Tau pathology and relative cerebral blood flow are independently associated with cognition in Alzheimer’s disease

Denise Visser 1, Emma E. Wolters 1,2, Sander C. J. Verfaillie 1, Emma M. Coomans 1, Tessa Timmers 1,2, Hayel Tuncel 1, Juhan Reimand 2, Ronald Boellaard 1, Albert D. Windhorst 1, Philip Scheltens 2, Wiesje M. van der Flier 2,3, Rik Ossenkoppele 2,4, Bart N. M. van Berckel 1

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Abstract
Purpose We aimed to investigate associations between tau pathology and relative cerebral blood flow (rCBF), and their relationship with cognition in Alzheimer’s disease (AD), by using a single dynamic [18F]flortaucipir positron emission tomography (PET) scan.

Methods Seventy-one subjects with AD (66 ± 8 years, mini-mental state examination (MMSE) 23 ± 4) underwent a dynamic 130-min [18F]flortaucipir PET scan. Cognitive assessment consisted of composite scores of four cognitive domains. For tau pathology and rCBF, receptor parametric mapping (cerebellar gray matter reference region) was used to create uncorrected and partial volume-corrected parametric images of non-displaceable binding potential (BPND) and R1, respectively. (Voxel-wise) linear regressions were used to investigate associations between BPND and/or R1 and cognition.

Results Higher [18F]flortaucipir BPND was associated with lower R1 in the lateral temporal, parietal and occipital regions. Higher medial temporal BPND was associated with worse memory, and higher lateral temporal BPND with worse executive functioning and language. Higher parietal BPND was associated with worse executive functioning, language and attention, and higher occipital BPND with lower cognitive scores across all domains. Higher frontal BPND was associated with worse executive function and attention. For [18F]flortaucipir R1, lower values in the lateral temporal and parietal ROIs were associated with worse executive functioning and attention, and lower occipital R1 with lower language and attention scores. When [18F]flortaucipir BPND and R1 were modelled simultaneously, associations between lower R1 in the lateral temporal ROI and worse attention remained, as well as for lower parietal R1 and worse executive functioning and attention.

Conclusion Tau pathology was associated with locally reduced rCBF. Tau pathology and low rCBF were both independently associated with worse cognitive performance. For tau pathology, these associations spanned widespread neocortex, while for rCBF, independent associations were restricted to lateral temporal and parietal regions and the executive functioning and attention domains. These findings indicate that each biomarker may independently contribute to cognitive impairment in AD.

Keywords [18F]flortaucipir PET · Relative cerebral blood flow · Tau · Cognition · Alzheimer’s disease

Denise Visser and Emma E. Wolters contributed equally to this work.

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Denise Visser d.visser2@amsterdamumc.nl

1 Department of Radiology & Nuclear Medicine, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands

2 Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands

3 Department of Epidemiology and Biostatistics, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands

4 Clinical Memory Research Unit, Lund University, Lund, Sweden
Introduction

[18F]Flortaucipir is the most widely studied PET tracer to date for detecting AD-specific tau pathology [1]. Most studies with [18F]Flortaucipir used static scan protocols, which allow semi-quantitative estimates such as the standardized uptake value ratio (SUVR) [1]. Advantages of static over dynamic scanning protocols include the relatively short scan duration and computational simplicity which facilitates clinical applicability [2]. On the other hand, dynamic acquisition allows optimal quantitative accuracy and additionally enables computation of parametric images of tracer delivery, which can be interpreted as a proxy of relative tracer flow or relative cerebral blood flow (rCBF) (i.e. $R_1$) [2–9]. $R_1$ represents the ratio between the rate constant for ligand transfer from blood to tissue ($K_f$) in the tissue of interest and the reference region [4–8], which is strongly correlated with metabolic activity derived from [18F]FDG PET [4, 5, 9]. A dynamic [18F]Flortaucipir PET scan may thus not only provide accurate information on (regional) quantification of tau pathology, but also yields information on rCBF.

Previous studies demonstrated that high levels of regional tau pathology [10–12], as well as low levels of rCBF (as measured with [18F]FDG PET or MRI) [9, 13], correlate with cognitive impairment in various domains. However, rCBF has not been investigated yet using [18F]Flortaucipir $R_1$. Investigating tau pathology and rCBF simultaneously by using dynamic [18F]Flortaucipir PET might yield valuable information, since both pathophysiological mechanisms may contribute to cognitive impairment in AD.

The aims of this study are to investigate the (regional) association between tau pathology and rCBF, and their (independent) associations with cognitive functioning in patients with AD.

