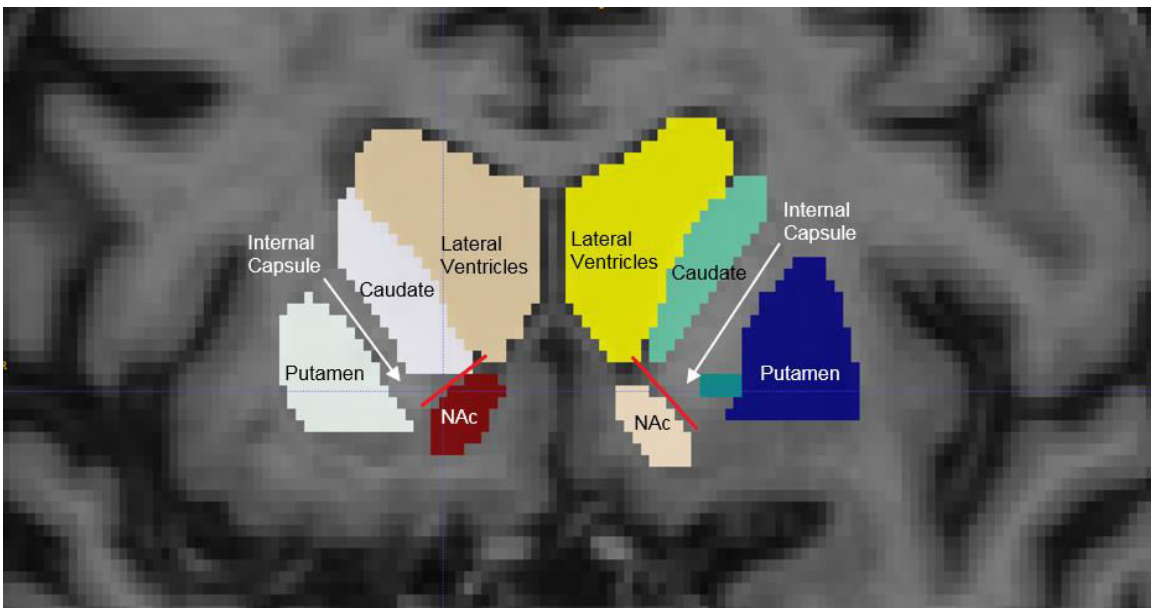


Figure 2.5: Boundary dividing Nucleus Accumbens from Caudate

The separation of Nucleus Accumbens from putamen can also be done in a similar way as it is separated from caudate. For separating putamen from Nucleus Accumbens, a vertical line is drawn downwards from the point where the line drawn for distinguishing caudate from NAc meets the internal capsule. Also, in the sagittal view, the Nucleus Accumbens and putamen are never present in the same slice. In other words, the putamen starts to arrive only when Nucleus Accumbens is totally vanished from the slices.

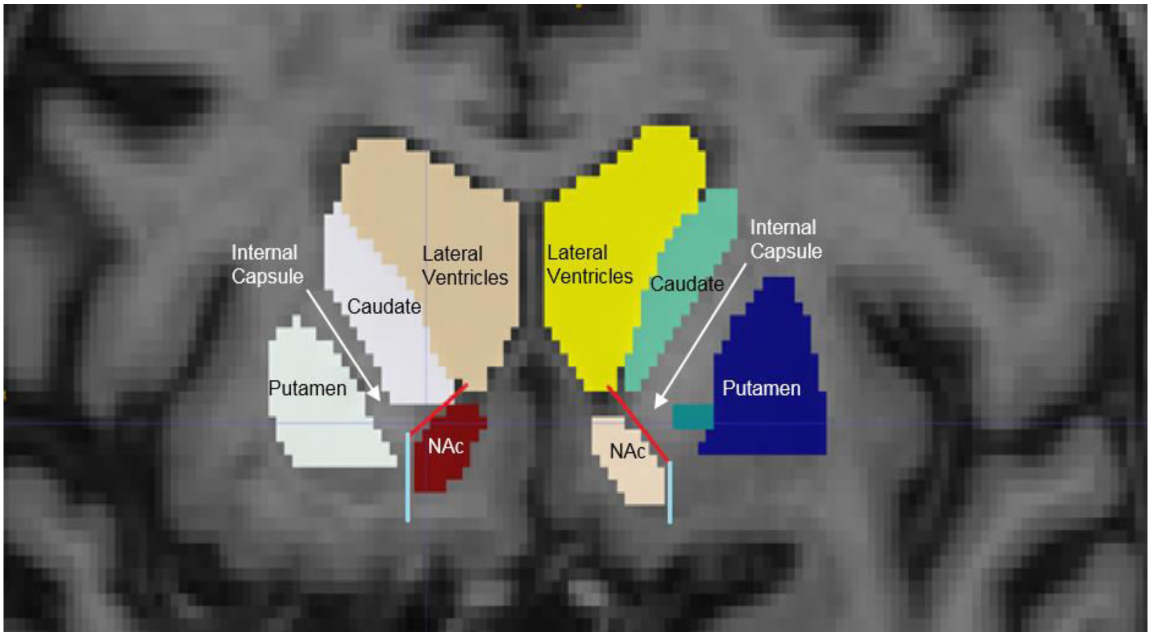
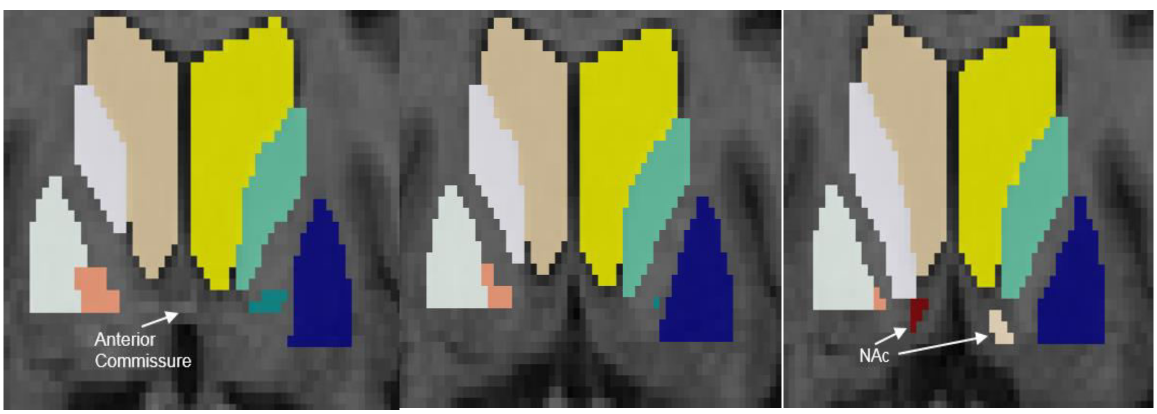


