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Disrupted dorsal mid-insula activation during interoception across psychiatric disorders

Camilla L Nord, PhD[1], **Rebecca P Lawson, PhD**[2,1], **Tim Dalgleish, PhD**[1,3]

[1]Medical Research Council Cognition and Brain Sciences Unit, University of Cambridge, 15 Chaucer Road, Cambridge, CB2 7EF

[2]Department of Psychology, University of Cambridge, Downing Site, Cambridge, CB2 3EB

[3]Cambridgeshire and Peterborough NHS Foundation Trust

Abstract

Objective—Maintenance of bodily homeostasis relies on interoceptive mechanisms in the brain to predict and regulate bodily state. While many experiments report altered neural activation during interoception in specific psychiatric disorders, it is unclear whether a common neural locus underpins transdiagnostic interoceptive differences.

Methods—We conducted a meta-analysis of neuroimaging studies comparing psychiatric groups against healthy controls to identify brain regions exhibiting convergent 'disrupted activation' during interoception. We searched bibliographic, neuroimaging, and preprint databases through to May 2020. We extracted 306 foci from 33 studies, including 610 controls and 626 patients with schizophrenia, bipolar or unipolar depression, post-traumatic stress disorder, anxiety, eating disorders, and substance use disorders. Data were pooled using a random-effects model implemented by the activation likelihood estimation algorithm. Our pre-registered primary outcome was the neuroanatomical location of the convergence of peak voxel coordinates.

Results—We found convergent 'disrupted activation' specific to the left dorsal mid-insula ($Z=4.47$, $p=0.0000038$; peak: -36, -2, 14; volume: 928mm^3). Studies directly contributing to the cluster included patients with bipolar, anxiety, major depression, anorexia, and schizophrenia, and task probes assessing pain, hunger, and interoceptive attention. A series of conjunction analyses against extant meta-analytic datasets revealed that this mid-insula cluster was anatomically distinct from brain regions involved in affective processing and from regions altered by psychological or pharmacological interventions for affective disorders.

Conclusions—We report a transdiagnostic, domain-general difference in interoceptive processing in the left dorsal mid-insula. Disrupted mid-insular activation may represent a neural marker of psychopathology and a putative target for novel interventions.

Correspondence to: Camilla L Nord.

Please address correspondence to: Dr Camilla Nord, 15 Chaucer Road, Cambridge, CB2 7EF, Camilla.nord@mrc-cbu.cam.ac.uk, Phone: +44(0)1223 767481.

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Introduction

Arguably the most vital function of the nervous system for survival is to detect and regulate the body's internal state to maintain key physiological variables within viable operating ranges. Interoception provides our sense of the physiological condition of the internal milieu (1), and requires the brain to integrate temporally and spatially complex information carried by afferent projections from diverse bodily systems. Mapping the body's internal state often occurs entirely outside of conscious awareness until an urgent bodily need arises—a lack of oxygen, for instance, or a pressing need for food or water (2). Altered interoceptive processes are reported in many neuropsychiatric conditions, including addiction (3, 4), anxiety and depression (5, 6), eating disorders (7–11), panic disorder (12–15), and somatoform disorders (16–18). Theoretical models have proposed that disrupted cortical processing drives such alterations in interoceptive processing, conferring vulnerability to a range of mental health symptoms (2, 19–22).

Homeostatic regulation requires the brain to perform two functions: monitoring (what is my current bodily state with respect to viable physiological operating parameters?) and prediction (how will putative actions change this bodily state?) (20). One class of influential theories posits that prospective control (allostasis) is used to avoid potential departures from homeostatic operating ranges (2, 19, 20, 23, 24). To support prospective regulation of bodily state, a neural circuit involving the anterior insula cortex, anterior cingulate cortex, and orbitofrontal cortex is thought to receive bodily state information from the mid- and posterior insula, and send predictions to the hypothalamus, brainstem, and spinal cord nuclei (19, 20, 23, 25, 26). This circuitry allows arbitration between external environmental information and the state of the internal milieu (physiology, motivational state, and so on) (20, 23, 25–27).

In light of the increasing recognition that dimensions of psychopathology cut across traditional nosological boundaries (28, 29), disruptions in interoception may originate from a transdiagnostic perturbation within this neural circuitry. The anatomical location of this disruption would shed light on the origins of behavioural transdiagnostic disruptions in interoception (30). For example, convergent disrupted signalling in the primary interoceptive cortex – usually attributed to the posterior insula – would indicate a common alteration in bodily state representation across disorders (31). In contrast, altered activity in the anterior insula might indicate a transdiagnostic disruption in abstract representation of affective state (31), perhaps the aspect of interoceptive processing most strongly implicated in psychopathology (32–34). Alternatively, disruptions at the top level of the hierarchy – in anterior prefrontal regions – would support recent theories suggesting aberrant interoceptive meta-cognition (that is, confidence in one's own ability to regulate homeostasis)(19).

To date, the vast majority of individual neuroimaging studies measuring neural correlates of interoception in psychiatric conditions are limited in their ability to identify such

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transdiagnostic mechanisms due to study- and sample-specificity. Neuroimaging meta-analysis is a powerful technique to aggregate data across studies to identify if there exist any common 'loci of disruption' that manifest across psychiatric disorders (35, 36). This approach has particular significance for interoception due to the rationale that diverse interoceptive signals, assayed with a variety of tasks, are nevertheless integrated in common neural regions (31). Establishing if the diverse measures and samples in individual neuroimaging studies converge on a neuroanatomical locus could eventually facilitate development of novel transdiagnostic interventions translated from basic neuroscience.

