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Correlations between working memory effectiveness and depression levels after pharmacological therapy

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Summary

Aim: The goal of the study was to identify possible associations between spatio-visual performance and verbal working memory, evaluated on admission, with the remission degree, assessed by the HDRS after 8-week pharmacotherapy with SSRI in a group of patients with depression.

Material and methods. 141 subjects were examined (patients with depressive disorders, DD: n=86, healthy subjects, CG: n=55). TMT and the Stroop Test were used.

Results. CG obtained higher results vs. DD-I patients (the evaluation started on the therapy onset) in the Stroop Test, RCNb/time (p<0.001), NCWd/time (p<0.001), NCWd/errors (p<0.001), TMT B/time (p=0.009). CG demonstrated higher results than DD-II patients (following eight weeks of pharmacological treatment) in the Stroop Test, RCNb/time and NCWd/time (p<0.001). Compared to DD-I group, DD-II group achieved better results in the Stroop Test, NCWd/time (p=0.03), NCWd/errors (p<0.001), TMT, A (p<0.001), B (p<0.001). The lowest performance levels in the Stroop Test NCWd/time (p=0.02), NCWd/errors (p=0.04) and in TMT, A/time (p=0.01), may have been related to the highest depression levels after pharmacological treatment.

Conclusions. 1.Depressive disorders are associated with deteriorated efficiency of visual and verbal working memory. 2.Antidepressant treatment resulted in improved of visual and verbal working memory. 3.The better performance in the Stroop Test and in TMT on the first day of treatment may have influenced the noted reduction in severity of depressive symptoms after treatment with SSRI.

Key words: depression, working memory, SSRI

Introduction

The most evident symptoms of depressive disorders include those visible in the emotional sphere. However, depression disturbs the cognitive functions of affected patients as well [1, 2, 3]. Cognitive function impairments as observed in these patients, can be of various character and severity (from selective, specific and mild deficits to

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generalized and pronounced changes) [4, 5]. According to some authors, patients with mild depression demonstrate slight intellectual function impairment only, while in patients with „severe depression", impairment of cognitive functions with preserved good intellectual level is more frequently observed [6]. Deterioration of cognitive functions (primarily episodic memory) is treated as a potential risk factor for depressive disorder to occur within a 3-year prognostic period [7].

Working memory enables short-time information storage, making it available for processing and use during undertaken actions. Working memory dysfunctions are observed both in patients with recurrent depressive disorders and in those in the depressive phase of bipolar affective disorder, as well as in the first-degree relatives of the subjects in question [8]. Executive functions are responsible for our planning, undertaking and carrying out of activities, situation biased information screening and for short-term information storage with recorded action criteria, as well as with new action principles [9, 10]. Many researchers believe that executive functions play a crucial role in an appropriate performance of an individual, coordinating all other cognitive processes [11]. Executive function impairment becomes evident particularly in elderly patients with depression [12], but may also be observed in younger subjects [13]. These deficits exert negative effects not only on psychological test performance levels but also on the capacity of affected patients to cope with everyday life situations, as well as on decreased remission levels [4, 14].

Aim

The goal of the study was to identify possible associations between spatio-visual performance and verbal working memory, evaluated on admission, with the remission degree, assessed by the Hamilton Depression Rating Scale (HDRS) after 8-week pharmacotherapy with selective serotonin reuptake inhibitors (SSRI) in a group of patients with diagnosed depression.

Material and methods

The reported study was carried out in a group of 141 subjects (women n = 86, 60.99%; men n=55, 39.01%) aged 20-62 (M=44.12 yrs, SD=12.39). The participants were divided into 2 groups: patients with depressive disorders (DD, n=86) and healthy subjects (comparison group, CG, n=55). Education was measured by the number of years of completed education (years at school). Considering the characteristic features of the Polish education system, the education period ≤9 yrs was considered primary education, 10–12 yrs - secondary and >12 yrs - higher education. See Table 1 – *next page* for demographic characteristics of the study group and for disease course data.

