Common and specific large-scale brain changes in major depressive disorder, anxiety disorders, and chronic pain: a transdiagnostic multimodal meta-analysis of structural and functional MRI studies

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INTRODUCTION

Major depressive disorder (MDD), anxiety disorders (ANX), and chronic pain (CP) are closely-related disorders with both high degrees of comorbidity among them and shared risk factors. Considering this multi-level overlap, but also the distinct phenotypes of the disorders, we hypothesized both common and disorder-specific changes of large-scale brain systems, which mediate neural mechanisms and impaired behavioral traits, in MDD, ANX, and CP. To identify such common and disorder-specific brain changes, we conducted a transdiagnostic, multimodal meta-analysis of structural and functional MRI-studies investigating changes of gray matter volume (GMV) and intrinsic functional connectivity (iFC) of large-scale intrinsic brain networks across MDD, ANX, and CP. The study was preregistered at PROSPERO (CRD42019119709). 320 studies comprising 10,931 patients and 11,135 healthy controls were included. Across disorders, common changes focused on GMV-decrease in insular and medial-prefrontal cortices, located mainly within the so-called default-mode and salience networks. Disorder-specific changes comprised hyperconnectivity between default-mode and frontoparietal networks and hypoconnectivity between limbic and salience networks in MDD; limbic network hyperconnectivity and GMV-decrease in insular and medial-temporal cortices in ANX; and hypoconnectivity between salience and default-mode networks and GMV-increase in medial temporal lobes in CP. Common changes suggested a neural correlate for comorbidity and possibly shared neuro-behavioral chronification mechanisms. Disorder-specific changes might underlie distinct phenotypes and possibly additional disorder-specific mechanisms.

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across studies. Particularly, we investigated properties of intrinsic brain networks, namely intrinsic functional connectivity (iFC), measured by correlated infra-slow blood oxygenation fluctuations of resting-state functional MRI-data [18], and regional gray matter volume (GMV), measured by voxel-based morphometry (VBM) of structural MRI-data [19].

Given this brief outline of our approach, we want to clarify two of its critical points, namely why we restricted our approach to MDD, ANX, and CP, and why we focused on intrinsic brain networks, characterized by GMV and iFC, as neural correlates. Concerning disorder selection, first, comorbidity levels among MDD, ANX, and CP are much higher than those with other disorders: for example, comorbidity between CP and MDD or ANX, respectively, is about 50–60% [2–4], and comorbidity of MDD and ANX is also 50–60% [5]. Comorbidity rates with, for example, other psychiatric disorders are considerably lower, such as substance use disorder 10–30% [2, 3, 5] or schizophrenia and bipolar disorder ca. 30% [5, 20, 21]. Second, MDD, ANX, and CP share major risk factors: for example, chronic and/or acute life stress overlap strongly between MDD, ANX, and CP [6, 13]. Third, high comorbidity without a clear chronological sequence of disorders (MDD can precede CP, but also the other way round) as well as shared risk factors suggest one or several shared neuro-behavioral chronication mechanisms across MDD, ANX, and CP; such shared mechanisms might be complemented by additional distinct neuro-behavioral mechanisms reflecting distinct phenotypes of each disorder. Currently, one of the most promising candidates for a shared mechanism is maladaptive chronic ‘threat’ behavior [13, 22–26] (also called ‘defensive behavior’ [22], “avoidant behavior” [13], or ‘negative-valence behavior’ [27]): in brief, low mood, anxiety, and pain all lead to avoidance and (social) withdrawal and therefore protection from (anticipated) threatening situations [13, 14, 16, 28–30]—if these processes become detached from threats, i.e., if they chronify, they can result in maladaptive threat behavior, such as in MDD, ANX, and CP. Other promising candidates for separate [17, 31, 32] or common basic neuro-behavioral mechanisms in MDD, ANX, and CP comprise, among others, aberrant reward [33] or salience [34] processing. Since these suggested mechanisms usually focus on explaining behavioral traits of depression, anxiety, and pain, most of these models—indeed of the exact nature of the underpinning neural mechanism—can be applied best to MDD, ANX, and CP, where these symptoms are more prominent and critical than in other neurological/psychiatric disorders. In this study, we did not directly probe specific behavioral aspects of such supposed neuro-behavioral mechanisms; instead, we focused on common and disorder-specific large-scale neural correlates, which allow to speculate about possible common and disorder-specific neuro-behavioral mechanisms supported by these neural correlates, thereby preparing future studies.

