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Resting-state functional connectivity correlates of anxiety co-morbidity in major depressive disorder

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ABSTRACT

Major depressive disorder (MDD) is frequently co-morbid with anxiety disorders. The co-morbid state has poorer functional outcomes and greater resistance to first line treatments, highlighting the need for novel treatment targets. This systematic review examined differences in resting-state brain connectivity associated with anxiety comorbidity in young- and middle-aged adults with MDD, with the aim of identifying novel targets for neuromodulation treatments, as these treatments are thought to work partly by altering dysfunctional connectivity pathways. Twenty-one studies met inclusion criteria, including a total of 1292 people with MDD. Only two studies included people with MDD and formally diagnosed co-morbid anxiety disorders; the remainder included people with MDD with dimensional anxiety measurement. The quality of most studies was judged as fair. Results were heterogeneous, partly due to a focus on a small set of connectivity relationships within individual studies. There was evidence for dysconnectivity between the amygdala and other brain networks in co-morbid anxiety, and an indication that abnormalities of default mode network connectivity may play an underappreciated role in this condition.

1. Introduction

Major depressive disorder (MDD) is one of the leading contributors to disability worldwide (Vos, 2020), and affects 1 in 7 people during their lifetime (Kessler and Bromet, 2013). MDD is the most common psychiatric diagnosis in people who die by suicide (Hawton et al., 2013). Up to 30% of people with MDD do not respond to first line treatments (Al-Harbi, 2012), highlighting the need for novel treatment options. Whilst treatment resistance in MDD is likely to be a multifaceted phenomenon, patient co-morbidities may be an important consideration (Kautzky et al., 2019). In particular, co-morbid anxiety disorder is relatively common in MDD and is associated with poorer functional outcomes, increased suicidality, and greater illness chronicity, as well as greater resistance to current treatments (Andrade et al., 2003; Fava et al., 2008; Fawcett et al., 1990; Kaufman and Charney, 2000).

Non-invasive neuromodulation techniques, such as transcranial magnetic stimulation (TMS), transcranial direct- or alternating-current stimulation, and transcranial ultrasound, may be able to overcome the limitations of current pharmacological treatments (Lewis et al., 2016). These techniques have high patient acceptability (Li et al., 2021) and are inherently flexible, meaning that characteristics of the stimulation, such as the targeted brain area, could potentially be adjusted based on patient characteristics such as co-morbidities. At present, much of this flexibility is unused. The left dorsolateral prefrontal cortex (DLPFC) is by far the most common site of stimulation in MDD (Perera et al., 2016), regardless of patient co-morbidities. Neuromodulation techniques are thought to exert clinical benefit primarily by inducing changes in communication, or "connectivity", between the targeted brain area and other key brain networks (To et al., 2018). This is consistent with the conceptualisation of psychiatric disorders as reflecting dysfunctions of inter-region brain connectivity rather than single region activity (Menon, 2011). Therefore, abnormalities of connectivity associated with co-morbid anxiety could be used to suggest novel neuromodulation targets for the co-morbid state.

The DLPFC is a key hub of the fronto-parietal executive control and dorsal attention networks (ECN), involved in functions such as decision

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making and working memory (Dosenbach et al., 2008). Other key networks include the default mode network (DMN) - involved in internally directed mental activity and rumination (Raichle, 2015) - and the cingulo-opercular salience network (SN), involved in assigning importance to external and internal stimuli (Seeley et al., 2007). The most common methodology for measuring brain connectivity is functional magnetic resonance imaging (fMRI). Brain areas whose activity time courses are positively correlated are thought to be working together as a network and are said to exhibit high "functional connectivity" (van den Heuvel and Hulshoff Pol, 2010) (FC).

Reviews of FC have documented wide-spread abnormalities in MDD alone. These include increased connectivity between the ECN and DMN (Kaiser et al., 2015), increased connectivity between the SN and the anterior DMN, and decreased connectivity between the posterior DMN and ECN (Mulders et al., 2015). In addition, it is suggested that the alterations in the SN leads to the abnormal balance of functional connectivity between the DMN and ECN (Dai et al., 2019). It is unclear how connectivity between these networks would be altered in the presence of co-morbid anxiety. It is also unclear whether co-morbid anxiety would be associated with the same connectivity changes previously identified in anxiety states alone, given the changes already associated with MDD. In a recent meta-analysis of FC changes in anxiety alone, Xu et al. (2019) identified hypo-connectivity between the amygdala and both the ECN and DMN, hypoconnectivity between the ECN and DMN, and hypo-connectivity between the SN and a sensorimotor network, as significant features. Thus, DMN-ECN connectivity has been found to increase, and decrease, in MDD alone, and anxiety disorders alone, respectively, whilst connectivity with the amygdala has been particularly implicated in anxiety.

