Accountability in Methodology and Analysis for Clinical Trials Involving Quantitative Measurements of MR Brain Images

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Abstract: Quantitative measurements of macroscopic neural anatomy that are obtained from MRI scans are beginning to be used in clinical trials. This paper describes procedures and software features that ensure the demonstrable validity of these measurements. In addition to describing mechanisms that provide data integrity and security throughout the image analysis pipeline, we present "SegMentor", a system that provides accountability for neuroanatomical measurement techniques. Employing these methods results in neuromorphometrics that are suitable as surrogate endpoints for diagnosis and for measuring response to treatment.

Keywords:

Quantitative 3D Macroscopic Neuromorphometry, MRI Brain Segmentation, Clinical Trial.

1 Introduction

Investigators in pharmaceutical drug trials are familiar with the interpretation of medical images by radiologists, but this can only provide a qualitative or roughly quantified judgment. Because of advances in digital imaging involving better image quality, faster computers at lower cost, DICOM, Teleradiology, picture archiving and communication systems (PACS), and efforts such as the Human Brain Project [1-3], now precise *quantitative* image measurements can also help with drug discovery and in measuring drug efficacy. In this paper, we focus on diagnosis and assessing response to treatment of brain disorders that involve macroscopic structural brain changes as seen in MRI.

To provide neuroanatomical measurements and localizations, volumetric brain scans must be segmented: specified regions in the images that correspond to neuroanatomical structures are identified and delineated. By using precise anatomical definitions and paying careful attention to the details of how anatomy appears in MR images, the resulting measurements produce statistically significant findings. Furthermore, the identification of brain regions and the localization of their boundaries in structural MRI can be used as a frame of references for fusing and measuring multiple imaging modalities including fMRI, PET, M/EEG, MR spectroscopy, and Diffusion-weighted MRI to provide an integrated structural and functional analysis over time. Comprehensively measured area, volume, and shape along with their averages, variances, and the covariances of interrelated structures can be compiled in databases and correlated with outcomes in specific disorders to provide an enormous amount of information. Compare this, for example, with the qualitative radiological assessment of an autistic brain where the observation of standard topology without obvious holes or bright spots is categorized as "normal".

A search for references in the medical literature using the keywords "brain", "volume" and "magnetic resonance" produces many hundreds of citations that involve schizophrenia, epilepsy, multiple sclerosis, Alzheimer's disease, tumors, depression, Huntington's disease, obsessive

compulsive disorder, ADHD, autism, HIV, alcoholism, mood disorders, borderline personality disorder, and many other areas. Investigations can measure individual regions or ratios of region volume (e.g. one specific region normalized against the entire brain or one disease impacted region against a control region), but a comprehensive morphometric analysis comes closest to harvesting the rich information available in an MRI scan.

Interest in using quantitative measurements in MRI in clinical trials was seen as early as July, 1993 when the Food and Drug Administration licensed Interferon beta-1b for the treatment of certain patients with multiple sclerosis: lesion areas measured in MRI brain scans were used as surrogate endpoints [4]. On April 15-16 1999, a multidisciplinary, international conference was hosted by the NIH and FDA called "Biomarkers and Surrogate Endpoints: Advancing Clinical Research and Applications". In the section on Neuroimaging Markers, quantitative measurements were described for trials involving Multiple Sclerosis and Alzheimer's disease. This year, the PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group measured the total area of lesions in MRI in clinical trials involving interferon-beta-1a [5]. Currently, Dr. Brigitte Widemann and Dr. Nicholas Patronas of the National Institutes of Health Clinical Center Diagnostic Radiology Department are evaluating the usefulness of volumetric MRI analysis in a National Cancer Institute trial to learn more about the natural history of plexiform neurofibromas in patients with neurofibromatosis type 1 (NF1) [6].

For the purpose of making good quality measurements, we define neuroanatomical segmentation as the extraction of a precise, comprehensive, 3D morphological description of specific neuroanatomical structures of a subject's brain that is obtained robustly and practically from volumetric image data (see [7]). We believe that complete automation of this task is still an unsolved problem. Olabarriaga and Smeulders agree that interaction is often necessary in their survey of interaction in segmentation [8]. Operator interaction can range from completely manual drawing to manually guided oversight of the final result. Besides the more obvious difficulties with analyzing low signal scans, or those with lots of noise or artifacts, practical problems that may necessitate manual intervention include missing data, unexpected data formats, and varying acquisition parameters.

