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A Systematic Review and Meta-Analysis of Resting-state fMRI in Anxiety Disorders: Need for Data Sharing to Move the Field Forward

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Abstract

Anxiety disorders are among the most prevalent psychiatric disorders. Neuroimaging findings remain uncertain, and resting state functional magnetic resonance (rs-fMRI) connectivity is of particular interest since it is a scalable functional imaging modality. Given heterogeneous past findings for rs-fMRI in anxious individuals, we characterize patterns across anxiety disorders by conducting a systematic review and meta-analysis. Studies were included if they contained at the time of scanning both a healthy group and a patient group. Due to insufficient study numbers, the quantitative meta-analysis only included seed-based studies. We performed an activation likelihood estimation (ALE) analysis that compared patients and healthy volunteers. All analyses were corrected for family-wise error with a cluster-level threshold of $p < .05$. Patients exhibited hypo-connectivity between the amygdala and the medial frontal gyrus, anterior cingulate cortex, and cingulate gyrus. This finding, however, was not robust to potential file-drawer effects. Though limited by strict inclusion criteria, our results highlight the heterogeneous nature of reported findings. This underscores the need for data sharing when attempting to detect reliable patterns of disruption in brain activity across anxiety disorders.

Keywords

neuroimaging; anxiety; meta-analysis; resting-state; fMRI

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Declaration of interest

The authors report that they have no conflict of interest.

1. Introduction

Anxiety disorders, which are highly prevalent (Kessler et al., 2005), are classified into several distinct diagnoses: specific phobia (SPH), generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), separation anxiety disorder, selective mutism, and agoraphobia (American Psychiatric Association, 2022). These disorders share core features but possess other unique characteristics related to fear, anxiety, or avoidance. Most patients present for treatment with comorbidities, particularly among those with anxiety or mood disorders (Brown et al., 2001). This systematic review and meta-analysis compare functional connectivity in healthy people and patients with anxiety disorders.

Anxiety pathophysiology models build on evidence from various studies to implicate multiple brain structures across distinct diagnoses. These structures include the amygdala, nucleus accumbens, bed nucleus of the stria terminalis (BNST), and regions of the prefrontal cortex, as well as the insula and parietal cortex (LeDoux & Pine, 2016). With respect to brain imaging studies, two reports describe findings from a meta-analysis of task-based findings related to an individual anxiety disorder. One of these reports is based on 36 task-fMRI studies in SAD, which revealed hyperactivation in patients in the bilateral amygdala, parietal regions, right insula, ACC, left dlPFC and mPFC, as well as clusters in occipitotemporal regions (Brühl et al., 2014). These regions somewhat overlap with findings from a second report, a meta-analysis limited to specific phobia, which demonstrated a greater response to phobic stimuli in the left amygdala, globus pallidum, right thalamus and left insula (Ipser et al., 2013). Similarly, systematic reviews in PD (Sobanski & Wagner, 2017) and GAD (Goossen et al., 2019) also implicate differences in activation of the regions involved in fear and threat response (for review see: (Penninx et al., 2021)). An alternative method for assessing patterns in brain activity is resting state fMRI (rs-fMRI) in which data are collected while the subject rests, obviating the need for a specific task; studies using rs-fMRI are less prone to researcher-introduced heterogeneity than studies using task-based design.

Resting state fMRI has become a widely used method for investigating clinical biomarkers and novel treatment targets (Cole et al., 2020). However, as with task-based paradigms, inconsistent analysis of rs-fMRI data across studies yields inconsistent findings (Canario et al., 2021). Rs-fMRI has been used to study the functional connectivity between distinct brain regions. Seed-based rs-fMRI represents one established approach, which uses the time series of the voxels within one or more “seeds” or regions-of-interest (ROIs) to examine correlations with all other voxels in the brain. Some such studies use an atlas to extract signals from ROIs defined by prior research; other studies use more complex approaches, such as graph-based statistics (Rubinov & Sporns, 2010). When considering alternatives to functional connectivity, other methods have been developed, which quantify fluctuations in local brain activity during the course of the rs-fMRI scan (Zuo & Xing, 2014). Only recently have researchers sought to combine data across studies using different approaches to data collection or analysis. As a result, no “gold-standard” exists for rs-fMRI measurement and analysis.

In a previous meta-analysis of rs-fMRI, Xu and colleagues (2019) concluded that studies of rs-fMRI in anxiety showed hypo-connectivity within and between various regions. This included the connectivity that the affective network showed with the executive control and default mode networks; connectivity among seeds in the default mode and executive control networks, as well as within the salience network. The current report builds on this past report. Specifically, Xu et al. (2019) included heterogeneous samples that carry unclear implications for research on therapeutics. Some of the included studies did enroll subjects based on the presence of an anxiety disorder diagnosis, but other studies failed to assess the presence of a diagnosis or included subjects based only on the presence of ratings on anxiety scales (Geng et al., 2016; He et al., 2016; Kim et al., 2014). Research on therapeutics typically enrolls subjects based on the presence of an anxiety disorder diagnosis.

In the current meta-analysis, the main goal was to investigate anxiety disorders to maximize the relevance for therapeutics. Accordingly, only studies that compared participants with the diagnosis of an anxiety disorder to controls were included. Moreover, the previous meta-analysis utilized an arbitrary cluster size threshold to indicate statistical significance. This approach leads to excessive false positives, especially when including a limited number of studies (Eickhoff et al., 2016). In the current meta-analysis, we utilized a permutation-based procedure that provides adequate control over the error rate. Finally, we adopted a procedure to investigate the robustness of the ALE findings against publication bias. The aim of the present study is to conduct a systematic review of rs-fMRI in anxiety disorders and perform a coordinate-based meta-analysis of rs-fMRI if enough studies are found. Moreover, since each of the many types of rs-fMRI analysis methods carry inherently different implications (Zang et al., 2015) we aimed to conduct different meta-analysis for each method.

Our desire to use imaging findings to inform the treatment of anxiety disorders led us to limit inclusion to studies of subjects with a clinical diagnosis. As noted, there is evidence of some overlap in neuroimaging findings among anxiety diagnosis, although this overlap appears in distinct meta-analyses using different methods. A secondary aim of this study was to perform one separate meta-analysis by diagnostic category if enough records were retrieved. Additionally, only studies that reported whole-brain family-wise error rate corrected results are to be included, given the considerable risk for spurious findings (Eklund et al., 2016). The inclusion of studies that did not use whole-brain methods would violate the assumption of a coordinate-based meta-analysis (Müller et al., 2018). We expect to find several reports using methodologies that may not be directly comparable and provide the reader a concise review of the methods used in rs-fMRI anxiety research. We expect that the meta-analysis will show connectivity alterations that overlap with regions implicated in fear and threat processing.

2. Methods

2.1. Screening

The methods for this review were registered in PROSPERO (CRD42022310833). PubMed was used for the literature research on the 24th of February of 2022 with the following search strategy: (anxiety OR anxious OR “panic disorder” OR “ generalized anxiety disorder” OR “specific phobia” OR “social anxiety disorder”) AND (rest OR resting OR rs)

AND (fMRI OR MRI OR bold). A total of 1007 records were then exported to a reference library manager (Zotero) We designed our search strategy with the catchall “Anxiety” or “Anxious” terms; however, during the review process we included the search terms “selective mutism”, “agoraphobia” and “separation anxiety”. We performed this new search on March 21st, 2023, resulting in an additional 219 records, totaling 1226 records.

