Compensating for choroid plexus based off-target signal in the hippocampus using 18F-flortaucipir PET

Daria Pawlik\textsuperscript{a,b}, Antoine Lezy\textsuperscript{a}, Olof Strandberg\textsuperscript{a}, Ruben Smith\textsuperscript{a,b}

\textsuperscript{a} Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, Sweden
\textsuperscript{b} Department of Neurology, Skåne University Hospital, SE-20502 Malmö, Lund, Sweden

1. Introduction

Alzheimer’s disease (AD) is the most common neurodegenerative disease, affecting an estimated 46 million people worldwide (Prince et al., 2016). The largest risk factor for AD is age; and due to the rapid growth in the number of elderly individuals, the prevalence of AD is predicted to exceed 81 million by 2040 (Ballard et al., 2011). AD is characterized by the extracellular deposition of amyloid-\(\beta\) (A\(\beta\)), the accumulation of intracellular insoluble paired helical filament (PHF) tau, and cognitive decline (Braak and Braak, 1991; De-Paula et al., 2012; Iqbal et al., 2016). The cognitive deterioration go hand in hand with the development of tau pathology in the brain (Bennett et al., 2004). Over the past years, tau specific tracers have been developed for use with positron emission tomography (PET) brain imaging (Lezy et al., 2019; Villedagone et al., 2015). The tau tracer 18F-flortaucipir has been shown to mirror post mortem brain tau-burden in AD (Lowe et al., 2020; Smith et al., 2018) and can be used to track disease progression (Harrison et al., 2019; Jack et al., 2018). The most commonly used tau PET tracer this far has been 18F-flortaucipir (Baker et al., 2017; Chien et al., 2013), but new ligands such as 18F-MK-6240 (Walji et al., 2016), 18F-PI-2620 (Kroth et al., 2019) and 18F-RO948 (Wong et al., 2018) have recently been developed.

Tau pathology in AD typically begins in the transentorhinal cortex, before spreading to the medial (hippocampus and parahippocam-
pal gyrus and lateral temporal lobes and the remaining neocortex (Braak and Braak, 1991). Given that the hippocampus is affected by tau pathology early on in AD, mapping the hippocampal distribution of tau is of interest. A problem when analysing hippocampal tau using 18F-flortaucipir PET, however, is the presence of binding in the adjacent choroid plexus, where PHFs are not seen (Lowe et al., 2016). This off-target signal complicates accurate signal quantification in the hippocampus and has been suggested to be due to Biondi ring tangles, age-related structures that are not associated with AD pathology but that resemble neurofibrillary tangles (NFTs) (Ikonomovic et al., 2016; Wen et al., 1999).

Several studies have proposed methods to correct for this off-target choroid plexus signal using 18F-flortaucipir (Baker et al., 2017; Lee et al., 2018; Wolters et al., 2018), but no effect on diagnostic performance have been reported. Our aim herein was to determine whether reducing hippocampal off-target signal derived from the choroid plexus using a novel method would result in improved group separation (cognitively impaired [CI]; mild cognitive impairment [MCI] and AD dementia) vs cognitively unimpaired [CU] subjects) using hippocampal SUVR, and whether this would improve the correlations between 18F-flortaucipir hippocampal SUVR and cognitive measures. As choroid plexus off-target binding has been shown to be lower using the novel tau-PET tracer 18F-RO948, as compared to 18F-flortaucipir (Smith et al., 2019), we created a hippocampal binary mask including voxels where 18F-flortaucipir retention was significantly higher than that for 18F-RO948 in subjects having undergone both 18F-flortaucipir and 18F-RO948 PET. As an alternative approach the choroid plexus region of interest (ROI) was expanded based on the resolution of the PET-camera into three additional masks. These four masks, thought to represent hippocampal voxels affected by off-target spill-over from the choroid plexus, were then applied as exclusion masks to 18F-flortaucipir scans from the Swedish BioFINDER study.

