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AGE-ADJUSTED NORMATIVE DATA AND DISCRIMINATIVE VALIDITY OF COGNITIVE TESTS IN THE UKRAINIAN ADULT PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Вікові нормативні дані та дискримінаційна валідність когнітивних тестів в українській когорті дорослих пацієнтів з великим депресивним розладом

Abstract

Purpose of the study. *We aimed: 1) to compare cognitive functioning in patients with major depressive disorder (MDD) and healthy controls (HC) in the Ukrainian adult population by the results of neuropsychological assessment, that included Perceived Deficit Questionnaire (PDQ-5), Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test Part B (TMT-B), Digit Symbol Substitution Test (DSST); 2) to obtain age-adjusted normative data of RAVLT, TMT-B, and DSST tests; 3) to explore the diagnostic utility of PDQ-5, RAVLT, TMT-B, and DSST tests to separate patients with MDD from HC; 4) to provide cutoff scores of the PDQ-5, RAVLT, TMT-B, and DSST tests, stratified by age, that discriminate MDD patients from HC, based on the sensitivity (Se) and specificity (Sp) of the obtained scores.*

Materials and methods. *130 MDD medication-free patients (according to DSM-5) and 70 HC were enrolled in the study. Psychopathological (by Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression Severity (CGI-S)) and neuropsychological (by PDQ-5, RAVLT, TMT-B, DSST) parameters were analyzed in all subjects. To assess between-group differences parametric and non-parametric tests were used (T-test, Mann-Whitney test, chi-squared test). Areas under the curve (AUC) of receiver operating characteristic (ROC) were calculated to determine if the results of PDQ-5, RAVLT, TMT-B, and*

Реферат

Мета дослідження. *Ми мали на меті: 1) порівняти когнітивне функціонування пацієнтів з великим депресивним розладом (ВДР) та осіб групи здорового контролю (ГК) в українській когорті людей дорослого віку за результатами нейропсихологічної оцінки, яка включала опитувальник суб'єктивного когнітивного дефіциту (Perceived Deficit Questionnaire – PDQ-5), тест Рея на слухове запам'ятовування вербальної інформації (Rey Auditory Verbal Learning Test – RAVLT), тест послідовних з'єднань, частина В (Trail Making Test Part B TMT-B), тест заміни символів цифрами (Digit Symbol Substitution Test – DSST); 2) отримати нормативні дані тестів RAVLT, TMT-B та DSST з урахуванням віку; 3) дослідити діагностичну цінність тестів PDQ-5, RAVLT, TMT-B та DSST для відокремлення пацієнтів з ВДР від ГК; 4) отримати граничні показники тестів PDQ-5, RAVLT, TMT-B та DSST, стратифіковані за віком, які з оптимальною чутливістю (Se) та специфічністю (Sp) відділяли пацієнтів із ВДР від ГК.*

Матеріали та методи. *В дослідження було залучено 130 пацієнтів з ВДР (згідно з критеріями DSM-5), що не приймали фармакотерапію та 70 осіб ГК. У всіх учасників були проаналізовані психопатологічні (за шкалами депресії Монтгомері-Асберг (MADRS) та загальної клінічної оцінки (CGIS)) та нейропсихологічні (за PDQ-5, RAVLT, TMT-B, DSST) параметри. Для оцінки*

DSST tests` performance could discriminate MDD patients from HC. Cutoff scores, which separated MDD patients from HC with empirical optimal Se and Sp, were derived from the ROC curves. The statistical threshold was set at p < 0.05.

Results. *Surveyed groups were comparable in age, gender, and level of education. Besides the expected statistical difference in MDD patients and HC on MADRS and CGI-S scores, sufficient distinction in neuropsychological test performance was found between the comparison groups. MDD participants were significantly worse (p < 0,0001) in subjective (PDQ-5) as well as objective cognitive functioning (RAVLT subtests, DSST, TMT-B scores). Significant differences between MDD and HC groups, established during objective cognitive testing, were specific to each age group, despite the general trend of deterioration of cognitive performance with age. ROC analysis was used to examine the utility of PDQ-5, RAVLT, TMT-B, and DSST tests to discriminate MDD patients from HC. AUC-ROCs showed that all cognitive measures included in this study adequately differentiated between the performance of HC and MDD patients. We also provided cutoff scores for five age groups in discriminating MDD patients from HC, based on the Se and Sp of the prescribed scores. The age ranges for each group were as follows: Group 1 – 18–24 years; Group 2 – 25–34 years; Group 3 – 35–44 years; Group 4 – 45–54 years; Group 5 – 55–65 years. For PDQ-5 cutoff scores were: in the whole sample > 3,5 points (Se 90%, Sp 91%); Group 1 > 3,5 points (Se 100%, Sp 83 %); Group 2 > 3,5 points (Se 93%, Sp 89%); Group 3 > 2,5 points (Se 89%, Sp 83%); Group 4 > 2,5 points (Se 100%, Sp 84%); Group 5 > 3,0 points (Se 90%, Sp 100%). For immediate recall of the RAVLT cutoff scores were: in the whole sample < 56,5 words (Se 85%, Sp 82%); Group 1 < 57 words (Se 100%, Sp 73%); Group 2 < 59,5 words (Se 85%, Sp 70%); Group 3 < 59,5 words (Se 91%, Sp 83%); Group 4 < 57,5 words (Se 86%, Sp 74%); Group 5 < 53,5 words (Se 94%, Sp 80%). For proactive interference of the RAVLT cutoff scores were: in the whole sample < 6,5 words (Se 66%, Sp 72%); Group 2 < 7,5 words (Se 83%, Sp 63%); Group 3 < 6,5 words (Se 70%, Sp 75%); Group 4 < 6,5 words (Se 72%, Sp 74%); an unsatisfactory quality of the models for groups 1 and 5 did not allow to determine the cutoff scores for these age groups. For retroactive interference of the RAVLT cutoff scores were: in the whole sample < 13,5 words (Se 86%, Sp 76%); Group 2 < 13,5 words (Se 85%, Sp 89%); Group 3 < 13,5 words (Se 82%, Sp 92%); Group 4 < 13.5 words (Se 82%, Sp 74%); Group 5 < 12,5 words (Se 94%, Sp 80%); Group 1 had an unsatisfactory quality of the model. For TMT-B cutoff scores were: in the whole sample > 63 s (Se 70%, Sp 68%); Group 1 > 61 s (Se 91%, Sp 64%); Group 2 > 58,5 s (Se 73%, Sp 60%); Group 3 > 58,0 s (Se 83%, Sp 83%); Group 5 > 71,5 s*

