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Elucidating the association between depression, anxiety, and cognition in middle-aged adults: Application of dimensional and categorical approaches

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ABSTRACT

Background: In older adults, depressive and anxiety symptoms are associated with dementia risk, and represent a manifestation of the dementia prodrome. Understanding how these symptoms are related to cognition in midlife may inform risk models of dementia.
Methods: This study examined the relationship between depressive and anxiety symptoms, and cognition, in a sample (n= 2,657) of participants enrolled in the Healthy Brain Project. Depressive and Anxiety symptoms were assessed using the Depression Anxiety and Stress Scale, Hospital Anxiety and Depression Scale, and centre for Epidemiological Studies Depression Scale. Objective cognition was assessed using the Cogstate Brief Battery and subjective cognition assessed using the Alzheimer's disease Cooperative Study Cognitive Function Instrument.
Results: Somatic- and panic-related anxiety symptoms were associated significantly with poorer attention; while tension- and panic-related anxiety were associated significantly with poorer memory. Having clinically meaningful anxiety or depressive symptoms was associated with increased subjective cognitive concerns (d=-0.37). This was further increased for those with clinically meaningful anxiety and depressive symptoms (d = -1.07).
Limitations: This study reports cross-sectional data, and uses a sample enriched with individuals with a family history of dementia who are therefore at a higher risk of developing dementia compared to the general population. Additionally, biological markers such as cortisol, Aβ, and tau were unavailable.
Conclusion: The results support the hypothesis that depressive and anxiety symptoms may increase risk of cognitive decline. Further, they suggest that using depression and anxiety as clinical markers may be helpful in identifying the earliest signs of cognitive decline.

1. Introduction

In older adults, depressive and anxiety symptoms are associated with increased risk of cognitive impairment, vascular dementia (VD) and Alzheimer's disease (AD) (Becker et al., 2018; Cherbuin et al., 2015; Deckers et al., 2015; Diniz et al., 2013; Gimson et al., 2018). When levels of depressive symptoms reach clinically-meaningful thresholds, they become associated with increased risk of mild cognitive impairment (MCI) and AD dementia, with risk ratios ranging from 1.05 to 4.39 (Almeida et al., 2017; Jiro et al., 2016; Rasmussen et al., 2018). The presence of depression and anxiety in mid-life is also associated with a doubled risk of developing dementia in later life, with meta-analytic estimates indicating that relative risk ratios for dementia range from 1.3 to 2.7 (Becker et al., 2018; Prince et al., 2013; Santabárbara et al., 2019, 2019). Prospective studies in middle-aged adults also indicate that clinically meaningful anxiety levels are associated with an increased risk

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of dementia diagnosis over 10 years, with odds ratios ranging from 1.48 to 7.4 (Gimson et al., 2018).

It is likely that the risk for dementia from depressive and anxiety symptoms reflects that these symptoms are neurobehavioral expressions of early neuropathological abnormalities, or that they arise as a response to the emergence of early disease related cognitive dysfunction, or both (Brzezińska et al., 2020; Gulpers et al., 2016; Wiels et al., 2020). Therefore, elucidation of the extent to which depressive and anxiety symptoms relate to subjective and objective cognition in adults who do not meet any criteria for symptomatic neurodegenerative disease, in their midlife when occult neuropathology is unlikely, may help inform risk models of cognitive impairment and dementia. However, several issues in the current literature should be addressed to allow a more precise understanding of these relationships.

First, in individuals whose day-to-day function is normal, depressive and anxiety scores may be minimal, thus yielding total or symptom scores equivalent to zero. Zero inflation of symptom data may restrict modeling of relationships with cognition through limiting the statistical power of analyses. One way to overcome this limitation is to measure dimensions of the anxiety and depressive construct using multiple measures of depressive and anxiety symptoms, and to examine the responses across multiple questionnaires for commonalities and potential underlying or latent factors. This could improve the reliability of identifying individual and subsyndromal symptoms, as well as their relationships to objectively measured and self-rated cognition (Sunderland et al., 2018).

Second, in otherwise cognitively normal older adults, subjective concerns about cognition are related more strongly with elevated depressive and anxiety symptoms (Balash et al., 2013; Dux et al., 2008; Mitchell et al., 2014). It is thus important to clarify the relationships between depressive and anxiety symptoms, cognition, and subjective cognitive concerns.

Finally, as the greatest risk factor for AD is increasing age, it is important to determine the extent to which any relationships observed between depressive and anxiety symptoms, cognition, and subjective cognitive concerns, also change with increasing age. This will provide information on how the effects of age on AD risk is moderated by depressive and anxiety symptoms.