In their recent systematic review of TMS in anxiety and trauma-related disorders, Cirillo et al. (2019) found four studies in generalised anxiety disorder (GAD) and two in panic disorder. These suggested that *right* DLPFC may be an effective treatment target for isolated anxiety disorders, and there is evidence from clinical service data of benefit of TMS to right DLPFC for anxiety symptoms in people with MDD (Griffiths et al., 2019). Other potential treatment sites for MDD with co-morbid anxiety disorders remain to be explored. Since any sufficiently superficial cortical area could be stimulated with TMS, a means of identifying the most promising treatment sites is required.

Despite the prevalence of co-morbid anxiety in people MDD, most neuroimaging research has used co-morbidity as an exclusion criterion. The current review looks at studies examining FC correlates of anxiety in people with MDD, with the goal of identifying novel treatment targets for people with MDD who have co-morbid anxiety disorders. In the first instance, we examine studies that have contrasted FC between patients with MDD alone and patients with MDD plus a formally diagnosed anxiety disorder (specifically, generalised anxiety, social anxiety, panic disorder, or agoraphobia, or the "anxious distress" specifier of DSM-5). In the second instance, we examine studies that have assessed correlations between dimensional anxiety measurements and FC in patients with MDD.

2. Methods

2.1. Study identification, inclusion, and exclusion criteria

This systematic review was completed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). A comprehensive database search was completed using Embase and MEDLINE, from inception up to October 2020 (this search was repeated on 21st January 2022 to identify articles published in the interim). The search strategy included the following: (functional connectivity/ OR functional connect* OR effective connect* OR fmri connect* OR connectom*) AND (depress* OR depression/) AND (anxiety/ or anxiety disorder/ OR anxi*). Reference lists from relevant studies and reviews were also examined to add further studies meeting the eligibility criteria.

Studies were included if they met either of the following criteria: 1) Studies comparing fMRI functional or effective (i.e., directed) connectivity, measured in the task-free state, between an adult MDD and co-morbid anxiety disorder group versus a single-disorder group (this is the criterion for "Analysis 1"); 2) Studies examining univariate correlations between FC or effective connectivity, measured in the task-free state, and a dimensional measure of anxiety in an adult MDD sample (this excluded multivariate, e.g., canonical correlation analyses, in which the contribution of anxiety to the relationship may be unclear) (this is the criterion for "Analysis 2"). For Analysis 1, included anxiety disorders were GAD, social anxiety disorder (SAD), panic disorder (PD), or agoraphobia (that is, conditions under "Anxiety or fear-related disorders" in ICD-11, aside from specific phobia or disorders unique to childhood), or the "anxious distress" specifier of DSM-5 MDD. We also included only studies that examined connectivity in the resting-state and without an intervention (such as medication or a psychological intervention). All studies were limited to original peer reviewed articles published in English. In the Results, we further split Analysis 2 into 2a – whole brain connectivity studies, 2b – amygdala seed region connectivity studies, 2c - cingulate and insula seed region studies, and 2d – other seed region studies. We excluded studies focussing solely on older adults (65 +), since depression is often intertwined with cognitive impairment in this age group (Rodda et al., 2011), as well as studies focussing solely on children or adolescents (under 18), as normal brain connectivity is still developing in this age group (Marek et al., 2015).

2.2. Study screening and data extraction

2.2.1. Step 1

Titles were assessed for inclusion (with a lenient inclusion threshold) by one of four reviewers (PMB, LW, CB or WJC). Step 2. Two of the four reviewers then independently assessed abstracts, with initial agreement between reviewers at 92%. In doubt or if consensus was not agreed at this stage, then these abstracts were included for full article review. Step 3. Full-text articles were split between the four reviewers and assessed for inclusion, then checked by a second reviewer. Initial agreement at the full article review stage was 89%, with disagreements resolved by discussion between the four reviewers.

