Lack of association between bridging integrator 1 (BIN1) rs744373 polymorphism and tau-PET load in cognitively intact older adults

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Abstract

Introduction: The bridging integrator 1 (BIN1) rs744373 risk polymorphism has been linked to increased [18F]AV1451 signal in non-demented older adults (ie., mild cognitive impairment [MCI] plus cognitively normal [CN] individuals). However, the association of BIN1 with in vivo tau, amyloid beta (Aβ) burden, and cognitive impairment in the asymptomatic stage of Alzheimer’s disease (AD) remains unknown.

Methods: The BIN1 effect on [18F]AV1451 binding was evaluated in 59 cognitively normal (CN) participants (39% apolipoprotein E [APOE] ε4) from the Flemish Prevent AD Cohort KU Leuven (F-PACK), as well as in 66 Alzheimer’s Disease Neuroimaging Initiative (ADNI) CN participants, using voxelwise and regional statistics. For comparison, 52 MCI patients from ADNI were also studied.

Results: Forty-four percent of F-PACK participants were BIN1 rs744373 risk-allele carriers, 21% showed high amyloid burden, and 8% had elevated [18F]AV1451 binding. In ADNI, 53% and 50% of CNs and MCIs, respectively, carried the BIN1 rs744373
1 | INTRODUCTION

Genome-wide association studies (GWAS) have shown that bridging integrator 1 (BIN1, or amphiphysin 2 [AMPH2]) is the second most strongly associated genetic susceptibility locus for late-onset Alzheimer’s disease (AD) [rs744373, odds ratio (OR): 1.15 to 1.17; population-attributable risk: 6%] after apolipoprotein E (APOE).1,2 The association of BIN1 with late-onset AD has been shown to remain significant even after adjustment for APOE, suggesting that the BIN1 risk allele contributes independently to AD risk.3 Current knowledge about BIN1 and its spatial association with AD pathology (ie., neurofibrillary tangles [NFTs] and amyloid beta [Aβ]) comes mainly from post mortem studies assessing different AD stages, that is, Braak stages 1 to VI.4,5 Overall, BIN1 seems to be a modulator of tauopathy, with generally little impact on Aβ.5–6

The introduction of tau positron emission tomography (PET) for in vivo imaging, such as [18F]AV14517, enables AD tauopathy imaging in vivo. One previous study investigated the association between BIN1 rs744373 and in vivo tau-PET, Aβ burden, and cognitive impairment in 89 older adults from Alzheimer’s Disease Neuroimaging Initiative (ADNI); 49 cognitively normal (CN) and 40 mild cognitive impairment (McI) participants. The BIN1 rs744373 risk allele was associated with increased [18F]AV1451 binding.8 No association was found between the BIN1 rs744373 risk allele and Aβ PET. BIN1 carriers had reduced memory, an effect mediated by globally increased [18F]AV1451 binding.8 According to a follow-up paper, BIN1 risk-allele carriers show accelerated tau-PET accumulation at higher Aβ levels.9

The primary objective of the current study was to assess whether the effect of BIN1 rs744373 polymorphism on tau could be confirmed in a study cohort consisting exclusively of CN older adults. Enrichment for APOE ε4 carrier status ensured that the F-PACK cohort was at increased risk for AD. In addition, we verified whether the reported effect8 could be reproduced in ADNI CN and McI. As a secondary objective, the association between BIN1 rs744373 and cognition was assessed within F-PACK CNs.

2 | METHODS

2.1 | Study sample

Sixty CN older adults were community-recruited between October 2015 and December 2018. Forty-four individuals were part of the first wave of recruitment for the Flemish Prevent AD Cohort KU Leuven (F-PACK), a larger longitudinal community-recruited study cohort of 180 CN older individuals.10 Sixteen participants were novel participants who were recruited based on the same procedures and criteria as used for the F-PACK cohort. Together these 60 individuals will be referred to below as the “F-PACK participants.” The local Ethics Committee for Clinical Studies UZ/KU Leuven approved the study. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

All participants were included via advertisement in newspaper and online requests for volunteers for scientific research including brain imaging. The inclusion criteria for all participants at baseline were age between 50 and 80 years, a Mini-Mental State Examination (MMSE) score ≥27, a Clinical Dementia Rating (CDR) global score of zero, and a history of cancer, a contraindication for MRI or exposure to radiation for research procedures within the year prior to PET.

F-PACK participants were stratified at inclusion based on APOE ε4 genotype such that the proportion of APOE ε4 carriers was around
RESEARCH IN CONTEXT

1. Systematic Review: Previous findings in non-demented participants (mild cognitive impairment [MCI] plus cognitive normals [CN]) have reported that BIN1 rs744373 is associated with increased tau-tracer binding. However, the association of BIN1 with in vivo tau in the asymptomatic stage of Alzheimer’s disease (AD) remains unknown.

2. Interpretation: The current study in CN older adults, enriched for apolipoprotein E (APOE) z4, ensured that the cohort was at increased risk for AD. In addition, we verified whether the previously reported effect could be reproduced within Alzheimer’s Disease Neuroimaging Initiative (ADNI) CNs and MCIs. The BIN1 effect on [18F]AV1451 binding could not be confirmed. Large effect sizes were observed in late-stage tau-vulnerable regions in patients with MCI, suggesting that BIN1 exerts its effect in the MCI stage of AD, when tau aggregates progressively spread throughout the brain.

3. Future Directions: These findings highlight that a distinction should be made between asymptomatic, MCI, and dementia stages of AD, when studying how the BIN1 risk polymorphism influences AD pathogenesis.

