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FEATURED ARTICLE

Repetitive negative thinking is associated with amyloid, tau, and cognitive decline

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Abstract

Introduction: The Cognitive Debt hypothesis proposes that repetitive negative thinking (RNT), a modifiable process common to many psychological risk factors for Alzheimer's disease (AD) may itself increase risk. We sought to empirically examine relationships between RNT and markers of AD, compared with anxiety and depression symptoms.

Methods: Two hundred and ninety-two older adults with longitudinal cognitive assessments, including 113 with amyloid-positron emission tomography (PET) and tau-PET scans, from the PREVENT-AD cohort and 68 adults with amyloid-PET scans from the IMAP+ cohort were included. All participants completed RNT, anxiety, and depression questionnaires.

Results: RNT was associated with decline in global cognition ($P = .02$); immediate ($P = .03$) and delayed memory ($P = .04$); and global amyloid (PREVENT-AD: $P = .01$; IMAP+: $P = .03$) and entorhinal tau ($P = .02$) deposition. Relationships remained after adjusting for potential confounders.

Discussion: RNT was associated with decline in cognitive domains affected early in AD and with neuroimaging AD biomarkers. Future research could investigate whether modifying RNT reduces AD risk.

KEYWORDS

Alzheimer's disease, amyloid, cognition, depression, repetitive negative thinking, rumination, tau, worry

1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive neurological disease. In early stages, AD is characterized by the aggregation of amyloid beta (Aβ) and hyperphosphorylated tau proteins in the brain,[1] and worsening memory.[2,3] In the absence of disease-modifying treatments, there is an urgent need to identify modifiable risk factors that are associated with these biomarkers, which can be targeted to prevent future AD.

In recent decades, a number of psychological risk factors for cognitive decline and AD have been identified.[4] These include depression[5-7] and anxiety.[8-10] While these risks have generally been considered independently, the Cognitive Debt hypothesis suggests that a mechanism frequently present in these psychological risk factors—repetitive negative thinking (RNT)[11]—may underlie the risk associated with each factor.[4]

Repetitive negative thinking (also termed perseverative cognition) is a behaviorally measurable cognitive process that

encompasses future- (worry) and past- (rumination) directed thoughts,[12] and describes the thought *process* rather than its time orientation or content. It is relatively stable[13] but like other traits, can also be modified through intervention.[14,15] While RNT is a comparatively new term, its components, rumination and worry, have been associated with memory and executive function in diverse populations.[16-22] The behavioral evidence, we suggest, implicates RNT as a potential common pathway that contributes to increasing AD risk. RNT's relationship with neurobiological AD markers, amyloid and tau, has not yet been empirically examined; however, memory-related worries have been associated with higher amyloid burden in individuals with subjective cognitive decline.[23,24] The current study sought to examine the relationship between (1) RNT and longitudinal cognitive change, and (2) RNT and AD pathologies using neuroimaging markers of Aβ and tau, compared to the relationships between symptoms of depression and anxiety and these markers.

HIGHLIGHTS

- Psychological risks for Alzheimer's disease (AD) often involve repetitive negative thinking (RNT).
- The Cognitive Debt hypothesis proposed that RNT itself may increase risk of AD.
- RNT is associated with amyloid and tau deposition in non-demented adults.
- RNT predicts decline in cognitive domains affected early in AD.
- Empirical evidence supports RNT as a marker of increased AD risk.

RESEARCH IN CONTEXT

1. Systematic review: We reviewed the literature using traditional sources (eg, PubMed and GoogleScholar). Although the associations between psychiatric symptoms such as depression and anxiety, and markers of AD risk are increasingly studied, investigation of a thinking style that may be central to these associations has been largely neglected.
2. Interpretation: Our results suggest that RNT is associated with cognitive and neuropathological markers of AD. Importantly, these are the first data to provide proof-of-principle support for the Cognitive Debt hypothesis that RNT is an important marker of dementia risk.
3. Future directions: These findings call for experimental interventions to determine (a) the causal relationship between RNT and AD biomarkers, and (b) whether reducing RNT impacts risk of developing AD.

2 | METHODS AND MATERIALS

2.1 | Participants

2.1.1 | PREVENT-AD cohort

Two hundred and ninety-two cognitively normal participants from the Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer's Disease (PREVENT-AD) cohort (see supporting information) provided data for the longitudinal cognitive analyses, a subset of whom had undergone Aβ and tau positron emission tomography (PET) scans (N = 113, Table 1).

All participants were aged 55 or older, in good physical and cognitive health, had a parent or at least two siblings with past or current AD dementia, and were apolipoprotein E (APOE) genotyped. Detailed medical examinations were undertaken by research nurses before enrolment to ensure eligibility for study participation. Participants must have completed a measure of RNT to be included in analyses.

