Amyloid Profile Continued Support with Brain Phantom Development
Larry Pierce, David Haynor, John Sunderland, Paul Kinahan
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Title: Amyloid Profile Continued Support with Brain Phantom Development
PI: Paul E. Kinahan
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Primary goals and objectives

To design and construct a prototype brain Digital Reference Object (DRO) phantom with properties appropriate for testing software used to characterize amyloid uptake patterns in a quantitative fashion. The result can be used to help develop methods to be used in the PET amyloid profile and to test current commercial and academic amyloid analysis software in a consistent fashion.

Summary of Main Results

1. The PET Amyloid DRO was completed and was evaluated by four experts. The unanimous consent was that the DRO provides a realistic appearance of a PET brain image of amyloid binding radiotracer, as well as ground truth information for evaluation of image analysis software. There is, however, room for some improvements:

   - Due to the complexities of converting a reference MRI imaging to a PET amyloid binding radiotracer image, some adjustments and corrections should be made in a future version of the PET Amyloid DRO.

   - The PET image should be accompanied with corresponding CT and MRI images.

   - The radiotracer concentration and biodistribution should be adjustable to model different PET-amyloid imaging agents.

2. Due to the project evolution, there are now small differences between the underlying structures of the PET Amyloid DRO and the template used for the physical phantom. These should be merged in a future version of the PET Amyloid DRO.

3. Since we now have IRB-approved access to roughly 250 de-identified high-resolution MRI series of patients with known or suspected Alzheimer's disease or other dementias with comparable brain anatomies, it would be feasible to construct a library of PET Amyloid DROs with different characteristics.

Overview

This project is the digital phantom (reference object) part of the Brain Phantom Development Project in support of the QIBA PET Amyloid Profile. The physical phantom is being developed by John Sunderland as a linked, but administratively separate, joint project (Subaward HHSN268201300071C (X-1)).

It has become clear during the course of discussions on constructing a PET Amyloid Profile that currently available brain phantoms are inadequate and ill-designed for quantitative assessment of amyloid tracer uptake, and that amyloid imaging, in particular, and the field of neuro-PET imaging in general, would significantly benefit from parallel development of both a digital and physical brain phantom designed to test quantitative approaches to PET amyloid imaging.

The proposed project was an academic/industry cooperative effort to design, develop, and manufacture these prototype brain phantoms that will be specifically designed to meaningfully test promising quantitative amyloid imaging and analysis approaches, including but not exclusively SUVr.

This was the first part of a two-phase project designed as follows:

1) The development of a PET Brain Digital Reference Object (DRO) with separate gray and white matter anatomies, with well-defined reference regions for SUVr (the amyloid metric currently identified for the profile) calculations. This work leveraged off of the significant foundational PET DRO work already performed. Paul Kinahan led this effort.

2) The development of an amyloid specific physical brain phantom whose design would be modeled directly from the final version of the Brain DRO using porous high density polyethylene. John Sunderland led this effort, and a separate report will be provided for this component.

Proposed Timeline and Deliverables

0-Month

- Returned, signed Sub-award Agreement

3-Month

- Design phase of Brain DRO – Defining concentrations/contrasts using pooled information from the amyloid tracer manufacturers.

6-Month

- Implement prototype brain DRO. On-site UW testing using various commercial amyloid analysis software.

12-Month

- Test prototype Amyloid Brain DRO. External testing of Brain DRO using a single amyloid analysis platform.

- Compiling of Prototype Brain DRO results different Amyloid analysis software analyzed at different sites.

Project Details

The construction of the Amyloid PET DRO was based on the following steps, each of which is described in turn. Following the construction was the evaluation phase, which is described separately.