Data were extracted from the included full text articles and inputted into a data extraction sheet by one of the four reviewers. This included sample characteristics (sample size, diagnosis, inclusion/exclusion criteria, medication status), neuroimaging information (acquisition parameters, region of interest (ROI) definitions and whether these were defined a priori or post-hoc, quality control information, reporting thresholds, and whether global normalisation was used), a description of findings and any further information on limitations, or potentially relevant articles found in the full text article reference lists. Given the methodological and analytic heterogeneity of the studies that met the inclusion criteria, we did not conduct a formal meta-analysis and instead report a narrative synthesis of all the findings. To aid this synthesis, we assigned brain regions in the included studies to networks using a validated atlas (Power et al., 2011). Specifically, we used the network label of the nearest neighbour of the reported region centroid amongst the 264 ROIs of Power et al. One study (Ma et al., 2020) provided assignments according to an alternative atlas (Yeo et al., 2011), rather than reporting centroids, and the reported assignments were used. Otherwise, where centroids were not provided, centroids of reported region labels were, where possible, derived from the Neuromorphometrics atlas in SPM 12. Information on co-ordinates and labels are given in the Tables.

2.3. Assessment of study quality

Study quality was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Heart,

Lung, 2014). This tool was used recently by Amidi and Wu (2019) in their systematic review of studies examining structural brain imaging outcomes of non-central nervous system cancers. A list of all items, with notes on their application in the current review, is presented in Table S1 (summary, and study-by-study, information on which criteria were met is presented in Figs. S1/2). Of the fourteen items in the tool, three (Q. 6, 7, and 13) were omitted due to the cross-sectional nature of the included studies. Quality was assessed by the reviewer conducting data extraction as well as one other reviewer. Each criterion was assessed as met or not met. Where information was not provided, that criterion was determined as not met. Question 11 - "Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?" – was deemed met if studies mentioned imaging pipeline validation and assessment of image quality (only one study met this criterion). Question 14 - "Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposures and outcomes?" was deemed met if at least one confounder was accounted for, and multiple comparisons correction was performed for the extracted results. Studies were deemed good quality if more than seven criteria were met, fair quality if four to seven criteria were met, and poor quality if fewer than four criteria were met (thresholds as a proportion of included items were the same as Amidi and Wu (2019).

3. Results

3.1. Overview of included studies

A total of 1252 articles were screened for eligibility. After duplicate removal, and exclusion at the title and abstract stage, 181 articles were selected for full-text review (Fig. 1). In total, 21 of these articles met the inclusion criteria for the systematic review, including a total of 1292 patients with a diagnosis of MDD. Only three studies (Oathes et al., 2015; Pannekoek et al., 2015; Price et al., 2017) included patients with a formally-diagnosed comorbid anxiety disorder – one of these was assigned to Analysis 2 since it divided patients into subgroups on the basis of FC measures (Price et al., 2017). Two studies (Qiao et al., 2020; Zhao et al., 2020) split patients into low and high anxiety sub-groups using scores on an "anxiety/somatization" subset of the Hamilton Depression Rating Scale (HAMD) questionnaire (Hamilton, 1960) – these were also assigned to Analysis 2 as patients lacked a specific co-morbid anxiety disorder diagnosis. The remaining studies explored correlations between FC and a dimensional measure of anxiety. Twelve of the dimensional studies used the Hamilton Anxiety Rating Scale (HAMA) measure of anxiety (Hamilton, 1959), three studies used an anxiety/somatization HAMD sub-score and one used the Beck Anxiety Inventory (BAI) (Beck et al., 1988). For clarity of reporting, Analysis 2 studies were divided into those that reported whole brain connectivity (2a), those that focused on amygdala connectivity (2b), those that focused on cingulate/insula connectivity (2c; included together since dorsal anterior cingulate and anterior insula are both key components of the salience network (Seeley et al., 2007), and those that focused on other areas (2d). A summary of the significant relationships between FC and anxiety from the included studies is presented in Fig. 2 (relationships involving the amygdala, DMN, ECN, and SN are included; solid green arrows indicate connectivity relationships that increased with increasing anxiety, whilst dotted red arrows indicate relationships that decreased with increasing anxiety; the letters next to the arrows indicate the studies that identified the relationship – these letters match those in the first column of Tables 1–5).

