

Introduction

Theory of mind (ToM), being an essential contributor to the ability to understand other people's emotions and intentions, forms the basis for a healthy social life. Patients with a depression tend to show difficulties disengaging from self-centered thoughts, resulting in poor social understanding, a dysregulation of their social behavior and even social isolation (Rochat, et al, 2012). Indeed, previous research has shown alterations in theory of mind (ToM) functioning in acute depression (Harkness, et al, 2011; Zobel, et al, 2010), but also in remission (Inoue, et al, 2004; Yamada, Inoue and Kanba, 2015). A recent meta-analysis found that twelve out of eighteen studies in major depressive disorders (MDD) identified deficits in relevant ToM domains (Bora and Berk, 2016). However, as highlighted by the authors, due to limited clinical information regarding these samples and the diversity of ToM tasks, potentially moderating factors have remained underexplored. One paradigm that has been found particularly useful to tackle (cognitive) ToM deficits in mental disorders is the so-called "animated triangles task" (Abell, et al, 2000), which is designed to induce automatic attributions of intention and agency in a way that excludes language understanding. Due to its robust activation of ToM-related cortical networks and reliability across subjects, it is one of the tasks used in the Human Connectome Project with the aim to unify research methods and investigate large samples (Barch, et al, 2013). Only in two earlier studies, the animated triangles task in depression has been used, showing deficits in the performance of acutely and chronically ill patients as well as in those having a first episode of depression (Ladegaard, et al, 2014a,b). In these two previous investigations, the assessed samples had co-morbid disorders (Ladegaard, et al, 2014a: generalized anxiety disorder (52.5%), panic disorder 29.5%; Ladegaard, et al, 2014b: two-thirds of the patients had one or more axis I co-morbid condition, with generalized anxiety and panic disorder being the most

prevalent in both). Even though this represents clinical reality, studying a depression-only sample and assessing the severity of the disorder along with different personality traits can help to clarify the inconsistencies in the previous literature assessing ToM abilities, as well as reveal the mechanisms underlying a putative deficit (Kret and Ploeger, 2015).

In the current study we therefore investigated patients with an MDD without psychiatric comorbidities regarding their ToM abilities. Assuming that the profile of deficits in depression might be different, i.e. less dependent on the state of the illness as compared to other neurodevelopmental psychiatric disorders such as schizophrenia, we also addressed the impact of factors known to be associated with ToM performance. These factors include psychopathology (Bora and Berk, 2016), neurocognitive functioning (Lee, et al, 2014), empathy abilities (Vollm, et al, 2006) and attachment styles (Pos, et al, 2015).

Methods

Participants

Forty in-patients participated in the study and were diagnosed with the Structured Clinical Interview for DSM-IV (SCID-I) as well as on the basis of the patient chart by an experienced clinician. Two patients had to be excluded due to co-morbid disorders, leaving a sample of thirty-eight. Patients fulfilled the criteria for a first or recurrent MDD of at least medium severity (≥ 8 points on the Hamilton Depression Rating Scale (HDRS), 21-item version; Hamilton, 1960). The mean duration of illness was 3.4 (5.4) years with a range of 0.2-20 years. All other axis-I psychiatric disorders, most importantly anxiety disorders, were used as exclusion criteria. Patients with any history of serious internal medical or neurological disorders, serious head injury, illegal drug use or alcohol abuse were excluded from the study. Thirty-two patients received antidepressant medication (SNRI: 7; SSRI: 6; NaSSA: 4; tricyclic antidepressant: 2; MAO-antagonist: 2; NDRI: 1; mood stabilizer:1; atypical antipsychotic: 1; combination with atypical antipsychotic: 16; combination of SNRI and NaSSA: 4; additional mood stabilizer: 3; SNRI and melatonin-derivative:1; four-fold medication of SSRI, SNRI, melatonin derivative and mood stabilizer or atypical antipsychotic: 4; low-dose benzodiazepine: 1). Forty healthy controls matched for age, gender and education duration were recruited. Control subjects had no history of mental disorders (as verified with a SCID-I) or any first-degree relatives with mental disorders. All participants were native speakers of German. The groups did not differ in age and gender (see **Table 1**). The study protocol was approved by the local ethics committee (2012-495-f-S) according to the Declaration of Helsinki (<http://www.wma.net/en/30publications/10policies/b3/>, accessed July 4, 2019 and written informed consent was obtained from all participants prior to their enrolment in the study.

