[18F]Flortaucipir PET Across Various MAPT Mutations in Presymptomatic and Symptomatic Carriers

Author(s):
Emma E. Wolters, MD, PhD1,2; Janne M. Papma, PhD3; Sander C.J. Verfaillie, PhD1; Denise Visser, MSc1; Emma Weltings, MSc1; Colin Groot, PhD2; Emma L. van der Ende, MD3; Lucia A.A. Giannini, MD3; Hayel Tuncel, MSc1; Tessa Timmers, MD, PhD1; Ronald Boellaard, PhD1; Maqsood Yaqub, PhD1; Danielle M.E. van Assema, MD, PhD4; Dennis A Kuijper, MSc4; Marcel Segbers, MSc4; Annemieke J.M. Roemuller, MD, PhD5; Frederik Barkhof, MD, PhD5; Albert D Windhorst, PhD1; Wiesje M. van der Flier, PhD2,7; Yolande A.L. Pijnenburg, MD, PhD2; Philip Scheltens, MD, PhD2; Rik Ossenkoppele, PhD8,9; Bart N.M. van Berckel, MD, PhD1; John C. van Swieten, MD, PhD3; Harro Seelaar, MD, PhD1

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Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

Published Ahead of Print on July 1, 2021 as 10.1212/WNL.0000000000012448
Corresponding Author:
Emma E. Wolters
ee.wolters@amsterdamumc.nl

Affiliation Information for All Authors: 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 Neurology, Alzheimer Center, Erasmus MC University Medical Center, Rotterdam, the Netherlands; 4. Department of Radiology & Nuclear Medicine, Erasmus MC University Medical Center, Rotterdam, the Netherlands; 5. Department of Pathology, Amsterdam Neuroscience, Amsterdam UMC, location VUMc, Amsterdam, The Netherlands; 6. Institutes of Neurology & Healthcare Engineering, UCL, London, United Kingdom; 7. Department of Epidemiology and Biostatistics, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands; 8. Clinical Memory Research Unit, Lund University, Lund, Sweden

Contributions:
Emma E. Wolters: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Janne M. Papma: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Sander C.J. Verfaillie: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Denise Visser: Major role in the acquisition of data
Emma Weltings: Major role in the acquisition of data
Colin Groot: Analysis or interpretation of data
Emma L. van der Ende: Major role in the acquisition of data
Lucia A.A. Giannini: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Hayel Tuncel: Analysis or interpretation of data
Tessa Timmers: Major role in the acquisition of data
Ronald Boellaard: Drafting/revision of the manuscript for content, including medical writing for content
Maqsood Yaqub: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Danielle M.E. van Assema: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Dennis A Kuijper: Major role in the acquisition of data
Marcel Segbers: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Annemieke J.M. Roemuller: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Frederik Barkhof: Drafting/revision of the manuscript for content, including medical writing for content
Albert D Windhorst: Drafting/revision of the manuscript for content, including medical writing for content
Wiesje M. van der Flier: Drafting/revision of the manuscript for content, including medical writing for content
Yolande A.L. Pijnenburg: Drafting/revision of the manuscript for content, including medical writing for content
Philip Scheltens: Drafting/revision of the manuscript for content, including medical writing for content
Bart N.M. van Berckel: Drafting/revision of the manuscript for content, including medical writing for content
content; Study concept or design
John C. van Swieten: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design
Rik Ossenkoppele: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Harro Seelaar: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

Number of characters in title: 94

Abstract Word count: 250

Word count of main text: 4498

References: 50

Figures: 6

Tables: 1

Supplemental: Strobe checklist

Statistical Analysis performed by: Emma E Wolters, MD, PhD, Location: Amsterdam UMC, Amsterdam.

Search Terms: [ 29 ] Frontotemporal dementia, [ 122 ] PET, [ 199 ] All Neuropsychology/Behavior

Acknowledgements: [ <SUP>18</SUP> F]Flortaucipir PET scans were made possible by Avid Radiopharmaceuticals Inc. The brain tissue and CSF were obtained from The Netherlands Brain Bank (NBB), Netherlands Institute for Neuroscience, Amsterdam. The material has been collected from the donor that has written informed consent for brain autopsy and the use of the material and clinical information for research purposes has been obtained by the NBB. The SCIENCe project receives support from Gieskes Strijbis fonds and stichting Dioraphte. WF holds the Pasman chair. Several authors of this publication are members of the European Reference Network for Rare Neurological Diseases - Project ID No 739510

Study Funding: ZonMw Memorabel grant

Disclosures: EE Wolters, JM Papma, SCJ Verfaillie, D Visser, E Weltings, C Groot, EL van der Ende, LAA Giannini, H Tuncel, T Timmers, R Boellaard, M Yaqub, DME van Assema, DA Kuijper, M Segbers, AIM Rozemuller, AD Windhorst, YAL Pijnenburg, JC van Swieten, R Ossenkoppele, reports no disclosures. Wm van der Flier receives grant support from ZonMw, NWO, EU-FP7, Alzheimer Nederland, CardioVascular Onderzoek Nederland, Stichting Dioraphte, Gieskes-Strijbis Fonds, Boehringer Ingelheim, Piramal Neuroimaging, Roche BV, Janssen Stellar, Combinotics. All funding is paid to the institution. WvdF holds the Pasman chair. BNM van Berckel receives research support from ZonMw, AVID radiopharmaceuticals, CTMM and Janssen Pharmaceuticals. He is a trainer for Piramal and GE. He receives no personal honoraria. F Barkhof is editorial board member of Brain, European Radiology, Neurology®, Multiple Sclerosis Journal, and Radiology; performed consultancy and received personal compensation and honoraria from Bayer-Schering Pharma and Genzyme; received compensation (personal and to institution) and honoraria from Biogen-IDE, TEVA, Merck-Serono,
Abstract

Objective
To assess the $[^{18}F]$flortaucipir binding distribution across MAPT mutations in presymptomatic and symptomatic carriers.