50% per 5-year age bin.11 The same criteria were applied for the 16 newly recruited cases except for the genetic stratification, as this was unknown at inclusion. All participants are invited for a 2-yearly neuropsychological assessment for a 10-year period.

To verify the reproducibility of the previously reported effect of BIN1 on [18F]AV1451 binding,8 we analyzed data from 66 CN older adults from ADNI Phase 3 (ADNI3; ClinicalTrials.gov ID: NCT02854033). Inclusion criteria were MMSE ≥27, CDR = 0, and neuropsychological test scores within published norms at ADNI recruitment. There were 101 CN individuals with baseline data. Eleven individuals were removed based on the baseline age/cognitive inclusion criteria, 17 were removed due to lack of GWAS data, six were removed due to lack of scan availability (five from missing tau-PET and one from missing structural MRI), and one was removed due to issues with scan processing (inferior cerebellum out of the field of view). In total, 66 individuals remained for analyses. Additionally, we analyzed data from 52 ADNI3 MCI patients: 171 individuals had available baseline data, 19 were removed based on the baseline age criteria, 93 were removed due to lack of GWAS data, 3 were removed due to scan availability (two from lack of amyloid- and tau-PET and 1 from missing structural MRI), and 4 were removed due to insufficient tau-PET frames. Hence, a total of 52 individuals remained for analyses. All eligible ADNI3 participants had [18F]AV1451 tau-PET, amyloid-PET, T1-weighted structural MRI, GWAS data, and CDR and MMSE available. Approximately 52% of the ADNI participants in the current study were also part of the previous study.8 Additionally inclusion here, as opposed to the previous study, related to the fact we included either of two amyloid-PET tracers instead of only [18F]Florbetapir. Furthermore, we did not include individuals >80 years, hence some cases were included in the previous report but not in our analysis.

2.2 | Neuropsychological assessment

All F-PACK participants underwent baseline and follow-up testing for general cognition (CDR and MMSE), episodic memory, language, fluid intelligence/reasoning, and executive functioning (Supplementary Material). Cognitive test results that were acquired near the [18F]AV1451 scan date have been used in further analyses. Based on the neuropsychological follow-up data, the CDR of three F-PACK participants evolved to a total score of 0.5 with corresponding MMSE scores of 26, 26, and 29 of 30.

2.3 | Genotyping

For the BIN1 rs744373 polymorphism, participants with the G allele were classified as BIN1 rs744373 risk (4 GG, 22 AG), and those with the A allele (33) were BIN1 rs744373 normal (Supplementary Material).

For ADNI, we analyzed DNA from peripheral blood using the Illumina Infinium Global Screening Array v2.13 The BIN1 rs744373 genotype was extracted from ADNI GWAS data using PLINK (version 1.9, URL: www.cog-genomics.org/plink/1.9/), and included 35 CN BIN1 risk carriers (30 AG, 5 GG) and 26 MCI BIN1 carriers (21 AG, 5 GG).

2.4 | Imaging

2.4.1 | Structural magnetic resonance imaging

A structural T1-weighted MRI was acquired on a 3T Philips Achieva scanner (Philips, Best, The Netherlands) (3-D turbo field echo sequence, 32-channel Philips sensitivity encoding head coil: coronal inversion recovery prepared 3-D gradient-echo images, inversion time (TI) 900 millisecond, echo time (TE)/repetition time (TR) 4.6 ms/9.6 ms, flip angle 8°, voxel size 0.98 x 0.98 x 1.2 mm3). Bias correction was performed to remove intensity non-uniformities.

For ADNI images (https://ida.loni.usc.edu): T1-weighted structural MRI was recorded using an accelerated Magnetization Prepared Rapid Gradient Echo Imaging sequence, TI 900 ms, TR 2300, voxel size 1 x 1 x 1 mm3 (http://adni.loni.usc.edu/methods/documents/mri-protocols/).

