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Research / Araştırma

Comparison of First Episode and Recurrent Major Depression Patients in Terms of Cognitive Function

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ABSTRACT

Comparison of first episode and recurrent major depression patients in terms of cognitive function

Objective: Cognitive impairment is one of the most important causes of disability in depression. There are conflicting results about the nature of cognitive impairment with some studies finding a difference between first episode (FE) and recurrent depression (RD) and a correlation between cognitive impairment and depression severity while others do not. Our aim was to compare cognitive function in FE and RD patients and to see if cognitive impairment is correlated with depression severity and number of depressive episodes.

Method: Unmedicated 33 FE and 37 RD outpatients with no additional Axis I disorder or physical disorder likely to affect cognition were included into the study and cognitive function was evaluated with verbal memory, verbal fluency, Stroop, Benton facial recognition and Boston naming tests.

Results: There were no cognitive differences between FE and RD groups or between RD patients with more or less than 3 depressive episodes. But severely depressed patients had lower naming and immediate memory scores. Depression severity was positively correlated with Stroop color word reading time and negatively correlated with verbal memory learning score. Perseveration scores were positively correlated with total depressive episode duration.

Discussion: Depression severity seems to be more effective on cognitive function than the number of depressive episodes. Results indicate that simple attention, encoding, learning, naming and mental speed is affected negatively from depression severity and cognitive flexibility was negatively affected by total depressive episode duration supporting prefrontal dysfunction hypothesis in depression.

Key words: Depression, cognition, first episode, recurrent

ÖZET

İlk atak ve rekürren major depresyon hastalarının kognitif işlevler açısından karşılaştırılması

Amaç: Kognitif bozukluk, depresyonun yeti yitimine yol açan önemli nedenlerindendir. Ancak literatürde, depresyondaki kognitif bozukluk ve doğası hakkında çelişkili sonuçlar mevcuttur. İlk atak (İA) ve rekürren depresyon (RD) hastaları arasında kognisyon açısından fark bulan ve bulmayan çalışmalar, kognitif bozukluğun depresyon şiddetinden bağımsız olduğunu gösteren ve göstermeyen çalışmalar vardır. Bu araştırmada, İA ve RD hastalarının kognitif işlevler açısından karşılaştırılması, atak sayısının ve depresyon şiddetinin kognitif işlevlere etkisinin incelenmesi amaçlanmıştır.

Yöntem: Psikiyatri polikliniğine ayaktan başvuran, ek psikiyatrik/nörolojik bozukluğu olmayan, kognitif işlevleri etkileyebilecek bedensel hastalığı bulunmayan, ilaç kullanmakta olmayan 33 İA ve 37 RD hastası sözel bellek süreçleri, sözel akıcılık, Stroop, Benton yüz tanıma, Boston adlandırma testleri ile değerlendirilmiştir.

Bulgular: İA ve RD grupları arasında, 3'ten fazla ya da az atak geçiren RD hastaları arasında kognitif işlevler açısından bir fark yoktu. Ancak ağır depresyonu olan hastaların kendiliğinden adlandırdıkları kelime sayıları ve anlık bellek puanları daha düşüktü. Depresyon puanı Stroop renkli kelimeleri okuma süresiyle pozitif, Sözel Bellek Süreçleri Testi öğrenme puanıyla negatif biçimde koreleydi. Perseverasyon puanı da toplam depresif atak süresiyle pozitif biçimde koreleydi.

Sonuç: Depresif atak sayısından ziyade depresyon şiddeti bilişsel işlevler üzerinde daha belirleyici görünmektedir. Depresyon şiddetlendikçe basit dikkat, kodlama, adlandırma, mental hız ve öğrenme bozulmakta; depresyon süresi uzadıkça da kognitif esneklik azalmaktadır. Bu bulgular, depresyonda prefrontal bir işlev bozukluğu olduğu hipotezini desteklemektedir.

Anahtar kelimeler: Depresyon, kognisyon, ilk atak, rekürren

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INTRODUCTION

Major depression is a common disorder, affecting approximately one in ten of the population at some time in their lives (1). The core symptoms are depressed mood and/or loss of interest but there is substantial evidence that cognitive function is also impaired (2).

Depressive patients may have severe, global cognitive defects or focal, discrete cognitive deficits or they may be cognitively intact (3). Their cognitive status is dependent on their age, depression severity, premorbid cognitive state or whether they have a comorbid condition or on their depression subtype (bipolar, unipolar, atypical, melancholic, psychotic, dysthymic) (3). As a rule, patients with bipolar or psychotic depression are more impaired than other subtypes (4). However, even mildly depressed patients without complicating factors are more impaired, as a group, than healthy people (5).

