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The relationship between "Eyes Reading" ability and verbal memory in bipolar disorder

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ABSTRACT

In psychiatric disorders, neurocognitive impairments are prevalent and have been associated with poor outcome. Deficits in Theory of Mind (ToM, "mentalising") have also been observed in bipolar disorder (BD); however, the literature shows inconsistent data. The aim of this study was to explore ToM performance in a well-characterized sample of euthymic individuals with BD and its relationship with neurocognitive function. One hundred sixteen euthymic patients with BD between 18 and 74 years (mean age = 42.4, SD = 13.8) and 79 healthy controls (mean age = 39.8, SD = 16.5) were investigated with an extensive neurocognitive test battery (Trail Making Test A/B, d2 Test of Attention, Stroop Color-Word Test, California Verbal Learning Test, Multiple Choice Vocabulary Test). Additionally, all participants were given the Reading the Mind in the Eyes Test (RMET) to measure affective ToM, the ability to make assumptions about other people´s feelings. Overall, "Eyes Reading" performance was not impaired in individuals with BD compared with controls. However, a significant relationship between RMET and verbal memory in BD was shown, particularly in males. Data showed worse RMET performance in patients with memory deficits compared to patients without memory deficits and controls. Due to cross-sectional data, no conclusions can be made with respect to cause and effect.

1. Introduction

Theory of Mind (ToM) is an essential social cognition ability and relates to the cognitive capacity to attribute mental states to self and others (Goldman, 2012). ToM plays a significant role in effective and adaptive psychosocial functioning and can be impaired in some severe mental disorders, including schizophrenia (Bora et al., 2009a), autism spectrum disorder (Baron-Cohen, 2000) as well as affective disorders (Bora and Berk, 2016). Generally, we distinguish between cognitive and affective ToM. Both are mediated by dissociable prefrontal networks. According to the neuroanatomical–neurochemical model of ToM, which was proposed by Abu-Akel and Shamay-Tsoory (2011), two neural systems are involved in processing other people's beliefs and intentions (cognitive component) and others' emotions and feelings (affective component).The first refers to the ability of understanding other´s beliefs and intentions, the latter refers to the ability to make assumptions about other people´s emotions and feelings (Shamay-Tsoory and Aharon-Peretz, 2007). In recent years, it was in the interest of research to distinguish between the two proposed ToM components, usually in disorders actually known to be associated with impaired ToM function, mainly psychiatric disorders including schizophrenia (e.g., Shamay-Tsoory et al., 2007), autism (e.g., Baron-Cohen, 2000), anorexia nervosa (e.g., Adenzato et al., 2012), depression (e.g., Russel et al., 2009), and borderline personality disorder (e.g., Arntz et al., 2009), but also in neurodegenerative diseases including Alzheimer's and Parkinson's disease (Poletti et al., 2012).

Although the cognitive and affective ToM hypothesis is widely agreed, affective ToM is by others acknowledged as "cognitive empathy" allowing one to make inferences about mental or emotional states of others, whereas "affective empathy"means the ability to share the emotional experiences of others (Cox et al., 2011). Cox et al. (2011) outlined that in various psychiatric disorders different disruptions in affective and cognitive empathy might exist. Whereas schizophrenia, depersonalization and narcissism seem to be characterized by impairments in affective but not in cognitive empathy, autism, BD and borderline traits seem to be associated with deficits in cognitive but not in affective empathy. However, a recent meta-analysis found BD to be associated with both cognitive and affective ToM tasks (Bora et al., 2016a,b).

In sum, there are numerous tasks measuring ToM ability; however,

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they are heterogeneous, differing in psychometric properties and task type (verbal or visual). The Reading Mind in the Eyes Test (RMET; Baron-Cohen et al., 2001) is considered the prototypical task for the assessment of affective ToM, and requires participants to match emotion and mental state based on the eye region of faces. It is described in more detail below.

1.1. Cognitive function in BD

In recent years, a bulk of meta-analytic reviews (Bourne et al., 2013; Robinson et al., 2006; Solé et al., 2017; Torres et al., 2007) have demonstrated that neurocognitive impairments are accompanied by poor psychosocial functioning in bipolar disorder (BD), even during euthymia. Strong to moderate effect sizes have been reported for executive dysfunction and deficits in memory functions as well as attention in BD. As cognitive deficits are a core feature of BD, they are currently discussed as trait vulnerability factors of BD. Previous research (Arts et al., 2008; Bora et al., 2009b) suggests neuropsychological deficits also in early stages of BD as well as in first-degree relatives. Currently, the existence of neurocognitive subtypes in BD is in discussion, as not all patients exhibit cognitive dysfunction (Bora et al., 2016a,b). It is assumed there are those who were cognitively impaired before illness onset. Moreover, there are those who show a cognitive decline during the various stages of affective illness. There are, however, patients with BD who do not demonstrate any cognitive impairment at all (Burdick et al., 2014), suggesting the existence of cognitive subgroups within bipolar individuals (Volkert et al., 2015). To conclude, in all cases, cognitive deficits are highly related to clinical outcome measures, they limit quality of life dramatically and favor relapse of mood episodes in patients with affective disorders (Majer et al., 2004; Tse et al., 2014).