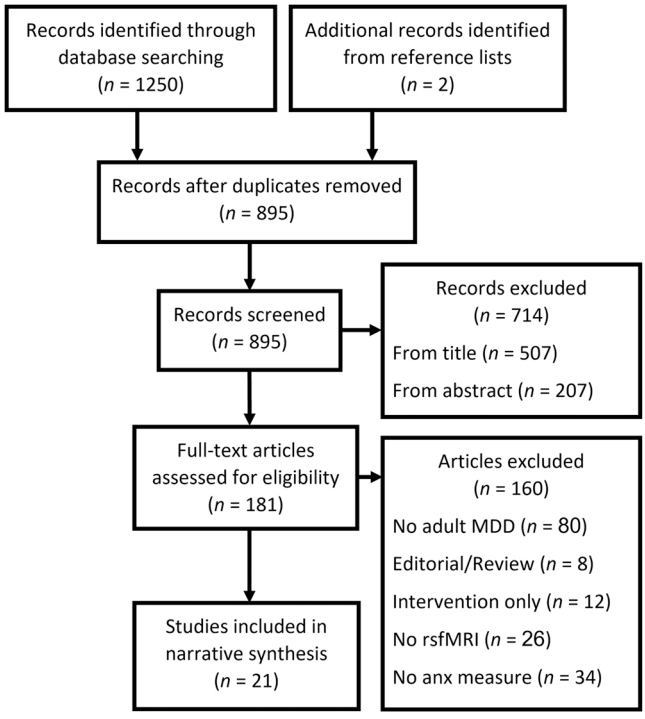

Fig. 1. PRISMA flow diagram of the systematic review search, screening, and selection process (Moher et al., 2009).

3.2. Quality of included studies

Across the twenty-one included studies, a mean of five out of the eleven quality assessment criteria were met (range 3–8). Most studies were judged as fair quality; two were judged as good quality and one as poor quality. Both studies included in Analysis 1 ensured that patient

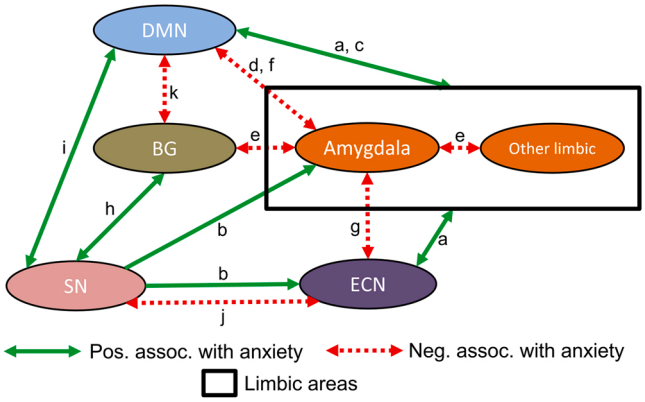

Fig. 2. Summary of relationships between functional connectivity and anxiety from the included studies. BG: basal ganglia; DMN: default mode network; ECN: executive control network; SN: salience network. Only relationships involving the above networks are included. Green solid arrows indicate positive associations with connectivity, red dotted arrows indicate negative relationships. Most studies report undirected connectivity (i.e., functional connectivity), indicated by the double-headed arrows, one study (Price et al., 2017) reported directed (effective) connectivity. The black box encloses amygdala and nearby limbic structures to demonstrate how the model accounts for findings of greater DMN/ECN-limbic/subcortical connectivity and decreased DMN/ECN-amygdala connectivity associated with increased anxiety in MDD. Across the included studies, regions within a given network showed connectivity-anxiety correlations in the same direction. They are thus considered together. Future work should seek to provide a more fine-grained description, which may indicate differences in correlations for specific network sub-regions. Letters next to arrows correspond to study superscripts in Tables 1–5 and show the studies finding each significant relationship. *a:* Pannekoek et al. (2015); *b:* Price et al. (2017), *c:* Ma et al. (2020), *d:* Ramasubbu et al. (2014), *e:* Yang et al. (2017), *f:* He et al. (2019), *g:* Qiao et al. (2020), *h:* Wu et al. (2016), *i:* Peng et al. (2018), *j:* Peng et al. (2020), *k:* Bai et al. (2018).

