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The impact of depression on language function in individuals with Alzheimer's disease: a pre/post-treatment design

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Abstract

Background It is uncertain whether depression might affect cognitive function in Alzheimer's disease (AD). Most of studies on the effect of depression treatment on cognitive function in AD were briefly evaluated by Mini-Mental State Examination (MMSE). MMSE is poor sensitive to detect cognitive change. This study examined the cognitive response to depression treatment in AD via multi-domain assessment. In addition, we explored whether effect of depression treatment in AD is different those of late-life depression (LLD).

Methods This study include AD patients with depression (AD + D) and without depression (AD − D), LLD patients (LLD), and healthy controls (HC). The patients were treated according to their diagnosis for 16 weeks: acetylcholinesterase inhibitors (AChEIs) and selective serotonin reuptake inhibitors (SSRIs) for AD + D, AChEIs for AD − D, and SSRIs for LLD. The cognitive changes from pre- to post-treatment were compared between AD + D and AD − D or LLD and HC. An independent sample *t* test was performed to compare the degree of change between the groups. Paired *t* tests were used to determine cognitive function changes in each depression treatment responder group.

Results At baseline, AD + D had more impairment in language function compared to AD − D, and LLD had greater deficit in executive function than HC. After depression treatment, more impaired cognitive domains at baseline were improved in AD + D and LLD, respectively. Moreover, AD + D showed an improvement in the global cognitive function (MMSE).

Conclusions Results indicated that language function was influenced by depression in AD, which is first evidence for specific cognitive domain related to depression in AD. Our finding indicates that depression could negatively impact cognitive function, and depression treatment may have beneficial cognitive effect in both AD and LLD. This study suggests the importance of early detection and treatment of depression in AD and LLD.

Trial registration Clinical Research Information Service, CRIS, ID#: KCT0004041, Registered 5 June 2019, retrospectively registered after first patient enrollment date (4 March 2014) https://cris.nih.go.kr/cris/search/detailSearch.do?seq=14140&status=5&seq_group=14140&search_page=M.

Keywords Alzheimer's disease, Depression, Cognitive function

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Background

Depression is one of the most common comorbidities in patients with Alzheimer's Disease (AD). It has been estimated that 10–20% of AD patients have major depression, and an additional 40–50% of patients experience depressive symptoms [50]. The comorbidity of depression in AD patients is associated with greater impairment in activities of daily living (ADL) [61], worse quality of life (QOL) [22], increased behavioral disturbances [41], and suicidal risk [53]. Previous studies have suggested that depression in AD contributes to poor prognosis of AD [3, 48, 60].

Several cross-sectional comparisons indicate that AD patients with depression (AD + D) have more cognitive impairment than AD patients without depression (AD − D) [3, 66]. In contrast, other studies reported no differences in cognitive function between AD + D and AD − D [18, 21, 25, 34, 38]. An experimental study design is required to examine the casual relationships between AD, depression, and cognitive function, but few such studies have been conducted [47].

A clinical review of the literature and meta-analyses several studies, which have evaluated the impact of antidepressant treatment on cognitive function among AD patients with depression, suggested conflicting results [36, 47].

Some studies have shown an improvement in global cognitive function after use of serotonin reuptake inhibitors (SSRIs; citalopram, escitalopram, fluoxetine, and paroxetine) or tricyclic antidepressants (TCAs; amitriptyline) medication in AD patients with depression [52, 63]. However, it is not known which specific cognitive domains are improved from these studies, because cognitive function was only assessed globally with the Mini-Mental State Examination (MMSE). MMSE is used to measure global cognitive function as a brief and simple screening tool, but its use has not been extended to encompass diverse cognitive domains [7].

In contrast, several studies have reported that cognitive function was unchanged despite a reduction in depressive symptoms or recovery after SSRIs (sertraline) [40, 43] or TCAs (imipramine) medication treatment [49] in AD + D. In two of these studies, cognitive function was also evaluated broadly using the MMSE [40, 49]. MMSE is not an appropriate measure to detect cognitive alteration, because it has intrinsic limitations as tool for tracking cognitive changes [51]. Another study using a number of cognitive measurements including MMSE, the Alzheimer's Disease Assessment Scale–Cognitive Subscale, Letter Fluency, Backward Digit Span, Symbol Digit Modalities Test, and Finger Tapping Test, found that sertraline treatment did not have a significant effect on any cognitive functions [43]. As a result, specific cognitive domains related to depression in AD are yet unknown. Because most previous studies focused on examining the efficacy of antidepressants as a primary outcome, cognitive function was only briefly evaluated using the MMSE. Thus, to clarify whether depression treatment in AD affects cognitive function, it is necessary to conduct a more detailed evaluation including a variety of cognitive domains.

Unlike depression in AD, it has been widely suggested that late-life depression (LLD) without dementia could induce cognitive impairment in the elderly [64, 67, 69]. Cognitive deficits in attention, executive function, and information processing speed are commonly noted in LLD [3, 13, 32, 67]. According to meta-analysis, the use of antidepressants to treat LLD has a moderate but not robust effect [44], while the efficacy of antidepressants for treatment of depression in AD has not been demonstrated [45, 47]. The clinical reviews of literature and meta-analysis, which included randomized controlled trials (RCTs) for efficacy of antidepressants vs. placebo with AD, identified only partial or no clinical benefits in treating depression in AD [36, 39, 45, 47]. As a result, it has been hypothesized that pathogenic mechanisms of depression in AD may be fundamentally different from those without AD [9, 11, 17]. Therefore, the effect of depressive treatment on cognitive function in AD is likely different from those in LLD.

As mentioned above, in most previous studies, cognitive response to depression treatment in AD was crudely measured by the MMSE, which showed conflicting results. To evaluate the influence of depression treatment on cognitive function more sensitively, diverse cognitive domains must be investigated using a comprehensive neuropsychological test battery.

