Detached empathic experience of others' pain in remitted states of depression – An fMRI study

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ARTICLE INFO

ABSTRACT

Background: Major depressive disorder is strongly associated with impairments and difficulties in social interactions. Deficits in empathy, a vital skill for social interactions, have been identified as a risk factor for relapse. However, research on empathy in remitted states of depression is scarce. We chose a social neuroscience approach to investigate potentially altered neural processes involved in sub-components of empathy in remitted states of depression. We expected aberrations in cognitive components of empathy, based on previous reports regarding their role as risk factors for relapse.
Methods: Employing functional magnetic resonance imaging and a pain empathy task (video clips of painful medical treatments), we compared behavioral and neural empathic responses of unmedicated remitted depressive patients (N = 32) to those of untreated acutely depressed patients (N = 29) and healthy controls (N = 35). Self-report ratings of pain evaluation and affect-sharing were obtained.
Results: Compared to controls and acutely depressed patients, remitted depressive patients reported higher pain evaluation and showed increased activity in the right temporo-parietal junction. This region, which is central to self-other distinction and which has been linked to adopting a detached perspective, also exhibited reduced connectivity to the anterior insula. Furthermore, we observed reduced activity in regions involved in emotion processing (amygdala) and perception of affective facial expressions (fusiform face area, posterior superior temporal sulcus).
Conclusions: Remitted states of depression are associated with a detached empathic style in response to others' pain, characterized by increased self-other distinction, lowered affective processing, and reduced connectivity between empathy-related brain regions. Although this may prevent emotional harm in specific situations, it may reduce opportunities for positive experiences in social interactions in the long run.

1. Introduction

Psychiatric disorders such as major depressive disorder (MDD) are strongly associated with impairments and difficulties in social interactions (Hirschfeld et al., 2000), leading to their conceptualization as "disorders of social interaction" in influential theoretical work (Redcay and Schilbach, 2019). According to an emerging view, such impairments substantially contribute to recurrence, and may even represent a pre-morbid vulnerability factor for psychiatric conditions (Schilbach, 2016). One crucial social ability on which we focused here is empathy, a multi-faceted skill that allows to correctly perceive and interpret the emotional states of others. Broadly defined, empathy entails isomorphic sharing of another person's affective state, which can be elicited by either direct observation or imagination of the other's emotion, while being aware that the other is the origin of one's emotional state (self-other distinction) (de Vignemont and Singer, 2006). Overly negative

interpretations of others' emotions and other failures in empathizing impact social interactions and might be particularly relevant for the case of MDD. The resulting avoidance of social interactions may protect from harm and negative emotions or mood in a particular moment. However, these maladaptive coping mechanisms might lead to a lack of opportunities for successful social interactions and positive experiences as well as social reinforcement in the long run (Trew, 2011, for review).

The core symptoms of depression are loss of interest in activities (anhedonia) and depressed mood, and it is associated with impaired cognitive function, including predominantly executive function, memory and attention (Otte et al., 2016), as well as attentional biases towards negative information (Peckham et al., 2010). Upon remission, significant moderate cognitive deficits appear to persist in the domains of executive function and attention (see *meta*-analysis; Rock et al., 2014). Deficits in attention may be relevant to empathic processing, as modulations of top-down attention in a pain empathy task have been demonstrated to influence activity in regions associated with both cognitive and affective aspects of empathy (Gu and Han, 2007; Lamm et al., 2007b). Previous research has linked acute states of depression to higher self-reported empathic distress and lowered perspective taking (Schreiter et al., 2013, for review).

Recent theory identified both cognitive and affective aspects of empathy as important factors for developing depression (Kuehner, 2017), but also emphasized the heterogeneity of results when it comes to comparisons between acutely depressed patients and healthy controls, which may be caused by medication effects, for example (Berecz et al., 2016). Lately, a large-scale questionnaire study including over 3000 participants tested the relationship between (sub)clinical levels of depression and empathy, and found low self-reported cognitive empathy (cognitive empathy scale of the empathy components questionnaire; (Batchelder et al., 2017)) to be associated with more depressive symptoms (Bennik et al., 2019). While most cognitive functions tend to normalize (at least in younger adults) after remission from depression, cognitive perspective taking (an important component of what is sometimes referred to as cognitive empathy) has been reported to stay impaired (Ladegaard et al., 2016). Such mentalizing deficits are frequent in remitted depressive patients (e.g., regarding cognitive perspective taking; Harkness et al., 2010 or false-belief tasks; Inoue et al., 2004), and have been identified as a risk factor for relapse (Inoue et al., 2006). Despite these indications for a role of aberrant empathic processing in recurrence, no systematic experimental test of neural and behavioral empathic differences in remitted states of depression has been carried out yet. Discovering such a trait marker would allow for further testing its potential role in pre-morbid depression vulnerability. In general, previously experienced episodes of MDD are another strong predictor of future MDD episodes (Kessing et al., 2004), which suggests that patients either possess a cognitive or biological predisposition for developing depression (vulnerability hypothesis; Abramson et al., 1999), or that they suffer an impairment due to previously experienced MDD episodes (neuroprogression hypothesis; Moylan et al., 2013).

