Comparing cognitive dysfunction in euthymic patients with first episode and recurrent episodes of major depression

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Background
Euthymic patients with major depressive disorder demonstrate cognitive deficits in executive function, attention, and memory, but to date, limited amount of work has compared patients with first-episode depression (FED) with patients with recurrent episodes of depression (RED), and no studies have been conducted in the Egyptian population.
Aim
The aim was to compare cognitive functions between euthymic patients after FED and patients with RED.
Participants and methods
A total of 60 euthymic participants (30 with FED and 30 with RED) were administered a battery of cognitive tasks, including the Wechsler Adult Intelligence Scale, Wechsler Memory Scale, and Wisconsin Card Sorting Test.
Results
Patients with RED performed significantly poorly than patients with FED on tasks measuring abstract thinking, verbal memory, working memory, verbal immediate recall, and executive functions (which included tasks for conceptualization, cognitive flexibility, shifting, planning, and sustained attention).
Conclusion
There are significant differences in performance on cognitive functions between euthymic patients with FED and RED across memory tasks and executive functions but with relative sparing of tasks of general intelligence. Poorer cognitive functions may possibly be associated with recurrent episodes.

Keywords:
euthymic, executive functioning, first episode depression, intelligence, major depressive disorder, memory, recurrent episodes of depression

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Introduction

Major depressive disorder (MDD) is a common disorder that affects more than 300 million people worldwide and is ranked by the WHO as the single largest cause of global disability (WHO, 2017). It has a high rate of chronicity and recurrence, leading to decreased productivity and absenteeism, resulting in significant economic burden (Gilmour and Patten, 2007).

Only a subset of individuals with MDD (30–40%) reach symptomatic remission after adequate treatment, and many patients do not reach premorbid levels of functioning (Bortolato *et al.*, 2016). Cognitive dysfunction may be the primary mediator of functional impairment in MDD and refers to deficits in attention, verbal and non-verbal learning, short-term and working memory, visual and auditory processing, problem solving, processing speed, and motor functioning (McIntyre *et al.*, 2013). Cognitive deficits were found to be present in both first and recurrent episodes of MDD (Lee *et al.*, 2012), with cognitive symptoms present during 85–94% of the length of depressive episodes and 39–44% of the length of periods of remission (Conradi *et al.*, 2011). MDD was found to have a clinically significant effect on psychomotor speed, declarative memory, working memory, executive functions, and attention (Papakostas, 2014), and cognitive deficits have been shown to persist even beyond the acute stages of illness in MDD (Bora *et al.*, 2013). Meta-analyses in first-episode depression (FED) have shown significant cognitive deficits for psychomotor speed, attention, visual learning, memory, and all aspects of executive functioning (Lee *et al.*, 2012), with remission associated with normalization of function in processing speed, learning and memory,

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autobiographical memory, shifting, and intelligence quotation (IQ) but persistent impairment in inhibition and verbal fluency (Ahern and Semkovska, 2017). With recurrent episodes of depression (RED), there is a decrease in cognitive function, and interepisode cognitive function is related to the number of previous episodes (Conradi *et al.*, 2011). Dotson *et al.* (2010) demonstrated that depression in general, and particularly recurrent depression, was a risk factor for developing later dementia. It has therefore been suggested that cognitive impairments are one of the main reasons for the lag between syndromal and functional recovery in patients with MDD (McIntyre *et al.*, 2013), which may lead to the loss of productivity and an increased economic burden of the illness (Gilmour and Patten, 2007). Hence, there has been increasing recognition that symptomatic remission is an insufficient goal of treatment for MDD and that return to premorbid psychosocial functioning should be the target (Zimmerman *et al.*, 2004).

Egypt is the most populated Arab country with a population of almost 95 million people (~1% of the world's population and ~20% of all Arabs) (Population of The World, 2019). MDD has been shown to have a high prevalence in the Middle East (Ferrari *et al.*, 2013), and in Egypt, it has a prevalence of 2.7% (Ghanem *et al.*, 2009). Few studies in Egypt have looked at cognitive dysfunctions in MDD. Abdel Aal *et al.* (2018) demonstrated deficits in working memory, short-term memory, and information processing, and Sarhan *et al.* (2015) demonstrated deficits on all domains of the Wechsler Adult Intelligence Scale (WAIS) and Wechsler Memory Scale. Both studies were conducted in Egyptian patients with symptomatic MDD. To the best of our knowledge, no previous studies have specifically compared cognitive dysfunction in euthymic patients with first episode compared with RED. Therefore, we aimed to investigate the patterns of cognitive dysfunction in euthymic patients with MDD and investigate differences between patients experiencing FED compared with those with RED. We hypothesized that there is greater cognitive impairment in euthymic patients with RED compared with patients with a first episode of depression (FED).