We therefore examined differential neural activation across a collated transdiagnostic sample of patients and controls during a variety of interoceptive probes, synthesised from multiple neuroimaging studies using neuroimaging meta-analysis. This allowed us to uncover: (1) whether there exists a common interoceptive 'locus of disruption' across psychiatric disorders and across interoceptive domains; and (2) where this locus sits within established interoceptive brain circuitry.

We additionally explored two secondary aims: first, does this 'locus of disruption' overlap with the brain's affect circuitry, a wide-reaching network thought to be critical to psychopathology? Previous work might suggest some overlap: emotional experience is profoundly influenced by bodily state (32), and interoceptive accuracy (assessed by heartbeat detection) is associated with better affect regulation (33) and verbalisation (37). We assessed this by quantitatively contrasting our findings with a large existing database of neuroimaging studies of emotion processing (38).

Second, does this 'locus of disruption' overlap with the neural targets of existing evidence-based psychiatric interventions? We assessed this by contrasting our findings with two previous meta-analyses of the neural effects of psychological (39) and pharmacological (40) interventions in transdiagnostic affective disorder populations. We would expect a conjunction of our meta-analyses' results if an interoceptive processing 'locus' was altered by one of the treatment types.

Methods

We conducted a meta-analysis of neuroimaging studies comparing psychiatric groups against healthy controls to identify brain regions exhibiting convergent 'disrupted activation' during interoception.

Inclusion criteria and search protocol

The meta-analysis protocol was preregistered (Prospero ID: CRD42020176791). Records were identified through bibliographic (PubMed/MEDLINE, PsycINFO, EMBASE), neuroimaging (NeuroSynth, BrainMap Sleuth, brainspell), and preprint databases (PsyArXiv bioRxiv), supplemented by reference tracing. Two raters screened all records. Experiments were eligible if they: (1) included an interoceptive probe during neuroimaging data acquisition (see definition below; interoceptive domains and contrasts in Table S1); (2) included at least two groups differentiated according to a psychiatric criterion (current or past diagnosis, or scores on a psychiatric dimension (clinical groups in Table S1); (3) used

a whole-brain sequence; and (4) reported whole-brain coordinates in a defined stereotaxic space (e.g. Talairach or Montreal Neurological Institute [MNI]). Our initial analysis included adolescents (aged 13 and above), although we confirmed our results in an adult-only sample.

We defined interoception according to previously published criteria: a sensing of the physiological condition or state of the body, including tickle, itch, skin temperature, hunger, thirst, heat, pain, and organ integrity. Following established neuroimaging meta-analysis guidelines (41) we included only one contrast per study. If more than one was reported, we selected the contrast most specific to interoception to minimise the contribution of other neural systems to our results (typically the primary contrast in the study: for example, *interoceptive attention>exteroceptive attention* identifies activation specific to top-down focused interoceptive attention; in contrast, if the authors also reported *interoceptive focus>fixation,* a fixation baseline does not control for attention-related activation (42)). If multiple contrasts were equally relevant to interoception, we used the first contrast reported. See Table S1 for specific contrasts: note that some studies involve assessment of brain activation during top-down interoceptive attention to specific organ systems, while others involve assessment of brain activation during bottom-up perturbation of specific sensory signals such as pain or hunger.

In line with the transdiagnostic motivation behind our analysis, Criterion 2 (clinical group) was intended to capture an inclusive array of mental health problems, and included (for example) patients diagnosed with psychiatric disorders, patients with high levels of a clinically-significant trait (e.g. problem substance use; high anxiety), and recovered or weight-restored patients with anorexia nervosa (see Supplemental Materials 1 and Table S1 for search terms, criteria, and specific diagnoses)

Data (peak voxel coordinates for whole-brain between-group comparisons or group interaction effects during interoception, sample size, demographic characteristics, and contrast information) were extracted from eligible records, and all coordinates double-checked by a second rater for accuracy. We obtained unreported whole-brain data via corresponding authors. All coordinates reported in Talairach space were converted into MNI space (43).

With respect to inclusion/exclusion, 637/642 (99.2%) record abstracts were classed concordantly between the two raters (ICC=0.969, 95%CI = 0.964—0.974, $p<0.001$). Discrepancies were resolved by discussion.

Activation Likelihood Estimation (ALE) Meta-analysis

We implemented the revised ALE algorithm, which compares the convergence of reported coordinates with those expected under random spatial association (44–46). The ALE algorithm treats foci as three-dimensional Gaussian probability distributions centred at the given coordinates and scaled according to the sample size, and performs random-effect inference, testing for above-chance clustering between experiments (44–46). ALE results were thresholded at a cluster-level family-wise-error (FWE)-corrected threshold of $p<0.05$ (cluster-forming threshold at voxel-level $p<0.001$; 1000 threshold permutations).

Conjunction analyses were set at a minimum volume of 50mm^3 (p=0.05, 1000 p-value permutations).

Maps were overlaid onto a standard brain in MNI space (Colin 27, a stereotaxic average of 27 single-subject anatomical scans, skull stripped) using Mango software (http://ric.uthscsa.edu/mango).

Primary analysis

The resulting cluster-corrected ALE map identified transdiagnostic patterns of 'disrupted activation' during interoception for psychiatric participants versus controls (36) (our primary, pre-registered analysis).