Detailed justification for each analytic choice appears in the preregistration (www.crd.york.ac.uk/prospero/display_record.php?RecordID=310833). Briefly summarized, we sought original research articles that compared resting-state fMRI data between a group of healthy subjects and subjects with an anxiety disorder. Exclusion criteria comprised a) studies including only a subset of data from larger studies included in the meta-analysis (Overlapping sample); b) studies failing to use a structured diagnostic interview; c) treatment and longitudinal studies failing to report findings from pre-treatment, baseline data, d) studies of anxiety in the context of medical conditions (i.e.: anxiety in patients with cancer), and e) studies with fewer than 10 patients (i.e.: case studies or case series targeting subject-specific alterations in the fMRI exam).

Additional exclusion criteria followed from our use of an ALE analysis framework. As also noted in section 2.3, this framework requires input data from studies reporting findings as coordinates in standard space. We therefore excluded studies that failed to report findings as standard-space coordinates for activation differences between patients and controls. Ample additional literature exists on resting-state fMRI in anxiety disorders, which could not be accommodated in the ALE analysis. While such work was not included in our quantitative analysis, we did prepare a systematic review that summarizes this literature. Finally, we recorded the information on data preprocessing, fMRI measure used for comparison, and additional clinical measures such as anxiety rating scales.

Some aspects of our final analysis deviated from procedures outlined in the preregistration. This addressed problems encountered during the initial phases of the analysis. For example, after the initial screening, we also included results from studies reporting regional activity metrics, such as amplitude of low frequency fluctuations (ALFF), fractional ALFF, and regional homogeneity (ReHO). This is because many retrieved papers used these methods, and the reported results were generally compatible with the requirements of an ALE meta-analysis (reported findings with standard brain coordinates).

Any meta-analysis must balance statistical power, which reflects the number of included experiments, and the heterogeneity of the pooled studies. This is especially true in ALE analysis where errant results can be driven by a small number of studies (Eickhoff et al., 2016). Noted experts emphasize the need for neuroimaging meta-analyses to combine studies that appear as homogeneous as possible with respect to the process investigated (Müller et al., 2017). To follow this recommendation, we chose not to combine the coordinates of results from distinct studies using one of the many different rs-fMRI methods with different characteristics and interpretations (for review see: (Zuo & Xing, 2014)). In the systematic review, we restricted our focus to studies that included a control group, given our desire to report alterations in anxiety disorders, and we eliminated studies focused exclusively on machine learning methods. Not only were all machine-learning studies ROI-

based, making them unsuitable for ALE analysis, but they also focused on model predictive accuracy rather than case-control differences in functional connectivity. This makes them less relevant than studies using other methods, such as graph-based analyses. These studies were included in the systematic review since they focus on functional connectivity between patients and controls, even though they are ROI-based and omitted from the ALE analysis. Finally, functional connectivity methods, such as independent component analysis (ICA), were not considered when they failed to reach the experiment-number threshold for a quantitative meta-analysis.

Studies were included in the review if they contained both a patient group with a primary diagnosis of an anxiety disorder and a healthy comparison (HC) group with no psychiatric diagnoses at the time of assessment. From the total number of studies retrieved (n = 1226), 13 were excluded for being written in a language other than English, 4 were excluded for being book chapters or videos, and 1 was excluded for being marked as retracted. The remaining 1208 studies were screened; of these, 74 studies were excluded because they did not use resting state fMRI, 37 were excluded because they were reviews, and 27 were animal studies. 931 studies were excluded because they did not include a primary diagnosis of an anxiety disorder such as generalized anxiety disorder (GAD), social anxiety disorder (SAD), separation anxiety disorder, panic disorder, agoraphobia, selective mutism, and/or specific phobia. For example, studies were excluded if they only included healthy participants, if they only used self-report measures of anxiety from a general population, or if the focus was on a major medical diagnosis other than anxiety or on another psychiatric diagnosis, such as major depressive disorder. Of the remaining studies that included a primary diagnosis of an anxiety disorder, 33 were excluded because they did not compare anxiety patients to healthy controls (HC).

Studies were eligible for inclusion if they possessed an intervention; however, we did exclude five such studies because they only reported post-treatment data but lacked data from a pre-intervention baseline. We also excluded five additional studies that did not include correction for multiple testing in their analyses. Other reasons for exclusion included reliance exclusively on machine learning (n = 4), enrolling fewer than 10 patients (n = 3), as well as incomplete data (n = 2) for studies with ongoing data collection (Barendse et al., 2019; Seok et al., 2020) and failure to report baseline case-control differences (n=1) from a study in a longitudinal cohort (van Tol et al., 2021).

For the quantitative meta-analysis, studies were excluded if they did not report their findings in a standard coordinate space (n = 7). Studies were also excluded if they did not conduct a whole-brain analysis (n = 27), such as occurs when using a small volume correction and when examining ROI-to-ROI or seed-to-ROI connectivity. Additionally, some of the analytic approaches appeared in insufficient number to reach the proposed threshold of 17 experiments for a modality specific analysis and therefore excluded from the meta-analysis. These include granger causality analysis (n = 3), independent component analysis (n = 5), or interhemispheric connectivity (n = 2). These studies were still included in the systematic review section of this work.

After excluding studies for the above criteria, a total of 42 suitable studies were identified, including 30 using seed-based methods. The number of non-seed-based studies (n = 12) was deemed insufficient to allow for quantitative meta-analysis; thus, the meta-analysis was limited to the 30 studies using a seed-based method (see Figure 1 for PRISMA (Page et al., 2021) diagram).

2.2. Data extraction and coding

Once the studies were selected, their reported findings were organized into structured text files. These included any peak voxel coordinates reported as significant and that were corrected for multiple comparisons. Any coordinates that were not already reported using the Montreal Neurological Institute (MNI) space, such as those using the Talairach space, were converted to MNI using GingerALE (Lancaster et al., 2007). Also included in the text files is the number of subjects in the smallest study group, as recommended in ALE documentation.

2.3. Activation likelihood estimation

GingerALE software v 3.0.2 (https://brainmap.org/ale/) was used to conduct coordinate-based meta-analysis of resting-state fMRI activation (Eickhoff et al., 2009). Activation likelihood estimation (ALE) analysis treats each coordinate activation reported in studies as the peak of a spatial probability distribution. ALE analysis requires the reporting of coordinate, not allowing for the inclusion of negative findings. This means that the coordinate is used as a best point estimate, while accommodating for spatial uncertainty inherent to the imaging acquisition and processing. For every study included, the coordinate information is used to build a map. Each peak coordinate is smoothed into neighboring voxels by means of a Gaussian kernel. The size of the kernel is dependent on the sample size of the smallest group in a given study. The kernel size increases with decreasing sample sizes, thus reflecting the precision of the estimate by accounting for higher spatial uncertainty and less statistical power. Coordinate-based meta-analysis is dependent on the assumption that all voxels have the same chance of being activated. Therefore, included studies should use the same coverage, i.e., use of regions of interest would violate this assumption (Müller et al., 2018). Studies that do not provide adequate thresholding for whole-brain analysis were therefore excluded. ALE maps are obtained by computing the union of activation probabilities across experiments for each voxel. Convergence of foci is distinguished from random clustering of foci by testing against the null hypothesis of random spatial association between experiments. Cluster-level family-wise error correction was used to account for whole-brain comparisons. Cluster-level family-wise correction involves the use of an uncorrected p-value threshold and employing a cluster-extent threshold that controls for the chance of observing a cluster of that size if foci were distributed at random. The threshold for cluster-forming was set at $p < 0.001$ and the cluster extent threshold was set at $p<0.05$ with 1000 permutations (Eickhoff et al., 2009; Laird et al., 2005). The peak coordinates reported in each study were entered for two contrasts: HC > Anxiety and HC < Anxiety. In order to account for possible “file-drawer effect” we have applied the Fail Safe N (FSN) method, which quantifies the robustness of an ALE analysis by introducing noise studies to the data and repeating the analysis with the same parameters. The minimum number of noise studies to introduce in the analysis can be

defined by estimating the “file drawer” effect in the imaging literature. We have used 30% of the included experiments as the minimum FSN (Acar et al., 2018).