The overarching aim of this study was to examine the relationship between depressive and anxiety symptoms, and cognition, assessed objectively and from subjective reports, in a large sample of participants enrolled in the Healthy Brain Project (HBP) (Lim et al., 2019). The first aim was to determine associations between depressive and anxiety symptoms and cognition and subjective cognitive concerns in middle-aged adults. The first hypothesis was that individuals with higher levels of depressive and anxiety symptoms would show worse attention and memory and report greater subjective cognitive concerns, when compared to individuals who exhibited little to no psychological symptoms. The second aim was to explore a novel approach to exploring relationships between anxiety and depressive symptoms on cognition and subjective cognitive concerns. This approach included utilizing data from multiple measures of depression and anxiety symptoms, examining how these measures aggregate via factor analysis, and then examining whether the factors identified predict cognitive performance or subjective cognitive concerns. The third aim was to evaluate the role of age in moderating the relationship between depressive and anxiety symptoms and cognition.

2. Methods

2.1. Participants

A total of 2657 participants enrolled in the HBP (healthybrainproject.org.au) were included in this analysis. The HBP sample consists of community-dwelling adults aged 40–70 years. Recruitment, enrolment, inclusion and exclusion of HBP participants have been described in detail elsewhere (Lim et al., 2019). Briefly, participants were eligible for enrolment if they were residing in Australia; were fluent in English; did not have a diagnosis of AD, Parkinson's disease, Dementia with Lewy Bodies, or other known diagnosis of dementia; had no history of major traumatic brain injury or other neurological disease or insult; did not have a diagnosis of a major psychiatric condition (e.g., schizophrenia, uncontrolled major depressive disorder, or other psychiatric disorder); and did not use any of the Australian government's Therapeutic Goods Administration approved medication for the treatment of AD (e.g., donepezil, rivastigmine or other approved medication). The HBP was approved by the human research ethics committee of Melbourne Health. As recruitment for the HBP is ongoing, the current study only includes data that has been collected up to the third formal Data Freeze (April 2020). The final sample for this study (n = 2657) comprised of participants who had completed both cognitive testing and surveys assessing depressive and anxiety symptoms.

2.2. Measures

Demographic and medical history. All measures were administered online via the HBP website. Demographic information and medical history including: date of birth, sex, years of education, annual income, employment status, ethnicity, residential address (from which we determined whether they resided in a metropolitan or rural/regional area according to the Australian Bureau of Statistics' classification), family history of dementia, and personal and family history of psychological disorders, were self-reported.

Depression and anxiety questionnaires. Depressive and anxiety symptoms were assessed using the *Hospital Anxiety and Depression Scale* (HADS) (Snaith and Zigmond, 1986; Zigmond and Snaith, 1983), *Depression, Anxiety and Stress Scale* (DASS) (Lovibond and Lovibond, 1995), and the *Center for Epidemiologic Studies Depression Scale* (CES-D) (Radloff, 1977). Together, these scales contribute 48 depression-related items and 28 anxiety-related items. Severity of psychological symptoms in the sample were measured as a categorical variable ("mood screen"). Categorization was based on whether participants met the thresholds recommended for clinically meaningful levels of symptoms on one or more of the depression and anxiety screening questionnaires (where "negative screen" = no clinically meaningful results on any depressive or anxiety measure; "positive screen for depression or anxiety" = at least one clinically meaningful result on a depression or anxiety measure; "positive screen for depression and anxiety" = clinically meaningful scores on both a depression and anxiety screening measure). The thresholds indicating elevated depressive and anxiety scores were $\geq$8 for the HADS-A and HADS-D scales, $\geq$10 for the DASS-D scale, $\geq$8 for the DASS-A scale, and $\geq$16 for the CES-D scale (Lovibond and Lovibond, 1995; Vilagut et al., 2016; Zigmond and Snaith, 1983). Composite scores were also created to evaluate low mood. Total scores for the depression scales (HADS-D, DASS-D and CES-D) were averaged to create a depression composite, and total scores for the anxiety scales (HADS-A and DASS-A) were averaged to create an anxiety composite.

Cognition. Cognition was assessed objectively using the Cogstate Brief Battery (CBB) optimized for remote unsupervised application (Darby et al., 2014; Mackin et al., 2018; Perin et al., 2020). Participants were directed to complete the CBB online via the HBP website where the time for completion of the CBB was ~20 min x223C. The CBB consists of four tests: Detection (DET) to measure psychomotor function, Identification (IDN) to measure visual attention, One Card Learning (OCL) to measure visual learning, and the One-Back (OBK) test to measure visual working memory. These tests have been described in detail previously (Lim et al., 2012). Primary outcome measures for the DET and IDN tests was reaction time in milliseconds (speed) and for the OCL and OBK was the proportion of correct answers (accuracy). An Attention Composite was computed by standardizing and averaging the sign reversed performance measures for the DET and IDN tasks. A Memory Composite was computed by standardizing and averaging the performance

measures for the OCL and OBK tasks (Lim et al., 2012). For each test standardization occurred using the baseline mean and standard deviation of the entire CN sample.

