Depressive symptoms as a risk factor for memory decline in older adults: a longitudinal study using the dual change score model

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Abstract

Background: the direction of the longitudinal association between depression and memory remains a topic of intense debate. A unidirectional association where depression impacts the change in memory (or vice-versa) and a bidirectional association where the trajectories of both dimensions affect each other lead to different clinical implications. Method: This study aimed to investigate the directionality of the depression-memory association in a sample of 2,057 older adults aged between 60 to 99 years old from the Virginia Cognitive Aging Project (VCAP). We used the bivariate dual change score model to investigate the directionality of the association between episodic memory and three dimensions of depression (somatic, depressed affect, and positive affect) throughout ten years (five measurement points), controlling for age, education, and gender. Results: slight decline is observed for memory and stability for depression over the ages of 60 – 99. All depression scales at a given time-point predicted the subsequent change in memory with a negative association, meaning that higher depression is linked with a steeper decline in memory by the next time-point (γ_{Dep} = 1.768; SE = 0.566; $p < 0.05$). The opposite model in which memory predicted depression and the bidirectional model were both much weaker than the depression predicting memory model. Conclusions: Our findings support a unidirectional association with depression preceding an accelerated decline in memory in older adults. We discuss the clinical implications for depression as a risk factor for a subsequent memory decline.

Keywords: memory, depression, relationship, aging

Word count: 6122

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Introduction

How our mood is affected by the aging process and whether depressive symptoms influence cognitive decline has been a topic of intense debate due to its clinical implications. Variability in the trajectory of depression is expected among older adults, with the mean of depressive symptoms increasing (Sutin et al., 2013) but the prevalence of depressive disorder declining with age (Byers, Yaffe, Covinsky, Friedman, & Bruce, 2010). It coincides with a well-documented decline in memory performance among older adults (Salthouse, 2019), which justifies investigating a potential association between depression and memory among older people (Bielak, Gerstorf, Kiely, Anstey, & Luszcz, 2011; Dong et al., 2016; Oi, 2017).

In general, cross-sectional and longitudinal studies have demonstrated that higher scores in self-reported depressive symptoms are associated with lower scores in objective memory measures and with an accelerated cognitive decline (Gale, Allerhand, & Deary, 2012; Kommer et al., 2013; Wang, Yip, Lu, & Yeh, 2017). However, findings have been mixed regarding the directionality of this association for healthy aging. Changes in memory have been reported as predicting changes of depression (M → D) (Jajodia & Borders, 2011; Perrino, Mason, Brown, Spokane, & Szapocznik, 2008) in the same way that the opposite direction, i.e., changes in depression predicting changes in memory (D → M), have been supported by the literature (Brailean et al., 2017; Chodosh, Kado, Seeman, & Karlamangla, 2007; Gale et al., 2012; Oi, 2017). There are also evidence for a bidirectional association in which changes in both constructs predict a change in the other (Bielak et al., 2011).

Investigating the temporal ordering of this association allows a deeper understanding of the dynamic between depression and memory during aging. Therefore, this study investigated the directionality of longitudinal associations between memory and depression in older adults using a set of Bivariate Dual Change Score Models (BDSCM) (McArdle & Hamagami, 2001) in a subsample from the Virginia Cognitive Aging Project (VCAP).

Association Between Memory and Depression

While typical trends in cognitive aging assume a general age-related decline for multiple abilities, in particular the fluid ones (Salthouse, 2019), the pattern of change for depressive symptoms for healthy adults is variable: some longitudinal studies show a significant increase in depressive symptoms from around the age of 60, preceded by a decrease in self-reported symptoms around the age of 50 to 60 years old (Gale et al., 2012; Oi, 2017; Sutin et al., 2013). In contrast, the late years of lifespan have been reported as the happiest ones, with a continuous decrease in depressive symptoms from the age of 50 to the oldest ages (Salthouse, 2010). Since variability in the trajectory of depression is expected around the age of 60, when a steeper decline in cognitive performance is also expected (Salthouse, 2019), investigating a possible relationship between depression and cognition is justified.

Depressive symptoms and memory are pointed by the literature as coexistent phenomena in older adulthood. In general, longitudinal studies have demonstrated that higher scores in self-rating depressive symptoms are associated with lower memory scores and an accelerated memory decline (Brailean et al., 2017; Chodosh et al., 2007; Gale et al., 2012; Oi, 2017; Perrino et al., 2008). However, the reasons for this association are less understood and a key research question to advance in this matter is to investigate whether the trajectories of depression and cognition are

strongly associated and the direction of this association. Over the last decades, the pool of evidence has pointed out three possible directions.

In the first one, depression is reported as a predictor of the rate of change in memory (D → M). This finding supports the hypothesis of depression as a risk factor or a prodromal stage of dementia (Butters et al., 2008). Numerous studies support that a higher level of depressive symptoms in a given time-point is associated with subsequent memory performance, predicting an accelerated memory decline (Gale et al., 2012; Köhler et al., 2010; Oi, 2017). The longitudinal trajectory of depression has also been associated with subsequent diagnosis of dementia, i.e., older adults with a pattern of high and increasing depressive symptoms are at increased risk for dementia (Kaup et al., 2016).

Chodosh et al. (2007) showed that a higher baseline level of depression was strongly associated with an accelerated seven-year decline in cognitive performance, indicated by the sum score of standard tests, including a measure of delayed recall (memory). Gale et al. (2012) also reported that greater depression was associated with a slightly faster rate of cognitive decline (assessed by the sum score of verbal memory, prospective memory, verbal fluency, and attention), and this association remained significant over 6-years of follow-up for people aged 60-80 years. Using data from the Health and Retirement Study, Oi (2017) found that, among later cohorts, the worsening of depressive symptoms contributed to a steeper memory decline, with the intercept and slope of depression scores predicting individual trajectories of memory performance. Wilson, Arnold, Beck, Bienias, and Bennett (2008), in their prospective 13-year study, reported that from a sample of 917 those who subsequently developed Mild Cognitive Impairment (MCI) (n=319) had a significantly higher baseline level of depressive symptoms than those who did not develop MCI (n = 368). Using the Bivariate Dual Change Score Model to

investigate the directionality of depression-cognition association, Bielak et al. (2011) also concluded that depressive symptoms precede changes in perceptual speed. Either the opposite direction (perceptual speed to depressio) and the bidirectional model showed poorer fit to the data.