Figure 2.6: Boundary separating Nucleus Accumbens from Putamen

Further, Nucleus Accumbens is closely related to Anterior Commissure as well. Anterior Commissure is one of the two tracts that connects hemispheres. When Anterior Commissure disappears from the coronal view, the Nucleus Accumbens starts to appear after a few slices (generally one or two) of the anterior commissure and makes up the most posterior slices of NAc.



(a) First slice having Anterior Commissure (b) Second Slice (c) Third Slice NAc appears

Figure 2.7: Three continuous slices depicting appearance of NAc after Anterior Commissure in Coronal View

Globus Pallidus is interconnected with Putamen. In the sagittal view, Nucleus Accumbens starts to appear when Globus Pallidus has started to disappear from the view and is having its last slices.

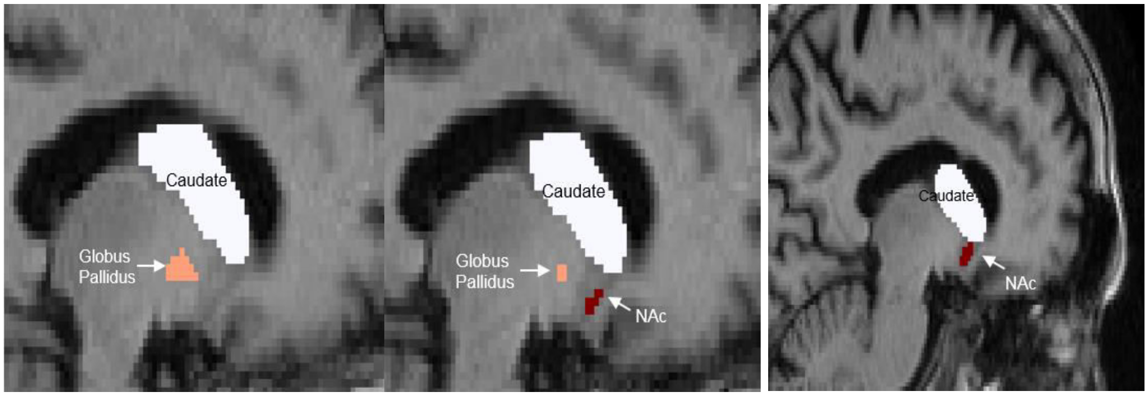


Figure 2.8: 3 continuous slices depicting appearance of NAc after disappearance of Globus Pallidus in Sagittal View

Similarly, in the coronal view, Nucleus Accumbens appear when Globus Pallidus starts to disappear and is overcome by internal capsule and putamen.

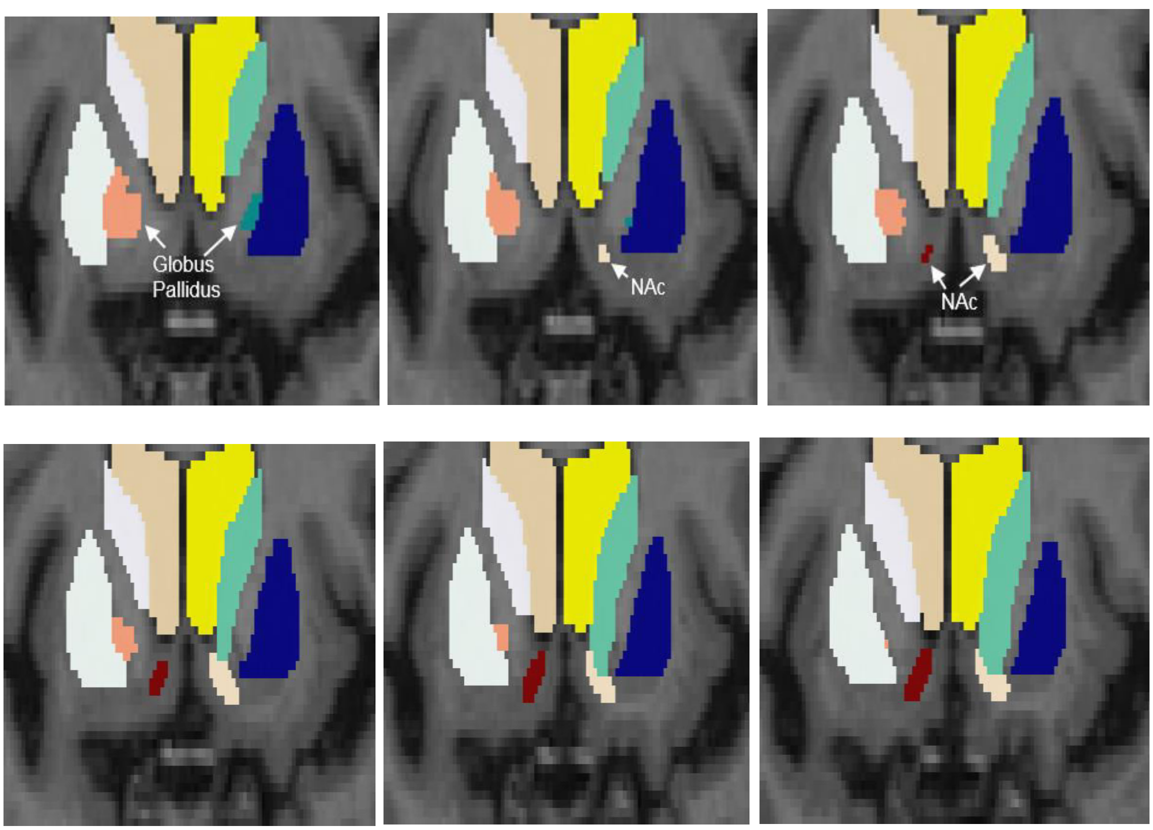


Figure 2.9: Six continuous slices depicting appearance of NAc in coronal plane after disappearance of Globus Pallidus.

