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RESEARCH ARTICLE

The *BIN1* rs744373 Alzheimer's disease risk SNP is associated with faster Aβ-associated tau accumulation and cognitive decline

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Abstract

Introduction: The *BIN1* rs744373 single nucleotide polymorphism (SNP) is a key genetic risk locus for Alzheimer's disease (AD) associated with tau pathology. Because tau typically accumulates in response to amyloid beta (Aβ), we tested whether *BIN1* rs744373 accelerates Aβ-related tau accumulation.

Methods: We included two samples (Alzheimer's Disease Neuroimaging Initiative [ADNI], n = 153; Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably [BioFINDER], n = 63) with longitudinal ^{18}F-Flortaucipir positron emission tomography (PET), Aβ biomarkers, and longitudinal cognitive assessments. We assessed whether *BIN1* rs744373 was associated with faster tau-PET accumulation at a given level of Aβ and whether faster *BIN1* rs744373-associated tau-PET accumulation mediated cognitive decline.

Results: *BIN1* rs744373 risk-allele carriers showed faster global tau-PET accumulation (ADNI/BioFINDER, $P < .001$/$P < .001$). We found significant Aβ by rs744373 interactions on global tau-PET change (ADNI: β/standard error [SE] = 0.42/0.14, $P = 0.002$;

BioFINDER: β/SE = −0.35/0.15, P = .021), *BIN1* risk-allele carriers showed accelerated tau-PET accumulation at higher Aβ levels. In ADNI, rs744373 effects on cognitive decline were mediated by faster global tau-PET accumulation (β/SE = 0.20/0.07, P = .005).

Discussion: *BIN1*-associated AD risk is potentially driven by accelerated tau accumulation in the face of Aβ.

KEYWORDS
Alzheimer's disease, amyloid, BIN1, tau

1 | INTRODUCTION

Alzheimer's disease (AD) is the most common cause of late-onset dementia, characterized by cerebral amyloid beta (Aβ) plaques, tau tangles, and neurodegeneration.[1] As shown by genome-wide association studies (GWAS), late-onset AD has a strong genetic component, with ≈30 genetic risk loci identified to date.[2,3] The rs744373 single nucleotide polymorphism (SNP) in the *BIN1* gene (i.e., bridging integrator 1) shows strong associations with AD dementia.[2–5] Thus, understanding the pathomechanism of *BIN1* rs744373-related AD risk can provide important insight into AD pathophysiology and help uncover novel therapeutic targets.

The *BIN1* gene encodes the nucleoplasmic adaptor protein BIN1, which is predominantly expressed in brain and muscle tissue[6] and is involved in the regulation of membrane curvature,[7] clathrin-mediated endocytosis,[8,9] presynaptic vesicle release,[10] and neuronal excitability.[11,12] Previous pre-clinical,[8,9,13] *post mortem*,[13–15] and biomarker studies[8,16,17] demonstrated BIN1 involvement in the development of tau pathology, which is considered a major driver of neurodegeneration[18] and cognitive decline in AD.[19] Preclinical work has shown that the BIN1 protein is involved in trans-neuronal tau pathology spreading,[8,9] for example, via modulating the secretion and endocytosis of tau-containing vesicles.[8,9] Similarly, BIN1 is found both in and on the surface of tau-harboring exosomes in cerebrospinal fluid (CSF) samples of AD patients.[8] *Post mortem* assessments revealed upregulated cerebral BIN1 mRNA expression in AD,[15] which was correlated with greater tau[14,20] but not Aβ pathology.[20] Similarly, we reported previously that *BIN1* rs744373 risk allele carriers show elevated positron emission tomography (PET)-assessed tau, but not Aβ pathology.[16] Together, these studies indicate that BIN1 is involved in AD as a modulator of tau rather than Aβ pathology. However, these studies leave unaddressed whether *BIN1* risk influences in vivo tau accumulation rates at a given level of Aβ, thereby increasing dementia risk.

In the current independently validated longitudinal tau-PET study, our primary goal was to assess whether *BIN1* rs744373 risk-allele carriers show faster tau accumulation in response to more abnormal Aβ markers (i.e., an interaction between *BIN1* rs744373 and Aβ measures on longitudinal global tau-PET change) and whether faster *BIN1* rs744373-related global tau accumulation rates mediate faster global cognitive decline in risk-allele carriers. We addressed this in two independent samples with longitudinal tau-PET, including 153 participants of the Alzheimer's Disease Neuroimaging Initiative (ADNI) with PET-assessed Aβ levels and 63 participants of the Swedish Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably (BioFINDER) study with CSF Aβ assessments.

2 | METHODS

2.1 | Participants: ADNI

We included 153 ADNI participants with longitudinal partial volume effect-corrected ^{18}F-Flortaucipir tau-PET, longitudinal cognition, and ^{18}F-Florbetapir/^{18}F-Florbetaben amyloid-PET obtained within 6 months of the first tau-PET visit. Subjects were classified by ADNI as cognitively normal (CN, N = 94, Mini-Mental State Examination [MMSE] > 24, Clinical Dementia Rating [CDR] = 0, non-depressed) or mildly cognitively impaired (MCI; N = 59, MMSE > 24, CDR = 0.5, objective memory-loss on the education adjusted Wechsler Memory Scale II, preserved activities of daily living). *BIN1* rs744373 status was extracted from whole-genome sequencing (Illumina Infinium Global Screening Array v2) data, as described previously.[21] Subjects were labeled as *BIN1*-risk (N = 67) when carrying≥1 rs744373 G-allele. For amyloid-PET, we used FreeSurfer-derived global standardized uptake value ratios (SUVRs) normalized to the whole cerebellum. Aβ status was determined at pre-established cut-offs, that is, 1.11 for Florbetapir and 1.08 for Florbetaben.[22] Global Florbetaben/Florbetapir-PET SUVRs were linearly transformed to Centiloids to allow SUVR pooling across tracers (http://www.gaain.org/centiloid-project).[23] Ethical approval was obtained by ADNI; all participants provided written informed consent.

2.2 | Participants: BioFINDER

For validation, we included 63 CN (n = 40), MCI (n = 8), or AD dementia participants (n = 15) from BioFINDER with partial volume effect-corrected longitudinal ^{18}F-Flortaucipir tau-PET and baseline cerebrospinal fluid-derived Aβ_{42}/Aβ_{40} levels (EUROIMMUN AG). Aβ positivity was defined using a pre-established A$\beta_{42/40}$ ratio cut-off < 0.10.[24] BioFINDER participants were fluent in Swedish and classified as CN (MMSE > 28, criteria of MCI or dementia not fulfilled), MCI (MMSE > 24, objective memory impairment in delayed word-list

recall), or AD dementia according to Diagnostic and Statistical Manual of Mental Disorders 3rd edition revised (DSM-III-R) dementia criteria and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for AD. Exclusion criteria were substantial systemic illness, refusing lumbar puncture, or substantial alcohol abuse. An in-depth summary of BioFINDER inclusion/exclusion criteria and assessments has been described previously,[25] genetic assessments are described in the supporting information. All participants provided written informed consent. Ethical approval was provided by the Lund University ethics committee.

2.3 | Tau-PET analysis

For details on neuroimaging acquisition please see supporting information. In brief, PET images were coregistered to FreeSurfer-processed T1-weighted structural magnetic reference imaging (MRI). Mean tau-PET uptake was extracted for Desikan-Killiany atlas regions[26] and intensity normalized to an inferior cerebellar gray reference.[27] Partial volume-effect correction was performed using the geometric transfer matrix approach, as described previously for tau-PET.[28]

2.4 | Regions of interest and estimation of longitudinal tau-PET change

To determine *BIN1* rs744373 effects on tau accumulation, we computed tau-PET SUVRs for different pre-established regions of interest (ROIs).[29,30] For primary analyses, we used a global ROI, summarizing neocortical tau-PET SUVRs (i.e., all cortical FreeSurfer regions excluding the hippocampus).[16] We selected global tau-PET for our primary analysis, because we previously found that *BIN1* rs744373 effects on cross-sectional tau-PET uptake were global and not restricted to a particular brain region.[16] For exploratory analyses, we determined tau-PET SUVRs for a temporal meta-ROI (i.e., Braak I, III, and IV),[30] an early AD meta-ROI (fusiform and posterior cingulate cortex), and a late AD meta-ROI (inferior temporal, orbitofrontal, middle occipital), which were previously shown to capture early versus late AD-related longitudinal tau accumulation.[29] Early and late-AD meta-ROIs were constructed in FreeSurfer space using anatomical information provided by previous work using a different brain atlas (see Table S1 in supporting information for FreeSurfer ROIs included in each summary ROI).[29] Hippocampal/subcortical ROIs were excluded from all analyses due to Flortaucipir off-target binding.[31] To determine longitudinal tau-PET changes, we fitted linear-mixed models with tau-PET SUVRs as the dependent variable and time (i.e., years from baseline) as the independent variable, controlling for random slope and intercept.[32] From these models, we derived subject-specific slope estimates for annual tau-PET SUVR change.