(1) Find a high resolution MRI images from a patient or subject with appropriate brain structure
(2) Segmentation of needed regions from brain MRI image
(3) Assigning appropriate values to segmented regions
(4) Adding plausible levels of blurring and noise to mimic PET image characteristics
(5) Saving the final image in an appropriate DICOM structure

<u>(1) High resolution MRI images</u>

We evaluated the following sources:

Zubal Brain Phantom

A dedicated head phantom was created by manually segmenting 124 transverse MRI were outlined. The transverse T2 slices, recorded in a 256x256 matrix have isotropic voxel dimensions of 1.5 mm. This dedicated head phantom contains 62 index numbers designating neurological and taxonomical structures in the brain, as well as anatomical regions. The final volume is contained within a 256x256x128 byte array.

The image data is free to download at noodle.med.yale.edu/zubal. Unfortunately the license for the image data states:

> "... do not pass along any part of the phantom to anyone else (they can download a copy directly)"

> " … our phantom data is "free-ware" and cannot be used for commercial business."

Based on the above restrictions we decided that the licensing was too uncertain.

Allen Brain Institute

Free java viewers and data are available at human.brain-map.org/mri_viewers/data. However the data are from subjects with "... no known history of neuropsychiatric or neurological conditions".

These data were judged not suitable for an amyloid-positive neuroanatomy.

The Whole Brain Atlas

Free java viewers are available at www.med.harvard.edu/aanlib. Unfortunately the license for the image data states:

"Commercial reproduction or multiple distribution of any kind is prohibited."

Based on the above restrictions we decided that the licensing was too uncertain.

BrainWeb

The McConnell Brain Imaging Centre (BIC) of the Montreal Neurological Institute, McGill University provides a Simulated Brain Database (SBD). The SBD contains a set of realistic MRI data volumes produced by an MRI simulator. These data are freely downloadable at www.bic.mni.mcgill.ca/ServicesBrainWeb/HomePage. However the MRI data are based on two anatomical models: normal and multiple sclerosis (MS).

These data were judged not suitable for an amyloid-positive neuroanatomy.

Alzheimer's Disease Neuroimaging Initiative (ADNI)

Images from the North American ADNI study participants, including Alzheimer's disease patients, mild cognitive impairment subjects and elderly controls, are available from the Laboratory of Neuro Imaging (http://loni.usc.edu). We corresponded with Dr. Boyco who

offered to act on our behalf, but did not hear back. Although this was promising, when we evaluated the data (after registering) it was difficult to find high-quality MRI image sets that were suitable for segmentation.

University of Washington patient images

AT UW the neuroradiology team maintains a database of approximately 250 (currently) image sets of high-resolution MRI series of patients with known or suspected Alzheimer's disease or other dementias. Evaluation of these images conformed that they have suitable brain anatomies. And each patient image set contains high resolution 1 mm slices in each of the three primary orientations (transverse, sagittal, and coronal).

Explanation of the project delay: An IRB application was submitted in January 2015 to gain access to the images and allow distribution of de-identified versions for this project. This lead to the delay in the project as the UW has two IRB boards, and the first one we used (as we were directed) eventually decided that the IRB application should be reviewed by the other IRB board. This was done, but we did not gain IRB approval until late July 2015. This lead to delays for both this project and for the companion project lead by John Sunderland, as the brain image template was used for the physical phantom construction.

At UW the neuroradiology team uses a commercial neuroimage analysis package called 'NeuroQuant' by Cortechs Labs (http://www.cortechslabs.com/neuroquant), which automatically segments and measures volumes of the hippocampus, ventricles and other brain structures and compares these volumes to norms. We tested the software with several patient image sets, and had the results confirmed by an experienced neuroradiologist. Sample patient images from the UW database are shown in Figure 1, and a sample report from the NeuroQuant product literature is shown in Figure 2.
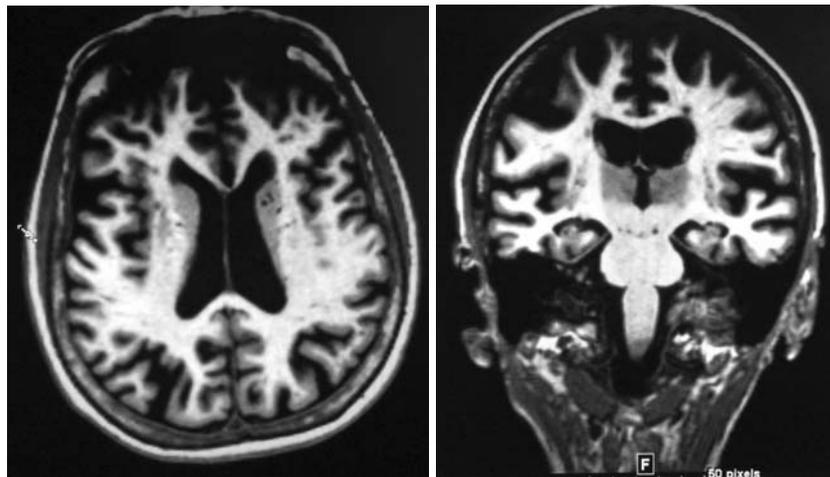