2.1.2 | IMAP+ cohort

Data from 68 adults that were either cognitively healthy or with subjective cognitive decline from the Multi-Modal Neuroimaging in Alzheimer's Disease (IMAP+) study were used in the Aβ neuroimaging replication study (Table 1). Cognitively healthy participants were recruited from the general population and those with subjective cognitive decline were recruited from local memory clinics (see Perrotin et al.[25] for details). All performed in the normal range in neuropsychological tests, had no clinical evidence of major neurological or psychiatric disorder, had a Mini-Mental State Examination (MMSE) $\geq$ 28, and were APOE genotyped. Participants must have completed a measure of RNT and undergone an Aβ-PET scan to be included in the analyses.

2.2 | Standard protocol approvals, registrations, and patient consents

PREVENT-AD was approved by the Institutional Review Board of the McGill University Faculty of Medicine, and conducted in accordance with the World Medical Association, Declaration of Helsinki. Participants provided written consent before participation.

IMAP+ (Caen, France) was approved by the regional ethics committee (Comité de Protection des Personnes Nord-Ouest III) and is registered with ClinicalTrials.gov (number NCT01638949). All participants gave written informed consent before the examinations.

TABLE 1 Demographic, clinical, and biological characteristics of the PREVENT-AD and IMAP+ cohorts

		PREVENT-AD cohort		
	Variable	Cognitive Trajectory Substudy N = 292	Neuroimaging Substudy N = 113	IMAP+ cohort N = 68
Demographics	Age, years	62.3 (4.9)	67.5 (5)	67.6 (9.4)
	Sex, female n (%)	212 (73%)	85 (75%)	33 (49%)
	Education,years	15.39 (3.4)	15.07 (3.2)	12.9 (3.7)
	APOE, ε4+ n (%)	114 (39%)	45 (40%)	16 (24%)
	MMSE	–	28.84 (1.2)	28.96 (1.1)
	MoCA	28.07 (1.5)	–	–
Psychiatric symptoms	GAI anxiety score	2.86 (4.3)	2.0 (3.6)	–
	GDS depression score	1.63 (2.2)	1.28 (1.9)	–
	STAI-B anxiety score	–	–	36.76 (8.0)
	MADRS depression score	–	–	1.59 (2.2)
Neuroimaging AD markers	Global Aβ, [^{18}F]-NAV4694 SUVR	–	1.32 (0.3)	–
	Global Aβ, [^{18}F]-AV45 SUVR	–	–	0.94 (0.2)
	Aβ +/-[a]	–	18 / 95	12 / 56
	Entorhinal cortex tau, [^{18}F]-AV1451 SUVR	–	1.08 (0.1)	–
	Inferior temporal cortex tau, [^{18}F]-AV1451 SUVR	–	1.16 (0.1)	–
RNT	PTQ: closest to PET scan	–	16.42 (9.6)	19.4 (10.9)
	PTQ: 1st administration	17.0 (10.5)	16.8 (9.5)	–

Data are presented as mean (standard deviation) of participants unless otherwise indicated.
Abbreviations: Aβ, amyloid beta; APOE, apolipoprotein E; GAI, Geriatric Anxiety Inventory; GDS, Geriatric Depression Scale; IMAP+, Multi-Modal Neuroimaging in Alzheimer's Disease; MADRS, Montgomery-Asberg Depression Rating Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PREVENT-AD, Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer's Disease; PTQ, Perseverative Thinking Questionnaire; RNT, repetitive negative thinking; STAI-B, State-Trait Anxiety Inventory part B; SUVR, standard uptake volume ratio.
[a]Aβ positivity was determined using cohort specific cutoffs (see supporting information for detail).

2.3 | Behavioral measures

2.3.1 | Repetitive negative thinking

The 15-item self-report Perseverative Thinking Questionnaire (PTQ)[26] was used in PREVENT-AD and IMAP+, either in the original English form or translated into French by native speakers. Participants respond to questions about how they typically think about negative experiences using Likert scales that range from 0 (never) to 4 (almost always). All items are positively scored, and higher scores reflect higher levels of RNT. Total scores range from 0 to 60. The PTQ was designed to measure content-independent levels of RNT and has been validated for use in both clinical and non-clinical populations.[26]

2.3.2 | Depression

PREVENT-AD

Participants completed the 15-item Geriatric Depression Scale (GDS), which screens for depressive symptoms in older adults, and has a maximum total score of 15.[27]

IMAP+

Participants completed the Montgomery and Asberg Depression Rating Scale (MADRS), a 10-item semi-structured interview that measures depressive symptoms. It has a maximum total score of 60,[28] and correlates highly with the GDS.[29]

2.3.3 | Anxiety

PREVENT-AD

Participants completed the 20-item Geriatric Anxiety Inventory (GAI) self-report questionnaire, which screens for anxiety symptoms in older adults and has a maximum total score of 20.[30]

IMAP+

Participants completed the trait subscale of the State-Trait Anxiety Inventory (STAI-B), a 20-item self-report questionnaire that assesses habitual anxiety tendencies. Scores range from 20 to 80,[31] and correlate with the GAI.[30]

2.3.4 | Cognition

The MMSE and the Montreal Cognitive Assessment (MoCA) are screening tools for assessing global cognitive function in older adults. The MMSE was completed by participants in PREVENT-AD and IMAP+ who underwent neuroimaging scans, and the MoCA was completed by the PREVENT-AD participants at enrolment who completed cognitive tests.

