RESEARCH PAPER

Depressive symptoms influence global cognitive impairment indirectly by reducing memory and executive function in patients with mild cognitive impairment

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ABSTRACT

Background Depressive symptoms negatively influence global cognition in the elderly; however, the mechanism of this effect remains unclear.

Objective To investigate whether depressive symptoms influence global cognitive function in patients with mild cognitive impairment (MCI) and mild Alzheimer's disease (AD) by impeding specific neuropsychological abilities and under what conditions this effect might occur.

Method A sample of 259 participants (104 cognitively normal elderly controls, 66 patients with MCI and 89 patients with mild AD) underwent a comprehensive neuropsychological assessment. Global cognitive impairment was indexed by the composite of Mini-Mental State Examination and Montreal Cognitive Assessment scores and severity of depressive symptoms was measured with the Geriatric Depression Scale (GDS).

Results Among patients with MCI, greater severity of depressive symptoms was associated with greater global cognitive impairment, with a moderate effect size. A mediation analysis revealed that patients with MCI experiencing depressive symptoms may exhibit global cognitive impairment because their depressive symptoms were reducing their capacity for working memory, episodic memory and non-speed-based executive functions. A moderation analysis indicated that this effect was consistent across age, gender, years of education and APOE-e4 status for working memory and episodic memory, and was observed in patients with MCI older than 65 years for executive functions. In cognitively normal elderly adults and patients with AD, depressive symptoms were not associated with global cognitive impairment.

Conclusions Depressive symptoms influence global cognitive function in patients with MCI indirectly by reducing mental space, mental flexibility and their capacity for consolidating and retrieving memories. These findings may guide clinicians to better diagnose and manage cognitive impairment in the context of concomitant depressive symptoms.

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INTRODUCTION

Depressive symptoms have detrimental effects on disease prognosis for patients with mild cognitive impairment (MCI), enhancing cognitive decline and increasing their risk of developing dementia, particularly Alzheimer's disease (AD).[1 2] Despite the numerous studies demonstrating a link between depressive symptoms and cognitive impairment in these patients,[1–5] the specific mechanisms by which depressive symptoms affect cognitive impairment remain largely unexplored.

One proposed mechanism for the effect that depressive symptoms have on global cognition focuses on the vulnerability of specific neuropsychological abilities. This perspective argues that depressive symptoms decrease the availability of mental resources for 'effortful' neuropsychological abilities, such as processing speed, working memory and other executive functions.[6–8] These abilities form the foundation for a majority of cognitive tasks and have been found to play a key role in the effect that depression has on cognitive impairment in geriatric patients with depression.[9 10]

In patients with MCI and AD, depressive symptoms spare very few neuropsychological abilities.[11] A meta-analysis has identified that major depressive symptoms in patients with dementia have large adverse effects on executive functions, memory and attentional abilities, and medium effect on language abilities.[11] Over time, depressive symptoms exacerbate existing neuropsychological difficulties in patients with MCI and AD,[12] and the magnitude of these effects appears to be moderated by individual characteristics. For example, older age, female gender, greater educational attainment and APOE-e4 genotype have been found to enhance the effect of depressive symptoms on neuropsychological impairments in the ageing population.[11 13–15]

While the relationship between depressive symptoms, global cognition and neuropsychological functioning is well established in patients with MCI and AD, it remains unclear whether depressive symptoms have direct effects on global cognition or whether the effect is indirect via specific neuropsychological abilities. Such insights may provide novel and imperative information for clinicians to better diagnose and manage cognitive impairment in their patients, and may also guide clinical trials aimed at improving cognitive impairment associated with depressive symptoms.

The present study used an integrated analytical model to investigate whether the relationship between depressive symptoms and global cognitive impairment in patients with MCI and AD is mediated by specific neuropsychological abilities, namely executive function, working memory,

processing speed, episodic memory and language abilities; and whether individual characteristics moderate this relationship, such as age, gender, educational attainment and APOE-e4 genotype.

