



Featured Article

Synergistic interaction between amyloid and tau predicts the progression to dementia

Tharick A. Pascoal^a, Sulantha Mathotaarachchi^a, Monica Shin^a, Andrea L. Benedet^{a,b}, Sara Mohades^a, Seqian Wang^a, Tom Beaudry^a, Min Su Kang^a, Jean-Paul Soucy^c, Aurelie Labbe^{d,e}, Serge Gauthier^{f,g}, and Pedro Rosa-Neto^{a,c,f,g,h,*}, for the Alzheimer's disease Neuroimaging Initiative¹

^aTranslational Neuroimaging Laboratory, The McGill University Research Centre for Studies in Aging, Montreal, Canada

^bCAPES Foundation, Ministry of Education of Brazil, Brasilia, Brazil

^cMontreal Neurological Institute, Montreal, Canada

^dDouglas Hospital Research Centre, McGill University, Montreal, Canada

^eDepartment of Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, Canada

^fAD Research Unit, The McGill University Research Centre for Studies in Aging, Montreal, Canada

^gMcGill University, Montreal, Canada

^hDepartment of Neurology and Neurosurgery, McGill University, Montreal, Canada

Abstract

Introduction: Recent literature proposes that amyloid- β and phosphorylated tau (p-tau) synergism accelerates biomarker abnormalities in controls. Yet, it remains to be answered whether this synergism is the driving force behind Alzheimer disease (AD) dementia.

Methods: We stratified 314 mild cognitive impairment individuals using [¹⁸F]florbetapir positron emission tomography amyloid- β imaging and cerebrospinal fluid p-tau. Regression and voxel-based logistic regression models with interaction terms evaluated 2-year changes in cognition and clinical status as a function of baseline biomarkers.

Results: We found that the synergism between [¹⁸F]florbetapir and p-tau, rather than their additive effects, was associated with the cognitive decline and progression to AD. Furthermore, voxel-based analysis revealed that temporal and inferior parietal were the regions where the synergism determined an increased likelihood of developing AD.

Discussion: Together, the present results support that progression to AD dementia is driven by the synergistic rather than a mere additive effect between amyloid- β and p-tau proteins.

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Keywords:

Alzheimer disease; Amyloid-PET; Mild cognitive impairment; Neuropsychological tests; Phosphorylated tau

¹Data used in preparation of this article were obtained from the AD Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

*Corresponding author. Tel.: +1-514-761-6131, ext.3407; Fax: +1-514-888-4050.

E-mail address: pedro.rosa@mcgill.ca

<http://dx.doi.org/10.1016/j.jalz.2016.11.005>

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1. Introduction

Alzheimer disease (AD) is characterized by the progressive accumulation of extracellular amyloid- β (A β) plaques, intracellular inclusions of hyperphosphorylated tau in tangles, and neuronal degeneration [1]. The most widely accepted model of AD progression proposes a cascade of neuropathological events in which abnormal levels of A β , neurofibrillary tangles, and neurodegeneration precede dementia [1]. The idea of pathophysiological progression was incorporated by the

National Institute on Aging and the Alzheimer's Association criterion for predementia phase of AD, which recognizes that the coexistence of abnormal A β and neurodegeneration biomarkers better identify mild cognitive impairment (MCI) patients who will progress to dementia [2]. This notion has been supported by recent observations demonstrating that MCI A β + individuals with neurodegenerative changes, measured by brain hypometabolism or atrophy, have higher rates of neuropsychological decline as compared with MCI biomarker negative participants [3–5]. Yet, a key question that remains unanswered is whether the highest rate of progression to dementia in MCI A β + individuals with downstream cascade abnormalities is due to a synergistic effect between the coexistent brain pathologies or simply the sum of their deleterious effects. This question is particularly important in the context of the two hallmark proteinopathies underlying AD [6]. Although A β and phosphorylated tau (p-tau) proteins well characterize AD pathophysiology, brain hypometabolism or atrophy may be found in several other brain disorders associated with neuronal loss [2,7].

Given the emphasis of the current literature on the combination of A β and neuronal degeneration biomarkers [3–5,8], the clinical fate of MCI patients with abnormal A β plus p-tau proteins is scarcely known. The importance of characterizing the synergistic effect between A β and p-tau on the development of dementia goes beyond the understanding of the mechanisms of disease progression. Determination of such synergism has immediate implications for the population enrichment of clinical trials testing anti-amyloid or anti-tau therapy. For example, if A β and p-tau synergistically determine dementia, the enrichment of clinical trial populations with carriers of both pathologies would increase the rate of clinical progression without loss of therapeutic effectiveness. Conversely, if A β and p-tau simply add their deleterious effects on cognitive decline, carriers of both pathologies would lead to a reduced therapeutic effectiveness of an intervention targeting only one of these proteinopathies, given the residual effect of the untreated protein on the clinical course of the disease.

Although several studies have shown that A β and p-tau independently predict disease progression [9,10], a hypothetical framework proposes that both proteinopathies synergistically potentiate downstream neurodegeneration [11]. The presence of such a synergism would suggest that the effect of A β and p-tau on the progression of AD taken together is greater than the sum of their separate effects at the same level. In fact, recent findings from our laboratory support this framework showing that the synergistic effect between brain A β and p-tau rather than neurodegeneration drives AD-related metabolic decline in a cognitively normal population [12]. Similarly, *in vivo* studies conducted in controls have suggested that p-tau modulates the link between A β and brain atrophy or behavioral changes [13–15], whereas animal model literature has demonstrated a synergistic effect between A β and p-tau peptides, leading to downstream synaptic and neuronal dysfunctions [16].

