Journal of Psychiatric Research 153 (2022) 206–212

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Impaired socio-affective, but intact socio-cognitive skills in patients with treatment-resistant, recurrent depression

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ARTICLE INFO

Keywords:
Treatment-resistant depression
Affective empathy
Compassion
Theory of mind
EmpaToM
Social isolation

ABSTRACT

Background: Social withdrawal is a key symptom of depression. The resulting loss of social reinforcement in turn contributes to chronic, recurrent courses of the disease. However, it is not clear whether depressed patients have less motivation to socially interact, or whether their skills in doing so are impaired. The current study investigates potential skill deficits in patients with treatment-resistant depression (TRD).
Methods: 15 TRD patients and 19 age- and sex-matched healthy controls performed the EmpaToM, a paradigm which includes naturalistic video stimuli of either neutral or emotional valence and which differentiates between socio-affective (affective empathy, compassion) and socio-cognitive (theory of mind) skills.
Results: Controlling for the baseline affective state in neutral situations, TRD patients displayed significantly reduced affective empathy towards emotional situations compared to healthy controls. Furthermore, TRD patients were less compassionate in both neutral and emotional situations. In contrast, socio-cognitive skill performances did not differ between patients and healthy controls.
Limitations: Further studies might explore socio-affective and socio-cognitive skills in TRD patients using socio-affective/-cognitive tasks involving face-to-face social interactions.
Conclusion: Our study revealed a specific socio-affective deficit in TRD patients, while showing intact socio-cognitive skills. Patients were less able to affectively resonate with others (affective empathy) and exhibited generally reduced feelings of compassion. These deficits might interfere with providing and receiving social support. Our study contributes to a better understanding of the underlying causes of social withdrawal and stresses the need to specifically address pervasive socio-affective deficits in psychotherapy of TRD patients.

1. Introduction

The importance of social interactions for our mental health has recently been demonstrated by rising rates of depressive symptoms during social-contact restrictions while fighting the COVID-19 pandemic (Ettman et al., 2020; Schiller et al., 2021). Indeed, impaired social interactions and the concomitant loss of positive social reinforcement have long been recognized as key drivers in the development and maintenance of major depressive disorder (Libet and Lewinsohn, 1973). Empirical evidence supports this assumption, as a reduced number of positive social interactions, social conflicts and social malintegration have been identified as risk factors for chronic, recurrent depression (Hölzel et al., 2011; Visentini et al., 2018) as well as resistance to antidepressive treatments (Fekadu et al., 2012; Hallgren et al., 2017). Treatment-resistant depression (TRD) is a severe and in most cases persistent condition that affects 30% of depressive patients undergoing conventional treatment methods (Rush et al., 2006), and that is associated with high burdens for the patients themselves and society (Bewernick et al., 2012; Gaynes et al., 2020). One might only be able to improve this condition by developing individualized treatment strategies that target specific underlying mechanisms (Akil et al., 2018) of which one pillar might focus on dysfunctional social interactions

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https://doi.org/10.1016/j.jpsychires.2022.07.025
Received 22 March 2022; Received in revised form 3 June 2022; Accepted 5 July 2022
Available online 7 July 2022

(Fekadu et al., 2012). It therefore appears crucial to illuminate what causes the loss and impairment of social interactions in patients with chronic, recurrent, and treatment-resistant depression. Until today, it is still unclear whether such patients have less motivation to socially interact (Kupferberg et al., 2016) or whether they have impaired social skills (Beer and Ochsner, 2006; Weightman et al., 2014) to do so. To better understand the impact of social skill deficits in depression, the current study investigates potential social skill deficits in a rarely studied sample of patients with TRD using a recently developed naturalistic paradigm (EmpaToM (Kanske et al., 2015)) that enables specific differentiation between socio-cognitive (theory of mind (ToM)) and socio-affective skills (affective empathy and compassion).