Depressive symptoms, however, have not always been reported as preceding cognitive decline. The second direction of this dynamic association states that lower initial levels of memory performance are associated with an increase in depression over time (M → D), supporting the hypothesis that depressive symptoms in older adults are reflecting a mood reaction caused by one's awareness of cognitive loss (Jajodia & Borders, 2011; Kommer et al., 2013; Perrino et al., 2008). Perrino et al. (2008) suggest that a growing cognitive impairment may also negatively impacts the individual's capacity to regulate mood and engage in activities that could prevent depressive symptoms or promote coping, like participation in social activities. Cognitive impairment may also make the individual more prone to cognitive distortions associated with depressive moods, like magnifying negative details of life events (Beck & Clark, 1988; Sachs-Ericsson, Schatschneider, & Blazer, 2006).

Jajodia and Borders (2011) examined the relationship between a single measure of immediate/delayed recall with depressive symptoms. Using a dynamic change score approach to test unidirectional and bidirectional models, the authors found that the best model in terms of relative fit had memory as the leading variable. That is, memory preceded the rate of change of depressive symptoms with a better initial memory performance associated with a greater decrease in depressive symptoms over time, but the contrary was not true: depressive symptoms did not reliably predict the rate of change of memory. Brailean et al. (2017) reached a similar conclusion with memory (delayed recall test) predicting a further steeper increase in depressive affect,

supporting the unidirectional hypothesis from memory to depression. The decline in processing speed was also associated with an increase in somatic symptoms of depression over time, suggesting that a neurodegenerative common cause may associate depression and cognition. Using the BCSM, Aichele and Ghisletta (2019) reported a time-ordered effect such that low baseline scores in a single recall test preceded subsequent 2-year increases in depressive symptoms in a large sample of 107,599 adults.

Despite the large number of research supporting the negative association between memory and depressive symptoms, a few studies also reported no longitudinal association between depression and cognition for healthy older adults (e.g., Ganguli, Du, Dodge, Ratcliff, & Chang, 2006; Dufouil, Fuhrer, Dartigues, & Alpérovitch, 1996) and no systematic change in depression before and after Alzheimer's disease (AD) diagnosis (Wilson et al., 2008). These findings suggest that cognition and depression are independent phenomena, and their co-existence might be explained by common causes underlying major depression and dementia, like vascular risk factors (Butters et al., 2008; Panza et al., 2010), cerebrovascular lesions (Alexopoulos, 2005), and damage on the hypothalamic-pituitary-adrenal-stress axis (Butters et al., 2008; Lupien et al., 1998).

The mixed results reported by the field may reflect methodological differences between studies, like the length of observation periods, rates of follow-up, assessments of depressive symptoms, possible bias in AD diagnosis, and the control of confounding demographic and clinical variables (Panza et al., 2010). The use of unappropriated statistical approaches to answer questions about the directionality of this association may also explains the mixed results of the field (Grimm, 2007). Many studies relied on longitudinal growth curve (LGC) models (Brailean et al., 2017; Kommer et al., 2013; Oi, 2017) or regression models (Chodosh et al., 2007; Gale et

al., 2012) to examine whether depression precedes cognitive decline or vice-versa. Fewer studies relied on a more appropriate approach to answer directionality questions using a dual change score (DCS) model (e.g., Aichele & Ghisletta, 2019; Jajodia & Borders, 2011; Perrino et al., 2008).

Grimm (2007) points out that questions that could be answered by LGC models can also be answered using the DCS models, with the latter presenting the advantage of "dealing with multiple processes over time. This additional benefit is that the model directly examines time-dependent change as the latent differences are the outcome of interest and can be predicted by previous scores" (p. 333). Therefore, the DCS approach, in particular the bivariate dual change score model (BDCS; McArdle & Hamagami, 2001) allows the investigation of a crucial developmental question: whether a latent variable X at time t is a predictor of the changes in a latent variable Y and vice-versa. This can be accomplished by investigating the fit of competing models, each with a different directionality represented by the coupling parameter (that if set to zero indicates that a given latent variable does not predict changes in a second latent variable). The time-lagged predictions are unique to the BDCS model and cannot be estimated using LGC models.

Present Study

The current study investigates the directionality of the association between three dimensions of depression (somatic symptoms, depressive affect, and positive affect) and measures of episodic memory using data from the Virginia Cognitive Aging Project (VCAP) with the participants ranging from 60 to 99 years old. The group was accessed in five time-points

throughout ten years in 2.5 year-interval between the assessments. Not all time-points from VCAP were used due to missing data and dropout rates.

Following the findings that established a cross-sectional association between depressive symptoms and cognitive functioning (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008) a negative association between high levels of depressive symptoms and cognitive abilities at baseline is expected. Given the mixed results about the directionality of this association, the present study aims to explore which of the two dimensions (memory or depression) best predicts the other over time, using the BDSC model. This study tests three hypotheses: 1) if depressive symptoms are mood reaction to the awareness of the cognitive loss expected with age, we expect that memory performance at time t predicts the change of depression at time t+1 (M → D); 2) if depressive symptoms are a risk factor for cognitive decline, we expect that depression at time t predicts the change in memory at time t+1 (D → M); 3) if depression and memory share a common etiology, we would expect a parallel association between the trajectories of depressive symptoms and memory (bidirectional coupling); and 4) no longitudinal association between memory and depression.

Method

Participants

The sample was composed of 2,057 participants ranging from 60 to 99 years old at the first measurement point (Mean = 70.25; SD = 7.74), with 16.23 years of education on average (SD = 2.85). For a summary of the recruitment strategies and data collection, see Salthouse (2019). Regarding the selectivity attrition for this sample, Salthouse (2014a) reported that returning participants had higher cognitive performance at an initial measurement occasion

among adults older than 50 years old, possibly due to a greater dropout of older participants with lower cognitive performance. At the first time-point, the average performance was calculated for memory (M = 13.37; SD = 7.42), for CES-D scale (M = 8.56; SD = 0.37), and for each dimension of CES-D scale: a) Somatic: (M = 3.50; SD = 9.01); b) Depressed Affect: (M = 1.62; SD = 5.44); and c) Positive Affect: (M = 1.82; SD = 5.23). Among respondents, 62% (n = 1280) were females, and none of the participants met the cognitive impairment criteria for the MMSE (score of ≤ 23 points, (Tombaugh & McIntyre, 1992). Clinically relevant depressive symptoms were found for 2.5% of the participants (score ≥ 16, (Beekman et al., 1997)). Table 1 presents the mean and standard deviation for our sample across the five time-points.

Table 1

Means and Standard Deviations for Study Variables Across Waves

Variables	Wave 1	Wave 2	Wave 3	Wave 4	Wave 5
Memory	13.37 (7.42)	15.60(4.63)	15.66(4.71)	15.65(4.76)	15.78(4.71)
CES-D	8.56(0.37)	7.86(6.83)	8.23(7.02)	8.30(6.85)	8.58(7.69)

Note: Standard deviations are in parentheses.