Subjective cognitive concerns. Subjective cognitive concerns were assessed using a modified version of the self-report section of the Alzheimer's disease Cooperative Study (ADCS) – CFI (Ferris et al., 2006; Walsh et al., 2006). The CFI is a 14-item self-report instrument that asks about common cognitive concerns reported in older adults. As the CFI was designed for use in older adults, some items were modified to include ecologically valid questions about subjective experiences of memory and thinking at work, and other aspects relevant to middle-aged individuals' lives (Lim et al., 2019). The CFI has been shown to be sensitive in identifying objective cognitive decline over time in individuals who were cognitively normal at baseline (Amariglio et al., 2015).

2.3. Data analysis

All analyses were conducted using R version 3.5.0 and IBM SPSS (version 25). Significance was defined at $p < .05$ for all analyses. However, to protect against the risk to Type I error, effect sizes were also computed for each comparison and those considered trivial ($d<0.1$) were not interpreted irrespective of the associated p-value.

To determine the effect of depressive and anxiety symptoms on attention, memory, and subjective cognitive concerns, a series of one-way analysis of covariance (ANCOVA) tests were conducted with mood group as the predictor; age, sex and education as covariates; and the Attention Composite, Memory Composite, and CFI total score as dependent variables. A series of regressions (age, sex and education as covariates) with the depression and anxiety composite scores were also conducted to determine their effects on each cognitive outcome.

To examine the effect of depressive and anxiety factor scores on cognition and subjective cognitive concerns, responses to all individual questions pertaining to depressive and anxiety symptoms from all questionnaires were submitted to exploratory factor analyses (EFA). The first EFA evaluated the pooled depressive items from the three depression scales (HADS-D, DASS-D, CES-D), and the second examined the pooled anxiety items from the two anxiety scales (HADS-A, DASS-A). Bartlett's test of sphericity and the Kaiser-Meyer-Olkin Measure of Sampling Adequacy were calculated to ensure that the data were suitable for EFA (Bartlett, 1954; Kaiser, 1960). Components with eigenvalues greater than one were selected for the extraction. As expected in a non-clinical sample, depression and anxiety symptom scores observed in the HBP sample were positively skewed. Principal axis factoring (PAF) with Kaiser normalization and oblimin rotation was therefore selected as the method of extraction as PAF is robust to non-normality in data (Costello and Osborne, 2005). Factors were interpreted through subjective appraisal of item loadings. Items with loading values >0.32 were retained (Tabachnick and Fidell, 2001). Cross-loading items were excluded if the loading value difference between items was <0.20 (Matsunaga, 2010). Factor scores were calculated by averaging each component's scale items (DiStefano et al., 2009). Three separate linear regressions were conducted to determine the contribution of each depressive and anxiety factor score on memory, attention, and subjective cognitive concerns. Each model included the depressive and anxiety factor scores, and age, sex, and education as covariates.

Finally, to examine the potential role of age in moderating the relation between depressive and anxiety symptoms, and measures of cognition, participants who screened positive or negative for depressive and/or anxiety symptoms (i.e., "mood screen") were categorised further into three age groups (40–50 years old, 51–60 years old, 61–70 years old). A series of one-way analysis of covariance (ANCOVA) tests were conducted with the interaction between mood group and age group as the predictor; sex and education as covariates; and attention, memory, and CFI total score as the dependent variables. A series of planned comparisons were conducted to compare the least square means of performance (attention, memory, and CFI total score) of each mood-age group, and effect sizes (Cohen's d) were reported.

3. Results

3.1. Demographic characteristics

Demographic characteristics of the sample are provided in Table 1. Participants who screened positive for the presence of depressive and/or anxiety symptoms were associated with younger age, lower levels of education and lower annual income. These individuals were also more likely to report a personal and first- and second-degree family history of diagnosed psychological disorder(s). However, they were less likely to report European ethnicity or engagement in full-time employment, compared to those with normal mood. As expected, they were also more likely to score highly on the depressive and anxiety composites, and all factor scores compared to the normal mood group.

3.2. Relationship between depressive and anxiety symptoms, and cognition

Results of the ANCOVA analyses are presented in Table 2. After adjusting for age, sex, and education, statistically significant differences between mood groups were observed for the Attention Composite ($F(2,2522) = 4.55$, $p = .011$), Memory Composite ($F(2,2523) = 10.19$, $p <0.001$), and CFI total score ($F(2,2314) = 145.68$, $p < .001$). Individuals who screened positive for depression or anxiety performed worse than individuals with normal mood only on the Memory Composite and the CFI total score (Table 2, Fig. 1). Individuals who screened positive for depression and anxiety performed worse than individuals who screened negative, on all outcome measures, with the difference between groups, by convention, moderate in magnitude for the Attention and Memory Composites, and very large, for the CFI total score (Table 2; Fig. 1).