Despite our initial plan of conducting one separate analysis for each diagnostic category, insufficient experiment numbers precluded implementation of a reasonably powered meta-analysis for each diagnostic category. It is recommended that ALE analysis have a minimum of 17 studies. Therefore, the meta-analysis was performed including any anxiety diagnosis, for all seed-based findings. We also performed a secondary meta-analysis of amygdala-seed based studies, although this analysis only includes 14 studies, below the 17-study threshold. As this analysis included fewer studies, we have used $p < 0.05$ for both cluster and extent thresholds. This cluster threshold has been shown to be adequate to control for false positives when at least 17 to 20 studies are included; however the results must be interpreted carefully, as they might be driven by a small number of studies (Eickhoff et al., 2016). Additionally, each cortical and striatal seeds with available coordinates was grouped by network according to a 7 networks parcellation described in (Thomas Yeo et al., 2011) and (Choi et al., 2012). Each seed was classified according to the label of the MNI coordinate provided. If the seed voxel was unlabeled, we identified the closest ROI centroid to that seed, and classified according to that centroid. We did not consider seeds that averaged the signal of multiple ROIs, when the included ROIs were labeled in distinct networks. The most used seeds were from the default mode, salience, and control networks; however, none of these networks included more than 10 studies. Therefore, we did not perform a network-specific ALE analysis (suppl Table 1).

3. Results

Resting-state studies in anxiety disorders employed different methodological approaches. The most common approach was seed-based connectivity analysis, with the amygdala being the most common seed (Table 1 and 2). Other methods found were ReHO, ALFF, ICA, Graph-based measures, and voxel-mirrored homotopic connectivity. These studies are summarized in Table 3. The overall group sizes of the studies are generally small, ranging from 10 to 118 patients. There is little consistency in software used to preprocess and analyze the images, with DPABI (http://rfmri.org/dpabi), DPARSF (http://rfmri.org/DPARSF), FSL (https://fsl.fmrib.ox.ac.uk/fsl), and SPM (https://www.fil.ion.ucl.ac.uk/spm/) being the most common choices. One important methodological choice involves the methods used to control head movement during the scan: most included studies reported how they controlled for movement, usually by regressing out the variance associated with movement, although there were variable thresholds for excluding participants based on movement.

3.1. Coordinate-based meta-analysis

There were too few studies in each diagnostic group to conduct a specific meta-analysis for each anxiety disorder. In the coordinate-based ALE meta-analysis, we included studies reporting significant results using (a) any seed and (b) the amygdala as a seed (for both analyses, studies are described in Table 1).

29 studies were included in the ‘any seed’ analysis, with a cumulative number of 1506 subjects (770 healthy, 736 anxious). 25 studies had significant results that could be included

in the healthy > anxious contrast, with a total of 604 subjects included in the analysis (see Methods: data extraction and coding above), and 18 studies were included in the healthy < anxious contrast, with a total of 410 subjects. The analysis of papers using any seed (a) rendered no significant results for either contrast (healthy > anxious or healthy < anxious).

14 studies were included in the 'amygdala seed' analysis, with a total of 572 subjects (283 healthy, 289 anxious). 10 studies had significant results that could be included in the healthy > anxious contrast, with a total of 184 subjects, and 10 studies were included in the healthy < anxious contrast, with a total of 191 subjects. We found no significant clusters in which patients exhibited hyperconnectivity relative to controls in the amygdala seed-based meta-analysis. However, there was one significant cluster in which anxious individuals exhibited significant hypoconnectivity relative to healthy controls. This cluster (Figure 2) spans the bilateral medial frontal gyrus, the right cingulate gyrus, and the left anterior cingulate cortex (Table 4). However, this analysis was not robust to a potential file-drawer effect with an FSN < 3. Additionally it was driven by findings of 6 foci (out of 36) in 5 studies, 3 in GAD (Du et al., 2021; Makovac et al., 2016; Pace-Schott et al., 2017), one in SAD (Jung et al., 2018) and one transdiagnostic (Hahn et al., 2011) study.

3.2. ALFF and fALFF

The amplitude of low frequency fluctuations (ALFF) is the calculated power of very low frequencies (0.01 to 0.08 Hz) calculated by using a Fourier transform (H. Yang et al., 2007). The power frequencies are then standardized by the subject's mean ALFF value across voxels. Fractional ALFF (fALFF) computes ALFF as a fraction of the observed power in all frequencies (Yu-Feng et al., 2007). In GAD, patients showed lower ALFF in the right postcentral and right precentral gyrus (Shen et al., 2020), with another study showing higher ALFF in the dorsomedial prefrontal cortex (DMPFC), left precuneus/posterior cingulate cortex (PCU/PCC) and bilateral dorsolateral prefrontal cortex (DLPFC) (W. Wang et al., 2016). There is some overlap with regions with lower ALFF in the prefrontal and parietal regions in SAD patients (C. Yuan et al., 2018; Y. Zhang et al., 2015); however, there are not enough studies to conduct a meta-analysis or draw stronger conclusions.

3.3. ReHO

Regional Homogeneity (ReHO) is a method for assessing local functional connectivity between a given region, or "node," and its nearest neighbor by estimating the time consistency of the BOLD signal. In GAD patients, studies have largely identified decreased ReHo in anterior regions including the inferior frontal gyrus (S. Li et al., 2018), the orbital middle temporal gyrus, middle frontal gyrus, and anterior cingulate (Xia et al., 2017). Results in GAD are paralleled by a more limited literature in other anxiety disorders, with findings of decreased ReHO in frontal regions of subjects with SAD (Qiu et al., 2011), whereas PD patients showed an increased ReHO in the precuneus and occipital gyrus (Lai, 2018).

3.4. Other Methods

ICA (or group ICA - GICA) is commonly used to identify patterns of spatiotemporal fluctuations in the fMRI signal in all included individuals in a study. The resulting group

maps are then used in a regression into each subject fMRI data. This results in one regressor for each component identified in the group ICA. Those regressors are then used to model each subject's time series, resulting in subject-specific spatial maps that can be compared across groups (Calhoun et al., 2001; Nickerson et al., 2017). One of the advantages of this approach is that it is data-driven, not depending on a priori seed selection, though there are few studies available in anxiety disorders and most studies find some alteration in anxiety disorders, albeit in different network and regions (Table 3).

