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Neuropsychological Performance in Remitted Major Depressive Disorder Patients: A Case-Control Study

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Abstract

Background: Neurocognitive deficits in Major Depressive Disorder (MDD) might hamper social readjustment and impede full recovery. Their reversibilityafter remission remains controversial.Diverge results are mainly explained by methodological biases.The aim of the present study was to (1) examine the cognitive performance in a well-defined homogenous group of MDD patients in remitted state and to (2) determine clinical features associated with cognitive deficits.

Methods : We recruited thirty outpatients meeting the DSM-IV criteria of former MDD, 18 to 60 years-old, free from axis-I comorbid disorders and regularly consulting in the psychiatry department of Farhat Hached University Hospital, Sousse, Tunisia. Patients were in state of clinical remission for at least three months with HDRS score below 7 at the time of assessment. They were compared to thirty control subjects matched for age, sex, level of instruction and IQ. Participants were assessed for attention and processing-speed, working memory, verbal fluency, non-verbal memoryand executive functions.

Results: Remitted MDD patients displayed cognitive dysfunction in attention and processing-speed, non-verbal memory and executive functions. Patients with a single depressive episode showed a general intact cognitive performance. A positive correlation was found between number of previous depressive episodes and longer duration of the illness respectively with attention and processing-speed, mental flexibility and non-verbal memory performance.

Conclusions: Our results further reinforce the hypothesis of long-lasting cognitive impairment in remitted MDD patients.Findings suggest that cognitive dysfunction cannot be considered as trait marker but appears to be sensitive to depressive recurrence.

Keywords: Major depressive disorder; Cognitive functioning; Memory; Executive functions; Attention; Impairment; Long-lasting

Introduction

Major depressive disorder (MDD) is a common and disabling condition often characterized by a recurrent and chronic course. Although definitions give primacy to depressed mood,cognitive dysfunction is considered as a core symptom of the disease.

In the acute phase, cognitive impairment in the areas of attention, processing speed, memory and executive functions has been widely reported in the litterature [1,2]. In their recent review, Mc Intyre et al. pointed out the mediating role of cognitive deficits in psychosocial impairment and notably workforce performance in MDD patients [3]. Long-lasting deficits can hamper social readjustment and impede full recovery. Thus focusing onneurocognitive profile of MDD patients after recovery has great clinical implications.

Data on the evolutionary course remains controversial. A common empirical understanding has been that cognitive impairment restores as depression heals.This assumption has been questioned the last decade and a growing body of evidence implies that impairment observed during episodes of illness is long lasting [4,5]and persists in remission in various cognitive domains, such as attention [6,7] executive functioning [7-9] and memory [10-12]. Some domains such as sustained attention were even considered to be trait-markers of the disease [7]. Several studies failed to replicate these results [13-15] and some authors considered cognitive deficits as state-markers phenomena.

Diverging results can be explained mainly by methodological biases. In addition to the relative lack of longitudinal studies, the heterogeneity of clinical samples might be pointed out as potential factor responsible for controversial results. In fact, numerous studies included late-onset depression patients and earlier-onset ones [9,16]. Some authors considered together patients remitted from MDD and from other affective disorders such as bipolar disorder, schizoaffective disorder and dysthymia [17]. Almost all did not investigate comorbid psychiatric conditions especially anxiety disorders wich can affect cognitive functions [18].

Contradictory results could also be explained by the lack of consensus to define MDD and to state full-remission.Some authors did not consider manual's diagnostic criteria to establish the MDD diagnosis. To state remission, some investigators used self-assessment scales. Even when performing psychometric evaluation, there was no consensus concerning cut-off scores to define remission. Number of studies examined together patients partly and fully remitted. In several studies, temporal duration of euthymic mood has not been specified and some authors examined cognitive functions in patients at discharge without specifying duration of remission.

The aim of the present study was to (1) examine the cognitive performance in a well-defined homogenous group of MDD patients in

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a remitted state and to (2) determine clinical features associated with cognitive deficits.

