**Supplementary Material**

**Common and disorder-specific neurofunctional markers of dysregulated empathic reactivity in major depression and generalized anxiety disorders**

Xu et al.

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**Supplementary methods**

**Participants and experimental protocols**

N = 107 participants were enrolled in the study after providing written informed consent. N = 35 patients with generalized anxiety disorder (GAD) and n = 37 patients with major depressive disorder (MDD) were recruited at the Sichuan Provincial People’s Hospital and The Fourth People’s Hospital of Chengdu (Chengdu, China). All patients were diagnosed by an experienced psychiatrist according to DSM-IV criteria (Sichuan Provincial People’s Hospital) or ICD-10 (Fourth People’s Hospital of Chengdu). Diagnosis according to DSM-IV was confirmed by an experienced psychologist by means of the Mini International Neuropsychiatric Interview (M.I.N.I.) for DSM-IV [1]. All patients were unmedicated and had not previously received a diagnosis of or treatment for a psychiatric disorder. The diagnostic assessments were conducted during initial admission to the hospitals by experienced psychiatrists and suitable patients underwent the fMRI assessments during the period of further diagnostic clarification without receiving any treatment (<5 days after admission). The following exclusion criteria were applied to all participants, including controls: (1) history of or current episode of the following axis I disorders according to DSM criteria: post-traumatic stress disorder, PTSD, feeding and eating disorders, substance use disorders, bipolar disorder, and mania, (2) history of or current clinically relevant medical or neurological disorder, (3) acute (within six weeks before the assessments) or chronic use of medication, (4) acute suicidal tendencies, (5) contraindications for MRI assessments, (6) left handedness, and, (7) excessive motion during MRI assessment (head motion >3mm). All participants were provided written informed consent after detailed explanation of the study procedures and were informed that they could withdraw from study participation at any time without negative consequences. To facilitate valid data acquisition, and reduce the burden for the participants, participants were explicitly asked before each assessment (e.g. MRI scanning, questionnaire assessment) whether their current status (e.g. exhaustion, emotional state) allowed proceeding with the assessments. The study and all procedures had full approval from the local ethics committee and adhered to the latest revision of the Declaration of Helsinki.

**Dimensional assessment of symptom load, childhood trauma exposure and empathy**

Anxiety and depressive symptom load were further dimensionally assessed in all participants using the Penn State Worry Questionnaire (PSWQ) [2] and Beck Depression Inventory II (BDI-II) [3]. To further control for potential confounding effects of different levels of early life stress exposure on brain structure and function (see e.g. review by Teicher et al., 2016) [4], including social cognitive processing [5], and interactions of early life stress with depressive symptom load on brain activation (see e.g. recent study by Yu et al., 2019) [6], the Childhood Trauma Questionnaire (CTQ) [7] was administered. In addition, previous studies consistently indicated that depression enhanced personal distress [8,9] which reflecting the levels of distress and discomfort experience in response to suffering of others, therefore the personal distress subscale of the Interpersonal Reactivity Index (IRI) [10] was additionally administered to examine emotional empathy differences between groups on the dispositional level.

**Experimental paradigm**

A previously validated blocked-design affective and physical pain empathy fMRI paradigm was employed to assess neural pain empathic reactivity [11]. During the paradigm participants are visually presented with physical (e.g. cutting a finger with a scissor) and affective (painful facial expressions) pain stimuli as well as corresponding control stimuli (physical control, e.g. cutting papers with a scissor; affective control, neutral facial expression) [12]. The stimuli have been validated in previous studies and demonstrated to robustly engage the pain empathic networks, including the insular and cingulate cortex [11,13,14]. Facial stimuli presented facial expressions from Chinese subjects and were balanced for gender of the faces [13].In total the paradigm included 64 pictures divided into 16 blocks with each containing 4 blocks displaying 4 stimuli from the same category per block. Stimuli were presented for 3s each and the average jittered inter-block interval was 10s (8-12s). Participants were asked to passively view the stimuli to further account for potential cognitive differences between the groups and reduce the burden for the participants. Although the decision to employ a passive viewing paradigm may allow better control of potential confounding effects of cognitive impairments during the acute symptomatic stage the use of a passive viewing paradigm also comes at the cost of limited control over the visual engagement of the participants and potential between group differences in this respect.