Therefore, we investigated cognitive alterations between AD + D and AD − D via multi-domain assessment, including language function, memory, constructional praxis, and executive function, as well as global cognitive function in the MMSE, along with depression treatment. The effects of antidepressant treatment on each cognitive domain were also examined. In addition, we examined whether the effect of depression treatment in AD is different from that in LLD.

Specifically, this study examined the following by multi-domain assessment: (i) whether cognitive function is different according to the presence or absence of depression in AD group or elderly without dementia group and (ii) whether cognitive function changes after depression treatment in AD + D group or LLD group, and, if so, which cognitive domains are related to depression.

Methods

Participants

The participants were recruited from the Dementia Clinic of Chuncheon Sacred Heart Hospital. The inclusion criteria for the AD patient group (AD + D or AD − D) were as follows: (a) diagnosis of AD: met the criteria for AD via the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [4]; and neuropsychological tests that used the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K) [35]; (b) the diagnosis of depression for AD patients: three or more symptoms on the Olin Diagnosis Criteria for Depression in Alzheimer's disease [46]; and (c) a score of 0.5–2 on the Clinical Dementia Rating (CDR) Scale [26].

Moreover, depression in the elderly without dementia was assessed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [5].

The patients who met any of the following criteria at screening were excluded: (a) a history of taking antidepressants within 4 weeks; (b) treatment with memantine medication for at least 4 weeks; and (c) Parkinson's disease, stroke, brain tumor, or normal brain pressure hydrocephalus.

Eligible participants were enrolled 2 years (March 2014 to June 2016). A total of 95 participants were included in this study. Participants consisted of patients with newly diagnosed AD and LLD, as well as healthy controls with non-demented and non-depressed volunteers: 29 AD patients with depression (AD + D), 36 AD patients without depression (AD − D), 15 patients with late-life depression (LLD), and 15 healthy controls (HC) were included in the final sample.

All participants and their caregivers provided written informed consent. The Ethics and Medical Research Committee of Chuncheon Sacred Heart Hospital approved the study protocol.

Procedures

All participants were scheduled at baseline and at 4, 8, and 16 weeks. Depressive symptoms were rated at every visit, while cognitive function, overall functioning, and other psychosocial factors were examined at the baseline and final visits.

Clinical groups received treatment with Acetylcholinesterase inhibitors (AChEIs; donepezil) (for AD) and/or selective serotonin reuptake inhibitors (SSRIs; escitalopram) (for depression) according to diagnosis during the 16 weeks: AChEIs and SSRIs for AD + D, AChEI for AD − D, and SSRIs for LLD.

Assessments

Depressive symptoms evaluations

Depressive symptoms in AD + D and LLD were objectively assessed by the Cornell Scale for Depression in Dementia (CSDD) [1] and the 17-item Hamilton Rating Scale for Depression (HAMD) [68], respectively. Because depression in AD has a different presentation [36], the dementia-specified CSDD was used to evaluate depression in AD patients. The CSDD is a validated clinician-administered instrument specifically designed to rate the symptoms of depression in dementia patients [1]. The HAMD is a widely used clinician-rated scale of depression in older adults; however, its validity has not been established for late-life depression[37]. Subjective depressive symptoms in both groups were measured using the Short Geriatric Depression Scale-Korean version (SGDS-K) [6]. The GDS is a self-report inventory specifically designed to measure depression among older adult population [8]. Higher scores reflect more severe feelings of depression. Treatment response was defined as a $\geq$ 50% reduction in CSDD for AD + D and HAMD score for LLD.

Cognitive function evaluations

Cognitive function was assessed using several subtests from CERAD-K neuropsychological assessments and the Seoul Neuropsychological Screening Battery (SNSB) [28]. The neuropsychological measurement comprised nine subtests from CERAD-K and seven subtests from the SNSB. The subtests from CERAD-K; the Mini-Mental State Examination-Korean version (MMSE-KC), Korean version of Short Blessed test (SBT-K), Word Fluency, Korean version of Boston Naming Test (K-BNT), Word List Memory, Word List Recall, Word List Recognition, Constructional Praxis, and Constructional Recall. The subtests from the SNSB; Digit Span Forward (DSTF) and Backward (DSTB), Contrasting Program, Go/No-Go, Semantic Fluency, Phonemic Fluency, and the Stroop color test. Higher scores on all subtests, with the exception for SBT-K, indicate a better cognitive function.

Other evaluations

Activities of Daily Living (ADL) were measured using the Seoul Instrumental Activities of Daily Living (S-IADL) [33] for AD patients and LLD patients, and Blessed Dementia Scale–Activities of Daily Living (BDS–ADL) [35] for AD patients. Behavioral disturbances of AD patients were evaluated using the Neuropsychiatric Inventory (NPI) [29]. Lower S-IADL, BDS–ADL, and NPI scores indicate better functioning. Quality of life was assessed with the Korean version of the World Health Organization-Five Well-Being Index (WHO-5) [31].

Higher scores on the WHO-5 indicate a higher level of well-being. Suicidal ideation was assessed using the Suicidal Ideation Scale (SIS) [24]. Higher scores on the SIS indicate higher suicidal ideation. Suicidality was measured using the corresponding module of the Mini-International Neuropsychiatric Interview. A suicide risk score, based on the number of items endorsed was recorded [56].

Statistical analyses

For the descriptive statistics, a Fisher's exact test was used. To assess differences in cognitive function between groups at baseline, analysis of covariance (ANCOVA) with covariates of age, sex, and the duration of education was conducted. An independent sample *t* test was performed to compare the degree of change between the groups. Paired *t* tests were used to determine cognitive function changes in each treatment responder group. Cohen's d (for a *t* test) and/or partial eta squared (η_p^2) (for an ANCOVA) were reported as a measure of effect size. The statistical analysis was performed usi148ng SPSS Statistics 23.0.