The qualification of depressive patients into the study group was based on the diagnostic criteria of ICD-10 (F 32.0-7.32.2, F 33.0-F 33.8) [15]. All the subjects from the DD group were examined in the course of their hospitalisation. The study group included both subjects, hospitalised for the first time for depressive episode and depression treatment-naïve, and those, treated for many years before and with multiple

Table 1. Demographic characteristics of the group with depressive disorders (DD) vs. the comparison group (CG) and the data concerning the course of disease

Characteristics		DD n = 86			CG n = 55		
		n	%	(± SD)	n	%	(± SD)
Gender	Female	52	60.47	-	34	61.82	-
	Male	34	39.54	-	21	38.18	-
Age in years	-	-	-	47.01 (± 9.25)	-	-	44.95 (± 10.21)
Education level	Primary	32	37.21	-	4	7.27	-
	Secondary	40	46.51	-	33	60.00	-
	High	14	16.28	-	18	32.73	-
Disease	Disease duration in years	-	-	5.89 (± 5.64)	-	-	-
	Number of depression episodes	-	-	7.52 (± 6.11)	-	-	-

n – numbers of patients; ± SD – standard deviation

hospitalisation episodes in history, the latter admitted for various degrees of health deterioration. The presence of axis I and II disorders, other than depressive episode, and the diagnosis of somatic diseases, injuries of the central nervous system (CNS) or drugs, which could have affected the cognitive functionality, were regarded as exclusion criteria. In all the included cases, history was obtained, using the standardized Composite International Diagnostic Interview (CIDI) [16]. Additionally, the number of depression episodes and the disease duration periods were recorded in each patient.

During hospitalization at the Department, all the patients received antidepressant pharmacotherapy (in monotherapy), including drugs of the SSRI (Sertonic Selective Reuptake Inhibitors) group: 54 patients received fluoxetin, the onset dose (20 mg/day, the maximal dose: 60 mg/day, the mean dose: *M*=35 mg/day, *SD*=9.5), 8 patients received sertraline (the onset dose: 50 mg/day, the maximal dose: 200 mg/day, the mean dose: *M*=130 mg/day, *SD*=14.7), 12 patients were administered citalopram (the onset dose: 20 mg/day, the maximal dose: 40 mg/day, the mean dose: *M*=31 mg/day, *SD*=4.3), 12 patients received paroxetin (the onset dose: 20 mg/day, the maximal dose: 60 mg/day, the mean dose: *M*=32 mg/day, *SD*=3.9). The mean duration of the disease for DD patients had been *M*=7.63 years, *SD*=8.31 years, the mean number of hospitalization episodes for depressive disorders *M*=2.72, *SD*=2.29, the mean number of depression episodes *M*=7.05, SD=7.54.

The selection of the comparison group was random. The comparison group (CG) consisted of 55 healthy subjects with family history negative for psychiatric disorders. The healthy controls included community volunteers, enrolled into the study on the criteria of the psychiatric CIDI interview [16]. Controls with other psychiatric diagnoses, concerning axis I and II disorders, were excluded from the study. Subjects with a history of neurological or psychiatric disorders or a family history of mood disorders, substance abuse or dependence, were also excluded.

Neither the group with depressive disorders nor the comparison group demonstrated any statistically significant differences with respect to age, gender, racial/ethnic background or the mean education period ($p>0.05$). All the patients and control subjects were native, unrelated Poles, inhabitants of the central Poland. An informed, written consent for participation in the study was obtained from each subject, according to the protocol, approved by the Bioethical Committee of the Medical University of Łódź (No RNN/603/08/KB).

Method

The Trail Making Test (TMT) and Stroop's Tests were used in the study. Part A of TMT was applied for evaluations of psychomotor speed, while part B was used for assessments of spatio-visual performance, working memory and executive functions [17, 18, 19].

The Stroop test (Colour Word Interference Test) was performed with the use of paper cards. The test is used for working memory evaluations. The Stroop Test consists of two parts: RCNb (reading colour names in black) and NCWd (naming colour of word – different). In the reported study, the duration of each test part performance was measured and the number of errors, made in the NCWd part, was counted [20].

The severity of depression was assessed by the 21-item Hamilton Depression Rating Scale (HDRS) [21, 22]. Depressive symptom intensity levels were classified by the grades, specified in the study by Demyttenaere and De Fruyt [23]. The HDRS scale was also used for clinical improvement evaluations after applied pharmacotherapy, with HDRS scores after 8 weeks of therapy as improvement indicators vs. depression levels (in HDRS scale). The psychic status improvement and the efficacy of applied therapy were evaluated in two aspects: the response to therapy and disease remission. A response to therapy was defined as ≥ 50% depression symptom reduction vs. the base level, while HDRS score < 7 was regarded remission.

