Reference region quality control as a critical aspect of amyloid measurement using PET imaging

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Background

The cerebellar cortex, often used as the primary reference region to evaluate PET amyloid burden, profoundly impacts all region of interest standardized uptake value ratio (SUVR) measures. However, it is vulnerable to numerous sources of artifact that must be considered in obtaining and interpreting results. These sources include truncation of the PET image due to subject positioning; image noise at the edge of the scanner axial field of view (FOV); differences in scatter correction; subject motion; differences in scanner sensitivity and reconstruction methods used; and differences in signal intensity at various locations within the same reference region. Since differences in reference region value of even a few percent can impact longitudinal measurements in clinical trials or alter the classification of a border-line amyloid positive classification, quality control is of great importance.

Objectives

The objectives of our study were to identify the frequency of occurrence of sources of reference region artifact in a multi-center data set (ADNI) and to characterize their impact upon volume of interest and SUVR results, with the goal of providing practical guidelines for analysis.

Methods

We examined cerebellar attributes of 226 PiB scans from 103 ADNI subjects imaged at 13 sites with 6 different PET scanner models (100 scans acquired on HR+, 53 HRRT, 35 GE Advance, 15 GE Discovery, 23 Biograph HiRes). Clinical diagnoses at time of PiB scan were: Normal (NL, 53), MCI (107), and AD (66); mean age 77(SD 7) yrs.

The PiB images used in this study were the pre-processed files available for download from ADNI as of August 2011. PiB images were obtained from the 50 – 70 minute summed frames. Using Statistical Parametric Mapping (SPM8), each subject's baseline MRI was coregistered to the corresponding baseline FDG and all available PiB scans and spatially normalized to MNI space by high-dimensional warping (DARTEL) with the standard template included in the VBM8 toolbox[1]. The subject-specific transforms obtained were applied to each coregistered PiB scan. Initial testing was conducted on unsmoothed images in order to understand behavior by scanner prior to influencing inter-slice signal levels.

A full gray matter cerebellum volume of interest (VOI) was overlaid upon each image to classify the reference region as follows: (a) *multi-slice truncated,* where PET image truncation had occurred to a degree that excluded VOI voxels beyond a minority of the lowest VOI slice, (b) *at edge of FOV,* where the VOI was within 1 cm of the inferior edge of the PET scan, or (c) *fully included*. Two cerebellar VOIs were then applied for sampling: (a) a probabilistic gray matter VOI (21 2 mm slices, Figure 1), and (b) a gray matter VOI created for each subject by intersecting a whole cerebellum mask to each subject's spatially normalized, thresholded gray matter MRI segment (27 2mm slices, Figure 2). A multi-slice subcortical white matter VOI was also applied for comparison to cerebellar values (Figure 1).

Each slice was measured as a separate VOI. Image assessment and measurement were conducted using PMOD software[3]. Variance was assessed using (a) all available scans, (b) all scanners, one scan per subject, and (c) across scanner models.

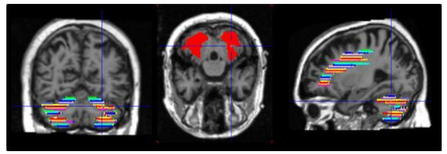


Figure 1. Probabilistic multi-slice gray matter cerebellum VOI and subcortical white matter VOI.

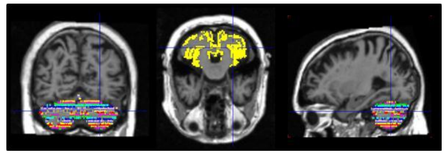


Figure 2. Individually gray matter thresholded cerebellum VOI.

Since cerebellar truncation typically takes place at an oblique angle, actual cases where subjects had no truncation in one scan but multi-slice truncation in another scan were tested, whereby in one case two different cerebellar VOIs matching the subject's available anatomy in each scan were used, and in the second case the same truncated cerebellar VOI was used for both scans.

Results

Frequency of Occurrence of Truncation and FOV Edge Location

Of the 226 scans, 4% had multi-slice truncation causing sampling outside tissue (Fig 3), and 12% additional scans had reference region overlap with scan edge where artifact is known to occur (Fig. 4).

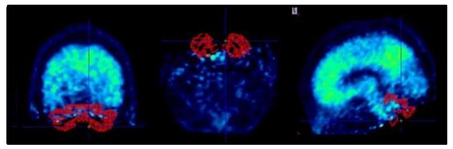


Figure 3. Example of multi-slice cerebellar truncation. VOI in red shows location of cerebellar cortex if no truncation had occurred.

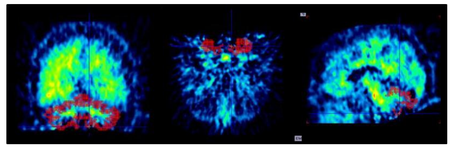
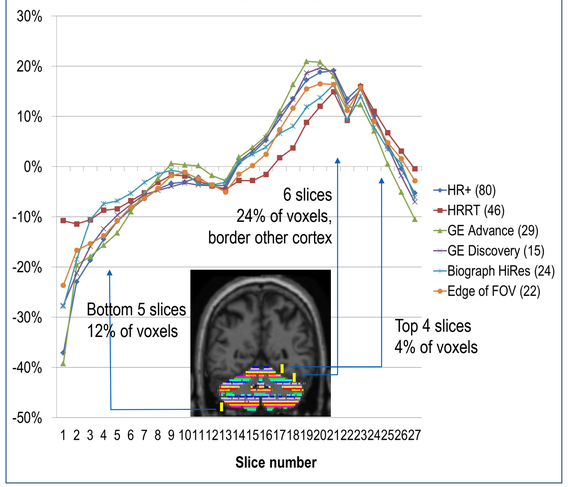


Figure 4. Example of reference region location at edge of FOV.