1.2. ToM function in BD

As with individuals with schizophrenia, ToM dysfunction in BD is prevalent, and has been similar to cognitive deficits, considered as trait markers of this illness (Bora et al., 2009b; Samamé et al., 2012). Comparing patients with schizophrenia with bipolar patients on “Eyes Reading” performance, no significant differences were found; however patients with BD tend to be slightly less impaired than patients with schizophrenia (Donohoe et al., 2012). Recent literature indicates that ToM ability was significantly impaired also in relatives of persons with BD (Berecz and Tényi, 2016; Bora and Özerdem, 2017), leading experts to assume that social cognition deficits are possible endophenotypic markers of BD. Some studies using the RMET to measure ToM in BD (Bora et al., 2005; Budak, 2011; Cusi et al., 2012; Donohoe et al., 2012) have demonstrated impaired ToM in euthymic patients with BD, whereas others (Duman, 2014; Ibanez et al., 2012; Purcell et al., 2013; Robinson, 2010; Shamay-Tsoory et al., 2009; Thaler et al., 2013) found no difference between euthymic BD patients and healthy controls. In literature, cognition and social cognition were initially expected to be distinct domains (Bora et al., 2009a; Sprong et al., 2007), but there are also authors supposing that ToM is basically a function of cognitive deficits or at least closely related (e.g., Baker et al., 2014; Peterson and Miller, 2012).

A recent meta-analysis (Bora et al., 2016a,b) demonstrated significant but modest cognitive/affective ToM impairments in remitted BD patients. These authors suggested such impairments might be comparable to neuropsychological deficits observed in the literature and theorized that there might be a partial overlap between neurocognitive and socio-cognitive function in BD Bora et al. (2016a,b). However, they merely examined the effect of general cognition on ToM impairment; they did not focus on cognitive subdomains such as attention, executive functions or verbal memory. According to Bora et al. (2016a,b) there is a need for further studies investigating the separability of neurocognition and social cognition. In 2005, Olley et al. showed that ToM ability was significantly associated with executive dysfunction in BD, they suggested a fronto-subcortical pathway dysfunction and interpreted the decreased ToM function as a related trait deficit in BD. However, only 15 BD subjects were included in those analyses using the Story comprehension and the cartoon comprehension ToM task. A study by Bora et al. (2005), enrolling 34 remitted individuals with BD, indicated that RMET was related to executive dysfunctions, sustained attention and memory function, which were suggested to be at least partly responsible for ToM deficits in BD.

All in all, Bora et al. (2016a,b) recommended performing studies with larger sample sizes and more power to further explore the association of cognitive subdomains on ToM performance. This was also suggested in regard of findings that ToM is proposed to be of clinical significance in BD, since ToM function is considered to be connected to issues relating to family, relationships, leisure activities and work activity. Recently, associations between ToM impairments and decreased life functioning in individuals with BD have been described (McKinnon et al., 2010; Montag et al., 2010; Purcell et al., 2013), but were not consistently observed (Barrera et al., 2013; Olley et al., 2005).

Based on all these considerations, the aim of this study was to examine whether: (a) there are deficits in ToM, measured by RMET, in a cohort of euthymic BD patients, (b) ToM function is related to different aspects of cognitive functioning (verbal learning and memory, attention, psychomotor processing speech, executive functions) as well as clinical symptoms (depressive symptoms, illness duration, the number of affective episodes, history of psychosis, previous suicide attempts, global functioning), and (c) cognitive function affects ToM only in BD or even in healthy individuals. We hypothesized that individuals with BD would perform worse in the RMET compared to healthy controls. Moreover, we assumed there is a substantial association between ToM and cognitive functioning as well as clinical functioning in BD. In this regard, it is possible that neurocognitive dysfunction serves as a prerequisite for ToM impairments.

2. Material and methods

2.1. Participants and procedures

A total of 116 euthymic patients with BD and 76 healthy control subjects with no history of substance abuse or other medical, psychiatric, or neurological disorder participated in the study. The patients were between 18 and 74 years old (mean age = 42.37, SD = 13.80), 51.7% were females. A total of 56.9% had an education of high school level or higher. The half of the patients lived in partnership and 53.4% had children. In the control group the mean age was 39.8 years (SD = 16.48; range = 18–76 years) and 63.3% were females, 68.4% had a high school level or higher, 60.8% lived in partnership, and 53.2% had children. All participants signed an informed consent, and the study was approved by the Ethical Committee of the Medical University of Graz in accordance with the Helsinki Declaration of 1975. All euthymic BD patients were recruited from the dedicated outpatient center of bipolar disorders at the Department of Psychiatry of the Medical University Graz. This investigation is part of the larger “BIPFAT”-study investigating fat metabolism, brain function and cognitive abilities in BD (see our previous report, Lackner et al., 2016).

2.2. Measures

Clinical symptom characteristics included illness duration, the number of affective episodes, history of psychosis and suicide attempts). Additionally, the GAF score (Global Assessment of Functioning; Jones et al., 1995) was obtained. Depressive symptoms were assessed with the Beck-Depression Inventory (BDI; Wintjen and Petermann, 2010). Euthymia was one inclusion criterion of the “BIPFAT”-study and was classified for the current analysis via the Hamilton Depression Scale (HAMD, Hamilton, 1976) with a score under 9

and the Young Mania Rating Scale (Young et al., 1978) with a score under 6. The patients were treated with mood stabilizers including lithium (n = 40), atypical antipsychotics (n = 68), typical antipsychotics (n = 15), and antiepileptics (n = 37).

2.2.1. Instruments

All participants were investigated with a computerized version of the Reading Mind in the Eyes Test (RMET; Baron-Cohen et al., 2001). The RMET measures the ability to recognize emotions in others by viewing black-and-white photographs of the eye region of faces from just above the eyebrows to halfway down the bridge of the nose (Baron-Cohen et al., 2001). The RMET consists of 36 stimuli; Participants had to select one from four emotional adjectives that correspond to the presented eye-pair. A list of definitions for all the descriptors was provided and participants were encouraged to consult the list whenever they felt uncertain about the meaning of a word. In this study, the number of correct answers was used as an indicator of ToM ability.