After accounting for the effects of age, sex and education, the anxiety composite, but not the depression composite, was associated with attention (β (SE) = −0.136 (0.01), $p <0.001$), and memory (β (SE) = −0.141 (0.01), $p <0.001$) performance. Both the anxiety composite (β (SE) = 0.195 (0.07), $p <0.001$) and depression composite (β (SE) = 0.230 (0.06), $p <0.001$) were associated significantly with CFI total score. Age was also associated significantly with performance on the Attention Composite (β (SE) = −0.294 (0.002), $p <0.001$), Memory Composite (β (SE) = −0.093 (0.002), $p <0.001$), and CFI total score (β (SE) = 0.079 (0.016), $p <0.001$). Education was associated significantly with performance on the Attention Composite (β (SE) = 0.065 (0.005), $p = .001$) and Memory Composite (β (SE) = 0.101 (0.004), $p <0.001$), and CFI total score (β (SE) = −0.052 (0.032), $p = .007$).

3.3. Identification of depression and anxiety factors

The derived component structure of the depressive and anxiety scale items and additional details regarding the results of the EFA are included in a supplement. EFA of the depression scale items yielded five depression factors with Eigenvalues greater than one, which in combination, explained 65.37% of the variance. The factors were defined as: Apathy, Fatigue, Negative Affect, Positive Affect, and Low Self-Esteem. EFA of the anxiety scale items resulted in three anxiety factors with Eigenvalues greater than one, which in combination, explained 47.90% of the variance. These factors were defined as: Tension, Somatic Symptoms, and Panic.

3.4. Association of depression and anxiety factors with cognition

Results of linear regressions are presented in Table 3. These analyses indicated that, after adjusting for age, sex, and education, the anxiety factor scores 'somatic' and 'panic' were associated significantly with poorer attention; while 'tension' and 'panic' were associated

Table 1
Demographic characteristics of the sample by depressive and anxiety symptoms.

	Negative Screen (n = 1629)	Screen Positive for Depression OR Anxiety (n = 683)	Screen Positive for Depression AND Anxiety (n = 345)	
	Mean (SD)	Mean (SD)	Mean (SD)	p
Age	57.27 (6.96)	56.60 (6.93)	54.66 (7.18)	<0.001
Education (years)	16.17 (3.39)	15.83 (3.47)	15.35 (3.59)	<0.001
Annual Income (self) ('000's)	68.32 (35.24)	65.12 (34.55)	60.12 (34.39)	<0.001
HADS Depression	1.80 (1.63)	3.73 (2.17)	7.55 (2.64)	<0.001
HADS Anxiety	2.16 (1.73)	4.18 (2.11)	9.85 (2.64)	<0.001
DASS Depression	1.56 (1.89)	4.64 (3.74)	12.76 (7.11)	<0.001
DASS Anxiety	1.29 (1.47)	2.88 (2.09)	8.29 (4.59)	<0.001
CES-D Total	12.71 (1.71)	17.75 (3.16)	20.88 (5.36)	<0.001
Anxiety Composite Score	3.45 (2.68)	7.06 (3.50)	18.14 (5.92)	<0.001
Depression Composite Score	16.07 (3.55)	26.13 (6.28)	41.19 (11.88)	<0.001
Anxiety (somatic)	−0.30 (0.38)	−0.04 (0.58)	1.00 (1.36)	<0.001
Anxiety (tension)	.41 (0.55)	−0.11 (0.62)	−1.3 (0.75)	<0.001
Anxiety (panic)	.33 (0.28)	.11 (0.46)	−1.18 (1.41)	<0.001
Depression (apathy)	−0.46 (0.46)	.06 (0.74)	1.51 (0.99)	<0.001
Depression (fatigue)	−0.33 (0.23)	−0.08 (0.67)	1.23 (1.58)	<0.001
Depression (negative affect)	−0.50 (0.43)	.29 (0.77)	1.21 (1.07)	<0.001
Depression (positive affect)	−0.33 (0.39)	.16 (0.84)	.78 (1.18)	<0.001
Depression (low self-esteem)	−0.45 (0.28)	.19 (0.79)	1.19 (1.05)	<0.001
	N (%)	N (%)	N (%)	p
Female	1208 (74.2%)	533 (78.0%)	259 (75.1%)	.142
European	1283 (78.8%)	516 (75.5%)	245 (71.0%)	.008
Residing in Regional/Rural Australia	430 (26.4%)	204 (29.9%)	101 (29.3%)	.181
Employed Full Time	586 (36.0%)	240 (35.1%)	117 (33.9%)	<0.001
History of diagnosed psychological disorder (any)	130 (8.0%)	102 (14.9%)	116 (33.6%)	<0.001
Diagnosed with 2 or more psychological disorders	25 (1.5%)	28 (2.1%)	52 (15.0%)	<0.001
First-degree family history of psychological disorders	686 (42.1%)	326 (47.7%)	225 (65.2%)	<0.001
Second-degree family history of psychological disorders	256 (15.7%)	122 (17.9%)	96 (27.8%)	<0.001
First- or second-degree family history of dementia	1041 (63.9%)	414 (60.6%)	231 (67.0%)	.106

