HIPPOCAMPAL VOLUME ASSESSMENT

Using Analyze

AnalyzeDirect

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Introduction

The volume of the hippocampus is a commonly used structural MRI measurement in brain research. Many studies focus on changes in hippocampal volume associated with a wide variety of neurological and psychiatric conditions including depression[1], posttraumatic stress disorder (PTSD)[2,3], borderline personality disorder (BPD)[4], schizophrenia[5,6], alcohol abuse[7], and Alzheimer's[8], Parkinson's and Huntington's diseases[9].

It is as yet unclear what mechanisms underlie the decrease in hippocampal volume associated with major depressive disorder (MDD)[9]. Cross-sectional studies are incapable of determining definitively whether decreased hippocampal volume is caused by MDD or is a contributing factor to MDD, so it is recommended that longitudinal studies be conducted to determine the causal relationship between MDD and hippocampal volume[10]. Decreased hippocampal volume in MDD patients may lead to recollection memory impairment. It may also be related to an increase in glucocorticoids caused by stressful events and exacerbated by decreased inhibition of the hypothalamic-pituitary-adrenal (HPA) axis as a result of decreased hippocampal volume[1,11]. It has been found that antidepressants used during episodes of depression may protect the hippocampus from decreasing in size[12] and that there is an association between duration of depression and reduced hippocampal volume[13,14].

Decreased hippocampal volume has been identified in Vietnam veterans with PTSD, and hippocampal volume was directly correlated with combat exposure. This correlation may be explained by combat stress causing PTSD, which in turn damages the hippocampus, or by an increased likelihood of individuals with smaller hippocampi either being assigned to combat units or developing PTSD when exposed to combat stress [2]. Decreased hippocampal volume has not been found to be a necessary risk factor for developing PTSD and does not occur within six months of the onset of PTSD. The lower hippocampal volume observed in some PTSD patients may be related to chronic or complicated PTSD or related distress. The frontal lobe may be the area of the brain most significantly affected by PTSD, rather than the hippocampus[3]. In adults who sustained childhood trauma in the form of abuse or maltreatment, hippocampal volume is reduced[15]. This effect is not observed until adulthood, suggesting there is a delay between the childhood causal factors and the reduced hippocampal volume effect[16,17].

Hippocampal volume is frequently used in the study of Alzheimer's disease (AD) and as such may be developed into a standardized biomarker for dementia and AD[18,19]. The volume of the hippocampus, adjusted for age and gender, has been found to best discriminate controls from early-onset AD cases in comparison to other medial temporal lobe structures[20]. However, a stronger correlation was found between change in hemispheric volume measurements (whole brain and ventricle) and cognitive performance compared to the correlation between medial temporal lobe volume decrease and cognitive performance[21]. MRI-based hippocampal volume measurement may become a useful diagnostic tool in cases of memory impairment which may indicate early-onset AD[20], and measurement of whole brain atrophy rates may be preferable for some clinical trials, especially considering that it can more easily be automated[21].

Findings from the Nun Study have shown that hippocampal volume as measured by postmortem MRI was able to identify differences between Braak stages of AD pathology as determined by histopathology. This suggests that hippocampal volume could be used to identify AD at early stages in patients long before they show clinical symptoms. This should be considered along with findings that 43-67% of individuals fulfill neuropathologic criteria for diagnosis of AD at autopsy yet never exhibited dementia[22]. Measurements of hippocampal volume from MRI have been used to show that patients with mild cognitive impairment (MCI) who have smaller hippocampal volume are more likely to convert to AD than MCI patients with larger hippocampi[23].

In order to be widely used as a biomarker in clinical practice and clinical trials, hippocampal segmentation will have to be automated, but the gold standard of hippocampal segmentation remains manual tracing[18]. The bottom line is that structural volume measurements as determined by MRI provide a more reliable assessment of AD progression than cognitive tests alone. Imaging should be used in conjunction with standard cognitive tests in AD therapeutic trials[21].

The population in the developed world is increasingly aging, and researchers are trying to confirm ways of preventing or reversing cognitive atrophy. One group found that higher fitness levels were associated with increased left and right hippocampal volume in nondemented adults, which was also associated with increased performance on spatial memory tests[24]. Spatial navigation training maintained hippocampal volume in both younger and older men, while controls experienced a decline in hippocampal volume over time[25].

Insulin resistance is a cause of cardiovascular disease, diabetes, and obesity, which are in turn risk factors for dementia and AD[26]. Insulin receptors in the central nervous system are mostly located in or near the hippocampus, and a negative correlation has been demonstrated between insulin resistance and hippocampal volume[27].

Note that the sample data set shown is a 1.5 Tesla T1-weighted MR image. Because of the relatively low field strength, the boundaries of the hippocampus are not always clear due to partial volume effects. Data acquired at a higher field strength such as 3T or even 7T would have a higher resolution and signal-to-noise ratio, and an atlas of the hippocampus has even been created from 9.4T postmortem scans[28] . Partial volume effects can also be reduced by acquiring the data orthogonal to the long axis of the hippocampus.

Using a higher field strength would also allow for the segmentation of the hippocampus into its subregions, which is not shown in this guide. In particular, reduced hippocampal tail volume has been observed in patients with MDD and schizophrenia[29,30]. This guide focuses on the steps necessary to segment hippocampi and measure total hippocampal volume in Analyze.

Preprocessing Steps

There are a number of data preprocessing steps that will aid in manual hippocampus segmentation. It is recommended to reslice the data orthogonal to the AC-PC line for consistency. In addition, upsampling the data through interpolation to create a smaller voxel size will allow you to define hippocampal regions more precisely.

Finally, cropping or subregioning the data to zoom in on the region containing the hippocampus will reduce the size of the data set, as well as speed up processing and rendering times, especially on slower systems.

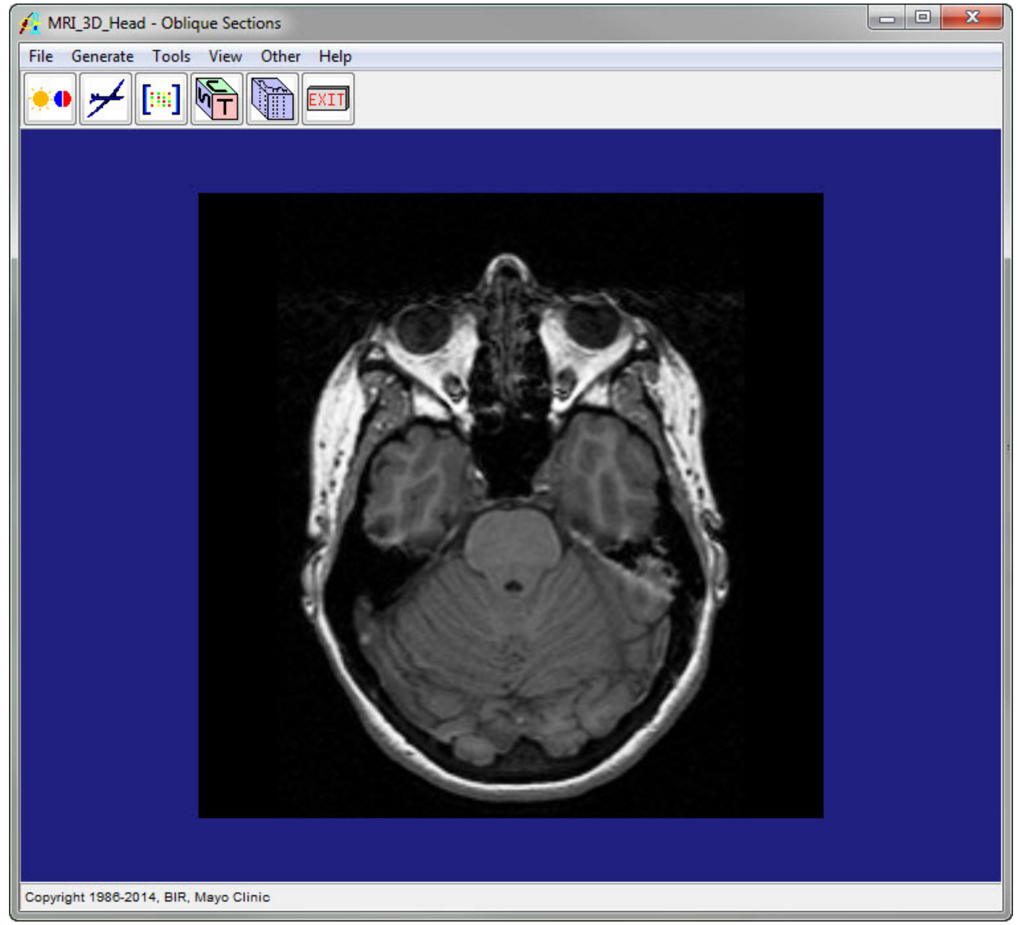
Manual AC-PC Alignment of Brain Data

According to the current standards set by EADC (European Alzheimer's Disease Consortium) and ADNI (Alzheimer's Disease Neuroimaging Initiative)[31,32], the structural MRI brain data should be AC-PC aligned before segmentation.

