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Common and Disorder-Specific Neurofunctional Markers of Dysregulated Empathic Reactivity in Major Depression and Generalized Anxiety Disorder

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Anxiety disorders and depression are highly prevalent, debilitating, and commonly comorbid mental disorders. Epidemiological, symptomatic, and pathogenetic perspectives suggest a particularly strong relationship between generalized anxiety disorder (GAD) and major depressive disorder (MDD), leading to a continuous debate about their nosological and neurobiological uniqueness [1]. Traditional case control studies in either MDD or GAD patients suggest shared dysregulations in emotional and cognitive domains and underlying amygdala-frontal circuits [1, 2], while initial studies have reported disorder-specific dysregulations in the insular and ventrolateral prefrontal cortex (vlPFC) [3]. During recent years, dysregulations in social processes, such as emotional empathy, have gained increasing attention as transdiagnostic etiological and diagnostic factors for internalizing disorders, including both depression and anxiety [4]. Expression of emotional empathy is dependent on the integrity of the anterior insula (AI) and adjacent ventral frontal regions, but while initial evidence suggests that empathic experience is impaired in MDD [5], common and distinct neural alterations in this domain between MDD and GAD and whether these vary between physical and affective pain observation have not been examined.

To this end, the present neuroimaging study examined neural empathic reactivity and everyday empathic experience in unmedicated, treatment-naïve first-episode GAD ($n = 35$) and MDD ($n = 37$) patients and healthy controls (HC, $n = 35$) by means of a validated blocked-design emotional (pain) empathy fMRI paradigm [6] employing visually presented physical and affective pain stimuli, as well as corresponding control stimuli (Fig. 1a). To account for potential cognitive alterations during the symptomatic state, participants were asked to passively view the stimuli. Following initial quality assessments, 30 sociodemographically matched individuals per group entered the final analysis (online suppl. Fig. S1 and Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000504180). Categorical diagnostics were conducted during hospital admission and independently confirmed by a standardized clinical interview according to DSM IV criteria. In addition, GAD and MDD symptom load was dimensionally assessed using validated self-report scales (Penn State Worry Questionnaire, PSWQ; Beck Depression Inventory II, BDI-II), indicating that depressive symptom load was higher in MDD compared to both, GAD patients and HC, while GAD symptom load was higher in both patient groups relative to HC (all $ps_{Bonferroni\text{-}corrected} < 0.001$) but comparable between patient groups ($p > 0.1$). MRI data collection, preprocessing, and modeling adhered to evaluated standard protocols (online suppl. material). The main interaction contrast of interest ([affective pain > affective control] > [physical pain > physical control]) was subjected to a voxel-wise mixed ANOVA, including group as between-subject factor (FWE-$p_{cluster} = 0.05$, whole-brain). Results of this categorial strategy revealed a significant interaction effect of diagnosis in a cluster predominantly located in the right dorsal anterior insula (rdAI) spreading into the adjacent vlPFC (FWE-$p_{cluster} = 0.023$, $k = 119$). Post hoc analyses demonstrated that compared to HC, MDD patients exhibited exaggerated neural reactivity during affective pain yet attenuated reactivity during physical pain observation in this region, whereas GAD patients did not (Fig. 1b). Based on the contribution of both the insula and right amygdala to emotional empathy [7], functional connectivity alterations between these regions were examined in MDD relative to HC (contrast [affective pain > affective control] > [physical pain > physical control]) which revealed aberrant rdAI-right basolateral amygdala (rBLA) functional communication in MDD (FWE-$p_{svc} < 0.05$, $k = 5$, MNI peak coordinates *x/y/z*: 24/3/−30, Fig. 1c). Post hoc analyses revealed decreased rdAI-rBLA functional connectivity during affective yet increased connectivity during physical pain observation in MDD patients relative to HC. Further exploratory voxel-wise ANOVAs separately examined empathy-specific neural activation differences ([physical pain > physical control]; [affective pain > affective control]) and revealed that both diagnostic groups demonstrated decreased bilateral dorsomedial prefrontal cortex (dmPFC, FWE-$p_{cluster} = 0.05$, $k = 95$, Fig. 1d) reactivity during observation of physical pain. To explore empathic differences in daily life, the personal distress scale from the Interpersonal Reactivity Index was assessed, revealing that MDD patients reported higher discomfort when confronted with suffering of others compared to both, HC and GAD patients (Fig. 1e, online suppl. Table S1).