Результати. Групи порівняння достовірно не відрізнялись за віком, статтю та рівнем освіти. Окрім очікуваної статистичної різниці між групами ВДР та ГК за загальними балами MADRS та CGIS, виявлена значуща різниця в когнітивному функціонуванні за опитувальником PDQ-5, а також за об'єктивним нейропсихологічним тестуванням (RAVLT, TMT-B та DSST). Пацієнти з ВДР у порівнянні з особами ГК мали значно гірші результати тесту RAVLT (субтести на негайне пригадування, проактивну та ретроактивну інтерференцію), TMT-B та DSST. Суттєві відмінності між групами ВДР та ГК, виявлені під час виконання об'єктивних когнітивних тестів, зберігались для кожної вікової категорії, незважаючи на загальну тенденцію погіршення когнітивних показників з віком. ROC-аналіз був використаний для вивчення діагностичної цінності тестів PDQ-5, RAVLT, TMT-B, DSST для розрізнення пацієнтів з ВДР від ГК. AUC-ROCs продемонстрували, що всі когнітивні тести, включені у це дослідження, мали відмінну або дуже гарну або гарну якість моделі для відмежування пацієнтів з ВДР від ГК. Також були отримані граничні результати тестів PDQ-5, RAVLT, TMT-B, DSST з оптимальними значеннями Se та Sp для дискримінації хворих з ВДР від ГК у п'яти вікових групах. Вікові діапазони для кожної групи були наступними: 1 група – 18–24 роки; 2 група – 25–34 роки; 3 група – 35–44 роки; 4 група – 45–54 роки; 5 група – 55– 65 років. Граничні показники для PDQ-5 були: у всій вибірці > 3,5 балів (Se 90%, Sp 91%); 1 групі > 3,5 балів (Se 100%, Sp 83%); 2 групі > 3,5 балів (Se 93%, Sp 89%); 3 групі > 2,5 балів (Se 89%, Sp 83%); 4 групі > 2,5 балів (Se 100%, Sp 84%); 5 групі > 3,0 балів (Se 90%, Sp 100%). Граничні показники для субтесту RAVLT на негайне пригадування: у всій вибірці < 56,5 слів (Se 85%, Sp 82%); 1 групі < 57 слів (Se 100%, Sp 73%); 2 групі < 59,5 слів (Se 85%, Sp 70%); 3 групі < 59,5 слів (Se 91%, Sp 83%); 4 групі < 57,5 слів (Se 86%, Sp 74%); 5 групі < 53,5 слів (Se 94%, Sp 80%). Граничні показники для субтесту RAVLT на проактивну інтерференцію: у всій вибірці < 6,5 слів (Se 66%, Sp 72%); 2 групі < 7,5 слів (Se 83%, Sp 63%); 3 групі

(Se 90%, Sp 80%); Group 4 had an unsatisfactory quality of the model. For DSST cutoff scores were: in the whole sample < 58.5 points (Se 74%, Sp 63%); Group 2 < 59,5 points (Se 71%, Sp 67%); Group 3 < 60,5 points (Se 78%, Sp 83%); Group 4 < 53,5 points (Se 68%, Sp 72%); groups 1 and 5 had an unsatisfactory quality of the model.