Note. Total N= 2657. Chi-square analyses were used to test differences between groups for categorical variables, and analysis of variance was used to test differences between groups for continuous variables. HADS = Hospital Anxiety and Depression Scale; DASS = Depression Anxiety and Stress Scale; CES-D = Center for Epidemiological Studies Depression Scale.

significantly with poorer memory (The magnitudes of these associations are presented in Table 3). None of the depressive factor scores were associated with performance on either Attention or Memory composite scores. However, 'fatigue' was found to be a significant predictor of CFI total score. Further, all three anxiety factor scores (somatic, tension and panic) were associated significantly with CFI total scores. In all models, age and education were associated significantly with the Attention and Memory composite scores, and CFI total score, while sex was not.

3.5. Role of age in moderating relation between depressive and anxiety symptoms and cognition

Table 4 summarises the results of an ANCOVA examining relationships between increasing age and mood groups on cognition and subjective cognitive concerns. The least square means of each outcome, for each age and mood group and the magnitudes of any differences detected in the analyses, are illustrated in Fig. 2. After accounting for the effects of sex and education, a statistically significant interaction of age group and mood group was observed for the Memory Composite only. Planned comparisons revealed no differences in memory with increasing severity of depressive and anxiety symptoms in the 40–50 years age group (Fig. 2). In the 51–60 years age group, individuals who screened positive for depression or anxiety showed worse memory than those who screened negative, but individuals who screened positive for depression and anxiety had equivalent memory to those who screened positive for depression or anxiety. In the 61–70 years age group, individuals who screened positive for both depression and anxiety had significantly worse memory than those with only one of those symptoms, with this impairment moderate in magnitude (Fig. 2). There was a stronger effect of age than depressive and anxiety symptoms on the Attention Composite, with performance reduced significantly only in individuals who screened positive for both depression and anxiety in the 61–70 years age group. There was a stronger effect of depressive and anxiety symptoms than age for the CFI total score, with individuals who screened positive for both depression and anxiety reporting higher levels of subjective cognitive concerns, irrespective of their age group (Fig. 2).

4. Discussion

The hypothesis that individuals with higher levels of depressive and anxiety symptoms would have poorer cognition was supported partially. Poorer cognition, particularly in memory, was observed in individuals with clinically meaningful levels of depressive or anxiety symptoms. Specifically, individuals with high levels of depressive or anxiety symptoms exhibited worse memory than those in the normal mood group, however the magnitude of this difference was very small (d= 0.09) and therefore would not be detectable in clinical assessment. Individuals with both high depressive and anxiety symptoms showed worse memory and attention than individuals in the normal mood group, with the magnitude of these differences small but meaningful (d ~x223C 0.28). When global estimates of anxiety and depressive symptoms were considered simultaneously, and after accounting for the effects of age, sex and education, higher anxiety (but not depressive) symptoms were associated more strongly with poorer attention and memory. Investigation of the sub-domains of anxiety symptoms showed that somatic- and panic-related anxiety symptoms were associated more strongly with levels of attention while tension- and panic-related anxiety symptoms were associated more strongly with levels of memory. The strong relationship between anxiety symptoms and poorer attention and memory in middle-aged adults is consistent with our observations in preclinical AD, where even subclinical anxiety symptoms were associated with increased decline in memory over 4.5 years (Pietrzak et al., 2015). Consideration of relationships between anxiety levels and cognition over increasing age indicated that clinically meaningful depressive and/or anxiety symptoms were associated with poorer memory function, in individuals aged 51–60 years and 61–70 years.

Table 2
Differences in performance between mood groups (categorical) on attention, memory and subjective cognitive concerns.

	Attention Composite		Memory Composite		Subjective Cognition	
	(df) F	*p*	(df) F	*p*	(df) F	*P*
Age	(1,2522) 243.42	<0.001	(1,2523) 28.86	<0.001	(1,2314) 16.11	<0.001
Sex	(1,2522) 0.69	.406	(1,2523) 3.24	.072	(1,2314) 0.15	.697
Education	(1,2522) 12.95	<0.001	(1,2523) 26.83	<0.001	(1,2314) 9.98	.002
MoodGroup	(2,2522) 4.55	.011	(2,2523) 10.19	<0.001	(2,2314) 145.68	<0.001
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
Negative Screen	0.055 (0.87)	1559	0.06 (0.75)	1560	0.22 (0.95)	1442
Positive Screen depressive / anxiety	−0.02 (0.86)	642	−0.02 (0.76)	642	−0.14 (0.94)	585
Positive Screen depressive + anxiety	−0.18 (0.87)	327	−0.16 (0.76)	327	−0.80 (0.96)	293
	Cohen's d (95% CI)		Cohen's d (95% CI)		Cohen's d (95% CI)	
Positive Screen depressive / anxiety	0.09 (−0.20,0.11)		−0.09 (−0.17, −0.08)		−0.37 (−0.47, −0.10)	
Positive Screen depressive + anxiety	−0.27 (−0.39, −0.12)		−0.28 (−0.40, −0.12)		−1.07 (−1.20, −0.13)	