METHODS

Sampling, screening and procedure

Participants were recruited from tertiary neurology centres in Singapore between 2013 and 2016. Diagnosis of mild probable AD was based on the National Institute on Ageing - Alzheimer's Association (NIA-AA) Criteria and included patients with a Clinical Dementia Rating Scale (CDR)[17] of 1. MCI was diagnosed based on the NIA-AA criteria[18] and included amnestic and non-amnestic patients with a CDR of 0.5. Controls included elderly community volunteers who were cognitively normal, had a CDR of 0 and did not have any other significant neurological, psychiatric or systemic disease. Diagnoses for disease groups were made by cognitive neurologists using structural MRI as a supportive biomarker, and all classifications were corroborated by a comprehensive neuropsychological evaluation as detailed below. Exclusion criteria for all participants included (1) a history of alcohol or drug abuse, (2) a current or known history of major depression (Diagnostic and Statistical Manual Fourth Edition Revised), (3) comorbid neurodegenerative diseases (eg, Parkinson's disease), (4) cerebrovascular disease (eg, CAA and prior stroke) and (5) neuropsychiatric conditions (eg, psychosis); thus, any reported depressive symptoms were subsyndromal and unrelated to a premorbid psychiatric disorder. The study received approval from the institutional Ethics Committee and informed consent was received from the patients themselves or their next of kin.

Measures

Global cognitive function was indexed by a composite of the Mini Mental State Examination (MMSE)[19] and the Montreal Cognitive Assessment (MOCA).[20] The composite score for global cognitive function was obtained by taking the average of the combined z scores of MMSE and MOCA.

Depressive symptoms were indexed by the Geriatric Depression Scale (GDS).[21] The GDS is a self-reported questionnaire consisting of 15 yes/no items. A higher score indicates more severe depressive symptoms and a score of 5 or more indicates a significant degree of depressive symptoms.[22]

Mediators, moderators and covariates

Mediators of the relationship between depressive symptoms and global cognition included five neuropsychological abilities: frontal executive function, working memory, processing speed, episodic memory and language abilities. Some abilities were measured with speed and non-speed-based tasks given that depressive symptoms have been found to mostly impair speeded tasks in patients with AD.[11]

Frontal executive function based on speed was measured with the Colour Trails 2 test.[23] The non-speeded frontal executive assessment was measured with the Frontal Assessment Battery (FAB).[24]

Working memory/attention was measured using the visual and verbal measures of immediate recall from the Wechsler Memory Scale-IV.[25] No differences have been found between the effects of depression on both verbal and visual memory;[11] therefore, a composite score was created using z-scores of visual and verbal immediate recall.

Processing speed was measured with the Symbol Search component from the Wechsler Adult Intelligence Scale-IV.[26]

Episodic memory was measured using the visual and verbal measures of delayed recall from the Wechsler Memory Scale-IV.[25] A composite score was created using z-scores of visual and verbal delayed recall.

Language ability based on speed was measured with the Animal Fluency task.[27] The non-speed language assessment was measured with the Boston Naming Test.[28]

Moderators and covariates of the relationship between depressive symptoms and global cognition included individual characteristics that have been found to influence depression and cognitive impairment, namely age, gender, years of education and the APOE-e4 genotype.[11 15] *APOE* genotyping was performed using TaqMan SNP genotyping assay and ABI 7900HT PCR system from Applied Biosystems.[29]

Statistical analysis

All data analysis was conducted using SPSS Statistics, Release V.20.0.0 (Corp I. IBM SPSS Statistics for Windows, Version 20.0. Armonk, New York: IBM Corp, 2011).

Group differences

Differences between diagnostic groups and differences between participants with high versus low GDS scores were assessed with χ^2 for categorical variables and one-way analysis of variance for continuous variables with a Tukey post hoc test.

Covariates

A bivariate correlation was conducted for each diagnostic group to determine covariates. A significant correlation between the covariate and the primary outcome, global cognition, indicated that the variable would be included as a covariate in the conditional process model.

Conditional process modelling

To investigate whether the relationship between depressive symptoms and global cognition is mediated by specific neuropsychological abilities, we applied Preacher, Rucker and Hayes'[30] conditional process model using Hayes'[30] SPSS macro PROCESS (model 58). Conditional process modelling integrates the mediation and moderation processes. Mediation quantifies the path by which depressive symptoms are related to global cognition, while moderation quantifies the conditions under which depressive symptoms will be related to global cognition. Bonferroni correction was applied for all steps in the conditional process model, with the significance value set at $p<0.025$.

Mediation

To ensure suitability to use mediation analysis, the significance of the three direct pathways (paths a, b and c as illustrated in figure 1) was assessed using linear regression analysis. Each direct pathway was confirmed for each neuropsychological ability and for each diagnostic group. If the three pathways were significant, mediation analysis was used to investigate whether path c was still significant after controlling for the mediator (represented in figure 1 as path c'). If path c reduced in significance after controlling for the mediator, partial mediation was implied; if path c was no longer significant in the presence of the mediator, full mediation was implied. A Bias Corrected (BC) bootstrap estimation with 1000 resamples was used as a non-parametric approach for effect-size estimation and hypothesis testing.[31] Here, a CI that did not contain zero indicated that the relationship between X and Y was mediated by the neuropsychological ability under investigation. Effect sizes of the