Concerning neural correlates, we focused on intrinsic brain networks, i.e., highly consistent whole-brain patterns of coherent ongoing brain activity, such as the so-called default-mode network [35, 36]. Intrinsic brain networks can be characterized by iFC among constituting regions and by GMV of these regions. We focused on intrinsic networks characterized by iFC and GMV since these neural correlates are large-scale and comparatively stable, both reflecting a “history” of acquired/learned (impairments of) behavior and shaping future behavior [37]; therefore, they might mediate between microscopic mechanistic changes and behavioral functions and are predictive for longer-term behavioral traits such as low mood or anxiety [7]. For this reason, task-based activation data, which reflect rather short-term reactions to external stimuli, were not investigated. Furthermore, other measures characterizing intrinsic networks, like structural connectivity, were not considered to keep pairwise multi-modal overlap analyses simple. Regarding iFC, we restricted our approach to whole-brain seed-to-voxel iFC-data as a kind of “simple” iFC, since more complex iFC-approaches, like graph analysis or dynamic iFC, cannot be integrated easily into meta-analyses of network-iFC.

We tested (i) which changes of regional GMV and network-iFC are common across MDD, ANX, and CP; (ii) which changes are specific (i.e., significantly more pronounced) to one of the three disorders; and (iii) whether and where specific GMV- and iFC-changes overlap [38]. This approach is ‘transdiagnostic’ since it respects current diagnostic categories of MDD, ANX, and CP (while acknowledging their limitations), but also looks for commonalities across these categories [39].

MATERIALS AND METHODS
To test our hypotheses, we employed well-established Multilevel Kernel Density Analysis (MKDA) for coordinate-based meta-analysis of brain imaging-studies (open-source code available at https://github.com/canlab/Canlab_MKDA_MetaAnalysis) [17, 40]. We followed the analytic approach of grouping seed-based iFC-effects according to “seed networks”, which was first introduced by [11] and since then applied by several studies [12, 38, 41]. Since we [38, 41] and others have already described this approach in detail, we only give a brief description of our current approach (details in Supplementary Methods).

Literature search and study selection
The meta-analysis was registered at PROSPERO (registration number: CRD42019119709; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=119709). Studies were searched until January 01, 2020 in PubMed, Web of Science, EMBASE, and reference lists of reviews and eligible articles, using the keywords (rest* OR intrinsic) AND connect* AND seed* AND [disorder name] for the iFC meta-analysis and (“VBM” OR “voxel-based morphometry”) AND [disorder name] for the GMV meta-analysis (disorder-specific details in Table S1). All English-language publications of whole-brain VBM and whole-brain seed-to-voxel iFC comparing patients with MDD, ANX, or CP (with explicit diagnosis of the respective disorder, e.g., using DSM-5) to healthy subjects were selected following MOOSE guidelines for meta-analyses of observational studies (Fig. 1, Table S2) [42]; furthermore, a PRISMA checklist is attached. Briefly, exclusion criteria were (i) methods other than VBM or seed-based iFC; (ii) no whole-brain analysis; (iii) neurological (other than CP) or severe medical comorbidity (psychiatric comorbidity was no exclusion criterion); (iv) no peak-coordinates reported in standard space. In longitudinal or intervention/challenge studies, only baseline results were considered. We made no restrictions concerning age, illness duration, symptom severity, or medication status to ensure maximal study coverage, but we conducted several control analyses later on. For further details about inclusion/exclusion criteria, study quality control, and control variables, see Supplementary Methods.

