

Comparison of Theory of Mind between Patients with Major Depressive Disorder and Stimulant-Induced Depressive Disorder

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Abstract

Objective: Theory of mind (ToM) denotes the ability to understand the mental state of others and perceive their unique beliefs and emotions. In this study, we compared ToM between individuals with major depressive disorder (MDD) and stimulant-induced depressive disorder (SIDD).

Method: This cross-sectional, causal-comparative study included patients with MDD or SIDD admitted to Ostad Moharary Neuropsychiatric Hospital between January and June 2022. Each diagnosis was confirmed through a semi-structured interview conducted by a single attending psychiatrist according to the DSM-5 criteria. After consecutive sampling of 110 individuals, 51 patients completed the study in each group. Demographic characteristics were recorded, and the Persian version of the revised Reading the Mind in the Eyes Test (RMET) was used to evaluate ToM. Statistical analysis was performed using SPSS v.25, employing the t-test, chi-squared test, linear regression, and analysis of covariance (ANCOVA).

Results: Our analysis included 102 subjects (65.7% male) with a mean age of 35.17 ± 7.54 years. The two groups were similar in age, gender, marital status, working status, occupation, economic class, and ethnicity ($P > 0.05$). The RMET scores were 12.94 ± 4.03 and 11.86 ± 3.15 in the MDD and SIDD groups, respectively ($P = 0.135$). Almost all patients had low RMET scores (< 22); only two individuals in the MDD group achieved normal scores (22–30). ANCOVA revealed no significant confounding effects between the independent variables. Furthermore, regression analysis revealed that the level of education had a significant linear relationship ($\beta = 0.249$) with the RMET score ($P = 0.021$).

Conclusion: Hospitalized patients with MDD and SIDD have similar ToM deficits, as measured by the RMET.

Keywords: *Major Depressive Disorder; Psychometrics; Substance-Related Disorders; Theory of Mind*

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Theory of mind refers to the ability to understand the mental state of others and perceive their unique beliefs and emotions (1). With a correct theory of mind, one can comprehend what others think, wish, or intend (2). A sound theory of mind is critical for adapting to the complex social environment within which we exist (3). However, individuals suffering from depression have a significant impairment in their theory of mind (4). According to empirical evidence from research on psychological morbidities such as major depressive disorder or autism spectrum disorder, cognitive difficulties and theory of mind deficits can damage social functioning (2, 5, 6). Hence, part of the failure of patients suffering from depression in their interactions with others may be explained by their impaired ability to accurately interpret other people's mental states and emotions (7). Besides damaging one's relationships and productivity, depression can also lead to suicide and substance abuse (4).

Substance abuse is a major problem that places an immense psychosocial and economic burden on human societies (8). After marijuana, stimulants and their derivatives rank second in terms of substance abuse (9), sounding the siren for healthcare systems. According to clinical studies, substance abuse is associated with a myriad of mental, emotional, mood, and behavioral disorders (10). In particular, the present study focuses partly on stimulant-induced depressive disorder, described by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). This disorder is characterized by depressed mood or markedly diminished interest or pleasure, developing during or shortly after stimulant use or withdrawal, with the stimulant itself being able to induce these symptoms (11). However, the link between this disorder and theory of mind is yet to be explored.

Major depressive disorder (a separate DSM-5 entity where the condition cannot be attributed to the impacts of a substance) is one of the most common comorbidities, identified as both a cause and effect of substance abuse (12). While depression is bidirectionally linked with substance abuse, symptoms of depression are also linked with deficits in theory of mind, including cognitive, affective, visual, verbal, and reasoning abilities (3, 7, 13-17). In particular, major depressive disorder is linked with a remarkable defect in one's ability to recognize other people's mental states. This defect is referred to as "mindblindness," where one has remarkable difficulty understanding things in relation to themselves from the point of view of others (2). Such people have problems with social interactions, along with difficulties in understanding the intentions of others and comprehending how their behavior affects others (18, 19).

Although disorders in social interactions experienced by people with depression are known to therapists and researchers, defects in social functions, as the most

recognized feature of major depressive disorder, have sparsely been examined in this population. Assessing the quality of these patients' capability to decipher other people's mental states can have significant therapeutic implications with the aim of improving social functioning. Although the connection between depression and theory of mind has been investigated to some extent (4), stimulant-induced depressive disorder has not been explored in this context as a distinct entity. Therefore, the present study sought to assess theory of mind in patients with (i) major depressive disorder, and (ii) stimulant-induced depressive disorder, before (iii) exploring differences in theory of mind between these groups.