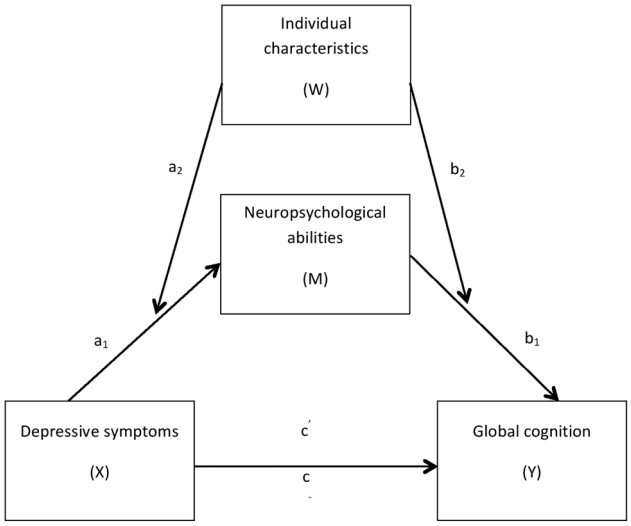

Figure 1 Path diagram for the conditional process model. X=Independent variable, Y=Outcome variable, M=Mediator and W=Moderators. The model assesses whether the effect of depressive symptoms (X) on global cognition (Y) is mediated by neuropsychological abilities (M) across different individual characteristics (W), such as age, gender, APOE-e4 and years of education.

indirect effects were assessed using Preacher and Kelley's κ^2,[32] which was interpreted according to Cohen's[33] r^2guidelines of small (0.01), medium (0.09) and large (0.25) effect sizes.

Moderation

To determine moderation of mediation effects, we assessed the interaction of moderator variables (W in figure 1) with depressive symptoms (X), neuropsychological abilities (M) and global cognition (Y) independently. If interactions between WMX and WMY were significant, then we noted that moderation has occurred and we proceeded to test how the indirect effects vary across different levels of the moderator. Here, a 95% CI that contained zero was used to indicate a significant effect. Each moderator was assessed separately for each mediator and each diagnostic group.

Severity of depressive symptoms

To investigate the severity of depressive symptoms, the sample was split based on having either high GDS scores (GDS≥5) or low GDS scores (GDS≤4). Here, linear regression analyses were used to determine whether the criteria for a mediation analysis were met (X→M and X→Y).

RESULTS

Patients

The final sample consisted of 259 participants, whose demographic characteristics are presented in table 1.

Primary group differences

Differences between diagnostic groups

Table 1 displays that patients with AD were significantly older and had less years of education than controls and patients with MCI. No differences were observed for gender of APOE-e4 carriers ($p>0.025$). As expected, patients with AD performed significantly worse on all neuropsychological assessments, followed by patients with MCI and then controls. Depressive symptoms were significantly greater in patients with AD compared to controls.

Differences between patients with high and low GDS scores

Table 2 shows that for controls and patients with AD, individual characteristics and performance on neuropsychological tests did not differ across patients with high and low GDS scores ($p>0.025$). For patients with MCI, those with a high GDS score had less years of education and greater cognitive impairment than those with low GDS scores.

Covariates

A correlation analysis indicated that the outcome measure, global cognition, was significantly associated with years of education in patients with MCI ($r=0.37$, $p<0.01$) and was thus used as a covariate for analyses with patients with MCI. For patients with AD, global cognition was significantly associated with gender ($r=0.24$, $p<0.025$), years of education ($r=0.26$, $p<0.01$) and APOE-e4 ($r=-0.25$, $p<0.01$), and was thus used as covariates for analyses with patients with AD. Covariates were not related to global cognition in controls.

Mediation analysis

Controls

Direct pathways

For controls, GDS scores were not related to global cognition (path c, $p>0.025$) and GDS scores were not related to any of the neuropsychological abilities (path a, $p>0.05$). These insignificant relationships were not moderated by age, gender, years of education or APOE-e4.

Patients with MCI

Direct pathways

Table 3 displays that for patients with MCI, GDS scores were negatively related to global cognition, even after controlling for years of education and accounted for 21% of the variance in global cognition (path c; $F(1, 64)=9.23$, $p<0.025$). This suggests that increased severity of depressive symptoms was associated with more global cognitive impairment when controlling for years of education. Additionally, GDS scores were negatively associated with non-speed executive functions (FAB), episodic memory (WMS-IV-Delayed recall) and working memory/attention (WMS-IV-Immediate recall) (path a), but not related to speed-based executive functions (Colour trails 2), processing speed (Symbol Search) or speed and non-speed-based language abilities (Animal Fluency and Boston Naming Test, respectively; $p>0.025$). All cognitive abilities were significantly associated with global cognition ($p<0.025$).