Data extraction
For the GMV-meta-analysis, peak-coordinates of between-group effects were extracted from included GMV-studies (Tables S3–S5). For the iFC-meta-analysis, we took the following previously-used approach to meta-analytically investigate network-iFC based on whole-brain seed-to-voxel iFC input studies (Tables S6–S8) [11, 38]: first, we extracted the center-coordinates of seed regions-of-interest from included iFC-studies. Second, we assigned each seed—based on its anatomical location—to one out of seven networks from a widely-used parcellation based on iFC-data from 1000 healthy subjects, comprising visual (VIS), primary-sensormotor (PSM), dorsal attention (DAN), salience (SAL), limbic (LIM), frontoparietal (FPN), and default-mode (DMN) networks (Fig. S1) [36, 43, 44]. Since no similar network-parcellation was available for thalamus, studies using only thalamus or hypothalamus seeds were excluded (3 studies in total). Third, peak-coordinates of iFC between-group effects were extracted from included studies and grouped according to the network-assignment of the respective seed, yielding one list of between-group iFC-effects per network.

Meta-analysis
MKDA meta-analysis of both GMV and network-iFC was conducted [11, 40] following our previous work on transdiagnostic multimodal meta-analysis of structural and resting-state fMRI-studies across psychiatric disorders [38]. For iFC, meta-analyses were only conducted for networks with at least
GMV-changes and seed-network-related iFC-changes common to MDD, ANX, and CP were identified via a two-step procedure: (i) Identification of consistent GMV-increase/decrease and iFC-hyper/hypoconnectivity, respectively, separately for MDD, ANX, and CP compared to healthy controls, using MKDA-meta-analysis (p < 0.05 FWER-corrected). (ii) Conjunction analysis to detect common GMV-increase/decrease and iFC-hyper/hypoconnectivity across MDD, ANX, and CP (p < 0.005 FWER) and based on cluster size (extent-based threshold, p < 0.05 FWER) and based on cluster size (extent-based threshold, p < 0.05 FWER) are reported, for these thresholds convey complementary information [11, 38]. We tested for common (i.e., observed in all three disorders) and specific (i.e., more pronounced in one disorder than in the other two disorders) changes in MDD, ANX, and CP.

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Common and specific gray matter volume changes

Specific gray matter volume changes are depicted along the gray oval line; they were calculated by pairwise MKDA meta-analytic contrasts (e.g., MDD > ANX and MDD > CP) and subsequent conjunction across these pairwise result maps (p < 0.00005). Common gray matter volume changes across each disorder and healthy controls (e.g., MDD > HC) and subsequent conjunction across single-disorder results (p < 0.0015). For each contrast, meta-analytic regional result clusters are shown on the left. Their overlap with intrinsic brain networks [36, 43, 44] is displayed on the right: GMV-decrease is shown in the outer ring, GMV-increase in the inner ring of each diagram; color intensity reflects the size of spatial overlap (the more voxels, the stronger the color—a colorscale is added to each plot). ANX anxiety disorder, CP chronic pain, HC healthy controls, MDD major depressive disorder.

GMV-changes

Common GMV-changes. Common GMV-decreases in MDD, ANX, and CP were found in bilateral insula (left > right), dorsomedial PFC (dmPFC), bilateral anterior cingulate cortex (ACC), supplementary motor area, superior temporal gyrus (STG), and lateral PFC. GMV-decreases were mostly located in DMN (57%), SAL (26%), and PSM (15%) (Fig. 2, Table S15). Speciﬁc GMV-decreases were detected in bilateral hypothalamus, thalamus (mediodorsal, ventral lateral, and ventral anterior nuclei [48]), striatum (putamen, ncl. accumbens), and insula (left: whole, right: posterior), right amygdala (mainly centromedial/superﬁcial nuclei [49]), and left hippocampus (anterior and posterior), parahippocampal gyrus, temporal pole, and ventrolateral PFC (vIPFC). GMV-decreases were mainly located in DMN (37%), SAL (19%), LIM (16%), PSM (15%), and VIS (10%) (Fig. 2, Table S15).

CP. Specific GMV-increases were detected for bilateral hippocampus (left: whole, right: posterior), parahippocampal gyrus, and ncl. accumbens, left amygdala (basolateral and centromedial [49]) and putamen, as well as right cerebellar hemisphere. Results were mainly located in LIM (33%) and DMN (31%). Speciﬁc GMV-decreases were found in right anterior insula, mainly located in SAL (66%) and FPN (27%) (Fig. 2, Table S15).

iFC-changes

IFC-meta-analyses were conducted for PSM, SAL, LIM, FPN, and DMN networks, because common GMV-decrease overlapped with these networks (Fig. 2) and at least three studies per disorder were available for them (Table S11) [11, 38].