Clinical and neuropsychological assessment

Intellectual performance was assessed by way of the Multiple Choice Vocabulary Intelligence Test (MWT-B) that estimates crystallized intelligence (Lehrl, 1999). The Trail-Making Test (TMT-A and B) was used as a cognitive flexibility measure assessing visual attentional abilities and processing speed as well as executive functioning (Reitan, 1958). The Adult Attachment Scale (AAS) measures adult attachment styles, namely “secure”, “anxious” and “avoidant” (Collins and Read, 1990). From these styles, three scores were derived. The “closeness” score indicates greater feelings of comfort with closeness and intimacy. The “anxiety” score points at worries about being rejected or unloved. Lastly, the “depend” score indicates more comfort with depending on others and a belief that others will be available when needed. As an empathy measure we administered the Interpersonal Reactivity Index (IRI; Davis, 1980). This scale features four subscores, i.e. perspective taking (PT), fantasy (FS), empathic concern (EC) and personal distress (PD). The PT score measures the tendency to spontaneously adopt the psychological point of view of others, while the FS score assesses the ability to imagine the emotional status of fictional characters. The EC score assesses "other-oriented" feelings of sympathy and concern and the PD subscore measures "self-oriented" feelings of personal anxiety and unease in tense interpersonal settings. In the German version a general empathy score can be calculated (Paulus, 2006). The State-Trait Anxiety Inventory (STAI-S/STAI-T) is a commonly used measure of trait and state anxiety (Spielberger, et al, 1970). We found significant differences between groups on verbal IQ, HDRS, the TMT-A, the STAI-S, the AAS and the IRI FS (see **Table 1**).

(**Table 1** about here)

The “animated triangles” task

The computer-assisted “animated triangles” task consists of silent animated videos (see <https://sites.google.com/site/utafrih/research> for examples, accessed July 4, 2019), presenting a big red and a small blue triangle, which move on a framed white screen. Three types of animations (Video Condition) were displayed in random order: 1) random movement (RM) sequences, in which the triangles move around purposelessly; 2) goal-directed (GD) sequences, in which one triangle acts and the other one reacts, without any indication of discerning the other's thoughts/intentions; and 3), ToM sequences in which the triangles interact as if they were discerning each other's thoughts/intentions. We used a shortened version of the task with nine videos (3 Video Exemplars per condition) that lasted 24 seconds each. This version has successfully been used before with patients with schizophrenia (Bliksted, et al, 2016). Prior to the experiment, participants were informed through a standardized text about the procedures and practice sessions that would be performed. Then the videos were presented in randomized order. After each sequence participants were asked to describe the proceedings freely, with no hints given by the experimenter. The answers were recorded and afterwards evaluated by an expert rater (K.K.) who was blind to the diagnosis. Scoring was performed in three dimensions: intentionality (INT) (mental-state-related terms used, 0–5 points), appropriateness (APP) (correctness of descriptions, 0–2 points) and length of answers (LEN) (0–4 points).