2.5 | Cognitive assessments

In ADNI, we included the AD assessment scale total score (i.e., Alzheimer's Disease Assessment Scale Cognitive subscale [ADAS13]) as our primary measure of global cognition, which is widely used in clinical routine and trials.[33] As secondary measures, we used more specific measures. That is, the memory composite ADNI-MEM,[34] as well as the Preclinical Alzheimer Cognitive Composite (PACC), which is tailored to detect earliest AD-related cognitive changes[35] by combining episodic memory, executive function, and global cognitive measures. Cognition was assessed at the tau-PET visits. In BioFINDER, only longitudinal data for the MMSE, that is, a screening tool for global cognition, were available as a primary measure of interest for a subset of 59/63 subjects. Cognitive change rates were computed using linear mixed models, with cognition as the dependent variable and time (i.e., years from baseline) as the independent variable, controlling for random slope and intercept,[32] yielding subject-specific slope estimates for annual cognitive changes.

RESEARCH IN CONTEXT

1. **Systematic review**: The *BIN1* rs744373 single nucleotide polymorphism (SNP) is a key genetic risk factor for Alzheimer's disease (AD). Previous studies have suggested that altered BIN1 and *BIN1* rs744373 are associated with tau pathology, and thus AD risk.
2. **Interpretation**: In two independent samples, we show that carriage of the *BIN1* rs744373 risk allele was associated with faster rates of brain-wide tau accumulation, especially at more abnormal amyloid beta (Aβ) levels. Further, *BIN1* rs744373 was associated with faster cognitive decline that was mediated by tau accumulation. Our findings suggest that *BIN1* rs744373 is associated with elevated AD risk via accelerating tau pathology accumulation in the face of abnormal Aβ levels.
3. **Future direction**: By which molecular mechanisms does *BIN1* rs744373 alter BIN1 function and thus enhance AD risk?

2.6 | Statistics

Baseline characteristics were compared between groups (i.e., CN vs. MCI/AD dementia) stratified by *BIN1* risk, using analyses of variance (ANOVAs) for continuous measures and chi-squared tests for categorical measures. Tau-PET SUVRs and CSF Aβ_{42} levels (i.e., in BioFINDER) were log-transformed to approximate a normal distribution. Primary analyses were conducted for global tau-PET SUVRs. Exploratory analyses were conducted for the temporal meta-ROI or early/late AD meta-ROIs.[29] For validation, all analyses were performed separately in ADNI and BioFINDER.

We tested first whether (1) *BIN1* risk was associated with faster tau accumulation and whether (2) *BIN1* risk moderated the association between Aβ and tau accumulation. For (1) we used analyses of covariance (ANCOVAs) to determine *BIN1* rs744373 effects on annual

tau-PET change, controlling for age, sex, education, apolipoprotein E (*APOE*) ε4 status , Aβ levels (i.e., Centiloid in ADNI and $A\beta_{42}$ levels in BioFINDER), diagnosis at baseline, maximum follow-up duration, and baseline tau-PET. This analysis was conducted in the pooled Aβ+/Aβ− sample and in Aβ+ only for exploratory reasons. For (2), we tested the *BIN1* rs744373 x Aβ interaction (i.e., Centiloid in ADNI and CSF $A\beta_{42}$ in BioFINDER) on tau accumulation rates using linear regression controlling for age, sex, education, *APOE* ε4 status, diagnosis at baseline, and maximum follow-up duration. This analysis was conducted again across Aβ+/Aβ− subjects for each sample.

Last, we assessed whether *BIN1* rs744373 was associated with cognitive decline in ADAS13 (primary outcome) or ADNI-MEM and PACC (secondary outcomes) in ADNI or with changes in MMSE (primary outcome) in BioFINDER, and whether these effects were mediated by tau accumulation rates, using causal mediation analyses as implemented in the R-package *mediation* (https://www.rdocumentation.org/packages/mediation/versions/4.5.0). Mediation models were controlled for age, sex, education, Aβ levels, diagnosis, *APOE* ε4 status, maximum follow-up duration, baseline cognition, and baseline tau-PET. Significance and 95% confidence intervals (CI) of mediation effects were determined using 1000 bootstrapping iterations. All analyses were conducted in *R* version 3.6.1. Effect size estimates (i.e., Cohen's $f_{partial}$) were computed for all ANCOVA and regression models using the *effectsize* R-package (https://cran.r-project.org/web/packages/effectsize/index.html).

3 | RESULTS

Sample characteristics stratified by *BIN1* risk and clinical status are shown in Table 1. For clinical status, MCI (ADNI/BioFINDER: n = 59/8) and AD dementia (ADNI/BioFINDER: n = 0/15) groups were labeled as cognitively impaired. The *BIN1* rs744373 risk-allele frequency was 40.2% in ADNI (67/153 subjects) and 49.2% in BioFINDER (31/63 subjects); 86/153 ADNI subjects and 51/63 BioFINDER subjects were Aβ+. There were no differences in Aβ levels (i.e., Centiloid in ADNI and CSF $A\beta_{42}$ in BioFINDER) between *BIN1* rs744373 risk versus reference-allele carriers, as shown by ANCOVAs controlling for age, sex, education, *APOE* ε4 status, and diagnosis (ADNI: $P = .16$; BioFINDER: $P = .34$), suggesting that *BIN1* risk is not associated with Aβ levels. When using baseline tau-PET data, we could replicate the previously reported association between *BIN1* risk-allele carriage and cross-sectionally higher global tau-PET levels in ADNI (Cohen's $f_{partial} = 0.26$, $P = .002$, ANCOVA controlling for age, sex, education, Centiloid, *APOE* ε4, and diagnosis) and BioFINDER (Cohen's $f_{partial} = 0.29$, $P = .032$, ANCOVA controlling for age, sex, education, CFS $A\beta_{42}$, *APOE* ε4, and diagnosis). In a subset of the BioFINDER sample with available global Flutemetamol amyloid-PET data (n = 60), we could confirm higher cross-sectional tau-PET levels, controlling for age, sex, education, global amyloid-PET SUVR, *APOE* ε4, and diagnosis (Cohen's $f_{partial} = 0.30$, $P = .036$).[16] Tau-PET follow-up was 1.59 ± 0.76 years in ADNI and 2.32 ± 0.96 years in BioFINDER. Surface renderings of baseline tau-PET SUVR data are shown in Figure 1. As expected, Aβ+ subjects showed faster global tau accumulation than Aβ−- subjects (ADNI: $P < .001$, Cohen's $f_{partial} = 1.23$, BioFINDER: $P < .001$, Cohen's $f_{partial} = 1.36$), controlling for age, sex, education, *APOE* ε4 status, maximum follow-up time, diagnosis, and baseline global tau levels.