Results

Characteristics of sample

Table 1 shows the demographic and clinical characteristics of the entire sample. Within the AD group, there were no differences in demographic and clinical characteristics between AD + D and AD − D. Within the elderly group without dementia, the LLD and HC did not differ in age, sex and clinical characteristics. However, the educational level of the HC group was significantly higher than that of the LLD group ($p=0.006$).

Comparison of cognitive function and other clinical data at baseline

Table 2 presents the differences in cognitive function between subgroups (the depressed subgroup and the non-depressed subgroup) of the AD group and the elderly group without dementia at baseline. Each subgroup with depression showed poor cognitive performance in some domains compared to the subgroup without depression. The mean score of K-BNT, which is a language function test, was lower in AD + D compared to AD − D ($F=5.346$, $p=0.024$, $\eta_p^2=0.082$). The mean score of MMSE-KC, which measures global cognitive function, in LLD was lower than that of HC ($F=4.327$, $p=0.048$, $\eta_p^2=0.148$). The LLD group had lower mean scores of Contrasting, Go/No-Go, and Semantic Fluency tests, which are executive function tests, compared to HC group ($F=5.346$, $p=0.029$, $\eta_p^2=0.176$, $F=15.980$, $p=0.000$, $\eta_p^2=0.390$, and $F=5.385$, $p=0.030$, $\eta_p^2=0.197$, respectively).

There were also significant differences in other factors between the depressed and the non-depressed, in both the AD and the elderly without dementia groups. AD + D had higher mean scores on the NPI ($t=3.401$, $p=0.001$, Cohen's $d=0.86$), SIS ($t=4.273$, $p=0.000$, Cohen's $d=1.12$), and Suicidality ($t=3.883$, $p=0.001$, Cohen's $d=1.02$) assessments and lower mean scores on the WHO-5 ($t=-6.386$, $p=0.000$, Cohen's $d=-1.56$) compared to AD − D. The LLD group showed higher mean scores on the S-IADL ($t=5.465$, $p=0.000$, Cohen's $d=2.00$) and Suicidality ($t=2.181$, $p=0.042$, Cohen's $d=0.80$) and lower mean scores on the WHO-5 ($t=-6.623$, $p=0.000$, Cohen's $d=-2.42$) compared to the HC group.

Table 1 Demographic characteristics and clinical features of overall group ($N=95$)

	AD		Elderly without dementia		*p* value	
	AD + D ($n=29$)	AD − D ($n=36$)	LLD ($n=15$)	HC ($n=15$)	AD + D vs. AD − D	LLD vs. HC
Age (years, mean ± *SD*)	76.34 ± 6.81	78.86 ± 5.06	70.80 ± 5.56	74.27 ± 5.31	0.505	0.151
Sex (female/male)	24/5	26/10	13/2	13/2	0.316	1.000
Education (years, means ± SD)	3.24 ± 3.74	4.78 ± 4.44	3.27 ± 2.92	13.73 ± 16.46	0.414	0.006
CDR					0.281	
0.5 (*n*, %)	13 (44.8)	20 (55.6)	–	–		
1 (*n*, %)	16 (55.2)	14 (38.9)	–	–		
2 (*n*, %)	0	2 (5.6)	–	–		

All variables were compared by fisher's exact test

AD + D, Alzheimer's disease with depression; AD − D, Alzheimer's disease without depression; LLD, late-life depression; HC, healthy controls; SD, standard deviation; CDR, Clinical Dementia Rating

Table 2 Comparison of cognitive function and other clinical data according to group at baseline