In addition, an extensive neurocognitive test battery was performed.

The Trail Making Test A/B (TMT A/B; Reitan, 1992) is a neuropsychological test of visual attention and task switching measuring psychomotor processing speech (TMT A) and cognitive flexibility (TMT B).

The d2 test of Attention (d2R; Brickenkamp et al., 2010) is a neuropsychological measure of selective and sustained attention and visual scanning speed.

The Stroop Color-Word Test (Bäumler and Stroop, 1985) measures cognitive processing and attention in the first and second condition (Stroop word-reading, Stroop color-naming) and executive function in the third condition (Stroop interference).

Verbal learning and memory was assessed with the California Verbal Learning Test (CVLT; Niemann et al., 2008), which is a measure of episodic verbal learning and memory. The CVLT generates a wide variety of measures: immediate Recall (trial 1–5), short-delay free recall, short-delay cued recall, long-delay free recall, and long-delay cued recall.

The Multiple Choice Vocabulary Test; Lehrl, 2005) to measure premorbid IQ was used.

2.3. Analysis

Sociodemographic and clinical characteristics of BD patients and healthy controls were compared using independent sample t-tests or Chi-square tests (see Table 1). As we were able to find an association between obesity and cognitive impairments earlier (Lackner et al., 2016), body mass index (BMI) was introduced as a co-variable in all analyses. Premorbid IQ was worse in bipolar individuals compared to controls (see Table 2) and is known to affect ToM function (Baker et al., 2014), and was therefore additionally introduced as a control variable. No differences between men and women in both samples were found in premorbid IQ and age. Cognitive function was compared using analyses of co-variance (MANCOVAS) with Group and Gender as independent factors controlled for age, premorbid IQ, and BMI.

To test differences in RMET performance between individuals with BD and healthy controls, an analysis of covariance (ANCOVA) was performed including Group and Gender as independent factors and RMET as a dependent variable. Age, BMI, and premorbid IQ were introduced as control variables. Additionally, to test associations between RMET performance and cognitive markers, partial correlation analyses were conducted, controlling for age and premorbid IQ in individuals with BD and healthy controls. To test associations between RMET performance and other clinical parameters (e.g., number of affective episodes, BDI, GAF, BMI) in the group of individuals with BD, partial correlation analyses were conducted, controlling for age and premorbid IQ.

In a next step ANCOVAs were performed, to test if there were differences in RMET performance between participants with cognitive deficits versus those without deficits. This was done by introducing the variable cognitive deficits (yes/no) as a third factor into the above described model. Cognitive deficits were classified according to percentile ranks from the manuals. A rank under 25 was considered as below average. The analyses were done using the CVLT short-delay free recall scores and the CVLT long-delay free recall scores ("memory deficits"), the TMT A ("attention deficits"), and the TMT B ("executive function deficits").

Table 1
Descriptive Statistic (Means and standard deviations).

	BD n = 116	Controls n = 79	
Females	60	50	$\chi 2$ = 2.56, n.s.
Age [years] Mean (SD)	42.8 (14.35)	40.8 (16.56)	t = 0.91, n.s.
BMI [kg/m^2] Mean (SD)	28.7 (6.41)	24.7 (4.72)	t = 4.6**
Completed high school (n)	59	51	$\chi 2$ = 8.0, n.s.
Premorbid IQ Mean (SD)	111.2 (13.7)	116.1 (15.2)	t = −2.30*
Illness duration [years] Mean (SD)	18.4 (12.17)		
Number of depressive episodes Mean (SD)	15.0 (15.7)		
Number of manic episodes Mean (SD)	9.9 (13.6)		
BDI Mean (SD)	15.9 (11.7)		
HAMD Mean (SD)	4.2 (4.9)		
YMRS Mean (SD)	1.4 (3.2)		
GAF Mean (SD)	69.6 (12.6)		
History of psychosis [yes] (%)	23.3		
Previous suicide attempts [yes] (%)	31		

Note: Results from independent sample t-tests and chi-square tests, BD = Bipolar disorder, BMI = body mass index, BDI = Beck Depression Inventory, HAMD = Hamilton Depression Scale, YMRS = Young Mania Rating Scale, GAF = Global Assessment of Functioning.

** $p < 0.001$.

* $p < 0.05$.

3. Results

3.1. Descriptive statistics

Table 1 shows the demographic and clinical characteristics of the participant groups. Patients and controls differed in BMI and premorbid IQ showing higher BMI and lower premorbid IQ in the sample of BD patients. No differences were found in age or education.

3.2. Cognitive function in patients with BD and controls

Multivariate analyses testing differences in cognitive functioning between individuals with BD and controls (factor Group) as well as men and women (factor Gender) controlling for age, premorbid IQ and BMI revealed significant group effects **in attention tasks** (TMT A, Stroop word-reading, Stroop color-naming, d2 concentration test; Wilks' Lambda = 0.97, $F(3/174)$ = 5.546, p = 0.001, $Partial\ \eta^2$ = 0.09), **and executive function tasks** (TMT B, Stroop interference task; Wilks' Lambda = 0.98, $F(2/172)$ = 10.27, $p < 0.001$, $Partial\ \eta^2$ = 0.11) indicating a worse cognitive performance in TMT A, Stroop color-naming, d2 concentration test, and TMT B in the BD sample compared with controls (see the univariate results in Table 2). In multivariate analyses, age and premorbid IQ were identified as significant confounders for attention (Age: Wilks' Lambda = 0.72, $F(3/174)$ = 22.10, $p < 0.001$, $Partial\ \eta^2$ = 0.28; Premorbid IQ: Wilks' Lambda = 0.91, $F(3/174)$ = 6.03, p = 0.001, $Partial\ \eta^2$ = 0.94) showing better attention in younger participants and those with higher premorbid IQ.

