Short report

Anxiety symptoms, cerebral amyloid burden and memory decline in healthy older adults without dementia: 3-year prospective cohort study

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Summary

Although beta-amyloid, anxiety and depression have been linked cross-sectionally to reduced memory function in healthy older adults without dementia, prospective data evaluating these associations are lacking. Using data from an observational cohort study of 178 healthy older adults without dementia followed for 3 years, we found that anxiety symptoms significantly moderated the relationship between beta-amyloid level and decline in verbal (Cohen's $d = 0.65$) and episodic (Cohen's $d = 0.38$) memory. Anxiety symptoms were additionally linked to greater decline in executive function, irrespective of beta-amyloid 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 beta-amyloid.

Declaration of interest

None.

Beta-amyloid accumulates incrementally with age and is abnormally elevated in the majority of individuals who meet criteria for mild cognitive impairment or Alzheimer's disease.[1] Abnormal levels of beta-amyloid are also seen in about 30% of healthy older adults without dementia[2] and are associated with clinically significant decline in episodic memory over 18–36 months.[3] Anxiety and depression are also linked to increased beta-amyloid in healthy older adults without dementia, as well as in adults with mild cognitive impairment or Alzheimer's disease,[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 beta-amyloid-related decline in episodic memory and related cognitive domains in otherwise healthy older adults. Given that anxiety and depression are amenable to treatment, their identification as determinants or moderators of beta-amyloid-related cognitive decline in healthy older people is important for managing preclinical and prodromal phases of Alzheimer's disease prior to the availability of anti-amyloid therapies. We evaluated whether elevated anxiety and depressive symptoms moderated the effect of elevated beta-amyloid on cognitive decline in one of the largest cohorts of healthy older adults without dementia who have undergone assessment with ^{11}C-Pittsburgh Compound B (PiB) and whose clinical status was followed prospectively over 3 years. We hypothesised that elevated anxiety and depressive symptoms at baseline would be associated with increased memory decline over the 3-year period of assessment, and that this effect would be independent of traditional risk factors for cognitive decline (such as age, education, IQ and apolipoprotein E (APOE) genotype).

Method

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. Participants were recruited from among the healthy older adults without dementia enrolled in the AIBL study (i.e. 25% of the group who completed PiB imaging, see the online supplement for further details of selection and exclusion criteria, and approval of the study).

Beta-amyloid imaging with positron emission tomography (PET) was conducted using PiB. Imaging was conducted over a 30 min acquisition period that was started 40–70 min after the injection of PiB. The PET standardised uptake value (SUV) data were summed and normalised to the cerebellar cortex SUV, yielding a region-to-cerebellar ratio termed SUV ratio (SUVR). The PiB SUVR levels reflect the mean of beta-amyloid in frontal, post-cingulate, lateral temporal and occipital cortices. The SUVR was classified dichotomously as either negative or positive on the basis of SUVR < or ≥ 1.5. An 80 ml blood sample was also obtained from each participant, 0.5 ml of which was sent to a clinical pathology laboratory for APOE genotyping.

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

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] (see online supplement for details of tests). Subjective memory impairment was assessed dichotomously ('No' or 'Yes') using the question: 'Do you have difficulties with your memory?'

Descriptive statistics were generated to summarise sample characteristics. To evaluate the relationship 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 (score ≥ 8 on anxiety items of the HADS), depressive symptoms (score ≥ 8 on depression items of the HADS) and PiB screening status (SUVR < v. ≥ 1.5 (PiB− v. PiB+)),[3] APOE genotype (ε4 carrier v. 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 participants who completed a baseline assessment, 163 (91.6%) completed an 18-month and 138 (77.5%) a 36-month follow-up. Online Table DS1 shows demographic and clinical characteristics of the sample. We found that PiB+ status was associated with greater decline in episodic, verbal and visual memory over the 3-year study period (Online Table DS2). Anxiety symptoms moderated the relation between PiB status and decline in episodic (Cohen's $d = 0.38$) and verbal (Cohen's $d = 0.65$) memory, such that the participants who were PiB+ with elevated anxiety symptoms showed significantly greater decline relative to those who were PiB+ without elevated anxiety symptoms (Table DS3). 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 × PiB status were not significant for any of the cognitive measures. Depressive symptoms were significantly associated with subjective memory complaints (87.5% ($n = 7$) of the depressive symptoms group v. 51.8% ($n = 87$) of the no depressive symptoms group reported subjective memory complaints, $\chi^2(1) = 3.91$, $P = 0.048$), but anxiety symptoms were not (52.2% ($n = 12$) of the anxiety symptoms group v. 53.9% ($n = 83$) of the no anxiety symptoms group reported subjective memory complaints, $\chi^2(1) = 0.02$, $P = 0.88$).

