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Heterogeneity of late-life depression: relationship with cognitive functioning

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ABSTRACT

Background: Late-life depression is a heterogeneous disorder, whereby cognitive impairments are often observed. This study examines which clinical characteristics and symptom dimensions of late-life depression are especially impacting on specific cognitive domains.

Methods: Cross-sectional data of 378 depressed and 132 non-depressed older adults between 60–93 years, from the Netherlands Study of Depression in Older adults (NESDO) were used. Depressed older adults were recruited from both inpatient and outpatient mental healthcare institutes and general practices, and diagnosed according to DSM-IV-TR criteria. Multivariable associations were examined with depression characteristics (severity, onset, comorbidity, psychotropic medication) and symptom dimensions as independent variables and cognitive domains (episodic memory, processing speed, interference control, working memory) as dependent variables.

Results: Late-life depression was associated with poorer cognitive functioning. Within depressed participants, higher severity of psychopathology and having a first depressive episode was associated with poorer cognitive functioning. The use of tricyclic antidepressants, serotonergic and noradrenergic working antidepressants, and benzodiazepines was associated with worse cognitive functioning. Higher scores on the mood dimension were associated with poorer working memory and processing speed, whereas higher scores on a motivational and apathy dimension were associated with poorer episodic memory and processing speed.

Conclusions: Heterogeneity in late-life depression may lead to differences in cognitive functioning. Higher severity and having a first depressive episode was associated with worse cognitive performance. Additionally, different domains of cognitive functioning were associated with specific symptom dimensions. Our findings on the use of psychotropic medication suggest that close monitoring on cognitive side effects is needed.

Key words: late-life depression, cognition, clinical characteristics, symptom dimensions

Introduction

Late-life depression is often associated with cognitive impairment. The impact of comorbid cognitive problems is high and associated with worse treatment response (Pimontel *et al.*, 2012). Cognitive impairment in late-life depression is predominately expressed in slowed information processing speed, executive dysfunctioning, and memory problems (Thomas and O'Brien, 2008). These cognitive problems sometimes persist after recovering from depression and may lead to mild cognitive impairment or dementia (Jorm, 2000). Late-life depression, however, is a heterogeneous disorder. Specific aspects of late-life depression may thus be differentially related to cognitive functioning. Studying clinical characteristics such as severity, onset, comorbidity, and the use of psychotropic medication may provide a better understanding of the link between late-life depression and cognitive functioning. Heterogeneity of late-life depression might also be seen in the presence

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of specific symptom dimensions (Hegeman *et al.*, 2012), which might be associated with decrements in different domains of cognitive functioning.

Several studies examined specific clinical characteristics of late-life depression and cognitive functioning. However, differences in the adjustment for relevant confounders and the use of different cognitive domains have led to inconsistent results. For instance, a greater depression severity is consistently negatively associated with processing speed and executive functioning (Butters, 2004; Sheline *et al.*, 2006), whereas the association with memory functioning is not always observed (Sheline *et al.*, 2006). A higher recurrence of depressive symptoms was associated with an increased risk of dementia (Dotson *et al.*, 2010). However, few studies examined the recurrence of depressive symptoms in association with impaired cognitive functioning without dementia (Paterniti *et al.*, 2002). In addition, some studies observed a higher age of onset to be associated with cognitive impairment (Rapp *et al.*, 2005) whereas other studies examining clinical characteristics simultaneously did not observe this association (Butters, 2004; Sheline *et al.*, 2006).

Comorbidity of late-life depression and anxiety disorders is high. A review of Beaudreau and O'Hara (2008) showed that late-life anxiety is associated with cognitive dysfunctioning, especially (episodic) memory. However, few studies considered the comorbidity between depressive and anxiety symptoms in association with cognitive functioning. A study among 79 depressed older adults observed more memory decline when comorbid anxiety was present (DeLuca *et al.*, 2005). In contrast, in community-dwelling older adults, Bierman *et al.* (2005) observed a U-shape relationship of anxiety symptoms after adjusting for depressive symptoms, where mild anxiety symptoms facilitated episodic memory but severe anxiety symptoms impaired episodic memory. A recent study of Pietrzak *et al.* (2012) observed that symptoms of worrying in community-dwelling older adults were associated with impairments in visual and paired associate learning but not with verbal memory and processing speed.

Older adults with depression often use psychotropic medication, which has shown to be associated with cognitive impairment. A review of Peretti *et al.* (2000) showed that tricyclic antidepressants (TCAs) were consistently associated with impaired cognitive function. Another review observed a consistent association with attention and processing speed whereas an association with memory function was less consistent and only observed at higher doses (Tannenbaum *et al.*, 2012). This study also showed that benzodiazepines were associated with cognitive impairment, especially in older adults, which is supported by a population-based epidemiological study (Bierman *et al.*, 2007).

The association between symptom dimensions of late-life depression and cognitive functioning received little attention. Baune *et al.* (2007) studied this association in community dwelling older adults and observed a depressive symptom dimension to be associated with impaired processing speed and motor function, and a somatic dimension only with processing speed. In addition, a study of 89 depressed older adults showed that apathy was associated with executive functioning and processing speed (Feil *et al.*, 2003) whereas a study with 29 depressed older adults found no association between apathy and cognitive functioning (Lampe and Heeren, 2004).

The first aim of this study is to replicate the general established association between late-life depression and several domains of cognitive functioning. We expect that older depressed persons have poorer memory, processing speed, and executive functioning compared to non-depressed older adults. The second aim is to examine which clinical characteristics of depression contribute independently to poorer cognitive function in late-life depression. The third aim is to explore whether specific symptom dimensions of late-life depression are associated with different domains of cognitive functioning.

