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Causal associations between depression symptoms and cognition in a community-based cohort of older adults

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Running head: Depression and cognition

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Abstract

Objectives: To evaluate the temporal association between depression symptoms and cognitive function in older adults over a 4 year period.

Design: Longitudinal cross-lagged.

Setting: Population-based.

Participants: 896 community-dwelling adults aged 70 to 97 years.

Measurements: Depression symptoms and cognitive domains including processing speed, verbal fluency, face and word recognition, episodic memory, and simple and choice RT.

Results: Cross-lagged structural equation models suggested that initial depression symptoms affected subsequent processing speed, simple and choice RT, but that cognition did not predict depression symptoms over time. The associations between depression and cognitive variables were attenuated when the models were adjusted for sensory impairment, physical health and locus of control.

Conclusions: The findings suggest that causally, depression precedes cognitive impairment in this age group, and that the association is related to physical health and perceptions of a lack of control thereover.

Introduction

The association between late life depression and cognition is well recognized, with cross-sectional studies indicating poorer cognitive function in more depressed older persons (e.g., 1, 2-4) and longitudinal research showing depression is associated with more precipitous cognitive decline over time (e.g., 5, 6-11). However, less information is available about the causal relationship between late life depression and cognition. Does depression give rise to cognitive deficits or do perceptions of cognitive impairment with increasing age precipitate depression? A meta-analysis (12) concluded there had been insufficient research examining depression arising from cognitive decline and one of the few studies since examining causal relations (11) found that in 64 to 85 year olds, depressive symptoms at baseline were associated with greater decline in global cognition and episodic memory over 3.5 years. Notably in this investigation, baseline cognitive scores did not predict change in depression over the same period suggesting that depression temporally precedes cognitive decline.

In the present study, our goals were twofold. First, we used a cross-lagged design (e.g., 13) spanning four years to investigate temporal relations between depression symptoms and a range of cognitive domains including processing speed, executive function and episodic memory in a large population-based sample of older adults. As depression may be an early marker of dementia (for review see 14), we took low global cognition scores into account in models estimating effects over time as they may be indicative of cognitive impairment and incipient dementia. Second, as there is evidence that physical fitness and health may account for associations between depression and cognitive function (e.g., 14, 15), we included in our analyses several potential explanatory variables relating to physical health status; specifically, health histories, functional daily activities, and visual and auditory impairment. Finally, it is likely that perceived control over physical health in old age will also impact on psychological wellbeing (16). This is particularly important as, for example, cardiovascular health is

implicated in both depression and dementia (14). As failing health that accompanies aging is likely to precipitate perceptions that physical decline (e.g., hypertension, heart disease) is beyond the control of the individual, we measured locus of control, in the expectation that perceived lack of control (i.e., an external locus of control) may also account for depression-cognition associations.

Method

Participants

The Canberra Longitudinal Study is an epidemiological survey of mental health and cognitive functioning in older people. Participants were sampled from the compulsory electoral roll for the cities of Canberra and Queanbeyan, Australia, with 69% responding. The baseline assessment was completed by 896 community-dwelling adults (456 men and 440 women) aged 70-97, with the sample stratified by age and gender. Participants were followed up every four years, with up to four assessments administered between 1990 and 2002. At the four year follow-up assessment, 185 (20.6%) participants were deceased and 100 (11.2%) did not complete an assessment, resulting in a sample of 611 at follow-up. The four year assessment was conducted a mean of 3.6 years after the initial assessment (*SD* = 0.13 years, range 39-50 months). Approval for the research was obtained from the Ethics in Human Experimentation Committee of The Australian National University. Further details of the study design are provided by Christensen et al. (17).

Procedure

Interviews were conducted by trained professional interviewers, who administered a comprehensive survey and conducted physical assessments. Baseline assessments lasted

approximately two hours, and covered background characteristics, physical health and disease status, mental health status and cognitive performance. Follow-up assessments were similar in length and content.