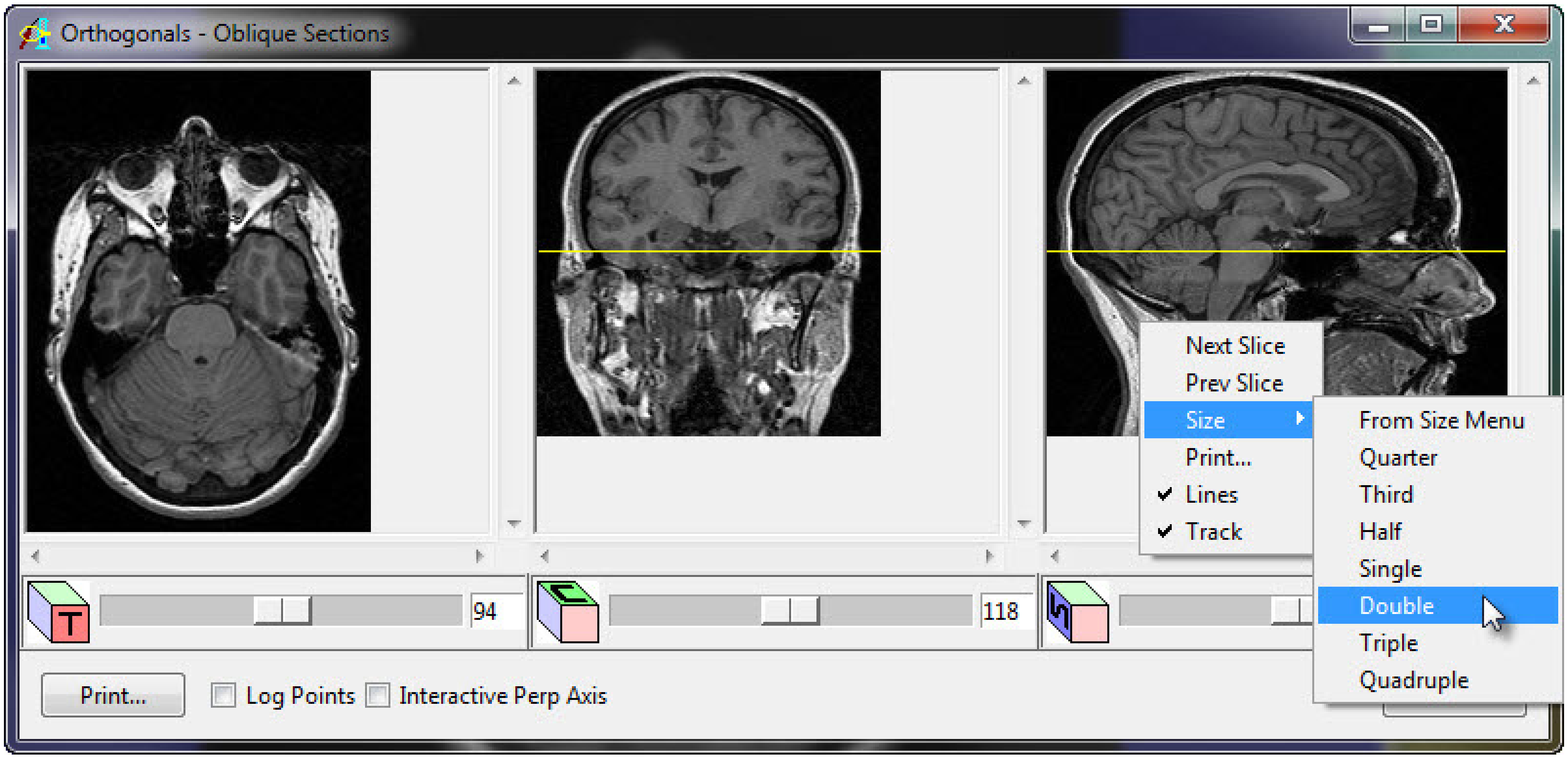
The brain data can be aligned along the AC-PC axis as described in the following section, or as described in the Oblique Sections: Manual AC-PC Realignment document.

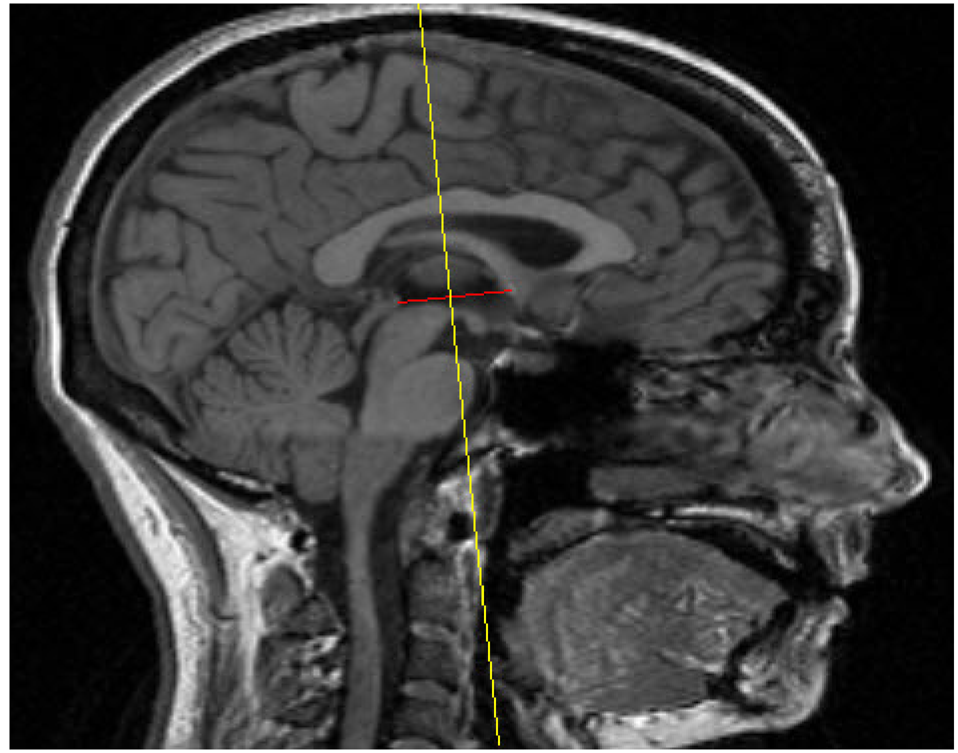
For users who have access to the Mayo 3D Brain Atlas add-on module, there is a tool specifically designed for easy AC-PC alignment of data, which is described in steps 3-8 of the Mayo 3D Brain Atlas Training Guide document.

Load the MRI_3D_Head.avw data set from the TutorialData folder or your MRI brain data set into Analyze. Open the data set in Oblique Sections (**Display > Oblique Sections**).



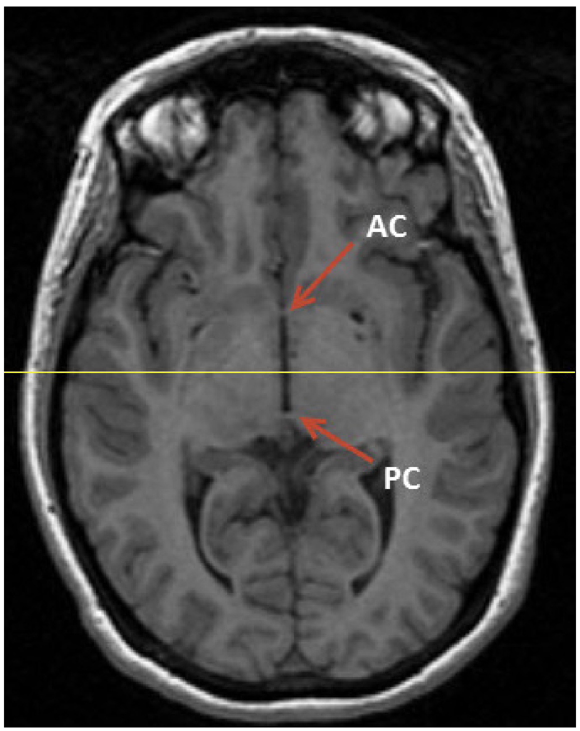
Open the Orthogonals tool from the Oblique Sections module window (**Tools > Orthogonals**). In order to better visualize the sagittal view in which the AC-PC axis will be defined, change the size of that view to double by right-clicking on the image, selecting Size, then selecting Double.





