

Research article Ερευνητική εργασία

The relationship of Theory of Mind with symptoms and cognitive impairment in bipolar disorder: A prospective study*

N. Ioannidi,¹ G. Konstantakopoulos,^{1,2} D. Sakkas,³ P. Oulis^{† 1}

¹First Department of Psychiatry, Athens University Medical School, Eginition Hospital, Athens, Greece

²Section of Cognitive Neuropsychiatry, Department of Psychosis Studies, Institute of Psychiatry, King's College London, UK

³Department of Psychiatry, General Hospital "G. Gennimatas", Athens, Greece

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Previous studies in bipolar disorder suggest patients' deficient performance in Theory of Mind tasks, both during manic or depressive episodes and in remission. However, most of the extant studies were cross-sectional and did not control for potential confounders such as residual symptoms or co-existent deficits in other cognitive functions. The present study is the first prospective study that assessed the effect of remission on Theory of Mind (ToM) in patients with Bipolar Disorder (BD) controlling for other cognitive deficits. ToM was assessed in 29 patients with BD type I during an episode of the illness and in remission as well as in 29 healthy controls. The two groups were pair-matched for gender, age and education level. Three tests with different levels of complexity were used to assess ToM: First Order False Belief Task, Hinting Task and Faux Pas Recognition Test. Concomitantly, a comprehensive battery of neuropsychological tests was administered to all participants assessing general intelligence, working memory, attention, speed processing, verbal learning, and memory and executive functions. The Hamilton Rating Scale for Depression, Young Mania Rating Scale, Brief Psychiatric Rating Scale, and GAF were also administered to the patients. Differences between patients –in acute phase and in remission– and the control group on neuropsychological tests were tested using one-way ANOVA with post hoc Bonferroni corrections. The effect of other cognitive deficits on patients' ToM dysfunction was controlled for using general linear models. The patients

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showed significantly lower performance in all ToM tests during the acute phases as compared to the control group (p values from 0.001 to 0.014). However, these impairments did not persist beyond acute mood episode, except patients' poor performance on Faux Pas ($p=0.001$). Additionally, patients had poorer performance compared to control group in verbal learning and memory ($p<0.001$) as well as visuospatial working memory ($p<0.001$) during both the acute and the euthymic phases of the illness. Patients also had poorer performance than healthy controls in immediate memory ($p=0.026$) and executive functions ($p=0.001$), however only during episodes of illness. Differences in Faux Pas did not remain statistically significant when the effect of verbal memory and visuospatial working memory was controlled for. Differences in other ToM tests during episodes did not remain statistically significant, when other cognitive functions that were found impaired in patients during episodes, were controlled for. The findings of this study support the hypothesis that ToM dysfunction in BD is associated with mood symptoms and it might reflect underlying cognitive deficits rather than representing a specific trait marker of the disorder.

Key words: Theory of Mind, social cognition, cognitive dysfunction, bipolar disorder, remission.

Introduction

Theory of Mind (ToM), the ability to understand mental states of other people (such as beliefs and intentions), is one of the key components of social cognition.^{1,2} Many studies have offered evidence for ToM dysfunction in schizophrenia and two recent meta-analyses found large effect sizes of the differences between schizophrenia patients and healthy controls in ToM performance.^{3,4} ToM dysfunction has a significant negative impact on social functioning of these patients, probably in a greater extent than any other concurrent cognitive deficit.⁵ Moreover, ToM deficits in schizophrenia persist beyond the acute phase of the disorder⁶⁻¹³ and they may be independent of concomitant deficits in other cognitive functions, such as general intelligence, memory, attention and executive functions.^{7,14-16}

More recently, the examination of ToM in bipolar disorder (BD) has been the focus of relevant research, as ToM impairments could be associated with psychosocial dysfunction in this disorder too. Significant deficits in ToM tests were found during the acute phases of the illness (mania or depression) in both adults¹⁷⁻²⁰ and pediatric patients with BD²¹ as well as in subsyndromal phases.²² Moreover, some studies in remitted patients with BD found that they exhibit poorer performance in some ToM tests compared with healthy controls.²³⁻³⁰ However, other studies have not found ToM impairment in BD patients in both remission¹⁷ and mania,³¹ while in most of the studies that they used multiple ToM tests BD patients

performed worse than controls only in some of these tests and not in others.^{18,19,22,25,27,28,30,32} Therefore, the available evidence on ToM impairment as a stable characteristic of BD is far from robust, and a number of methodological issues in this line of research as well as the effect of potential confounding factors should be further examined.

Regarding the methodological shortcomings of previous studies, it should be noted that some of them used mixed samples of patients with BD and major depression^{18,23} or patients with BD type I and II,^{22,27,30,32} although it has been found that the type of disorder can significantly affect ToM performance.²¹ Moreover, the studies in non-acute phases of BD used different criteria for the definition of euthymia and/or remission.^{19,25,28,30} Thus, it is not clear whether patients' ToM dysfunction in these studies was not related with residual symptoms. On the other hand, studies that examined the effect of symptoms on ToM performance in BD patients found a significant correlation with the severity of both manic^{21,32} and depressive²² symptoms. To our knowledge, there has been as yet no prospective study that directly examined the effect of remission in ToM performance in patients with BD.

The potential impact of deficits in other cognitive functions on ToM dysfunction in BD was examined in previous studies, although only two of these assessed a wide range of cognitive abilities and found an association between executive functions and ToM deficits.^{24,25} There is also evidence that ToM dysfunc-

tion in BD is associated with sustained attention deficits.^{26,29} Hence, in contrast to previous findings in schizophrenia, both symptoms and overall cognitive functioning might be determinants of ToM in BD. Therefore, recent reviews^{33,34} and a meta-analysis³⁵ on ToM deficits in BD highlighted that the role of subclinical symptoms, general cognitive deficits and other possible confounding factors should be further investigated in order to determine whether ToM dysfunction is a stable feature of the disease.