3.1 | BIN1 risk is associated with faster tau accumulation

For our major hypothesis, we found that *BIN1* risk-allele carriers had faster global tau-PET accumulation in ADNI ($P < .001$, Cohen's $f_{partial} = 1.04$, Figure 2A) and BioFINDER ($P < 0.001$, Cohen's $f_{partial} = 0.50$, Figure 2B), controlling for age, sex, education, continuous Aβ levels, *APOE* ε4 status, diagnosis, maximum follow-up time, and baseline global tau levels in the pooled Aβ+/Aβ− group. When tested in Aβ+ only, *BIN1* rs744373 effects on tau accumulation rates were stronger than in the larger Aβ+/Aβ−- group (ADNI: $P < .001$, Cohen's $f_{partial} = 1.26$, Figure 3A; BioFINDER: $P < .001$, Cohen's $f_{partial} = 0.86$, Figure 3B). *BIN1* effects on tau accumulation rates in BioFINDER remained consistent when repeated in the amyloid-PET subsample, that is, controlling for global amyloid-PET instead of CSF Aβ levels (Aβ+/Aβ−-: Cohen's $f_{partial} = 0.53$. < 0.001; Aβ+: Cohen's $f_{partial} = 1.04$, $P < .001$). In region-specific subanalyses, we found congruent *BIN1* risk effects on tau accumulation for the temporal meta ROI (ADNI: $P < .001$, Cohen's $f_{partial} = 0.98$, Figure 2C; BioFINDER: $P < .001$, Cohen's $f_{partial} = 0.74$, Figure 2D) and the early AD meta ROI (ADNI: $P < .001$, Cohen's $f_{partial} = 0.48$, Figure 2E; BioFINDER: $P < .001$, Cohen's $f_{partial} = 0.57$, Figure 2F). For the late meta ROI, *BIN1* risk effects on tau accumulation were only significant in ADNI (ADNI: $P < .001$, Cohen's $f_{partial} = 0.98$, Figure 2G), but not in BioFINDER ($P = .115$, Cohen's $f_{partial} = 0.22$, Figure 2H). Again, *BIN1* rs744373 effects on tau accumulation rates were pronounced in Aβ+ consistently for the temporal meta ROI (ADNI: $P < .001$, Cohen's $f_{partial}$: 1.17, Figure 3C; BioFINDER: $P < .001$, Cohen's $f_{partial} = 1.22$, Figure 3D), the early AD meta ROI (ADNI: $P < .001$, Cohen's $f_{partial} = 0.61$, Figure 3E; BioFINDER: $P < .001$, Cohen's $f_{partial} = 0.92$, Figure 3F) and the late AD meta ROI (ADNI: $P < .001$, Cohen's $f_{partial} = 1.12$, Figure 3G; BioFINDER: $P = .016$, Cohen's $f_{partial} = 0.40$, Figure 3H). Together, *BIN1* rs744373 risk-allele carriage is associated with faster tau accumulation rates, especially in the face of abnormal Aβ levels. In subanalyses stratified by diagnosis and Aβ status, we found consistent significant (i.e., $P < .05$) *BIN1* rs744373 effects on global tau-PET accumulation in all stratified subgroups (i.e., CN, CN Aβ+, MCI, MCI Aβ+) of the ADNI sample. In BioFINDER, significant *BIN1* effects on global tau change (i.e., $P < .05$) were detected in the CN Aβ+ and the cognitively impaired Aβ+ group, but not in the pooled Aβ+/Aβ−- CN or CN Aβ− group (see Table S2 and Figure S1 in supporting information). These findings support the view that *BIN1* effects on tau accumulation are strongest in the face of abnormal Aβ. Group-average tau change rates stratified by *BIN1* risk are presented in Tables S3 and S4 in supporting information for ADNI/BioFINDER.

TABLE 1 Sample characteristics

ADNI (N = 153)	*Cognitively normal BIN1 reference allele (n = 54)*	*Cognitively normal BIN1 risk allele (n = 40)*	*Cognitively impaired BIN1 reference allele (n = 32)*	*Cognitively impaired BIN1 risk allele (n = 27)*	*P-value*
Age	71.2 ± 6.0	71.4 ± 4.7	69.9 ± 7.9	70.5 ± 6.3	.740
Sex (f/m)	30/24	19/21	17/15	9/18	.280
Education	16.7 ± 2.3	17.1 ± 2.3	16.3 ± 2.7	16.2 ± 2.9	.540
ADAS13	11.7 ± 4.8[c,d]	11.7 ± 5.5[c,d]	16.0 ± 6.3[a,b]	16.7 ± 5.8[a,b]	<.001
ADNI-MEM	1.0 ± 0.6[c,d]	1.1 ± 0.6[c,d]	0.6 ± 0.7[a,b]	0.2 ± 0.5[a,b]	<.001
PACC	0.5 ± 2.4[c,d]	0.4 ± 3.5[c,d]	-3.0 ± 3.9[a,b]	-4.4 ± 4.1[a,b]	<.001
Centiloid (M/SD)	33.7 ± 35.9	42.1 ± 40.4	40.7 ± 41+5	50.1 ± 48.9	.390
Amyloid-PET tracer (Flor-betapir/Florbetaben)	36/18	28/12	21/11	21/6	.729
Aβ status (neg./pos.)	26/28	17/23	15/17	9/18	.622
APOE ε4 status (neg./pos.)	30/24	24/16	19/13	11/16	.411
Number of visits	2.4 ± 0.7	2.3 ± 0.5	2.4 ± 0.7	2.4 ± 0.6	.87
Flortaucipir-PET follow-up time in years (M/SD)	1.7 ± 0.8	1.5 ± 0.6	1.6 ± 0.9	1.5 ± 0.8	.77
BioFINDER (N = 63)	***Cognitively normal BIN1 reference allele (n = 21)***	***Cognitively normal BIN1 risk allele (n = 19)***	***Cognitively impaired BIN1 reference allele (n = 11)***	***Cognitively impaired BIN1 risk allele (n = 12)***	***P-value***
Age	75.1 ± 5.4[d]	74.8 ± 5.6	72.5 ± 7.4	68.8 ± 8.6[a]	.047
Sex (f/m)	7/14	11/8	2/9	7/5	.092
Education	12.1 ± 3.8	11.6 ± 4.2	12.5 ± 4.0	11.6 ± 2.3	.927
CDR-SB	0.1 ± 0.4[c,d]	0.03 ± 0.1[c,d]	5.4 ± 5.1[a,b]	5.6 ± 4.4[a,b]	<.001
CSF Aβ42/40	0.08 ± 0.04[d]	0.09 ± 0.04[c,d]	0.05 ± 0.02[b]	0.05 ± 0.02[a,b]	.001
Aβ status (neg./pos.)	5/16	7/12	0/11	0/12	.022
APOE ε4 status (neg./pos.)	13/8	11/8	3/8	4/8	.154
Number of visits	2.1 ± 0.3	2.3 ± 0.5	2.2 ± 0.4	2.2 ± 0.4	.373
Flortaucipir-PET follow-up time in years (M/SD)	2.1 ± 0.6	2.7 ± 1.2	2.3 ± 1.0	2.2 ± 1.0	.235

[a]sig. different from cognitively normal, BIN1 reference allele ($P < .05$).
[b]sig. different from cognitively normal, BIN1 risk allele ($P < .05$).
[c]sig. different from cognitively impaired, BIN1 reference allele ($P < 0.05$).
[d]sig. different from cognitively impaired, BIN1 risk allele ($P < .05$).
[e]The BioFINDER cognitively impaired BIN1 reference allele group included five MCI and six AD dementia patients.
[f]The BioFINDER cognitively impaired BIN1 reference allele group included three MCI and nine AD dementia patients.
Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; ADAS13, Alzheimer's Disease Assessment Scale cognitive subscale; ADNI-MEM, Alzheimer's Disease Neuroimaging Initiative memory composite; *APOE*, apolipoprotein E; CDR-SB, Clinical Dementia Rating, Sum of Boxes; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; PACC, Preclinical Alzheimer Cognitive Composite; PET, positron emission tomography; SD, standard deviation.

3.2 | BIN1 risk moderates the association between baseline Aβ and tau accumulation

We next tested whether *BIN1* risk is associated with accelerated Aβ-related tau accumulation. Specifically, we determined the interaction between *BIN1* rs744373 and Aβ levels (i.e., Centiloid in ADNI and CSF $A\beta_{42}$ in BioFINDER) on global tau accumulation rates in the pooled Aβ+/Aβ−= groups. Using linear regression, we found significant *BIN1* rs744373 by Aβ interactions for ADNI (β/standard error [SE] = 0.42/0.14, $P = .002$, Cohen's $f_{partial} = 0.25$, Figure 4A) and BioFINDER (β/SE = −0.35/0.15, $P = .021$, Cohen's $f_{partial} = 0.30$, Figure 4B), controlling for age, sex, education, *APOE ε4* status, diagnosis, and maximum follow-up time. As illustrated in Figure 3A and B, *BIN1* rs744373 risk-allele carriers showed faster tau accumulation at more abnormal Aβ levels than reference-allele carriers. Results remained consistent in BioFINDER when testing the *BIN1* rs744373 x global amyloid-PET interaction in the subsample with available amyloid-PET (β/SE = 0.31/0.15, $P = .045$, Cohen's $f_{partial} = 0.26$). In region-specific subanalyses, we found congruent *BIN1* rs744373 x Aβ interactions on tau accumulation rates for the temporal meta ROI

