Impaired cognition in depression and Alzheimer (AD): a gradient from depression to depression in AD

Alterações cognitivas na depressão e na doença de Alzheimer: um gradiente da depressão até a doença de Alzheimer

Narahyana Bom de Araujo[1,2], Helena Sales Moraes[1,2], Heitor Silveira[1,2], Cynthia Arcoverde[6],
Paulo Eduardo Vasques[1,2], Maria Lage Barca[4], Anne-Brita Knapskog[4], Knut Engedal[4],
Evandro Silva Freire Coutinho[3], Andrea Camaz Deslandes[1,2], Jerson Laks[2,5]

ABSTRACT

Objective: To assess cognition in major depressed (MD), Alzheimer's disease (AD), and depression in AD elderly. **Method:** Subjects were evaluated by Mini Mental, Rey Auditory Verbal Learning Test, Rey Complex Figure, Digit Span, Similarities, Trail Making A/B, Verbal Fluency and Stroop. One-way ANOVA and multivariate models were used to compare the performance of each group on neuropsychological tests. **Results:** We evaluated 212 subjects. Compared to MD, attention, working memory, processing speed and recall showed significantly better in controls. Controls showed significantly higher performance in all cognitive measures, except in attention compared to AD. Verbal fluency, memory, processing speed and abstract reasoning in MD was significantly higher compared to AD. AD was significantly better in general cognitive state than depression in AD. All other cognitive domains were similar. **Conclusion:** A decreasing gradient in cognition appeared from the control to depression in AD, with MD and AD in an intermediate position.

Keywords: Alzheimer's disease, depression, neuropsychological tests and cognition.

RESUMO

Objetivo: Avaliar a cognição em idosos com depressão Maior (DM), doença de Alzheimer (DA) e Depressão na DA. **Método:** Utilizou-se o Mini Mental, Rey Auditory Verbal Learning Test, Figura de Rey, Dígitos, Semelhanças, Trail Making A/B, Fluência Verbal e Stroop. ANOVA one-way e modelos multivariados foram utilizados para comparar o desempenho dos grupos. **Resultados:** Foram avaliados 212 sujeitos. Comparado com DM, controles apresentaram desempenho significativamente melhor na atenção, memória de trabalho, velocidade de processamento e evocação. Os controles apresentaram desempenho significativamente superior em todas as avaliações, exceto na atenção comparado com DA. Fluência verbal, memória, velocidade de processamento e raciocínio abstrato na DM foi significativamente maior comparado com DA. DA foi significativamente melhor no estado cognitivo geral comparado a depressão na DA, os outros domínios foram semelhantes. **Conclusão:** Observou-se um gradiente decrescente na cognição dos controles até a Depressão na DA, com os grupos DM e DA com desempenhos intermediários.

Palavras-chave: doença de Alzheimer, depressão, testes neuropsicológicos e cognição.

Alzheimer's disease (AD) and major depression (MD) are the most common neuropsychiatric disorders in the elderly and several patients have both disorders[1]. The relation between MD and AD may have several directions: MD

may be a risk factor for dementia[2], a comorbid disorder with dementia, or even a neuropsychiatric syndrome in AD, regardless of the severity of dementia[3].

It is known that the cognitive impairment is more common in depressed elderly than in younger people with depression[4]. The impairment in speed of information processing, in attention/concentration, and in executive functions are the most important cognitive features in geriatric depression[4]. However, these problems are the very same cognitive problems which appear in mild cognitive impairment and in mild AD and MD[1,5], making it difficult to distinguish both disorders when depression is present[5].

In addition, several studies have focused on the severity of cognitive impairment within the spectrum ranging from normal aging, MD, cognitive dysfunction, mild cognitive impairment, and dementia[6,7]. The cognitive performance of older persons with MD is thought to be in between the performance observed in healthy and dementia subjects. As already pointed out, the main cognitive changes in MD are observed in attention and executive functions, whereas immediate and delayed recall are more characteristic impairments of dementia in Alzheimer's disease[5]. However, older adults with MD may have prominent deficits in memory too, as well as AD patients have significant deficits in executive function[5]. When dementia is associated with depression, there are conflicting results in the literature. Some studies have shown that depression in dementia is associated with reduced cognitive performance when compared with AD without depression[8,9] and others found no difference in cognitive function between AD and depression in AD[10,11].