PREVENT-AD

The Repeatable Battery for Assessment of Neuropsychological Status (RBANS)[32] was used to measure cognitive performance. The RBANS consists of 12 cognitive tests which yield a global score and five domain-specific index scores: immediate memory, delayed memory, attention, spatial cognition, and language. All measures are standardized, with a mean score of 100 and standard deviation of 15 (see Randolph et al. [32] for details). Cognitive performance was measured at 12-month intervals for up to 48 months, using different test versions at each time point to minimize practice effects.

2.4 | Image acquisition and processing

PREVENT-AD

Participants underwent PET imaging using [^{18}F]-NAV4694 to assess Aβ burden and [^{18}F]-AV1451 to assess tau burden. T1-weighted magnetic resonance imaging (MRI) from an MPRAGE sequence were used to assist with PET processing (see supporting information for detailed procedures). Briefly, for both Aβ and tau scans, the mean standardized uptake value ratio (SUVR) for each participant was extracted across both hemispheres from the cortical Desikan-Killiany regions. A global neocortical Aβ index value was calculated by taking the mean SUVR in typical AD signature regions,[33] namely medial and lateral regions in the frontal, parietal, and temporal lobes. The inferior temporal and entorhinal cortical regions were selected as regions of interest (ROIs) for tau-PET analyses because of autopsy and imaging evidence for early pathological deposition in these regions, and sensitivity to differentiate impaired versus non-impaired individuals.[34,35]

IMAP+

The procedures for imaging data handling, transformation, and determination of amyloid positivity are similar to those used in[36] and described in the supporting information. Briefly, [^{18}F]-AV45florbetapir-PET images were corrected for partial volume effects and spatially normalized to generate SUVRs. The global neocortical Aβ index was obtained in each individual from the florbetapir-PET SUVR images using a neocortical mask.[37]

2.5 | Statistical analyses

The associations between RNT and potential confounders (ie, demographic characteristics, MMSE/MoCA, symptoms of depression and anxiety) were investigated using separate linear regression models with RNT as the outcome. APOE status was dichotomized into ε4-positive and ε4-negative.

In PREVENT-AD, the assessment of RNT was added to an ongoing study. All participants filled in the questionnaire in Autumn 2016 (see supporting information for detailed information about timing of RNT data collection relative to neuroimaging and cognitive assessments). A second measure of RNT was completed 1 year later by 200 (68%) participants. The relative stability of RNT over time was examined to address whether the collection time of the first RNT assessment in relation to the cognitive assessments would influence temporality assumptions of the study. This was done by computing the intraclass correlation coefficient (ICC) for RNT across the interval between the two RNT measurements. We further examined whether change in RNT was associated with amyloid and tau levels using the models described below.

The relationship between RNT and change in cognition over time was examined using linear mixed effects models, which are robust to unbalanced and incomplete data in longitudinal designs.[38] These models allowed for the inclusion of all eligible data points for a given analysis. Missing data in PREVENT-AD reflect in large part the ongoing study recruitment (ie, follow-up visits have yet to be conducted, rather than participant dropout). Logistic regression analyses showed no associations with any variable and missing data across time points, and that only sex was associated with missing data at individual time points. Sex was included as a covariate in the models along with other potentially confounding variables.

Separate models were fitted for each of the six raw composite scores from the RBANS (global cognition, immediate memory, delayed memory, attention, visuospatial cognition, and language), with fixed effects of RNT, time (0, 12, 24, 36, and 48 months) and the interaction between RNT and time as the main explanatory variables. Similar models were fitted with either depression or anxiety and their respective interactions with time as the main explanatory variable, and cognitive scores as the outcome. All models included fixed effects of sex, age at enrolment, educational level, APOE status, and their interactions with time as covariates, permitting both absolute values of the cognitive outcomes and their trajectories over time to vary according to different values of these measures. A random effect of individual was specified to account for repeated measures on participants over time. An unstructured residual covariance matrix allowed the residual variation at each time point and the covariances between pairs of time points to remain unconstrained. Models were estimated using restricted maximum likelihood. Linearity checks were performed and, where there was evidence of departure from linearity, quadratic terms were included in the model.