Methods

Study sample

Data from the Netherlands Study of Depression in Older persons (NESDO) were used. NESDO is a multi-site prospective cohort study, including 378 depressed and 132 non-depressed older persons (60–93 years). Recruitment of depressed older persons was from both mental healthcare institutes (86.2%) and general practices (13.8%) in order to include persons with late-life depression in various developmental and severity stages. Depressed persons were included when they fulfilled the DSM-IV-TR criteria for major depression (95.0%), dysthymia (26.5%), or minor depression (5.0%). Non-depressed persons were recruited from general practices and were included when no lifetime diagnosis of depression was present. Exclusion criteria for both groups were a primary clinical diagnosis of dementia, psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder, a Mini-Mental State Examination score (MMSE) below 18 (out of 30 points), and insufficient command of the Dutch language. Data collection of the baseline

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measurement started in 2007 and was finished in 2010. The population and methods of the NESDO study have been described in detail elsewhere (Comijs *et al.*, 2011). The study was approved by the ethical boards of the participating institutes and written informed consent was obtained from all participants.

To examine differences in cognitive functioning between persons with and without depression, both groups were included ($n = 510$). When investigating the clinical characteristics and symptom dimensions of late-life depression, only persons with a current DSM-IV diagnosis (past six months) of major depression, dysthymia, or minor depression were included ($n = 378$).

Measurements

Depressive psychopathology

Diagnoses of major depression and dysthymia were assessed with the Composite International Diagnostic Interview (CIDI; World Health Organization (WHO) version 2.1; lifetime version) according to DSM-IV-TR criteria. The CIDI is a structured clinical interview and has high validity for depressive and anxiety disorders (Wittchen, 1994). Questions were added to determine the research DSM-IV research diagnosis of current minor depression.

Clinical characteristics of late-life depression

The severity of depressive symptoms was assessed with the Inventory of Depressive Symptomatology (IDS) (Rush *et al.*, 1996). The age of onset of the first depressive episode and the number of depressive episodes were assessed with the CIDI. The age of onset of the first depressive episode was used as a continuous measure. The number of depressive episodes was asked whereby only the periods were counted when symptom-free periods in between were at least two months. This was dichotomized into one and more than one episodes. The severity of anxiety symptoms was assessed with the Beck Anxiety Index (BAI) (Beck *et al.*, 1988) and symptoms of worrying were examined with a revised version of the Worry Scale (Wisocki *et al.*, 1986).

Psychotropic medication used daily in the previous week was determined by inspection of the medication containers and classified according to the Anatomical Therapeutic Chemical (ATC) classification (World Health Organization Collaborating Centre for Drug Statistics Methodology, 2010). The use of selective serotonin reuptake inhibitors (SSRIs; ATC code: N06AB), TCAs (ATC code: N06AA), and serotonergic and noradrenergic working antidepressants (SNRIs, antidepressants classified as N06AX) were dichotomized into yes/no. When benzodiazepines (ATC codes: N03AE, N05BA, N05CD, N05CF) were used for more than 50% of the time, the use was considered present and this variable was dichotomized into yes/no.

Symptom dimensions

To examine different symptom dimensions of late-life depression, subscales of the IDS and the scores of the Apathy Scale (AS) were used (Starkstein *et al.*, 1992). Three homogenous subscales of the IDS were shown to have a good fit with factor analyses in the NESDO study. This three-factor structure consists of a mood (nine items), motivational (five items) and somatic factor (eight items) with adequate internal consistencies (α coefficient: 0.93, 0.83, 0.70, respectively; Hegeman *et al.*, 2012).

Cognitive functioning

Episodic Memory was assessed with the 10-word test, a modified version of the auditory verbal learning test (Rey, 1964). In five trials the respondent had to recall as many words as possible and after a distraction period of 20 minutes the respondent was asked to name the words learned before again. The episodic memory domain consists of the immediate sum score of the five trials (range: 0–50) and the delayed recall score (range: 0–10).

Processing speed was assessed with cards I and II of the abbreviated version of the Stroop color-word test (Stroop, 1935). This test consisted of three subtasks; the first card (I) had color words (red, blue, green, yellow) printed in black, the second card (II) had colored patches of the same colors, and the last card (III) had color words printed in incongruent colored ink. The time to read the words on card I and name the colors on card II reflected processing speed.

Interference control was assessed with the interference score of the abbreviated version of the Stroop color-word test. This score was calculated by the following formula: $(t\text{III} - 0.5 \times (t\text{I} + t\text{II})) / (0.5 \times (t\text{I} + t\text{II}))$ (t = time in seconds) (Klein *et al.*, 1997).

Working memory was assessed with the subtest digit span from the Wechsler Adult Intelligence Scale (Wechsler, 1958). Respondents were asked to recall numbers forward and backwards, and the number of correct digits both forwards (range: 0–12) and backwards (range: 0–10) were used.

Possible confounders

Variables known to be associated with both late-life depression and cognitive functioning are age, sex, education, alcohol use, smoking status, and

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chronic diseases. Therefore, these were included in the analyses as confounders. Detailed information about age, sex, and number of years of education was collected. The number of drinks per day was used as measure for alcohol use and categorized into 0, more than 0 and less than 2, and 2 or more drinks per day. More than 0 and less than 2 drinks per day was used as the reference category because in previous research by our study group and the Longitudinal Aging Study Amsterdam it was observed that next to high alcohol use, alcohol abstinence was associated with depression possibly due to benzodiazepine use and poorer health (Comijs *et al.*, 2012; van den Berg *et al.*, 2013).

