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RESEARCH ARTICLE

Neural mechanisms underlying social recognition and theory of mind in adolescent patients with bulimia nervosa and transdiagnostic comparison with anorexia nervosa

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Abstract

Introduction: Theory of mind (ToM) is important for social interactions and typical development and has been found to be impaired in patients with anorexia nervosa (AN) and bulimia nervosa (BN). Hypoactivation in fronto-temporal brain regions seems to be the underlying neural mechanism in AN while whole-brain analyses in BN are lacking.

Methods: We used the well-validated social recognition task fMRI paradigm to assess ToM in a total of 72 female adolescents (16 BN, 18 AN and 38 matched healthy controls [HC]).

Results: Compared to HC_{BN}, patients with BN showed hyperactivity during ToM-activity in the right frontal pole, middle temporal gyrus and left

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; BDI, beck depression inventory; BMI, body mass index; BN, bulimia nervosa; CREST, cognitive remediation and emotion skills training; DSM-V, diagnostic and statistical manual of mental disorders V; EDI-2, eating disorder inventory; fMRI, functional magnetic resonance imaging; FWE, family wise error; GLM, general linear model; HC, healthy controls; IQ, intelligence quotient; MANTRA, Maudsley model of anorexia nervosa treatments in adults; MATLAB, matrix laboratory; mPFC, medial prefrontal cortex; MR, magnetic resonance; RO-DBT, radically open dialectical behavioural therapy; SIAB-EX, structured clinical interview for the assessment of AN and BN; SSRI, selective serotonin reuptake inhibitor; STS, superior temporal sulcus; ToM, theory of mind; TPJ, temporoparietal junctions.

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temporal pole and differed fundamentally from hypoactivation in these regions observed in patients with AN before and after short-term weight rehabilitation. Interaction and overlap analyses confirmed that similar regions were affected in opposite directions in both diseases. Hyperactivations in BN in the right middle temporal gyrus and right frontal pole were associated with clinical BN-severity markers binging and purging frequency.

Discussion: The hyperactivation in BN suggest different underlying neural mechanisms for ToM compared to AN. Hyperactivity might correspond to a different but also ineffective cognitive style in patients with BN when approaching social interactions. These important transdiagnostic differences are relevant for future brain-targeted therapeutic approaches.

KEYWORDS
anorexia nervosa, bulimia nervosa, eating disorders, social recognition, theory of mind

Highlights

- Theory of mind (ToM) and social recognition have been found to be impaired in patients with anorexia nervosa (AN) and bulimia nervosa (BN)
- In our study patients with BN showed hyperactive fronto-temporal brain activations compared to controls during a social recognition tasks, in contrast to patients with AN that showed hypoactivation
- Hyperactivation in patients with BN was associated with illness severity, potentially signifying reduced neural efficacy and helping to explain impaired social interaction found clinically, however, opposite brain alterations suggest transdiagnostically different underlying mechanisms and directions for brain-directed therapy

1 | INTRODUCTION

Bulimia nervosa (BN) is a severe eating disorder (diagnostic and statistical manual of mental disorders V [DSM-V]) that mostly occurs in female adolescents and young adults (American Psychiatric Association, 2013). Patients suffering from BN show recurrent episodes of binge eating, followed by pathological compensatory behaviours (purging) to prevent weight gain, including self-induced vomiting and laxative misuse. Similar to patients with anorexia nervosa (AN), patients with BN frequently exhibit a distorted body image and weight phobia, and thus, attempt to lose weight (Herpertz-Dahlmann, 2015).

Recent findings suggest that deviations in societal information processing are an important factor in the onset and maintenance of eating disorder pathologies, and they contribute to unfavourable long-term outcomes (Agras et al., 2000; Schulte-Rüther et al., 2012; Strober et al., 1997). Typically described social problem areas include reduced social skills and difficulties in interpersonal problem solving (Arcelus et al., 2013), as well as lowered cognitive empathy found in AN (Kerr-Gaffney et al., 2019). It has been suggested that the majority of the patients with a binge/purging psychopathology (e.g., patients with BN) are more strongly characterised by negative social interactions and conflicts, interpersonal distrust and ineffective problem-solving strategies. Restrictive eating pathology (more pronounced in patients with AN) is more strongly associated with a fear of negative evaluation, negative social comparison and avoidance of expressing emotion (Arcelus et al., 2013). This resonates well with findings of a higher impulsivity in patients with BN than in AN, found to be associated with symptom severity (Seitz et al., 2013; Svedlund et al., 2019). Contrary to BN, higher levels of social withdrawal were reported in AN (Adambegan et al., 2012; Nickel et al., 2019).

In addition to overall social problem areas, more specific impairments in social cognition have been described, and they appear to play an important role in the aetiology and pathophysiology of AN and BN (Bora & Kose, 2016; Simonsen et al., 2020). Social cognition abilities are important for successful social relationships. Patients with deficits in these have difficulties perceiving and interpreting information about themselves and others and how to decipher social situations (Bora & Kose, 2016), and they are thus more likely to struggle during social interactions. One important aspect of social cognition is the 'theory of mind' (ToM) ability, that is, the metacognitive ability to appreciate the mental states of other people, such as their beliefs, intentions and desires. Deficits in this ability may impair patients in understanding and accepting different perspectives of others, including the notion that one's own body image may be different from how others perceive it (Frith & Frith, 2005). Furthermore, such a deficit may influence one's own insight into the need for treatment (Bora & Kose, 2016; Vandereycken, 2006), further complicating the initiation and course of therapeutic interventions.

On the behavioural level, ToM abilities were found to be impaired in patients with AN (Bora & Kose, 2016; Sedgewick et al., 2019; Simonsen et al., 2020) and BN (Dejong et al., 2013; Kenyon et al., 2012). A recent review (Mason et al., 2021) and a meta-analysis (Bora & Kose, 2016) revealed the strongest social cognition deficits in acute AN with medium to large effect sizes and somewhat smaller effects in BN and recovered AN. In patients with AN, the duration of illness, reduced body mass index (BMI) and depressive symptoms are associated with the severity of ToM deficits. Other studies have also demonstrated a relationship between ToM deficits and bulimic symptoms in patients with BN (Sacchetti et al., 2019). One hypothesis of the authors is to interpret ED symptoms as maladaptive coping strategies to overcome social cognition inabilities.