Studies have shown cognitive impairment (CI) almost in every cognitive domain in depression like attention, memory, language function, executive functions and visuo-spatial function, but recent research have demonstrated especially specific cognitive deficits in tests of sustained attention (6,7). Meta-analysis revealed intermediate effect size of depression on tests of psychomotor speed and tests that require sustained attention (8). The attentional deficits of depressive patients were more evident in effortful tasks like working memory tests (9,10) suggesting that attention is more likely to be affected from the current clinical state.

Another specific area of CI in depression is memory. Studies have demonstrated problems with immediate memory (encoding), long term memory (retrieval), recognition and recall (11-13). Meta-analyses revealed that depression had the largest effect on measures of encoding and retrieval from episodic memory (8). Since depressed patients are generally more impaired on effortful than automated tasks (14), explicit memory (relatively effortful) was found to be more impaired than implicit memory (relatively automatic) in depressive patients (15,16). Likewise, depressive patients had particular difficulties in memory tasks requiring sustained effort, such as list learning and free recall, indicating that these memory deficits could be associated with degree of depression (17). But, other researchers like Bearden et al. (2006) suggested that these impairments did not appear to be secondary to clinical state, but rather related to the past course of the patient's illness and number of previous episodes (18,19). Thus, verbal memory impairment seems at least to a degree trait-related, in contrast to attentional dysfunction, which appears to be state-dependent (3). But, unlike verbal memory, visuo-spatial function and visual memory seems to be generally preserved in depression since visual memory tasks are carried out automatically as compared to verbal memory tasks which require sustained attention and effort (20,21).

Language functions and naming ability also tend to be preserved in depression though impairments in verbal fluency have been noted (6,22). Fossatti et al. (22) found verbal fluency impairments in depressive patients but this was associated with reduced ability to shift mental set on card sorting tests, suggesting that verbal fluency impairments were not primary but reflective of general executive problems in depression.

Executive dysfunction can also be seen in depression, although not to the degree seen in schizophrenia patients (7,21). Depressive patients can exhibit executive deficits in tests of inhibition, problem solving and planning (23). Cognitive inhibition deficits in depression can cause depressed patient to process information that is irrelevant or counterproductive and thus reduce his or her cognitive capacity to deal effectively with depressive thinking and mood control (23). As such, impairment in cognitive inhibition was shown to be significantly associated with the level of depression (24). Several studies have also found evidence of problem solving impairments in depressive patients. In card sorting tasks, depressive patients have difficulty with hypothesis testing and cognitive flexibility. Increase in perseveration scores -indicating a state of cognitive rigidity- can prevent depressive patients from coping with life events, thus perpetuating depressive mood by prolonging stress exposure (23). Studies have shown that, impairments in

measures of cognitive flexibility were associated with relapse and recurrence of depression and with residual depressive symptoms (23).

All above mentioned findings show CI in many cognitive domains in depression and this is consistent with the "global and diffuse impairment in brain functions" hypothesis, but recent evidence suggested that executive deficits associated with frontal lobe dysfunction might be particularly prominent in depression (14). In support of this, brain-imaging studies showed reduced blood flow, especially in medial prefrontal cortex and dorsal anterior cingulate cortex, subserving executive impairments in depression (25).

Although there are plenty of studies about CI in depression, a small number of studies (26-31) compared first episode (FE) and recurrent depression (RD) with conflicting results. Some of these studies found a difference between FE and RD while others did not and some of them found a correlation between CI and depression severity while others did not. Because of this, we aimed to compare FE and RD patients in terms of cognitive function to see if previous depressive episodes have a scarring effect on cognition or if cognition is more affected from current depression severity.

METHOD

This is a cross-sectional study of cognitive function in FE and RD patients. This study is part of an ongoing, prospective study comparing cognitive function, stressful life events, temperament and character, genetic polymorphisms, inflammation biomarkers and neurotrophic factors in major depressive patients.

Sample

Patients were recruited from outpatient clinics of Abant Izzet Baysal University, Faculty of Medicine and Izzet Baysal Mental Health Hospital, between 16.04.2009 and 05.05.2010. Major depressive patients who scored above 17 from Beck Depression Inventory were invited to participate in the study. Those who agreed to participate gave written informed consent. Patients were excluded if they had a psychotic/bipolar depression, comorbid psychiatric/neurological disorder, history of head trauma, and any somatic disorder likely to affect cognitive function, mental/physical incapacity to understand and fill in questionnaires, psychotropic medication, emergent clinical condition like suicide risk, recent treatment with electroconvulsive therapy, iron, folate, vitamin B12 deficiency and hypothyroidism. 73 patients were included in the study at first, but 3 of them were excluded later due to hypomanic shift, Lyme disease and severe cognitive impairment at dementia level. As a result, the study was completed with 70 major depressive patients, 33 of which were FE and 37 RD. The study was approved by the Ethical Comittee of Abant Izzet Baysal University Faculty of Medicine.