2.3. Problems Faced

1. Nucleus Accumbens is a small part of the brain placed adjacent to caudate and putamen and is closely related to these parts such that there is no clear distinction between them.

   As seen in Figure 2.10, there is no clear distinction can be seen between the caudate and NAc. This lead to confusion in segmenting the boundary voxels of NAc which are near to the Caudate. To our convenience, Caudate was already segmented and helped us in knowing the boundary voxels. Also, the protocol mentioned above was followed to segment the boundaries of NAc.

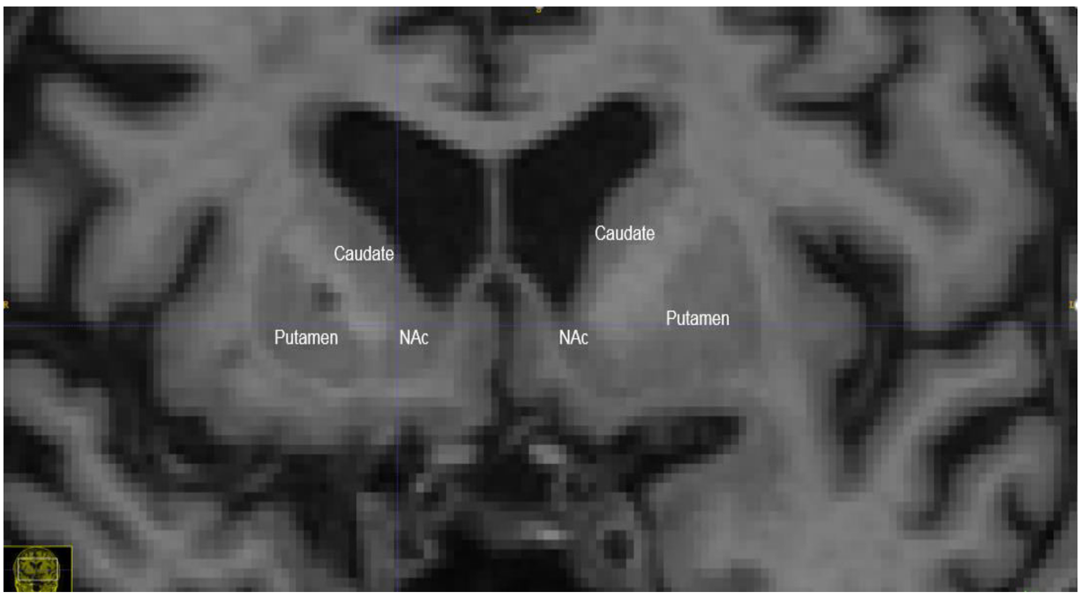
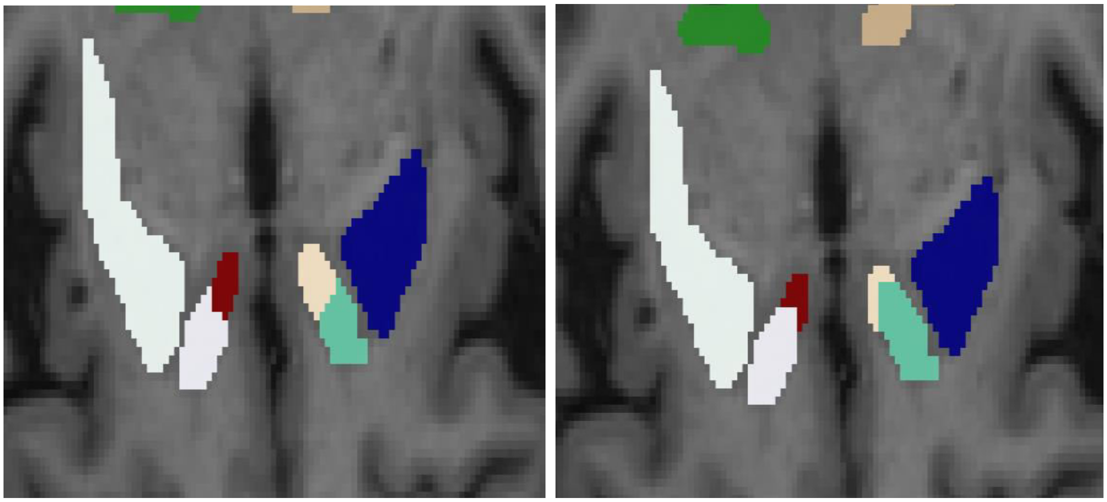


Figure 2.10: No clear distinction between Caudate and Nucleus Accumbens

2. The FS-LDDMM method propagates the manually segmented templates over the rest of the templates resulting into the segmentations which are nearly accurate and smooth. When this approach is applied over Nucleus Accumbens, the mapped segmentations of NAc gets fused into caudate. These segmentations need to be corrected further manually such that NAc no longer merges into caudate.



(a) NAc fused with Caudate (FS-LDDMM) **(b) NAc corrected manually**

Figure 2.11: Fused parts between NAc and Caudate corrected manually

3. Nucleus Accumbens is termed as the neighbor of caudate. But in some cases, there is large gap between the caudate and nucleus accumbens, and in some cases the Nucleus Accumbens seems to be dislocated little above than the normal position.