Participants and methods

Operational definition of euthymia

We used a cross-sectional observational comparative study where we defined euthymia as patients who fulfilled the Diagnostic and Statistical Manual of mental disorders 4th edition (DSM IV) criteria for major depression and obtained a score less than 7 on Hamilton Rating Scale for Depression and reported being euthymic for at least 6 months.

Site of the study

The study was carried out at the outpatient department of the Institute of Psychiatry, Ain Shams University Hospitals, Cairo, Egypt. We recruited potential participants who attended for follow-up and medication renewal. They were then screened to determine their eligibility for participation in the study.

Study population

We recruited 60 Egyptian male and female participants (30 with FED and 30 with RED), aged 18–50 years, who met the DSM-IV criteria for major depression and the operational definition for euthymia. We excluded participants who had a co-morbid axis I disorder, significant uncontrolled medical or neurological diseases, learning disabilities, those who received electroconvulsive therapy in the previous 6 months, and participants who could not read and write. We also excluded patients with psychotic features in previous episodes, as they may confer increased risk to develop cognitive dysfunction (Bortolato *et al.*, 2015). The sample size of 30 participants for each study group was calculated using the Epi-Info program Version 7.1.5 (2015).

Ethical considerations

The study was conducted according to the Helsinki Declaration of 1975, and it was approved by the Research and Ethics Committee of Ain Shams University. Participants signed an informed consent form detailing the research process, the confidentiality, and voluntariness of the participation.

Tools

The Structured Clinical Interview for DSM-IV (First et al., 1996)

This was used to confirm psychiatric diagnosis of major depression according to DSM-IV criteria. We used the translated Arabic version (El Missiry *et al.*, 2003).

The Hamilton Rating Scale for Depression (Hamilton, 1960)

This was used to measure the severity of depressive symptoms, with a score of 0–7, indicating euthymia.

The Wechsler Adult Intelligence Scale (Wechsler, 1981)

This was used as an individually administered test of general intelligence reflecting both verbal and performance abilities and as a broad assessment of

cognitive functions. It consists of 11 separate subtests, which are broken down into the verbal scale (six subtests) and the performance scale (five subtests). Each patient received a full-scale IQ score, a verbal IQ score, a performance IQ score, and scaled scores on each of the subtests. We used the Arabic standardized version (Melika, 1996).

The Wechsler Memory Scale (Wechsler, 1987)

This was used to assess memory functions and includes information and orientation questions, eight short-term memory tasks, and four delayed recall trials. Summary scores include general memory, verbal memory, visual memory, attention/concentration, and delayed recall. These indices reflect disturbances in memory function and also show certain disease-associated patterns of memory impairment.

Wisconsin Card Sorting Test, computerized version (Heaton and Saff, 2003)

This was used to assess abstraction ability and the ability to shift cognitive strategies in response to changing environmental contingencies and as a measure of frontal lobe executive function; it also provides information on several aspects of problem-solving behavior beyond such basic indices.

Procedure

Recruited patients who fulfilled the criteria of the study and who gave informed consent were enrolled. They were further assessed by two senior psychiatrists to confirm the diagnosis before applying the neuropsychological battery, which was performed by an experienced clinical psychologist.

Statistical analyses

Data were recorded and analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows, Version 18.0 (2011) (IBM, Armonk, New York, USA). The results were tabulated, grouped, and statistically analyzed using the Student's *t*-test to assess the statistical significance between the two study group means (quantitative data). The χ^2-test was used to test the significance of the differences between the frequencies of different observations (qualitative data). A *P* value of less than 0.05 was used to indicate statistical significance.

Results

Socio-demographic and clinical characteristics

A total of 60 eligible participants with major depressive disorder (MDD) participated in the study, of whom 48 (80%) were males and 12 (20%) were females. The first patient group included 30 participants (24 males and six females) in the euthymic phase of MDD after FED. The second patient group included 30 participants (24 males and six females) in the euthymic phase of MDD after RED.

The FED group was significantly younger than RED group (P=0.001). Years of education were comparable across the two groups (P=0.4), and none of the patients in FED group was married compared with 53.33% of the patients in RED group (P<0.001). There were no significant differences regarding the mean age of the first episode in both groups, whereas RED group had significantly longer duration of the last episode (5.733 months) compared with only 4.733 months in the FED group (P=0.003). Overall, 80% of the FED group did not report a history of childhood abuse compared with 46.67% of the RED group (P=0.007), whereas 93.3% of the FED group reported a family history of depression compared with the 73.33% of the RED group (P=0.002). There were no significant differences in the medication received by the two studied groups.