In the sagittal view, on the mid-sagittal slice, click on the PC, then drag the red line to the location of the AC and release the mouse button. The yellow line will be generated as the orthogonal plane.

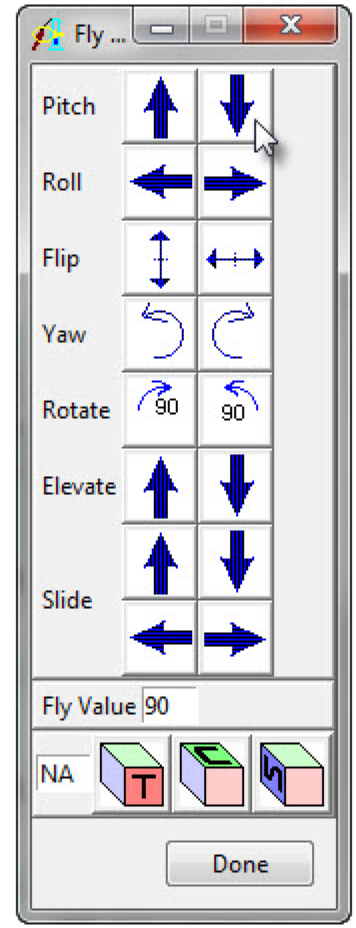
This step can be repeated if necessary to define the correct plane. If you wish to view the orthogonal plane interactively, check the **Interactive Perp Axis** option in the Orthogonals window.



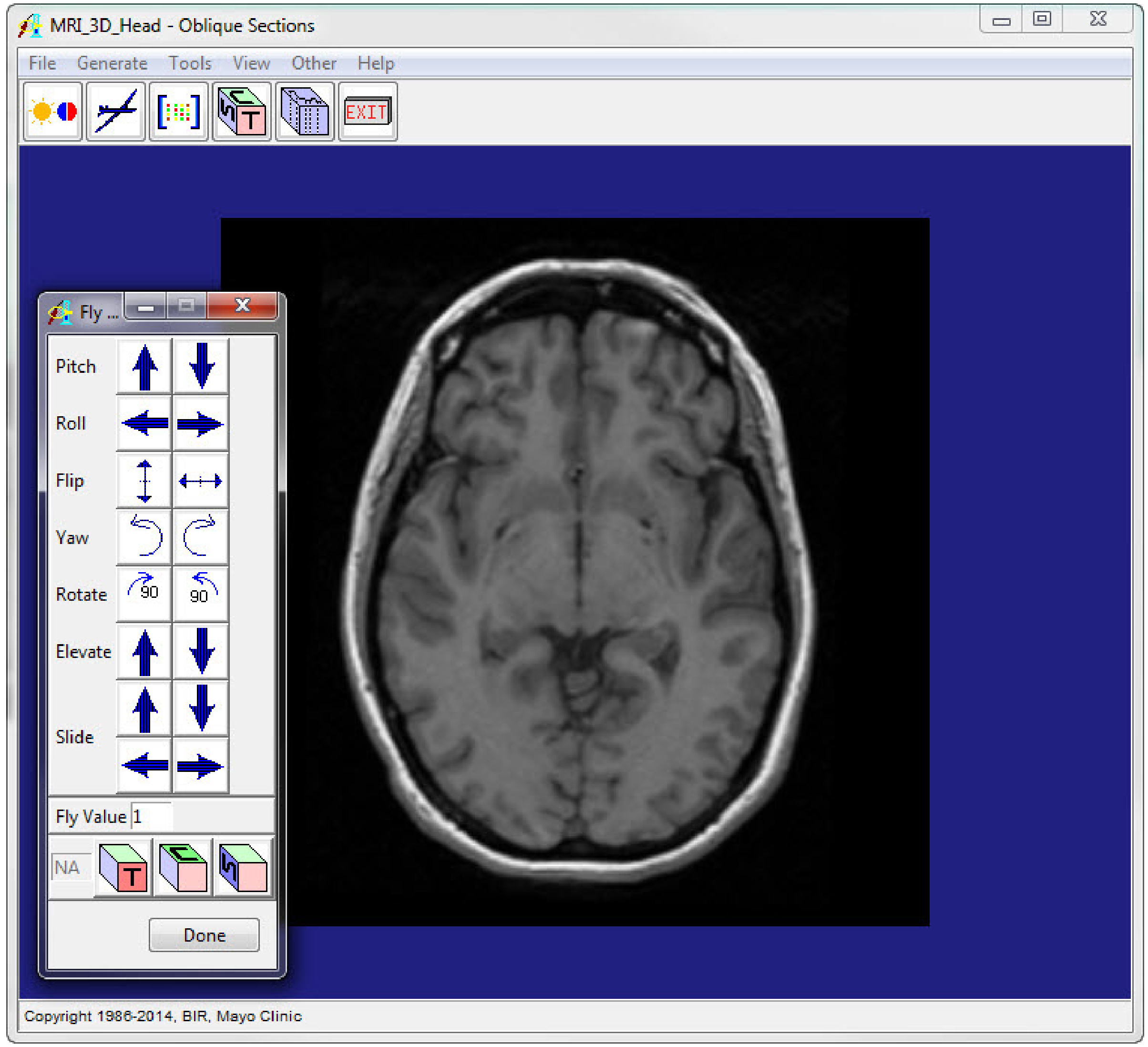
Correct AC-PC alignment can be checked for by viewing the transverse slice in the Orthogonals window. The AC and PC should both be clearly visible.

Open the Fly tool from the Oblique Sections window (**Generate > Fly**). Change the **Fly Value** to **90** degrees at the bottom of the Fly tool window, and click one of the Pitch buttons.

The oblique image in the main Oblique Sections window should have the anterior part of the brain at the top. If it is upside-down, then click the same Pitch button twice to flip the oblique plane by **180** degrees.

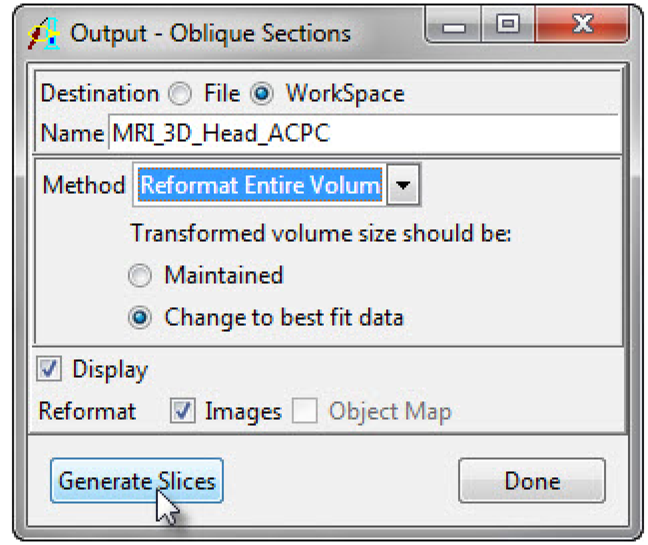


Change the Fly value to a small value between 1-5 degrees. Use the Roll and Yaw buttons to make small adjustments to the oblique plane such that the brain structures appear symmetrical.



To output the data set resliced along the oblique plane, open the Output window (**File > Output**). Rename the data set and choose where to save the resliced data.

Change the method to "**Reformat Entire Volume**" and select "**Change to best fit data**." Click Generate Slices to output the reformatted data to the specified location.