Materials and Methods

The study population of this cross-sectional, causal-comparative study included all patients with major depressive disorder or stimulant-induced depressive disorder who were admitted to Ostad Moharary Neuropsychiatric Hospital, affiliated with Shiraz University of Medical Sciences, Shiraz, Iran. Between January and June 2022, the participants were sampled via consecutive sampling.

The inclusion criteria for this study encompassed patients hospitalized for either major depressive disorder or stimulant-induced depressive disorder, aged between 25 and 50 years, who could read and write in the Persian language. On the other hand, the exclusion criteria ruled out individuals with any history of neurological diseases or severe head trauma resulting in loss of consciousness, as well as those who were unwilling to participate. Participation in this study was voluntary, and patients could exit at any time.

Each patient was diagnosed based on the DSM-5 criteria by a single attending psychiatrist (L. R. J.) through a semi-structured clinical interview (11). Major depressive disorder was defined according to five or more of the following symptoms that last for two weeks or more: depressed mood, anhedonia (at least one of the first two symptoms must be present), significant weight change, insomnia or oversleeping, psychomotor agitation or retardation, fatigue or lack of energy, feeling worthless or excessively guilty, reduced concentration, and frequently dwelling on death. Additionally, these symptoms were accompanied by a significant deterioration in social functioning, upon the condition that these symptoms cannot be attributed to a substance or alternative medical problem. Moreover, substance-induced depressive disorder was diagnosed according to the DSM-5 criteria, with the key difference from major depressive disorder being that the depressed mood or anhedonia develops during or shortly after substance use or withdrawal, and the substance is able to produce the symptoms. To meet the diagnostic criteria, the disorder should not be better described as a depressive disorder not related to substance use, should not occur exclusively during an episode of delirium, and should

cause significant distress to or impairment of normal functioning. Finally, the specific substance (or substance category) should be specified in the diagnosis. In this case, “stimulant-induced depressive disorder” was diagnosed when the diagnostic criteria were fulfilled in relation to the use of amphetamine or other stimulants.

The sample size was selected according to Research Methods in Psychology and Educational Sciences, which recommends a minimum sample size of 15 in each group for causal-comparative research (20). We aimed for a slightly higher sample size to compensate for any missing or incomplete data. Patient selection was made through consecutive sampling by a head nurse external to the research group. The study commenced with a total of 110 participants: 56 with major depressive disorder and 54 with stimulant-induced depressive disorder. However, five patients from the former group and three from the latter group withdrew from the study as they did not wish to complete the questionnaire. Finally, 51 patients with major depressive disorder and 51 with stimulant-induced major depressive disorder completed the study.

To evaluate the participants' theory of mind, we utilized the Persian version of the revised Reading the Mind in the Eyes Test (RMET) (21). This 15-minute neuropsychological assessment was developed by Baron-Cohen *et al.* and includes images of famous actors and actresses. In each of the 36 items, one must look at the eyes of the person and select which of four terms best describes their intention or mental state. In each image, mental states with similar emotional capacities are presented. The maximum score that can be achieved by selecting the best term in all 36 cases is 36, while the minimum is 0. The average person achieves a score between 22-30; those with scores under 22 have a poor perception of mental states, while those with scores above 30 are highly skilled in decoding facial expressions around the eyes (22). In terms of the reliability and validity of the Persian version of this test, various studies have found its Cronbach's alpha coefficient to be approximately 0.73 (23-25). Although Khorashad *et al.* noted poor internal consistency (Cronbach's alpha 0.371), their detailed analysis led them to conclude that the test items are generally acceptable for Iranian adults (26).

The Data were analyzed using SPSS version 25 (IBM, USA). Any missing data were excluded from the individual analyses. Descriptive statistics were provided in the form of either mean and standard deviation or median and interquartile range, as appropriate. The normality of test scores was confirmed using the Kolmogorov-Smirnov test. To compare the mean scores of the two groups, we used the independent t-test. The chi-squared test was utilized to compare the correct response rate on each test item between the two groups. Analysis of covariance (ANCOVA) was employed to check for confounding effects of group, age, occupation, and education on the RMET score. Linear regression

was used to determine the effects of age, group, and education on the RMET score. A significance level of 0.05 was considered in all cases.