Statistical measures

All statistical analyses were performed with IBM SPSS Statistics 23. With the program G-Power (<http://www.gpower.hhu.de/>, accessed July 4, 2019), we calculated a minimal group size of 22 per group for an effect size of $d = 1.05$ (intentionality (INT)

score). Our sample was thus sufficiently large to identify group differences in ToM functioning. The demographic and questionnaire data were first checked for their normal distribution with Kolmogorov-Smirnov tests. As a result, gender was analyzed with the Mann-Whitney-U-Test, other group differences were investigated by independent sample t-tests. For the analysis of the animated triangles task we used a multilevel model for nested data with Video Exemplars (3) nested into Video Condition (3), nested within Individuals (see also Kret and de Gelder, 2013; Kret and de Dreu, 2013). The benefit of this method is that all data can be included in the model without having to average over experimental conditions, as is the case in an ANOVA or regression. In addition, because this method allows the inclusion of random factors more variance in the data can be explained, making this a very powerful, more precise method. Thus, each rating score for all animations of each participant was fed into the analysis, with rating scores for INT, APP and LEN as the three dependent variables, respectively. In our multilevel analysis, gender was shown to have an impact on ToM performance and was therefore used in all further analyses as a factor. Thus, in addition to the fixed factors Video Condition (ToM, GD, RM animations), Group (patients, control group) and Gender (male, female), the interactions between those factors were included in the statistical model. Random effects for Individuals and Individuals X Video Condition as well as their intercepts were also included. Starting with a full model, non-significant factors were dropped one by one, starting with higher order interactions. Finally, questionnaire scores were fed into the final models to specifically investigate their impact on ToM functioning and whether potential group differences could be (partly) explained by these other factors. As the factors Group and the questionnaire scores highly correlate, raising the problem of collinearity, questionnaire scores could not be entered into the same model as the Group factor.

Results

Of particular interest for the current study are putative differences between MDD patients and healthy controls regarding the INT ratings, as ascribing intentions to objects is a characteristic of the phenomenon of interest, that is, ToM functioning. We will first briefly describe the results of the other two Rating Types and then focus on the INT ratings.

Appropriateness Ratings

The analysis for the Appropriateness (APP) ratings revealed no main effect of group ($F(1, 690) = 1.3, p < .3$) nor any interaction with group. However, a main effect for Video Condition was observed ($F(2, 690) = 13.2, p < .001$). On average, the most appropriate language was used in the GD condition, where the interaction of triangles is based less on mental state than on the ToM animations. However, as the score has a very narrow range (0-2), the results could represent a methodological artefact.

Length Ratings

The analysis for the dependent variable Length (LEN) also revealed no main effect of group ($F(1, 690) = 0.2, p < .7$) nor any interaction with group, showing that patients had a normal production of speech. A main effect was observed in the Video Condition ($F(2, 690) = 45.3, p < .01$) with descriptions of ToM Videos being longer than for GD and RM animations (and GD descriptions being longer than descriptions of RM videos.)

Intentionality Ratings

It is of crucial interest to the current study whether the groups differed in their tendency to ascribe social intentions (intentionality, INT) to the animated triangles. The higher the score on INT, the more social attributions participants assigned to the animations. Usually, healthy people assign social intentions to a higher degree to the animated triangles in those animations that were specifically designed to appear social, i.e. in the ToM condition. This is not the case in the condition where the shapes move in a goal-directed (GD), non-emotional manner or move randomly (RM). First of all, our multilevel analysis identified a main effect of Video Condition ($F(2, 690) = 400.5, p < .001$) with corrected post-hoc pair-wise comparisons showing that the ToM Video Condition yielded higher INT ratings than the other two Video Conditions (GD, RM), suggesting that our manipulation worked. More interestingly, we found a significant three-way interaction between Video Condition X Gender X Group ($F(2, 690) = 5.3, p = .005$), showing that healthy women performed significantly better than healthy men and female MDD patients (and a trend towards significance with regard to depressed men) exclusively in the most relevant condition, i.e. the ToM condition. Here, people typically ascribe social intentions to the animated triangles, which is indicative for higher ToM functioning.

This raises the question: did depressed women perform less well than healthy women due to their depression or can other differences in personality explain this difference? As can be seen in **Table 1**, the two groups not only differed in their diagnosis, but also on multiple questionnaire scores and clinical variables. In order to test whether these differences could explain weaker ToM performance in depressed women as compared to healthy women, we ran the same statistical model as described above, but replaced “Group” with the respective questionnaire score. For the sake of brevity, we focus in the following on significant effects of these questionnaire scores only. All further results can be found in supplementing tables.