Methods

Recruitment of participants

Patients were recruited from the Amsterdam Dementia Cohort of the Alzheimer Center Amsterdam [14]. All subjects underwent a standardized dementia screening, including medical and neurological examination, informant-based history, assessment of vital functions, screening laboratory tests, neuropsychological evaluation, MRI, lumbar puncture and/or amyloid-β positron emission tomography (PET), after which diagnoses were determined in a multidisciplinary consensus meeting [14]. For this study, patients with a diagnosis of Alzheimer’s disease (AD) dementia [15] or mild cognitive impairment (MCI) due to AD [16] were included. For all subjects, AD biomarkers in cerebrospinal fluid (CSF) and/or Aβ PET were abnormal (CSF Aβ42 < 813 pg/mL [17] and/or abnormal Aβ PET (on visual read)). According to the NIA-AA Research Framework [18], all subjects are considered in the AD pathophysiological continuum. Subjects were excluded if they had severe traumatic brain injury, abnormalities on MRI likely to interfere with segmentation of tau PET and participation in drug trial with a tau or Aβ-targeting agent.

All procedures were in accordance with the ethical standards of the Medical Ethics Review Committee of the Amsterdam UMC VU Medical Center and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Image acquisition

All participants underwent a single dynamic [18F]Flortaucipir PET scan at the Amsterdam UMC VU Medical Center on an Ingenuity TF PET-CT scanner (Philips Medical Systems, Best, The Netherlands) within 1 year from their neuropsychological examination. [18F]Flortaucipir was synthesized at the Amsterdam UMC VU Medical Center, using a protocol described in detail previously [19]. The scan protocol started with a low-dose CT for attenuation correction, followed by a 234 ± 14 MBq [18F]flortaucipir bolus injection (injected mass 1 ± 1 μg). Simultaneously with tracer injection, a 60-min dynamic emission scan was initiated. After a 20-min break and following a second low-dose CT for attenuation correction, an additional dynamic emission scan was performed during the interval 80–130 min post-injection. During scanning, head movements were restricted by a head holder with band and head position was regularly checked. PET scans were reconstructed using a matrix size of 128 × 128 × 90 and a final voxel size of 2 × 2 × 2 mm³. All standard corrections for dead time, decay, attenuation, randoms and scatter were performed. Both scan sessions were co-registered into a single dataset of 29 frames (1 × 15, 3 × 5, 3 × 10, 4 × 60, 2 × 150, 2 × 300, 4 × 600 and 10 × 300 s), in which the last 10 frames belonged to the second PET session.

In addition, all subjects underwent structural MRI on a 3.0 Tesla (3 T) Philips medical systems’ Ingenuity TF PET-MRI. The protocol included an isotropic structural 3D T1-weighted image using a sagittal turbo gradient-echo sequence (1.00 mm³ isotropic voxels, repetition time = 7.9 ms, echo time = 4.5 ms, and flip angle = 8°), and a 3D fluid-attenuated inversion recovery (FLAIR) image (1.04 × 1.04 × 1.12 mm voxels, repetition time = 4800 ms, echo time = 278.8 ms, flip angle 90°).

PET and MR analyses

Using Vinci software (Max Plank Institute, Cologne, Germany), T1-weighted MR images were co-registered to their individual PET scans in native space. To delineate
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[18F]flortaucipir with excellent test-retest repeatability demonstrated that, when compared to full kinetic modelling, RPM dynamic 130 min PET data [22]. Our group previously demonstrated that, when compared to full kinetic modelling, RPM is the most optimal simplified parametric method for [18F]flortaucipir [23] with excellent test-retest repeatability [24]. PET images were partial volume-corrected using Van Cittert iterative deconvolution methods (IDM), combined with highly constrained back-projection (HYPR) [25]. A moving frame composite image was used for HYPR to better sustain the temporal information while denoising [26]. Uncorrected data are presented throughout the paper and partial volume-corrected data are presented in the Supplementary material.

For voxel-wise analyses, using Statistical Parametric Mapping (SPM) version 12 software (Wellcome Trust Center for Neuroimaging, University College London, UK), we warped all native space parametric BPND and R1 images to Montreal Neurological Institute (MNI152) space, by using the transformation matrices derived from warping the co-registered T1-weighted MRI scans to MNI space. Warped images underwent quality control for transformation errors.