This study is the first prospective study examining the effect of remission on ToM in BD. ToM performance was evaluated in patients with BD type I during episode and was reassessed in euthymia. The potential impact of coexisting deficits in a wide range of cognitive domains on ToM dysfunction in BD was also examined.

Material and method

Participants and procedures

Twenty-nine patients (12 male and 17 female) aged 22–65 years meeting the DSM-IV-TR criteria for BD type I,³⁶ 16 of them being in depressive and 13 in manic episode, were recruited along with 29 healthy participants. Patient and control groups were matched for gender, age and education level. The clinical sample was recruited from the psychiatric departments of the General Hospital "G. Gennimatas" and the Eginition Hospital in Athens. Healthy participants were recruited from local communities. Clinical and neuropsychological evaluation of the patients was held in two phases. The first assessment was conducted shortly after their admission to the hospital, while the second assessment was performed at least 4 weeks after discharge (mean 7.2 ± 3.4 weeks) and only if the patients met the criteria for euthymia (see below). All patients were receiving medication at the time of assessment. In particular, all of them were receiving mood stabilizers (lithium, divalproex sodium, etc.), and the majority of them were additionally on antipsychotics, antidepressants or benzodiazepines. Exclusion criteria for all participants included: age beyond 60 years old, intellectual disability, history of head injury, history of a serious neurological disorder or a systemic illness with known neurological complications, alcohol or substance abuse (other

than nicotine) within the last month or alcohol or substance dependence (other than nicotine) in the last 6 months preceding their inclusion in the study, and receiving electroconvulsive therapy within the last 6 months. Inclusion criteria for the control subjects were no personal history of psychiatric disorder or family history of psychosis or bipolar disorder. All participants were Greek native speakers. All participants had been informed about the research procedures and given written informed consent as approved by the local Ethics Committee. Additional information for patients was obtained from their medical records and treating physicians.

Clinical assessment

Symptom severity in patients with BD was evaluated by valid and widely used clinical scales: (a) the Brief Psychiatric Rating Scale (BPRS),³⁷ which assesses psychotic symptoms, (b) the Hamilton Depression Rating Scale (HDRS),³⁸ which assesses depressive symptomatology, and (c) the Young Mania Rating Scale (YMRS),³⁹ which assesses manic symptomatology. Euthymia was defined by a score of 6 or less at the YMRS and a score of 8 or less at the HDRS. Finally, the patient's psychosocial functioning was assessed by the Global Assessment of Functioning (GAF).⁴⁰

Neuropsychological assessment

A neuropsychological battery assessing a wide range of cognitive functions was administered to all participants. The Vocabulary subscale (WAIS-Vocabulary) from Wechsler Adult Intelligence Scale (WAIS)⁴¹ was used to estimate general intellectual ability, because it is considered as the scale with the highest correlation with individual's general intelligence. The Block Design (WAIS-Block design) and Digit Span (WAIS-Digit span) subscales were used to assess visuospatial and verbal working memory, respectively. Executive functions were examined using three different tasks: the Stroop Color-Word test (Stroop),⁴² the Wisconsin Card Sorting Test – 64 version (WCST),⁴³ and the Trail Making Test, part A & B (Trails).⁴⁴ The Stroop-Interference, WCST-Categories, WCST-Perseverative errors and Trails-B were used as indicators of executive functioning. Moreover, the Stroop-Word and Trails-A scores were used in this study as measures of sustained attention and processing speed. Verbal learning and memory were

assessed by the Rey Auditory Verbal Learning Test (RAVLT)⁴⁵ scores – immediate memory, learning curve, immediate and delayed recall, recognition.

ToM assessment

ToM was evaluated by the following three tests in order of increasing complexity:

- a. *The First Order False Belief task.*^{7,46,47} This test consists of two stories that are read aloud to the subject followed by two questions. The first question refers to one of the characters' mistaken belief regarding the situation. Correct answer to this question requires the knowledge of the mental state of the hero (ToM question). The second question is a measure of story comprehension regarding another aspect of the situation and can be answered correctly without using ToM skills (reality question).
- b. *The Hinting task.*^{7,46,47} This test requires the subject's ability to infer the real intentions behind direct speech. The original test consists of 10 stories (4 of which are only used in this study) describing an interaction between two characters in which one of them drops an obvious hint. The subject is then asked what the character really meant when he/she said this. For each correct response two points are given. If the subject fails to give the correct response, an even more obvious hint is added to the story and one point is given for each correct response.
- c. *The Faux Pas Recognition Test (Faux Pas).*⁴⁸ A Faux Pas occurs when someone says something without thinking that the person who hears it may not want to hear it or be offended or hurt by it. The test consists of 20 stories arranged in random order – 10 stories with social cognition mistakes and 10 control stories. In the present study, the sum of correct error detections and correct rejections in control stories (non-Faux Pas stories) were measured (Faux Pas-recognition score).

Statistical analyses

The normality of distribution was examined by the means of Shapiro-Wilk test. None of the variables showed non-normal distribution; therefore, exclusively parametric tests were used. For comparisons between BD patients and healthy controls in demo-

graphic characteristics t-test was used for quantitative variables and χ^2 test for gender. The differences in clinical variables between episodes and euthymia and in neuropsychological variables between manic and depressive episodes were tested by t-test. The differences between patients –whether in the acute phase or in remission– and controls in neuropsychological performance were tested using one-way ANOVA with paired contrasts corrected for multiple comparisons using Bonferroni corrections. To examine ToM impairment after controlling for the potential influence of other cognitive deficits, comparisons in ToM performance were repeated using general linear models in which other neuropsychological variables were entered as covariates. All results at a p level <0.05 were considered significant, unless otherwise noted. Statistical analyses were performed using IBM SPSS Statistics version 20.