	AD		Elderly without dementia		AD + D vs. AD − D		LLD vs. HC	
	AD + D (mean ± SD)	AD − D (mean ± SD)	LLD (mean ± SD)	HC (mean ± SD)	*p* value	Cohen's d/η_p^2	*p* value	Cohen's d/η_p^2
Depressive symptoms								
CSDD	14.92 ± 6.95	1.75 ± 2.05	–	–	0.000	2.57	–	–
HAMD	–	–	14.13 ± 5.48	0.20 ± 0.56	–		0.000	3.58
SGDS-K	11.55 ± 3.16	2.44 ± 2.48	9.67 ± 3.81	1.07 ± 1.58	0.000	3.21	0.000	2.95
Cognitive function								
MMSE-KC	16.03 ± 2.97	17.31 ± 3.58	24.33 ± 3.01	27.07 ± 2.74	0.242	0.023	0.048*	0.148
Word Fluency	6.52 ± 2.90	7.39 ± 3.37	11.07 ± 2.63	13.67 ± 2.82	0.474	0.009	0.169	0.074
K-BNT	4.76 ± 2.31	6.61 ± 3.17	9.00 ± 2.70	11.27 ± 2.43	0.024*	0.082	0.237	0.055
Word List Memory	8.00 ± 3.18	8.48 ± 3.154	16.71 ± 4.97	18.40 ± 3.36	0.550	0.008	0.287	0.047
Word List Recall	1.42 ± 1.35	1.18 ± 1.13	5.57 ± 2.03	5.40 ± 1.77	0.602	0.006	0.932	0.000
Word List Recognition	4.05 ± 3.40	4.52 ± 3.02	8.71 ± 3.22	9.07 ± 1.03	0.456	0.012	0.364	0.034
Constructional Praxis	5.93 ± 2.15	6.89 ± 2.36	8.60 ± 1.84	9.47 ± 1.81	0.358	0.014	0.706	0.006
Constructional Recall	1.14 ± 1.41	1.19 ± 1.83	3.40 ± 1.84	6.13 ± 3.38	0.736	0.002	0.262	0.050
SBT-K	20.32 ± 5.73	17.69 ± 6.72	5.07 ± 5.85	2.33 ± 2.77	0.234	0.024	0.422	0.026
DSTF	4.17 ± 0.82	4.46 ± 1.07	4.93 ± 1.34	5.80 ± 1.37	0.822	0.001	0.398	0.029
DSTB	2.21 ± 1.06	2.37 ± 1.03	2.73 ± 1.34	3.47 ± 0.92	0.845	0.001	0.135	0.087
Contrasting Program	10.08 ± 7.46	11.86 ± 7.06	17.47 ± 3.52	19.87 ± 0.35	0.491	0.009	0.029*	0.176
Go/No-Go	8.96 ± 6.61	9.69 ± 6.43	12.87 ± 6.12	19.93 ± 0.26	0.927	0.000	0.000***	0.390
Semantic Fluency	15.71 ± 4.12	14.91 ± 6.65	24.85 ± 5.46	33.43 ± 6.96	0.335	0.017	0.030*	0.197
Phonemic Fluency	7.200 ± 7.24	7.44 ± 8.14	17.08 ± 11.20	28.13 ± 10.05	0.820	0.001	0.241	0.062
Stroop color	24.08 ± 16.15	32.56 ± 18.52	62.85 ± 22.09	79.27 ± 20.40	0.251	0.040	0.325	0.042
Others								
S-IADL	18.00 ± 9.40	18.36 ± 8.37	4.40 ± 2.41	0.73 ± 0.96	0.872	−0.04	0.000***	2.00
BDS–ADL	2.17 ± 1.85	1.97 ± 1.41	–	–	0.623	0.12	–	–
NPI	7.36 ± 5.00	3.53 ± 3.86	–	–	0.001**	0.86	–	–
WHO-5	28.41 ± 22.46	60.03 ± 17.91	21.60 ± 17.75	66.13 ± 19.06	0.000***	−1.56	0.000***	−2.42
SIS	7.55 ± 3.10	5.08 ± 0.28	6.00 ± 2.73	4.67 ± 1.29	0.000***	1.12	0.098	0.62
Suicidality	4.83 ± 6.57	0.08 ± 0.28	2.13 ± 2.92	0.33 ± 1.29	0.001**	1.02	0.042*	0.80

The cognitive functions were compared by ANCOVA after controlling for age, sex, and educational duration. Psychosocial and other variables were compared by independent sample *t* test. Effect sizes were calculated using Cohen's d (for an independent sample *t* test) and/or partial eta squared (η_p^2) (for an ANCOVA)

AD + D, Alzheimer's disease with depression; AD − D, Alzheimer's disease without depression; LLD, late-life depression; HC, healthy controls; SD, standard deviation; CSDD, Cornell Scale for Depression in Dementia; HAMD, Hamilton Rating Scale for Depression; SGDS-K, Short Geriatric Depression Scale-Korean version; MMSE-KC, Korean version mini-mental state examination; K-BNT, Korean version of the Boston Naming Test; SBT-K, Korean version of Short Blessed test; DSTF, Digit Span Forward; DSTB, Digit Span Backward; S-IADL, Seoul Instrumental Activities of Daily Living; BDS-ADL, Blessed Dementia Scale–Activities of Daily Living; WHO-5, Korean version of the World Health Organization-Five Well-Being Index; SIS, Suicidal Ideation Scale

*$p < .05$, **$p < .01$, ***$p < .001$

Comparison of changes in cognitive function at 16 weeks

To determine the effect of depression treatment on clinical factors, we first analyzed whether depressive symptoms were significantly reduced after 16 weeks in AD + D and LLD subgroups with depression. In both AD + D and LLD, the mean score of depressive symptoms (as measured by CSDD for AD + D or HAMD for LLD) within each subgroup was significantly diminished from baseline to final ($t = 6.807$, $p = 0.000$, Cohen's $d = 1.605$ and $t = 8.639$, $p = 0.000$, Cohen's $d = 2.396$, respectively). Figure 1 indicates CSDD mean score changes during 16 weeks of treatment in both AD groups. In addition, the mean score of SGDS-K in both groups (i.e., AD + D and LLD) was significantly reduced ($t = 5.684$, $p = 0.000$,

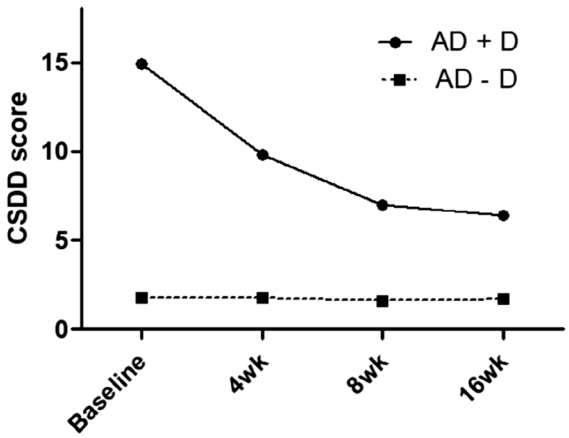

Fig. 1 Cornell scale for depression (CSDD) mean score changes in both Alzheimer's disease (AD) groups during 16 weeks of treatment

Cohen's $d=1.340$ and $t=8.215$, $p=0.000$, Cohen's $d=2.279$, respectively).

Table 3 presents a comparison of the mean scores on cognitive changes from baseline to final measurement for all neuropsychological tests between AD + D and AD − D or LLD and HC. The AD + D group showed a greater improvement in scores on the MMSE-KC (Fig. 2) and K-BNT (Fig. 3) than the AD − D group ($t=2.169$, $p=0.034$, Cohen's $d=0.542$ and $t=2.945$, $p=0.005$, Cohen's $d=0.756$, respectively). The LLD group showed a significant improvement on the Go/No-Go test as compared to the HC group ($t=3.144$, $p=0.007$, Cohen's $d=1.147$).