Discussion

Consistent with prior work,[3] this study revealed that abnormal levels of beta-amyloid were associated with decline in episodic, verbal and visual memory in healthy older adults without dementia. Anxiety, but not depressive, symptoms moderated the effect of high beta-amyloid burden on decline in episodic and verbal memory. Specifically, among individuals with abnormal beta-amyloid, those with elevated anxiety symptoms showed a significantly greater decline in episodic and verbal memory over a 3-year study period than those without. This additional deleterious effect of anxiety symptoms was, by convention, moderate in magnitude even after statistical adjustment for well-known determinants of cognitive decline. Anxiety symptoms were unrelated to subjective memory complaints at baseline, which suggests that these symptoms were more general in nature and likely reflective of generalised anxiety symptoms such as worry, fearfulness and restlessness.[8] Notably, results of this study did not support our hypothesis that anxiety and depressive symptoms at baseline would be associated with increased memory decline over the 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 beta-amyloid burden and memory decline among healthy older adults with elevated beta-amyloid. 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 is needed.

That anxiety symptoms moderated the relationship between beta-amyloid 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 beta-amyloid 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] As the prevalence of ε4 carriers in the AIBL sample was, by design, high (40.5%), additional research in population-based samples of healthy older adults is required. Further research is also needed to elucidate neurobiological mechanisms that mediate the relation between beta-amyloid, anxiety symptoms and cognitive decline; and evaluate the effect of treating elevated anxiety symptoms in mitigating memory decline in normal ageing and preclinical Alzheimer's disease.

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References

1 Price JL, Morris JC. Tangles and plaques in nondemented aging and ''preclinical'' Alzheimer's disease. *Ann Neurol* 1999; **45**: 358–68.

2 Rowe CC, Ellis KA, Rimajova M, Bourgeat P, Pike KE, Jones G, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging* 2010; **31**: 1275–83.

3 Lim YY, Ellis KA, Pietrzak RH, Ames D, Darby D, Harrington K, et al. Stronger effect of amyloid load than APOE genotype on cognitive decline in healthy older adults. *Neurology* 2012; **79**: 1645–52.

4 Lavretsky H, Siddarth P, Kepe V, Ercoli LM, Miller KJ, Burggren AC, et al. Depression and anxiety symptoms are associated with cerebral FDDNP-PET binding in middle-aged and older nondemented adults. *Am J Geriatr Psychiatry* 2009; **17**: 493–502.

5 Ramakers IHGB, Verhey FRJ, Scheltens P, Hampel H, Soininen H, Aalten P, et al. Anxiety is related to Alzheimer cerebrospinal fluid markers in subjects with mild cognitive impairment. *Psychol Med* 2013; **43**: 911–20.

6 Murrough JW, Iacoviello B, Neumeister A, Charney DS, Iosifescu DV. Cognitive dysfunction in depression: neurocircuitry and new therapeutic strategies. *Neurobiol Learn Mem* 2011; **96**: 553–63.

7 Eysenck MW, Derakshan N, Santos R, Calvo MG. Anxiety and cognitive performance: attentional control theory. *Emotion* 2007; **7**: 336–53.

8 Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; **52**: 69–77.

9 Harrington K, Lim YY, Ellis KA, Copolov C, Ames D, Darby D, et al. The association of Aβ amyloid and composite cognitive measures in healthy older adults and MCI. *Int Psychogeriatr* 2013; **25**: 1667–77.

10 Beaudreau SA, O'Hara R. Late-life anxiety and cognitive impairment: a review. *Am J Geriatr Psychiatry* 2008; **16**: 790–803.

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