The Relationship of Verbal Working Memory and Theory of Mind in First Degree Relatives of Patients with Schizophrenia and Bipolar Disorder

Mehmet Onur YÜCEL1, Halise DEVRİMÇİ ÖZGÜVEN2, Ayşegül SAKARYA3, Bora BASKAK4, Erguvan Tuğba ÖZEL KIZIL5, Direnç SAKARYA6, Seda HARAN7

SUMMARY

Objective: We aimed to compare Theory of Mind (ToM) functions and investigate the relationship between ToM functions and verbal working memory (VWM) in first degree relatives of bipolar disorder and schizophrenia patients.

Method: The sample consisted of first degree relatives of patients with bipolar disorder (n=22), schizophrenia (n=28), and age, gender, education and total IQ matched healthy volunteers (n=27) without a family history of schizophrenia or bipolar disorder. We administered the Auditory Consonants Test (ACT) to evaluate VWM, first and second order false belief tests (ToM-1, ToM-2), Faux Pas Test (FPT), and Hinting Test (HT) to evaluate different domains of ToM functions.

Results: Both groups with relatives of schizophrenia and bipolar patients performed significantly lower in all components of ToM and VWM tests compared to the control group. When VWM scores were employed as covariate in the analyses, the FPT difference between the groups remained significant, HT difference regressed to a marginal level, and the difference between ToM-1 and ToM-2 disappeared.

Conclusion: To our knowledge, this is the first study indicating the presence of ToM impairment among first degree relatives of bipolar disorder patients similar to relatives of schizophrenia patients. VWM performance seems to affect first and second order ToM functions in relatives of patients with schizophrenia and bipolar disorder. On the other hand, FPT and HT domains seem to be independent of VWM performances in these groups. FPT and HT impairments may be familial vulnerability markers that are independent from neurocognitive impairment.

Keywords: Schizophrenia, bipolar disorder, theory of mind, working memory, endophenotypes

INTRODUCTION

Although schizophrenia and bipolar disorder were once conceptualized as separate disorders, the belief that these disorders belong to the same spectrum and have many similarities has been increasingly more prominent (Tamminga et al 2009). This belief has been supported by many diagnostic validators of schizophrenia, bipolar disorder, and schizoaffective disorder. Schizophrenia and bipolar disorder are clustered together in families at a substantial rate and genom-wide association studies have reported that many susceptibility loci are shared by these disorders (Lichtenstein et al 2009, Cardno and Owen 2014). If there are shared genes, it will be valuable to search for familial susceptibility markers that have phenotypic value. To the best of our knowledge, no previous study has tested neurocognitive and social cognitive features together as familial susceptibility markers.

Many studies which compared healthy relatives of schizophrenic patients with healthy controls regarding several cognitive functions found cognitive deficits both in schizophrenia...
patients and their relatives although they were milder in relatives (Chen et al. 1998, Laurent et al. 2000, Sitskoorn et al 2004, Barrantes-Vidal et al 2007). Research on bipolar patients and their relatives is relatively sparse but similar results have been found for these subjects (Glahn et al. 2003, Zalla et al. 2004, Ferrier et al. 2004, Szöke et al. 2006, Christensen et al. 2006, Hill 2008). On the other hand, there are very few studies that compared relatives of schizophrenia and bipolar patients according to several clinical features and cognitive dysfunctions (Quraishi and Frangou 2002, Altshuler et al. 2004, Krabbendam et al. 2005). For example Zalla et al (2004) demonstrated that relatives of schizophrenia and bipolar disorder patients had similarly slow visual attention.

Dysfunction in working memory has been demonstrated to be one of the cognitive endophenotypes that have the highest effect size in meta-analytic studies of schizophrenia patients and their first-degree relatives (Snitz et al. 2006, Kalkstein et al. 2010). There are fewer studies on bipolar patients and their relatives; the ones that exist indicate the presence of disorders in verbal working memory (Balanzá-Martínez et al. 2008).