Assessment of general intellectual abilities

Except on the similarities subtest (which measures abstract thinking), there was no statistically significant difference between patients with FED and those with RED on all other domains of the WAIS, which measured visual perception, visiomotor coordination, psychomotor speed, storage of mathematical process, and total verbal and performance abilities (Tables 1 and 2).

Assessment of memory functions

On the Wechsler Memory Scale, patients with RED showed significantly poorer scores on subtests measuring verbal memory (P<0.001), verbal immediate recall (P=0.006), working memory (P<0.001), and visual immediate recall (P=0.001) compared with patients with FED. Subtests measuring verbal and visual delayed recall showed no significant difference between the two groups (Table 2).

Assessment of executive functions

On the Wisconsin Card Sorting Test, patients with FED obtained significantly higher scores than patients with RED on the total correct scores, conceptual level responses, categories completed, and % conceptual level response, reflecting that they were better in conceptualization, planning, and problem solving. On the contrary, patients with RED obtained higher scores on perseveration responses, perseverative errors, and % perseverative responses, reflecting that they were worse on tasks measuring shifting and cognitive flexibility (Table 3).

Table 1 Sociodemographic data and clinical characteristics

	Groups (mean±SD) or [*n* (%)]		Tests used	*P*
	FED (*N*=30)	RED (*N*=30)		
Age (years)	30.973±8.431	38.078±8.578	*t*-test: –3.617	0.001*
Years in education	11.324±4.06	10.631±4.07	*t*-test: 0.736	0.464
Age at first MDD episode	23.000±5.645	22.733±5.711	*t*-test: 0.182	0.856
Duration of last episode (months)	4.733±1.413	5.733±1.081	*t*-test: –3.080	0.003*
Global assessment of function	91.333±2.249	88.333±5.774	*t*-test: 3.81	0.008*
Sex				
Female	6 (20.00)	6 (20.00)	χ^2: 4.448	0.108
Male	24 (80.00)	24 (80.00)		
Marital status				
Single	30 (100)	14 (46.67)	χ^2: 22.044	<0.001*
Married	0	16 (53.33)		
Occupation				
Unemployed	0	0	χ^2: 25.155	<0.001*
Employed	18 (60.00)	30 (100)		
Student	12 (40.00)	0		
Family history of depression				
No	28 (93.33)	22 (73.33)	χ^2: 9.231	0.002*
Yes	2 (6.66)	8 (26.67)		
Medications				
Not prescribed	4 (13.33)	0	χ^2: 4.333	0.115
Antidepressants	22 (73.33)	26 (86.67)		
Antidepressants +Antipsychotics	4 (13.33)	4 (13.33)		
Childhood abuse				
No	24 (80.00)	14 (46.67)	χ^2: 7.177	0.007*
Yes	6 (20.00)	16 (53.33)		

FED, first-episode depression; RED, recurrent episodes of depression. **P* statistically significant.

Table 2 Wechsler Adult Intelligence Scale and Wechsler Memory Scale: comparison between patients with first episode and recurrent episode

Wechsler Adult Intelligence Scale	FED group (*n*=30) (mean±SD)	RED group (*n*=30) (mean±SD)	*t* test FED and RED	Functions measured
Performance subscales				
Picture completion	10.733±1.964	9.633±2.312	0.134	Visual perception
Block design	10.233±2.861	8.867± 2.700	0.750	Visio motor coordination
Digit Symbol	12.867±1.042	9.933±2.912	0.637	Psychomotor speed immediate memory
Verbal subscales				
Comprehension	13.133±2.556	12.400±2.238	0.957	Social common severe
Arithmetic	9.433±4.739	8.300±3.554	0.412	Storage of mathematical process
Similarities	10.500±2.623	7.833±2.842	0.015*	Abstract thinking
Verbal IQ	99.033±16.106	97.100±12.172	0.717	Total verbal ability
Performance IQ	106.133±13.328	104.000±10.072	0.671	Total performance ability
Total IQ	103.367±14.717	101.100±11.143	0.794	Intellectual ability
Wechsler Memory Scale				
Digit Span-Forward Score	8.300±1.685	5.600±1.694	<0.001*	Verbal memory
Digit Span-Backward Score	7.600±1.133	4.933±1.461	<0.001*	Working memory
Verbal Paired Association I	18.200±3.367	15.333±2.510	0.006*	Verbal immediate recall
Verbal Paired Association II	6.400±1.221	5.800±1.495	0.189	Verbal delayed recall
Visual Paired Association I	13.533±3.598	9.800±4.715	0.001*	Visual immediate recall
Visual Paired Association II	5.767±2.192	5.267±2.083	0.612	Visual delayed recall

FED, first episode depression; IQ, intelligence quotation; RED, recurrent episodes of depression. **P* statistically significant.