Accordingly, age (Wilks' Lambda = 0.80, $F(2/172)$ = 21.45, $p < 0.001$, $Partial\ \eta^2$ = 0.20) and premorbid IQ (Wilks' Lambda = 0.88, $F(2/172)$ = 12.32, $p < 0.001$, $Partial\ \eta^2$ = 0.13) were significant

Table 2
Differences in ToM function and cognition between patients and controls: Group and Gender effects.

	BD		Controls		Group (F)	Gender (F)
	Males $n = 54$	**Females** $n = 57$	**Males** $n = 27$	**Females** $n = 48$		
ToM						
RMET [correct responses] (M, SD)	20.7 (4.8)	21.5 (4.5)	22.1 (4.2)	23.7 (4.1)	2.09	**4.69***
Total (M, SD)	21.2 (4.7)		23.1 (4.1)			
Attention	$n = 51$	$n = 57$	$n = 27$	$n = 48$		
TMT A [sec] (M, SD)	40.5 (20.2)	31.5 (11.2)	27.5 (10.7)	27.7 (9.3)	**8.77****	5.85*
Total (M, SD)	35.7 (16.5)		27.4 (9.9)			
Stroop word-reading [sec] (M, SD)	32.8 (6.8)	30.7 (5.5)	28.7 (6.1)	30.0 (3.9)	n.s.	n.s.
Total (M, SD)	31.7 (6.2)		29.5 (4.9)			
Stroop color-naming [sec] (M, SD)	51.9 (8.7)	48.2 (10.7)	44.0 (8.7)	45.1 (5.8)	**11.87****	n.s.
Total (M, SD)	49.9 (10.0)		44.6 (6.9)			
d2 concentration test [concentration score] (M, SD)	145.8 (43.4)	155.8 (40.9)	182.6 (55.3)	185.7 (49.1)	**13.23*****	n.s.
Total (M, SD)	150.6 (42.2)		185.1 (50.9)			
Executive functions	$n = 49$	$n = 56$	$n = 27$	$n = 48$		
TMT B [sec] (M, SD)	82.0 (45.9)	73.1 (30.0)	60.6 (21.7)	62.7 (23.2)	**20.53*****	n.s.
Total (M, SD)	77.2 (38.0)		61.7 (22.5)			
Stroop interference [sec] (M, SD)	89.0 (27.8)	80.7 (20.8)	65.9 (11.3)	68.2 (11.0)	n.s.	n.s.
Total (M, SD)	86.2 (27.1)		68.2 (10.9)			
Verbal learning and memory	$n = 52$	$n = 57$	$n = 27$	$n = 48$		
CVLT trial 1–5 [correctly recalled items] (M, SD)	49.4 (12.4)	55.9 (12.5)	53.9 (12.6)	60.4 (10.4)	n.s.	**16.33*****
Total (M, SD)	52.9 (12.8)		58.3 (11.7)			
CVLT short-delay free recall [correctly recalled items] (M, SD)	9.8 (3.6)	11.5 (3.4)	11.1 (3.3)	13.1 (2.3)	n.s.	**15.82*****
Total (M, SD)	10.7 (3.6)		12.4 (2.8)			
CVLT short-delay cued recall [correctly recalled items] (M, SD)	10.8 (3.3)	12.2 (3.1)	11.8 (3.0)	13.7 (2.0)	n.s.	**15.23*****
Total (M, SD)	11.5 (3.3)		13.1 (2.5)			
CVLT long-delay free recall [correctly recalled items] (M, SD)	10.7 (3.5)	12.4 (3.4)	11.3 (3.6)	13.4 (2.2)	n.s.	**18.30*****
Total (M, SD)	11.6 (3.5)		12.7 (2.9)			
CVLT long-delay cued recall [correctly recalled items] (M, SD)	10.9 (3.5)	12.8 (2.9)	11.7 (3.3)	13.8 (2.0)	n.s.	**20.92*****
Total (M, SD)	11.9 (3.3)		13.1 (2.7)			

Note: Significant univariate results from multivariate analyses of co-variance (controlled for age, premorbid IQ, and body mass index); ToM = Theory of Mind, RMET = Reading Mind in the Eyes Test, TMT A = Trail Making Test A, TMT B = Trail Making Test B, CVLT = California Verbal Learning Test, BD = Bipolar disorder.

*** $p < 0.001$.

** $p < 0.01$.

* $p < 0.05$.

confounders for executive functioning.

No group difference was found in **verbal learning and memory** (Wilks' Lambda = 0.95, $F(5/173) = 1.80$, $p = 0.116$, *Partial* $\eta^2 = 0.05$); however, a gender effect was found (Wilks' Lambda = 0.89, $F(5/173) = 4.42$, $p = 0.001$, *Partial* $\eta^2 = 0.11$) showing better performance in all CVLT conditions in women compared to men (see Table 2). Again, age and premorbid IQ were significant covariates for verbal learning and memory (Age: Wilks' Lambda = 0.73, $F(5/173) = 12.59$, $p < 0.001$, *Partial* $\eta^2 = 0.27$); Premorbid IQ: Wilks' Lambda = 0.83, $F(5/173) = 6.97$, $p < 0.001$, *Partial* $\eta^2 = 0.17$).