Methods

Participants

For the purpose of the study, we recruited thirty outpatientsmeeting the DSM-IV criteria of former MDD, free from any comorbid axis-I psychiatric disorder,between 18 and 60 years-old and regularly consulting in the psychiatry department of Farhat Hached university hospital, Sousse, Tunisia.

The MDD diagnosis was performed by the attending physician and confirmed using the Structured Clinical Interview for DSM-IV Axis-I Disorders, MINI-PLUS [19], adapted and validated for Tunisian Arabic dialect.

Patients had either suffered a single episode (n=13) or recurrent depressive episodes (n=17).At the time of testing, all patients were in a state of clinical remission for at least three months and the Hamilton-Depression-Rating-Scale score was below 8 based on Frank's remission criteria [20].

Patients were compared to thirtycontrol subjects matched for age, sex, level of instruction and IQ level, free from any psychiatric disorders as shown by the MINI-PLUS interview.

Subjects with history of substance abuse or dependance, neurological disorder, dementia, head trauma or electroconvulsive therapy within the last 12 months were excluded. Premorbid intelligence was measured by the Standard Progressive Matrices (PM-38) [21] and subjects with QI<70 were ruled out.

The study protocol wereapproved by the Institutional Review Hospital Board Committee. All participants gave informed consent after the nature of the procedure was fully explained.

Neuropsychological assessment

Since there is no specific battery assessing neurocognitive functions in patients with mood diorders, we chose to explore major cognitive domains expected to be altered in depression [4] using neuropsychological tests wich showed relevance in previous studies and wich are validated in our socio-cultural context. Assessment was performed by the same trained administrator and lasted approximately two hours.Tests were administered in the same sequence for all participants.

- The Trail Making Test (TMT) consists of two subtests [22,23]. The TMT-part A (TMT-A) is commonly used to assess selective attention and psychomotor speed while the TMT-part B (TMT-B) is to gauge cognitive flexibility and set-shifting. The TMT-A requires connecting as fast as possible 25 encircled numbers randomly spread across a sheet of paper in an ascending sequence. The TMT-B requires connecting 25 targets by alternating between letters and numbers in the shortest possible time.Duration in seconds necessary to complete the test is scored.
- The verbal fluency test [24] requires participants to generate in 120 seconds as many words as possible respecting two conditions : category (fruits and animals) and phonemic (validated arabic characters are "ba" and "qaf"). The number of correct words generated is taken into account for assessment. Semantic fluency were used to assess verbal memory and phonemic fluency to assess executive functions.Verbal fluency was used to explore mental flexibility, ability to inhibit the production of irrelevant items and the development of effective research strategies in semantic memory.
- The Digit span forward and backward are subtests of the Wechsler scalesthat explore the working memory [25]. In the forward section, the patient repeats the numbers as read to him/herby the examiner (for short-term memory evaluation). In the backward section,the patient is instructed to reverse the numbers read to him/her (for working memory evaluation). The number of items that a person can recall is scored.
- The Rey-Osterrieth-Complex-Figure-Test (RCFT) [26] is commonly used to measure non-verbal learning and memory (RCFT-recall score) and visual-constructional ability (RCFT-copy score).Because of the complexity of the figure, the RCFT has been said also to reflect executive functions such as planning abilities.

Statistical analysis

The Data analysis was performed using SPSS 19.0 software (SPSS Inc., Chicago, USA).In order to compare group frequencies and means, khi 2 test and t-tests for independent samples were applied.The Fisher exact test was used for comparison of small effectives.

Beyond the above primary analysis providing confirmatory statistical evidence, further secondary and exploratory analyses were performed. Post-hoc analysiswas performed when significant difference was found in the multivariate analysis.Correlations between cognitive performance and clinical features were evaluated with the Spearman coefficient.A p-level <0.05 was set as a value of statistical significance.

Results

Sample sizes were small since, among patients eligible for the study, some refused to participate and some others dropped out because of refusal to undertake the comprehensive assessment.

Socio-demographic and clinical characteristics

The patients were on average 42, 2 years old. The two groups were matched for age, sex, level of instruction and IQ and they did not differ in terms of marital and occupational status, family history of psychiatric disorder and burden of medical illness.