Unadjusted linear regressions were used to examine the relationships among RNT, Aβ, and tau. Log-10 transformed global Aβ index

or tau (entorhinal or inferior temporal) values were specified as the outcome variable in each model with RNT as the exposure. Similar models were fitted with depression or anxiety as the exposure. Where evidence of an association was observed, an adjusted model was constructed by adding known predictors of Aβ as covariates: age, APOE status, cognitive function (measured using MMSE).[39]

3 | RESULTS

Baseline RNT was not associated with age, MMSE, MoCA, education, or APOE status in either cohort (all $P > .05$); however, it was associated with sex in the PREVENT-AD cohort with women showing higher levels (unstandardized $\beta = 3.44$, 95% confidence interval [CI] 0.76 to 6.17, $P = .012$, female: mean = 17.97, standard deviation [SD] = 10.63, male: mean = 14.54, SD = 9.6). RNT was positively associated with depressive symptoms (PREVENT-AD: unstandardized $\beta = 2.06$, 95% CI 1.56 to 2.56, $P < .001$; IMAP+: unstandardized $\beta = 1.46$, 95% CI 0.31 to 2.61, $P = .01$) and anxiety symptoms (PREVENT-AD: unstandardized $\beta = 1.32$, 95% CI 1.09 to 1.56, $P < .001$; IMAP+: unstandardized $\beta = 0.79$, 95% CI 0.52 to 1.06, $P < .001$). Stability measures of RNT measured at a 1-year interval returned an ICC of 0.75 (95% CI 0.69 to 0.8), considered to show "good" reliability,[40] indicating that scores were relatively stable.

3.1 | Cognitive decline: PREVENT-AD

Of the total sample, cognitive data were available for 288 (98.6%) participants at baseline, 242 (82.9%) at 12 months, 150 (51.4%) at 24 months, 101 (34.6%) at 36 months, and 45 (15.4%) at 48 months. Eleven participants withdrew after baseline, one participant withdrew after the 12-month visit, and one participant was excluded after the 24-month visit (total withdrawal/exclusion 4.4%); the remainder were yet to complete follow-up visits. Because we found strong evidence of an acceleration in decline over time for immediate memory and a deceleration for language we opted to retain quadratic terms for time in models for all six cognitive scores. We found evidence of a faster decline in cognition over time with greater RNT (Table 2 and Figure 1). Global cognition declined 0.40 points per year more quickly for each 1 SD increase on the PTQ scale (standardized $\beta = -0.40$, 95% CI −0.74 to −0.05, $P = .02$). Similar differences in rate of change per additional SD increase on the PTQ scale were observed for both immediate memory (standardized $\beta = -0.62$, 95% CI −1.16 to −0.08, $P = .03$) and delayed memory (standardized $\beta = -0.47$, 95% CI −0.93 to −0.02, $P = .04$). There was weak evidence for a negative association with language (standardized $\beta = -0.40$; 95% CI −0.84 to 0.05, $P = .08$), and no evidence of any difference in rate of change for attention or visuospatial cognition, and likewise little evidence of an association between overall levels of cognition and RNT (all $P \geq .05$).

We found evidence of a faster decline of global cognition with greater depression symptoms (standardized $\beta = -0.46$, 95% CI −0.82 to −0.09, $P = .01$) and weak evidence for decline in immediate memory (standardized $\beta = -0.55$, 95% CI −1.12 to −0.03, $P = .06$) and delayed memory (standardized $\beta = -0.41$, 95% CI −0.89 to 0.07, $P = .09$). We also found evidence of a faster decline of global cognition with greater anxiety symptoms (standardized $\beta = -0.34$, 95% CI −0.68 to −0.00, $P = .05$) and delayed memory (standardized $\beta = -0.57$, 95% CI −1.00 to −0.14, $P = .009$).

3.2 | Amyloid: PREVENT-AD and IMAP+

We found evidence of a positive relationship between RNT and Aβ in the PREVENT-AD cohort, with higher RNT associated with greater Aβ deposition. This finding was replicated in the IMAP+ cohort. By contrast, no evidence of a relationship between depression or anxiety symptoms and Aβ were found in either cohort (Table 3).

PREVENT-AD

In the unadjusted model RNT was associated with global Aβ (standardized $\beta = 0.23$, 95% CI 0.05 to 0.41, $P = .014$), and this relationship was still evident after adjustment for age, APOE status ,and cognitive function (standardized $\beta = 0.19$, 95% CI 0.01 to 0.38, $P = .04$, Figure S1a in supporting information). In the subset of participants who completed the PTQ twice, an increase in RNT was weakly associated with lower global Aβ in the unadjusted model (N = 89; standardized $\beta = -0.20$, 95% CI −0.40 to 0.01, $P = .06$), and significantly associated with lower global Aβ in the adjusted model (N = 88; standardized $\beta = -0.28$, 95% CI −0.48 to −0.09, $P = .004$).

