SCAN FDG PET Processing

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Summary

Our goal was to identify the most important hypometabolic regions that are indicative of pathological or metabolic change in MCI and AD. We identified a set of pre-defined regions of interest (MetaROIs) based on coordinates cited frequently in other FDG studies comparing AD, MCI, and Normal subjects. Because these regions are based on a literature review and not anatomy, these MetaROIs are alternatives to other template-based ROIs (e.g. AAL regions). These five MetaROI volumes were then combined into a composite MetaROI; this composite MetaROI was deemed sufficient as the singular FDG MetaROI due to the similar quantification shown across all five MetaROIs.

The FDG PET processing pipeline does not require an MRI and is completed in template space. Our MRI-free pipelines consist of (1) a linear registration of individual PET scans to a MNI152 T1 template, (2) non-linear spatial normalization to a tracer-specific PET template, (3) mean intensity quantification within regions of interest (ROIs), and (4) intensity normalization to create standardized uptake value ratios (SUVRs) in relation to a reference region.[1] For FDG, the MetaROI is intensity normalized by the top 50% of voxels in a pons/vermis reference region. As with all our MRI-free datasets, we also provide SUVRs for ROIs in the Normalized Probability Desikan-Killiany Atlas (NPDKA), described below.

Methods

Creation of MetaROIs

We developed the set of MetaROIs by identifying regions cited frequently in FDG-PET studies of AD and MCI patients. We conducted a PubMed meta-analysis in April 2007 using all permutations of the following search terms: AD or Alzheimer's; MCI or Mild Cognitive Impairment; FDG-PET or FDG or glucose metabolism. Within the studies identified by these terms we isolated those that listed coordinates representing results of cross-sectional and/or longitudinal voxelwise analyses in which FDG uptake differed significantly between groups, changed in the same individuals over time, or correlated with cognitive performance. This resulted in a total of 292 MNI or Talairach coordinates and (if available) their accompanying Z-scores or T-values, of which 209 were from cross-sectional or correlational studies and 31 were

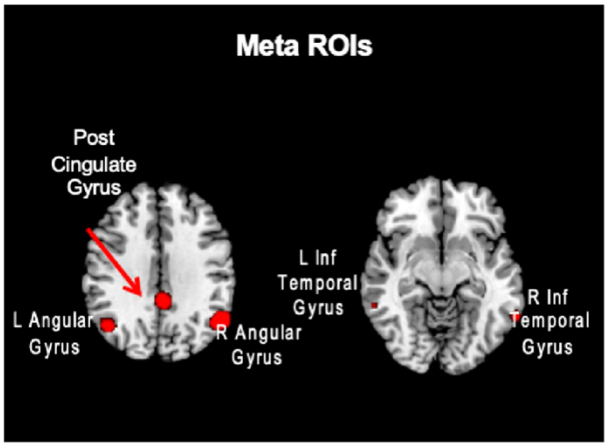

Figure 1. The five MetaROI regions used to create the composite FDG MetaROI.

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coordinates from longitudinal studies. See Supplementary Table 1 in Landau et al., Neurobiology of Aging, 2009 [2] for the list of studies used to generate the MetaROIs.

The following steps were carried out separately for (1) the set of coordinates from cross-sectional or correlational studies and (2) the set of coordinates from longitudinal studies. All coordinates were transformed into MNI space. Then intensity values were generated for coordinates that reflected a combination of the Z-score or T-value associated with the coordinate and the degree to which coordinates within the same region overlapped (indicating repeated citations of the same region across studies). All T-values were transformed to approximate Z-scores. Then, overlapping Z-scores, when they occurred, were added. The volumes were smoothed with a 14mm FWHM smoothing kernel. Finally, the volume was then intensity normalized using the maximum value, resulting in a map with values between 0 and 1. The cross-sectional coordinate map was then thresholded at 0.50, and this resulted in a set of four regions located in right and left angular gyri, bilateral posterior cingulate gyrus, and left middle/inferior temporal gyrus. Because the longitudinal map was composed of far fewer coordinates than the cross-sectional map and therefore had less regional consistency among coordinates, we thresholded the coordinate intensity values at a higher threshold (0.75), which resulted in a single ROI in right middle/inferior temporal gyrus. (An additional longitudinal FDG ROI in the prefrontal cortex was identified, but it did not meet our cluster size criterion (20 voxels) and signal to noise in this region was insufficient for analysis.)

The final five MetaROIs that resulted from this procedure (Left Angular Gyrus, Right Angular Gyrus, Bilateral Posterior Cingular, Left Inferior Temporal Gyrus, Right Inferior Temporal Gyrus) were binarized and combined into the single composite FDG composite MetaROI.

Acquisition of FDG PET data from LONI

We download SCAN FDG images from LONI in the most fully pre-processed format (Step 4; frames realigned and averaged, linear transformation to straighten out the head, standardized voxel size and smoothed to 6mm resolution). In the table below, LONI series descriptions are listed for each acquisition-time currently available for FDG. Each FDG image is processed according to its full acquisition window such that the primary acquisition window (30-60) is used preferentially, with the shorter acquisition window (30-45) used when the primary acquisition is unavailable (Table 1).

Table 1. SCAN FDG PET LONI Series Descriptions. Primary acquisition time is in bold.