**MRI data acquisition**

MRI data were collected on a 3.0 Tesla GE MR750 system (General Electric Medical System, Milwaukee, WI, USA). Functional time series were acquired within a single run using T2\*-weighted echo planar imaging (sequence parameters, TR = 2000ms, TE = 30ms, flip angle = 90°, acquisition matrix = 64 × 64, thickness = 3.4mm, FOV = 240 × 240 mm, gap = 0.6mm, slices = 39).High-resolution whole-brain T1-weighted images were additionally obtained to exclude subjects with apparent brain pathologies and to improve normalization of the functional time series (sequence parameters, TR = 6ms, TE = minimum, flip angle = 9°, acquisition matrix = 256 × 256, thickness = 1mm, FOV = 256 × 256mm, slices = 156). ﻿

**MRI data processing**

MRI data was processed and analyzed using SPM12 (Wellcome Trust Center for Neuroimaging, University College London, London, United Kingdom). To allow magnet-steady images the first 6 functional volumes were discarded. Preprocessing for the remaining functional images included slice timing, realigning to correct for head motion, normalization into Montreal Neurological Institute (MNI) employing a two-step procedure implementing the segmentation of the T1 images and application of the resulting transformation parameters to the functional time series resampled at 3mm3 voxel size and spatial smoothing using an 8mm full-width at half-maximum (FWHM) Gaussian kernel. A two-level random effects general linear model (GLM) analysis was employed to the fMRI data for statistical analyses [15].

For the blood-oxygen-level-dependent (BOLD) analysis of brain activation the first level design matrix included separate regressors for the four experimental conditions were modelled using a box-car function (‘affective pain’, ‘affective control’, ‘physical pain’, ‘physical control’) that were convolved with the canonical hemodynamic response function (HRF). To further control motion-related artifacts the six head-motion parameters were included in the design matrix. The inter-block interval served as implicit baseline. The main interaction contrast of interest [(affective pain > affective control) > (physical pain > physical control)] and empathy-specific contrasts [affective pain > affective control]; [physical pain > physical control] were subjected to second level group-level analysis. Between-group differences in pain empathic neural reactivity were determined using a voxel-wise whole-brain mixed ANOVA in SPM with the contrast [(affective pain > affective control) > (physical pain > physical control)] and group as between-subject factor (corrected for multiple comparison using FWE cluster-level correction and p <.05, initial cluster forming threshold p <.001, as recommended by Woo et al., 2014 [16] and Slotnik, 2017 [17]).

 SM on the contribution of both,To further determine alterations on the network level, a generalized form of context-dependent psychophysiological interaction analysis (gPPI) [18] was conducted to determine group differences in task-dependent functional connectivity. In comparison to standard PPI approaches the generalized approach allows to model more than two conditions in the same design matrix thus allowing to model the entire experimental space and in turn leading to improved specificity to true-negative findings while increasing sensitivity to true-positive findings [18]. For the functional connectivity analysis the seed region was determined based on the results from the BOLD level analysis using an independently defined mask for the right dorsal anterior insula (from Uddin, 2014, details see also paragraph on **Neural pain empathic functional connectivity** provided below). The mask was employed to extract the signal time series and hemodynamic deconvolution was performed to account for the effects of canonical hemodynamic response function (HRF). In accordance with the BOLD level analysis the first level design matrix for the gPPI analysis included separate regressors for the four experimental conditions (‘affective pain’, ‘affective control’, ‘physical pain’, ‘physical control’)**,** the corresponding psychophysiological interaction terms as well as the six head-motion parameters. In accordance with the BOLD level analysis the main contrast of interest [(affective pain > affective control) > (physical pain > physical control)] was computed and subsequently subjected to the second level analysis.

In addition to this categorical approach employing the diagnostic groups, an additional confirmatory dimensional analysis was employed to examine associations between depressive (BDI-II scores) and GAD (PSWQ scores) symptom load in the entire sample. To this end individual parameter estimates for pain empathic neural reactivity and functional connectivity were extracted from the underlying contrasts. To account for the non-normal distribution of the BDI II scores (﻿Kolmogorov-Smirnov, *p*< 0.05) and the association between BDI-II and PSWQ scores in the entire sample (Spearman’s rho = 0.769, *p*<0.001), and to facilitate determination of symptom-specific associations Permutation Analysis of Linear Models as implemented in the FSL PALM-alpha110 toolbox (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM>, number of permutations = 5,000) [19] were employed that controlled for the other symptom dimension (BDI-II association controlled for PSWQ scores, PSWQ association controlled for BDI-II scores). For reasons of transparency simple associations (BDI-II, Spearman correlation; PSWQ, Pearson correlation) are initially reported.