Mediation

Conditions to test mediation were only satisfied for non-speed executive function, episodic memory and working memory/attention. Table 3 shows that when controlling for non-speed executive functions (FAB) and years of education, the direct path between GDS scores and global cognition was no longer significant, indicating full mediation. Approximately 34% of global cognition variance was accounted for by GDS scores, non-speeded executive function (FAB) and years of education ($F(2,63)=13.87$, $p<0.00$). The indirect coefficient was significant ($b=-0.04$, $SE=0.02$, BC 95% CI −0.13 to -0.02), indicating that for every one point increase in GDS score, global cognition decreased by 0.04 points when mediated by non-speed executive functions. This was a medium sized effect ($\kappa^2=0.14$, $SE=0.06$, 95% CI 0.04 to 0.28).

Table 2 shows that when controlling for episodic memory (WMS-IV-Delayed recall) and years of education, the direct

Table 1 Group differences on demographic and neuropsychological data

Mean (SD)	Controls (N=104)	MCI (N=66)	AD (N=89)	F value
Age (years)	63.27 (6.81)	65.19 (SD=6.95)	71.05 (SD=7.90)	28.9*
Gender (males, %)	45 (43)	28 (42)	50 (56)	4.11†
Years of education	12.87 (3.41)	11.07 (SD=3.03)	9.44 (SD=4.05)	26.51*
Race (%)				47.38†,*
Chinese	97 (93)	63 (96)	70 (78)	
Malay	2 (2)	0	7 (8)	
Indian	4 (4)	3 (4)	9 (11)	
Other	1 (1)	0	3 (3)	
Employment (%)				28.41†,‡
Unemployed	20 (19)	28 (42)	26 (29)	
Employed	15 (14)	5 (9)	6 (7)	
Retired	4 (4)	2 (3)	10 (11)	
Homemaker	57 (55)	28 (42)	35 (38)	
Student	6 (6)	2 (3)	8 (9)	
Other	1 (1)	0	4 (5)	
APOE-e4 carrier	18 (17)	18 (27)	42 (47)	0.58
Neuropsychological assessments				
MMSE (Score range 0–30)	28.65 (1.47)	27.43 (1.57)	22.93 (4.31)	105.40*
MOCA (Score range 0–30)	27.85 (1.92)	25.50 (2.51)	19.22 (5.14)	151.593*
Colour Trails Test (seconds)	95.17 (25.31)	121.50 (38.69)	223.12 (119.33)	75.69*
Frontal Assessment Battery (score range 0–18)	17.00 (0.95)	16.11 (1.77)	13.52 (2.94)	83.97*
WMS-IV-Immediate Recall (score range 0–34)	25.88 (2.88)	21.68 (4.23)	13.88 (6.21)	165.46*
WAIS-IV-Symbol Search (score range 0–60)	29.18 (7.14)	24.12 (6.16)	14.32 (7.14)	112.50*
WMS-IV-Delayed Recall (score range 0–34)	22.18 (4.90)	16.18 (6.27)	6.71 (7.33)	151.49*
Animal Fluency task§	16.53 (3.22)	13.63 (3.28)	9.95 (3.65)	90.38*
Boston Naming Test (score range 0–30)	26.63 (2.11)	23.64 (3.99)	19.82 (5.74)	64.71 *
Depressive symptoms (median (SD), range)				
High depressive symptoms (GDS ≥5)	7 (2.51), 5–7	6 (1.44), 5–9	6 (2.08), 5–12	2.12
Low depressive symptoms (GDS <5)	1 (1.20), 0–4	1 (1.30), 0–4	2 (1.27), 0–4	7.55*

For all neuropsychological measures, a higher score equates to better performance.
*Significant at the p<0.00 level.
†=χ^2.
‡Significant at the p<0.025 level.
§No score range was implemented for the animal fluency task. For depressive symptoms, a higher score equates to greater depressive symptoms.
¶Significant at the p<0.01 level.
MMSE, Mini Mental State Examination; MOCA, Montreal Cognitive Assessment.

path between GDS scores and global cognition was no longer significant, indicating full mediation. Approximately 28% of global cognition variance was accounted for by GDS scores, episodic memory (WMS-IV-Delayed recall) and years of education ($F(2,63)=8.58$, $p<0.00$). The indirect coefficient was significant (b=−0.03, SE=0.05, BC 95% CI −0.09 to −0.00), indicating that for every one point decrease in GDS score, global cognition decreased by 0.03 points when mediated by episodic memory. This was a small to medium sized effect ($\kappa^2=0.08$, SE=0.05, 95% CI 0.00 to 0.21).