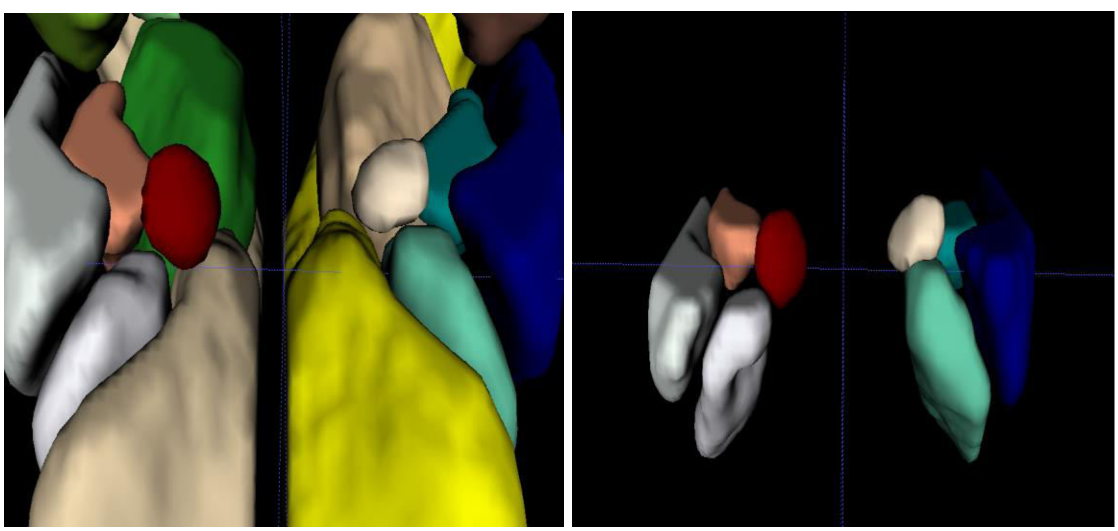


Figure 2.12 (a): Larger gap between NAc and Caudate; Figure 2.12 (b): NAc dislocated

Figure 2.9 shows two cases, one in which there is more gap than normal between Nucleus Accumbens and Caudate. In second case, Nucleus Accumbens is dislocated little above the normal position. Some other example of such cases is shown as follows:

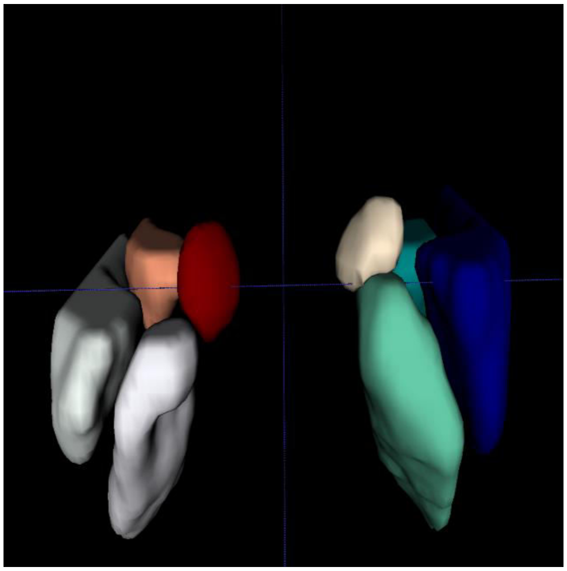
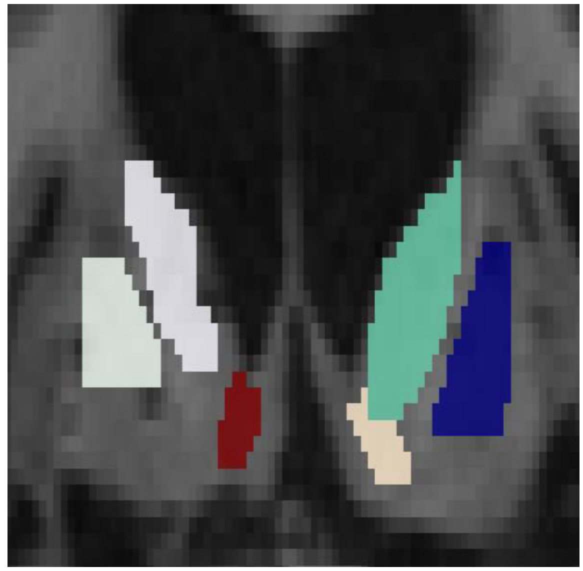



Fig 2.13 (a): Large gap between NAc and Caudate **Fig 2.13 (b): Segmentation showing the gap**

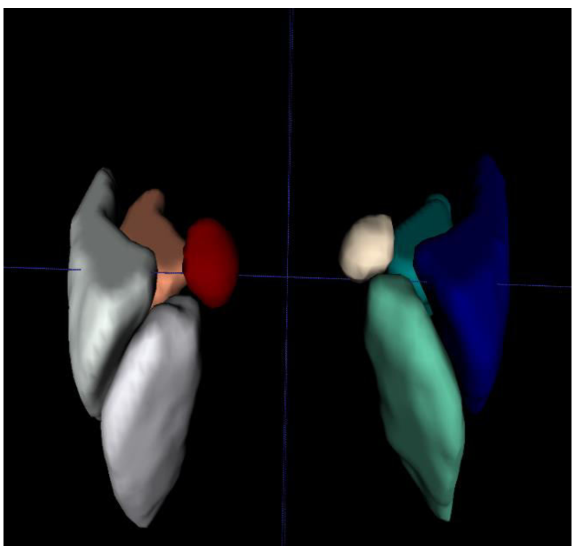
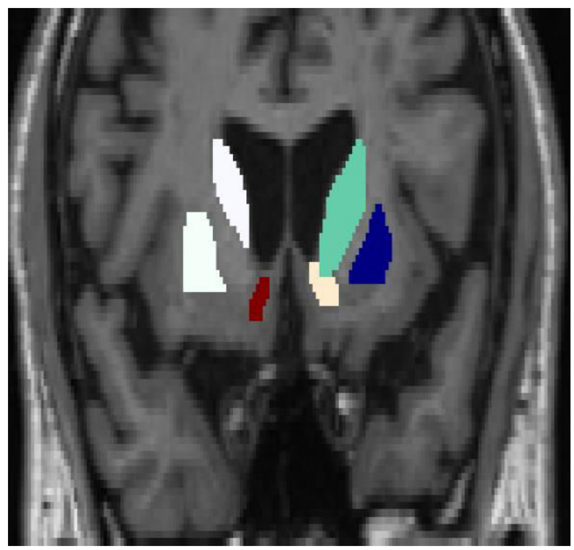