Comparison of cognitive changes between pre- and post-treatment according to the depression treatment responder group

The response rate of depression treatment was 62.07% (18 of 29) in AD + D (defined as a ≥ 50% reduction in CSDD score) and 86.67% (13 of 15) in LLD (defined as a ≥ 50% reduction in HAMD score). At 16 weeks, we examined the changes in cognitive function before and after treatment according to the response to depression treatment to confirm whether the improvements in cognitive function in some domains were indeed due to the treatment effect of the medication.

Table 4 indicates the comparison of mean changes in cognitive function before and after treatment within the depression treatment responder group in AD + D and LLD, respectively. The responders to depression treatment in AD + D showed a significant improvement in scores on the MMSE-KC ($t=-2.317$, $p=0.033$, Cohen's $d=-0.546$) and the K-BNT ($t=-2.197$, $p=0.042$, Cohen's $d=-0.518$). The responders to depression treatment in the LLD group showed a significant improvement in the MMSE-KC ($t=-2.379$, $p=0.035$, Cohen's $d=-0.660$) and Go/No-Go test ($t=-2.264$, $p=0.043$, Cohen's $d=-0.628$). In contrast, in non-responders to depression treatment of the two groups (AD + D and LLD), there was no difference in pre- and post-treatment scores in any cognitive domains.

Comparison of changes others clinical data at 16 weeks

As shown in Table 3, after 16 weeks, AD + D showed a decrease in scores in SIS ($t=4.911$, $p=0.000$, Cohen's $d=1.29$) and Suicidality ($t=3.733$, $p=0.001$, Cohen's $d=0.98$) compared to AD − D. The responders to depression treatment in AD + D showed a significant decrease in scores on the NPI ($t=3.264$, $p=0.005$, Cohen's $d=0.769$), SIS ($t=3.370$, $p=0.004$, Cohen's $d=0.794$), and Suicidality ($t=2.163$, $p=0.045$, Cohen's $d=0.510$) (Table 4). The LLD group showed a decrease in scores on the S-IADL ($t=3.495$, $p=0.003$, Cohen's $d=1.36$) and an improvement in scores on the WHO-5 ($t=4.127$, $p=0.000$, Cohen's $d=1.53$) (Table 3). The similar results are presented in the analysis within depression treatment responders in LLD (Table 4).

Discussion

In this study, the difference in cognitive function between AD + D and AD − D or LLD and HC was examined, and cognitive domains in response to depression treatment were measured using a comprehensive neuropsychological test battery.

At the baseline assessment, the subgroups with depression (i.e., AD + D or LLD) showed greater deficit in some domains, such as language function in AD or executive function in LLD, than those without depression (i.e., AD − D or HC) (Table 2). AD + D had greater impairment in language function (as measured by K-BNT) than AD − D. LLD showed more deficit in global cognitive function (as measured by MMSE-KC) and executive function (as measured by contrasting program, Go/No-Go, and semantic word fluency test) than HC. These cognitive differences could not be explained through a cross-sectional comparison. Hence, we observed changes in cognitive function after the antidepressant treatment. We found that more impaired cognitive domains (i.e., language function for AD + D or executive function for LLD) at baseline in subgroups with depression were improved compared to those without depression, respectively (Table 3), following the depression treatment. We also identified similar results in the analysis within the depression treatment responders of two subgroups with depression for each group (Table 4), which means that these outcomes were the result of cognitive alterations from a real effect of depression recovery. Furthermore, two depression treatment response groups showed

Table 3 Comparison of changes in clinical variables between pre- and post-treatment