For regional analyses, the following bilateral ROIs were created a priori based on the Hammers atlas [20] (in subject space): medial temporal (hippocampus, parahippocampal and ambient gyrus), anterior temporal lobe medial part), lateral temporal (superior temporal gyrus, middle and inferior temporal gyri), parietal (inferolateral remainder of parietal lobe, superior parietal gyrus, gyrus cinguli posterior part), occipital (cuneus, lingual gyrus, lateral remainder of occipital lobe) and frontal (middle frontal gyrus, orbitofrontal gyri, superior frontal gyrus) regions.

As a measure of vascular pathology, white matter hyperintensities (WMHs) were visually rated by an experienced rater on subjects’ FLAIR image using the Fazekas scale, with scores ranging from 0 to 3 [27].

Cognition

Cognitive domain scores were created by averaging Z-transformed test-scores (based on the current sample) of corresponding tests for memory (Immediate Recall of the Dutch version of the RAVLT, Delayed Recall of the Dutch version of the RAVLT and Visual Association Test-A), executive functioning (Stroop Colour Word test I and II, Digit Span Backwards and Trail Making Test (TMT)-B), language (Category Fluency Animals and Visual Association Test-Naming) and attention (TMT-A, Stroop Colour Word test I and II and the Digit Span Forward) [28]. Tests on which lower scores indicated better performance (TMT-A and -B, Stroop Colour Word test I, II and III) were inverted. Domain scores were only calculated if two or more tests within a domain were available.

Statistical analyses

To assess the correlations between [18F]flortaucipir BPND and $R_1$ with age, sex, education and Fazekas score, a correlation matrix was created using Spearman correlations. A $p$ value below 0.05 was considered statistically significant.

To examine the regional associations between [18F]flortaucipir BPND and $R_1$, linear regression analyses, adjusted for age and sex, were performed. To assess the contribution of white matter damage in these associations, analyses were additionally adjusted for Fazekas score.

To assess voxel-wise associations between [18F]flortaucipir BPND or $R_1$ and cognition, voxel-wise regression analyses using SPM12 were performed. Analyses were adjusted for age, sex and education. A $p$ value below 0.001 (uncorrected) was considered statistically significant for voxel-wise analyses. Additionally, a more conservative family-wise error (FWE) correction at $p < 0.05$ was applied.

To investigate regional associations between [18F]flortaucipir BPND or $R_1$ and cognition (dependent variables), linear regression analyses, adjusted for age, sex and education (model 1), were used. Subsequently, we entered [18F]flortaucipir BPND and $R_1$ simultaneously in the model to assess their independent associations with cognition (model 2).

For all regional analyses, we report the level of significance both with and without correction for multiple comparisons using the Benjamini-Hochberg procedure with a false discovery rate (FDR) Q value of 5%. A $p$ value below 0.05 was considered statistically significant. All regional and voxel-wise analyses were repeated with partial volume-corrected data.

Results

Participants

A total of 71 subjects (MCI due to AD: $n = 10$, and AD dementia: $n = 61$) with a mean age of $66 ± 8$ years and MMSE score of $23 ± 4$ were included (Table 1). By study design, all subjects had abnormal amyloid biomarkers. [18F]Flortaucipir BPND values were highest in parietal ($0.55 ± 0.43$) regions and $R_1$ values were lowest in medial temporal regions ($0.68 ± 0.06$) (Table 1). [18F]Flortaucipir BPND and/or $R_1$ showed statistically significant correlations with age and education (Table 2), but not with sex.
Supplementary Table 1.

Scores to the model did not notably change the results of scatterplots for these associations. Addition of Fazekas

Regional associations with cognition

Regional linear regression analyses (model 1) revealed that higher medial temporal BP$_{ND}$ was associated with worse memory performance (−0.43 [−0.66 to −0.20]), higher lateral temporal BP$_{ND}$ with worse scores on executive functioning (−0.26 [−0.52 to −0.02]) and language (−0.37 [−0.66 to −0.11]), and higher parietal BP$_{ND}$ with worse executive functioning (−0.46 [−0.81 to −0.23]), language (−0.34 [−0.76 to −0.03]) and attention (−0.50 [−0.89 to −0.25]) (Fig. 3). Higher BP$_{ND}$ in the occipital ROI was associated with worse memory (−0.27 [−0.54 to −0.00]), executive functioning (−0.26 [−0.53 to −0.01]), language (−0.40 [−0.73 to −0.14]) and attention (−0.37 [−0.67 to −0.10]) performance, and higher BP$_{ND}$ in the frontal ROI with worse executive functioning (−0.34 [−0.65 to −0.13]) and attention (−0.33 [−0.67 to −0.08]). After FDR correction, the majority of significant associations remained (Table 4; Fig. 3).