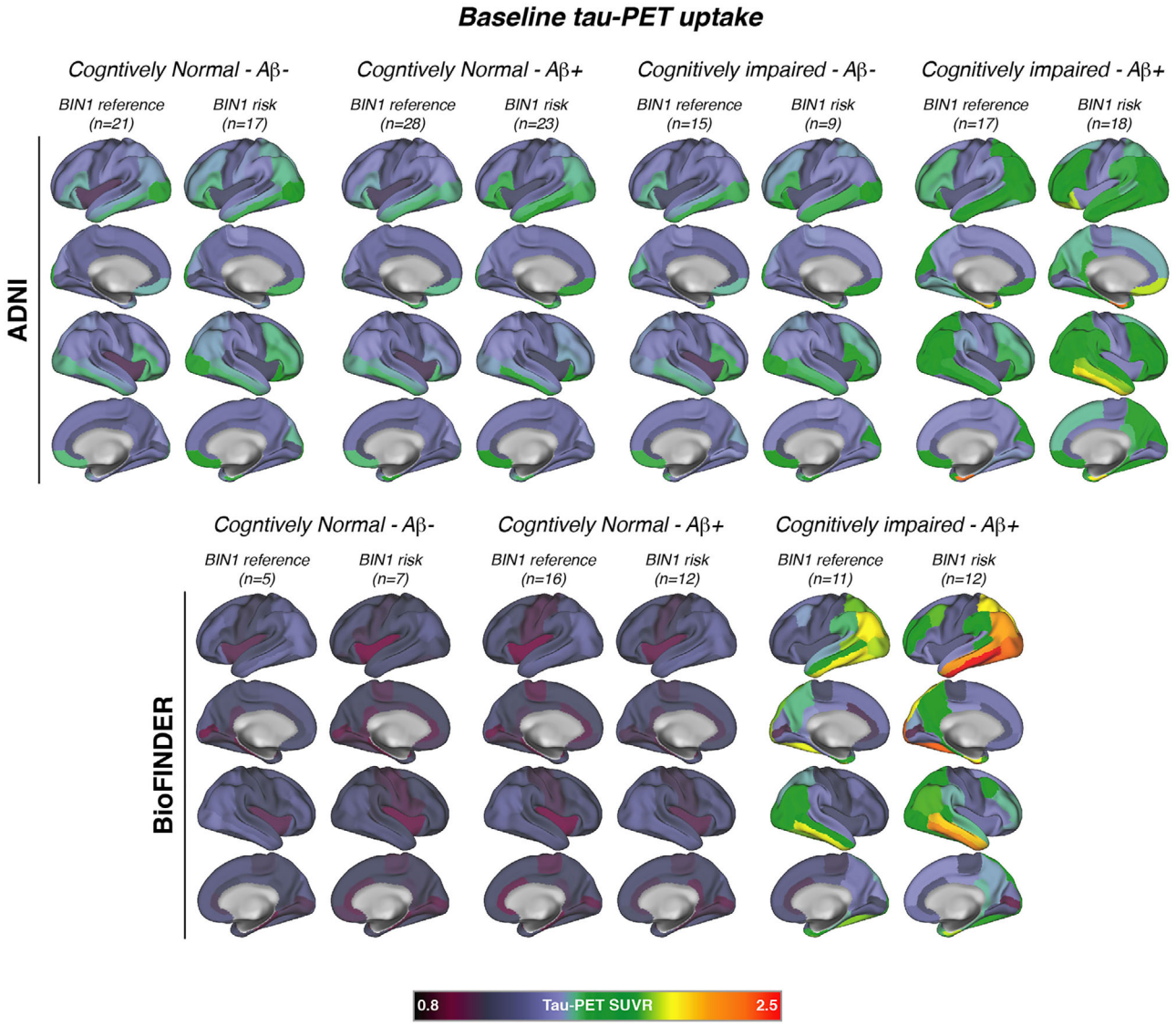

FIGURE 1 Surface renderings of tau-positron emission tomography uptake (i.e., standardized uptake value ratios) at baseline, stratified by diagnosis, amyloid beta (Aβ) status and *BIN1* rs744373 risk-allele carriage

(ADNI: β/SE = 0.40/0.13, P = .003, Cohen's $f_{partial}$ = 0.24, Figure 4C; BioFINDER: β/SE = −0.36/0.14, P = .009, Cohen's $f_{partial}$ = 0.34, Figure 4D), the early AD meta ROI (ADNI: β/SE = 0.38/0.14, P = .006, Cohen's $f_{partial}$ = 0.23, Figure 4E; BioFINDER: β/SE = -0.34/0.15, P = .026, Cohen's $f_{partial}$ = 0.29, Figure 4F), and the late AD meta ROI (ADNI: β/SE = 0.38/0.14, P = .007, Cohen's $f_{partial}$ = 0.22, Figure 4G; BioFINDER: β/SE = −0.37/0.16, P = .025, Cohen's $f_{partial}$ = 0.29, Figure 4H). These results suggest that *BIN1* risk is associated with accelerated Aβ-associated tau accumulation. For exploratory purposes, we repeated the above-described analyses for each FreeSurfer ROI (see Figure S2 in supporting information) at an exploratory ROI-based alpha threshold of 0.05. These analyses show that regional *BIN1* x Aβ interactions were strongest for temporo-parietal and inferior frontal brain regions in ADNI and for the cingulate cortex, insula, and frontal regions in BioFINDER.

3.3 | Effects of BIN1 risk on cognitive decline are mediated by faster tau accumulation

Last, we tested whether *BIN1* risk was associated with faster cognitive decline, and whether this association was mediated by faster tau accumulation. In ADNI, *BIN1* rs744373 risk-allele carriers showed faster cognitive decline, consistently for the primary outcome ADAS13 (P = .031, Cohen's $f_{partial}$ = 0.18, Figure 5A), and for the secondary outcomes ADNI-MEM (P = .026, Cohen's $f_{partial}$ = 0.19, Figure 5B) and PACC (P = .008, Cohen's $f_{partial}$ = 0.23, Figure 5C; ANCOVAs controlling for age, sex, education, *APOE* ε4 status, maximum follow-up time, Centiloids, diagnosis, baseline tau, and baseline cognition). In BioFINDER, no significant (P > 0.05) *BIN1*-related differences in longitudinal MMSE changes were detected, potentially due to ceiling effects in this mostly cognitively normal cohort. Thus, all remaining