Between-group differences in the IRI personal distress scale were examined using an ANOVA model as implemented in SPSS 22 including diagnostic category (MDD, GAD, HC) as between-subject factor. To further examine association between IRI personal distress and individual parameter estimates for pain empathic neural reactivity and functional connectivity (extracted parameter estimates) Permutation Analysis of Linear Models were employed.

**Supplementary results**

**Exclusion criteria, initial quality assessments and final sample**

Study exclusion criteria, inspection of data quality and the independent diagnostic interview led to exclusion of n = 17 subjects due to (1) technical issues during fMRI data acquisition (n = 6), excessive head motion (> 3mm, n = 2), MDD and GAD diagnosis not validated by the M.I.N.I. or presence of a co-morbid previous or current disorder in the M.I.N.I. according to the exclusion criteria (PTSD, n = 2, OCD, n = 1 (as primary diagnosis, GAD not confirmed by the M.I.N.I.), substance use disorder, n = 1, bulimia nervosa, n = 1, agoraphobia, n = 1, (as primary diagnosis, MDD diagnosis not confirmed in the M.I.N.I.), acute suicidal tendencies, n = 1, and mania, n = 2). The final sample for all fMRI analyses included n = 30 subjects per group (GAD, MDD, HC, total n = 90) specific details of exclusion according to diagnostic group (MDD, GAD, HC) are additionally provided in **Fig. S1**. All patients in the GAD group received the primary diagnosis GAD, all patients in the MDD group received the primary diagnosis MDD according to DSM criteria across the diagnostic assessments. Given the high prevalence of unipolar depressive and anxiety-associated disorders in GAD or MDD, respectively, a secondary diagnosis in these disorders that was additionally determined by the M.I.N.I. interview was thus not considered as exclusion criterion. N = 16 patients in the GAD (total n = 30) group and n = 14 (total n = 30) patients in the MDD group did not exhibit an additional psychiatric diagnosis. The following secondary diagnoses were determined by the M.I.N.I. interview: social phobia (GAD, n = 3; MDD, n = 3), obsessive compulsive disorder (GAD, n = 2; MDD, n = 2), panic disorder (GAD, n = 4; MDD, n = 1), agoraphobia (GAD, n = 4; MDD, n = 4), MDD (n = 7 in the GAD group), GAD (n = 6 in the MDD group). To further account for co-morbidity the categorical approach (comparing MDD, GAD and HC) was flanked by a dimensional analysis strategy examining associations with MDD and GAD symptom load in the entire sample (pooling the data from MDD, GAD, and HC). All healthy controls were not diagnosed with a psychiatric disorder in the M.I.N.I. interview. Some patients (and one HC) reported being too exhausted to continue with the self-report questionnaire following the MRI assessments. The number of subjects per group therefore varies from 30 to 26 (BDI II, PSWQ), 29-23 (CTQ, IRI) respectively. Importantly, testing differences in the ratio of participants that discontinued the self-reported questionnaires did not reveal significant differences between the patient groups (Chi-square test, all ps> .05, detailed numbers provided in **Table S1**). To examine potential between-group differences in head motion during fMRI assessment mean framewise displacement (FD) according to Power et al., 2012 [20] was calculated. A univariate ANOVA with group as between subject factor (GAD, MDD, HC) and did not reveal significant mean FD differences between the groups (F2,87 = 1.35, *p* = 0.26).

**Demographic data and dimensional symptom load**

Participants in GAD, MDD, and HC group were of comparable age (*p*=0.26), gender distribution (x2 = 0.09), and education level (*p*=0.48).Univariate ANOVA for depressive symptom load revealed a significant main effect of group (BDI-II, *F2,82* =73.62, *p*< 0.001, *η2p= 0.64*) with post-hoc analyses indicating that depressive symptom load was higher in both, GAD and MDD patients compared to HC, and in MDD compared to GAD patients (*p* values, GAD vs HC <.001, MDD vs HC <.001, GAD vs MDD <.001). Examining GAD symptom load revealed a significant main effect of group (PSWQ, *F2,82* = 51.79, *p*<0.001, *η2p= 0.56*)with GAD symptom load being significantly higher in both patient groups relative to HC, but not significantly different between the two patient groups (*p* value, GAD vs HC <.001, MDD vs HC <.001, GAD vs MDD = 0.12, details see **Table S1**).

