

ORIGINAL ARTICLE

Improvement in neurocognitive functions and serum brain-derived neurotrophic factor levels in patients with depression treated with antidepressants and yoga

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ABSTRACT

Context and Aims: Impairment in cognition is well-known in patients with major depressive disorder. This study examined the effect of yoga therapy with or without antidepressants and antidepressants alone on certain neuropsychological functions in patients with depression. Correlation between changes in neuropsychological test performance and serum brain-derived neurotrophic factor (BDNF) levels was also explored.

Materials and Methods: Antidepressant-naïve/antidepressant-free outpatients with depression received antidepressant medication alone ($n = 23$) or yoga therapy with ($n = 26$) or without ($n = 16$) antidepressants. Depression was assessed using the Hamilton Depression Rating Scale. Neuropsychological tests included digit-span forward and backward, Rey Auditory Verbal Learning Test, and Trail Making Tests (TMT-A and B). These tests were administered before and 3 months after the treatment in patients, and once in healthy comparison subjects ($n = 19$).

Statistical Analysis: Baseline differences were analyzed using independent sample *t*-test, Chi-square, and one-way ANOVA. Paired *t*-test was used to analyze the change from baseline to follow-up. Pearson's correlation was used to explore the association of change between 2 variables.

Results: Patients had impaired performance on most neuropsychological tests. After 3 months, there was significant improvement – patients' performance was comparable to that of healthy controls on majority of the tests. Significant inverse correlation was observed between increase in BDNF levels and improvement in TMT "A" duration in Yoga-alone group ($r = -0.647$; $P = 0.009$).

Conclusions: To conclude that, Yoga therapy, alone or in combination with medications, is associated with improved neuropsychological functions and neuroplastic effects in patients with depression.

Key words: Antidepressants, brain-derived neurotrophic factor, cognition, depression, Rey Auditory Verbal Learning Test, yoga

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INTRODUCTION

Depression is a highly prevalent mental disorder characterized by sadness of mood, anhedonia, negative cognitions and retardation of motor behavior, and cognitive process impairment in neurocognition is well-known in patients with major depressive disorder.^[1] Patients with depression experience neuropsychological impairment in several domains including verbal learning, memory, attention, motor speed, and executive functions.^[2-6] Studies show inconsistent results regarding the influence of antidepressant medications on neurocognitive functioning of patients with depression. While some studies report improved cognitive functioning,^[7] other studies report no significant improvement after antidepressant medications.^[8,9]

Brain-derived neurotrophic factor (BDNF), a key modulator of neuroplastic changes, has been implicated in the pathophysiology of depression^[10] through the stress pathway.^[11,12] Decreased serum BDNF levels were observed in medication-free patients with depression in comparison to healthy controls.^[13,14] Serum BDNF level has been shown to increase with antidepressant treatment.^[15-17] In addition, decreased serum BDNF levels were significantly correlated with reduced hippocampal volume in moderately depressed patients.^[18] Further, decreased serum BDNF levels were associated with better performance in attention and psychomotor speed tested using Trail Making Test (TMT) in patients with major depression.^[19] In this context, abnormal neuroplasticity has been proposed as an important pathophysiological mechanism underlying depression.^[20] There is a need to look at complementary and alternative approaches as a treatment option in patients with depression.

Yoga is an effective treatment for depression.^[21] It has also been shown to improve cognitive functions. Sahaj Yoga practice (one type of meditation) improved the cognitive domains of verbal working memory, attention span, and visual-motor speed in addition to improvement in executive functions in patients with depression.^[22] In a recent study, regular practice of yoga has been shown to enhance serum BDNF levels and reduction in depression scores in patients with depression.^[23] Further, the practice of yoga is reported to increase hippocampal volume in elderly participants.^[24]

Little is known about the changes in cognitive impairment in depression with practice of generic yoga. We compared the effect of yoga therapy with or without antidepressants, and antidepressants alone, on certain neuropsychological functions in patients with depression. Further, we examined the association between neuropsychological functions, serum BDNF levels, and severity of depression.