Measures

Memory. Memory was evaluated using six tests: 1) Paired Association test (Salthouse, Fristoe, & Rhee, 1996): participants hear six pairs of unrelated words. They are then presented with the first word in each pair and asked to recall the second word; 2) Logical Memory (Wechsler, 1997): participants listen to two different stories and are asked to repeat as many details as they can recall; 3) Word Recall (Wechsler, 1997): participants heard a list of words and were asked to recall the words in any order throughout three trials. After a second list being presented and recalled, the participants are asked to recall the first list; 4) Delayed Memory Word Recall (Wechsler, 1997): participants are asked to recall a list of words presented four times

earlier; 5) Delayed Memory Paired Associates: the participants are asked to recall the second word in the associates pairs presented earlier after being prompted with the first word in each pair; 6) Delayed Memory Logical Memory test (Wechsler, 1997): participants are asked to recall as many details as possible from stories presented earlier in two conditions (no cue and cue) (Wechsler, 1997). For each time point, sum scores of each measure were calculated by summing the scores of the individual tests: total score of memory at time t = score in the paired association test at time t + score in the logical memory test at time t + score in the word recall test t time t).

Depression. Depression was assessed using the full version (20-items) of the Center for Epidemiological Studies-Depression scale (CES-D) (Radloff, 1977). Participants reported how often they experienced symptoms of depression in the past week on a Likert scale of four points: 0 = “rarely or never”; 1 = “some of the time”; 2 = “occasionally”; 3 = “mostly or always”. A cutoff score of 16 points was used to identify participants with high depressive symptoms (Beekman et al., 1997). The original study of the CES-D scale reported a four-factor structure with depressed affect, positive affect, somatic symptoms, and interpersonal difficulties dimensions (Radloff, 1977). The interpersonal difficulties factor, however, has been recognized as a poor measure (Carleton et al., 2013), and for this reason, it was excluded from our analyses. Based on preview studies that have reported a differential association between the dimensions of depression and memory (Brailean et al., 2017), the present study analyzed the directionality of memory-depression association for somatic symptoms, depressed affect (DA), and positive affect (PA).

Data analysis

In this study, the reciprocal and directional relationships between memory and depression are addressed using the longitudinal structural equation modeling framework via the bivariate

dual change score model (McArdle & Hamagami, 2001). The BDCS model combines methodological aspects of growth curve models and autoregressive cross-lagged models, capturing time-sequential associations within each developmental process. The following paragraphs summarize how BDCSM can be used to investigate the longitudinal relationship between depression and cognition. We propose the following BDCS model to capture the dynamical directional relations of cognition and depressive symptoms. Let D and M be two repeatedly measured variables.

$$D_{it} = d_{it} + e_{D_{it}},$$

$$M_{it} = m_{it} + e_{m_{it}}, (1)$$

where D_{it} and M_{it} represent the observed scores of depressive symptoms and memory for person i ($i = 1, \dots, N$ with N denoting sample size) at time t ($t = 1, \dots, T$ with T denoting measurement occasions). Equation (1) shows that the observed scores of D_{it} and M_{it} can be written as functions of their theoretical true scores d_{it} and m_{it} and time-specific residuals $e_{D_{it}}$ and $e_{m_{ij}}$.

Assume autoregressive relationships or event-contingency in cognition and depressive symptoms, the true score at the current time t is a function of the true score at the immediately preceding time $t - 1$ plus the true change and can be represented as

$$d_{it} = d_{i(t-1)} + \delta d_{it},$$

$$m_{it} = m_{i(t-1)} + \delta m_{it}. (2)$$

Equation (2) shows that the true cognitive score at the current time t is equal to the true cognitive score at time $t-1$ plus the true change in cognition. The same logic applies to the repeatedly-measured scores for depressive symptoms.

As mentioned previously, the BDCSM focus on the changes in trajectory and therefore the latent changes (i.e., δd_{it} and δm_{it}) are typically the outcomes of the interest in BDCS. Based on the dual change score model, one typical form of the bivariate change equations can be represented as:

$$\delta d_{it} = \beta_{d0} \times S_{di} + \beta_{d1} \times d_{i(t-1)} + \beta_{d2} \times m_{i(t-1)},$$
$$\delta m_{it} = \beta_{m0} \times S_{mi} + \beta_{m1} \times m_{i(t-1)} + \beta_{m2} \times d_{i(t-1)}, (3)$$

where S_{di} and S_{mi} represent the rates of change, similar to the latent slope factors in growth curve analysis. These terms are constant across time and are usually allowed to covary. The second sources of latent difference come from the variables of their previous states, which are summarized in the proportional change parameters β_{d1} and β_{m1}. The second sources show that cognitive scores at the previous time point m affect the cognitive scores at its next state. Similarly, the current scores for the depressive symptoms are partially affected by depressive symptoms from its previous time point $d_{i(t-1)}$. Additionally, there is a third part that contributes to the latent changes in cognition and depressive symptoms, which makes the BDCSM advantageous to determine the directional relationships between cognition and depressive symptoms. These unique sources of latent difference are captured in the coupling parameters γ_{d2} and γ_{m2}, demonstrating the amounts of latent differences that are explained by the previous state of the other variable. In other words, γ_{d2} determines whether memory is a leading indicator of changes in depressive symptoms and vice versa for γ_{m2}.

In summary, the BDCS model is represented in Equations (1), (2), and (3) and will be used for the analysis in the study. From the model representations, we see that it is advantageous to apply the BDCS model to understand the reciprocal and directional relationship between depressive symptoms and memory. First, the BDCSM share the benefits of GCM in that both models study the intraindividual change and interindividual differences in change (i.e., S_{di} and S_{mi} in the model representation). Besides, the BDCSM answer additional research questions that traditional GCM cannot answer as it examines the separate time-dependent changes in depressive symptoms and cognition, where their previous time scores can predict their later developments in depression and memory, respectively (i.e., the proportional change parameters β_{d1} and β_{m1}). Furthermore, the BDCS allows the changes in one latent factor, the depressive symptoms, to covary with the previous status of the other latent factor, memory, which leads to the estimation of the directional relationship between the memory and depressive symptoms (i.e., the coupling parameters γ_{d2} and γ_{m2}). Significant coupling parameters are evidence of decisive relations of one variable affecting the other variable.

Measurements of memory and depressive symptoms were collected for five time points over ten years. Everyone in the sample was measured approximately at the same time. Longitudinal score change models were fitted to the five repeated measurements of memory and each of the depression dimensions (somatic, DA, and PA) as a function of five time-points. Different restrictions were imposed on the models to determine the directionality of memory-depression association. For each pair of dimensions (e.g., memory and somatic symptoms), four BDSC models were fitted: no coupling, unidirectional M → D, unidirectional D → M, and full coupling (bidirectional) model. For the BDCS full coupling model, all coupling parameters were freely estimated. In the unidirectional BDCS models, only one of the coupling parameters was estimated, and the other fixed to zero. Therefore, to test the directionality from memory to

depression, only the coupling parameter M→D was estimated; and from depression to memory, only the coupling parameter D→M was estimated. Figure 1 portrays the model diagram used in this study.