Conclusions. *Patients with an active episode of MDD demonstrate as subjective as objective cognitive impairments as compared to HC. Cognitive dysfunction in the Ukrainian cohort of MDD patients is characterized by mild impairments in working memory; moderate impairments in alternating attention; and moderate impairments in executive functioning. PDQ-5 and neuropsychological tests, such as RAVLT (subtests for immediate recall, proactive and retroactive interference), TMT-B, and DSST show from excellent to good diagnostic value for separating patients with MDD from HC. PDQ-5, RAVLT, TMT-B, and DSST and obtained age-adjusted cutoffs of those tests could be used by clinicians in everyday practice as a method to secure a more valid assessment of cognitive function in MDD patients.*

Keywords: *Major depressive disorder; cognitions; PDQ-5; RAVLT; DSST; TMT-B.*

< 6,5 слів (Se 70%, Sp 75%); 4 групі < 6,5 слів (Se 72%, Sp 74%); незадовільна якість моделей для груп 1 та 5 не дозволила визначити граничні показники виконання субтесту для цих вікових груп. Граничні показники для субтесту RAVLT на проактивну інтерференцію: у всій вибірці < 13,5 слів (Se 86%, Sp 76%); 2 групі < 13,5 слів (Se 85%, Sp 89%); 3 групі <13,5 слів (Se 82%, Sp 92%); 4 групі < 13,5 слів (Se 82%, Sp 74%); 5 групі < 12,5 слів (Se 94%, Sp 80%); 1 група мала незадовільну якість моделі. Граничні показники для TMT-B: у всій вибірці > 63 с (Se 70%, Sp 68%); 1 групі > 61 с (Se 91%, Sp 64%); 2 групі > 58,5 с (Se 73%, Sp 60%); 3 групі > 58,0 с (Se 83%, Sp 83%); 5 групі > 71,5 с (Se 90%, Sp 80%); 4 група мала незадовільну якість моделі. Граничні показники для DSST: у всій вибірці < 58,5 (Se 74%, Sp 63%); 2 групі < 59,5 (Se 71%, Sp 67%); 3 групі <60,5 (Se 78%, Sp 83%); 4 групі <53,5 (Se 68%, Sp 72%); групи 1 і 5 мали незадовільну якість моделі.

Висновок. *Пацієнти з активним епізодом ВДР в порівнянні з ГК мають як суб'єктивні, так і об'єктивні когнітивні порушення. Когнітивна дисфункція в українській когорті хворих на ВДР характеризується легкими порушеннями робочої пам'яті; помірними порушеннями уваги; та помірними порушеннями виконавчих функцій. Опитувальник PDQ-5 та нейропсихологічні тести, такі як RAVLT (субтести на негайне пригадування, проактивну та ретроактивну інтерференцію), TMT-B та DSST мають від відмінної до гарної діагностичну цінність для відокремлення пацієнтів з ВДР від ГК. Тести PDQ-5, RAVLT, TMT-B та DSST та отримані з урахуванням віку граничні показники цих тестів можуть бути використані клініцистами у повсякденній практиці як метод, що забезпечує більш достовірну оцінку когнітивних функцій у пацієнтів із ВДР.*

Ключові слова: *великий депресивний розлад; когнітивні функції; PDQ-5; RAVLT; DSST; TMT-B.*

INTRODUCTION

Major Depressive Disorder (MDD) is one of the most important theoretical and applied problems of modern psychiatry, given its prevalence and socioeconomic implications [1]. MDD ranks second in the structure of mental disorders, and the socioeconomic burden caused by it is largely related to the loss or decline in productivity of affected individuals [2, 3]. The need to restore the functioning of patients with MDD in the workplace, society, and family encourages the search for factors that negatively affect it. Among them, cognitive dysfunction occupies a prominent place, which, along with affective and somatic symptoms, is a structural part of the clinical picture of MDD [4].

Cognitive dysfunction in affective disorders hasn't been studied much until the last two decades, although cognitive impairments are widespread in patients with MDD. They are found in 94% of patients with an acute depressive episode (DE) and 44% of patients with symptomatic remission [5]. It is proved that cognitive impairments directly affect the work productivity and social functioning of patients and impede functional recovery [6, 7, 8, 9]. Nevertheless, only 38% of psychiatrists in their daily practice use cognitive instruments to screen patients; of these, only 3% were actually appropriate for use in MDD [10]. Therefore, there is a need for a standardized method for evaluating cognitive dysfunction.

It is now known that from clinical and phenomenological points of view, cognitive

deficits in MDD are mainly manifested in the domains of memory [K. Hinkelmann et al., 2012], executive functions, attention and psychomotor speed [12, 13, 14]. At the same time, there is ample evidence of the cultural specificity of neuropsychological disorders, which is found in ongoing research in different countries [15–19]. Studies of the specifics of cognitive impairment in MDD in the Ukrainian patient population are absent.

An applied task is the validation of diagnostic tools for cognitive dysfunction of the Western neuropsychology (Perceived Deficit Questionnaire – PDQ-5, Rey Auditory Verbal Learning Test RAVLT, Trail Making Test Part B TMT-B, Digit Symbol Substitution Test DSST) in the Ukrainian cohort of patients with MDD to objectify cognitive deficit. Solving this problem will significantly improve the diagnosis of cognitive deficits in persons with MDD in the daily practice of Ukrainian psychiatrists.