2.4.2 | [18F]AV1451 PET

F-PACK participants received a dynamic [18F]AV1451 PET scan on a Biograph PET/computed tomography (CT) scanner (16-slice CT; Siemens, Erlangen, Germany). [18F]AV1451, synthesized in-house
according to previously standard procedures under full GMP, was injected in an antecubital vein (average dose of 183 ± 6 MBq). Prior to PET acquisition, a low-dose CT scan of the head (11 mAs) was performed for attenuation correction. Random, scatter, and decay corrections were applied. The first two participants received a 0 to 90-minute scan, rebinned into 26 frames: 4 × 15 s, 4 × 60 s, 2 × 150 s and 16 × 300 s. The scanning period was extended to a 0 to 100-minute scan in all subsequent participants. Images were reconstructed using ordered subset expectation maximization (4 iterations × 16 subsets) as 28 frames in total: 4 × 15 s, 4 × 60 s, 2 × 150 s, and 18 × 300 s frames and realigned using Statistical Parametric Mapping (SPM) version 12 software (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm) running on Matlab 2014b (Mathworks, Natick, MA, USA) to correct for head motion. One subject was retrospectively excluded from the analyses because of an orbitofrontal post-traumatic lesion on MRI. The maximum overall movement threshold for translation and rotation was set at 3 mm and 3 degrees, respectively. For each of these 59 F-PACK participants, a mean [18F]AV1451 PET image of the first 5 minutes following tracer injection was created and was used to coregister MRI to PET data. The MRI was then segmented using SPM12, which also included the calculation of the deformation field to warp the data to Montreal Neurological Institute space. Partial volume correction (PVC, 6 mm full-width half-maximum [FWHM]) was applied on the normalized [18F]AV1451 PET frames and deformation field to warp the data to Montreal Neurological Institute space. Partial volume correction (PVC, 6 mm full-width half-maximum [FWHM]) was applied on the normalized [18F]AV1451 PET frames and realigned using Statistical Parametric Mapping (SPM) version 12 software (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm) running on Matlab 2014b (Mathworks, Natick, MA, USA) to correct for head motion. One subject was retrospectively excluded from the analyses because of an orbitofrontal post-traumatic lesion on MRI. The maximum overall movement threshold for translation and rotation was set at 3 mm and 3 degrees, respectively. For each of these 59 F-PACK participants, a mean [18F]AV1451 PET image of the first 5 minutes following tracer injection was created and was used to coregister MRI to PET data. The MRI was then segmented using SPM12, which also included the calculation of the deformation field to warp the data to Montreal Neurological Institute space. Partial volume correction (PVC, 6 mm full-width half-maximum [FWHM]) was applied on the normalized [18F]AV1451 PET frames and realigned using Statistical Parametric Mapping (SPM) version 12 software (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm) running on Matlab 2014b (Mathworks, Natick, MA, USA) to correct for head motion. One subject was retrospectively excluded from the analyses because of an orbitofrontal post-traumatic lesion on MRI. The maximum overall movement threshold for translation and rotation was set at 3 mm and 3 degrees, respectively. For each of these 59 F-PACK participants, a mean [18F]AV1451 PET image of the first 5 minutes following tracer injection was created and was used to coregister MRI to PET data. The MRI was then segmented using SPM12, which also included the calculation of the deformation field to warp the data to Montreal Neurological Institute space. Partial volume correction (PVC, 6 mm full-width half-maximum [FWHM]) was applied on the normalized [18F]AV1451 PET frames using a modified Müller-Gärtner procedure and Logan graphical analysis to derive parametric distribution volume ratios (DVR) images with a subject-specific inferior cerebellar mask as reference region (Supplementary Material). PVC was applied as it has been shown with a subject-specific inferior cerebellar mask as reference region to improve the results of tau deposition. PVC-normalized DVR images were masked with an intracranial volume brain mask to remove extracerebral noise. For voxelwise analyses, images were smoothed with a 6 mm isotropic FWHM Gaussian 3D kernel. When calculating standardized uptake value ratios (SUVRs; as per the method described below for the tau thresholds), six participants were excluded (due to movement or data only until 90 minutes); hence only 53 F-PACK [18F]AV1415 SUVs were used.

For ADNI, [18F]AV1451 was injected (370 MBq ± 10%) and PET images were recorded 75 to 105 minutes post injection (p.i.), reconstructed as 6 × 5 minutes frames. Four of the six frames (80 to 100 minutes p.i.) were used to be consistent with F-PACK processing. No dynamic data were available for ADNI, so SUVs with a subject-specific inferior cerebellar reference region were calculated as described below. PVC with the original Müller-Gärtner procedure and smoothing for voxelwise analyses were also applied, as with F-PACK.

Regional [18F]AV1451 measures
Unsmoothed PVC [18F]AV1451 DVR images were intersected with the gray matter–masked Brainnetome parcellations to obtain subject-specific regional measures of tau deposition in neuropathologically established tau-vulnerable regions. The eight regions were entorhinal and perirhinal cortex, hippocampus, parahippocampus, fusiform cortex, inferior temporal cortex, middle temporal gyrus, precuneus, and inferior parietal lobule (atlas labels: Supplementary Material). The early metaVOI consisted of entorhinal, perirhinal, hippocampus, parahippocampus, fusiform gyrus, and inferior temporal gyrus, weighted for the voxel size of each subregion. To determine amyloid-PET positivity in the F-PACK participants, SUVs were converted to Centiloids (CLs), using the formula: Centiloid = 132.53 × [11C]PIB SUVR40-60 minutes − 147.64 (Supplementary Material). Based on a neuropathologically validated binary threshold of 23.5 CLs, F-PACK participants were binarized based upon amyloid status.

For determining amyloid positivity in ADNI participants with [18F]Florbetaben, we used a threshold of 1.29, derived from an independent data set, as described previously. For [18F]Florbetapir amyloid positivity, an independent data set of [18F]Florbetapir-PET 50-60 minutes p.i. from the Global Alzheimer’s Association Interactive Network (GAIN) was analyzed (Table S1). The optimal [18F]Florbetapir threshold to distinguish AD cases from controls was 1.308, calculated using “cutpointr” (https://github.com/thie1e/cutpointr).

For tau-PET positivity, median PVC [18F]AV1451 SUV values of an independent data set of [18F]AV1451 SUV values of an independent data set were entered into “cutpointr,” which estimated the optimal threshold per VOI.

3 | STATISTICAL ANALYSES

All statistical analyses were conducted with R statistical software, version 4.0.2 (2020-06-22) (The R Foundation for Statistical Computing, https://www.r-project.org/) and R studio. The correction of two-tailed P values for multiple comparisons was performed using Bonferroni, that is, dividing the α-value of 0.05 by the number of tests. Outliers were assessed using the Grubb’s test.