Follow-up analyses

We quantitatively compared the cluster-corrected map of 'disrupted activation' in interoception with results from three previous meta-analyses:

(1) We conducted a conjunction and contrast ALE analysis testing convergence between 'disrupted activation' and core affect circuitry (38) from a previous meta-analysis (data obtained through correspondence). This sample (N=3587; 216 studies; 3867 individual foci) consisted of whole-brain neuroimaging tasks of valenced emotion processing (compared to neutral conditions) measured using fMRI or PET. After thresholding the initial ALE map of this meta-analysis data (p<0.05 FWE cluster-corrected; cluster-forming p<0.001; 1000 threshold permutations), we conducted a conjunction/contrast analysis of this map and the interoception 'disrupted activation' corrected map (min. volume: 50mm^3; p=0.05, 1000 p-value permutations). See Supplemental Materials 3 for full description.

(2) We also conducted a conjunction and contrast ALE analysis testing convergence between 'disrupted activation' and regions altered during antidepressant treatment (N=343; 24 studies; 200 foci) (40) and psychological therapy (N=276; 17 studies; 200 foci) (39) for affective disorders (data obtained through correspondence). These studies' samples included patients with an affective disorder diagnosis (depression, anxiety, social phobia/anxiety, post-traumatic stress disorder, obsessive-compulsive disorder, and panic disorder) treated with either selective serotonin or noradrenaline reuptake inhibitors, or psychological therapy (most commonly cognitive behavioural therapy, CBT), with neural activation measured using valence processing tasks (see diagnosis, treatment, and imaging contrast: Table S7; S9). Again, we ran individual meta-analyses on each dataset (p<0.05 FWE cluster-corrected; cluster-forming p<0.001; 1000 threshold permutations) before conducting a conjunction/contrast analysis of this map and the interoception 'disrupted activation' corrected map (min. volume: 50mm^3; p=0.05, 1000 p-value permutations). See Supplemental Materials 4-5 for full description.

Results

Thirty-three eligible records were identified (Figure 1) containing data from 33 separate experiments (306 foci). Approximately 17-20 experimental datasets are needed for ALE to be adequately powered to detect small effects, and ensure results are not driven by single experiments (47).

Our sample included 626 patients and 610 controls (See Supplemental Materials 1 and Table S1). All 33 included experiments used functional magnetic resonance imaging (fMRI). Mean ages ranged from 16.1-43.2 (psychiatric group) and 16.5-43.6 (control group). The majority of experiments included psychiatric participants not currently taking psychotropic medication (25/33; one study did not report medication status), and most screened for past psychiatric disorders in their healthy control group (27/33; six studies did not report diagnostic interviews).

Tasks in the final experiment set either measured top-down assessments of interoceptive attention (including heartbeat counting (K=1) as well as general attentional focus on specific organs (K=4)), or bottom-up perturbations of sensory signals (breathing load (K=10), pain (K=8), affective touch (K=5), and hunger (K=5)). No studies incorporated interoceptive accuracy (or any other interoceptive behavioural measure) into their neuroimaging analyses.

Transdiagnostic disrupted activation

Synthesising across all studies revealed a single cluster of disrupted activation between psychiatric and control participants in the left dorsal mid-insula (Z=4.47, p=0.0000038; peak: -36, -2, 14; volume: 928mm^3) (Figure 2; Table S2). Studies falling within the cluster included patients with unipolar and bipolar depression, anxiety, remitted anorexia, and schizophrenia (among others), including tasks assessing heartbeat detection, hunger, pain, and interoceptive focus. The same cluster was apparent in the sub-sample including only adult participants (Z=4.58, p=0.0000024; volume: 1088mm^3; Table S2). See Table S3 for clusters apparent at the uncorrected threshold (p<0.001), including right dorsal mid-insula clusters.

See Supplemental Materials 2, Table S4, and Table S5 for exploratory analyses split by disorder grouping and hyper- (patients>controls) versus hypo-activation (controls>patients); these analyses are underpowered (41) and included only for completeness. A small number of the included studies (K=4) used tasks involving verbal probes (e.g. the word “STOMACH”), which could have contributed to the laterality of this result (see Supplemental Table S1 for list of studies involving verbal probes).

Comparison of transdiagnostic disrupted activation and affect circuitry

We performed a conjunction analysis to assess whether there was any overlap and/or significant differences in convergence between our results and results obtained from the largest database of affect task-based neuroimaging studies. We extracted whole-brain contrasts across all participants with a neutral affect baseline from this database (see Supplemental Materials 3 for protocol). ALE analysis was performed on 3867 foci originating from 249 experiments.

The conjunction analysis revealed no regions of significant overlap (Figure 3). However, the left dorsal mid-insula (Z=2.75, p=0.003, peak: -20, -18, -20; volume: 872mm^3) and the left entorhinal/perirhinal cortex (Z=3.29, p<0.001, peak: -34, -4, 16; volume: 272mm^3) were preferentially activated in disrupted interoceptive activation, compared to general affect processing. Conversely, a number of regions were preferentially activated during affect processing compared to disrupted interoception (Table S6), most notably a very large cluster in the left hemisphere that included a peak in the left anterior insula (Z=3.29, p<0.001; insula peak= -33.7, 25.7, -7.7; volume: 30064mm^3). This indicates that our identified transdiagnostic neural locus of differential interoceptive processing is distinct from brain regions implicated in affective processing.