Results

Demographic and clinical characteristics of the sample are presented in table 1. There were no significant differences between patients and healthy controls in gender, age and education level. As expected, patients had significantly higher scores in all clinical scales –HDRS, YMRS, and BPRS– and significantly lower GAF score during mood episodes than in remission.

The comparison between patients undergoing a manic episode and those in a major depressive episode did not reveal statistically significant differences in any of the neuropsychological tests. Accordingly, patients undergoing a mood episode irrespective of polarity were considered as a single group in further analyses. Neuropsychological performance of the groups and the results of ANOVA and post hoc comparisons are presented in table 2. Patients with BD exhibited significant deficits in general intellectual ability (WAIS-Vocabulary), visuospatial working memory (WAIS-Block design), verbal learning (RAVLT-Learning curve), short and long term verbal memory (RAVLT-Immediate and Delayed recall) both in mood episodes and in remission compared to healthy controls. Patients' performance was impaired only during mood episodes in the verbal component of immediate memory (RAVLT-Immediate memory) and in executive functions – in particular,

Table 1. Demographic and clinical characteristics of patients with bipolar disorder (BD) and healthy controls.

	<i>BD Patients (n=29)</i> <i>Mean (SD)</i>	<i>Healthy Controls (n=29)</i> <i>Mean (SD)</i>	<i>Statistics</i>	<i>p</i>
Gender (Women), n (%)	17.0 (58.6)	17.0 (58.6)	$\chi^2=0.00$	1.000
Age (years)	44.2 (11.8)	44.9 (13.0)	$t=0.21$	0.833
Education (years)	12.7 (4.0)	12.4 (3.7)	$t=-0.27$	0.786
Age at onset (years)	28.1 (7.4)	–		
Duration of illness (years)	16.3 (10.0)	–		
Hospitalizations	3.4 (3.4)	–		
HDRS (n=16)			$t=8.40$	<0.001
Episode	23.7 (7.9)			
Remission	6.7 (1.4)			
YMRS (n=13)		–	$t=14.12$	<0.001
Episode	30.5 (5.1)			
Remission	5.5 (1.0)			
BPRS		–	$t=5.92$	<0.001
Episode	42.9 (9.9)			
Remission	28.8 (7.0)			
GAF		–	$t=-9.27$	<0.001
Episode	38.8 (9.9)			
Remission	65.8 (11.6)			

HDRS=Hamilton Depression Rating Scale, *YMRS*=Young Mania Rating Scale, *BPRS*=Brief Psychiatric Rating Scale, *GAF*=Global Assessment of Functioning

Table 2. Neuropsychological performance of patients with bipolar disorder (BD) during episode and in remission, in comparison with healthy controls (one-way ANOVA and post hoc Bonferroni corrections).

	<i>Healthy controls</i> <i>(n=29)</i> <i>Mean (SD)</i>	<i>BD-Episode</i> <i>(n=29)</i> <i>Mean (SD)</i>	<i>BD-Remission</i> <i>(n=29)</i> <i>Mean (SD)</i>	<i>F</i> <i>(df=2.87)</i>	<i>p</i>	<i>Pairwise comparisons</i>
WAIS-Vocabulary	11.93 (1.89)	10.07 (2.09)	9.92 (2.26)	8.18	0.001	E,R<HC
WAIS-Block design	10.55 (1.68)	7.96 (1.91)	8.15 (1.76)	18.48	<0.001	E,R<HC
WAIS-Digit span	9.61 (2.87)	8.07 (2.21)	8.23 (2.49)	3.07	0.052	NS
Stroop-Word	94.58 (16.77)	82.57 (19.21)	87.73 (19.27)	3.14	0.048	NS
Stroop-Interference	1.69 (9.02)	-1.61 (9.08)	-1.50 (9.38)	1.19	0.311	NS
RAVLT-Immediate memory	7.00 (2.46)	5.45 (1.90)	6.54 (2.18)	3.81	0.026	E<R,HC
RAVLT-Learning curve	13.48 (2.60)	10.38 (2.65)	11.15 (2.85)	10.34	<0.001	E,R<HC
RAVLT-Immediate recall	11.93 (3.44)	7.86 (3.18)	8.92 (3.65)	10.97	<0.001	E,R<HC
RAVLT-Delay recall	12.28 (3.24)	7.69 (3.13)	9.38 (3.35)	14.87	<0.001	E,R<HC
RAVLT-Recognition	19.45 (6.45)	16.21 (6.67)	18.38 (6.32)	1.88	0.160	NS
WCST-Categories	3.03 (1.27)	1.69 (1.28)	2.23 (1.53)	7.17	0.001	E<HC
WCST-Perseverative errors	11.11 (8.67)	20.31 (9.99)	14.27 (8.00)	7.77	0.001	E>R,HC
Trails A	47.00 (29.71)	72.14 (60.32)	52.27 (31.90)	2.70	0.074	NS
Trails B	109.59 (80.54)	181.52 (87.68)	165.54 (92.92)	5.43	0.006	E>HC
False belief task	1.71 (0.66)	1.17 (0.85)	1.58 (0.58)	4.50	0.014	E<HC
Hinting task	7.11 (1.03)	5.52 (1.72)	6.61 (1.74)	8.04	0.001	E<HC
Faux Pas-Recognition	10.47 (1.94)	12.32 (2.33)	13.91 (2.78)	8.26	0.001	E<R<HC

E=Patients during episode, *R*=Patients in remission, *HC*=Healthy controls, *NS*=Not Significant differences

set shifting (WCST-Categories and Perseverative errors, Trails-B). Regarding ToM assessment, patients had significantly poorer performance than healthy controls in all tests during the episode but only in Faux Pas during remission.

