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Anxiety symptoms moderate the effect of cerebral amyloid on memory decline in healthy, non-demented older adults: A three-year prospective cohort study

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Summary

While beta-amyloid (Aβ), anxiety and depression have been linked cross-sectionally to reduced memory function in healthy, non-demented older adults, prospective data evaluating these associations are lacking. Using data from an observational cohort study of 178 healthy, non-demented older adults followed for three years, we found that anxiety symptoms significantly moderated the relation between Aβ level and decline in verbal (Cohen's d=.65) and episodic (Cohen's d=.38) memory. Anxiety symptoms were additionally linked to greater decline in executive function, irrespective of Aβ and other risk factors. These findings suggest that interventions to mitigate anxiety symptoms may help delay memory decline in otherwise healthy older adults with elevated Aβ.

Introduction

Beta-amyloid (Aβ) accumulates incrementally with age and is abnormally elevated in the majority of individuals who meet criteria for mild cognitive impairment (MCI) and Alzheimer's disease (AD)[1]. Abnormal levels of Aβ are also observed in approximately 30% of healthy, non-demented older adults[2] and are associated with clinically significant decline in episodic memory over 18-36 months.[3] Anxiety and depression are also linked to increased Aβ in healthy, non-demented older adults, as well as in adults with MCI and AD,[4,5] and are known to deleteriously affect episodic memory and related cognitive functions, such as attention and executive function.[6,7] Taken together, these observations suggest that anxiety and depression may contribute to Aβ-related decline in episodic memory and related cognitive domains in otherwise healthy older adults. However, prospective data evaluating this possibility are lacking. Given that anxiety and depression are amenable to treatment, their identification as determinants or moderators of Aβ-related cognitive decline in healthy older persons is important for managing preclinical and prodromal phases of AD prior to the availability of anti-amyloid therapies.

In this study, we evaluated whether elevated anxiety and depressive symptoms moderated the effect of elevated Aβ on cognitive decline in one of the largest cohorts of healthy, non-demented older adults who have undergone assessment with ^{11}C-Pittsburgh Compound B (PiB) and whose clinical status was followed prospectively over three years. We hypothesized that elevated anxiety and depressive symptoms at baseline would be associated with increased memory decline over the three-year period of assessment, and that this effect would be independent of traditional risk factors for cognitive decline (e.g., age, education, IQ, and apolipoprotein E [*APOE*] genotype).

Method

Sample. A total of 178 older adults who completed PiB imaging as part of the Australian Imaging, Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing[2] participated in this study. Participants were recruited from among the healthy, non-demented older adult group enrolled in the AIBL study (i.e., 25% of the group who completed PiB imaging). Exclusion criteria included: schizophrenia; depression (15-item Geriatric Depression Score ≥ 6); Parkinson's disease; cancer (except basal cell skin carcinoma) within the last two years; symptomatic stroke; uncontrolled diabetes; current regular alcohol use exceeding two standard drinks per day for women or four per day for men. For each assessment, a clinical review panel considered all available medical, psychiatric, and neuropsychological information to confirm the cognitive health of each participant. Selection of healthy older adults into the full AIBL cohort was controlled to ensure: (a) a wide age distribution from 60 years through to the very elderly, and (b) that approximately 50% had subjective memory complaint; for the 25% of this cohort who completed PiB imaging, an additional criterion was added to enrich the sample with *APOE* ε4 carriers: (c) that approximately 50% of the sample were *APOE* ε4 carriers. The study was approved by and complied with the regulations of the institutional research and ethics committees of Austin Health, St. Vincent's Health, Hollywood Private Hospital, and Edith Cowan University. All participants provided written informed consent prior to participating in the study.

PET Imaging and APOE genotyping. Aβ imaging with PET was conducted using ^{11}C-Pittsburgh Compound B (PiB). Imaging was conducted over a 30-minute acquisition period that was started 40-70 minutes after the injection of PiB. PET standardized uptake value (SUV) data were summed and normalized to the cerebellar cortex SUV, yielding a region-to-cerebellar ratio termed SUV ratio (SUVR). PiB SUVR levels reflect the mean of Aβ in frontal, post-cingulate, lateral temporal, and occipital cortices. In line with previous studies, SUVR was classified dichotomously as either negative or positive on the basis of SUVR < or ≥ 1.5. An 80ml blood sample was also obtained from each participant, 0.5ml of which was sent to a clinical pathology

laboratory for *APOE* genotyping.