ToM (also known as mentalizing or perspective-taking) is one of the most important higher socio-cognitive skills referring to the ability to understand and infer the mental states of others including their intentions, beliefs, and desires, as well as to make predictions about their behavior (Premack and Woodruff, 1978). Socio-affective skills, on the other hand, describe the induction of an affective state by sharing a counterpart's feelings (affective empathy) or in form of positive feelings of warmth and care (compassion) (Kanske et al., 2015). It is important to differentiate between these skills, as ToM, affective empathy, and compassion are associated with the activation of distinct neural networks: ToM: anterior cingulate cortex, medial prefrontal cortex; Affective empathy: anterior, right insula, inferior frontal gyrus; Compassion: ventral striatum (Kanske et al., 2015; Schurz et al., 2021). Some studies suggest that both socio-cognitive (Bora and Berk, 2016; Kupferberg et al., 2016) and socio-affective skills (Kupferberg et al., 2016; Schreiter et al., 2013) might be impaired in patients with depression and make a relapse more probable (Inoue et al., 2006; Yamada et al., 2015), but recent findings are inconsistent (Banzhaf et al., 2018; Domes et al., 2016; Guhn et al., 2020; Hoffmann et al., 2016; Mattern et al., 2015). These inconsistencies may be attributable to the application of distinct tasks and sample characteristics. In particular, there are still no ecologically valid, objective measures of social skills in response to actual social scenes that could supplement findings from self-report measures potentially more prone to biases (e.g., impression management, self-deception) (Dziobek et al., 2008; Gerdes et al., 2010; Schreiter et al., 2013).

The EmpaToM was recently developed providing such an objective, naturalistic measure. This task assesses social skills by analyzing an invidual's response to videos of actors describing neutral and emotional social scenes. As real social interactions involve dynamic facial expressions and emotional prosodies (Dziobek, 2012), the use of video stimuli significantly increases this test's ecological validity (Kanske et al., 2015). Moreover, the EmpaToM differentiates between affective empathy, compassion and ToM while controlling for general cognitive functioning. In addition to a validation study (Kanske et al., 2015), the EmpaToM has been applied in younger individuals compared to older ones (Reiter et al., 2017), in aggressive men compared to a control sample (Winter et al., 2017) and most recently in a clinical sample of patients with obsessive-compulsive disorder compared to a healthy control group (Kämpf et al., 2022) – evidence that this test effectively reveals deficits in specific social skills.

Therefore, in the current study, we aimed to illuminate the role of specific social skill deficits in TRD. For that purpose, we compared the performance in the EmpaTom between patients with TRD (n = 15) and age- and gender-matched healthy controls (HC) (n = 19). Given that recent studies using ecologically valid objective measures of social skills (i.e., photorealistic stimuli (Banzhaf et al., 2018; Guhn et al., 2020)) reported no impairments in socio-cognitive skills, we also expected to detect no such differences when using even more dynamic social stimuli (i.e., videos). Rather, we hypothesized that patients with TRD would display specific deficits in socio-affective skills. In affective empathy terms, this hypothesis relies on the results of behavioral studies (Banzhaf et al., 2018; Guhn et al., 2020). While evidence on specific compassion deficits in patients with TRD is lacking, we expected to detect such a difference, considering that feelings of compassion are associated with a specific activation cluster in the ventral striatum (Kanske et al., 2015), a region known to be less activated in depression and linked to depressive symptoms (e.g., anhedonia, loss of motivation, negative mood) (Russo and Nestler, 2013).

2. Material and methods

Participants and recruitment. Patients with TRD were considered for this subproject if they had been enrolled in the FORESEE III study („Efficacy Study of Deep Brain Stimulation in Patients With Treatment Resistant Major Depression", registered at clinicaltrials.gov with identifier: NCT03653858) between September 2018 and September 2020. The FORESEE III study's inclusion criteria were a primary diagnosis of major depressive disorder (unipolar or bipolar) with at least four previous or one chronic depressive episode (> two years), a minimum score of 21 on the 28-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967) and a <45 score in the Global Assessment of Functioning (GAF) (Jones et al., 1995). Patients were classified as treatment-resistant if they had failed to respond to adequate trials of primary antidepressants from at least three different classes, adequate trials of augmentation/combination of a primary antidepressant using at least two different augmenting or combination agents, an adequate trial of electroconvulsive therapy as well as an adequate trial of individual psychotherapy (for details see clinicaltrials.gov or previous publications (Coenen et al., 2019; Schlaepfer et al., 2013)).