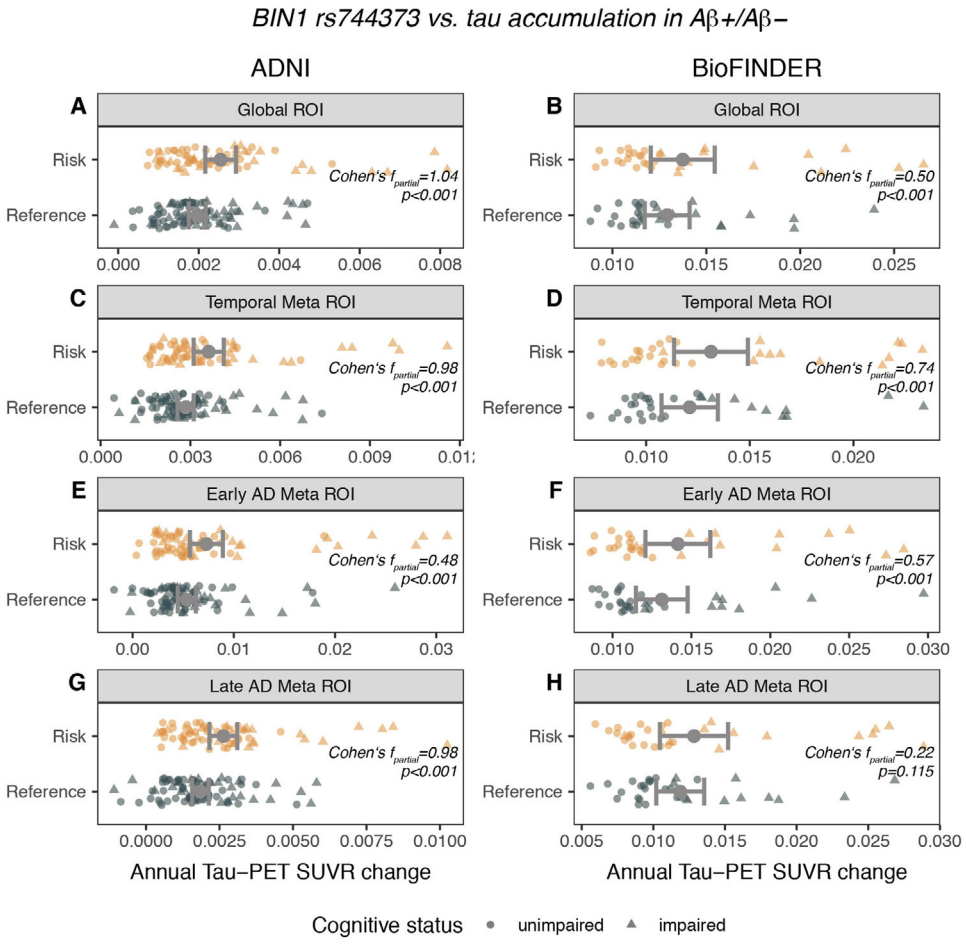

FIGURE 2 Differences in tau accumulation rates between *BIN1* rs744373 risk-allele and reference-allele subjects for Alzheimer's Disease Neuroimaging Initiative (ADNI; A, C, E, G) and Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably (BioFINDER; B, D, F, H) for the pooled amyloid beta (Aβ)+/Aβ− sample. *P*-values indicate significance of group differences and were derived from analyses of covariance controlling for age, sex, education, apolipoprotein E (*APOE*) ε4 status, Aβ levels (i.e., Centiloid in ADNI and cerebrospinal fluid $A\beta_{42}$ in BioFINDER), maximum follow-up duration, diagnosis, and baseline tau levels of the respective regions of interest (ROIs). The gray dots and whiskers represent the mean plus/minus standard error. AD, Alzheimer's disease; PET, positron emission tomography; SUVR, standardized uptake value ratio

mediation analyses were restricted to ADNI subjects. Regression analyses in ADNI showed further that annual cognitive change rates were associated with global tau accumulation rates in all cognitive tests (ADAS13: β/SE = 0.20/0.07, P = .005, Cohen's $f_{partial}$ = 0.23, Figure 5D; ADNI-MEM: β/SE = −0.09/0.03, P = .004, Cohen's $f_{partial}$ = 0.23, Figure 5E; PACC: β/SE = −0.18/0.05, P < .001, Cohen's $f_{partial}$ = 0.29, Figure 5F). In bootstrapped mediation analyses (see Figure 5G), we found that *BIN1* risk effects on cognitive decline were mediated by faster global tau accumulation for ADAS13 (β = 0.084 [95% CI: 0.011, 0.19], P = .016, proportion mediated = 34.8%), ADNI-MEM (β = −0.037 [95% CI: −0.078, −0.010], P = .010, proportion mediated = 46.6%) and PACC scores (β = −0.071 [95% CI: −0.145, −0.020], P = .002, proportion mediated = 57.5%). All mediation effects were full mediations, because bootstrapped average direct effects of *BIN1* risk on cognitive changes were non-significant for all models when the mediator was included (all P > 0.05, see Figure 5G). This suggests that *BIN1*-risk for cognitive decline is driven by faster tau accumulation rates.

4 | DISCUSSION

In this independently validated longitudinal tau-PET study, we assessed whether *BIN1* rs744373, that is, a key genetic risk factor for late-onset AD,[2–5] is associated with faster Aβ-related tau accumulation thereby increasing AD risk. In two independent samples of cognitively normal and cognitively impaired elderly subjects, we observed faster tau accumulation in rs744373 risk-allele versus reference-allele carriers, and this effect was particularly pronounced in Aβ+. In contrast, *BIN1* risk was not related to baseline Aβ levels. Higher baseline Aβ levels were associated with faster subsequent tau accumulation, yet this association was stronger in *BIN1* rs744373 risk-allele versus reference-allele carriers. That is, per unit increase of Aβ, the increase in tau-PET is higher in *BIN1* risk-allele versus reference-allele carriers, suggesting that *BIN1* effects on tau act downstream of Aβ. In ADNI, we observed, further, that associations between *BIN1* risk and longitudinal decline in global cognition, memory, and a preclinical

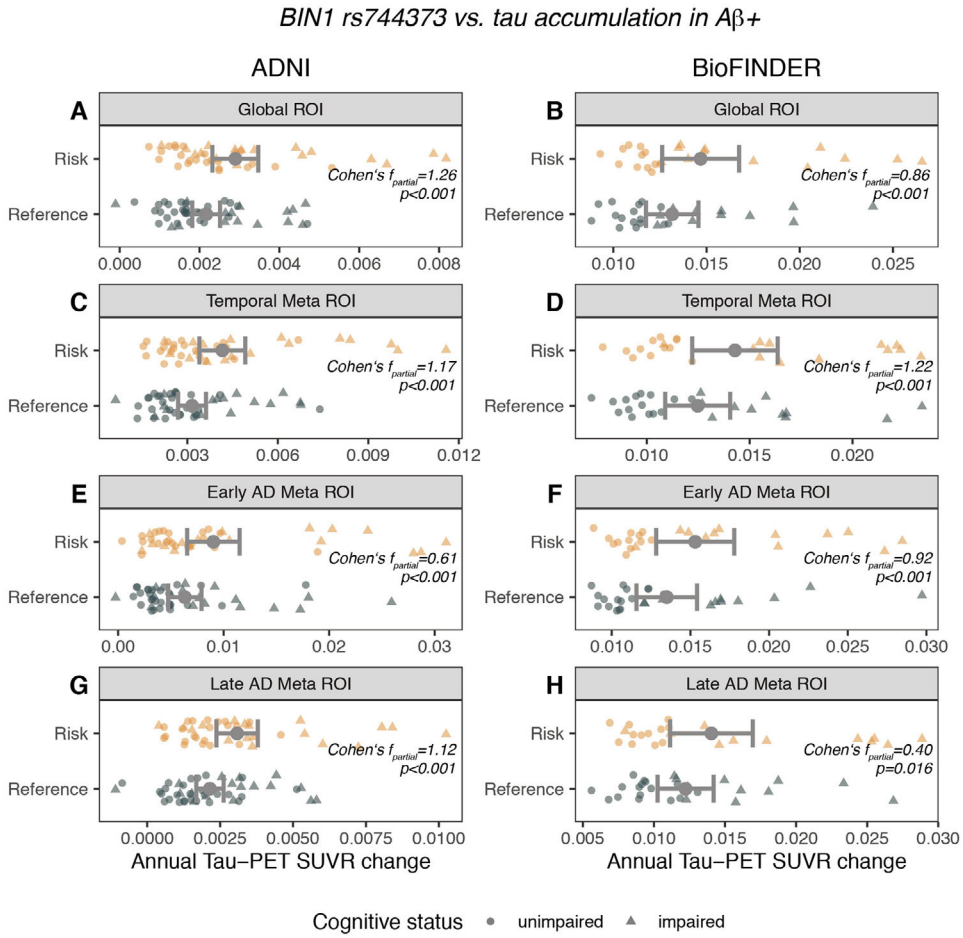

FIGURE 3 Differences in tau accumulation rates in amyloid beta (Aβ)+ BIN1 risk- versus reference-allele carriers for Alzheimer's Disease Neuroimaging Initiative (ADNI; A, C, E, G) and Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably (BioFINDER; B, D, F, H). *P*-values indicate significance of group differences and were derived from analyses of covariance controlling for age, sex, education, apolipoprotein E (*APOE*) ε4 status, Aβ levels (i.e., Centiloid in ADNI and cerebrospinal fluid $A\beta_{42}$ in BioFINDER), maximum follow-up duration, diagnosis and baseline tau levels of the respective regions of interest (ROIs). The gray dots and whiskers represent the mean plus/minus standard error. AD, Alzheimer's disease; PET, positron emission tomography; SUVR, standardized uptake value ratio

AD cognitive composite[35] were mediated by faster tau accumulation. Together, we demonstrate that *BIN1* risk is associated with accelerated Aβ-associated tau accumulation, thereby increasing the risk for cognitive decline. These results provide an important contribution to understanding how *BIN1* relates to AD pathogenesis.[2–4]