Common iFC-changes. We detected no signiﬁcant clusters of common hyper- or hypoconnectivity across disorders (Fig. 3, Table S17). As control, pairwise conjunctions showed, exclusively, overlapping LIM-hypoconnectivity in right insula for MDD and ANX and in left medial PFC for ANX and CP (Figs. S10–S11).

Specific iFC-changes. MDD. We identiﬁed speciﬁc hyperconnectivity between DMN and left dlPFC. DMN-hyperconnectivity was located in PSM (70%), SAL (18%), and DMN (12%), indicating DMN-FPN, DMN-SAL, and within-DMN-hyperconnectivity (Fig. 3, Table S19). Speciﬁc hypoconnectivity was observed between DMN and right ventral putamen, amygdala (mostly basolateral, also parts of centromedial [49]), and anterior insula. DMN-hypoconnectivity was mainly located in SAL (53%), FPN (25%), and LIM (15%), indicating LIM-DN, LIM-FPN, and FPN-LIM. A similar pattern was also observed for LIM-SAL, LIM-DN, and LIM-FPN (Fig. 3, Table S19).

ANX. Speciﬁc hyperconnectivity was detected between LIM and right cerebellum, angular/supramarginal gyrus, and occipital cortex. LIM-hyperconnectivity was mainly located in PSM (39%), SAL (26%), LIM (14%), and DMN (10%), indicating LIM-PSM, LIM-SAL, within-LIM, and LIM-DMN-hyperconnectivity (Fig. 3, Table S19).

CP. We found speciﬁc hypoconnectivity between SAL and bilateral dmPFC, ACC, posterior cingulate cortex, precuneus, and
DISCUSSION

Using coordinate-based meta-analysis, we provide first-time evidence for common and specific large-scale brain changes in major depression, anxiety disorders, and chronic pain. Common changes concerned gray matter volume loss in insular and prefrontal cortices of default-mode and salience networks, suggesting a neural correlate for comorbidity and possibly shared chronication mechanisms. Specific gray matter volume and intrinsic functional connectivity changes of each disorder concerned default-mode, salience, limbic and sensorimotor networks; these changes might underlie distinct phenotypes and suggest additional disorder-specific mechanisms.

Common GMV-decrease across major depression, anxiety disorders, and chronic pain

We found common GMV-decreases in insula and dorsomedial prefrontal/anterior cingulate cortices, mostly located within DMN and SAL networks (Fig. 2). Leave-one-out jackknife and post-hoc control analyses showed that results were not significantly influenced by any single study, comorbidity across included disorders, demographic/clinical variables (age, gender, medication), or methodological issues (modulation during VBM, global-signal-regression, non-significant studies).

Our result of common GMV-decrease facilitates new mechanistic and clinical insights. First, our study extends previous single-disorder meta-analyses of GMV-changes in MDD [8], ANX [9], and CP [10]; via conjunction analysis, we showed directly, for the first time to our knowledge, an overlap between disorder-individual GMV-decreases in medial PFC/ACC and insula, which had already been shown individually for the disorders; on the other hand, there was no overlap of GMV-increase.

High comorbidity levels across MDD, ANX, and CP (50–60%) [2–5]) without a clear chronological sequence of disorders (MDD can precede CP, but also the other way round) as well as

Regional overlap between specific GMV-changes and specific iFC-changes

Only for CP, we identified one small overlapping cluster (18 voxels): specific GMV-decrease converged with specific PSM-FPN-hypoconnectivity on right vlPFC (Fig. S12, Table S20).

Control analyses

Jackknife analyses showed no disproportionate influence of any single study on results ($\chi^2$-tests: $p \geq 0.85$ in the GMV-meta-analysis, $p \geq 0.51$ in the iFC-meta-analysis), meaning that the density-statistic of each significant result cluster did not change significantly after iteratively leaving out one study. Results were not significantly influenced by comorbidity across included disorders (GMV: $p \geq 0.60$, iFC: $p \geq 0.28$), age (GMV: $p \geq 0.16$, iFC: $p \geq 0.30$); influence of non-adult studies: GMV: $p \geq 0.85$, iFC: $p \geq 0.84$, gender (GMV: $p \geq 0.52$, iFC: $p \geq 0.53$), or medication (GMV: $p \geq 0.48$, iFC: $p \geq 0.37$), nor by methodological factors like modulation during VBM (global-signal-regression: $p \geq 0.64$) or global-signal-regression during iFC-analysis ($p \geq 0.63$). Moreover, including studies without significant results did not change meta-analysis results (Fig. S13).