Measures

A range of cognitive tests that offered broad coverage within the constraints of the wider study was administered at each interview. Full details of the measures and the rationale for their inclusion, is provided elsewhere (17). *Speed of processing* was measured by the Symbol-Letters Modalities Test (SLMT), a task similar to Smith's Symbol-Digit Modalities Test (18) and Wechsler's Digit-Symbol Substitution (19). The number of correct symbol-letter pairs made in 90 seconds was summed. *Verbal fluency* was assessed as the number of animals named in 30 seconds. *Face and word recognition* tasks were based on the Rivermead Behavioural Memory Test (20). An *episodic memory* task consisted of four brief episodic memory tasks testing word, face, name and address recall and figure reproduction (21). To facilitate comparisons between these five tests, scores were standardized to a common metric, with a mean of 100 and standard deviation of 10 for the full sample at baseline.

Simple and choice reaction time (RT) were both assessed over 20 trials. The simple RT trials consisted of ten left hand stimuli followed by ten right hand stimuli. Choice reaction time trials consisted of a random combination of left- and right-hand stimuli. Interstimulus intervals ranged from 0.5 to 2.0s. Further detail of the RT protocol is provided by Christensen et al (22). Initially, RTs for incorrect trials were removed together with unusually fast responses (<150 ms) and those greater than the age group mean + 3 age groups *SD*s. These exclusions resulted in the loss < 2.1% of trials across the sample. Age group means and *SD*s were computed for age ranges 70 to 75, 76 to 80, 81 to 85 years, and 86 years and older. *Mean RT* and *intraindividual standard deviation* (ISD) were then calculated as measures of

central tendency and intraindividual variability respectively. A regression procedure was used to compute the ISD, based on previously established methods (e.g., 23), whereby residuals were saved having partialled out time-on-task effects, age group effects, and their interaction. The residuals obtained for ISDs were then standardized and converted into t-scores.

Depression symptoms were assessed using the Goldberg Depression Scale (24) at both time points. This scale comprises nine items that measure symptoms of depression in the four weeks prior to reporting (specifically, low energy, loss of interest, loss of confidence, hopelessness, inefficient thinking, poor appetite, early waking, feeling slowed up and feeling worse in the morning). The number of "yes" responses were summed to derive a score (range 0-9), with higher scores reflecting a greater severity of depression. A number of other variables were included in the models to account for potential confounding. *Age, gender and years of highest educational attainment* were reported during the initial interview. *Potential presence of preclinical dementia* (the subclinical phase of the disease prior to formal diagnosis) was identified using the Mini-Mental State Examination (MMSE, 25), based on a score of <24 out of 30 (e.g., 26) at any of the four assessment time points. This measure has been shown to exhibit adequate sensitivity and specificity to dementia in community samples (e.g., 27). Physical health was assessed using a *health history* measure, derived from the count of diseases from a list of 16 options (e.g., diabetes, cancer, heart disease, hypertension), and a *functional ability scale* assessing a range of Activities of Daily Living (ADL), with scores ranging from 0 to 22. Sensory impairment was assessed on the basis of self-report, with *visual impairment* rated as "poor" or "blind" corrected vision and *hearing impairment* assessed as requiring a hearing aid and/or rating hearing as "poor". *Locus of control* was measured using the 17-item Locus of Control of Behaviour scale (28), with scores reflecting mean ratings across the items (range 0-6). Higher scores indicate the self as locus of control while lower scores indicate external locus of control.