Lower lateral temporal and parietal $R_1$ was associated with lower scores on executive functioning (0.27 [0.04 to 0.50]; 0.36 [0.15 to 0.60]), language (0.30 [0.04 to 0.57]; 0.28 [0.02 to 0.57]) and attention (0.33 [0.08 to 0.57]; 0.48 [0.26 to 0.71]) (Table 4; Fig. 3). Lower $R_1$ in the occipital ROI was associated with worse language (0.28 [0.03 to 0.57]) and attention (0.31 [0.07 to 0.59]) performance. By applying the FDR correction, the significant associations between lower $R_1$ in the parietal ROI and worse executive functioning remained, as well as the significant associations between lower $R_1$ in the lateral temporal, parietal and occipital ROI and worse attention scores (Table 4; Fig. 3). Scatterplots for a selection of these associations are presented in Fig. 1.

Finally, to examine the independent effects of tau pathology and rCBF on cognitive functioning, linear regression analyses including both [18F]flortaucipir BP$_{ND}$ and $R_1$ were performed (model 2) (Table 4). Results revealed that higher medial temporal BP$_{ND}$ was independently associated with worse memory (−0.44 [−0.67 to −0.20]), higher lateral temporal

### Associations between [18F]flortaucipir BP$_{ND}$ and $R_1$

Higher [18F]flortaucipir BP$_{ND}$ was associated with lower $R_1$ within the lateral temporal (stβ = 0.32 [95% CI −0.56 to −0.08]), parietal (−0.43 [−0.72 to −0.14]) and occipital (−0.53 [−0.78 to −0.29]) ROI (Table 3). Higher BP$_{ND}$ in the occipital ROI was also associated with lower $R_1$ in the parietal ROI (−0.38 [−0.64 to −0.12]). All associations remained significant after FDR correction (Table 3). Figure 1 shows a selection of scatterplots for these associations. Addition of Fazekas scores to the model did not notably change the results (Supplementary Table 1).

### Voxel-wise associations with cognition

Voxel-wise analyses (model 1) revealed that, in general, higher [18F]flortaucipir BP$_{ND}$ was associated with worse cognition (Fig. 2). More specifically, higher medial temporal BP$_{ND}$ associated with worse memory performance, and higher (orbito-)frontoparietal BP$_{ND}$ with worse scores on executive functioning (Fig. 2). Higher inferior temporal BP$_{ND}$ associated with worse language performance and higher (middle-)frontoparietal and occipital BP$_{ND}$ with worse attention scores (Fig. 2). After FWE correction, sparse associations with higher BP$_{ND}$ in the medial temporal regions and worse memory performance remained, as well as higher BP$_{ND}$ in the temporal (fusiform cortex) regions and worse language scores (data not shown). Associations between higher BP$_{ND}$ in the parietal and frontal regions and worse attention also survived FWE correction (data not shown).

Overall, lower $R_1$ associated with worse cognition (Fig. 2). In more detail, lower fronto-temporoparietal $R_1$ associated with worse scores on executive functioning and to a sparser extent with worse language performance (Fig. 2). Lower temporoparietal $R_1$ associated with worse attention scores (Fig. 2). None of the associations survived FWE correction (data not shown).
Table 2  Correlation matrix (Spearman’s rho) for BPND and R1 and (possible) covariates age, sex, education and Fazekas score