Methods
We compared regional $[^{18}F]$flortaucipir binding potential ($BP_{ND}$) derived from a 130-minute dynamic $[^{18}F]$flortaucipir PET scan, in nine (pre)symptomatic MAPT mutation carriers (4 with P301L[1 symptomatic], 2 with R406W[1 symptomatic]; 1 presymptomatic L315R, 1 presymptomatic S320F and 1 symptomatic G272V carrier) with 30 cognitively normal controls and 52 Alzheimer’s disease patients.

Results
$[^{18}F]$flortaucipir $BP_{ND}$ images showed overall highest binding in the symptomatic carriers. This was most pronounced in the symptomatic R406W carrier in whom tau binding exceeded the normal control range in the anterior cingulate cortex, insula, amygdala, temporal, parietal and frontal lobe. Elevated medial temporal lobe $BP_{ND}$ was observed in a presymptomatic R406W carrier. The single symptomatic and one of the three presymptomatic P301L carriers showed elevated $[^{18}F]$flortaucipir $BP_{ND}$ in the insula, parietal and frontal lobe compared to controls. The symptomatic G272V carrier exhibited a widespread elevated cortical $BP_{ND}$, with at neuropathological examination a combination of 3R pathology and encephalitis. The L315R presymptomatic mutation carrier showed higher
frontal BP\textsubscript{ND} compared to controls. The BP\textsubscript{ND} values of the S320F presymptomatic mutation carrier fell within the range of controls.

**Conclusion**

Presymptomatic \textit{MAPT} mutation carriers already showed subtle elevated tau binding, whereas symptomatic \textit{MAPT} mutation carriers showed a more marked increase in \textsuperscript{\textit{[\textit{18}F]}flortaucipir BP\textsubscript{ND}. Tau deposition was most pronounced in R406W \textit{MAPT} (pre)symptomatic mutation carriers, which is associated with both 3R and 4R tau accumulation. Thus, \textsuperscript{\textit{[\textit{18}F]}flortaucipir may serve as an early biomarker for \textit{MAPT} mutation carriers in mutations that cause 3R/4R tauopathies.
Introduction

Frontotemporal dementia (FTD) is a clinically and pathologically heterogeneous neurodegenerative disorder, characterized by behavioral changes\(^1\) and/or language difficulties.\(^2\) Mutations in the micro-tubule-associated protein tau gene (\textit{MAPT}) are a frequent cause of familial FTD. Alternative mRNA splicing from the \textit{MAPT} gene produces six different tau isoforms, including three (3R, 3 isoforms) and four (4R, 3 isoforms) repeat tau, which are found in equal amounts in the normal adult brain. Mutations in the \textit{MAPT} gene may affect the normal function of the tau protein (exon 9-13) or alter the balance between 3R and 4R (exon 10). Therefore, exon 10 mutations like P301L, typically lead to an abundance of 4R tau. Mutations outside exon 10 usually affect all isoforms, with most \textit{MAPT} mutations resulting in a combined 3R/4R tauopathy (e.g. L315R, S320F). This sometimes results in 3R/4R paired helical filaments (PHFs) of tau comparable to Alzheimer's disease (AD) tauopathy (e.g. in R406W), while other mutations (e.g. G272V) lead to an increased aggregation of 3R tau only.\(^3\) Imaging biomarkers could help to assess the regional distribution of tau pathology in (pre)symptomatic \textit{MAPT} mutations carriers years before symptom onset.

\([^{18}\text{F}]\text{flortaucipir}\) is a positron emission tomography (PET) tracer with high affinity to tau aggregates, offering the opportunity to examine the heterogeneity of tau pathology observed in \textit{MAPT} mutations carriers.\(^4,5\) \([^{18}\text{F}]\text{flortaucipir}\) binds with high affinity to PHFs in AD.\(^4,5\) Previous studies of \([^{18}\text{F}]\text{flortaucipir}\) in \textit{MAPT} mutations carriers have shown frontal and temporal tau PET uptake primarily in combined 3R/4R tau pathology, but not exclusively.\(^6,12\) Only few \([^{18}\text{F}]\text{flortaucipir}\) studies have included presymptomatic \textit{MAPT} carriers\(^8,13\) and showed elevated as well as negligible cortical tau pathology. The identification of appropriate biomarkers to detect FTD prior to symptom onset is crucial and could advance the development of disease-modifying drugs and evaluation of early intervention. Therefore, the aim of this study was to use \([^{18}\text{F}]\text{flortaucipir}\) PET to assess regional distribution of tau across \textit{MAPT} mutations in presymptomatic and symptomatic carriers.
Methods

Recruitment of participants

Patients with 50% risk of developing familial FTD, were recruited from Dutch families with MAPT mutations from the FTD-RisC study, as previously described. Briefly, as part of the FTD-RisC study, all participants underwent annual or biannual follow-up standardized clinical assessment, including neuropsychological testing and brain MRI. All participants with a possible MAPT mutation were considered except for those who met exclusion criteria: (1) significant cerebrovascular disease on MRI (e.g. territorial infarct), (2) major traumatic brain injury, (3) major psychiatric or neurological disorders other than behavioral variant FTD (bvFTD) (4) current substance abuse. We included a total of 13 participants; DNA genotyping revealed 9 MAPT mutation carriers and 4 non-carriers (healthy controls from a MAPT mutation family). The clinical investigators (HS/JvS) and participants were blinded for the participants’ genetic status, except for those that underwent predictive testing at their own request. For confidentially reasons, sex is not provided, and age range is provided in Table-1.