	AD		Elderly without dementia		AD + D vs. AD − D		LLD vs. HC	
	AD + D (mean ± SD)	AD − D (mean ± SD)	LLD (mean ± SD)	HC (mean ± SD)	*p* value	Cohen's *d*	*p* value	Cohen's *d*
Depressive symptoms								
CSDD	8.15 ± 7.46	0.06 ± 2.28	–	–	0.000***	1.467	–	–
HAMD	–	–	11.20 ± 7.24	−0.20 ± 1.08	–	–	0.000***	2.202
SGDS-K	3.76 ± 4.60	−1.25 ± 4.42	6.54 ± 4.29	−0.86 ± 2.18	0.000***	1.110	0.000***	2.175
Cognitive function								
MMSE-KC	1.93 ± 3.37	0.08 ± 3.45	0.73 ± 3.08	0.13 ± 2.03	0.034*	0.542	0.534	0.235
Word Fluency	1.24 ± 3.17	0.60 ± 3.27	1.15 ± 2.48	1.00 ± 2.50	0.431	0.199	0.870	0.060
K-BNT	1.48 ± 2.50	−0.06 ± 1.43	0.00 ± 2.48	0.13 ± 1.30	0.005**	0.756	0.864	0.065
Word List Memory	2.26 ± 5.44	1.16 ± 3.40	1.17 ± 2.95	1.07 ± 3.73	0.374	0.242	0.940	0.029
Word List Recall	0.95 ± 1.68	0.28 ± 1.30	0.50 ± 1.78	1.13 ± 1.73	0.120	0.446	0.360	0.358
Word List Recognition	1.67 ± 4.19	0.47 ± 3.41	0.83 ± 2.33	0.53 ± 0.83	0.278	0.314	0.646	0.171
Constructional Praxis	0.28 ± 1.67	0.67 ± 1.99	−0.08 ± 1.55	0.07 ± 1.44	0.401	0.212	0.801	0.100
Constructional Recall	0.04 ± 1.43	−0.50 ± 1.78	1.62 ± 3.25	0.60 ± 3.27	0.199	0.334	0.419	0.312
SBT-K	2.25 ± 5.64	−0.31 ± 5.88	0.54 ± 5.93	1.27 ± 2.22	0.084	0.444	0.662	0.163
DSTF	0.04 ± 0.91	0.34 ± 0.91	−0.08 ± 0.95	0.13 ± 1.06	0.215	0.329	0.588	0.208
DSTB	−0.04 ± 0.62	0.17 ± 0.95	−0.15 ± 0.80	0.13 ± 1.30	0.341	0.261	0.497	0.304
Contrasting Program	2.46 ± 7.92	3.06 ± 5.66	1.69 ± 3.25	0.13 ± 0.35	0.736	0.087	0.110	0.674
Go/No-Go	2.08 ± 7.92	0.63 ± 5.67	4.33 ± 5.96	−0.60 ± 1.18	0.414	0.210	0.007**	1.147
Semantic Fluency	2.00 ± 5.53	0.70 ± 5.10	2.25 ± 3.72	2.43 ± 4.03	0.362	0.244	0.908	0.046
Phonemic Fluency	2.47 ± 5.04	2.03 ± 4.12	1.92 ± 7.28	0.67 ± 5.88	0.757	0.095	0.625	0.188
Stroop color	5.54 ± 12.49	6.08 ± 12.22	8.82 ± 19.91	−0.43 ± 9.00	0.889	0.043	0.134	0.598
Others								
S-IADL	0.14 ± 7.92	−0.39 ± 7.75	3.00 ± 2.97	−0.07 ± 1.14	0.788	0.07	0.003**	1.36
BDS–ADL	−0.09 ± 1.75	−0.55 ± 1.71	–	–	0.300	0.27	–	–
NPI	2.82 ± 4.80	0.85 ± 5.61	–	–	0.148	0.38	–	–
WHO-5	2.90 ± 28.04	−2.91 ± 22.38	34.93 ± 20.08	4.29 ± 19.87	0.360	0.23	0.000***	1.53
SIS	2.90 ± 3.08	0.08 ± 0.28	1.33 ± 3.24	−0.36 ± 1.34	0.000***	1.29	0.080	0.68
Suicidality	3.69 ± 5.27	0.03 ± 0.38	1.33 ± 3.06	0.36 ± 1.34	0.001**	0.98	0.270	0.41

The cognitive function, psychosocial and other variables were compared by Independent sample *t* test. Effect sizes were calculated using Cohen's *d*

AD + D, Alzheimer's disease with depression; AD − D, Alzheimer's disease without depression; LLD, late-life depression; HC, healthy controls; SD, standard deviation; CSDD, Cornell Scale for Depression in Dementia; HAMD, Hamilton Rating Scale for Depression; SGDS-K, Short Geriatric Depression Scale-Korean version; MMSE-KC, Korean version mini-mental state examination; K-BNT, Korean version of the Boston Naming Test; SBT-K, Korean version of Short Blessed test; DSTF, Digit Span Forward; DSTB, Digit Span Backward; S-IADL, Seoul Instrumental Activities of Daily Living; BDS-ADL, Blessed Dementia Scale–Activities of Daily Living; WHO-5, Korean version of the World Health Organization-Five Well-Being Index; SIS, Suicidal Ideation Scale

*$p < .05$, **$p < .01$, ***$p < .001$

improvement on global cognitive function (Table 4), whereas the treatment non-response groups did not show cognitive change in any domains. Our findings suggest that depression may lead to a decline in cognitive function, and successful treatment of depression can recover cognitive impairment in AD and in the elderly population without dementia.

Previous studies found that depression impacts the cognitive progression of AD [60] and that depression treatment enhances global cognitive function in AD [52, 63]. However, in these studies, it was not specified which cognitive domains were related to depression, because a brief cognitive screening tool, MMSE, was used to assess cognitive functioning. In the current study, we identified more specific domain, such as language function, that are impacted by depression in AD + D. The Boston Naming Test (BNT), one of the subtests used to measure language function in our study, is an instrument to assess confrontation naming ability, and it is commonly used to measure language function in AD patients [10]. Language impairment on the BNT is one of the primary determinants of cognitive decline in AD [19] and a common

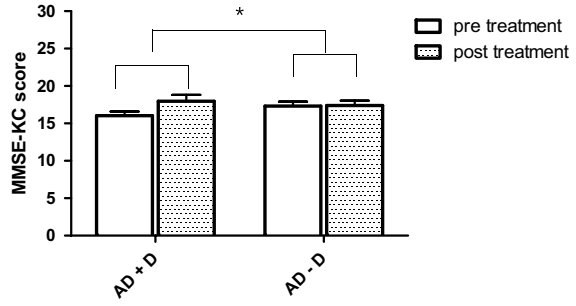

Fig. 2 AD + D group exhibited significantly greater increase on mean change score of MMSE-KC than AD − D ($t = 2.169$, $p = 0.034$). The bars indicate standard deviations

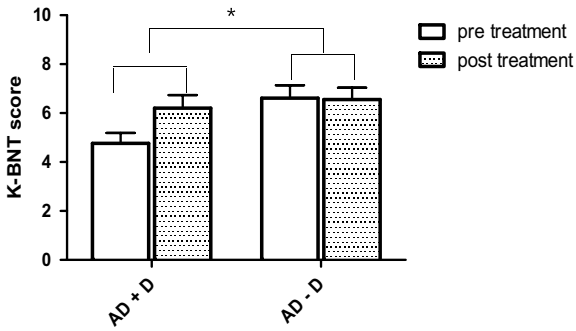

Fig. 3 After depression treatment, the AD + D group showed greater significant improvement in mean change score of K-BNT compared with AD − D group ($t = 2.945$, $p = 0.005$). The bars indicate standard deviations

symptom among individuals with dementia [62]. The language impairment is often found in the early stage of AD and deteriorates over the course of disease [58, 65].