Other methods used to analyze rs-fMRI in anxiety disorders are graph measures and interhemispheric connectivity. In short, graph measures aim to estimate how different parts of the brain are connected. Each ROI is currently referred to as a node, and the connections between each ROI are edges. There are a number of graph measures that can be derived to assess connectivity, making the direct comparison between studies difficult. This can lead to conflicting conclusions, such as SAD exhibiting higher or lower connectivity in different studies (X. Yang et al., 2019; Zhu et al., 2017).

Granger Connectivity Analysis (GCA) is a method that attempts to consider the directionality of the connection; hence it is possible to test the connection from a region to another part of the brain. One study using GCA in SAD reports multiple alterations between both the left and right amygdala and several brain regions, including a decrease in the effective connectivity from the frontal cortex and inferior temporal gyrus to the right amygdala (Liao, Qiu, et al., 2010).

Results investigating effective connectivity with rs-fMRI might be influenced by preprocessing steps, such as high-pass filtering, TR (Repetition time) of the acquisition (Smith et al., 2011), and vascular effects on the BOLD signal (Webb et al., 2013), which hinders the interpretation of these findings.

4. Discussion

The meta-analysis revealed no consistent anxiety-related associations when using all seeds. Of note, studies with the amygdala as a seed region did show altered connectivity with the mPFC, including portions of the anterior cingulate cortex, but this finding was not robust against publication bias. The systematic review identified many rs-fMRI methodologies used to investigate anxiety disorders, including ALFF, ReHO, ICA, and graph-based measures. Findings suggest differences exist in the brain connectivity of anxious groups compared to healthy controls in several brain regions and networks. This resembles other findings implicating distributed disturbances rather than regional or network specific findings in anxiety (Linke et al., 2021).

ALE analysis relies on the reported peak activation to test for above chance clustering between experiments (Eickhoff et al., 2009). The findings should be interpreted as probability of an effect in the cluster considering the reported peaks, in a way that generalizes to the population of studies analyzed. However, with a small number of experiments, it is possible that two studies can account for over 80% of the ALE score even with cluster-wise correction (Eickhoff et al., 2016). Additionally, most included studies

have small samples, which can lead to inflated effect sizes and results. This in turn might influence meta-analytic results (Szucs & Ioannidis, 2020). In neuroimaging, this is further complicated by different available pre-processing pipelines, software, and strategies to deal with movement and to account for multiple testing (Botvinik-Nezer et al., 2020). We only included results from analyses that were corrected for multiple statistical tests, since the publication of uncorrected statistical maps is uncommon. The availability of such data would provide more information for meta-analytical work.

The results of the amygdala meta-analysis were based on a small n (only 10 studies in each contrast) with 5 papers contributing to the cluster. This cluster was not significant after introducing 3 noise studies. This indicates that the findings are not robust against file-drawer effects, a fact that is particularly concerning for a seed-based analysis. One could imagine a scenario in which authors selectively report findings from one of many analyzed seeds, focusing selectively on the amygdala and brain regions previously linked to amygdala function (Samartsidis et al., 2020).

The cluster found largely overlaps with previous findings in task-based fMRI showing altered amygdala-PFC connectivity (Gold et al., 2020) and in animal models of anxiety. The results also partially overlap with a cluster between the amygdala and the left vmPFC described in Xu et al. (2019). Interestingly, the amygdala and the PFC do have an anatomical connection (Folloni et al., 2019). While the amygdala is linked by task-based studies to fear acquisition and response, the mPFC is related to fear extinction and recall, specifically through connections to the basolateral amygdala (Phelps et al., 2004; Vouimba & Maroun, 2011). Although the evidence provided in this meta-analysis is limited, when combined with prior evidence, it merits that amygdala-PFC connectivity should be further studied in larger samples.

Beyond identifying a possible circuit to be examined in future, larger studies, the current report provides other valuable insights. The report highlights inconsistent methodology and small sample sizes as pressing problems in brain imaging research, including for data from treatment-seeking patients, where putative effect sizes are expected to be larger than in studies recruiting patients from the community. Existing approaches to coordinate-based meta-analysis do not provide comparable measures of effect size that arise from other types of meta-analysis. In fact the findings of coordinate-based meta-analysis may be useful to inform the analysis plan and preregistration of such studies, helping to avoid selective reporting of ROI-based findings (Gentili et al., 2021).

Despite finding many published studies, our review highlights difficulties scientists face when synthesizing data from these studies through meta-analytical methods. Addressing the need for comparability in brain imaging methods provides one avenue for addressing these difficulties (Nichols et al., 2017). Other avenues involve an increasing focus on open-science initiatives, such as pre-registration, as well as data and code sharing to further increase standardization in ways that would facilitate data synthesis (OPEN SCIENCE COLLABORATION, 2015).

Inconsistent methods across studies targeting the same research question suggest absence of a standard approach to addressing the question. Inconsistent methods in most areas of neuroimaging remain a concern for the field (Poldrack et al., 2017). This reflects unresolved questions about the best way to adjudicate relative advantages and disadvantages of the many approaches. Different analytical methods probe diverse aspects of the data and their many possible relations with disorders. In some instances, lack of methodological consistency across studies reflects imprecision in hypotheses (Botvinik-Nezer et al., 2020; Poldrack et al., 2017). While such diversity of research approaches increases the chances of discovery, it poses challenges for systematic reviews and meta-analyses. Such disparities make it challenging to identify patterns and trends across studies. Consortia might address this problem by implementing mega-analyses (Zugman et al., 2022). With this approach, reanalysis of data from multiple sites is implemented, using consistent methods in one, large analysis. This offers a viable solution to this problem, and it highlights the importance of collaboration among sites worldwide.

The ENIGMA consortium is a leading initiative in the field as it has successfully conducted many studies using these strategies (Thompson et al., 2022). Findings from structural studies might also guide future work with rs-fMRI. For example, the ENIGMA-Anxiety working group utilized a mega-analytic approach, in an attempt to maximize sensitivity to group differences while adopting a relatively conservative statistical approach (Harrewijn et al., 2021; Zugman et al., 2022). Comparable efforts might utilize rs-fMRI and would benefit from integrating in their analysis pipelines methods that show more consistent results in clinical studies. Moreover, ENIGMA has successfully combined data from clinically focused studies with data from large scale studies such as the ABCD study. ABCD (Casey et al., 2018), UK biobank (Alfaro-Almagro et al., 2018), Generation R (Jaddoe et al., 2006), PNC (Satterthwaite et al., 2014), BHRC (Salum et al., 2015), c-VEDA (Sharma et al., 2020) and the NKI-Rockland (Nooner et al., 2012) are all examples of studies that are geared towards collecting neuroimaging data from a large number of research subjects, though there are limitations in these large data studies as well. The phenotypic characterization is usually less detailed compared to studies with small samples and the acquisition methods are still different between cohorts; however, most of those studies make their data available to bona-fide researchers.