HC participants were recruited via an online questionnaire (placed in the Intranet of the University Hospital of Freiburg, University of Freiburg and distributed via e-mail to different mailing lists). Participants were selected if they had no current or previous history of neurological and psychiatric disorder, no current or previous psychiatric or psychotherapeutic treatment and no current alcohol or drug abuse. HC (n = 21) were matched to the TRD group manually by selecting a participant of the same gender and the least age discrepancy from the available pool of healthy participants. HC were excluded with a BDI >10 to guarantee a healthy population free of depressive symptoms. We had to exclude two participants because of this exclusion criterion, leaving a sample of 19 HC.

A group of 21 patients with TRD signed the informed consent form of the current subproject (registered at Deutsches Register Klinischer Studien (DRKS) with identifier DRKS00019092). Six patients subsequently had to be excluded from further analysis. Four patients did not participate in the EmpaToM as they experienced significant difficulties performing the EmpaToM test trials (e.g., attention problems). Another two patients were excluded after the data assessment. One patient responded indifferently with the score "0" to the conditions, and was therefore excluded due to non-compliance. The second patient was excluded because of random response behavior. Thus, 15 patients with TRD remained in the analysis.

Procedure. For the TRD group, a single test session was conducted during an acute, depressive episode two to four weeks before implanting the deep brain stimulation system. HC were tested once. Test session lasted a total of 90–120 min. After having signed the informed consent form, the severity of depressive symptoms was assessed via objective and subjective ratings and the EmpaToM was conducted. To compare intelligence quotients, both groups completed the Multiple Choice Vocabulary Test („Mehrfachwahl-Wortschatz-Test") (Lehrl et al., 1995) whose sum score can be transformed into a premorbid intelligence quotient (IQ, M = 100, SD = 15). The study was approved by the University of Freiburg's Ethics Commitee (affirmative vote 12/21/2017 – document number 579/17). This research was conducted in accordance with the Helsinki Declaration as revised 1989.

2.1. Measures

Severity of Depression. Severity of depression was assessed both by an

expert and by the patients themselves. *Hamilton Depression Rating Scale (HDRS)* (Hamilton, 1967) and *Montgomery-Åsberg Depression Rating Scale (MADRS)* (Montgomery and Åsberg, 1979) have attained the status of a gold standard for the objective assessment of symptom severity in depression (Venn et al., 2006). The *Beck Depression Inventory (BDI-II)* (Hautzinger et al., 2006) is a self-rating questionnaire of depressive symptoms.

Socio-affective and Socio-cognitive Skills. The *EmpaToM* is a recently developed computerized task first published by Kanske et al. (2015) and applied in several studies (Kämpf et al., 2022; Reiter et al., 2017; Winter et al., 2017). It measures affective empathy, compassion, and ToM, thereby differentiating between socio-affective (affective empathy, compassion) and socio-cognitive (ToM) skills. It is a naturalistic paradigm with videos differing in the emotionality of their content (neutral vs. emotionally negative). After the presentation of the videos, participants are asked to rate their own current affect (valence rating/affective empathy) („How do you feel?") and feelings of compassion („How much compassion do you feel?") on a dimensional scale ranging from „negative" to „positive" or „none" to „very much". Thereafter, they have to answer a multiple-choice question either demanding ToM inference ("Anna thinks that …") or factual reasoning (nonToM) ("It is correct that …"; for a detailed description, see Kanske et al. (2015)) (see Fig. 1). After four training videos, a total of 48 videos are presented taking about 45 min to finish the test. The test comprises four conditions (12 trials per condition) with two categories of videos (neutral and emotional) and two categories of multiple-choice questions (ToM and non-ToM). Note that the time to respond was adapted and prolonged for 2 s in the current study based on response time findings from a pilot assessment with five patients classified as TRD. The time to answer the rating questions (affective empathy, compassion and confidence) was changed from originally 4–6 s, and the time to answer the multiple choice question was adapted from originally 14–16 s.