IMAP+

In the unadjusted model RNT was associated with global Aβ (standardized $\beta = 0.26$, 95% CI 0.02 to 0.49, $P = .03$), and this relationship likewise remained in the model adjusted for age, APOE status, and cognitive function (standardized $\beta = 0.24$, 95% CI 0.02 to 0.47, $P = .03$, Figure S1b). Further adjustment for cognitive status (healthy vs subjective cognitive decline [SCD]) did not affect the results (standardized $\beta = 0.25$, 95% CI 0.02 to 0.47, $P = .03$), Adjusting for the time lag between RNT and neuroimaging assessments in participants with these data available slightly reduced the association (standardized $\beta = 0.22$, 95% CI −0.03 to 0.47, $P = .08$).

3.3 | Tau: PREVENT-AD

We found evidence of a positive association between RNT and tau deposition in the entorhinal but not inferior temporal cortex, with higher RNT associated with greater tau deposition. We found no evidence of a relationship between either depressive or anxiety symptoms

TABLE 2 Cross-sectional and longitudinal relationships between (a) RNT and cognition, (b) depressive symptoms and cognition, (c) anxiety symptoms and cognition

	Global Cognition		Immediate Memory		Delayed Memory		Attention		Spatial cognition		Language	
Variable	**Est. (95% CI)**	***P***	**Est. (95% CI)**	***P***	**Est. (95% CI)**	***P***	**Est. (95% CI)**	***P***	**Est. (95% CI)**	***P***	**Est. (95% CI)**	***P***
(a)	RNT											
RNT	−0.05 (−1.03 to 0.94)	.93	0.24 (−0.92 to 1.39)	.69	0.52 (−0.33 to 1.37)	.23	−1.58 (−3.22 to 0.05)	.06	0.23 (−1.16 to 1.61)	.75	0.36 (−0.63 to 1.35)	.48
Time	1.49 (−2.94 to 5.92)	.51	2.25 (−4.76 to 9.26)	.53	6.21 (0.41 to 12.01)	.04	1.40 (−5.50 to 8.31)	.69	−4.92 (−12.47 to 2.63)	.20	2.34 (−3.36 to 8.04)	.42
Time^2	−0.10 (−0.42 to 0.22)	.54	−0.82 (−1.25 to −0.39)	<.001	−0.60 (−0.96 to −0.24)	.001	−0.27 (−0.69 to 0.16)	.22	0.32 (−0.19 to 0.83)	.22	0.99 (0.63 to 1.35)	<.001
RNT × Time	−0.40 (−0.74 to −0.05)	.02	−0.62 (−1.16 to −0.08)	.03	−0.47 (−0.93 to −0.02)	.04	−0.08 (−0.62 to 0.45)	.77	−0.03 (−0.60 to 0.55)	.93	−0.40 (−0.84 to 0.05)	.08
(b)	Depressive symptoms											
Depression symptoms	0.09 (−0.89 to 1.07)	.85	−0.05 (−1.20 to 1.09)	.93	0.36 (−0.50 to 1.21)	.41	−0.45 (−2.08 to 1.18)	.59	0.17 (−1.21 to 1.55)	.81	0.34 (−0.65 to 1.33)	.50
Time	1.52 (−2.86 to 5.90)	.50	2.83 (−4.24 to 9.90)	.43	6.58 (0.70 to 12.45)	.03	1.40 (−5.58 to 8.39)	.69	−4.75 (−12.31 to 2.82)	.22	2.35 (−3.54 to 8.23)	.43
Time^2	−0.13 (−0.46 to 0.19)	.42	−0.87 (−1.31 to −0.44)	<.001	−0.63 (−0.99 to −0.27)	.001	−0.28 (−0.71 to 0.14)	.19	0.31 (−0.20 to 0.83)	.23	0.99 (0.63 to 1.36)	<.001
Depression symptoms × Time	−0.46 (−0.82 to −0.09)	.01	−0.55 (−1.12 to 0.03)	.06	−0.41 (−0.89 to 0.07)	.09	−0.16 (−0.73 to 0.41)	.57	−0.11 (−0.72 to 0.50)	.73	−0.18 (−0.66 to 0.30)	.47
(c)	Anxiety symptoms											
Anxiety symptoms	0.33 (−0.64 to 1.30)	.50	−0.17 (−1.30 to 0.96)	.77	0.76 (−0.07 to 1.59)	.07	−0.46 (−2.09 to 1.16)	.58	0.45 (−0.91 to 1.82)	.51	0.50 (−0.47 to 1.47)	.31
Time	1.17 (−3.37 to 5.71)	.61	2.48 (−4.57 to 9.53)	.49	6.08 (0.33 to 11.84)	.04	1.54 (−5.41 to 8.49)	.66	−4.90 (−12.43 to 2.64)	.20	2.15 (−3.70 to 8.01)	.47
Time^2	−0.12 (−0.43 to 0.20)	.47	−0.84 (−1.27 to −0.41)	<.001	−0.60 (−0.96 to −0.25)	.001	−0.27 (−0.70 to 0.15)	.21	0.32 (−0.19 to 0.83)	.22	1.0 (0.64 to 1.36)	<.001
Anxiety symptoms × Time	−0.34 (−0.68 to −0.00)	.05	−0.41 (−0.93 to 0.11)	.12	−0.57 (−1.00 to −0.14)	.009	0.29 (−0.23 to 0.80)	.27	−0.20 (−0.75 to 0.35)	.47	−0.24 (−0.67 to 0.20)	.29

All estimates are adjusted for age, sex, education, and APOE status.