Regarding the patients with DD, HDRS, the Stroop Test and TMT were applied at the therapy onset (on admission) and after 8 weeks of its continuation. All the patients were examined on admission, i.e., at the symptomatic phase, before or shortly after previous antidepressant drug regime modification. In the control group, the Stroop Test and the Trail Making Test were performed in single examination. Examination of patients by the above-mentioned tests was done by the same person in each particular case: the same psychologist examined the patients with the Stroop Test and TMT, including an evaluation of obtained results, while the HDRS test was performed by the same physician-psychiatrist.

Statistical analysis

Statistical analysis of the collected material utilized descriptive methods, as well as a statistical conclusion. In order to describe the studied group of patients and the control group, structural indexes were calculated in the qualitative analysis of characteristics. In order to estimate the average values for the quantitative characteristics, arithmetic means (*M*) were calculated. Standard deviation (*SD*) was adopted as the measure of scatter.

The Lilliefors (Kolmogorov-Smirnov) test for normality was used to evaluate distribution normality of the studied variables. The test values turned out to be statistically insignificant, thus providing no foundations to reject the distribution normality hypothesis.

The t-test for dependent groups was used to evaluate differences in the degree of depressive disorders and of the Stroop Test and TMT performance levels in the group of DD patients, both on admission (DD-I) and after 8 weeks of the therapy continuation (DD-II). Differences in the Stroop Test and the Trail Making Test performance levels were assessed between the DD (DD-I, DD-II) group and the control group, using the t test for independent samples.

The differences in the mean scores, obtained by the tested subjects in each study group, were evaluated by the one-way ANOVA analysis. The procedure of multiple comparisons was employed to see which groups were responsible for the one-way ANOVA results.

The relationships between spatio-visual performance levels and verbal working memory, evaluated on admission, with the remission degrees, assessed by the HDRS after eight (8) weeks of pharmacological treatment, were expressed as Pearson's correlation coefficients (Pearson's r). In all the statistical methods, the p value for statistical significance was: $p<0.05$,

Results

On admission, 6 subjects met the Hamilton Depression Rating Scale score criteria for mild depression episode, 19 for moderate one and 61 for severe depression episode. On the day of discharge, 40 subjects did not meet the Hamilton Depression Rating Scale criteria for depressive disorder, 34 met the HDRS criteria for mild depression, 8 for moderate and 4 for severe depression (see Figure 1). Figure 2 demonstrates the final evaluation of therapy efficacy in the HDRS scale (see Figure 2 – *next page*).

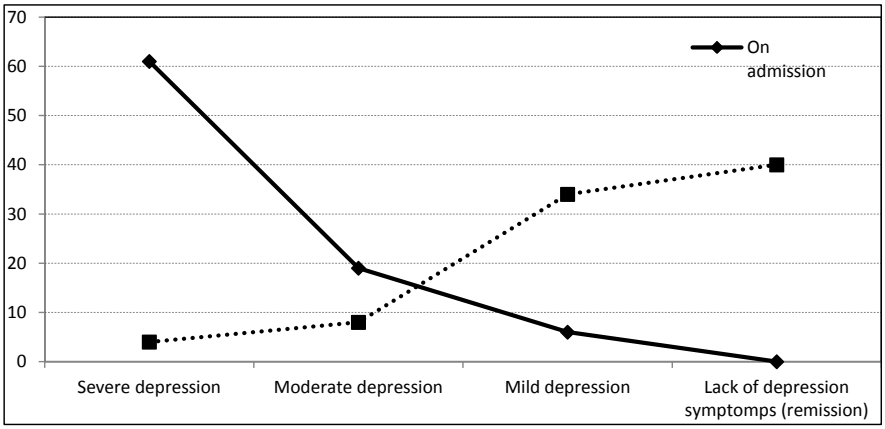

Figure 1. **Enhancement of depression symptoms in the study group (n = 86) on admission and discharge.**
Lack of depression symptoms: 0-7 points, mild depression: 8-12 points, moderate depression: 13–17 points, severe depression: 18–29 points [23].