2. Materials and methods

2.1. Participants

We analysed two separate cohorts: cohort A was recruited from the Swedish BioFINDER-2 study (clinical trial no. NCT03174938) and underwent both 18F-flortaucipir and 18F-RO948 PET, as defined below. This cohort was used to generate the choroid plexus mask. Cohort B was drawn from the BioFINDER study (clinical trial no. NCT01208675) and underwent only 18F-flortaucipir PET. Cohort A (n = 30) included four controls, three patients with mild cognitive impairment (MCI), eight patients with other neurodegenerative diseases (four progressive supranuclear palsy (Hoglinger et al., 2017), one corticobasal degeneration (Armstrong et al., 2013), one dementia with Lewy bodies (McKeith et al., 2017), one semantic variant primary progressive aphasia (Gorno-Tempini et al., 2011) and one with unspecified dementia) and 15 patients with AD dementia. Cohort B (n = 145) included 66 cognitively unimpaired (CU; S4 controls and 12 with subjective cognitive decline) and 79 cognitively impaired (CI) participants (29 with MCI due to AD (i.e. Aβ+ MCI) and 50 with AD dementia).

Inclusion criteria for CU were: (1) 26–30 points on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) at the screening visit, (2) not fulfilling criteria for MCI or any dementia and (3) fluency in Swedish. MCI patients were eligible if they (1) scored 22–30 on the MMSE, (2) did not fulfil criteria for dementia, (3) had objective memory impairment according to Delayed Word Recall test from the Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) (Rosen et al., 1984), (4) were Aβ+ based on either CSF Aβ42 or 18F-flutemetamol PET and (5) fluent in Swedish. AD dementia patients fulfilled criteria for dementia according to DSM-IV-TR criteria (American Psychiatric Association, 2000) and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association criteria for probable AD (McKhan et al., 2011). Exclusion criteria were (1) the presence of significant neurologic or psychiatric disease, other than the inclusion diagnosis, (2) significant systemic illness making it hard to participate, (3) refusing lumbar puncture or (4) alcohol abuse. All participants gave written informed consent to participate in the study. Ethical approval was given by the Regional ethics committee at Lund University, Sweden. Imaging procedures were approved by the Radiation protection committee at Skåne University Hospital and by the Swedish Medical Products Agency.

2.2. Image acquisition and analysis

All subjects underwent magnetic resonance imaging (MRI) on 3.0 T MR scanners (Siemens MAGNETOM Prisma [cohort A]; Siemens Skyra [cohort B]), acquiring T1-weighted magnetization-prepared rapid gradient echo (T1-MPRAGE) and fluid-attenuated inversion recovery (FLAIR) images. MRI images were processed by removal of non-brain tissue (brain extraction) and segmented into gray and white matter. Parcellation into regions of interest (ROIs), including hippocampus and choroid plexus ROIs, were performed using the Desikan-Killiany atlas in FreeSurfer 6.0 (http://surfer.nmr.mgh.harvard.edu/). In cohort A, 18F-flortaucipir and 18F-RO948 PET were performed on a GE Discovery MI scanner (General Electric Medical Systems). Participants were injected with 341.5 ± 53.1 MBq of 18F-flortaucipir or 364.5 ± 20.4 MBq of 18F-RO948, with LIST-mode emission data acquired 80–100 min or 70–90 min post injection, respectively. The average interval between 18F-flortaucipir and 18F-RO948 scans was 32.7 ± 33.1 days. In cohort B, 18F-flortaucipir PET scans were acquired in LIST-mode on a GE Discovery 690 PET scanner (General Electric Medical Systems), 80–100 min after a bolus injection of ~ 370 MBq of 18F-flortaucipir. For both cohorts, a low dose CT scan was performed immediately prior to the PET scan for attenuation correction (Hahn et al., 2017). After binning LIST-mode data into 4 × 5 min time frames, PET-images were motion corrected, summed and co-registered to their corresponding T1 MR images. SUVR images were calculated using the inferior cerebellar cortex as reference region (Baker et al., 2017). Partial volume error (PVE) correction was performed using the Geometric Transfer Matrix (GTM) (Rouset et al., 1998) approach combined with a region-based voxel-wise method, producing voxel-wise PVE corrections (Thomas et al., 2011). All FreeSurfer segmented anatomical regions were included in the GTM ROI set including WM, and CSF.