Note: All estimates, apart from time, are standardized. Time indicates year. Participants, N = 292. Observations, N = 826.

Abbreviations: APOE, apolipoprotein E; CI, confidence interval; RNT, repetitive negative thinking.

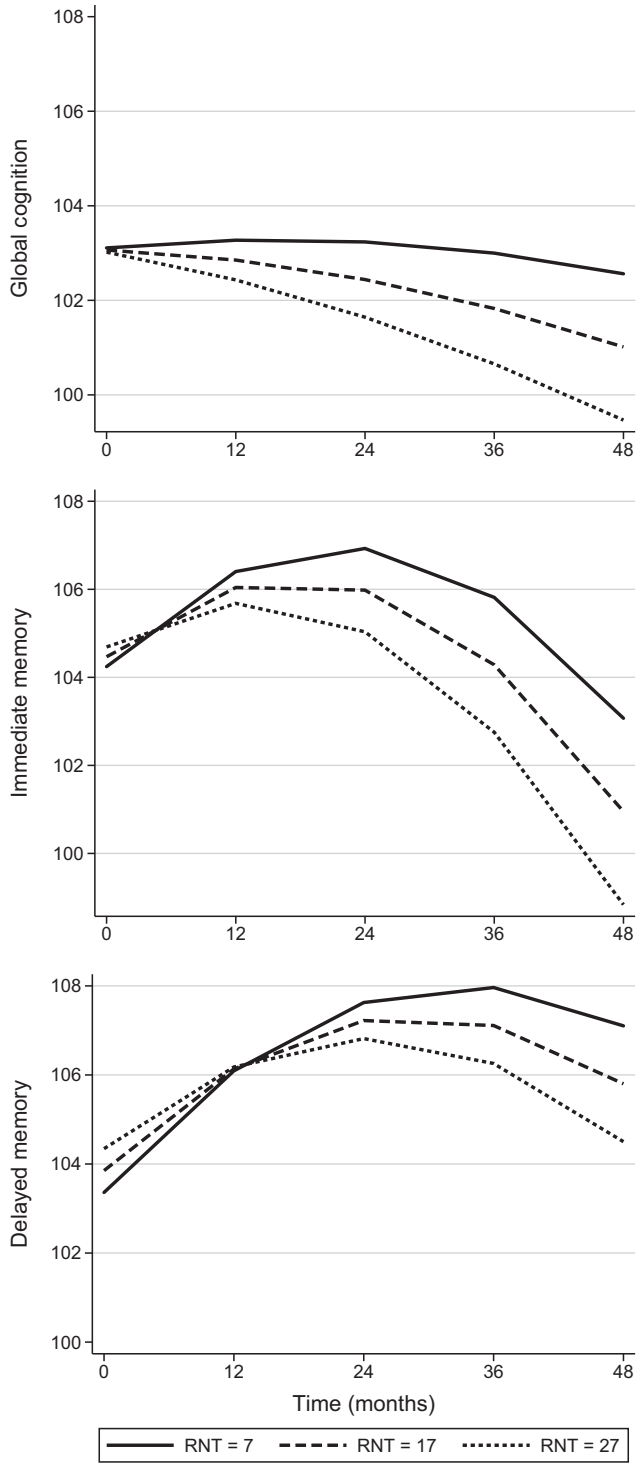

FIGURE 1 Predicted cognitive scores over time for participants with repetitive negative thinking (RNT) scores of 7, 17, and 27 on the Perseverative Thinking Questionnaire (PTQ; approximating −1 standard deviation [SD], mean, and +1 SD RNT scores in our sample). Estimates are for a female participant aged 62.5 years at entry to the study, with some undergraduate education and no APOE ε4 allele from the PREVENT-AD cohort. Note: Education was converted into categories to avoid curvature adjustments for this variable: (1) Elementary to high school, (2) some undergraduate, (3) some postgraduate, and (4) postgraduate, where "some" indicates that the course was started, but not completed

and either measure of tau (Table 3). In the unadjusted model RNT was associated with entorhinal tau (standardized $\beta = 0.23$, 95% CI 0.05 to 0.41, $P = .02$), and evidence of this relationship remained in the model adjusted for age, APOE status, and cognitive function (standardized $\beta = 0.19$, 95% CI 0.01 to 0.37, $P = .04$, Figure S1c). In the subset of participants who completed the PTQ twice, an increase in RNT was not associated with entorhinal or inferior temporal cortical tau in unadjusted or adjusted models (all $P \geq .05$).