Statistical Analysis. Variables of interest were compared between HC and patients with TRD using univariate and mixed ANOVAs. For variables violating normal distribution, Mann Whitney U-Tests are reported. For affective empathy and compassion, mixed ANOVAs were calculated with the within-subjects factor "emotion" (neutral vs. emotional) and the between-subjects factor "group" (HC vs. TRD patients). To compare ToM abilities, the accuracy of performance in the multiple-choice question was calculated with a mixed ANOVA with the two within-subjects factors "emotion" (neutral vs. emotional) and "task" (factual reasoning vs. theory of mind) and the between-subjects factor "group" (HC vs. patients with TRD). Results are reported with Greenhouse Geiβer correction. Considering that traditional null-hypothesis significance testing is used to detect group differences, we performed equivalence testing (Goertzen and Cribbie, 2010; Rogers et al., 1993) to further explore ToM performance in both samples setting the smallest effect size of interest to a large effect (bounds of d = −.80 (lower) and d = 0.80 (upper)). We used the two one-sided tests procedure for Welch's tests for independent samples (Lakens et al., 2018). For all statistical comparision, p-values smaller than 0.05 were considered significant (two-tailed).

3. Results

Sample Description. Importantly, for the purpose of this study, HC and patients with TRD did not differ in age, intelligence, or gender (all $p > .05$; for demographics on both groups, see Table 1). Note that the TRD group exhibits high depression scores in both the self-rating (BDI-II) ($M = 39.33$, $SD = 6.18$) and expert ratings assessed with MADRS ($M = 32.73$, $SD = 6.18$) and HDRS-28 ($M = 28.67$, $SD = 4.79$).

Affective Empathy (EmpaTOM). We first calculated a mixed ANOVA to analyze whether HC and patients with TRD (between-subjects factor "group") differed in their affective responses across conditions of the EmpaToM (within subjects-factor "condition": neutral vs. emotional). The emotional videos of the EmpaToM successfully induced affective responses, as indicated by a main effect of "condition" with individuals across groups reporting more negative affect after watching emotionally negative videos ($M_{Emo} = 0.20$, $SD_{Emo} = 0.43$) compared to neutral ones ($M_{Neut} = -1.25$, $SD_{Neut} = 0.70$) ($F(1,32) = 101.21$, $p < .001$, $\eta^2 = 0.76$) (see Fig. 2). Importantly, while HC and patients with TRD did not differ in their overall affective response (main effect of "group": $F(1,32) = 1.03$, $p = .318$, $\eta^2 = 0.03$), they did show a differential increase in their negative affect after viewing emotionally negative vs. neutral videos

Table 1
Demographic and clinical characteristics.

	TRD	HC	Statistical test
			F, p, η^2 U, z, p
N	15	19	
Sex (male/female)	7/8	9/10	
Age (years) (SD)	45.00 (9.61)	47.58 (10.67)	$F(1,32) = 0.53$, $p = .470$, $\eta^2 = .02$
MWT (sum score) (SD)	30.33 (3.31)	31.63 (2.29)	$F(1,32) = 1.83$, $p = .186$, $\eta^2 = .05$
IQ (SD)	112.00 (13.75)	117.47 (11.87)	$F(1,32) = 1.55$, $p = .222$, $\eta^2 = .05$
HAMD-28* (SD)	28.67 (4.79)	0.63 (0.76)	$U = 0$, $z = -5.02$, $p < .001$
MADRS* (SD)	32.73 (6.18)	0.74 (0.93)	$U = 0$, $z = -5.03$, $p < .001$
BDI-II* (SD)	39.33 (6.18)	1.58 (2.09)	$U = 0$, $z = -5.01$, $p < .001$

Note. TRD = treatment-resistant depression, HC = healthy controls, SD = standard deviation, MWT = Multiple Choice Vocabulary Test („Mehrfachwahl-Wortschatz-Test"), HAMD-28 = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, BDI-II = Beck Depression Inventory II. *Variables are not normally distributed.