Acquisition Time	**LONI Series Description**
30-45	FDG Coreg, Avg, Rigid Reg to Std Img/Vox Size, 30-45*, 6mm Res
30-60	FDG Coreg, Avg, Rigid Reg to Std Img/Vox Size, 30-60*, 6mm Res

Calculation of SUVRs

The standard [15O]-H2O PET template provided in SPM5 was used for spatial normalization of SCAN FDG PET images. After images are registered to the MNI152 T1 template and then warped to template space, we sample regional means within template space ROIs. A whole brain atlas was developed to sample template space Desikan-Killiany ROIs equivalent to those produced by Freesurfer in native space (Figure 2; for more information see NPDKA section below). In addition to this atlas, the FDG MetaROI and the top 50% pons/vermis reference region are provided at the front of the dataset. This top 50% pons/vermis reference region is derived from a hand-drawn pons/cerebellar vermis region that was hand-drawn on a T1 template in MNI space. **The FDG PET dataset is intensity normalized by the top 50% pons/vermis reference region, visible as a column of 1's. Any SUVR can be renormalized once by dividing the region by another reference region.**

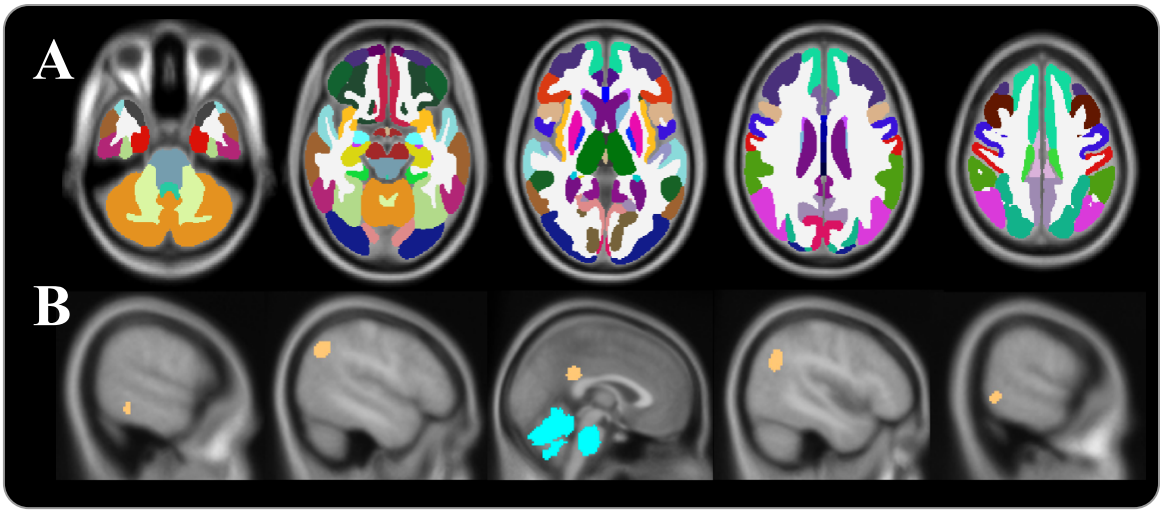

Figure 2. (A) Normalized Probability Desikan-Killiany atlas (NPDKA) based on the Desikan-Killiany atlas and derived from an average of 200 Freesurfer 7.1 segmentations. (B) The pons/vermis (turquoise) and FDG MetaROI (peach) masks. These masks exist in MNI-152 space and are used to sample SUVRs from SCAN FDG PET images after MRI-free spatial normalization.

NPDKA Regional SUVRs

The purpose of the normalized probability Desikan-Killiany atlas (NPDKA) was to provide template-space SUVRs for the 111 Freesurfer-defined ROIs used in our MRI-dependent, native space pipeline[3]. The NPDKA regional SUVRs reported in the dataset are intensity normalized to the top 50% pons/vermis reference region.

The NPDKA (Figure 2A) was derived from Freesurfer v7.1 Desikan-Killiany segmentations of 200 cognitively normal, Aβ-negative ADNI participants. Template-space probability maps were created for each region first by 1) warping each segmentation to MNI-152 space using the parameters from the T1 (SPM12 normalize), 2) lightly smoothing each ROI mask with a 1.5mm FWHM gaussian kernel to clean the edges, 3) averaging the ROI masks across the 200 subjects, and 4) normalizing each ROI between 0 and 1 by dividing out the highest voxel probability. ROI

probability maps were combined into a single whole brain atlas by assigning each voxel to the ROI whose probability map was the highest for that voxel.

FAQs

1. ***Are the SUVRs in these datasets already intensity normalized?***
Yes. The SUVRs are already normalized by the top 50% pons/vermis reference region. This is observable as a 1.000 SUVR in the column "TOP50PONSVERMIS_SUVR".

2. ***Can I intensity normalize the SUVRs using a different region?***
To use a different reference region, re-normalize once with the provided values (divide original SUVRs by new reference region mean). For more information, see the "Calculation of SUVRs" section above.

3. ***Can I merge SCAN data with ADNI data?***
Yes, SCAN and ADNI use an identical FDG processing pipeline and can therefore be merged.

Version Information

This is our first FDG PET processing methods document for SCAN.

Dataset Information

This methods document applies to the following datasets available from the SCAN repository:

Dataset Name
UC Berkeley – FDG MetaROI NPDKA Analysis
UC Berkeley – MRI-free NPDKA Appendix

References

1. Landau, S. M., Ward, T. J., Murphy, A., Iaccarino, L., Harrison, T. M., La Joie, R., ... & Alzheimer's Disease Neuroimaging Initiative. (2022). Quantification of amyloid beta and tau PET without a structural MRI. *Alzheimer's & Dementia*.
2. Landau SM, Harvey D, Madison CM, et al. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. Neurobiol Aging 2009.
3. Landau, SM, Murphy, A, Lee, JQ, et al. Florbetapir (AV45) processing methods. *LONI ADNI*. 2022; 1-7.

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