MATERIALS AND METHODS

Subjects

Data for this study were obtained from participants, who took part in a three-group, single-blind comparative trial; the detailed methodology of the trial is presented elsewhere.^[23] Briefly, patients with depression with a score of 11 or more on Hamilton Depression Rating Scale (HDRS) and score of 2 or less on the suicide item of HDRS^[25] were recruited from the outpatient department of psychiatry in an academic psychiatric center. They were aged between 18 and 55 years. Diagnosis of major depressive disorder was made according to the DSM-IV criteria. The diagnosis was confirmed by a psychiatrist using the Mini International Neuropsychiatric Interview.^[26] Patients were either antidepressant-naïve or not on antidepressants for at least 1 month. Patients with mental retardation, substance abuse disorders (except nicotine and caffeine), organic disorders such as dementia, epilepsy, or cerebrovascular accidents, psychosis and bipolar disorder were excluded from the study. None of them had received yoga as treatment before. The patients had no indications for electroconvulsive therapy (e.g., catatonia, severe, treatment-resistant depression). Written informed consent to take part in the study was obtained from all study participants. The study was approved by the Institutional Ethics Committee.

One hundred and thirty-seven patients with depression were recruited in the main study.^[23] Of these, 65 patients' neuropsychological assessment data were available for baseline as well as 12 weeks follow-up. There were three naturalistic groups of patients: Medication-alone ($n = 23$), yoga therapy-alone ($n = 16$), and medications + yoga therapy ($n = 26$). The duration of the follow-up was 12 weeks. Out of the 32 age and education-matched healthy subjects, neuropsychological performance data was available for 19. None of the healthy controls had any psychiatric/medical disorder or alcohol/drug use disorders.

Yoga therapy procedure

A yoga module developed and validated for depression was used in this study.^[27] The participants of both the yoga groups attended Yoga sessions daily for 2 weeks at Yoga therapy center of NIMHANS, where a yoga professional taught them the yoga practices. Each session of training/practice lasted for about 1 h. They were then asked to come to perform yoga practices in the yoga therapy center twice a week for the next 2 weeks. The participants were instructed to continue the yoga practices at home thereafter, except for one booster session at every month held at the yoga therapy center. Home practices were monitored by a family member for the next 2 months. They were also instructed to maintain a log of each day's yoga at home filled by the family members. The yoga professional was formally trained with a graduate medical degree (5 years) in yoga and naturopathy with 2 years' postgraduate degree in yoga. Efforts were made to maintain 100% attendance. The patients receiving

yoga were encouraged to report any untoward event that they had experienced during the course of the study.

Antidepressant medication

During the 3 months of study, the patients on antidepressant medications received a consultation with their respective psychiatrists. Antidepressant type and dose were not controlled. However, the medications, their dosage, and changes, if any, were noted. The treatment remained unchanged in nearly all patients. Antidepressants administered were escitalopram (10–15 mg/day; $n = 63$), fluoxetine (20–40 mg/day; $n = 30$), duloxetine (60 mg/day; $n = 1$), sertraline (50–100 mg/day; $n = 3$); amitriptyline (25–100 mg/day; $n = 13$), mirtazapine (7.5–15 mg/day; $n = 4$). In addition, some patients were given benzodiazepines (lorazepam up to 3 mg/day or alprazolam 1.5 mg/day). The researcher had a telephonic conversation with all the participants to inquire regarding their medication/yoga practice compliance at home.

Assessments

A trained rater blind to the group status of the patients (resident in psychiatry) assessed the severity of depression using HDRS. Neuropsychological functions were assessed by another researcher (Naveen GH). Patients and healthy controls had minimum 5 years of schooling and could read English letters and numerals. The following neuropsychological tests were administered before starting the treatment and at the end of 3 months: (1) Rey auditory verbal learning test,^[28,29] (2) digit span test,^[30] and (3) TMT.^[31-33]

Statistical analysis

In this paper, we present an analysis of data from patients in whom neuropsychological test data are available

at baselines as well as at 3-month follow-up ($n = 65$). Baseline differences between patients and controls with respect to sociodemographic data, serum BDNF levels, and neuropsychological test scores were analyzed using independent sample *t*-test and Chi-square test. Baseline comparisons across three groups of patients with respect to sociodemographic details, illness characteristics, serum BDNF levels, and neuropsychological changes were assessed using Chi-square test and one-way ANOVA. Paired *t*-test was used to analyze the change, from baseline to follow-up, in HDRS, BDNF, as well as in neuropsychological test scores. Pearson's correlation was used to explore the association of change in serum BDNF levels with change in neuropsychological test scores.