To summarise, ToM deficits could play a substantial role in both the aetiology and pathophysiology of AN and BN, but only very few studies have investigated ToM in patients with BN (Bora & Kose, 2016) and hardly anything is known about differential contributing factors to ToM in both disorders.

The neural processes underlying ToM processing have been well studied in healthy controls (HCs). Several studies have consistently described activation in brain regions associated with ToM, including the medial prefrontal cortex (mPFC), posterior cingulate/precuneus, bilateral temporoparietal junctions (TPJ) and anterior temporal lobes (Gallagher et al., 2000; Schurz et al., 2014). A few studies have investigated neural substrates of ToM in adults and adolescents with AN (McAdams & Krawczyk, 2011; Schulte-Rüther et al., 2012), while only one study has been performed in adults with BN (McAdams & Krawczyk, 2013). Most findings in patients with AN suggest hypoactivation in the mPFC, temporal and parietal brain regions (McAdams & Krawczyk, 2011; Schulte-Rüther et al., 2012) in both acute and recovered patients and more severe neurofunctional deficits predict worse clinical outcomes at the 1-year follow-up (Schulte-Rüther et al., 2012). Leslie et al. (2020) did not replicate these findings in a larger sample, however, they used a slightly different version of the paradigm (Frith Happe task) which varied in terms of instructions (Abell et al., 2000). They found an association between the complexity of the ToM stimuli and extra-striatal BOLD-response. McAdams and Krawczyk (2013) used an ROI approach and observed hypoactivation in the right TPJ of adults with BN but did not find differential effects in the mPFC. However, there is a striking lack of investigations of ToM in early manifestations of BN in adolescent and young adult patients on the one hand and whole brain analyses on the other hand.

Taken together, social cognitive processing, ToM abilities and their neural substrates are particularly relevant topics for investigation across different eating disorders. Increasingly, transdiagnostic investigations of brain activation studies have revealed specific patterns of hyperactivation and hypoactivation and their relation to symptom clusters (McTeague et al., 2020). However, respective studies focussing on eating disorders are scarce. Notable differences between neural substrates of AN vs BN may have the potential to substantially inform clinical practice and translation because they suggest that some therapeutic strategies might be more effective for specific neurobehavioural phenotypes (McTeague et al., 2020).

The present study aimed to investigate the neural substrates of ToM processing in adolescent and young adult patients with BN, including a transdiagnostic comparison with patients with AN before and after weight rehabilitation. Considering previous findings of behavioural deficits in ToM in patients with BN, we expected aberrant brain activation patterns in particular in mPFC, TPJ and anterior temporal lobe regions in patients with BN compared to those in HCs. Furthermore, we explored the association of brain activation with symptoms of eating disorder severity in patients with BN. Given the qualitative differences in social difficulties in patients with BN compared to patients with AN, we were interested whether these relate to distinct ToM brain activation patterns in BN vs An.

2 | METHODS

2.1 | Participants

Twenty-two female adolescent and young adult patients with BN according to DSM-IV, aged 15–23 years and 20 HCs (HC_{BN}), matched for age and intelligence quotient (IQ), participated in this study. Six patients and two HC_{BN} were excluded post hoc from the study due to technical difficulties that impacted data acquisition during the scanning procedure ($n = 4$) or due to excessive movement ($n = 4$; Power, 2017), leaving a total sample of 16 BNs and 18 HC_{BN}. The patients were consecutively recruited by the in- and outpatient clinics of the Department of Child and Adolescent Psychiatry of Aachen University Hospital, Germany, which is a specialist centre for eating disorders. Six patients were inpatients and ten outpatients (eight former inpatients) at the time of the study. BN-associated symptoms were assessed with a structured clinical interview for the assessment of AN and BN (structured interview for eating disorders [SIAB]-EX, diagnoses and parametric eating disorder psychopathology [Fichter & Quadflieg, 1999] patients only) and the eating disorder inventory (EDI-2, 91 items/11 subscales of eating disorder psychopathology [Garner et al., 1991]). The exclusion criteria included a history of psychosis or autism spectrum disorder (ASD), severe substance abuse, and IQ < 80, however, taking medication was acceptable. HC_{BN} were enrolled via local advertisements that did not state the aims of the study. The HC_{BN} exclusion criteria included current psychiatric disorders or lifetime eating disorders and an IQ < 80. Additionally, the Beck depression inventory (BDI) was administered.

Three patients showed improvement after inclusion with respect to acute symptoms (binging and vomiting frequencies) but still satisfied the criteria for atypical BN at the time of the magnetic resonance (MR) assessment. Four patients were diagnosed with a current major depressive episode, two of whom received serotonin reuptake inhibitors during the study. For the demographic and clinical data of the enrolled participants, see Table 1. Furthermore, we included a sample of 18 patients diagnosed with AN according to DSM-IV and 20 HCs (HC_{AN}) which has been previously published (Schulte-Rüther et al., 2012) in our final analysis for comparison. In short, all the patients with AN were recruited as inpatients at the Aachen University Hospital and diagnosed based on DSM-IV by a board-certified psychiatrist. Assessments were conducted longitudinally at admission (T1) and discharge (T2) after short-term weight recovery and included the EDI-2 and BDI. Age- and IQ-matched HC_{AN} were recruited locally via advertisements, were confirmed to not have any lifetime psychiatric diagnoses and were assessed once.

The current study was approved by the local Ethics Committee of Aachen University Hospital in accordance with the Declaration of Helsinki. All the participants and their legal guardians (if applicable) provided informed written consent before being included in the study.

2.2 | Social attribution task

While lying in the scanner, participants performed a social attribution task designed to induce ToM processing that was similar to the task established by Heider and Simmel (1944) but optimised for functional magnetic resonance imaging (fMRI; Vandewouw et al., 2021; Wager & Nichols, 2003), because it uses the optimal block length frequency (with interspersed low-level baseline blocks) for blocked fMRI designs. Such design types have been proven as particularly sensitive also for low sample size and clinical group comparisons. A total of 24 15.1-s video clips of three white geometric shapes moving on a black background around a box were presented to the participants. The video clips were grouped into three conditions (eight videos per condition) and presented in a randomised order. The first condition implied that the geometric shapes behaved in a way suggesting personal agency and reciprocal contingent social interaction. After each video, participants were asked to indicate whether all shapes were 'friends' via a button press with the left or right index finger. In the two other (non-ToM) conditions, the shapes were either (1) circling at various speeds like 'bumper cars' or (2) moved along simple trajectories governed by Newtonian physics like billiard balls ('physical'). After each of these non-ToM clips, participants were asked to decide whether all the shapes were equally 'strong'.