Note. Magnitude of difference (Cohen's d) reported for each mood group when compared to normal mood group.

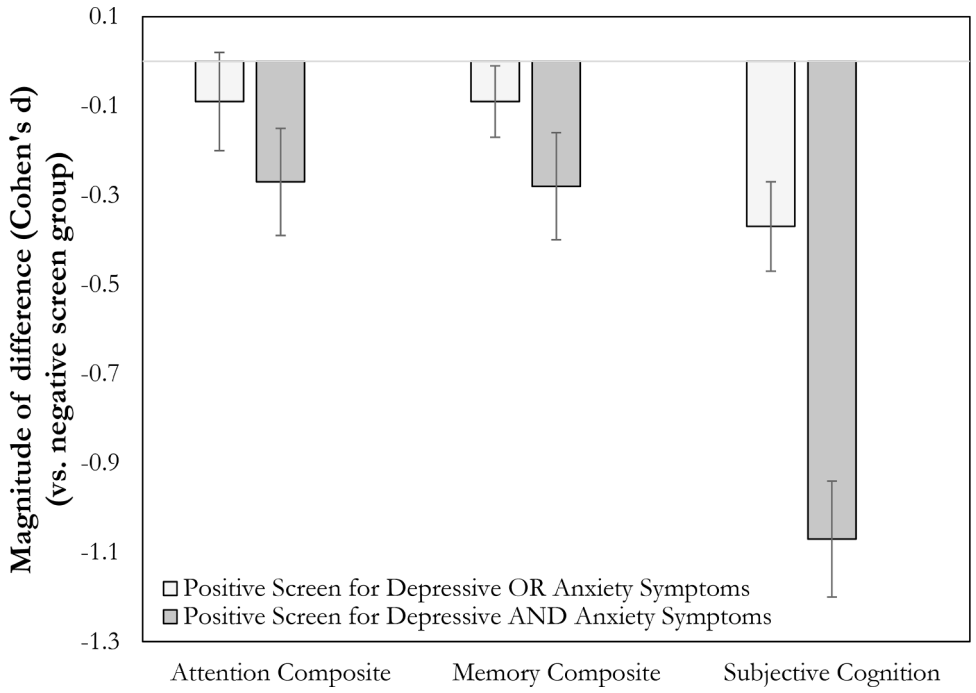

Fig. 1. Magnitude of difference (Cohen's d) in cognition and subjective cognitive concerns between those who screened negative, and those who screened positive for depression and/or anxiety (error bars represent 95% CIs).

Table 3
Contribution of anxiety and/or depressive symptom factor scores on objective and subjective cognitive concerns.

	Attention Composite			Memory Composite			Subjective Cognitive Concerns		
	β (SE)	Partial η^2	*p*	β (SE)	Partial η^2	*p*	β (SE)	Partial η^2	*P*
Age	−0.29 (0.02)	8.40%	<0.001	−0.09 (0.20)	0.86%	<0.001	−0.08 (0.02)	0.74%	<0.001
Sex	0.04 (0.04)	0.03%	.407	−0.09 (0.05)	0.14%	.061	0.03 (0.04)	0.02%	.541
Education	0.06 (0.02)	0.45%	.001	0.10 (0.02)	0.995%	<0.001	0.05 (0.02)	0.24%	.018
Anxiety (somatic)	−0.06 (0.02)	0.26%	.011	−0.02 (0.02)	0.02%	.457	−0.08 (0.02)	0.56%	<0.001
Anxiety (tension)	−0.02 (0.02)	0.05%	.278	−0.06 (0.02)	0.26%	.011	−0.08 (0.03)	0.45%	.001
Anxiety (panic)	−0.07 (0.03)	0.33%	.004	−0.07 (0.03)	0.26%	.011	−0.13 (0.03)	0.93%	<0.001
Depression (apathy)	–	–	–	–	–	–	0.01 (0.03)	0.01%	.644
Depression (fatigue)	–	–	–	–	–	–	−0.24 (0.03)	3.39%	<0.001
Depression (negative affect)	–	–	–	–	–	–	−0.03 (0.03)	0.040%	.340
Depression (positive affect)	–	–	–	–	–	–	−0.02 (0.02)	0.03%	.441
Depression (low self-esteem)	–	–	–	–	–	–	−0.02 (0.02)	0.04%	.345

Table 4
Effect of Age and Mood groups on objective and subjective cognitive outcomes.