Here, in a longitudinal analysis conducted in amnesic MCI individuals, we tested the hypothesis that the synergism between A β aggregation and tau hyperphosphorylation determines progression from amnesic MCI to AD dementia.

2. Materials and methods

2.1. Database description and study participants

Data used in the preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database. ADNI was launched in 2003 as a public-private partnership, led by a principal investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), cerebrospinal fluid (CSF), and clinical assessment can be combined to measure the progression of MCI and early AD.

For the present study, we selected 314 ADNI-GO/2 participants meeting the criteria for single-domain or multidomain amnesic MCI, who underwent lumbar puncture and [18 F]florbetapir PET imaging at baseline as well as neuropsychological assessments at both baseline and at a 2-year follow-up. The eligibility criteria for selecting MCI were participants who had a Mini-Mental State Examination (MMSE) score equal to or greater than 24, a clinical dementia rating of 0.5, subjective and objective memory loss, and absence of other neuropsychiatric disorders [17]. (Further information about the inclusion/exclusion criteria may be found at www.adni-info.org [accessed September 2016].)

2.2. CSF analyses

The multiplex xMAP Luminex platform (Luminex Corp, Austin, TX, USA) was used to quantify p-tau at threonine 181 using INNO-BIA AlzBio3 immunoassay kit-based reagents (Innogenetics, Ghent, Belgium). All of the CSF p-tau data used in this study were obtained from the ADNI files "UPENNBBIOMK5-8.csv." The data were statistically rescaled based on the baseline assay analysis that was used to define the CSF p-tau threshold [18]. We considered a subject positive for tau hyperphosphorylation if the CSF p-tau value was above the ADNI published threshold (>23 pg/mL) [19,20]. (Further details can be found at www.adni-info.org [accessed September 2016].)

2.3. MRI/PET methods

The schematic representation of the image analysis methods is presented in Fig. 1. The [18 F]florbetapir standardized uptake value ratio (SUVR) was obtained using the cerebellum gray matter and global white matter as reference regions. A global [18 F]florbetapir SUVR value for each subject was estimated by averaging the precuneus, prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate cortices. The cutoff value was established based on the 10th percentile of the [18 F]florbetapir SUVR

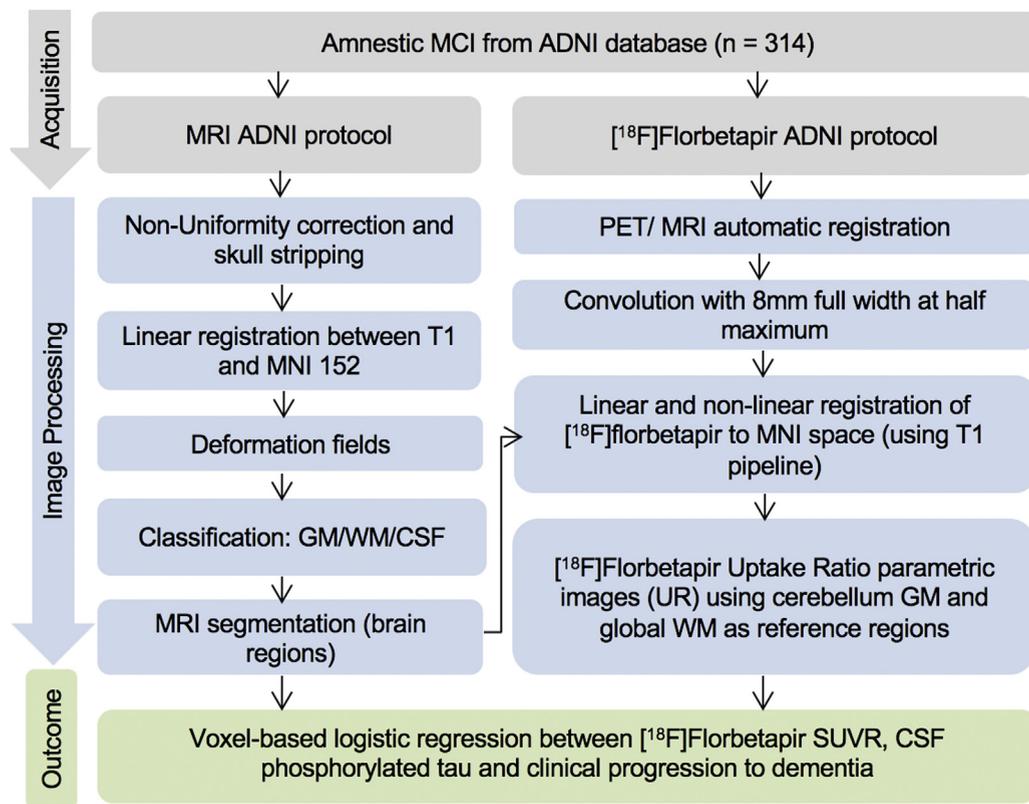


Fig. 1. Schematic representation of the image analysis methods. Abbreviations: ADNI, Alzheimer's disease Neuroimaging Initiative; CSF, cerebrospinal fluid; GM, gray matter; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography; SUVR, standardized uptake value ratio; WM, white matter.

distribution of the ADNI AD population ($n = 90$), which corresponds to 90% sensitivity for a diagnosis of AD. This approach was based on previous publications that performed similar types of analyses in individuals segregated by $A\beta$ and neurodegeneration biomarkers [3–5]. Using this approach, individuals were considered positive for $A\beta$ deposition if [^{18}F]florbetapir SUVR > 1.12 . Finally, gray-matter density was computed at every voxel using voxel-based morphometry. (Details about ADNI image acquisitions may be found at www.adni-info.org [accessed September 2016].)