Fig 2.14 (a): NAc dislocated **Fig 2.14 (b): Segmentation of NAc dislocation**

During the segmentation of 74 templates, 4 such cases were observed in which the caudate and Nucleus Accumbens were having an abnormal relationship. That is, in two of the cases the Nucleus Accumbens seem to have dislocated and moved little above than the normal position. The other two cases observed that there is more space than normal between Caudate and NAc. The four templates I which this was observed were:

- ADNI74.77
- ADNI74.102
- ADNI74.1081
- ADNI74.1090

CHAPTER 3:

Results and Discussion

3.1. Cross-validation

The dice coefficient is used for comparing the performance of FreeSurfer and FSLDDMM segmentation method. Dice coefficient helps in validating how similar two images are. Dice coefficient can be defined as the size of the overlap of the two segmentations divided by the total size of the two objects. The Dice coefficient is computed for all 74 segmentations done by FreeSurfer and FS-LDDMM method. The manual segmentations are considered as the ground truth, related to which the FreeSurfer and FS-LDDMM segmentations are compared. The results of the cross-validations show that the segmentations done using FS-LDDMM method are more like the manual segmentations. Whereas, the segmentations done by FreeSurfer gives very low Dice coefficient, which shows that these segmentations are dissimilar to the manual segmentations performed.

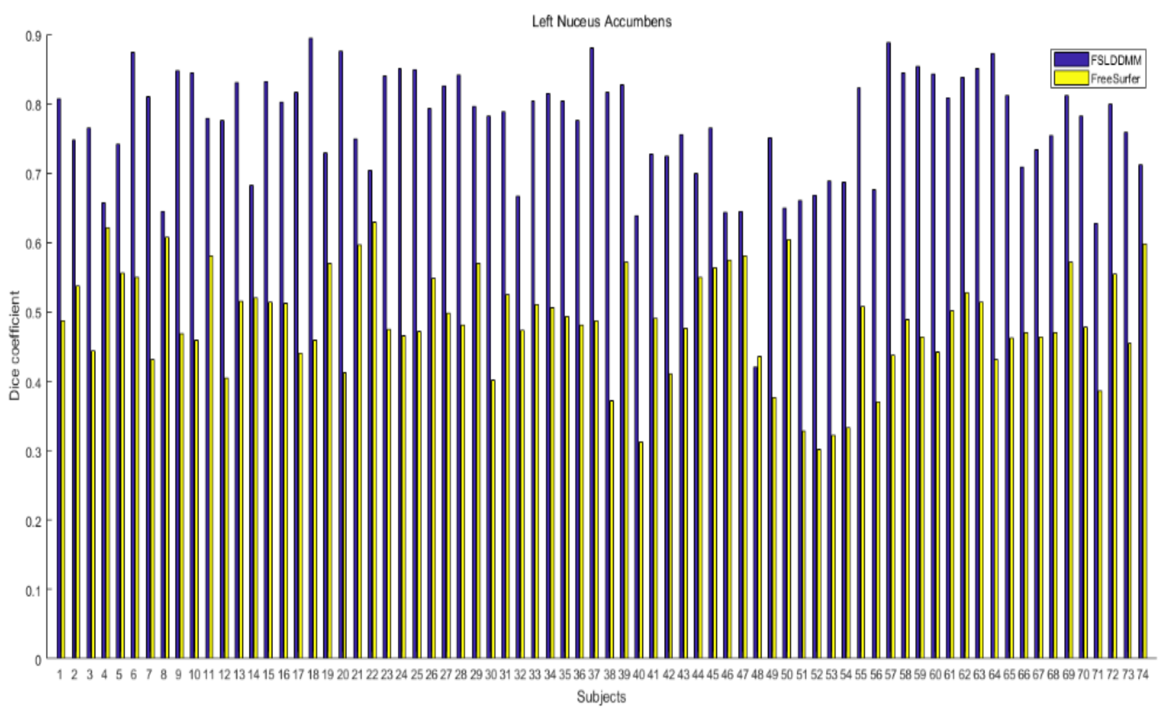


Figure 3.1 (a): Cross-validation results for Left NAc

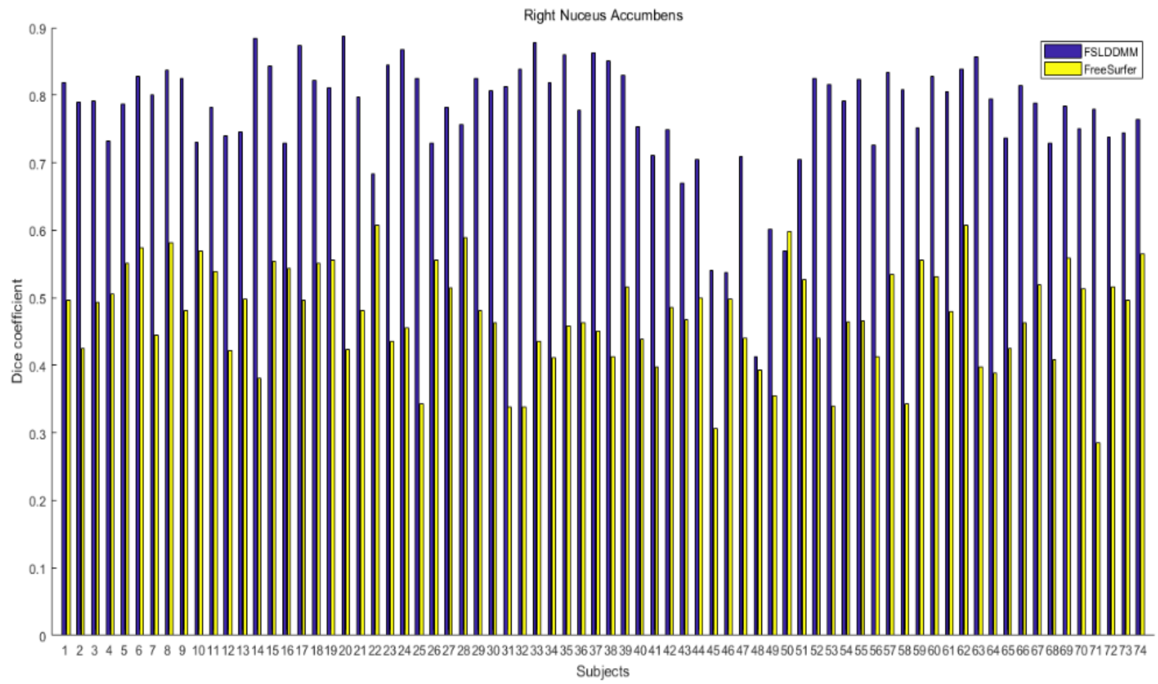


Figure 3.1 (b): Cross-validation results for Right NAc

It can be clearly seen from the Figure 3.1, the Dice coefficient of all the segmentations done by FSLDDMM are greater than the Dice coefficient of FreeSurfer segmentations. Further, it is also clear from Figure 3.2, the average Dice coefficient of FreeSurfer segmentation is below 0.5 for both left and right Nucleus Accumbens, which is very low as compared to the average Dice coefficient of FSLDDMM segmentations which is around 0.8.

