ADNI Alzheimer's Disease Neuroimaging Initiative

Flortaucipir (AV-1451) processing methods

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December 2019 reference region correction summary

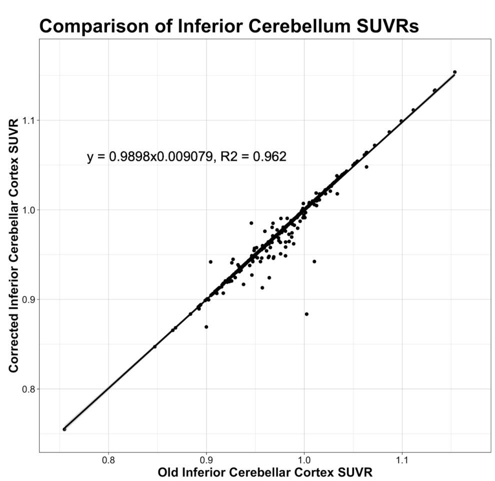
Our previous (pre-December 2019) UC Berkeley flortaucipir (AV1451) datasets were affected by an image processing problem in which the most inferior slices of the inferior cerebellar cortex reference region were missing in approximately 13% of the scans. This issue was caused due to a malfunction with our warping of the SUIT template defined inferior cerebellum to the native-space MRI image. In summary, the bounding box that was applied to the post-warping native-space inferior cerebellum was too conservative for some of the scans, and this led to the cropping of the most inferior slices.

We have corrected this issue, and created new PVC and non-PVC flortaucipir datasets with corrected inferior cerebellum SUVRs. **Based on our analyses of the old vs the corrected SUVRs (see below), we anticipate that this correction would have a minimal effect on most analyses because the old and revised SUVRs have an average R^2 value of approximately 0.995.**

Summary of old vs corrected flortaucipir SUVRs

Included below are comparisons of our AV1451 SUVR quantifications with the old and revised inferior cerebellum definitions for both the default AV1451 and Partial Volume Corrected AV1451 datasets.

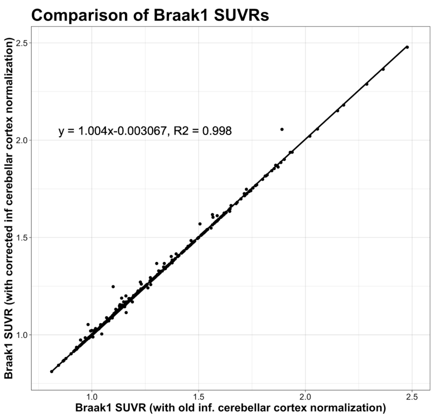
Old inferior cerebellum SUVR vs corrected inferior cerebellum SUVR

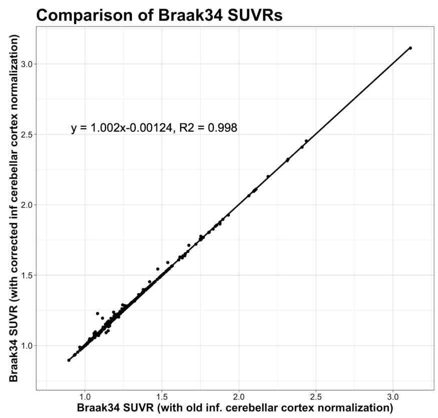


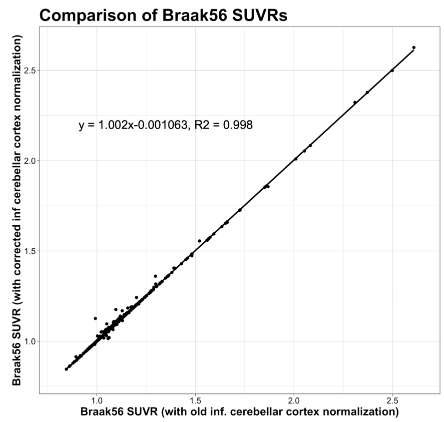
The previous and revised inferior cerebellum cortex SUVRs exhibit a close linear relationship of y=0.9898x+0.0091 and an R^2 correlation of 0.962.

Scatter plots showing previous non-PVCed Braak region SUVRs (with old inf cerebellar cortex normalization) vs corrected Braak region SUVRs (with corrected inf cerebellar cortex normalization)

As shown in the figures below, the R^2 correlations between the non-PVCed Braak stage regions using the previous cerebellar cortex reference region vs the updated cerebellar cortex reference regions are 0.998 for Braak1(entorhinal cortex), Braak34 and Braak56.







Our PVCed Braak stage data using the corrected reference region (not shown) has similar correlations that range from 0.992 (Braak 1; entorhinal cortex) to 0.996 (Braak 56) and 0.997 (Braak 34).

Flortaucipir analysis overview

ADNI flortaucipir regional summary data are updated regularly and uploaded to LONI by our group. Our image analysis pipeline includes the flortaucipir scan and an MPRAGE for each subject that is usually acquired at the same visit as the flortaucipir image. This MPRAGE is segmented and parcellated with Freesurfer (version 5.3.0) to define a variety of regions of interest in each subject's native space. We then coregister each flortaucipir scan to its corresponding MPRAGE and calculate mean flortaucipir uptake within each Freesurfer-defined region. Mean regional uptake can be calculated across several regions of interest (e.g. Braak stage composite regions – see below) and divided by a reference region (cerebellar GM or hemispheric WM) to generate flortaucipir SUVRs.