| Correlation matrix (Spearman’s rho) | Age       | Sex       | Education | Fazekas score | BP ND medial temporal | BP ND lateral temporal | BP ND parietal | BP ND occipital | BP ND frontal | R1 medial temporal | R1 lateral temporal | R1 parietal | R1 occipital | R1 frontal |
|-------------------------------------|-----------|-----------|-----------|---------------|----------------------|-----------------------|----------------|----------------|---------------|-------------------|-------------------|-------------|-------------|-----------|
| Age                                 | 1.00      |           |           |               |                      |                       |                |                |               |                   |                   |             |             |           |
| Sex                                 | -0.09     | 1.00      |           |               |                      |                       |                |                |               |                   |                   |             |             |           |
| Education                           | -0.05     | -0.03     | 1.00      |               |                      |                       |                |                |               |                   |                   |             |             |           |
| Fazekas score                       | 0.48<sup>‡</sup> | -0.15 | -0.07 | 1.00 | | | | | | | | | | | |
| BP ND medial temporal               | 0.02      | -0.04     | -0.25<sup>§</sup> | 0.14 | 1.00 | | | | | | | | | | |
| BP ND lateral temporal              | -0.31<sup>†</sup> | -0.05 | -0.17 | 0.01 | 0.68<sup>‡‡</sup> | 1.00 | | | | | | | | | |
| BP ND parietal                      | -0.64<sup>‡‡</sup> | 0.04 | 0.00 | -0.19 | 0.32<sup>‡‡</sup> | 0.73<sup>‡‡</sup> | 1.00 | | | | | | | | | |
| BP ND occipital                     | -0.46<sup>‡‡</sup> | -0.01 | -0.01 | -0.19 | 0.32<sup>‡‡</sup> | 0.62<sup>‡‡</sup> | 0.84<sup>‡‡</sup> | 1.00 | | | | | | | | |
| BP ND frontal                       | -0.47<sup>‡‡</sup> | -0.01 | -0.02 | -0.03 | 0.49<sup>‡‡</sup> | 0.77<sup>‡‡</sup> | 0.82<sup>‡‡</sup> | 0.57<sup>‡‡</sup> | 1.00 | | | | | | | |
| R1 medial temporal                  | -0.38<sup>‡‡</sup> | 0.03 | -0.01 | -0.21 | -0.10 | -0.04 | 0.29<sup>‡</sup> | 0.14 | 0.20 | 1.00 | | | | | |
| R1 lateral temporal                 | -0.11     | 0.18      | 0.01      | -0.20 | -0.19 | -0.30<sup>‡</sup> | -0.04 | -0.03 | -0.12 | 0.67<sup>‡</sup> | 1.00 | | | | |
| R1 parietal                         | 0.17      | 0.09      | 0.02      | -0.14 | -0.10 | -0.32<sup>‡</sup> | -0.37<sup>‡</sup> | -0.40<sup>‡</sup> | -0.27<sup>‡</sup> | 0.21 | 0.68<sup>‡‡</sup> | 1.00 | | | | |
| R1 occipital                        | 0.08      | -0.01     | -0.03     | -0.15 | -0.01 | -0.13 | -0.20 | -0.42<sup>‡</sup> | 0.02 | 0.24<sup>‡</sup> | 0.45<sup>‡</sup> | 0.77<sup>‡‡</sup> | 1.00 | | | | |
| R1 frontal                          | -0.11     | 0.19      | -0.03     | -0.23 | -0.18 | -0.16 | 0.08 | 0.13 | -0.06 | 0.64<sup>‡</sup> | 0.81<sup>‡‡</sup> | 0.52<sup>‡‡</sup> | 0.22 | 1.00 | | |

<sup>*p < 0.05, †p < 0.01, ‡p < 0.001, §p<sub>FDR</sub> < 0.05</sup>
BPND with worse language (−0.31 [−0.60 to −0.04]) performance, and higher parietal BPND with worse scores on executive functioning (−0.36 [−0.70 to −0.11]) and attention (−0.36 [−0.72 to −0.10]). Higher occipital BPND was independently associated with worse language (−0.33 [−0.68 to −0.03]) and higher frontal BPND with lower scores on executive functioning (−0.33 [−0.64 to −0.11]) and attention (−0.31 [−0.66 to −0.06]). Most significant associations survived FDR correction (Table 4). For \([^{18}F]\)flortaucipir \(R_1\), lower values in the lateral temporal ROI were independently associated with worse attention (0.28 [0.03 to 0.54]), while low \(R_1\) values in the parietal ROI were with lower scores on executive functioning (0.27 [0.06 to 0.50]) and attention (0.39 [0.17 to 0.62]). After FDR correction, the association between lower \(R_1\) in the parietal ROI and worse attention remained (Table 4).

![Graphs showing scatterplots between \([^{18}F]\)flortaucipir BPND and/or \(R_1\) and/or cognition. BPND non-displaceable binding potential, stβ standardized β, punc uncorrected p value, p(fdr) p value corrected for multiple comparisons using the Benjamini-Hochberg procedure with a false discovery rate (FDR) Q value of 5%. A p value below 0.05 was considered statistically significant](image.png)