Discussion

Cognitive dysfunction is among the most frequently reported residual symptoms in depression, which is an important mediator of functioning, including workplace performance, psychosocial functioning, and quality of life (Ekman *et al.*, 2013; Bortolato

Table 3 Wisconsin Card Sorting Test comparison between patients with first episode and recurrent episode

Wisconsin Card Sorting Test	FED group		RED group		*t* test	Function measured
	Mean	SD	Mean	SD	FED and RED	
Trials administered	98.433	35.979	98.800	23.131	0.998	
Total correct	78.200	10.675	65.333	6.712	<0.001*	
% error	24.600	10.108	29.067	13.075	0.181	
Preservative responses	17.667	9.393	30.433	19.915	0.004*	Capacity to learn from experience Concept formation, Executive function, Learning to learn, Mental flexibility, Planning, Problem solving, Set shifting, Sustained attention
% preservative responses	15.400	7.103	25.667	15.448	0.002*	
Preservative errors	15.733	7.887	24.333	16.174	0.006*	
% nonpreservative errors	12.600	5.130	9.400	3.318	0.012*	
conceptual level responses	73.200	8.822	57.967	5.702	<0.001*	
% conceptual level responses	71.600	14.393	60.733	20.517	0.014*	
Categories completed	5.000	1.702	4.667	1.422	0.661	

FED, first episode depression; RED, recurrent episodes of depression. **P* statistically significant. Failure to maintain set.

et al., 2016; Woo *et al.*, 2016). Cognitive dysfunction in depression remains largely under-recognized, unmonitored, and under-treated (McAllister-Williams *et al.*, 2017; Zuckerman *et al.*, 2018). Thus, recognition and management of cognitive dysfunction remains an unmet need in the treatment of MDD and should be addressed in the therapeutic approach of depression (Albert *et al.*, 2016).

Our study aimed to assess cognitive functions among euthymic patients with MDD with FED compared with patients with RED.

Overall, our findings showed that euthymic patients with RED showed significant impairment of cognitive functions compared with patients with first episode across tests of memory and executive functions, with relative sparing on tests of general intelligence.

Mixed results have been demonstrated regarding the presence of cognitive dysfunction in euthymic patients with major depression (Wang *et al.*, 2006; Delaloye *et al.*, 2010). Hasselbalch *et al.* (2013) reported persistent deficits in cognitive functions in a large systematic review of 11 studies involving 500 patients with MDD in remission. Hammar *et al.* (2010) suggested that persistent cognitive dysfunction in euthymia is not an epiphenomena of mood symptoms but is rather a core persisting phenomenon.

Similar to our findings, Talarowska *et al.* (2015) reported significant differences in performance on cognitive tasks among patients with RED compared with patients with FED. Vanderhasselt and De Raedt (2009) suggested that deficits of cognitive function with each depressive episodes after symptom remission may be a scar of cognitive control. Other interpretations of the coexistence of cognitive deficits and depressive illness were suggested by Sarapas *et al.* (2012) who stated that it may be a trait-like relationship and as a state effect. de Diego-Adeliño *et al.* (2013) added that the worsening of cognitive performance in patients with RED may be related to the presence of structural and functional changes in the hippocampus and frontal lobes, which appear after frequent episodes.

Regarding general intellectual abilities, our study did not find significant differences in the WAIS subtests between the two studied euthymic groups except in similarities subtest, which reflected worse abstract ability in the RED group. Although general intelligence seems to be impaired in acute episodes of depression, it is not considered a primary disturbance in euthymic phase (Marazziti *et al.*, 2010), which was consistent with our results. In a meta-analysis involving 994 patients with FED, Ahern and Semkovska (2017) denoted that small to large impairments were observed in IQ functions in patients with FED compared with healthy controls, which normalized with remission of symptoms.

Memory functions

Patients with FED performed significantly better compared with patients with RED on tests of memory functions, namely, verbal memory, working memory, immediate recall, and visual immediate recall. Similar to our study, Talarowska *et al.* (2015) demonstrated that FED group performed better than RED group on auditory-verbal memory, auditory-verbal immediate and delayed memory, and the ability to learn, and that these differences were visible from as early as the second episode of a MDD.