2.4. Cognitive measurements

The Logical Memory subtest of the Wechsler Memory Scale was used to assess immediate recall memory (LMI) and 30-minute delayed recall memory (LM30). Psychomotor speed processing was assessed with the Trail Making Test part A (TMT-A). The performance of participants on the Trail Making Test part B (TMT-B) was assessed to examine executive function. Category fluency animals were used to evaluate language. To assess the global cognitive performance, we used MMSE and Alzheimer's disease Assessment Scale–Cognitive Subscale (ADAS-Cog) scores. For TMT-A and TMT-B tests, and ADAS-Cog higher scores indicate poorer performance. (Details about tests acquisition may be found at www.adni-info.org [accessed September 2016].)

2.5. Biomarker-based stratification of participants

For analysis purposes, we divided the 314 MCI participants into four biomarker groups using the previously described [^{18}F]florbetapir and p-tau thresholds. At baseline, out of 314 individuals, 47 (15%) were biomarker negative ($A\beta^-/p\text{-tau}^-$), 37 (12%) had only abnormal [^{18}F]florbetapir ($A\beta^+/p\text{-tau}^-$), 62 (20%) had only abnormal p-tau ($A\beta^-/p\text{-tau}^+$), and 168 (53%) showed abnormal [^{18}F]florbetapir and p-tau ($A\beta^+/p\text{-tau}^+$).

2.6. Statistical methods

The statistical analyses were performed using the R Statistical Software Package version 3.1.2 with RMINC library (<http://www.r-project.org/>; accessed September 2016). Neuropsychological test scores were analyzed using z-scores anchored in normative data obtained from the ADNI cognitively normal controls ($n = 162$). Controls had a MMSE of 24 or greater, a CDR of 0, had no neuropsychiatric diagnosis including MCI and dementia, and performed the same protocols for data collection as the studied MCI population. All analyses involving neuropsychological measurements were repeated for each of the seven neuropsychological tests at baseline as well as for longitudinal changes between baseline and follow-up, where cognitive progression was measured using the difference between z-scores.

Analysis of covariance (ANCOVA) was performed to test for significant differences between groups (coded as a factor with four levels) on neuropsychological functions. *P* values were corrected for multiple comparisons using Bonferroni, and a significance level of .05 was used to interpret the results. Post hoc analysis provided significant differences between groups.

To evaluate the synergistic effect between A β and p-tau on neuropsychological changes, ANCOVA models were fitted using both biomarkers as main effects as well as an interaction term between biomarkers.

$$\begin{aligned} \Delta NPS = & \beta_0 + \beta_1(\text{florbetapir status}) + \beta_2(\text{ptau status}) \\ & + \beta_3(\text{florbetapir status} * \text{ptau status}) \\ & + \text{covariates} + \text{error} \end{aligned}$$

To evaluate if A β and p-tau values predict cognitive changes across biomarker groups, a stratified linear regression analysis was performed in each of the four biomarker groups using change in test as the outcome and biomarker levels as the main covariate. Another model was fitted to evaluate if the effect of biomarker levels on cognitive changes differed significantly between the biomarker groups by adding in the model a main effect for biomarker groups, as well as an interaction term between biomarker groups and biomarker levels.

$$\begin{aligned} \Delta NPS = & \beta_0 + \beta_1(\text{florbetapir SUVR or ptau continuous}) \\ & + \beta_2(\text{biomarker groups}) + \beta_3(\text{florbetapir SUVR} \\ & \text{or ptau continuous} * \text{biomarker groups}) \\ & + \text{covariates} + \text{error} \end{aligned}$$

Subsequently, to characterize the effects of abnormal A β and p-tau status on the clinical progression to dementia, a logistic regression analysis was performed using progression as the outcome, biomarker status as the two main effects, and an interaction term between biomarkers.

2.7. Voxel-based logistic regression analysis

Furthermore, to identify the brain regions susceptible to the synergism between A β and p-tau, a voxel-based logistic regression model was built to test the interactive and main effects between CSF p-tau status and [¹⁸F]florbetapir SUVR at every brain voxel on the likelihood of developing dementia [21], assuming the probability of progression as \hat{p} , (progression=1).

$$\begin{aligned} \log\left(\frac{\hat{p}}{1-\hat{p}}\right) = & \beta_0 + \beta_1(\text{florbetapir SUVR}) + \beta_2(\text{ptau status}) \\ & + \beta_3(\text{florbetapir SUVR} * \text{ptau status}) \\ & + \text{covariates} + \text{error} \end{aligned}$$

The voxel-based statistical parametric maps were corrected for multiple testing. Statistical significance was defined using a Random Field Theory at a threshold of

$P < .001$ [22]. We further adjusted the voxel-based model for the gray-matter density at every voxel to correct our results for gray-matter atrophy effects [21].

All analyses were adjusted for age, gender, years of formal education, *APOE* $\epsilon 4$ status, and baseline neuropsychological scores (only for models involving longitudinal changes), and varying intervals between cognitive assessments were also considered in the models.