Using the Adult Attachment Scale (AAS) “depend” score instead of the Group factor, we found a three-way interaction between Video Condition x Gender x AAS “depend” score ($F(2, 690) = 4.2, p < .02$) with women who were higher on AAS “depend” scoring lower in the ToM video condition and higher in the RM video condition (see **Figure 1**). Moreover, men showed exactly the opposite relationship. An analysis with the AAS “closeness” score yielded very similar findings, also with a three-way interaction between Video Condition x Gender x AAS “closeness” score ($F(2, 690) = 4.1, p < .02$), again showing that women with higher “closeness” scores performed more poorly on the ToM video condition and better on the RM video condition. In a next model, we assessed whether the AAS “anxiety” score revealed similar effects, but this was not the case ($F(2, 690) = 2.8, p < .07$). Similarly, no other score on which the two groups differed, e.g. the HAMD or STAI scores, could explain the group difference regarding the INT ratings.

(**Figure 1** about here)

Taken together, the results demonstrate that out of all groups healthy women perform with the highest rate of mental-state-related terms used on the animated triangles task. This gender effect was observed on the intentionality ratings with regard to ToM animations, the most important measure for social interactional abilities. Dissimilarities between the groups were observed and were mainly driven by differences in attachment styles with regard to the “depend” and the “anxiety” subscale on the AAS, which measure aspects of the same construct and are thus highly correlated. One possible explanation might be that female MDD patients would perform as strongly as healthy controls if they did not show a pattern of attachment styles different to that of their healthy counterparts. However, as a mere correlation

does not allow causal inferences this remains speculation. Possibly, a third variable might influence both attachment style and depressed symptomatology, or even the other way around.

Discussion

In this study we investigated a sample of patients with an MDD on a ToM task and compared them to healthy controls. Moreover, we assessed the patients with a number of cognitive tests and questionnaires related to factors that might have an impact on ToM performance. A major strength of the present study is our focus on the recruitment of a sample unbiased by comorbid diagnoses such as anxiety disorders. Our findings demonstrate that patients with depression do not have distinct deficits in ToM task performance as a whole group. We have identified a ToM performance difference, however, between healthy female controls and female MDD patients. Our negative findings regarding differences between the groups comply with the results of several previous studies. For example, Wilbertz et al. (2010) used a video-measure of ToM (MASC) and did not find significant differences between chronically depressed patients and healthy controls. In a study using the “Reading the Mind in the Eyes” task in a sample of patients with chronic and episodic depression, van Randenborgh and colleagues (2012) also found no ToM deficits. Doody et al. (1998) investigated different mental disorders on a second-order false-belief task and could not confirm any specific deficits in affective disorders. Nevertheless, there are other studies that indicate a performance deficit on the animated triangles task (Ladegaard, et al, 2014a,b) or other ToM tasks (Uekermann, et al, 2008; Zobel, et al, 2010) in patients with MDD. In three of these studies patients with comorbid anxiety disorders were included. It is possible therefore that results were biased by anxious symptomatology. In the fourth study the authors used a task