Finally, a confirmatory dimensional approach was employed to examine associations between MDD and GAD symptom load, and personal distress with rdAI pain empathic reactivity and connec-

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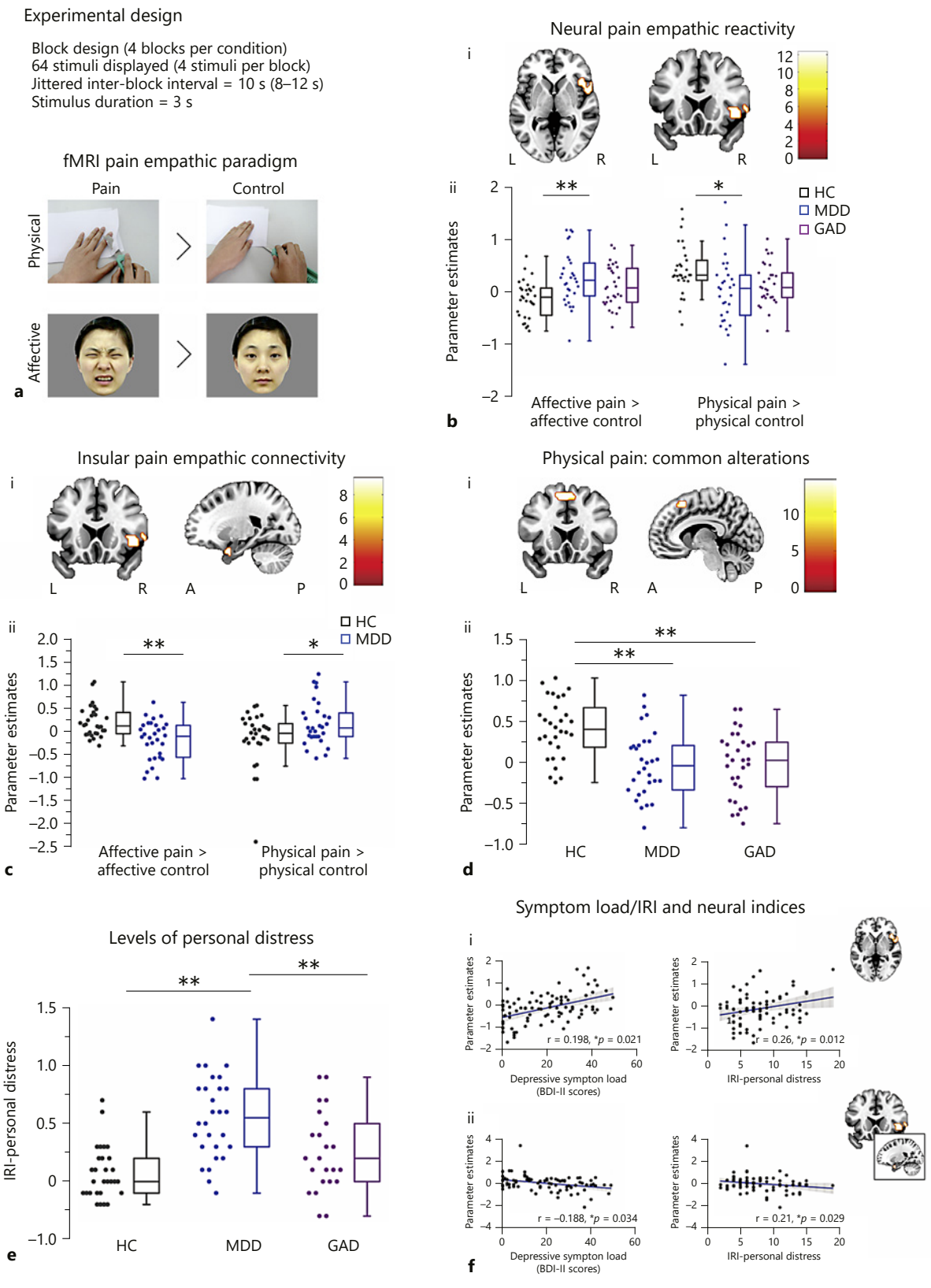

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tivity using extracted neural indices from the entire sample. In accordance with the categorical findings, higher depressive symptom load and personal distress were associated with both rdAI empathic reactivity (BDI-II: $r = 0.19$, $p = 0.021$; IRI-personal distress: $r = 0.26$; $p = 0.012$) and rdAI-rBLA connectivity (BDI-II: $r = -0.188$, $p = 0.034$, IRI-personal distress: $r = -0.21$; $p = 0.029$, Fig. 1f), whereas associations with GAD symptom load failed to reach statistical significance ($p > 0.05$, controlled for MDD symptom load).

In summary, the present findings demonstrate MDD-specific dysregulations in empathic reactivity, emphasizing that MDD and GAD can be differentiated by neurofunctional and everyday dysregulations in this domain, thereby emphasizing the validity of distinct diagnostic and neuropathological entities. The AI is a key hub for interoception-emotion integration and its activation both tracks the level of negative emotional experiences in self and others [8] as well as conveys aversive visceral information to the basolateral amygdala to facilitate avoidance learning [9]. Alterations in this network may therefore indicate dysregulated MDD-specific interoception-emotion integration during empathic processing. Exaggerated rdAI reactivity and elevated personal distress in response to socially transmitted suffering may specifically reflect a failure to disengage from affective suffering of others potentially mirroring the negative affective state experienced during depression. Attenuated rdAI reactivity during physical pain observation may in contrast reflect a decreased capacity for emotionally sharing other's physical pain, possibly associated to increased pain perception thresholds in MDD [10]. Altered rdAI-rBLA communication in this context may reflect biased aversive learning and subsequent adaptation of future behavior. Together these alterations may constitute a risk factor for the development and maintenance of depression. An exploratory empathy-specific analysis further revealed that during observation of physical pain both diagnostic groups exhibited attenuated engagement of the dmPFC – a frontal system involved in the cognitive regulation of negative affect – suggesting that deficient implementation of volitional top-down control may represent a common neurofunctional impairment across both diagnostic entities.