Anxiety and depressive symptoms. Anxiety and depressive symptoms were assessed at the baseline visit using the Hospital Anxiety and Depression Scale (HADS). A total score ≥ 8 on the anxiety and depression items are indicative of clinically elevated anxiety and depressive symptoms, respectively.[8]

Neuropsychological assessment. Comprehensive neuropsychological evaluations were conducted at baseline, and at 18- and 36-month follow-ups. Composite indices of episodic memory, verbal memory, visual memory, executive function, language, attention, and visuospatial function were derived based on theory and clinical consensus.[9] The *Episodic Memory* composite score was comprised of scores on the California Verbal Learning Test, Second Edition (CVLT-II) delayed recall and Rey Complex Figure Test (RCFT) 30 minute delayed recall tests. The *Verbal Memory* composite score was comprised of scores on Logical Memory delayed recall, CVLT-II delayed recall, and CVLT-II d' measures. The *Visual Memory* composite score was comprised of scores on the RCFT 3-minute delayed recall, RCFT 30-minute delayed recall, and RCFT recognition tests. The *Executive Function* composite score was comprised of scores on the Stroop Colors/Dots, Letter Fluency (FAS), and Category Switching (Fruit/Furniture) tests. The *Language* composite score was comprised of scores on the Category Fluency (Animals/Boys' Names) and Boston Naming tests. The *Attention* composite score was comprised of scores on the Digit Span, Stroop Dots, and Digit Symbol Coding tests. The *Visuospatial* composite score was comprised of scores on the RCFT Copy and Clock Drawing tests. Factor analyses revealed strong loadings (i.e., all factor loadings ≥ .47) of each of the component measures on these composite scores.

Subjective memory complaint. Subjective memory impairment was assessed dichotomously (i.e., "No" or "Yes") using the question: "Do you have difficulties with your memory?"

Data analysis. Descriptive statistics were generated to summarize sample characteristics. To evaluate the relation between baseline anxiety and depression, other risk factors, and change in cognitive functioning over the 3-year study period, we conducted a series of linear mixed-effects models using maximum likelihood estimation and an unstructured covariance matrix. Baseline anxiety symptoms (i.e., score ≥ 8 on anxiety items of the HADS), depressive symptoms (i.e., score ≥ 8 on depression items of the HADS), and PiB screening status (standardized uptake value ratio [SUVR] < vs. ≥ 1.5 [PiB- vs. PiB+]),[3] *APOE* genotype (ε4 carrier vs. non-ε4 carrier), age, education, IQ, and subjective memory complaint were entered as fixed factors; participant as a random factor; and composite cognitive test scores as dependent variables in separate analyses. Cohen's d values were computed to estimate effect sizes of group differences.

Results

Of the 178 healthy, non-demented older adults who completed a baseline assessment, 163 (91.6%) completed an 18-month follow-up and 138 (77.5%) completed a 36-month follow-up. Table 1 shows demographic and clinical characteristics of the sample. PiB+ status was associated with greater decline in episodic, verbal, and visual memory over the 3-year study period (Table 1). Anxiety symptoms moderated the relation between PiB status and decline in episodic (Cohen's d=.38) and verbal (Cohen's d=.65) memory, such that PiB+ older adults with elevated anxiety symptoms showed significantly greater decline relative to PiB+ older adults without elevated anxiety symptoms; baseline anxiety symptoms were also associated with lower overall attention and executive function scores, and greater decline in executive function over time, irrespective of PIB status. The main effect of elevated depressive symptoms and

interactions of elevated depressive symptoms by time, PiB status, and time x PiB status were not significant for any of the cognitive measures. Depressive symptoms were significantly associated with subjective memory complaints (87.5% of the depressive symptoms group vs. 51.8% of the no depressive symptoms group reported subjective memory complaints, [$X^2(1)=3.91$, $p=.048$]), but anxiety symptoms were not (52.2% of the anxiety symptoms group vs. 53.9% of the no anxiety symptoms group reported subjective memory complaints, [$X^2(1)=0.02$, $p=.88$]).

Discussion

Consistent with prior work,[3] results of this study revealed that abnormal levels of Aβ were associated with decline in episodic, verbal, and visual memory in healthy, non-demented older adults. They extend this work by demonstrating that anxiety, but not depressive, symptoms moderated the effect of high Aβ burden on decline in episodic and verbal memory. Specifically, among individuals with abnormal Aβ, those with elevated anxiety symptoms showed a significantly greater decline in episodic and verbal memory over a 3-year study period than those without elevated anxiety symptoms. This additional deleterious effect of anxiety symptoms was, by convention, moderate in magnitude even after statistical adjustment for well-known determinants of cognitive decline, including age, education, IQ, *APOE* genotype, depressive symptoms, and subjective memory complaints. Anxiety symptoms were unrelated to subjective memory complaints at baseline, which suggests that these symptoms were more general in nature and likely reflective of generalized anxiety symptoms, such as worry, fearfulness, and restlessness.[8] Notably, results of this study did not support our hypothesis, based on extant literature, that anxiety and depressive symptoms at baseline would be associated with increased memory decline over the 3-year study period. Instead, anxiety symptoms predicted overall attention and executive function, and decline in executive function in the full sample; and

moderated the association between high Aβ burden and memory decline among healthy, non-demented older adults with elevated Aβ. The low prevalence of depressive symptoms (4.5%) may, at least in part, account for the lack of association between these symptoms and cognitive change; additional research with more clinically diverse samples will be useful in evaluating the direct and moderating effect of depressive symptoms on cognitive change in preclinical AD.