2.3. Generation of a hippocampal mask adjusted for off-target choroid plexus signal

Following spatial normalization to the MNI-152 template, hippocampal retention between 18F-flortaucipir and 18F-RO948 was compared within cohort A using voxelwise paired t-tests in SPM12 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK). The comparison was made within a hippocampal mask obtained from the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Clusters larger than 20 voxels (k > 20) where 18F-flortaucipir hippocampal signal was significantly higher than that for 18F-RO948 (p < 0.05, family wise error (FWE) corrected) were then used to create a binary mask, presumably representing hippocampal voxels affected by spill-over from off-target binding in the choroid plexus (Fig. 1). No significant clusters were seen when performing the contrast 18F-RO948 > 18F-flortaucipir. The final hippocampal mask was then transformed back into individual space for each subject within cohort B and used as an exclusion mask when sampling the hippocampus in 18F-flortaucipir PET images, providing an estimate of hippocampal 18F-flortaucipir SUVR, corrected for choroid plexus spill-in. On average, the mask excluded 16% of voxels from the right hippocampus and 20% of voxels from the left hippocampus (calculated in subject space).
2.4. Creation of an alternative subject specific hippocampal mask

As an alternative to the tau PET ($^{18}$F-flortaucipir > $^{18}$F-RO948) derived mask, we also examined a native space-based approach. Here, we smoothed the FreeSurfer derived choroid plexus ROI in native space for each participant using a 5 mm kernel (the approximate resolution of the scanner). We then applied thresholds of 0.25, 0.50 or 0.75 to the smoothed ROI to generate choroid plexus exclusion masks that were then applied to FreeSurfer hippocampal ROIs. To evaluate the diagnostic performance of this method (CI vs. CU), we performed ROC analyses using the resulting hippocampal ROI values (i.e. masked using the masks from thresholds of 0.25, 0.50 and 0.75, without and with PVEc).

2.5. Cognitive testing

Subjects from cohort B underwent cognitive testing with the MMSE to measure global cognition and the ADAS-Cog Delayed Word Recall test measured on a scale of 0–10 (where a score of 0 indicates no memory impairment and 10 indicates severe impairment of short-term memory), to get an estimate of episodic memory function.

2.6. Statistics

All analyses, except creation of the off-target mask in SPM (as described above), were performed in R (v.3.5.1; https://www.R-project.org/), with significance set at $p < 0.05$, two-sided. Demographic data was analysed with unpaired t-tests or Fisher’s exact tests. As described in the preceding section, for the voxelwise comparison of $^{18}$F-flortaucipir and $^{18}$F-RO948, a voxelwise paired two-sample t-test was used, as implemented in SPM12. Resulting voxelmaps were thresholded at a significance level of $p < 0.05$, FWE corrected ($k > 20$). The following analyses were run using $^{18}$F-flortaucipir hippocampal SUVR (with and without adjustment for choroid plexus spill-in) and using both non-PVE corrected data and data with a GTM-based PVE-correction: 1) linear regression to assess the relationship with choroid plexus SUVR; 2) comparison of area under the receiver operating characteristic curve (AUC) values to assess the diagnostic performance; and 3) linear regression to assess the association with cognition, adjusting for age, sex and education. AUC and correlation coefficients between the different conditions (with and without adjustment for choroid plexus and PVE correction) were compared using confidence interval (Diedenhofen and Musch, 2015; Zou, 2007) and bootstrapping ($n = 1000$) (Hanley and McNeil, 1982, 1983; Robin et al., 2011) approaches. Power calculations (assuming $\alpha = 0.001$, power=0.80) using correlations with cognition (MMSE and ADAS-Cog Delayed Recall, adjusted for age, sex and education) between the different conditions (Non-PVEc and PVEc; with and without masking) were also performed. In addition to AUC, sensitivity/specificity and diagnostic accuracy (i.e. true outcomes/all outcomes) are reported for Youden index (CI vs. CU) derived cutoffs in Supplementary Table 1. Lastly, given the association between age and $^{18}$F-flortaucipir uptake in the choroid plexus (Schöll et al., 2016), we also analyzed the relationship between non-PVEc SUVR values in the choroid plexus and age in cohort B using linear regression.