Multimodal synopsis: common and specific large-scale brain changes

Results from a network perspective are summarized in Fig. 4, representing a synopsis of results from Figs. 2 and 3, thus providing an overview of which networks were multimodally affected.

F. Brandl et al.
shared risk factors suggest shared neuro-behavioral chronication mechanisms and underlying neural correlates. Common GMV-decrease might represent just such a neural correlate of high comorbidity, possibly reflecting a ‘common core’ of large-scale brain changes across the three disorders. This ‘common core’ might predispose/increase the probability for further disorder-specific changes (possibly underlying distinct disorder phenotypes) in the future, leading to further disorder(s) as comorbidity.

Second, common GMV-decrease in medial PFC/ACC and insula suggests shared neurobehavioral disease-mechanisms across MDD, ANX, and CP. One (but not the exclusive) candidate for such a common mechanism is maladaptive chronic threat behavior [13, 22–26], since medial PFC and insula have been implicated in both the learning/persistence and the control of human threat behavior [46, 50]. Therefore, impairments of medial PFC and insula circuits might play an important role in the chronicification and maintenance of negative moods, anxiety, and pain – presumably via impaired control/downregulation of threat behavior -, leading to MDD, ANX, and CP, respectively. Other possible candidates for common mechanisms comprise aberrant reward processing [33] or aberrant salience processing [34]. For example, a recent review posited that deficits in reward processing and learning, as shared vulnerability factors for MDD, ANX, and CP, underlie negative moods, anxiety, and reduced pain mitigation by external rewards, and are associated with a brain network comprising medial PFC and cingulo-insular cortices [33]. Since we did not directly test for neuro-behavioral mechanisms in our study, our results should mainly be seen as a starting point for future studies specifically testing these hypotheses in MDD, ANX, and CP.

Third, our study extends and contrasts with recent transdiagnostic meta-analyses of a wider range of psychiatric disorders (e.g., comparing MDD and ANX with schizophrenia or bipolar disorder instead of CP) [38, 41, 51]: (i) we also included chronic pain studies—although psychiatric disorders and chronic pain are intimately related, they are often addressed by distinct research communities, which our work tries to integrate; (ii) we restricted disorder selection to MDD, ANX, and CP (excluding, e.g., schizophrenia or bipolar disorder) based on higher comorbidity among themselves than with other disorders, shared risk factors, and possible mechanistic overlaps; (iii) we combined GMV- and iFC-analyses in one framework. We found common GMV-changes across MDD, ANX, and CP in insular, medial-prefrontal, and cingulate cortices. These changes are also present across several other psychiatric disorders, e.g., also in schizophrenia [41, 51], possibly hinting at brain region-pleiotropy, i.e., many-to-many-mappings between brain structure/systems/circuits and behavioral/cognitive functions [52]. For example, functions associated with insula and cingulate cortex are allostasis, interoception, and detection of salient stimuli [34, 53], which are important for threat behavior, but also, for example, for reward processing. Hence, these regions are implicated in various disorders.

No common iFC-changes

In contrast with common GMV-decrease, we identified no common iFC-changes (Fig. 3). Single-disorder meta-analytic iFC-changes (the basis for transdiagnostic tests) were largely well consistent with previous meta-analyses investigating iFC-changes in MDD, ANX, and CP separately [11, 12], confirming the reliability of our approach (Supplementary Discussion). So why were there no common iFC-changes across all three disorders? From a general methodological perspective, firstly, GMV and iFC reflect distinct brain features or clusters of features (i.e., single-region brain structure vs. bi-/multi-regional correlated blood oxygenation), which are not necessarily correlated, particularly since some disorders might be impaired in only one feature but
not in the other. So, if there is no multi-modal overlap of changes, one can only conclude that distinct regions are aberrant regarding different features. Secondly, underlying factors of blood oxygenation-based fIC are heterogeneous: beyond neuronal processes, a couple of hemodynamic, vascular, and mediating control processes (e.g., astrocytes) underpin general neuro-vascular coupling between neuronal activity and blood oxygenation, which underlies BOLD fIC [54]. These factors might distinctively contribute to aberrant fIC for different disorders, networks, or regions, inducing larger heterogeneity for fIC-findings than for GMV-findings, which in turn might prevent common fIC-changes across all three disorders.