So, it seems that the severity of the cognitive decline follows a gradient according to the interaction of depression and dementia. It is reasonable to hypothesize that patients with depression in DA are the ones with most impairment, whereas dementia would be in between depression and depression in AD. This is possibly due to an increasing hippocampal neuropathology when depression is superimposed to dementia, suggesting an interaction between depression and neuropathology processes in AD[12].

Therefore, the purpose of the present study is to assess the cognitive impairment in older persons with MD, AD, and with depression in AD.

METHOD

Subjects

Patients were diagnosed by psychiatrists at the university center. For diagnosis, psychiatrists used the DSM-IV[13] and the NINCDS-ADRDA[14] to AD, and the DSM-IV criteria[13] to MD. Imaging and laboratory evaluation were required and a screening using the Mini Mental State Examination (MMSE), the clock test, and the verbal fluency test was applied. After the diagnosis, patients were selected according to the inclusion/exclusion criteria. The inclusion/exclusion criteria were: subjects with comorbid neurological or clinical disorders were excluded from the sample, as well as those subjects who had important physical limitations, and visual or hearing impairment. The healthy elderly were recruited from an exercise program at the same university campus in Rio de Janeiro. Control participants included individuals who were designated cognitively normal by clinical evaluation and MMSE and without neurological or psychiatric diseases. A total of 212 elderly patients (≥60 years) were included in the final sample (MD=61; AD=46; depression in AD=43; healthy elderly=62).

The severity of depression in each disorder was measured by the Brazilian validated versions of the Hamilton Depression Scale (cutoff scores - mild: 8-13; moderate: 14-18; severe: 19-22)[15] and Cornell Scale for Depression in Dementia Scale (CSDD)[16]. Severity of dementia was rated with the Clinical Dementia Rating Scale (stages 1 to 3)[17]. In addition, all subjects were assessed with the MMSE, verbal fluency test using the animal category (VF), Digit span and Similarities subtests of the WAIS-R, Stroop Test, Rey Auditory Verbal Learning Test (RAVLT) and Rey Complex Figure.

Hamilton Depressive Scale

The Hamilton Depressive Scale is a multiple item questionnaire used to provide an indication of severity of depression. The Brazilian version has 17 items, each item is scored from 0 to 4 according to the severity of the symptom[15]. The following topics are evaluated: depressed mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss, genital symptoms, somatic symptoms and awareness of the disease. Scores higher than 25 indicate severe classification, scores between 18 and 24 define a classification moderate, scores between 7 and 17 indicate mild rating, and scores below 7 represent remission or absence of depression[15].

Cornell Scale for Depression in Dementia Scale (CSDD)

The CSDD was developed to assess signs and symptoms of major depression in patients with dementia. This scale has 19 items, each item is rated for severity on a scale of 0-2 (0=absent, 1=mild or intermittent, 2=severe).CSDD evaluates mood, behavioral disorders, physical signs, cyclic functions and ideational disorder[16].

Clinical Dementia Rating (CDR)

The CDR is a scale used to assess the severity of dementia. This scale assesses a patient's cognitive and functional performance in six areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Scores in each area are combined to obtain a final score ranging from 0 through 3 (0=absence, 1=mild, 2=moderate, 3=severe)[17].

Cognitive function assessment
Mini-Mental State Examination

The MMSE is a brief screening test for cognitive capabilities that evaluates orientation (spatial and time), attention, concentration, memory, calculation, language, and praxis[18].

Verbal Fluency

The VF test is a one-minute assessment in which the patient is asked to name as many animals as he can. This test assesses executive functions, semantic memory and linguistic abilities[19].

Digit span

The digit span subtest is divided in two parts, the first portion assesses attention and immediate memory and the second portion assesses working memory. A series of number sequences are presented to the subject. In the first portion of the test, the subject is asked to reproduce the exact sequence, whereas in the second portion he/she is asked to repeat the sequence backwards[20].

Similarities

In Similarities, the subject is asked in what way two objects or concepts are alike. This test assesses abstract reasoning and verbal comprehension[20].