3. Results

3.1. Participants

Participant characteristics are provided in Table 1. CI and CU participants did not differ significantly in terms of sex and years of education, but the CU group was slightly older ($p < 0.05$). As expected, subgroups in cohort B differed significantly in MMSE scores and in the percentage of subjects classified as Aβ positive ($p < 0.001$).

3.2. Relation to choroid plexus SUVR and diagnostic performance

Using linear regression, we found a significant relationship between SUVR values in the hippocampus (unmasked) and the choroid plexus, using both non-PVE corrected ($r = 0.28$, $p < 0.001$) and PVE corrected data ($r = 0.18$, $p < 0.05$) (Fig. 2A and B). After applying the hippocampal mask to the data, this correlation was no longer significant (non-PVE corrected: $r = 0.13$, $p = 0.11$; PVE corrected: $r = 0.09$, $p = 0.26$, Fig. 2C and D). Non-PVEc $^{18}$F-flortaucipir SUVR values in the choroid plexus were significantly associated with age, though the strength of the relationship was lower ($r = 0.21$, $p < 0.001$) (Supplementary Fig. 1). Mean choroid plexus and hippocampus $^{18}$F-flortaucipir SUVR values are included in Supplementary Table 2.

Next, we evaluated the diagnostic performance of $^{18}$F-flortaucipir hippocampal SUVR for separating CI from CU subjects, using ROC analyses. Using unmasked hippocampal SUVRs and no PVE-correction, this analysis gave an area under the curve (AUC) of 0.79 (95% Confidence Interval (C.I.), 0.72 – 0.87). After PVE correction, the AUC was 0.80 (95% CI., 0.72 – 0.87). When applying the hippocampal mask, AUCs increased to 0.84 for non-PVE corrected data (95% CI., 0.77 – 0.91, $p < 0.001$ compared to non-masked), and 0.83 for PVE corrected data (95% CI., 0.77 – 0.90, $p < 0.001$ compared to non-masked) (Fig. 3). We found similar effects when accounting for age (Supplementary Fig. 2). AUC values for additional comparisons (AD dementia and MCI versus controls, as well as between AD dementia and MCI) are reported in Supplementary Fig. 3. Results for the various conditions are summarized in Table 2.

3.3. Relationship between $^{18}$F-flortaucipir hippocampal SUVR and cognition

To study the relationship between $^{18}$F-flortaucipir PET hippocampal signal and cognition, we correlated hippocampal SUVR values with MMSE and ADAS-Cog Delayed Word Recall test scores. These analyses showed significant associations between SUVR and MMSE scores using unmasked and masked data ($p < 0.001$), both without and with PVE correction (Fig. 4, Table 3). However, correlation coefficients improved significantly when using masked hippocampal SUVR values for both non-PVE corrected ($r = −0.48$ vs. $r = −0.52$, $p < 0.001$) and PVE corrected data ($r = −0.49$ vs. $r = −0.53$, $p < 0.001$). Correlation analysis using the ADAS-Cog Delayed Word Recall test scores showed similar results (Supplementary Fig. 4), with masked hippocampal SUVRs resulting in stronger correlation coefficients for both non-PVE corrected data.
Table 1
Participant characteristics.

