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# *DAT1* and *BDNF* polymorphisms interact to predict Aβ and tau pathology

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ABSTRACT

Previous work has associated polymorphisms in the dopamine transporter gene (rs6347 in *DAT1/SLC6A3*) and brain derived neurotrophic factor gene (Val66Met in *BDNF*) with atrophy and memory decline. However, it is unclear whether these polymorphisms relate to atrophy and cognition through associations with Alzheimer's disease pathology. We tested for effects of *DAT1* and *BDNF* polymorphisms on cross-sectional and longitudinal β-amyloid (Aβ) and tau pathology (measured with positron emission tomography (PET)), hippocampal volume, and cognition. We analyzed a sample of cognitively normal older adults (cross-sectional n = 321) from the Alzheimer's Disease Neuroimaging Initiative (ADNI). *DAT1* and *BDNF* interacted to predict Aβ-PET, tau-PET, and hippocampal atrophy. Carriers of both "non-boptimal" *DAT1* C and *BDNF* Met alleles demonstrated greater pathology and atrophy. Our findings provide novel links between dopamine and neurotrophic factor genes and AD pathology, consistent with previous research implicating these variants in greater risk for developing AD.

## 1. Introduction

β-amyloid (Aβ) pathology is a central component of Alzheimer's disease (AD) and has been associated with a cascade of events including hyperphosphorylated tau proteins, neurodegeneration, and cognitive deficits (Hardy and Higgins, 1992). Identifying factors that influence pathological disease progression will be critical for understanding individual differences in AD risk and identifying candidate targets for intervention (Karran et al., 2011). Dysfunctional neurotransmitter activity is strongly implicated in AD, with most research focused on acetylcholine and norepinephrine (Berry and Harrison, 2023; Ciampa et al., 2022; Hampel et al., 2018; Jacobs et al., 2021). However, emerging lines of evidence identify the suboptimal dopamine function observed in AD (Pan et al., 2019) as a potential exacerbator of AD pathophysiology. In AD models, declines in dopamine signaling are associated with impaired memory and hippocampal plasticity (Nobili et al., 2017). Notably, dopamine agonists have been shown to reverse Aβ-mediated reductions in hippocampal plasticity (Yuan Xiang et al., 2016). Dopamine may also exert protective effects against Aβ-induced neurotoxicity as in vivo studies demonstrate dopamine and its metabolites can disassemble Aβ fibrils and inhibit Aβ aggregation (Li et al., 2004).

The dopamine transporter (DAT) protein is a key regulator of dopamine signaling (Jaber et al., 1997), as it controls extracellular dopamine levels through reuptake into the presynaptic neuron (Vaughan and Foster, 2013). A single nucleotide polymorphism (SNP; rs6347) in the DAT gene (*DAT1/SLC6A3*; T > C substitution, minor allele frequency ~.27; Phan et al., 2020) is located on chromosome 5 in exon 9. The minor C allele of rs6347 occurs at a higher frequency in AD patients compared with healthy controls and is linked to faster ventricular expansion and lower scores on the Mini Mental State Exam (MMSE) in both healthy controls and clinically-diagnosed AD patients

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(Roussotte et al., 2015). Further, the C allele is associated with more severe dementia compared with the T allele in patients with clinical diagnoses of AD (Lin et al., 2012). However, cognitive decline and atrophy may be present in aging absent of pathology or in other forms of dementia. It is unclear whether rs6347 is related to cognition and atrophy through links with AD pathology or through other pathways that are not associated with AD.

Brain-derived neurotrophic factor (BDNF) is a growth factor critical for the development and maintenance of neurons (Gorski et al., 2003). BDNF is most highly concentrated in the hippocampus (Yan et al., 1997) and is richly expressed in the dopaminergic midbrain and striatal regions (Fenner et al., 2014; Seroogy et al., 1994). In AD, Aβ impairs BDNF signaling (Jerónimo-Santos et al., 2015), and lower BDNF levels are related to greater tau burden in autopsy studies (Ginsberg et al., 2019). One polymorphism in the *BDNF* gene (Val66Met, rs6265) has been repeatedly associated with AD (Franzmeier et al., 2021; Lim et al., 2013). Val66Met is a SNP located on chromosome 11 (minor allele frequency =.19; Phan et al., 2020) that results in a methionine (Met) amino acid substitution for valine (Val) at codon 66. Met carriers who are also Aβ positive exhibit more severe declines in hippocampal volume and episodic memory compared with Val/Val carriers who are Aβ positive and individuals who are Aβ negative with any *BDNF* genotype (Lim et al., 2013). This suggests that sub-optimal *BDNF* function may exacerbate the negative effects of AD pathology. It is worth noting that there are substantial inconsistencies in reported *BDNF* Val66Met results, including null effects (Ji et al., 2015) and findings suggesting the Val/Val allele is implicated in AD (Voineskos et al., 2011). We expand upon these inconsistencies in the Discussion. The mechanisms underlying *BDNF*'s impact on AD trajectories is an area of active research, though evidence suggests *BDNF* may support resistance to neurodegeneration, in part, through modification of dopamine signaling (Meisner et al., 2008; Zhu et al., 2015).

While *BDNF* Val66Met is a contributor to AD polygenic risk scores (Porter et al., 2018), dopamine polymorphisms are rarely considered despite links between dementia and *DAT1* rs6347 (Roussotte et al., 2015). Neither *BDNF* nor *DAT1* polymorphisms have been identified in genome-wide association studies of AD, and likely have small effects independently. There is considerable functional interaction between BDNF and the dopamine system as most mesencephalic dopamine-producing neurons express the high affinity BDNF receptor tyrosine kinase receptor B (TrkB; Numan and Seroogy, 1999). Relevant to cognition, studies in rodent models have defined conjoint effects of BDNF and dopamine signaling on memory (Rossato et al., 2009). In humans, effects of dopamine genetic polymorphisms on episodic memory depend on *BDNF* genotype in aging (Papenberg et al., 2019), and *DAT1***BDNF* interactions predict trait neuroticism, a well-known risk--factor for dementia (Hünnerkopf et al., 2007). Together, these studies motivate further examination of the interactive effects of *BDNF* and *DAT1* on AD.