Table 1
Analysis 1 – functional connectivity (FC) associations of major depressive disorder (MDD) with a co-morbid anxiety disorder, versus MDD alone.

Analysis 1	Sample	Severity	Exclusions	Scanning	Analyses/ROIs	Extracted results
Oathes 2015	DSM-IV criteria (1) MDD ($N = 12$, age ± SD 28 ± 7 y, 67% female) (2) GAD (N17, 30 ± 8 y, 77%) (3) MDD+GAD (N23, 33 ± 11 y, 65%) (4) HC (N38, 34 ± 10 y, 71%)	MASQ scales (GD/AA/AD): MDD (33/23/91) GAD (29/27/73) MDD + GAD (39/32/88) HC (16/19/47)	Antidepressants in last 6 weeks, benzodiazepines in last 48 h, substance abuse, PTSD, history of neurological, psychotic, or bipolar illness, head trauma/ LoC	8-minute 3 T eyes-closed rsfMRI. TR/TE 2 s/30 ms. Maximum tolerated motion 3 mm/3°	*A priori* ROIs from atlases, or co-ordinates or ICA masks from previous studies/cohorts. Pair-wise FC matrices submitted to PCA, yielding six components	No significant differences ($p <$ 0.05 uncorrected) in any of the FC principal components between groups. Subsequent dimensional analyses collapsed across groups so beyond scope of review
[a]Pannekoek 2015	DSM-IV criteria (1) MDD (N37, 36 ± 10 y, 49%) (2) ANX (N30, 33 ± 8 y, 73%; PD, SAD, or GAD) (3) MDD+ANX (N25, 35 ± 11 y, 76%) (4) HC (N48, 40 ± 9, 63%)	81% antidep-naïve. MADRS/ BAI scores: MDD (11.7/8.8) ANX (10.4/14.2) MDD+ANX (19.0/16.8) HC (1.1/2.1)	Current psychotropic medication, history of other axis-I disorders, major internal/ neurological disorders, hypertension, substance abuse or dependence in past year, age < 18 or > 57	7.5-minute 3 T eyes-closed rsfMRI. TR/TE 2.3 s/30 ms. Maximum tolerated motion 3 mm. Voxel time courses submitted to group ICA	Four ICA components selected representing DMN, SN, sensory-motor and limbic networks (incl. amygdala and hippocampus). Used as seeds in FC analysis. Excluded GN. Controlled for age and gender ($p < 0.05$ FWE-corrected)	MDD+ANX versus MDD/ANX: ↑ FC between limbic network and two clusters – posterior DMN (bilateral precuneus, posterior cingulate, MNI centroid: 7, −56, 10, DMN) and inferior/middle frontal gyrus (MNI: 35, 6, 31, ECN)

3 T: 3-Tesla; BAI: Beck Anxiety Inventory; DMN: default mode network; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Volume IV; ECN: executive control network; FWE: family-wise error; GAD: generalised anxiety disorder; GN: global normalisation; HC: healthy control participants; ICA: independent component analysis; LoC: loss of consciousness; MADRS: Montogmery-Åsberg Depression Rating Scale; MASQ: Mood and Anxiety Symptom Questionnaire – GD (General Distress), AA (Anxious Arousal), AD (Anhedonic Depression); MNI: Montreal Neurological Institute co-ordinates; PCA: principal component analysis; PD: panic disorder; PTSD: post-traumatic stress disorder; ROI: region of interest; rsfMRI: resting-state functional magnetic resonance imaging; SAD: social anxiety disorder; SN: salience network; TE: echo time; TR: repetition time.
Superscript letters preceding author names identify studies contributing to relationships depicted in Fig. 2. MNI centroids are given where provided, with network labels assigned as per the nearest neighbour in the Power et al. atlas.

groups being compared were recruited from the same source. Whilst Analysis 2 focussed on anxiety associations within patient groups, and, in each case, patient groups were recruited from the same sources, twelve of the studies selected regions, or connectivity values, of interest based on prior comparisons between patients and controls – in seven of these studies, recruitment differed between patients and controls and there were no details of a matching process. Only one study reported details of imaging analysis pipeline validation, five mentioned assessment of image quality. Seven studies controlled for multiple comparisons and at least one confounder in the analyses that were extracted. Only one study referred to outcome blinding – that is, specifying the analyses of FC associations without knowing patient anxiety disorder diagnosis or dimensional anxiety level so as not to inadvertently bias the analysis parameters used (in that study, bias was reduced by pre-specifying the analysis process). No study reported sample size justification. Additional information on quality of included studies is contained in Supplemental Information.