Taking into account the considerations outlined above, the objectives of our study were: 1) to compare cognitive functioning in MDD patients and healthy controls in the Ukrainian population by the results of PDQ-5, RAVLT, TMT-B, and DSST; 2) to obtain age-adjusted normative data of RAVLT, TMT-B, and DSST tests for adults; 3) to explore the diagnostic utility of these tests to separate patients with MDD from HC; 4) to provide cutoff scores of the tests, stratified by age, that discriminate cognitively HC from MDD patients, based on the sensitivity and specificity of the obtained scores.

MATERIALS AND METHODS

Study design. This was a case-control study, which included 205 participants aged 18 to 65 years. Outpatients (n = 130) with MDD diagnosis according to DSM-5 criteria [20] were recruited through Zaporizhzhia Regional Clinical Psychiatric Hospital, Ukraine. Eligibility criteria for the study participants were described elsewhere [21]. Before entering the study, all patients had received no actual antidepressant medication. Subjects were excluded if they had any other psychiatric diagnosis, high suicidal risk, substance dependence/abuse over the past year, significant neurological disorders, head trauma, unstable medical conditions, history of endocrine diseases, psychotic symptoms, the risk for the hypomanic switch [21]. Seventy-five healthy controls (HC) with no current psychiatric disorder were enrolled within the same period that the MDD patients were included. HC were excluded based on the use of medications and/or illicit drugs; the intake of alcohol within 48 hours of the study visit; and the presence of an unstable medical condition, which could affect cognitive function [21].

The study was approved by the local ethics committee and performed following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and registered at ClinicalTrials.gov (NCT03187093). All participants gave written informed consent after study procedures were explained and before participation.

Clinical Assessments. Depression severity was evaluated using Montgomery-Asberg Depression Rating Scale (MADRS) [22] and Clinical Global Impression Severity (CGI-S) scale [23]. Assessment of the severity of depression according to MADRS was as follows: 0–11 points – no depression, 12–23 points – mild depression, 24–34 points – moderate depression, 35–60 points – severe depression [22]. An integrative assessment of the severity of the patien`s condition was done using a subscale "Severity" of the CGI [23]. CGI-S score is based on the general clinical experience of a physician regarding a specific population of patients. The severity of the patient's condition over the past seven days on the CGI-S subscale was graded as follows: 1 – normal; 2 – borderline mentally ill; 3 – mildly ill; 4 – moderately ill; 5 – markedly ill; 6 – severely ill; 7 – among the most extremely ill patients.

Neuropsychological Assessments. Patients` subjective cognitive functioning was assessed using the Ukrainian version of PDQ-5, a validated 5-item self-report scale measuring perceived difficulties in executive functioning, concentration, and memory, ranging from 0 to 4 (table 1) [24]. The questionnaire estimates subjective symptoms over the past week and its total score ranges from 0 to 20, with higher scores reflecting greater severity.

The objective neuropsychological investigation included several tests that proved their validity concerning quantitative and qualitative parameters of cognitive deficits in patients with MDD: RAVLT; TMT-B; and DSST [8, 25, 26]. The tests were administered using paper and pencil.

RAVLT is used to analyze verbal learning and memory, including immediate memory, retroactive and proactive interference effects, and encoding versus retrieval. In our study, we administered Ukrainian translation of the World Health Organization/University of California Los Angeles version of the RAVLT (table 2) [27]. The test consists of two lists (A and B), containing 15 words each. All test words were selected from five categories and included three examples for a separate category. The words of List A are read with a one-second interval between words for five consecutive trials, each trial is followed by a free-recall. The total number of words across the five trials is defined as an immediate recall. On completion of Trial 5, an interference list of 15 new words (List B) is presented, followed by a free-recall test of that list – to assess proactive

interference. Immediately after this, delayed recall of the List A is tested without further presentation of the words – to assess retroactive interference. After a 30-minute delay period, the examinee is again required to recall the words from List A – to evaluate delayed recall. Finally, a list with 30 words is presented, which includes those from List A and 15 new items, and the person has to identify the words from List A – to assess recognition.

Table 1

Ukrainian version of Perceived Deficit Questionnaire 5 (PDQ-5)

How often in the last 7 days...	Never	Occasionally 1– 2 times	Sometimes 3-–5 times	Often 1r/day	Very often > 1p/day
You had difficulty planning things?	0	1	2	3	4
Was it difficult for you to concentrate on what you were reading?	0	1	2	3	4
You forgot what number it was today until you checked it out?	0	1	2	3	4
After talking on the phone, you forgot what you were talking about?	0	1	2	3	4
You suddenly notice that you don't think about anything?	0	1	2	3	4