The goal of the current study is to establish relationships among AD pathology, atrophy, cognition, and genetic polymorphisms that have previously been implicated in risk for AD but lack direct links to Aβ and tau pathology. We focused our analyses on a large sample of cognitively normal older adults, as studying healthy individuals is key to understanding the relative risk for developing AD and many interventions target the pre-clinical stage of AD (van Bokhoven et al., 2021). We first hypothesized that *DAT1* rs6347 and *BDNF* Val66Met would relate to Aβ and tau pathology such that individuals carrying one or more "non-optimal" variants (i.e., *DAT1* CC and *BDNF* Met) would exhibit higher PET measures of pathology. Second, we hypothesized that carriers of non-optimal variants would display lower hippocampal volume and worse cognition.

## 2. Methods

### 2.1. Participants

Our cross-sectional sample consisted of 321 cognitively normal adults over the age of 60 (mean age=73.8 years, SD=7.0, range=61.2–94.4; 56% female) from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Inclusion criteria for cognitively normal participants included scoring above the education cutoffs for the Logical Memory component of the Wechsler Memory Scale ($\geq$ 3 for 0–7 years of education, $\geq$ 5 for 8–15 years of education, and $\geq$ 9 for 16 or more years of education), Mini Mental State Exam = 24–30, Clinical Dementia Rating = 0, Geriatric Depression Scale $\leq$ 5, no significant impairments in cognitive function or daily activities, and no history of depression within the last year. Participants had at least 12 years of education and had no major medical illnesses or MR contraindications. For cross-sectional analyses we used each participant's first tau-PET scan and the Aβ-PET scan closest to the first tau-PET. Participants were required to have known rs6347 and rs6265 genotypes, [18 F]Flortaucipir tau PET and Aβ PET ([18 F]Florbetapir or [18 F]Florbetaben PET). A subset of these participants with at least one follow-up scan or session were included in longitudinal analyses (Aβ: n = 235; tau: n = 135; MRI: n = 215, cognition: n = 236). Due to smaller longitudinal sample sizes, we consider longitudinal analyses to be exploratory and the results should be interpreted with caution. For longitudinal Aβ analyses, mean age= 74.4 years, SD= 7.0, range= 61.2 – 91.5. For longitudinal tau analyses, mean age= 74.1, SD= 6.5, range= 62.4 – 90.5. For longitudinal MR analyses, mean age= 74.5, SD= 6.9, range= 61.2 – 91.5. For longitudinal cognitive analyses, mean age= 73.8, SD= 7.0, range= 61.2 – 94.4. All participants provided informed consent.

### 2.2. Genetic data

DNA from peripheral blood samples was genotyped using either the Ilumina Omni 2.5 M BeadChip or the Ilumina Global Screening Array v2. Genotype data was in Hardy-Weinberg equilibrium for *DAT1* rs6347 and *BDNF* Val66Met (rs6347: 178 T homozygotes (55%), 111 heterozygotes (35%), and 32 C homozygotes (10%); Val66Met: 208 Val homozygotes (65%), 100 heterozygotes (31%), and 13 Met homozygotes (4%)). Due to a low number of *BDNF* Met/Met carriers, we grouped together any individuals carrying a Met allele (Met/Met and Val/Met), as done previously (Lim et al., 2013).

### 2.3. Aβ and tau PET acquisition and processing

Documentation on PET data acquisition and processing is available on the ADNI website (https://adni.loni.usc.edu/). PET imaging was performed at multiple sites using one of several different scanners: GE Healthcare PET/CT or PET only, Philips Medical Systems PET/CT or PET only, or Siemens Medical Solutions PET/CT or PET only. There were no differences in radiotracer yield, acquisition time, or number of frames across different scanners or sites. There were also no differences in imaging protocols across different sites.

To measure tau pathology, participants were given a 10 mCi ± 10% bolus injection into an antecubital vein 75–105 min before scanning. Dynamic acquisition frames were obtained over 30 min (6 x 5 min frames). [18 F]Flortaucipir standardized uptake ratios (SUVRs) were calculated by coregistering each participant's PET scan to the MRI scan closest to the PET scan. MRI scans were reconstructed and segmented using FreeSurfer (v.7.1.1). [18 F]Flortaucipir scans were partial volume corrected using the Geometric Transfer Matrix (Rousset et al., 1998) and an inferior cerebellar reference region. Our analyses included tau ROIs measured in the entorhinal cortex, which is one of the earliest sites of cortical tau accumulation (Braak and Braak, 1985; Kaufman et al., 2018), and a meta-temporal lobe region consisting of the entorhinal cortex, amygdala, fusiform, parahippocampal gyrus, inferior temporal

gyrus, and middle temporal gyrus (Jack et al., 2020).

Aβ was measured with two different PET tracers ([18 F]Florbetapir and [18 F]Florbetaben) depending on when participants joined ADNI. Participants received a bolus injection of either 10 mCi ± 10% (Florbetapir) or 8.1 mCi ± 10% (Florbetaben) and dynamic acquisition frames were obtained over 20 min of continuous scanning (4 x 5 min frames) either 50 min (Florbetapir) or 90 min (Florbetaben) post-injection. Using the Aβ-PET scan closest in time to baseline [18 F]Flortaucipir, PET images were coregistered to the MRI scan closest to the Aβ-PET scan and a cortical summary region was created (including frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal regions). SUVRs were calculated by dividing the cortical summary region by the whole cerebellum, which was used as the reference region for both cross-sectional and longitudinal analyses. SUVRs were normalized to the amyloid centiloid scale to enable comparison of scans obtained using the two different tracers (Royse et al., 2021).