Before each video, a condition-specific instruction cue appeared for 3 s. Of note, our experimental tasks require ToM processing only during the dedicated ToM task ('are they friends' vs. 'equally strong/heavy'), thus maximising the ToM related neural activations in ToM vs. nonToM contrasts. Furthermore, it requires focused attention during the full period of the stimulus video because even the last second can change the required response. In contrast, in other variations of the task (see example in Leslie et al., 2020) a single multiple choice decision was used across all conditions (requiring a decision about the type of video). This type of instruction may induce ToM-processing even during non-ToM conditions and the initial parts of the video may suffice to make the decision, both potentially resulting in less statistical power to detect subtle group differences.

TABLE 1 Demographics and clinical characteristics of female adolescents with bulimia nervosa, anorexia nervosa and respective healthy control

	Bulimia nervosa (*N* = 16) BN	**Healthy controls (*N* = 18) HC_{BN}**	**Anorexia nervosa admission (*N* = 18) AN_{T1}**	**Anorexia nervosa discharge (*N* = 18) AN_{T2}**	**Healthy controls (*N* = 20) HC_{AN}**
Age (years)	17.81 (2.74) [15; 23]	17.5 (1.42) [15; 19]	15.69 (1.55) [12.58; 17.83]	16.03 (1.53) [12.88; 18.25]	15.85 (1.96) [12.25; 18.78]
IQ (points)	102.67 (10.22) [86; 118]	102.78 (7.67) [93; 124]	107.41 (7.75) [90; 120]	108.08 (5.84) [99; 120]	110.06 (15.95) [90; 135]
Body mass index (kg/m^2)	20.17 (2.30) [17.3; 24.8]	21.51 (2.57) [16.9; 27]	15.85 (1.55) [16,17; 19.87]	18.01 (1.06) [16.17; 19.87]	22.25 (3.38) [18.33; 32.14]
EDI 2 (total score)	338.50 (77.51) [204; 463]	198.11 (55.52) [135; 334]	262.29 (56.14) [130; 350]	248.56 (64.22) [130; 350]	–
BDI 2 (total score)	24.29 (15.40) [1; 48]	3.61 (5.12) [0; 21]	21.76 (10.52) [0; 28]	10.88 (8.87) [0; 28]	–
SIAB (total sum)	85.06 (30.02) [34; 152]	–			
Objective binge episodes (over last 2 weeks)	3.60 (8.99) [0; 35]	–			
Vomiting episodes (over last 2 weeks)	4.25 (8.96) [0; 35]	–			
Laxative use (last 2 weeks)	0.31 (0.87) [0; 3]	–			
ToM social (% correct)	83.06 (13.63) [50; 100]	77.28 (14.33) [50; 100]	81.39 (10.42) [63; 100]	81.25 (11.54) [50; 100]	78.40 (12.66) [50; 100]
ToM physical (% correct)	69.00 (19.28) [38; 100]	69.72 (15.65) [38; 88]	54.23 (15.35) [13; 75]	61.11 (18.10) [29; 100]	64.63 (17.31) [25; 88]
ToM bumper (% correct)	63.56 (15.44) [38; 88]	56.5 (16.29) [25; 88]	54.04 (23.79) [13; 100]	54.86 (22.34) [25; 100]	54.56 (17.67) [25; 88]

Abbreviations: BDI 2, Beck depression inventory 2; EDI 2, eating disorder inventory 2; SIAB, structured interview for eating disorders; ToM, theory of mind.

With respect to behavioral data, group differences were calculated between average correct rating of BN versus HC_{BN}, AN_{T1} versus HC_{AN} and AN $_{T2}$ versus HC_{AN} using two-sided *T*-tests after checking for meeting the normality assumptions using Kolmogorov-Smirnoff tests. 2 × 2 ANOVAs were used to compare BN, HC_{BN}, AN_{T1} and HC_{AN} and HC_{AN} as well as BN, HC_{BN}, AN_{T2} and HC_{AN}.

2.3 | MR technical parameters

All the MR measurements of the participants with BN and the respective HC were acquired with a 3-T TRIO MR scanner (Siemens, Erlangen, Germany) using a standard circular polarised (CP) head coil (TxRX-coil) at Aachen RWTH University Hospital. MR measurements of patients with AN and their respective HC were acquired using an identical Siemens TRIO scanner and CP head coil at Research Center Jülich.

For functional imaging of the BN sample, gradient-echo echoplanar T2*-weighted images (EPIs) were acquired (time to echo [TE] 30 ms, repetition time [TR] = 2424 ms, $\alpha = 80°$, field of view [FOV] = 192 mm, voxel size = 3 × 3 × 3 mm^3, matrix size = 64 × 64, 40 transverse slices, ascending slice acquisition, interleaved) in one session (approximately 12 min). A number of participants had 34 instead of 40 transverse slices (nBN = 14 nHC = 8). An additional regressor was used in later second-level analyses to correct for potential differences. Identical scanning parameters and sequences were used for both timepoints of the AN sample, with the exception of a slightly different α of 90° and non-interleaved ascending slice acquisition.

Anatomical images were acquired using a standard T1-weighted 3D magnetisation-prepared, rapid acquisition gradient echo (MP-RAGE) pulse sequence and a 1 × 1 × 1 mm^3 resolution.

2.4 | Behavioural and fMRI data analysis

Statistical analysis of the behavioural data was conducted with SPSS 25. Descriptive variables referring to the sample (demographic variables, diagnostic parameters, questionnaire data and video correct/incorrect answers) were analysed with two-tailed student's *t*-tests.

Analysis of the functional imaging data was performed with SPM12 v7771 (Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB R2019b (Mathworks, Natick, MA) running in a Debian (Sid) environment. Default SPM settings were used unless stated otherwise.