In this paper, we discuss accountability by presenting the program "NVM," one example of the many available software packages designed to make quantitative measurements in MR brain images [1]. We briefly describe the general features of this software, but focus on features developed specifically to provide accountability for clinical trials. This software is the most recent incarnation in a lineage dating back to 1985 that has been developed by researchers the Center for Morphometric Analysis at Massachusetts General Hospital. NVM succeeds the program "cardviews," which succeeded "seg," which was a successor of a general set of anatomic analysis programs developed originally by David N. Kennedy, Pauline A. Filipek and Verne S. Caviness, Jr. A body of literature has been created using these software tools [9-33].

NVM can display multiple views of 3D volumetric MR image data with arbitrary zoom and 3D slice rotation. By default, it shows preset coronal, sagittal, axial and "tile" (all slice) views. The operator can adjust brightness & contrast, display multiple data sets overlaid on one another, and use various tools to create outlines around neuroanatomical structures. Using the Contour tool, a click on a voxel creates isointensity contours everywhere in the current slice image (using that voxel's intensity), and dragging the mouse dynamically adjusts the intensity of that contour. Contours can be edited using the Draw, Erase, and Arrow (selection) tools. Contours are converted to "Outlines" by extracting them and giving them a neuroanatomical label. Outlines can then be displayed with or without a fill color. Once outlines have been created and labeled, their volumes are saved as a spreadsheet to allow statistical analysis.

Histograms can be taken over selected outlines or over an entire image, and clicking on the histogram creates isointensity contours. The

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[1] A list of software packages is available at http://www.cma.mgh.harvard.edu/tools/. NVM is available as Open Source (see http://neuromorphometrics.com).

Landmark tool is used for cropping, positional normalization, and registration of multiple data sets. After cropping, only the important image data is loaded and displayed. Positional Normalization involves setting three landmarks (the mid-sagittal point, and the anterior and posterior commisures). The result is to reslice the data into a standard frame of reference where the slices show the coronal view aligned with the AC-PC axis (as in the Talairach coordinate system [34]).

2 Validity, Integrity and Security

To use neuromorphometrical measurements in clinical trials, the integrity of all images, accompanying data and analysis results must be demonstrably maintained such that nothing is lost, inappropriately released, or corrupted. But more importantly, all data must be shown to have been generated using valid methods.

Data integrity and security can be maintained by adhering to a defined set of procedures that involve logging and signing off of all actions, continual consistency and completeness checks, and redundant archiving. Initially received data must be inspected to be sure it is correct and complete: automated checks for the presence and sizes of files must be accompanied by image quality examinations. Once in the analysis pipeline, calculating and matching checksums must confirm data file integrity. Actual results must be matched with expected outcomes whenever possible by using, for example, range checks on measurements, or by making sure that sub-volumes add up to their total volume. In addition to all data, all documentation and software must also be archived. Data and log files should be digitally signed and even encrypted to insure accountability, integrity, and security.

Even if it is assumed that a measurement method accurately produces values that correlate with veridical anatomical volumes, all data integrity procedures are worthless if the method is not reproducible because it is incompletely defined or improperly executed. This is often the case when applying neuroanatomical measurement methods that are described in academic publications because there is not enough room to present comprehensive details along with results. Moreover, slight differences in the interpretation of the definition of an anatomical boundary or differences in the perception of how that boundary appears in a sliced MR image can significantly alter the final measurement. In short, a method cannot be learned and then reproduced just by reading a paper; it also takes some months of training and validity checking. To demonstrate the accountability of a neuroanatomical measurement method, it must be comprehensively documented in addition to being accurately conveyed. The remainder of this paper describes software features and practices that we have developed to provide accountability in methodology and analysis by insuring measurement validity, and data integrity and security.

3 General Data flow

3.1 Pre-Analysis

When data is received, it must be done so over a secure channel. This can be via the physical transfer of media (such as tapes, CDs or DVDs), over a dedicated transmission line, or else by using a virtual private network (VPN) over the Internet. Before analysis, or even before initial transmission, the data must be stripped of identifying patient information to protect confidentiality. Along with the subject's name, in high resolution imaging data, the subject's face may also be able to be used for identification and may therefore also need to be removed or masked. As in any blind investigation, an internal tracking identifier must be assigned and should be random to prevent operator bias. All data must be checked for completeness and to make sure it has been appropriately acquired.