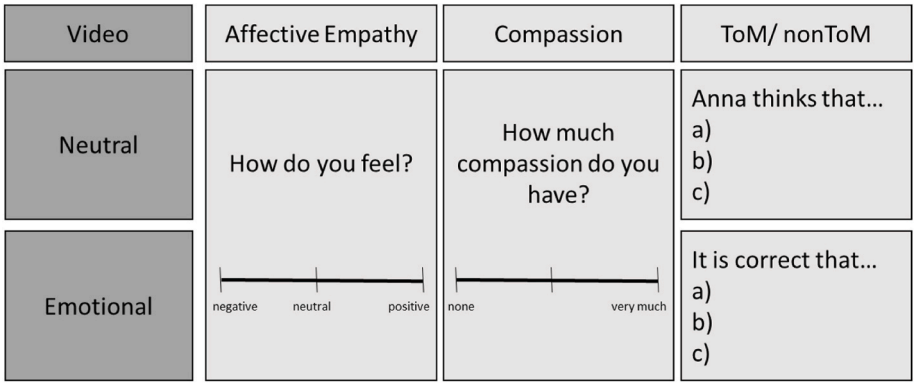

Fig. 1. Schematic overview of the EmpaToM design. Videos are presented with either neutral or emotional (negative) valence followed by ratings of affective empathy, compassion and a multiple-choice question requiring theory of mind or factual reasoning (nonToM). For detailed information see Kanske et al. (2015).

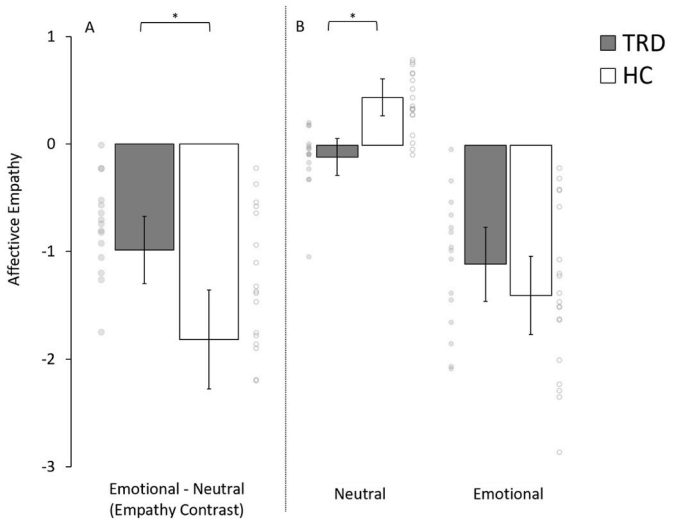

Fig. 2. Affective Empathy in patients with treatment-resistant depression (TRD) and healthy controls (HC). Error bars represent 95% confidence intervals. Asteriks indicate a statistically significant difference ($p < .05$, two-sided). Small gray dots represent individual data points. **A:** Difference in the mean affect rating between emotional (negative) and neutral videos (affective empathy responsiveness) (emotional-neutral) in patients with TRD (gray bar, n = 15) and HC (white bar, n = 19). Patients with TRD experienced significantly reduced affective responsiveness. **B:** Affect ratings for neutral (left side) and emotional videos (right side) ranging from positive (max = 3) to negative (max = −3). Note that more negative ratings in the emotional condition indicate stronger affective empathy. Patients with TRD started from a less positive baseline affective response towards neutral videos. Excluding the outlier (>2.5 SD, neutral condition, TRD sample) did not affect the reported findings.

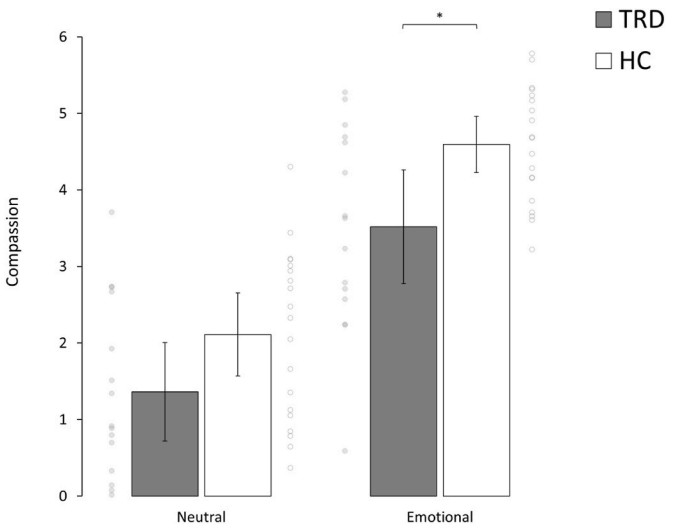

Fig. 3. Compassion in patients with treatment-resistant depression (TRD) and healthy controls (HC). Error bars represent 95% confidence intervals. Asteriks indicate a statistically significant difference ($p < .05$, two-sided). Small gray dots represent individual data points. Shown are compassion ratings for each condition (neutral; emotional) ranging from none (min = 0) to very much (max = 6) in patients with TRD (gray bar, n = 15) and HC (white bar, n = 19). Patients with TRD showed reduced compassion across experimental conditions with a statistically significant difference in the emotional ($F(1,32) = 8.71$, $p = .006$, $\eta^2 = 0.21$) but not in the neutral condition ($F(1,32) = 3.62$, $p = .066$, $\eta^2 = 0.10$).