Before analysis, function imagining data was carefully inspected for the prescence of artefacts and other over data quality issues. Functional images were realigned using rigid-body transformation and slice-timed (Sladky et al., 2011) with respect to slice 6. All functional volumes were co-registered to the mean realigned and slice-timed functional image. The mean functional image was segmented and spatially normalised (with respect to the tissue probability maps provided by SPM according to the Montreal Neurological Institute template), and resulting normalization parameters were applied to the functional images which are thereafter smoothed with an 8 mm (full-width-half maximum) isotropic Gaussian kernel.

Individual first-level models were established by modelling all functional blocks, separately per condition. The models included estimated realignment parameters as regressors to account for residual variance related to movement. Boxcar functions (aligned with the onset and duration of the video blocks) were convolved with a canonical model of the haemodynamic response function for each condition separately. First-level analyses included modelling of a 128s high-pass filter to account for low-frequency noise in the fMRI data. Parameter estimates of the resulting general linear model (GLM) were calculated for each voxel and each regressor. Simple contrasts of these regressors (against fixation cross baseline) were used for the second level models.

For population inference, whole-brain second-level models were computed using a flexible factorial ANOVA with subject and group (HC_{BN}, BN, HC_{AN}, AN) as independent factors and condition (social, physical, bumper) as a non-independent within-subject factor assuming non-sphericity for all factors (non-sphericity correction using modelling of covariance components as implemented in SPM12). The number of slices was additionally entered as a covariate to account for potential confounds. Specific effects at each voxel were tested by applying the appropriate linear contrasts to the parameter estimates. Analyses were performed separately for AN_{T1} and AN_{T2}. For reporting, a strict voxelwise threshold was applied ($p < 0.05$ familywise error (FWE) correction). According to our previous publication (Schulte-Rüther et al., 2012), we reported results pertaining to the factor task by comparing the ToM condition against the collapsed non-ToM conditions, testing for both hyper- and hypo-activation with respect to ToM ($contrast_{hyperactivation}$: 2 × social − (bumper + physical); $contrast_{hypoactivation}$: (bumper + physical) − 2 × social)).

Rendered images were created using BSPMVIEW (v.20180918) implemented in MATLAB R2019b.

AN_{T1}, AN_{T2} and HC_{AN} data from Schulte-Rüther et al. (2012) were reanalysed using the exact same

analysis settings and pipeline as the BN and HC_{BN} data to allow for a direct statistical comparison. A single exception was made for the slice timing procedure because the two datasets differed in the order of slice acquisition (interleaved for BN, ascending for AN).

To account for any potential residual differences due to data acquisition and processing, we only considered direct group comparisons between BN and AN in relation to their respective HC comparison groups.

2.4.1 | ToM-network

First, we assessed the overall network involved in ToM processing by contrasting the ToM condition against the non-ToM conditions across the newly acquired dataset of BN and HC_{BN} combined.

2.4.2 | BN versus HC

Next, we used the respective ToM versus non-ToM contrast and compared differences between BN and HC_{BN}, that is, hypo- or hyperactivation in patients with BN compared to HC_{BN}, by assessing the group × task interaction contrasts. Results were reported at a statistical threshold of $p < 0.05$, FWE-corrected across the whole brain.

In light of previous reports of hypoactivation in ToM-related processing in eating disorders, including our own study (Schulte-Rüther, 2012), we performed an additional VOI analysis to allow for a more lenient threshold in order to test for any indication of hypoactivation. VOIs were generated by expanding existing FWE-significant clusters of the previous AN_{T1} versus HC_{AN} data by relaxing the multiple comparison correction to $p < 0.001$ uncorrected. Using this procedure, 5 VOI masks were generated, comprising medical temporal and mPFC regions and were used for small volume correction across these respective regions, respectively.

To explore the possibility that the observed effects may be due to potentially confounding effects, the above whole brain analysis was repeated excluding patients with major depression or selective serotonin reuptake inhibitor (SSRI) medication, respectively (see supplementary materials for more details). Individual beta-values for each participant were extracted for all the whole brain FWE-corrected significant clusters for visual inspection using custom-made scripts. In an exploratory analysis, these beta values were also used to check for a potential role of a prior diagnosis of AN in patients with BN. We compared the eight patients with a prior AN diagnosis with eight without a priori diagnosis using two-sided independent Mann-Whitney-U-tests.

2.4.3 | AN versus HC

To compare the activation patterns related to ToM in patients with BN to the patterns in patients with AN, we first replicated the analyses reported by Schulte-Rüther et al. (2012), which suggested hypoactivation in ToM-related areas compared to HC. To account for the potential effects of starvation, we performed the analyses separately for the T1 measurement (acute starvation) and the T2 measurement after short-term weight recovery. For this purpose, AN_{T1} versus HC_{AN} and AN_{T2} versus HC_{AN} ToM versus non-ToM were compared, and the results are reported at a threshold of $p < 0.05$ FWE-corrected across the whole brain.

2.4.4 | BN versus AN

To perform direct statistical comparisons for the difference in ToM-related processing between patients with BN and AN, we also compared the respective group-specific effects of patients with AN and BN (determined by comparison to their own respective HC group) using the contrasts (BN-HC_{BN}) versus (AN-HC_{AN}) for the ToM versus non-ToM comparisons. Again, the analyses were performed separately for both T1 and T2 on a whole brain level and were FWE-corrected.

2.4.5 | Beta-plots and clinical correlations

Furthermore, the extracted beta-values were used to calculate the ToM-specific contrast values for each of the clusters that showed significant differences between patients with BN and HC_{BN}. We performed correlation analyses to check for associations of brain activation with clinical variables within patients with BN. One-sided Spearman's rank correlations were used to analyse the association with BN severity (number of objective binges, vomiting and laxative use in the last 2 weeks).