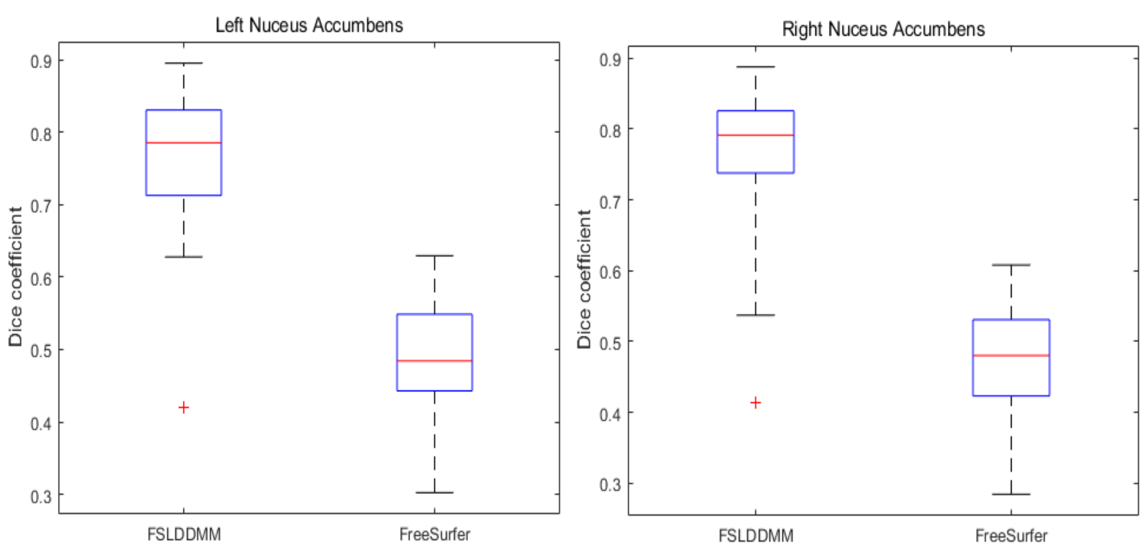


Figure 3.2: Cross-validation results for Left and Right NAc

3.2. Quickchecks

The Quickchecks were obtained for segmentations done by FreeSurfer, FS-LDDMM and manual segmentations.

Figure 3.3 shows Quickchecks for segmentations done by FreeSurfer, FS-LDDMM method and manually. It can be seen in Figure 3.3 (a) clearly that segmentations done by FreeSurfer is not accurate. Further the 3D view also depicts that both left and right NAc are very rough and inaccurately segmented.