(interaction effect of "condition" x "group": $F(1,32) = 8.98$, $p = .005$, $\eta^2 = 0.22$). Specifically, starting from an already more negative affect ($M_{TRD} = -0.11$, $SD_{TRD} = 0.30$) than HC ($M_{HC} = 0.44$, $SD_{HC} = 0.36$) towards neutral videos ($F(1,32) = 22.19$, $p < .001$, $\eta^2 = 0.41$), patients with TRD reported less of an increase in negative affect towards emotionally negative vs. neutral videos ($M_{TRD} = -1.09$, $SD_{TRD} = 0.62$) compared to HC ($M_{HC} = -1.38$, $SD_{HC} = 0.75$) ($F(1,32) = 8.98$, $p = .005$, $\eta^2 = 0.22$). These findings indicate that patients with TRD exhibit less affective responsiveness to emotionally negative events, possibly driven by a more negative affective baseline state.

Compassion (EmpaTOM). Next, we analyzed differences in self-reported compassion using the same ANOVA as described above. As expected, compassion was enhanced towards emotionally negative ($M_{Emo} = 1.78$, $SD_{Emo} = 1.19$) compared to neutral videos ($M_{Neut} = 4.12$, $SD_{Neut} = 1.17$) (main effect "condition": $F(1,32) = 171.46$, $p < .001$, $\eta^2 = 0.84$) (see Fig. 3). Different than affective responses, groups did not differ in their increases in compassion across conditions ($M_{TRD} = 2.16$, $SD_{TRD} = 0.91$; $M_{HC} = 2.48$, $SD_{HC} = 1.11$) (interaction effect "condition" x "group": $F(1,32) = 0.86$, $p = .362$, $\eta^2 = 0.03$), but rather in the general compassion reported ($M_{TRD} = 2.44$, $SD_{TRD} = 1.65$; $M_{HC} = 3.35$, $SD_{HC} = 1.58$) (main effect "group": $F(1,32) = 7.39$, $p = .010$, $\eta^2 = 0.19$). Patients with TRD thus experience generally weaker positive feelings of warmth and care towards others (regardless of their emotional situation) in comparison to HC.

Theory of Mind (EmpaTom). In the final step, we analyzed group differences in ToM, calculating a mixed ANOVA with the between-subjects factor "group" and the within-subjects factors "condition" and "task" (factual reasoning/nonToM vs. ToM). General performance did not differ between conditions across groups, but tasks did (main effect "condition": $F(1,32) = 0.56$, $p = .461$, $\eta^2 = 0.02$; main effect "task": $F(1,32) = 12.39$, $p = .001$, $\eta^2 = 0.28$). The significant difference between questions requiring ToM or factual reasoning/nonToM was demonstrated by a task-specific deficit in patients with TRD ($M_{TRD} = 0.15$, $SD_{TRD} = 0.15$) compared to HC ($M_{HC} = 0.01$, $SD_{HC} = 0.11$) (interaction effect "task" x "group": $F(1,32) = 9.74$, $p = .004$, $\eta^2 = 0.23$) (see Fig. 4). Post-hoc analyses indicated that patients with TRD ($M_{TRD} = 0.50$, $SD_{TRD} = 0.10$) performed worse than HC ($M_{HC} = 0.65$, $SD_{HC} = 0.15$) in answering factual reasoning questions ($F(1,32) = 10.96$, $p = .002$, $\eta^2 =$