4 | DISCUSSION

The current study sought to empirically test the Cognitive Debt hypothesis by investigating, in cognitively intact older adults, the relationship between RNT and markers of AD: cognitive decline, and neuroimaging measures of Aβ and tau. We found that higher levels of RNT were associated with more rapid decline in global cognition, immediate and delayed memory over a 48-month period. Further, RNT was associated with higher levels of tau in the entorhinal cortex (a region of early aggregation), and with global brain amyloid in two independent cohorts. While we found evidence of associations between depression and anxiety symptoms and cognitive change, RNT was the only predictor consistently associated with decline in multiple AD-related cognitive domains. We found no evidence for any relationship between anxiety and depression with neuroimaging AD biomarkers.

While cognitive impairment in preclinical AD can be spread across cognitive domains,[2] two consistent and strong predictors of progression to AD are deficits in episodic memory and global cognition.[2,41,42] The findings from our study show a relationship between RNT and decline in these specific cognitive domains, supporting the proposal that RNT is associated with AD risk. These findings also build on previous work showing worse cognitive performance in adults with high rumination[18] and worry,[21] and extend them to focus on domains specific to AD, namely episodic memory.

In our study, RNT was also associated with global Aβ burden in two independent cohorts of cognitively intact adults that used different tracers and processing methods, and even after accounting for the known predictors of Aβ deposition—age, APOE ε4 status, and cognitive function.[39] RNT was also associated with symptoms of depression and anxiety; however, neither of these symptoms were themselves associated with Aβ pathology.

The inferior temporal and entorhinal cortices have been highlighted as key regions of tau inception and predictors of cognitive impairment based on autopsy data[34,43] and more recent neuroimaging research.[35,44] With increasing evidence that entorhinal tau deposition occurs early,[45] and that inferior temporal cortical deposition occurs later in the pathological AD cascade,[34,35,44] one could argue that RNT's association with entorhinal tau supports its role as an early marker of AD. Alternatively or additionally, as only relatively young, cognitively intact participants were included in this study, they have relatively low levels of tau. Tau deposition may, therefore, not yet have extended from the entorhinal cortex to the inferior temporal region. However, this alternative proposal seems unlikely given that age was

TABLE 3 Variance in neuroimaging biomarkers of Alzheimer's disease (AD) explained by putative psychological AD risk factors

(a)		Amyloid		Tau				(b)		Amyloid	
		Global Aβ [18F]-NAV4694		Entorhinal cortex [18F]-AV1451		Inferior temporal cortex [18F]-AV145				Global Aβ [18F]-AV45	
Variable		Standardized Beta (95% CI)	*P*	Standardized Beta (95% CI)	*P*	Standardized Beta (95% CI)	*P*	Variable		Standardized Beta (95% CI)	*P*
		Unadjusted models								Unadjusted models	
1	RNT	0.23 (0.05 to 0.41)	.01	0.23 (0.05 to 0.41)	.02	0.15 (−0.03 to 0.34)	.11	1	RNT	0.26 (0.02 to 0.49)	.03
3	Depression symptoms	−0.10 (−0.29 to 0.09)	.3	0.1 (−0.09 to 0.28)	.31	0.04 (−0.15 to 0.23)	.69	3	Depression symptoms	0.2 (−0.04 to 0.44)	.1
2	Anxiety symptoms	0.09 (−0.09 to 0.28)	.32	−0.03 (−0.22 to 0.16)	.77	−0.01 (−0.19 to 0.18)	.95	2	Anxiety symptoms	0.12 (−0.12 to 0.36)	.33
		Adjusted model								Adjusted model	
1	RNT	0.19 (0.01 to 0.38)	.04	0.19 (0.01 to 0.37)	.04	0.12 (−0.07 to 0.31)	.22	1	RNT	0.24 (0.02 to 0.47)	.03
	Age	0.17 (−0.02 to 0.36)	.09	0.21 (0.02 to 0.4)	.03	0.19 (−0.00 to 0.39)	.05		Age	0.33 (0.10 to 0.57)	.007
	APOE	0.26 (0.08 to 0.44)	.006	0.17 (0.01 to 0.35)	.06	0.14 (−0.05 to 0.33)	.14		APOE	0.32 (0.09 to 0.55)	.007
	MMSE	0.05 (−0.14 to 0.24)	.58	−0.03 (−0.22 to 0.16)	.75	0.02 (−0.18 to 0.22)	.84		MMSE	0.08 (−0.15 to 0.32)	.47

(a) Predictors of global cortical Aβ and regional tau in the PREVENT-AD cohort, and (b) predictors of globalAβ in the IMAP+ cohort replication study. Standardized beta values are displayed to allow for direct comparison of each variable's contribution. Unadjusted models examine RNT, anxiety, and depressive symptoms as independent explanatory variables in separate models. Only RNT explained AD biomarker variance and was therefore retained in the adjusted model. The adjusted model included RNT, Age, APOE status, and MMSE, and all variables were adjusted for each other.