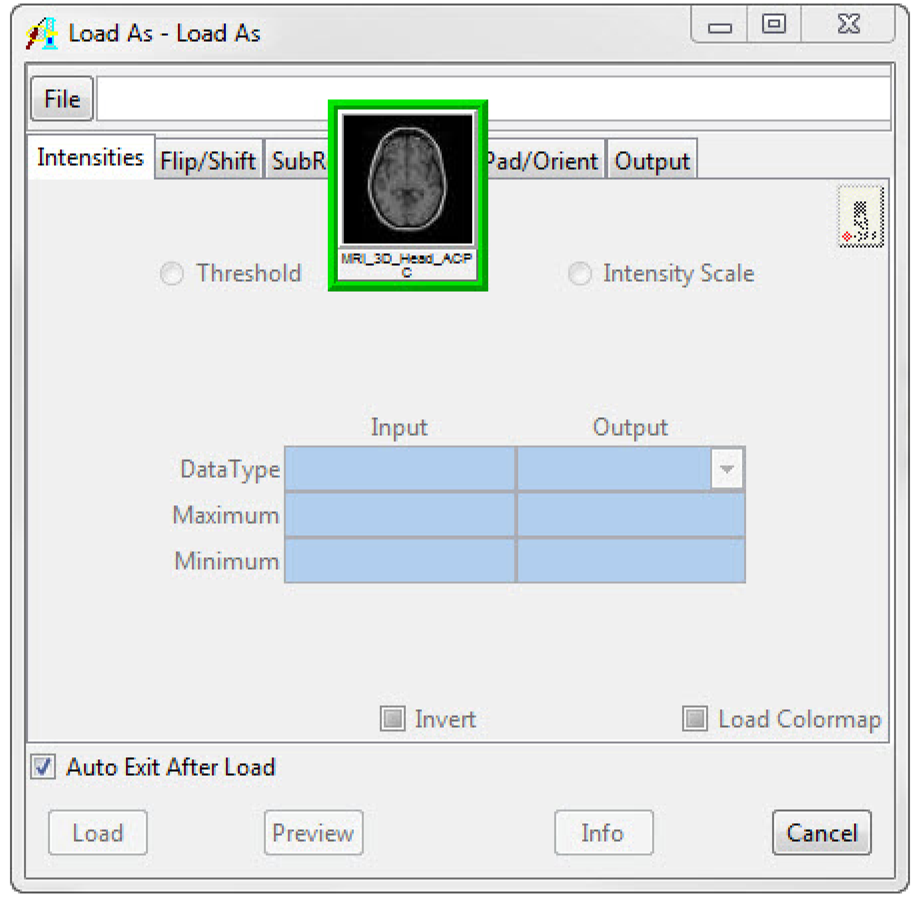


Upsampling and Cropping for Improved Segmentation

The hippocampus is a relatively small structure compared to the whole brain. For this reason, unless the data was taken at an extremely high resolution, the definition of the hippocampal region in the original data set will likely not be completely precise due to large voxel size compared to the size of the hippocampus.

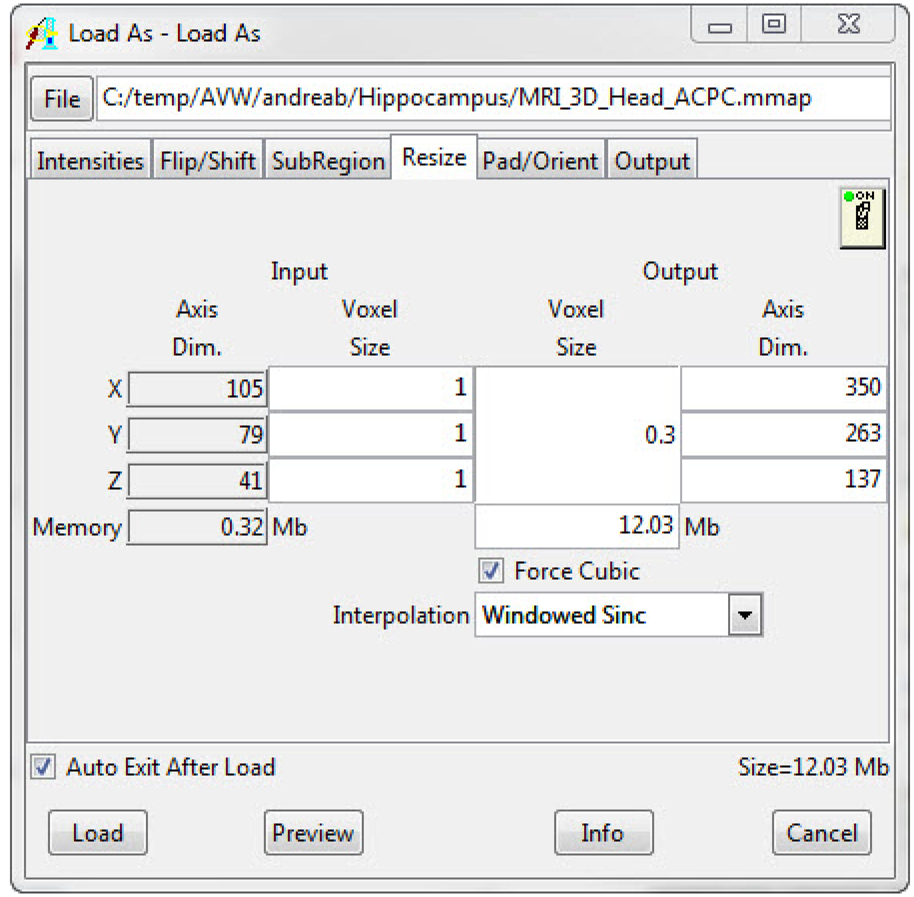
To be able to precisely define the hippocampus, the data can be upsampled or interpolated to create a smaller voxel size. This can be done using the Load As module.

Open Load As (**File > Load As**) and drag the reformatted data set from the workspace into the File area of the window. Alternatively, click the File button and select the location of the reformatted data set on disk.



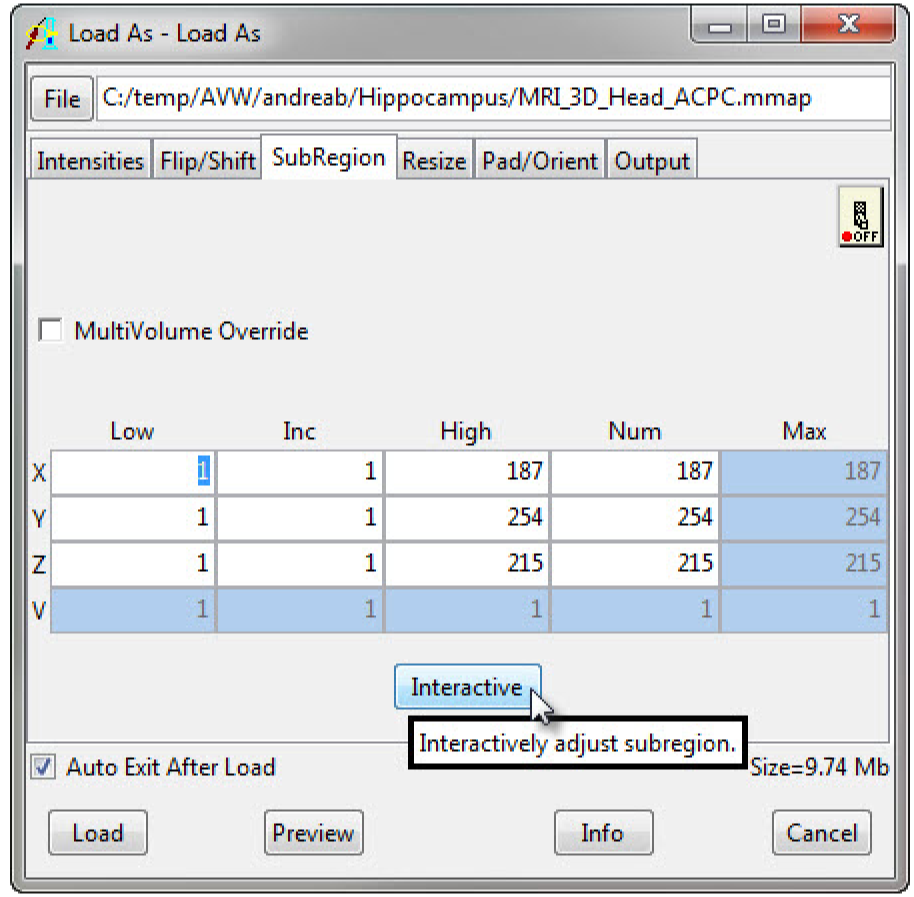
Navigate to the Resize tab and check the **Force Cubic** checkbox. Choose an interpolation type from the dropdown menu. Cubic Spline and Windowed Sinc are recommended as they will best preserve the data as it is interpolated.

You will need to choose a voxel size. To change the voxel size, click in the Voxel Size box and type in a new voxel size. The box showing the size of the data set will automatically update.



To zoom in on the region of the data containing the hippocampi, the data set can be subregioned or cropped. This will also reduce the size of the data set which can speed up processing times on slower systems. If you do not wish to crop the data set, click **Load** to apply the upsampling changes.

To crop the data set, navigate to the SubRegion tab and click the **Interactive button**.