Smoking status was dichotomized into "smoker" (current smoker) and "non-smoker" (never smoked and former smoker). The number of chronic diseases was assessed by self-report questions about the presence of somatic diseases (cardiac diseases, cerebrovascular accident, hypertension, peripheral artherosclerosis, diabetes mellitus, chronic non-specific lung disease, liver diseases, thyroid diseases, epilepsy, intestinal diseases, arthritis/arthrosis, and cancer). The number of chronic diseases for which people were under treatment or received medication was counted. The accurateness of self-reports of these diseases was shown to be adequate and independent of cognitive impairment in comparison with data obtained from general practitioners (Kriegsman *et al.*, 1996).

Statistical analyses

Differences in demographics and clinical characteristics between depressed and non-depressed older adults were compared by using χ^2 analysis for dichotomous variables, student's *t*-tests for normally distributed variables, and Mann–Whitney U tests for non-normally distributed variables.

The scores on the Stroop task were transformed (1/(Stroop card I), 1/(Stroop card II), natural logarithm (Stroop interference score)) to obtain a near-normal distribution. The other cognitive measures showed a normal distribution. To observe if the separate cognitive tasks covered the separate cognitive domains, an exploratory factor analysis was performed on the seven cognitive measures (immediate recall, delayed recall, Stroop I, Stroop II, interference Stroop, digit span forwards, digit span backwards). We used oblique rotation (promax) because the final factors were expected to be intercorrelated. Factors were extracted on the basis of high primary loadings on one factor, lower loadings on the other factors, differences between factor loadings at least 0.20, eigenvalues (>0.7) (Jolliffe, 1972), observation of the scree plot, and interpretability of the factors. *Z*-scores from the separate cognitive tasks were calculated, and the mean *z*-scores of the cognitive tasks representing one cognitive domain were computed. Participants were excluded when one of the tasks representing one domain was missing.

To examine differences in cognitive functioning between depressed and non-depressed older adults, separate ANCOVA analyses were performed with the different cognitive tasks and domains as outcome variable and depressed versus non-depressed as independent variable. Effect size measures (Cohen's *d*) describing the difference between older adults with and without depression in cognitive functioning were determined. To observe whether the severity of depressive symptoms in the total group (both depressed and non-depressed) was associated with cognitive functioning, linear regression analyses were performed with depression severity as the independent variable and the single cognitive domains as the outcome variable.

Subsequently, in persons with current depression diagnosis ($n = 378$), linear regression analyses were performed with the clinical characteristics as independent variables and the single cognitive domains as the outcome variable. For each cognitive domain, multivariable models were analyzed with all clinical characteristics showing bivariable significant associations ($p < 0.10$) with cognitive functioning.

In addition, in persons with a current depression diagnosis, separate linear regression analyses were performed for each symptom dimension and cognitive domain to test whether different symptom dimensions of late-life depression (mood, motivation, somatic, apathy) were associated with different domains of cognitive functioning. All analyses were adjusted for age, sex, education, alcohol use, smoking status, and chronic diseases.

Results

Differences in demographics, clinical characteristics, symptom dimensions, and confounders between depressed and non-depressed older adults are shown in Table 1.

Table 2 shows the factor loadings, eigenvalues, and explained variances of the exploratory factor analysis. Four factors were retained according to the established criteria. These four factors explained 86.0% of the total variance and showed four theoretical domains. These four domains were interpreted as episodic memory (immediate and delayed recall), processing speed (Stroop cards I and II), and two domains of executive functioning: interference control (interference score of the Stroop) and working memory (digit span forwards

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Table 1. Characteristics of the study sample

	N	DEPRESSED PERSONS ($n = 378$)	NON-DEPRESSED CONTROLS ($n = 132$)	t, χ^2, or Z	p
Demographics					
Age, mean (SD)	510	70.7 (7.4)	70.1 (7.2)	− 0.90	0.37
Female, *n* (%)	510	250 (66.1)	81 (61.4)	0.98	0.32
Education in years, mean (SD)	510	10.4 (3.4)	12.5 (3.5)	5.79	<0.001
Clinical characteristics					
Depression severity, mean (SD)	502	30.1 (13.0)	7.8 (6.4)	− 25.4	<0.001
Age of onset, mean (SD)	354	48.2 (20.5)	–		
History of depression, *n* (%)	362	178 (49.7)	–		
Anxiety severity, mean (SD)	476	17.5 (11.4)	4.1 (5.5)	− 17.1	<0.001
Worrying, median (IQR)	476	4 (10)	0 (2)	− 9.1	<0.001
Psychotropic medication, *n* (%)					
TCA, *n* (%)	508	82 (21.9)	2 (1.5)		
SSRI, *n* (%)	509	105 (27.9)	1 (0.8)		
SNRI, *n* (%)	509	104 (27.5)	0		
Benzodiazepines, *n* (%)	510	150 (39.7)	4 (3.0)		
Symptom domains, mean (SD)					
Mood symptoms	500	8.96 (5.21)	1.20 (1.96)	− 24.2	<0.001
Motivational symptoms	490	5.01 (3.13)	0.68 (1.20)	− 22.1	<0.001
Somatic symptoms	501	9.79 (4.22)	4.91 (3.06)	− 14.0	<0.001
Apathy symptoms	477	17.2 (5.6)	10.2 (4.6)	− 13.9	<0.001
Confounders					
Alcohol use, *n* (%)	500				
- no alcohol use		150 (40.3)	17 (13.3)	23.9	<0.001
- >0 and <2 per day		194 (52.5)	84 (65.6)	ref	
- 2 or more per day		28 (7.5)	27 (21.1)	7.36	0.007
Smoking, *n* (%)	507	100 (26.7)	11 (8.3)	19.2	<0.001
Chronic diseases, mean (SD)	509	1.94 (1.41)	1.55 (1.17)	− 3.14	0.002

TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonergic and noradrenergic working antidepressants.