Table 3 shows that when controlling for working memory/attention (WMS-IV-Immediate recall) and years of education, the direct path between GDS scores and global cognition was no longer significant, indicating full mediation. Approximately 30% of global cognition variance was accounted for by GDS scores, working memory (WMS-IV-Immediate recall) and years of education ($F(2,63)=13.51$, $p<0.00$). The indirect coefficient was significant (b=−0.06, SE=0.02, BC 95% CI −0.13 to −0.03), indicating that for every one point decrease in GDS score, global cognition decreased by 0.06 points when mediated by working memory/attention. This was a medium sized effect ($\kappa^2=0.15$, SE=0.05, 95% CI 0.06 to 0.27).

Conditional process modelling

Age was found to moderate the indirect effect that depressive symptoms had on global cognitive impairment through non-speed executive functions (FAB). The total variance accounted for by GDS, age, non-speed executive functioning and years of education was 38% and the effect was statistically significant from zero only for those older than 65 years (b=−0.06, SE=0.03, BC 95% CI −0.12 to −0.02). This finding indicates that depressive symptoms may exert their effect on global cognitive impairment through non-speed executive functions only for patients with MCI older than 65 years. Conditional process modelling was not significant for any of the other neuropsychological abilities ($p>0.025$).

Final model for patients with MCI

Figure 2 illustrates the parsimonious final mediation model for patients with MCI. Depressive symptoms were shown to exert their effect on global cognitive impairment through three specific neuropsychological abilities, namely non-speed based executive function, working memory and episodic memory. Figure 2 illustrates that depressive symptoms had the largest

Table 2 Differences between patients with high and low GDS scores

	Controls		MCI		AD	
	High GDS (N=11)	Low GDS (N=93)	High GDS (N=13)	Low GDS (N=53)	High GDS (N=25)	Low GDS (N=64)
Mean (SD)						
Age	65.53 (5.34)	63.01 (6.95)	65.14 (5.98)	65.21 (7.22)	70.30 (7.05)	71.34 (8.24)
Males	6	39	6	22	11	39
Years of education	12.81 (3.60)	12.88 (3.41)	9.54 (2.50)	11.45 (3.05)*	10.12 (4.11)	8.75 (3.99)
Race						
Chinese	11	82	12	51	19	51
Malay	0	2	0	0	2	5
Indian	0	4	1	2	2	7
Other	0	1	0	0	2	1
Employment						
Unemployed	3	17	6	22	3	23
Employed	1	14	2	3	1	5
Retired	1	3	0	2	3	7
Housewife	3	54	5	23	11	24
Student	2	4	0	2	5	3
Other	1	0	0	0	2	2
APOE-e4 carrier	4 (36%)	14 (15%)	3 (23%)	15 (28%)	11 (44%)	31 (48%)
Neuropsychological assessments						
MMSE	28.27 (1.62)	28.69 (1.47)	26.08 (1.32)	27.77 (1.50)*	22.68 (5.21)	23.03 (3.96)
MOCA	28.55 (2.07)	27.77 (1.90)	23.62 (2.50)	25.96 (2.32)*	20.08 (5.16)	18.89 (5.14)

High GDS included GDS scores ≥5; low GDS included GDS scores ≤4.
For both global cognitive measures, a higher score equates to better performance.
*Significant at the p<0.025 level.
MMSE, Mini Mental State Examination; MOCA, Montreal Cognitive Assessment.

effect on episodic memory, where a one point increase in depressive symptoms was associated with a 2.15 point decrease in episodic memory. Effect size estimates indicated that working memory/attention had the largest mediation effect between depressive symptoms and global cognition, regardless of age, gender, years of education and APOE-e4 status.

Patients with AD

Causal pathways

For patients with AD, GDS was not related to global cognitive impairment (path c, $p<0.025$) or individual neuropsychological abilities (path a, $p<0.025$) when controlling for covariates. These insignificant relationships were not moderated by age, gender, years of education or APOE-e4.

Severity of depressive symptoms

To determine whether severity of depressive symptoms influenced the mediation effect, the sample was split into those with high GDS scores (GDS ≥5) and low GDS scores (GDS <5), see table 2. We note that splitting the group by severity of depressive symptoms and diagnostic group limits power; however, any trends would indicate important preliminary findings that may guide subsequent research.