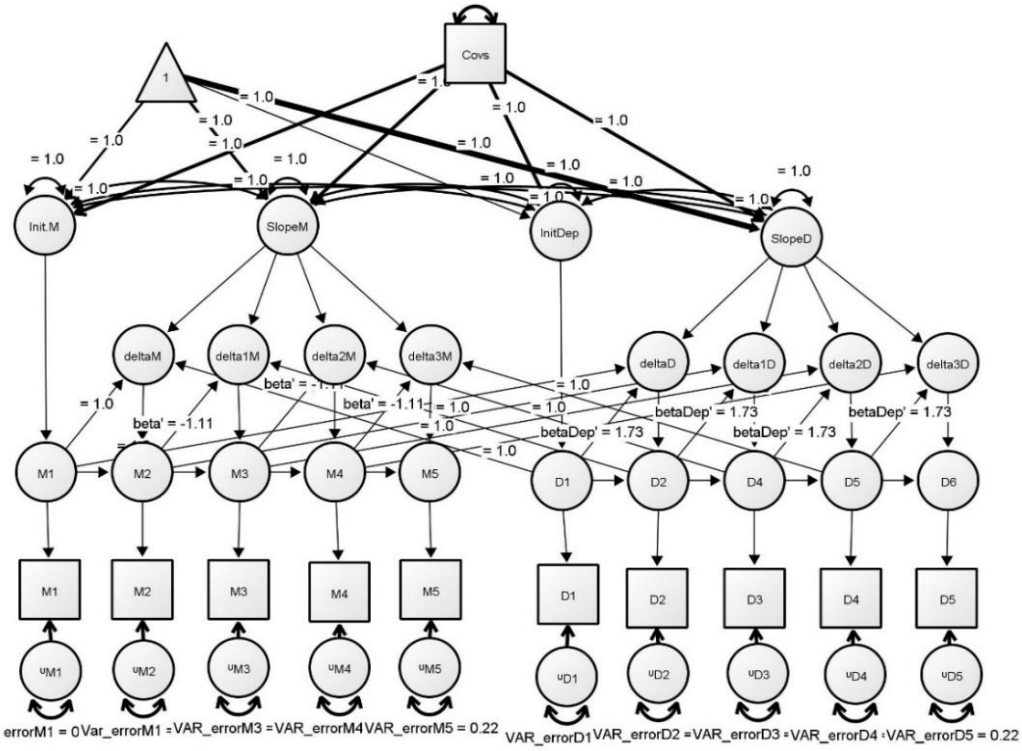

Figure 1. Bivariate dual change score model diagram. Squares depict the observed variables and circles represent the latent variables. Regression weights are shown by one-headed arrows and variance and covariance by two-headed arrows. An autoregressive parameter is exemplified by the arrow connecting *M1* to *deltaM*, while an example of a coupling parameter is the arrow connecting *M1* to *deltaD*.

Additionally, univariate dual change score models were employed to examine longitudinal trajectories for both memory and depression. Following the guidelines from Grimm, An, McArdle, Zonderman, and Resnick (2012), four models were specified: proportional change, constant change, the dual change (including both proportional and constant change parameters), and the changes-to-changes model, in which changes in time [t] influences changes in time [t + 1].

All analyses were implemented in R (Team, 2017). The BDCSM graph (Figure 1) was implemented on Onyx (von Oertzen, Brandmaier, & Tsang, 2015), a graphical user interface for SEM that uses R in the background. Model fit was evaluated based on the guidelines proposed by Hu and Bentler (1999) for good fit. To compare the four models and choose the final, we adopted the same holistic approach proposed by Nelson, Jacobucci, Grimm, and Zelinski (2020) which includes the analysis of the Akaike Information Criterion (AIC) (Akaike, 1987) and the Bayesian Information Criterion (BIC) (Raftery, 1995) with lower values indicating better model fit. Following the Nelson et. al (2020) approach, we defined meaningful improvements in model fit as a difference in the model's information criteria higher than 10 points. In the case of equal model fit or difference between information criteria lower than 10, we chose in favor of the simplest model.

Covariates

To control for potentially cofounder variables in the association between depression and memory, predictors of the latent change variables were included in each final model. The influence of age, education, and gender were investigated. Baseline age was calculated to the participant's date of birth, and education was assessed by the number of years the participant attended formal education.

Ethical Standard

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and received research ethics committee approval.

Results

Univariate dual change score models

Univariate dual change score models were applied for estimating the univariate trajectories of memory and depression. For memory, the dual change and the changes-to-changes models presented adequate fit to the data (CFI = 1, RMSEA = .00; 90% CI .04 – .005), and the difference between information criteria was lower than 10 (subtracting the dual change model information criteria values from those of the changes to changes model, $\Delta AIC = 1.204$; $\Delta BIC = 5.144$). Selecting in favor of the simpler model, the dual change model was retained as the final. Regarding memory's trajectory across age, the mean of the constant change component was 0.003 (SE = 0.036, p = 0.937), combined with a proportional change parameter of -0.774 (SE = 0.09, $p < 0.001$) as shown in Table 2.

Table 2

M*emory Univariate Dual Change Score Model Fits*

Model	**AIC**	**BIC**	**RMSEA/CFI**
Constant change	4345.313	4368.954	0.113 / 0.883
Proportional change	4378.909	4394.670	0.131 / 0.823
Dual	4277.115	4304.696	0.000 / 1.000
all	4278.319	4309.840	0.000 / 1.000

This resulted in a trajectory that shows a non-significant change from 60 to 99 years old in memory. Figure 2 plots the expected latent scores for memory based on the univariate dual change score model. The oldest age group (> 75 years old) shows a lower performance over time-points, and both groups of age present a steeper decline from time-point 1 to time-point 2.