3. Results

Demographics and key population characteristics are summarized in Table 1. The biomarker groups did not differ in age, gender, or years of education. The proportion of *APOE* $\epsilon 4$ carriers was higher in A β +/p-tau+ (63%) than in the other three groups (24%) ($P < .001$).

3.1. Synergistic effect between A β and p-tau predicts the rate of cognitive decline in MCI individuals

ANCOVA models revealed that the A β +/p-tau+ group had the worst baseline score and the highest rate of decline in most of the neuropsychological tests when compared with all other biomarker groups (Fig. 2). Interestingly, the baseline and longitudinal cognitive performances of the A β +/p-tau- and A β -/p-tau+ groups were similar to those of the biomarker negative group (Fig. 2). Notably, our regression models confirmed that the synergistic interaction, rather than the sum of individual contributions of A β + and p-tau+ status, determined worse baseline performance or higher rate of impairment over time on the MMSE, ADAS-Cog, LMI, LM30, and TMT-B for the A β +/p-tau+ group ($P < .05$).

3.2. A β and p-tau values predict cognitive decline only among MCI A β +/p-tau+ individuals

Stratified regression analysis revealed that high [¹⁸F]florbetapir SUVR values predicted poorer longitudinal performance in all neuropsychological tests in A β +/p-tau+ group (Table 2). By contrast, [¹⁸F]florbetapir SUVR values did not predict longitudinal changes on any of the tests in biomarker negative, A β +/p-tau- and A β -/p-tau+ groups, or in models evaluating these three groups together. Interaction models between [¹⁸F]florbetapir SUVR values and biomarker groups confirmed that the prediction slope of [¹⁸F]florbetapir SUVR was significantly higher in A β +/p-tau+ as compared to the other biomarker groups in all neuropsychological tests (MMSE, $P = .002$; ADAS-Cog, $P = .001$; LMI, $P = .04$; LM30, $P < .0001$; TMT-A, $P = .03$; TMT-B, $P = .04$; Category Fluency, $P = .03$).

Stratified regression analysis revealed that high CSF p-tau continuous values predicted worse scores in MMSE, ADAS-Cog, LMI, and LM30 only in the A β +/p-tau+ group (Table 2). Interaction models between CSF p-tau values and the biomarker groups showed that the effects of CSF p-tau values in predicting declines in LMI

Table 1
Demographics and key characteristics of the amnesic MCI population

Characteristics	A β -/p-tau-	A β +/p-tau-	A β -/p-tau+	A β +/p-tau+	P values
No.	47	37	62	168	
Age, years, mean (SD)	71 (7.6)	70.2 (7.2)	71 (8.1)	72.6 (7.1)	.16
Male, no. (%)	31 (66)	17 (46)	33 (54)	87 (52)	.34
APOE ϵ 4, no. (%)	9 (19)	11 (30)	15 (24)	105 (63) ^{a,b,c}	<.0001
Education, years, mean (SD)	17.1 (2.2)	15.6 (2.4)	16.3 (2.7)	16.4 (2.6)	.05
[¹⁸ F]Florbetapir, mean SUVR (SD)	1.07 (0.04)	1.18 (0.07) ^{a,c}	1.05 (0.05)	1.34 (0.11) ^{a,b,c}	<.0001
CSF p-tau, mean pg/mL (SD)	18.5 (3.9)	17.4 (4)	37 (12.8) ^{a,b}	53.5 (24.1) ^{a,b,c}	<.0001
Diagnostic at follow-up, no. (%)					
Cognitively normal	2 (4)	3 (8)	1 (2)	6 (4)	.45
MCI	43 (92)	33 (89)	59 (95)	108 (64)	—
Dementia	2 (4)	1 (3)	2 (3)	54 (32) ^{a,b,c}	<.0001

Abbreviations: MCI, mild cognitive impairment; A β , amyloid- β ; p-tau, phosphorylated tau; SD, standard deviation; SUVR, standardized uptake value ratio; CSF, cerebrospinal fluid.

NOTE. P values indicate the values assessed with analyses of variance for each variable except gender, APOE ϵ 4, and diagnostic at follow-up, where a contingency chi-square was performed. Post hoc analysis provided significant differences between groups: ^afrom A β -/p-tau-; ^bfrom A β +/p-tau-; ^cfrom A β -/p-tau+.

and LM30 were significantly higher in A β +/p-tau+ when compared with other biomarker groups ($P < .01$).

3.3. Synergistic effect between A β and p-tau predicts progression from MCI to AD

Although A β + and p-tau+ status independently predicted dementia ($P < .05$), a significant interaction term with no significant main effects between A β and p-tau status on progression to dementia revealed that A β +/p-tau+ individuals showed a rate of progression greater than the sum of the independent contributions of A β + and p-tau+ ($P < .05$).

Furthermore, a multivariate logistic regression revealed that the presence of A β +/p-tau+ was the strongest factor associated with developing dementia with a 14.1-fold (95% CI 5.7–38, $P < .0001$) increase in likelihood of progression. APOE ϵ 4 status (OR = 5.7, 95% CI 3.1–12, $P < .0001$) also predicted likely progression to dementia. Furthermore, [¹⁸F]florbetapir SUVR values (OR = 2.0, 95% CI 1.31–3.1, $P = .001$) and CSF p-tau values (OR = 1.47, 95% CI 1.14–1.96, $P = .004$) predicted dementia exclusively in A β +/p-tau+ group.