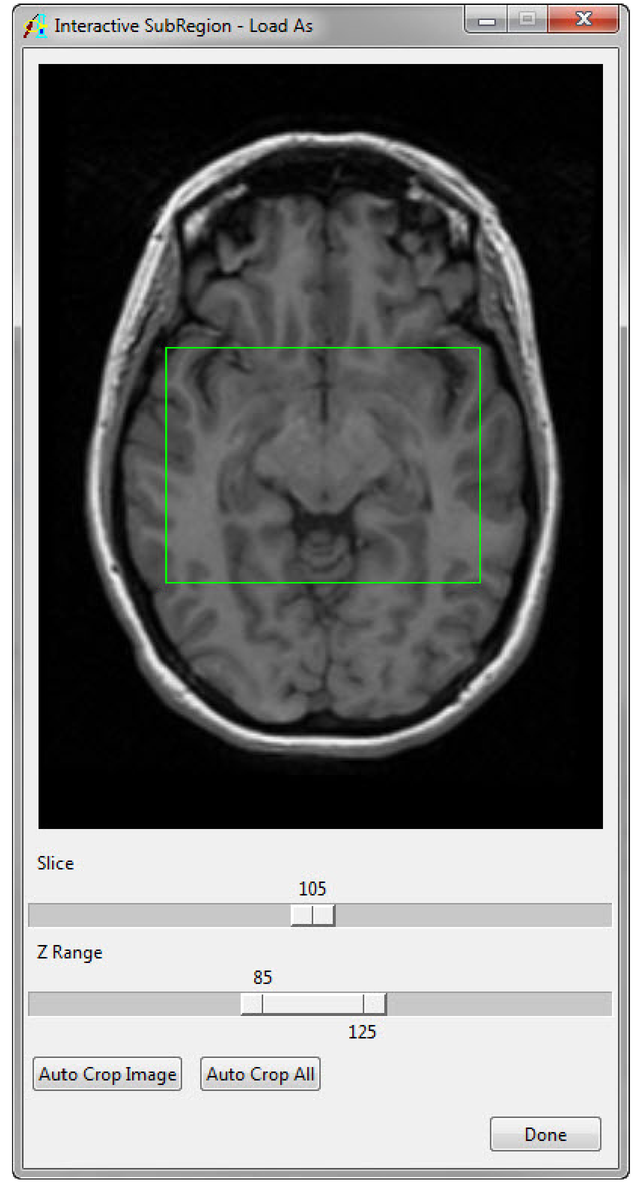


To crop the data set in 3D, first define a rectangular region on the transverse view that is shown. Each side of the region can be defined by clicking in the image near that side of the window and moving the green line to the desired position.

To define the dorsal and ventral limits of the 3D region, select a Z range of slices using the lower bar. It is difficult to determine these limits simply by looking at the Interactive SubRegion window, so the reformatted data set can be opened on the side in Volume Edit and the slices can be reviewed in order to determine the limits in all three dimensions of the region containing the hippocampi.

Once the region has been defined, click **Done** to close the Interactive SubRegion window. The chosen ranges will be shown in the Load As window.

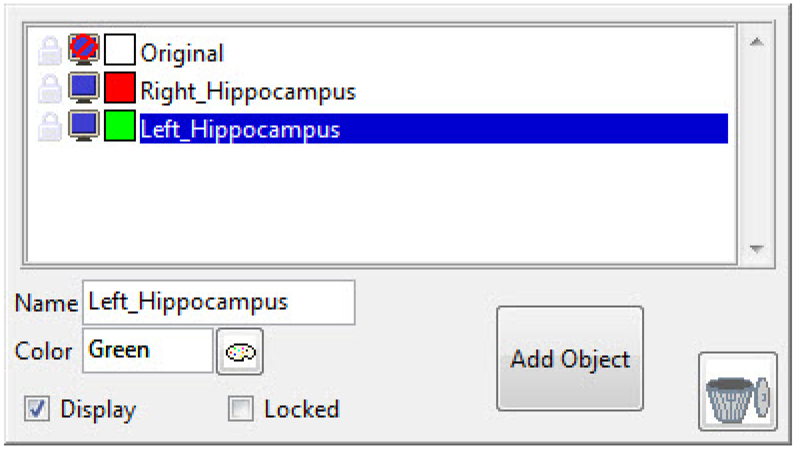
Click the **Load button** to load the data into the Analyze workspace. When prompted, click "**Create New**" to create a separate preprocessed data set. You may wish to rename the preprocessed data set once it is loaded, according to your own naming conventions.



Manual Segmentation of the Hippocampus

The segmentation will be performed primarily in the coronal view, from rostral to caudal. The EADC-ADNI Harmonized Protocol for Manual Hippocampal Segmentation (HarP) requires 3D navigation for frequently checking anatomical structures against the sagittal and transverse view during the segmentation process. For this reason, the segmentation is best performed using the Volume Edit module, which includes 3D linked cursor functionality.

Open the AC-PC aligned, preprocessed T1 MRI brain data set in Volume Edit (**Segment > Volume Edit**). Click the **Add Object** button to add two new objects and name them **Right_Hippocampus** and **Left_Hippocampus**.



The segmentation method will not be described in anatomical detail here, as that is beyond the scope of this document. Please refer to the EADC-ADNI protocol for detailed instructions on manual hippocampus segmentation.

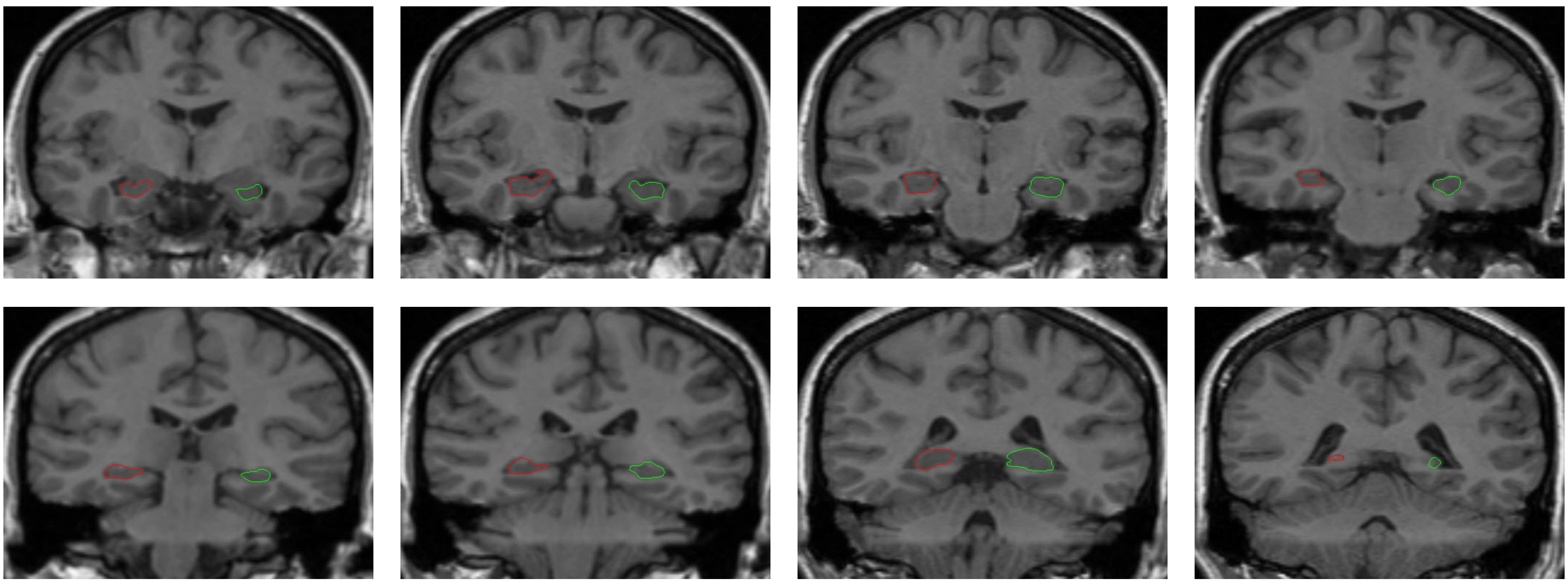
Note: Analyze uses a left-handed coordinate system, so the sagittal images as seen in Analyze are mirror images of the sagittal view as seen in the EADC-ADNI Protocol.

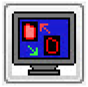
Use the manual trace tool to delineate hippocampal tissue. To do this, select the object to be defined, Right_Hippocampus or Left_Hippocampus, then click on the **Trace tool** under the Manual tab, and trace around the hippocampus.

Mistakes can be fixed by clicking the Undo button and retracing the contour. The Nudge Edit tool can also be used to expand the hippocampus contour (by clicking inside the hippocampus and dragging out along the inside of the contour) or to nudge the contour back from the outside (by clicking in the Original object and dragging along the outside of the contour). The size of the Nudge Edit tool can be adjusted by holding down the middle mouse button and moving the mouse.

