# Computational quantification of white matter hyperintensities

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## Abstract:

Hyperintensities in the neural white matter are areas of especially high contrast and are detectible by fluid attenuation magnetic resonance imaging(FLAIR). These hyperintense regions are associated with normal aging of the brain, but they can also indicate neurological diseases such as early dementia and Alzheimer’s. Building upon earlier work, we develop a Python based software tool to automatically quantify the volume of hyperintense regions, providing information that can be used to aid researchers by giving anatomical data that they can correlate to patient diagnoses. In order for our work to be more general and ported to other scanning hardware, we develop a semi-automatic calibration mechanism that leads to proper threshold values for a given scanner.

## Keywords: neuroimaging, Python, white matter hyperintensities

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## 1 Introduction:

## 1.1 White matter hyperintensities:

White Matter Hyperintensities(WMH) are artifacts from MRI scans appearing as voxels with extraordinarily high contrast in the white matter regions of the brain. They are most detectable with fluid attenuation inversion recovery(FLAIR) scans, and, while WMH regions correlate with the normal aging of the brain, they can also indicate, when appearing in excess, neurological and cognitive disorders.

Researchers involved in a study of patients with symptoms of dementia or other cognitive impairments would be interested in whether there was an anatomical correlation with the diagnosis. For this purpose, we have developed a software tool to automatically quantify the volume of WMH artifacts in an MR scan. Our tool gives the researchers the volume of the WMH for an entire three-dimensional scan.

## 1.2 Automatic detection of WMH

Our software tool is based on previous work in the automatic detection of WMH regions developed by(Hulsey 2008)for a master’s thesis andprovides an algorithm implemented with a bash based script, calibrated to a particular scanner, that calls programs from the FSL suite of software(Smith et. al, 2004; Woolrichet. al., 2009). This approach uses MPRAGE images to develop a set of binary masks towards the general goal of isolating the white matter of the brain. As MPRAGE MR scans are inadequate for delineating WMH, these generated masks are thencoregistered to the FLAIR image space.

Using the transformation matrix generated by the FSL tool FLIRT (Jenkinson and Smith, 2004), it generates FLIRT based masks from the MPRAGE binary masks. Using the tool fslstats, again part of the FSL suite, it determines the mean and standard deviation of the contrast values for the peripheral cerebral white matter tissue.

Once these values are acquired, Hulsey’s algorithm adds the mean to the standard deviation multiplied by lower and upper thresholds, 3.0 and 3.5 in the original paper, giving two values. The upper threshold added to the mean multiplied by 3.5 is applied to the FLAIR cerebral tissue mask, and the lower threshold is likewise multiplied and applied to the entire FLAIR white matter mask generating two binary three dimensional images. Hulsey adds the two together generating a single binary three-dimensional scan containing the regions afflicted by WMH.

There are many limitations in Hulsey’s approach, the most prominent being that it is extremely time consuming as the tools used in the algorithm are computationally expensive and must be run sequentially in the order given by the bash script. Hulsey’s approach is also inadequate when applying it to new scanners. We found that Hulsey’s values for upper and lower thresholds dramatically underestimated the extent of the WMH. In fact, running the script with the default values detected no WMH in even cases with extraordinarily obvious effected regions. Furthermore, because of the computational cost of running the program, manually trying new threshold values to find the ideal for our scanning hardware was temporally prohibitive. Lastly, we found that when we applied Hulsey’s algorithms to our scans, it detected erroneous regions, i.e., areas known not to be white matter, as WMH.

## 1.3 Python approaches to neuroimaging

Python is a multi-paradigm programming language that is increasingly being used in the sciences. The primary attractions to Python are its power, brevity, ease of use, interactivity, the inclusiveness of its library, and the ease in which one can interact with third party modules. A Python based suite of software, NIPY, has been developed to aid in neuroimaging with especial emphasis on fMRI analysis. Nipype (Gorgolewski, 2011) was developed under this suite and specializes in interfacing with existing neuroimaging software tools such as FSL, SPM, and FreeSurfer.

Nipype allows one to create a workflow, linking nodes together with the output of one being the input to another. After a workflow is defined, it is run, and with each step, software artifacts are created and stored in the workflow directory, enabling one to easily debug and validate an algorithm if necessary.

We also make use of the tool NiBabel, also in the NIPY suite that allows one to easily import images of a variety of types, e.g., NIFTI, which we use in our volumetric analysis.

## 2 Methodology

## Figures:

See these guidelines for figures:more

## 2.1 Context

Our lab was contracted by an investigator in the department of psychology to study a potential anatomical correlation between patients who had been labeled with various cognitive impairments such as early dementia.