RESULTS

Table 1 presents baseline comparison of sociodemographic details and neuropsychological assessment between patients and controls. There were no significant differences between patients and controls with respect to sociodemographic details, except that females were significantly over-represented in the control group. Patients' scores on neuropsychological tests were significantly poorer than that of healthy controls on most neuropsychological tests except digit span backward and trail making error "A." Serum BDNF levels were significantly lower in patients.

As shown in Table 2, patients in the three treatment groups were not significantly different with respect to baseline sociodemographic details and illness characteristics. However, there was a significant difference across 3 group with respect to education ($P = 0.03$); patients in the yoga alone group had higher education levels than those in the other two.

Table 1: Sociodemographic details, serum brain-derived neurotrophic factor levels, and performance of patients and controls on cognitive function tests

Parameter	Mean (SD)		t^*/χ^2	P
	Patients ($n=65$)	Controls ($n=19$)		
Age (years) [#]	34.60 (8.85)	32.84 (9.14)	0.326	0.745
Gender (%)				
Males [^]	38 (58.46)	05 (26.31)	6.081	0.013
Females [^]	27 (41.53)	14 (73.68)		
Education (years) [#]	11.86 (3.58)	12.89 (4.06)	-1.071	0.287
Serum BDNF [#]	19.32 (6.22) ($n=51$)	23.58 (6.81) ($n=13$)	-2.162*	0.03
Neuropsychological functions [#]				
Digit span forward	3.81 (1.12)	4.58 (1.21)	-2.56*	0.012
Digit span backward	2.30 (1.00)	2.68 (1.25)	-1.39	0.167
Trail making duration "A" (s)	60.32 (25.70)	43.11 (12.89)	3.95*	<0.001
Trail making error "A"	0.31 (0.66)	0.32 (0.47)	-0.050	0.960
Trail making duration "B" (s)	174.83 (100.66)	122.05 (55.53)	2.184*	0.032
Trail making error "B"	2.03 (2.33)	0.68 (0.74)	2.471*	0.016
RAVLT total score	41.70 (9.42)	55.05 (9.81)	-5.370*	<0.001
RAVLT distraction list B	4.20 (2.15)	5.32 (1.85)	-2.2036*	0.045
RAVLT immediate recall	8.67 (2.95)	11.37 (3.05)	-3.47*	0.001
RAVLT delayed recall	7.72 (2.62)	11.11 (2.55)	-4.97*	<0.001

[#]Continuous variables-independent samples *t*-test, [^]Expressed as number (percentage as whole %). RAVLT – Rey auditory verbal learning test; SD – Standard deviation

Baseline comparison between three treatment groups were not significantly different with respect to neurocognitive test characteristics, except on digit span backward ($P = 0.03$), where the medication-alone group performed poorly.

As shown in Table 3, there was a significant improvement in performance on most neuropsychological tests at follow-up. However, significant changes were observed more in the yoga-alone and yoga with antidepressant medication group in comparison with medication group alone. Further, the performance of controls and patients

at follow-up on neuropsychological tests did not show any significant differences between patients and controls with respect to performance in most of the neuropsychological tests. Patients scored similarly to healthy controls on most of the neuropsychological tests except trail making error "A" ($P = 0.01$), and Rey Auditory Verbal Learning Test total score ($P = 0.02$).

As reported in the previous publication,^[23] there was a significant increase in serum BDNF level from baseline to 3-month follow-up in patients. Mean (standard deviation)

Table 2: Comparison of the three treatment groups across demographic, illness, serum brain-derived neurotrophic factor characteristics

Variable	Medication (n=23)	Yoga with medication (n=26)	Yoga only (n=16)	F/ χ^2	P
Gender					
Male	13	16	09	0.169	0.919
Female	10	10	07		
Age (years)	30.96 (5.94)	33.81 (10.77)	37.06 (8.08)	2.352	0.104
Duration of illness (months)	23.87 (20.61)	20.31 (22.95)	21.81 (27.73)	0.141	0.869
Age of onset (years)	28.70 (6.25)	31.48 (10.25)	35.50 (7.59)	3.109	0.052
HDRS	18.17 (4.15)	18.12 (5.00)	16.88 (4.09)	0.479	0.622
BDNF	21.99 (6.03)	17.14 (5.79)	19.71 (6.22)	2.920	0.064
Education number of years	10.48 (3.35)	12.12 (3.70)	13.44 (3.14)	3.587	0.034
Drug naïve/drug-free (%)					
Naïve	16 (69.56)	18 (69.23)	10 (62.05)	0.262	0.877
Free	7 (30.43)	8 (30.76)	6 (37.5)		
Diagnosis					
Moderate depression	22 (95.65)	15 (57.69)	12 (75)	5.91	0.657
Family history of Depression	5 (21.73)	6 (23.07)	4 (25)	2.67	0.613
Medication (%)					
Escitalopram	13 (56.52)	18 (69.23)	-	3.971	0.410
Fluoxetine	7 (30.43)	5 (19.23)	-		
Amitriptyline	3 (11.53)	1 (3.84)			
Sertraline	0	1 (3.84)			
Mirtazapine	0	1 (3.84)			

