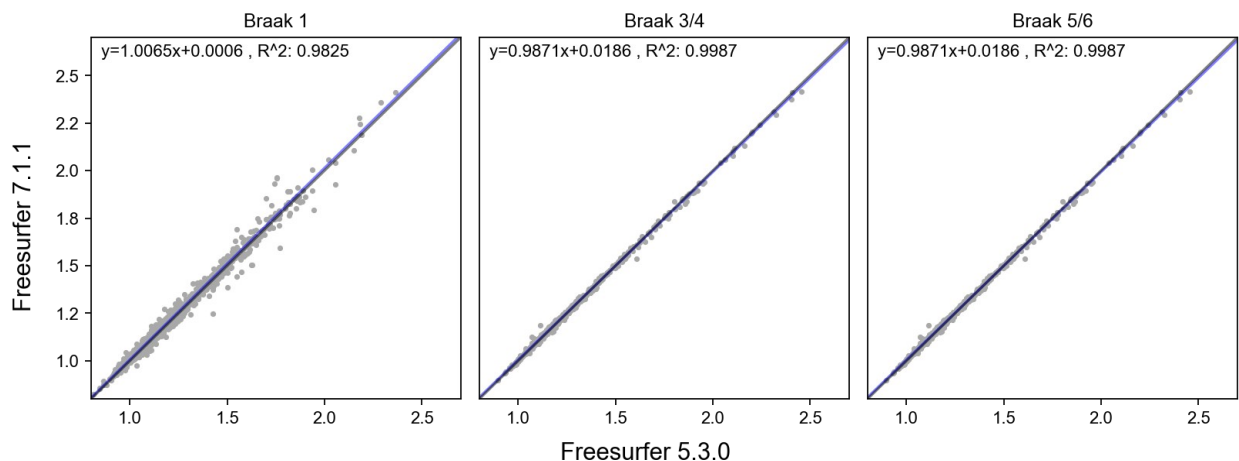


## Flortaucipir (AV-1451) processing methods

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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 ( $^{18}\text{F}$ ) 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 Koeppel 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 Koeppel during his pre-processing procedures (see Jagust et al. Alz & Dementia 2015 and PET preprocessing info at [adni.loni.usc.edu](http://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 Koeppel 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 (mm<sup>3</sup>). 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>) (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\_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\_isthmusing  
1035 L\_insula  
1009 L\_inferiortemporal  
1033 L\_temppole  
2015 R\_middletemporal  
2002 R\_caudantcing  
2026 R\_rostantcing  
2023 R\_postcing  
2010 R\_isthmusing  
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

**Meta-temporal ROI [8]**

18 L\_amygdala  
1006 L\_entorhinal  
1007 L\_fusiform  
1009 L\_inferiortemporal  
1015 L\_middletemporal  
54 R\_amygdala  
2006 R\_entorhinal  
2007 R\_fusiform  
2009 R\_inferiortemporal  
2015 R\_middletemporal



**Cerebellar Gray Matter**

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

**Eroded subcortical WM**

This region is eroded by smoothing 8mm<sup>3</sup> 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:

Dataset Name	Date Submitted
<u>UC Berkeley - AV1451 Analysis [ADNI1,GO,2,3]</u>	14 January 2021
<u>UC Berkeley - AV1451 Partial Volume Corrected Analysis [ADNI2,3]</u>	14 January 2021

## References

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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.
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