**fMRI results**

**Neural pain empathic reactivity (BOLD level analysis)**

The voxel-wise whole-brain ANOVA revealed a significant interaction effect of diagnostic group (cluster-level, *K* = 119, FWE-*p* = 0.023, **Fig.3a**) in a cluster predominantly located in the right dorsal anterior insula (peak located at MNI coordinates *x/y/z*: 42/18/-3, specifically the right dorsal AI subregion, localized according to Uddin, 2014) [21] spreading into the adjacent right ventrolateral prefrontal cortex (inferior frontal gyrus, peak located at MNI *x/y/z*:57/18/3). To disentangle the group and empathy specific alterations parameter estimates from the cluster were extracted and subjected to post-hoc analyses examining empathy-specific(affective pain >affective control; physical pain >physical control) differences between the groups which revealed significantly exaggerated reactivity of this region in the MDD patients compared to HC (parameter estimates, MDD = 0.267, HC = -0.129, *p* = 0.002) in response to affective pain stimuli but attenuated reactivity towards physical painful stimuli (parameter estimates, MDD = 0.037, HC = 0.431, *p* = 0.013), whereas GAD patients exhibited no differences compared to HC (all ps>0.08), and MDD (all ps> 0.58).

**Neural pain empathic functional connectivity**

To explore alterations on the level of functional connectivity in the MDD patients a PPI analysis was performed using an independently defined mask for the right dorsal anterior insula (from Uddin, 2014, rdAI mask, visual inspection of the maps and overlay revealed a high overlap with the identified activation cluster from the BOLD level analysis) as seed region and a concordant contrast of interest as for the BOLD level analysis [(affective pain > affective control) > (physical pain > physical control)]. The corresponding voxel-wise whole-brain ANOVA comparing MDD patients with controls revealed a initial uncorrected significant interaction effect in the right amygdala (*k* = 11, *x/y/z*: 21/6/-30, *p*uncorr<.001). Based on previous studies reporting that right hemispheric lesions of the amygdala and insula lead to impaired emotional empathy [22] and impaired emotional relevance detection during emotional face processing [23] as well as a previous study demonstrating the functional relevance of the anterior insula-right amygdala pathway for enhanced emotional empathy following oxytocin administration [24] further analysis focused on this pathway using a small volume correction (svc) employing an atlas based probabilistic mask for the entire right amygdala (svc p <.05, FWE peak level correction) [25]. Given the functional heterogeneity of the amygdala significant voxels within the amygdala were subsequently mapped on the amygdala sub-regional level by employing a probabilistic mapping approach based on cytoarchitectonic maps of the amygdala subregions [25]. To increase the spatial specificity and localization within the amygdala a peak level correction approach was employed (svc p <.05, FWE peak level correction). Results revealed significant connectivity between right dorsal anterior insula and right basolateral amygdala (*k* = 5, *x/y/z*: 24/3/-30, FWE-*psvc*< 0.05, cytoarchitectonically mapped onto the basolateral subregion according to ANATOMY toolbox) [25]. Additional control analyses (concordant voxel-wise ANOVA in SPM) revealed no significant differences for the contrast of interest in the GAD patients as compared to HC.

**Exploratory analysis: examination of empathy-specific neural pain empathic reactivity**

Separate examination of empathy-specific group differences using separate whole-brain voxel-wise ANOVAs with the empathy specific contrasts [physical pain >physical control] and [affective pain > affective control]revealed a significant main effect of group located in the bilateral dorsomedial prefrontal cortex (dmPFC, peak located at *x/y/z*: 3/24/54, *k* = 95, cluster level FWE-*p* = 0.05) under the contrast [physical pain > physical control]. Post hoc comparisons by means of subjecting extracted parameter estimates from this cluster to an SPSS ANOVA with the between subject factor group (MDD/GAD/HC) revealed that both MDD and GAD patients exhibited decreased neural pain dmPFC empathic reactivity compared to HC (MDD vs HC, *p*<0.001, GAD vs HC, *p*<0.001), suggesting a common neural alteration in response to physical pain in MDD and GAD patients. In contrast, no significant group differences for affective pain observation were observed ([affective pain >affective control]).