Table 2. Factor loadings, eigenvalues, and explained variances of the exploratory factor analysis on the separate cognitive tasks

	FACTORS			
	1	2	3	4
Immediate recall	**0.91**	0.44	0.39	0.31
Delayed recall	**0.94**	0.32	0.21	0.17
Stroop I	0.35	**0.91**	0.36	− 0.02
Stroop II	0.38	**0.92**	0.30	0.19
Digit span forwards	0.23	0.26	**0.88**	0.08
Digit span backwards	0.31	0.37	**0.85**	0.19
Stroop interference	0.24	0.09	0.14	**0.99**
Eigenvalues	2.89	1.15	1.06	0.84
% of variance	41.31	16.49	15.12	11.95

The primary loading for each item is printed bold.

and backwards). Few participants were excluded because of missing scores on one of the two tasks forming one domain (episodic memory: $n = 1$; processing speed: $n = 3$; working memory; $n = 3$). The interference control score was reversed to make sure that higher *Z*-scores reflect better cognitive performance in all domains of cognitive functioning.

In Table 3 it is shown that depressed older adults have lower scores on the cognitive domains episodic memory, processing speed, and interference control but not on working memory, compared with non-depressed control participants. These results were largely comparable to the differences observed by the separate cognitive tasks. The associated effect sizes were modest, with the lowest effect size for episodic memory ($d = 0.23$) and the highest for interference control ($d = 0.34$). In the total group, higher severity of depressive symptoms was associated with poorer cognitive functioning on all four cognitive domains.

Table 4 shows the associations between clinical characteristics of depression and the four domains of cognitive functioning in the depressed group. A higher severity of depressive and anxiety symptoms was associated with lower scores on

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Table 3. Associations between depression status and depression severity with cognitive functioning

	DEPRESSED PERSONS ($n = 378$) MEAN (SE)	NON-DEPRESSED CONTROLS ($n = 132$) MEAN (SE)	F	p	COHEN'S D	ASSOCIATION WITH DEPRESSION SEVERITY		
						β	t	p
Episodic memory								
Immediate recall	31.8 (0.34)	33.4 (0.61)	4.56	0.03	0.24	−0.16	−3.52	<0.001
Delayed recall	5.89 (0.11)	6.37 (0.20)	4.05	<0.05	0.22	−0.14	−2.89	0.004
Z-score episodic memory	− 0.04 (0.05)	0.17 (0.08)	5.17	0.02	0.23	−0.16	−3.52	<0.001
Processing speed								
Stroop card I	20.5 (0.28)	19.6 (0.50)	2.19	0.14	0.17	−0.05	−1.08	0.28
Stroop card II	26.6 (0.34)	24.3 (0.61)	10.81	0.001	0.35	−0.22	−4.79	<0.001
Z-score processing speed	− 0.05 (0.05)	0.20 (0.08)	6.92	0.01	0.27	−0.15	−3.20	0.001
Interference control								
Z-score interference control	− 0.07 (0.05)	0.26 (0.09)	9.57	0.002	0.34	−0.14	−2.98	0.003
Working memory								
Digit span forward	8.17 (0.09)	8.09 (0.16)	0.18	0.68	0.05	−0.10	−2.03	0.04
Digit span backward	5.29 (0.10)	5.41 (0.17)	0.34	0.56	0.06	−0.07	−1.54	0.12
Z-score working memory	0.004 (0.04)	0.013 (0.08)	0.01	0.92	0.01	−0.10	−2.11	0.04

Notes: Adjusted for age, sex, education, alcohol use, smoking status, and chronic diseases.
Degrees of freedom ANCOVA analysis; Episodic memory: 486, Processing speed: 474, Interference: 467, Working memory: 478.
Degrees of freedom Regression analysis; Episodic memory: 485, Processing speed: 473, Interference: 466, Working memory: 477.

episodic memory, processing speed, and working memory; worrying was associated only with slower processing speed. Recurrent episodes as opposed to first episodes were associated with better episodic memory performance. Regarding the use of psychotropic medication, TCAs were associated with poorer episodic memory, slower processing speed, and poorer interference control, and the use of SNRIs and benzodiazepines with slower processing speed.

High correlations were present between depression severity and anxiety severity ($r = 0.58$, $p < 0.001$), and worrying ($r = 0.41$, $p < 0.001$), and the individual significant effects disappeared when depression severity and anxiety or worrying were examined together. Therefore, only depression severity, being the strongest bivariable predictor of the psychopathological variables, was added to the multivariable models. The multivariable models (Table 4) showed that a greater severity of depression, a first depressive episode, and the use of TCAs were associated with worse episodic memory functioning. A greater severity of depression, the use of TCAs, SNRIs, and benzodiazepines was associated with slower information processing speed. The use of TCAs was also associated with poorer interference control, whereas only depression severity was associated with poorer working memory.