While the initial literature search resulted in many studies, only a few were suitable for inclusion in the comparison between patients and controls. Common reasons for exclusion included a study’s failure to employ a whole-brain approach or present results using a coordinated-based tabulation of results, both of which are needed in ALE. It also should be noted that analyses for most methodologies failed to meet a commonly used threshold of 17 studies for an ALE analysis. The presence of these factors also precluded a diagnosis-specific meta-analysis. As opposed to some meta-analysis methods, ALE meta-analysis can only establish possible convergence of findings. The results should be interpreted as regions linked to a diagnostic condition across experiments. As such, we interpret our findings as reflecting a failure to detect convergent results. By adopting a similar approach to the one taken by Harrewijn et. al. (2021) and discussed by (Zugman et al., 2022), it may be possible to overcome this limitation and leverage other data from individual studies investigate rs-fMRI in generalized anxiety disorder (GAD) and other anxiety disorders. This

approach would be particularly well suited for evaluating suggestive findings on amygdala-PFC connectivity identified in our exploratory ALE analysis. With this future approach, the findings from such mega-analyses can then inform clinically focused, smaller studies.

5. Conclusion

In this review, we demonstrate that current evidence reveals altered connectivity between the amygdala and the prefrontal regions in anxious patients. However, this finding might be driven by publication bias. Despite the large number of published articles, summarizing results is difficult due to the diversity of methods employed. Future studies should consider pooling individual participant data and standardizing preprocessing and analytical approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- There are numerous studies investigating rs-fMRI and anxiety; however, the methodologies are inconsistent.
- Anxiety patients show hypoconnectivity between the amygdala and the medial prefrontal cortex.
- This finding is not robust against possible publication bias. Thus, no strong findings manifest in available literature.
- More studies are needed with standardized methods and larger sample sizes.

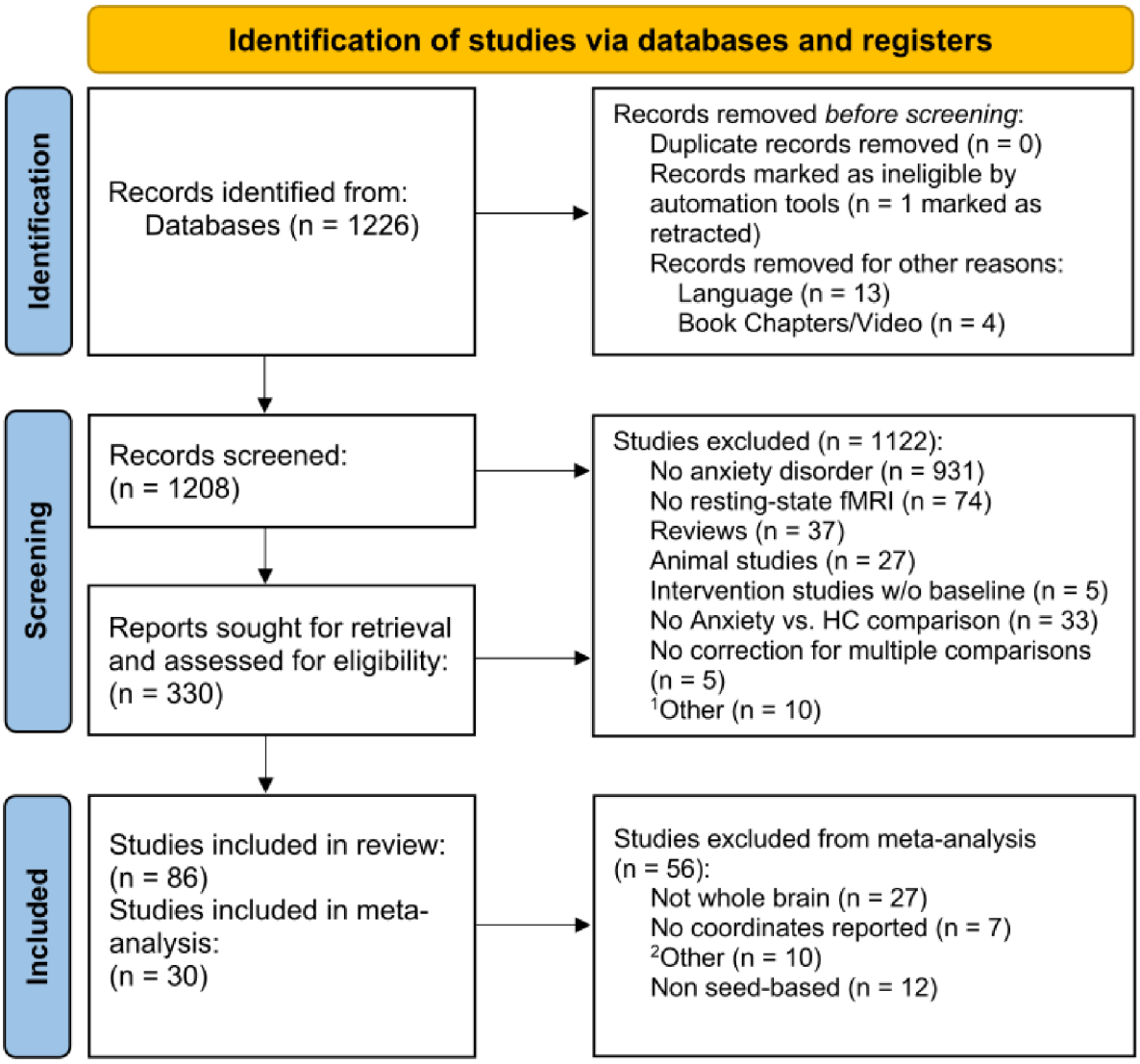

Figure 1:
PRISMA diagram
[1]Longitudinal cohort with no baseline results n=1, prospective/ongoing n=2, case studies n=3, machine learning n=4; [2]granger causality analysis n=3, independent component analysis n=5, interhemispheric connectivity n = 2