3.3. Differences in ToM between patients with BD and controls

The first ANCOVA indicated no significant difference in the RMET between patients and controls; however, there was a difference between men and women. Males performed worse on the RMET compared with females (see Table 2). No interaction Group x Gender was observed ($F(1/179) = 0.17$, $p = 0.193$; Partial $\eta^2 = 0.01$). Age was identified as a significant confounding factor ($F(1/179) = 44.74$, $p < 0.001$; Partial $\eta^2 = 0.20$), as was premorbid IQ ($F(1/179) = 12.66$, $p < 0.001$; *Partial* $\eta^2 = 0.07$).

3.4. Association between ToM and cognitive parameters in patients with BD

In Table 3, the correlation coefficients between RMET and cognitive functioning in individuals with BD and controls are displayed. RMET was positively associated with CVLT parameters trial 1–5, and the short-and long-delay free recall condition. No significant associations were found with ToM function and attention (TMT A, TMT A, Stroop word-reading, Stroop color-naming, d2 concentration test) or executive

Table 3
Associations between ToM (RMET) and cognitive function as well as illness parameters in individuals with BD.

	*ToM*RMET
Cognitive variables	*r* (*p*)
TMT A	−0.02 (0.874)
TMT B	−0.04 (0.729)
d2 concentration test	−0.01 (0.960)
Stroop word-reading	−0.01 (0.911)
Stroop color-naming	0.00 (0.972)
Stroop interference	−0.06 (0.542)
CVLT trial 1–5	**0.20 (0.046)***
CVLT short-delay free recall	**0.20 (0.049)***
CVLT short-delay cued recall	0.20 (0.055)
CVLT long-delay free recall	**0.21 (0.040)***
CVLT long-delay cued recall	0.19 (0.056)
Illness parameters	
Illness duration	0.19 (0.641)
BMI	0.11 (0.307)
BDI	0.14 (0.203)
GAF	0.02 (0.835)
Number of depressive episodes	0.17 (0.126)
Number of manic episodes	0.04 (0.746)
History of psychosis	0.02 (0.885)
Number of previous suicide attempts	0.02 (0.885)

Note: Partial correlation analysis controlled for age and premorbid IQ in individuals with bipolar disorder (BD, $n = 96$); TMT A = Trail Making Test A, TMT B = Trail Making Test B, CVLT = California Verbal Learning Test; BMI = Body Mass Index, BDI = Beck Depression Inventoy, GAF = Global Assessment of Functioning. Bold values indicate significant correlations;

* $p < 0.05$.

Table 4
Associations between ToM (RMET) and cognitive function in controls.

	ToM RMET
Cognitive variables	*r* (*p*)
TMT A	0.03 (0.815)
TMT B	0.02 (0.838)
d2 concentration test	0.14 (0.255)
Stroop word-reading	0.05 (0.687)
Stroop color-naming	0.02 (0.869)
Stroop interference	−0.07 (0.553)
CVLT trial 1–5	0.22 (0.066)
CVLT short-delay free recall	0.19 (0.101)
CVLT short-delay cued recall	0.19 (0.101)
CVLT long-delay free recall	0.16 (0.173)
CVLT long-delay cued recall	0.17 (0.151)

Note: Partial correlation analysis controlled for age and premorbid IQ in healthy controls (CG, $n = 70$). TMT A = Trail Making Test A, TMT B = Trail Making Test B, CVLT = California Verbal Learning Test.

variables (TMT B, Stroop interference).

3.5. Association between ToM and cognitive parameters in controls

In the control group, no significant associations between cognitive function and ToM were found (see Table 4).

3.6. Cognitive deficits in patients with BD versus controls

Table 5 gives the frequencies of cognitive deficits (*n*) in the two groups (patients with BD versus healthy controls). In the BD group, 45.7% had a deficit in the TMT A (versus 16.5% in the control group) and 44% of the patients in the TMT B (versus 29.1% of controls). In the BD group, 50% had impairments on the CVLT short-delay free recall (versus 29.1% in the control group) and 41.4% had impairments on the CVLT long-delay free recall (versus 36.7% in the control group). Chi-square tests demonstrated that individuals with BD had more deficits in TMT A, TMT B and CVLT short-delay free recall. No differences between patients and controls were found in the CVLT long-delay free recall condition.

3.6.1. Effects of memory deficits on ToM performance in patients with BD
3.6.1.1. Effect of CVLT short-delay free recall deficit. ANCOVAS, computing the difference between patients and controls in the RMET (which included the effects of CVLT short-delay free recall deficits), demonstrated higher RMET performance in those without CVLT short-delay free recall deficits ($F(1/168) = 5.53$, $p = 0.020$, *Partial* $\eta^2 = 0.03$). Additionally, there was a significant interaction of CVLT short-delay free recall deficits x Gender x Group ($F(1/168) = 5.20$, $p = 0.024$, *Partial* $\eta^2 = 0.03$), indicating worse RMET performance in bipolar men with memory deficits compared with bipolar men without memory deficits and bipolar women with and without deficits, as well as controls (see Fig. 1A).

3.6.1.2. Effect of CVLT long-delay free recall deficit. Similarly, there was a significant difference in the RMET between those with deficits in the CVLT long-delay free recall condition compared to those without deficits in this task ($F(1/168) = 1.75$, $p = 0.025$, *Partial* $\eta^2 = 0.03$), with the latter showing better RMET performance (see Fig. 1B). There were two interaction effects. First, there was an interaction of CVLT long delay free recall deficits x Group ($F(1/168) = 4.08$, $p = 0.045$, *Partial* $\eta^2 = 0.02$), indicating a worse RMET performance in BD patients with cognitive deficits compared with BD patients without cognitive deficits and controls. Second, an interaction Long-delay free recall deficit x Group x Gender ($F(1/168) = 3.94$, $p = 0.049$, *Partial* $\eta^2 = 0.02$) was seen, showing also a worse RMET performance in bipolar men with deficits in long-delay free recall compared to those without deficits, both BD females/males and controls (see Fig. 1).