Here, we only report on the MAPT mutation carriers, including 6 presymptomatic and 3 symptomatic carriers. All symptomatic and 5 presymptomatic carriers were aware of their mutation status. All symptomatic mutation carriers met diagnostic criteria for bvFTD, and other clinical phenotypes (i.e. primary progressive aphasia) were not observed in symptomatic carriers. Diagnostic criteria were supported by extensive neuropsychological assessment, behavioral testing, supportive neuroimaging findings and after a multidisciplinary consensus meeting of the Erasmus University Medical Center. Mutation carriers were considered presymptomatic when diagnostic criteria for bvFTD were not met. We classified mutation carriers as converters if they met the following criteria: (i) progressive deterioration of behavior and/or language by observation or history (as provided by a knowledgeable informant); (ii) significant functional decline (evidenced by increased CDR® plus NACC-FTLD sum of boxes scores at the first or second follow-up visit and CDR® plus NACC-FTLD score ≥1); and (iii) cognitive deficits in at least one domain of the neuropsychological assessment. Neuropsychological assessment covered the following...
cognitive domains: language, processing speed, executive functioning, memory, social
cognition, visuconstructive ability and orientation as described before (see for separate
neuropsychological tests, data available from Dryad, eTable-1, https://doi.org/10.5061/dryad.3tx95x6g1). We furthermore report the MMSE, Frontal
Assessment Battery (FAB), CDR® plus NACC-FTLD and CDR® plus NACC-FTLD sum of boxes. Symptomatic MAPT mutations included P301L (n=1), R406W (n=1) and G272V (n=1). Presymptomatic MAPT mutations included P301L (n=3), R406W (n=1), L315R (n=1) and S320F (n=1). We grouped mutation carriers based on their coding exon, expected tau isoforms and number of carriers within the MAPT mutation. First, we present P301L mutations, involving exon 10, which mainly is associated with the 4R isoform of tau. Second, we present exon 13 R406W mutation carriers, which tend to form both 3R and 4R tau pathology, comparable to AD. Third, we present presymptomatic MAPT mutations carriers of exon 11 (L315R and S320F), which tend to form 3R/4R. Finally, we present MAPT mutation exon 9 carrier (G272V), which is composed of 3R tau.

Additionally, to assess whether tau PET binding of MAPT mutation carriers deviates from the distribution of cognitively normal controls and of AD patients, we included two reference groups that were previously described in greater detail. First, we included 30 cognitively normal controls (66±8 years, 50% female, MMSE 29±1) of the SCIENCe study. Second, we included 52 participants diagnosed with AD (66±8 years, 48% female, MMSE 23±3), who met core clinical criteria according to the National Institute on Aging and Alzheimer’s Association. All controls were amyloid negative and all AD were amyloid positive based on visual assessment of [18F]florbetapir PET scans and/or CSF biomarkers.

**Imaging and processing**

All MAPT mutation carriers underwent a single dynamic 130 minute [18F]flortaucipir PET scan on a Siemens Biograph mCT PET/CT (Siemens, Erlangen, Germany). The scanning protocol consisted of two dynamic PET scans of 60 and 50 minutes respectively, with a 20-minute break in between. The first 60-minute dynamic acquisition started simultaneously with a bolus injection 229±7 MBq [18F]flortaucipir (injected mass 1.26±0.47µg, details for
MAPT mutation carriers). PET list mode data were rebinned into a total of 29 frames and were reconstructed using an OSEM 3D Time-Of-Flight enabled iterative reconstruction (4i21s) with a matrix size of 400x400x111 and a final voxel size of 2.036x2.036x2.0 mm³, including standard corrections for dead time, decay, attenuation, randoms and scatter. Each PET dataset consisted of in total 29 frames; the last 10 frames stemmed from the second PET scan session. The second 50 minute PET acquisition was co-registered to the first dynamic PET scan using Vinci software. Finally, PET scans from the Siemens scanner were additionally smoothed using a Gaussian filter (4mm FWHM) in order to correspond to smoothing kernels of the SCIENCe and AD dataset (Philips Ingenuity TF PET/CT).

In addition, for gray matter segmentation purposes, all MAPT mutation carriers underwent a 3D-T1-weighted sequence MRI scan on a Philips 3 Tesla Achieve MRI scanner (Philips Medical Systems, Best) using an 8-channel SENSE head coil. Except for the scanner type, details of [¹⁸F]flortaucipir image and MR acquisition of the SCIENCe and AD datasets are comparable and have been described elsewhere.¹⁶

We co-registered native 3D-T1 MR images to the averaged images of frame 8–29 of the dynamic PET scan using Vinci software. We defined the volumes of interest (VOIs, including separate VOIs for left and right hemisphere) on MRI scans using PVElab according to the probabilistic Hammers brain atlas.¹⁸ Time activity curves were generated and [¹⁸F]flortaucipir binding potential (BP_{ND}) was extracted using receptor parametric mapping (RPM)¹⁹ and SUVr images were generated for the time interval 80-100 minutes post injection, while using cerebellar gray matter as a reference region. RPM also allows for the additional quantification of Rᵣ images. Rᵣ is a proxy for relative cerebral blood flow (rCBF)²⁰ and since hypoperfusion has been observed previously in (pre)symptomatic MAPT mutation carriers,²¹ we investigated Rᵣ in a secondary analysis to assess the regional distribution of rCBF.

Methods of regional/ voxel wise analysis are described in detail in eAppendix 1 (data available from Dryad, https://doi.org/10.5061/dryad.3tx95x6g1). In short, we created a priori 9 VOIs (anterior cingulate cortex [ACC], insula, amygdala, frontal, medial/lateral temporal/parietal regions) and compared these regional BP_{ND}/Rᵣ /SUVr values between

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MAPT mutation carriers and controls/AD. Analyses were performed using R (version 3.5.3, R Development Core Team 2019).