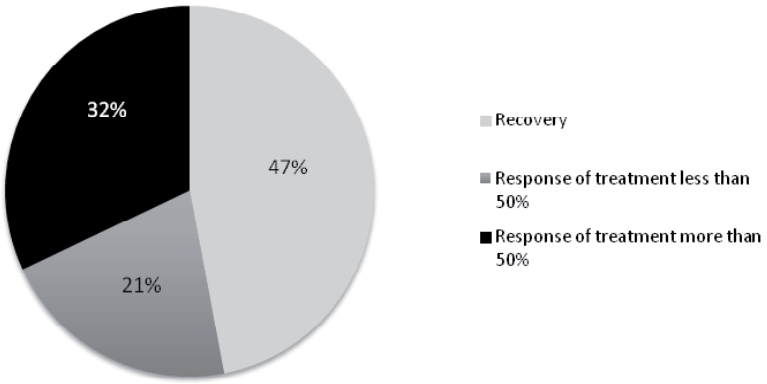

Figure 2. **Evaluation of therapy efficacy in the study group (n = 86) by the HDRS scale**

Statistically significant differences were found in the intensity of depression symptoms, measured by the HDRS in DD group on therapy onset (DD-I) vs. the examination results after 8 weeks of treatment (DD-II) (p<0.001) (see Table 2). Considering the 8-week pharmacotherapy period, DD patients presented with better outcomes of both cognitive function tests vs. the results on therapy onset (see Table 2).

The comparison group obtained significantly higher scores than DD-I patients in the Stroop Test (see Table 2) and in the Trail Making Test. The comparison group obtained significantly better results than DD-II patients in the Stroop Test. On the other hand, no statistically significant differences were found between the groups, regarding TMT results.

Table 2. **Results of tests in the control group and in the patients with depression, evaluated on therapy onset and after 8 weeks of its continuation.**

Variable	DD-I	CG	t	p
	(±SD)	(±SD)		
Stroop Test / RCNb time (s)	34.39 (±16.19)	21.38 (±3.34)	5.87	p*<0.001
Stroop Test / NCWd time (s)	83.47 (±17.23)	52.82 (±10.69)	4.09	p*<0.001
Stroop Test / NCWd (errors)	4.58 (±5.84)	1.82 (±2.21)	3.36	p*<0.001
TMT / A time (s)	60.18 (±47.68)	47.24 (±24.98)	1.72	p=0.09
TMT / B time (s)	112.91 (±58.55)	85.19 (±53.96)	2.65	p*=0.009
Variable	DD-II	CG	t	p
	(±SD)	(±SD)		

table continued on next page

Stroop Test / RCNb time (s)	34.42 (±16.38)	21.38 (±3.34)	5.78	p*<0.001
Stroop Test / NCWd time (s)	70.65 (±37.25)	52.82 (±10.69)	3.41	p*<0.001
Stroop Test / NCWd (errors)	2.54 (±4.98)	1.82 (±2.21)	0.97	p=0.33
TMT / A time (s)	48.58 (±23.95)	47.24 (±24.08)	-1.65	p=0.11
TMT / B time (s)	86.89 (±38.27)	85.19 (±53.96)	-0.19	p=0.85
Variable	DD-I	DD-II	t	p
	(±SD)	(±SD)		
HDRS	22.31 (±6.56)	7.64 (±5.17)	22.12	p*<0.001
Stroop Test / RCNb time (s)	34.39 (±16.19)	34.42 (±16.38)	0.89	p=0.378
Stroop Test / NCWd time (s)	83.47 (±17.23)	70.65 (±37.25)	2.26	p*=0.03
Stroop Test / NCWd (errors)	4.58 (±5.84)	2.54 (±4.98)	4.15	p*<0.001
TMT / A time (s)	60.18 (±47.68)	48.58 (±23.95)	4.47	p*<0.001
TMT B time (s)	112.91 (±112.91)	86.89 (±38.27)	3.97	p*<0.001

HDRS – Hamilton Depression Rating Scale; TMT – Trail Making Test; DD-I – patients with depressive disorders, examined on therapy onset; DD-II – DD patients after 8-week therapy;CG – control group; ± SD – standard deviation; p*– statistically significant, $p < 0.05$;

The one-way ANOVA demonstrated statistically significant differences in the mean values among particular groups for each of the analysed results in the Stroop Test and TMT: Stroop Test RCNb/time (*s*): F=17.333, p<0.0001; Stroop Test NCWd/time (*s*): F=9.036, p<0.0001; Stroop Test RCNb/errors: F=1.479, p=0.231; Stroop Test NCWd/errors: F=6.257, p=0.002; TMT A/time (*s*): F=4.969, p=0.007; TMT B/time (s): F=6.249, p=0.002. See Table 3 – *on next table* for detailed results of the Stroop Test and TMT for particular groups.