	Attention Composite		Memory Composite		Subjective Cognition	
	(df) F	*p*	(df) F	*p*	(df) F	*p*
Sex	(1,2517) 0.249	.618	(1,2518) 3.245	0.072	(1,2309) 0.028	0.868
Education	(1,2517) 16.008	<0.001	(1,2518) 29.714	<0.001	(1,2309) 9.964	.002
Mood Group	(2,2517) 4.499	.011	(2,2518) 10.228	<0.001	(2,2309) 145.956	<0.001
Age Group	(2,2517) 105.460	<0.001	(2,2518) 14.231	<0.001	(2,2309) 10.665	<0.001
Mood x Age Group	(4,2517) 0.458	.767	(4,2518) 2.770	0.026	(4,2309) 1.082	0.364

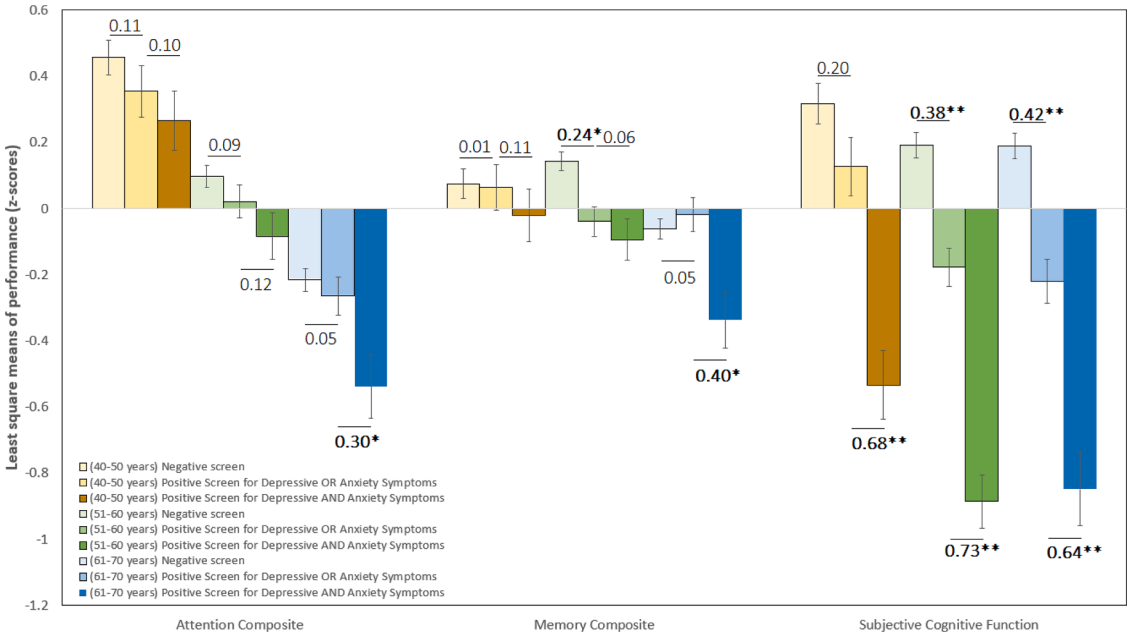

Fig. 2. Effect of age and mood group on each objective and subjective outcome (error bars represent standard error; Cohen's d values are presented above/below each comparison; * indicates $p < .05$ and ** indicates $p < .001$).

Thus, when considered together, the results of this study suggest that age moderates the effect of anxiety symptoms on cognition, potentially contributing to a decline in cognitive performance over time.

In middle-aged adults, studies suggest that proteinopathic changes associated with AD have begun, although individuals are unlikely to reach established thresholds of abnormality for Aβ or tau (Sutphen et al., 2015). The observation that clinically meaningful anxiety symptoms are related to memory impairment, particularly in late-middle-aged adults, suggest that elevated anxiety may be also an early indicator of preclinical disease, or that it may be related to the pathogenesis of AD. We and others have postulated that the presentation of elevated anxiety early in AD may reflect a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Canet et al., 2019; Pietrzak et al., 2017). It is possible that the anxiety factor scores identified in this study (i.e., panic, tension, somatic symptoms) may be accompanied by elevated levels of circulating cortisol. This is due to the observed association between pathological anxiety, and dysregulation of the HPA axis (Fiksdal et al., 2019). Animal studies have also shown that HPA dysregulation (e.g., through prolonged exposure to glucocorticosteroids) can promote AD neuropathological changes. In humans, high plasma cortisol levels have been shown to be associated with increased rates of cognitive decline in Aβ+ cognitively normal older adults (Ouanes and Popp, 2019; Pietrzak et al., 2017). Others have hypothesised that anxiety may increase AD risk through cortisol-mediated hippocampal neurotoxicity, as elevated cortisol levels have been found in older adults with clinically meaningful anxiety (Mantella et al., 2008). Elevated anxiety can also exacerbate vascular risk factors such as inflammation and oxidative stress which can, in turn, drive increased cognitive decline (Machado et al., 2014).