that taps only partly into cognitive ToM, but uses a humor-processing paradigm instead, which might explain different results. While there have been contradictory discussions on whether women are more adept at using social skills than men (Russel, et al, 2007), a recent study of depressed women showed a reduced performance on ToM tasks (Fischer-Kern, et al, 2013). However, other studies did not report a gender-specific deficit. In the current study specific focus was put on the assessment of factors that are known to impact ToM performance. Generally, our clinically stabilized patients with MDD showed insecure attachment styles, lower empathy scores and a slowing on attention-based tasks. HDRS ratings, indicating a medium severity of depressed symptoms in patients, empathy abilities and cognitive slowing were not correlated with task performance. On the other hand, individuals who had less dependent and anxious attachment styles rated higher on intentionality. Pos and colleagues (2015) pointed out the significance of attachment styles in ToM in the psychotic spectrum, paralleling our results in MDD. Trustful, less dependent attachment in relationships seems to help perform on the ToM task. On the other hand, it might be assumed that female MDD patients would have performed just as well as healthy women if they had not shown an attachment pattern different from that of the healthy controls. Patients with high dependence and anxiety in relationships might monitor their surroundings more closely or more sensitively in order to be able to react as swiftly as possible, thus performing better, as shown here, on the random movement animations (Donges, et al, 2012). On the other hand, this might have distracted them from the relevant details which are necessary for ToM interactions. In respect of experience with the task in other mental disorders (Bliksted, et al, 2016) and considering effect sizes as found in Ladegaard et al. (2014a), our sample size has to be considered more than appropriate for measuring the effect of interest, specifically on the intentionality score. While ratings have been performed by

an independent blind expert rater, the employment of a single rater limits the generalizability of the study results. Also, almost all patients had been medicated, which might have influenced the results. At the same time, medication is considered to have beneficial effects on affective processing in depression (Greer, et al, 2014). Taken together, in our sufficiently large sample of well-characterized patients with MDD we found no differential deficits in patients on a ToM task as a group. In female healthy controls however, performance was stronger than that of the female MDD patients. This performance deficit in women with an MDD was correlated with attachment styles. Such personality traits could further enhance vulnerability to social cognitive dysfunction. Future studies may expand on our observations by addressing the role of different subgroups in differential social cognitive deficit patterns in MDD.

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Tables

	MDD	HC	Significance
Age (years)	40.3 (11.4)	39.7 (10.9)	F (2, 76) = .04, $p = .8$
Gender	♂21, ♀17	♂23, ♀17	$u = .9$
HDRS	15.1 (6.2)	.7 (1.2)	F (2, 74) = 48.5, $p < .001$
IQ (MWT-B)	109.2 (11.2)	116.5 (16.5)	F (2,75) = 9.9, $p = .03$
Education (years)	11.6 (1.5)	11.8 (1.5)	F (2,76) = 1.3, $p = .5$
IRI (FS)	10.8 (3.8)	11.4 (2.9)	F (2, 75) = 5.3, $p = .03$
IRI (EC)	14.5 (2.8)	13.5 (2.4)	F (2, 75) = .4, $p = .6$
IRI (PT)	12.7 (2.9)	13.8 (2.6)	F (2, 75) = .7, $p = .4$
IRI (PD)	13.2 (2.7)	8.9 (2.2)	F (2, 75) = 1.8, $p = .2$
IRI empathy	38.0 (7.0)	38.7 (6.0)	F (2, 75) = .4, $p = .6$
TMT-A	32.8 (17.0)	26.1 (8.5)	F (2, 75) = 4.4, $p = .04$
TMT-B	79.9 (79.4)	60.6 (28.4)	F (2, 75) = 2.3, $p = .1$
AAS Depend	18.8 (5.0)	11.0 (4.4)	F (2,77) = 21.4, $p < .001$
AAS Closeness	14.0 (5.0)	10.2 (4.4)	F (2,77) = 21.2, $p < .001$
AAS Anxiety	15.4 (3.7)	9.7 (3.3)	F (2,77) = 24.6, $p < .001$
STAI-Trait	61.4 (9.9)	34.0 (7.4)	F (1, 74) = 2.4, $p = .1$
STAI-State	48.3 (11.3)	33.3 (7.6)	F (1, 75) = 7.2, $p = .01$

Table 1: Clinical, performance and questionnaire data in patients with MDD and healthy controls (HC) in means and standard deviations. Abbreviations: HDRS (Hamilton Depression rating Scale); MWT-B (Multiple Choice Vocabulary Intelligence Test); IRI (Interpersonal Reactivity Index); FS (Fantasy Scale); EC (Empathic

concern); PT (Perspective taking); PD (Personal distress); TMT (Trail-Making Test); AAS (Adult Attachment Scale); STAI (State-Trait-Anxiety Inventory).