Analysis

Cross-lagged structural equation models (13, 29) were estimated using Mplus v6.12 (30). These models are illustrated in Figure 1. The relationships of particular interest were the effects of baseline depression symptoms on follow-up cognition, and baseline cognition on follow-up depression symptoms. The models also accounted for cross-sectional associations of cognition with depression symptoms, the correlations of depression estimates across the two time points and the correlation of cognition effects across the two time points. Adjustments were made in the models for age, gender, education and possible dementia, with follow-up adjustments made for visual impairment, hearing impairment, disease count, ADL score and locus of control. Initially, separate models were estimated for each of the nine cognition variables. Additional adjustment (physical health, sensory impairment, locus of control) was only examined for those models where depression symptoms and cognition had longitudinal associations. Models were estimated using all available data, such that sample sizes for the analyses ranged from 753-894. Missingness was due to participants not completing a cognitive measure (8-10% non-completion on RT measures, <5% missingness on other measures) and missing depression data (3%). Standard errors were estimated in Mplus based on maximum likelihood with a sandwich estimator for robustness to violations of non-normality.

Results

For descriptive purposes, participants with more than two depression symptoms were compared to those with fewer (or missing) symptoms following a cut point identified by the authors of the scale (24) and work in the present sample suggesting this to be associated with high sensitivity (88%) while maintaining reasonable specificity of 68% (31). Sample

characteristics for these subgroups are shown in Table 1. Individuals with more than two depression symptoms tended to have greater external locus of control, lower functional ability, poorer processing speed, slower simple/choice RT and higher simple/choice RT variability. Males were less likely to be depressed than females and individuals reporting visual impairment were less likely to be depressed than those without impairment. There were no differences between depression groups in terms of age, education, hearing impairment, possible dementia, and the remaining cognitive measures.

The cross-lagged models of depression symptoms and cognition are shown in Table 2, with adjustment for age, gender, education and possible dementia. Estimates refer to unstandardized linear regression estimates. The *p* values are based on *z* scores, derived by dividing each estimate by its standard error, which are based on robust maximum likelihood estimates. There were negligible effects of initial cognitive performance on subsequent depression symptoms, with processing speed the sole exception. Conversely, however, there were effects of initial depression symptoms on subsequent cognitive performance in multiple domains, specifically processing speed, mean simple RT and mean choice RT. For example, Wave 1 depression significantly predicted Wave 2 mean simple RT; higher depression scores were associated with slower RTs. Specifically, each additional depression symptom endorsed at Wave 1 was associated with a decrease of 0.75% in processing speed performance, 6.6 ms slowing of mean simple RT and 7.7 ms slowing of mean choice RT. By contrast though, the association between Wave 1 mean simple RT and Wave 2 depression was nonsignificant. There was also a non-significant trend in the relationship between depression symptoms and intraindividual variability on the simple RT task. In addition to these core findings, the models suggested consistent depression scores from baseline to follow-up (r = 0.49), a finding repeated with the majority of cognitive measures (range: r = 0.23 to r = 0.69). There were also baseline cross-sectional relationships between depression symptoms and cognition

on processing speed, verbal fluency, simple/choice RT mean and simple/choice RT variability. These cross-sectional relationships were less pronounced at follow-up, with only the simple RT mean/variability effects remaining.

To examine possible explanations for the relationship between depression symptoms and cognition, models were re-estimated for the three tasks where depression showed a significant longitudinal relationship with cognition: processing speed, simple RT mean and choice RT mean. Measures of sensory impairment (visual and hearing), physical health (disease count and ADL score) and locus of control were added to the model. These extended models, shown in Table 3, indicate that the additional adjustments accounted for a large proportion of the relationship between depression symptoms and cognition. The only remaining significant effect was that between baseline depression and subsequent mean simple RT. Nonsignificant trends were obtained for mean choice RT, processing speed and the effect of processing speed on depression, that were highly attenuated from the effects observed in Table 2.