Stroop

In this test patients are required to name the ink color in which incongruent color names are printed. The instrument assesses selective attention and concentration, cognitive flexibility and inhibitory control[21].

RAVLT

In the RAVLT, there is a sequence of 30 substantives with 15 substantives in each list (list A and list B). The list A is read aloud to the subject five consecutive times. After each reading the subject must say the words to remember. Then a list of interference, list B, is read to the subject, after he/she must say the words to remember (B1). The examiner asks the subject to recall the words from list A (A6). After a 20 or 30 minutes, the examiner asks the subject to remember the words from list A (attempt A7). Then a recognition list (RL) is read and the subject is asked to indicate if the word belongs to list A, or not[22]. The instrument assesses recent memory, verbal learning, susceptibility to interference, retention of information and recognition memory[22].

Rey-Osterriech Complex Figure

The Rey-Osterrieth complex figure (Rey Figure) is a test used to investigate visual memory, visuospatial ability and some aspects of planning and executive function. In the present study only the copying task was used. The figure was placed in front of the patient and he was asked to copy the figure as accurately as possible[23].

The study was approved by the Ethics Committee of the Institute of Psychiatry of the *Universidade Federal do Rio de Janeiro*, and all participants signed informed consent forms before any procedure.

Statistical analysis

A descriptive statistics was initially calculated for the demographic and clinical characteristics of the patients. Kolmogorov-Smirnov and the Levene's tests were used to investigate the normality and homoscedasticity of the neuropsychological data, respectively. One-way ANOVA with post-hoc Tukey test (parametric data) and Kruskall-Wallis with post-hoc Tamhane (non-parametric data) were used to compare the neuropsychological tests among the groups (MD, AD, depression in AD).

Multivariate regression models were fitted to compare the performance of each group on neuropsychological tests adjusting the data by gender, age, and education. As the attempt to normalize the distribution of the scores failed, negative binomial models were employed with the coefficients expressing the ratio of means of each group compared to the control group.

The analysis was conducted using SPSS® for Windows (version 17.0) and Stata 12. The significance level accepted in this study was $p < 0.05$.

RESULTS

Table 1 presents the demographic and clinical characteristics across the four groups. In all groups, most participants were women. The patients in the AD group were significantly older than in the MD and the control group. Also, MD patients were significantly older than the control group and significantly younger than the depression in AD group. Inversely, education level of the control group was significantly higher than in any other group, whereas the comparison among the other groups revealed no statistical difference with this regard.

As expected, patients with MD and depression in AD showed higher scores on depression symptoms. MD patients had a longer disease duration, followed by the patients of the AD and depression in AD groups. All groups were classified predominantly as mild cases.

Table 2 presents the results of the neuropsychological tests by participant groups. The cognitive performance of the groups showed a decreasing gradient. The control group was the most preserved one, followed by the MD group, the AD and finally by the depression in AD.

	Control N=62	MD N=61	AD N=46	Depression in AD N=43
Age (years)[a]	68.55 (±5.97)	70.89 (±7.30)	76.09 (±6.34)	75.86 (±7.6)
Education (years)	10.32 (±4.14)	8.18 (±3.91)[b]	7.37 (±4.45)[b]	6.56 (±3.87)[b]
Duration of disease (years)	–	7 (0-40)	4 (1-11)	4 (1-10)
Depressive symptoms x (sd)	2.17 (±2.32)	12.21 (±4.03)	3.46 (±2.08)	11.23 (±4.64)
Gender (%)				
Female	82.69	81.97	80.43	70.45
Disease Severity (%)				
Mild	-	62.29	67.39	37.21
Moderate	-	34.43	21.74	34.88
Severe	-	3.28	10.87	27.91

N: number of patients; MD: major depression; AD: Alzheimer disease;[a]Significant differences among groups control vs AD (p<0.001); control vs depression in AD (p<0.001); MD vs AD (p=0.001); MD vs depression in AD (p=0.001); [b]Significant difference compared to control group (p<0.05).