ANCOVAS showed no significant effects of attention and executive function deficits on ToM performance. There was an interaction Gender x Attention deficit ($F(1/175) = 4.03$, $p < 0.046$, *Partial* $\eta^2 = 0.02$), indicating that women without attention deficits had a better performance in the RMET compared with women with attention deficits and men (with and without deficits). No other interactions, group or gender effects were found.

3.7. Association between ToM and illness parameters in patients with BD

In the group of BD participants, RMET correlated negatively with age ($r = -0.32$, $p = 0.001$) as well as with illness duration ($r = -0.19$, $p = 0.047$). Illness duration was no longer related to RMET when controlling for age ($r = 0.04$, $p = 0.641$). RMET correlated positively with premorbid IQ ($r = 0.34$, $p = 0.001$). In partial correlation analyses controlling for age and premorbid IQ, RMET was not associated with BMI, BDI, GAF, number of depressive episodes, number of manic episodes, history of psychosis, or number of previous suicide attempts (see Table 5).

4. Discussion

The aim of this study was to investigate ToM performance (measured with the RMET) in a well-characterized euthymic BD group of participants. Additionally, we wanted to examine the relationship between "Eyes Reading" ability and cognitive parameters including attention, executive function, and verbal memory in individuals with BD versus controls and to show associations between ToM and illness parameters. We found a relationship between verbal memory and ToM performance, indicating impaired ToM only in bipolar patients with marked memory deficits.

In contrast to some prior studies (Bora et al., 2005; Budak, 2011; Cusi et al., 2012; Donohoe et al., 2012; Wiener et al., 2011), we did not find a worse RMET performance in individuals with BD compared to

Table 5
Frequencies (n) and group differences (BD versus controls) in deficits in cognitive test variables.

		TMT A		TMT B		CVLT short-delay free recall		CVLT long-delay free recall	
		Deficit	No Deficit	Deficit	No Deficit	Deficit	No Deficit	Deficit	No Deficit
BD	Males	31	23	26	28	34	18	32	20
	Females	22	35	25	32	22	32	15	39
Controls	Males	5	22	8	19	13	13	16	10
	Females	8	40	15	33	9	39	13	35
Group differences		$\chi2 = 18.55^{***}$		$\chi2 = 4.64^{*}$		$\chi2 = 9.23^{**}$		$\chi2 = 0.56$	

Note: Cell distribution concerning the frequencies of cognitive deficits in the sample and differences between patients and controls. BD = Bipolar disorder, TMT A = Trail Making Test A, TMT B = Trail Making Test B, CVLT = California Verbal Learning Test.
*** $p < 0.001$.
** $p < 0.01$.
* $p < 0.05$.

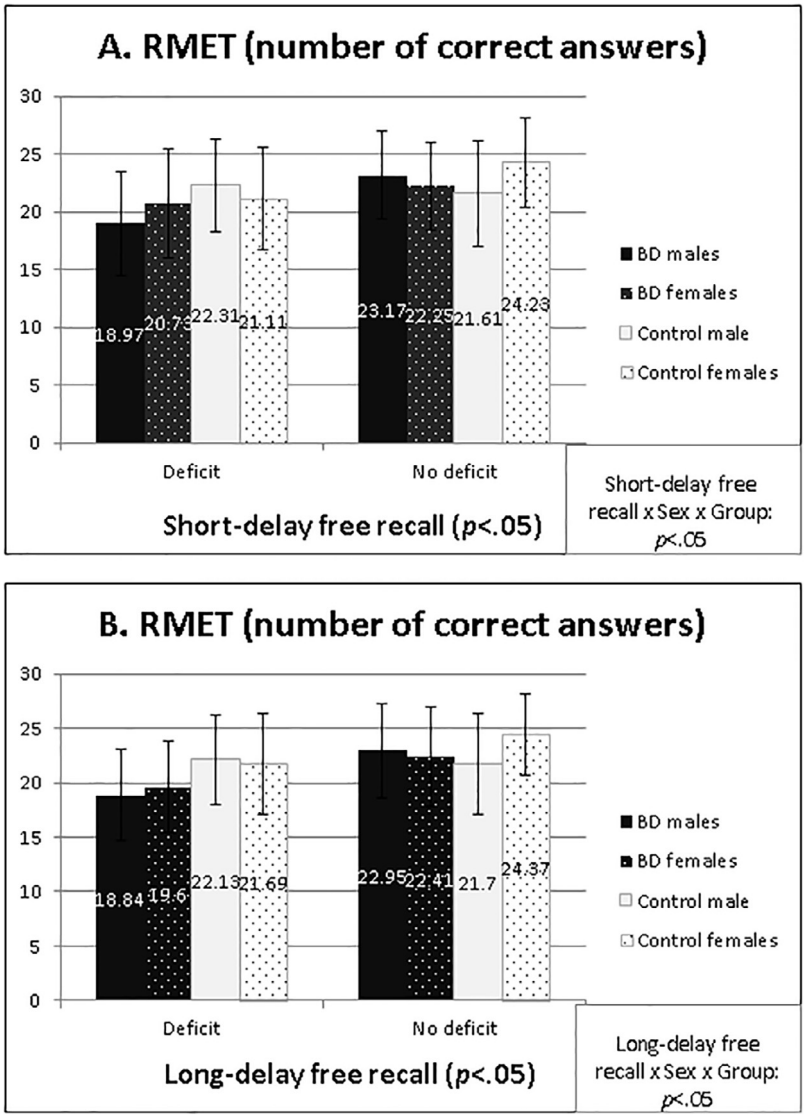

Fig. 1. Number of correct answers in the RMET comparing individuals with BD and healthy controls depending on gender and memory deficits (A: CVLT short-delay free recall and B: CVLT long-delay free recall). Analyses were controlled for age, premorbid IQ, and BMI. Females are displayed in dotted bars. *Note: BD = Bipolar disorder, RMET = Reading Mind in the Eyes Test, CVLT = California Verbal Learning Test.*