Comparison of transdiagnostic disrupted activation with neural changes following evidence-based treatments

We performed a conjunction analysis to assess whether there was any overlap and/or significant differences in convergence between our results and regions modified by antidepressant medication treatment (40) (data from 24 experiments measuring activation during processing of affective material before and after antidepressant treatment; 200 foci; Supplemental Materials 4; Table S7). We found no regions of overlap. However, the cluster in the left dorsal mid-insula (Z=2.33, p=0.010; peak: -42, 2, 10; volume: 408mm^3) was preferentially activated in disrupted interoception compared to neural changes following antidepressant treatment (Figure 4), while changes following antidepressant treatment preferentially converged on the bilateral amygdala (right: Z=1.87, p=0.031; peak: 34, -6, -22; volume: 256mm^3; left: Z=2.23, p=0.013; peak: -22, 2, -22; volume: 256mm^3) and the medial globus pallidus (Z=2.23, p=0.013; peak: -15, -6, -10.5; volume: 408mm^3) (Table S8).

A conjunction analysis comparing our interoception data with regions modified by psychological therapy (39) (data from 17 experiments measuring task-based or resting-state activation before and after psychological therapy in mood and anxiety disorders; 120 foci; see Supplemental Materials 5; Table S9) showed neither significant overlap nor differential convergence between disrupted interoceptive activation and changes following psychological therapy (see Table S10 for uncorrected (p<0.001) results; there was no significant convergence, but at the uncorrected threshold the dorsal mid-insula was preferentially involved in disrupted interoception compared to psychological therapy).

Discussion

Influential theories propose a role for disrupted interoception across multiple psychiatric disorders (3, 19, 20, 48). Identifying common neural disruptions in interoception across traditional diagnostic categories could identify targets for novel transdiagnostic treatments. We used ALE meta-analysis to map the convergence of disrupted neural processing during interoception across psychiatric disorders and a variety of interoceptive probes. This revealed a transdiagnostic, domain-general convergence of disrupted activation in the left dorsal mid-insula. Studies comparing patients with unipolar and bipolar depression, anxiety, anorexia, and schizophrenia to healthy controls all showed differences that fell within this mid-insular cluster. Our follow-up conjunction and contrast analyses demonstrated that

this cluster is spatially distinct from general affect circuitry and regions of neural change following current evidence-based psychological and pharmacological treatments. Altered processing of interoceptive information in the dorsal mid-insula may therefore represent a hitherto unidentified transdiagnostic common locus of disruption (19).

The locus of transdiagnostic differential neural activation we report is located on the precentral gyrus of the mid-insula (49). Non-human primate studies have established that the insula is comprised of three cytoarchitectonic subregions: a ventral-anterior agranular area, a mid-insular dysgranular zone, and a dorsal-posterior granular area (27, 50, 51). Human *in vivo* probabilistic tractography (52) and anatomical tracing studies in macaques (27) have revealed a graduated pattern of connectivity: agranular anterior insula projects to inferior frontal regions, and some anterior temporal areas, while granular posterior insula projects primarily to posterior superior and middle temporal areas (52). In contrast, the mid-insular dysgranular zone possess a hybrid connectivity pattern: the precentral insular gyrus projects to both frontal and temporal regions (27, 52), and its afferent inputs likewise originate from a hybrid of regions projecting to anterior and posterior insula (53). Moreover, while anterior and posterior insula show dense within-subregion connectivity (52), the mid-insula region identified here, in particular the precentral insular gyrus, projects to (27, 52) and receives input from (53) both anterior and posterior insula. This makes the mid-insula well placed to serve as an intermediary between the processing of sensory representation of bodily state in the posterior insula (31) and the abstract representation of affective state in the anterior insula (34), where the latter, as demonstrated empirically in our conjunction analysis, appears to be spatially distinct from our identified region of interoceptive dysfunction) (31, 34, 38).

This functional anatomy of the precentral insular gyrus makes it an ideal candidate for the locus of processing of interoceptive prediction errors, which occur following a mismatch between generative expectations of physiological state and incoming signals from the body (19, 23, 25, 26). Influential theories have suggested that expectations of physiological state are communicated via projections from the ventral-anterior insula and fronto-cingulate regions to the mid- and posterior insula, with the mid- and posterior insula encoding any mismatch between these prior expectations and signals from the body (i.e., interoceptive prediction errors) (19, 23, 25, 26).

The dorsal mid-insula could represent a common ‘locus of disruption’ emerging from other (domain- or pathology-specific) interoceptive changes. Some pathologies might originate from a primary dysfunction in interosensory signalling (e.g., an increased sensitivity to interoceptive stimuli, resulting in a higher weighting of prediction errors (54)) while others might stem from increased precision of prediction models, at the expense of prediction error signals (thought to be encoded by neuromodulators (55) or local GABAergic mechanisms (56)). We speculate that the unique hybrid architecture of the dysgranular dorsal mid-insula makes it a possible anatomical candidate for encoding of interoceptive prediction errors. This hypothesis requires testing in future studies employing tasks that manipulate the expectancy of interoceptive associations and fit learning models to trial-by-trial prediction errors (a paradigm commonly employed in exteroceptive predictive processing studies, for

example (57)). This approach could delineate the putative role of the dysgranular mid-insula in interoceptive predictive processing in in psychiatric populations.