At baseline, all the patients used a pharmacologic treatment and the modal patient was taking two medications (antidepressant and anxiolytic). During the assessment 83, 3% of our patientsused a psychiatric medication and 76, 7% was under antidepressant monotherapy (TCA=7; SSRI=14; SNRI=4).

Socio-demographic and clinical characteristics of the participants are summarized in (Tables 1 and 2).

Neuropsychological assessment

The cognitive performance of both groups is presented in (Table 3).

An additional time was necessary for patients to achieve the TMT-A (64,6 ± 23,7 vs. 52,8 ± 22,0 ; p=0,05)and the TMT-B (153,8 ± 69,9 vs. 94,4 ± 49,9 ; p=0,001) subtests showing impairment in attention and processing speed and lowered cognitive flexibility.

Patients generated significantly fewer words than controls in phonemic verbal fluency test (19,1 ± 6,6 vs. 27,0 ± 8,9 ; $p<10^{-3}$) suggesting lowered flexibility and inhibition.

	Remitted MDD	Healthy controls	Statistics	
	(n=30)	(n=30)	t-test/chi²	p
Age (years)	42,2 ± 10,3	42,6 ± 10,6	-0,13	0,893
Sex (Male/female)	5/25	5/25	1,00	1,00
Instruction's level Primary/ Secondary/ University	9/13/8	9/13/8	1,00	1,00
IQ	96,3 ± 10,4	96,7 ± 11,0	-0,13	0,896
HAMD score	3,0 ± 2,1			
Age of onset (years)	34,4 ±10,8			
Single/recurrent episode (s)	13/17			

Table 1: Demographic and clinical characteristics of the sample.

	Single episode MDD	Recurrent MDD patients	Statistics	
	(n=13)	(n=17)	t-test/chi²	p
Age (years)	41,6 ± 10,0	42,7 ± 10,8	-0,29	0,769
Sex (Male/female)	2/11	3/14	0,02	0,633
Instruction's level Primary/ Secondary/ University	3/5/5	6/8/3	1,68	0,430
IQ	98,7 ± 12,9	94,4 ± 8,0	1,12	0,272
HAMD score	3,6 ± 1,8	2,5 ± 2,3	1,47	0,153
Duration of the disease (years)	1,9 ± 0,8	12,2 ± 10,3	-3,57	0,001
Number of previous episodes	1,0 ± 0,0	3,2 ± 1,6	-4,89	$< 10^{-3}$
Cumulative duration of espisodes	9,7 ± 5,0	16,9 ± 9,7	-2,41	0,022
Duration of remission (months)	7,8 ± 6,2	20,2±17,5	-2,41	0,022
Cumulative duration of pharmacotherapy (months)	13,3 ± 7,0	56,0 ± 48,5	-3,13	0,004

Table 2: Demographic and clinical characteristics of patients with single episode MDD and with recurrent MDD.

Neurocognitive domains/measures	Remitted MDD	Healthy controls	Statistics	
	n=30	n=30	t-test	P[a]
	Mean (SD)	Mean (SD)		
Attention/ processing speed				
TMT-A (seconds)	64,6(23,7)	52,8 (22,0)	2,00	0,05
Working memory				
Digit forward	5,4 (0,9)	5,8 (1,3)	-1,43	0,157
Digit backward	4,2(0,9)	4,1(1,5)	0,304	0,762
Verbal memory				
Semantic fluency (words generated)	32,2(5,4)	35,4 (6,8)	-1,95	0,056
Non-verbal memory				
RCFT-recall score	14,3 (7,5)	20,8 (6,9)	-3,50	0,001
Executive functions				
TMT-B (seconds)	153,8 (69,9)	94,4(49,9)	3,67	0,001
Phonemic fluency (words generated)	19,1 (6,6)	27,0 (8,9)	-3,89	$< 10^{-3}$
RCFT-copy score	32,0 (4,1)	34,7 (2,6)	-3,06	0,003
RCFT-copy duration (seconds)	275,8 (160,5)	175,2 (68,1)	3,15	0,003

Table 3: Performance on neurocognitive tests by remitted MDD patients and healthy control individuals.