Social neuroscience has made considerable advances in revealing the neural processes involved in empathy (Lamm et al., 2019; Marsh, 2018), and techniques such as functional magnetic resonance imaging (fMRI) allow to disentangle the subcomponents of empathy and their potential alterations in clinical conditions (Cacioppo et al., 2014). While viewing others in negative affective states, activity in a set of brain regions can be observed, each of which are thought to support different functions in the process of empathy. Bilateral anterior insula (AI) and anterior midcingulate cortex (aMCC) are mainly associated with affect sharing (*affective empathy*) (Lamm et al., 2011), while regions such as the medial prefrontal cortex and precuneus are involved in *mentalizing* or *perspective taking* processes (i.e., "cognitive empathy"). *Self-other distinction* (online control of self and other representations, for setting one's own emotions apart from those of others), a defining feature of empathy (Singer and Lamm, 2009), has been linked to the right temporo-parietal junction (rTPJ), an area that has also been associated with attentional biases in

depression (Everaert et al., 2012; Gupta and Kar, 2012). Inhibitory transcranial magnetic stimulation of the rTPJ impaired performance in false-belief tasks (Krall et al., 2016), while increasing activity in this region by means of intermittent theta-burst stimulation led to reduced mimicry, suggesting that increased activity in the rTPJ is associated with enhancement of representations of the self over those of the other (Duffy et al., 2019). In a similar vein, excitatory transcranial direct current stimulation of this region led to increased self-other distinction as measured by two independent socio-cognitive tasks involving imitation and perspective taking (Santiesteban et al., 2012). Very recently, it was shown that the TPJ plays a central role in adopting a detached perspective while watching emotional movies, as compared to a condition in which the same participants were instructed to actively empathize (Borja Jimenez et al., 2020). We focused on the rTPJ, as there is considerably more empathy-related evidence as compared to the left TPJ (Lamm et al., 2016; but see also Quesque and Brass, 2019).

The aforementioned studies investigated healthy adult samples, but there are few studies which investigated the neural correlates of empathy during acute or remitted states of depression (Fujino et al., 2014; Rütgen et al., 2019). In the present study we aimed at revealing a potential socio-affective neural trait marker for depression. Such differences in empathic responding should be present in symptom-free states under both the vulnerability and the neuroprogression hypothesis, but should scale with the number of episodes and/or duration of disease only if the neuroprogression hypothesis is true (though this would not contradict the vulnerability hypothesis). To elucidate our research question, we recruited 32 remitted MDD patients (stable remission > three months; unmedicated) for a high-field 7 T fMRI study. We compared their behavioral and neural responses to an empathy for pain task to the responses of the samples included in our previous study (Rütgen et al., 2019): unmedicated acutely depressed patients (N = 29) and healthy controls (N = 35). We additionally employed an electrical pain task to control for domain-general (versus empathy-specific) effects on the processing of negative affective states. Notably, empathy for pain recruits a core network consisting of AI and aMCC, which is also centrally involved in the processing of self-experienced pain (Lamm et al., 2011; Rütgen et al., 2015, 2021; Zhou et al., 2020). Finding similar group differences in AI/aMCC in both tasks would allow to relate our findings to a rather general response to negative or painful affective states, while exclusive modulation of the empathy task would rather speak for a more specific effect on the level of social cognition. We also investigated whether socio-affective neural processing might be influenced by previously suffered episodes. To explore potential differences on the neural level in an unrestricted, yet reliable fashion, we mainly focused our analysis on whole-brain activity comparisons employing stringent thresholds. We further investigated differences in task-related effective connectivity and, finally, focused on regions of interest that had been shown to be modifiable by antidepressant treatment in our previous study (Rütgen et al., 2019). We hypothesized that remitted states of depression would be characterized by impaired perspective taking, based on the above-mentioned evidence regarding their role as risk factors for relapse. Despite a lack of specific previous evidence on the neural level, reduced activity in regions associated with mentalizing was conceivable. We expected these differences to emerge when comparing remitted patients to both healthy controls and unmedicated acutely depressed patients, as our previously published comparison between the latter groups had revealed no significant differences in empathic responding (more precisely, reduced empathic responding was only observed after three months of antidepressant treatment).

2. Methods and materials

This cross-sectional study was part of a larger project previously reported (Hahn et al., 2013; Seidel et al., 2015). Participants completed the below-mentioned tasks (the pain task was always completed before the empathy task, with three unrelated tasks in between) during a 7 T

fMRI session. Participants of both patient groups were medication free for at least three months preceding the study. Acutely depressed patients started their antidepressant therapy after the fMRI session.

2.1. Participants

Patients with acute MDD (aMDD; unmedicated), remitted patients with depression (rMDD, unmedicated patients with stable remission for at least three months were included after psychiatric screening by an experienced psychiatrist; Hamilton Depression Scale < 8 (HAMD[24]; Hamilton, 1960)) and healthy controls (HC) were recruited from the local community, through the outpatient clinic of the Department of Psychiatry and Psychotherapy, Medical University of Vienna, or using advertisement. Only patients without psychiatric axis I and II comorbidities were included. All study participants (age range 18–50 years) gave written informed consent before participating. See Table 1 for sample characteristics. See Supplement M1 for details on recruitment and exclusion criteria. The study was registered as a clinical trial, approved by the Ethics Committee of the Medical University of Vienna and was conducted in compliance with the Declaration of Helsinki.

2.2. Experimental tasks and trial structure

2.2.1. Empathy task

An established empathy for pain task (Lamm et al., 2007a) was employed (see Fig. 1). Participants viewed 24 video clips (duration: 3 s), each showing the face of a single individual (12f/12 m), whose facial expression transitioned from a neutral expression into a painful reaction in response to painful sound administration. Participants were told that the depicted people suffered from a neurological disorder (*tinnitus aurium*), which was treated by repeatedly delivering intense auditory stimulation. They were instructed to empathize with the patients while watching the videos. The task run lasted about 6:30 min. Participants were asked to rate the degree of unpleasantness for the patients displayed in the videos (*pain evaluation* rating), and the degree of unpleasantness for themselves (*self-experienced unpleasantness* rating). These ratings measured both cognitive-evaluative (pain evaluation) and affect-sharing (self-experienced unpleasantness) aspects of empathy (Lamm and Majdandžić, 2015; Shamay-Tsoory, 2011). See Supplement M2 for a more detailed description of the task.

Table 1
Sample characteristics.