Two aspects of the location of our common cluster are surprising. The first is its laterality: previous literature strongly suggests a right lateralisation of interoception (1). Whilst our uncorrected results do include multiple smaller clusters in the right insula and claustrum, it is possible that this general lateralisation of function is not reflected in right lateralisation of disrupted function, or that low power in the included studies resulted in weaker clustering on the right (see *Limitations*). In addition, it is surprising that our result does not overlap with the very extensive affect network, given the strong overlap of interoceptive-frontotemporal regions subserving interoception and emotion in general (32, 58). We suggest that this originates from our locus occurring lower in the interoceptive hierarchy than might have been expected: the affect circuitry results clearly show a large, highly significant cluster in the anterior, but not mid- or posterior insula.

Limitations and future directions

The locus of disruption we report appears common across several disorders in our analysis: patients with unipolar and bipolar depression, anxiety, anorexia, and schizophrenia all fell within the cluster identified. Nevertheless, there might still exist anatomically distinct processing alterations in discrete disorders or specific transdiagnostic dimensions. The current literature did not contain sufficient data to provide the statistical power necessary for robust disorder-specific sub-analyses. In addition, due to the nature of our meta-analytic approach, it was not possible to conduct meta-regression analyses to examine the influence of sex and age on interoceptive differences in psychiatric disorders (59). This is because ALE tests for convergence of activation between studies, with no incorporation of different effect sizes (e.g., fMRI *Z*-score), a prerequisite for meta-regression (59). The exploration of latent variables that underlie our activation differences is an important avenue for future research. Although we conducted exploratory sub-group analyses of different symptom domains (see Supplemental Material), these sub-group analyses (as well as any future sub-group analyses testing effects of gender or age) will require a larger number of included studies to achieve sufficient statistical power, and so remain a key question for future studies.

In addition, conclusions from the existing literature are limited by the fact that certain interoceptive domains are measured significantly more in some disorders than others: disorder-specific results in the literature might partially be driven by task differences. By aggregating across studies that measure different interoceptive functions (nociception, respiration, cardiac attention, sensory touch, etc.), our meta-analysis is unable to disentangle the contribution of these task differences themselves. We did not have the statistical power to analyse convergent disrupted activation within specific interoceptive domains, despite the strong likelihood that different interoceptive channels are not necessarily integrated (42, 60). Therefore, we were unable to identify how the functional role of the insula (or any other region) in psychiatric disorders might differ across different features of interoception. Therefore, our result represents only a transdiagnostic, cross-domain alteration; in reality, transdiagnostic alterations could be observed within specific interoceptive domains. For

example, in the respiratory domain, animal work has identified acid-sensing ion channels in the basolateral amygdala and bed nucleus of the stria terminalis that drive carbon-dioxide-evoked fear behaviour; genetic variations in the sensitivity of these ion channels in humans relate to susceptibility to carbon dioxide challenge and, potentially, panic attacks (reviewed in (61)).

Future neuroimaging work can better elucidate how interoceptive processing in the mid-insula (and elsewhere in interoceptive brain circuitry) might differ between particular (clusters of) disorders or symptom dimensions, consistent with recent dimensional neuroimaging approaches (62, 63). This would enable future neurocognitive treatment development focussed on interoceptive loci and designed to modulate disrupted interoceptive processing, similar to the application of novel brain stimulation interventions to target particular transdiagnostic neurocognitive mechanisms (64, 65). This potential is further supported by our finding that neither antidepressant medication nor psychological therapy appear to evoke activation changes in this mid-insular region, albeit using mostly non-interoceptive tasks. This highlights the need for treatment studies employing interoceptive probes. However, existing interoceptive measures are limited in many respects: tasks often employ explicit interoceptive manipulations (e.g. (66)), while interoception itself is usually unconscious (67), require invasive perturbation approaches (e.g. (68)); and the timescales of interoceptive signals range vastly between systems (e.g. respiratory versus gastric systems). Sophisticated computational approaches go some way toward parameterising disruptions in interoceptive signalling (19), but still suffer from many of the above limitations, and also usually require extremely lengthy procedures to estimate computational parameters.

Interoceptive processing is multidimensional. A recent consensus definition identified eight aspects of interoception: interoceptive *attention* (observing one's internal bodily sensations), *detection* (reporting the presence or absence of a consciously-reported sensation), *magnitude* (perceived intensity of a sensation), *discrimination* (localising a sensation to a particular interoceptive channel), *accuracy* (how correct one's monitoring of sensations is), *insight* (metacognitive evaluation of one's interoceptive performance – i.e. the correspondence between accuracy and confidence), *sensibility* (a trait measure, the self-assessed tendency to focus on interoceptive stimuli), and self-report (assessed with psychometric questionnaires which can be state or trait assessments). These dimensions share some features in common, but likely have relatively distinct neural mappings (2, 69). All studies in this meta-analysis probed brain activation either using bottom-up perturbations of sensory signals (for example, aversive breathing load, affective touch, hunger, or pain), or by top-down interoceptive attention instructions (e.g., 'focus on your bladder'). No studies incorporated interoceptive accuracy, discrimination, or any another interoceptive behavioural measure into their neuroimaging analyses; future studies will need to establish how the neural representation of specific interoceptive dimensions differs in psychiatric disorders.