Nonetheless, the statistically significant results among all groups were observed in the overall cognitive state as evaluated by the MMSE. The control group showed a significant higher cognitive performance in all functions compared to AD and depression in AD. Moreover, the control group showed significantly better results in the assessment of

	Control N; Median (min-max)	MD N; Median (min-max)	AD N; Median (min-max)	Depression in AD N; Median (min-máx)	X^2 (p) Post hoc
MMSE (score)	62; 29 (24-30)	61; 28 (21-30)	46; 19 (2-28)	43; 13 (0-27)	152.589 (<0.001) [b]p<0.001 [c]p<0.001 [d]p<0.001 [e]p<0.001 [f]p<0.001 [g]p=0.025
Verbal fluency[a]	62; 17.85 (4.89)	61; 15.90 (3.85)	46; 9.98 (5.15)	43; 7.37 (5.56)	52.705 (<0.001) [c]p<0.001 [d]p<0.001 [e]p< 0.001 [f]p<0.001
Digit span (score)	62; 10 (4-23)	61; 8 (4-15)	44; 7 (0-17)	43; 6 (0-14)	53.848 (<0.001) [b]p<0.001 [c]p<0.001 [d]p<0.001 [f]p<0.001
Digit forward (score)	62; 5.5 (2-13)	61; 4 (1-9)	44; 4 (0-11)	43; 4 (0-8)	24.304 (<0.001) [b]p=0.003 [c]p=0.006 [d]p<0.001
Digit backward (score)	62; 5 (1-10)	61; 4 (2-9)	44; 3 (0-6)	43; 2 (0-7)	65.059 (<0.001) [b]p=0.002 [c]p<0.001 [d]p<0.001 [e]p=0.009 [f]p<0.001
Stroop points (sec)	59; 15 (10-32)	61; 23 (12-50)	37; 28 (13-71)	34; 38,5 (13-226)	66,756 (<0.001) [b]p<0.001 [c]p<0.001 [d]p<0.001 [f]p=0.012
Errors-stroop points	59; 0 (0-2)	61; 0 (0-0)	37; 0 (0-7)	34; 0.5 (0-19)	33,769 (<0.001) [d]p=0.008 [f]p=0.007 [g]p=0.021

Continue

Continuation

Stroop words (sec)	59; 20 (12-32)	61; 25 (13-59)	37; 34 (15-108)	34; 49.5 (14-144)	75,628 (<0.001) [a]p<0.001 [c]p<0.001 [d]p<0.001 [e]p=0.030 [f]p<0.001
Errors-stroop words	59; 0 (0-1)	61; 0 (0-2)	37; 0 (0-24)	34; 1.5 (0-23)	51.105 (<0.001) [d]p<0.001 [f]p=0.002
Stroop colors (sec)	59; 31 (19-58)	61; 38 (18-126)	37; 48 (20-118)	35; 57 (21-249)	46.931(<0.001) [b]p=0.001 [c]p<0.001 [d]p<0.001 [f]p=0.008
Errors-stroop colors	59; 0 (0-18)	61; 0 (0-13)	37; 4 (0-24)	35; 7.5 (0-24)	64,621(<0.001) [c]p=0.004 [d]p<0.001 [e]p=0.001 [f]p<0.001
RAVLT[a](list A1-A5)	62; 43.82 (12.51)	61; 36.28 (11.03)	42; 19.24 (8.99)	40; 13.57 (10.52)	81.633(<0.001) [b]p=0.003 [c]p<0.001 [d]p<0.001 [e]p<0.001 [f]p<0.001
RAVLT B	62; 5 (1-12)	61; 5 (0-10)	41; 2 (0-5)	40; 1 (0-5)	102.852 (<0.001) [b]p=0.40 [c]p<0.001 [d]p<0.001 [e]p<0.001 [f]p<0.001
RAVLT A6	62; 8.5 (2-14)	61; 7 (0-13)	41; 1 (0-6)	40; 0 (0-6)	129.420 (<0.001) [b]p=0.004 [c]p<0.001 [d]p<0.001 [e]p<0.001 [f]p<0.001
RAVLT A7	62; 9 (0-15)	61; 6 (0-14)	41; 0 (0-7)	40; 0 (0-4)	130.106(<0.001) [c]p<0.001 [d]p<0.001 [e]p<0.001 [f]p<0.001
RAVLT LR	62; 14 (4-18)	60; 13 (5-15)	37; 11 (0-15)	26; 6.5 (0-15)	53.187 (<0.001) [c]p<0.001 [d]p<0.001 [e]p=0.001 [f]p<0.001
Similarities[a]	62; 16.16 (5.55)	61; 16.18 (5.85)	25; 8.24 (5.47)	12; 5.25 (3.49)	25.279 (<0.001) [c]p<0.001 [d]p<0.001 [e]p<0.001 [f]p<0.001
Rey figure	61; 31 (8-36)	60; 26.5 (3-34)	22; 18 (0-34)	14; 6.5 (0-34)	29.344(<0.001) [b]p=0.008 [c]p=0.004 [d]p=0.003 [f]p=0.025