As data is accepted into the analysis pipeline, various automated "sanity" checks should be performed to prevent partial installation that can lead to database corruption. For instance, simple checks should be done for the presence of all slices of each scan and the existence of sufficient disk space to store all images and results, both in their primary locations and in backup and archive locations. Backup disks (or tapes, etc.) should be physically separate from primary storage disks/computers, and archive locations should be geographically separate.

Image data will likely need to be converted from the received format into the standard local format. As a last step before the actual analysis, the initial data and the converted data should be archived. This, and all other steps must be logged, and the operator should electronically sign the logs and other data files.

3.2 Analysis

Much of the analysis may be automated. But, as mentioned above, the real world does not always allow the automation to perform adequately without any user intervention. Minimally, the operator must start the automated analysis and then check that the output is as expected. In other cases, there must be user input iterated with automated analysis (again, see [8] for a survey). Finally, the operator must check that the analysis was complete. The automated analysis itself should be designed to follow a similar cycle of computing and checking result against expectations.

When using NVM to analyze brain scans, an initial automated program is run which removes intensity inhomogeneities and estimates the main tissue border intensities (for the gray-white matter boundary, gray-CSF boundary, and for the exterior of the brain). These results are then loaded into NVM (as "AutoContours" which are described below) and the operator segments (outlines) the desired neuroanatomical structures. Finally, another automated program is run which calculates volumes, places the results in the proper location and logs these accomplishments.

At any time, the logs can be examined to determine the current status of the project. An additional logging task is to create summary reports (for instance by generating web pages). When regularly checked, these will help detect problems early so that they can be corrected with minimal effort.

Another important check of both the analysis pipeline and the methods is to analyze the same subject multiple times. The most comprehensive way to do this is to acquire multiple scans of some small number of subjects and put them through the complete analysis. As long as there are no obvious distinguishing marks in the redundant scans, the operator should remain blind. If multiple scans cannot be obtained, the same scan can be analyzed twice.

4 Specific NVM Features

There are a number of features of NVM that help insure that the analysis proceeds properly and smoothly. One simple example is to display the resulting segmentations in multiple orthogonal 3D slices as the analysis proceeds; this makes more accurate segmentations because the operator can better understand the 3D shapes being measured.

4.1 Contours & Outlines

Another helpful feature is a conceptual separation between "contours" and "outlines" that facilitates complicated editing operations. Contours represent temporary editable lines that are "extracted" to become outlines. Seven differently colored contours can be created and edited (i.e. different colors serve as different editing buffers). A contour of one color can be converted to other colors, which allows, for instance, parts of the contour to be erased while others are kept. Contours can also be used as auxiliary lines that are drawn in one view to indicate a location as they pass through an orthogonal view (e.g. drawn in a sagittal plan for reference in a coronal image). Outlines represent the final description of a neuroanatomical structure and have an associated text label, color and "seed point" inside the contour. Unlike contours, outlines are a list of points that must be both connected and closed.

4.2 Histogram "Mid-peak" method

The Histogram tool provides a feature that facilitates repeatability of manually guided segmentations. A histogram taken over a region that covers two different tissue types can have two distinct peaks, one corresponding to each tissue type. The intensity between these two peaks can be used to create an isointensity contour to divide the two different tissues. The variance of the intensities around the peaks plays no part in choosing the mid-peak intensity since the estimation of the variance is less robust compared to the estimate of the peak location. Partial voluming has a greater effect on the variance than the mean intensity of a peak and this is made worse because the histogram regions usually

contain only a small number of voxels. Ignoring the variances allows the histogram mid-peak method to give more reproducible results [35]. The histogram tool automatically calculates the mid-peak value when the operator clicks on one peak and drags to the other. The mid-way intensity between the peaks is then used to generate isointensity contours.

4.3 AutoContours

The "AutoContour" feature in NVM increases reliability and speed for manually guided segmentation. This feature involves a list of intensities associated with names such as "gray-white boundary". When the operator selects the name, the corresponding isointensity contour is drawn. The operator then edits the contours as necessary and finally extracts the result as an outline. AutoContour intensities can be automatically estimated (before the main analysis as mentioned above), or may be set by the operator. These intensities can be set to different values at different slices and then the value used at a given slice is interpolated between the values at the set slices. The main benefit of this feature is to have an AutoContour create an isointensity contour every time the operator changes to a different slice. Then contours are automatically created at the interpolated or set intensity. Multiple AutoContours can be assigned to different colors and they will all be drawn after changing the slice. The general procedure is to set initial values for an AutoContour at the middle, the ends, and then in between set slices as necessary to make this intensity match the desired neuroanatomical boundary through the whole brain. Then the operator proceeds slice by slice from one end of the brain to the other and, after switching to a slice, the isointensity contours will be drawn at their proper intensities.