Ethical Considerations

All procedures in this study were in line with the institutional protocols and the Declarations of Helsinki. Participation in this study was completely voluntary, and the subjects could withdraw at any time. Informed consent was provided before inclusion in this study, and patient anonymity was ensured. The Ethics Committee of Shiraz University of Medical Sciences approved our proposal (IR.SUMS.MED.REC.1400.440).

Results

The demographic characteristics of the 102 study participants with a mean overall age of 35.17 ± 7.54 years (65.7% male) are presented in Table 1. As evident, the two groups were comparable regarding age, gender, marital status, working status, occupation, economic class, and ethnicity ($P > 0.05$). However, the groups differed in terms of education, such that those with stimulant-induced depressive disorder were less educated than those with major depressive disorder ($P = 0.025$) (Table 1).

Regarding the RMET scores, participants in the major depressive disorder group achieved a mean score of 12.94 ± 4.03 with a range of 6–24. In the stimulant-induced depressive disorder group, the mean score was 11.86 ± 3.15 , ranging from 5 to 20. Evidently, the mean scores were similar between the groups ($P = 0.135$), although those with major depressive disorder performed slightly better. In terms of RMET score categories, all patients in the stimulant-induced depressive disorder group had scores below 22, indicating deficits in their theory of mind. On the other hand, two patients in the major depressive disorder group had scores within the normal range (22–30), while the remaining also had deficits in theory of mind. The two groups were comparable in terms of the categorized RMET scores ($P = 0.153$).

In Table 2, we present the correct response rate for each question categorized by group. It is evident that the correct response rates were generally low, with both groups performing similarly on most questions. Nonetheless, the major depressive disorder group performed significantly better on nine items, while the stimulant-induced depressive disorder group performed better on only two items (Table 2).

The results of ANCOVA indicated that age, education, group, and occupation had no significant confounding effects on the RMET score (Table 3). Within the linear regression model, the level of education demonstrated a significant linear relationship ($\beta = 0.249$) with the RMET score ($P = 0.021$). However, the other variables in the model had no significant effects on the RMET score (Table 4).

Table 1. Demographic Characteristics of Participants in the Major Depressive Disorder and Stimulant-Induced Depressive Disorder Groups

	Major Depressive Disorder	Stimulant-Induced Depressive Disorder	P-value
Age , years, mean \pm SD	33.95 \pm 7.19	36.39 \pm 7.88	0.105
Gender , male, n (%)	30 (58.8%)	37 (72.5%)	0.144
Marital Status , n (%)			
Single	18 (40.0%)	26 (52.0%)	0.392
Married	22 (48.9%)	22 (44.0%)	
Divorced	4 (8.9%)	1 (2.0%)	
Widowed	1 (2.0%)	1 (2.0%)	
Education , n (%)			
Primary	11 (22.0%)	21 (41.2%)	0.025*
Secondary	17 (34.0%)	23 (45.1%)	
Tertiary	22 (44.0%)	7 (13.7%)	
Currently Working , yes, n (%)	20 (42.0%)	21 (40.8%)	0.905
Occupation , n (%)			
Employed	14 (34.1%)	6 (16.7%)	0.024
Freelance	12 (29.3%)	23 (63.9%)	
Student	5 (12.2%)	0 (0.0%)	
Other	10 (24.4%)	7 (19.4%)	
Economic Class , n (%)			
Lowest	2 (4.0%)	11 (21.6%)	0.057
Low	12 (23.5%)	12 (24.0%)	
Middle	31 (62.0%)	25 (49.0%)	
High	5 (10.0%)	2 (3.9%)	
Highest	0 (0.0%)	1 (2.0%)	
Ethnicity , n (%)			
Fars	26 (53.1%)	38 (74.5%)	0.247
Lur	8 (16.3%)	4 (13.7%)	
Turk	7 (14.3%)	3 (5.9%)	
Kurd	3 (6.1%)	1 (2.0%)	
Baluch	1 (2.0%)	0 (0.0%)	
Arab	2 (4.1%)	2 (3.9%)	
Other	2 (4.1%)	0 (0.0%)	

*P < 0.05

Table 2. Number of Individuals with the Correct Response to each Question of the Reading the Mind in the Eyes Test