First, we show faster tau accumulation in *BIN1* rs744373 risk- versus reference-allele carriers, while controlling for baseline levels of Aβ, tau-PET, *APOE* ε4, and other confounds. Faster tau accumulation in *BIN1* rs744373 risk-allele carriers was consistently detected across different pre-defined ROIs capturing whole-brain, temporal, or AD stage-specific tau accumulation.[29,30] This brain-wide result pattern is consistent with our cross-sectional work,[16] suggesting global rather than spatially restricted *BIN1* risk effects on tau. This supports the view that BIN1 is generally associated with tau accumulation rather than region-specific vulnerability. In contrast, we did not detect *BIN1* effects on Aβ levels. This is a critical extension of previous cross-sectional work relating *BIN1* risk-SNPs including rs744373 to elevated brain-wide tau-PET,[16] CSF p-tau,[8,17] *post mortem* tau,[15] but not Aβ pathology. Accelerated tau accumulation at a given level of Aβ may thus result in previous reports of cross-sectionally elevated tau levels in *BIN1* risk-allele carriers.[8,15–17] While our initial findings on *BIN1* rs744373 versus tau accumulation were obtained in pooled Aβ−/Aβ+ groups using Aβ levels as a covariate, subgroup analyses revealed strongest effects in Aβ+ subjects, highlighting pronounced *BIN1* risk for tau accumulation at abnormally elevated Aβ levels. This pattern was also observed when exploratorily stratifying the analyses by diagnostic groups, where strongest *BIN1* risk effects were found in both cognitively normal Aβ+ and cognitively impaired Aβ+ groups, while effects were less strong for the mixed Aβ+/Aβ− CN group of the ADNI sample and non-significant for the mixed Aβ+/Aβ− CN group in BioFINDER. This result pattern is further supported by a significant *BIN1* rs744373 by Aβ interaction in both samples, in which tau accumulation was stronger in *BIN1* risk-allele versus reference-allele carriers at a given level of Aβ. Strikingly, this interaction was consistently found despite using different assays for Aβ across samples (i.e., PET vs. CSF). This suggests that fibrillary Aβ deposition may be an important starting condition for *BIN1* risk to

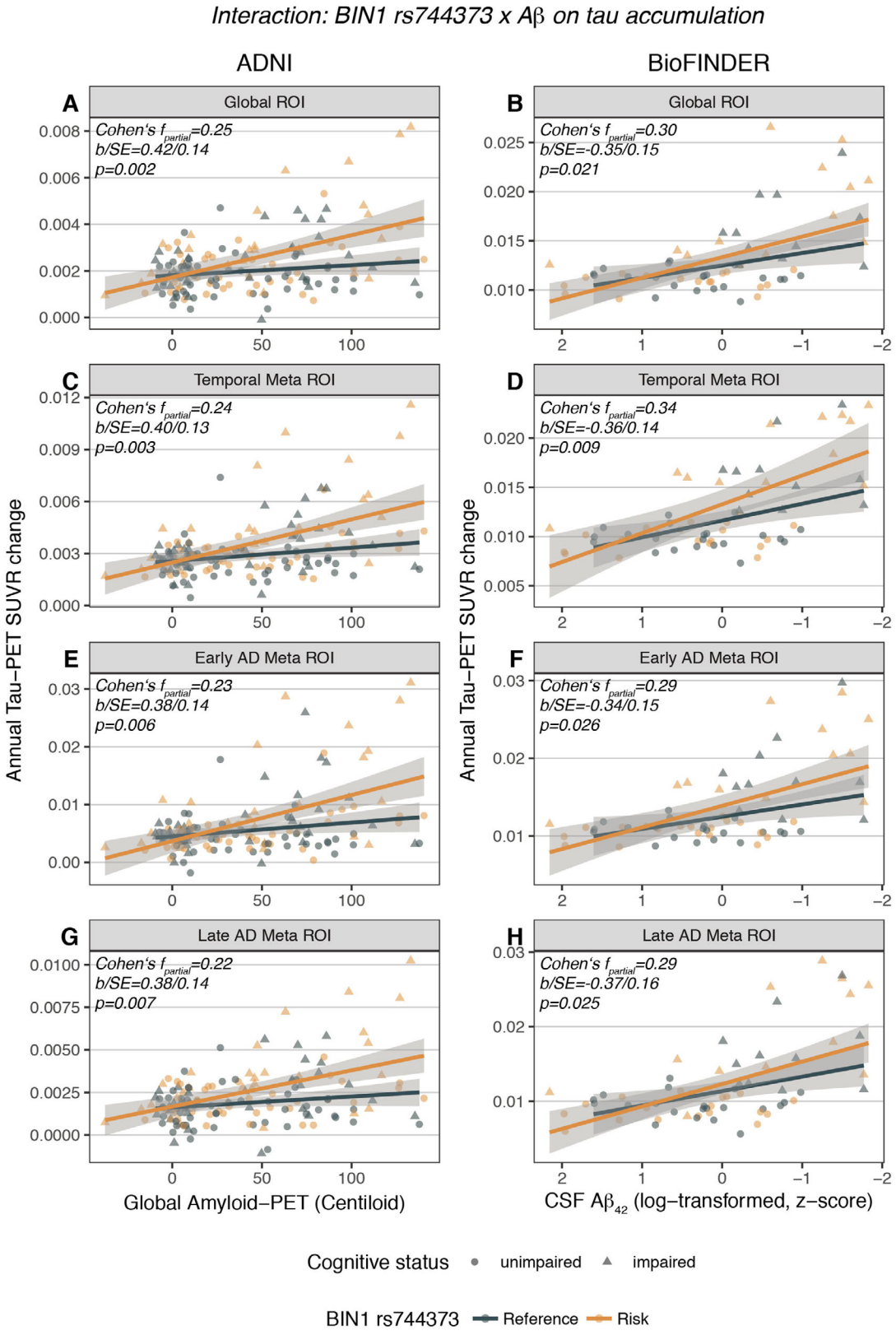

FIGURE 4 Interaction effects for the BIN1 rs744373 by amyloid beta (Aβ) interaction on tau accumulation rates for Alzheimer's Disease Neuroimaging Initiative (ADNI; A, C, E, G) and Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably (BioFINDER; B, D, F, H). *P*-values indicate significance of interaction effects and were derived from linear regression models controlling for age, sex, education, apolipoprotein E (*APOE*) ε4 status, maximum follow-up duration, diagnosis, and baseline tau levels of the respective regions of interest (ROIs). Gray shaded areas indicate standard errors of the regression bars. Note that the x-axis in for cerebrospinal fluid $A\beta_{42}$ in BioFINDER has been swapped for visualization purposes. AD, Alzheimer's disease; PET, positron emission tomography; SUVR, standardized uptake value ratio