For longitudinal analyses, participants had an average of 3.19 follow up Aβ-PET scans (SD=1.41, range=2–6) and there was an average follow up time (time between first and last scan) of 4.99 years (SD=3.00, range=1.52–11.01) for Aβ-PET. There was an average of 2.60 follow up tau-PET scans (SD=.77, range=2–5), with an average follow up time of 2.83 years (SD=1.37, range=.80–5.86).

### 2.4. Hippocampal volume

T1-weighted MRIs are available in the ADNI database. Analyses relied on FreeSurfer software (version 7.0.0). Automatic segmentation of subcortical regions is based upon an atlas of probabilistic information on the location of structures, as previously described (Fischl et al., 2002). Right and left hippocampal volumes were segmented separately and added together to create a bilateral volume. Estimated total intracranial volume was used as a covariate in analyses involving hippocampal volume to adjust for differences in head size. Longitudinal change in hippocampal volume was assessed in a subset of n = 215 participants with a mean follow-up time of 4.04 years (SD=2.69, range=.98–10.51) and a mean of 3.87 follow-up scans (SD=2.40, range=2–9).

### 2.5. Cognitive assessments

Cognitive measures included the ADNI University of Washington (UW) Memory (Crane et al., 2012) and Executive Function (EF) (Gibbons et al., 2012) composites and the Preclinical Alzheimer's Cognitive Composite (PACC) (Donohue et al., 2014) Cross-sectional cognition was measured at the cognitive testing session closest to the baseline [18 F] Flortaucipir PET scan. Longitudinal cognition was measured using all sessions after the baseline [18 F]Flortaucipir scan (n = 236 participants). Mean follow-up time was 2.47 years (SD=.98, range=.96–5.56). Mean number of follow up sessions was 2.98 (SD=1.28, range=2–8).

### 2.6. Statistical analyses

We first investigated whether carrying both "non-optimal" genotypes was associated with higher Aβ and tau pathology by testing *DAT1* **BDNF* interactions on Aβ and tau PET, as well as main effects of *DAT1* and *BDNF*. We used multiple regression models with cross-sectional and longitudinal measures of pathology as dependent variables. Longitudinal change in pathology over time was analyzed using linear mixed effects modeling with both random slope and random intercept in the lme4 R package. Individual slopes for each participant were extracted from the model and used as dependent variables in linear regression analyses testing for *DAT1* **BDNF* interactions on longitudinal change in pathology (Model 1 in the SPSS PROCESS Macro). We next conducted an exploratory moderated mediation analysis to test whether Aβ mediates the effects of the polymorphisms on tau pathology. This analysis involved a bias-corrected and accelerated (BCa) 95% confidence intervals bootstrap estimation (10,000 samples). We used the moderated mediation model to test whether *DAT1* rs6347 (independent variable, X) affects tau-PET (dependent variable, Y) both directly and indirectly through effects of rs6347 on Aβ-PET (mediator, M), and whether this mediation is moderated by *BDNF* Val66Met (moderator, W). The moderated mediation was run using Model 8 in the PROCESS Macro (version 4.0; Hayes, 2013) in SPSS (version 28.0.1.1). Finally, we used multiple regression models to test for direct and interactive effects of the polymorphisms on cross-sectional and longitudinal hippocampal volume and cognition. All regression analyses and the moderated mediation included age, sex, and years of education as covariates. Longitudinal models also adjusted for number of follow-up scans/sessions, and mean follow-up time. Effect sizes were calculated using Cohen's $f^2$.

Based on our cross-sectional sample size (n = 321), a sensitivity analysis using G*Power (version 3.1, Faul et al., 2007) revealed a sensitivity to detect small effect sizes ($f^2$ =.041, 80% power, alpha.05, Fixed Model $R^2$ increase).

## 3. Results

### 3.1. Sample characteristics

Participant demographics, genotype information, baseline tau-PET SUVRs, and Aβ-PET centiloids closest to baseline tau-PET are presented in Table 1. Linear regression models with each genotype as the predictor demonstrated no genotype differences in age, years of education, MMSE score, GDS score, or PET measures (see Table 1 for p-values). Additionally, logistic regression models revealed no associations between genotype and sex, no associations between genotype and Aβ status (rs6347: p = .31; Val66Met: p = .35), and no associations between rs6347 and Val66Met genotypes (p = .44).

*3.2 Carriers of both DAT1 CC and BDNF Met genotypes exhibit higher Aβ and tau pathology*.

We first investigated *DAT1* **BDNF* interactions predicting cross-sectional and longitudinal Aβ-PET. *DAT1* and *BDNF* interacted to predict cross-sectional Aβ-PET (t(314) = 2.35, p = .019, $f^2$ = .02; Figure 1A**, left;** Table 2A) such that individuals carrying both "non-optimal" genotypes (DAT1 CC and BDNF Met) exhibited higher Aβ centiloids. Carriers of both *DAT1* CC and *BDNF* Met showed numerically larger rates of increase in longitudinal Aβ, but this was not statistically significant (t(226) = 1.69, p = 0.09, $f^2$ = .01; Figure 1A**, right;** Table 2B). Direct effects of *DAT1* rs6347 and *BDNF* Val66Met on cross-sectional and longitudinal Aβ-PET were null (cross-sectional: rs6347 p = .16, Val66Met p = .13; longitudinal: rs6347 p = .26, Val66Met p = .91; adjusting for age, sex, and years of education).