Figure 1. Sections through a T1w MRI patient image after processing by NeuroQuant. This patient was from the UW database and illustrates anatomical characteristics of Alzheimer's disease (e.g. enlarged sulci etc.). The colors code different segmented regions.

In the processed images each voxel has is stored as six bytes, two for red, two for green, and two for blue. Only 7 bits are used for the dynamic range of the data given in these images. So each pixel is labeled as red, green, and blue values, each between 0 and 127. The gray matter is tagged as red voxels.

PATIENT INFORMATION

Patient ID:	Patient Name:		Sex: M	Age: 84
Accession Number:	Referring Physician:		Exam Date:	

MORPHOMETRY RESULTS
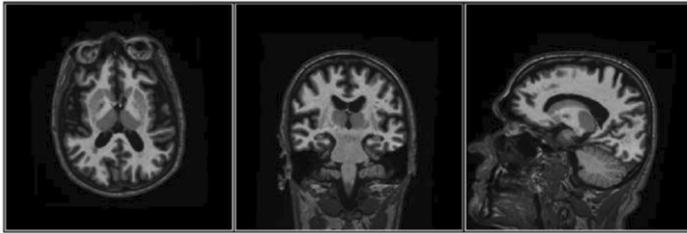
Hippocampal Occupancy Score (HOC)		0.64	
Brain Structure	Volume (cm³)	% of ICV (5%-95% Normative Percentile*)	Normative Percentile*
Hippocampi	6.42	0.40 (0.30-0.45)	70
Lateral Ventricles	46.12	2.88 (2.22-5.48)	33
Inferior Lateral Ventricles	3.56	0.22 (0.16-0.33)	52

AGE-MATCHED REFERENCE CHARTS*
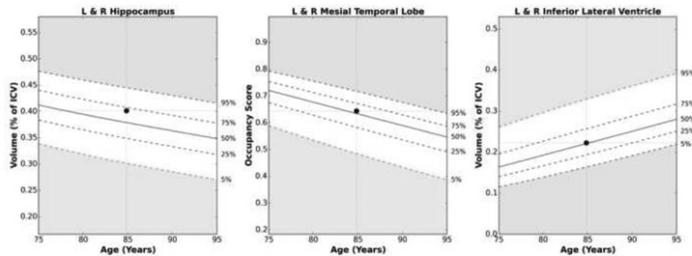
*Charts and normative values are provided for reference purposes only.

Figure 2. The NeuroQuant report tool provides detailed brain structure volume for the whole brain, lateral ventricles and thalami and age-matched reference charts for cortical gray matter, cerebral white matter, white matter hypointensities, third ventricle, hippocampi and inferior lateral ventricles. The normative percentile is given as the structure relates to a normative population of healthy individuals with the same imaging parameters. Figure is reproduced from the NeuroQuant product literature.

A potential advantage of the using the NeuroQuant report tool is matching patient images to the hypothesized progression of characteristics of Alzheimer's disease (Figure 3). To this end we selected a sample patient image for evaluation that exhibited marked structural anatomy (Figure 1) to be the basis for an amyloid PET positive reference object.