5 Embodying Anatomical Methods: SegMentor

"SegMentor" is the most important and novel feature of NVM. Its purpose is to explicitly define and embed neuroanatomical measurement methods into the software. SegMentor not only provides on-line, context-sensitive instructions and definitions, but also assists with segmentation. SegMentor records, plays, and allows viewing and editing of scripts that provide information to the user and also control the rest of the program. It also allows images and text to be captured as web pages to help document segmentation procedures as part of SegMentor scripts.

With SegMentor, a neuroanatomical measurement method is represented by a collection of XML and HTML documents. XML documents consist of two main types of information: 1) short text descriptions designed to remind the operator what to do next, and 2) macro language instructions. Each step in the script has a link to specific HTML document location that provides help on that step in the script. The interpreted macro language has a C language-like structure. Most commands are simply calls to NVM subroutines so that a script can control everything the user can control through the NVM user interface. Scripts can call system commands and can set the text displayed in two buttons in the SegMentor window that allow the operator to jump to different locations within that script.

A typical scenario for running a SegMentor script proceeds as follows. First, a "to do" list (also an XML file) is loaded and this indicates which XML files to display and execute, and in what order. This allows scripts to have "tasks" which are groups of "sub-tasks". Each sub-task has a button in the task list window and that button causes the sub-task's script to be run. Each sub-task (a separate SegMentor script) has a check box to indicate when that sub-task is done. The first sub-tasks are "prerequisites" that must be checked before the rest of the non-prerequisite sub-task buttons are activated.

When a sub-task button is pressed its script is executed, the first command in that script is usually to display a short text message in the SegMentor window explaining what the script is about to do. At this point, the operator can press the "help" button to launch a browser to display a specific local web page (as determined in the script). The operator follows the instructions in the SegMentor window and finally presses the Enter or "a" (advance) key in image window to execute the next step in the script. In between text messages, the script will usually execute NVM subroutines to prepare the program for the next necessary operator intervention.

```
<?xml version="1.0"?>
<segmentorscript>
<showtext goon="no" doonload="yes" url="HippoICC/index.html">
This SegMentor script will guide you through the
segmentation of the Hippocampus and Intracranial
Cavity.
Hit the Enter key (with the main window selected
and the mouse over an image) to begin...
</showtext>
<task label="Hippocampus" url="HippoICC/index.html">
  <needs>
    <name>Segmentation Lines</name>
    <filename>xml/01.seglines.xml</filename>
  </needs>
  <choice>
    <condition_text>Hippocampus Part 1</condition_text>
    <filename>xml/02.anthippo.xml</filename>
  </choice>
<choice>
    <condition_text>Hippocampus Part 2</condition_text>
    <filename>xml/03.midhippo.xml</filename>
  </choice>
  <choice>
    <condition_text>Hippocampus Part 3</condition_text>
    <filename>xml/04.posthipthal.xml</filename>
  </choice>
  <choice>
    <condition_text>Hippocampus Part 4</condition_text>
    <filename>xml/05.posthip.xml</filename>
  </choice>
</task>
…
```

Listing 1: Example "To Do" List XML file (showing only the first task).

The goal here is to save time and effort for the user– a SegMentor script automates segmentation as much as possible except for difficult steps that need to be done using the operator's experience and anatomical knowledge. In this sense, the SegMentor script performs "bottom-up" low-level automation. Furthermore, since SegMentor can control all operations of NVM, scripts can be written to test the features of NVM and thereby improve software validation.

The following demonstrates how a neuroanatomical segmentation method for measuring the hippocampus can be embodied in a collection of SegMentor scripts. First, the "To Do" list XML file is opened. Listing 1 shows the contents of this file, which indicate that there is one prerequisite and four parts to segmenting the hippocampus. In this example, there are five separate sub-tasks grouped into the first task. The "Segmentation Lines" sub-task must be completed first, then the four parts can be completed in any order but the default is to run through the tasks in order. The first command in Listing 1 is to display an introductory text message in the SegMentor window. It also sets up links to general help information in an HTML file for this script. Following this is a task definition. The first sub-task is a "needs", which is a prerequisite. The next sub-tasks are the four parts. Figure 1 shows the "To Do List" window that can be called up from the main SegMentor window that is shown in Figure 2.