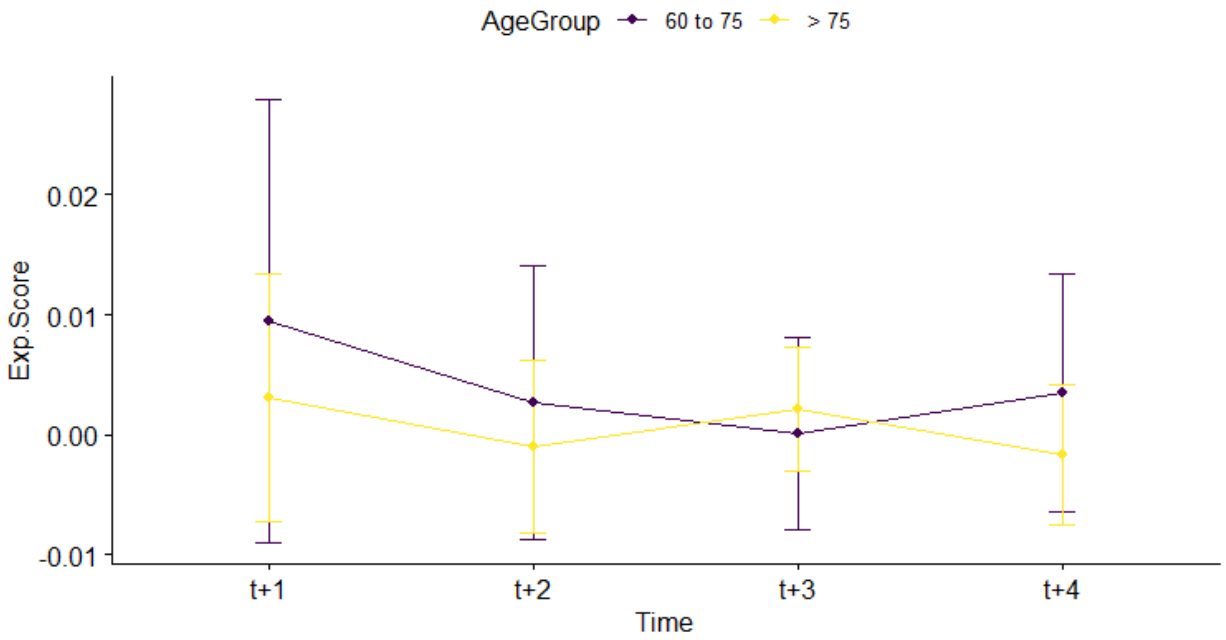

Figure 2. Expected latent scores based on the univariate dual change score model for memory across measurement occasions. t+1 = latent score mean for timepoint 2; t+2 = latent score mean for timepoint 3; t+3 = latent score mean for timepoint 4; t+4 = latent score mean for timepoint 5. The yellow line represents the age group from 60 to 75 years old. The black line represents the age group > 75 years old.

For depression, information criteria (Table 3) also indicated that the dual change and the change-to-change model fit equally well, with a difference lower than 10 points between criteria (subtracting the dual change model information criteria values from those of the changes-to-changes model, ΔAIC = -0.737; ΔBIC = -4.678). Selecting in favor of the simpler model, the dual change model was retained as the final. Regarding the trajectory of depressive symptoms across age, the mean of the constant change component was 0.001 (SE = 0.022, p = 0. 965), combined with a proportional change parameter of -0.477 (SE = 0.440, p = 278) resulted in a trajectory that shows stabilization.

Table 3

Depression Univariate Dual Change Score Model Fits

Model	**AIC**	**BIC**	**RMSEA/CFI**
Constant change	4113.898	4137.539	0.000 / 1.000
Proportional change	4116.379	4132.139	0.018 / 0.997

Dual	4113.592	4141.173	0.000 / 1.000
all	4114.329	4145.851	0.000 1.000

Figure 3 shows the expected latent scores from the dual change model. It is possible to observe that the oldest age group (> 75 years old) presents lower depressive scores, and both groups of age show a pattern of stabilization of depressive symptoms over the five time points.

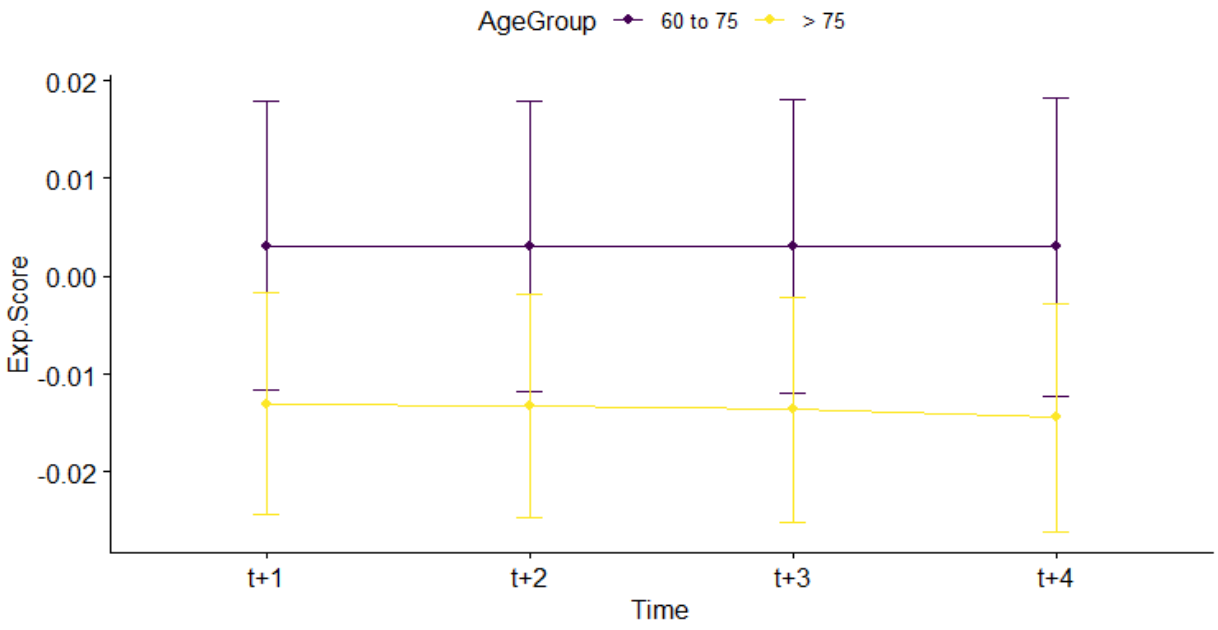

Figure 3. Expected latent scores for depression based on the univariate dual change score model across measurement occasions. Exp.Score = mean of latent scores for CES-D. t+1 = latent score mean for timepoint 2; t+2 = latent score mean for timepoint 3; t+3 = latent scores for timepoint 4; t+5 = latent score mean for timepoint 5. The yellow line represents the age group from 60 to 75 years old. The black line represents the age group > 75 years old.

Bivariate dual change score models

In this section, the directionality of the association between depressive symptoms and memory is reported. The relative fit indices AIC and BIC (sample-sized adjusted) were used to determine which model showed the best fit to the data. Specifically, the selection protocol

employed by Nelson et.al (2020) was adopted to choose the final model. The estimates for each parameter of the four models are shown in Table 4 and the fit indices for all models are presented in Supplemental Material. It is important to note that the positive affect (PA) dimension of the CES-D scale is inverted; therefore, a lower score represents, actually, a high level of PA.