Procedure

Patients' diagnoses were first confirmed by the investigators according to DSM IV criteria with a structured interview (SCID-I). FE depression was diagnosed if there was only one episode of depression at time of enrollment, while RD was diagnosed if there were at least two depressive episodes with at least two month interval in between, with no history of hypomanic or manic episode according to DSM IV criteria. The investigators again performed evaluation of depressive and anxious symptomatology. Cognitive testing was administered the next day by a trained psychologist and pharmacotherapy was started then after.

Measures

Sociodemographic Form: It was prepared by the investigators. Age, sex, education, marital status, working status, monthly income, social security type, age of depression onset, number of depressive episodes, duration of the current depressive episode, depression subtype, history of psychiatric drug treatment, electroconvulsive treatment, hospitalization, suicide, alcohol and drug abuse, family history for psychiatric disorders were evaluated.

Structured Clinical Interview for Axis I Disorders (SCID-I): It is a clinician administered structured interview to diagnose Axis I disorders according to DSM IV criteria. Turkish validation was made by Corapcioglu et al. (32).

Beck Depression Inventory (BDI): It is a self-rating instrument developed by Beck (33). It is composed of 21 items scored from 0-3. Cut-off value for depression is 17 (34). Turkish validation was made by Hisli (35).

Hamilton Depression Scale (HAM-D): It is a 17-item clinician rated instrument developed by Hamilton (36). Scores of 0-7 means no depression, 8-15 means mild, 16-27 means moderate, 28 and over means severe depression (37). Turkish validation was made by Akdemir et al. (38).

Hamilton Anxiety Scale (HAM-A): It is a 14-item clinician rated scale developed by Hamilton (39). Scores of 0-4 means no anxiety, 4-17 means mild, 18-24 means moderate and above 25 means severe anxiety (40). Turkish validation was made by Yazıcı et al. (41).

Global Assessment of Functionality Scores (GAF): It is a clinician rated instrument to assess functionality and scored between 0-100 (42).

Verbal Memory Test (VMT): This is a Turkish test to evaluate verbal memory. It was developed and tested in reliability and validity by Oktem (43). The test was composed of A, B, C lists which were composed of 15 test words on the front page and a recognition list composed of 45 words (15 target words and 30 similar words) on the back page. On the front page, under the 15 target words were 10 horizontal lines for acquisition trials. In brief, subjects were asked to recall as many words as possible in any order on an initial oral 15-word list (list A). This procedure was repeated 10 times consecutively (trials 1-10 or acquisition trials), with the score for each trial being the number of words correctly recollected. Immediate recall was usually measured based on the number of words recollected on the first trial (trial 1). Total learning score was the sum of words recalled in the ten free-recall trials and delayed recall was the number of the words recalled following a 30-40 minute time interval (43).

Stroop Test: It was first developed by John Ridley Stroop and then various versions were developed (44). In this study, a version developed by the Neuropsychiatry Laboratory of Istanbul University Faculty of Medicine was used. Norm study of this test was made by Tumac (45). Attention, processing (mental) speed and inhibition of irrelevant stimuli were assessed by this test. Three cards were used in Stroop paradigm. The first card (Color) consisted of colored dots (green, yellow, red, blue) in random order and the subject was instructed to name the color of the dots as fast as possible. On the second card (Word) words, such as green, blue, yellow and red were written in black ink. The subject was asked to read the words as fast as possible. The third card (Color-Word) consisted of words of color, all written in incongruent colors, such as the word ''GREEN'' being written in "RED" The subject was asked to name the color of each word (RED), ignoring the word information (GREEN), as fast as possible. The data were scored as naming time in seconds, number of errors and number of self corrected errors. Reading the word is an automated behavior, so it takes time to discard the irrelevant name in favor of the color. This time difference between part 3 and part 2 constitutes the "interference time". Increase in this interference time indicates a deficiency in inhibition of irrelevant stimuli.