|                | Cohort A | Cohort B |        |        |        |
|----------------|----------|----------|--------|--------|--------|
|                | All subjects | All subjects | CU | CI | p-value * |
| n              | 30 | 145 | 66 | 79 |        |
| Age            | 71.4 ± 8.6 | 72.1 ± 8.3 | 74.0 ± 6.9 | 70.5 ± 9.0 | <0.01 |
| Sex (M/F, %)   | 16/14 (46.7) | 77/68 (47.3) | 30/36 (53.7) | 47/32 (41.5) | 0.10 |
| Education      | 11.6 ± 4.8 | 12.1 ± 3.5 | 12.1 ± 3.7 | 12.1 ± 3.4 | 0.87 |
| MMSE           | 23.5 ± 4.3 | 25.5 ± 5.1 | 29.0 ± 1.1 | 22.4 ± 5.3 | <0.001 |
| ADAS-Cog Delayed Word Recall | NA | 4.9 ± 3.4 | 2.3 ± 1.9 | 7.4 ± 2.6 | <0.001 |
| *Aβ+ (No., Total No.,%) | 22/27 (81.5) | 105/145 (72.4) | 29/66 (43.9) | 79/79 (100) | <0.001 |

Legend: *Aβ* - Amyloid-β; ADAS - Alzheimer’s Disease Assessment Scale; CI – cognitively impaired; CU – cognitively unimpaired; F – female; M – male; MMSE – Mini-Mental State Examination. * Comparison CI vs. CU in cohort B.

Fig. 2. Correlations of *18F*-flortaucipir hippocampus SUVRs against choroid plexus SUVRs for: unmasked, non-PVE corrected data (A); masked, non-PVE corrected data (B); unmasked, PVE corrected data (C); and, masked, PVE corrected data (D). PVE – partial volume error; SUVR – standardized uptake value ratio.

Table 2
*18F*-Flortaucipir PET hippocampal SUVR and the relation to choroid plexus SUVR and diagnostic performance.

|                | Unmasked SUVR |        |        |        |        |        |        |        |        |        |        |
|----------------|----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
|                | r   | p-value | AUC | 95% C.I. | r   | p-value | AUC | 95% C.I. |        |        |
| No*Hippocampus vs. CP SUVR | 0.28 | <0.001 | – | – | 0.13 | 0.01 | – | – |        |        |
| PVE*Separation CI/CU | – | <0.001 | 0.79 | 0.72 – 0.87 | – | – | 0.84 | 0.77 – 0.91 |        |        |
| Separation CI/CU, adjusted for age | – | <0.001 | 0.80 | 0.73 – 0.87 | – | – | 0.85 | 0.78 – 0.91 |        |        |
| PVE*Hippocampus vs. CP SUVR | 0.18 | <0.05 | – | – | 0.09 | 0.26 | – | – |        |        |
| Separation CI/CU | – | <0.001 | 0.80 | 0.72 – 0.87 | – | – | 0.83 | 0.77 – 0.90 |        |        |
| Separation CI/CU, adjusted for age | – | <0.001 | 0.82 | 0.75 – 0.89 | – | – | 0.86 | 0.79 – 0.92 |        |        |

AUC, area under the receiver operating characteristic curve; CI, cognitively impaired; CU, cognitively unimpaired; C.I., confidence interval; CP, choroid plexus; SUVR, standardized uptake value ratio. * Comparison unmasked vs. masked.
**Fig. 3.** Receiver operating characteristic curves for differentiating cognitively impaired from cognitively unimpaired participants based on hippocampal $^{18}$F-flortaucipir SUVR. AUC – area under the curve; C.I. – confidence interval; PVEc – partial volume error correction; SUVR – standardized uptake value ratio.

**Fig. 4.** Correlations between cognitive scores and hippocampal $^{18}$F-flortaucipir SUVR. Correlations with MMSE for unmasked, non-PVE corrected data (A); masked, non-PVE corrected data (B); unmasked, PVE corrected data (C); and, masked, PVE corrected data (D). PVE – partial volume error; SUVR – standardized uptake value ratio.
for the separation of CI and CU subjects and improved correlations with cognitive measures more than the use of PVE correction alone.