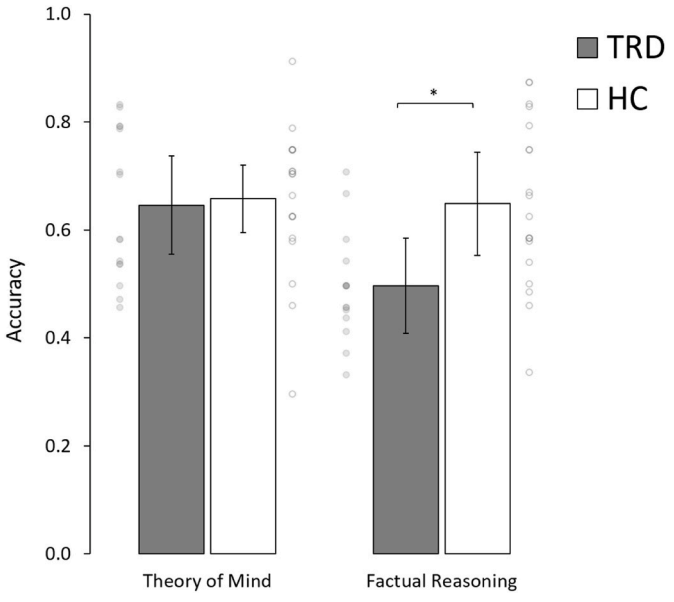

Fig. 4. Group differences in Theory of Mind (ToM) and Factual Reasoning performance. The y-axis indicates the accuracy of multiple-choice answers (range from 0 to 1) with higher accuracy levels indicating more correct answers in patients with TRD (gray bar, n = 15) and HC (white bar, n = 19). Error bars represent 95% confidence intervals. Asteriks indicate a statistically significant difference ($p < .05$, two-sided). Small gray dots represent individual data points. Notably, patients with TRD were not impaired in their ToM, but rather int their factual reasoning performance.

0.26) while no differences appeared when answering ToM questions ($M_{TRD} = 0.65$, $SD_{TRD} = 0.14$; $M_{HC} = 0.66$, $SD_{HC} = 0.14$; $F(1,32) = 0.06$, $p = .808$, $\eta^2 = 0.00$; equivalence testing: $T(30.07) = 2.07$, $p = .024$). This finding indicates general cognitive deficits, but intact ToM abilities in patients with TRD.

4. Discussion

This study investigated socio-affective and socio-cognitive skills in a unique sample of patients suffering from TRD using an ecologically valid measure that includes dynamic social stimuli. Compared to healthy controls, patients with TRD showed impairments in socio-affective, but not in socio-cognitive skills (theory of mind). Specifically, these patients demonstrated less affective responsiveness to emotionally negative events in comparison to neutral ones (i.e., impaired affective empathy). Furthermore, they had overall weaker feelings of warmth and care towards others (impaired compassion). The socio-affective skill deficits in patients with TRD we observed might contribute to their disease-maintaining withdrawal from social interactions.

By disentangling affective empathy from compassion and theory of mind, our study enables a more nuanced understanding of social deficits in individuals with depression. *First*, we demonstrated that patients with TRD did not adapt their affective response to others' negative emotional experience to the same degree as healthy controls. Specifically, they reported a smaller decrease in negative affect in response to emotionally negative events in comparison to their already more negative affective state in response to emotionally neutral events. This finding also illustrates the need to account for existing negativity bias in depression when assessing affective responses (Bourke et al., 2010; Everaert et al., 2012; Weightman et al., 2014). By highlighting impaired affective reactivity to others' negative emotions in patients with TRD, our study delivers additional evidence of reduced self-reported and neural affective responses to videos displaying others' pain in depressed individuals (Fujino et al., 2014). We also observed differences in the *second* socio-affective skill we assessed, namely compassion. By definition, compassion transcends affective empathy (i.e., sharing others' affect) by evoking positive feelings of care that include feeling motivated to help others (Kanske et al., 2015). In fact, our sample's patients were less compassionate than healthy controls. It is possible that affective-empathy deficits contribute to the deficits in compassion, because being compassionate with others is hard to do if one cannot fully share another person's feelings (Singer and Klimecki, 2014; Vignemont and Singer, 2006). In line with this idea, we noted a significant correlation between compassion and affective responsiveness in patients with TRD ($r = 0.61$, $p = .016$) as well as in our healthy sample ($r = 0.54$, $p = .016$). Alternatively, the impaired compassionate responding in depression could also be caused by a blunted response to positive social interactions from the neuroendocrinological reward system (e.g., helping others) (Germine et al., 2011; Hsu et al., 2015; Rottenberg and Hindash, 2015). *Third*, and finally, patients with TRD showed intact ToM skills in our study, although equivalence testing did not permit us to exclude differences in ToM skills of small or medium effect sizes. In contrast, patients showed significant neurocognitive deficits in their factual reasoning abilities. Considering that ToM is important in everyday social interactions (Kupferberg et al., 2016), relatively intact ToM skills might represent an important resource in these patients to compensate for socio-affective deficits, thereby maintaining some social relationships despite severe depressive symptoms.