Move through the coronal slices, defining the Right_Hippocampus and Left_Hippocampus objects using the Trace tool and checking against anatomical landmarks as described in the EADC-ADNI protocol. Save the object map periodically during the segmentation process.

A few representative coronal slices with the right and left hippocampal objects defined are shown below, from rostral to caudal.

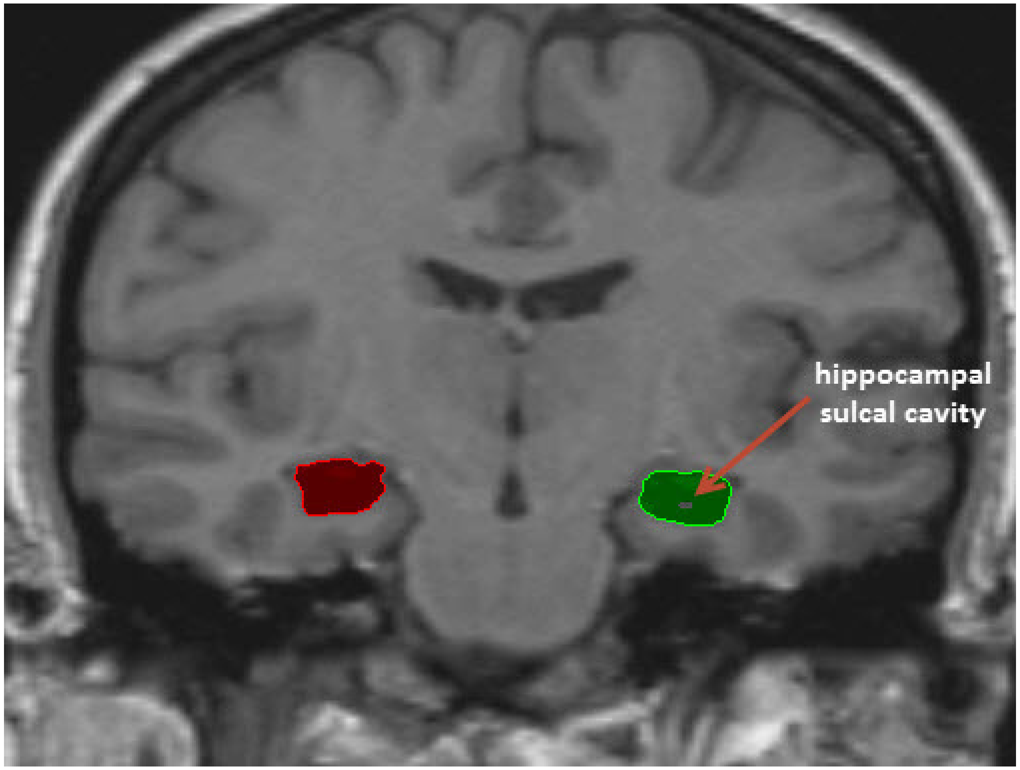


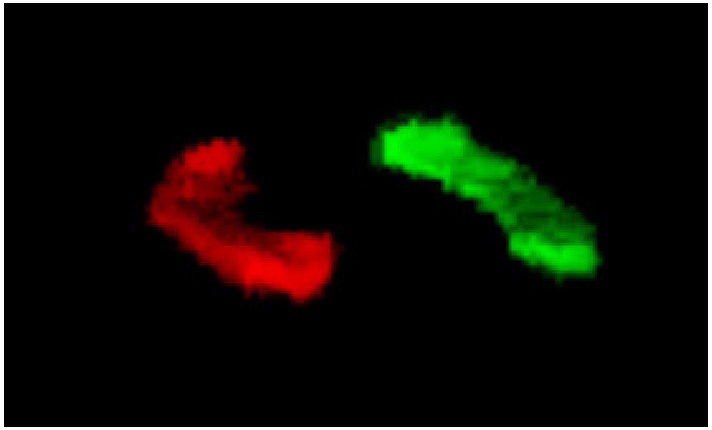


A hippocampal sulcal cavity[33–35] appears on one of these slices, the segmentation of which can be more clearly seen by toggling the display using the Toggle Region Display Powerbar button.

To exclude a region from the hippocampus object, the draw tool (under the Manual tab) can be used to assign such a cavity to the Original object.

An example rendering of the segmented hippocampi is shown below on the right.





Note: Hippocampal subregions can be manually segmented by adding further objects and assigning voxels to these objects using manual tools as described for the whole hippocampi above.

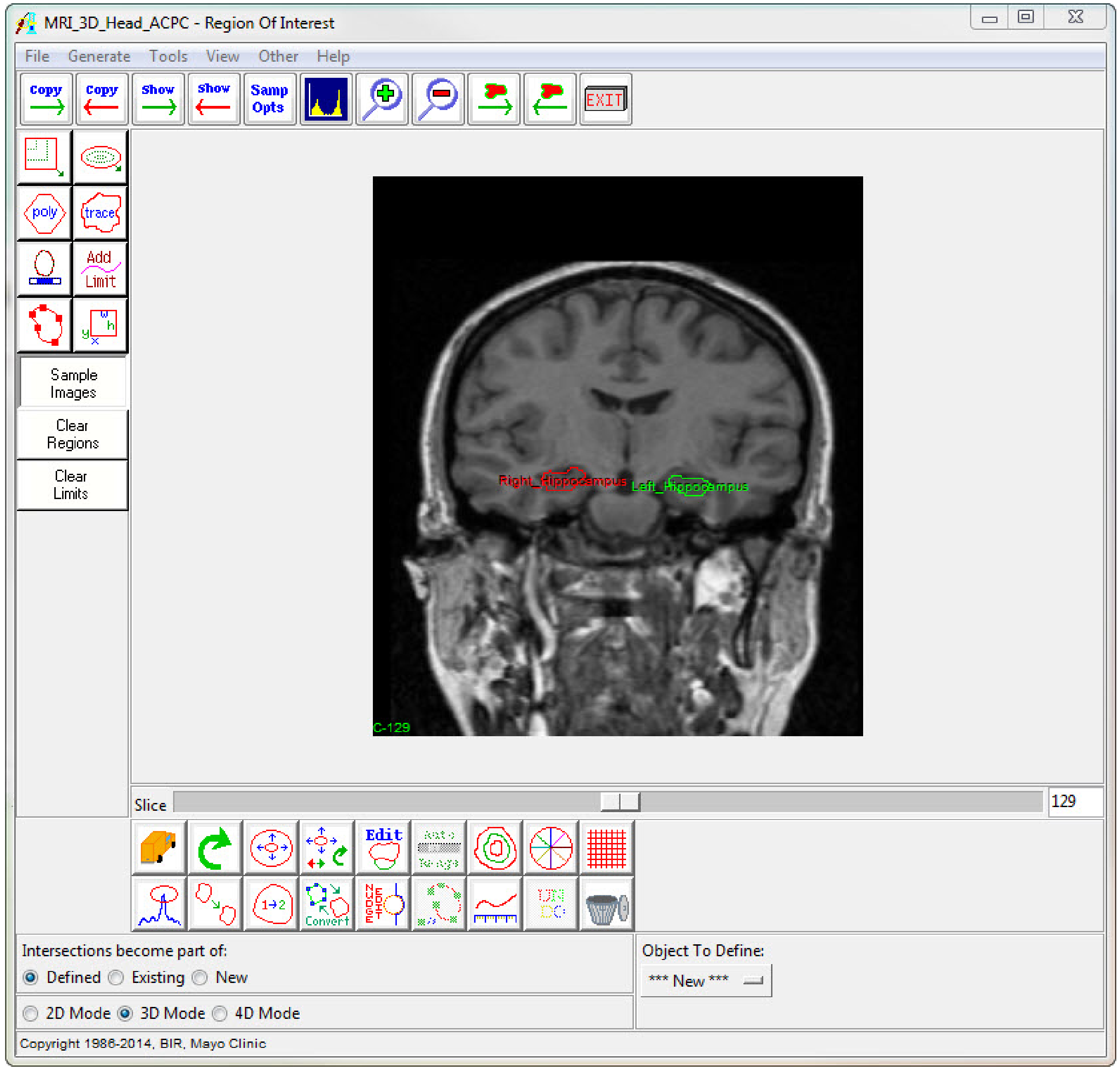
Measurement of Hippocampal Volume

As discussed in the introduction, the volume of the hippocampus is the measurement of interest. The volume will be measured in the Region of Interest (ROI) module of Analyze.

Open the data set in the ROI module (**Measure > Region of Interest**).

Load the object map saved at the end of the segmentation (**File > Load Object Map**).