At baseline, in our study, the AD + D group had more impaired language function than the AD − D group, but it was unclear whether language dysfunction was caused by neurodegenerative changes or temporarily damaged due to depression. After depression treatment, a significant improvement in language function was observed in AD + D compared to AD − D; hence, it is plausible that some degree of language impairment in AD + D stems from depression. This finding implies that language function in AD might be vulnerable to depression, which could contribute to poor prognosis of AD. Despite the high prevalence of depression in AD, the evaluation and treatment of depression in clinical settings is often overlooked. Our findings suggest the importance of evaluation and treatment of depression in AD patients, since comorbid depression in AD could contribute to a decline in cognitive functioning.

Cognitive domain influenced by depression in AD + D was different from those with LLD. It is presumed that regions of brain affected by depression may differ between AD and LLD. In AD, the medial temporal lobe of the brain is the first area to exhibit atrophy [14, 20, 27, 30], which is characterized by the most extensive pathological change in AD [59]. Depression is known to be neurotoxic to medial temporal lobe structures and can contribute to their atrophy [16, 42, 57]. There is evidence for significant effects of depressive symptoms on medial temporal lobe structure in AD patients with depressive symptoms [15, 17]. In our study, AD patients with depression showed greater naming disturbance. It is well-known that naming difficulty is associated with lesions in the medial temporal lobe [12, 23]. It could be postulated that depression in AD might aggravate atrophy of the medial temporal lobe, which may in turn lead to more impaired language function. It is inferred that if depression is not adequately treated in AD, the medial temporal lobe atrophy might become worse, causing poorer prognosis of disease.

Also, in LLD, we identified depression may impact the executive function. There are previous reports of frontal lobe abnormalities in LLD [2, 54]. In this respect, it is likely that depression's impact on the regions of brain is different in AD from in LLD. To clary determine, longitudinal studies on structural changes in the brain following depression treatment may be helpful.

AD + D had lower response rates to depression treatment than LLD (AD + D, 62.07%, LLD 86.67%) (Table 4), which is consistent with findings of a previous study [44]. In a meta-analysis study, the efficacy of selective serotonin reuptake inhibitors (SSRIs) treatment in AD + D appeared to be quite weak [55], while SSRIs are generally considered to be as the first choice antidepressant for LLD. In our study, low levels of antidepressant response rate in AD + D compared to LLD could be evidence supporting the concept that depression in AD has a different pathogenic mechanism from depression in the elderly with normal cognition [9, 11].

Overall, this study demonstrated that the patterns of depression seen in AD differed from typical depression seen in the elderly without dementia, specifically regarding the affected cognitive domains and antidepressant response rate. From our results, depression in AD might be thought of as a different subtype of depression. Future studies should explore the possibility of differences in pathophysiology between AD + D and LLD to determine whether depression in AD patients requires a different therapeutic approach. Moreover, this study demonstrated that depression treatment had beneficial effects on decreasing behavioral disturbances and suicide-related factors in AD patients with depression, and improving ADL and QOL in the elderly with LLD (Tables 3, 4).

Table 4 Comparison of changes in clinical variables between pre- and post-treatment in depression treatment responder groups

	Responders in AD + D ($n = 18$)				Responders in LLD ($n = 13$)			
	Baseline (mean ± SD)	After 16 weeks (mean ± SD)	*p* value	Cohen's *d*	Baseline (mean ± SD)	After 16 weeks (mean ± SD)	*p* value	Cohen's *d*
Depressive Symptoms								
CSDD	14.44 ± 7.58	3.50 ± 3.13	0.000**	1.605	–	–	–	–
HAMD	–	–	–		14.54 ± 5.62	1.38 ± 1.26	0.000***	2.396
SGDS-K	11.11 ± 3.69	5.61 ± 0.88	0.000***	1.340	9.69 ± 4.11	2.00 ± 1.78	0.000***	2.279
Cognitive function								
MMSE-KC	16.28 ± 3.29	18.28 ± 4.75	0.033*	−0.546	24.15 ± 3.21	25.69 ± 3.66	0.035*	−0.660
Word Fluency	7.28 ± 2.82	8.33 ± 3.53	0.138	−0.367	11.15 ± 2.76	12.69 ± 3.38	0.052	−0.599
K-BNT	4.67 ± 2.38	6.06 ± 2.96	0.042*	−0.518	9.45 ± 2.95	10.00 ± 3.52	0.441	−0.242
Word List Memory	7.60 ± 3.24	8.80 ± 3.19	0.493	−0.226	17.40 ± 5.46	18.10 ± 5.20	0.472	−0.238
Word List Recall	1.10 ± 0.88	1.80 ± 1.14	0.132	−0.523	6.10 ± 1.79	6.60 ± 1.65	0.440	−0.255
Word List Recognition	4.67 ± 2.92	5.00 ± 3.35	0.818	−0.079	9.70 ± 0.68	9.90 ± 0.32	0.343	−0.316
Constructional Praxis	5.78 ± 2.44	5.94 ± 2.31	0.687	−0.097	8.55 ± 1.86	8.73 ± 2.49	0.676	−0.130
Constructional Recall	1.06 ± 1.48	0.82 ± 1.85	0.509	0.164	3.45 ± 2.02	5.27 ± 2.72	0.101	−0.544
SBT-K	20.18 ± 5.87	18.88 ± 7.38	0.165	0.353	4.92 ± 6.09	5.23 ± 5.45	0.843	−0.056
DSTF	4.29 ± 0.85	4.41 ± 0.94	0.608	−0.127	4.85 ± 1.28	4.85 ± 1.07	1.000	0.000
DSTB	2.24 ± 1.09	2.18 ± 0.95	0.718	0.089	2.62 ± 1.39	2.77 ± 1.09	0.502	−0.192
Contrasting Program	9.12 ± 7.43	10.82 ± 8.01	0.376	−0.221	17.77 ± 3.56	19.00 ± 2.74	0.143	−0.434
Go/No-Go	9.00 ± 6.86	9.76 ± 5.72	0.685	−0.100	14.00 ± 5.46	17.00 ± 3.27	0.043*	−0.628
Semantic Fluency	16.06 ± 4.29	18.35 ± 7.87	0.114	−0.405	25.50 ± 4.99	27.00 ± 5.66	0.160	−0.484
Phonemic Fluency	7.90 ± 8.36	10.60 ± 10.30	0.056	−0.694	20.56 ± 10.48	22.11 ± 13.69	0.590	−0.187
Stroop color	25.44 ± 15.65	34.56 ± 17.34	0.062	−0.721	61.58 ± 22.58	66.08 ± 30.30	0.604	−0.154
Others								
S-IADL	17.22 ± 8.82	16.78 ± 9.58	0.833	0.050	4.23 ± 1.79	2.08 ± 2.25	0.005**	0.950
BDS–ADL	1.72 ± 1.22	1.97 ± 1.34	0.535	−0.149	–	–	–	–
NPI	6.17 ± 4.13	3.22 ± 5.01	0.005**	0.769	–	–	–	–
WHO-5	31.78 ± 26.48	40.67 ± 15.78	0.243	−0.285	21.23 ± 18.86	60.62 ± 15.99	0.000***	−2.301
SIS	6.67 ± 2.57	4.50 ± 2.01	0.004**	0.794	6.00 ± 2.92	4.62 ± 1.39	0.177	0.398
Suicidality	4.56 ± 8.17	1.33 ± 3.17	0.045*	0.510	2.38 ± 3.07	0.85 ± 1.73	0.114	0.472