Are the flortaucipir data in our dataset already intensity normalized?

Yes, the regional flortaucipir means in our dataset are SUVRs, as are the pre-processed images available for download from LONI, but we strongly recommend "re-intensity normalizing" the regional SUVRs in our dataset using one of the reference regions in our dataset, since the initial intensity normalization applied during pre-processing did not use precise anatomical information.

The Stage 3 flortaucipir images as well as the Stage 4, fully pre-processed flortaucipir images ("AV1451 Coreg, Avg, Std Img and Vox Siz, Uniform Resolution") are SUVR images that have been ***approximately*** intensity normalized using an atlas-space cerebellar cortex region defined by Bob Koeppe during his pre-processing procedures (see Jagust et al. Alz & Dementia 2015 and http://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/#pet-pre-processing-container). These procedures include defining an atlas-space cerebellar cortex region using a coregistered FDG or MPRAGE scan and reverse normalizing this region back onto the native space flortaucipir image. Because this initial intensity normalization carries with it some noise associated with the warping procedures, we defined native-space reference regions (as well as regions of interest) more precisely using Freesurfer. We then suggest replacing (e.g. dividing out) the initial intensity normalization carried out by Bob Koeppe with a subsequent intensity normalization using our Freesurfer-defined / native space reference regions as described in the methods below.

Note that the Freesurfer-defined cortical SUVRs listed in our dataset include *only* Bob Koeppe's cerebellar cortex intensity normalization, so in order to generate SUVRs that take advantage of our Freesurfer-based reference regions, you have to divide a region of interest SUVR mean (e.g. Braak12) by one of the reference regions we provide in our dataset (we recommend our inferior cerebellar cortex region).

Method

Acquisition of flortaucipir and MRI image data from LONI

We download flortaucipir data from LONI in the most fully pre-processed format (series description in LONI Advanced Search: "AV1451 Coreg, Avg, Std Img and Vox Siz, Uniform Resolution"). Each subject's pre-processed flortaucipir image is coregistered using SPM to that subject's MRI image (series description: ADNI 1 scans *N3;* and ADNI GO/2 scans *N3*) that was closest in time to the flortaucipir scan. Typically the MRI and PET images are within 3 months, but when a concurrent MRI is not available we use an MRI scan acquired at another visit.

Calculation of flortaucipir SUVR

We have investigated a number of strategies for quantifying and staging tau using flortaucipir *[1-4]*. This ADNI UC Berkeley flortaucipir dataset includes a broad set of regional flortaucipir means and their corresponding Freesurfer-defined volumes (in mm^3). This set includes cortical and subcortical regions of interest and reference regions such as cerebellar grey matter and eroded hemispheric WM. Additionally, we approximate uptake in the anatomical Braak stages [5] by calculating volume-weighted means of groups of FreeSurfer-defined regions, specified in the "Braak ROIs" section.

As described in the box above, flortaucipir SUVRs can be calculated by dividing a region of interest (with or without an adjustment for regional volume) by a reference region.

Flortaucipir Partial Volume Correction

We also provide a separate dataset with flortaucipir data corrected for partial volume effects using the Geometric Transfer Matrix (GTM) approach [6] as implemented for flortaucipir by Suzanne Baker [1, 2]. The GTM approach we are currently using models all FreeSurfer-defined ROIs (see list below) as well as regions in which off-target binding is common (e.g. choroid plexus) in order to reduce contamination from these regions into neighboring regions of interest.

In order to reduce the influence of off-target flortaucipir binding that has been observed in the dorsal cerebellum, we defined an **inferior cerebellar GM reference region** using the SUIT template [7] (http://www.diedrichsenlab.org/imaging/suit.htm) and reverse-normalized this region back to each subject's native space as described in Baker et al. NeuroImage 2017[2].

In our flortaucipir PVC and nonPVC datasets, we use the individual Freesurfer-defined SUVRs and volumes to calculate weighted averages of the following composite regions (Braak I, Braak III/IV, Braak V/VI) that approximate the spread of tau as depicted by Braak and Braak [5] and described in Scholl et al. [4] and Maass et al [3]. **Note that we have recently stopped including Braak II (hippocampus) in our analyses as we have observed that this region is contaminated by off-target binding in the choroid plexus that we do not feel can be adequately corrected by partial volume correction.**

We recommend normalizing either composite (e.g. Braak) or individual PVC ROI values by a PVCed reference region (e.g. inferior cerebellar grey matter) to ensure standardized units.