Group	rMDD	aMDD	HC	p
N	32	29	35	
Age, Years, Mean ± S.E.M.	27.34 ± 1.35	29.62 ± 1.76	27.41 ± 1.30	.51[1]
Sex	23 females, 9 males	21 females, 8 males	23 females, 12 males	.89[2]
Age of onset (y)	21.9 ± 1.3	21.4 ± 1.7	–	.81[3]
Number of episodes (n)	1.8 ± 0.2	3.4 ± 0.4	–	.001[3]
Duration of disease (years)	6.1 ± 0.8	9.6 ± 1.7	–	.07[3]
Period between end of last episode and current episode (months)	–	6.5 ± 2.0	–	
Previous medication[4] (unclear/yes/no)	10/14/8	3/14/12	–	
Handedness (r/l)	31/1	27/2	34/1	
Hamilton Depression Scale[5], Mean ± S.E.M.	1.6 ± 0.48	25.9 ± 1.19	0.3 ± 0.09	

rMDD = Remitted MDD patients; aMDD = Major depressive disorder patients; HC = healthy control participants.

[1] ANOVA.
[2] chi-square.
[3] *t*-tests comparing rMDD and aMDD.
[4] patient groups were medication free for at least three months preceding the study; "previous" refers to the time before this period.
[5] HAMD[24].

2.2.2. Electrical pain task

Participants also underwent an electrical pain task, as previously published (Hahn et al., 2013; Seidel et al., 2015). In this task, no subjective ratings were obtained. For a detailed description of the task, see Supplement M2.

2.3. Questionnaires

The HAMD, the Interpersonal Reactivity Index (IRI; Davis, 1983), the Emotion Contagion Scale (ECS-D; Doherty, 1997) and the Emotion Regulation Questionnaire (ERQ; Gross and John, 2003) were administered before the experimental sessions. Questionnaire data were analyzed separately for each questionnaire and its subscales with four ANOVAs with *Group* (rMDD/aMDD/HC) as the between-subjects factor. In case of significant main effects, post-hoc independent samples *t*-tests were carried out. Spearman correlations between questionnaire scales and number of episodes, age at first episode, as well as duration of disease were calculated. Benjamini-Hochberg (false discovery rate) correction for multiple testing was applied.

2.4. Behavioral data analysis

The two types of ratings in the empathy task (pain evaluation, self-experienced unpleasantness) were analyzed separately with planned independent samples *t*-tests between rMDD and aMDD/HC. Previously published comparisons between aMDD and HC are also reported for reasons of completeness.

2.5. fMRI data analysis

Image acquisition and preprocessing are detailed in Supplement M3. First-level and second-level analyses were performed with SPM12 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm), adopting a general linear model approach. In the empathy task, the first-level design matrix of each subject contained regressors for videos, ratings, and instructions. In the electrical pain task, first-level regressors comprised four stimulation (pain, no-pain, uncertain pain, uncertain no-pain) and three anticipation (certain pain, certain no-pain, uncertainty) conditions. Anticipation was not of interest and therefore orthogonalized to the respective stimulation regressors. Regressors were convolved with the canonical hemodynamic response function and its temporal and dispersion derivatives.

2.5.1. Empathy task

We employed two main analyses: The first one was a whole-brain analysis to identify group differences in an unrestricted fashion. We ran whole-brain cluster-level corrected analyses for the contrasts rMDD > aMDD and rMDD > HC (and reverse contrasts; whole-brain FWE-corrected $p < .05$). The second analysis was specifically focused on the ROIs that were used in our previously published comparison of aMDD and HC (Rütgen et al., 2019). Parameter estimates were extracted (REX-toolbox: http://web.mit.edu/swg/software.htm) from all participants in 10-mm spherical ROIs, centered (as in the previous study) on three clusters reported in the *meta*-analysis by Lamm et al. (2011): anterior midcingulate cortex (aMCC; coordinates: x:−2/y:23/z:40), left anterior insula (lAI; −40/22/0) and right anterior insula (rAI; 39/23/−4). Video > baseline first-level contrasts were used. These values were entered into a two-way mixed-model ANOVA (*ROI*: lAI/aMCC/rAI; *Group*: rMDD/aMDD/HC), followed up by separate one-way ANOVAs per ROI (in line with Rütgen et al., 2019). Based on recommended standards for testing brain-behavior correlations (Rousselet and Pernet, 2012), Spearman correlations between ROI data and behavioral ratings were calculated.

2.5.2. Empathy task: effective connectivity analysis

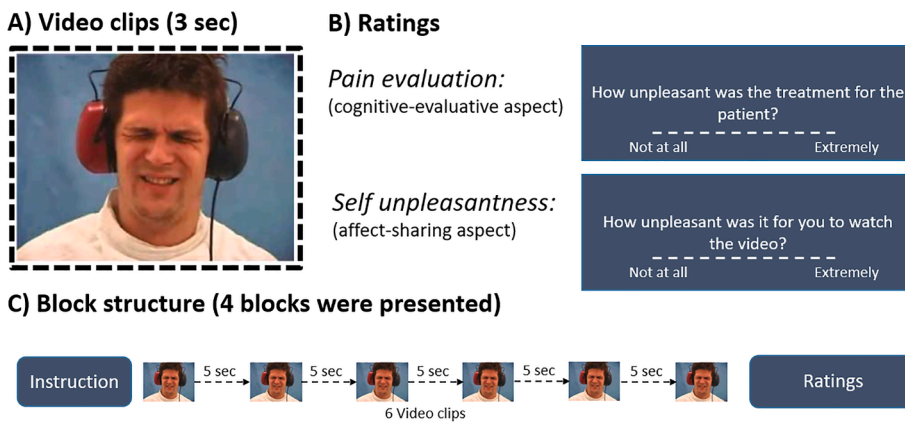This analysis aimed at assessing differences in task-dependent

A) Video clips (3 sec)

B) Ratings

Pain evaluation:
(cognitive-evaluative aspect)

> How unpleasant was the treatment for the patient?
> Not at all ———————————— Extremely

Self unpleasantness:
(affect-sharing aspect)

> How unpleasant was it for you to watch the video?
> Not at all ———————————— Extremely

C) Block structure (4 blocks were presented)