HDRS – Hamilton depression rating scale; BDNF – Brain-derived neurotrophic factor

Table 3: Baseline and 12 weeks comparison of neuropsychological functions in patients with depression and comparison of these changes in all patients at follow-up and controls

Neuropsychological functions	Time	Medication (n=23)	Yoga + medication (n=26)	Yoga (n=16)	Healthy controls
Digit span Test Forward	Baseline	3.45 (0.91)	3.88 (1.17)	4.19 (1.22)	4.58 (1.21)
	12 weeks	3.64 (1.002)	4.58 (1.06)*	5.00 (1.26)*	
Digit span test backward	Baseline	1.95 (0.78)	2.27 (0.77)	2.81 (1.37)	2.68 (1.25)
	12 weeks	2.41 (1.00)*	2.88 (0.816)*	3.69 (1.44)*	
Trail making duration A	Baseline	65.48 (20.09)	57.45 (26.77)	57.56 (31.11)	43.11 (12.89)
	12 weeks	55.35 (18.73)*	45.81 (14.91)*	42.13 (17.25)*	
Trail making error A	Baseline	0.43 (0.89)	0.23 (0.43)	0.25 (0.57)	0.32 (0.47)*
	12 weeks	0.04 (0.209)	0.00 (0.00)*	0.00 (0.00)	
Trail making duration B	Baseline	181.78 (96.04)	159.2 (90.78)	190.13 (123.38)	122.05 (55.53)
	12 weeks	166.4 (81.17)	121.9 (58.41)*	146.25 (116.43)*	
Trail making error B	Baseline	2.61 (2.80)	1.27 (1.31)	2.60 (2.66)	0.68 (0.74)
	12 weeks	1.87 (2.22)	0.77 (1.07)	0.87 (1.40)*	
RAVLT total score	Baseline	40.21 (10.12)	42.76 (9.44)	42.18 (8.65)	55.05 (9.81)*
	12 weeks	44.26 (10.38)	52.04 (7.79)*	51.81 (10.36)*	
RAVLT distraction list B	Baseline	3.74 (1.54)	4.60 (2.50)	4.25 (2.32)	5.32 (1.85)
	12 weeks	3.57 (1.16)	5.76 (2.60)	5.69 (1.58)*	
RAVLT immediate recall	Baseline	8.33 (2.82)	8.40 (3.13)	9.50 (2.85)	11.37 (3.05)
	12 weeks	9.43 (2.87)	11.36 (2.79)*	11.31 (2.54)*	
RAVLT delayed recall	Baseline	7.39 (2.40)	8.08 (2.88)	7.63 (2.57)	11.11 (2.55)
	12 weeks	8.91 (3.27)	10.48 (2.66)*	10.50 (2.80)	

* $P < 0.05$ cell values are mean (SD). SD – Standard deviation; RAVLT – Rey auditory verbal learning test

serum BDNF level of patients at follow-up (21.36 [6.53] ng/ml) was comparable to that of controls (23.58 [6.81] ng/ml; $t = 1.09$; $P = 0.28$). In addition, the correlation coefficients were in the expected direction: the higher the increase in serum BDNF, the better was the test performance. However, they were statistically nonsignificant except in one case: there was a significant negative correlation between increase in BDNF levels and reduction in TMT “A” duration, in the Yoga-alone group [Figure 1; $P = 0.009$; $r = -0.647$].

DISCUSSION

Patients with depression in this study had impaired performance on most neuropsychological tests when compared to healthy controls. Their performance improved significantly following treatment – improvement was observed across all three treatment groups, antidepressants alone, antidepressants and yoga, and yoga alone. Neuropsychological performance of patients “normalized” after 3 months of treatment. There was a significant increase in the serum BDNF levels in these patients. The increase in serum BDNF correlated with improvement in performance in most neuropsychological tests although it reached statistical significance in only one of the tests of psychomotor speed (Trail-making test A duration) in patients who received yoga alone as treatment.