3 | RESULTS

3.1 | Clinical and behavioural data

The clinical data of the patients with AN and BN and their respective HCs are summarised in Table 1. The samples of patients and HCs were well matched for age

and IQ. In addition to increased eating disorder symptoms, patients with BN also showed higher depressive symptoms than their HC_{BN}. There was no difference in the ability to correctly rate the three categories of videos between BN (ToM: 77.3%, non-ToM 83.1%) or AN (ToM: 78.4%, non ToM 81.4%), and their respective HC ($ToMHC_{AN}$: 54%, non-$ToMHC_{AN}$ 54.9%; $ToMHC_{BN}$: 56.5%, non-$ToMHC_{BN}$ 69.7%) nor a difference between BN and AN (all $p > 0.05$).

3.2 | fMRI data

3.2.1 | ToM-network

In the combined analysis of both groups, BN and HC_{BN}, the contrast between ToM versus non-ToM confirmed neural activation in the mPFC, frontal pole, posterior and anterior temporal gyrus, TPJ, temporal pole, fusiform gyrus and inferior and superior frontal gyrus typically associated with ToM-related processing (Figure 1).

3.2.2 | BN versus HC

We did not find any significant results at the whole-brain level, that would indicate reduced activation in patients with BN. Even when investigating region of interest analysis with increased detection power using predefined VOIs, we did not find any significant hypoactivation in patients with BN. However, when comparing BN > HC_{BN}, we did find voxel-level FWE-corrected hyperactivation in the whole-brain analysis in the mPFC, the middle temporal gyrus/superior temporal sulcus (STS), temporal pole and hippocampus (Figure 2, Table 2). Beta plots of the three significant regions within the ToM-network (whole-brain analysis) confirmed the pattern of increased activation for the ToM condition in patients with BN versus HC_{BN} (Figure 2). Excluding patients with major depression or SSRI medication did not significantly change the results (supp. Figures 7 and 8, supp. Table 1). Exploratory analysis did not reveal any differences in beta-values between patients with BN and prior AN and those without (data not shown).

3.2.3 | AN versus HC

We separately compared the contrast ToM versus non-ToM for AN at admission (AN_{T1}) and at discharge after short-term weight recovery (AN_{T2}) with HC. In HC > $AN_{T1,}$ we uncovered five hypoactive regions in medial temporal and mPFC regions that confirmed our previous analysis by Schulte-Rüther et al. (2012). Of these, three regions were in close proximity to hyperactive regions in patients with BN (Figure 3; for beta plots, see supp. Figure 1) that were also well inside the ToM network. When comparing HC > AN_{T2}, we found a similar pattern of four significant regions that again confirmed the hypoactivation previously found by Schulte-Rüther et al. (2012), and these regions were again in close proximity to the hyperactive regions in patients with BN (supp. Figure 2).

3.2.4 | BN versus AN

The direct comparison of BN versus acute AN (relative to their respective HC: BN-HC_{BN} vs. AN_{T1}-HC_{AN}) revealed seven significant frontal, temporal and temporoparietal clusters in the whole-brain analysis (Figure 3, supp. Figure 3 and Table 2). Beta-plot analyses showed

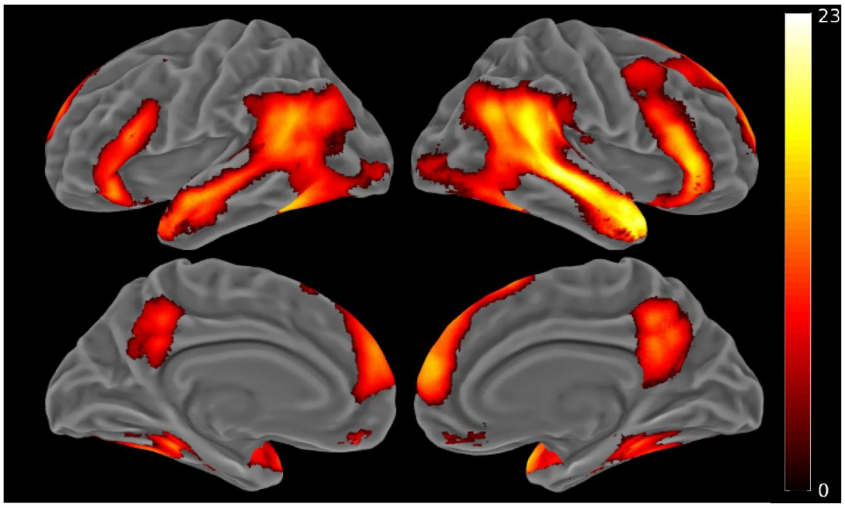

FIGURE 1 ToM-network: ToM versus non-ToM in BN and HC_{BN} combined. Whole brain analysis, FWE corrected $p < 0.05$ [Colour figure can be viewed at wileyonlinelibrary.com]