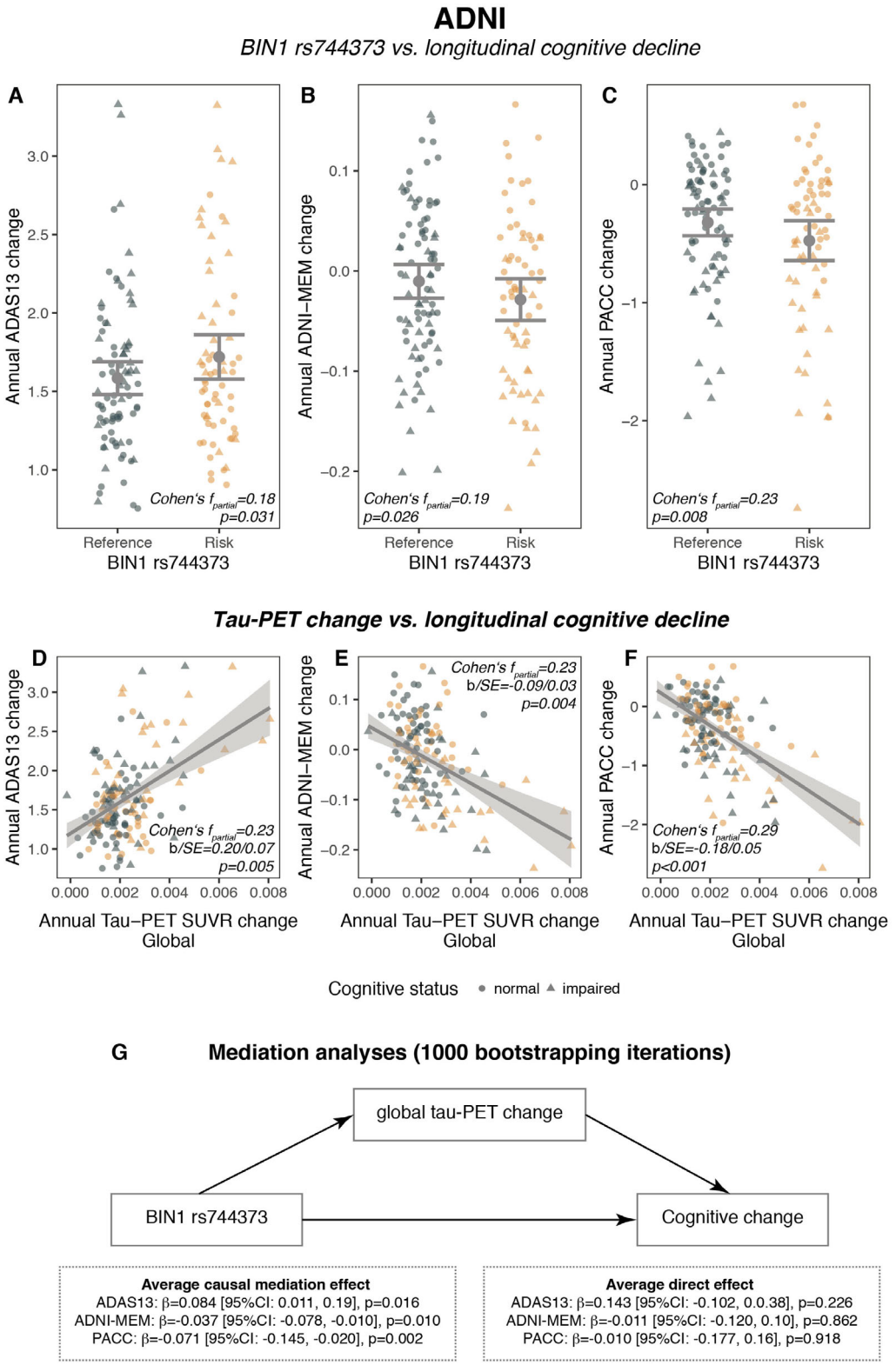

FIGURE 5 A-C, Effects of BIN1 rs744373 risk- versus reference-allele carriage on annual cognitive change rates. *P*-values indicate analysis of covariance (ANCOVA)-derived group differences. D-F, Associations between global tau-positron emission tomography (PET) change and change in cognition. *P*-values were derived from linear regression. G, Mediation analyses to test whether effects of BIN1 rs744373 risk-allele carriage on cognitive decline are mediated via global tau change rates. Parameter estimates are shown for the average causal mediation effect as well as the average direct effect. Confidence intervals and *P*-values for the mediation analyses were determined on 1000 bootstrapped samples. All models (i.e., ANCOVAs, regression, mediation) were controlled for age, sex, education, amyloid beta (Aβ) levels (Centiloid), baseline tau, diagnosis, apolipoprotein E (*APOE*) ε4 status, maximum follow-up duration, and baseline cognition. ADAS13, Alzheimer's Disease Assessment Scale cognitive subscale; ADNI-MEM, Alzheimer's Disease Neuroimaging Initiative memory composite; PACC, Preclinical Alzheimer Cognitive Composite

accelerate tau accumulation, which is congruent with GWAS evidence linking *BIN1* risk SNPs to AD,[2–4] that is, an Aβ-associated tauopathy,[1] rather than to other primary tauopathies.[36]

In AD, Aβ accumulation is assumed to precede[37] and initiate tau spreading.[1,38] Pre-clinical[39] and clinical studies[40,41] have shown that tau spreads across neuronal connections in an activity-dependent manner.[42] Aβ deposition has been shown to induce neuronal hyperexcitability,[43] which is associated with increased tau secretion and assumed to be a critical mechanism that drives tau spreading.[44] Supporting this, recent pre-clinical work reported that Aβ-induced neuronal hyperexcitability enhances tau spreading across connected neurons.[45] For BIN1, pre-clinical studies revealed that BIN1 overexpression promotes the secretion of tau-containing exosomes from neurons,[8] that is, a critical tau transmission route.[46] Similarly, exosomes containing both hyperphosphorylated tau and BIN1 have been detected in the CSF of AD patients,[8] and BIN1 has been shown to modulate clathrin-mediated endocytosis of tau-containing vesicles.[9] Thus, BIN1 may act downstream of Aβ in the neuronal secretion and uptake of tau-containing vesicles thereby modulating tau spreading. This effect may be particularly pronounced in the face of Aβ-related neuronal hyperexcitability and tau secretion that enhance tau spreading.[45] In addition, BIN1 overexpression has been shown to further increase neuronal excitability,[10] which may add to Aβ-associated activity-dependent tau spreading in AD.[42] Consequently, it will be critical to characterize how genetic *BIN1* risk relates to BIN1 protein function, neuronal excitability, and tau spreading. Preliminary work has related rs744373 risk-allele carriage to elevated *BIN1* mRNA expression in brain tissue from epilepsy patients,[47] and similarly, a *post mortem* study in AD has linked another *BIN1* risk-SNP 1 kb upstream of rs744373 to elevated *BIN1* mRNA expression.[15] It is thus possible that *BIN1* risk modulates BIN1 expression and tau pathology, yet, this remains to be elucidated by studying molecular/cellular consequences of genetic *BIN1* risk. Here, it will be of particular importance to clarify further whether the *BIN1* rs744373 SNP, which is in a non-coding region, is causally linked to increased tau pathology or whether rs744373 is tagging a functional variant in proximity. A better characterization of the molecular *BIN1* rs744373 consequences and associated cellular mechanisms holds high potential to increase our understanding in the development of tau pathology.

Last, we report that *BIN1* risk is associated with faster cognitive decline, mediated by faster tau accumulation in ADNI. These findings extend previous reports of *BIN1* risk being associated with poorer memory[16,48] and faster global cognitive decline,[49] providing further evidence that *BIN1* rs744373 contributes to AD dementia risk via tau pathology. It must be considered though that the association between tau accumulation and cognitive decline remains correlational in nature and was restricted to ADNI, because there was no association between *BIN1* risk and MMSE changes in the smaller and mostly cognitively normal BioFINDER group, hence mediation analyses were not possible. This is potentially associated with the limited sensitivity of the MMSE to detect subtle longitudinal cognitive changes in the mostly cognitively normal subjects of the BioFINDER sample. Still, our results provide a putative pathomechanistic link between *BIN1* rs744373 and GWAS-identified risk for AD dementia.[2–4]

As a cautionary note, we highlight that multiple *BIN1* SNPs are associated with elevated AD risk.[5] *BIN1* rs744373 has been, however, robustly associated with AD risk,[5] hence we specifically focused on this risk SNP. Still, other *BIN1* SNPs have been associated with *post mortem*-assessed tau pathology[15] and AD dementia, hence other *BIN1* risk SNPs may be involved in tau pathology as well.[5] Further, we used Flortaucipir tau-PET, which shows considerable off-target binding in subcortical regions and choroid plexus.[31] While these regions were excluded, we caution that our findings await replication using second-generation tau-PET data, with a better off-target binding profile. In addition, the current study includes only CSF/PET proxies for late-stage fibrillar Aβ. Previous preclinical studies have shown, however, that BIN1 is involved in intracellular amyloid precursor protein trafficking, thus our findings do not contradict BIN1 involvement in early phases of the amyloid pathway.[50] We'd like to also caution that the replication sample is relatively small (N = 63), hence we explicitly encourage replication in larger cohorts. Larger cohorts with a reasonable number of homozygous *BIN1* rs744373 risk-allele carriers will also allow to assess potential gene-dose dependent *BIN1* rs744373 effects on tau accumulation.

Together, this independently validated study shows that *BIN1* rs744373 is associated with faster tau accumulation, particularly in the face of abnormal Aβ, thereby mediating faster cognitive decline. These findings provide a link between GWAS-identified AD risk and AD progression. Here, it will be of particular interest for future studies to assess how *BIN1* effects on tau pathology compare to other established genetic AD risk factors (e.g., *APOE*) and whether there are synergistic effects between Aβ-associated risk factors and *BIN1*. Because tau is a key driver of cognitive decline, we encourage future studies to characterize the specific molecular mechanisms linking *BIN1* risk to tau pathology, which may yield novel targets for interventions. Modulating tau pathology will likely become a critical focus for AD intervention research in addition to Aβ-modulating trials.