**Table 3** Regional association between \([^{18}F]\)flortaucipir BPND (rows) and \(R_1\) (columns)

| \([^{18}F]\)flortaucipir \(R_1\) | Medial temporal | Lateral temporal | Parietal | Occipital | Frontal |
|--------------------------------|----------------|-----------------|----------|-----------|--------|
| \([^{18}F]\)flortaucipir BPND |                |                 |          |           |        |
| Medial temporal                | −0.10 [−0.32 to −0.13] | −0.21 [−0.44 to −0.02] | −0.11 [−0.35 to −0.13] | 0.03 [−0.21 to −0.27] | −0.18 [−0.41 to −0.05] |
| Lateral temporal               | −0.15 [−0.38 to −0.08] | −0.32 [−0.56 to −0.08] | −0.24 [−0.49 to −0.01] | −0.10 [−0.35 to −0.16] | −0.19 [−0.43 to −0.06] |
| Parietal                       | 0.10 [−0.18 to −0.38] | 0.14 [−0.44 to −0.16] | 0.43 [−0.72 to −0.14] | 0.29 [−0.59 to 0.00] | 0.04 [−0.26 to −0.33] |
| Occipital                      | 0.02 [−0.24 to −0.27] | 0.07 [−0.34 to −0.20] | 0.38 [−0.64 to −0.12] | −0.53 [−0.78 to −0.29] | 0.13 [−0.13 to −0.40] |
| Frontal                        | 0.12 [−0.12 to −0.36] | 0.18 [−0.43 to −0.08] | 0.23 [−0.49 to −0.03] | 0.09 [−0.18 to −0.35] | −0.14 [−0.40 to −0.11] |

Model is adjusted for age and sex. Standardized β’s with 95% confidence intervals are reported. BPND non-displaceable binding potential. *\(p<0.01\), †\(p<0.001\), ‡\(p_{FDR}<0.05\).
Additional analyses

Overall, partial volume-corrected data yielded slightly higher values for both $[^{18}F]$flortaucipir BP$_{ND}$ and $R_I$ (Supplementary Table 2), but results from regression analyses remained essentially comparable (Supplementary Tables 3 & 4; Supplementary FIGs. 1 & 2).

Discussion

The present study used a single dynamic $[^{18}F]$flortaucipir PET scan to examine the relationship between tau pathology, rCBF and cognition in AD. The main finding is that high levels of tau pathology and low levels of rCBF were independently associated with worse cognitive performance across various domains.

![Fig. 2 Voxel-wise associations between $[^{18}F]$flortaucipir BP$_{ND}$ or $R_I$ and cognition. Voxel-wise regression analyses were performed, adjusted for age, sex and education. Voxels with a significant ($p < 0.001$, uncorrected) association are displayed. BP$_{ND}$ non-displaceable binding potential, A anterior, P posterior, R right, L left.](image)

**Tau pathology and rCBF are independently associated with cognition in AD**

An important finding in the present study is that tau pathology and rCBF, at least in part, independently contribute to cognitive deficits in AD. A previous study demonstrated that tau pathology was also independently associated with specific cognitive impairment in AD in the context of neurodegeneration [29]. This leads to the notion that tau pathology may impact cognitive performance directly, but also indirectly through a variety of mechanisms [29]. One such mechanisms might be rCBF, since some of the associations found between $[^{18}F]$flortaucipir BP$_{ND}$ and cognition in the present study disappeared when $R_I$ was included in the model simultaneously. Other factors possibly explaining the tau pathology-independent associations between rCBF and cognition in AD might be the presence of other down- or upstream pathological factors like tau-independent atrophy, vascular
pathology or other proteinopathies. Vascular damage for example might lead to impaired rCBF, possibly causing an increase in amyloid-β accumulation, which in turn can lead to inflammation and neuronal dysfunction, leading to cognitive deficits [30]. Further research is required, however, to gain knowledge about the mechanisms explaining the tau-independent relationships between rCBF and cognition in AD.

**Associations between tau pathology, rCBF and cognition**

Strong (regional) associations between tau pathology and cognitive deficits in AD have been established by multiple (imaging) studies [10–12, 31], and results of the present study are generally in line with previous findings. As expected, tau pathology in the medial temporal regions showed strong associations with memory, while tau pathology in temporoparietal regions was associated with language. High levels of tau pathology in frontal regions were associated with more anteriorly based cognitive functions, like executive function and attention.