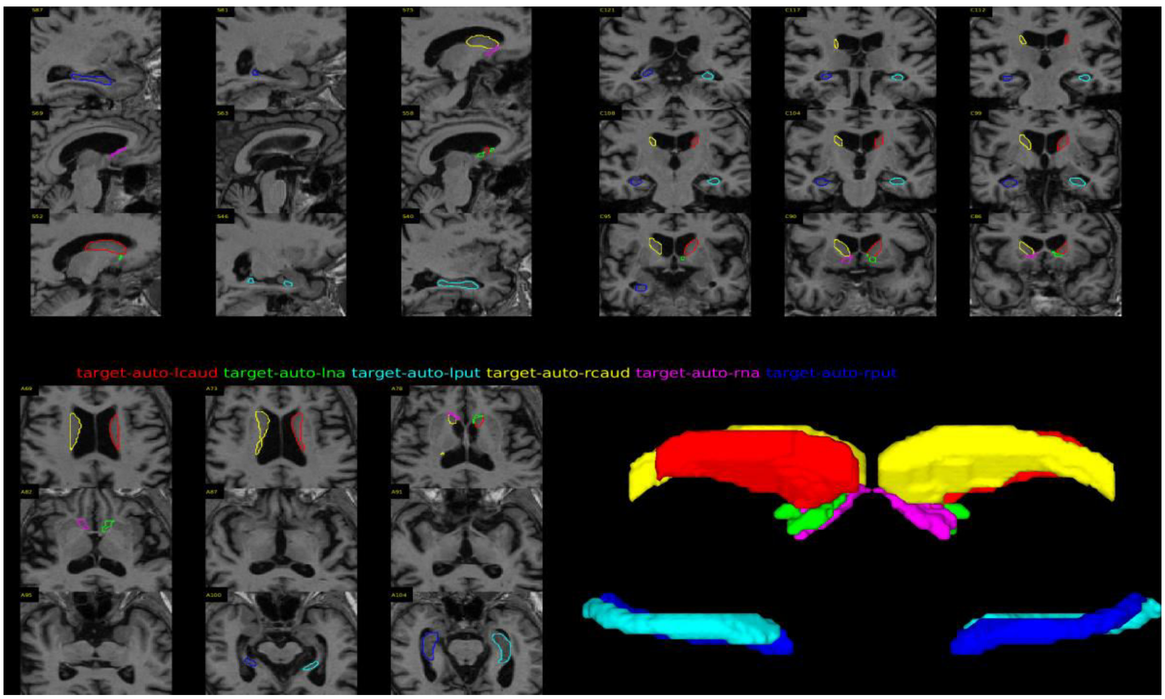


Figure 3.3: (a). Quickchecks for FreeSurfer segmented Nucleus Accumbens

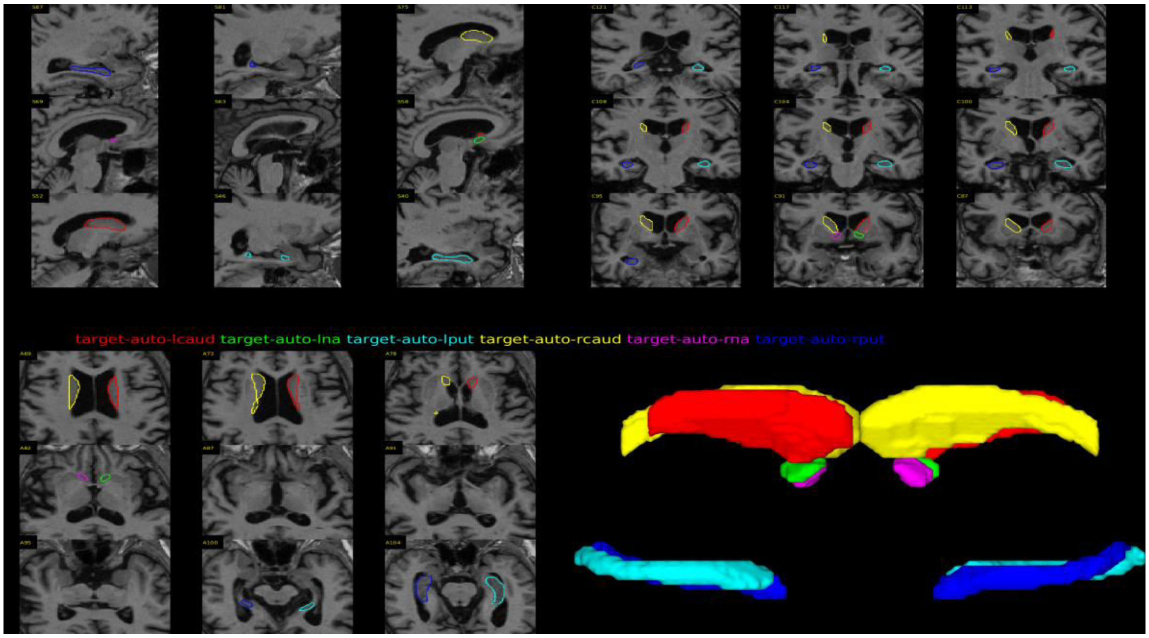


Figure 3.3: (b) Quickchecks for FS-LDDMM segmented Nucleus Accumbens

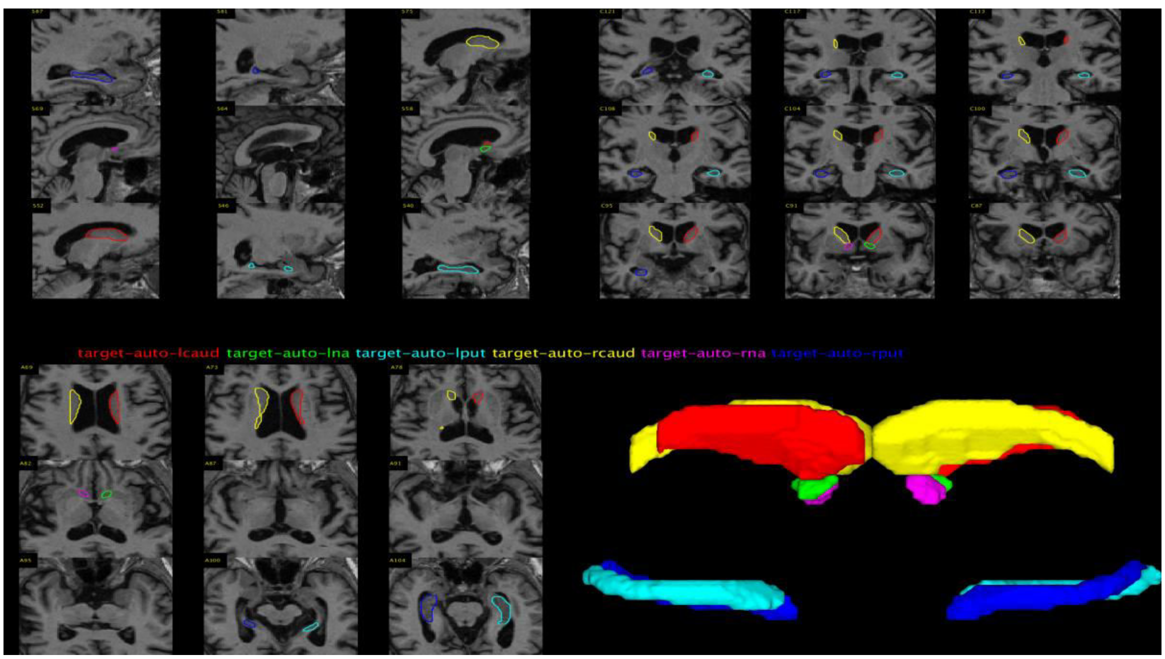


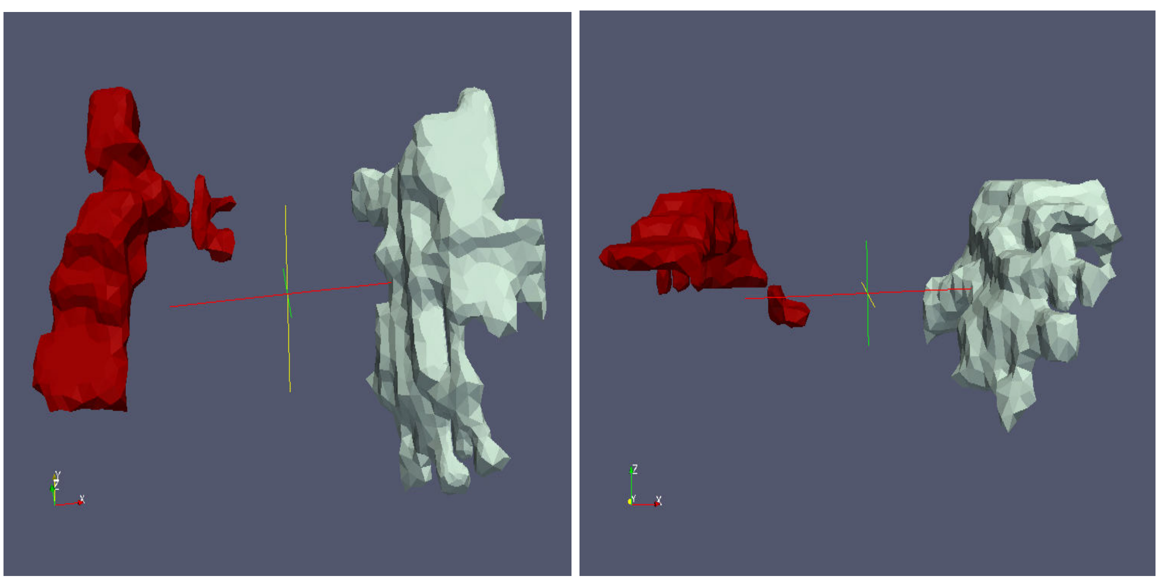
Figure 3.3: (c). Quickchecks for manually segmented Nucleus Accumbens

The segmentations done by FS-LDDMM method are smooth and are more accurately segmented than FreeSurfer segmentations. Since, FS-LDDMM method resulted into merging of NAc with Caudate, manually segmentations were done. The manually segmented segmentation is shown in Figure 3.3 (c). Manually segmented NAc is smoother, accurate and do not merge with Caudate.

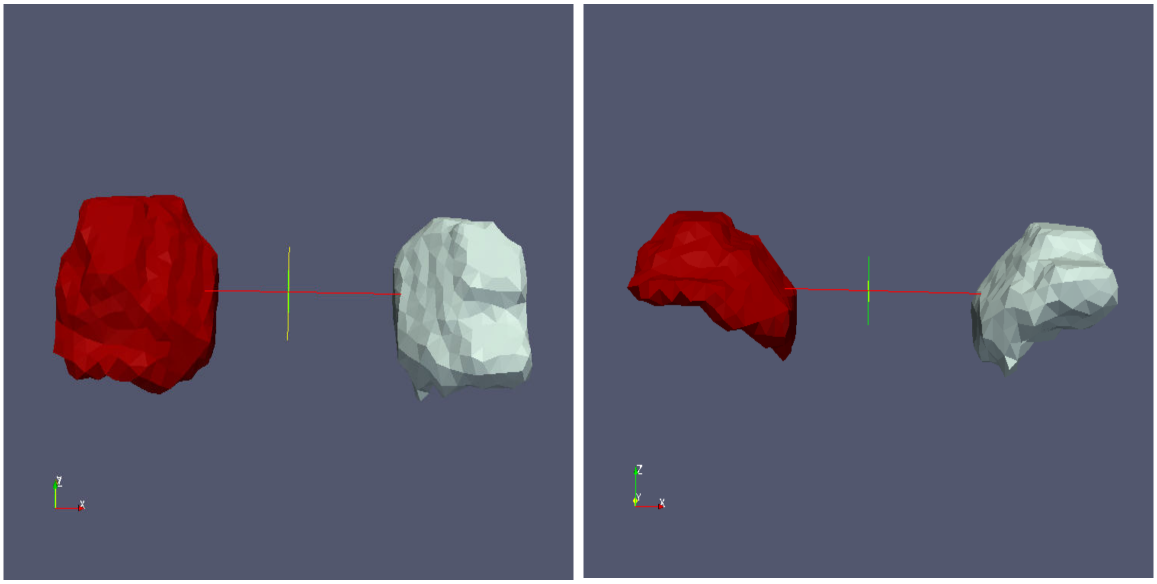
3.3. Three- Dimensional Visualization

In order to get more accurate view of the segmentation, the three-dimensional visualization of segmentations was created using Paraview. The three-dimensional visualization helps to analyze the segmentation by looking at the segmentations from various aspects which was not possible in ITK Snap.

Figure 3.2 displays the three-dimensional visualization of Nucleus Accumbens. It can be clearly seen from the 3D visualization that the FreeSurfer segmentation are inaccurate, rough and discontinuous. On the other hand, the 3D visualization of manual segmentation depicts that they are accurate, smooth and robust.



(a). 3D Visualization of FreeSurfer Segmented Nucleus Accumbens



(b). 3D Visualization of Manually Segmented Nucleus Accumbens

Figure 3.4: 3D Visualization using Paraview

CHAPTER 4:

Conclusion and Checks for Future Manual Segmentations