Together with a previous study reporting that altered AI reactivity during a pain empathy task differentiates autism and alexithymia [6], the present findings suggest that neurofunctional markers in this domain may have the potential to segregate symptom-specific dysregulations.

Fig. 1. a Pain empathic neural reactivity was assessed using a validated pain empathy fMRI paradigm. **b** (i) Voxel-wise whole-brain ANOVA using cluster level FWE correction revealed a significant interaction effect in the right dorsal anterior insula (rdAI) spreading into the adjacent ventrolateral prefrontal cortex (vlPFC) (z = −1, y = 18, respectively). (ii) Post hoc analysis indicating that MDD patients exhibited increased affective pain empathic reactivity and decreased physical pain empathic reactivity compared to HC; * $p < 0.05$, ** $p < 0.005$. **c** (i) Voxel-wise region of interest analysis employing FWE correction on the peak level to increase regional specificity revealed a significant interaction effect for rdAI connectivity located in the right basolateral amygdala (rBLA) (y = 18, x = 20, respectively). (ii) Post hoc analysis revealed that MDD patients exhibited decreased functional connectivity during affective pain empathic reactivity and increased connectivity during physical pain empathic reactivity compared to HC; * $p < 0.05$, ** $p < 0.005$. **d** (i) Exploratory empathy-specific ANOVAs revealed a significant interaction effect in the dorsomedial prefrontal cortex (dmPFC) (y = 22, x = -5, respectively), with (ii) post hoc analysis indicating that both, MDD and GAD patients exhibited reduced dmPFC pain empathic reactivity compared to HC; ** $p < 0.005$. **e** Higher personal distress scores in MDD patients compared to both, HC and GAD; ** $p < 0.005$. **f** (i) Associations between rdAI activation and (ii) rdAI-rBLA connectivity with depressive symptom load and IRI personal distress in the entire sample; * $p < 0.05$.

Disclosure Statement

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Author Contributions

X.X. and J.D. contributed equally to this work. X.X., B.B., and K.M.K. designed the experiment. X.X. prepared the study protocols and procedures. X.X., B.Z., C.L., Y.C., F.X., and J.D. performed the clinical assessments and acquired data. X.X., F.Z., X.Z., J.L., and B.B. analyzed the data. X.X., B.B., K.M.K., and R.P.E. interpreted the data and drafted the manuscript. All authors commented on and gave final approval to the final version of the manuscript.

References

1 Maron E, Nutt D. Biological markers of generalized anxiety disorder. Dialogues Clin Neurosci. 2017 Jun;19(2):147–58.
2 Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH. Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of base line activation and neural response data. Am J Psychiatry. 2012 Jul;169(7):693–703.
3 Etkin A, Schatzberg AF. Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in generalized anxiety and major depressive disorders. Am J Psychiatry. 2011 Sep;168(9):968–78.
4 Tone EB, Tully EC. Empathy as a "risky strength": A multilevel examination of empathy and risk for internalizing disorders-CORRIGENDUM. Dev Psychopathol. 2016 Nov;28 4pt2:1567.
5 Schreiter S, Pijnenborg GH, Aan Het Rot M. Empathy in adults with clinical or subclinical depressive symptoms. J Affect Disord. 2013 Aug;150(1):1–16.
6 Li J, Xu L, Zheng X, Fu M, Zhou F, Xu X, et al. Common and Dissociable Contributions of Alexithymia and Autism to Domain-Specific Interoceptive Dysregulations: A Dimensional Neuroimaging Approach. Psychother Psychosom. 2019;88(3):187–9.
7 Leigh R, Oishi K, Hsu J, Lindquist M, Gottesman RF, Jarso S, et al. Acute lesions that impair affective empathy. Brain. 2013 Aug;136(Pt 8):2539–49.
8 Singer T, Critchley HD, Preuschoff K. A common role of insula in feelings, empathy and uncertainty. Trends Cogn Sci. 2009 Aug;13(8):334–40.
9 Uematsu A, Kitamura A, Iwatsuki K, Uneyama H, Tsurugizawa T. Correlation between activation of prelimbic cortex, basolateral amygdala, and agranular insular cortex during aversive taste memory formation. Cereb Cortex. 2015 Sep;25(9):2719–28.
10 Dickens C, McGowan L, Dale S. Impact of depression on experimental pain perception: a systematic review of the literature with meta-analysis. Psychosom Med. 2003 May-Jun;65(3):369–75.