healthy controls in general. This is in line with some other studies using the RMET in euthymic or remitted bipolar patients (Duman, 2014; Purcell et al., 2013; Robinson, 2010). Nevertheless, we also wanted to test whether ToM deficits might be secondary to different aspects of cognition. First, the findings showed a relation between RMET performance and verbal memory function. Second, the existence of verbal memory impairments seems to be a crucial factor in ToM deficits in BD. Our analyses revealed that individuals with memory deficits, both in the short-delay free recall condition as well as the long-delay free recall condition, performed poorer in the RMET than those without deficits. This indicates a considerable overlap between impaired verbal memory function and poor RMET performance and was in accordance with recent findings, suggesting a strong association between ToM function and marked verbal memory deficits in BD (Bora et al., 2016a,b; Martino et al., 2011). No associations were found with other cognitive domains, e.g., executive function or attention.

The link between verbal cognitive function and ToM was highlighted before by Peterson and Miller (2012), who found associations between RMET and verbal IQ. According to the authors, the relation between verbal IQ and RMET performance could be driven by cognitive abilities related to verbal-reasoning and verbal working memory. Peterson and Miller (2012) suggest that the RMET requires implicit social-perceptual processes. Although the RMET asks explicitly to name mental states, it is suggested that the mere presentation of the eye region of faces may trigger fast and automatic spontaneous reasoning about the person's mental state. Other researchers have also argued that ToM ability rests on the integration of automatic implicit processes with more cognitively mediated explicit processes, which require the expenditure of mental effort (e.g., Frith and Frith, 2008).

It can be supposed that individual differences on implicit task performance are influenced to a certain degree by differences in verbal abilities. Moreover, verbal memory predicted ToM and emotion recognition ability in autistic individuals before (Buitelaar et al., 1999). Even so, participant differences in vocabulary knowledge could be the deciding factor. To exclude this possibility, a vocabulary test could be included in future studies. Peterson and Miller (2012) also recommend including other measures of verbal ability (e.g., verbal-reasoning and verbal working memory tests) to better understand the relationship between RMET and verbal cognitive functioning. Surprisingly, in our study, no associations between RMET and verbal memory were found in control persons. Hence, the investigation of cognitive tasks in concordance with fMRI data during ToM task processing would be

fundamental. ToM is suggested to involve a widespread neural network, including temporoparietal regions, the precuneus, temporal cortex, cingulate areas, and the prefrontal cortex (Lissek et al., 2008). A preliminary neuroimaging study by Malhi et al. (2008) found an altered activation in parts of this network, in particular the insula, inferior frontal, supramarginal and angular gyri, and temporal cortex, during a social cognition task. In numerous studies (Adolphs, 2001; Shaw et al., 2004; Stone et al., 2003; Völlm et al., 2006) affective networks, particularly the amygdala, were found to be involved in the ability to appreciate the other's emotional states and the RMET. The hippocampus is traditionally assumed to be central for memory functions (Kesler et al., 2013; Van Petten, 2004); The amygdala might also play a role in this context. In healthy individuals, amygdala volume was unrelated to memory function, whereas in BD, higher amygdala volume was predictive of memory function (Killgore et al., 2009).

In fact, we can only speculate about the precise processes involved (implicit and explicit processes) or brain regions activated in the relationship between RMET and verbal memory in contributing to performance differences. Further research is needed to spread our understanding of the interaction between brain networks and the impairments in memory function and social cognition domains in participants with serious mental illness.

There might exist subtypes regarding ToM ability, as it is assumed to exist for neurocognition (Burdick et al., 2014). However, in accordance with the suggestions of Bora et al. (2009c), we rather conclude that ToM deficits in BD might reflect underlying memory deficits, as opposed to representing a specific BD trait marker. The extent to which ToM impairment can be considered a valid endophenotypic marker for BD is lack of empirical research and further investigating ToM performance in groups with a heightened genetic loading for the disorder (e.g., first degree relatives) would be significant. To finally answer the question of whether cognitive and socio-cognitive dysfunction are a state or a trait marker of BD, more longitudinal studies in this area are urgently needed.

Given the overall finding that women had higher ToM abilities as well as memory function than men, the analyses clearly showed that bipolar men with memory deficits had the worst RMET performance compared with the other groups. These findings indicate that, especially in male patients with BD, both aspects seem to be cumulated. In general, it appears that bipolar men are at particular risk for cognitive abnormality, even decline. There might be a cumulative effect of BD, male sex and verbal memory deficits on ToM ability. This higher risk in bipolar men with subsequent immunological links to neurodegenerative factors such as oxidative stress parameters and tryptophan breakdown have been more than once observed in our study group (Bengesser et al., 2015; Platzer et al., 2017). The use of social cognitive training embedded in cognitive training can potentially improve ToM function, especially in males with BD. However, standardized socio-cognitive training programs for bipolar populations are lacking. In schizophrenia, on the one hand, “targeted” interventions (e.g., the FAR training program by Wölwer et al. (2005), and on the other hand, “broad-based” interventions, which incorporate multiple domains such as the Social Cognition and Interaction Training (SCIT) by Roberts and Penn (2009), were evaluated. Meta-analytic research of 19 controlled studies by Kurtz and Richardson (2011) concluded that socio-cognitive training programs improve facial affect recognition (FAR) in the moderate-large range, while producing a smaller but significant effect on ToM. However, no effects on positive and negative symptoms specific to schizophrenia could be found. Interestingly, longer duration of illness predicted greater responses to socio-cognitive trainings. There was no evidence that training programs of longer duration or higher intensity, or programs that treat multiple domains of social cognition, rather than a single domain, produce larger effects on socio-cognitive measures (Kurtz and Richardson, 2011).