The overall progression rate to probable AD dementia of this study was 19% over 2 years. Among A β -/p-tau-, A β +/p-tau-, A β -/p-tau+, and A β +/p-tau+ participants, the progression rate was 4%, 3%, 3%, and 32%, respectively (Fig. 3). Out of 59 participants who converted to dementia, 54 (92%) were A β +/p-tau+ at baseline.

3.4. Synergistic effect between A β and p-tau in temporoparietal regions predicts progression from MCI to AD

Voxel-based logistic regression analysis revealed that lateral and basal temporal and inferior parietal cortices are the brain regions where the synergistic effect between [¹⁸F]florbetapir SUVR and CSF p-tau determined the increased likelihood of progression from amnesic MCI to AD dementia over a 2-year period (Fig. 4).

4. Discussion

In this study, we found that amnesic MCI A β +/p-tau+ individuals had the highest rate of cognitive decline and progression to dementia, as compared to all other biomarker groups. Remarkably, our regression models confirmed that a synergistic rather than additive effect between A β and p-tau determined greater cognitive decline and clinical progression in amnesic MCI A β +/p-tau+. Furthermore, we found that only among amnesic MCI A β +/p-tau+ individuals, did the baseline values of A β and p-tau biomarkers predict cognitive and clinical impairments. Finally, a voxel-based analysis revealed that the temporal and inferior parietal cortices were the brain regions vulnerable to the synergism between A β and p-tau peptides.

Overall, our results suggest the synergism between A β and p-tau as an important element involved in the progression from amnesic MCI to AD dementia. This finding extends previous studies conducted in cognitively normal persons demonstrating that the synergism between A β and p-tau determines functional and structural abnormalities [12–15]. Interestingly, the temporal and inferior parietal cortices described here as the structural substrates in which the A β and p-tau synergistic effect conferred an increased likelihood of clinical progression, are well known as vulnerable brain regions in patients who progressed from MCI to dementia [23]. Indeed, the synergistic effect between A β and p-tau reported here is well supported by molecular studies describing synaptic and neuronal damages as consequences of the synergistic interactions between A β and tau peptides [16,24,25].

This study revealed that the link between A β levels and progression to AD dementia depends on the p-tau status. This finding sheds light on the literature showing conflicting results reporting the association between A β and cognition. Although the majority of studies describe a modest association in early disease stages [26–30], others suggest that A β