A power calculation was performed using the R package “pwr” to determine whether the sample size had sufficient power to...
measure the association between \(\text{BIN1} \) and \([^{18}\text{F}]\text{AV1451}\) tau-PET levels based on an analysis of variance (ANOVA) design on data reported in Franzmeier et al. in ADNI CNs. Based on the power analysis, a sample of 59 individuals per group would be required to reach a power of 80% at \(\alpha = 0.05\) to replicate the reported \(\text{BIN1} \) rs744373 effect on global tau burden (effect size \(= 0.26\)). Similarly, one would need to include 48 individuals per group to reach a power of 80% at \(\alpha = 0.05\) for detecting a \(\text{BIN1} \) rs744373 effect on global tau burden (effect size \(= 0.29\)) in BioFINDER CNs. In the pooled F-PACK and ADNI CNs cohort, we included 61 \(\text{BIN1} \) rs744373 non-risk carriers and 58 \(\text{BIN1} \) rs744373 risk carriers.

Prior to any statistical analyses, normality of data was assessed using Shapiro-Wilk tests. When a variable deviated from normality (\(\alpha <0.05\)), a natural logarithm transformation (\(\ln\)) was performed to approach normality. For F-PACK, only \([^{18}\text{F}]\text{AV1451}\) DVR values in the precuneus were log-transformed. However, log-transformed precuneus \([^{18}\text{F}]\text{AV1451}\) DVR values did not fulfill normality either, so non-parametric statistics have been used for this region. Demographic variables were normally distributed. Of the cognitive data set, letter verbal fluency, Raven's Progressive Matrices and the total learning scores of Auditory Verbal Learning Test and Buschke Selective Reminding Test were normally distributed; all other cognitive data were log-transformed. However, only Trial Making Test B/A scores were normally distributed after log-transformation. For the remaining cognitive data, non-parametric statistics were used.

For ADNI CN, \([^{18}\text{F}]\text{AV1451}\) SUVR data were normally distributed for all regions except for entorhinal and perirhinal cortex. Log-transformation improved the distribution of perirhinal but not entorhinal SUVRs. This was the same when pooling F-PACK and ADNI CNs. For ADNI MCI, only the hippocampal \([^{18}\text{F}]\text{AV1451}\) SUVRs were normally distributed as well as log-transformed entorhinal and perirhinal cortical \([^{18}\text{F}]\text{AV1451}\) SUVRs. Thus, non-parametric statistics have been used for those regions not normally distributed. Demographic variables were compared between \(\text{BIN1} \) groups (ie, normal vs risk-allele), within and between cohorts, using Welch two-sample t-tests for continuous measures and chi-square tests for categorical measures. To assess the effect of age, education, and sex on \([^{18}\text{F}]\text{AV1451}\) values, independent Pearson/Spearman correlational analyses and Chi-square tests were performed, corrected for the number of regions assessed (\(N = 9\)). Robust \(\text{d} \) effect sizes with corresponding 95% CIs were calculated using the R package "WRS2".

For ADNI, the same statistical approach was used as described for F-PACK, to assess the replicability of the reported findings. F-PACK and ADNI CNs were pooled (\(N = 119\)), and \(\text{BIN1} \) groups were compared with a similar statistical approach (depending on normality) as described in the Methods section.

### 3.2 Secondary outcome analysis

We performed the same regional and global analysis on the amyloid positive and amyloid negative subgroups of the pooled cohort to assess whether amyloid positivity influenced the \(\text{BIN1} \) effect on tau positivity. As a complimentary analysis, we also performed two-way ANOVAs for each of the regions of interest with amyloid status and \(\text{BIN1} \) status as factors, as well as with an interaction term of both variables.

To assess the hypothesis that the reported effect of \(\text{BIN1} \) exerted its effect in a disease stage-dependent manner, \(\text{BIN1} \) groups were also compared within the ADNI MCI cohort.

To investigate the effect of \(\text{BIN1} \) on cognitive performance in the F-PACK cohort, we used Mann-Whitney U tests or Welch two-sample t-tests, depending on normality.

### 4 RESULTS

Characteristics of F-PACK participants (Table 1)—ADNI CN and MCI participants (Table S2)—and pooled CNs (Table S3) were stratified for the \(\text{BIN1} \) rs744373 polymorphism.

In the F-PACK cohort, based on a neuropathologically validated binary threshold of 23.5 CLs, 12 participants (21%) were amyloid positive. Thresholds for tau positivity are provided in Table S4. Five F-PACK participants (8%) were tau positive on the metaVOI (threshold: 1.39) and four participants (7%) were positive on the early metaVOI (threshold: 1.39). Demographic variables did not differ between \(\text{BIN1} \) groups in F-PACK (Table 1).

In ADNI CNs, 15 participants (23%) were amyloid positive (7 based upon \([^{18}\text{F}]\text{Florbetapir-PET}\) and 8 using \([^{18}\text{F}]\text{Florbetaben-PET}\)). One participant was tau positive (2%). No significant differences were observed in demographic characteristics between \(\text{BIN1} \) groups in the ADNI CNs (Table S2), or in the pooled CNs (Table S3).

In ADNI MCI, 25 (51%) were amyloid positive (11 with \([^{18}\text{F}]\text{Florbetapir}\) and 14 with \([^{18}\text{F}]\text{Florbetaben}\)). Eighteen patients (35%) were tau positive. \(\text{BIN1} \) non-carriers were significantly older than risk-allele carriers (\(P = .04\)) (Table S2).