Kruskal-Wallis Test (Values in median and minimum-maximum); *Anova Oneway (Values in mean and standard deviation)
[a]significant difference from control group compared to MD; [b]significant difference from control group compared to AD; [c]significant difference from control group compared to Depression in AD; [d]significant difference from MD compared to AD; [e]significant difference from MD compared to Depression in AD; [f]significant difference from AD compared to Depression in AD.
MD: major depression; AD: Alzheimer disease; MMSE: Mini Mental state examination; RAVLT: Rey Auditory verbal learning test.

attention and working memory (Digit Span, Digit Forward, Digit Backward), processing speed (Stroop), learning and verbal memory (RAVLT A1-A5), immediate recall (RAVLT B), recall after interference (RAVLT A6) and visuospatial ability and planning (Rey Figure) as compared to the MD group.

The MD group showed a significantly higher performance in verbal fluency (FV), in all memory evaluations (Digit Backward, RAVLT A1-A5; RAVLT B; RAVLT B; RAVLT A6; RAVLT A7; RAVLT LR), as well as in processing speed (Stroop words), inhibitory control (Errors-stroop colors), and abstract reasoning (Similarities) when compared to the AD group. The MD group showed a significant higher cognitive performance in all functions compared to depression in AD, except for the assessment of attention (Digit Forward).

As some factors such as age, education, and gender may influence the cognitive performance, we calculated the adjusted ratio of means of the scores using the control group as the reference (Table 3). For example, in Table 3 the observed ratio of means for MMSE (0.97, 0.65 and 0.51) indicates that the mean of the MD group is 3% smaller than in the control group (1-0.97). Nevertheless, this finding was not statistically significant (p=0.45). On the other hand, for the AD group, the mean of MMSE was 45% smaller than in the control group (1-0.65), reaching statistical significance (p<0.001).

Unlike the unadjusted data (Table 2), the difference in cognitive performance between the MD and control groups was no longer statistically significant for the cognitive status (MMSE), learning and verbal memory (RAVLT A1-A5), immediate recall (RAVLT B1), visual spatial ability and planning (Rey figure) after the control for gender, age, and education (Table 3). When the AD group was compared to the

Table 3. Ratio of means adjusted for age, gender, and education (Reference: control group).

