



The effectiveness of integrated neurocognitive therapy on neuropsychological functions in patients with major depressive disorder

Sara Farzi¹, *Azar Kiamarsi²; Ali Akbar Saremi³; Reza Kazemi¹

¹Department of Psychology, Ardabil Branch, Islamic Azad University, Ardabil, Iran.

²Department of Psychology, Rasht Branch, Islamic Azad University, Rasht, Iran.

³Department of Psychology, Torbat-e-Jam Branch, Islamic Azad University, Torbat-e-Jam, Iran.

Abstract

Introduction: Neuropsychological dysfunctions are a major factor in severe mental disorders, including depression. The present study aimed to investigate the effectiveness of Integrated Neurocognitive Therapy (INT) on neuropsychological functions of individuals with major depressive disorder.

Materials and Methods: In this cross-sectional study, 25 patients with major depressive disorder referring to psychiatric and rehabilitation clinics in Mashhad-Iran were selected by purposive sampling method. Data were collected using the Stroop Color-Word Test and Go/No-Go test in the pretest, posttest, and 3-month follow-up phases. Subsequently, the patients in the experimental group underwent integrated neurocognitive therapy for 20 sessions of 90 minutes each (twice a week). Repeated measures analysis of variance and Bonferroni post-hoc test were used for data analysis.

Results: The results showed that the interaction effect between Go/No-Go scores (omission error) and group ($F=2.15$, $P=0.148$) was not significant, but the interaction effect between Go/No-Go scores (commission error) and group was significant ($F=5.04$, $P=0.011$). After analyzing the Stroop test data, the results also indicated that the interaction effect between Stroop scores (interference errors) and group ($F=0.90$, $P=0.416$) was not significant, and the interaction effect between Stroop scores in the subscale (interference time) and group ($F=1.68$, $P=0.198$) was significant.

Conclusion: Based on the results, integrated neurocognitive therapy can be effective in improving some neuropsychological functions of patients with major depressive disorder and can be used.

Keywords: Cognitive rehabilitation, Executive functions, Integrated neurocognitive therapy, Inhibition, Major depressive disorder

Please cite this paper as:

Farzi S, Kiamarsi A, Saremi AA, Kazemi R. The effectiveness of integrated neurocognitive therapy on neuropsychological functions in patients with major depressive disorder. *Journal of Fundamentals of Mental Health* 2026 Mar-Apr; 28(2): 125-132. DOI: 10.22038/jfmh.2026.90853.3279

Introduction

Major Depressive Disorder (MDD) stems from a complex interplay of social, cognitive, and biological factors. Research has historically encountered challenges in operationalizing the high-risk or clinical status of past depression, with the complexity and heterogeneity of this illness often cited as an argument against such operationalization (1). MDD is a prevalent, often recurrent or chronic syndrome associated with elevated risks of suicide, comorbidity, and

reduced life expectancy (2). Despite the functional impairment that manifests early in the illness trajectory, MDD is frequently diagnosed with significant delays. The current scarcity of reliable instruments that comprehensively assess the multifaceted dimensions related to depression has directed part of the research toward emphasizing the importance of early depression detection and highlighting preventative strategies.

Structural and functional neuroimaging studies, alongside clinical investigations, have indicated alterations in the functioning of the Central Nervous System (CNS) in individuals with depression. According to this paradigm, the prefrontal cortex plays a crucial role in the generation of depressive symptoms. Neuropsychological deficits and functional impairments in patients with MDD, specifically deficits in non-verbal learning and problem-solving skills, are correlated with the risk of suicidal behavior (3,4). Reduced capacity for the engagement of the Dorsolateral Prefrontal Cortex (DLPFC) suggests that top-down cognitive control over affective responses is compromised in MDD, indicating that depression has a detrimental effect on the neurocognition (5). The intricate interaction between depressive symptoms and cognitive dysfunction underscores the necessity for comprehensive research into its various facets.

In recent years, novel paradigms, such as the Integrative Neurocognitive Approach (INT), have emerged, representing a major evolution in therapeutic methodologies. This approach offers exciting new insights into the close and reciprocal relationship between mindfulness, relationships, and the brain. Mindfulness, through enhancing neurocognitive integration in the medial prefrontal cortex area, leads to positive cerebral changes (6). Neurocognitive integration is a brain pattern associated with a sense of well-being; an integrated brain state fosters the most flexible, adaptive, and stable possible states within a dynamic and complex system. This clinical method is employed to improve the neuropsychological functions in MDD. The objective of the current study is to investigate the efficacy of the INT in treating individuals diagnosed with MDD and to answer the fundamental question: Is integrative neurocognitive therapy effective in improving the neuropsychological functions of Major Depressive Disorder?