We next tested whether *DAT1* and *BDNF* would interact to predict cross-sectional and longitudinal tau-PET (entorhinal and meta-temporal ROIs). Similar to the Aβ analyses, participants carrying both *DAT1* CC and *BDNF* Met exhibited the highest tau SUVR and the greatest rates of longitudinal increase. *DAT1***BDNF* significantly predicted cross-sectional and longitudinal entorhinal tau (cross-sectional: t(314) = 2.49, p = .013, $f^2$ = .02; longitudinal: t(126) = 3.44, p = .0008, $f^2$ = .07; Figure 1B**;** Table 2C, D) and meta-temporal tau (cross-sectional: t(314) = 3.34, p = .0009, $f^2$ = .03; longitudinal: t(126) = 3.26, p = .001, $f^2$ = .09; Figure 1C**;** Table 2E, F). Paralleling Aβ-PET analyses, direct effects of *DAT1* rs6347 and *BDNF* Val66Met on cross-sectional and longitudinal tau-PET were null for entorhinal ROIs (cross-sectional entorhinal: rs6347 p = .06, Val66Met p = .07; longitudinal entorhinal: rs6347 p = .14, Val66Met p = .50) and meta-tau ROIs (cross-sectional meta-ROI: rs6347 p = .06, Val66Met p = .40; longitudinal meta-ROI: rs6347 p = .17, Val66Met p = .98).

Given the interactive effects of *DAT1* and *BDNF* on both Aβ and tau pathology, we conducted a moderated mediation analysis to test whether Aβ mediates the relationship between the polymorphisms and tau. This analysis is in line with prominent models describing the role of

**Table 1**
Participant characteristics at first tau-PET scan.

| Variable | Total (N = 321), 35% Aβ+ | rs6347 CC (N = 32), 44% Aβ+ | rs6347 TC (N = 111),36% Aβ+ | rs6347 TT (N = 178),34% Aβ+ | p-value (comparing rs6347 genotypes) | rs6265 Met carriers (N = 113),39% Aβ+ | rs6265 Val/Val (N = 208),34% Aβ+ | p-value (comparing rs6265 genotypes) |
|---|---|---|---|---|---|---|---|---|
| N female (%) | 179 (56) | 17 (53) | 58 (52) | 104 (58) | .35 | 48 (42) | 94 (45) | .64 |
| Age, years (SD) | 73.8 (7.0) | 72.4 (7.1) | 73.9 (7.1) | 73.9 (7.1) | .38 | 73.0 (7.2) | 74.2 (6.8) | .14 |
| Education, years (SD) | 16.9 (2.3) | 16.6 (2.4) | 16.6 (2.4) | 17.2 (2.2) | .06 | 17.2 (2.3) | 16.7 (2.2) | .16 |
| MMSE (SD) | 29.1 (1.2) | 29.1 (1.1) | 29.0 (1.4) | 29.1 (1.2) | .50 | 29.2 (1.2) | 29.0 (1.2) | .23 |
| GDS (SD) | 0.7 (1.2) | 0.8 (1.6) | 0.7 (1.0) | 0.8 (1.3) | 0.71 | 0.7 (1.1) | 0.8 (1.3) | 0.34 |
| FBP/FBB in centiloids (SD) | 21.8 (30.7) | 25.4 (29.5) | 23.7 (33.1) | 19.9 (29.4) | .23 | 24.5 (33.0) | 20.3 (29.4) | .25 |
| Entorhinal FTP SUVR (SD) | 1.1 (.1) | 1.2 (.2) | 1.1 (.1) | 1.1 (.1) | .13 | 1.2 (.1) | 1.1 (.1) | .07 |

Abbreviations: MMSE, Mini Mental State Exam; GDS, Geriatric Depression Scale; FBP/FBB, Florbetapir/Florbetaben Aβ-PET normalized to the centiloid scale; FTP SUVR, Flortaucipir standardized uptake value ratio (tau-PET measured in the entorhinal cortex).

Aβ in AD, which suggest that Aβ contributes to tau spread (Hardy and Higgins, 1992; Karran et al., 2011). The moderated mediation was performed on cross-sectional data only, as there were few participants with both longitudinal Aβ and longitudinal tau. The moderated mediation model (Figure 2) demonstrated that *BDNF* Val66Met significantly moderated the mediation among DAT1 rs6347, Aβ-PET, and tau-PET (moderated mediation index =.02, 95% CI [.002,.036]), adjusting for age, sex, and years of education as covariates. As demonstrated by our multiple regression analyses, *BDNF* Val66Met significantly moderates relationships between *DAT1* and Aβ-PET, as determined by a significant conditional indirect effect of *DAT1* and *BDNF* on tau-PET through Aβ-PET as a mediator. The conditional indirect effect is demonstrated by a significant effect of *DAT1* on Aβ-PET for *BDNF* Met carriers (b=−.015, 95% CI [−.03, −.003]) but not for *BDNF* Val/Val homozygotes (b=.002, 95% CI [−.006,.020]), and a significant relationship between Aβ and tau PET measures (b=.002, 95% CI [.001,.002]). These results indicate that *DAT1* rs6347 and *BDNF* Val66Met together relate to both amyloid and tau pathology and may have a synergistic effect in which carrying both rs6347 C and Val66Met Met relates to higher pathology.

We replicated this moderated mediation using tau-PET measured within the temporal lobe tau meta-ROI (Jack et al., 2020), rather than entorhinal tau-PET. This analysis yielded similar significant results (moderated mediation index=.012, 95% CI [.002,.025]), indicating a significant moderating effect of *BDNF* Val66Met on the *DAT1*→Aβ→tau mediation such that individuals carrying both *DAT1* CC and *BDNF* Met demonstrate higher Aβ and temporal lobe tau pathology. As there were four outliers in the tau meta-ROI data (greater than three SD above the mean), we also re-ran this analysis after removing these potentially influential datapoints (n = 318 participants included in analysis) and found that there was still a significant moderated mediation (moderated mediation index=.010, 95% CI [.002,.021]), suggesting that the effect is not driven by individuals with highest tau-PET values.