The neuropsychological profiles of patients during the episode of the disorder and in euthymia are graphically illustrated in figure 1. Patient's z scores presented in this graph were calculated using means and standard deviations of the healthy control group.

In order to examine the effect of other cognitive deficits on patients' ToM performance general linear models were created. In each of these models, a ToM task was the dependent variable and the group of participants (patients with BD/healthy controls), along with their scores on other neuropsychological tests, were entered as independent variables (see Table 3). Regarding Faux Pas test, scores in other tests in which euthymic patients showed significantly poorer performance than healthy controls were entered as covariates. This analysis revealed that differences in Faux Pas performance were no longer statistically significant when the effect of WAIS-Block de-

sign, RAVLT-Immediate recall and delayed recall were controlled for, whereas these differences remained significant after controlling for the effect of WAIS-Vocabulary and RAVLT-Learning curve. The impact of other cognitive deficits on patients' performance on ToM tests during episodes was also tested with general linear models. Scores in other tests in which patients performed significantly poorer than healthy controls during episodes were entered as covariates. The difference in performance on the False Belief test did not remain statistically significant when WAIS-Vocabulary and Block design, RAVLT-Learning curve, Immediate and Delayed recall, WCST-Categories and Perseverative errors and Trails-B were entered as covariates. Furthermore, performance differences on Hinting task did not remained statistically significant when WAIS-Block design was entered as covariate (table 3).

Discussion

The present study is the first to examine prospectively ToM and cognitive functioning in patients with BD-I during episodes and in euthymia. In order to as-

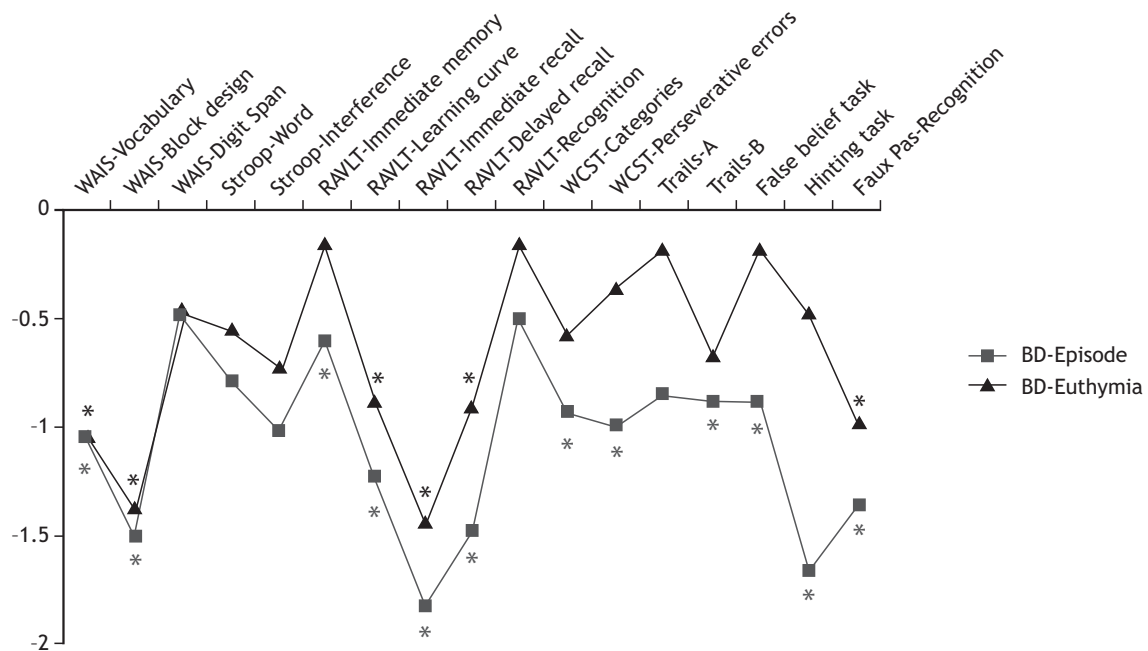


Figure 1. The impact of remission on cognitive functioning: Performance of patients with bipolar disorder (BD) during episode and in euthymia (z-scores). Asterisks indicate statistically significant differences between patients and healthy controls.

Table 3. The impact of other cognitive functions on ToM in patients with bipolar disorder (BD): The effect of study group (bipolar patients/healthy controls) in general linear models with scores in other neuropsychological tests entered as covariates.