The hypothesis that higher levels of depressive and anxiety symptoms would be associated with increased subjective cognitive concerns was also supported. In middle-aged adults, clinically meaningful anxiety or depressive symptoms were associated with increased subjective cognitive concerns of a moderate magnitude (d=−0.37; Fig. 2). In individuals with high levels of both anxiety and depressive symptoms, the extent of subjective cognitive concerns was increased further and substantially (d = −1.07; Fig. 2). Both depressive and anxiety global composites, anxiety factor scores (panic, tension, somatic) and one depressive factor score (fatigue) were associated with increasing levels of subjective cognitive concern. This is consistent with a previous report in older adults, where depressive and anxiety symptoms contributed to the severity of subjective cognitive concerns (Buckley et al., 2013). Further, these findings are also consistent with established literature which reports that subjective cognitive concerns are frequently comorbid with depressive symptoms and often present as the primary symptom of depression in older adults (Burmester et al., 2016; Jessen et al., 2014; Molinuevo et al., 2017).

Examination of the relationships between older age and poor mood revealed that individuals with high depressive and anxiety symptoms reported higher subjective cognitive concerns, irrespective of their age group. Considering the strong relationship between subjective cognitive concerns and affect, it will be important to ascertain whether subjective cognitive concerns represent a separate disease process from that of depression (Mascherek et al., 2020; Zlatar et al., 2018). The finding in the current study that only anxiety symptoms were associated with cognition, whereas both depressive and anxiety symptoms were associated with subjective cognitive concerns, suggests that subjective

cognitive concerns may be an indicator of psychopathology as opposed to reflecting true changes in cognition, as the presence of psychological symptoms does not appear to be associated with subjective cognition in the same pattern as that observed for objective cognition.

The results of this study should be interpreted in the context of its limitations. First, this study only reports data collected cross-sectionally at baseline, and future studies examining the extent to which changes in anxiety and/or depression is related to changes in cognition will further inform on the contribution of abnormal mood symptomatology to the development of cognitive decline and progression to dementia, or its prodrome, MCI. Second, while the HBP is a community-based sample, it is significantly enriched with individuals with a family history of dementia. The sample in this study is therefore at a higher risk of developing dementia compared to the general population, and thus the generalizability of our results may be limited. However, it should be noted that the HBP sample does include individuals across multiple states in Australia, including regional areas, as well as a large range of ages, education levels and occupational attainment, which allows for a broad spectrum of the Australian population to be represented. Finally, the HBP was designed to assess and monitor a large sample of community-based Australians, and as such, biological markers of cortisol, Aβ, tau or other markers of HPA-axis dysregulation (e.g., inflammatory cytokines) are currently unavailable as participants will be required to attend a medical facility to enable the collection of such biomarkers. However, the advent of blood biomarkers will allow for the collection of such disease markers in the future, which will in turn assist in elucidating the biological drivers of the relationship between anxiety and memory impairment in middle-aged adults.

These limitations notwithstanding, this study supports the hypothesis that depressive and anxiety symptoms may increase the risk of developing AD-related cognitive dysfunction and dementia. It also provides support for literature which suggests that depressive and anxiety symptoms may be a clinical marker of dementia, and that screening for these symptoms can be a means of identifying people experiencing or at risk of cognitive decline (Creese et al., 2021, 2019). However, additional longitudinal investigations are needed to evaluate the generalizability of these results, as well as exploring the effect of psychological symptoms on other cognitive domains. Further research examining other biological factors involved in AD dementia onset and progression such as Aβ and tau, and their relationship to psychological symptoms may provide further insights about the moderating effect of these symptoms on dementia risk, onset, and progression. Lastly, studies examining the efficacy of treatment for anxiety and depressive symptoms as an intervention to mitigate cognitive decline may now be warranted.

Author statement

S Perin, J Lai and YY Lim designed the study. RF Buckley and YY Lim are responsible for the design and conduct of the Healthy Brain Project. S Perin and YY Lim conducted all statistical analyses and interpretation of the data. S Perin and YY Lim prepared the manuscript. S Perin, MP Pase, L Bransby, RF Buckley, N Yassi, RH Pietrzak, P Maruff, and YY Lim drafted and revised the manuscript. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

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Declaration of Competing Interest

P Maruff is a full-time employee of Cogstate Ltd., the company that provides the Cogstate Brief Battery. All other investigators have no relevant disclosures to report.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.10.007.

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