Freesurfer-defined region codes for Braak ROIs

Braak 1 and 2 composite region (Braak12):

Braak 1
1006 L_entorhinal
2006 R_entorhinal

Braak 2 (We have concluded that this region is contaminated by off-target binding in the choroid plexus and have eliminated it from most of our analyses although we have provided the data in our dataset)
17 L_hippocampus
53 R_hippocampus

Braak 3 and 4 composite region (Braak34):

Braak 3
1016 L_parahippocampal
1007 L_fusiform
1013 L_lingual
18 L_amygdala
2016 R_parahippocampal
2007 R_fusiform
2013 R_lingual
54 R_amygdala

Braak 4
1015 L_middletemporal
1002 L_caudantcing
1026 L_rostantcing
1023 L_postcing
1010 L_isthmuscing

1035 L_insula
1009 L_inferiortemporal
1033 L_temppole
2015 R_middletemporal
2002 R_caudantcing
2026 R_rostantcing
2023 R_postcing
2010 R_isthmuscing
2035 R_insula
2009 R_inferiortemporal
2033 R_temppole

Braak 5 and 6 composite region (Braak56):

Braak 5
1028 L_superior_frontal
1012 L_lateral_orbitofrontal
1014 L_medial_orbitofrontal
1032 L_frontal_pole
1003 L_caudal_middle_frontal
1027 L_rostral_middle_frontal
1018 L_pars_opercularis
1019 L_pars_orbitalis
1020 L_pars_triangularis
1011 L_lateraloccipital
1031 L_parietalsupramarginal
1008 L_parietalinferior
1030 L_superiortemporal
1029 L_parietalsuperior
1025 L_precuneus
1001 L_bankSuperiorTemporalSulcus
1034 L_tranvtemp
2028 R_superior_frontal
2012 R_lateral_orbitofrontal
2014 R_medial_orbitofrontal
2032 R_frontal_pole
2003 R_caudal_middle_frontal
2027 R_rostral_middle_frontal
2018 R_pars_opercularis
2019 R_pars_orbitalis
2020 R_pars_triangularis
2011 R_lateraloccipital
2031 R_parietalsupramarginal
2008 R_parietalinferior
2030 R_superiortemporal
2029 R_parietalsuperior
2025 R_precuneus
2001 R_bankSuperiorTemporalSulcus
2034 R_tranvtemp

Braak 6
1021 L_pericalcarine
1022 L_postcentral
1005 L_cuneus
1024 L_precentral
1017 L_paracentral
2021 R_pericalcarine
2022 R_postcentral
2005 R_cuneus
2024 R_precentral
2017 R_paracentral

PVC input regions

All Braak regions listed above

Other non-Braak-related regions used as PVC input

Choroid plexus: 31, 63
28 Left-VentralDC
30 Left-vessel
60 Right-VentralDC
62 Right-vessel
77 WM-hypointensities
80 non-WM-hypointensities
85 Optic-Chiasm
1000 ctx-lh-unknown
1004 ctx-lh-corpuscallosum
2000 ctx-rh-unknown
2004 ctx-rh-corpuscallosum

Not included in PVC model (set to zero). Note that bone, soft tissue, and CSF outside the brain are omitted and are all implicitly set to zero [2]

4 Left-Lateral-Ventricle
5 Left-Inf-Lat-Vent
14 3rd-Ventricle
15 4th-Ventricle
24 CSF
43 Right-Lateral-Ventricle
44 Right-Inf-Lat-Vent
72 5th-Ventricle

Inferior Cerebellar Gray Matter definition

8 Left-Cerebellum-Cortex
47 Right-Cerebellum-Cortex

SUIT ROI numbers used for Inferior Cerebellar Gray definition [7]

Inferior cerebellar inclusion mask: SUIT codes 6, 8-28, 33, 34
Superior cerebellar exclusion mask (bilateral lobules I-VI): SUIT codes 1-5, 7

Version Information

This document supersedes our previous document dated 2019-09-05. Specific changes in our methods are summarized at the beginning of this document.

Dataset Information

This methods document applies to the following dataset(s) available from the ADNI repository:

Dataset Name	Date Submitted
UC Berkeley - AV1451 Analysis [ADNI1,GO,2,3]	13 December 2019

References

1. Baker, S.L., et al., *Reference Tissue-Based Kinetic Evaluation of 18F-AV-1451 for Tau Imaging.* J Nucl Med, 2017. 58(2): p. 332-338.
2. Baker, S.L., A. Maass, and W.J. Jagust, *Considerations and code for partial volume correcting [(18)F]-AV-1451 tau PET data.* Data Brief, 2017. 15: p. 648-657.
3. Maass, A., et al., *Comparison of multiple tau-PET measures as biomarkers in aging and Alzheimer's disease.* Neuroimage, 2017. 157: p. 448-463.
4. Scholl, M., et al., *PET Imaging of Tau Deposition in the Aging Human Brain.* Neuron, 2016. 89(5): p. 971-982.
5. Braak, H. and E. Braak, *Neuropathological stageing of Alzheimer-related changes.* Acta Neuropathol, 1991. 82(4): p. 239-59.
6. Rousset, O.G., Y. Ma, and A.C. Evans, *Correction for partial volume effects in PET: principle and validation.* J Nucl Med, 1998. 39(5): p. 904-11.
7. Diedrichsen, J., *A spatially unbiased atlas template of the human cerebellum.* Neuroimage, 2006. 33(1): p. 127-38.

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