Theyneeded significantly more time to copy the RCFT (275,8 ± 160,5 vs. 175,2 ± 68,1 ; p=0,003). They scored significantly less on the copy (32,0 ± 4,1 vs. 34,7 ± 2,6 ; p=0,003) and the delayed recall (14,3 ± 7,5 vs. 20,8 ± 6,9 ; $p<10^{-3}$) of the RCFT indicating impairment in visual–constructional function and non-verbal memory.

There were no statistical differences between the two groups in semantic fluency and digit span tests demonstrating a preserved verbal memory and working memory performance.

Associations between neurocognitive and psychiatric parameters

There was no significant correlation between performance on any cognitive test and residual depressive symptoms. No association was found between cognitive function and the age of the onset of the disease.

Focusing on the impact of depressive recurrence on cognitive function, we compared cognitive performance between the MDD patients with history of single episode of depression and those with the recurrent major depressive episodes.Data is shown in (Table 4).

Patients with a single depressive episode showed a general intact cognitive performance compared to control subjects.

Considering the recurrent MDD group, a longer duration of the illness was correlated with a lowered performance on TMT-B

Neurocognitive domains/measures	Recurrent MDD n = 17 Mean (SD)	Single episode MDD n= 13 Mean (SD)	Healthy controls n = 30 Mean (SD)	ANOVA F	ANOVA p	Post hoc[a]
Attention/ processing speed						
TMT-A (seconds)	74,2 (23,3)	52,1 (18,2)	52,8 (22,0)	6,0	0,004	**G1>G2,G3**
Working memory						
Digit forward	5,2 (0,7)	5,6 (1,1)	5,8 (1,3)	1,4	0,252	
Digit backward	4,2 (0,8)	4,3 (1,1)	4,1 (1,5)	0,05	0,944	
Verbal memory						
Semantic fluency (words generated)	31,3 (4,64)	33,4 (6,5)	35,4 (6,8)	2,32	0,107	
Non-verbal memory						
RCFT-recall score	13,0 (6,2)	16,0 (8,8)	20,8 (6,9)	6,8	0,002	**G1<G2,G3**
Executive functions						
TMT-B (seconds)	166,6 (71,4)	137,9 (67,4)	94,4 (49,9)	7,5	0,001	**G1>G2,G3**
Phonemic fluency (words generated)	17,8 (3,9)	20,7 (8,8)	27,0 (8,9)	8,1	0,001	**G1<G2,G3**
RCFT-copy score	30,5 (4,5)	33,8 (2,6)	34,7 (2,6)	8,7	$< 10^{-3}$	**G1<G2,G3**
RCFT-copy duration (seconds)	288,7 (169,7)	259,0 (152,6)	175,2 (68,3)	5,1	0,009	**G1>G2,G3**

G1= recurrent MDD patients, G2=single episode MDD patients, G3=healthy control individuals
[a] The threshold for significance was p<0.05

Table 4: Performance on neurocognitive tests by single episode MDD patients and recurrent MDD patients.

(r=0,553 ; p=0,033) and RCFT-delayed recall (r=-0,658 ; p=0,004). The number of depressive episodes was correlated only with TMT-A performance(r=0,684 ; p=0,002). The cumulative duration of depressive episodes showed no significant correlation with any cognitive test.

Discussion

In our study, we demonstrated a persistent impairment in a wide range of neurocognitive domains including attention and processing speed, non-verbal memory, phonemic fluency and executive functions.

Studies that focused on attention performance in remitted MDD patients yielded contradictory results [6,7,13,27,28]. Neu et al. [13], using the TMT-A in a longitudinal study, demonstrated attention and psychomotor speed improvement after recovery from a major depressive episode with melancholic features. Xu et al. [27], examining longitudinally a mixed sample of first episode and recurrentMDD,found that remission of unipolar depressionwas not followed by processing speed function recovery. In our study, we demonstrated a significant correlation between TMT-A performance and number of previous depressive episodes. Taken together these results can suggest that multiple depressive episodes can progressively deteriorate attention and processing speed function.