Additionally, our meta-analysis limited its clinical sampling to psychiatric disorders and related symptoms. The statistical constraints of our meta-analysis approach, which require group differences studies in order to construct a map of convergent 'different activation' between groups (41, 45) required us to exclude the large number of studies on interoception

in healthy individuals alone, which has been formative in the field's mechanistic understanding of interoceptive processes (reviewed in (42)). We also did not include, for example, pain disorders (70, 71), functional gastrointestinal disorders (72), functional neurological disorders (16), or connective tissue conditions (73), though, unsurprisingly, interoception also differs across these and other conditions involving a markedly different bodily experience. As such, our analysis cannot adjudicate whether differential activation in the mid-insula represents a common locus for *all* disorders where interoceptive differences are implicated, or whether it is specific to the mental health conditions we examined here. That said, in chronic pain disorders, pain-related mental health indices predict quality of life over and above physical pain variables (74, 75) suggesting (76) that the role of interoceptive disruption in disorders not classically considered psychiatric may not be as distinct from the present data as one might assume. Nevertheless, the degree to which this role is distinct or overlaps with the role of disrupted interoception in psychiatric disorders remains to be uncovered.

Lastly, but crucially, many studies included in this meta-analysis, as in the wider neuroscience field (77, 78), are underpowered to detect all but relatively large effect sizes. This increases the likelihood that at least some of the coordinates included in our meta-analysis represent false positives. The cluster-level thresholding we employ helps to mitigate the potential contribution of false positives: a simulation of 120,000 ALE meta-analyses shows this technique can control for excessive contribution of single experiments as long as 17 or more experiments are included (47). However, small sample sizes in contributing studies also means true effects could be excluded or under-represented in our meta-analysis due to lack of power in the original studies (i.e., false negatives). This can only be remedied by multiple large-scale neuroimaging studies characterising interoception in patient groups in future.

Conclusion

Empirical work and theoretical models have proposed a core disruption in interoceptive neural processing across psychiatric disorders. Most previous neuroimaging work consists of studies in discrete diagnostic groups using a single interoceptive probe and is thus poorly suited to identifying common loci of disruption. Here we report a transdiagnostic, domain-general locus of disruption in the dorsal mid-insula. We propose, in the interoceptive predictive coding framework, that mid-insular convergence could reflect a disruption in interoceptive prediction error signalling that represents a common pathway of interoceptive dysfunction across disorders with quite distinct pathologies. Other computational frameworks have identified similar regions in the neural computation of punishment or loss magnitude (79), a process also implicated in many neuropsychiatric disorders (e.g. (80–84)). The particular convergence of activation differences we identify in the dorsal mid-insula projects to both frontal and temporal regions, making it a putative intermediary between posterior insula representation of bodily state and anterior insula representation of affective state (31, 32). This common pathway almost certainly represents only part of the neural changes underpinning disrupted interoception in psychiatric disorders. A fuller understanding of the complex psychopathology- and domain-specific changes in interoceptive processing will require robust, well-powered assessments of

multiple interoceptive domains psychiatric dimensions, and ideally incorporation of these measures into trials of current and novel treatment approaches.

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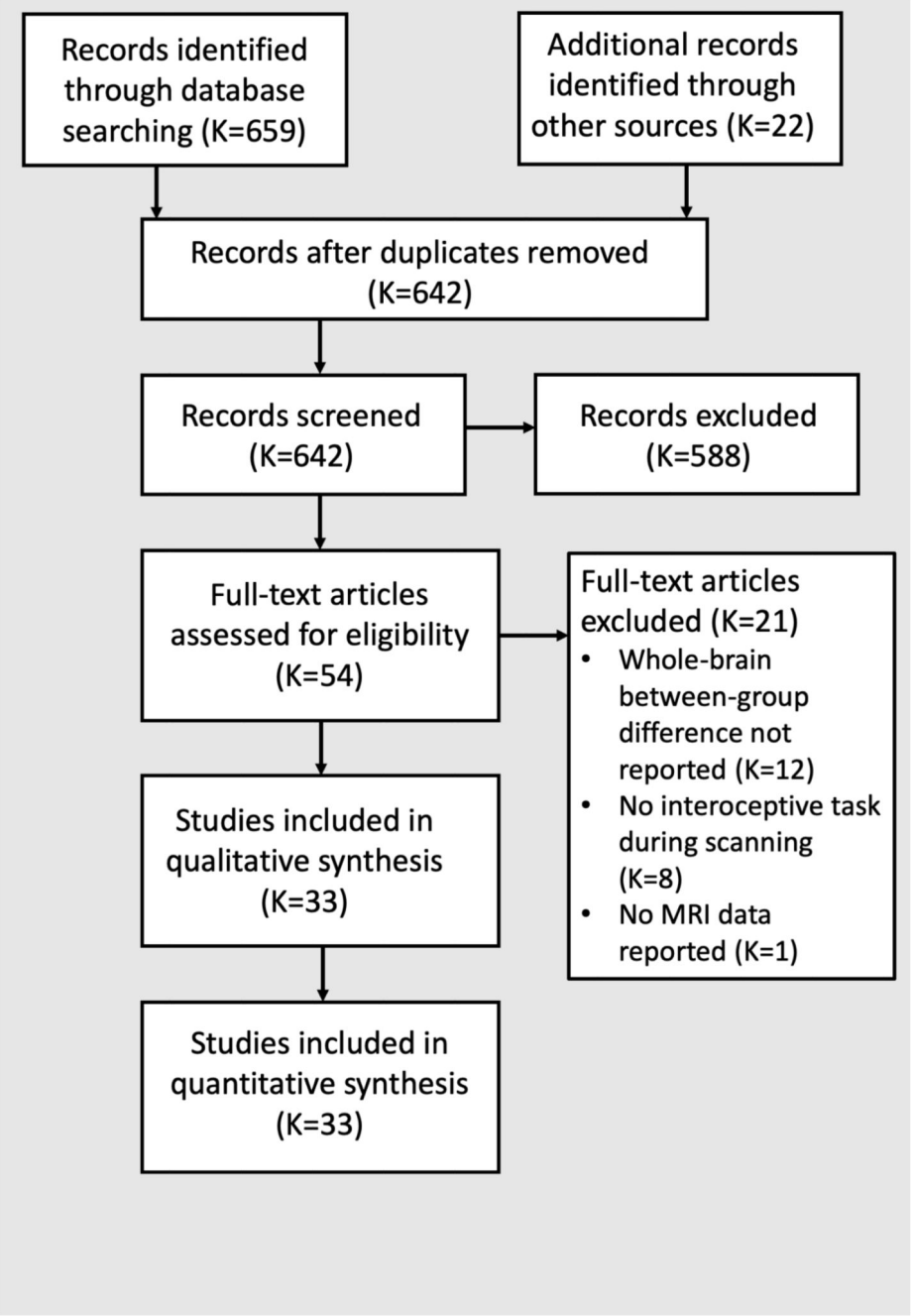