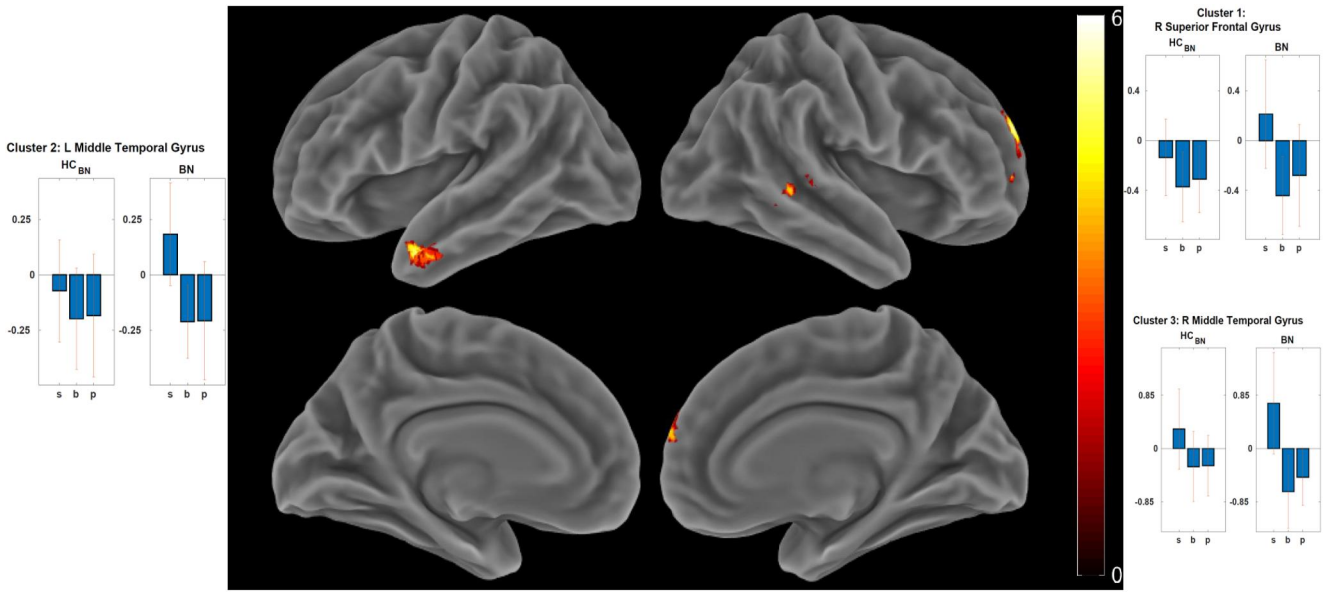

FIGURE 2 Hyperactivity in patients with BN: BN versus HC_{BN} (ToM vs. non-ToM). Significant clusters of the whole brain analysis, FWE corrected $p < 0.05$, are depicted here $p < 0.001$ uncorrected for display purposes only. Beta-plots of significant clusters include separate mean beta scores for both groups and s (social), b (bumper) and p (physical) respectively. Greater activation for social compared to bumper and physical (ToM vs. non-ToM) supports regions being part of the ToM-network depicted in Figure 1 [Colour figure can be viewed at wileyonlinelibrary.com]

consistently higher activation in patients with BN in the ToM-condition compared to patients with AN in all seven regions.

The direct comparison of patients with BN and patients with AN_{T2} after short-term weight recovery (BN-HC_{BN} > AN_{T2}-HC_{AN}) revealed very similar findings compared to AN_{T1} (Table 2 and supp. Figure 4).

The close proximity of the BN > HC_{BN}, HC_{AN} > AN and BN > AN findings is visualised in a joint overlay with AN_{T1} (Figure 3 and supp. Figure 5) and AN_{T2} (supp. Figure 6). Additionally, correcting the above analyses for age did not significantly change the results (supp. Figure 9 + 10, supp. Table 2).

3.2.5 | Association with clinical measures

For patients with BN only, hyperactivation in the right middle temporal gyrus/STS was associated with illness severity marker binging (Spearman's rho: 0.490, *p*: 0.032) and laxative abuse (Spearman's rho: 0.570, *p*: 0.011), while hyperactivation in the right medial prefrontal gyrus was associated with laxative abuse (Spearman's rho: 0.460, *p*: 0.037).

4 | DISCUSSION

The present study is the first to investigate the neural signatures of ToM in adolescent and young adult patients with BN. We found significant hyperactivation in BN > HC_{BN} in areas encompassing the mPFC/frontal pole, temporal pole and middle temporal gyrus/STS. Importantly, the extent of hyperactivation was associated with different illness severity measures. This pattern contrasts with hypoactivation in similar regions in patients with AN, suggesting important transdiagnostic distinctions in the neurobehavioural phenotypes across these two types of eating disorders.

Similar to our previous study of patients with AN (Schulte-Rüther et al., 2012) and other studies using similar or adjusted stimuli and paradigm (Leslie et al., 2020; Schultz et al., 2003), we did not observe behavioural group differences in reaction times or the percentage of correct choices for the employed task and all participants were able to successfully perform the task. Thus, the fMRI results can be interpreted with respect to differences in functional brain organisation and are unlikely to reflect potential nonspecific differences, such as attention to the task or processing speed.

Patients with BN did not show any *hypo*activation compared to HC_{BN} for the ToM videos (even in a more lenient VOI analysis) but rather robust *hyper*activations in the right mPFC/frontal pole, middle temporal gyrus/STS and temporal pole (Table 2, Figure 2). The mPFC, in particular the anterior rostral mPFC, is considered to be one of the most important regions for representing mental states and predicting others' behaviour (Gallagher et al., 2000). This region has been characterised as the main hub for 'mentalising', that is, representing the

TABLE 2 Peaks of significant group differences

Anatomical region	H	k	x	y	z	t
$BN > HC_{BN}$						
Medial PFC/frontal pole	R	9	16	58	24	5.26
Middle temporal gyrus/temporal pole	L	6	−52	2	−26	5.25
Middle temporal gyrus/STS	R	2	58	−36	0	5.18
White matter	L	1	−26	−30	0	4.98
Hippocampus	L	1	−36	−32	−6	4.88
$HC_{AN} > AN_{T1}$						
Medial temporal gyrus/temporal pole	R	67	56	6	−20	6.40
Middle temporal gyrus/STS	R	120	48	−20	−8	6.17
Middle temporal gyrus/temporal pole	L	5	−56	2	−14	5.39
Cerebellum (VII)	L	11	−22	−78	−38	5.33
Medial PFC/frontal pole	R	8	2	56	22	4.97
$HC_{AN} > AN_{T2}$						
Middle temporal gyrus/temporal pole	R	17	56	8	−18	5.89
Middle temporal gyrus/temporal pole	L	6	−56	2	−14	5.49
Middle/superior temporal gyrus	R	21	62	−16	−4	5.18
Superior temporal gyrus	R	1	62	−6	−4	4.86
Interactions $BN\text{-}HC_{BN} > AN_{T1}\text{-}HC_{AN}$						
Middle temporal gyrus	R	250	48	−22	−8	6.43
Medial PFC	R	75	46	36	−10	6.06
Posterior PFC	R	20	8	18	64	5.80
Medial PFC/frontal pole	R	37	14	58	26	5.77
Medial temporal gyrus/temporal pole	R	29	50	12	−26	5.52
Medial temporal gyrus/temporal pole	L	5	−56	2	−14	5.21
Superior temporal gyrus	R	13	48	−40	24	5.17
Medial PFC	R	5	42	26	−16	4.90
Interactions $BN\text{-}HC_{BN} > AN_{T2}\text{-}HC_{AN}$						
Medial temporal gyrus/temporal pole	R	12	52	12	−22	5.63
Medial PFC/frontal pole	R	19	14	58	26	5.63
Medial temporal gyrus/temporal pole	L	12	−52	2	−24	5.53
Middle temporal gyrus	R	14	56	−36	0	5.45
Middle temporal gyrus	L	8	−56	0	−12	5.42
Middle temporal gyrus	R	14	60	−12	−10	5.33
Middle temporal gyrus	R	8	50	−22	−8	5.11
Superior medial gyrus	L	6	−8	58	14	4.95

Note: Analyses FWE-corrected at $p < 0.05$ for multiple comparisons at the voxel level.