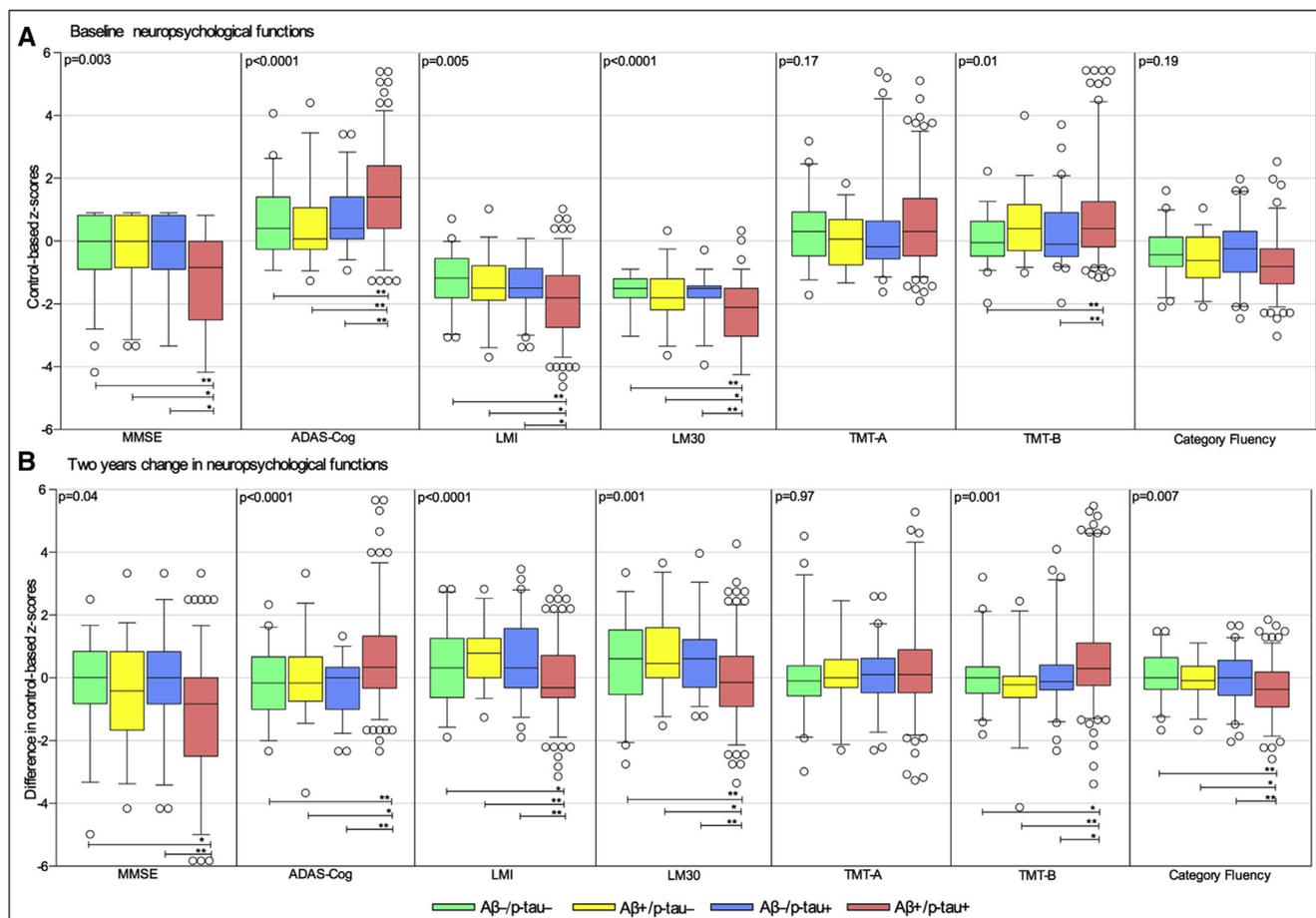


Fig. 2. The amnesic MCI $A\beta^+/p\text{-tau}^+$ individuals present the lowest baseline scores and the highest rate of decline in most neuropsychological functions. The values are presented in z-scores anchored in normative data of a cognitively normal population. In the box and whisker plots, the lower and upper boundaries show the 25th and 75th percentiles, respectively, whereas the horizontal line shows the median. The dots represent mild cognitive impairment (MCI) individuals less than the fifth or higher than the 95th percentile. Bonferroni-corrected P values for multiple comparisons indicate the values assessed with analyses of covariance adjusted for age, gender, years of education, APOE $\epsilon 4$ status, and baseline neuropsychological test score for longitudinal analysis. Post hoc multiple comparison analysis provided significant differences between biomarker groups for each neuropsychological test at $*P < .05$ and $**P < .001$. (A) At baseline, the $A\beta^+/p\text{-tau}^+$ group presented the lowest baseline scores in Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), logical memory immediate recall (LMI), and 30-minute delayed recall (LM30). The $A\beta^+/p\text{-tau}^+$ group showed worse performance in the Trail Making Test part B (TMT-B) than the $A\beta^-/p\text{-tau}^-$ and $A\beta^-/p\text{-tau}^+$ groups. (B) The $A\beta^+/p\text{-tau}^+$ group presented the highest longitudinal impairment in all neuropsychological tests except TMT-A and MMSE. $A\beta^+/p\text{-tau}^+$ group showed higher decline in MMSE than $A\beta^-/p\text{-tau}^-$ and $A\beta^-/p\text{-tau}^+$ groups. Notably, $A\beta^-/p\text{-tau}^-$, $A\beta^+/p\text{-tau}^-$, and $A\beta^-/p\text{-tau}^+$ groups did not differ from each other in any baseline or longitudinal cognitive performance. Abbreviations: $A\beta$, amyloid- β ; p-tau, phosphorylated tau.

levels strongly predict cognitive decline in populations with a high probability to present p-tau abnormalities [9,13]. Interestingly, $A\beta$ levels fail to predict time-to-progression to dementia in MCI $A\beta^+$ individuals with evidences of brain hypometabolism or atrophy [4]. One might claim that $A\beta$ levels represent an important predictor of forthcoming dementia, particularly in predementia persons with p-tau abnormalities [2].

Suspected non-Alzheimer disease pathophysiology (SNAP) has emerged as an important concept referring to patients showing a biomarker signature of neurodegeneration without $A\beta$ abnormalities [9]. As the concept of SNAP arises in our study as the group of MCI $A\beta^-/p\text{-tau}^+$ individuals [9], we would like to comment on the clinical progression of this population. Previous studies have

demonstrated that in SNAP MCI, characterized by the presence of neuronal degeneration evidenced by brain hypometabolism or atrophy, the rate of cognitive decline is higher than in MCI individuals who are biomarker negative and comparable to MCI carriers of $A\beta$ -plus neurodegeneration [4–6]. In contrast, we demonstrate here that SNAP MCI $A\beta^-/p\text{-tau}^+$ subjects clinically progress at a rate similar to that of MCI subjects who are biomarker negative. This reduced rate of progression of our SNAP MCI $A\beta^-/p\text{-tau}^+$ population may be explained by the fact that CSF p-tau reflects neurofibrillary tangles pathology rather than neuronal degeneration [7]. Importantly, the clinical stability of MCI $A\beta^-/p\text{-tau}^+$ participants supports the synergism between $A\beta$ and p-tau pathologies as a key element triggering AD dementia [1,10]. The reduced rate of clinical progression

Table 2
Predictive biomarker effects on neuropsychological functions in amnesic MCI participants according to biomarker groups

Tests	A β -/p-tau-		A β +/p-tau-		A β -/p-tau+		A β +/p-tau+	
	[¹⁸ F]Florbetapir	CSF p-tau						
MMSE (SE)	0.23 (1.07)	-0.34 (0.95)	-0.16 (0.53)	0.96 (1.26)	0.83 (0.61)	-0.5 (0.3)	-1.16 (0.25)**	-0.36 (0.15)*
ADAS-cog (SE)	-1.49 (1.87)	2 (2.08)	-0.04 (0.97)	1.87 (2.3)	-0.39 (0.94)	0.82 (0.42)	0.99 (0.45)*	0.52 (0.26)*
LMI (SE)	2.5 (2.24)	-4.1 (2.5)	0.3 (0.98)	-0.79 (2.55)	1.6 (1.28)	0.1 (0.67)	-1.39 (0.32)**	-0.68 (0.19)**
LM30 (SE)	0.42 (2.77)	-6.9 (3)	2 (1.19)	-2.5 (2.9)	1.7 (1.37)	-0.43 (0.65)	-1.30 (0.39)**	-0.79 (0.23)**
TMT-A (SE)	5.6 (8.2)	4.2 (9.2)	-11.7 (5.9)	-8.9 (14)	-3.7 (3.78)	1.5 (1.88)	5.30 (1.6)*	1.11 (1.04)
TMT-B (SE)	6.2 (21.4)	36 (23)	-11.45 (15.5)	-17 (36)	18.33 (17.58)	-3.5 (8.5)	16.62 (5.9)*	4.95 (3.75)
Category Fluency (SE)	-3.33 (2.2)	-6.14 (2.5)	1.73 (1.26)	-1.6 (3.08)	-0.93 (1.57)	0.29 (0.76)	-2.25 (0.48)**	-0.52 (0.24)