Figure 1. Flow diagram of study selection.

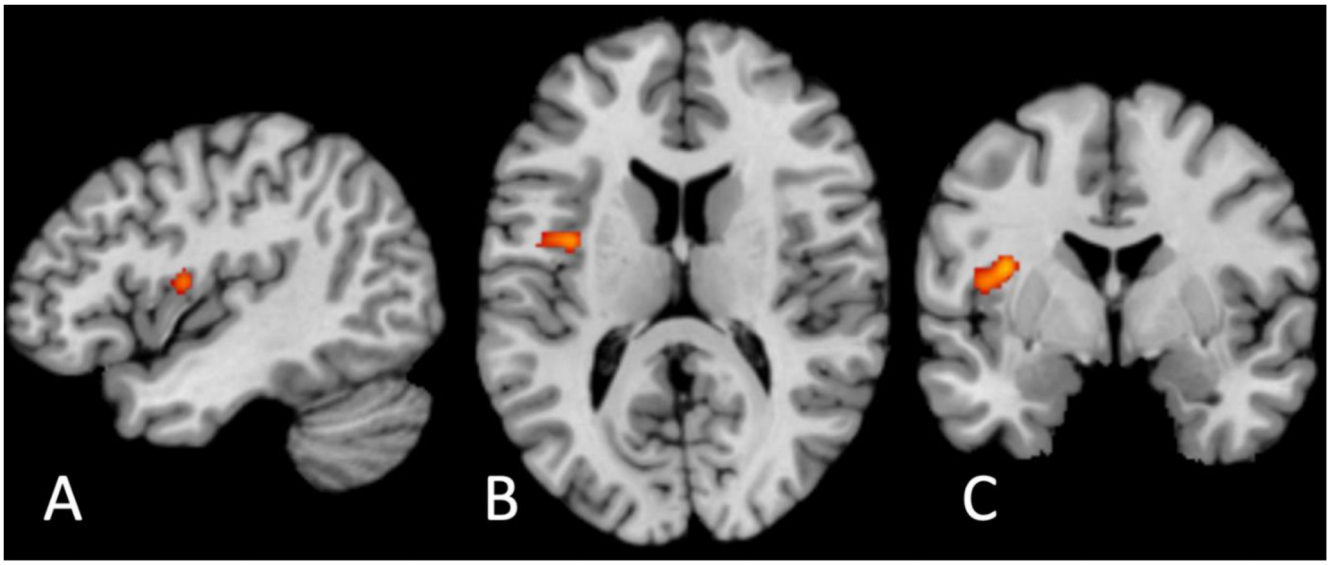

Figure 2. Transdiagnostic disrupted activation between psychiatric and control participants during interoceptive processing derived from ALE meta-analysis (k=33).

A single significant cluster was found (p<0.05 FWE-corrected; cluster-forming threshold p<0.001; 1000 threshold permutations) in the left dorsal mid-insula (Z=4.47, p=0.0000038; peak: -36, -2, 14; volume: 928mm^3) viewed in sagittal (A), axial (B), and coronal (C) sections.

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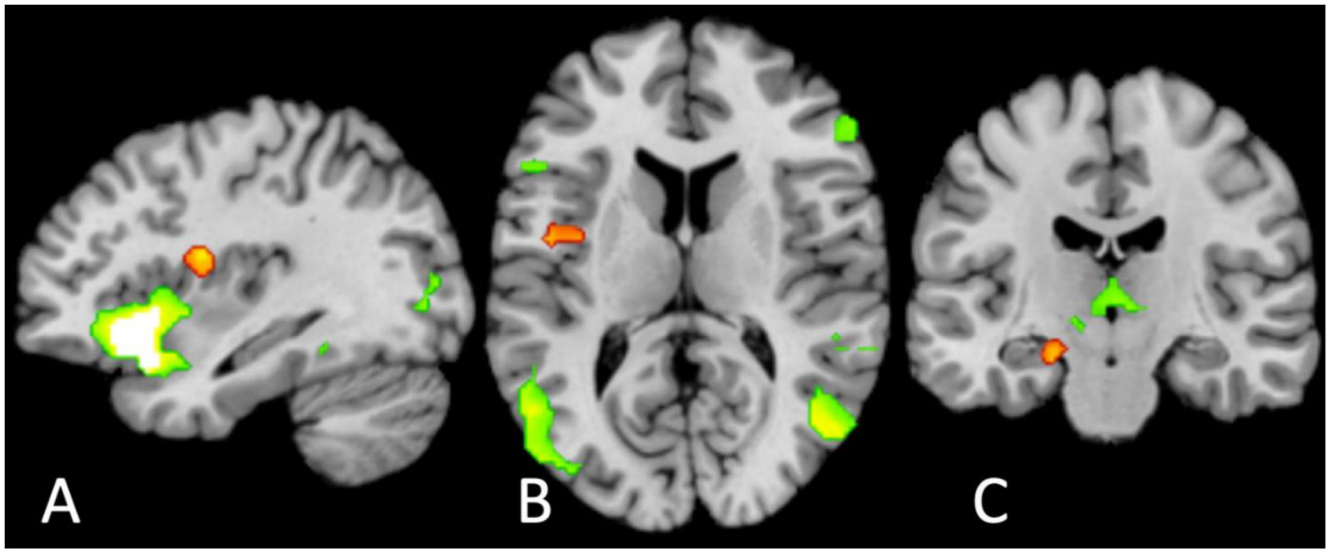