Benton Facial Recognition Test (BFRT): It was developed by Arthur Benton (1909-2006) to evaluate prosopagnosia (46). It assesses visual perception, visual memory, visuo-constructive abilities, as well as perception of spatial relations and memory for newly learned material. Memory for spatial events are carried out automatically, it doesn't require sustained effort. This test was composed of 22 pages of black-and-white photographs of adult faces depicted in full frontal orientation (but without shoulders or other identifying cues). Shown beneath each target face were six other

black-and-white photographs of choice faces, which had been taken under full or partial light and in full frontal or three-quarter profile orientation. From the six items, only one choice face matched the target. The respondent was asked to identify which choice face was identical to the target face. The total number of correct responses on this matching-to-sample test of facial discrimination was the primary outcome for this study. Turkish standardization in adults was made by Keskinkilic (47).

Boston Naming Test (BNT): It is an 85-item test developed by Kaplan et al. (48) to evaluate language functions, specifically naming ability. In this study, a shortened version of this test, developed by Neuropsychology Laboratory of Istanbul University, Faculty of Medicine was used. During the test participants were asked to name 31 items shown in the pictures. A semantic cue about the identity of the object was given if the item was misperceived. A phonemic cue (the first letter of the object) was given if the participant recognized the object but stated that he/she could not know the name. The semantic and phonemic cues were recorded at the end of the test.

Verbal Fluency Tests (VFT): Verbal fluency is evaluated by counting names (45). Total number of items counted in 60 seconds indicates the ability to continue a behavior and the number of repeats indicates perseveration (49). There are 3 subtests.

- Animal Name Counting: The participant was asked to generate as many words as possible from a certain semantic category like "animals" in 60 seconds. Animal classes like domestic animals, wild animals, birds, and insects were given. If the same animal name was repeated in different animal categories it was accepted as a perseveration. Total number of the animal names and perseverations were recorded (45). Norm study in different age and education groups was made by Tumac (45).

- Controlled Oral Word Association Test (COWAT): It evaluates phonemic fluency (45). Participants were asked to generate as many words as possible beginning with the letters K, A, and S in 60 seconds. Proper names and variations of the same word with different endings (e.g., eat, eating) were not counted. Total number of words generated forms each three letters and perseverations were recorded. Turkish standardization of this test was made by Tumac (45).

- Category Fluency Test: It evaluates semantic fluency. Participants were asked to generate examples from two semantic categories: Human names and fruit names, one after other. Total numbers of semantic couples generated in 60 seconds were recorded. If the participant could not follow the semantic category order it was recorded as category perseveration. Repeating any name was recorded as perseveration (45).

Statistical Analysis

SPSS 13.0 was used for statistical analysis. Categorical variables were compared with chi-square test. Continuous variables were compared with t-test if the distribution was normal and with Mann-Whitney U test if the distribution was not normal. Pearson test was used for correlation analysis. Statistical significance was accepted at a p value of 0.05. Education that was a confounding factor was controlled with ANCOVA if applicable. Significant differences in cognitive tests found by t-tests were taken as dependent variables and linear regression analysis was applied to find out which independent sociodemographic or clinical variables predicted these differences in cognitive tests.

RESULTS

There was no sex difference between the two groups but RD group was significantly older and more educated then FE group (Table 1). Age of onset was significantly lower in RD patients (25.14±7.78) compared to FE patients (29.30±8.33, p=0.034). There was no difference in terms of the duration of current depressive episode between the two groups, but total duration of depression (16.17 months) and history of psychotropic medication

Table 1: Comparison of sociodemographic variables of first epizode (FE) and recurrent depression (RD) groups

Sociodemographic variables	FE (n=33)	RD (n=37)	t	χ^2	p
Sex [Female (n (%)]	26 (78.8)	30 (81.1)		0.05	0.811
Age (Min:17, Max:57)	30.1±8.5	34.9±10.6	-2.107		0.039

Continuous variables are presented as mean±sd, categorical variables are presented as n (%), χ^2: Chi Square Test, t: Student t test

Table 2: Comparison of psychiatric history of first epizode (FE) and recurrent depression (RD) groups

Psychiatric History	FE (n= 33)	RD (n= 37)	t/z	χ^2	P
Age at onset	29.30±8.33	25.14±7.78	2.165		0.034
Number of depressive episodes	1.00	2.78±1.08	-7.688		<0.001
Duration of the current depressive episode (months)	8.02±6.59	6.18±6.88	-1.460		0.144
Duration of the total depressive period (months)	8.03±6.69	16.17±8.65	-4.134		<0.001
Previous psychiatric drug treatment n (%)	7 (%21.2)	22 (%59.4)		10.51	0.001
History of suicide n (%)	3 (%9.1)	8 (%21.6)		2.068	0.150
History of alcohol-substance abuse n (%)	1 (%3.0)	3 (%8.3)		0.887	0.346
History of smoking n (%)	11 (%33.3)	16 (%44.4)		0.892	0.345
Family history of psychiatric disorder n (%)	23 (%69.7)	24 (%64.9)		0.185	0.667
Family history of depressive disorder n (%)	16 (%69.6)	20 (%83.3)		1.242	0.265
Family history of suicide n (%)	11 (%33.3)	4 (%10.8)		5.255	0.022
Family history of alcohol-substance abuse n (%) (%)	13 (%39.4)	15 (%40.5)		0.010	0.922
Suicidal feature of current episode n (%)	4 (%12.1)	6 (%16.2)		0.239	0.625
Atypical feature of current episode n (%)	28 (%84.8)	31 (%83.8)		0.015	0.903
Melancoholic feature of current episode n (%)	3 (%9.1)	3 (%8.1)		0.021	0.883