Abbreviations: MCI, mild cognitive impairment; A β , amyloid- β ; p-tau, phosphorylated tau; MMSE, Mini-Mental State Examination; SE, standard error; LMI, Logical Memory immediate recall; LM30, Logical Memory 30-minute delayed recall.

NOTE. The results are presented in change (slope coefficient) of neuropsychological test score per standard deviation of baseline biomarker. For the Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-cog), Trail Making Test part A (TMT-A) and B (TMT-B) greater values reflect worse cognition. The models were adjusted for age, gender, years of education, *APOE* $\epsilon 4$ status, baseline test score, and Bonferroni-corrected for multiple comparisons. It is important to emphasize that [¹⁸F]florbetapir and p-tau values did not significantly predict longitudinal cognition in biomarker negative, A β +/p-tau-, and A β -/p-tau+ individuals. Significance at * $P < .05$; ** $P < .001$.

of our SNAP MCI A β -/p-tau+ group as compared to that observed in previous studies may be due to the presence of a significant proportion of MCI individuals who are in the early clinical stages of MCI in the ADNI-GO/2 cohort [11,12]. This is consistent with studies on cognitively normal individuals showing that SNAP progresses at a rate similar to that of biomarker negative subjects [3,13]. Furthermore, it is possible that the cognitive decline observed in SNAP MCI in previous studies, defined by less-specific biomarkers for AD such as brain hypometabolism or atrophy, was driven by other pathophysiological

processes such as TDP-4, alpha-synuclein inclusions, and hippocampal sclerosis [14,15]. Together, these results support that SNAP MCI individuals characterized by the presence of p-tau pathology, different from those with SNAP MCI defined by neuronal degeneration biomarkers, clinically progress at rates comparable to those seen in MCI biomarker negative individuals.

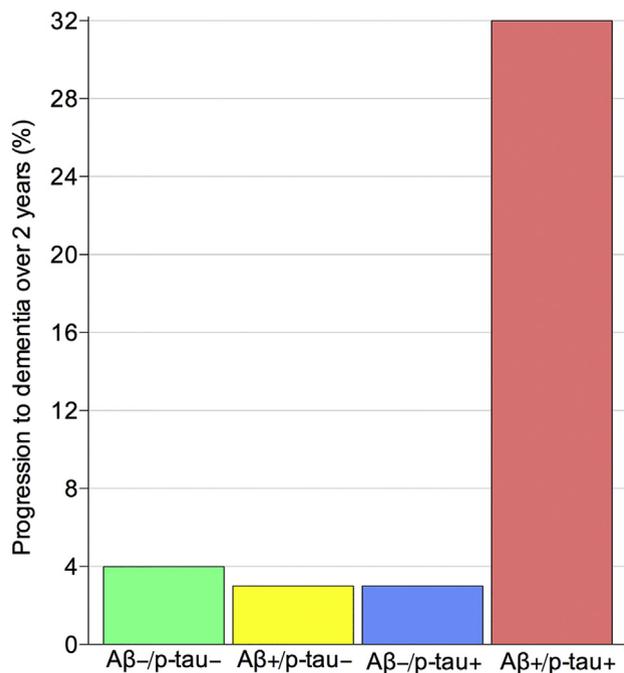


Fig. 3. A β +/p-tau+ individuals drove the rate of progression to dementia over 2 years in the amnesic MCI population. Abbreviations: A β , amyloid- β ; MCI, mild cognitive impairment; p-tau, phosphorylated tau.

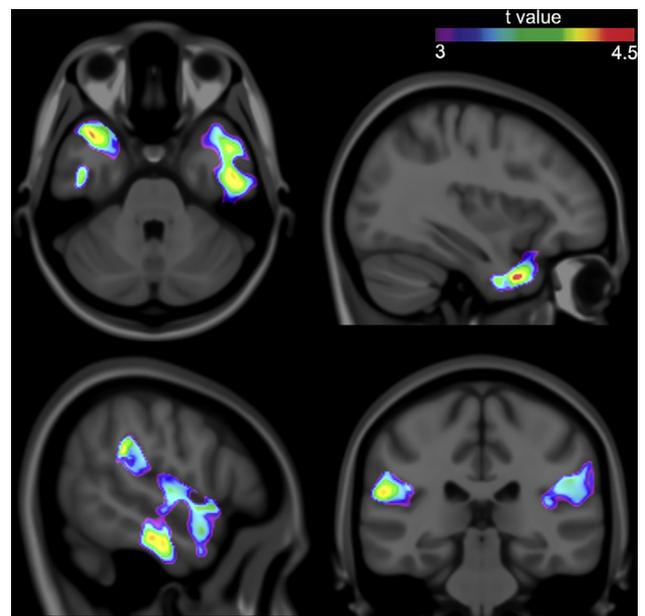


Fig. 4. Synergistic effect between [¹⁸F]florbetapir SUVR and CSF p-tau in temporal and inferior parietal cortices predicts progression to dementia. T-statistical parametric map, after correcting for multiple comparisons (random field theory at $P < .001$), overlaid in a structural magnetic resonance scan revealed that lateral and basal temporal and inferior parietal cortices were the brain regions where the synergism between [¹⁸F]florbetapir standardized uptake value ratio (SUVR) and cerebrospinal fluid (CSF) phosphorylated tau (p-tau) status was associated with an increased likelihood of progression to Alzheimer disease (AD) dementia over 2 years.