One study by Lahera et al. (2013) evaluated the effects of a 18–24-week, group based SCIT program, originally developed for individuals with schizophrenia, on different social cognition measures in BD and found significant improvements in emotion perception (measured with the Face Emotion Identification Task and the Face Emotion Discrimination Task) and ToM (measured with the Hinting Task). However, no improvement in social functioning was observed.

Santiesteban et al. (2012) tested two contrasting theoretical ToM training approaches by training adults either to imitate or to inhibit imitation. It is suggested that imitation, and its neural substrate the mirror neuron system, may play a crucial role in supporting higher-order socio-cognitive abilities such as ToM. An intervention promoting the triggering of corresponding motor representations by action observation (imitation training) could enhance the ability to represent the mental states of others. In contrast, it is suggested by others that ToM ability is related not to imitation, but to the inhibition of imitation. The distinction and control of representations pertaining to the self and the other, rather than the mirror neuron system, is considered at the core of higher-order socio-cognitive functions. When inhibiting the tendency to imitate another person's behavior, the observer must distinguish between their own action intentions and those of the observed person, which results in performing their own motor intention rather than that of the other. In their studies, Santiesteban et al. (2012) observed that imitation-inhibition training could improve ToM, this was not seen after either imitation training or training in general inhibitory control. Thus, such findings could be taken into account when developing new ToM training approaches in bipolar populations.

Concerning the relevance of socio-cognitive functioning in everyday life, some studies found an association between social cognition impairment and psychosocial functioning in BD (McKinnon et al., 2010; Montag et al., 2010; Purcell et al., 2013), which might be related to social problems and problems at work. In the present study, no association between the Global Assessment of Functioning or other illness variables (i.e., number of affective episodes, depressive symptoms) and ToM ability was found. The lack of association with such illness-related factors indicates that ToM function might not be as much affected by neurodegenerative processes as initially assumed. No associations also were found with psychotic symptoms. This again emphasizes that ToM might not be used as a trait marker for psychosis in BD (Wolf et al., 2010).

Against our assumptions and evidence from recent studies, in both BD (Bora et al., 2005; Olley et al., 2005) and other clinical populations (Baez et al., 2015), as well as in healthy individuals (Aboulafia-Brakha et al., 2011; Ahmed and Miller, 2011), social cognition was not related to executive function. Benson and Sabbagh (2010) reported that already in preschool children the understanding of mental states was related to some aspects of executive functioning, in particular response-conflict tasks (including the Stroop Test). However, the authors argued that this does not apply to ToM ability related to the understanding of intentions or desires. In line with our findings, other authors (e.g., Wolf et al., 2010) also consider ToM as independent from executive functioning in BD. We can only speculate that executive functioning might be related to social cognition only in more complex ToM tasks, for example, story or cartoon comprehension tasks as used by Olley et al. (2005). As the RMET is a verbal task requiring in a certain way verbal abilities, an association with the verbal memory function (CVLT) and verbal IQ (MWTB) is quite logical. The evaluation of non-verbal ToM in this context could shed more light on the role of verbal ability in socio-cognitive functioning.

4.1. Limitations

There are some limitations regarding the current study. First, as this study was cross-sectional, no conclusions can be made with respect to cause and effect. Second, there might be medication effects that possibly could have influenced cognitive performance and ToM performance. Third, studies which may investigate to what extent ToM deficits in BD are of clinical significance, and how ToM is associated with

social functioning in BD using more notable scales, are needed. The additional use of other advanced ToM tasks, in particular testing non-verbal ToM, would be a next step. Fourth, there is a certain overlap of this study to Bora´s studies, nevertheless, our results add significantly to the current literature. Bora et al. highlighted in 2016 the need for more studies investigating the separability of neurocognitive subdomains and ToM performance by performing studies with comprehensive neuropsychological tasks and large sample sizes, such as this study was.

4.2. Conclusion

A recently assumed overlap between neurocognition and ToM function, a higher-order form of social cognition, representing the understanding of thoughts, emotions and intentions of others, has been observed in this study. The main result was that RMET performance, measuring the ability to read the emotions of others through the eyes, was associated with marked deficits in verbal memory function in symptom-free intervals of BD. Euthymic bipolar men with verbal memory deficits, in particular, performed more poorly in the RMET compared with bipolar men without memory deficits, bipolar females and controls. Illness parameters (illness duration, number of affective episodes, global functioning, history of psychotic symptoms) were not related to ToM ability in BD. Summing up, the results support the hypothesis that in individuals with BD, “Eyes Reading” is linked to poor memory function, especially in male patients.

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Authors' contributions

ND: Supervised testing, performed the statistical analyses and wrote the first draft of the paper. **ER**: Contributed in study planning and was responsible for the study. **MP/FF/AB/RQ/SB/CH/AR/RH**: Were responsible for data collection and analyses and helped with the revisions of the paper. **RP:** Was responsible for data management. **BW/EW:** Were responsible for RMET analyses. **HPK:** Edited the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors have no conflict of interest.

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Supplementary materials

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