Question	Stimulant-Induced Depressive Disorder, n (%)	Major Depressive Disorder, n (%)
1	11 (21.6%)	9 (18.0%)
2	13 (26.0%)	23 (46.9%)*
3	18 (35.3%)*	7 (14.0%)
4	14 (28.6%)	23 (50.0%)*
5	15 (29.4%)*	6 (11.8%)
6	21 (41.2%)	32 (62.7%)*
7	10 (19.6%)	8 (15.7%)
8	16 (31.4%)	21 (41.2%)
9	22 (43.1%)	27 (54.0%)
10	20 (39.2%)	16 (31.4%)
11	25 (50.0%)	20 (39.2%)
12	21 (41.2%)	28 (54.9%)
13	5 (9.8%)	6 (11.8%)
14	22 (43.1%)	37 (72.5%)*
15	18 (35.3%)	29 (58.0%)*
16	17 (34.0%)	32 (62.7%)*
17	13 (26.0%)	12 (23.5%)
18	21 (32.0%)	32 (62.7%)*
19	11 (22.0%)	14 (28.0%)
20	10 (19.6%)	15 (29.4%)
21	19 (38.0%)	23 (46.0%)
22	13 (25.5%)	17 (35.4%)
23	9 (17.6%)	8 (16.3%)
24	8 (15.7%)	7 (14.3%)
25	21 (41.2%)	16 (32.0%)
26	9 (17.6%)	18 (36.7%)*
27	17 (34.0%)	20 (40.0%)
28	30 (60.0%)	24 (49.0%)
29	21 (42.0%)	14 (28.0%)
30	14 (28.6%)	21 (42.0%)
31	22 (44.9%)	22 (44.0%)
32	17 (34.0%)	11 (22.0%)
33	22 (44.0%)	24 (48.0%)
34	20 (40.0%)	12 (24.0%)
35	26 (53.1%)	21 (42.0%)
36	14 (28.6%)	5 (10.0%)*

*P < 0.05, chi-squared test

Table 3. Analysis of Covariance Model Output for Determining the Confounding Effects of Group, Age, Occupation, and Education on the Reading the Mind in the Eyes Test Score

Source	Type III Sum of Squares	df	Mean Square	F	P-value
Corrected Model	1039.471 ^a	66	15.750	0.492	0.841
Intercept	1071.210	1	1071.210	33.475	0.109
Group	25.739	1	25.739	0.804	0.535
Age	344.567	31	11.115	0.347	0.900
Occupation	31.942	4	7.985	0.250	0.884
Education	221.885	8	27.736	0.867	0.686
Group * Age	178.348	11	16.213	0.507	0.812
Group * Occupation	46.153	2	23.076	0.721	0.640
Group * Education	66.248	5	13.250	0.414	0.819
Error	32.000	1	32.000		
Total	12720.000	68			
Corrected Total	1071.471	67			

a. R Squared = 0.970 (Adjusted R Squared = -1.001). df: degrees of freedom. F: F-statistic.

Table 4. Linear Regression Model for Determining the Effects of Age, Group, and Education on the Reading the Mind in the Eyes Test Score

	Coefficients ^a					
	Unstandardized Coefficients		Standardized Coefficients		t	P-value
	B	Std. Error	Beta			
(Constant)	7.825	2.372			3.298	0.001
Age	0.024	0.046	0.056		0.526	0.601
Group	1.720	0.915	0.209		1.879	0.064
Education	0.285	0.121	0.249		2.359	0.021

a. Dependent Variable: Reading the Mind in the Eyes Test (RMET) Score

Discussion

Theory of mind is regarded by Wellman as a prerequisite for understanding the social environment and a necessity for engaging in competitive social behaviors (1). The present study compared theory of mind between patients with major depressive disorder and stimulant-induced depressive disorder. The two groups were well-matched in terms of demographic characteristics except for education level. We found that both groups had a defect in theory of mind according to the RMET, although patients with major depressive disorder achieved slightly higher scores, possibly mediated by their higher education level.

Previous studies have shown that patients with major depressive disorder have impaired abilities in various aspects of theory of mind, including cognitive, affective, visual, verbal, and reasoning tasks, compared to healthy controls (3, 7, 13-17). In these patients, deficits in theory

of mind are mostly reported in the symptomatic phase, becoming more pronounced as the symptoms of depression worsen (3, 7, 13-17). Our results align well with the literature as we demonstrated significant deficits in theory of mind among patients hospitalized due to major depressive disorder or stimulant-induced depressive disorder. Nonetheless, contrary to the general trend, some studies have found that individuals with depression perform equally or even better than controls on the RMET; however, these studies mostly included patients with mild/subclinical, remitted, or unspecified types of depression (13, 14, 17, 27, 28). Some researchers note that such individuals may have increased sensitivity in recognizing negative emotions compared to positive ones (7). However, our patients can be assumed to have had severe forms of depression as they all required hospitalization. This severity of depression could explain their significant deficits in

theory of mind given the direct link between the severity of depression and the severity of the deficits (4).