Controls and patients with MCI

Depressive symptoms were not related to global cognitive impairment in either the high or low GDS group ($p>0.025$). This was consistent across age, gender, years of education and APOE-e4 genotype.

Patients with AD

The relationship between high GDS scores and global cognitive impairment was trending and negative ($b=-0.87$, $SE=0.57$, $R^2=0.09$, $F(1,23)=2.30$, $p=0.14$), while controlling for covariates. This suggests that as severe depressive symptoms increase, global cognition becomes more impaired. On the other hand, low GDS scores were positively trending on significance with global cognitive impairment only for males with AD ($b=0.67$, $SE=0.35$, $t(60)=1.91$, $p=0.06$), while controlling for covariates. This suggests that increases within the low range of low depressive symptoms in males with AD were associated with greater global cognition.

For each diagnostic group, the relationship between high and low GDS and specific neuropsychological abilities was trending (see online supplementary appendix). Given the trending nature of these findings, criteria for conditional process modelling were not met.

DISCUSSION

Our findings demonstrate that in patients with MCI, greater severity of depressive symptoms was associated with greater global cognitive impairment. This association had a moderate effect, indicating that an increase in depressive symptoms caused a noticeable decline in global cognition. We further demonstrated that patients with MCI who exhibit depressive symptoms may experience global cognitive impairment because their depressive symptoms have reduced their capacity for working memory, episodic memory and executive function. This effect was consistent across age, gender, years of education and APOE-e4 genotype for all neuropsychological abilities except for executive functions, which was relevant only for patients with MCI older than 65 years. In cognitively normal elderly adults and patients with AD, depressive symptoms were not associated with global cognitive impairment.

Further exploratory analysis investigated the effects of high (GDS ≥5) and low (GDS ≤4) depressive symptoms on global

Table 3 Mediation model of depression on global cognitive impairment through specific cognitive abilities for patients with MCI

	Unstandardised estimate	SE	t	Mediation
Path c (X→Y)	−0.13	0.05	−2.51*	
Executive functions-speeded				
Path a (X→M)	1.52	5.7	0.27	
Path b (M→Y)	0.00	0.00	0.73	No mediation
Path c′ (X→M→Y)	Criteria not met			
Executive functions—non-speed				
Path a (X→M)	−0.57	0.25	−2.20†	
Path b (M→Y)	0.09	0.02	4.01‡	Full mediation
Path c′ (X→M→Y)	−0.08	0.05	−1.68	
Working memory/attention				
Path a (X→M)	−1.75	0.59	−2.98*	
Path b (M→Y)	0.04	0.00	3.73‡	Full mediation
Path c′ (X→M→Y)	−0.10	0.05	−2.08	
Processing speed				
Path a (X→M)	−0.81	0.90	−0.90	
Path b (M→Y)	−0.00	0.03	−0.02	No Mediation
Path c′ (X→M →Y)	Criteria not met			
Episodic memory				
Path a (X→M)	−2.15	0.93	−2.29†	
Path b (M→Y)	0.02	0.07	2.98‡	Full mediation
Path c′ (X→M→Y)	−0.09	0.05	−1.83	
Language–speed				
Path a (X→M)	−0.32	0.48	−0.66	
Path b (M→Y)	0.01	0.01	0.90	No mediation
Path c′ (X→M →Y)	Criteria not met			
Language–non-speed				
Path a (X→M)	−1.17	0.57	−2.05	
Path b (M→Y)	0.04	0.01	3.79‡	No mediation
Path c′ (X→M→Y)	Criteria not met			

X=Independent variable (depressive symptoms), Y=outcome variable (cognition) and M=mediator (neuropsychological ability). Path a=the effect of depressive symptoms on the neuropsychological ability, Path b=the effect of the neuropsychological ability on global cognition, Path c=the direct effect of depressive symptoms on global cognition and Path c′=the effect of depressive symptoms on global cognition when the effect of the neuropsychological ability is removed. All reported SEs were bootstrapped except for Path c (X→Y).
*Significant at the p<0.01 level.
†Significant at the p<0.025 level.
‡Significant at the p<0.00 level.

cognition. For controls and patients with MCI, neither high nor low depressive symptoms were related to global cognitive impairment. For patients with AD, a trend indicated that further increases in depressive symptoms in patients already experiencing a high range of depressive symptoms were associated with greater cognitive impairment. Alternatively, for male patients with AD experiencing a low range of depressive symptoms, increases in depressive symptoms were associated with less cognitive impairment. We note that these trends need to be considered with caution and further validation is required in a larger sample.