Abbreviations: H, hemisphere; k, cluster size; L, left; R, right.

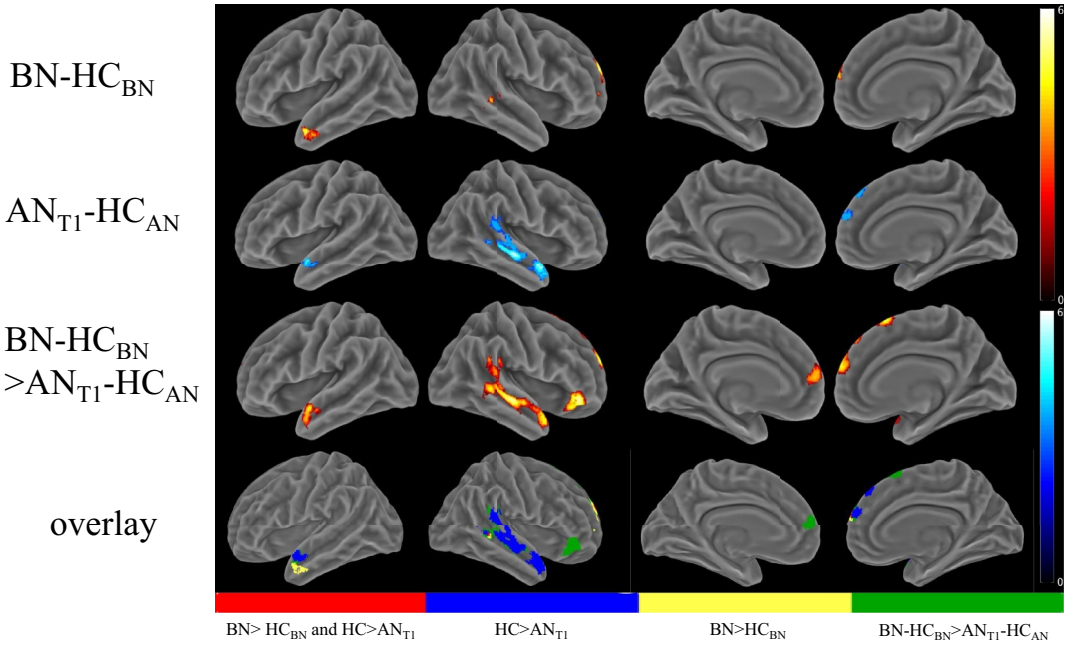

FIGURE 3 Close proximity of hyperactivity in patients with BN and hypoactivity in patients with AN at admission. First row: hyperactivity in patients with BN: BN-HC$_{BN}$. Second row: hypoactivity in patients with AN: AN$_{T1}$-HC$_{AN}$. Third row: direct comparison of BN with AN$_{T1}$ (and their respective HC) BN > HC$_{BN}$ versus AN$_{T1}$ > HC$_{AN}$. Fourth row: overlay demonstrating close proximity of hyper- and hypoactive regions. BN > HC$_{BN}$ in yellow, HC$_{AN}$ > AN$_{T1}$ in blue, both BN > HC$_{BN}$ and HC$_{AN}$ > AN$_{T1}$ in red, BN > AN$_{T1}$ (including respective HC) not overlapping with the first two in green. All group comparisons used ToM versus non-ToM of significant clusters of the whole brain analysis, FWE corrected $p < 0.05$. Here $p < 0.001$ uncorrected is used for display purposes [Colour figure can be viewed at wileyonlinelibrary.com]

mental states of oneself and other people as decoupled from reality (Amodio & Frith, 2006; Mitchell et al., 2006). Regions at the temporal pole have been characterised as 'semantic hubs' that are important for bringing together semantic and autobiographical memory and binding emotional reactions to preprocessed sensual input (Olson et al., 2007; Simmons & Martin, 2009). These are thus essential for mentalising processes by integrating semantic and autobiographic memories with the patient's momentary socioemotional reaction (Frith & Frith, 2006). The middle temporal gyrus/STS has been implicated in the interpretation of relevant social cues and is also often activated in ToM experiments (Gallagher et al., 2000; Schulte-Rüther et al., 2012).

In light of the absence of behavioural differences for the employed task, hyperactivity in these brain regions could either signify primary alterations and overactivity within this network associated with ToM abilities (e.g., as a predisposition or consequence of the disease) or may reflect secondary compensatory activity due to initially less effective neural networks (i.e., more effort is needed for the same behaviour/task). More research is warranted to clarify which of these potential explanations may hold true. In all cases, the observed pattern may signify a distinct neurobehavioural phenotype associated with acute BN in adolescents. Supporting a clinical importance of these alterations, hyperactivity in the mPFC and medial temporal gyrus/STS was also associated with markers of illness severity such as the extent of binging and purging symptoms.

Recent findings support the idea that increased activation in brain areas relatd to ToM tasks are associated with increased everyday social affect and cognition (Hildebrandt et al., 2021). Future studies should thus investigate whether patients with BN have a tendency for 'overthinking' ambiguous social situations and whether this may contribute to observed deficits in social cognition (Bora & Kose, 2016). On the other hand, patients with BN show an elevated level of impulsivity (Mobbs et al., 2008; Rosval et al., 2006) and impulsivity is known to be negatively associated with ToM abilities (Pineda-Alhucema et al., 2018). It is furthermore associated with higher symptom severity and more comorbidities, such as attention-deficit/hyperactivity disorder (ADHD), risk-taking behaviour (Seitz et al., 2013) and features found in borderline personality disorder (Sacchetti et al., 2019). Generally, patients with high values of impulsivity tend to arrive at quicker interpretations and give themselves less time to resolve ambiguous situations, also in social situations. Future studies should further investigate a potential link between overactivity in brain areas related to social difficulties in every day life and impulsivity.