Table 2

Ukrainian translation of RAVLT

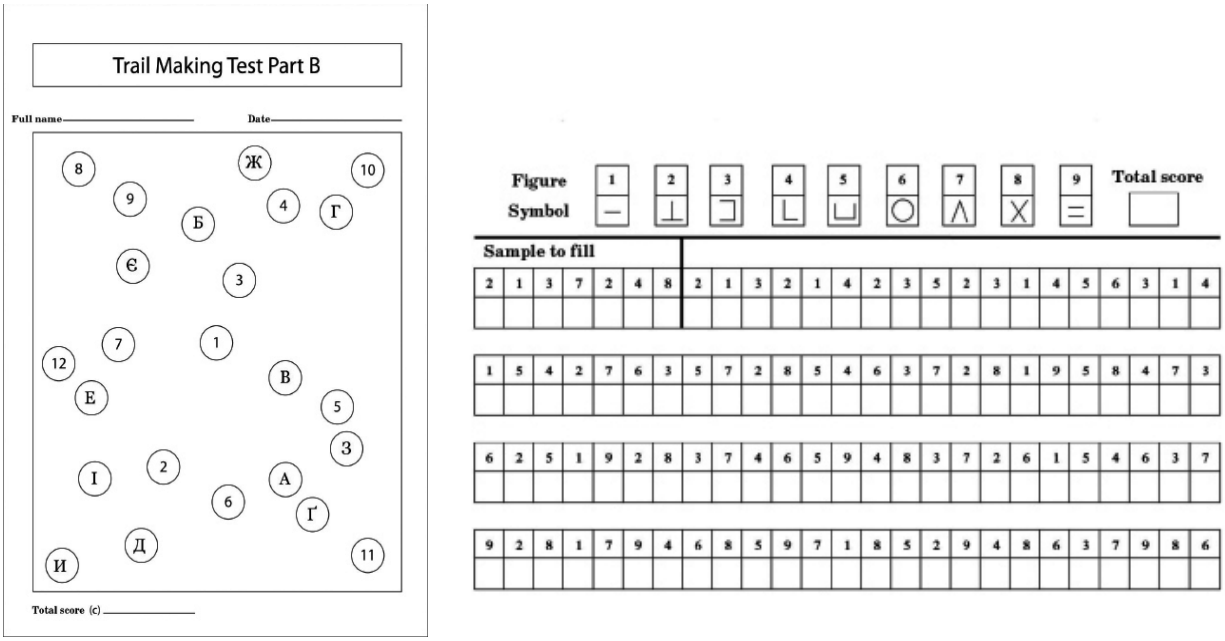
List A	List B	List of words for recognition	
Shoulder	Boot	Mirror	Lose
Cat	Monkey	Ax	Tree
Ax	Bowl	Than	Shoulder
Bed	Cow	Candle	Nose
Plane	Finger	Motorcycle	Sun
Ear	Dress	Hammer	Truck
Dog	Spider	Watch	Eye
Hammer	Cup	Chair	Fish
Chair	Bee	Plane	Ear
Auto	Leg	Turtle	Bike
Eye	Hat	Horse	Snake
Horse	Hat	Leg	Bench
Than	Kettle	dog	Bus
Watch	Mouse	Table	Bed
Bike	Hand	Cat	Auto

TMT-B allows detecting violations of information processing speed, switching attention, and executive functions [25]. To perform the test, a patient is provided with a drawing with circles with inscribed numbers from 1 to 12 and letters of the alphabet from A to L (fig. 1a). The TMT-B requires to connect alternately numbers and letters in ascending order (1 A, 2B...12L). During the test, the researcher immediately points out errors, and the participant needs to correct them before proceeding. The faster the test is passed, the better. Criteria for assessing the performance of the test are as follows: 0-60 s – excellent; 61– 72 s – normal; 73-105 s – violation of moderate severity; ≥ 106 s – severe cognitive impairment [28]. In this interpretation of the test, the patient`s age is not taken into account.

The DSST test was used to assess executive functions, information processing speed, memory, concentration, and switching attention. During the test, the participant has to copy in the spaces below the lines of numbers the characters that correspond to each digit according to the key located at the top of the page (fig. 1b) [25]. The overall score is the number of correct characters over 90 seconds.

Statistical analyses. Statistical analyses were carried out using SPSS Statistics (IBM) v.20.0. The results were presented as median (interquartile range) or means (SDs) or percentages. The statistical significance of between-group comparisons was

determined using nonparametric and parametric criteria when appropriate (Mann-Whitney test, chi-squared test, T-test). Thereafter, the receiver operating characteristic (ROC) analysis was performed to build ROC curves for cognitive tests to determine their diagnostic value to discriminate patients with MDD from HC. A ROC-curve shows the level of sensitivity and specificity for each possible threshold value and allows to display the dependence of the number of truly positive results from false positives. The areas under the curves (AUC), their standard errors, and the 95% confidence intervals for each cognitive test were calculated. The larger the area between the curves, the higher the sensitivity and specificity of the test, i.e. it is more accurate. In an ideal test, the curve passes through the upper left or lower right corner, indicating that the proportion of true positive test results is approaching 100%. AUC is used to quantify the clinical significance of the test. The quality of the test can be judged on an expert scale for AUC values: 0,9–1,0 – excellent quality of the model; 0,8–0,9 – very good quality; 0,7–0,8 – good quality; 0,6–0,7 – average quality; 0,5–0,6 – unsatisfactory quality. Cutoff scores with empirical optimal sensitivity and specificity were derived from the ROC curves. The statistical threshold was set at $p < 0,05$.



a b

Figure 1. Ukrainian variants of TMT-B (a) and DSST (b) tests

RESULTS AND DISCUSSION

Table 1 demonstrates the main demographic and neuropsychological characteristics of MDD and HC groups. Surveyed cohorts were comparable in age, gender, and level of education. The mean years of education in MDD patients and HC was about 15 years. The severity of depression (according to MADRS and CGI-S) was significantly more prominent in MDD patients than in HC.