Continuous variables are presented as mean±sd, categorical variables are presented as %), χ^2: Chi Square Test, t: Student t test, z: Mann Whitney U test

Table 3: Comparison of psychiatric questionnaires of first epizode (FE) and recurrent depression (RD) groups

Psychiatric questionnaire scores	FE (n= 33)	RD (n= 37)	t/z	P
BDI	29.39±8.61	27.89±7.19	0.790	0.432
HAM-D Cognitive	13.12±2.36	11.97±2.50	1.971	0.053
HAM-D Vegetative	12.60±3.34	12.38±3.39	0.358	0.722
HAM-D Total	25.70±4.72	24.35±4.90	1.247	0.217
Depression severity				
HAM-D ≥28 (%)	12 (36.3)	8 (21.6)	1.857	0.173
HAM-A Psychic	8.12±2.03	8.53±3.11	-0.648	0.519
HAM-A Somatic	10.18±3.05	11.81±4.18	-4.169	<0.001
HAM-A Total	18.30±4.68	20.33±6.93	-1.413	0.162
GAF	55.88±7.31	56.46±9.22	-0.290	0.773

Continuous variables are presented as mean±sd, categorical variables are presented as n (%), BDI: Beck Depression Inventory,
HAM-D: Hamilton depression Scale, HAM-A: Hamilton Anxiety Scale, GAF: Global Assessment of Functionality Scale, t: Student t test, z: Mann Whitney U test

(59.4%) were significantly higher in RD group (p<0.001). Most of the patients used selective serotonin reuptake inhibitors or serotonin-noradrenalin reuptake inhibitors and none of them used a mood stabilizer before. Again, none of them were hospitalized or received electroconvulsive treatment. Both of the groups were also similar in terms of sucide and alcohol-substance abuse. Family history was similar as well with the exception of suicide history, where FE patients' family members had higher ratios of suicide attempt compared to RD group (33.3% vs 10.8%, p=0.022). The suicidal, atypical and melancoholic features of the current depressive episode did not differ between the two groups (Table 2).

There were no differences between the two groups in terms of depression and anxiety severity and

Table 4: Comparison of neurocognitive test scores between the first epizode (FE) and recurrent depression (RD) groups

Neurocognitive test scores	FE (n= 33)	RD (n= 37)	t/z	p
Verbal fluency- Fruit name score	8.77±2.50	9.38±1.97	-1.133	0.261
Verbal fluency – Fruit name- Category perseveration	0.42±0.90	0.24±0.68	-1.103	0.270
Verbal fluency –Fruit name perseveration	0.30±0.68	0.38±0.68	-0.589	0.556
Verbal fluency – Animal name score	21.79±4.97	22.59±4.89	-0.684	0.496
Verbal fluency – Animal name perseveration	0.58±0.75	0.73±1.19	-0.160	0.873
Verbal fluency - KAS total score	34.03±13.58	41.49±14.99	-2.171	0.033*
Verbal fluency - KAS total perseveration	0.88±1.24	0.70±1.02	-0.493	0.622
BNT Spontaneously named items	26.24±2.94	28.49±2.33	-3.560	<0.001
BNT Total named items	29.64±1.34	30.27±1.07	-2.142	0.032
VMT Immediate recall (IR)	6.39±2.14	7.00±1.80	-1.290	0.201
VMT Total learning score (TL)	124.79±14.83	129.57±9.78	-1.608	0.112
VMT Delayed recall (DR)	12.61±1.94	12.73±1.69	-0.285	0.776
Stroop- Color reading time	48.70±16.30	45.10±13.10	1.028	0.308
Stroop- Word reading time	35.91±11.8	33.65±8.28	0.973	0.334
Stroop- Color/word reading time	82.91±27.82	78.97±19.45	0.692	0.491
Stroop- Interference time	47.06±24.91	45.24±16.15	0.366	0.716
Stroop- Total number of mistakes	0.82±1.57	0.51±1.45	-1.381	0.167
BFRT- Total score	47.30±3.64	46.57±3.58	0.836	0.406