Instruction → 5 sec → 5 sec → 5 sec → 5 sec → 5 sec → Ratings

6 Video clips

Fig. 1. Empathy task description. In this task originally developed by Lamm and colleagues (Lamm et al., 2007a), participants were told that they would view videos of tinnitus patients undergoing painful noise treatment. A) Example video clip: transition from neutral to painful expression within 3 sec (adapted from Lamm et al., 2007a). B) Subjective ratings collected during the task: pain evaluation (upper part; cognitive-evaluative aspect of empathy) and self-experienced unpleasantness (lower part; affect-sharing aspect). C) Block structure: Four blocks with 6 video clips each were presented in total. After viewing initial instructions, participants saw six video clips in a row, separated by 5 s. Each video was presented for 3 s and was followed by a 5 s inter-trial interval, plus a 0–300 ms random jittering. Twice per block, ratings were collected via visual-analogue scales. Two 15-seconds baseline periods were recorded at the beginning and at the end of the task.

connectivity between groups, using the generalized form of context-dependent psychophysiological interactions (gPPI; McLaren et al., 2012). We decided to restrict this analysis to classical empathy regions (rTPJ, bilateral AI, aMCC, medial prefrontal cortex, precuneus) that also showed significant group differences on the whole-brain level as seed regions. Physiological (BOLD) activity of each participant in the rTPJ ROI was defined as the principal eigenvariate of a mask of the anterior rTPJ (as overlap analysis revealed large parts of the group differences in activity in the anterior compared to the posterior part; mask derived from *meta*-analysis by Krall et al. (2015)). Single-subject PPI contrast images were then entered into two-sample *t*-tests at the second level.

2.5.3. Empathy task: regression analysis

To test whether the number of previously experienced episodes and duration of disease had an influence on brain activity in response to empathy for pain, we performed multiple regression analysis as implemented in SPM12. Duration of disease and number of episodes were used as regressors in separate models. All analyses were carried out separately for both patient groups (aMDD, rMDD). A whole-brain cluster-level correction approach with an initial height threshold of $p = .001$ uncorrected was chosen.

2.5.4. Electrical pain task

Parameter estimates were extracted from the same 10-mm spherical ROIs (lAI, rAI, aMCC). Pain > baseline and No-pain > baseline first-level contrasts were entered into a three-way mixed model ANOVA (factors *Intensity:* pain/no-pain; *ROI*: lAI/aMCC/rAI; *Group*: rMDD/aMDD/HC). As in the empathy task, follow-up one-way ANOVAs per ROI were carried out.

3. Results

3.1. Questionnaire results

Mean questionnaire scores ± S.E.M., as well as *p*-values of post-hoc tests are listed in Supplemental Table T3. As for the empathy-related subscales, rMDD reported significantly higher levels of personal distress compared to HC, but lower levels than aMDD. However, neither empathic concern nor perspective taking showed any variation. Concerning emotion regulation, rMDD and HC showed comparable values of ERQ suppression and ERQ reappraisal, while aMDD significantly differed from both other groups regarding these scales (lowest in reappraisal, highest in suppression). rMDD reported higher levels of emotional contagion by joy as compared to aMDD, but were not significantly different from HC. See Supplement R1 for one-way ANOVA results.

3.2. Correlations

IRI personal distress correlated positively with number of MDD episodes ($rs = 0.448$, $p < .001$), duration of disease ($rs = 0.448$, $p < .001$) and negatively with age at first episode ($rs = -0.389$, $p = .004$). ERQ suppression was positively correlated with duration of disease ($rs = 0.302$, $p = .043$).

3.3. Behavioral data

The independent samples *t*-tests on *self-experienced unpleasantness* ratings showed no differences for any of the group comparisons (all *p*-values > 0.644); mean ± S.E.M. per group: HC = 49.36 ± 3.43; aMDD = 51.64 ± 3.45; rMDD = 50.78 ± 3.39.

The independent samples *t*-tests on *pain evaluation* ratings showed that rMDD (Mean ± S.E.M. = 79.06 ± 1.63) reported higher pain evaluation than both HC ($t(65) = -2.02$, $p = .047$, *Cohen's d* = 0.49) and aMDD ($t(59) = -2.16$, $p = .034$, *Cohen's d* = 0.56). HC (Mean ± S.E.M. = 74.29 ± 1.69) and aMDD (Mean ± S.E.M. = 73.27 ± 2.15) did not differ significantly from each other ($p = .710$). See Fig. 2 for illustration of behavioral results.

3.4. fMRI data

3.4.1. Empathy Task: Whole-Brain analysis

The empathy task reliably activated previously reported regions (Lamm et al., 2007a) in a similar manner in all three experimental groups, comprising e.g., bilateral AI, aMCC, rTPJ, amygdalar and peri-amygdalar regions and bilateral occipital cortices, among others. The whole-brain group comparisons (rMDD > HC; rMDD > aMDD) mainly revealed clusters in the rTPJ and right occipital cortex. The reverse contrasts showed stronger activation in the posterior superior temporal sulcus (pSTS), bilateral fusiform face area (FFA), left visual association cortex, and left amygdala (HC > rMDD & aMDD > rMDD), and in the right amygdala (aMDD > rMDD). See Table 2 for full results and Fig. 3A for visualization of whole-brain results. Differences between aMDD and HC were reported previously (Rütgen et al., 2019).