### 3.2. *DAT1 and BDNF interact to predict change in hippocampal volume*

After determining that *DAT1* CC and *BDNF* Met variants are related to higher pathology, we investigated whether these same variants would relate to lower hippocampal volume. Bilateral hippocampal volume was measured using FreeSurfer-derived ROIs (Figure 3A). All regression analyses included age, sex, years of education, and estimated total intracranial volume as covariates. There was no *DAT1*BDNF* interaction on cross-sectional hippocampal volume (p = .68). However, there was a significant *DAT1*BDNF* interaction on longitudinal change in hippocampal volume (t(205) = −2.19, p = .03, $f^2$ = .02; Figure 3B). Individuals carrying both non-optimal genotypes exhibited greater decline in hippocampal volume over time. Similar to analyses of PET data, there were no main effects of *DAT1* rs6347 and *BDNF* Val66Met on hippocampal volume (cross-sectional: rs6347 p = .53, Val66Met p = .60; longitudinal: rs6347 p = .97, Val66Met p = .17).

### 3.3. *DAT1 and BDNF genotypes do not relate to cognition*

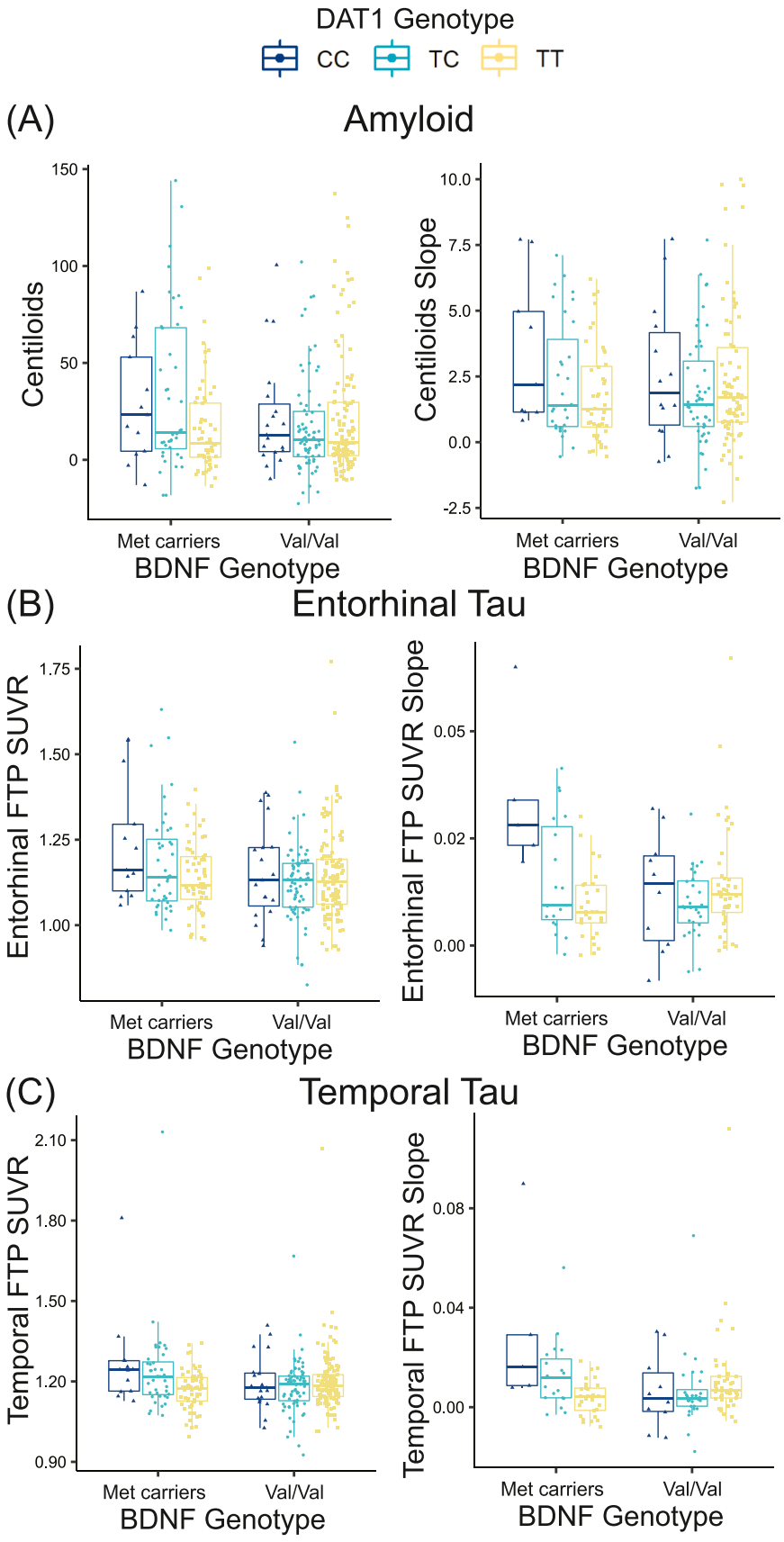
*DAT1* and *BDNF* did not interact to predict any cross-sectional cognitive measures (UW Memory: p = .65, UW EF: p = .51, PACC: p = .87). Similarly, *DAT1 *BDNF* did not predict longitudinal change in cognition (UW Memory: p = .77, UW EF: p = .22, PACC: p = .87). There were no main effects of *DAT1* rs6347 or *BDNF* Val66Met on UW Memory (cross-sectional: rs6347 p = .82, Val66Met p = .80; longitudinal: rs6347 p = .39, Val66Met p = .95), UW Executive Function (cross-sectional: rs6347 p = .71, Val66Met p = .23; longitudinal: rs6347 p = .20, Val66Met p = .76), or PACC (cross-sectional: rs6347 p = .85, Val66Met p = .58; longitudinal: rs6347 p = .55, Val66Met p = .97).