Besides the expected statistical difference in MDD patients and HC on MADRS and CGIS total scores, a significant distinction in cognitive functioning was found when assessed subjectively (PDQ-5) as well as objectively by neuropsychological testing (RAVLT, TMT-B, and DSST) (table 3). Significant differences were obtained between the comparison groups when examining different aspects of memory using the RAVLT test. It was found that MDD patients performed significantly worse on subtests for immediate recall, proactive and retroactive interference, which indicated the presence of memory problems. In terms of severity, these violations were mild according to the metanorms of the test [29]. At the same time, the indicators of long-term memory (delayed recall and delayed recognition of verbal information) in the MDD group were normal according to Schmidt et al., although lower than in the HC [29]. Thus, the dysmnestic syndrome in patients with MDD was characterized by mild impairments of working memory while maintaining its long-term performance. These violations were also confirmed by subjective patients` assessment of the presence of cognitive symptoms (subscales “forget the current date” and “forget the phone call conversation” of PDQ-5). Our results on verbal memory have some discrepancies with the meta-analytical data of Ahern et al., who also did not find impairments in delayed recognition of verbal information in

patients with MDD, but showed only a tendency to small disturbances in immediate recall and minor significant disturbances in delayed recall (in our study, patients also significantly differed from healthy individuals in this indicator, but their results corresponded to the normative data) [30].

Table 3

Demographic and clinical characteristics of comparison groups

	MDD n = 130	HC n = 75	p
Demographic characteristics			
Women, n (%)	88 (68,3)	44 (56,3)	0,19[a]
Age, years*	38,7 (11,9)	37,5 (12,1)	0,47[b]
Education, years*	14,6 (2,0)	15,0 (1,6)	0,10[b]
Clinical assessments			
Mood symptoms			
MADRS total score (0–60)	28 (22–33)	3 (0–5)	< 0,0001[c]
CGI-S score	4 (4–5)	1 (1–1)	< 0,0001[c]
Patient-reported cognitive symptoms			
PDQ-5 total score (0–20)	8 (5–11)	1 (0–2)	< 0,0001[c]
MADRS «concentration difficulties» (0–6)	4 (3–4)	0 (0–1)	< 0,0001[c]
PDQ-5 «have trouble getting things organized» (0–4)	2 (1–3)	0 (0–1)	< 0,0001[c]
PDQ-5 «have trouble concentrating on what you were reading» (0–4)	2 (1–3)	0 (0–1)	< 0,0001[c]
PDQ-5 «forget the date unless you looked it up» (0–4)	2 (1–3)	0 (0–1)	< 0,0001[c]
PDQ-5 «forget what you talked about after a telephone conversation» (0–4)	1 (0–2)	0 (0–0)	< 0,0001[c]
PDQ-5 «fell like your mind went totally blank» (0–4)	0 (0–2)	0 (0–0)	< 0,0001[c]
Performance-based cognition			
RAVLT immediate recall total score, number of words (0–75)	49 (44–55)	63 (58–68)	< 0,0001[c]
RAVLT proactive interference score, number of words (0–15)	6 (5–7)	8 (6–9)	< 0,0001[c]
RAVLT retroactive interference score, number of words (0–15)	11 (9–13)	15 (14–15)	< 0,0001[c]
RAVLT delayed recall score, number of words (0–15)	11 (9–13)	15 (13–15)	< 0,0001[c]
RAVLT delayed recognition score, number of words (0–15)	15 (14–15)	15 (15–15)	< 0,0001[c]
TMT-B, number of seconds	74 (60–90)	58 (43–68)	< 0,0001[c]
DSST, number of correct symbols	51 (43–59)	62 (54–68)	< 0,0001[c]

Note: *data are presented as median (upper-lower quartile) unless otherwise stated; * data are presented as means (SD); a Chi-square test; b T-test for independent samples; c Mann–Whitney U–test*

The TMT-B test was used to assess alternating attention. The test revealed significant differences between groups of patients and healthy individuals. It was found that the average time spent on the test was significantly higher in the group of patients with MDD compared with HC (table 3). According to the normative data of the authors of the test, attention disorders in patients with MDD were on average moderate in severity, while HC performed tasks at an excellent level [28]. Impairments in attention in patients with current DE were assessed on average as moderate by the researcher (the MADRS item «concentration difficulties»), as well as by the patients themselves (relevant item of PDQ-5). Similar cognitive impairments on the TMT-B test were found in a general cohort of patients with MDD in recent studies and two meta-analyses, as well as in the elderly with MDD [12, 30, 31, 32, 33, 34].