Materials and Methods

This cross-sectional study, initially, a pre-test was administered. Subsequently, patients in the experimental group underwent 20 sessions of 90 minutes each of the intervention, selected based on purposive (non-probability) sampling, who attended psychological and rehabilitation clinics. The statistical population comprised referred clients to psychiatric and rehabilitation clinics in Mashhad- Iran, who received a

diagnosis of MDD according to the DSM-5 diagnostic criteria. Recruitment was facilitated by posting flyers in these centers. Only clients deemed in need of treatment by a psychiatrist were included in this design. Due to limitations in sample access and the prediction of potential attrition, a sample size of 40 individuals was initially selected using non-probability purposive sampling based on Cohen's table, considering a statistical power of 80%, an alpha level of 0.05, and an effect size of 0.2. This yielded an estimate of 20 participants per group. Fifteen individuals were withdrawn from the study due to pre-existing medical conditions, non-adherence to the protocol, or symptom recurrence. Finally, the remaining 25 participants were randomly allocated to either the experimental group (n= 13) or the control group (n= 12). All participants met the inclusion criteria: a diagnosis of MDD according to DSM-5, an age range between 20 and 60 years, and a minimum of a junior high school education. Exclusion criteria included absence from two consecutive sessions, intellectual disability, comorbidity with another mental or physical disorder, or symptom relapse.

Research instruments

A) *Demographic Questionnaire:* This questionnaire was developed by the researcher to determine the demographic profiles of the subjects such as age and marital status.

B) *Beck Depression Inventory-II (BDI-II):* Beck et al. developed this inventory in 1996. This tool is used to measure the severity of depression in adults diagnosed with a depressive disorder. Scores are rated on a four-point Likert scale from "none" (0) to "high" (3) based on the severity reported by the patient (7). Fathi et al. used this scale on 94 individuals from the Iranian population, yielding a Cronbach's alpha coefficient of 0.93 and a test-retest reliability coefficient of 0.81 over a 5-week interval, indicating suitable validity for use in the Iranian population (8).

C) *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/DSM-5):* A flexible interview developed by First, Spitzer, Gibbon, and Williams (1992). This interview has demonstrated good validity for diagnosing psychiatric disorders. The Persian version of the SCID-I has reported good psychometric properties (9).

D) Beck Hopelessness Scale (BHS): Beck et al. designed this scale in 1974 as a tool to measure hopelessness at the University of Pennsylvania's Center for Cognitive Therapy and administered it to diverse patient samples. The questionnaire consists of 20 true/false statements that assess an individual's pessimism and is considered a strong predictor of potential suicide, covering three critical aspects of feelings about the future: loss of motivation and expectations. This tool was used in Iranian populations (10).

E) Stroop Computerized Color-Word Test: This test was first designed and used by John Ridley Stroop in 1935 to assess selective attention and cognitive flexibility (11). The Stroop test is a classic measure of attentional processing and the ability to shift cognitive set, consisting of 7 stages (12).

F) Go/No-Go Task: This task measures behavioral inhibition and includes two stimulus categories. Participants must respond to one category (go) and withhold a response to the other (no-go). Three separate scores are derived from this test: percentage of commission error, percentage of inappropriate inhibition, and

reaction time. The reliability of this test has been reported as 0.87 (13).

G) Captain's Log Cognitive Rehabilitation Software: This is one of the software programs designed to enhance cognitive functions in areas such as visual recognition, auditory recognition, number perception, sequential conceptual patterns, and various types of memory (visual memory, auditory memory, working memory, memory sequencing). It was first introduced in 2000 by the Brain Train company in the USA. Bangirana et al. (14) showed that this software program can improve the learning of children with brain injury resulting from severe malaria. This software can also be used to assess the efficacy of computer-based cognitive therapy on the psychological problems of adults and to increase prefrontal cortex activity (15).

Siegel's Integrative Neurocognitive Therapy (INT) Protocol (Table 1) was administered in the present research by a Ph.D. student in psychology under the supervision of the second author—a Ph.D. in cognitive neuroscience—to ensure fidelity to the INT methodology.