Figures

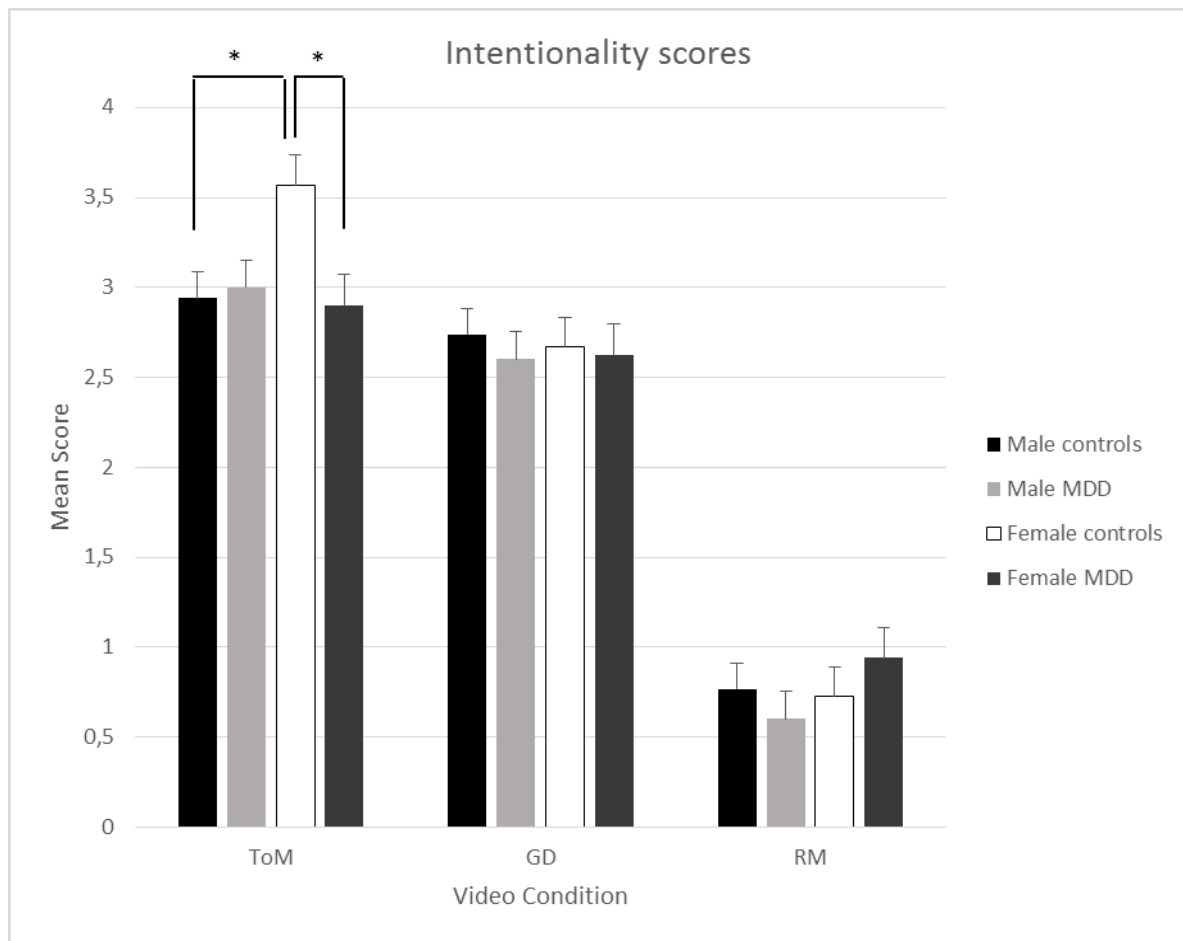


Figure 1: Gender differences on the ToM INT score: healthy women perform better on the INT ToM score than men or female MDD patients. (* indicates a significant group difference)