Listing 2 below shows the first part of the script called by "Hippocampus Part 2" in the task list

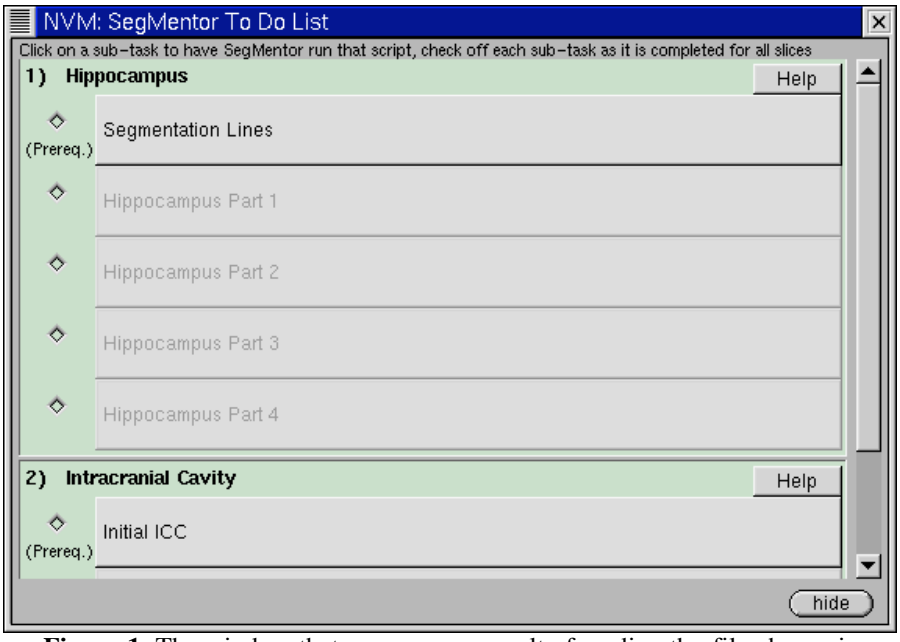

Figure 1: The window that appears as a result of reading the file shown in Listing 1. The prerequisite button "Segmentation Lines" is active for Task 1 while the other four buttons are not because the prerequisite must be finished before the others can be done. Task 2 is for the segmentation of the intracranial cavity.

shown in Listing 1. Figure 3 shows the resulting SegMentor window. Again, the first command is a "showtext" instruction. The next command is to run the macro interpreter ("interpretC") and call a sequence of NVM subroutines. The first two select the label "Hippocampus" in the label tool and checks the box in that tool so that every contour extracted will have that label assigned (with "Right" and "Left" appended automatically). The instruction "SMI_SetCurContour(0);" sets the current contour color to red (the first one). Then the script makes sure all of these contours are cleared, and does the same for yellow contours. Following this, it chooses the contour tool so that the operator has only to click on a voxel and the red isointensity contour will be drawn. The last two commands clear the text and actions for the script-controlled buttons.

The next "showtext " command tells the operator what has happened and what to do next. The following "interpretC" command does what the text describes, and then sets the tool back to the Contour tool (since the operator had to also use the Arrow tool), and then turns on the first script-controlled button ("MiscGoToButton") by setting its text to "do again" and by setting the jump target to the statement labeled "DoAgain" (which is the first "interpretC" command in the file).