(2) Segmentation of Brain Structures

The primary goal is to segment the gray matter, white matter, and cerebrospinal fluid (CSF) regions within a brain that has anatomical characteristics of Alzheimer's disease, so appropriate PET image values can be assigned. This could not by done completely (thus simply) with NeuroQuant, since it does not explicitly identify white matter.

This segmentation necessitates a pre-processing method (known as "skull stripping") where the brain is extracted from the MRI image volume and the muscle, eyes, and other non-brain anatomy are removed from the volume. The process of skull-stripping is non-trivial and there are many software packages for performing this task. We tested 3D Slicer, FSL-BET, and NeuroQuant software packages in an attempt to perform the skull-stripping preprocessing step.
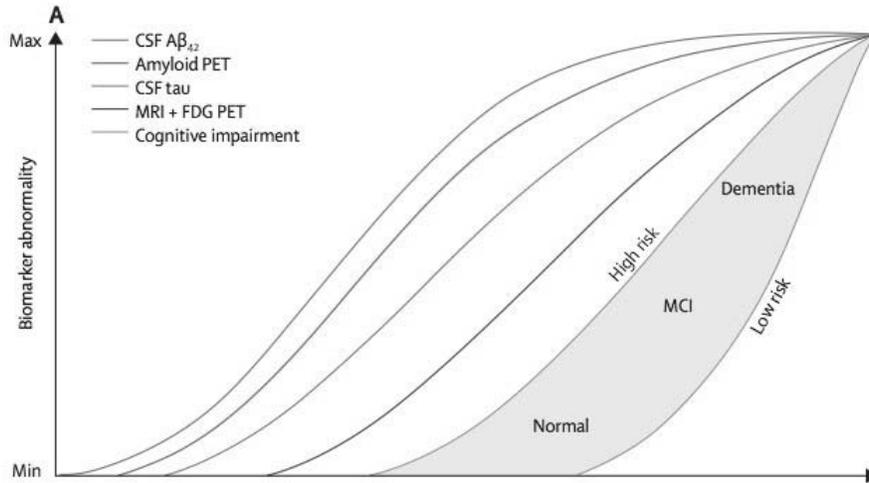
Figure 3. Potential method to link structural MRI features to amyloid PET biomarker signal levels (modified from fig. 5 of J et al. Lancet Neurol, vol. 12, no. 2, pp. 207–216, Feb. 2013). Hypothetical model of dynamic biomarkers of the A|zheimer's disease pathological cascade over time (years). Neurodegeneration is measured by FDG PET and structural MRI, which are drawn concordantly (dark blue). By definition, all curves converge at the top right-hand comer of the plot, the point of maximum abnormality. Cognitive impairment is illustrated as a zone (light green-hued area) with low-risk and high-risk borders. Aβ = amy|oid β. FDG = fluorodeoxyglucose. MCI=mild cognitive impairment.

Unfortunately, none of these software packages proved useful in for the pre-processing step. The 3D Slicer and FSL packages tended to remove wanted anatomy (regions of brain) or leave unwanted anatomy (e.g. eyes, muscle) within the image volume (Figure 4). Despite exhaustive tuning of the software parameters, an acceptably-extracted brain volume was not obtained with either software package.
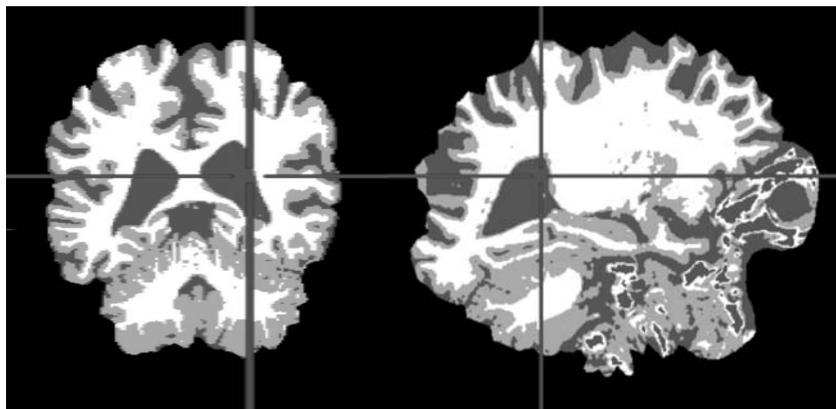