Continuous variables are presented as mean±sd, categorical variables are presented as n (%), *Difference for the KAS score disappeared when education was controlled by ANCOVA test (p=0.44). BNT: Boston Naming Test, VMT: Verbal Memory Test, BFRT: Benton Facial Recognition Test, t: Student t test, z: Mann Whitney U test

Table 5: Comparison of neurocognitive test scores between mild and severely depressed patients

Neurocognitive test scores	HAM-D<28 (n=50)	HAM-D≥28 (n=20)	t	p
BNT Spontaneously named items	28.00±2.45	26.00±3.31	2.782	0.007
VMT Immediate recall (IR)	7.06±2.00	5.85±1.63	2.398	0.019

Continuous variables are presented as mean±sd, BNT: Boston Naming Test, VMT: Verbal Memory Test, t: Student t test

functionality except for significantly increased somatic anxiety scores in the RD group (Table 3).

RD group's total KAS score and the number of total and spontaneously named items were significantly higher than the FE group, but when education was controlled by ANCOVA test, the difference for KAS score disappeared (p=0.44). RD and FE groups did not differ in terms of other cognitive tests as well (Table 4). When the RD group was divided into two subgroups according to the number of previous depressive episodes (<3 vs ≥3 episodes), no difference was found between these two sub groups in terms of any cognitive test. But when all sample was divided into two groups according to depression severity (HAMD<28 vs HAMD≥28 points), severely depressed group named significantly lesser objects in BNT (26.00±3.31 vs 28.00±2.45) (p=0.007) and their immediate recall scores were significantly lower (5.85±1.63 vs 7.06±2.00, p=0.019) in VMT when compared to mildly depressed group (Table 5).

Correlation analysis showed a positive correlation between HAM-D score and Stroop Color-Word reading time (r=0.236, p=0.005) and a negative correlation between HAMD-D score and Total Learning Score in VMT (r=-0.278, p=0.02). Animal perseveration scores were positively correlated with total duration of the depressive episode (r=0.286, p=0.026).

The significant difference in total KAS score between the RD and FE groups was analyzed further by linear regression analysis to find out its potential predictors and it was found out that total KAS score was predicted by education (p<0.001), while the significant difference in immediate recall score between the mild and severely depressed groups was predicted by both education (p<0.001), depression severity (p=0.012) and presence of a stressor (p=0.032)(Table 6).

Table 6: Linear regression analysis for the predictors of immediate recall score

Dependent variable	VMT Immediate recall score		
	Beta	R^2	P
Independent variables			
Age	0.068	0.483	0.663
Sex	0.148		0.177
Total education	0.424		0.001*
Family history of depression	-0.042		0.701
Family history of suicide	0.074		0.507
Total duration of depressive episode	-0.164		0.188
Presence of a stressor factor	0.230		0.032*
Age of onset	-0.251		0.115
Depression severity	-0.289		0.012*

*Total education, depression severity and presence of a stresor factor predicted VMT immediate recall score.

DISCUSSION

There are plenty of studies about CI in major depression but a scarce number of studies in the literature compared FE and RD for cognitive function. Our results indicated that there were no differences between FE and RD patients in terms of psychomotor speed, attention, verbal fluency, verbal and visual memory and visuo-spatial functions. Somewhat similar to our study, Basso and Bornstein (27) compared relatively young 20 FE and 46 RD inpatients and reported that RD group demonstrated verbal memory deficits involving immediate recall, delayed recall and total learning relative to FE group and published norms, but no other significant difference was found across the battery examining psychomotor speed, verbal fluency, visuo-spatial functions and visual memory like our study. In a geriatric population, Rapp et al. (26) also compared late-onset 19 FE depression, 21 RD and 42 healthy controls (HC) and showed specific deficits in attention and executive function in FE patients and episodic memory deficits in RD patients, suggesting a specific frontal lobe dysfunction in FE and a temporal lobe dysfunction in RD. Fossati et al. (29) also compared 23 FE, 28 RD patients with 18 bipolar (BP) depressed patients and 88 HC on a verbal episodic memory test and FE depression patients were found to be similar to HC while RD and BP patients exhibited verbal memory deficits of free recall, cued recall and recognition. These findings suggested that number of depressive episodes had a negative influence on verbal memory performance of acutely depressed patients (29). MacQueen et al. (19) also indicated that memory performance was not predicted by indices of current mood state, but rather by past number of depressions, being a more trait-like character. But unlike these studies, Wang et al. (28) could not find any difference in verbal memory functioning between 57 FE, 42 RD patients and 46 HC, and no difference were obtained between FE and RD groups as well, similar to our study. One reason for this could be the similarity of depression severity in both FE and RD groups, since they were both moderately depressed individuals similar to our study. Because verbal memory impairments may only be present in more severe depression, and among hospitalized patients (28) we may not have been able to find a difference between these two groups.