**Dimensional analyses: associations between dorsal anterior insula activation and connectivity with symptom load**

Results from the simple correlation analyses revealed that both depressive and GAD symptom load were positively associated with pain empathic neural reactivity in the right dorsal anterior insula (BDI, df = 83, Spearman’s rho = 0.397,*p*<0.001; PSWQ, df = 83, Pearson r = 0.442, *p*<0.001) and negatively associated with the connectivity between this region and the right basolateral amygdala (BDI, df = 83, Spearman’s rho = -0.28, *p* = 0.009; PSWQ, df = 83, Pearson r = -0.276, *p* = 0.011). After controlling PSWQ, the association between depressive symptom load and both, activation indices (df = 83, r = 0.198, *p* = 0.021) and connectivity indices remained significant (df = 83, r = -0.188, *p* = 0.034). In contrast, associations between the PSWQ and both neural indices failed to reach significance after controlling for BDI scores (df = 83, activation r = 0.139, *p* = 0.075; connectivity, r = -0.038, *p* = 0.354).

**Interpersonal reactivity index - personal distress**

A univariate ANOVA with the between-subject factor diagnostic group (MDD, GAD, HC) revealed a main effect of group (*F2,77 = 17.14*, *p*<0.001) with post-hoc tests indicating that MDD patients reported elevated personal distress as compared to both HC, (MDD = 10.54, HC = 5.72, *p*<0.001) and GAD patients (GAD = 7.48, *p*=0.003), whereas GAD patients and controls reported comparable personal distress (*p*>0.1). Examining associations between personal distress and neural indices revealed that higher personal distress was positively associated with insula pain empathic reactivity (r = 0.26; p = 0.012) and negatively associated with insula-amygdala connectivity (r = -0.21; p = 0.029).

**Further analyses and results**

**Exploratory analysis of altered dmPFC connectivity during physical pain empathy**

Given that both, GAD and MDD patients exhibited decreased neural pain empathic reactivity in the dmPFC compared to HC during physical pain observation network level alterations of this region were explored. To this end a first level gPPI model that employed the dmPFC as seed region (the significant cluster from the BOLD level between-group comparison) was performed. In line with the BOLD level analysis [physical pain >physical control] was considered as contrast of interest and subjected to a second level ANOVA including group as factor (GAD, MDD, HC). Results from this analysis revealed no significant between group differences in dmPFC functional connectivity.

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**Supplementary table and figure**

**Fig. S1** Flow diagram showing the reasons for exclusion separately for the diagnostic groups in accordance with the study exclusion criteria

**Table S1** Demographics, symptom load, early life stress and personal distress

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | HC(N=30) | GAD(N=30) | MDD(N=30) |  |  |  |  |
| Male | N = 11 | N = 14 | N = 6 |  |  |  |  |
|  | Mean(SEM) | Mean(SEM) | Mean(SEM) | *F* | GAD vs HC | MDD vs HC | GAD vs MDD |
| Age (years) | 27.07 (1.76) | 30.70 (1.46) | 28.30 (1.50) | *F2,87=*1.37 | >.3 | >.3 | >.3 |
| Education (years) | 14.10 (0.61) | 14.32 (0.64) | 13.23 (0.75) | *F2,87=*0.74 | >.9 | >.9 | >.8 |
| PSWQ | 39.53 (1.73)(N=30) | 58.08 (1.86)(N=26) | 63.45 (1.76)(N=29) | *F2,82=*51.79\*\* | <.001\*\* | <.001\*\* | =.12 |
| BDI-II |  5.67 (1.57)(N=30) | 23.15 (1.69)(N=26) | 32.38 (1.60)(N=29) | *F2,82=*73.62\*\* | <.001\*\* | <.001\*\* | <.001\*\* |
| CTQIRI –personal distress | 43.35 (2.08)(N=29)5.72 (0.58)(N=29) | 50.30 (2.33)(N=23)7.48 (0.65)(N=23) | 53.82 (2.11)(N=28)10.54 (0.59)(N=28) | *F2,77=*6.48\*\**F2,77=*17.14\*\* | =.086=.15 | =.002\*\*<.001\*\* | =.80=.003\*\* |

PSWQ = Penn State Worry Questionnaire; BDI-II = Beck depression Inventory II; CTQ = Childhood Trauma Questionnaire; IRI = Interpersonal Reactivity Index; Given that some participants did not completed all questionnaires (details see also: Exclusion criteria, initial quality assessments and final sample) the number of subjects that indicated the respective analysis is reported for each measure.\*\**p*<.005