### 4.1 Whole-brain voxelwise \([^{18}\text{F}]\text{AV1451}\) and \(\text{BIN1} \) polymorphism

In the whole-brain voxelwise analysis based on F-PACK CN, there was no significant effect of \(\text{BIN1} \) on \([^{18}\text{F}]\text{AV1451}\) binding at the
TABLE 1 Characteristics of F-PACK cognitively normal study participants stratified for BIN1 rs744373 polymorphism

| Characteristic                              | BIN1 rs744373 normal | BIN1 rs744373 risk | Statistics |
|---------------------------------------------|----------------------|-------------------|------------|
| N                                           | 33                   | 26                | —          |
| Age (years)                                 | 70 (55-83)           | 70.5 (59-81)      | T = -0.096, P = .92 |
| Sex (female/male)                           | 17/16                | 16/10             | X² = 0.26, P = .61 |
| Education (years)                           | 13 (8-19)            | 14.5 (8-21)       | T = -0.42, P = .68 |
| APOE ε4 (carrier/non-carrier)               | 13/20                | 10/16             | X² < 0.1, P = 1.0 |
| Composite [11C]PIB DVR                      | 1.08 (0.98-1.41)     | 1.07 (0.98-1.52)  | U = 461, P = .49 |
| Centiloids                                  | 9.94 (-8.35-82.57)   | 4.31 (-9.01-92.11) | U = 444, P = .52 |
| MMSE (/30)                                  | 29 (27-30)           | 29.5 (26-30)      | U = 406.5, P = .88 |
| CDR                                         | 0 (0-0.5)            | 0 (0-0.5)         | U = 409, P = .43 |
| AVLT total learning (/75)                   | 49 (27-71)           | 48.5 (28-73)      | T = -0.062, P = .95 |
| AVLT delayed recall (%)                     | 86.7 (37.5-100)      | 89.2 (16.7-107.1) | U = 433, P = .80 |
| Buschke mean score                          | 8.0 (2.4-11.3)       | 8.4 (4.1-11.5)    | T = -0.14, P = .89 |
| Buschke delayed recall (/15)                | 8.0 (2.0-12)         | 8.0 (0.0-12)      | U = 389, P = .72 |
| Boston Naming Test (/60)                    | 56 (45-60)           | 56 (48-60)        | U = 464, P = .59 |
| Letter verbal fluency (#/min)               | 33 (11-63)           | 34.5 (14-52)      | T = -0.17, P = .86 |
| Animal verbal fluency (#/min)               | 21 (14-42)           | 21.5 (13-50)      | U = 448.5, P = .77 |
| PALPA49 associative-semantic (/30)           | 27 (21-30)           | 28 (24-30)        | U = 412, P = 0.80 |
| Trial making test B/Aa                      | 2.3 (1.5-5.5)        | 2.7 (1.5-4.98)    | T = -0.84, P = .41 |
| Raven’s progressive matrices (/60)          | 43 (29-58)           | 43 (13-57)        | T = 1.02, P = .31 |

Abbreviations: AVLT, Auditory Verbal Learning Test; CDR, Clinical dementia rating scale; DVR, distribution volume ratio; MMSE, Mini-mental State Examination; N, number; PALPA49, Psycholinguistic Assessment of Language Processing in Aphasia subtest 49.

Data are median and range (minimum to maximum) for continuous variables and proportions for categorical variables.

Total sample size = 59 except for [11C]PIB and Centiloids: N = 58.

Age is at the timepoint of [18F]AV1451-PET.

Statistics: Welch two-sample t-test (T) or Wilcoxon rank sum test with continuity correction (U), depending on normality. For categorical variables, chi-square (χ²) has been calculated.

P-values are two-tailed and uncorrected.

For this particular variable, log-transformed values have been used as statistical input.

4.2 Regional analysis of [18F]AV1451 values and BIN1 polymorphism

At the regional level, there was no significant effect of BIN1 on [18F]AV1451 DVRs in F-PACK (Figure 1A, Table 2). Likewise, there were no significant differences for BIN1 regarding [18F]AV1451 binding in ADNI CNs (Figure 1B, Table 3) or ADNI MCIs (Figure 1F, Table 4), or in pooled CNs (Figure 1C, Table 5).

4.3 Regional analysis of [18F]AV1451 values and BIN1 polymorphism stratified for amyloid

We performed the same regional and global analysis on the amyloid positive and amyloid negative subgroups, respectively, of the pooled cohort of F-PACK and ADNI CN individuals. There were 21 amyloid-positive cases (see Methods). Of these 21 amyloid positive individuals, 11 were BIN1 rs744373 risk carriers and 10 were non-carriers. There were 98 amyloid negative individuals: 47 were BIN1 risk carriers and 51 were non-carriers. As with the main analyses, there was no effect of BIN1 status on [18F]AV1451 SUVR in either of the two subgroups (amyloid positive: Pcorr > 2.47; amyloid negative: Pcorr > 1.02), Figure 1D and E. Furthermore, two-way ANOVAs did not yield any significance with any of the regions assessed (Pcorr > 1.31).

pre-set threshold. Lowering the threshold to voxelwise uncorrected P < .001 did not reveal any significant voxels either. Similarly, negative results were obtained in ADNI CN, MCI, as well as in pooled CNs.
FIGURE 1  Regional analysis of $[18F]$AV1451 values and BIN1 rs744373 polymorphism. Median values are plotted for BIN1 rs744373 normal (green) and BIN1 rs744373 risk-allele groups (red), with the horizontal axis at 0. (A) F-PACK DVR values, (B) ADNI cognitively normal (CN) SUVR values, (C) pooled ADNI and F-PACK CN SUVR values, (D) pooled ADNI and F-PACK CN amyloid-positive SUVR values, (E) pooled ADNI and F-PACK CN amyloid-negative SUVR values, (F) ADNI mild cognitive impairment SUVR values. F-PACK DVR: Total N = 59, ADNI CN: N = 66, pooled CN: N = 119 (21 amyloid-positive), ADNI MCI: N = 52. DVR, distribution volume ratio; InfTemp, inferior temporal gyrus; IPL, Inferior parietal lobule; MidTemp, middle temporal; metaVOI, meta volume of interest; PVC, partial volume corrected; SUVR, standardized uptake volume ratio.