Nucleus Accumbens belongs to the basal ganglia part of the brain and is termed as the brain’s pleasure center because it plays an important role in pleasure and reward activity. A template library was created by manually segmenting the Nucleus Accumbens so that it can be used with a multi- atlas segmentation algorithm like FS-LDDMM to segment large number of images acquired from patients with neurodegenerative disorders to get better understanding of the diseases. The segmentation of Nucleus Accumbens is done by first creating a segmentation protocol because there is no clear distinction between NAc and its neighboring parts. The protocol created helps in determining the boundary voxels and thus distinguishing NAc from Caudate and Putamen.

Various aspects are needed to be kept in mind while segmenting Nucleus Accumbens. NAc is generally traced in coronal view, and the axial and sagittal helps in aiding the segmentation. Before beginning with segmentation, the contrast of the image is adjusted so that the borders between the gray and white matter are clear and consistent. Moreover, proper image contrast helps in viewing the boundary between NAc and its neighboring parts. Further, all three views should be taken into consideration while labelling any voxel. This is because some voxels that seems to be the part of the structure in one view, makes an improper structure when other views are seen. Considering all three views also helps in viewing the voxel intensity difference in neighboring voxels and thus helps in deciding whether the voxel should be part of the structure or not. Further, the 3D view can also help in analyzing the overall structure and any voxel changes to be done accordingly.

Further, the segmentations performed and with the help of the FS-LDDMM algorithm, any kind of disorder with the Nucleus Accumbens can be detected by providing a clear distinction between a normal case and a Nucleus Accumbens with any abnormality. The early detection of any minor disorder can help in treating the disease before it becomes life threatening.

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