Social cognition refers to all skills used to structure the framework of relation between self and others and to flexibly direct social behaviors. Theory of mind (ToM), which is an important component of social cognition, is the ability to comprehend mentalistic conditions (thoughts, beliefs, and intentions) someone comes across with and to refer them to their real owner (Frith 1992). Many methods exist in the literature to evaluate ToM, however, there is not a ToM battery which is widely accepted. However, a study by Scherzer et al (2012) suggests that ToM should be assessed as a structure consisting of several dimensions. Researchers have modelled different ToM dimensions and found that a model that involves testing false beliefs, recognizing faux pas (RFP), and understanding hints (UH) had the highest ability to differentiate between patients and healthy controls. Testing false beliefs is divided into two functions by primary and secondary ToM tests. Primary ToM function (ToM-1) is defined as the ability to detect false beliefs of others (Wellman and Woolley 1990). This first order ToM component develops at 4-5 years of age. Second order ToM function (ToM-2) is named as “thought about thoughts” and develops at 6-7 years of age (Perner and Wimmer 1985). This function is the ability of a person to understand someone else’s false belief about an external event. For example, the subject understands whether person A knows that person B’s idea is false. RFP is the ability to detect faux pas, and develops between 9-11 years of age (Stone et al 1998). This function is the ability to detect that a person does not understand what he said or did something wrong in a situation and that he would be ashamed if he had recognized his mistake. Hence, this skill involves having empathy about how someone else feels. UH is the ability to understand hints in a conversation between two characters and to predict the real intents (Corcoran et al 1995); It is believed to develop at similar ages with RFP. The UH tests assesses the ability to understand the real intents under indirect verbal statements. Schizophrenia and bipolar disorder have similarities according to cognitive dysfunctions. ToM dysfunctions have been found in schizophrenia patients and their first degree relatives (Pinkham et al 2003, Janssen et al. 2003, Irani et al. 2006). In patients with bipolar disorder, ToM dysfunctions have been demonstrated both during illness periods and during euthymic periods (Bora et al. 2005, Inoue et al. 2004, Wölf 2010). A study demonstrated impairment in ToM function especially in ToM tests using verbal material in relatives of bipolar patients (Reynolds et al. 2014).

The aim of this study is to compare ToM function in first degree relatives of schizophrenia and bipolar patients. Our hypothesis is that ToM dysfunction, compared with controls, is present in both groups of relatives. On the other hand, ToM is a function of social cognition. Whether or not social cognitive functions have dimensions coinciding qualitatively with neurocognitive functions is a debated topic (Blakemore et al. 2004). There is evidence suggesting that working memory performance affects ToM functions in healthy children and adults (Mutter et al. 2006, McKinnon and Moskovitch 2007). In addition, impairment in working memory is an important endophenotype both in schizophrenia and bipolar disorder and working memory dysfunctions may affect ToM function or its assessment procedure. Moreover this effect may be different in schizophrenia and bipolar disorder. For example, a recent study (Lee et al 2013) demonstrated that in schizophrenia neurocognitive and social cognitive features were similarly impaired whereas in bipolar disorder neurocognitive impairment was prominent while social cognitive function was relatively preserved. Accordingly, the aim of this study is to assess whether verbal working memory (VWM) and ToM impairments are similar in schizophrenia and bipolar patients.

**METHOD**

**Sample**

This study included first degree relatives (mother, father, sibling or child) of schizophrenia or bipolar disorder patients with psychotic features (22 relatives of bipolar patients and 28 relatives of schizophrenia patients) diagnosed using DSM-IV criteria who were treated as outpatients or inpatients at the Psychiatry Department of Ankara University Medical School. Inclusion criteria were age between 18-65 years, education of at least eight years, and absence of a previous psychiatric or neurologic illness. The control group included 27 healthy volunteers who had similar age, sex education and IQ values, did not have any familial history of schizophrenia and/or bipolar disorder, and who did not have any psychiatric disorder.
The WAIS-R (Wechsler Adult Intelligence Scale-Revised) was applied to all subjects by a clinical psychologist. Subjects who scored below normal levels in verbal, performance or total IQ or who had a higher than 15 points difference between verbal and performance IQ scores were excluded. Written and verbal informed consents were taken from all patients. The study was approved by Ankara University Medical School Research Ethics Committee.