Table 1. Summary of INT protocol (16)

Session	Content
1	Determination of depression severity and provision of therapeutic recommendations; diagnostic assessment via psychological testing
2	Identification of cognitive issues in the client's behavior and adaptation to capabilities, along with the assessment of executive functions through neuropsychological evaluation
3	Description of the rationale for the therapy. Objective: Familiarization with the general content of the sessions and fostering motivation to commence treatment
4	Establishing harmonious interaction and training on operating the Captain's Log software. Therapy homework: Writing therapeutic goals in the goals and expectations worksheet.
5	Training in attention stabilization skills, enhancement of attention and concentration abilities, and conceptual reasoning. Therapy homework: The circle of awareness, aiming for cognitive integration, and performing the conceptual discrimination game (The Ugly Duckling)
6	Strengthening synaptic integration, identification of rigid states: description of the manual brain model and the function of the left and right hemispheres, aiming for horizontal integration. Therapy homework: Journaling thoughts, feelings, and mental imagery; practicing visual pattern recognition (What's Next?).
7	Opening affective communication pathways and enhancing internal resources. Objective: Vertical integration. Therapy homework: Consistent performance of mindfulness meditation tailored to attentional capacity and playing Captain's Log skill games, such as Max's Match (symbolic matching) and Tower Power (size discrimination)
8	Exploration of the feeling of helplessness. Repetition of exercises to fully improve the targeted executive functions; presentation of the next exercise upon mastery. Expanding the window of tolerance (stay with it, repeated body scan) with the goal of vertical integration. Playing reinforcement games to compensate for weaker game performances. Therapy homework: Consistent performance of mindfulness meditation tailored to attentional capacity
9	Identifying unresolved memory representations and making sense of traumatic memories in the presence of a attuned other, aiming for memory integration. Therapy homework: Consistent performance of mindfulness meditation and the memory pattern recall game (Puzzle Power)
10	Attaining an "earned secure" life narrative and comprehending/making meaning of childhood experiences, aiming for narrative integration. Therapy homework: Consistent performance of mindfulness meditation and repetition of the previous session's exercise
11	Achieving a coherent life story narrative and enhancing attention skills. Cultivating self-compassion with the goal of narrative integration. Consistent performance of mindfulness meditation and specific exercises for visuospatial-auditory recall (Where's My Car) and paired word lists (Lost and Found)

12	Examining the formation of mental states and their acceptance through the identification of multiple selves, aiming for state integration. Exercises from prior sessions are repeated, and the next exercise is introduced upon learning. Therapy homework: Observing different self-states or unresolved conflicts and repeating the previous session's games
13	Trauma restructuring, enhancement of inhibitory skills, attentional shifting, and visual processing speed; locating the core self with the aim of state integration. Journaling the experience of mindful observation and playing the auditory scanning game (Mystery Messages)
14	Strengthening accepting skills, enhancing inhibitory skills, attentional shifting, and visual processing speed. Promoting receptivity over reactivity with the goal of interpersonal integration. Therapy homework: Identifying and journaling reactive situations and repeating the previous session's game
15	Converging the mind to restructure the brain, enhancing inhibitory skills, attentional shifting, and visual processing speed. Letting go of the certainty illusion, aiming for time integration. Therapy homework: Playing symbol search games (The Great Hunt) and visual scanning (Smart Detective) to reinforce cognitive inhibitory function
16	Expanding the inner territory: broadening identity and addressing any residual vulnerabilities. Introduction to the concept of meta-minding (or 'overarching awareness') to cultivate skills in mindfulness and freedom. Therapy homework: Repetition of the previous session's games
17	Clarification of any ambiguous teachings from past sessions, bridging techniques, and review of exercise execution with the client. Discussion regarding symptom recurrence to support the client and prepare them for returning to daily life, focusing on acceptance and management of their condition. Therapy homework: Noting favorite exercises and logging the client's self-experience of the neurocognitive integration state
18	Discussion of remaining conflicts, reflection on achieved progress, and emphasis on continuing techniques beneficial to the client. Therapy homework: Worksheet for favorite exercises and teachings prioritized by the client themselves.
19	Measurement of symptom severity and depression levels (Post-test)
20	Measurement of neuropsychological functions (Post-test)

Results

In term of demographic variables, the groups were homogeneous regarding marital status (experimental group: 69% married; control group: 67% married) ($P = 1.000$). The mean age for the experimental group was 38.85 ± 9.04 years, and for the control group was 36.58 ± 9.73 years ($P = 0.552$).