The different symptom dimensions of late-life depression were observed to have different associations with cognitive functioning (Figure 1). A higher score on the mood dimension was associated with worse working memory ($B = -0.02$, $t(350) = -2.44$, $p = 0.02$) and processing speed ($B = -0.02$, $t(349) = -2.17$, $p = 0.03$), a higher score on the motivational dimension and AS were both associated with worse episodic memory (motivational: $B = -0.05$, $t(350) = -3.11$, $p = 0.002$; apathy: $B = -0.03$, $t(336) = -3.35$, $p = 0.001$), and processing speed (motivational: $B = -0.05$, $t(342) = -3.34$, $p = 0.001$; apathy: $B = -0.02$, $t(330) = -2.27$, $p = 0.02$). A higher score on the somatic dimension was only associated with poorer working memory ($B = -0.02$, $t(351) = -2.17$, $p = 0.03$).

Discussion

In this large cohort of depressed and non-depressed older adults it was shown that depressed older adults have poorer cognitive functioning. A higher severity of psychopathological symptoms, having a first depressive episode, and the use of TCAs, SNRIs, and benzodiazepines was associated with worse cognitive performance. Poorer functioning in different cognitive domains was observed for specific symptom dimensions.

Our results contribute to the growing body of research emphasizing on impaired cognitive functioning in late-life depression (Thomas and O'Brien, 2008). In the depressed group, the severity of depressive, anxiety, and worry symptoms showed

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Table 4. Bivariable and multivariable associations between clinical characteristics and cognitive functioning among currently depressed older adults ($n = 378$)

	EPISODIC MEMORY				PROCESSING SPEED				INTERFERENCE CONTROL				WORKING MEMORY			
	B	*d.f.*	*t*	*p*	*B*	*d.f.*	*t*	*p*	*B*	*d.f.*	*t*	*p*	*B*	*d.f.*	*t*	*p*
Bivariable models																
Severity																
Depression severity	−0.01	358	−2.66	0.01	−0.01	350	−2.37	0.02	−0.004	343	−0.87	0.39	−0.01	351	−2.26	0.03
Onset																
Age of onset	−0.001	336	−0.26	0.80	0.002	328	0.94	0.34	−0.002	322	−0.70	0.48	0.001	330	0.54	0.59
History of depression	0.18	340	1.99	<0.05	0.07	332	0.72	0.48	0.03	326	0.31	0.76	0.06	333	0.62	0.53
Comorbidity																
Anxiety severity	−0.01	335	−2.66	0.01	−0.01	329	−2.64	0.01	−0.01	322	−1.39	0.17	−0.01	328	−2.01	<0.05
Worrying	−0.01	335	−1.58	0.12	−0.01	329	−1.98	<0.05	−0.003	322	−0.46	0.65	−0.004	328	−0.63	0.53
Psychotropic medication																
TCA	−0.45	358	−4.04	<0.001	−0.28	350	−2.45	0.02	−0.29	343	−2.26	0.02	0.07	351	0.62	0.54
SSRI	0.16	358	1.57	0.12	0.24	350	2.28	0.02	0.09	343	0.76	0.45	−0.01	351	−0.09	0.93
SNRI	0.00	359	−0.001	0.99	−0.25	351	−2.34	0.02	0.02	344	0.20	0.85	−0.11	352	−1.12	0.27
Benzodiazepines	−0.19	359	−1.87	0.06	−0.30	351	−3.00	0.003	0.04	344	0.33	0.75	−0.14	352	−1.47	0.14
Multivariable models																
Depression severity	−0.01	335	−2.36	0.02	−0.01	344	−2.55	0.01					−0.01	351	−2.26	0.03
History of depression	0.18	335	1.99	<0.05												
TCA	−0.46	335	−4.10	<0.001	−0.25	344	−1.97	0.05	−0.29	343	−2.26	0.02				
SSRI					0.16	344	1.35	0.18								
SNRI					−0.25	344	−2.17	0.03								
Benzodiazepines	−0.10	335	−1.00	0.32	−0.21	344	−2.00	<0.05								

Notes: Adjusted for age, sex, education, alcohol use, smoking status, and chronic diseases.
TCA = tricyclic antidepressants; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonergic and noradrenergic working antidepressants.