Although the association between CBF and cognition in AD has not been studied using this [18F]Flortaucipir PET approach before, other studies investigated these associations by using [18F]FDG PET or MRI techniques (such as arterial spin labeling (ASL)) to measure (proxies of) CBF [13, 32]. These studies demonstrated that in AD, reduced CBF is generally associated with worse global cognition [13, 32] and not with domain-specific cognitive impairments (memory, executive function, language, attention and visuospatial functioning) [13]. Nonetheless, it was also demonstrated that most associations with cognition were found for low CBF in parietal and frontal areas [13].

| Table 4 | Regional associations between [18F]Flortaucipir BPND and $R_I$ and cognition |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Memory ($n = 71$) | Executive functioning ($n = 64$) | Language ($n = 59$) | Attention ($n = 64$) |
| **Model 1** | | | |
| Medial temporal BPND | $-0.43^{**}$ [−0.66–−0.20] | $-0.08$ [−0.34–−0.16] | $-0.17$ [−0.48–−0.12] | $0.00$ [−0.28–−0.28] |
| $R_I$ | $-0.04$ [−0.30–−0.22] | $0.03$ [−0.22–−0.28] | $0.10$ [−0.18–−0.38] | $0.07$ [−0.21–−0.35] |
| Lateral temporal BPND | $-0.22$ [−0.48–−0.04] | $-0.26^{*}$ [−0.52–−0.02] | $-0.37^{**}$ [−0.66–−0.11] | $-0.25$ [−0.54–−0.02] |
| $R_I$ | $0.03$ [−0.22–−0.27] | $0.27^{*}$ [0.04–0.50] | $0.30^{*}$ [0.04–0.57] | $0.33^{**}$ [0.08–0.57] |
| Parietal BPND | $-0.23$ [−0.52–−0.07] | $-0.46^{**}$ [−0.81–−0.23] | $-0.34^{*}$ [−0.76–−0.03] | $-0.50^{**}$ [−0.89–−0.25] |
| $R_I$ | $0.06$ [−0.18–−0.30] | $0.36^{**}$ [0.15–0.60] | $0.28^{*}$ [0.02–0.57] | $0.46^{**}$ [0.26–0.71] |
| Occipital BPND | $-0.27^{*}$ [−0.54–−0.00] | $-0.26^{*}$ [−0.53–−0.01] | $-0.40^{**}$ [−0.73–−0.14] | $-0.37^{**}$ [−0.67–−0.10] |
| $R_I$ | $0.13$ [−0.12–0.37] | $0.17$ [−0.06–0.43] | $0.28^{*}$ [0.03–0.57] | $0.31^{**}$ [0.07–0.59] |
| Frontal BPND | $-0.14$ [−0.40–−0.12] | $-0.34^{**}$ [−0.65–−0.13] | $-0.21$ [−0.57–−0.09] | $-0.33^{**}$ [−0.67–−0.08] |
| $R_I$ | $-0.12$ [−0.37–0.13] | $0.15$ [−0.09–0.40] | $0.13$ [−0.15–0.41] | $0.13$ [−0.13–0.40] |
| **Model 2** | | | |
| Medial temporal BPND | $-0.44^{**}$ [−0.67–−0.20] | $-0.08$ [−0.34–−0.17] | $-0.17$ [−0.48–−0.12] | $0.01$ [−0.28–−0.29] |
| $R_I$ | $-0.09$ [−0.33–0.15] | $0.03$ [−0.23–0.28] | $0.10$ [0.19–0.38] | $0.07$ [−0.21–−0.35] |
| Lateral temporal BPND | $-0.23$ [−0.51–−0.04] | $-0.19$ [−0.46–0.05] | $-0.31^{*}$ [−0.60–−0.04] | $-0.16$ [−0.45–0.11] |
| $R_I$ | $-0.05$ [−0.30–0.21] | $0.21$ [−0.02–0.46] | $0.22$ [−0.04–0.49] | $0.28^{*}$ [0.03–0.54] |
| Parietal BPND | $-0.23$ [−0.55–−0.09] | $-0.36^{**}$ [−0.70–−0.11] | $-0.27$ [−0.68–0.05] | $-0.36^{*}$ [−0.72–−0.10] |
| $R_I$ | $-0.00$ [−0.26–0.25] | $0.27^{*}$ [0.06–0.50] | $0.22$ [−0.05–0.52] | $0.39^{**}$ [0.17–0.62] |
| Occipital BPND | $-0.26$ [−0.57–0.04] | $-0.21$ [−0.52–0.07] | $-0.33^{*}$ [−0.68–−0.03] | $-0.27$ [−0.59–0.03] |
| $R_I$ | $0.02$ [−0.25–0.28] | $0.09$ [−0.17–0.37] | $0.15$ [−0.13–0.46] | $0.20$ [−0.07–0.50] |
| Frontal BPND | $-0.16$ [−0.42–0.11] | $-0.33^{**}$ [−0.64–−0.11] | $-0.20$ [−0.56–0.10] | $-0.31^{**}$ [−0.66–−0.06] |
| $R_I$ | $-0.14$ [−0.39–0.11] | $0.11$ [−0.12–0.34] | $0.11$ [−0.16–0.39] | $0.09$ [−0.17–0.35] |