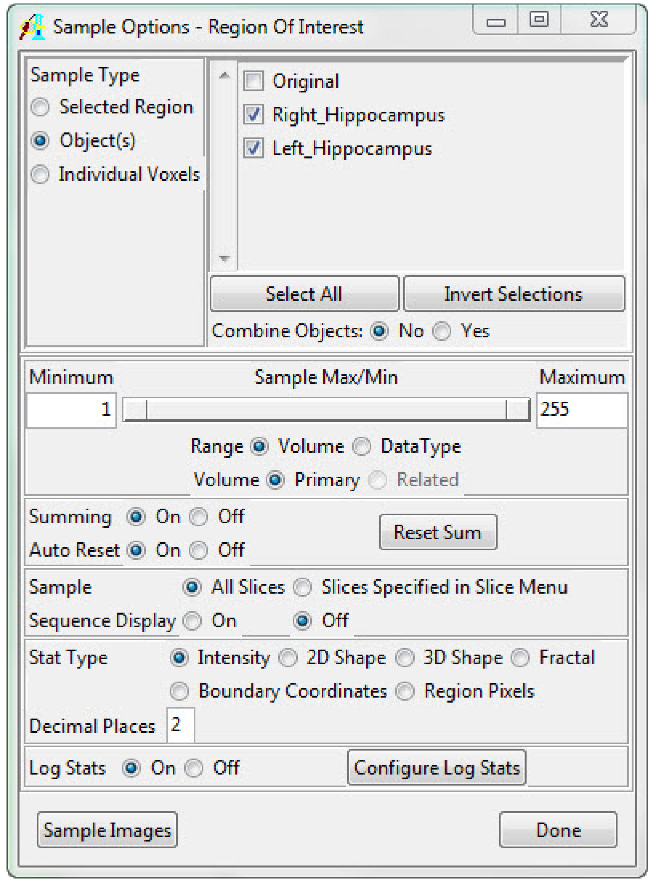
To change the orthogonal orientation shown, navigate to **Generate > Orientation** and select one of the orientations. Navigate through the slices using the slice slider bar.

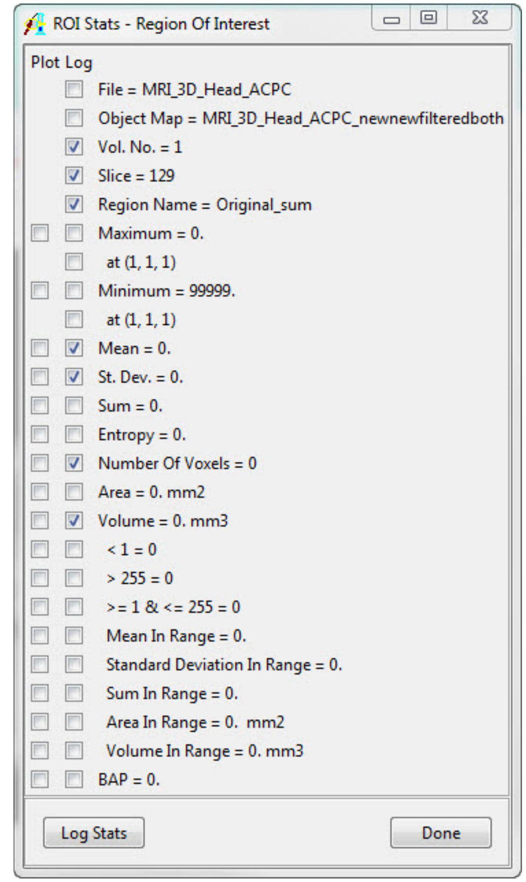


To open the measurements tool, click **Generate > Sample Options**.

In the Sample Options window, set the following parameters:

- **Sample Type** to Object(s)
- Select the Objects **Right HC** and **Left HC**
- **Summing** to **On**
- **Sample** to **All Slices**
- **Sequence Display** to **Off**
- Choose the desired number of decimal places
- **Log Stats** to **On**
- Click on the **Configure Log Stats** button



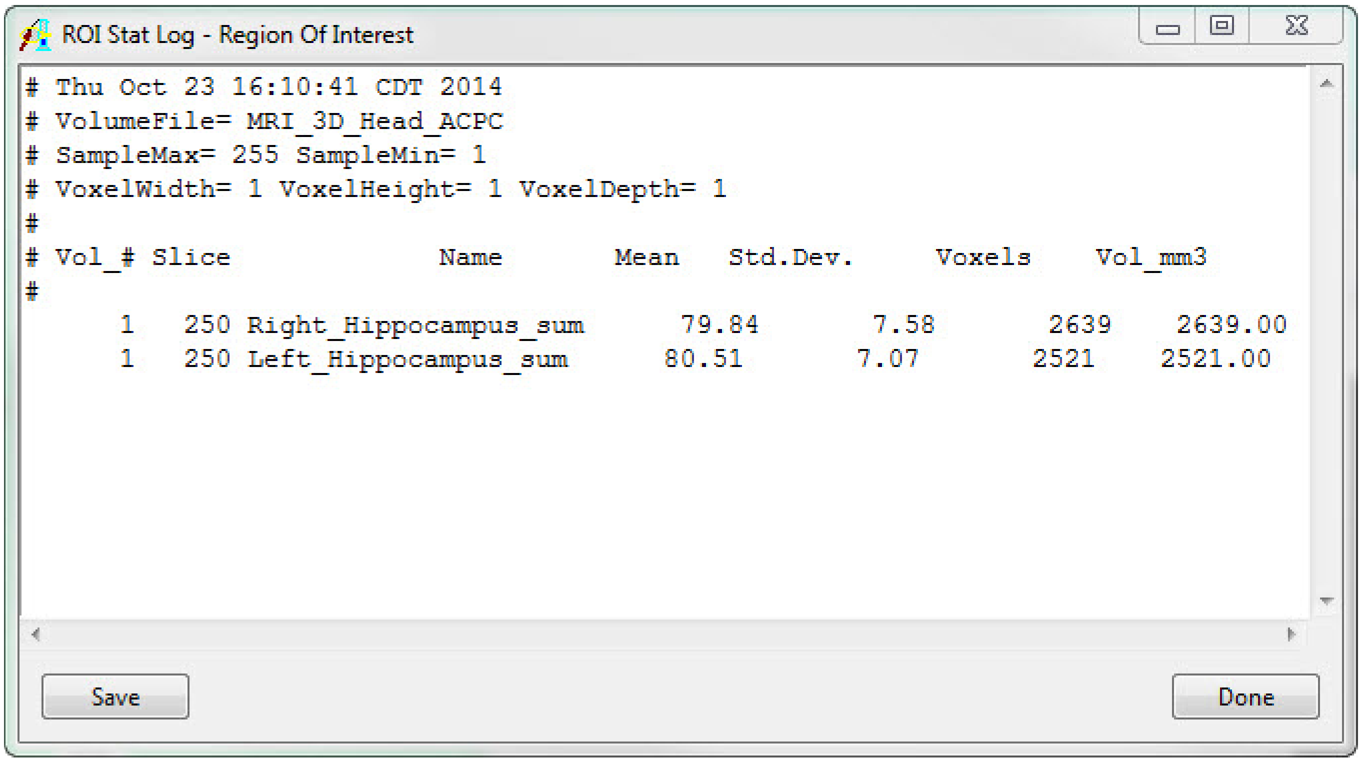


The ROI Stats window will open, showing the measurements that can be generated. Uncheck the Area measurement, as this is not applicable.

The correct settings for the Sample Options and ROI Stats windows are shown to the right.

Click the Sample Images button at the bottom of the Sample Options window. This will initiate the measurement routine. The ROI Stat Log window will open and return the following for each object: mean intensity value, standard deviation of intensity, number of voxels and the corresponding volume in cubic millimeters.

Click Save to output the measurements as a .stats file, which can then be opened in a spreadsheet and used for further analysis.



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References

1. Campbell, S., Marriott, M., Nahmias, C. & MacQueen, G. M. Lower Hippocampal Volume in Patients Suffering From Depression: A Meta-Analysis. *Am. J. Psychiatry* **161**, 598–607 (2004).
2. Gurvits, T. V *et al.* Magnetic Resonance Imaging Study of Hippocampal Volume in Chronic, Combat-Related Posttraumatic Stress Disorder. *Biol. Psychiatry* **40**, 1091–1099 (1996).
3. Bonne, O. *et al.* Longitudinal MRI Study of Hippocampal Volume in Trauma Survivors With PTSD. *Am. J. Psychiatry* **158**, 1248–1251 (2001).
4. Schmahl, C. G., Vermetten, E., Elzinga, B. M. & Bremner, J. D. Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. *Psychiatry Res. Neuroimaging* **122**, 193–198 (2003).
5. Nelson, M. D., Saykin, A. J., Flashman, L. A. & Riordan, H. J. Hippocampal Volume Reduction in Schizophrenia as Assessed by Magnetic Resonance Imaging. *Arch. Gen. Psychiatry* **55**, 433 (1998).
6. Velakoulis, D. *et al.* Hippocampal Volume in First-Episode Psychoses and Chronic Schizophrenia. *Arch. Gen. Psychiatry* **56**, 133 (1999).
7. De Bellis, M. D. *et al.* Hippocampal Volume in Adolescent-Onset Alcohol Use Disorders. *Am. J. Psychiatry* **157**, 737–744 (2000).
8. Vemuri, P. *et al.* Alzheimer's Disease Diagnosis in Individual Subjects using Structural MR Images: Validation Studies. *Neuroimage* **39**, 1186–1197 (2008).