**Neuropathology**

Neuropathology was available in one patient (symptomatic G272V carrier), who died aged 45, 10 months after the $[^{18}F]flortaucipir$ PET. The Netherlands Brain Bank performed brain autopsy according to their Legal and Ethical Code of Conduct. Tissue blocks were taken from the left hemisphere from all cortical lobes hippocampus (both left and right), amygdala, basal ganglia, substantia nigra, pons, medulla oblongata, cerebellum, and cervical spinal cord, and were embedded in paraffin blocks. Immunohistochemistry was performed as previously described. In addition, immunochemical staining with AT-8 (Thermo Fisher Scientific, MN1020; dilution 1:200), RD3 (Millipore clone 8E6/C11, 05-803), RD4 (Millipore, clone 1E1/A6, 1:1000), CD3 (DAKO, A0452, 1:150) and HLA-DR (DAKO, M0775, 1:100) antibodies were performed in a subset of slides. Silver-staining using the Gallyas method was performed on hippocampal and temporal tissue sections.

**Standard Protocol Approvals, Registrations, and Patient Consents**

All procedures were in accordance with the ethical standards of the Medical Ethics Review Committee of the Amsterdam UMC location VU Medical Center and the Erasmus University Medical Center according to the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants.

**Data Availability**

Data not published within the article is available in a public repository and include digital object identifiers (https://doi.org/10.5061/dryad.3tx95x6g1). Anonymized data used in the present study may be available upon request to the corresponding author.

**Results**

**Demographics**
Demographic and clinical characteristics of the (pre)symptomatic MAPT mutation carriers are presented in Table-1. Further details of screening, behavioral, and neuropsychological test results are presented in eTable-1 (data available from Dryad, eTable-1, https://doi.org/10.5061/dryad.3tx95x6g1)

**(pre)symptomatic P301L mutation carriers**

Figure-1 shows voxel-wise and regional \[^{18}F\]flortaucipir BP\textsubscript{ND} images/values and corresponding MRI images of (pre)symptomatic P301L mutation carriers (panel A-B,E-F) versus controls (panel C,E) and AD (panel D,F) as a reference group.

The symptomatic P301L carrier showed visually higher BP\textsubscript{ND} than the presymptomatic P301L cases, with highest BP\textsubscript{ND} in the orbitofrontal cortex, inferior temporal and parietal lobe (Fig-1 A). Regional \[^{18}F\]flortaucipir BP\textsubscript{ND} in the insula, frontal, medial/lateral temporal and parietal lobe was higher than in controls (Fig-1E).

Presymptomatic P301L cases showed variable \[^{18}F\]flortaucipir BP\textsubscript{ND}, ranging from minimal (case 2) to widespread tau higher binding in frontoparietal regions, including precuneus and posterior cingulate (case 3) (Fig-1A). All regional BP\textsubscript{ND} values of presymptomatic P301L case 2 and 3 fell within the distribution of controls. Presymptomatic P301L case 4 showed increased \[^{18}F\]flortaucipir BP\textsubscript{ND} in ACC, insula, frontal and medial/lateral parietal lobe compared to the range of values in controls (Fig-1E), but within the range of AD (Fig-1F).

**(pre)symptomatic R406W mutation carriers**

Figures 2-4 show the voxel-wise \[^{18}F\]flortaucipir BP\textsubscript{ND} images (panel A) and regional \[^{18}F\]flortaucipir BP\textsubscript{ND} values (panel C-D) in (pre)symptomatic mutation carriers versus controls (C) and AD (D) as a reference group. Voxel-wise images of control and AD reference groups are shown in Figure-1 panel C and D, respectively.

The symptomatic R406W patients revealed higher BP\textsubscript{ND} than the presymptomatic R406W carrier, with highest tau binding in the medial temporal lobe, temporal pole, amygdala and frontoparietal regions on voxel-wise \[^{18}F\]flortaucipir BP\textsubscript{ND} images (Fig-2A). Regionally, BP\textsubscript{ND}
in ACC, insula, amygdala, frontal, medial/lateral temporal and medial parietal lobe was elevated compared to the distribution of controls (Fig-2C), and equal to the AD range (Fig-2D).

The presymptomatic R406W carrier showed tau binding largely restricted to the medial temporal lobe. Regional values confirmed this observation with regional medial temporal tau values exceeding the range of controls. Additionally, there was higher BP\textsubscript{ND} in the amygdala compared to the values observed in controls (Fig-2C). For both R406W carriers, regional BP\textsubscript{ND} fell within the AD range (Fig-2D).

**Presymptomatic S320F, L315R mutation carriers**

Minimal BP\textsubscript{ND} was observed in presymptomatic carriers. Small areas of elevated [\textsuperscript{18}F]flortaucipir BP\textsubscript{ND} appeared in the orbitofrontal and parieto-occipital regions in the S320F mutation carrier (Fig-3A), although regional BP\textsubscript{ND} fell within range of controls and AD. The L315R mutation carrier showed higher frontal BP\textsubscript{ND} compared to the distribution of controls (Fig-3C), but did not exceed the BP\textsubscript{ND} range in AD (Fig-3D).

**Symptomatic G272V carrier including clinical presentation and neuropathology**

The symptomatic G272V carrier exhibited a widespread cortical higher tau binding, with increased BP\textsubscript{ND} values in the ACC, insula, frontal and medial/lateral parietal lobe in the G272V mutation carrier, relatively sparing the temporal lobe (Fig-4A) compared to the distribution in controls. All regional [\textsuperscript{18}F]flortaucipir BP\textsubscript{ND} values fell within range of AD (Fig-4D).