A possible explanation for these findings may be related to the effect of major depression on memory. Maeshima *et al.* (2012) investigated patients with single and recurrent major depressive episodes and found that at the time of initial remission, scores of both logical memory and visual reproduction were significantly lower in both patient groups compared with healthy controls. At follow-up after 3 years, memory dysfunction of the single-episode group disappeared, whereas scores in the recurrent group remained significantly lower than those of the single-episode group and controls (Maeshima *et al.*, 2012). This might explain why patients with RED performed worse than patients with FED in our study.

Smith *et al.* (2013) found no association between the number of episodes in euthymic patients with MDD and deficits in cognitive performance including working and verbal memory. However, they also noted that the lack of association may be masked by the participants' level of education (Smith *et al.*, 2013). Similarly, the meta-analysis by Ahern and Semkovska (2017) showed that compared with healthy controls, remission in patients with FED was associated with a normalization of function in learning and memory (especially autobiographical memory) but that lower FED age was associated with more impairment in word-list delayed memory (Ahern and Semkovska, 2017).

In the current study, patients with RED obtained significantly lower scores on tasks measuring verbal immediate recall, visual immediate recall, abstract thinking, and working memory. Previous studies demonstrated that patients with FED performed better than patients with RED on auditory-verbal memory, auditory-verbal immediate, and delayed memory and the ability to learn, and that these differences were visible from as early as the second episode of MDD (Talarowska *et al.,* 2015). Verbal memory was an area of consistent impairment in patients with remitted MDD and one of the cognitive deficits that were the principal mediators of occupational impairment in these patients (Woo *et al.*, 2016).

Executive functions

Executive functions involve handling novel situations, planning, decision-making, error correction, abstract ability, and shifting of response to changing environmental situations (Marazziti *et al.*, 2010). In the current study, we reported more impairment of executive functions in patients with RED versus patients with FEB in terms of conceptualization, shifting, planning, cognitive flexibility, and problem solving.

Using other tools of assessment such as trail-making test and stroop test, Talarowska *et al.* (2015) found that patients with FED performed better compared with patients with RED on tests of executive functions, and those differences were already visible from the second episode of depression. The findings that patients with euthymic/remitted MDD exhibited deficits in executive functions compared with healthy controls has been demonstrated in numerous studies (Biringer *et al.*, 2005; Paelecke-Habermann *et al.*, 2005; Smith *et al.*, 2013). The meta-analysis by Bora *et al.* (2013) looked at 27 studies that included 895 participants and concluded that healthy controls significantly outperformed euthymic patients with MDD on all cognitive domains, including the Wisconsin Card Sorting Test (except for perseveration), with late-onset cases showing more pronounced deficits on some executive functions. Ahern and Semkovska (2017) found a significant difference in patients with FED compared with healthy controls on executive functions, with normalization of set-shifting with remission of symptoms. Previous studies reported marked impairment in inhibition (Ahern and Semkovska, 2017) and difficulties in cognitive flexibility, with cognitive rigidity preventing patients from coping with life events (Marazziti *et al.*, 2010).

Conclusion and clinical implications

The current study demonstrated that euthymic patients with recurrent major depression have significantly more impaired cognitive functions than those with first episode across memory and executive functions, with relative sparing of general intelligence. The cognitive control in depression may be reduced after recurrence of depressive episode, and it seems that cognitive symptoms may have a progressive nature and might leave a scar after each episode. In clinical practice, we suggest that it should be mandatory to screen for and treat cognitive dysfunctions in addition to mood symptoms to achieve functional as well as symptomatic recovery in depression.

Strengths and limitations

The novelty of this study is that, to the best of our knowledge, it is the first study in Egypt to investigate cognitive dysfunctions among euthymic patients with major depression after first and recurrent episodes. However, this study was limited by the number of participants and by the cross-sectional nature of the study where we could not infer any direct causal effect

between MDD and cognitive functions. It is unclear from our study if cognitive symptoms preceded depression (trait marker) or developed and progressed after recurrent episodes (state marker). A longitudinal study following up participants over the course of their illness should help address these limitations. Another limitation was is that we did not compare patients with healthy controls. Further studies that address differences in cognitive functions between healthy participants and euthymic patients with depression and that explore the relation of cognitive functions to clinical course, functioning, and outcome can help in identification and prediction of relapse, which ultimately can help inform us about unmet needs in the management of patients with depression.

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Conflicts of interest

There are no conflicts of interest.

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