3.4.2. Empathy Task: ROI analysis

The two-way mixed-model ANOVA revealed a significant main effect of *ROI* ($F(2,186) = 34.71$, $p < .001$, $\eta^2_p = .272$), as well as a trend for a main effect of *Group* ($F(2,93) = 2.81$, $p = .066$, $\eta^2_p = .057$). The interaction was not significant ($p = .178$). Follow-up planned one-way ANOVAs per ROI revealed a significant main effect of *Group* for the lAI ($F(2,93) = 3.21$, $p = .045$, $\eta^2_p = .065$). *One-way* ANOVAs for the remaining ROIs were not significant (all *p*-values > 0.178). Follow-up independent samples *t*-tests for group differences in lAI revealed
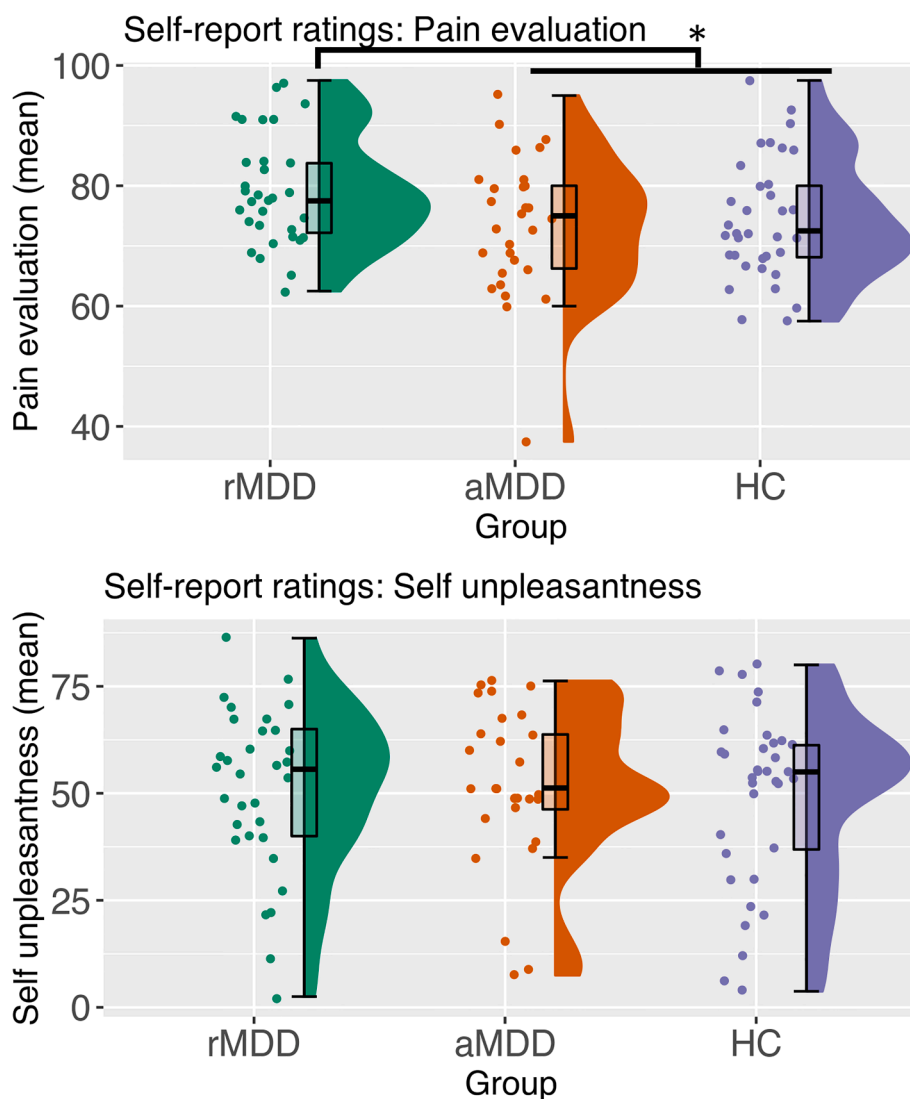
Self-report ratings: Pain evaluation

Self-report ratings: Self unpleasantness

Fig. 2. Self-report ratings of pain evaluation and self-unpleasantness. Raincloud plots (including boxplots) illustrating the distribution of the data and single data points. rMDD showed significantly higher pain evaluation as compared to both other groups. Asterisks mark significant independent-samples *t*-test results (*p* < .05). Values are mean ratings. Note that an outlier (>3 SD) in the pain evaluation data of the aMDD group was retained, as winsorizing did not affect the results. Figure created with ggplot2 R package (Wickham, 2009).

significant differences between rMDD and aMDD ($t(59) = 2.41, p = .019$, *Cohen's d* = 0.63) and a trend for a difference between rMDD and HC ($t(65) = 1.81, p = .075$, *Cohen's d* = 0.45). These differences were driven by lower values in the rMDD group (Mean ± S.E.M. = 0.67±0.13) compared to the other groups (Mean ± S.E.M.: HC: 0.99±0.12; aMDD: 1.11±0.13). No significant differences were observed between aMDD and HC ($p = .478$). No significant correlations between ROI data and behavioral ratings were observed (all $rs < 0.142$; all *p*-values > 0.168). See Supplemental Fig. F1 for illustration of fMRI ROI results.

3.4.3. Empathy Task: Effective connectivity

Following up the whole-brain analyses, we assessed effective connectivity of brain areas strongly associated with empathic processing that showed significant group differences. Using the rTPJ as seed region revealed connectivity differences to the right superior temporal gyrus and bilateral AI (aMDD > rMDD). Comparing HC > rMDD revealed connectivity differences to rAI. In the reverse contrast, significantly different connectivity to the occipital cortex was found (rMDD > HC). Comparisons between aMDD and HC revealed no significant differences in connectivity. See Fig. 3B for visualization of effective connectivity results. Clusters are reported in Supplemental Table T4.

3.4.4. Empathy Task: Regression analysis

Using number of episodes or duration of disease as regressors on

whole-brain activity during pain empathy did not yield significant correlations.

3.4.5. Electrical pain Task

Neither the three-way mixed-model ANOVA nor the follow-up one-way ANOVAs per ROI revealed main effects of *Group* (all *p*-values > 0.709), or interactions with that factor. See Supplemental Results R2 for details.

4. Discussion

In the present study, we aimed at identifying a potential socio-affective trait marker for depression. To this end, we investigated neural and behavioral responses of remitted patients with depression to a pain empathy task. Compared to groups of unmedicated acutely depressed patients and healthy controls, unmedicated rMDD patients showed higher pain evaluation ratings, higher activity in the right temporoparietal junction (rTPJ), and lower activity in areas associated with the processing of emotions and emotional facial expressions. The rTPJ, a brain area that has been consistently associated with self-other distinction and related social-cognitive functions (Quesque and Brass, 2019), showed lower connectivity to the AI in rMDD. We interpret this pattern of results as a detached style in responding to others' negative affect, which results in lowered affective processing of empathically

Table 2
fMRI results. Significant clusters (cluster-level *FWE-corrected*) resulting from whole-brain comparisons between rMDD and aMDD/HC (whole-brain *FWE-corrected, p* < .05). See Supplemental Table T2 for comparisons between aMDD and HC.