The finding of impaired neuropsychological test performance is consistent with a number of previous studies that have compared the performance of patients with depression and healthy controls.^[2-6] Improvement in the test performance has also been noted in many previous studies.^[7,34,35] This is the first study to demonstrate improvement in cognitive functions with yoga therapy alone in depression. This finding is not surprising, given that a number of previous studies have shown that cognitive functions show substantial improvement with yoga in patients with other conditions and healthy controls.^[22,36-38] A significant increase was noted in serum BDNF level as reported in our previous paper. The direction of correlation between increase in serum BDNF level was in the expected direction – the

more the increase in serum BDNF level, the better was the performance in neuropsychological test performance across all tests and groups although it did not reach the level of statistical significance in most cases. Given that the sample sizes were small in each of the subgroups of patients; this perhaps reflected a type-II error.

There was a significant negative correlation between increase in serum BDNF level and duration of time taken to complete the TMT “A” in Yoga-alone group. This reflects the positive effect of yoga on both serum BDNF level and psychomotor speed. The lack of statistical significance in correlations in other groups perhaps reflects possible confounding effects of antidepressants on this correlation. Yoga may have different biological mechanisms that operate with mood-elevation, reduction in cortisol, and BDNF enhancement pathways. A recently published article demonstrated a significant correlation between increase in serum BDNF and reduction in serum cortisol levels in patients with depression.^[39] These mechanisms could have mediated the effect of yoga on neuropsychological test performance. Stress reduction mechanisms, by way of quieting the HPA axis, may be particularly relevant to the effect of yoga in reducing depression.

Studying antidepressant-naïve or antidepressant-free patients with depression and the use of neuropsychological tests standardized for local population are the important strengths of this study. The person who assessed the neuropsychological performance of the patients was not blind to the treatment status of the patients. Although this may be perceived as a drawback of the study since the tests provide fairly objective measures of neuropsychological functioning of patients, there was little scope for systematic bias. Some additional limitations of the study need to be mentioned: use of a limited set of neuropsychological tests, a substantial number of dropouts and the possibility of higher education levels in the Yoga group influencing the results. Further, other factors such as lifestyle modification by participants after exposure to yoga such as better nutrition, more attention to physical exercise, and sleep hygiene might have influenced the results in terms of better neuropsychological functions and BDNF levels. The reader may also refer to a recent critical review that summarizes the current evidence for efficacy, plausible mechanisms of action and future research directions in the area of yoga as an intervention in depression.^[40] Attending the yoga training may have increased the participants’ awareness and receptiveness to adopt health promotion strategies.

Future studies could look at into the biochemical mechanisms by which yoga practice increases serum BDNF levels and also association between serum BDNF levels\neuropsychological functions and volumetric changes in the hippocampus, as the reduction of hippocampal volume is seen in patients with depression. This study provides preliminary evidence

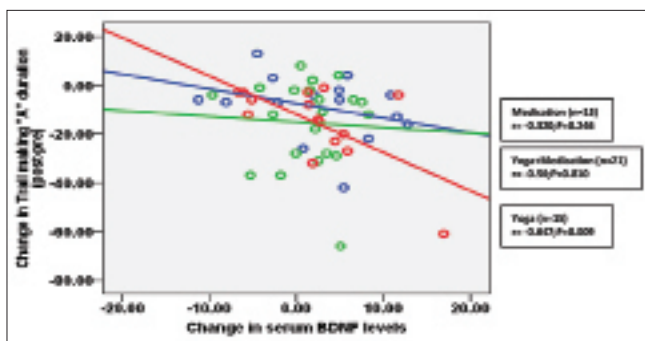


Figure 1: Correlation between change in brain-derived neurotrophic factor levels and Trail Making test “A” duration in patients with depression

for the effect of yoga therapy on cognitive performance of patients with depression and a possible correlation with neuroplastic mechanisms. The evidence suggests that yoga may be incorporated in clinical settings as a mind-body intervention to enhance the cognition and BDNF levels in patients with depression. The findings of this study need replication in larger samples with the use of more comprehensive neuropsychological assessments.

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Conflicts of interest

There are no conflicts of interest.

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