Given that dysfunctional social interactions seem to play a key role in TRD (Bergfeld et al., 2018; Calati et al., 2019; Hölzel et al., 2011; Visentini et al., 2018), our finding of concomitant, specific socio-affective deficits might also have translational value. First, it supports the view that treatment approaches targeting dysfunctional social interactions may be of particular benefit when treating patients with TRD. Interestingly, the cognitive behavioral analysis system of psychotherapy (CBASP) focusing on interpersonal interaction deficits (McCullough, 2003) has been specially designed to achieve long-term symptom reductions in individuals with chronic depression (Negt et al., 2016). Yet there seems to be room for improvement regarding the efficacy of these approaches in boosting social functioning (Renner et al., 2014). Based on our findings, a successful treatment of social interaction deficits should include working on deficits in affective empathy and compassion. Indeed, recent findings suggest that it is possible to improve socio-affective skills through training (Aguilar-Raab et al., 2018; Klimecki et al., 2014). However, as socio-affective skills are clearly to some degree "hard-wired" in our biology (for a review, see (Kupferberg et al., 2016)), it may also prove fruitful to combine psychotherapeutical strategies with psychopharmacological or neurobiological treatment approaches, following the concept of a biopsychosocial treatment model (Meyer-Lindenberg et al., 2011). For example, intranasal administration of the neuropeptide oxytocin is known to facilitate empathy- and compassion-related processes in both healthy individuals (Bartz et al., 2010; Hurlemann et al., 2010; Schiller et al., 2020; Schiller and Heinrichs, 2018) and those with depression (MacDonald et al., 2013); deep brain stimulation of brain regions linked to the processing of social rewards (e.g. ventral striatum) (Russo and Nestler, 2013) has been associated with short- and long-term improvements in social functioning (Kennedy et al., 2011; Merkl et al., 2016; Schlaepfer et al., 2013).

As a key strength, this study applied an ecologically valid and objective measure of various social skills. It thereby complements research that has relied on self-report measures (for review see (Schreiter et al., 2013)) or tasks based on static images (for a review, see (Bora and Berk, 2016)) to assess social functioning in depression. Moreover, this study focused on a sample of patients rarely studied and that differ from patients with episodic depression (Domes et al., 2016) by displaying more persistent social skill deficits. Alongside these strengths, our study also has limitations. One could further enhance the ecological validity of the findings reported here by studying social performance during actual face-to-face interactions. Future studies might also include larger samples of patients with TRD, patients with less treatment-resistant forms of depression, patients with recurrent depression currently in remission, and patients with episodic depression in order to clarify whether social skill deficits are the cause or the consequence of depressive symptoms, and whether they are particularly pronounced in patients with TRD. Furthermore, it might prove fruitful to include measures of social motivation to clarify how deficits in social skill and social will interact in driving social interaction problems in individuals with depression.

5. Conclusions

In sum, while socio-cognitive skills were intact in patients with TRD, their socio-affective skills (i.e., affective empathy and compassion) were significantly impaired. These socio-affective deficits might hamper both the provision and receiving of support during functional social interactions with others and, in the long-term, contribute to social withdrawal and result in exacerbating depressive symptoms in patients with TRD. As patients with TRD are in a severe condition, it is essential that we develop and optimize individualized treatment strategies to improve their quality of life. Our research indicates that such strategies need to specifically address socio-affective deficits by involving innovative psychotherapeutic (e.g., social skills training) or biological (e.g., hormone application, deep brain stimulation) treatment approaches.

Contributors

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Role of the funding source

This research project did not profit from any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Dora M Meyer for supporting us in the data collection and for conscientiously proof reading the manuscript.

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