Note: PREVENT-AD participants, N = 113 for unadjusted amyloid and tau models, N = 111 for adjusted models. IMAP participants, N = 68 for unadjusted and adjusted models.

Abbreviations: Aβ, amyloid beta; APOE, apolipoprotein E; CI, confidence interval; IMAP+, Multi-Modal Neuroimaging in Alzheimer's Disease; MMSE, Mini-Mental State Examination; PREVENT-AD, Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer's Disease; RNT, repetitive negative thinking.

associated with tau deposition in both inferior temporal and entorhinal cortices.

One explanation for RNT's association with Aβ and tau is via the stress pathway. Indeed, RNT is associated with indicators of stress (eg, elevated blood pressure, cortisol) and has been called a behavioral marker of chronic physiological stress.[46] Evidence from the human, animal, and cellular literature suggest that stress and glucocorticoids contribute to Aβ and tau pathogenesis,[47-49] and risk for AD.[50] As RNT levels are relatively stable in absence of intervention, engaging in this cognitive process may chronically activate the stress response, thereby increasing vulnerability to AD.

This study has some limitations. The PREVENT-AD cohort was created to study individuals at elevated risk of dementia (ie, with at least one first-degree relative with AD); therefore, the findings from the current study may not be generalizable to a broader population of older adults. RNT was assessed at different time points and sometimes retrospective to cognitive testing. While RNT levels may have changed over the course of participation, and ideally multiple measures of RNT over time preceding the cognitive assessments are needed to assess stability, we did show that RNT was relatively stable over a 1-year interval. Due to the ongoing nature of the PREVENT-AD study, data were often unavailable for the follow-up cognitive testing. It is important to note that data were largely unavailable due to follow-up visits not yet being conducted, rather than participant dropout, therefore were less likely to be influenced by survivor bias. However, we cannot be sure that the missing data did not bias estimates of magnitude and direction of cognitive trajectories. We tried to mitigate this possibility by using multilevel models of longitudinal data and including factors associated with missingness as covariates. Further, and in line with a widely held view in epidemiology, we did not correct for multiple comparisons.[51] Rather our approach was to transparently report the number of analyses performed.

It should be noted that the means and variances in depression and anxiety scores were relatively lower than seen in the RNT measure in the cohorts that were examined in this study. In a more clinically diverse population, correlations with the depression and anxiety scores may also have been significant. Alternatively, as depression and anxiety were associated with cognitive decline but not amyloid or tau, it may be these symptoms are more indicative of age- or non-specific dementia-related decline whereas RNT may be a more precise marker for AD. Indeed a recent systematic review examining the relationship between depression and Aβ reported equivocal findings,[52] and a separate review examining depression and tau found no evidence of a relationship.[53] Far less research has focused on anxiety; however, there is a small body of evidence reporting relationships between anxiety and AD biomarkers.[54,55] The relatively high degree of variance in RNT levels in two independent populations indicates that the PTQ may be a useful tool to measure AD risk in non-clinical populations. Further replication of these findings along with development of established cut-offs, sensitivity, specificity, and predictive value data must be performed before recommending an RNT questionnaire as a screen for inclusion of high-risk participants in future clinical trials.

Despite the Cognitive Debt hypothesis' proposal that RNT increases risk for AD, the opposite may also be true. Aβ and/or tau may aggregate first, disrupt neural circuitry, which then leads to a difficulty in disengaging from thoughts and elevated RNT (reverse causality). If this were the case, one might expect that higher levels of amyloid and tau would be associated with increases in RNT; however, the preliminary results presented here do not support this argument. Still, this was an observational study with relatively few participants meeting criteria for substantial amyloid deposition (ie, Aβ positive) and no means to assess causality. Investigations using data from longitudinal birth cohorts with multiple neuroimaging measures, or intervention studies, would help address these questions.

In this first empirical investigation of the Cognitive Debt hypothesis, we find evidence for a relationship between RNT, cognitive decline, Aβ and tau burden in cognitively intact older adults. While it is not known whether reducing RNT would reduce risk of AD, this is certainly an avenue worth exploring. Behavioral interventions known to reduce RNT, such as talking therapies[14] or mindfulness,[15] could be examined with cognitive and/or pathological AD markers as outcomes. Ongoing preventative clinical trials targeting the emotional dimension of dementia risk and aging will be able to directly examine these questions (eg, Marchant et al.[56]).

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CONFLICTS OF INTEREST

All authors report no conflicts of interest.

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SUPPORTING INFORMATION

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

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