Figure 3. Conjunction analyses indicating significant differences in convergence between disrupted transdiagnostic interoceptive activation and general affect circuitry.

Disrupted interoceptive activation differed significantly from general affect circuitry in the left dorsal mid-insula (visible in A and B) (Z=3.29, $p<0.001$; peak: -34, -4, 16; volume: 872mm^3) and the left entorhinal/perirhinal cortex (visible in C) (Z=2.75, $p=0.003$, peak: -20, -18, -20; volume: 272mm^3) (shown in orange). General affect circuitry preferentially activated a large cluster including the left anterior insula (visible in A) and bilateral inferior frontal gyri, occipito-temporal regions (visible in B) and thalamus (visible in C). There were no regions of significant overlap (see Table S5 for full list of regions).

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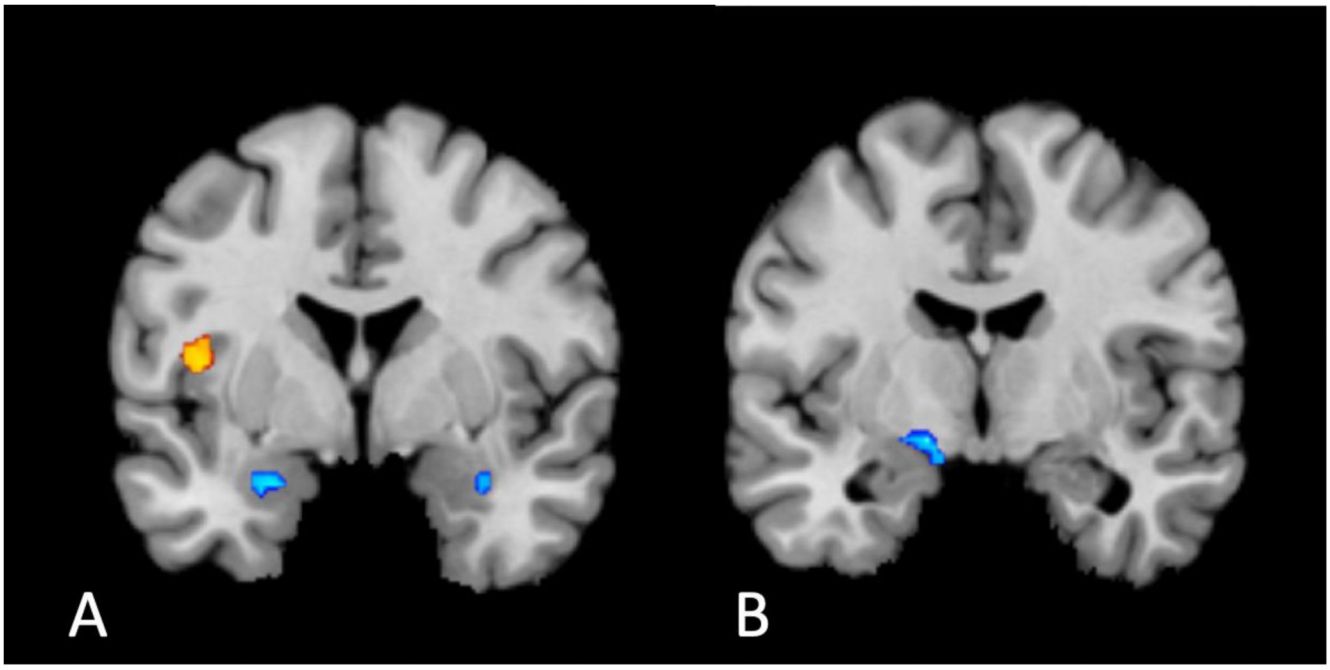

Figure 4. Conjunction analysis revealing significant differences in convergence between disrupted interoceptive activation and regions of neural change following treatment with antidepressant medication.

Disrupted interoceptive activation differed significantly from the neural changes associated with antidepressant medication treatment in the left dorsal mid-insula (orange cluster, visible in A) (Z=2.33, p=0.01; peak: -42, 2, 10; volume: 408mm^3). Changes following antidepressant treatment preferentially converged on clusters in the bilateral amygdala (right: Z=1.87, p=0.031; peak: 34, -6, -22; volume: 256mm^3; left: Z=2.23, p=0.013; peak: -22, 2, -22; volume: 256mm^3) (blue cluster, visible in A) and the medial globus pallidus (Z=2.23, p=0.013; peak: -15, -6, -10.5; volume: 408mm^3) (blue cluster, visible in B). There were no significantly overlapping regions.