Models are adjusted for age, sex and education. [18F]Flortaucipir BPND and $R_I$ were included in the model separately (model 1) and simultaneously (model 2). Standardized β’s with 95% confidence intervals are reported. BPND non-displaceable binding potential. $^{*}p<0.05$, $^{*}p<0.01$, $^{*}p<0.001$, $^{*}p_{FDR}<0.05$
CBF and cognition. Standardized regression coefficients ranged from 0.22 till 0.42 across the cognitive domains in the former study \[13\], and ranged from 0.27 till 0.48 in the present study, indicating comparable effect sizes.

Regional association between tau pathology and low rCBF

Relative CBF is tightly correlated with measures of metabolic activity such as \[^{18}F\]FDG PET \[4, 5, 9\]. Earlier studies investigating \[^{18}F\]flortaucipir and \[^{18}F\]FDG PET in AD found considerable overlap between higher levels of tau tracer uptake and lower levels of metabolic activity \[11, 33\], with moderate correlation coefficients across 30 predefined brain regions. The present study used \(R_f\) as proxy for rCBF, and in line with the previously described study \[33\], we also found spatial overlap between high levels of tau pathology and low rCBF, with comparable standardized regression coefficients. The overlap of high levels of tau pathology and low levels of rCBF was in both studies not completely uniform across all brain regions, suggesting that both measures represent complementary aspects of AD pathology \[33\]. A potential explanation might be that tau pathology may develop prior to or even (partially) drive impaired metabolic activity or CBF, creating a time-lag between both pathological mechanism leading to topographical differences \[34\]. Alternatively, other pathological processes besides tau pathology may contribute to impaired metabolic activity or CBF, such as other proteinopathies. Vascular pathology has been linked to AD \[35\] and might have an impact on for example rCBF. However, in our study, the influence of vascular pathology showed to be negligible, since no correlation between Fazekas score and tau pathology or rCBF was found, and addition of Fazekas score to the regression model assessing the association between tau pathology and rCBF did not notably change results.

Strengths and limitations

This study has several strengths, including the use of \[^{18}F\]flortaucipir \(R_f\) as a measure of CBF, since this tracer has not been used in this context before, while \[^{18}F\]flortaucipir currently is the most widely used tracer for tau pathology in AD. Another strength is that both measures were derived from a single dynamic \[^{18}F\]flortaucipir PET scan, thereby circumventing the need for a dual-tracer study and avoiding
bias caused by time-lags between measures of tau pathology and rCBF. Furthermore, analyses were repeated with partial volume-corrected data, and results remained essentially comparable; hence, we feel that our findings are not biased by atrophy to a large extent.

This study also has some limitations. The AD patients in this study were relatively young, which might hamper generalizability of results to older patient populations. Also, because our sample included only ten ‘MCI due to AD’ patients, further research is needed to elucidate potential differences in the BPND-R1 relationship between diagnostic groups. Furthermore, it might be difficult to draw firm conclusions about the performance of [18F]flortaucipir R1 compared to other measures of CBF due to the lack of a golden standard for measuring CBF. At last, this study has a cross-sectional design, which excluded the possibility to investigate whether the associations found between tau pathology, rCBF and cognition in AD represent causality. Therefore, longitudinal designs are required.

Conclusion

This study demonstrates that tau pathology and rCBF derived from a single dynamic [18F]flortaucipir PET scan are associated in a region-specific matter, with high levels of tau pathology being generally present in areas with low levels of rCBF. Lower cognitive scores are associated with higher levels of tau pathology and lower levels of rCBF. A substantial amount of these associations remained present when correcting for the other PET measure, indicating that tau pathology and rCBF (at least in part) independently contribute to cognitive deficits in AD. Besides, this study indicates that the use of dynamic [18F]flortaucipir PET might sometimes be preferable, since accurate quantification of tau pathology and an additional functional measure like rCBF can be derived from a single scan.

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Compliance with ethical standards

Conflict of interest Visser, Wolters, Verfaillie, Coomans, Timmers, Tuncel, Reimand, Boellaard, Windhorst and Ossenkoppele declare that they have no conflict of interest.

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No other potential conflicts of interest relevant to this article exist.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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