Statistical analysis (see Table 4 – *on next table*) revealed significant relationships between HDRS scores after and cognitive functions before the administered treatment. The lowest performance in the Stroop Test, part NCWd/time (p=0.02), NCWD/errors (p=0.04), and TMT, part A/time (p=0.001) evaluated on admission, was connected with the highest depression level after pharmacological treatment.

Table 3. **The level of significance of the differences for particular groups in the performance on the Stroop Test and TMT.**

Stroop Test / RCNb time (s)			
	DD-I	DD-II	CG
DD-I		p=0.999	p*<0.001
DD-II	p=0.999		p*<0.001
CG	p*<0.001	p*<0.001	
Stroop Test / NCWd time (s)			
	DD-I	DD-II	CG
DD-I		p*=0.01	p*<0.001
DD-II	p*=0.01		p*=0.02
CG	p*<0.001	p*=0.02	
Stroop Test / NCWd (errors)			
	DD-I	DD-II	CG
DD-I		p*=0.002	p*=0.004
DD-II	p*=0.002		p=0.742
CG	p*=0.004	p=0.742	
TMT / A time (s)			
	DD-I	DD-II	CG
DD-I		p*=0.01	p=0.169
DD-II	p*=0.01		p=0.557
CG	p=0.169	p=0.557	
TMT / B time (s)			
	DD-I	DD-II	CG
DD-I		p*=0.012	p*=0.017
DD-II	p*=0.012		p=0.986
CG	p*=0.017	p=0.986	

TMT – Trail Making Test; DD-I – patients with depressive disorders, examined on therapy onset; DD-II – DD patients after 8-week therapy; CG – control group; p*– statistically significant, $p < 0.05$

Table 4. **The Pearson's (Pearson's r) correlation coefficient for value of the Stroop Test, TMT before treatment and HDRS after pharmacological treatment.**

	HDRS	
Variable	Pearson's r	p
Stroop Test / RCNb time (s)	0.155	p=0.346
Stroop Test / NCWd time (s)	0.359	p*=0.02
Stroop Test / NCWd (errors)	0.318	p*=0.04
TMT / A time (s)	0.395	p*=0.01
TMT / B time (s)	0.206	p=0.207

HDRS – Hamilton Depression Rating Scale; TMT – Trail Making Test; p*– statistically significant, $p < 0.05$

Discussion

The presented study is one of the few attempts, utilizing the results of cognitive function tests for the prognosis of depressive symptom remission. The obtained results indicate that depressive disorders are associated with failures of irrelevant information deletions from the working memory and with impaired executive functions. In comparison with healthy subjects, depressive patients achieved significantly poorer results in the applied tests, also assessing the spatio-visual and verbal working memory (see Tables 2 and 3). Considering the 8-week pharmacotherapy period, DD patients presented with better outcomes in both cognitive function evaluating tests vs. the base values on therapy onset (see Table 2 and Table 3), however, the obtained results were still weaker vs. CG. The study by Herrera-Guzmán et al. [24], Vasic et al. [25] (employing the Sternberg Item Recognition Paradigm), Joormann et al. [26] (verbal test, based on the N-back test principle), Walter et al. [27] (verbal test, based on the N-back test principles) and Hugdahl et al. [28], (a test with the use of arithmetic exercises), despite different diagnostic tools, also indicate working memory deficits among depressive patients. Following Alexopoulos et al. [29] late-life depression is associated with executive dysfunction, which persists even after depressive episode remission. Baba et al. [30] aimed at investigating whether remitted major depressive disorders, observed in adult and elderly patients, show different executive dysfunction patterns. Relative to depressive patients and healthy comparison subjects, remitted patients were more impaired in Behavioral Assessment of the Dysexecutive Syndrome, which measured executive functions. Moreover, mild cognitive impairment and depression can more than double the risk for dementia of Alzheimer type vs. non-depressive subjects [31]. Rosenberg et al. [32] demonstrated also that depressive symptoms increased the risk for MCI (mild cognitive impairment) in subjects without previously noted symptoms of disturbed cognitive functions (436 non-demented women, 70-79 years old, were examined). In turn, those results were not confirmed by Matsuo et al. [33] or Rose et al. [34] (both tests were performed with the visual version of the N-back test).