Brain region (s)	k	peak x	peak y	peak z	t value	p value (FWE-corr.)
rMDD > aMDD						
rTPJ	1120	60	−40	21	16.93	**<0.001**
R Inferior Occipital Gyrus	2930	48	−72	4	16.50	**<0.001**
L Middle Occipital Gyrus	968	−34	−90	9	9.81	**<0.001**
L Middle Occipital Gyrus	195	−42	−76	6	8.85	**<0.001**
R Superior parietal lobule	363	30	−51	57	8.59	**<0.001**
R Precentral G	176	53	2	43	8.19	**<0.001**
L Sup. Temp. Gyrus	206	26	−72	31	8.08	**<0.001**
aMDD > rMDD						
Posterior STS	1083	58	−63	10	16.25	**<0.001**
L FFA	380	−38	−55	−14	15.54	**<0.001**
Bil. Cuneus	4670	−6	−93	16	12.42	**<0.001**
R FFA	224	42	−46	−9	11.19	**<0.001**
L Amygdala	1163	−18	−10	−11	9.33	**<0.001**
R Amygdala	732	24	4	−15	8.39	**<0.001**
R Middle Frontal Gyrus	147	36	8	51	7.92	**<0.001**
rMDD > HC						
rTPJ	485	58	−39	22	13.06	**<0.001**
R Inferior Occ. Gyrus	576	42	−69	4	10.70	**<0.001**
R Precentral Gyrus	645	53	0	40	10.36	**<0.001**
R Middle Temporal Gyr.	367	52	−24	−14	8.32	**<0.001**
R Superior Parietal Lobule	239	32	−52	58	6.91	**<0.001**
HC > rMDD						
Bil. Cuneus	4109	−8	−94	15	16.68	**<0.001**
Posterior STS	1665	60	−64	10	15.74	**<0.001**
L FFA	1904	−38	−42	−17	13.09	**<0.001**
R FFA	644	42	−45	−9	12.06	**<0.001**
R Sup. Par. Lob.	527	26	−81	49	9.58	**<0.001**
L Amygdala	472	−21	−12	−9	9.35	**<0.001**

perceived emotions. We justify this interpretation and discuss our findings in greater detail in the following.

On a behavioral level, the rMDD group showed higher pain evaluation ratings than aMDD patients and healthy controls. In contrast, self-unpleasantness ratings were similar across all groups. In line with contemporary accounts of empathy (Coll et al., 2017b; Shamay-Tsoory, 2011), pain evaluation ratings result of cognitive evaluation rather than the actual affective impact that is elicited in the observer by sharing the other person's pain (the latter being reflected in self-unpleasantness ratings). This suggests that rMDD patients cognitively anticipate more pain for the other. In an attempt to avoid emotional harm or discomfort, they might lower their attention towards the target.

In line with this interpretation and the behavioral results, we found increased activity in the rTPJ in the rMDD group as compared to the other groups. This region is strongly implicated in self-other-distinction, but is also highly relevant to attentional processes (Corbetta et al., 2008). In general, rTPJ dysfunction has been suggested to increase vulnerability for various neuropsychiatric disorders (see review; Eddy, 2016). It was recently shown that inhibiting activity within the rTPJ by transcranial direct current stimulation leads to reduced empathy (Coll et al., 2017a) in terms of lowered subjective ratings of target pain and reduced amplitudes of the so-called late positive potential, an event-related potential that has been related to perspective taking and

motivational salience. The same study found no effect on neural components related to affect sharing, suggesting a specific role of the rTPJ in the allocation of attention between oneself and another person (see additional supportive evidence; Duffy et al., 2019; Krall et al., 2016). Our interpretation of a detached empathic style is also in line with a recent neuroimaging study (Borja Jimenez et al., 2020), in which participants were instructed to either take an empathic or detached perspective while watching emotional movies. Here, the TPJ was demonstrated to play a central role in adopting a detached perspective, as demonstrated by inter-subject correlation analyses. Higher expectations of others' pain (pain evaluation ratings) may thus lead the rMDD patients to either deliberately or unconsciously adopt a detached perspective.

In the reverse contrasts, we observed higher activity in acutely depressed patients and HC in a set of regions associated with the processing of emotions and affective facial expressions. First, we found higher activity in the left amygdala in both HC and aMDD patients, when compared to rMDD patients. The amygdala is a key region in depression, strongly involved in processing affective visual stimuli (Pessoa and Adolphs, 2010). Acutely depressed patients also showed higher activity in the right amygdala compared to rMDD patients. Second, pSTS was observed to be more active in the aMDD and HC group. This region has been implicated in the processing of biological motion and facial expressions (Hein and Knight, 2008), as well as in perspective taking, and it has been shown that its activity increases with the degree of social meaningfulness of a stimulus (Redcay, 2008). Third, regions involved in face processing (bilateral FFA) and visual attention (bilateral cuneus) were consistently activated more strongly in aMDD and HC groups, speaking for enhanced processing and higher attention towards experimental stimuli in these groups, as compared to rMDD patients. FFA and pSTS show high resting-state coupling and work in concert in facial expression processing (Turk-Browne et al., 2010). In summary, higher activity in this set of regions (amygdala, FFA, pSTS, cuneus) indicates enhanced processing of affective facial features in the aMDD and HC groups.