## 4. Discussion

We investigated relationships among AD-related pathology and two genetic polymorphisms that have previously been associated with increased risk for dementia but have not been directly related to pathology. Our analyses demonstrate that interactions between *DAT1* rs6347 and *BDNF* Val66Met predict PET measures of Aβ and tau pathology and change in hippocampal volume in cognitively normal older adults. Carriers of both rs6347CC and Val66Met Met demonstrated higher cross-sectional Aβ and tau pathology and greater longitudinal tau and hippocampal atrophy. Our findings extend previous research implicating these variants in AD vulnerability (Lin et al., 2012; Roussotte et al., 2015) by demonstrating associations with greater AD pathology. All of these analyses focused on cognitively normal older adults and demonstrated small effect sizes (Cohen's $f^2$ =.01–.09).

Our moderated mediation analysis suggests that together the *DAT1* and *BDNF* polymorphisms are related to higher Aβ pathology, which then contributes to higher tau pathology. While our analyses do not demonstrate causality, these findings are consistent with models of AD by which Aβ drives increases in tau pathology (Hardy and Higgins, 1992; Karran et al., 2011). Our results are also in line with work linking sub-optimal dopamine function to AD (Nobili et al., 2017; Pan et al., 2019), and research defining protective roles of *BDNF* (Buchman et al., 2016; Lim et al., 2013). Our study suggests that individuals carrying both "optimal" alleles (*DAT1* T and *BDNF* Val) may show greater resistance to AD-related pathology. While it is difficult to determine whether entorhinal tau in a cognitively unimpaired sample relates to AD or to primary age-related tauopathy (PART), we demonstrate consistent findings in a tau meta-ROI (Jack et al., 2020) consisting of temporal lobe regions, suggesting our results may be relevant to AD-related processes.

While we found no evidence that "optimal" alleles were associated with greater hippocampal volume cross-sectionally, our exploratory longitudinal analyses suggest that these alleles relate to less




*(caption on next page)*

**Fig. 1.** *DAT1* rs6347 interacts with *BDNF* Val66Met to predict cross-sectional and longitudinal Aβ and tau pathology such that individuals carrying both "non-optimal" alleles (*DAT1* CC and *BDNF* Met) exhibit higher Aβ Centiloids and tau SUVR compared with other genotypes. (A) *DAT1* and *BDNF* interact to predict cross-sectional Aβ-PET measured in centiloids (p = .019; left). The *DAT1*BDNF* interaction predicting longitudinal change in Aβ-PET did not reach significance (p = .09; right). (B) Significant *DAT1*BDNF* interactions predicting entorhinal tau-PET SUVR (cross-sectional: p = .013, left; longitudinal: p = .0008, right). (C) Significant *DAT1*BDNF* interactions predicting temporal lobe tau-PET (cross-sectional: p = .001, left; longitudinal: p = .001, right). The interaction effect on temporal lobe tau-PET remained significant after removing four outliers (p = .005).

**Table 2**
DAT1 rs6347 *BDNF Val66Met interactions on Aβ-PET (A), (B), entorhinal tau-PET (C), (D), and meta-temporal lobe tau-PET (E), (F).

| Variable | UnstandardizedCoef. | SE | t | p | 95% CI |
|---|---|---|---|---|---|
| (A) Aβ-PET (cross-sectional) | | $R^2$ = .070, F(6, 314) = 3.914, p = .0009 | | | |
| rs6347 *Val66Met | 12.273 | 5.219 | 2.352 | .019 | 2.004, 22.542 |
| rs6347 | -3.121 | 2.528 | -1.235 | .218 | -8.095, 1.852 |
| Val66Met | -5.012 | 3.527 | -1.421 | .156 | -11.951, 1.927 |
| Sex | 4.155 | 3.471 | 1.197 | .232 | -2.675, 10.985 |
| Age | .943 | .245 | 3.845 | .0001 | .460, 1.425 |
| Years Ed | -.586 | .749 | -.783 | .434 | -2.059,.887 |
| (B) Aβ-PET (longitudinal) | | $R^2$ = .048, F(8, 226) = 3.914, p = .188 | | | |
| rs6347 *Val66Met | .861 | .473 | 1.691 | .092 | -.133, 1.737 |
| rs6347 | -.257 | .229 | -1.119 | .265 | -.710,.196 |
| Val66Met | -.023 | .315 | -.074 | .942 | -.645,.598 |
| Sex | .358 | .316 | 1.131 | .259 | -.266,.981 |
| Age | .060 | .024 | 2.470 | .041 | .012,.108 |
| Years Ed | -.033 | .067 | -.493 | .622 | -165,.108 |
| Follow-up Time | -.106 | .154 | -.689 | .492 | -.410,.198 |
| Number of scans | .060 | .322 | .185 | .853 | -.575,.695 |
| (C) Entorhinal tau-PET (cross-sectional) | | $R^2$ = .058, F(6, 314) = 3.247, p = .004 | | | |
| rs6347 *Val66Met | .055 | .022 | 2.493 | .013 | .012,.098 |
| rs6347 | -.018 | .011 | -1.669 | .096 | -.039,.003 |
| Val66Met | -.025 | .015 | -1.703 | .090 | -.055,.004 |
| Sex | .005 | .015 | .328 | .743 | -.024,.034 |
| Age | .002 | .001 | 1.759 | .080 | -.0002,.004 |
| Years Ed | .007 | .003 | 2.115 | .035 | .0005,.013 |
| (D) Entorhinal tau-PET slope $R^2$ = .201, F(8, 126) = 3.956, p = .0003 | | | | | |
| rs6347 *Val66Met | .012 | .003 | 3.437 | .0008 | .005,.017 |
| rs6347 | -.003 | .001 | -1.988 | .049 | -.006, − .001 |
| Val66Met | -.002 | .002 | -.737 | .463 | -.006,.003 |
| Sex | .003 | .002 | 1.232 | .220 | -.002,.007 |
| Age | .0003 | .0002 | 1.928 | .056 | .00002.001 |
| Years Ed | .001 | .0004 | 1.129 | .199 | -.0003,.001 |
| Follow-up Time | -.001 | .001 | -1.663 | .099 | -.003,.0003 |
| Number of scans | .003 | .001 | 2.063 | .041 | .0001,.006 |
| (E) Meta-temporal tau-PET (cross-sectional) | | $R^2$ = .056, F(6, 314) = 3.108, p = .006 | | | |
| rs6347 *Val66Met | .067 | .020 | 3.344 | .0009 | .028,.106 |
| rs6347 | -.017 | .010 | -1.722 | .086 | -.036,.002 |
| Val66Met | -.010 | .014 | -.756 | .450 | -.037,.016 |
| Sex | -.0006 | .013 | -.046 | .964 | -.027,.026 |
| Age | .002 | .0009 | 1.455 | .147 | -.0005,.003 |
| Years Ed | .004 | .003 | 1.355 | .176 | -.002,.010 |
| (F) Meta-temporal tau-PET slope $R^2$ = .122, F(8, 126) = 2.181, p = .033 | | | | | |
| rs6347 *Val66Met | .014 | .004 | 3.265 | .001 | .006,.023 |
| rs6347 | -.003 | .002 | -1.274 | .205 | -.007,.001 |
| Val66Met | -.001 | .003 | -.232 | .817 | -.006,.005 |
| Sex | .0001 | .003 | .281 | .794 | -.001,.001 |
| Age | .0001 | .0002 | .505 | .614 | -.0003,.001 |
| Years Ed | .0001 | .001 | .228 | .820 | -.001,.001 |
| Follow-up Time | -.001 | .001 | -.811 | .419 | -.003,.001 |
| Number of scans | .003 | .002 | 1.476 | .143 | -.001,.007 |