<i>Variables</i>	<i>Adjusted R²</i>	<i>F*</i>	<i>p*</i>
Dependent: False Belief Task**			
WAIS-Vocabulary	0.19	2.50	0.119
WAIS-Block design	0.12	2.19	0.145
RAVLT-Immediate memory	0.10	4.30	0.043
RAVLT-Learning curve	0.18	1.24	0.270
RAVLT-Immediate recall	0.22	0.53	0.470
RAVLT-Delay recall	0.13	1.22	0.275
WCST-Categories	0.20	1.46	0.233
WCST-Perseverative errors	0.13	2.56	0.116
Trails B	0.17	2.69	0.107
Dependent: Hinting Task**			
WAIS-Vocabulary	0.32	6.64	0.013
WAIS-Block design	0.33	2.13	0.151
RAVLT-Immediate memory	0.26	10.85	0.002
RAVLT-Learning curve	0.25	7.90	0.007
RAVLT-Immediate recall	0.28	5.73	0.020
RAVLT-Delayed recall	0.28	4.42	0.040
WCST-Categories	0.25	9.39	0.003
WCST-Perseverative errors	0.21	10.97	0.002
Trails B	0.29	9.54	0.003
Dependent: Faux Pas – Recognition***			
WAIS-Vocabulary	0.19	4.24	0.018
WAIS-Block Design	0.20	2.12	0.127
RAVLT-Learning curve	0.21	3.53	0.034
RAVLT-Immediate recall	0.35	1.79	0.174
RAVLT-Delay recall	0.33	1.57	0.259

*Values correspond to study group (patients with BD/healthy controls) as an independent variable in each general linear model, **Patients' performance during episode, ***Patients' performance in remission

sess more accurately the impact of symptom remission on ToM, patients were reassessed only if they met strict criteria for euthymia. Moreover, the impact of concurrent cognitive deficits on patient's ToM performance was examined.

We found impairments in verbal immediate memory, verbal learning ability, short-term and long-term verbal memory as well as in executive functions –in particular, mental flexibility– during BD episodes in agreement with the findings of previous studies.^{49,50} Deficits in sustained attention have also been found with specific tests that were not included in our study battery. The significant deficits that were found in general intellectual ability and visuospatial

working memory, have also been identified in previous studies, mainly in the manic phase.⁵⁰ However, in our study these deficits remained significant after remission. The majority of previous studies in euthymia found deficits in executive functions, verbal learning and memory, processing speed and sustained attention.^{33,49–56} The findings of this study confirm only impairments in verbal memory and learning but not in the other aforementioned cognitive functions in euthymia. As it has been pointed out in reviews of the literature, findings vary considerably across the available studies.^{50,57}

Regarding ToM assessment, patients in a mood episode had significantly poorer performance in all

tests than healthy controls. Our findings are in line with studies of Kerr et al,¹⁷ and Bonstein et al,¹⁸ that found ToM impairment only in the acute phase of BD using false belief tests. Moreover, ToM deficits have been also found in other studies using false belief and hinting tests in patients with bipolar mania,^{19,20} with depression¹⁹ as well as in acute pediatric patients.²¹ To date, only one study did not find ToM deficits using cartoon stories in manic patients, whose symptoms however were of mild to moderate severity.⁵⁸ In euthymia, only patients' performance in the Faux Pas, the most complex of ToM tests administered, remained significantly poorer than in healthy controls. Otherwise, euthymic patients did not differ from normal controls in any other ToM test. In line with our findings, none of the previous studies has detected ToM dysfunction using false beliefs or ToM stories in euthymic patients^{17,23,25,26} and/or in patients with subsyndromal symptoms.²² Only in the study by Wolf et al¹⁹ euthymic BD patients performed worse than healthy controls in both first and second-order false belief stories as well as in hinting task. However, regarding hinting task, findings are contradictory: euthymic patients showed impaired performance in one study²⁴ while in another study no such impairment was detected.³² By contrast, all studies that used Faux Pas or other similar test in euthymic patients found impairments,²⁹ mainly in the cognitive^{27,28,30} but not in the emotional component of ToM.

The effect of cognitive functions on ToM during BD episodes has not been as yet systematically studied. Only a few studies have investigated specific effects on ToM performance in bipolar patients during acute phases and found no correlation with general intelligence (IQ),^{17,18,20} practical intelligence and executive functions.¹⁹ In the present study, it was found that in BD episodes, deficits in many cognitive functions (intellectual ability, visuospatial working memory, verbal learning and memory and executive functions) decisively contribute to patients' poor performance in false belief tasks. Moreover, working memory impairment significantly contributed to patients' poor performance in hinting task. In addition, differences between patients and control group in Faux Pas test, both during episodes and in remission, remained significant after controlling for other cognitive defi-

cits which also persist in remission, such as visuospatial working memory and verbal memory deficits. Two previous studies found no effect of executive functions and attention on ToM performance of BD patients in the Faux Pas test.^{28,29} However, unlike the present study, these studies were not prospective. Moreover, they did not examine patients' cognitive deficits, both in episodic relapse and in remission, as covariates. Based on our findings, ToM deficits that are present in both episodes and remission of BD might be secondary to underlying deficits in basic cognitive functions.

Among the limitations of our study we should acknowledge that its sample size, although adequate for comparisons between groups, was not large enough for the assessment of differences between depressed and manic patients. Moreover, the practice effect in repeated neuropsychological testing should be taken into account in the interpretation of the findings. Finally, as in all previous studies, it was not possible to eliminate the confounding effect of medication.

In conclusion, the findings of this study offer support to the hypothesis that ToM dysfunction in BD is associated with mood symptoms and is more likely to reflect other underlying cognitive deficits than to represent a stable characteristic of the disorder. The effect of ToM as a key component of social cognition on psychosocial functioning of patients with BD should be further investigated. However, our findings indicate that ToM may be a mediator in the relationship between basic cognitive deficits and social dysfunction that is observed in BD.⁵⁹ Consequently, therapeutic interventions targeting enduring cognitive deficits in the course of BD are crucial to improve both patients' social cognition and global functioning.