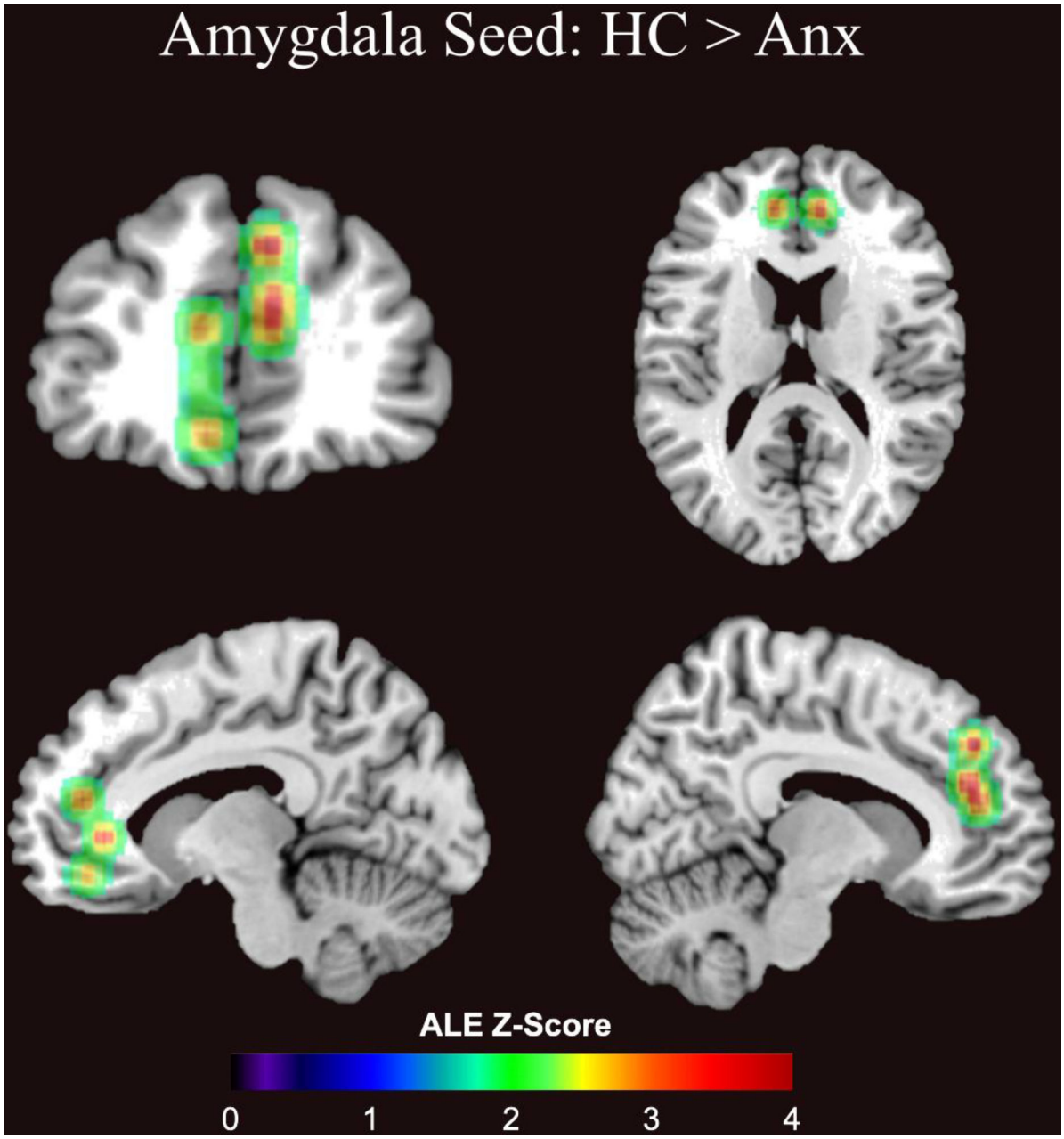

Figure 2:

Amygdala Seed-Based ALE Meta-analysis: healthy > anxious.

Results of amygdala seed-based papers. A single cluster emerged in healthy > anxious contrast. Cluster-corrected at $p < .05$ with 1000 permutations

Table 1 –

Included studies in meta-analysis.

Author/Date	Diag	n(Anx/HC)	Mean age (Anx/HC)	Field	Significance threshold	Findings
Amygdala						
Li et al. (2016)	GAD	22/21	39.9/38.5	3T	3dClustsim(pvox:0.005; clust size: 53)	Anx > HC *; HC > Anx *
Liu et al. (2015)	GAD	26/20	15.5/15.5	3T	Alphasim (pclust: 0.05)	HC > Anx: AMG (dlPFC). Anx > HC: AMG (R Cere, Ins, STG, Put, R AMG)
Makovac et al. (2016)	GAD	19/21	29.5/28.6	1.5T	Cluster corrected (pvox: 0.005; pclust: 0.05)	HC > Anx: AMG (SFG, PHG/ ACC, SMG)
Du et al. (2021)	GAD	38/20	41.1/39.1	3T	Alphasim (pvox:0.005; pclust: 0.05)	HC > Anx: AMG (ACC, IFG, PHG, Cere). Anx > HC: AMG (STG, Ins, PoCG)
Prater et al. (2013)	SAD	20/17	25.9/25.7	3T	AlphaSim(pvox:0.05; pclust: 0.05)	HC > Anx: R AMG (ACC)
Jung et al. (2018)	SAD	36/42	25.4/24.7	3T	FWE < 0.01 *	HC > Anx: L AMG (dlPFC). Anx > HC: L AMG (FG, Ins, SMG, Prec)
Pannekoek et al. (2013b)	SAD	12/12	34.8/34.0	3T	RFT (pvox:0.005; pclust: 0.05)	HC > Anx: R AMG (L MTG, L SMG, L OCC). Anx > HC: BL ACC (L Prec, L OCC)
Anteraper et al. (2014)	SAD	17/17	24.7/25	3T	pvox:0.05; pclust: 0.05 *	Anx > HC *
Pannekoek et al. (2013a)	PD	11/11	34.5/35.0	3T	RFT (pvox:0.005; pclust: 0.05)	HC > Anx *; Anx > HC *
Hamm et al.(2014)	Multi	33/23	13.9/14.6	3T	3dClustSim (pvox 0.001; pclust 0.05)	Anx > HC: R AMG (Ins); HC > Anx: L AMG (vmPFC; PCC)
Roy et al.(2013)	Multi	15/20	14.9/14.8	3T	RFT (pvox:0.005; pclust: 0.05)	HC > Anx: AMG (ACC, brstm, Cere). Anx > HC: AMG (vlPFC, mPFC, brstm, Cere)
Toazza et al.(2016)	Multi	18/19	17.9/16.7	3T	3dClustSim(pvox: 0.001; pclust 0.008)	Anx > HC: L BLA (R PrCG, R CG, Prec, R SFG)
Hahn et al.(2011)	Multi	10/27	28.6/27.7	3T	RFT (pvox:0.001; pclust: 0.05)	HC > Anx: L AMG (L OFC, L PCC/Prec). Anx > HC: R AMG (right OCC/AG)
Pace-Schott et al. (2017)	Multi	12/13	30.2/35	3T	3dClustSim (pvox: 0.001; pclust 0.05)	HC > Anx: L AMG (ACC)
Non-amygdala						
Wang et al. (2016)	GAD	28/28	32.9/33.2	3T	FDR p < 0.05	Anx > HC *; HC > Anx *
Yang et al. (2018)	GAD	34/26	16.9/16.5	3T	Monte Carlo (pvox: 0.001; clust size 48/50)	HC > Anx: R SMG (L FG, ITG, PHG, Prec); R SPG (SMA, MCG, SMG, SPG)
Cui et al. (2020)	GAD	32/30	33.1/31.0	3T	AlphaSim(pvox:0.002; pclust: 0.05)	HC > Anx *
Ma et al. (2019)	GAD	21/20	34.9/35.9	3T	AlphaSim(pvox:0.001; pclust: 0.05)	HC > Anx: PrGC (L STG). Anx > HC: PrGC (R IFG)