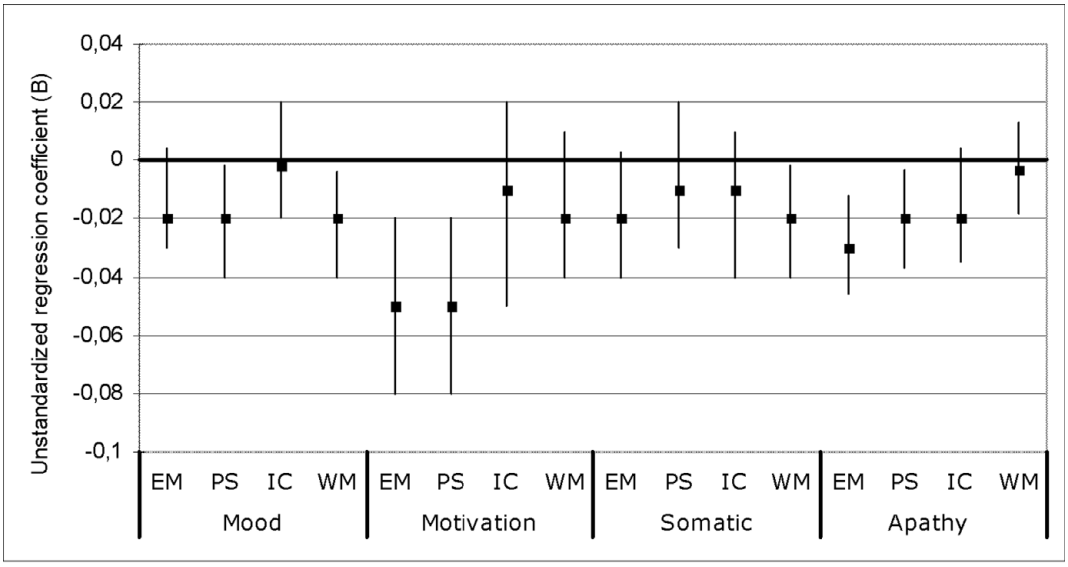


Figure 1. Associations between late-life depression symptom dimensions (mood, motivation, somatic, apathy) and cognitive functioning.

individually strong effects on cognitive functioning. However, these effects were no longer significant when examined together. This may indicate that high levels of anxiety and worrying reflect high severity of depression in our sample, and that high psychopathology severity was associated with poorer cognitive functioning in multiple cognitive domains.

Higher depression severity was associated with poorer episodic memory, processing speed, and working memory. Although some inconsistencies were observed in previous research, this is in line with studies whereby depression severity was associated with cognitive impairments when also other determinants of cognitive functioning in late-life depression were taken into account (Butters, 2004; Sheline *et al.*, 2006). The association between TCAs and poor cognitive functioning might be the result of the anticholinergic or antihistaminic effects of TCAs. This supports a preference for SSRIs in late-life depression compared to TCAs, which is in line with current Dutch psychiatry guidelines (Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ, 2008). Even though the use of SSRIs has increased enormously in the last decade, TCAs are still often used by older adults with depression (Sonnenberg *et al.*, 2008). Also, in the current study percentages of 21.9% were observed for TCAs compared to 27.9% for SSRIs. In addition, the use of SNRIs was associated with slower processing speed, which might be a direct effect of side effects such as tiredness and sleeplessness. Although we corrected for severity of depression, we cannot rule out the possibility that persons using TCAs and SNRIs, which are often used as second line following a non-response to SSRIs, have a more complex form of depression. In addition, in the Dutch psychiatry guidelines it is also stated that TCAs might be the first choice of antidepressant use when the depression severity is high, mainly when there are melancholic or psychotic features. Thus, it might be that TCAs and SNRIs are not causative factors itself in the association with cognitive functioning but might be the result of underlying depression complexity. In our sample also a high proportion of benzodiazepine use was observed (39.7%), which was also associated with slower processing speed. This is in line with results from a community-based study whereby especially chronic benzodiazepine use was associated with worse cognitive functioning (Bierman *et al.*, 2007). Overall, these results suggest that it is important to carefully consider the prescription of psychotropic medication in late-life depression and that close monitoring on cognitive side effects is necessary. The cross-sectional nature of the current study precludes more fine-grained analyses to determine whether antidepressant medication precedes poorer cognitive functioning. Follow-up data of the NESDO study could give more information about cognitive functioning in depressed persons versus persons in remission and the role of psychotropic medication in this association. This might help in disentangling the causative relationships between psychotropic medication and cognitive functioning.

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A history of depression was associated with better episodic memory, thus, a first depressive episode was associated with worse episodic memory. A first depressive episode in late life is associated with a later onset (mean age of onset first episode vs. history of depression: 56.2 vs. 40.8), and might be closer associated with underlying incipient neurodegenerative diseases (van Ojen *et al.*, 1995). However, in our study the age of onset of late-life depression was not associated with poorer cognitive function, which is in line with other research that excluded persons with dementia and examined multiple determinants of cognitive functioning together (Butters, 2004; Sheline *et al.*, 2006). Persons with a first depressive episode did not differ from persons with a recurrent depression on demographics, psychotropic medication, alcohol use, smoking status, and chronic diseases. However, persons with a first depressive episode had higher levels of worrying and motivational problems which might have contributed to a worse cognitive performance. Another explanation might be that the first episode already had a long duration, actually, about 30% of the persons with only one depressive episode reported a duration of more than 14 years. This suggests the presence of chronic depression which might be more unfavorable than experiencing recurrent episodes with symptom-free periods in between (Hetrick *et al.*, 2008).

Symptom dimensions of late-life depression were associated with poorer functioning in different cognitive domains, suggesting that heterogeneity of late-life depression may lead to problems in different domains of cognitive functioning. Although we performed multiple analyses, the probability that our findings can be explained by chance alone is very low. In addition, the findings in our study are not unexpected and consistent with other research, therefore we have not made a correction for multiple testing.

Higher scores on the mood dimension were associated with impairments on working memory and processing speed which might be explained by deficiencies in mental effort and attention when mood symptoms are prominent. This is in line with a population-based study of Baune *et al.* (2007) who observed slower processing speed among those scoring high on a depressive mood subscale. Alternatively, higher scores on the motivational symptom dimension was associated with poorer episodic memory and processing speed, which was in line with the associations found for the apathetic symptom dimension. This may suggest that apathetic/motivational symptoms of late-life depression are associated with poorer episodic memory and information processing speed. Feil *et al.* (2003) also observed apathy symptoms to be associated with slower processing speed. In addition, they observed that apathy symptoms were associated with worse executive functioning. However, the measures of executive functioning showing significant associations were closely related to processing speed and might as well reflect reductions in processing speed. Another explanation why we did not observe an association with executive functioning might be that apathy in late-life depression is more a marker of higher depression severity and less associated with neurodegenerative processes compared to apathy in non-depressed older adults. An apathy syndrome independent of late-life depression might have resulted in higher dysfunctioning in multiple cognitive domains including executive functioning.