Of note, our results are different from a previous study using the same task in adult patients with BN and AN that reported *hypo*activation in TPJ (McAdams & Krawczyk, 2013) in patients with both disorders and inconclusive results in the mPFC; however, that study focussed only on these two regions using a VOI and not a whole-brain approach. Furthermore, a fundamental difference between our study and the study of McAdams et al. is that their adult sample had a mean age of 28 years (18–42 years), while our patients were adolescents and young adults with a mean age of 17.8 years (15–23 years), suggesting that developmental aspects are likely to come into play. For example, several studies have shown an inverted U-shape association with increasing neural activation during ToM activity in adolescence and decreasing activation in adult ages (Dai & Scherf, 2019), particularly in areas such as the mPFC. Other studies have shown that atypical neural activity in clinical patients dynamically shifts with maturation, suggesting either primary disease-related changes with age or a differential speed of development (Morken et al., 2017). With respect to BN, a delay in ToM network maturation in patients with BN, including a delayed maturational decrease of adolescence-associated neural activity, could explain our hyperactive findings and the behavioural ToM deficits described in the literature.

Second, being adults, the patients in the study by McAdams et al. tended to have a longer duration of illness. This may suggest that the prolonged chronic stress of living with the disease, secondary compensatory changes or results of therapy could further modulate (and in this case: downregulate) reactivity in brain networks related to ToM, masking the initial hyperreactivity observed in our adolescent patients with BN. Investigating adolescents and young adults with mostly shorter illness durations avoids this potentially confounding influence. Longitudinal studies tracking the developmental trajectory of BN neural circuits, as well as the influence of the chronification of the disease, are needed to further elucidate these important issues.

A striking finding of this study is that we provide the first transdiagnostic characterisation of brain areas related to social cognition across eating disorder pathologies with marked differences in the patterns of hypo- and hyperactivation in adolescent and young adult patients with AN and BN. The hyperactivation in ToM-networks observed in patients with BN were in contrast to the hypoactivation observed in patients with AN by our group and others (McAdams & Krawczyk, 2013; Schulte-Rüther et al., 2012), or to no differences as found in Leslie et al. (2020). Using the exact same paradigm, we were able to analyse our BN data and previous AN data together in the same statistical model. The overlapping analysis of BN hyperactivation and AN hypoactivation (Figure 3 and supp Figures 5 and 6) and the direct comparison of brain activations in patients with BN versus AN, including their respective controls (Figure 3, supp Figures 3 and 4), revealed atypical patterns in patients in very similar regions but in opposite directions. This was found in comparison with both, acutely starved patients with AN as well as with weight recovered patients with AN ruling out a potentially confounding effect of low body weight or acute starvation often criticised in transdiagnostic studies that include patients with AN. Thus, it might be concluded that behavioural deficits in patients with BN with respect to ToM and social cognition are related to fundamentally different neural signatures compared to those found in patients with AN (Bora & Kose, 2016), suggesting dissociable neurobehavioural phenotypes. Patients with BN may tend to use a more active cognitive style for social recognition, which is potentially prone to more effort needed for the task. It remains to be elucidated if this also includes more metacognitions as well as impulsive overreacting and ad hoc jumping to conclusions on a behavioural basis. The identification of such relationships between neurobehavioural phenotypes, clinical symptomatology and difficulties in social cognition and interactions is of utmost importance to advance clinical care and needs to be researched further. Several therapeutic attempts have been made to treat ToM and social cognition deficits in patients with AN and BN, including 'mentalising-based psychotherapy' (Robinson et al., 2014) and 'cognitive remediation and emotion skills training' (CREST; Adamson et al., 2018; Tchanturia et al., 2015). Initial results suggest improvements in patients' abilities to label emotions, reduce social anhedonia and increase motivation to change. Other successful and effective programs, such as the 'Maudsley model of anorexia nervosa treatments in adults' (MANTRA; Schmidt et al., 2015) and 'radically open dialectical behavioural therapy' (RO-DBT; Lynch et al., 2013), also focus on social and emotional problems. Despite such partly encouraging results in improving social interaction abilities in eating disorder patients, the relative effectiveness of these therapeutic approaches in different types of eating disorders (such as BN and AN) and their relationship with cognitive style and neurobehavioural phenotypes should be studied in greater detail. By increasing our understanding of ToM deficits and their underlying neural processes, our study could spur new research to study the implications for clinically relevant behaviour and ultimately help inform the above programmes and clinicians to improve patient therapy in the realm of social interaction difficulties. Ideally, the therapeutic strategy

employed should be optimised for the neurobehavioural phenotype of the disorder (McTeague et al., 2020).

5 | STRENGTHS AND LIMITATIONS

First, our sample size is small, and we might have missed additional findings due to reduced detection power. A small sample size may furthermore be associated with less effects, thus rendering the current findings tentative replication in larger sample Second, due to the paradigm chosen, we could not show any behavioural differences in ToM-performance to be directly associated with underlying neurobiology. The main strengths of this study are the well-established social attribution task that was specifically optimised for fMRI-use regarding instructions, stimuli number and frequency and its identical use on all five patient and control samples, enabling us to directly compare differences in neural signals between these groups transdiagnostically.

6 | CONCLUSION

We aimed to elucidate the neural underpinnings of ToM deficits in adolescents and young adults with BN. Hyperactivation in key frontal and temporal ToM-regions were associated with clinical disease severity markers. Patients with AN showed, as previously demonstrated, hypoactivation in very similar regions, suggesting a markedly different underlying neural functioning. Further research needs to connect our brain findings with their corresponding behavioural consequences and to determine how these associations might differ in patients with BN and AN. If corroborated, our findings could have implications to address these deficits therapeutically in a more differentiated way.

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CONFLICT OF INTEREST DISCLOSURE

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings are available upon request from to the Data-Access Committee of Department of Child and Adolescent Psychiatry, University Hospital Aachen at KJP-Data-Access@ukaachen.de (due to sensitive patient data not publicly available).

ETHICS APPROVAL STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

PATIENT CONSENT STATEMENT

All study participants, and their legal guardians, provided informed written consent prior to study enrolment.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

The authors did not reproduce material from other sources.

CLINICAL TRIAL REGISTRATION

No applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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