Explaining the absence of common fIC-changes concretely with our data, we firstly see that the spatial outline of fIC-changes is distinct across disorders, i.e., across disorders, mostly different networks are affected. This distinct spatial outline is independent of network size or statistical power, since at least for default-mode network (≥14 studies for each disorder) and salience network (≥10 studies per disorder), power was well sufficient. Methodological heterogeneity is also a possible, but unlikely, explanation, since methods of fIC-calculation/preprocessing did not substantially differ across disorders or were controlled for in our control analyses. A possible functional implication of distinct fIC-changes could be that fIC might reflect disorder-specific functional impairments/phenotypes that are associated with given networks. This – albeit speculative - interpretation is supported by the observation of disorder-specific fIC-changes. Secondly, the strength and/or direction of fIC-changes differed across disorders, for example, for the auditory-sensorimotor network, we found hyperconnectivity in MDD, but hypoconnectivity in CP. This is a difficult topic as we do not have a clear interpretation of the quantitative nature of fIC-changes; therefore, we have to abstain from a functional interpretation.

Taken together, the absence of common fIC-changes might derive from a combination of factors, which should be clarified by future studies. Also, the relation between fIC and threat behavior should be tested directly in the future.

Specific GMV- and fIC-changes

In MDD, specific fIC-changes focused on DMN-FPN-hyperconnectivity (regionally located in dIPFC) and LIM-SAL-hypoconnectivity (in insula and ventral striatum) (Figs. 2–4). In ANX, specific changes focused on GMV-decrease in amygdala, hypothalamus, thalamus, striatum, hippocampus, and insula (overlapping with DMN, SAL, LIM, and PSM), and LIM-hyperconnectivity (predominantly with PSM and SAL, results located in parietal and cerebellar cortices). In CP, we found specific GMV-increase in hippocampus, amygdala, cerebellum, and ventral striatum (overlapping mainly with LIM and DMN) as well as GMV-decrease in insula (overlapping mostly with SAL and to a lesser degree with FPN), while specific fIC-changes centered on SAL-DMN-hypoconnectivity (in prefrontal-cingulate cortices) and to a lesser degree also on within-PSM-hypoconnectivity (in posterior insula and putamen).

Although disorder-specific results were largely consistent with previous single-disorder meta-analyses that separately compared MDD, ANX, and CP to healthy controls regarding GMV [8–10] and fIC [11, 12] (for details, see Supplementary Discussion), the direct comparisons between disorders are, to our knowledge, novel. Three observations require further discussion: first, we observed no specific GMV-changes in MDD, although GMV-changes in MDD versus healthy subjects (Figure S2, Supplementary Results and Discussion) were well compatible with previous meta-analyses [8, 55, 56]. The lack of MDD-specific findings appears to derive from the fact that GMV-changes in MDD overlapped strongly with changes in ANX and CP (all vs. healthy controls, respectively), hence no GMV-changes specific to MDD. From a more general perspective, the lack of specificity might derive from heterogeneity of MDD symptoms and their strong overlap with other disorders. Indeed, some meta-analyses detected no or only small converging effects across studies in MDD concerning GMV and also other measures like brain activity related to cognitive and emotional processing [57, 58].

Second, specific GMV-decrease in ANX overlapped with common GMV-decrease across disorders: within our concept of specificity, this means that GMV-decrease in ANX vs. HC overlapped with the other disorders’ changes vs. HC, but was significantly more pronounced. Future studies might further clarify the specificity of this finding, whether it is consistent across the course of ANX, and whether it is related to phenotypic specificity.

Third, we found specific GMV-increase in CP only, and particularly in hippocampus and amygdala, where ANX showed specific GMV-decrease. The functional significance of this difference remains to be investigated; however, recent data and meta-analyses suggest a prominent role of medial-temporal areas, particularly the hippocampus, in CP pathophysiology. For example, medial-temporal volume and pain-related activity are associated with CP intensity [59]. Interestingly, such a medial-temporal GMV-increase might have some potential for being a contrasting marker between CP and other psychiatric disorders; future comparison studies are needed to test its distinctive potential.