Aged 39 years, four years before the diagnosis of bvFTD, the mutation carrier had occasional word-finding problems and panic attacks.\textsuperscript{15} Neuropsychological testing and structural MRI were normal, and patient had CDR® plus NACC-FTLD score of 0.5 (≥1 is abnormal, i.e. symptomatic). Aged 41, patient developed mild memory problems and semantic paraphasias in spontaneous speech, although neuropsychological and behavioral testing remained within normal limits.
Aged 42, patient was unable to work due to difficulties with planning and remembering appointments, and complained about tiredness and depression. Six months before diagnosis, patient was shortly hospitalized for a manic episode after starting paroxetine for mood disturbances, which was quickly in remission after switching paroxetine to olanzapine and lorazepam. Aged 43 years, the diagnostic criteria of bvFTD were met, supported by observations of word-finding difficulties, phonological errors and neuropsychological questionnaires indicating mood problems, sleeping disturbances, euphoria, apathy, disinhibition, agitation and aberrant motor behavior. Additional neuropsychological assessment showed deficits in episodic memory, mental speed, attention and fluency, with CDR® plus NACC-FTLD score of 1 and asymmetric, right-sided temporal atrophy was found on MRI.

One-year post-diagnosis, patient was unable to perform activities of daily living and attended daycare four times a week and died aged 45 years by euthanasia, 10 months after the $[^{18}\text{F}]$flortaucipir PET.

**Neuropathology**

Brain section was carried out in the G272V patient. Macroscopically, there was very mild atrophy of the frontal lobes. The caudate nucleus was relatively small.

Microscopically, there was mild gliosis and spongiosis of layer II of the frontal cortex and cingulate gyrus. There was a slight increase in the number of glia cells in the white matter. All other cortical regions, basal ganglia and hippocampus showed no gliosis nor spongiosis.

Tissue immunohistochemistry with tau showed a small to moderate number of tau-immunoreactive (ir) positive neurons and some threads in a subset of regions (Fig-5 A-J). Tau burden was most severe in the hippocampus, followed by the temporal cortex and the frontoparietal cortex. In the hippocampus, a moderate number of tau-ir positive neurons and additional Pick body-like inclusions were found, particularly in the subiculum and CA1, and a small number in the dentate gyrus. The right hippocampus was more severely affected than the left hippocampus, where only sporadic inclusions were found in these areas, in line with
asymmetry in brain atrophy on MRI. The transentorhinal cortex was also moderately affected by neuronal tau-ir inclusions and threads, which were Gallyas negative. The temporal pole showed a few ramified astrocytes, some Pick body-like inclusions (max. 9 at 20x objective) and a few threads. The frontal cortex showed the same type of inclusions, but less abundant than in the temporal pole (max. 2 at 20x objective). Sporadic tau inclusions were also found in the inferior parietal lobule (max. 2-3 at 20x objective), limbic areas (amygdala, anterior cingulate gyrus) and in the basal ganglia (max. 2 inclusions at 20x objective in all regions), while they were absent in the occipital cortex. These inclusions also stained positively for 3R tau isoform, but not for 4R tau. Astrocytic inclusions were not stained positively with either 3R- or 4R tau antibodies.

In all cortical regions, basal ganglia, hippocampus, brainstem and cerebellum, there were several perivascular CD3-positive lymphocytic deposits with intraparenchymal infiltrates. Staining with HLA-DR showed severe immune activation of microglia and other myeloid cells around the vasculature and in the brain parenchyma. There was no apparent relationship between this diffuse immune activation, present throughout the entire brain, and the distribution of tau-ir inclusions. These findings of immune activation and infiltration (Fig-5 G-I) were compatible with a concurrent diagnosis of (auto-immune) encephalitis. There were no signs of a viral or bacterial encephalitis.

**Differential diagnosis of (auto-immune) encephalitis**

As the neuropathological diagnosis of (auto-)immune encephalitis was unexpected we retrospectively reviewed the clinical data, where there were no seizures or (sub)acute changes in behavior or cognition, apart from the paroxetine-induced manic period. Additional CSF collected for research purposes was evaluated and showed two years before diagnosis 24*10^6/L leukocytes (norm<5*10^6/L), of which 22*10^6/L were monocytes, in hindsight suggestive of a viral infection, (auto-immune) encephalitis or drug induced. However, there were no clinical signs of meningitis or encephalitis, nor T2/FLAIR abnormalities on MRI that would be suggestive for an auto-immune encephalitis and no drug use associated with pleocytosis at the time of CSF analysis. PCR for neurotrophic viruses and routine diagnostic
testing for immune-mediated encephalitis with immunohistochemistry, were negative. Leukocytes decreased over time and CSF showed a mild pleocytosis of 9*10^6/L (8*10^6 monocytes) at time of diagnosis.

Regional R₁ in (pre)symptomatic MAPT mutation carriers

Figure-6 (panel E-F) shows regional values of [¹⁸F]flortaucipir R₁ in (pre)symptomatic MAPT mutation carriers compared to average of controls (red boxplots) and AD (blue boxplots). The symptomatic P301L patient showed lower regional R₁ values in the ACC, frontal and lateral temporal lobe, when compared to control values (Fig-6). [¹⁸F]flortaucipir R₁ values in the G272V patient were elevated in all regions compared to both controls and AD, with exception of the ACC and medial temporal lobe (Fig-6). Regional R₁ values of the remaining presymptomatic P301L, R406W and S320F and symptomatic R406W carriers corresponded to the regional values of both controls and AD, with exception of the medial temporal lobe (Fig-6).

[¹⁸F]flortaucipir SUVr

To allow comparison of BP_{ND} with SUVR, we show in eFigures 1-4 (data available from Dryad, eFigures 1-4, https://doi.org/10.5061/dryad.3tx95x6g1) the voxel-wise [¹⁸F]flortaucipir SUVr images (panel A) and regional [¹⁸F]flortaucipir SUVr values (panel C-D) in (pre)symptomatic mutation carriers versus controls (panel C) and AD (panel D) as a reference group. The results were overall comparable between methods.