Several studies have previously suggested methods to correct $^{18}$F-flortaucipir hippocampal SUVR for spill-in from the choroid plexus (Baker et al., 2017; Lee et al., 2018; Maass et al., 2017; Wolters et al., 2018). Baker et al. created a specific subset of regions of interest (ROI) to compensate for regional atrophy and signal stemming from choroid plexus, skull and meninges (Baker et al., 2017). This approach, however, did not improve the separation of MCI and AD patients from Aβ-negative controls (Maass et al., 2017). Possibly, this may be due to the authors including the entorhinal cortex — a region less affected by off-target binding that performs well in differentiating CU from CI subjects — in their Braak I/II ROI. Lee et al. adjusted for choroid plexus binding by including it as a covariate when examining hippocampal SUVR and cognition, thereby improving the association to memory scores (Lee et al., 2018). This constitutes an alternative approach to correct for choroid plexus signal, however the effect on diagnostic performance has not been studied. Lastly, Wolters et al. first proposed a method for manually optimizing the hippocampal ROI (Wolters et al., 2018), followed by a semi-automatized method (Wolters et al., 2019) where ~40% of hippocampal voxels with the highest BP$_{ND}$ were removed. Both approaches reduced the relationship between $^{18}$F-flortaucipir retention in the choroid plexus and hippocampus, with the semi-automated method also increasing AUC values (CI vs. CU) and correlations with cognitive function. Though manually optimizing the hippocampal ROI is likely to be the most accurate method, it is also a labor intensive and investigator dependent approach. While similar to the semi-automated method presented by Wolters et al. our approach resulted in greater AUC and improved correlations to cognition, suggesting that our hippocampal exclusion mask is more selective for choroid plexus off-target signal.

Previous work comparing $^{18}$F-flortaucipir and $^{18}$F-R0948 using a head-to-head design showed no significant differences between tracers across cortical regions, except for the entorhinal cortex ($^{18}$F-R0948 > $^{18}$F-flortaucipir). SUVR values in the choroid plexus were higher for $^{18}$F-flortaucipir (Smith et al., 2019). These findings argue against the case that $^{18}$F-flortaucipir has a higher signal than $^{18}$F-R0948 throughout the brain overall — as opposed to specifically in the hippocampus — and support the idea that our voxelwise $^{18}$F-flortaucipir > $^{18}$F-R0948 operation reflects differences between tracers in choroid plexus off-target binding. The location of the mask along the dorsal surface of the hippocampus, just adjacent to the choroid plexus further suggests that the choroid plexus is the source of the increased signal in $^{18}$F-flortaucipir scans. In comparison to the adjusted hippocampal approach, the alternative subject specific method — derived by removing any voxels in the hippocampus in proximity to the choroid plexus — provided similar AUC values. As our adjusted hippocampal approach removes significantly fewer voxels than 0.25 threshold, however, it may prove more specific in removing off-target spill-over from the choroid plexus. Further work comparing these masks is required, however.

3.4. Evaluation of an alternative subject specific hippocampal mask

The three choroid plexus masks, generated in subject space using thresholds of 0.25, 0.50 and 0.75, removed 23%, 18% and 15% of hippocampal voxels, respectively. By comparison with 0.25 threshold, our adjusted hippocampal approach removed significantly fewer voxels (p < 0.001). Using linear regression, we examined relationships between subject specific hippocampal SUVR values (for thresholds of 0.25, 0.50 and 0.75, without and with PVEc) and choroid plexus SUVR (Supplementary Fig. 5). We found significant relationships using thresholds of 0.75 and 0.50 (p < 0.05, without PVEc) and trend level finding when using the 0.25 threshold (p = 0.07, without PVEc). Relationships for PVEc values for thresholds of 0.25, 0.50 and 0.75 were not significant.