Regarding the functional relevance of disorder-specific findings, we can only speculate, since we did not test the functional implications of these findings directly: disorder-specific changes might reflect distinct phenotypes of the disorders, which might be subserved by differential neuro-behavioral mechanisms complementing shared mechanisms. When considering maladaptive threat behavior as a possible shared mechanism, one could think of differentially pronounced impairments of parts of threat behavior [22]: e.g., Pavlovian fear conditioning, associated with, e.g., insular and cingulate cortices [60], which are more affected in ANX, or the cognitive regulation of aversive emotional states, often associated with prefrontal cortices [22, 46], which are more affected in MDD and CP. Future transdiagnostic functional studies are necessary to test these assumptions. Until then, several candidate interpretations and mechanisms remain possible, for example also negative valence [27] or a so-called ‘pain network’ [61, 62], which overlaps with CP-specific changes.

Limitations

First, disorder-specific effects were calculated by directly contrasting single-disorder effects, which were based on comparisons vs. healthy controls. However, the identification of disorder-specific abnormalities is optimized in meta-analyses that draw upon empirical studies that, themselves, directly compared between diagnostic groups. Therefore, future meta-analyses focusing on transdiagnostic studies are needed, although it will currently be difficult to find enough input studies for this question.

Second, the identification of disorder-specific effects might be confounded by high levels of comorbidity across disorders—here, in about one third of the included studies (Table S9) reflecting the high comorbidity levels in MDD, ANX, and CP patients. In control analyses, we found no significant influence of comorbidity on our results. However, confounding effects cannot be ruled out completely, since about 15% of studies did not report comorbidity information (Table S9) and, for example, MDD and ANX may be present in CP patients in only subtle or ‘forme fruste’ fashion and therefore not reported by studies.

Third, in DSM-5 as opposed to previous DSM versions, PTSD is no longer included under ANX due to (among others) etiological
MDD manifests itself in diverse symptoms, and CP encompasses negative results. This issue, which is inherent in most psychiatric diagnostic details on included conditions, see Supplementary Methods). The DMN). Similar iFC-profiles or function) were grouped together under the assumption of neuro-behavioral mechanisms [63]. Nevertheless, we conducted a large phenomenological/symptomatic overlap (for example, observed no clear trends in usage of specific iFC-targets [11, 38]). Future studies should test for the effects of individual studies on the results. In control analyses, we included only very few studies from before 2010. Possible disproportionate influences from these studies were ruled out by jackknife analyses, which tested for the effects of individual studies on the results. The paucity of pre-2010 studies made other post-hoc analyses impossible. Even after 2010, potential changes in usage of noise correction methods might confound results; however, we observed no clear trends in usage of specific methods (Table S21).

Eleventh, life stress as shared risk factor, as well as other unmeasured confounds, might constitute a confounding factor contributing to common brain changes. As it is hard to quantify, it is typically unmeasured; therefore, a control analysis was not possible. Twelfth, meta-analyses for iFC-networks were conducted if at least three studies per disorder were present, based on previous work [11, 38]. A low number of studies might potentially compromise statistical power. However, for networks with significant disorder-specific results, mostly more than 20 studies were present per disorder, ensuring sufficient power [66]. Thirteenth, a wide range of phenotypically distinct anxiety disorders were included within the ANX group. We conducted pairwise post-hoc control analyses (for methodology, see other post-hoc analyses above) comparing results in generalized anxiety disorder, panic disorder, and social anxiety disorder (for power reasons, no other sub-groups could be formed; also, analyses had to be restricted to GMV). No significant difference between sub-groups was found (p ≥ 0.16).

**Conclusion**

We found common reductions of gray matter volume in insula and medial PFC across MDD, ANX, and CP, suggesting a shared neural correlate for comorbidity and possibly neuro-behavioral chronification mechanisms. Disorder-specific changes across distinct brain networks might underlie distinct phenotypes and possibly add additional disorder-specific mechanisms.

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COMPETING INTERESTS
The authors declare no competing interests.

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