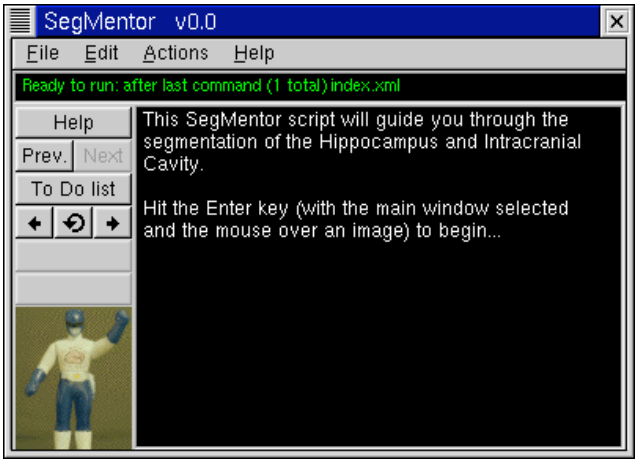

Figure 2: The main SegMentor window. The top line of text displays the current status ("Ready to run:…"). The large text area displays text from the script and the menus and buttons allow the operator to interact with the script. Two more buttons can appear and can be controlled by the script.

```
<?xml version="1.0"?>
<segmentorscript>
<showtext goon="no" doonload="yes"
url="HippoICC/html/hippocampus.html#MidNoAmig">
Hippocampus Part 2:
This is for segmenting the hippocampus when the
Amygdala is no longer present.
Hit the Enter key to continue...
</showtext>
<interpretC goon="yes" label="DoAgain">
<![CDATA[ int main(void) {
  SMI_ChooseLabel("R-L Hippocampus");
  SMI_SetAssignLabelButton(1);
  SMI_SetCurContour(0);
  SMI_ClearTheContour("Coronal","DELCONTKEY");
  SMI_SetCurContour(1);
  SMI_ClearTheContour("Coronal","DELCONTKEY");
  SMI_SetCurContour(0);
  SMI_SetTool("CONTOURTOOL");
  SMI_SetMiscGoToButton(1,"","");
  SMI_SetMiscGoToButton(2,"","");
}
]]></interpretC>
<showtext goon="no" url="HippoICC/html/hippocampus.html#MidNoAmig">
The Contour Tool has been selected and the red
contour has been chosen.
Create the medial border of the hippocampus
using a contour line.  Erase as appropriate,
and then use the Arrow Tool to select it.
Press the Enter key to continue and I will
promote it to yellow ("v") to save it for later
and then clear the red contour...
</showtext>
<interpretC goon="yes">
<![CDATA[ int main(void) {
  SMI_ProDeMoteContourSelection("Coronal","PROMOTE");
  SMI_ClearTheContour("Coronal","DELCONTKEY");
  SMI_SetTool("CONTOURTOOL");
  SMI_SetMiscGoToButton(1,"do again","DoAgain");
  }
]]></interpretC>
...
</segmentorscript>
```

Listing 2: Example SegMentor Script showing the first showtext and interpretC commands for the "Hippocampus Part 2" button seen in Figure 1.

6 Conclusions

By properly using the procedures and features described above, the resulting neuroanatomical measurements can be demonstrated to an auditing authority to be valid not only because every step in the analysis has been properly completed, but also because the methods have been completely documented and followed. The use of established procedures involving log files, digital signatures, checksums, consistency and completeness inspections, and various data and

result checking insure integrity and security. Beyond assurances about analysis techniques, the measurement methods themselves must also be accountable.

Olabarriaga and Smeulders [8] point out that difference in judgment decreases repeatability in segmentation and say that nothing can be done about this. However, we assert that good quality SegMentor scripts can change the way different operators judge boundaries (for instance) by providing detailed definitions of those boundaries. The scripts also increase repeatability because they take the operator through specific sequences of steps. Using SegMentor and the other features and procedures described herein, quantitative measurements of neuroanatomical structures will be accountable enough to be used as surrogate endpoints in clinical trials.

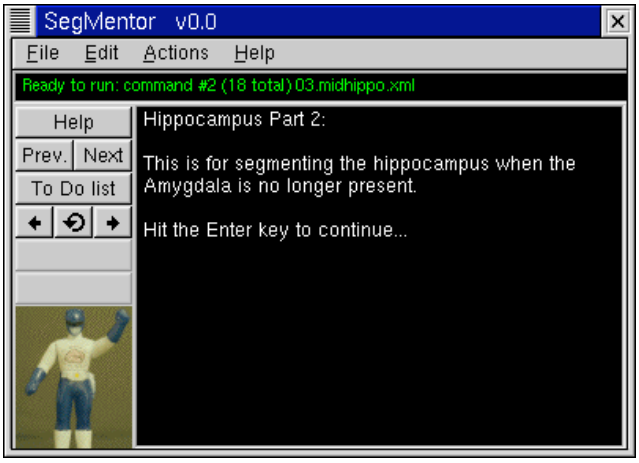

Figure 3: The main SegMentor window that results after pressing "Hippocampus Part 2" in the To Do List window.

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