Lasting memory impairments in euthymic MDD patients have been extensively reported in literature without specifying the mnemonic field affected [6,8,10-12,28]. Regarding visual memory, our results are consistent with those of Behnken et al. [10]. Using the RCFT to assess non-verbal memory and the SavageOrganizational Score to assess organizational strategies, they found persistent impairment and deficient use of organizational strategies in fully remitted MDD patients. They suggested that memory impairments were secondary to difficulties organizing non-verbal information while encoding information.

In the literature, data concerning long-term verbal memory is controversial [6,13,15,27]. Spared semantic fluency documented in our study associated with impairment of episodic verbal memory indicated in numerous studies [11,12,29] support the hypothesis of disrupted encoding processes underlying long-term memory dysfunction, information's retrieval being preserved.

Regarding working memory, our findings suggest intact cognitive performance in state of remission. After adequate antidepressant treatment, Xu G et al. patients displayed improvement in working memory as assessed by the digit span backward [27].The assumption that cognitive deficits observed in patients with MDD are due to a dysfunction of executive component of working memory [30] may therefore be challenged since that recovery of working memory was not followed by upturnof the others cognitive functions investigated in our study.

Consistent with previous data [7,8,11,27,31], we recorded residual impairments in all tests assessing executive functions.Remitted depressed patients showedflexibility, set-shifting and inhibition ability deficits.Compared to controls, they needed additional time to carry out required tasks.One possible explanation is that executive dysfunctions are mediated by slowing processing speed. Along with speeded-demanding tests dysfunctions, our patients showed visual-constructional and planning deficits suggesting that long-lasting cognitive impairment may be mediated by difficulties to generate and maintain adequate organizational strategies.

Focusing on the impact of recurrent depressive episodes on cognitive function, the main finding of our study was general intact cognitive performance in patients with a single depressive episode.This result allows us to challenge the trait-marker hypothesis previously advanced. Klimes- Dougan et al. when assessing high-risk children of mothers with MDD for memory and executive functions, failed to detect deficits suggesting that dysfunctions are related to depressive state rather than trait markers of the illness [32].Taken together, these findings allow us to suggest that in the earlier phase of the illness, cognitive deficits still reversible at least in patients with early-onset depression. This result must be interpreted with caution since we have not cognitively assessed our patients in the acute phase of the disease.

In the recurrent MDD group, a positive correlation was found between number of previous depressive episodes and attention and processing-speed performance. A longer duration of the illness was significantly correlated with altered mental flexibility and non-verbal long-term memory performance. Cognitive dysfunction in MDD after recovery proved to be related to the course of the illness and to be sensitive to depressive recurrence. A cumulative neurotoxic effect on brain-physiology has been postulated [33,34]. Underlying mechanism could be hippocampal and prefrontal cortex volume loss. Data is still controversial [34].

A main limitation in our study is that the majority of our patients were medicated during neuropsychological assessment. Iatrogenic characteristics may be a major confounding factor since deleterious effects on cognition have been suspected. This remain true especially with tricyclics witch may impair cognition through a potent anti-cholinergic effect [35]. More recent studies have suggested instead a neuroprotective effect of antidepressants [36,37]. Some papers described a beneficial effect on psychomotor slowing, attentional and executive functions [38] and an improvement in memory and attention skills [39] after SSRI treatment. Dual serotoninergic-noradrenergic reuptake inhibitors proved to be more efficient than SSRI to improve episodic and working performances [40].

Regarding these results and since that type and duration of antidepressant treatment and evolutionary course of MDD are closely interrelated,it seems unlikely that the cognitive dysfunctions observed in our patients are underpinned by neurotoxic effets of treatment. The assumption of accountability of cognitive dysfunction in recurrent depression seems more relevant.

Medication status stillhowever an inevitable methodological constraint specially for recurrent MDD patients.

Conclusion

In summary, our findings suggest that MDD patients in remission show long-lasting cognitive impairment in a broad range of domains including attention and psychomotor speed, non-verbal memory and executive functions.

The lack of cognitive deficits in MDD patients with a single depressive episode suggests that cognitive dysfunction cannot be considered as trait marker but appears to be sensitive to depressive recurrence.

To corroborate our hypothesis, there is a need for studies investigating longitudinally cognitive functioning in well-defined homogenous medication-free patient group in the future.

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