Table 4

Bivariate Dual Change Score Model Fits

Dimension	Fit indices	No coupling	Mem [t] → ΔSom [t + 1]	Som [t] → ΔMem [t + 1][a]	Bidirectional coupling
Somatic	-2LL	8284.583	8283.885	8254.266	8250.342
	Parameters	26	27	27	28
	AIC	8336.583	8337.885	8308.266	8306.342
	BIC	8482.937	8489.868	8460.249	8463.954
	aBIC	8487.380	8494.310	8464.692	8468.397
	RMSEA	0.011	0.011	0.004	0.002
	CFI	0.978	0.992	0.997	0.999
	Fit indices	No coupling	Mem [t] → ΔDA [t + 1]	DA [t] → ΔMem [t + 1][a]	Bidirectional coupling
Depressed Affect (DA)	-2LL	8272.593	8272.585	8251.327	8250.287
	Parameters	26	27	27	28
	AIC	8324.593	8326.585	8305.327	8306.287
	BIC	8470.947	8478.568	8457.31	8463.899
	aBIC	8475.389	8483.011	8461.753	8468.341
	RMSEA	0.015	0.015	0.012	0.012
	CFI	0.963	0.962	0.976	0.976
	Fit indices	No coupling	Mem [t] → ΔPA [t + 1]	PA [t] → ΔMem [t + 1][a]	Bidirectional coupling
Positive Affect (PA.)	-2LL	8290.581	8287.895	8281.224	8276.753

Parameters	26	27	27	28
AIC	8342.581	8341.895	8335.224	8332.753
BIC	8488.935	8493.878	8487.207	8490.366
aBIC	8493.378	8498.321	8491.65	8494.808
RMSEA	0.0	0.0	0.0	0.0
CFI	1.00	1.00	1.01	1.01

Note: Mem = Memory; Som = Somatic; DA = Depressed affect; PA = Positive affect. The models are depicted from the simplest to the more complex with the addition of one parameter in the sequence. The No coupling model is the simplest one. The Mem [t] → ΔDepression [t + 1] model tests the addition of the coupling parameter γ from memory at time $t - 1$ to each dimension of depression, whereas the model depression [t] → ΔMem [t + 1] tests the addition of the coupling parameter γ from each dimension of depression at time $t - 1$ to memory. The Bidirectional coupling model tests the addition of both coupling parameters. -2LL = Minus Two Log Likelihood; AIC = Akaike information criterion; BIC = Bayesian information criterion; aBIC = adjusted Bayesian information criterion.
[a] Final model

All BDCS models converged and presented an adequate fit to the data (CFI = 1, RMSEA = .00; 90% CI .04 – .005). The following paragraphs describe the model comparison procedures and present the estimated parameters of the final selected models. For the somatic symptoms dimension, removing the coupling parameter Somatic (Som) [t] → ΔMemory(Mem) [t + 1] from the bidirectional model resulted in a unidirectional model Mem → ΔSom. This removal significantly worsened model fit with the difference between the information criteria between both models being greater than 10 (ΔAIC = -31.543; ΔBIC = -25.914; ΔaBIC = -25.913). To test the opposite direction, the coupling parameter from memory to subsequent changes in somatic was removed, resulting in the unidirectional model Som [t] → ΔMem [t + 1]. This removal resulted in a similar model fit with the bidirectional model (ΔAIC = -1.924; ΔBIC = 3.705; ΔaBIC = 3.705). Thus, selecting in favor of the simplest model, Som [t] → ΔMem [t + 1] was chosen as the final model. This model showed a significant coupling effect (γ_{Som} = 1.768, SE = 0.566, $p < 0.05$) suggesting that somatic symptoms precede further memory decline, with a change of one standard deviation (SD) in somatic symptoms predicting a change of nearly 2 SDs

in memory. To illustrate the direction and strength of this relationship, Figure 4 depicts a vector field plot (Boker, & McArdle, 1995) between memory and somatic symptoms scale.

Table 5

BDCSM parameter estimates from the final model Somatic[t] → ΔMemory[t + 1]

Parameter	Estimate	SE.
Correlations		
Level of Memory w/ Slope of Memory	-0.172	0.147
Level of Somatic w/ Slope of Somatic	-0.680	0.363
Level of Memory w/ Level of Somatic	**0.264**	**0.046***
Level of Memory w/ Slope of Somatic	-0.322	-0.322
Level of Somatic w/ Slope of Memory	-0.575	0.312
Slope of Memory w/ Slope of Somatic	0.691	0.688
Proportional Changes		
Memory → ΔMemory (βm)	**-0.956**	**0.097***
Somatic → ΔSomatic (βs)	1.189	0.664
Coupling effects		
Somatic → ΔMemory (γ_S)	**1.768**	**0.566***

Note: Slope = constant change over five measurement points; Proportional changes and coupling effects represent score at a starting time as predictive of change in score at a subsequent time.
* significant at $p < 0.05$

