Flortaucipir (AV-1451) processing methods
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2021 Freesurfer version upgrade from 5.3.0 to 7.1.1
Starting with the January 2021 dataset, we are using regions of interest defined by Freesurfer v7.1.1. The decision to upgrade was made to keep our methods current with supported software. We report no major systematic difference to regional SUVR between the current and previous methods. The figure below shows the relationship between regional SUVRs defined using FS 5.3.0 and 7.1.1 Braak regions of interest [5] with inferior cerebellar grey matter as the reference region.

Flortaucipir analysis overview
ADNI flortaucipir (18F) regional summary data are updated regularly and uploaded to LONI by our group. Our image analysis pipeline includes one or more flortaucipir scans and a structural MRI scan for each subject. The MRI is segmented with Freesurfer (version 7.1.1) to define regions of interest in native space. We then coregister each flortaucipir scan to its corresponding bias-corrected T1 created by Freesurfer and compute the mean flortaucipir uptake within each region. Mean regional uptake can be averaged across several regions of interest (e.g. Braak stage composite regions – see below) and divided by a reference region such as inferior cerebellar GM (see details below) or hemispheric WM to generate flortaucipir SUVRs.
**Are the flortaucipir data in our dataset already intensity normalized?**

Yes. Regional flortaucipir means in our dataset are SUVRs that have already been intensity normalized by Bob Koepp during the generation of the pre-processed images available for download from LONI. 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 Koepp during his pre-processing procedures (see Jagust et al. Alz & Dementia 2015 and PET preprocessing info at adni.loni.usc.edu). 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. This initial intensity normalization carries with it some noise associated with the warping procedures, so we defined native-space reference regions (as well as regions of interest) more precisely using FreeSurfer. We recommend replacing (e.g. dividing out) the initial intensity normalization carried out by Bob Koepp with a subsequent intensity normalization using our FreeSurfer-defined, native space reference regions.

However, we recommend 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 take advantage of FreeSurfer-defined regional information.

In order to generate SUVRs that take advantage of our FreeSurfer-based target and reference regions, divide a region of interest SUVR mean (e.g. Braak1) by one of the reference regions we provide in our dataset. The recommended reference region for cross-sectional flortaucipir is the inferior cerebellar reference region (variable name: INFERIORCEREBELLUM_SUVR; see details about region definition below).

**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;*, ADNI GO/2 scans *N3*, and ADNI 3 *Accel*) acquired closest in time to the first flortaucipir scan.

*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 (mm³). This set includes cortical and subcortical regions of interest and reference regions such as inferior cerebellar grey matter and eroded hemispheric WM. 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. Additionally, we include a meta-temporal region, composed of FreeSurfer-
defined bilateral entorhinal, amygdala, fusiform, inferior and middle temporal cortices, outlined in the “MetaTemporal ROI” section [8].

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 (e.g. inferior cerebellar grey matter; see below for more details).

**Flortaucipir Partial Volume Correction**

We also provide a separate dataset with flortaucipir SUVRs corrected for partial volume effects using the Geometric Transfer Matrix (GTM) approach [6] as implemented 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](http://www.diedrichsenlab.org/imaging/suit.htm)) (see below for more details) 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 non-PVC datasets, we use the individual Freesurfer-defined SUVRs and volumes to calculate weighted averages of the following composite regions (Braak 1, Braak 3/4, Braak 5/6) 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]. We include both **Braak 1 (entorhinal) alone and Braak 1/2 (entorhinal and hippocampus)** but we note that the hippocampus is known to be contaminated by off-target binding in the choroid plexus. It is unclear whether this 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; see below for more details).

**Freesurfer-defined composite 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_amygda
da
2016 R_parahippocampal
2007 R_fusiform
2013 R_lingual
54 R_amygda
da

Braak 4
1015 L_middletemporal
1002 L_caudantcing
1026 L_rostan
tcing
1023 L_post
cing
1010 L_isthmus
cing
1035 L_insula
1009 L_inferiort
temporal
1033 L_temppole
2015 R_middletemporal
2002 R_caudantcing
2026 R_rost
tcing
2023 R_postcing
2010 R_isthmus
cing
2035 R_insula
2009 R_inferiort
temporal
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_lateraloc
cipital
1031 L_parietal
supramarginal
1008 L_parietalinferior
1030 L_superiortemporal
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<tr>
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<th>ROI Description</th>
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<tr>
<td>1029</td>
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<tr>
<td>1001</td>
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<tr>
<td>2028</td>
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<tr>
<td>2012</td>
<td>R_lateral_orbitofrontal</td>
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<tr>
<td>2014</td>
<td>R_medial_orbitofrontal</td>
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<tr>
<td>2032</td>
<td>R_frontal_pole</td>
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<td>2003</td>
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<td>2011</td>
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**Braak 6**

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<td>1022</td>
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<td>1005</td>
<td>L_cuneus</td>
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<td>R_postcentral</td>
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<td>2005</td>
<td>R_cuneus</td>
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<tr>
<td>2024</td>
<td>R_precentral</td>
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<td>2017</td>
<td>R_paracentral</td>
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**Meta-temporal ROI [8]**

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<tr>
<td>1006</td>
<td>L_entorhinal</td>
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<td>1007</td>
<td>L_fusiform</td>
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<tr>
<td>1009</td>
<td>L_inferiortemporal</td>
</tr>
<tr>
<td>1015</td>
<td>L_middletemporal</td>
</tr>
<tr>
<td>54</td>
<td>R_amygdala</td>
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<tr>
<td>2006</td>
<td>R_entorhinal</td>
</tr>
<tr>
<td>2007</td>
<td>R_fusiform</td>
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<tr>
<td>2009</td>
<td>R_inferiortemporal</td>
</tr>
<tr>
<td>2015</td>
<td>R_middletemporal</td>
</tr>
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</table>
Cerebellar Gray Matter
8    Left-Cerebellum-Cortex
47   Right-Cerebellum-Cortex

Eroded subcortical WM
This region is eroded by smoothing 8mm³ FWHM then applying a 0.7 threshold.
2    Left-Cerebral-White-Matter
41   Right-Cerebral-White-Matter

PVC input regions
All Braak regions listed above
Other non-Braak-related regions used as PVC input
31   Left-choroid-plexus
63   Right-choroid-plexus
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
**SUIT and FS ROI numbers used for Inferior Cerebellar Gray definition [7]**

This region is defined by an intersection between the SUIT inferior cerebellar and the freesurfer cerebellar gray matter masks, excluding the SUIT superior cerebellar mask.

Inferior cerebellar inclusion mask: SUIT codes 6, 8-28, 33, 34  
Superior cerebellar exclusion mask (bilateral lobules I-VI): SUIT codes 1-5, 7  
Freesurfer cerebellar gray matter: 8, 47

**Version Information**

This document supersedes our previous document dated 2020-02-04. 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:

<table>
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<td>UC Berkeley - AV1451 Analysis [ADNI1,GO,2,3]</td>
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<td>UC Berkeley - AV1451 Partial Volume Corrected Analysis [ADNI2,3]</td>
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**References**

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