Variance in Signal Intensity: Inferior to Superior Cerebellar Cortex

Measured values in cerebellar cortex increased from inferior to superior slices relative to average slice value and weighted average VOI value. The increase was consistent across scanners and subjects but degree of inferior slice reduction differed by scanner (Fig 5.).

Fig. 5 **Slice value %age above or below average cerebellar cortex slice value for 27 inferior to superior cerebellar cortex slices, 216 PiB scans**

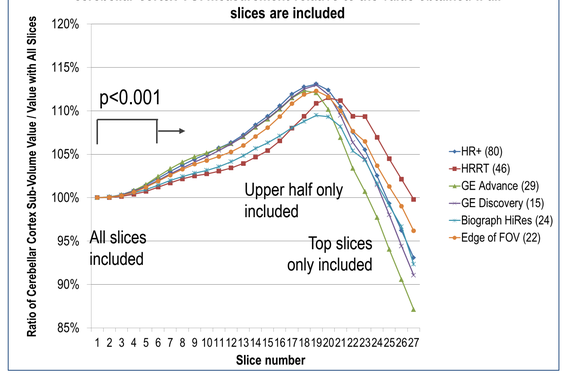


Results were consistent with the above when using only the first scan from each subject, and when using the probabilistic reference region mask rather than the subject-specific thresholded masks.

Impact of Using Different Reference Tissue to Compare Scans

Elimination of an increasing cumulative number of lower slices resulted in differences in overall VOI value of up to +/-13% on average (Fig. 6). Elimination of oblique sections of cerebellar cortex was found to produce differences in reference region value of up to 20%. Sampling slices outside of available tissue created much larger errors.

Fig. 6 **Impact of leaving out an increasing number of lower slices from the cerebellar cortex VOI measurement relative to the value obtained if all slices are included**

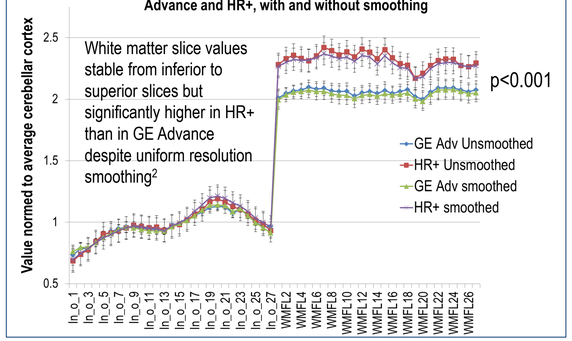


Use of a truncated reference region in measuring a first scan for a subject, and the whole reference region for a second scan, created artifactual changes in SUVR ranging from a few percent to 20%.

Impact of Scanner Changes With and Without Smoothing

Cerebellar cortex and subcortical white matter values (all normed to the average cerebellar cortex value) were compared in 6 subjects who changed from a GE Advance scanner to an HR+ scanner (Fig. 7)

Fig. 7 **Cerebellar Cortex (GM) and Subcortical White Matter (SWM) slice values (inferior to superior left to right) for 6 subjects having scans on both GE Advance and HR+, with and without smoothing**



Discussion and Conclusions

Truncation of cerebellar reference region tissue may occur in a minimum of 4% of amyloid imaging scans, and location at the edge of the scanner axial FOV in another 12% in multi-site, multi-platform trials.

Cerebellar cortex values vary significantly from inferior to superior slices, increasing throughout the lower 75% of slices. Lowest slices are most variable relative to average value and across scanners, and are most vulnerable to truncation and edge of FOV effects. Reference region definitions may consider omission of the bottom 1cm to minimize variance, as well as the uppermost 4 slices which also vary.

"Cerebellar cortex" definition (which slices included, erosion) varies and thus so do the SUVR values and cutoffs published across studies.

The use of different portions of cerebellar reference tissue across scans can impact SUVR values and conclusions regarding longitudinal change. and therefore must be limited or performed with caution.

Differences in raw cerebellar values may occur across scanners with significant impact upon SUVR values, requiring further investigation.

Quality control of reference region sampling is of key importance.

References

[1] Ashburner J, Friston K. (2000) Neuroimage 11:805–21

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Acknowledgements and Contact

Data used in this study were obtained from the ADNI database (www.loni.ucla.edu\ADNI). As such, ADNI investigators contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report (www.loni.ucla.edu\ADNI\Collaboration\ADNI_ Manuscript_Citations.pdf). This study was supported by Janssen Alzheimer Immunotherapy Research & Development, LLC, and Wyeth Research, which was acquired by Pfizer Inc. in October 2009.

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