Author/Date	Diag	n(Anx/HC)	Mean age (Anx/HC)	Field	Significance threshold	Findings
Ma et al. (2020)	GAD	22/21	34.6/36.2	3T	AlphaSim(pvox:0.001; pclust: 0.05)	Anx > HC: Hab (PMC, R vlPFC, mFC, L OFC). HC > Anx: Hab (L PCC, R Pulv)
Yu et al. (2023)	GAD	20/22	36.3/40.7	3T	RFT (pvox:0.001; pclust: 0.05)	HC > Anx: sgACC (R STG)
Minlan et al. (2017)	SAD	46/64	24.8/23.7	3T	FDR p < 0.05	HC > Anx: Cere (L PFC, L dmPFC, Thala)
Manning et al.(2015)	SAD	53/33	29.9/29.4	3T	FDR p < 0.05	HC > Anx: nACC (vmPFC); vmPFC (dlPFC). Anx > HC: nACC (ACC); vmPFC (ACC)
Liao et al. (2011)	SAD	18/18	22.6/21.8	3T	FDR p < 0.05	Anx > HC: R ITG (L OCC); R PHG (L MTG)
Cui et al.(2017)	SAD	23/20	22/21.6	3T	FDR p < 0.05	HC > Anx *
Zhang et al. (2022)	SAD	46/52	24.6/23.4	3T	RFT (pvox:0.001; pclust: 0.05)	Anx > HC *; HC > Anx *
Geiger et al. (2016)	SAD	18/15	29.5/28.4	3T	FDR p < 0.05 *	Anx > HC: L OFC (L AMG)
Yuan et al. (2018)	SAD	43/43	29/30.1	3T	RFT (pvox:0.005; pclust: 0.05)	HC > Anx: L prec (Cere, R ITG, R PHG, L mPFC)
Hang et al.(2022)	SPH	25/26	23.2/23.7	3T	RFT (pvox:0.01; pclust: 0.05)	HC > Anx: R FG (caudate, right PHG); L mSFG (L Cun)
Lee et al.(2021)	Multi	41/55	15.1/15.3	3T	FDR p<0.05	Anx > HC: DN (PoCG)
Dorfman et al. (2016)	Multi	35/36	13.2/13	3T	3dClustSim(pvox: 0.005; pclust 0.008)	HV > Anx *

Findings are reported by contrast, followed by the seed used and the location of the peak in parenthesis. RFT: random field theory, FDR: false discovery rate, Anx: anxious group, HC: healthy controls, R: right, L: left, AMG: amygdala, PFC: prefrontal cortex, dlPFC: dorsolateral prefrontal cortex, Cere: cerebellum, Ins: insula, STG: superior temporal gyrus, Put: putamen, SFG: superior frontal gyrus, PHG: parahippocampal gyrus, ACC: anterior cingulate cortex, SMG: supramarginal gyrus, OCC: occipital cortex, PoCG: postcentral gyrus, Prec: precuneus, MTG: middle temporal gyrus, vmPFC: ventromedial prefrontal cortex, brstm: brainstem, vlPFC: ventrolateral prefrontal cortex, mPFC: medial prefrontal cortex, PrCG: precentral gyrus, CG: cingulate gyrus, PCC: posterior cingulate cortex, AG: angular gyrus, FG: frontal gyrus, ITG: inferior temporal gyrus, SPG: superior parietal gryrus, MCG: middle cingulate gryrus, SMA: supplementary motor area, PMC: premotor cortex, mFC: medial frontal cortex, Pulv: pulvinar nucleus, Thala: thalamus, OFC: orbitofrontal cortex, nAcc: nucleus accumbens, Cun: cuneus, DN: dentate nucleus, sgACC: subgenual anterior cingulate cortex

*studies with more than 5 reported peaks.

Table 2:

Seed-based studies not included in meta-analysis.

Author(year)	Diag	n (Anx/HV)	Field	Analysis	Seeds	Reason excluded
Dong et al.(2019)	GAD	35/36	3T	Seed-based; GCA	BL AMG	GCA
Xu et al.(2021)	GAD	31/33	3T	Seed-based; ICC	R_MPFC, R put, L_DLPFC, AMG	Not whole-brain
Porta-Casteràs et al. (2020)	GAD	28/56	1.5T	Seed-based	BL BLA	Not whole-brain
Cha et al. (2014)	GAD	32/25	3T	Seed-based	vmPFC, AMG	Not whole-brain
Yuan et al. (2016)	SAD	15/19	3T	Seed-based	BL AMG	Not whole-brain
Yoon et al. (2016)	SAD	20/20	3T	Seed-based	AMG	Not whole-brain
Liao et al. (2010)	SAD	22/21	3T	Seed-based; GCA	BL AMG	GCA
Pang et al. (2021)	PD	19/18	3T	Seed-based; GCA	BL BNST	GCA
Shin et al. (2013)	PD	11/11	3T	Seed-based	paACC	No coordinates reported
Torrisi et al.(2019)	Multi	30/30	7T	Seed-based	BL BNST, BL CeA	Not whole-brain
Etkin et al.(2009)	Multi	16/48	3T	Seed-based	BLA, CMA	Not whole-brain
Jenks et al. (2020)	Multi	30/83	3T	Seed-based	AMG, BNST	Not whole-brain
Jin et al. (2023)	SAD	75/75	3T	Seed-based	BNST	No coordinates reported

GCA: granger causality analysis.

Table 3 –

Studies with methods other than seed-based.

Author (Year)	Diagnosis	n (Anx/HV)	Field	Software	Analysis	Results
Zhang et al. (2015)	SAD	20/18	3T	SPM	ALFF	ANX < HC: dlPFC, mPFC, STG, Ins ; ANX > HC: occipital gyrus
Chen et al.(2020)	GAD	33/25	3T	DPARSF; SPM	ALFF	ANX>HC: L Thal and L hippocampus.
Oathes et al.(2015)	GAD	17/38	3T	FSL; DPARSF	ALFF	ANX>HC: limbic/paralimbic regions.
Lai & Wu (2012)	PD	30/20	3T	DPARSF; SPM; REST	ALFF, fALFF	ANX<HC: middle occipital gyrus ANX>HC: R Put and R Thal.
Yuan et al.(2018)	SAD	15/19	3T	DPABI; DPARSF	ALFF	ANX<HC: Put, L supplementary motor area ANX>HC: R Inferior Parietal Lobule, L precuneus, R cerebellar posterior lobe
Cui et al.(2020)	GAD	56/55	3T	DPABI; DynamicBC	dALFF	ANX>HC: widespread increased dALFF
Shen et al (2020)	GAD	30/30	1.5T	DPARSF	ALFF; ReHo	ANX<HC ALFF R postcentral and precentral gyrus. ReHo bilateral precentral and R postcentral ANX>HC: ReHo L PCC
Li et al. (2018)	GAD	31/31	3T	DPARSF	ReHO	ANX<HC R inferior frontal gyrus and left caudate. ANX>HC: L cingulate gyrus
Xia et al. (2017)	GAD	31/36	3T	DPARSF	ReHO	ANX<HC R OFC, L ACC, R middle frontal gyrus, bilateral supplementary motor areas. ANX>HC: L MTG, L STG, R superior occipital gyrus
Qiu et al. (2011)	SAD	20/20	3T	SPM8	ReHO	ANX<HC bilateral angular gyrus and L mPFC
Lai (2018)	PD	53/54	3T	DPARSF	ReHO	ANX<HC bilateral precuneus
Xiong et al.(2020)	GAD	51/20	1.5T	DPABI; GIFT	ICA	ANX>HC: Increased R mPFC (DMN) and RSTL (SN)
Liao et al. (2010)	SAD	20/19	3T	SPM; GIFT	ICA	ANX<HC: FC in the SMN and VN.
Ergül et al. (2022)	SAD	21/21	3T	SPM; GIFT	ICA	ANX<HC: FC in L-OFC cortex in the SN; ANX>HV: L-SMG in the SN.
Zhang et al. (2022)	SAD	46/52	3T	DPARSF	ICA	ANX<HC: decreased inter-network connectivity in multiple networks; ANX>HV: increased connectivity SCN and multiple networks.
Ni et al.(2021)	PD	26/27	3T	DPABI; SPM	ICA	ANX < HC: Decreased R-ACC – DMN. L-PoCG, LPrCG – SMN
Li et al. (2019)	GAD	15/24	3T	DPABI; SPM	ICA; dFCD	No specific ANX – HV result reported**
Qiao et al. (2017)	GAD	20/20	3T	SPM	ICA; GCA	ANX < HC: frontal and temporal cortex. ANX > HC: AMG, Ins, Put, Thala.
Li et al. (2023)	Multi	38/21	3T	DPARSFA; SPM	ICA	Differences in the DMN and Precuneus network are GAD specific, the anterior DMN was PD specific.
Xu et al. (2021)	Multi	48/26	3T	REST; DPARSF; GIFT	ICA	The authors investigate the dynamic connectivity as states defined using networks identified with ICA. They find that one of the identified states occur more frequently in Anx patients
Linke et al.(2021)	Multi	83/55	3T	MRIQC; FMRIPREP	CCA	Two canonical variates captured a mix of anxiety with other psychopathology, one was specific to anxiety. canonical variates did not relate to specific resting-state networks