Clinical follow-up after one year

Five out of six presymptomatic carriers did not show clinical decline at follow up after one year. One P301L carrier (case 2) showed clinical decline and conversion to symptomatic bvFTD at the follow-up visit after the [¹⁸F]flortaucipir PET, which consisted of a cognitive...
assessment (data available from Dryad, eTable-1, https://doi.org/10.5061/dryad.3tx95x6g1) and MRI (data not shown). At time of [18F]flortaucipir PET scan this carrier did not meet clinical criteria, but did show a mild cognitive and behavioral impairment.
Discussion

Using dynamic \(^{18}\text{F}\)flortaucipir PET scanning, we quantified tau burden and examined regional distributions across a variety of MAPT mutations in presymptomatic and symptomatic carriers. We found elevated \(^{18}\text{F}\)flortaucipir binding compared to controls in both presymptomatic and symptomatic MAPT mutation carriers, which was most pronounced in the symptomatic and presymptomatic R406W MAPT mutation carriers with a combined 3R/4R tau aggregation.

The (pre)symptomatic R406W carriers showed increased tau binding in the amygdala, temporal lobe and frontoparietal regions, which is in line with previous studies in (pre)symptomatic R406W carriers showing frontal and temporal tau with relative sparing of the posterior cortical areas.\(^7\)\(^-\)\(^9\) The high binding in the R406W carriers is not surprising as this MAPT mutation consists of 3R and 4R tau, similar to those in AD.\(^3\)\(^,\)\(^23\) \(^{18}\text{F}\)flortaucipir binds with high affinity to AD tau\(^4\)\(^,\)\(^5\) and in vivo \(^{18}\text{F}\)flortaucipir retention is strongly associated with post mortem AD neurofibrillary tangle pathology,\(^7\)\(^,\)\(^24\)\(^,\)\(^25\) indicating that \(^{18}\text{F}\)flortaucipir is a reliable method for measuring combinations of 3R/4R PHFs of tau.

Notably, we also observed higher \(^{18}\text{F}\)flortaucipir binding in the P301L mutation carriers, a condition typically associated with 4R tau.\(^26\) Two carriers (one presymptomatic, one symptomatic) showed tau binding in the frontal lobe, insula and parietal lobe with additional tau binding in the inferior temporal lobe of the symptomatic P301L carrier. This is in line with previous studies showing inconsistent results in P301L carriers\(^8\)\(^,\)\(^9\)\(^,\)\(^27\) and other 4R tauopathies such as PSP\(^28\)\(^-\)\(^34\) varying from low to high binding in individual cases. Variations in tau uptake patterns may be explained by the presence of concomitant amyloid pathology\(^9\) or off-target binding.\(^28\)\(^,\)\(^31\)\(^-\)\(^33\) Furthermore, in vitro tau has not been associated with postmortem \(^{18}\text{F}\)flortaucipir uptake patterns in P301L carriers.\(^27\) Taken together, the evidence that \(^{18}\text{F}\)flortaucipir retention is caused by binding to 4R tau is inconclusive.

The presymptomatic S320F and L315R mutation carriers showed low tau binding not exceeding the range observed in controls. Although neuropathological case studies have shown a specific combination of 3R and 4R tau (one 3R band missing), this is different from
AD, which probably explains its low affinity. Additionally, these cases were presymptomatic, therefore these carriers may harbor amounts of tau below the detection threshold of tau PET. Our observation of subtly higher frontal tau uptake in the presymptomatic L315R mutation carrier >70 years old, possibly represents the first preclinical sign of tau pathology. As incomplete penetrance has been described in L315R families,\textsuperscript{35} tau PET uptake may highly depend on disease severity, as previous MAPT mutation carriers studies showed an increase in tau with advanced disease stage,\textsuperscript{9,11} in correspondence with results found across the AD spectrum.\textsuperscript{36,37}

The symptomatic G272V patient exhibited a widespread higher cortical tau binding, relatively sparing the temporal lobe. The gradient of \[^{18}\text{F}]\text{flortaucipir} binding did not correspond with postmortem 3R tau, as tracer uptake was most pronounced frontoparietal with sparing of the temporal lobe, while at neuropathological examination tau-ir inclusions were most pronounced -although still mild- in the temporal cortex and relatively sparse in frontoparietal lobes. However, the neuropathological findings were indicative for an encephalitis and the increased \[^{18}\text{F}]\text{flortaucipir} uptake may be the result of binding to non-specific targets related to neuroinflammation, such as microglial activation,\textsuperscript{38} gliosis or vascular permeability differences.\textsuperscript{39,40} In addition, virtually all regions showed higher rCBF to both controls and AD patients, which is in line with reported hyperperfusion/hypermetabolism in encephalitis patients.\textsuperscript{41,42}