Discussion and Conclusions

This is one of the first investigations to explicitly assess temporal associations between depression symptoms and cognitive function over time in a large population-based sample of adults aged 70 years and over at baseline. We also took several explanatory variables into account relating to physical health, functional activities of daily living, visual and hearing impairment, and locus of control. Our findings showed that depression symptoms predicted deficits on several cognitive variables at four-year follow up. Importantly, when the models were adjusted for the explanatory variables, cognition at Wave 1 did not predict depression at Wave 2 suggesting that depression symptoms temporally preceded the observed cognitive deficits. Moreover, when we took physical health, activities of daily living and locus of

control into account, most of the associations over time between Wave 1 depression symptoms and Wave 2 cognition became nonsignificant and effect sizes substantially diminished. Together, the findings suggest that depression temporally influences cognition in old age, but not vice versa, and that physical health may contribute to the association.

In terms of the cognitive mechanisms underlying the findings, theorists (e.g., 32, 33) propose that depression deleteriously affects cognitive performance due to reduced motivation and/or a narrowing of attention and increased distraction due to depression-related thoughts. Although we did not test cognitive mediating mechanisms in the present study, our findings suggest that a consequence of late life depression is a reduction in processing speed and in simple and choice RT tasks. This finding is consistent with work elsewhere (34) that suggests cognitive deficits in depression may arise out of general slowing rather than specific attentional deficits. Although we do not dismiss the possibility that attentional mechanisms contribute to depression-related cognitive deficits, the present findings suggest that a slowing of information processing is also a contributory factor. Finally, a previous study (11) also found depression to predict episodic memory declines, and similarly, we found a downward trend in this cognitive domain, albeit nonsignificant.

Importantly, we found that after adjusting for physical health, activities of daily living and locus of control, the associations between depression symptoms and cognitive variables became nonsignificant or diminished substantially. Although no one variable was primarily responsible for this finding, it is likely that experiencing physical ill health such as heart disease, cancer or hypertension, reduced ability to perform activities of daily living, and impaired vision and hearing, may contribute to later life depression. This finding is supported by work showing physical activity moderates the effects of depression on cognitive function (15) and also work implicating cardiovascular disease in both depression and dementia in old age (14). Moreover, when the occurrence of such diminishing health is perceived to be

beyond the control of the individual, our findings suggest that subsequent cognitive decline in the presence of depression may be partially attributable to this perception of external locus of control. Elsewhere, there is evidence that an individual's sense of control over their health plays an important role in depression (e.g., 35, 36).

A possible explanation for our findings that needs to be considered stems from evidence suggesting that depression may be an early marker of, and possibly a prodrome for, dementia (14), and that associated cognitive deficits are related to the preclinical phase of the disease rather than depression per se. Indeed, our previous investigation in this sample produced evidence consistent with this possibility (10). However, we believe this is unlikely in the present study as we were careful to adjust for low global cognition scores (MMSE<24) that are indicative of cognitive impairment and possible dementia. Although we cannot confirm that our participants were dementia-free either at the time of, or in the years following the study, this procedure reduces that likelihood considerably.

The use of a similar cross-lagged correlational approach has received criticism, as the causal influence is lagged in time (37) and the analysis does not reflect within-person change (38). However, the cross-lagged model used in the present study provides a rare opportunity to test causal relations between depression symptoms and cognition in a large sample of community-dwelling older adults and may provide new insights into the processes underlying this relationship. There are advantages and disadvantages to a range of methods for examining such relationships. In contrast to the bivariate growth curve approach used previously with this cohort (10), the cross-lagged analysis required no assumptions about the linearity of change in depression scores over time and provided clearer evidence for the direction of the observed effects. The lack of effects of cognition on subsequent depression meant that comparisons of the magnitude of associations (38) were unnecessary, further strengthening the evidence for directionality.