Figure 4.   An attempt at skull-stripping by the FSL-BET software package. Any anatomy remaining in the image volume is considered to be 'brain' by the software. The eyes and other non-brain anatomy are included, indicating that the software believes them to be part of the brain. Not visible are several regions of gray matter that have been excluded from the volume, indicating that those are not considered to be part of the brain.

The NeuroQuant software seemed to correctly identify different regions of the brain, but simply generates a color-coded map of the entire MRI volume (Figure 5). In these color-

coded volumes, the non-brain anatomy is color-coded identical to the white matter within the brain, making extraction difficult.
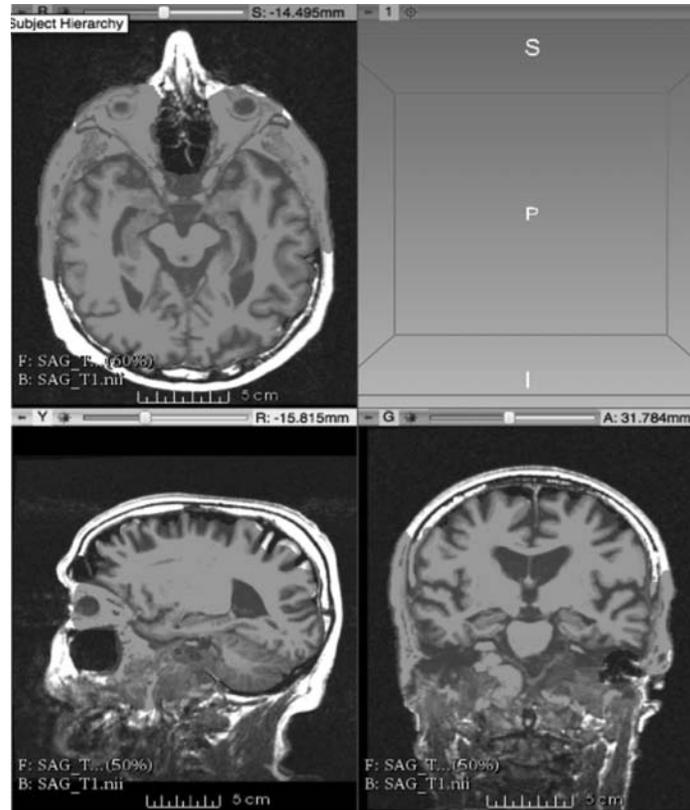

Figure 5. An attempt at skull-stripping using the 3D Slicer software. The region in red indicates what the software has tagged as 'brain'. Many non-brain regions such as the eyes have been labeled as 'brain', which some regions of gray matter have been labeled as 'not brain'.

To push the project forward, it was decided that the skull-stripping task would be performed via t very time-consuming manual segmentation and verification. Once the binary skull-stripping mask was generated (differentiating brain and non-brain anatomies), the NeuroQuant color-coded MRI image volumes were used to differentiate the gray matter, white matter, and CSF within the volume (Figure 6).