Before analyzing the treatment effect using repeated measures ANOVA, statistical assumptions were tested: The normality assumption for variables (Kolmogorov-Smirnov test) in both groups and both tests was

not rejected ($P > 0.005$). Homogeneity of variances (Levene's test) for both Stroop and Go/No-Go tests was not rejected ($P > 0.005$). For the Go/No-Go omission error subscale, the assumption of sphericity was rejected (Mauchly's Test) ($P = 0.026$). Therefore, the Greenhouse-Geisser correction with a value of 0.732 was applied. For all other subscales, the assumption of sphericity was accepted. The results of the repeated measures ANOVA are summarized below across the three measurement stages: Pre-test, post-test, and follow-up (Table 2).

Table 2. Results of repeated measures ANOVA (treatment effect)

Stroop test results			
Subscale	Main effect of time (overall change)	Interaction effect time $\times$ group (specific treatment effect)	Conclusion on INT efficacy
Time interference	$F = 6.19, P = 0.004$	$F = 1.68, P = 0.198$	INT treatment is not effective for this component
Error interference	$F = 1.72, P = 0.192$	$F = 0.90, P = 0.416$	INT treatment is not effective for this component
Go/No-Go test results			
Subscale	Main effect of time (overall change)	Interaction effect time $\times$ group (specific treatment effect)	Conclusion on INT efficacy
Commission error	$F = 6.89, P = 0.003$	$F = 5.04, P = 0.011$	INT treatment is effective for this component.
Omission error	$F = 1.00, P > 0.05$ adjusted	$F = 1.86, P > 0.05$ adjusted	-

In Stroop time interference, a significant change occurred across time points overall, but the interaction effect was non-significant, meaning this change was not specifically attributable to the INT intervention compared to the control group. For the Go/No-Go

commission error, both the main effect of time and the interaction effect were significant. This primary finding indicates that INT was effective in reducing commission errors (impulsivity/inhibition failure) in depressed patients. Post-hoc Bonferroni analysis for

commission error showed a significant reduction only between the follow-up and pre-test stages. Comparisons between pre-test/post-test and post-test/follow-up did not reach the significance level. Based on the statistical results, INT is effective in improving the commission error component of the Go/No-Go

Test (indicating improvement in inhibitory control/impulse control) in MDD patients. The treatment showed no significant effect on any component of the Stroop test (time interference or error interference) or the omission error component of the Go/No-Go test.

Table 3. Repeated measures ANOVA for Go/No-Go test (omission error)

Source of variation	SS	df	MS	F	P	Effect size (η_p^2)	Power
Within-subjects	Time	0.42	1.46	0.29	2.15	0.148	0.112
	Time $\times$ Group	0.42	1.46	0.29	2.15	0.148	0.112
	Error	3.33	24.90	0.13			
Between-subjects	Group	7.70	1.00	7.70	13.34	0.002	0.440
	Error	9.81	17.00	0.58			

In Table 3, the effect of time on Go/No-Go omission error scores was significant. Therefore, there was a significant difference in the mean scores across pre-test, post-test, and follow-up, regardless of the experimental group. However, within the within-subjects test, the interaction effect between Go/No-Go omission error scores and group was not significant. Thus, the difference in mean Go/No-Go omission error scores over different time points was not significant depending on the levels of the group variable. Furthermore, the effect of group on Go/No-Go omission error scores was significant. Therefore, regardless of the time of measurement, there was a significant difference in the mean Go/No-Go omission error scores between the experimental groups.

Based on the test results (interaction effect), it can be concluded that INT is not effective based on the Go/No-Go test (omission error) in MDD patients. Consequently, INT is effective based on the commission error scores in the Go/No-Go test and the time interference scores in the Stroop test in MDD patients. However, it showed no significant effect on the error interference dimension in the Stroop test and the omission error in the Go/No-Go test.

Discussion

This study evaluated the impact of Integrative Neurocognitive Therapy (INT) on the executive functions of 25 patients with MDD. According to the results, although some cognitive domains improved, persistent deficits were observed in specific variables, particularly Stroop Test time interference and Go/No-Go omission error. This positions the study as partly aligned with some research and contradictory to others.