9. Czéh, B. & Lucassen, P. J. What causes the hippocampal volume decrease in depression? Are neurogenesis, glial changes and apoptosis implicated? *Eur. Arch. Psychiatry Clin. Neurosci.* **257**, 250–60 (2007).

10. Videbech, P. & Ravnkilde, B. Hippocampal Volume and Depression : A Meta-Analysis of MRI Studies. *Am. J. Psychiatry* **161**, 1957–1966 (2004).

11. Bremner, J. D. *et al.* Hippocampal Volume Reduction in Major Depression. *Am. J. Psychiatry* **157**, 115–117 (2000).

12. Sheline, Y. I., Gado, M. H. & Kraemer, H. C. Untreated Depression and Hippocampal Volume Loss. *Am. J. Psychiatry* **160**, 1516–1518 (2003).

13. MacQueen, G. M. *et al.* Course of illness , hippocampal function , and hippocampal volume in major depression. *Proc. Natl. Acad. Sci. U. S. A.* **100**, 1387–1392 (2003).

14. Sheline, Y. I., Sanghavi, M., Mintun, M. A. & Gado, M. H. Depression Duration But Not Age Predicts Hippocampal Volume Loss in Medically Healthy Women with Recurrent Major Depression. *J. Neurosci.* **19**, 5034–5043 (1999).

15. Bremner, J. D. et al. Magnetic Resonance Imaging-Based Measurement of Hippocampal Volume in Posttraumatic Stress Disorder Related to Childhood Physical and Sexual Abuse — A Preliminary Report. *Biol. Psychiatry* **41**, 23–32 (1997).

16. Vythilingam, M. *et al.* Childhood Trauma Associated with Smaller Hippocampal Volume in Women With Major Depression. *Am. J. Psychiatry* **159**, 2072–2080 (2002).

17. Lupien, S. J. *et al.* Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. *Proc. Natl. Acad. Sci. U. S. A.* **108**, 14324–14329 (2011).

18. Jack, Jr, C. R. *et al.* Steps to standardization and validation of hippocampal volumetry as a biomarker in clinical trials and diagnostic criteria for Alzheimer's disease. Alzheimer's Dement. **7**, 474–485 (2011).

19. Nestor, S. M., Gibson, E., Gao, F.-Q., Kiss, A. & Black, S. E. A Direct Morphometric Comparison of Five Labeling Protocols for Multi-Atlas Driven Automatic Segmentation of the Hippocampus in Alzheimer's Disease. *Neuroimage* 50–70 (2013). doi:10.1016/j.neuroimage.2012.10.081.A

20. Jack Jr, C. R. *et al.* Medial Temporal Atrophy on MRI in Normal Aging and Very Mild Alzheimer's Disease. *Neurology* **49**, 786–794 (1997).

21. Jack Jr, C. R. *et al.* Comparison of Different MRI Brain Atrophy Rate Measures with Clinical Disease Progression in AD. *Neurology* **62**, 591–600 (2004).

22. Gosche, K. M., Mortimer, J. A., Smith, C. D., Markesbery, W. R. & Snowdon, D. A. Hippocampal volume as an index of Alzheimer neuropathology: Findings from the Nun Study. *Neurology* **58**, 1476–1482 (2002).

23. Jack, C. R. *et al*. Prediction of AD with MRI-Based Hippocampal Volume in Mild Cognitive Impairment. *Neurology* **52**, 1397–1403 (1999).

24. Erickson, K. I. *et al*. Aerobic Fitness is Associated with Hippocampal Volume in Elderly Humans. *Hippocampus* **19**, 1030–1039 (2009).

25. Lövdén, M. *et al*. Spatial navigation training protects the hippocampus against age-related changes during early and late adulthood. *Neurobiol. Aging* **33**, 620.e9–620.e22 (2012).

26. Craft, S. The Role of Metabolic Disorders in Alzheimer's Disease and Vascular Dementia: Two Roads Converged? *Arch. Neurol.* **66**, 300–305 (2009).

27. Rasgon, N. L. *et al*. Insulin resistance and hippocampal volume in women at risk for Alzheimer's disease. Neurobiol. Aging 32, 1942–1948 (2011).

28. Yushkevich, P. a. *et al*. A high-resolution computational atlas of the human hippocampus from postmortem magnetic resonance imaging at 9.4 T. Neuroimage 44, 385–398 (2009).

29. Maller, J. J. *et al*. Hippocampal volumetrics in treatment-resistant depression and schizophrenia: The devil's in De-Tail. *Hippocampus* **22**, 9–16 (2012).

30. Maller, J. J., Daskalakis, Z. J. & Fitzgerald, P. B. Hippocampal Volumetrics in Depression: The Importance of the Posterior Tail. *Hippocampus* **17**, 1023–1027 (2007).

31. Boccardi, M. *et al*. Delphi definition of the EADC-ADNI Harmonized Protocol for hippocampal segmentation on magnetic resonance. *Alzheimers. Dement.* (2014). doi:10.1016/j.jalz.2014.02.009

32. Frisoni, G. B. *et al*. The EADC-ADNI Harmonized Protocol for manual hippocampal segmentation on magnetic resonance: Evidence of validity. *Alzheimers. Dement.* (2014). doi:10.1016/j.jalz.2014.05.1756

33. Maller, J. J. *et al*. Hippocampal sulcal cavities: Prevalence, risk factors and relationship to memory impairment. *Brain Res.* **1368**, 222–230 (2011).

34. Maller, J. J. *et al*. Hippocampal sulcal cavities in depression and healthy individuals. *J. Affect. Disord.* **150**, 785–789 (2013).

35. Maller, J. J. & Reglade-Meslin, C. Longitudinal Hippocampal and Fornix Changes after Traumatic Brain Injury: Observations from Traditional Structural Magnetic Resonance Imaging. *J. Neurol. Neurophysiol.* **5**, (2014).

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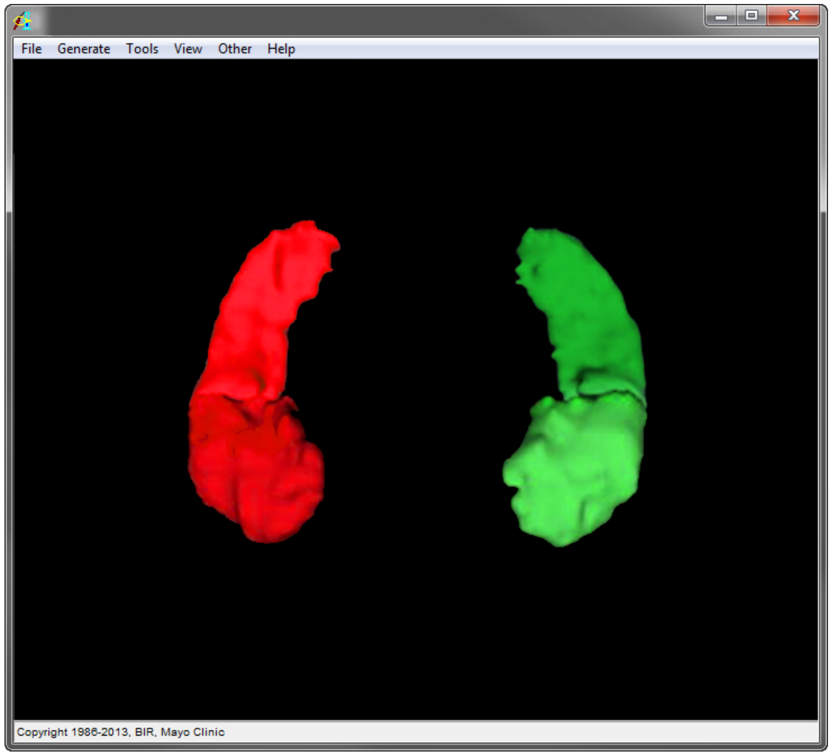

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