4.4  Cognitive differences depending on BIN1 polymorphism

Neuropsychological test scores of F-PACK participants did not differ significantly between BIN1 groups (Table 1). Without correction for the number of tests performed, APOE ε4 carriers performed worse on fluid intelligence testing compared to non-carriers ($T = 2.28, P = .026$) (data not shown).

5  DISCUSSION

The current study could not confirm the a priori hypothesis that the BIN1 rs744373 risk-allele was associated with elevated $[18F]$AV1451 binding in CN older adults. There was no effect in the CN amyloid positive subgroup either.

Amyloid- and tau-PET studies in CN older participants have revolutionized our insight into AD-related brain changes in the absence
of clinical symptoms. It is currently widely accepted that pathological changes span a long asymptomatic phase, of up to 20 years. This asymptomatic phase, currently mostly defined from amyloid-based measures, could offer a window of opportunity for intervention trials because disease-modifying drug therapies may be more successful when provided early in the disease course. Genetic screening for APOE ε4 has already been implemented as a selection criterion in amyloid-lowering drug trials in CNs. Given the failure of most amyloid-lowering drug trials, tau phosphorylation and aggregation are being increasingly considered as a drug target. Hence, research into the prevalence and risk factors for increased tau aggregation in CNs is of both fundamental and applied relevance.

Based on the previously reported findings in a cohort of 89 non-demented participants, BIN1 rs744373 seemed to be a potential genetic polymorphism candidate associated with increased tau tracer binding. However, in the current F-PACK and ADNI CN participants, this effect could not be replicated. Power calculations indicated that the sample size of the pooled cohort in the present study was sufficient to detect an effect of BIN1 on tau load using the previously reported findings; however, we were not able to demonstrate this. Here the focus was on CNs, which differs from the diagnostic groups studied by Franzmeier et al. The latter study pooled findings of 49 CN older subjects (49%) were amyloid positive and a significant proportion of the total group of participants were characterized by a Braak stage >IV, based on [18F]AV1451-PET (no tau-PET

### TABLE 2
Regional F-PACK ([18F]AV1451 DVR values, stratified for BIN1 rs744373 polymorphism

| Region                   | BIN1 rs744373 normal | BIN1 rs744373 risk | Statistics    | Robust d (95% CI) |
|--------------------------|----------------------|-------------------|---------------|------------------|
| Entorhinal               | 0.80 (0.63-0.91)     | 0.83 (0.63-1.00)  | T = −1.71     | −0.421 (−1.011, 0.104) |
| Perirhinal               | 0.89 (0.77-1.03)     | 0.91 (0.72-1.05)  | T = −1.03     | −0.259 (−0.718, 0.376) |
| Hippocampus              | 0.96 (0.74-1.11)     | 0.95 (0.78-1.13)  | T = 0.58      | 0.214 (−0.355, 0.709) |
| Parahippocampus          | 0.94 (0.80-1.11)     | 0.93 (0.78-1.09)  | T = 0.64      | 0.176 (−0.357, 0.777) |
| Fusiform gyrus           | 1.03 (0.93-1.16)     | 1.01 (0.90-1.19)  | T = −0.58     | −0.119 (−0.652, 0.409) |
| Inferior temporal        | 0.99 (0.89-1.13)     | 1.00 (0.85-1.12)  | T = −0.65     | −0.188 (−0.667, 0.343) |
| Middle temporal          | 0.99 (0.89-1.13)     | 1.00 (0.85-1.16)  | T = −0.47     | −0.106 (−0.742, 0.404) |
| Precuneus                | 1.03 (0.92-1.31)     | 1.03 (0.92-1.18)  | U = 433       | −0.0013 (−0.544, 0.548) |
| Inferior parietal lobe   | 0.99 (0.89-1.21)     | 0.98 (0.82-1.17)  | T = 0.50      | 0.116 (−0.445, 0.729) |
| Early metaVOI            | 0.997 (0.88-1.12)    | 0.99 (0.86-1.15)  | T = −0.25     | −0.033 (−0.615, 0.445) |
| MetaVOI                  | 0.99 (0.89-1.12)     | 0.996 (0.85-1.14) | T = −0.42     | −0.098 (−0.597, 0.509) |

Abbreviations: MetaVOI, meta volume of interest.
Data are median and range (minimum to maximum). Total N = 59.
Welch two-sample t-test (T) or Wilcoxon rank sum test with continuity correction (U).
P-values are two-tailed and uncorrected for the number of comparisons (N = 9).
For the Robust d (confidence interval) metric, a negative sign refers to the fact that the BIN1 rs744373 risk group has higher values than the BIN1 rs744373 normal group.
TABLE 3  Regional ADNI cognitively normal [18F]AV1451 SUVR values, stratified for BIN1 rs744373 polymorphism