The cognitive function, psychosocial and other variables were compared by Paired *t* test. Effect sizes were calculated using Cohen's *d*

AD + D, Alzheimer's disease with depression; AD − D, Alzheimer's disease without depression; LLD, late-life depression; HC, healthy controls; SD, standard deviation; CSDD, Cornell Scale for Depression in Dementia; HAMD, Hamilton Rating Scale for Depression; SGDS-K, Short Geriatric Depression Scale-Korean version; MMSE-KC, Korean version mini-mental state examination; K-BNT, Korean version of the Boston Naming Test; SBT-K, Korean version of Short Blessed test; DSTF, Digit Span Forward; DSTB, Digit Span Backward; S-IADL, Seoul Instrumental Activities of Daily Living; BDS-ADL, Blessed Dementia Scale–Activities of Daily Living; WHO-5, Korean version of the World Health Organization-Five Well-Being Index; SIS, Suicidal Ideation Scale

*$p < .05$, **$p < .01$, ***$p < .001$

This study had several strengths. We identified language impairment as a specific cognitive domain impacted by depression in those with AD, which improved through the treatment of depression via SSRIs. This is the first study to examine the specific cognitive domains impacted by AD and comorbid depression. We also found that a different cognitive function, specifically executive function, are affected in patients with late-life depression, but without dementia. Our research thus suggests that different therapeutic approaches may be required when treating depression in AD patients, compared to those required for treating patients without dementia. Our study, could consider the low antidepressant response rates in the AD patients with depression compared to those in patients with late-life depression, to support the concept that the pathogenic mechanism of AD-related depression could be different from depression in the elderly with normal cognition.

Our study had a few limitations. The small sample size might have limited the generalizability of the results. In the future, studies with larger samples are needed to determine the effect of depression treatment

on cognitive outcomes in AD patients. Another limitation was that the healthy control group had a significantly higher level of education than that of the LLD group. Although we statistically adjusted for age, sex, and education when analyzing cognitive function between the groups, considerable differences in the level of education might actually have influenced the psychometric assessment.

Nevertheless, the current study has demonstrated the effectiveness of treatment for depression in AD patients as well as elderly population without dementia regarding improvement in cognitive functioning (language and executive functioning). This is valuable as a frontier study in examining of the association between depression treatment and cognitive outcomes in AD.

In conclusion, our study demonstrated that depression treatment positively influences not only cognitive function but also overall functioning and other psychosocial factors in AD and LLD. Our findings have important clinical implication for diagnosis and treatment of depression in both AD patients and the elderly population without dementia.

Abbreviations

AD + D	Alzheimer's disease with depression
AD − D	Alzheimer's disease without depression
LLD	Late-life depression
HC	Healthy controls
AChEIs	Acetylcholinesterase inhibitors
SSRIs	Selective serotonin reuptake inhibitors
CSDD	Cornell Scale for Depression in Dementia
HAMD	Hamilton Rating Scale for Depression
SGDS-K	Short Geriatric Depression Scale-Korean version
MMSE-KC	Korean version mini-mental state examination
K-BNT	Korean version of the Boston Naming Test
SBT-K	Korean version of Short Blessed test
DSTF	Digit Span Forward
DSTB	Digit Span Backward
S-IADL	Seoul Instrumental Activities of Daily Living
BDS–ADL	Blessed Dementia Scale–Activities of Daily Living
WHO-5	Korean version of the World Health Organization-Five Well-Being Index
SIS	Suicidal Ideation Scale

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Author contributions
KHY conducted clinical and neuropsychological assessment of the patients, carried out the statistical analysis, and drafted the manuscript. YSM proofread the manuscript. DHK diagnosed and treated the diseases of patients and takes overall responsibility for the study. All authors read and approved the final manuscript.

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Availability of data and materials
The data sets analyzed in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study protocol was approved by the Ethics and Medical Research Committee of Chuncheon Sacred Heart Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare that there is no conflict of interests regarding the publication of this paper.

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