	Control (reference)	MD RR (CI) p-value	AD RR (CI) p-value	Depression in AD RR (CI) p-value
MMSE (score)	1	0.97 (0.91-1.04) 0.451	0.65 (0.60-0.72) <0.001	0.51 (0.46-0.56) <0.001
Verbal fluency	1	0.94 (0.83-1.07) 0.37	0.61 (0.52-0.72) <0.001	0.46 (0.38-0.55) <0.001
Digit span (score)	1	0.85 (0.76-0.96) 0.008	0.77 (0.66-0.89) <0.001	0.63 (0.53-0.74) <0.001
Digit forward (score)	1	0.85 (0.72-1.00) 0.054	0.86 (0.70-1.04) 0.13	0.76 (0.62-0.94) 0.01
Digit backward (score)	1	0.85 (0.72-1.01) 0.06	0.66 (0.53-0.82) <0.001	0.47 (0.37-0.62) <0.001
Stroop points (sec)	1	1.44 (1.22-1.71) <0.001	1.65 (1.35-2.03) <0.001	2.64 (2.16-3.23) <0.001
Errors-stroop points	1	0.93 (0.26-3.37) 0.91	1.54 (0.38-6.15) 0.54	37.06 (10.41-131.92) <0.001
Stroop words (sec)	1	1.41 (1.19-1.66) <0.001	1.89 (1.55-2.29) <0.001	2.76 (2.26-3.36) <0.001
Errors-stroop words	1	5.38 (1.02-28.27) 0.047	63.62 (11.66-347.00) <0.001	118 (22.74-621.11) <0.001
Stroop colors (sec)	1	1.34 (1.13-1.58) 0.001	1.47 (1.20-1.80) <0.001	2.07 (1.69-2.54) <0.001
Errors-stroop colors	1	0.77 (0.46-1.31) 0.340	3.48 (1.94-6.25) <0.001	5.47 (3.04-9.85) <0.001
RAVLT (list A1-A5)	1	0.91 (0.77-1.06) 0.240	0.50 (0.41-0.61) <0.001	0.36 (0.29-0.45) <0.001
RAVLT B	1	0.91 (0.77-1.07) 0.237	0.45 (0.35-0.58) <0.001	0.34 (0.26-0.45) <0.001
RAVLT A6	1	0.81 (0.69-0.95) 0.011	0.21 (0.16-0.28) <0.001	0.10 (0.07-0.15) <0.001
RAVLT A7	1	0.84 (0.68-1.04) 0.116	0.12 (0.68-1.04) <0.001	0.02 (0.01-0.05) <0.001
RAVLT LR	1	0.99 (0.89-1.10) 0.917	0.76 (0.66-0.87) <0.001	0.54 (0.46-0.65) <0.001
Similarities	1	1.09 (0.96-1.27) 0.187	0.57 (0.46-0.70) <0.001	0.39 (0.28-0.54) <0.001
Rey figure	1	0.93 (0.79-1.08) 0.353	0.73 (0.59-0.91) 0.005	0.49 (0.37-0.65) <0.001

RR: ratio of means; CI: confidence interval; MMSE: Mini Mental State Examination; RAVLT: Rey Auditory Verbal Learning Test; AD: Alzheimer disease; MD: major depression.

Table 4. Ratio of means after the adjustment for age, gender and education (Reference: MD group).

	MD (reference)	AD RR (CI) p-value	Depression in AD RR (CI) p-value
MMSE (score)	1	0.68 (0.60-0.76) <0.001	0.53 (0.47-0.59) <0.001
Verbal fluency	1	0.63 (0.52-0.76) <0.001	0.46 (0.37-0.57) <0.001
Digit total (score)	1	0.90 (0.77-1.05) 0.175	0.74 (0.62-0.87) <0.001
Digit forward (score)	1	1,00 (0.82-1.21) 0.991	0.89 (0.72-1.10) 0.300
Digit backward (score)	1	0.78 (0.63-0.98) 0.033	0.57 (0.44-0.73) <0.001
Stroop points (sec)	1	1.15 (0.94-1.42) 0.179	1.84 (1.49-2.27) <0.001
Erros-stroop points	1	1.74 (0.46-6.51) 0.411	44.14 (12.29-158.56) <0.001
Stroop words (sec)	1	1.34 (1.09-1.65) 0.005	1.96 (1.59-2.41) <0.001
Errors-stroop words	1	12.34 (4.16-36.64) <0.001	22.41 (8.17-61.42) <0.001
Stroop colors (sec)	1	1.09 (0.89-1.35) 0.401	1.55 (1.25-1.92) <0.001
Errors-stroop colors	1	4.66 (2.74-7.91) <0.001	7.96 (4.69-13.49) <0.001
RAVLT (list A1-A5)	1	0.55 (0.44-0.69) <0.001	0.39 (0.31-0.50) <0.001
RAVLT B	1	0.49 (0.38-0.62) <0.001	0.37 (0.28-0.49) <0.001
RAVLT A6	1	0.25 (0.18-0.34) <0.001	0.12 (0.08-0.17) <0.001
RAVLT A7	1	0.13 (0.087-0.20) <0.001	0.02 (0.01-0.06) <0.001
RAVLT LR	1	0.77 (0.66-0.91) 0.002	0.55 (0.45-0.68) <0.001
Similarities	1	0.50 (0.39-0.64) <0.001	0.34 (0.24-0.49) <0.001
Rey figure	1	0.78 (0.58-1.05) 0.105	0.53 (0.37-0.76) 0.001

RR: ratio of means; CI: confidence interval; MMSE: Mini Mental State Examination; RAVLT: Rey Auditory Verbal Learning Test; AD: Alzheimer disease; MD: Major depression.

control group controlling for the influence of gender, age, and education, the difference for attention performance (Digit forward) also was no longer statistically significant.