In the ROI analysis including the most relevant affect sharing regions (bilateral AI and aMCC), we found lower activity in the left AI in the rMDD group, suggesting lower affective responses to the pain of others. These lower values cannot be linked to a generally lowered response within this region irrespective of the applied tasks, as ROI analyses in the same brain regions revealed no group differences in an electrical pain task. Here, it should be noted that AI and aMCC have been demonstrated to be centrally involved in the processing of both pain empathy and self-experienced pain (Lamm et al., 2011; Rütgen et al., 2015, 2021; Zhou et al., 2020).

Analyses of group differences in effective connectivity using the rTPJ as a seed region further aid and corroborate our interpretation. These analyses revealed decreased connectivity between rTPJ and bilateral AI, medial frontal cortex, and right superior temporal gyrus when comparing the rMDD group to the aMDD group. Compared to the HC group, rMDD showed decreased connectivity between rTPJ and right AI. These connectivity profiles could be interpreted in two ways that are not mutually exclusive. On the one hand, reduced connectivity to the right AI might be interpreted as decreased neural processing within the ventral attention network (Corbetta et al., 2008). On the other hand, lowered rTPJ-AI connectivity has been argued to reflect decreased emotional salience of a situation (Preckel et al., 2018). More salient or emotionally more intense situations would engage attention to a higher degree. Here, it has to be noted that the anterior portion of the rTPJ (which was used as a seed for connectivity analyses; see methods section) was previously shown to be involved in both attention and social cognition, which is in contrast to the more specialized role of the posterior rTPJ in the social domain (Krall et al., 2015; see also Mars et al., 2012). It is difficult to disentangle specific effects on emotional salience and effects on attentional processes, as both may result in reduced affective responses (reduced left AI activity) and reduced processing of
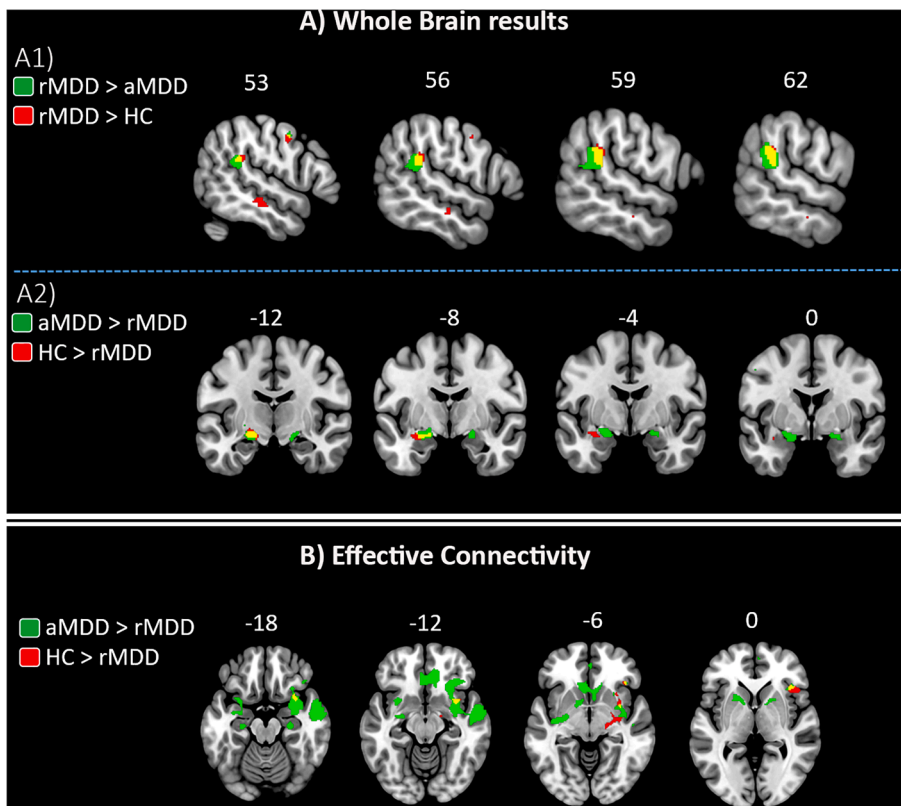
Fig. 3. Whole-brain (A) and effective connectivity (B) results. Panel A1) Map of higher activity in rMDD compared to aMDD (green) and HC (red), including a large partly overlapping cluster (yellow) in the rTPJ. Panel A2) Map showing reverse contrasts (aMDD > rMDD = green; HC > rMDD = red), including a partly overlapping cluster in the left amygdala (whole-brain FWE-corrected, $p < .05$). Panel B) Empathy Task – Effective Connectivity results. Clusters with higher connectivity to the rTPJ in aMDD (green) and HC (red), compared to rMDD, including an overlapping cluster (yellow) in the right AI (initial height threshold $p = .001$ uncorrected). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

affective facial features. Top-down attention has previously been demonstrated to have a significant impact on the neural processing of empathy (Gu and Han, 2007; Lamm et al., 2007b). Gu and Han demonstrated that experimentally lowering subjects' attention to a pain empathy task resulted in a substantial and widespread reduction of activity in various empathy-related regions (such as ACC, and right AI). Similarly, focusing on visual features of a painful scene led to marked reductions of AI and aMCC activity (Lamm et al., 2007b). Judging from the comparable activity across groups in the aMCC and right AI ROIs, and the higher activity in the occipital lobes in the rMDD group, we assume that our results cannot be fully explained by a pure lack of attention in the rMDD group. Still, we cannot exclude that rMDD patients had difficulties to focus their attention on specific parts of the faces associated with pain expressions (e.g., brows, mouth). In future studies, eye tracking may provide an answer to such questions.