The DSST test was used to objectively assess executive functions. The results of its completion in the comparison groups had statistically significant differences. Thus, patients with MDD reproduced significantly fewer symbols in the allotted period than those examined with HC. The degree of executive dysfunction in patients with MDD was on average moderate according to current standards [35] in contrast to healthy individuals, who have no executive dysfunction. This generally correlated with patients` subjective perceptions of their performance violations (PDQ-5 option). The mean DSST score in patients with MDD in our study (51) was similar to that reported

in Chinese (50,7) and Japanese patients with MDD (54,3) before starting antidepressant therapy, but higher than in comparable populations in the US and Europe (42.0 in the FOCUS study and 43,1 in the CONNECT study) [18, 19, 36, 37]. This may partially reflect cultural differences between different geographical populations.

Separately, it should be noted that significant differences between the MDD group and HC, found during the performance of objective cognitive tests, were maintained for each age category, despite the general trend of deterioration of cognitive performance with age (table 4). It is important to emphasize that in our study the HC performed all RAVLT subtests with better results than proposed metanorms by Schmidt [29]. This pattern was also observed in all age groups HC in the results of DSST [35].

Table 4

Performance of cognitive tests in different age groups

Cognitive test	Age groups, years									
	18–29		30–39		40–49		50–59		60–69	
	MDD n = 32	HC n = 22	MDD n = 45	HC n = 25	MDD n = 27	HC n = 15	MDD n = 18	HC n = 8	MDD n = 8	HC n = 5
RAVLT immediate recall	50,06 (7,54)*	61,10 (7,56)	49,77 (7,63)*	65,40 (6,83)	50,33 (6,41)*	63,33 (5,27)	47,47 (8,22)	53,13 (7,77)	40,13 (7,57)*	57,00 (7,14)
RAVLT proactive interference score	6,58 (1,39)*	7,81 (1,83)	5,91 (1,22)*	7,80 (1,76)	5,79 (1,62)*	8,00 (2,00)	5,48 (1,17)	5,75 (1,67)	5,25 (1,83)	7,20 (2,68)
RAVLT retroactive interference score	10,90 (2,50)*	13,43 (2,32)	10,82 (2,59)*	14,48 (1,05)	10,92 (2,64)*	14,33 (0,90)	10,00 (2,21)*	12,63 (2,56)	8,25 (2,12)*	12,40 (2,61)
RAVLT delayed recall score	11,10 (2,94)*	13,86 (2,10)	11,07 (2,39)*	14,40 (1,32)	10,92 (2,19)*	14,53 (0,92)	10,00 (2,76)	12,38 (3,02)	7,63 (2,50)*	12,40 (1,52)
RAVLT delayed recognition	14,30 (1,29)	14,81 (0,68)	14,27 (0,10)*	14,96 (0,20)	14,33 (0,87)*	14,80 (0,56)	12,84 (4,66)	14,50 (1,07)	13,50 (1,69)	15,00 (0,00)
TMT-B	71,03 (18,37)	62,67 (18,70)	73,00 (24,18)*	50,52 (21,08)	77,76 (17,36)*	57,21 (18,78)	90,37 (29,91)*	68,00 (12,17)	98,25 (30,87)	71,80 (17,51)
DSST	56,41 (9,27)*	63,05 (12,50)	52,61 (10,86)*	68,00 (13,34)	47,73 (10,70)*	60,00 (9,12)	42,32 (11,55)*	54,13 (8,15)	39,88 (10,04)	45,80 (6,91)
Results of DSST presented as median (upper-lower quartile)										
DSST	57 (53–63)	62 (54–71)	51 (45–60)	68 (62–73)	48 (39–53)	61 (56–67)	41 (33–56)	53 (48–61)	40 (33–49)	47 (39–52)

Note: *data are presented as means (SD) unless otherwise stated;* - $p < 0,05$ according to T-test for independent samples*

Afterward, using ROC analysis, we assessed the discriminatory ability of different cognitive tests for separating patients with MDD from healthy individuals by the scores of cognitive tests (table 5). The analysis was performed only for those tests, the performance of which by patients with an active DE was significantly worse according to the available normative data. The PDQ-5 test had an excellent quality of a model for differentiating patients with MDD from HC in the total sample, a total score of PDQ-5 > 3,5 provided the opportunity to separate patients with MDD from HC with a sensitivity of 90% and specificity of 91%. The RAVLT subtest for immediate recall had a very good diagnostic value for differentiating patients with MDD throughout the sample, the threshold score of the subtest < 56,5 words had a sensitivity of 85% and a specificity of 82% for the separation of patients with MDD from HC in the general sample. The RAVLT subtest for proactive interference showed good diagnostic value for separating patients with MDD from HC in the entire sample, the subtest threshold < 6,5 words with a sensitivity of 66% and a specificity of 72% separated patients with MDD from HC. The RAVLT subtest for retroactive interference had a very good diagnostic value for predicting MDD in the entire sample, a subtest threshold level < 13,5 words with optimal sensitivity and specificity of 86% and 76%, respectively, to separate healthy individuals from patients with MDD.