We further calculated the ratio of means adjusted for age, education, and gender using the MD group as the reference (Table 4). After the adjustment, the AD and depression in AD groups showed the same results observed in Table 2.

DISCUSSION

According to our initial hypothesis, the cognitive performance of the groups showed a decreasing gradient, from the control group as the most preserved one to the depression in AD group as the most affected one. The overall cognitive status as measured by the MMSE was the domain which obtained a statistically significant result among all groups. Furthermore, the MD group showed intermediate performance between the controls and the AD group in the overall cognitive state, as measured by verbal fluency and abstract reasoning. The patients with AD and MD showed no difference in attention and visuospatial ability and planning, i.e., an aspect of executive function.

Some studies have shown that there are significant differences between healthy elderly and MD patients[24,25] as well as between healthy elderly and AD patients[26]. Similar to our findings, other studies have found that MD elderly patients showed deficits in attention and in the executive function when compared to healthy elderly[27]. Additionally, AD patients showed impairment in different cognitive functions when compared to healthy elderly, including test performance of verbal fluency[28], abstract reasoning and memory[29].

The elderly with MD showed significant better results compared to the AD group in tasks that assessed memory function. Likewise, the AD group showed significantly higher result compared to the depression in AD group in overall cognitive status assessed by the MMSE. This is in line with several other studies which demonstrated that MD elderly have a better performance than AD patients, especially in tasks that assess information retention and recall[5], even though both groups have similar attentional deficits[5].

Studies which compared patients with depression in AD with healthy and MD elderly also observed an extensive cognitive impairment involving several functions including attention, executive function, and memory in the patients with both disorders compared with the healthy elderly and those with depression alone[30,31]. Also in line with our results, other studies have not found differences between patients with AD and depression in AD in specific cognitive functions such as verbal fluency, attention, executive functions and memory[10]. However, in the present study the AD group showed significantly better results compared to the depression in AD group in overall cognitive status assessed by the MMSE. A similar finding have also been reported by Rapp[8] et al.

To the best of our knowledge, only one other study[32] has compared all these groups of patients as we have done. However, their objective was to evaluate the usefulness of standardized neuropsychological tests in the psychometric differentiation of patients[32].

The present study has some limitations that should be acknowledged. First, the MD group was composed of elderly people with geriatric depression and recurrent depression. From previous research we know that patients with recurrent depression have atrophy of hippocampus and they have a higher risk of developing dementia. There is a strong link between geriatric depression and cerebrovascular changes,

which in turn could lead to vascular dementia. Some of the patients in the depressed group could have a subclinical dementia, either AD or vascular dementia. Moreover, we did not control for severity of dementia in the AD and depression in AD groups, including mild, moderate, and severe dementia, which may have influenced the cognitive performance. Also, the severity of depression in the MD and depression in AD groups was not controlled for. Finally, the cross-sectional design does not allow us to make any conclusion that there is a worsening along the spectrum which goes from healthy to Depression in AD groups. Longitudinal studies may come to a better understanding of this problem.

The severity gradient observed in some cognitive functions in this study may serve for further research using prospective designs. Also there is a clinical relevance in showing that cognitive functions may be further affected by depression in the presence of AD, meaning that treating depression in those cases is important to relieve some of the handicaps.

As the group of patients with both depression and AD had the worst performance in cognition this could indicate that these patients have the worst prognosis, or maybe also a faster progression of dementia than those suffering from AD without depression. Previous studies have shown that the conversion rate from MCI to dementia is higher among those with MCI with comorbid depression[33] and one clinic-pathological study also showed that AD patients with a history of depression in life had more plaques and tangles compared to AD patients with no history of depression in life[12]. Suggestions have been put forward that common low grade inflammation seen in depression and AD could explain this faster progression in patients with both disorders. Future longitudinal observational studies and treatment trials should examine this hypothesis.

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