Age, sex, education level, total WAIS-R scores and other sociodemographic features of the study and the control groups are given in Table 1. There was not a difference between groups according to these features.

Table 1. Sociodemographic features of the groups

<table>
<thead>
<tr>
<th></th>
<th>Relatives of bipolar disorder patients (n=22)</th>
<th>Relatives of schizophrenia patients (n=28)</th>
<th>Controls (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±sd)</td>
<td>35.41 ± 13.11</td>
<td>38.57 ± 12.60</td>
<td>33.44 ± 9.09</td>
</tr>
<tr>
<td>Level of education (years) (mean±sd)</td>
<td>12.25 ± 2.29</td>
<td>12.36 ± 2.50</td>
<td>12.93 ± 2.60</td>
</tr>
<tr>
<td>Total WAIS-R score (mean±sd)</td>
<td>94.33 ± 6.81</td>
<td>98.82 ± 9.83</td>
<td>98.48 ± 12.73</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>12/10</td>
<td>10/18</td>
<td>16/11</td>
</tr>
<tr>
<td>WAIS-R: Wechsler Adult Intelligence</td>
<td>5 (22.7%)</td>
<td>5 (17.9%)</td>
<td></td>
</tr>
<tr>
<td>WAIS-R: Wechsler Adult Scale-Revised</td>
<td>13 (59.1%)</td>
<td>19 (67.9%)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>9 (40.9%)</td>
<td>14 (50%)</td>
<td>18 (66.7%)</td>
</tr>
<tr>
<td>Single</td>
<td>11 (50%)</td>
<td>13 (46.4%)</td>
<td>8 (29.6%)</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>2 (9.1%)</td>
<td>1 (3.6%)</td>
<td>1 (3.7%)</td>
</tr>
</tbody>
</table>

*: One way analysis of variance  ** :Chi-square test

The interview started after the subject completed sociodemographic and clinical data forms about the patient and him/herself. Then Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I) was applied to evaluate if a psychiatric disorder existed in relatives of the patients. The interview continued with relatives who did not have a psychiatric diagnosis and others were excluded from the study. The SCID-I was developed by First et al (1997) and a Turkish validation and reliability study was performed by Ozkurkucgil et al (1999).

VWM and ToM functions were evaluated by the Auditory Consonants Test (ACT) and the ToM test, respectively. ACT assesses VWM (Brown 1958, Peterson and Peterson 1959). The Turkish validity and reliability study was performed by Anil et al (2003). The evaluation includes numbers of three consonant sets correctly remembered at 0, 3, 9 and 18 seconds and the sum of them. An increase in this sum means a higher VWM capacity.

The first of the ToM tests used in this study was developed by Perner and Wimmer (1985) to evaluate thought processes of subjects. The second test to evaluate ToM-1 was developed by Frith and Corcoran (1996) by choosing two tales from six which were used for the same purpose. In the first test to evaluate ToM-2, short tales developed by Bowler (1992) were adapted. In the second test to evaluate ToM-2, one of the six tales developed by Frith and Corcoran (1996) was chosen and adapted. The purpose of evaluating ToM-1 and ToM-2 using multiple and different tales was to prevent various characteristics (like location, subject, situation) of the tale to affect judgment procedure. After reading tales, skills of comprehension and correct evaluation of the subjects was assessed by naming, remembering, confirmation, reality, and reminding questions. The test was terminated in subjects who gave false answers to these questions and ToM evaluation was not performed. In this study, four subjects were excluded due to false answers to aforementioned questions. One of them was a relative of a bipolar patient and three were relatives of schizophrenia patients. The Hinting Test (HT) was developed by Corcoran et al (1995). The original test includes 10 tales and two of them were translated into Turkish. The subject’s ability to understand the hint in a dialogue between two cases was investigated by questions. Recognition of Faux Pas Test (RFPT) was developed by Baron and Cohen (1999). Its original version includes 10 tales and two of them were translated into Turkish. These tales are prepared to evaluate ToM functions and to avoid ceiling effect, tales that are appropriate to be used in adults were chosen. The ToM tests applied in this study were translated separately by three investigators and combined into a single text. Then back translation was performed and surface validity was confirmed. During translation cultural adaptation was also performed; however, cultural compatibility of the tests was not confirmed. This battery was developed by us and it was used in previous studies (Oner et al. 2009, Ozguven et al. 2010).