|          | BIN1 rs744373 normal | BIN1 rs744373 risk | Statistics | Robust d (95% CI) |
|----------|----------------------|-------------------|------------|------------------|
| N        | 31                   | 35                | —          | —                |
| Entorhinal | 1.168 (1.001-1.941)  | 1.139 (0.833-1.562) | U = 631  
  P = .260 | 0.274 (−0.265, 0.747) |
| Perirhinal | 1.136 (0.893-1.629)  | 1.062 (0.910-1.483) | T = 1.533  
  P = .131 | 0.318 (−0.11, 0.909) |
| Hippocampus | 1.032 (0.664-1.302)  | 1.040 (0.822-1.291) | T = −0.127  
  P = .899 | 0.082 (−0.417, 0.718) |
| Parahippocampus | 1.035 (0.837-1.298)  | 1.013 (0.839-1.219) | T = 0.529  
  P = .599 | 0.158 (−0.386, 0.793) |
| Fusiform gyrus | 1.135 (0.951-1.413)  | 1.136 (0.967-1.316) | T = 0.562  
  P = .576 | 0.089 (−0.391, 0.659) |
| Inferior temporal | 1.208 (0.981-1.460)  | 1.156 (1.024-1.433) | T = 0.759  
  P = .450 | 0.273 (−0.256, 0.880) |
| Middle temporal | 1.290 (1.086-1.531)  | 1.251 (1.061-1.506) | T = 0.480  
  P = .633 | 0.160 (−0.310, 0.630) |
| Precuneus | 1.154 (0.882-1.405)  | 1.125 (0.952-1.340) | T = 0.094  
  P = .925 | 0.026 (−0.518, 0.619) |
| Inferior parietal lobe | 1.207 (1.042-1.460)  | 1.232 (1.041-1.478) | T = −0.151  
  P = .880 | −0.026 (−0.527, 0.594) |
| Early metaVOI | 1.110 (0.876-1.381)  | 1.089 (0.947-1.284) | T = 0.530  
  P = .598 | 0.149 (−0.465, 0.597) |
| MetaVOI | 1.161 (0.915-1.412)  | 1.114 (0.975-1.321) | T = 0.654  
  P = .516 | 0.221 (−0.229, 0.684) |

Abbreviations: MetaVOI, meta volume of interest.
Data are median and range (minimum to maximum).
Total N = 66.
Welch two-sample T test (T) or Wilcoxon rank sum test with continuity correction (U).
P-Values are two-tailed and uncorrected for the number of comparisons (N = 9).
For the Robust d (with confidence intervals) metric, a negative sign refers to the fact that the BIN1 rs744373 risk group has higher values than the BIN1 rs744373 normal group.

threshold was calculated). The highest effect sizes occurred in later tau-sensitive regions, whereas earlier tau-sensitive regions such as the entorhinal cortex did not show a significant effect of BIN1.

Combined with the results observed here in CNs, the findings we obtained in the ADNI MCI group are in line with the hypothesis that the observed effect of the BIN1 rs744373 risk-allele was driven by the MCI group: although we did not find a significant association between [18F]AV1451 and BIN1 in the ADNI MCIs, there was a numerical difference observed for [18F]AV1451 binding in later tau-sensitive regions such as the precuneus and inferior parietal lobe, with high SUVRs in the BIN1 risk-allele group compared to BIN1 normals (Table 4). This can also be appreciated on Figure 1, which indicates that a subset of MCI patients are characterized by high [18F]AV1451 binding, likely driving cognition was mediated by globally increased [18F]AV1451 binding. This may be explained by its known association with AD rather than a direct effect on tau spread. This rationale is in fact further supported by Franzmeier et al., even though regression models were corrected for diagnosis by adding a dummy variable, the BIN1 rs744373 effect was significant after Bonferroni correction for Braak stage V and global tau, indicating effects on more progressed tau pathology, which accompanies the MCI stage of AD. BIN1 rs744373 risk-allele carriers had lower episodic memory scores than non-carriers in the Franzmeier et al. study. The effect on cognition was mediated by globally increased [18F]AV1451 binding. This is in line with the hypothesis that the results in the original study were driven by cognitively impaired participants with lower episodic memory scores and increased tau (ie, later-stage MCI patients).

Taken together, because the BIN1 polymorphism is a significant risk factor for clinical AD, pooling CN adults with MCI cases could potentially yield a spurious association, mediated by diagnostic group. Our data suggest that the BIN1 risk locus may exert its effect directly on tau spread only in a more advanced MCI stage or the effect of the risk locus on tau aggregation and spread may be below the detection threshold.
### TABLE 4
Regional ADNI mild cognitive impairment \(^{[18F]}\)AV1451 SUVR values, stratified for \(BIN1\) rs744373 polymorphism

| Region               | \(BIN1\) rs744373 normal | \(BIN1\) rs744373 risk | Statistics | Robust \(d\) (95% CI) |
|----------------------|---------------------------|------------------------|------------|------------------------|
| N                    | 26                        | 26                     | --         | --                     |
| Entorhinal           | 1.326 (0.867-2.429)        | 1.371 (0.987-1.993)    | \(T = 0.939\) | 0.179 (--0.456, 0.773) |
| Perirhinal           | 1.343 (0.889-2.246)        | 1.264 (0.930-2.117)    | \(T = 0.760\) | 0.222 (--0.363, 0.897) |
| Hippocampus          | 1.253 (0.838-1.755)        | 1.235 (0.835-1.868)    | \(T = 0.468\) | 0.148 (--0.428, 0.755) |
| Parahippocampus      | 1.135 (0.866-1.981)        | 1.164 (0.889-2.439)    | \(U = 332\) | --0.091 (--0.700, 0.483) |
| Fusiform gyrus       | 1.224 (0.963-2.219)        | 1.192 (1.012-3.472)    | \(U = 376\) | 0.132 (--0.469, 0.826) |
| Inferior temporal    | 1.302 (0.963-2.121)        | 1.246 (1.056-3.241)    | \(U = 357\) | 0.037 (--0.460, 0.672) |
| Middle temporal      | 1.356 (1.042-1.984)        | 1.329 (1.115-3.551)    | \(U = 313\) | --0.116 (--0.603, 0.637) |
| Precuneus            | 1.290 (0.989-1.965)        | 1.216 (0.994-3.081)    | \(U = 408\) | 0.390 (--0.218, 1.250) |
| Inferior parietal lobe| 1.361 (1.038-1.703)        | 1.287 (1.053-3.482)    | \(U = 389\) | 0.273 (--0.275, 0.926) |
| Early metaVOI        | 1.241 (0.923-1.948)        | 1.186 (0.977-2.695)    | \(U = 367\) | 0.103 (--0.504, 0.777) |
| metaVOI              | 1.264 (0.937-2.014)        | 1.219 (1.007-2.968)    | \(U = 365\) | 0.085 (--0.518, 0.705) |