We began our investigation by searching the literature to determine corollaries with neuro-anatomy and cognition and found that WMH lesions can be prominently comorbid with cognitive decline. Literature reviewed includes (Gunning-Dixon and Raz, 2000) which studies study the correlation of WMH with normal aging, excluding from their study patients with dementia or abnormal cognitive decline. They do conclude however that the presence and extent of WMH is related to cognitive decline, primarily the reduction in processing speed, though they were unable to conclude that WMH artifacts have bearing on intelligence.

(DeCarli et. al., 2005) study subjects diagnosed with cognitive impairments and find that the WMH regions in a study of 55 subjects range in volume from 1.1 to 63 mL.

(Yoshita et. al., 2006) study the relationship between WMH, normal aging, and mental impairments. They too found a relationship between WMH volumes and age, but controlling for age, WMH extent was associated with diagnosis of mild cognitive impairment or Alzheimer’s disease. Furthermore, they note that the location of WMH, whether in the periventricular regions or in the deep white matter has implications in the correlation to diagnosis.

## 2.2 Python implementation

We found Hulsey’s approach to WMH detection to be of limited use for our purposes. In order to calibrate our system, we had to run the program with many different threshold values representing the standard deviation that would demarcate WMH. Furthermore, there was an additional problem with our scanning hardware; it produced very high contrast regions in areas known to be outside of the white matter, e.g., on the periphery of the brain.

Hulsey’s program uses the bash shell to invoke software tools from the FSL suite. This is a perfectly valid approach, but it is slow and completely linear, executing commands in the sequence given. We made the decision to use a more robust programming language, Python, to develop a tool that could be later integrated into more complex, higher level programs.

We use Nipype to create a workflow by linking nodes, which interface to the FSL tools. The nodes have defined dependencies, as is discussed in (Gorgolewski, et. al., 2011), but aside from that, they can be run in any order as long as dependent nodes are executed later. Furthermore, this approach has the benefit of generating software artifacts for each step in the workflow, i.e. output files that one can examine in order to validate the algorithm. This last feature was very useful when we attempted to correct for erroneous WMH detection in non-white matter.

Because of these erroneous values in the non-white matter produced by our scanning hardware, it was initially difficult to get accurate volumes of the WMH. To remedy this, we developed a MATLAB based script that erodes the edges of the masks by a defined number of voxels in each direction. This script was invoked from within the Nipype framework as an intermediary layer in the registration of the MPRAGE masks to FLAIR space. Through this solution, no white matter was removed from the scans, and we were able to get accurate values for the volume of the WMH.

The volume of the WMH is very dependent upon the defined threshold values, i.e. the standard deviations that, when surpassed by the voxel contrast value, would register the voxel as WMH. It was necessary to develop a calibration mechanism to find the optimal values for the lower and upper standard deviation. To do this, we created a script that invoked our program repeatedly with different threshold values. From the output of this, we created a set of montages for each set of threshold variables that could be visually analyzed to determine the closest values that properly detect the WMH regions.

In adopting this tool to new hardware, it will be necessary to run this calibration script, and someone familiar with WMH should study the resulting montages, preferably a board certified neuro-radiolgist.

## 3 Analysis

## 3.1 Volumetric analysis

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| Subject | Diagnosis | WMH Volume |
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## 3.2 Example images

## 4 Further work

## 4.1 Differentiating between deep white matter and periventricular lesions

(Gunning-Dixon and Raz, 2000; Yoshita et. al., 2006) note that it is very difficult to differentiate between WMH lesions in the deep white matter and the periventricular area. Our program quantifies the volume of the WMH in all of the white matter, including the peripheral mixed tissue. Future work should concentrate on differentiating between these, as this data would be relevant for a researcher investigating anatomical relationships.

## 4.2 Integrating into larger workflows

By using Python and Nipype, our tool can easily be extended and integrated into more sophisticated neuroimaging algorithms. The detection of WMH volume levels is now possible, and other tools can make use of the output of our program. Furthermore, through the use of third-party Python tools, we can interface with, for example, patient databases on servers by either using Python's native networking APIs or one of the specialized tools that have been developed for health systems information.

## Conclusion

The detection of white matter hyperintensities is important to the work of researchers wishing to find anatomical correlations to neurological disorders. Much research has been done on the interplay between WMH, aging, and cognitive disease. It has been shown that WMH correlates highly with mental impairments, and by automating the detection of these hyperintensities, researchers are enabled to better understand the maladies afflicting their patients.

We have successfully implemented Hulsey’s algorithm, making improvements in enabling it to work on disparate hardware through the use of calibration tools. Furthermore, one can integrate our work into larger frameworks, further adding value to the Python-based approach.

We can conclude our paper by stating that Python has made our workflow more efficient, and has enabled us to implement Hulsey’s algorithm in a more robust manner.