Mediation model for patients with MCI

For patients with MCI, episodic memory was found to be the most vulnerable to depressive symptoms compared to the other investigated neuropsychological abilities (namely executive functions, working memory/attention, processing speed and language abilities). Episodic memory is believed to be the most disrupted neuropsychological ability in patients with MCI[34] and our findings support previous perspectives that argue that depressive symptoms may target the core neuropsychological difficulties that define neurodegenerative disorders.[35] Our measure of episodic memory relied on the ability to consolidate and retrieve verbal and visual information at a delayed time. Therefore, our findings suggest that one mechanism by which depressive symptoms impede global cognition in patients with MCI may be by reducing their capacity to consolidate and retrieve information.

Interestingly, even though episodic memory was most affected by depressive symptoms, it had the least mediating effect compared to working memory and executive functions. Working memory/attention exhibited the strongest relationship with global cognition and was also found to be the strongest mediator for the relationship between depressive symptoms and global cognitive impairment. The mediating effect of working memory/attention on the relationship between depressive symptoms and cognition is consistent with studies in geriatric patients with major depression,[10] suggesting that working memory may be principal to the effects of depression on cognition. Our test of working memory relied on the storage and manipulation of information,[36] and thus our findings suggest that one mechanism by which depressive symptoms impede global cognition in patients with MCI may be by reducing this mental space.

For patients with MCI older than 65 years, non-speed-based executive functions exhibited the second largest mediation effect between depressive symptoms and global cognitive impairment. We note that other neuropsychological abilities investigated in this study load on executive functions, such as working memory/attention. However, the specific test used to index non-speed

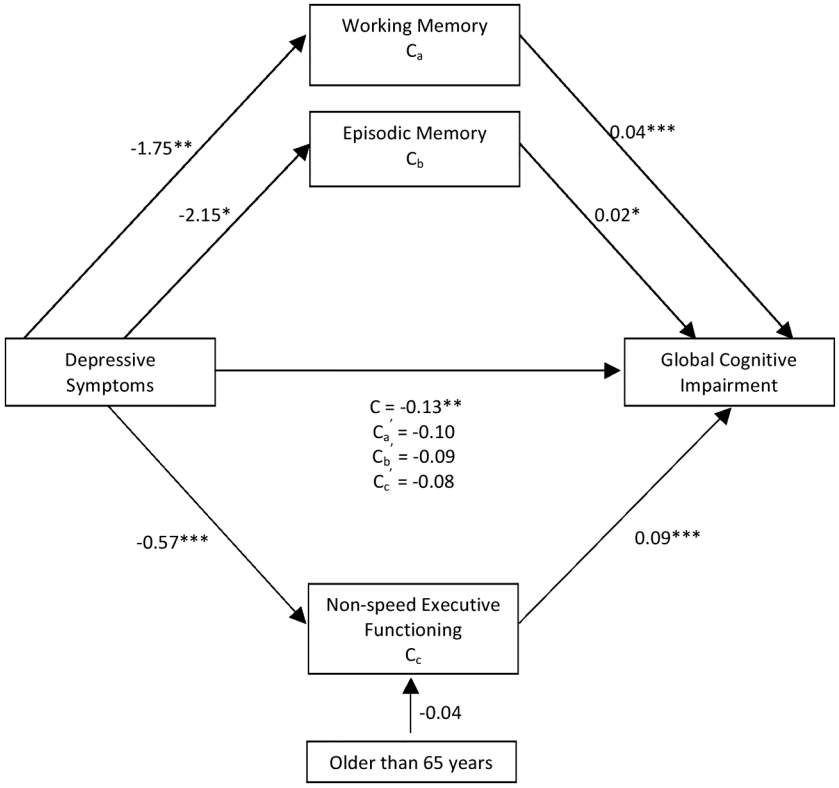

Figure 2 Final conditional process model for patients with MCI. Episodic memory was most vulnerable to depressive symptoms and working memory/attention had the largest mediation effect, regardless of age, gender, years of education and APOE-e4 status. Non-speed- based executive function was only a significant mediator for older patients with MCI.

executive function was focused on frontal lobe processes, such as inhibitory control and mental flexibility, while the working memory/attention task focused on encoding and retrieval of information. Thus, we propose that for older patients with MCI, one mechanism by which depressive symptoms may impede global cognition is by reducing capacity for mental flexibility.