In comparison of groups, one way analysis of variance (ANOVA) was used for continuous variables and Chi-square
and Fischer’s Exact tests were used for categorical variables.

For analysis of multiple variables, multiple variant analyses (MANOVA and MANCOVA) were used. Tukey’s test was used for post-hoc analyses. All statistical analyses were performed by SPSS 13.0 package program.

**RESULTS**

VWM and ToM scores of the study groups and F and p values are presented in Table 2. There was not a difference between groups at the 0th and 3rd seconds in ACT but there were significant differences in 9th and 18th seconds and total ACT values. Results of post-hoc tests showed that the difference was due to higher performance in controls than the two relative groups.

The three groups were different according to ToM-1 tests. Post-hoc analyses demonstrated that the difference was due to lower performance of the schizophrenia relatives group than the control group. The 3 groups were different according to ToM-2 tests and post-hoc analyses demonstrated that the difference was due to lower performance of the bipolar relatives group than the control group. The 3 groups were different according to RFPT total scores. Post-hoc analyses revealed that relatives of bipolar disorder and schizophrenia patients scored lower than the controls. Comparison of HT total points revealed that the 3 groups were different and post-hoc analyses revealed that the difference was due to lower performance of bipolar relatives than the control group.

To test whether VWM performance mediates the difference among groups according to ToM performance, the multiple analysis of covariance (MANCOVA) test was performed. Independent variables were the groups and ToM test scores and covariant was ACT total score. This analysis showed that the difference between groups in HT regressed to a marginal value, the difference between groups in RFPT scores persisted, and the difference between groups in ToM-1 and ToM-2 tests disappeared (Table 2).

**DISCUSSION**

This study suggests that first degree relatives of schizophrenia and bipolar disorder have similar impairments in both VWM and some dimensions of ToM. Although ToM tests used in this study have not been validated in Turkish, its ability to differentiate patient relatives and controls has been demonstrated. Thus, utility of these tests to evaluate theory of mind and the validity of Turkish version can be claimed indirectly.

Working memory impairments have been shown in relatives of schizophrenia patients in previous studies (Conklin et al. 2005, Vidal et al. 2007). Some of the studies detected working memory impairments in relatives of bipolar disorder patients (Ferrier et al. 2004, Goodwin et al. 2008), and some did not (Antilla 2007). Our study detected VWM impairments in this group similar to relatives of schizophrenia patients. Hence, VWM impairment may be a shared endophenotype for both of the diseases. Also, a similar pattern in relatives of bipolar and schizophrenia patients supports the idea that bipolar disorder and schizophrenia are two related disorders located in the same spectrum. But selection of relatives of psychotic bipolar patients might have approximated the performances of these two groups. Also, this finding in VWM cannot be generalized to other dimensions of working memory.

Multiple analysis of variance demonstrated that performance in ToM tests were lower in both groups than healthy controls. This finding was previously shown in relatives of schizophrenia patients (Pinkham et al. 2003, Janssen et al. 2003, Irani et al. 2006). Previous studies also showed ToM impairments in bipolar patients during remission (Bora et al. 2005). Our study makes a further step and supports the idea that ToM impairments may be an endophenotype for psychosis spectrum.