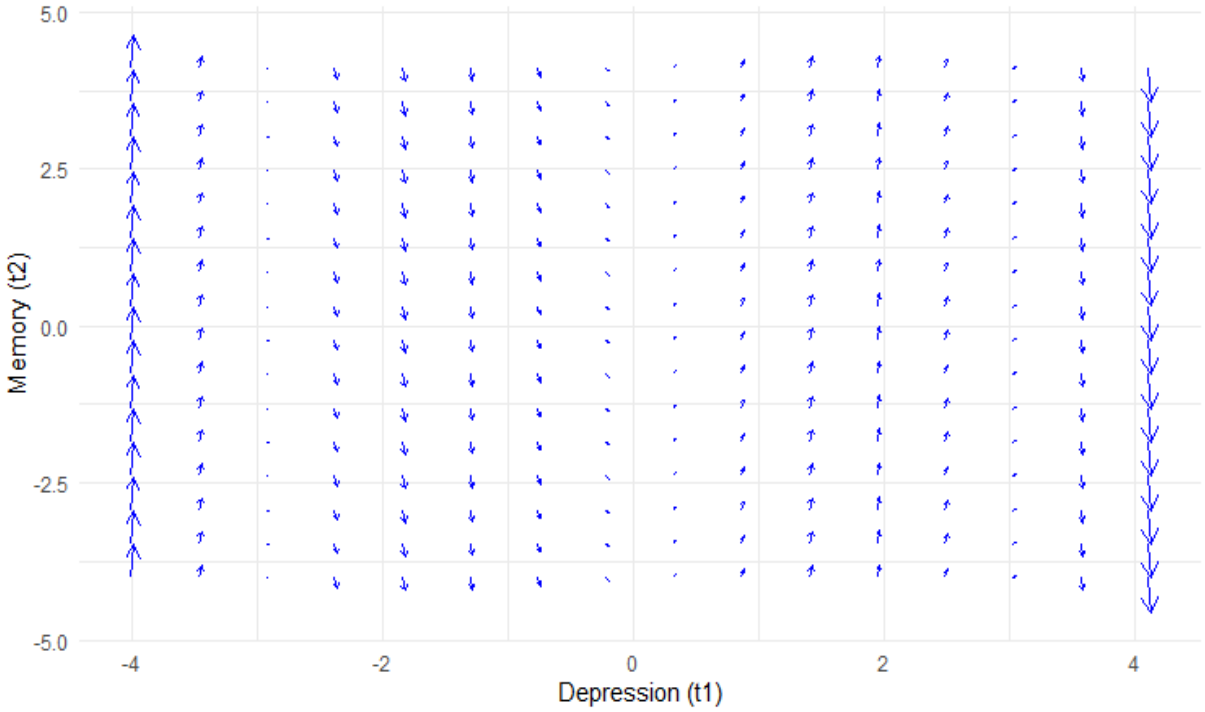

Figure 4. Vector field plot of the dynamic relationship between memory (change scores) and somatic symptoms (true scores). At lower levels of somatic symptoms (i.e., at a score of -4), memory tends to increase or decline less. At higher levels of somatic symptoms (i.e., at a score of 4), memory tends to decline.

For DA, removing the coupling parameter from prior DA to subsequent memory from the bidirectional model resulted in the model Mem [t] → ΔDA [t + 1], which significantly worsened the model fit with the difference between the information criteria being greater than 10 (ΔAIC = -20.298; ΔBIC = -14.669; ΔaBIC = -14.610). To test the opposite direction (DA → M), the coupling parameter from memory to subsequent changes in DA was removed, resulting in the model DA [t] → ΔMem [t + 1]. This removal resulted in a similar model fit (ΔAIC = 0.960; ΔBIC = 6.589; ΔaBIC = 6.588). Thus, selecting in favor of the simplest model, the unidirectional model DA [t] → ΔMem [t + 1] was chosen as the final model. This model showed a significant coupling effect from prior DA that predicts change in subsequent memory performance (γ_{DA} =

1.200, SE = 0.357, $p < 0.05$), meaning that a change of one SD in somatic symptoms predicts a change of nearly 1.2 SDs in memory.

Table 6

BDCSM parameter estimates from the final model DA [t] → ΔMemory[t + 1]

Parameter	Estimate	SE.
Correlations		
Level of Memory w/ Slope of Memory	-0.043	-0.043
Level of DA w/ Slope of DA	-0.119	0.158
Level of Memory w/ Level of DA	**0.287**	**0.049***
Level of Memory w/ Slope of DA	-0.061	0.083
Level of DA w/ Slope of Memory	-0.153	0.175
Slope of Memory w/ Slope of DA	0.044	0.063
Proportional Changes		
Memory → ΔMemory (βm)	**-1.056**	**0.119***
Somatic → ΔDA (β_{DA})	0.170	0.317
Coupling effects		
DA → ΔMemory (γ_{DA})	**1.200**	**0.357**

Note: Slope = constant change over five measurement points; Proportional changes and coupling effects represent score at a starting time as predictive of change in the score at a subsequent time.
* significant at $p < 0.05$

For PA, the bidirectional coupling model showed a significant coupling effect only from prior PA to change in memory (γ_{PA} = 0.940, SE = 0.408, $p < 0.05$). Removal of this coupling parameter resulted in the model Mem [t] → ΔPA [t + 1] with a similar model fit with differences between information criteria values being less than 10 (ΔAIC = -9.142; ΔBIC = -3.512; ΔaBIC = -3.513). To test the opposite direction (DA → M), the coupling parameter from prior memory to subsequent changes in PA was removed, resulting in the model PA [t] → ΔMem [t + 1]. This removal also resulted in a similar model fit (ΔAIC = -2.471; ΔBIC = 3.159; ΔaBIC = 3.158). Thus, both unidirectional models were favored with the employment of the simplest model selection criterion. Comparing them, the unidirectional model PA [t] → ΔMem [t + 1] presented

the lowest information criteria values and, for this reason, was chosen as the Final Model. This model showed a significant coupling effect from a change of one standard deviation in prior PA, predicting a change of 0.7 SD in memory (γ_{PA} = 0.703, SE = 0.294, p < 0.05).

Table 7

BDCSM parameter estimates from the final model Positive Affect → ΔMemory

Parameter	Estimate	SE.
Correlations		
Level of Memory w/ Slope of Memory	0.048	0.084
Level of PA w/ Slope of PA	-0.033	0.155
Level of Memory w/ Level of PA	**0.344**	**0.053***
Level of Memory w/ Slope of PA	-0.030	0.082
Level of PA w/ Slope of Memory	0.067	0.144
Slope of Memory w/ Slope of PA	0.021	0.028
Proportional Changes		
Memory → ΔMemory (βm)	**-0.929**	**0.101***
PA → ΔPA (β_{PA})	-0.040	0.299
Coupling effects		
PA → ΔMemory (γ_{PA})	**0.703**	**0.294***

Note: Slope = constant change over five measurement points; Proportional changes and coupling effects represent score at a starting time as predictive of change in score at a subsequent time.
* significant at p < 0.05

Covariate associations

The effects of age, education, and sex are provided in Supplementary Material. Higher educational level was associated with lower baseline levels of somatic symptoms (b = -0.149, SE = 0.044, p < 0.05), DA (b = -0.135, SE = 0.041, p < 0.05), lower long-term increases in DA (b = -0.333, SE = 0.104, p < 0.05) and lower long-term increase in memory (b = -0.331, SE = 0.105, p < 0.05). Women had better initial memory performance (b = 0.267, SE = 0.108, p < 0.05) and a larger long-term increase in memory (0.215, SE = 0.104, p < 0.05). There were neither significant sex-related differences in the baselines and slopes of depression nor significant differences found

for memory and depression across the ages of 60 to 99 years. The pattern of results remained the same after the inclusion of education, age, and sex in the final models. All models converged and presented a good fit, except for the models that included sex as a covariate. The dynamics reported did not alter with the inclusion of the covariates, with significant coupling effects found only from prior depression dimensions to a subsequent change in memory (Depression [t] → ΔMemory[t + 1].

Discussion

We investigated the time-ordered association between depressive symptoms and memory for older adults across ten years using the BDCSM that allows for the investigation of directionality hypotheses. The present study found a unidirectional effect in which three dimensions of depression predicted subsequent memory decline (D → M). Somatic symptoms was the dimension with the strongest association: a change in one SD of somatic symptoms predicted a change in almost two SDs in memory, followed by DA (1.2 SD) and PA (0.7 SD). The patterns of results did not alter after controlling for age, sex, and education. These findings agree with previous researches that supported a unidirectional association with depression leading the cognitive-depression association (Bielak et al., 2011; Gale et al., 2012; Kommer et al., 2013; Köhler et al., 2010; Oi, 2017).