The employed questionnaires yielded the following pattern of results. Both rMDD and aMDD patients reported higher levels of personal distress (this scale of the IRI indicates unpleasant feelings in response to observing others' negative experiences) compared to healthy controls, which is consistent with previous reports (Schreiter et al., 2013; Thoma et al., 2013). Increased personal distress is frequently reported in various neuropsychiatric conditions (Eddy, 2016, 2018). The fact that aMDD patients showed even higher levels than rMDD patients might be attributable to previously observed reporting biases during acute episodes of depression (Gupta and Kar, 2012; Morgado et al., 1991). Higher levels of personal distress were associated with a higher number of episodes and earlier age of onset, which may relate to the assumption that "every episode leaves a scar" (Monroe and Harkness, 2005). Suppression was positively correlated with the total duration of disease. Notably, results of these correlation analyses should be taken with caution, as groups significantly differed regarding personal distress and number of episodes. Also, neither number of episodes, nor duration of disease are accurate representations of an individual's total burden of disease: we did not collect individual durations of single episodes per patient, and

thus should not over-interpret group differences regarding these measures, or analyses involving them. We also abstain from claims that the differences between groups may be due to differences in the severity of (acute or previous) depression. We propose that future studies should attempt to incorporate more extensive measures of this aspect.

There is a striking similarity of the comparisons between rMDD to HC and rMDD to aMDD, both on the neural and the behavioral level. Although the focus of this study is on empathy in remitted states of depression, it is interesting to integrate its findings with our previous study (Rütgen et al., 2019), in which we found no relevant empathy-related differences between healthy controls and acutely depressed non-medicated patients (instead, previously reported empathy "deficits" in depressed patients appeared to be related to antidepressant treatment, as shown in a pre- vs. post-treatment comparison of affect-sharing ratings). This pattern of results converges in a framework provided by evolutionary accounts of depression, conceptualizing depression as an adaptive response to the environment: The attachment theory of depression (Gilbert, 2016) suggests that depression leads to appeasement-related behaviors in order to maintain relationships. In a similar vein, the social risk hypothesis (Allen and Badcock, 2003) argues that depressed states lead to the initiation of behaviors that reduce social risk, such as sending signals to others that reduce e.g. the risk of being excluded. Increased empathic sensitivity for others' emotions in the depressed state would be adaptive in such endeavors. Thus, the onset of an acute episode could actually result in enhanced empathic responses, which may explain why we did not observe a similar detached empathic style in the aMDD group. Clearly, only future prospective studies of empathic responding in vulnerable groups who undergo empathy assessments before and after the onset of an episode might reveal the functional and cognitive changes that occur at the transition from symptom-free states to acute states of depression. Seemingly normal responses in the depressed state do not imply that patients would respond similarly in symptom-free states, and the presented evidence suggests a tendency for lowered responses.

Having had an acute episode of depression is one of the strongest predictors of recurrence (Kessing et al., 2004), which could be due to a pre-existing vulnerability factor (vulnerability hypothesis), or due to detrimental changes suffered during the acute episode (neuro-progression hypothesis). The observed pattern of results may represent a trait marker for depression that might be tested in future prospective neuroimaging studies. Such studies might yield an answer to whether the observed pattern is specific to remitted states of depression or whether it represents a pre-morbid vulnerability factor. A recent prospective study (Bos et al., 2018) employing clinical interviews found evidence for pre-morbid impairments in social functioning before developing depression. Also, our whole-brain regression analysis did not provide evidence for a detrimental influence of the number of episodes or duration of disease on neural empathic responding.

The chosen research design certainly also comes with some limitations. First, our insights are limited to empathy for pain, but are not necessarily generalizable to empathy for other (either positive or negative) affective states. Second, we did not investigate prosocial behaviors, which have been reported to be altered during both remitted and acute states: in a recent study (Mohr et al., 2016), participants with prior or current depression (partly medicated) perceived more negative affect in distressed targets and showed more willingness to exert prosocial behaviors towards them. For recruitment, we used the standard HAMD cut-off scores for remission, which have previously been criticized for being too high (Zimmerman et al., 2005). Anyhow, our sample of remitted patients underwent a thorough psychiatric screening, was in stable remission and had HAMD values considerably smaller than the cut-off. Based on the whole-brain results, we focused on the rTPJ in our connectivity analyses, but future studies may also test for potential connectivity differences regarding the left TPJ, which has also been shown to be involved in social cognition (Quesque and Brass, 2019). Furthermore, the two kinds of ratings may not provide a clear-cut differentiation between cognitive-evaluative and affect-sharing aspects (e.g., cognitive pain evaluation may be influenced by one's own affective state), and may not measure fully independent underlying constructs (as shown by a modest correlation of $r = 0.419$ between them). They however put relative weight on and are deemed able to pick up differences between related facets of the multi-faceted experience of empathy, as also extensively documented in our own and others' previous work (Hartmann et al., 2021; Lamm et al., 2019; Rütgen et al., 2015, 2021; Zaki et al., 2016). Regarding generalizability of our results, the relatively narrow age range and the high proportion of female participants (>2/3) should be noted. Due to the relatively small and unbalanced sample sizes, we however abstained from computing sex/gender differences analyses. Lastly, we did not obtain subjective ratings in the electrical pain task, which would have allowed to evaluate group differences regarding the subjective experience of self-directed negative stimuli.

5. Conclusions

In summary, the results of this fMRI study on empathy in remitted states of depression show a consistent pattern for the remitted state: we observed more rTPJ activity, presumably related to increased self-other-distinction, and at the same time lower activity in the left AI and several regions associated with emotion and affective facial expression processing. Increased expectations of others' pain might lead rMDD patients to divert their attention from the targets to avoid emotional harm, which is in line with the questionnaire results of increased reappraisal for emotion regulation. These findings point to a detached style in perceiving others' emotions, which may be short-term protective, but might result in a lack of opportunities for rewarding social interactions in the long run (see Trew (2011)). Our insights may inform clinical practice and contribute to the conception of future depression relapse prevention programs targeting proper recognition of affective states.

Conflict of interest

RL received travel grants and/or conference speaker honoraria within the last three years from Bruker BioSpin MR, Heel, and support from Siemens Healthcare regarding clinical research using PET/MR. He is shareholder of BM Health GmbH since 2019. TV received travel grants and compensation for workshop participation from Pfizer and Eli Lilly and speaker honorary from Shire. CK received travel grants from Roche Austria GmbH and AOP Orphan. The remaining authors declare that they have no biomedical financial interests or potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102699.

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