Previous studies have emphasised the role of processing speed in mediating the effects of depression on cognition, particularly in elderly patients without cognitive impairment.[9 10] However, in this study, processing speed was not related to depressive symptoms. By comparing these previous studies[9 10] against this study, it becomes apparent that the underlying mechanism by which depressive symptoms exert their effect on global cognition may be different for cognitively impaired and cognitively intact elderly. Specifically, depressive symptoms in cognitively intact elderly participants may impair cognition by reducing processing speed,[9 10] while depressive symptoms in cognitively impaired adults may impair cognition by reducing mental space. This argument reinforces the perspective that early AD is not part of the normal ageing process.[37]

Depressive symptoms were not related to cognitive impairment in controls and in patients with AD

For the cognitively normal ageing population without major depression, we found that the experience of depressive symptoms may have limited effects on global cognitive functioning or specific neuropsychological abilities. We note, however, that our controls had limited variance on the neuropsychological tests which may have limited the findings.

For patients with AD, depressive symptoms did not influence global cognition or neuropsychological abilities, which is consistent with past studies in patients with AD with no major depression.[38 39] However, when considering patients with AD with a high degree of depressive symptoms (GDS scores ≥5), trends were consistent with past studies demonstrating that major depressive symptoms in patients with AD were associated with greater global cognitive impairment, compared to patients with AD without major depression.[1 2] While more research is required, these trends suggest that in patients with AD, severe depressive symptoms may play an important role in cognitive impairment, while less severe depressive symptoms may have limited effects in patients with AD.

Clinical implications

Depressive symptoms play an important role in cognitive outcomes and should be factored into clinician interviews, treatment programmes and research protocols addressing cognitive impairment. Our findings indicate that even in the presence of non-major depressive symptoms, neuropsychological abilities become exacerbated in patients with MCI and influence global cognition. As a result, clinicians are encouraged to interpret cognitive impairment in the context of concomitant depressive symptoms, particularly for difficulties with working memory/attention, episodic memory or executive functions. This is particularly important given that deficits within these neuropsychological domains have been strongly associated with conversion from MCI to AD.[40]

Our findings may guide intervention programmes by suggesting that in order to improve global cognition in patients with MCI experiencing non-major depressive symptoms, particular focus should be placed on improving available mental space, mental flexibility and the efficiency at which information can be consolidated into memory and retrieved. Given the significance of these skills to disease prognosis,[40] we propose that interventions targeting these skills have potential to slow the progression from MCI to AD in patients experiencing non-major depressive symptoms.

Previous clinical trials have shown that alleviating depressive symptoms have potential to improve global cognition in patients

with MCI.[41 42] Based on our findings, it is likely that antidepressant treatment may improve global cognition in patients with MCI by improving mental space and capacity for consolidating and retrieving information, regardless of age, gender, years of education and APOE-e4 genotype, and, in addition, by improving mental flexibility in older patients with MCI. Future research investigating the effects of antidepressant treatment on global cognition may benefit from considering the effects of depression on brain regions involved in executive functions and memory.

Limitations and future research

Our sample was restricted to patients with MCI and mild AD, which limits the generalisability of our results. We note that our MCI group included both amnestic and non-amnestic patients and, owing to limited statistical power, we were unable to analyse these groups separately. However, there is limited research suggesting that depressive symptoms affect amnestic and non-amnestic patients with MCI differently. We note that our measure of depressive symptoms was self-reported and, according to the reverse causality explanation of depression in dementia,[43] self-reported depressive symptoms may increase with the awareness of self-cognitive decline. Clinician-rated measures of depression (Hamilton Depression Rating scale and MADRS) have found inconsistent associations between depressive symptoms and cognition;[10 15] therefore, the rating method used to capture depressive symptoms must be considered when comparing findings across similar studies. A further limitation is that our findings regarding the relative strength of neuropsychological abilities on cognition is contingent on the specific neuropsychological test and its association with our measure of global cognition, MMSE and MOCA. Further research would benefit from investigating neuropsychological abilities using a composite of assessments.

Conclusion

This study found that in patients with MCI, depressive symptoms may indirectly influence global cognitive impairment by reducing working memory/attention and episodic memory, regardless of age, gender, educational attainment and APOE-e4 genotype, and by reducing executive function in patients older than 65 years. The capacity for episodic memory was found to be the most vulnerable to depressive symptoms; however, depressive symptoms were found to have their largest effect on global cognition by reducing working memory/attention. Comparatively, depressive symptoms in patients with AD were not found to affect global cognitive impairment; however, trends indicated that severe depressive symptoms may play an important role in cognitive impairment, while less severe depressive symptoms may have limited effects in patients with AD. Implications of these findings may guide clinicians to better diagnose and manage cognitive impairment in the context of concomitant depressive symptoms and, additionally, may guide treatment programmes and research focused on cognitive impairments associated with depressive symptoms.

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