Beyond statistical limitations, there are a number of further potential limitations to consider. First, there was a four-year lag (M = 3.6 years) between baseline and follow up, a period that may be considered too long to assess the causal linkage between depression and cognitive function. However, the depression symptoms test-retest reliability from baseline to follow up was high suggesting that consistency was good over the period of the investigation, and a previous study testing this association (11) assessed a similar period of time (3.5 years). Clearly though, future research is needed that tests the temporal association over both shorter and longer periods of time in order to gain insights into the precise chronology of depression-cognition relations in varying conditions. Second, the cognitive measures used in the present analysis were selected prior to the beginning of the study in 1990 with the aim of briefly assessing a range of abilities. Studies using more comprehensive measures of episodic memory in particular, along with other domains of cognitive functioning may find different outcomes. The inconsistency in episodic memory scores across the two time points may be due to the psychometric properties of the brief scale. Likewise, the brief assessment of depression symptoms, physical health (ADL, disease count) and mental state (MMSE) using brief epidemiological scales may result in different outcomes from the use of more comprehensive or clinical assessment tools. Third, our decision to focus on Waves 1 and 2 was decided by those waves providing the most data, highest retention and that by Wave 4, the majority of the participants were deceased. Additionally, by focussing on the younger old (as defined by mean age at Waves 1 and 2), there was a greater chance of uncovering the mechanisms involved and the work was more likely to be relevant to preventative intervention strategies. It would, though, obviously have been desirable to include Waves 3 and 4 in the analyses had sufficient data been available. Further, the practical constraints of the study meant that data relating to medication use (e.g., cognitive enhancers or anti-depressants) were unavailable and, therefore, could not be taken into account in our analyses.

Finally, we should note that the effect sizes were modest, indicating that although the relationship between depression and subsequent cognition appears robust, the magnitude of the effect over four years is unlikely to be of predictive significance in the clinical setting. That said, the mounting literature demonstrating strong links between depression and cognition suggests that assessment of depression symptoms should be considered in older adults when cognitive decline is present.

To conclude, the present findings suggest that late life depression precedes cognitive decline and that perceptions of poor physical health and reduced functionality in daily activities, may contribute to that decline. Although we cannot rule out that neuropathology associated with future dementia is the mechanism underlying this finding, the study provides important information on the causal association between depression and cognition in old age.

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Conflicts of interest

None

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Table 1: Descriptive statistics at baseline based on depression symptoms

	Low depression (≤2 symptoms) N = 599	Elevated depression (>2 symptoms) N=297		
	Mean (SD) or n (%)	Mean (SD) or n (%)	F or χ^2	*p*
Age	76.43 (4.82)	76.79 (5.17)	1.059	0.304
Gender = male	323 (53.9%)	133 (44.8%)	*6.640*	**0.010**
Years of education	11.39 (2.64)	11.28 (2.45)	0.344	0.557
Self as locus of control	4.32 (0.59)	4.10 (0.61)	23.234	**<0.001**
ADL score	1.41 (2.09)	2.76 (3.09)	57.779	**<0.001**
Disease count	2.51 (1.58)	3.43 (1.83)	61.026	**<0.001**
Possible dementia	114 (19.0%)	64 (21.5%)	*0.790*	0.374
Hearing impairment	429 (72.7%)	202 (68.0%)	*2.124*	0.145
Visual impairment	451 (76.4%)	167 (56.2%)	*38.194*	**<0.001**
Processing speed	100.67 (9.98)	98.67 (9.92)	7.695	**0.006**
Verbal fluency	100.43 (9.86)	99.10 (10.24)	3.526	0.061
Face recognition	99.98 (9.55)	100.04 (10.87)	0.008	0.928
Word recognition	99.95 (10.40)	100.10 (9.18)	0.040	0.842
Episodic memory	100.18 (10.01)	99.64 (9.98)	0.574	0.449
Simple RT mean	2.90 (0.94)	3.14 (1.10)	10.378	**0.001**
Simple RT ISD	4.88 (2.91)	5.53 (3.34)	8.164	**0.004**
Choice RT mean	3.39 (0.91)	3.67 (1.02)	15.270	**<0.001**
Choice RT ISD	5.78 (2.31)	6.18 (2.43)	5.173	**0.023**

Notes: **bold** values indicate $p < 0.05$; For X^2, df = 1and for *F*, df ranged from 1,757 to 1,895; W1: wave 1 (baseline); W2: wave 2 (follow-up); ADL: Activities of Daily Living scale; RT: reaction time; ISD: intraindividual standard deviation.