hippocampal atrophy. Similar discrepancies between cross-sectional versus longitudinal effects have been reported for aging studies evaluating hippocampal volume, which has suggested that longitudinal measures of hippocampal volume may, in some cases, be more sensitive than cross-sectional (Pfefferbaum and Sullivan, 2015). Previous analyses of the *DAT1* rs6347 polymorphism have found associations with longitudinal measures of ventricular volume, which were absent for cross-sectional analyses (Roussotte et al., 2015). While *BDNF* Val66Met has been linked to both cross-sectional and longitudinal hippocampal volume, some research suggests that this polymorphism relates best to longitudinal volume changes (Lim et al., 2017).

It is unclear why we observed genetic effects on pathology and hippocampal atrophy in the absence of effects on cognition. *BDNF* and *DAT1* polymorphisms have been previously linked with individual differences in cognitive function in aging (Baeuchl et al., 2019; van den Bosch et al., 2021) though genetic effects on cognitive function are often small and mediated by diverse factors (Dang et al., 2013). It is also possible that indirect effects of these polymorphisms on cognition (via effects on Aβ, tau and hippocampal atrophy) are only evident with greater disease progression, which would be in general agreement with observations that cognitive dysfunction temporally trails neurodegeneration and accumulation of Aβ and tau (Karran et al., 2011). As mentioned in the introduction, there are mixed findings regarding the role of *BDNF* in AD, which has often been studied in the context of *BDNF* interactions with *APOE*. Multiple studies suggest that carrying both *BDNF* Met and *APOE* e4 alleles relates to greater pathology (Adamczuk

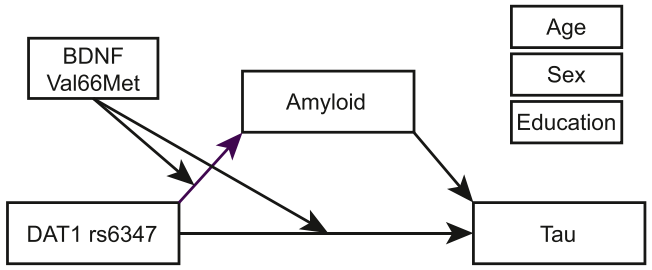



**Fig. 2.** Diagram illustrating exploratory moderated mediation model. Val66-Met moderates the mediation between rs6347, Aβ, and tau pathology, with age, sex, and years of education added to the model as covariates.

et al., 2013; Stonnington et al., 2020), while findings are more mixed for analyses focused on cognition (Stonnington et al., 2020; Ward et al., 2014). This is in line with evidence that *BDNF* may be more sensitive to early changes in pathology and neurodegeneration than to cognitive function (Lim et al., 2016; Stonnington et al., 2020).

*DAT1* and *BDNF* interacted to predict cross-sectional Aβ and tau and longitudinal tau, but, unexpectedly, there was no significant interaction predicting longitudinal Aβ ($p = .09$, $f^2 = .01$). While our exploratory moderated mediation suggested a path by which genetic effects on tau are mediated by Aβ, this was complicated by the lack of polymorphism effects on longitudinal Aβ. Additional research is needed to establish *DAT*1 **BDNF* effects on Aβ-independent, age-related tau accumulation. Important limitations of this work are the relatively small number of participants with both non-optimal genotypes and the small effect sizes observed throughout. Due to the small sample and small effect sizes, we do not want to strongly interpret this null result for longitudinal Aβ in the absence of replication in another PET dataset, or exploration within a larger fluid biomarker dataset.