Comparison of AUC values (without and with PVEc) using this subject specific method (Supplementary Fig. 6) to those using the adjusted hippocampal mask (without and with PVEc) and the unadjusted FreeSurfer hippocampal ROI (without and with PVEc) are summarized in Supplementary Table 4. These comparisons showed that the subject specific approach proved significantly better than the unadjusted FreeSurfer hippocampal ROI (without and with PVEc, p < 0.001). Comparison of non-PVEc data (i.e. subject specific vs. adjusted hippocampus) showed that the adjusted hippocampus ROI provided significantly higher AUC values than the 0.50 and 0.75 masks and a trend level finding (p = 0.07) using the 0.25 threshold. Comparison of PVEc data showed that the AUC from the adjusted hippocampus ROI was superior only to that from the 0.75 threshold (p < 0.05), with trend level findings for the remaining two thresholds (0.50, p = 0.06; 0.25, p = 0.07). Correlation analyses using thresholded hippocampal SUVR values with MMSE and ADAS-Cog Delayed Word Recall test scores showed similar results to those obtained using masked hippocampal SUVRs (Supplementary Table 5, Supplementary Figs. 7 and 8).

4. Discussion

The main findings of the present study were that the application of a hippocampal mask derived by taking hippocampal voxels where $^{18}$F-flortaucipir SUVR was significantly higher than $^{18}$F-R0948 SUVR removed the correlation between $^{18}$F-flortaucipir SUVR in the hippocampus and the choroid plexus (i.e. corrected hippocampal signal for off-target spill-in from the choroid plexus). Further, the use of masked $^{18}$F-flortaucipir hippocampal SUVR increased the diagnostic performance

| Unmasked SUVR | Masked SUVR |
|---------------|-------------|
| **r (95% CI)** | **p-value** | **r (95% CI)** | **p-value** |
| Norm hippocampus SUVR vs. MMSE | −0.44 (−0.56 – −0.30) | < 0.001 | −0.50 (−0.61 – −0.37) | < 0.001 |
| PVEc hippocampus SUVR vs. MMSE, adj. age, sex, educ. | −0.48 (−0.60 – −0.34) | < 0.001 | −0.52 (−0.63 – −0.39) | < 0.001 |
| Hippocampus SUVR vs. ADAS-Cog | 0.49 (0.35 – 0.61) | < 0.001 | 0.55 (0.42 – 0.66) | < 0.001 |
| Hippocampus SUVR vs. ADAS-Cog, adj. age, sex, educ. | 0.53 (0.40 – 0.64) | < 0.001 | 0.58 (0.46 – 0.68) | < 0.001 |
| PVEc hippocampus SUVR vs. MMSE | −0.45 (−0.57 – −0.31) | < 0.001 | −0.50 (−0.61 – −0.37) | < 0.001 |
| Hippocampus SUVR vs. MMSE, adj. age, sex, educ. | −0.49 (−0.61 – −0.35) | < 0.001 | −0.53 (−0.64 – −0.40) | < 0.001 |
| Hippocampus SUVR vs. ADAS-Cog | 0.53 (0.40 – 0.64) | < 0.001 | 0.58 (0.46 – 0.68) | < 0.001 |
| Hippocampus SUVR vs. ADAS-Cog, adj. age, sex, educ. | 0.56 (0.43 – 0.67) | < 0.001 | 0.60 (0.48 – 0.70) | < 0.001 |

ADAS-Cog, Delayed Word List Recall Test from the Alzheimer’s Disease Assessment Scale-Cognitive Subscale; adj. age, sex, educ., model adjusted for age, sex, and education; CI, confidence interval; MMSE, Mini-Mental State Examination; SUVR, standardized uptake value ratio. * Unmasked vs. masked.