A major strength of the current study is that a large and representative sample of currently depressed older adults with a diagnosis based on official DSM-IV diagnosis was examined and a wide range of clinical characteristics and cognitive domains was investigated. Some weaknesses should also be mentioned. First, cross-sectional data were used, therefore no causal inference can be made. Second, although persons with dementia were excluded, we cannot be sure that persons in very early stages of dementia were also excluded. Third, it might be difficult to state if a depressive episode was one long episode or several short episodes, and the number of depressive episodes might therefore be influenced by some recall bias. Finally, the most severely depressed or physically ill persons might be unwilling or unable to participate and conclusions should therefore not be generalized to the most severely depressed group.

To conclude, this large cohort of older depressed persons showed poorer cognitive function in late-life depression. Heterogeneity of late-life depression may lead to problems in different domains of cognitive functioning, whereby a higher severity of psychopathological symptoms, a history of depression, and differences in symptom dimensions are important characteristics. Our findings on the use of TCAs, SNRIs, and benzodiazepines suggest that close monitoring on cognitive side effects should be done when psychotropic medications are prescribed.

Conflict of interest

None.

Description of authors' roles

H.C. Comijs contributed to the conception and design of the study. N.C.M. Korten undertook

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the analyses. B.W.J.H. Penninx and H.C. Comijs assisted in the analyses. N.C.M. Korten made the first draft of the paper, and B.W.J.H. Penninx, R.M. Kok, M.L. Stek, R.C. Oude Voshaar, D.J.H. Deeg, and H.C. Comijs contributed to revising the paper critically for important intellectual content. All authors contributed to and have approved the final manuscript.

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References

Baune, B. T., Suslow, T., Arolt, V. and Berger, K. (2007). The relationship between psychological dimensions of depressive symptoms and cognitive functioning in the elderly – the MEMO-study. *Journal of Psychiatric Research*, 41, 247–254. doi:10.1016/j.jpsychires.2006.06.004.

Beaudreau, S. A. and O'Hara, R. (2008). Late-life anxiety and cognitive impairment: a review. *The American Journal of Geriatric Psychiatry*, 16, 790–803. doi:10.1097/JGP.0b013e31817945c3

Beck, A. T., Epstein, N., Brown, G. and Steer, R. A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology*, 56, 893–897. doi:10.1037/0022-006X.56.6.893.

Bierman, E. J. M., Comijs, H. C., Jonker, C. and Beekman, A. T. F. (2005). Effects of anxiety versus depression on cognition in later life. *The American Journal of Geriatric Psychiatry*, 13, 686–693.

Bierman, E. J. M., Comijs, H. C., Gundy, C. M., Sonnenberg, C., Jonker, C. and Beekman, A. T. F. (2007). The effect of chronic benzodiazepine use on cognitive functioning in older persons: good, bad or indifferent? *International Journal of Geriatric Psychiatry*, 22, 1194–1200. doi:10.1002/gps.1811.

Butters, M. A. (2004). The nature and determinants of neuropsychological functioning in late-life depression. *Archives of General Psychiatry*, 61, 587. doi:10.1001/archpsyc.61.6.587.

Comijs, H. C. *et al.* (2011). The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC Research Notes*, 4, 524.

Comijs, H. C., Aartsen, M. J., Visser, M. and Deeg, D. J. H. (2012). Alcoholgebruik onder 55-plussers in Nederland. *Tijdschrift voor Gerontologie en Geriatrie*, 43, 115–126. doi:10.1007/s12439-012-0018-9.

DeLuca, A. K. *et al.* (2005). Comorbid anxiety disorder in late life depression: association with memory decline over four years. *International Journal of Geriatric Psychiatry*, 20, 848–854. doi:10.1002/gps.1366.

Dotson, V. M., Beydoun, M. A. and Zonderman, A. B. (2010). Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology*, 75, 27–34. doi:10.1212/WNL.0b013e3181e62124.

Feil, D., Razani, J., Boone, K. and Lesser, I. (2003). Apathy and cognitive performance in older adults with depression. *International Journal of Geriatric Psychiatry*, 18, 479–485. doi:10.1002/gps.869.

Hegeman, J. M., Wardenaar, K. J., Comijs, H. C., de Waal, M. W., Kok, R. M. and van der Mast, R. C. (2012). The subscale structure of the Inventory of Depressive Symptomatology Self Report (IDS-SR) in older persons. *Journal of Psychiatric Research*, 46, 1383–1388. doi:10.1016/j.jpsychires.2012.07.008.

Hetrick, S. E., Parker, A. G., Hickie, I. B., Purcell, R., Yung, A. R. and McGorry, P. D. (2008). Early identification and intervention in depressive disorders: towards a clinical staging model. *Psychotherapy and Psychosomatics*, 77, 263–270. doi:10.1159/000140085.

Jolliffe, I. T. (1972). Discarding variables in a principal component analysis, I: Artificial data. *Journal of the Royal Statistical Society, Series C (Applied Statistics)*, 21, 160–173. doi:10.2307/2346488.

Jorm, A. F. (2000). Is depression a risk factor for dementia or cognitive decline? A review. *Gerontology*, 46, 219–227. doi:10.1159/000022163.