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N. Ιωαννίδη,¹ Γ. Κωνσταντακόπουλος,^{1,2} Δ. Σακκάς,³ Π. Ουλής^{† 1}

¹Α΄ Ψυχιατρική Κλινική Πανεπιστημίου Αθηνών, Αιγινήτειο Νοσοκομείο, Αθήνα

²Section of Cognitive Neuropsychiatry, Department of Psychosis Studies, Institute of Psychiatry, King's College London, UK

³Ψυχιατρική Κλινική, ΓΝΑ «Γεώργιος Γεννηματάς», Αθήνα

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Προηγούμενες μελέτες παρείχαν ευρήματα υπέρ της ύπαρξης δυσλειτουργίας της Θεωρίας του Νου (ΘτΝ) στη διπολική διαταραχή (ΔΔ), τόσο σε οξείες φάσεις της νόσου όσο και στην ύφεση. Ωστόσο, εμμένοντα υποκλινικά συμπτώματα και συνυπάρχοντα ελλείμματα άλλων νοητικών λειτουργιών αποτελούν πιθανούς συγχυτικούς παράγοντες των μελετών αυτών. Η παρούσα μελέτη αποτελεί την πρώτη προοπτική μελέτη με σκοπό να εκτιμήσει την επίδραση της ύφεσης στη ΘτΝ σε ασθενείς με ΔΔ, συνεξετάζοντας άλλες νοητικές λειτουργίες. Η ΘτΝ αξιολογήθηκε σε 29 ασθενείς με ΔΔ τύπου I κατά τη διάρκεια επεισοδίου και κατά την ύφεση της συμπτωματολογίας, καθώς και σε 29 υγιείς συμμετέχοντες. Οι δύο ομάδες εναρμονίστηκαν με αντιστοιχία ένας-προς-έναν ως προς το φύλο, την ηλικία και το επίπεδο εκπαίδευσης. Χρησιμοποιήθηκαν τρεις δοκιμασίες ΘτΝ με διαφορετικά επίπεδα πολυπλοκότητας: Δοκιμασία Εσφαλμένης Πεποίθησης Πρώτης Τάξης (First Order False Belief Task), Δοκιμασία υπαινιγμού (Hinting Task) και Δοκιμασία αναγνώρισης ατοπήματος (Faux Pas Recognition Test). Αξιολογήθηκαν παράλληλα με συστοιχία νευροψυχολογικών δοκιμασιών το γενικό νοητικό δυναμικό, η μνήμη εργασίας, η προσοχή, η ταχύτητα επεξεργασίας, η λεκτική μνήμη και μάθηση, και οι εκτελεστικές λειτουργίες. Χορηγήθηκαν στους ασθενείς οι κλινικές κλίμακες: Hamilton Rating Scale for Depression, Young Mania Rating Scale, Brief Psychiatric Rating Scale και GAF. Οι διαφορές μεταξύ των ασθενών –σε οξεία φάση και σε ύφεση– και της ομάδας ελέγχου στις νευροψυχολογικές δοκιμασίες, ελέγχθηκαν με τη δοκιμασία one-way ANOVA με post hoc Bonferroni διορθώσεις. Η επίδραση των άλλων νοητικών δυσλειτουργιών στα ελλείμματα των ασθενών σε δοκιμασίες ΘτΝ ελέγχθηκε μέσω γενικών γραμμικών μοντέλων. Οι ασθενείς εμφάνισαν σημαντικά χαμηλότερη επίδοση σε όλες τις δοκιμασίες ΘτΝ κατά την οξεία φάση σε σύγκριση με την ομάδα ελέγχου (τιμές p από 0,001 έως 0,014). Ωστόσο, τα ελλείμματα της ΘτΝ δεν διατηρήθηκαν κατά την ύφεση, παρά μόνο η χαμηλή επίδοση των νορμοθυμικών ασθενών στο Faux Pas ($p=0,001$). Επιπλέον, τόσο κατά τη διάρκεια των επεισοδίων όσο και κατά τη νορμοθυμία βρέθηκε δυσλειτουργία στη λεκτική μνήμη και μάθηση ($p<0,001$) και την οπτικοχωρική μνήμη εργασίας ($p<0,001$), σε σχέση με την ομάδα ελέγχου. Χαμηλότερες επιδόσεις στην άμεση μνήμη ($p=0,026$) και τις εκτελεστικές λειτουργίες ($p=0,001$) βρέθηκαν μόνο κατά τα επεισόδια της νόσου. Οι διαφορές στο Faux Pas δεν παρέμειναν στατιστικά σημαντικές, όταν συνεκτιμήθηκε η επίδραση της λεκτικής μνήμης και της οπτικοχωρικής μνήμης εργασίας. Η μειωμένη επίδοση των ασθενών στις υπόλοιπες δοκιμασίες ΘτΝ στα επεισόδια δεν παρέμεινε στατιστικά σημαντική όταν συνεκτιμήθηκαν άλλες νοητικές λειτουργίες στις οποίες οι ασθενείς εμφάνισαν έλλειμμα στα επεισόδια. Τα ευρήματα της παρούσας μελέτης υποστηρίζουν την υπόθεση ότι η δυσλειτουργία της ΘτΝ στη ΔΔ σχετίζεται με τα συναισθηματικά συμπτώματα και είναι πιθανότερο να αντανακλά υποκείμενα ελλείμματα άλλων νοητικών λειτουργιών παρά να αντιπροσωπεύει ένα σταθερό χαρακτηριστικό της διαταραχής.

Λέξεις ευρητηρίου: Θεωρία του Νου, κοινωνική νόηση, νοητική δυσλειτουργία, διπολική διαταραχή, ύφεση.