The TMT-B test demonstrated good diagnostic value for the separation of patients with MDD in the entire sample, the threshold level of test performance > 63 s had optimal sensitivity (70%) and specificity (68%) for the separation of healthy individuals from patients with MDD. The DSST test showed good diagnostic value for predicting MDD in the entire sample, the test score < 58,5 had optimal sensitivity and specificity (74% and 63%) to separate healthy individuals from patients with MDD. To the best of our knowledge, we were the first to obtain cutoff scores of those neuropsychological tests for discrimination MDD patients from HC.

Table 5

Discriminative validity of cognitive tests in the Ukrainian MDD patients

Age (years)	AUC	95% CI	P	Cutoff scores	Sensitivity	Specificity
PDQ-5 total score						
Whole sample	0,947 ± 0,015	0,918–0,977	< 0,0001	> 3,5	90%	91%
18–24	0,977 ± 0,025	0,929–1,000	< 0,0001	> 3,5	100%	83%
25–34	0,954 ± 0,024	0,908–1,000	< 0,0001	> 3,5	93%	89%
35–44	0,913 ± 0,041	0,833–0,994	< 0,0001	> 2,5	89%	83%
45–54	0,982 ± 0,017	0,948–1,000	< 0,0001	> 2,5	100%	84%
55–65	0,942 ± 0,050	0,845–1,000	0,003	> 3,0	90%	100%
RAVLT immediate recall (number of words)						
Whole sample	0,875 ± 0,026	0,825–0,926	< 0,0001	< 56,5	85%	82%
18–24	0,831 ± 0,094	0,646–1,000	0,009	< 57	100%	73%
25–34	0,895 ± 0,038	0,820–0,970	<0,0001	< 59,5	85%	70%
35–44	0,956 ± 0,031	0,894–1,000	<0,0001	< 59,5	91%	83%
45–54	0,800 ± 0,074	0,656–0,945	0,001	< 57,5	86%	74%
55–65	0,935 ± 0,065	0,807–1,000	0,004	< 53,5	94%	80%
RAVLT proactive interference (number of words)						
Whole sample	0,738 ± 0,039	0,662–0,814	< 0,0001	< 6,5	66%	72%
18–24	0,616 ± 0,123	0,375–0,856	0,36	-	-	-
25–34	0,758 ± 0,066	0,628–0,888	< 0,0001	< 7,5	83%	63%
35–44	0,795 ± 0,089	0,621–0,970	0,003	< 6,5	70%	75%
45–54	0,696 ± 0,087	0,525–0,867	0,03	< 6,5	72%	74%
55–65	0,694 ± 0,119	0,462–0,927	0,20	-	-	-
RAVLT retroactive interference (number of words)						
Whole sample	0,855 ± 0,029	0,797–0,913	< 0,0001	< 13,5	86%	76%
18–24	0,690 ± 0,121	0,452–0,928	0,13	-	-	-
25–34	0,900 ± 0,039	0,823–0,976	< 0,0001	< 13,5	85%	89%
35–44	0,945 ± 0,034	0,877–1,000	< 0,0001	< 13,5	82%	92%
45–54	0,795 ± 0,073	0,652–0,939	0,001	< 13,5	82%	74%
55–65	0,841 ± 0,129	0,589–1,000	0,023	< 12,5	94%	80%
TMT-B (time of completion, s)						
Whole sample	0,751 ± 0,036	0,681–0,822	< 0,0001	> 63	70%	68%
18–24	0,814 ± 0,098	0,622–1,000	0,01	> 61	91%	64%
25–34	0,673 ± 0,069	0,539–0,808	0,02	> 58,5	73%	60%
35–44	0,919 ± 0,040	0,841–0,997	< 0,0001	> 58,0	83%	83%
45–54	0,667 ± 0,087	0,497–0,836	0,07	-	-	-
55–65	0,821 ± 0,116	0,594–1,000	0,03	> 71,5	90%	80%
DSST (number of correct symbols)						
Whole sample	0,747 ± 0,036	0,676–0,817	< 0,0001	< 58,5	74%	63%
18–24	0,645 ± 0,132	0,386–0,903	0,25	-	-	-
25–34	0,755 ± 0,060	0,638–0,873	< 0,0001	< 59,5	71%	67%
35–44	0,867 ± 0,051	0,767–0,967	< 0,0001	< 60,5	78%	83%
45–54	0,739 ± 0,079	0,584–0,893	0,01	< 53,5	68%	72%
55–65	0,695 ± 0,117	0,465–0,924	0,19	-	-	-

CONCLUSIONS

1. Patients with an active episode of MDD demonstrate as subjective as objective cognitive impairments as compared to HC.

2. Cognitive dysfunction in the Ukrainian cohort of MDD patients is characterized by mild

impairments of working memory; moderate impairments in alternating attention; and moderate impairments in executive functioning

3. PDQ-5 and neuropsychological tests, such as RAVLT (subtests for immediate recall, proactive and retroactive interference), TMT-B, and DSST show from excellent to good diagnostic value for separating patients with MDD from HC

4. PDQ-5, RAVLT, TMT-B, and DSST and obtained age-adjusted cutoffs of those tests could be used by clinicians in everyday practice to assess the presence of cognitive dysfunction in MDD patients as a method to secure a more valid assessment of cognitive impairments specific to these patients

Conflict of Interest Statement. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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