It is unclear whether this patient had two rare disorders or that the MAPT mutation triggered an (auto-)immune response. There is no clear evidence in the literature to support the latter hypothesis, and none of the other G272V brain donors in our Rotterdam FTD cohort (n=5, data not shown) showed similar features of diffuse abundant perivascular lymphocytes and intra-parenchymal infiltrates. Although the role of a chronic neuroinflammatory response is increasingly recognized in FTD,\textsuperscript{43} elevated leukocyte levels in the CSF have not been observed in our FTD-RisC cohort in the presymptomatic phase or around conversion to symptomatic phases, nor has this been described by others research groups in the literature. Thus, these findings probably fall outside the clinicopathological manifestations of FTLD and are suggestive of a concurrent diagnosis of encephalitis.
To date, increasing evidence is available on identifying neuroimaging biomarkers for genetic FTD in an early phase. For example, recent work showed anterior cingulate abnormalities on both MRI and FDG-PET already in presymptomatic MAPT mutation carriers. However, information on combined in vivo and post-mortem pathological disease staging in MAPT carriers for tau specifically is still limited, due to the low occurrence of presymptomatic or early symptomatic MAPT carriers in clinical and research settings, especially with regard to neuropathological data. The combination of \( ^{18} \text{F}\)flortaucipir, rCBF and neuropathological data in presymptomatic and early symptomatic phases is unique and may help to understand to spread of tau accumulation in MAPT mutation carriers. \( ^{18} \text{F}\)flortaucipir uptake in R406W carriers is most robust. Although based on cross-sectional data, our study and previous \( ^{18} \text{F}\)flortaucipir PET studies in R406W carriers suggest that tau accumulation may start in the medial temporal lobe in the presymptomatic phase and finally spreads into the frontal and parietal lobe, as observed in our symptomatic R406W carrier. The P301L carriers showed a more frontoparietal \( ^{18} \text{F}\)flortaucipir binding pattern in the presymptomatic phase with involvement of temporal lobe only in the symptomatic phase. However, this should be interpreted with caution since P301L carriers, in line with literature, probably lack association between advancing of disease stage and tau uptake, as we found minimal tau binding in the symptomatic P301L carrier (case 2) that converted to symptomatic phase. In the early symptomatic G272V carrier, the highest neuropathological tau load in the right hippocampus, corresponded with the region of atrophy on MRI. Unfortunately only tissue blocks from the left hemisphere were available and showed very little amount of tau pathology, two years after onset, with the left frontal and parietal lobe similarly affected. It also must be considered that MAPT mutations show a great heterogeneity of pathological features, and G272V mutations have overall relatively low tau burden compared to other mutations, such as P301L. Possibly, a dynamic \( ^{18} \text{F}\)flortaucipir PET scan is of additional value to study disease spread providing an additional measure of rCBF. Previous rCBF dynamic PET studies with inclusion of bvFTD patients showed a good correlation between rCBF and FDG-PET hypometabolism patterns. Compared to controls, low rCBF in the ACC, lateral temporal and frontal lobe in the symptomatic P301L patient is largely in correspondence with a previous SPECT study in symptomatic MAPT mutation carriers.
Interestingly, borderline abnormal low ACC rCBF compared to controls was found in one presymptomatic P301L mutation carrier, confirming the results of a previous study that found glucose hypometabolism in the anterior cingulate of presymptomatic P301L carriers. More longitudinal (dynamic) tau PET studies in presymptomatic and symptomatic carriers in combination with different imaging techniques and in-depth neuropathological data are needed to give a better and more complete overview of pathology spreading in different disease stages and various MAPT mutations.

Strengths of this study include the performance of dynamic $^{[18]}$F-flortaucipir scans, which allows for simultaneous quantification of measures of both tau load and rCBF in presymptomatic and symptomatic carriers of various MAPT mutations and allowed for examining tau pathology/rCBF in a very early phase of the disease.

Limitations include the small number of carriers per mutation, which precluded statistical comparisons. Although the presence of amyloid pathology in MAPT carriers could not be ruled out, it is very unlikely given that the majority of the carriers were ~50 years (although one MAPT carrier was >70 years). Furthermore, there was neuropathological data available for only one case in this study, which is instrumental to better understand the binding properties of $^{[18]}$F-flortaucipir. However, several MAPT mutation cases have been described neuropathologically in other studies in combination with in vivo assessment of tau pathology using $^{[18]}$F-flortaucipir PET and show that $^{[18]}$F-flortaucipir binds predominantly to combined 3R/4R tauopathies which could be generalized to our study.

In conclusion, we found subtle increased tau binding in a significant proportion of the presymptomatic MAPT mutation carriers, whereas higher magnitude of $^{[18]}$F-flortaucipir binding was observed in symptomatic MAPT mutation carriers. Furthermore, increased tau load was mainly observed in those (pre)symptomatic mutation carriers with combined 3R/4R tau. Taken together, these findings suggests that $^{[18]}$F-flortaucipir PET may be used as an early biomarker in MAPT mutation carriers, in particular in a subset of MAPT mutation carriers.
carriers that include mutations that cause 3R/4R tauopathies. Thereby, [$^{18}$F]flortaucipir potentially binds to lower tau concentrations or non-specific targets, as we observed mild [$^{18}$F]flortaucipir signal in 3R/4R only MAPT mutation carriers. Future longitudinal [$^{18}$F]flortaucipir studies with postmortem confirmation will be essential to capture the complexity and progression of the in vivo findings observed with [$^{18}$F]flortaucipir in (pre)symptomatic MAPT mutation carriers.
Table 1: Overview of demographics of the MAPT mutation carrier characteristics

Fig 1. Voxel-wise $[^{18}\text{F}]$flortaucipir parametric BP$_{ND}$ images (A), T1 MR weighted images (B), regional $[^{18}\text{F}]$flortaucipir BP$_{ND}$ (C-D) values of (pre)symptomatic P301L carriers. Panel E-F (pre)symptomatic P301L mutation carriers (displayed individually) versus controls (C, E) and versus AD (D, F, both displayed as the average of the group). Open and closed squares depict presymptomatic and symptomatic P301L mutation carriers, respectively. The order of the presymptomatic cases is the same as the order of panel A and B (from left to right).
Fig 2. Voxel-wise \([^{18}F]\)flortaucipir parametric BP\(_{ND}\) images (A), T1 MR weighted images (B), regional \([^{18}F]\)flortaucipir BP\(_{ND}\) (C-D) values of (pre)symptomatic R406W mutation carriers. Panel C-D (pre)symptomatic R406W mutation carriers (displayed individually) versus controls (C) and versus AD (D, both displayed as the average of the group). Open and closed triangles depict presymptomatic and symptomatic R406W mutation carriers, respectively.
Fig 3. Voxel-wise $[^{18}F]flortaucipir$ parametric $BP_{ND}$ images (A), T1 MR weighted images (B), regional $[^{18}F]flortaucipir$ $BP_{ND}$ (C, D) values of the presymptomatic S320F, L315R mutation carriers.