Abbreviations: MetaVOI, meta volume of interest. Data are median and range (minimum to maximum). Total N = 52. Welch two-sample t-test (T) or Wilcoxon rank sum test with continuity correction (U). \(P\)-values are two-tailed and uncorrected for the number of comparisons (N = 9). For the Robust \(d\) (with confidence intervals) metric, a negative sign refers to the fact that the \(BIN1\) rs744373 risk group has higher values than the \(BIN1\) rs744373 normal group.

in the asymptomatic stage. Alternatively and more interestingly, our findings together with previous studies,\(^8,29–31\) may raise the possibility that genetic risk factors may exert their effect in a disease stage–dependent manner, for instance, only after symptoms appeared in a later disease stage.

### 5.1 Study limitations

The F-PACK sample size was relatively low. Hence, strict correction for multiple comparisons were applied to avoid false-positive findings. Moreover, we rectified this by analyzing pooled CN cohorts for validation of our original findings from the individual F-PACK and ADNI CN analyses.

Here, we focused on \(BIN1\) rs744373, since this single nucleotide polymorphism (SNP) is most frequently reported to be associated with AD risk across different GWASs.\(^1,2\) However, the rs59335482 SNP is the functional SNP of \(BIN1\), which is associated with increased \(BIN1\) mRNA expression in postmortem analyzed AD brains.\(^4\) rs744373 is in almost complete linkage disequilibrium with rs59335482 \((r^2 = 0.94)\), indicating that both SNPs have similar predictive value for AD risk and findings should not differ substantially between SNPs.

In conclusion, the effect of the \(BIN1\) rs744373 risk-allele on tau burden in CN individuals was not replicated. Our study highlights the importance of considering diagnostic status as well as disease stage when inferring effects of \(BIN1\) on in vivo tau aggregation.

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TABLE 5  Regional pooled cognitively normal [18F]AV1451 SUVR values, stratified for BIN1 rs744379 polymorphism

| BIN1 rs744373 normal | BIN1 rs744373 risk | Statistics | Robust d (95% CI) |
|----------------------|---------------------|------------|-------------------|
| N                    | 61                  | 58         |                   |
| Entorhinal           | 1.156 (0.772-1.941) | 1.151 (0.758-1.562) | $U = 1619$ | $P = .427$ | $-0.176$ (−0.566, 0.212) |
| Perirhinal           | 1.161 (0.893-1.629) | 1.172 (0.910-1.643) | $T = 0.667$ | $P = .506$ | $0.143$ (−0.266, 0.526) |
| Hippocampus          | 1.117 (0.664-1.322) | 1.087 (0.822-1.369) | $T = 0.719$ | $P = .473$ | $0.169$ (−0.143, 0.558) |
| Parahippocampus      | 1.123 (0.837-1.491) | 1.093 (0.839-1.450) | $T = 1.265$ | $P = .208$ | $0.192$ (−0.179, 0.518) |
| Fusiform gyrus       | 1.179 (0.951-1.452) | 1.186 (0.967-1.546) | $T = 0.701$ | $P = .485$ | $0.089$ (−0.262, 0.502) |
| Inferior temporal    | 1.233 (0.981-1.460) | 1.228 (1.024-1.484) | $T = 0.841$ | $P = .402$ | $0.213$ (−0.191, 0.569) |
| Middle temporal      | 1.261 (1.058-1.531) | 1.266 (1.018-1.522) | $T = 0.026$ | $P = .979$ | $0.045$ (−0.340, 0.445) |
| Precuneus            | 1.181 (0.882-1.541) | 1.178 (0.952-1.382) | $T = 0.789$ | $P = .432$ | $0.072$ (−0.339, 0.467) |
| Inferior parietal lobe| 1.202 (1.023-1.466) | 1.202 (0.978-1.478) | $T = 0.536$ | $P = .593$ | $0.072$ (−0.344, 0.446) |
| Early metaVOI        | 1.606 (0.876-1.404) | 1.164 (0.947-1.486) | $T = 0.753$ | $P = .453$ | $0.143$ (−0.206, 0.520) |
| MetaVOI              | 1.191 (0.915-1.412) | 1.189 (0.975-1.485) | $T = 0.815$ | $P = .417$ | $0.173$ (−0.227, 0.542) |

Abbreviations: MetaVOI, meta volume of interest.
Data are median and range (minimum to maximum).
Total N = 66.
Welch two-sample t-test (T) or Wilcoxon rank sum test with continuity correction (U).
$P$-values are two-tailed and uncorrected for the number of comparisons (N = 9).
For the Robust $d$ (with confidence intervals) metric, a negative sign refers to the fact that the BIN1 rs744373 risk group has higher values than the BIN1 rs744373 normal group.

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CONFLICTS OF INTEREST
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SUPPORTING INFORMATION

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