Author (Year)	Diagnosis	n (Anx/HV)	Field	Software	Analysis	Results
Liu & Lai (2022)	PD	60/60	3T	DPARSF	Graph theory	ANX<HC: degree centrality in the SFG
Yun et al. (2017)	SAD	28/27	1.5T	SPM	Graph theory	ANX<HC: degree in the MTG
Zhu et al. (2017)	SAD	42/42	3T	DPARSF; DPABI; SPM	Graph theory	ANX<HC: decrease in 49 connections.
Yang et al. (2019)	SAD	33/32	3T	SPM; DPARSF	Graph theory	ANX>HC: connectivity in circuit including dlPFC, vmPFC, Isn, PCC and OCC
Wu et al. (2021)	PD	31/33	3T	DPARSF; SPM	Graph theory	ANX<HC: nodal efficiency in the SFG, STG and middle frontal gyrus
Makovac et al. (2018)	GAD	16/16	1.5T	FSL	Graph theory	ANX<HC: global efficiency. ANX>HC betweenness centrality AMG and midline cortices
Liu et al. (2015)	SAD	20/20	3T	DPARSF	Graph theory	ANX<HC decreased connectivity of the precuneus. ANX>HC increased connectivity of fusiform gyrus
Meng et al. (2022)	GAD	41/45	3T	DPARSF	Graph theory	ANX<HC decreased degree centrality in L OFC, fusiform gyrus and PCC. ANX>HC increased degree centrality in cerebellum and L MTG
Guo (2021)	GAD	32/25	3T	DPARSF	Graph theory	ANX<HC decreased clustering coefficient, global, local efficiency, intermodular connections, rich club and feeder connections.
Chen et al. (2021)	GAD	57/57	3T	DPABI	FCS	ANX<HC decreased voxel-wise cerebral blood flow – functional connectivity correlation
Bijsterbosch et al. (2018)	GAD	23/27	3T	FSL;	ROI-to-ROI	Patients with major depressive disorder and anxiety analyzed together. STAI trait anxiety not related to resting-state predictor variables.
Ding et al. (2011)	SAD	17/19	3T	SPM; MarsBaR	ROI-to-ROI	ANX<HC: decreased positive connections in the frontal lobe and decreased negative connections between frontal and occipital lobes.
Rabany et al. (2017)	Multi	18/19	3T	CONN	ROI-to-ROI	ANX was associated with PCC-mPFC and R lateral parietal cortex - ACC.
Cui et al. (2016)	Multi	39/22	3T	SPM; DPARSF	ROI-to-ROI	ANX>HC: GAD increased hippocampus/PHG and fusiform connectivity. PD increased somatosensory and thalamus connectivity.
Zhou et al. (2022)	PD	38/40	3T	SPM	ROI-to-ROI	ANX>HC: increased Thala-Ins connectivity
Hong et al. (2023)	PD	62/40	3T	CONN; SPM	ROI-to-ROI	ANX>HC: increased Thala-postcentral gyrus connectivity
Li et al. (2023)	GAD	118/85	3T	DPARSF; SPM12	ROI-to-ROI	Multiple regions connectivity associated with anxiety symptoms, especially in the DMN and SN.
Wang et al. (2019)	GAD	30/30	3T	DPARSF; SPM; REST	VMHC	ANX<HC: decreased voxel-mirrored connectivity in PrCG, middle cingulate gyrus, and Ins/Put
Lai & Wu (2014)	PD	20/21	3T	DPARSF	VMHC	ANX<HC: decreased voxel-mirrored connectivity in PCC and precuneus.
Chen et al.(2020)	GAD	81/80	3T	DPABI	dFCD	ANX<HC: lower dFCD variability in R postcentral gyrus. ANX>HC: higher dFCD variability in dmPFC and L hippocampus
Cui et al. (2020)	GAD	74/74	3T	DPABI	DRePS	ANX<HC: decreased DRePS in the caudate, hippocampus, Ins, and fusiform gyrus

Author (Year)	Diagnosis	n (Anx/HV)	Field	Software	Analysis	Results
Wang et al. (2019)	GAD	47/38	3T	DPARSF	SampEn	ANX>HC: increased spatial complexity

ALFF: amplitude of low-frequency fluctuation, dALFF: dynamic amplitude of low-frequency fluctuation, CCA: canonical correlation analysis, fALFF: fractional amplitude of low-frequency fluctuation, ReHO: regional homogeneity, GCA: granger causality analysis, FCS: functional connectivity strength, ICA: independent component analysis, VMHC: voxel-mirrored homotopic connectivity, dFCD: dynamic functional connectivity density, FCD: functional connectivity density, SampEn: sample entropy, DRePS: dynamic regional phase synchrony. Anx: anxious group, HC: healthy controls, R: right, L: left, AMG: amygdala, PFC: prefrontal cortex, dlPFC: dorsolateral prefrontal cortex, Ins: insula, STG: superior temporal gyrus, Put: putamen, SFG: superior frontal gyrus, PHG: parahippocampal gyrus, ACC: anterior cingulate cortex, SMG: supramarginal gyrus, OCC: occipital cortex, PoCG: postcentral gyrus, MTG: middle temporal gyrus, vmPFC: ventromedial prefrontal cortex, mPFC: medial prefrontal cortex, dmPFC: dorsomedial prefrontal cortex, PrCG: precentral gyrus, PCC: posterior cingulate cortex, mFC: medial frontal cortex, Thala: thalamus, OFC: orbitofrontal cortex, nAcc: nucleus accumbens.

Table 4:

ALE results.

ALE Meta-Analysis Coordinates (Healthy > Anxious)							
	MNI Coordinates						
Cluster #	**x**	**y**	**z**	**ALE Score**	**z-score**	***p* value**	**Label**
1	8	42	36	0.009	3.865	< .001*	R Medial Frontal Gyrus
1	10	40	22	0.009	3.724	< .001*	R Cingulate Gyrus
1	−8	36	0	0.008	3.434	< .001*	L Anterior Cingulate
1	−8	44	14	0.007	3.060	0.001*	L Anterior Cingulate
1	−8	42	−14	0.007	2.939	0.002*	L Medial Frontal Gyrus

Single cluster with five foci emerged as significant in ALE meta-analysis of amygdala seed-based papers. MNI: Montreal Neurological Institute. R: right, L: left