Panel C-D presymptomatic S320F, L315R mutation carriers (displayed individually) versus controls (C) and versus AD (D, both displayed as the average of the group).
Fig 4. Voxel-wise $[^{18}F]$flortaucipir parametric BP$_{ND}$ images (A), T1 MR weighted images (B), regional $[^{18}F]$flortaucipir BP$_{ND}$ (C-D) values of the symptomatic G272V mutation carrier. Panel C and D the symptomatic G272V mutation carrier(displayed individually) versus controls(C) and versus AD (D, both displayed as the average of the group).
Fig 5. Neuropathological findings in the symptomatic G272V carrier with early tauopathy and concurrent (auto-)immune encephalitis

Neuropathological examination of the symptomatic G272V carrier showed findings consistent with an early tauopathy: moderate amounts of tau-ir neuronal inclusions and threads in the hippocampus and parahippocampal structures, specifically in the subiculum (a-b), transentorhinal cortex (c-d), and to a lesser extent in the dentate gyrus (e-f); these neuropathological findings were asymmetrical with greater involvement of the right hippocampus compared to the left hippocampus. Other brain regions, sampled exclusively in the left hemisphere, showed mild gliosis and spongiosis of the upper cortical layers, with moderate amounts of tau-ir neurons in the temporal cortex (g), fewer tau-ir neurons in the frontal cortex (h), in the parietal cortex (i), and in limbic and paralimbic areas, such as the amygdala (j) and the insular cortex (k). Additionally, neuropathological findings indicative of a concurrent (auto-)immune encephalitis were observed in all examined brain regions, with no apparent relationship to the distribution of tau inclusions: perivascular CD3-positive lymphocytic cuffing with infiltration in the adjacent brain parenchyma in the substantia nigra (l); CD3-positive lymphocytic infiltrates in the brain parenchyma in the cingulate gyrus (m); HLA-DR-positive patchy clustering of activated microglia and myeloid cells in the parahippocampal gyrus (n). Scale bar in large images a-d, g-i, l-n = 200 µm. Scale bar in small images a-d, g-i, l-n, and in images e-f, g-k = 20 µm.
Fig 6. Regional $^{[18}F$flortaucipir $R_1$ values of the (pre)symptomatic mutation carriers vs. controls and AD.

The symptomatic mutation carriers (squares) and presymptomatic carriers (triangles) (displayed individually and color coded per mutation) versus controls (red) and versus AD (blue, both displayed as the average of the group).


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</table>

*MMSE= Mini-Mental State examination at day of PET
### Appendix 1: Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>EE Wolters</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content</td>
</tr>
<tr>
<td>JM Papma</td>
<td>Erasmus MC University Medical Center, Rotterdam, the Netherlands</td>
<td>Design and conceptualized study; analyzed the data; Interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>SCJ Verfaillie</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>D Visser</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Major role in the acquisition of data</td>
</tr>
<tr>
<td>E Weltings</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Major role in the acquisition of data</td>
</tr>
<tr>
<td>C Groot</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Analyzed the PET data</td>
</tr>
<tr>
<td>EL van der Ende</td>
<td>Erasmus MC University Medical Center, Rotterdam, the Netherlands</td>
<td>Major role in the acquisition of data</td>
</tr>
<tr>
<td>L Gianni</td>
<td>Erasmus MC University Medical Center, Rotterdam, the Netherlands</td>
<td>Analyzed the neuropathological data, revised the manuscript for intellectual content.</td>
</tr>
<tr>
<td>H Tuncel</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Analyzed the PET data</td>
</tr>
<tr>
<td>T Timmers</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Major role in the acquisition of data</td>
</tr>
<tr>
<td>R Boellaard</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>M Yaqub</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Analyzed the data, revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>DME van Assema</td>
<td>Erasmus MC University Medical Center, Rotterdam, the Netherlands</td>
<td>Major role in the acquisition of data, revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>DA Kuijper</td>
<td>Erasmus MC University Medical Center, Rotterdam, the Netherlands</td>
<td>Major role in the acquisition of data</td>
</tr>
<tr>
<td>M Segbers</td>
<td>Erasmus MC University Medical Center, Rotterdam, the Netherlands</td>
<td>Major role in the acquisition of data</td>
</tr>
<tr>
<td>Name</td>
<td>Affiliation</td>
<td>Role</td>
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</tr>
<tr>
<td>AJM Rozemuller</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Analyzed the neuropathological data, revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>F Barkhof</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands UCL, London, United Kingdom</td>
<td>Revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>AD Windhorst</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>WM van der Flier</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>YAL Pijnenburg</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Ph Scheltens</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>BNM van Berckel</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands</td>
<td>Design and conceptualized study; Revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>JC van Swieten</td>
<td>Erasmus MC University Medical Center, Rotterdam, the Netherlands</td>
<td>Design and conceptualized study; Revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>R Ossenkoppele</td>
<td>Amsterdam UMC, Amsterdam, The Netherlands Lund University, Lund, Sweden</td>
<td>Design and conceptualized study; analyzed the data; Interpreted the data; revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>H Seelaar</td>
<td>Erasmus MC University Medical Center, Rotterdam, the Netherlands</td>
<td>Major role in the acquisition of data, Interpreted the data; revised the manuscript for intellectual content</td>
</tr>
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Symptomatic Carriers

Mutations in Presymptomatic and
MAPT

This information is current as of July 1, 2021