References

- Premack D, Woodruff G. Does the chimpanzee have a "theory of mind"? *Behav Brain Sci* 1978, 4:515–526
- Green MF, Penn DL, Bentall R, Carpenter WT, Gaebe W, Gur RC et al. Social Cognition in Schizophrenia: An NIMH Workshop on Definitions, Assessment, and Research Opportunities. *Schizophr Bull* 2008, 34:1211–1220
- Sprong M, Schothorst P, Vos E, Hox J, van Engeland H. Theory of mind in schizophrenia: meta-analysis. *Br J Psychiatry* 2007, 191:5–13
- Bora E, Yucel M, Pantelis C. Theory of mind impairment in schizophrenia: Meta-analysis. *Schizophr Res* 2009, 109:1–9
- Fett AK J, Viechtbauer W, Dominguez M, Penn DL, Van Os J, Krabbendam L. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. *Neurosci Biobehav Rev* 2011, 35:573–588
- Herold R, Tenyi T, Lenard K, Trixler M. Theory of mind deficit in people with schizophrenia during remission. *Psychol Med* 2002, 32:1125–1129
- Janssen I, Krabbendam L, Jolles J, van Os J. Alterations in theory of mind in patients with schizophrenia and non-psychotic relatives. *Acta Psychiatr Scand* 2003, 108:110–117
- Bora E, Gokcen S, Kayahan B, Veznedaroglu B. Deficits of social-cognitive and social-perceptual aspects of theory of mind in remitted patients with schizophrenia. Effect of residual symptoms. *J Nerv Ment Dis* 2008, 196:95–99
- Randall F, Corcoran R, Day I, Bentall R. Attention, theory of mind and causal attributions in people with persecutory delusions: A preliminary investigation. *Cognitive Neuropsychiatry* 2003, 8:287–294
- Kelemen O, Erdelyi R, Pataki I, Benedek G, Janka Z, Ker S. Theory of mind and motion perception in schizophrenia. *Neuropsychology* 2005, 19:494–500
- Inoue Y, Yamada K, Hirano M, Shinohara M, Tamaoki T, Iguchi H et al. Impairment of theory of mind in patients in remission following first episode of schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2006, 256:326–328
- Martino DJ, Bucay D, Butman JT, Allegri RF. Neuropsychological frontal impairments and negative symptoms in schizophrenia. *Psychiatry Res* 2007, 152:121–128
- Pousa E, Duñó R, Brnbion G, David A, Ruiz A, Obiols J. Theory of mind deficits in chronic schizophrenia: evidence for state dependence. *Psychiatry Res* 2008, 158:1–10
- Langdon R, Coltheart M, Ward PB, Catts SV. Mentalising, executive planning and disengagement in schizophrenia. *Cognitive Neuropsychiatry* 2001, 6:81–108
- Abdel-Hamid M, Lehmkaemper C, Sonntag C, Juckel G, Daum I, Brüne M. Theory of mind in schizophrenia: The role of clinical symptomatology and neurocognition in understanding other people's thoughts and intentions. *Psychiatry Res* 2009, 165:19–26
- Bozikas VP, Giannakou M, Kosmidis MH, Kargopoulos P, Kioseoglou G, Liolios D et al. Insights into theory of mind in schizophrenia: The impact of cognitive impairment. *Schizophr Res* 2011, 130:130–136
- Kerr N, Dunbar RIM, Bentall RP. Theory of mind in bipolar affective disorder. *J Affect Disord* 2003, 73:253–259
- Bonshtein U, Leiser D, Levine J. Naive theory impairment in schizophrenia. Is it domain specific? *J Nerv Ment Dis* 2006, 194:753–759
- Wolf F, Brune M, Assion H. Theory of mind and neurocognitive functioning in patients with bipolar disorder. *Bipolar Disord* 2010, 12:657–666
- Rossell SL, Van Rheenen TE. Theory of mind performance using a story comprehension task in bipolar mania compared to schizophrenia and healthy controls. *Cognitive Neuropsychiatry* 2012, in press
- Schenkel LS, Marlow-O'Connor M, Moss M, Sweeney JA, Pavuluri MN. Theory of mind and social inference in children and adolescents with bipolar disorder. *Psychol Med* 2008, 38:791–800
- McKinnon MC, Cusi AM, MacQueen GM. Impaired theory of mind performance in patients with recurrent bipolar disorder: Moderating effect of cognitive load. *Psychiatry Res* 2010, 177:261–262
- Inoue Y, Tonooka Y, Yamada K, Kanba S. Deficiency of theory of mind in patients with remitted mood disorder. *J Affect Disord* 2004, 82:403–409
- Bora E, Vahip S, Gonul AS, Akdeniz F, Alkan M, Ogut M et al. Evidence for theory of mind deficits in euthymic patients with bipolar disorder. *Acta Psychiatr Scand* 2005, 112:110–116
- Olley AL, Malhi GS, Bachelor J, Cahill CM, Mitchell PB, Berk M. Executive functioning and theory of mind in euthymic bipolar disorder. *Bipolar Disord* 2005, 7:43–52
- Lahera G, Montes MJ, Benito A, Valdivia M, Medina E, Mirapeix I et al. Theory of mind deficit in bipolar disorder: Is it related to a previous history of psychotic symptoms? *Psychiatry Res* 2008, 161:309–317
- Shamay-Tsoory S, Harari H, Szepeswol O, Levkovitz Y. Neuropsychological evidence of impaired cognitive empathy in euthymic bipolar disorder. *J Neuropsychiatry Clin Neurosci* 2009, 21:59–67
- Montag C, Ehrlich A, Neuhaus K, Dziobek I, Heekeren HR, Heinz A et al. Theory of mind impairments in euthymic bipolar patients. *J Affect Disord* 2010, 123:264–269
- Martino DJ, Strejilevich SA, Fassi G, Marengo E, Igoaet A. Theory of Mind and facial emotion recognition in euthymic bipolar I and bipolar II disorders. *Psychiatry Res* 2011, 189:379–384
- Barrera A, Vázquez G, Tannenhaus L, Lolicha M, Herbst L. Theory of mind and functionality in bipolar patients with symptomatic remission. *Rev Psiquiatr Salud Ment (Barc)* 2013, 6:67–74
- Sarfati Y, Hardy-Bayle MC, Brunei E, Widloecher D. Investigating theory of mind in schizophrenia: influence of verbalization in disorganized and non-disorganized patients. *Schizophr Res* 1999, 37:183–190
- Donohoe G, Duignan A, Hargreaves A, Morris DW, Rose E, Robertson D et al. Social cognition in bipolar disorder versus schizophrenia: comparability in mental state decoding deficits. *Bipolar Disord* 2012, 14:743–748
- Bora E, Yucel M, Pantelis C. Theory of mind impairment: a distinct trait-marker for schizophrenia spectrum disorders and bipolar disorder? *Acta Psychiatr Scand* 2009, 120:253–264
- Simon M, Varga E, Hajnal A, Schnell Z, Tényi T, Fekete S et al. Theory of mind deficits in euthymic patients with bipolar I disorder. Theoretical background and guidelines for neuroimaging research. *Psychiatr Hung* 2011, 26:178–187
- Samamé C, Martino DJ, Strejilevich SA. Social cognition in euthymic bipolar disorder: systematic review and meta-analytic approach. *Acta Psychiatr Scand* 2012, 125:266–280

36. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Text revision. American Psychiatric Publishing, Inc, Washington, DC, 2000
37. Burger GK, Calsyn RJ, Morse JA, Klinkenberg WD, Trusty ML. Factor structure of the expanded brief psychiatric rating scale. *J Clin Psychol* 1997, 53:451–454
38. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960, 23:56–62
39. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 1978, 133:429–435
40. American Psychiatric Association. *Diagnostic and Statistical Manual of mental disorders*. 4th ed. American Psychiatric Press, Washington, DC, 1994
41. Wechsler D. Wechsler Adult Intelligence Scale. *Psychological Corporation*. New York, 1955
42. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol* 1935, 18:643–662
43. Grant DA, Berg EA. A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card sorting problem. *J Exp Psychol* 1948, 38:404–411
44. Reitan R.M. Trail Making Test Results for Normal and Brain-Damaged Children. *Percept Mot Skills* 1971, 33:575–581
45. Rey A. *L'examen clinique en psychologie*. Presses Universitaires de France, Paris, 1964
46. Corcoran R, Mercer G, Frith CD. Schizophrenia, symptomatology and social influence: Investigating "theory of mind" in people with schizophrenia. *Schizophr Res* 1995, 17:5–13
47. Frith C, Corcoran R. Exploring "theory of mind" in people with schizophrenia. *Psychol Med* 1996, 26:521–530
48. Baron-Cohen S, O'Riordan M, Stone V, Jones R, Plaisted K. Recognition of faux pas by normally developing children and children with Asperger syndrome or high-functioning autism. *J Autism Dev Disord* 1999, 29:407–418
49. Malhi GS, Ivanovski B, Szekeres V, Olley A. Bipolar Disorder: It's All in Your Mind? The Neuropsychological Profile of a Biological Disorder- A review. *Can J Psychiatry* 2004, 49:813–819
50. Quraishi S, Frangou S. Neuropsychology of bipolar disorder: a review. *J Affect Disord* 2002, 72:209–226
51. Sole B, Bonnin CM, Torrent C, Martinez-Aran A, Popovic D, Tabare's-Seisdedos R et al. Neurocognitive impairment across the bipolar spectrum- a review. *CNS Neurosci Ther* 2012, 18: 194–200
52. Latalova K, Prasko J, Diveky T, Velartova H. Cognitive impairment in bipolar disorder. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2011, 155:19–26
53. Bora E, Vahip S, Akdeniz F, Gonul AS, Eryavuz A, Ogut M et al. The effect of previous psychotic mood episodes on cognitive impairment in euthymic bipolar patients. *Bipolar Disord* 2007, 9:468–477
54. Torres LJ, Defreitas VG, Defreitas CM, Kauer-Santanna M, Bond DJ, Honer WG et al. Neurocognitive functioning in patients with bipolar I disorder recently recovered from a first manic episode. *J Clin Psychiatry* 2010, 71:1234–1242
55. Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN et al. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord* 2006, 93:105–115
56. Martinez-Aran A, Vieta E, Reinares M, Colom F, Torrent C, Sanchez-Moreno J et al. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am J Psychiatry* 2004, 161:262–270
57. Jamrozinski K. Do euthymic bipolar patients have normal cognitive functioning? *Curr Opin Psychiatr* 2010, 23:255–260
58. Sarfati Y, Hardy-Bayle MC. How do people with schizophrenia explain the behaviour of others? A study of theory of mind and its relationship to thought and speech disorganization in schizophrenia. *Psychol Med* 1999, 29:613–620
59. Depp CA, Mausbach BT, Harmell AL, Savla GN, Bowie CR, Harvey PD, Patterson TL. Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. *Bipolar Disord* 2012, 14:217–226

Corresponding author: N. Ioannidi, Clinical Psychologist, MSc, Byron-Kessariani Community Mental Health Center, First Department of Psychiatry, Athens University Medical School, 14 Dilou street, GR-161 21 Vironas, Athens, Greece
 Tel: (+30) 210-76 40 111, Fax: (+30) 210-76 62 829
 e-mail: nikoleta_ioannidi@yahoo.gr