So, to test if CI was more related to depression severity, we subdivided all patients in our study into two groups according to depression severity. Results showed that more severely depressed group had significantly lower immediate recall scores on VMT and significantly lower number of spontaneously named items on BNT. Correlation analysis showed that immediate recall and total learning scores of VMT were negatively associated with HAMD score. Linear regression analysis also revealed that immediate recall score was predicted by depression severity. As a result, although we could not find a difference between FE and RD groups in terms of VMT, we found that immediate

recall and learning were negatively affected from depression severity. These findings were in line with Douglas and Porter's (50) assumption stating that verbal learning, verbal memory, fluency and psychomotor speed were the most sensitive cognitive domains to the clinical state, exhibiting a more state-like character, unlike MacQueen et al.'s (19) trait like character assumption. Our findings were also parallel to many studies in the literature demonstrating problems with immediate recall, delayed recall, recognition and list learning in depression (11-13,17). List learning is an effortful task and effortful tasks are known to be more impaired than automated tasks in depression (14). Accordingly, we could not find a difference between FE and RD groups or between mild and severely depressed groups in terms of visuo-spatial functions and visual memory, since these are automated tasks which do not require sustained attention and effort (20,21). Our finding was also in line with the meta-analysis revealing that depression had the largest effect on immediate and delayed recall from episodic memory (12). Even in euthymic depressive patients, Preiss et al. (51) found impairments in immediate recall, delayed recall, attention and executive function compared to HC, with no significant correlation between any cognitive test and number of depressive episodes, but with small-to-medium-sized correlations between delayed recall and depressive symptomatology. Partly similar to these findings, we found impairment in immediate recall, but not in delayed recall in severely depressed patients, may be because depressed states are frequently accompanied by intrusive, irrelevant and/or pessimistic thoughts that decrease immediate recall (encoding) or, may be because motivational decrease and apathy seen in severely depressed patients may cause indifference to the task impairing short-term attention and immediate recall (encoding), while performance on long term memory tasks (delayed recall) may remain unimpaired (43).

Thus, poorer performance of depressive patients on memory tests may either reflect basic memory impairments or a general inability to allocate cognitive effort to more demanding tasks, since memory problems in depression may be secondary to attentional dysfunctions, and reflect inability to concentrate (52,53). If we accept this impairment of encoding as a primary deficit in memory, this may indicate a medial temporal dysfunction. But if we accept this impairment of encoding as secondary to inattentiveness, then this may indicate a prefrontal dysfunction, since prefrontal cortex is mainly responsible from selective/sustained attention and higher executive functions like inhibition of irrelevant stimuli (54).

But when we compared FE and RD groups in terms of attention with Stroop test, we could not find a difference between these two groups, whilst Stroop word reading time was negatively correlated with HAM-D scores, indicating that mental speed was negatively affected from depression severity. This was in line with the meta-analysis showing intermediate effect sizes of depression on mental speed and sustained attention (8). Decrease in mental speed is an indicator of psychomotor retardation seen frequently in the majority of depressive patients (53). Habermann et al. (30) also could not find a difference between euthymic 20 FE and 20 RD patients with regard to attentional tasks but they found that euthymic depressive patients were more impaired in all tests related to attentional and executive functions when compared to 20 HC, so they suggested that attentional and executive dysfunction had a trait-like character. Since we did not evaluate our patients in the euthymic phase, we can not conclude that. But we can say that the decrease in immediate recall scores in severely depressed group may be due to the decreasing mental speed in severe depression.

As for executive functions, we used verbal fluency to test it. Karabekiroglu et al. (31) used verbal fluency and Wisconsin Card Sorting tests to evaluate executive functions and they found that both FE and RD patients showed executive dysfunction compared to HC, and that RD patients had significantly higher perseveration scores and lower word production compared to both FE patients and HC. Unlike Karabekiroglu et al. (31), we could not find a difference in terms of verbal fluency between FE and RD groups, but we found that animal name perseveration scores were positively correlated with total duration of depressive episode. Studies have shown that increase in perseveration scores may indicate a state of cognitive rigidity that may lead to

relapse and recurrence of depression and residual depressive symptoms (23). So, increase in total duration of depressive episode may cause a deficiency in cognitive flexibility and may prevent patients from coping with life events, thus perpetuating depressive mood by prolonging stress exposure (23). Thus the effect of a long lasting depressive episode may reflect sensitization to the cognitive impact of depression associated with increasing prefrontal dysfunction.