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CONFLICTS OF INTEREST

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REFERENCES

1. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med*. 2016;8:595-608.
2. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Abeta, tau, immunity and lipid processing. *Nat Genet*. 2019;51:414-430.
3. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat Genet*. 2019;51:404-413.
4. Seshadri S, Fitzpatrick AL, Ikram MA, et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA*. 2010;303:1832-1840.
5. Tan MS, Yu JT, Tan L. Bridging integrator 1 (BIN1): form, function, and Alzheimer's disease. *Trends Mol Med*. 2013;19:594-603.
6. Butler MH, David C, Ochoa GC, et al. Amphiphysin II (SH3P9; BIN1), a member of the amphiphysin/Rvs family, is concentrated in the cortical cytomatrix of axon initial segments and nodes of ranvier in brain and around T tubules in skeletal muscle. *J Cell Biol*. 1997;137:1355-1367.
7. Meunier B, Quaranta M, Daviet L, Hatzoglou A, Leprince C. The membrane-tubulating potential of amphiphysin 2/BIN1 is dependent on the microtubule-binding cytoplasmic linker protein 170 (CLIP-170). *Eur J Cell Biol*. 2009;88:91-102.
8. Crotti A, Sait HR, McAvoy KM, et al. BIN1 favors the spreading of Tau via extracellular vesicles. *Sci Rep*. 2019;9:9477.
9. Calafate S, Flavin W, Verstreken P, Moechars D. Loss of Bin1 Promotes the Propagation of Tau Pathology. *Cell Rep*. 2016;17:931-940.
10. De Rossi P, Nomura T, Andrew RJ, et al. Neuronal BIN1 Regulates Presynaptic Neurotransmitter Release and Memory Consolidation. *Cell Rep*. 2020;30:3520-3535.e7.
11. Voskobiynyk Y, Roth JR, Cochran JN, et al. Alzheimer's disease risk gene BIN1 induces Tau-dependent network hyperexcitability. *Elife*. 2020;9:e57354.
12. McAvoy KM, Rajamohamed Sait H, Marsh G, et al. Cell-autonomous and non-cell autonomous effects of neuronal BIN1 loss in vivo. *PLoS One*. 2019;14:e0220125.
13. Glennon EB, Lau DH, Gabriele RMC, et al. Bridging Integrator-1 protein loss in Alzheimer's disease promotes synaptic tau accumulation and disrupts tau release. *Brain Commun*. 2020;2.
14. Taga M, Petyuk VA, White C, et al. BIN1 protein isoforms are differentially expressed in astrocytes, neurons, and microglia: neuronal and astrocyte BIN1 are implicated in tau pathology. *Mol Neurodegener*. 2020;15:44.
15. Chapuis J, Hansmannel F, Gistelinck M, et al. Increased expression of BIN1 mediates Alzheimer genetic risk by modulating tau pathology. *Mol Psychiatry*. 2013;18:1225-1234.
16. Franzmeier N, Rubinski A, Neitzel J, Ewers M. Alzheimer's Disease Neuroimaging I. The BIN1 rs744373 SNP is associated with increased tau-PET levels and impaired memory. *Nat Commun*. 2019;10:1766.
17. Wang HF, Wan Y, Hao XK, et al. Bridging Integrator 1 (BIN1) Genotypes Mediate Alzheimer's Disease Risk by Altering Neuronal Degeneration. *J Alzheimers Dis*. 2016;52:179-190.
18. La Joie R, Visani AV, Baker SL, et al. Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. *Sci Transl Med*. 2020:12.
19. Hanseeuw BJ, Betensky RA, Jacobs HIL, et al. Association of amyloid and tau with cognition in preclinical Alzheimer disease: a longitudinal study. *JAMA Neurol*. 2019;76:915-924.
20. Holler CJ, Davis PR, Beckett TL, et al. Bridging integrator 1 (BIN1) protein expression increases in the Alzheimer's disease brain and correlates with neurofibrillary tangle pathology. *J Alzheimers Dis*. 2014;42:1221-1227.
21. Saykin AJ, Shen L, Yao X, et al. Genetic studies of quantitative MCI and AD phenotypes in ADNI: progress, opportunities, and plans. *Alzheimers Dement*. 2015;11:792-814.
22. Landau SM, Thomas BA, Thurfjell L, et al. Amyloid PET imaging in Alzheimer's disease: a comparison of three radiotracers. *Eur J Nucl Med Mol Imaging*. 2014;41:1398-1407.
23. Klunk WE, Koeppe RA, Price JC, et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement*. 2015;11:1-15.e1-.
24. Janelidze S, Zetterberg H, Mattsson N, et al. CSF Abeta42/Abeta40 and Abeta42/Abeta38 ratios: better diagnostic markers of Alzheimer disease. *Ann Clin Transl Neurol*. 2016;3:154-165.
25. Mattsson N, Smith R, Strandberg O, et al. Comparing (18)F-AV-1451 with CSF t-tau and p-tau for diagnosis of Alzheimer disease. *Neurology*. 2018;90:e388. e95.
26. Desikan RS, Segonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31:968-980.
27. Maass A, Landau S, Baker SL, Horng A, et al. Comparison of multiple tau-PET measures as biomarkers in aging and Alzheimer's disease. *Neuroimage*. 2017;157:448-463.
28. Baker SL, Maass A, Jagust WJ. Considerations and code for partial volume correcting [(18)F]-AV-1451 tau PET data. *Data Brief*. 2017;15:648-657.
29. Jack CR Jr, Wiste HJ, Schwarz CG, et al. Longitudinal tau PET in ageing and Alzheimer's disease. *Brain*. 2018;141:1517-1528.
30. Leuzy A, Smith R, Ossenkoppele R, et al. Diagnostic performance of RO948 F 18 tau positron emission tomography in the differentiation of Alzheimer Disease From Other Neurodegenerative Disorders. *JAMA Neurol*. 2020;77:955-965.
31. Lemoine L, Leuzy A, Chiotis K, Rodriguez-Vieitez E, Nordberg A. Tau positron emission tomography imaging in tauopathies: the added hurdle of off-target binding. *Alzheimers Dement (Amst)*. 2018;10:232-236.

32. Preische O, Schultz SA, Apel A, et al. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. *Nat Med*. 2019;25:277-283.
33. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11(suppl 2):S13-S21.
34. Crane PK, Carle A, Gibbons LE, et al. Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Brain Imaging Behav*. 2012;6:502-516.
35. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol*. 2014;71:961-970.
36. Chen JA, Chen Z, Won H, et al. Joint genome-wide association study of progressive supranuclear palsy identifies novel susceptibility loci and genetic correlation to neurodegenerative diseases. *Mol Neurodegener*. 2018;13:41.
37. Jack CR Jr, Holtzman DM. Biomarker modeling of Alzheimer's disease. *Neuron*. 2013;80:1347-1358.
38. Shin WS, Di J, Cao Q, Li B, et al. Amyloid beta-protein oligomers promote the uptake of tau fibril seeds potentiating intracellular tau aggregation. *Alzheimers Res Ther*. 2019;11:86.
39. Calafate S, Buist A, Miskiewicz K, et al. Synaptic contacts enhance cell-to-cell tau pathology propagation. *Cell Rep*. 2015;11:1176-1183.
40. Franzmeier N, Neitzel J, Rubinski A, et al. Functional brain architecture is associated with the rate of tau accumulation in Alzheimer's disease. *Nat Commun*. 2020;11:347.
41. Franzmeier N, Rubinski A, Neitzel J, et al. Functional connectivity associated with tau levels in ageing, Alzheimer's, and small vessel disease. *Brain*. 2019;142:1093-1107.
42. Wu JW, Hussaini SA, Bastille IM, et al. Neuronal activity enhances tau propagation and tau pathology in vivo. *Nat Neurosci*. 2016;19:1085-1092.
43. Busche MA, Eichhoff G, Adelsberger H, et al. Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. *Science*. 2008;321:1686-1689.
44. Pooler AM, Phillips EC, Lau DH, Noble W, Hanger DP. Physiological release of endogenous tau is stimulated by neuronal activity. *EMBO Rep*. 2013;14:389-394.
45. Rodriguez GA, Barrett GM, Duff KE, Hussaini SA. Chemogenetic attenuation of neuronal activity in the entorhinal cortex reduces Abeta and tau pathology in the hippocampus. *PLoS Biol*. 2020;18:e3000851.
46. Wang Y, Balaji V, Kaniyappan S, et al. The release and trans-synaptic transmission of Tau via exosomes. *Mol Neurodegener*. 2017;12:5.
47. Bungenberg J, Surano N, Grote A, et al. Gene expression variance in hippocampal tissue of temporal lobe epilepsy patients corresponds to differential memory performance. *Neurobiol Dis*. 2016;86:121-130.
48. Barral S, Bird T, Goate A, et al. Genotype patterns at PICALM, CR1, BIN1, CLU, and APOE genes are associated with episodic memory. *Neurology*. 2012;78:1464-1471.
49. Vivot A, Glymour MM, Tzourio C, Amouyel P, Chene G, Dufouil C. Association of Alzheimer's related genotypes with cognitive decline in multiple domains: results from the Three-City Dijon study. *Mol Psychiatry*. 2015;20:1173-1178.
50. Ubelmann F, Burrinha T, Salavessa L, et al. Bin1 and CD2AP polarise the endocytic generation of beta-amyloid. *EMBO Rep*. 2017;18:102-122.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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