Employing a correlation analysis, the relationship was evaluated between spatio -visual performance and verbal working memory, assessed on admission, with the remission degree, evaluated by HDRS after 8-week pharmacotherapy, (see Table 3). The model included with statistical significance: the Stroop Test, part NCWd (time and errors) and the Trail Making Test, part A. The obtained results allow for conclusion that better verbal working memory and visual-spatial coordination test performance, noted on the first day of treatment in the group of patients, correlated with a lower intensity of depressive symptoms (measured by the HDRS) after 8 weeks of pharmacological treatment with SSRI. Sheline et al. [11] examined 217 subjects, aged 60 years or more and meeting DSM-IV criteria for major *depression* – who scored 20 or more on the Montgomery-Asberg *Depression* Rating Scale (MADRS). All the patients received antidepressant pharmacotherapy (twelve weeks of sertraline treatment). Baseline episodic memory, language, *working memory*, processing speed and executive function factor scores predicted MADRS scores, controlling for age, *education*, the age of onset and race. Those factors remained significant predictors of decrease in MADRS sco-

res. Thirty-three percent of subjects achieved remission (MADRS ≤7). The remitters differed from nonremitters in baseline cognitive processing speed, executive function, language and episodic memory. In the study by Alexopoulos et al. [29], late-life depressed patients with deficits in Stroop Test had lower remission rates to citalopram than late-life depressed patients without deficits in Stroop performance. Han et al. [35] compared the intensity of depressive symptoms, measured by the Hamilton Depression Rating Scale and cognitive function of the patients, assessed by the Mini-Mental State Examination (MMSE). They found that an increase in the Hamilton Depression Rating Scale score by 1 was accompanied by deterioration of Mini-Mental State Examination performance by 0.03. On the other hand, Naismith et al. [36] confirmed that cognitive function impairment in depressive patients was a good predictor of subjectively assessed physical, mental and social fitness deterioration. Dunkin et al. [37] assessed the correlation between the patients' cognitive functions and therapeutic efficacy of SSRI in a group of 14 patients (mean age 41.9 years), treated for severe depressive episodes. In their opinion, worse performance in the Stroop Test and the Wisconsin Card Sorting Test (WCST), designed for assessments of working memory and executive functions, may be a predictor of low therapeutic efficacy of an SSRI drug. Studies by Withall et al. [38] indicate that poorer WCST performance in the WCST on admission to hospital correlates not only with worse therapeutic effects but also with worse social and occupational adaptation of the patients after discharge. According to Potter et al. [39], Baldwin et al. [40] and Story et al. [41], the level of cognitive function in older patients with depression (above 60 years of age) is associated with lower efficiency of antidepressant treatment and shorter periods of remission. However, in the authors' opinion, the intensity of depressive symptoms does not affect the above correlation. According to Modrego and Ferrández [31], patients with a poor response to antidepressants are at an especially increased risk for dementia. Kiosses and Alexopoulos [12] proposed that working memory and executive function assessment should become a routine examination procedure of patients above 60.

The wide age range of subjects and different duration of disease may be a limitation of our study. These variables can affect cognitive functions. The results of our preliminary study require further validation in subsequent research.

In summary, it should be emphasized that better understanding of the role of working memory and executive functions in the effectiveness of antidepressant treatment may enable earlier identification of patients with less beneficial therapeutic effects.

Conclusions

1. Depressive disorders are associated with deteriorated efficiency of visual and verbal working memory.
2. Antidepressant treatment resulted in improved of visual and verbal working memory.
3. The better performance in the Stroop Test and in TMT on the first day of treatment may have influenced the noted reduction in severity of depressive symptoms after treatment with SSRI.

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