Again, as part of the executive functions, we used Stroop test interference score to evaluate cognitive inhibition but we could not find a difference in terms of Stroop interference time between FE and RD groups and between mild and severe depression groups. Impairment in cognitive inhibition was shown to be significantly associated with the level of depression (23). But Habermann et al. (30) found that cognitive inhibition was more impaired in RD patients compared to FE patients. Ardal-Hammar et al. (55) also demonstrated cognitive inhibition impairment in both acute phase and at 10 year follow-up in RD group. The authors concluded that this impairment was long lasting when present in the acute phase of RD, and that impaired cognitive inhibition might be an irreversible vulnerability marker for RD. Although we have not followed up our patients for that long for now, cross-sectionally we could not find a difference in cognitive inhibition in the acute phase between FE and RD groups. The reason of this may be our small sample size.

Language functions, like naming, tend to be preserved in depression. We evaluated language function with Boston Naming test in our study but we could not find a difference in naming ability between FE and RD groups, while Boston naming scores were significantly lower in severely depressed group compared to mildly depressed ones. Usually, subtle deficits in language functioning and poor performance on BNT can be detected in the earliest stages of Alzheimer's disease (56). Thus, the impairment in naming ability that we detected in severely depressed group might be a vulnerability marker for Alzheimer's disease, because lately it has been documented that severe depression might precede dementia (57).

As a result, although we have not made a neuro-imaging study, in the light of fMRI studies, our results may suggest a prefrontal dysfunction in severe and long lasting depression. fMRI studies reveal that encoding and simple attention is mostly associated with left ventrolateral frontal activity and learning is more associated with left dorsolateral prefrontal activity while retrieval is mostly a right frontal function (58). In our study, we found that encoding was impaired while retrieval was preserved, suggesting a left prefrontal dysfunction. Again, fMRI studies report left frontal activation during verbal fluency tests (59,60). So, our finding of increased perseveration with longer lasting depression again suggests a left frontal dysfunction. Naming is also found to be associated with bilateral presilvian and left midfrontal activity (61) and our finding of decreased naming ability with severer depression again indicate a left prefrontal dysfunction. Stroop test performance was found to be mostly related with left lateral prefrontal cortex, left parietal/parieto-occipital cortex, and left anterior cingulate cortex activity (62). Although we could not find a difference in terms of interference time, positive correlation of Stroop color word reading time with depression severity also indicate a left prefrontal dysfunction. So, to sum up, all these findings of impaired encoding, simple attention, mental speed, naming and cognitive flexibility may suggest especially a left prefrontal dysfunction in severe and long lasting depression.

The main limitations of this study were its cross-sectional design, non-matching of the groups according to age and education and absence of a healthy control group. As a result, our ability to draw conclusions about depression related impairment in two groups is somewhat limited. Also, the cross-sectional design of this study does not permit conclusions about the state-trait hypothesis of CI in major depression. So, future research should investigate the course of cognitive deficits by means of longitudinal design in contrast to this cross-sectional study. The other limitation was that the majority of the participants were female, so the results can not be generalized to male patients. Again, majority of the patients had a typical feature which might have affected cognition. Lastly, not all of the

patients were drug-naive in FE group, 7 of them had used antidepressant medication in their index episode for a short time before enrollment to the study but they were all drug-free at time of enrollment. Again, the mean depressive episode duration was longer than 6 months in FE group and 2 of them had a suicide attempt in the index episode and 3 of them had a history of anxiety disorder in the past though none had a comorbid axis I disorder at time of enrollment. All these factors in FE group might have affected cognitive function. So, it would be best to homogenize the sample as much as possible but despite these shortcomings, strengths of this study was its well-controlled patient group composed of unmedicated (drug naïve and drug free), relatively young patients with no additional comorbid Axis I disorders or neurologic/somatic disorders likely to affect cognition or vitamin B12/folate deficiency and hypothyroidism.

Although we could not find a difference in cognitive function between FE and RD patients, a decrease in simple attention, encoding, naming and mental speed with increased severity of depression and an increase in perseveration scores with increased duration of depression in our study suggest a left prefrontal dysfunction in major depression. This study partially clarifies CI in major depression by identifying a subset of outpatients with severe depression, but state-trait hypothesis of cognitive function in major depression should be further clarified by prospective studies using neuro-imaging techniques.

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