This study has some methodological limitations. Biomarkers provide naturally continuous measurements; therefore, thresholds are invariably subject to conceptual and analytical idiosyncrasies and may change depending on the method of analysis used. However, the use of regression models with continuous biomarker values helped prevent our results from being driven by the use of more liberal or more conservative biomarker threshold. Additionally, we assessed the synergy between A β and p-tau across all brain voxels. To the best of our knowledge, this is the first study conducting a voxel-based logistic regression analysis to evaluate progression to dementia using A β PET imaging. Importantly, our results showing the synergism between amyloid- β and p-tau leading to downstream clinical progression do not exclude the possibility that these two proteinopathies might arise sequentially (e.g., amyloid- β triggering the spreading of tau over the neocortex early on in the pathophysiological progression [14]). Certainly, cell cultures and in vivo studies with long-term imaging of amyloid- β and p-tau in animal models and in humans could better investigate causal and temporal relationships between these proteins. It is also important to mention that the observations reported here do not prove a biological synergy between A β and p-tau proteins. Our overall progression rate to dementia was 19% over 2 years. Previous studies conducted in memory clinic cohorts have reported progression rate in MCI of up to 59% over 2 years [31]. This might be explained by the fact that the ADNI-GO/2 inclusion criteria include MCI individuals in a less-advanced disease stage as compared to these cohorts [32]. In fact, our findings are similar to a recent study involving MCI ADNI-GO/2 participants that reported an overall progression rate of 15% over 1.6 years [33]. Finally, regarding the population included in this analysis, it is important to emphasize that it represents a select group of amnesic MCI persons motivated to participate in a dementia study. As such, for reasons related to the study inclusion criteria and self-selection bias [34], these individuals may not represent the general MCI population. Therefore, it would be highly desirable to replicate our findings on a population-based cohort.

From a clinical perspective, if replicated, such a synergism has important implications in understanding the dynamics of progression to dementia. For example, the clinical stability of nondemented persons with biomarker abnormalities described in numerous cohorts [35,36] could be explained by the absence of convergence of the A β and p-tau pathways, postulated here to be crucial for imminent clinical progression in amnesic MCI. In addition, the combination of abnormal amyloid-PET and CSF p-tau biomarkers may represent a valuable strategy for the enrichment of amnesic MCI populations with individuals having a high probability of developing AD dementia in therapeutic clinical trials targeting A β or tau aggregates.

From a therapeutic perspective, one can derive important predictions from the existence of a synergistic interaction between A β and p-tau in AD. For example, one can predict that therapeutic interventions targeting either A β or p-tau pathology might similarly mitigate AD progression. Furthermore, the same synergistic model implies better effectiveness of a combined therapeutic approach targeting both, A β and p-tau, pathological pathways. However, it is important to mention that the synergism between pathological pathways might not always translate into synergistic effects of multiple treatments. Importantly, this model should be supported by further studies combining long-term sequential biomarker and clinical observations.

In conclusion, our results support the synergism between A β and tau pathologies as a driving force behind the clinical progression to AD dementia.

Acknowledgments

This work was supported by the Canadian Institutes of Health Research (CIHR; MOP-11-51-31), the Alan Tiffin Foundation, the Alzheimer's Association (NIRG-12-92090, NIRP-12-259245), Prevent-AD scholarship (TAP), Fonds de Recherche du Québec-Santé (FRQS; Chercheur Boursier, PR-N), S.G. and P.R.-N. are members of the CIHR-CCNA Canadian Consortium of Neurodegeneration in Aging. Data collection and sharing for this project was funded by the ADNI (National Institutes of Health grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; Euroimmun; F. Hoffmann-La Roche Ltd. and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research also provides funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the AD Cooperative Study at the University of California, San Diego. ADNI data were disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

RESEARCH IN CONTEXT

1. Systematic review: Cross-sectional and longitudinal studies conducted in animal models and in cognitively healthy individuals provide evidences suggesting that the interaction between amyloid- β (A β) and phosphorylated tau (p-tau) imposes neurodegeneration. However, the link between A β and p-tau as a determinant to the clinical progression to dementia remains unclear.
2. Interpretation: We tested the hypothesis that the synergistic interaction between A β and p-tau is a driving force behind the progression from amnesic mild cognitive impairment (MCI) to Alzheimer disease dementia. Our results support a framework in which A β and p-tau synergistic effect best predicts cognitive decline and dementia, as compared to the sum of their individual effects.
3. Future directions: Future clinical trials focusing on MCI should consider enrich study populations with individuals presenting the coexistence of A β and p-tau abnormalities, to include participants with a higher probability of developing dementia in short time frames.

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