In a study on 26 elderly patients with MDD indicated that these patients exhibited a significant reduction in cognitive inhibition when processing emotional stimuli (17). The findings of this current research confirm the ineffectiveness in improving executive functions in some indices. In the classic research conducted on 156 mood disorder patients, deficits in cognitive inhibition remained even after symptomatic recovery (18). This finding is consistent with some previous studies that have identified a distinct pattern of neural activity related to inhibition in depressed patients and emphasize that the assessment of inhibition in depression must systematically consider testing time to avoid confounding temporal effects (19,20). Mahmood Alilou et al. (21), in a study on 30 patients with hoarding-type OCD in Urmia treatment centers, believed that whether the subject provided a manual or verbal response to the stimulus affects the final outcome.

However, there are other studies showing that specific cognitive and behavioral interventions can help improve behavioral inhibition in these patients (22,24). Among these, a combination of the Stroop Test and N-Back in fMRI on MDD patients, demonstrated that cognitive training based on executive tasks led to significant improvement in prefrontal and attentional control networks. The Stroop test and similar tasks showed considerable effectiveness in modulating cognitive responses, which contradicts the current findings. Furthermore, based on imaging studies, concluded that attention and executive control disorders are widely documented in depressed patients, and cognitive training can have limited efficacy in rearranging neural

networks (26). This was confirmed, as in the research by Sagha et al. (27), which aimed to model the causal relationships of borderline personality disorder symptoms on 53 subjects, with cognitive inhibition skills acting as a mediator. Another research study has proven the efficacy of INT treatment on improving cognitive functions in 156 outpatients with schizophrenia and schizoaffective disorder (28). Overall, the current findings align with some research reporting limited efficacy, but they contrast with studies that report significant cognitive activation and retraining after executive treatments. This difference is likely due to the type of intervention, differences in depression severity, follow-up duration, or perhaps the absence of an initial deficit in these functions, the inappropriateness of the tools for precise assessment, and the ineffectiveness of the treatment on the mentioned variables. Although some research posits an alternative hypothesis of no correlation between cognitive processes and depression, explaining the ineffectiveness of certain cognitive interventions (29,30). Given the connection between neurocognition, social cognition, negative symptoms, and recovery, it is hoped that INT, by addressing the limitations of this study (linking neurocognition, social cognition, and negative symptoms), will yield better and more sustained treatment outcomes, significantly reducing clinical symptoms and increasing functional improvement in future studies. Additionally, larger sample sizes should be used, and the reliability of the subscales needs re-evaluation in more clinical settings. This research was conducted with the aim of introducing this technique for increased study and therapeutic use in the Iranian community, and the fact that the research was conducted only on patients with MDD in Mashhad City is considered one of the limitations of this study, requiring caution in generalizing the results. Moreover, events simultaneous with the research and the role of confounding variables were not examined in the current study. Given the fact that the experimenter and researcher were the same person in this study and the associated difficulties, it is suggested that in future studies,

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1. Long Z, Li J, Marino M. Brain structural changes underlying clinical symptom improvement following fast-acting treatments in treatment resistant depression. *J Affect Disord* 2025; 396(15): 52-60.

the experimenter and researcher should not be the same person.

Conclusion

Based on the outcomes, it is recommended to use integrative neurocognitive therapy for improving the neuropsychological functions of patients with major depressive disorder.

Acknowledgments

Gratitude is extended to all research participants and the officials of treatment centers and psychological clinics for their cooperation with the researcher.

Conflict of Interests

There is no conflict of interest.

Funding

No funding

Ethical Considerations

This article is derived from the first author's Ph.D. dissertation in public psychology at Islamic Azad University, Ardabil Branch. The current research was conducted after obtaining the ethics code from the Ethics Committee of Islamic Azad University, Ardabil Branch. To adhere to ethical considerations, at the beginning of the sessions, participants were given a brief explanation about the purpose of the study, the process of cooperation, the benefits, and advantages of participating in the study, and participants enrolled in the sessions based on personal consent. Furthermore, participants were assured about the confidentiality of their personal information. To maintain ethical standards, members of the control group were allowed to voluntarily undergo integrative neurocognitive therapy after the completion of the research, based on their own choice.

Code of Ethics

IR.IAU.ARDABIL.REC.1401.118

Authors' Contributions

The first author conducted this research and wrote the draft of the manuscript. The second and third authors designed and supervised the research process and involved in writing and editing the manuscript. The fourth author consulted in the research process and involved in revising the manuscript.

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