$(r = 0.48 \text{ vs. } r = 0.55; p < 0.001)$ and PVE corrected data $(r = 0.53 \text{ vs. } r = 0.58; p < 0.001)$ data. On the basis of these correlation findings (adjusted for age, sex and education) power analyses showed that the use of masked hippocampal SUVR values would result in the need for fewer subjects, as compared to the use of no mask, both without (MMSE and ADAS-Cog Delayed Word Recall: 11 and 10 fewer, respectively) and with PVEc (MMSE and ADAS-Cog Delayed Word Recall: 11 and 7 fewer, respectively) (Supplementary Table 3).
The main aim of this study was to analyze whether we could improve signal accuracy in the hippocampal ROI in 18F-flortaucipir PET scans and to assess whether this resulted in improved diagnostic performance (CU vs. CI) and the correlation between 18F-flortaucipir hippocampal SUVR and cognitive measures. In unmasked, non-PVE corrected data there was a clear correlation between choroid plexus retention and hippocampal SUVRs. Since the GTM method is one of the most frequently used methods to correct for PVE, we applied the hippocampal mask on both non-PVEc and PVEc (GTM) data to assess both the effect of PVE-correction alone and to examine whether the combination of PVEc and masking out choroid plexus signal would enhance data quality even more. As shown in Fig. 2B, PVEc alone was not enough to fully compensate for off-target spill-over signal from the choroid plexus. The correlation between hippocampus and choroid plexus SUVR disappeared after applying the choroid plexus mask, for both data without and with PVEc. The diagnostic performance for hippocampal ROI SUVRs in separating CI from CU groups improved with PVEc, however significantly better results were obtained after applying the off-target choroid plexus mask on hippocampal SUVR-data.

Correlations between neocortical 18F-flortaucipir SUVR and cognition are well established and have been described earlier (Cho et al., 2016; Pontecorvo et al., 2017). The relation between hippocampal SUVR and cognition, however, has not been investigated to the same extent. We wanted to examine if the relationship between hippocampal retention and cognition would improve after applying the choroid plexus off-target exclusion mask. We observed significant correlations between SUVRs and cognitive tests (MMSE and ADAS-Cog Delayed Word Recall test) for both non-PVEc and PVEc data in our cohort. The improvement of correlations by using PVE-correction alone was generally limited, indicating that PVEc using GTM has a small beneficial effect, but that it cannot on its own compensate for the strong off-target spill-in from the choroid plexus. As a result of masking, correlation coefficients improved significantly for both non-PVEc and PVEc values. The correlation of 18F-flortaucipir to ADAS-Cog Delayed Word Recall test were slightly higher than correlations to MMSE, which may reflect that delayed recall is a more hippocampal dependent cognitive measure relative to MMSE, which is a more global measure of cognition. Lastly, power analysis showed the need for fewer subjects using our off-target exclusion mask; though the differences were modest they may nevertheless be considered meaningful in the context of fewer PET scans and lower costs scans for a given study.

Limitations of the study included the relatively small size of the cohort used to create the choroid plexus off-target mask in the hippocampal ROIs, and the limited number of CI subjects in cohort B. The effects seen on cognition and diagnostic performance were significant but modest. Even though we used ROC analysis for separating CI from CU as a measure of diagnostic performance we would like to point out that for separating AD patients from controls or non-AD dementia other regions show higher AUC-values (Ossenkoppele et al., 2018) and are more suitable for differential diagnosis. Nonetheless, we believe that developing methods to more accurately measure hippocampal SUVR using 18F-flortaucipir is of great interest for studies focusing on the effect of medial temporal lobe tau accumulation on memory performance. Additional limitations include the use of SUVR instead of measures derived from dynamic data, and the use MMSE and ADAS-Cog Delayed Word Recall tests only; findings from the correlation analysis may have been stronger had we used cognitive measures with even greater dependence on hippocampal function. Lastly, while our method assumes that the off-target signal from the choroid plexus is removed from the hippocampus, this off-target component likely cannot be completely eliminated.

In conclusion, we show that correcting 18F-flortaucipir hippocampal SUVR for spill-in from the choroid plexus using an off-target mask is feasible, increases the diagnostic performance of hippocampal SUVRs and improves correlation with cognitive measures. Importantly, the proposed mask provided better results than applying PVE correction alone.

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Declaration of Competing Interest

DP, AL, OS and RS report no disclosures.

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Supplementary materials

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