Klein, M., Ponds, R. W., Houx, P. J. and Jolles, J. (1997). Effect of test duration on age-related differences in Stroop interference. *Journal of clinical and experimental neuropsychology*, 19, 77–82. doi:10.1080/01688639708403838.

Kriegsman, D. M., Penninx, B. W., van Eijk, J. T., Boeke, A. J. and Deeg, D. J. (1996). Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *Journal of Clinical Epidemiology*, 49, 1407–1417. doi:10.1016/S0895-4356(96)00274-0.

Lampe, I. K. and Heeren, T. J. (2004). Is apathy in late-life depressive illness related to age-at-onset, cognitive function or vascular risk? *International psychogeriatrics*, 16, 481–486. doi:10.1017/S1041610204000766.

Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ (2008). *Multidisciplinaire Richtlijn Depressie, Addendum Ouderen [Guidelines for Diagnostics, Treatment, and Counselling of a Depressive Disorder, Addendum Older Adults]*.

Paterniti, S., Verdier-Taillefer, M. H., Dufouil, C. and Alperovitch, A. (2002). Depressive symptoms and cognitive decline in elderly people. Longitudinal study. *The British Journal of Psychiatry*, 181, 406–410. doi:10.1192/bjp.181.5.406.

Peretti, S., Judge, R. and Hindmarch, I. (2000). Safety and tolerability considerations: tricyclic antidepressants vs. selective serotonin reuptake inhibitors. *Acta Psychiatrica*

https://doi.org/10.1017/S1041610214000155 Published online by Cambridge University Press

Scandinavica. Supplementum, 403, 17–25. doi:10.1111/j.1600-0447.2000.tb10944.x.

Pietrzak, R. H. *et al.* (2012). Mild worry symptoms predict decline in learning and memory in healthy older adults: a 2-year prospective cohort study. *American Journal of Geriatric Psychiatry*, 20, 266–275. doi:10.1097/JGP.0b013e3182107e24.

Pimontel, M. A., Culang-Reinlieb, M. E., Morimoto, S. S. and Sneed, J. R. (2012). Executive dysfunction and treatment response in late-life depression. *International Journal of Geriatric Psychiatry*, 27, 893–899. doi:10.1002/gps.2808.

Rapp, M. A., Dahlman, K., Sano, M., Grossman, H. T., Haroutunian, V. and Gorman, J. M. (2005). Neuropsychological differences between late-onset and recurrent geriatric major depression. *The American Journal of Psychiatry*, 162, 691–698. doi:10.1176/appi.ajp.162.4.691

Rey, A. (1964). *L'examen Clinique en Psychologie*. Paris, France: Presses Universitaire de France.

Rush, A. J., Gullion, C. M., Basco, M. R., Jarrett, R. B. and Trivedi, M. H. (1996). The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychological Medicine*, 26, 477–486. doi:10.1017/S0033291700035558.

Sheline, Y. I. *et al.* (2006). Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. *Biological Psychiatry*, 60, 58–65. doi:10.1016/j.biopsych.2005.09.019.

Sonnenberg, C. M., Deeg, D. J. H., Comijs, H. C., van Tilburg, W. and Beekman, A. T. F. (2008). Trends in antidepressant use in the older population: results from the LASA-study over a period of 10 years. *Journal of Affective Disorders*, 111, 299–305. doi:10.1016/j.jad.2008.03.009.

Starkstein, S. E., Mayberg, H. S., Preziosi, T. J., Andrezejewski, P., Leiguarda, R. and Robinson, R. G. (1992). Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 4, 134–139.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology: General*, 18, 643–662. doi:10.1037/h0054651.

Tannenbaum, C., Paquette, A. l., Hilmer, S., Holroyd-Leduc, J. and Carnahan, R. (2012). A systematic review of amnestic and non-amnestic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs. *Drugs & Aging*, 29, 639–658. doi:10.2165/11633250-000000000-00000.

Thomas, A. J. and O'Brien, J. T. (2008). Depression and cognition in older adults. *Current Opinion in Psychiatry*, 21, 8–13. doi:10.1097/YCO.0b013e3282f2139b.

van den Berg, J. F. *et al.* (2013). Correlates of alcohol abstinence and at-risk alcohol consumption in older adults with depression: the NESDO study. *The American Journal of Geriatric Psychiatry*, (in press). doi:10.1016/j.jagp.2013.04.006.

van Ojen, R., Hooijer, C., Bezemer, D., Jonker, C., Lindeboom, J. and van, T. W. (1995). Late-life depressive disorder in the community. I. The relationship between MMSE score and depression in subjects with and without psychiatric history. *The British Journal of Psychiatry*, 166, 311–315.

Wechsler, D. (1958). *The Measurement and Appraisal of Adult Intelligence*, 4th edn. Baltimore, MD: Williams & Wilkins Co. doi:10.1037/11167-000.

Wisocki, P. A., Handen, B. and Morse, C. K. (1986). The worry scale as a measure of anxiety among homebound and community active elderly. *The Behavior Therapist*, 9, 91–95. doi:10.1016/0022-3956(94)90036-1.

Wittchen, H. U. (1994). Reliability and validity studies of the WHO–Composite International Diagnostic Interview (CIDI): a critical review. *Journal of Psychiatric Research*, 28, 57–84.

World Health Organization Collaborating Centre for Drug Statistics Methodology (2010). *Anatomical Therapeutic Chemical (ATC) Classification*. Available at: http://www.whocc.no/atc_ddd_index.

https://doi.org/10.1017/S1041610214000155 Published online by Cambridge University Press