The mechanisms underlying this association are uncertain and have been a topic of intense debate: depressive symptoms have been reported either as a risk factor for subsequent development of dementia (Chodosh et al., 2007; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006; Richard et al., 2013; Saczynski et al., 2010) or as a prodromal stage (early symptom) of dementia (Panza et al., 2010; Vinkers, Gussekloo, Stek, Westendorp, & Mast, 2004). Butters et

al. (2008) advocate that both hypotheses (depression as a risk factor or a prodromal stage of dementia) are supported by large and robust evidence, and therefore they are not mutually exclusive. Barnes et al. (2012) showed that chronic depression during life is associated with an increased risk for developing dementia, particularly vascular dementia. Still, when the first depressive episode occurs in late life, it may reflect a prodromal stage of dementia.

At present, the authors know three other studies investigating the directionality of depression-memory association using the BDCSM. All these previous studies reached the same conclusion: a unidirectional association in which memory precedes depression over time for older adults (M → D). Jajodia and Borders (2011) used data from the Health and Retirement Study and reported that lower performance in a delayed recall test predicted increases in depression in a 2-year interval. Perrino et al. (2008) used a smaller sample of Hispanic Americans and also concluded that cognitive performance was related to subsequent depressive symptoms at every time point. Finally, Aichele and Ghisletta (2019) reported that the performance in a delayed recall test preceded a subsequent 2-year increase in depression.

Methodological differences may contribute to explain the inconsistencies between our results and past studies' findings, such as statistical analysis, variations in time-point frame, and measures. The quality of memory assessment and the longitudinal study's length are differences worth it to be commented. Our sample was assessed throughout ten years and five time-points, in contrast with the 2-year interval of Jajodia and Borders (2011) and Aichele and Ghisletta (2019), and the 3-year-interval of Perrino et al. (2008). The present study also relied on six memory measures to assess memory performance, instead of a single recall list test (Aichele & Ghisletta, 2019; Jajodia & Borders, 2011). Regarding the quality of the measurement assessment, the use of a single memory test to assess a broad cognitive domain is deemed as a significant limitation. The

use of single tests as a proxy for the performance on broad cognitive domains affects the robustness of the assessment (i.e., does not enable the adequate identification of broad latent variables). Compelling evidence against reliance on single tests was presented by Salthouse (2012), who investigated in which level of a cognitive hierarchical structure depressive symptoms presented the highest impact. Results showed that depressive symptoms were significantly related only with the highest levels of the model (g-factor and five cognitive abilities) rather than the level of observable variables (sixteen cognitive tests).

To investigate the impact of the quality of memory assessment in the directionality of memory-depression association, we run the same four BDCS models (no coupling, full coupling, and unidirectional models) using a single memory test of the VCAP memory battery to compare with our results using the complete memory battery. Using a single recall test (Word Recall), a different scenario was portrayed. Although all models have adjusted, no significant coupling effects were found between memory and the three depression dimensions. The differences between the model's information criteria were all lower than 10 points, with small differences in favor of the unidirectional model D → M for all depression dimensions. That contrasts with the results using the complete memory battery, supporting our claim that using single tests to assess the performance on broad cognitive domains affects the robustness of the cognitive assessment and may lead to different conclusions.

A possible explanation for depression plays an important role as a predictor of memory decline and be a potential risk factor for the development of dementia is that depressive symptoms might be a behavioral marker related to further cognitive pathologies. Malpetti et al. (2020) investigated the longitudinal association between apathy and cognitive decline over time and found that, among the presymptomatic patients of frontotemporal dementia, apathy predicted

the worsening of cognitive performance two years before dementia's diagnosis and was also associated with baseline low gray matter volume in frontal and cingulate regions. Although apathy can occur independently of depression and vice-versa (Husain & Roiser, 2018), a co-morbid relationship has been well-established among both conditions as either apathy and depression are associated with various somatic and neurological disorders that cause cognitive impairment (Andersson, Krogstad, & Finset, 1999; Van Reekum, Stuss, & Ostrander, 2005).

Findings from clinical literature suggest that the ability to recall important information is impaired over time in individuals who suffer from depression (Rock, Roiser, Riedel, & Blackwell, 2014). The cognitive effects of depressive symptoms may be explained by neurobiological mechanisms linked to memory problems, like the levels of corticosteroids, elevated during the depressive episode (Baumeister, Lightman, & Pariante, 2014). Animal literature has also shown that corticosteroids have a neurodegenerative effect on the hippocampus, a critical brain region for memory (Kim & Diamond, 2002). The literature has also suggested that depressed individuals tend to exhibit a mood bias that leads them to recall more negative information than non-depressed individuals (Elliott, Rubinsztein, Sahakian, & Dolan, 2002) and lack specificity in their autobiographical memories (Dritschel, Beltsos, & McClintock, 2014). These memory phenomena associated with depression may lead to abnormal memory functioning reflected in the objective memory performance of depressed individuals.

Although we found a unidirectional association with depression preceding memory decline, the cause of this association is not determined by this study as the demonstration of the time-ordered association between both constructs does not support causal inferences. This should be better explored by studies using clinical groups to investigate whether the longitudinal impact of depression on memory presents a different pattern among individuals with a clinical diagnosis

of depression, as well as whether depression is a risk factor for subsequent dementia. Other factors might influence both memory impairment and depression which limit the causal inferences that can be drawn.

This study aims to contribute to the field with important advances, like the robustness of the cognitive assessment conducted in a large sample and the use of a latent change score model to test the directionality of the association. Our findings, however, must be interpreted in light of some methodological limitations. First, the sample was not assessed through a formal diagnosis of depression, and there is no clinical data of risk factors linked to depression and cognitive impairment (Anstey, Sanden, Sargent-Cox, & Luszcz, 2007). Additionally, the sample attrition across time resulted in a sample with higher memory functioning, which may lead to a small association of initial levels of depression and memory performance (Salthouse, 2014b). The relatively high-functioning community sample may also explain the lower scores in depression among the oldest age groups in contrast with many other studies that report that depression increases among older adults (Gale et al., 2012; Oi, 2017; Sutin et al., 2013).

Conclusion

The present study applied models that directly tested the direction of the longitudinal association between memory and depression. We found that higher levels of all dimensions of depression (somatic symptoms, depressed affect, and positive affect) predicted a more rapid decline in memory, with a powerful effect found in particular for somatic symptoms. This pattern remained after controlling for age, education, and sex. Therefore, depressive symptoms may be considered a risk factor for further memory decline.

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Conflicts of Interest

None.

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