Additional research is needed to more clearly define the mechanisms by which BDNF and the dopamine system interact to influence AD pathology and hippocampal atrophy. BDNF.

maintains the health of dopamine-producing neurons via TrkB receptors (Numan and Seroogy, 1999) and regulates dopamine receptor expression (Guillin et al., 2001). Dopamine neurons can, in turn, increase BDNF expression via dopaminergic signaling (Okazawa et al., 1992). Thus, non-optimal function of dopamine and BDNF can create a "vicious cycle", magnifying deficits in each system. Broadly, non-optimal dopamine and BDNF signaling may create a more vulnerable environment in which Aβ and tau are more likely to accumulate. The positive impact of enhanced BDNF/TrkB signaling on dopamine system health has been studied in the context of excitotoxity in AD and Parkinson's disease models (Meisner et al., 2008; Zhu et al., 2015), which provides initial groundwork for establishing effects of these systems on hippocampal atrophy. Relevant to pathology, there is some evidence suggesting dopamine can disaggregate Aβ fibrils in vivo (Li et al., 2004), and that Aβ oligomers decrease BDNF expression (Garzon and Fahnestock, 2007). Optimal dopaminergic tone also plays a key role in stabilizing neural activity, with direct effects on hippocampal synaptic plasticity (Rossato et al., 2009; Yuan Xiang et al., 2016), and GABAergic inhibition (Seamans et al., 2001). Thus, dysregulation of dopamine and BDNF signaling may enhance pathology development and spread by increasing neural hyperactivity, a known promoter of Aβ and tau aggregation (Bero et al., 2011; Wu et al., 2016). Other indirect pathways may arise via associations with other neuromodulator systems. Increased dopamine transmission can prevent Aβ-induced internalization of acetylcholine receptors (Jürgensen et al., 2011), while the BDNF receptor TrkB supports neuroprotective effects of norepinephrine against Aβ toxicity (Liu et al., 2015). It will be critical to replicate our findings and extend them with in vitro research defining the cellular mechanisms that might drive associations between reduced BDNF, non-optimal dopamine function, and elevated AD pathology.

## 5. Conclusion

Understanding mechanisms that contribute to individual differences in Aβ and tau pathology in cognitively normal older adults will be critical for advancing our understanding of variation in AD risk. A recent

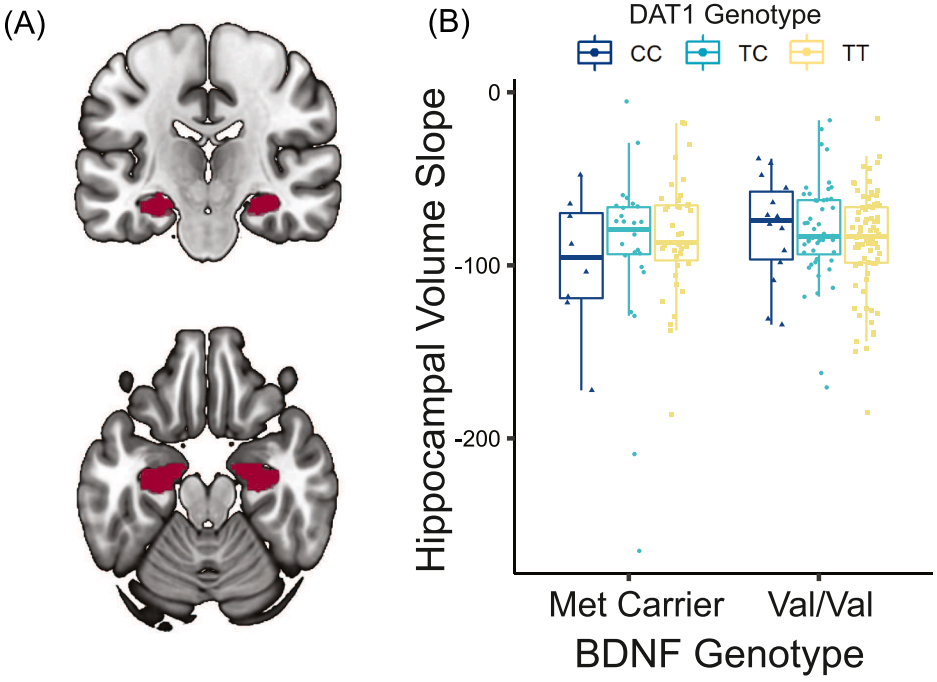



**Fig. 3.** Relationship between polymorphisms and change in hippocampal volume. (A) FreeSurfer-derived ROI of bilateral hippocampus overlaid on MNI152 template. (B) Significant *DAT1***BDNF* interaction predicting longitudinal change in hippocampal volume ($p = .03$, adjusting for age, sex, years of education, and total intracranial volume) such that individuals carrying both *DAT1* CC and *BDNF* Met demonstrate greater decline in hippocampal volume. Hippocampal slopes for individual participants were extracted from a linear mixed effects model.

review of AD drug trials highlighted the potential of genetic pathways as diagnostic indicators and targets of preventative drugs (van Bokhoven et al., 2021). Here, we demonstrate novel associations among polymorphisms in the dopamine transporter and *BDNF* genes, AD pathology, and hippocampal atrophy. Our results provide a direct link between AD pathology and variants of these genes previously associated with worse disease trajectories.

## CRediT authorship contribution statement

**Claire J. Ciampa:** Conceptualization, Formal analysis, Writing – original draft preparation, Writing – review & editing, Visualization **Thomas M. Morin:** Formal analysis, Writing – review & editing **Alice Murphy:** Data curation **Renaud La Joie:** Conceptualization, Supervision, Data curation, Writing – review & editing **Susan M. Landau:** Conceptualization, Supervision, Data curation, Writing – review & editing **Anne S. Berry:** Conceptualization, Supervision, Project administration, Writing – original draft preparation, Writing – review & editing.

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### *Conflicts of interest*

SM Landau is on the DSMB for Keife RX and the NIH IPAT study and has received speaking honoraria from Eisai. Authors CJ Ciampa, TM Morin, A Murphy, R La Joie, and AS Berry have nothing to disclose.

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