Table 2: Cross-lagged structural equation models of the relationship between depression symptoms and cognition, adjusted for age, gender, education and possible dementia

	Cognition W1 → Depression W2		Depression W1 → Cognition W2		Depression W1 ↔ Depression W2		Cognition W1 ↔ Cognition W2		Cognition W1 ↔ Depression W1		Cognition W2 ↔ Depression W2	
	Estimate	*p*	Estimate	*p*	Estimate	*p*	Estimate	*p*	Estimate	*p*	Estimate	*p*
Processing speed	-0.034	**<0.001**	-0.745	**<0.001**	1.503	**<0.001**	46.098	**<0.001**	-2.351	**<0.001**	-0.402	0.364
Verbal fluency	-0.012	0.083	-0.275	0.188	1.558	**<0.001**	48.066	**<0.001**	-1.378	**0.035**	-0.673	0.156
Face recognition	0.000	0.979	0.162	0.496	1.572	**<0.001**	26.044	**<0.001**	-0.145	0.831	-0.258	0.729
Word recognition	-0.007	0.433	-0.297	0.197	1.573	**<0.001**	44.165	**<0.001**	-0.621	0.295	1.073	0.051
Episodic memory	0.000	0.972	-0.312	0.096	1.573	**<0.001**	7.707	0.273	-0.870	0.188	-0.785	0.268
Simple RT mean	0.002	0.061	6.642	**0.004**	1.532	**<0.001**	1639.349	**<0.001**	20.181	**0.002**	12.597	**0.044**
Simple RT ISD	-0.019	0.552	0.123	0.052	1.532	**<0.001**	-0.052	0.853	0.421	**0.036**	0.848	**<0.001**
Choice RT mean	0.001	0.350	7.668	**0.004**	1.518	**<0.001**	3294.359	**<0.001**	23.510	**<0.001**	8.210	0.176
Choice RT ISD	0.061	0.102	0.089	0.124	1.518	**<0.001**	0.792	**0.007**	0.554	**<0.001**	0.240	0.069

Notes: **bold** values indicate $p < 0.05$; W1: Wave 1 (baseline); W2: Wave 2 (follow-up); RT: reaction time; ISD: intraindividual standard deviation; estimates refer to unstandardized linear regression estimates; p values based on z scores, derived by dividing each estimate by its standard error

Table 3: Cross-lagged structural equation models of the relationship between depression symptoms and cognition, adjusted for age, gender, education, possible dementia, sensory impairment, physical health and locus of control

	Cognition W1 → Depression W2		Depression W1 → Cognition W2		Depression W1 ↔ Depression W2		Cognition W1 ↔ Cognition W2		Cognition W1 ↔ Depression W1		Cognition W2 ↔ Depression W2	
	Estimate	*p*	Estimate	*p*	Estimate	*p*	Estimate	*p*	Estimate	*p*	Estimate	*p*
Processing speed	-0.018	0.050	-0.379	0.064	1.057	**<0.001**	36.888	**<0.001**	-0.709	0.149	-0.693	0.073
Simple RT mean	0.001	0.123	6.473	**0.012**	1.053	**<0.001**	3751.107	**<0.001**	5.777	0.360	10.540	0.063
Choice RT mean	0.001	0.220	5.952	0.050	1.052	**<0.001**	4135.912	**<0.001**	10.319	0.081	4.470	0.368

Notes: **bold** values indicate $p < 0.05$; W1: Wave 1 (baseline); W2: Wave 2 (follow-up); RT: reaction time; estimates refer to unstandardized linear regression estimates; p values based on z scores, derived by dividing each estimate by its standard error

Figure 1: Cross-lagged structural equation model