In addition the grey matter in the cerebellum was also manually segmented, as NeuroQuant classifies the cerebellum as a single object, as can be seen in Figure 2.
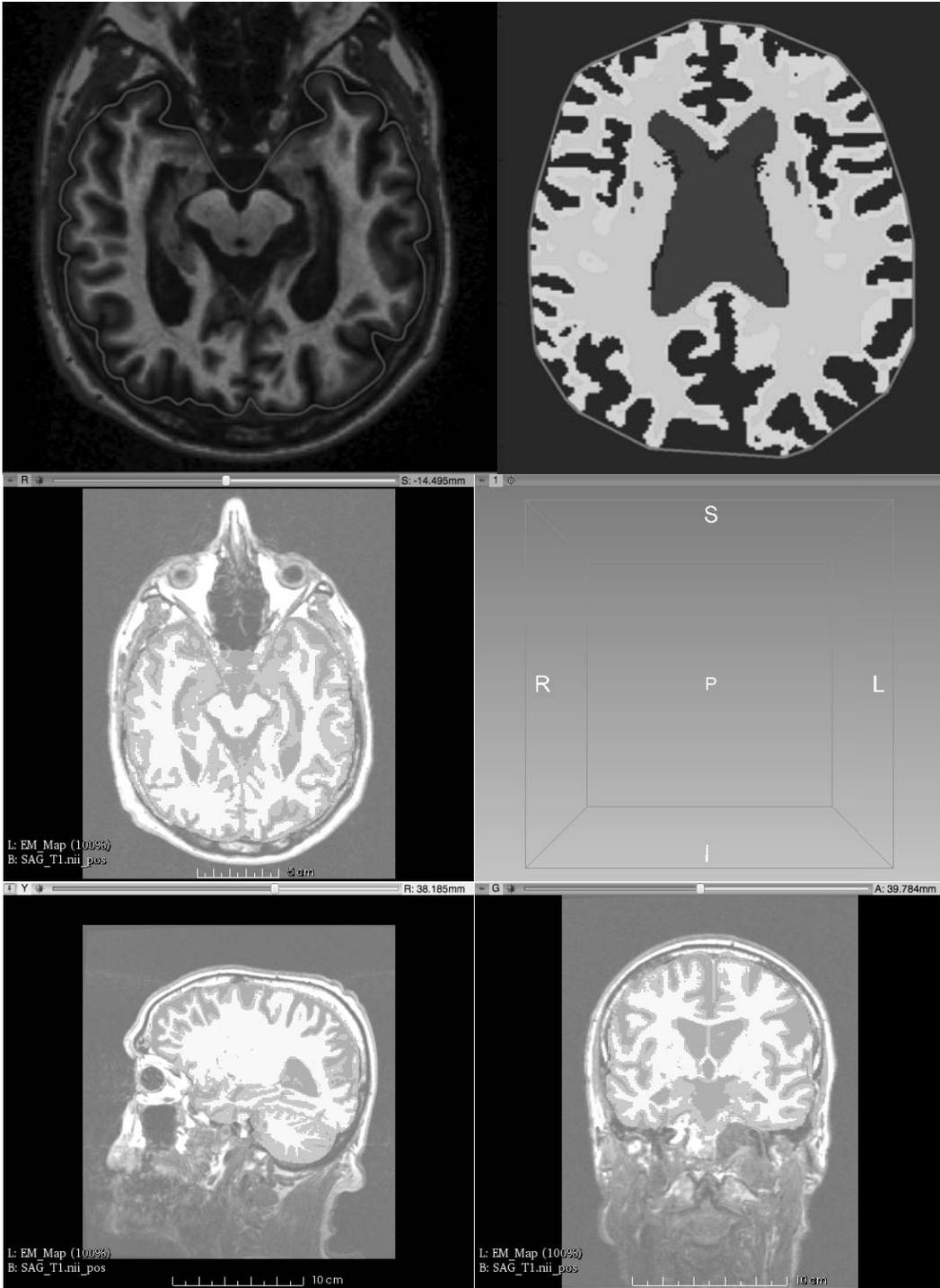
Figure 6. Processed image examples using manual segmentation and NeuroQuant

The gray matter is tagged as red voxels, which are easy to identify in the images. The CSV is tagged purple (at least in the interior regions). The white matter in the images is shown as white/gray voxels. Those have pixel values where the red, green, and blue are roughly equivalent. The problem is that all of the anatomy outside of the brain is also labelled with exactly the same grayscale values. Thus, more advanced techniques are needed do differentiate white matter and muscle, etc. There were problematic boundary