| Table 2. Comparison of the three groups according to ToM tests using multiple analysis of variance (MANOVA) and multiple analysis of covariance (MANCOVA) tests |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Relatives of bipolar patients (n=22) | Relatives of schizophrenia patients (n=28) | Controls (n=27) | Statistical significance (MANOVA) | Statistical significance (MANCOVA) |
| RFPT total point (mean±sd) | 5.68 ± 2.46 | 4.96 ± 2.28 | 7.77 ± 2.22 | F= 10.802 | F= 6.9 |
| HT total point (mean±sd) | 3.36 ± 0.84 | 3.68 ± 0.55 | 3.85 ± 0.46 | F= 3.786 | F= 2.93 |
| ToM-1 (mean±sd) | 8.22 ± 1.11 | 8.10 ± 1.16 | 8.74 ± 0.53 | F= 3.232 | F= 1.36 |
| ToM-2 (mean±sd) | 5.45 ± 1.05 | 5.89 ± 0.92 | 6.22 ± 0.85 | F= 4.082 | F= 1.99 |

* p<0.05, statistically significant

ToM: Theory of Mind
RFPT: Recognition of Faux Pas Test
HT: Hinting Test
disorders by detecting these impairments in healthy relatives of patients.

In the analysis to test the effect of working memory on ToM performance after addition of ACT score as a covariant, the difference between groups disappeared in ToM-1 and ToM-2 tests, regressed to a borderline value in HT, and only persisted in RFPT. Therefore, impairment in RFP may be a more specific candidate to be an endophenotype for both disorders. Persistence of the difference in HT performance between groups after covariance analysis at a marginal level may be due to type 2 error.

It is a general observation in diseases that the lastly obtained skills are lost the first. RFP and understanding hints are known to develop later than ToM-1 and ToM-2 skills (Stone et al. 1998). The observation that the impairment of detection of false beliefs in the relatives of patients who were evaluated by ToM-1 and ToM-2 tests was associated with VWM impairment rather than being a primary disturbance and independent of impairments in UH and RFP from VWM may be due to this fact. RFP and UH skills start to develop at 11-12 years at which puberty typically occurs, neuronal networks in the brain are revised, and not infrequently prodromal stages of bipolar disorder and schizophrenia start. Schiffman et al (2004) evaluated videos of 11-12 year old children while they were eating lunch. Children who would later be schizophrenics were found to have difficulties in social skills such as initiating a dialogue, or keeping eye contact while talking with someone. Although the specific neurobiological structures underlying theory of mind skills are not known yet, RFP and UH impairments in healthy relatives of the patients suggest that similar structural impairments occur in brains of the patients and their relatives.

High level ToM skills, like RFP and UH, are basic components that provide acceptance of a person in conditions involving conflict or solidarity in interpersonal relations. Impairment in these skills prevents the subject from behaving appropriately in a given situation. There are reports in the psychiatric literature that highlighted strange behavioral features of relatives of schizophrenia patients (Kretschmer 1970, Kety 1968). This appearance may reflect high level social cognitive dysfunction in these individuals. Although there are not similar descriptions regarding relatives of bipolar patients, our study suggests similar social-cognitive defects in this subject group.

Psychotic features are present in nearly half of bipolar disorder patients. There is growing evidence suggesting similarities between hereditary, neurobiological, and cognitive features of this patient group with other psychotic disorders (Valles et al. 2000, Bora et al. 2008, Allen et al. 2010). There are conflicting results in studies about social cognitive field. A study comparing bipolar disorder patients with a history of psychotic symptoms at remission with bipolar disorder patients without a history of psychotic symptoms and healthy controls found worse performance in executive functions and spatial working memory in bipolar disorder patients with a history of psychotic symptoms than the other two groups (Glahn et al. 2007). Also, there are studies that have suggested a power of psychotic features in predicting social cognitive functions beyond diagnostic categories and there are also there are studies that suggested the opposite (Van Hooren et al. 2008, Thaler et al. 2013a, Thaler et al. 2013b). We included first-degree relatives of bipolar patients in order to form a more homogeneous group that share common clinical features in schizophrenia-bipolar disorder spectrum and therefore that have a high probability to share a common genetic structure. Because this study included only relatives of bipolar patients who had a history of psychotic symptoms, these findings cannot be generalized to all bipolar patients.

REFERENCES