That anxiety symptoms moderated the relation between Aβ level and decline in episodic and verbal memory suggests that this interaction occurs at the level of the hippocampus. Elevated anxiety symptoms may moderate the effect of Aβ on these aspects of memory by increasing endogenous levels of glucocorticoids, which consequently damage the hippocampus and result in more pronounced memory decline over time.[10] Anxiety also diverts and preoccupies prefrontally-mediated attentional resources to fear- and threat-related information, which may in turn negatively affect encoding and retention of verbal information, as well as other prefrontally-mediated cognitive processes such as attention and executive function.[7,10]

While this study is limited by the relatively lower proportion of older adults who screened positive for depressive symptoms relative to anxiety symptoms, these results nevertheless suggest that mitigation of elevated anxiety symptoms may help delay episodic and verbal memory decline in healthy, non-demented older adults with elevated Aβ. Of note, because the prevalence of ε4 carriers in the AIBL sample of healthy older adults who underwent neuroimaging was, by design, high (40.7%), additional research in population-based samples of healthy older adults is needed to evaluate the generalizability of these results. Further research is also needed to elucidate neurobiological mechanisms that mediate the relation between Aβ, anxiety symptoms, and cognitive decline; and evaluate the effect of treating elevated anxiety symptoms in mitigating memory decline in normal aging and preclinical AD.

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Table 1. Sample characteristics and results of linear mixed-effects models examining the relation between cerebral Aβ, anxiety and depressive symptoms, and cognitive outcomes over a 3-year period in healthy older adults

Sample characteristics

	M (SD) or N (%)
Age	71.5 (7.4)
Female sex	89 (50.0%)
Education	
<=12 years	83 (46.6%)
13+ years	95 (53.4%)
WTAR IQ	111.7 (6.7)
MMSE	28.7 (1.2)
PiB SUVR > 1.5	55 (30.9%)
APOE ε4 carrier	72 (40.7%)
HADS anxiety score	4.1 (2.8)
Positive screen for anxiety	23 (12.9%)
HADS depression score	2.8 (2.3)
Positive screen for depression	8 (4.5%)
Subjective memory complaint	95 (53.7%)

Results of linear mixed-effect model analyses

	Episodic Memory		Verbal Memory		Visual Memory		Attention		Language		Visuospatial		Executive	
	F	p	F	p	F	p	F	p	F	p	F	p	F	p
PiB SUVR > 1.5	1.74	.19	**5.45**	**.020**	1.72	.19	.01	.94	.08	.77	.01	.94	.02	.90
Anxiety symptoms	.01	.99	2.08	.15	.15	.70	**4.96**	**.026**	.01	.98	.29	.59	**3.95**	**.047**
Depressive symptoms	.07	.79	.01	.93	.31	.58	.07	.79	3.74	.06	.31	.58	1.02	.31
Time	**12.85**	**<.001**	**20.67**	**<.001**	.32	.57	**3.95**	**.048**	**4.64**	**.032**	**30.42**	**<.001**	**5.82**	**.016**
PiB x Anxiety symptoms	1.69	.19	**4.98**	**.026**	1.75	.19	1.78	.18	.01	.95	.98	.32	.20	.65
PiB x Depressive symptoms	2.63	.11	.20	.66	3.43	.07	1.72	.19	3.07	.08	.27	.60	.56	.46
PiB x Time	**15.15**	**<.001**	**20.54**	**<.001**	**4.60**	**.033**	.01	.91	.87	.35	.46	.50	.01	.91
Anxiety symptoms x Time	1.82	.18	2.20	.14	.11	.74	2.04	.15	.01	.99	.56	.45	**4.41**	**.037**
Depressive symptoms x Time	.19	.66	.01	.94	.01	.99	.34	.56	.42	.51	.05	.83	.01	.97
PiB x Time x Anxiety symptoms	**4.20**	**.041**	**3.97**	**.047**	1.26	.26	1.74	.19	.06	.81	.97	.33	1.17	.28
PiB x Time x Depressive symptoms	1.26	.26	.28	.59	1.14	.29	.15	.70	2.22	.14	.17	.68	.01	,94

Adjusted slope estimates by PiB and Anxiety group					
	PiB-/Anxiety-	PiB-/Anxiety+	PiB+/Anxiety-	PiB+/Anxiety+	Pairwise comparisons
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	
Episodic memory	.14 (.09)	.26 (.25)	-.29 (.14)	-.65 (.35)	3,4<1; 4<3
Verbal memory	.18 (.09)	.21 (.25)	-.32 (.14)	-.93 (.34)	3,4<1; 4<3

Note. PiB level reflects mean of Aβ in frontal, post-cingulate, lateral temporal, and occipital cortices. Linear mixed-effects models are adjusted for age, education, IQ, *APOE* genotype, and subjective memory complaint.
WTAR=Wechsler Test of Adult Reading; MMSE=Mini-Mental State Examination; PiB SUVR=Pittsburgh Compound B Standardized Uptake Value Ratio; HADS=Hospital Anxiety and Depression Scale. SE=standard error.