Affective theory of mind performance may also be linked with the clinical characteristics of depression. As such, our investigation compared the performance of individuals with stimulant-induced depression disorder against those with major depressive disorder; however, no significant difference was found. Previous studies have linked suicidal behaviors (29), excessive rumination (30), anxiety (31), and psychotic features (32, 33) to impaired RMET performance among patients with depression. Hence, to interpret our results, it is plausible to consider that stimulant abuse itself may not remarkably influence theory of mind, with depression being a more important factor in this regard.

Depression is a condition that often co-occurs with substance use disorders (34, 35). While the DSM-5 criteria distinguish between major depressive disorder and substance-induced depressive disorder, studies on the latter are relatively limited. Furthermore, a proportion of patients diagnosed with substance-induced depressive disorder are later reclassified into the major depressive disorder group (36, 37). Few differences have been identified between these two entities in terms of risk factors, sociodemographics, and comorbidities (38, 39). Accordingly, we found that patients with major depressive disorder and stimulant-induced depressive disorder, besides performing almost equally on the RMET, were similar in terms of sociodemographic characteristics, except for education level. As the education level had a significant effect on the RMET score in our linear regression model, the slightly better performance of the major depressive disorder group may be due to their higher level of education. Further investigations of the differences between patients with stimulant-induced depressive disorder and major depressive disorder are essential, as there is a dearth of data on this matter.

Several researchers have looked at theory of mind in Iranian populations at the local level. In a study comparing normal individuals with patients diagnosed with major depressive disorder in Tabriz, Iran, Fakhari *et al.* found significantly lower RMET scores (12.35 ± 2.47 vs. 21.30 ± 2.47) in the major depressive disorder group (23). Similarly, the study of Nejati *et al.* in Tehran, Iran, also showed that individuals with major depressive disorder had lower scores than healthy controls on the RMET (17.40 ± 4.29 vs. 20.54 ± 2.51) (25). Our results are in line with the findings of these studies, although slight variations in scores may be due to differences in sampling procedures and study populations (e.g., hospitalized vs. outpatient). While our study did not include a control population, healthy individuals in a study conducted by Mahmoodaliloo *et al.* scored 22.57 ± 2.71 on the RMET (24). Thus, we can safely infer, in agreement with the local literature, that patients hospitalized due to major depressive disorder and stimulant-induced depressive disorder have a significant

deficit in theory of mind relative to the healthy population of Iranian adults. This aligns with a recent meta-analysis by Nestor *et al.*, which demonstrated that individuals with depression exhibit significant theory of mind deficits with medium effect sizes (4). These deficits may be explained by compromised skills in recognizing other people's mental and emotional states stemming from negative self-focused attention or self-absorption, negative biases, social withdrawal, or neurobiological abnormalities related to depression itself rather than its trigger (4).

Limitation

Like any investigation, our work had certain strengths and limitations. One key limitation was the lack of a control group, which was addressed by making comparisons with the data available in the literature. We also did not grade the severity of each disease, measure alternative aspects of theory of mind, or look into the impact of different clinical features. The small sample size was another limitation, attributed to the limited access to patients during the study period. Nonetheless, our work is the first to compare theory of mind between patients with stimulant-induced depressive disorder and major depressive disorder. Furthermore, all diagnoses were made by a single attending psychiatrist, and the eligibility criteria were robust. We hope that through further research, the exact psychosocial and neuropathological mechanisms underlying such deficits can be identified and ameliorated, ultimately leading to improved patient outcomes.

Conclusion

We conclude that patients hospitalized due to major depressive disorder or stimulant-induced depressive disorder have deficits in theory of mind as measured by the RMET, with no significant difference between them in this regard. Future studies should explore ways to correct such deficits in order to improve the social functioning of these patients.

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Conflict of Interest

This paper was extracted from the thesis of Mohammad Ali Tlais, written as part of the requirements of a

university degree, representing a potential conflict of interest. No other conflicts of interest exist.

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