3.3. Analysis 1 (MDD with co-morbid anxiety disorder versus MDD alone)

Two studies met the inclusion criteria for this analysis (Table 1). Pannekoek et al. (2015) examined FC between groups of brain areas (derived using data-driven "independent component analysis", ICA) in unmedicated patients with MDD (N = 37), an anxiety disorder (N = 30; PD, SAD, GAD), MDD plus an anxiety disorder (N = 25), or healthy controls (HCs, N = 48). FC between limbic areas (primarily amygdala, hippocampus) and two clusters was increased in the co-morbid group compared to either of the other patient groups and the control group. One cluster showing increased FC with limbic areas in the co-morbid group included primarily posterior DMN areas (including precuneus and posterior cingulate cortex, as well as intracalcarine cortex and lingual gyrus), whilst the other cluster included inferior frontal gyrus and middle frontal gyrus ("MFG", the site of DLPFC, a key ECN area) as well as right precentral gyrus. There were no significant differences between the two single-disorder patient groups or between the single-disorder patient groups and the control group, in their study (contrary to previous findings from the same group (Pannekoek et al., 2013b, 2013a), which may indicate low severity in the single disorder groups or be due to the range of anxiety disorders grouped together).

Oathes et al. (2015) computed FC between eight brain areas (either defined anatomically or from a previous ICA) and used principal component analysis to summarise pair-wise FC relationships between the areas with six principal components. They included unmedicated patients with MDD (N = 12), GAD (N = 17), MDD with co-morbid GAD (23), and healthy controls (N = 38). They found no differences in component values between groups. This may be due to the small sample size in each group. Subsequent dimensional analyses collapsed across groups so were outside of the scope of this review.

3.4. Analysis 2 (MDD with dimensional analysis of anxiety)

3.4.1. Analysis 2A (whole brain connectivity studies)

Four studies reported relationships between FC, calculated using a method that was not restricted to single seed regions or regions within a single brain network, and a dimensional measure of anxiety in patients with MDD (Table 2). In a sample of 80 unmedicated patients with MDD, Price et al. (2017) identified two separable patterns ("biotypes") of effective connectivity between a set of fifteen brain regions, chosen so as to span the DMN, ECN and SN. Effective, or directed, connectivity goes beyond FC to characterise the influence of one brain area on another, rather than solely assessing the correlation between the two areas. One biotype characterised by greater probability of anxiety disorder co-morbidity showed greater effective connectivity from the SN (dorsal anterior cingulate cortex – dACC – or insula) to the ECN (left DLPFC, right parietal) or limbic (right amygdala) systems, whereas the other,

Table 2
Analysis 2 A – whole brain functional connectivity (FC) studies in major depressive disorder (MDD), with dimensional analysis of anxiety.

2a Whole brain	Sample	Severity	Exclusions	Scanning	Analyses/ROIs	Extracted results
[b]Price 2017	DSM-IV criteria. MDD (N = 80, age ± SD 36 ± 11 years, 71% female)	24% severe depressive episode, 41% history of 3 + episodes, BDI mean ± SD 30.7 ± 9.5	Psychotropics in last two weeks. History of psychosis or manic/hypomanic episodes, alcohol excess in past two weeks, other ongoing health problems	7-minute 3 T eyes-open rsfMRI. TR/TE 1.5 s/27 ms. Timepoints with movement > 0.5 mm/0.5° omitted	15 ROIs selected a priori from anatomical atlases and previous studies. Clustering algorithm applied to ECs between all ROI pairs identified two subgroups (A/B), B characterised by greater anx dis. co-morbidity	Subgroup B showed ↑ EC from dACC (MNI centroid: 0, 17, 31, SN) to left DLPFC (−40, 20, 28, ECN) and right posterior parietal cortex (44, −50, 50, ECN), as well as from left anterior insula (39, 16, 1, SN) to right amygdala Greater HAMA associated with ↑ "participation coefficient" of right DLPFC (ECN, classified by authors with Yeo et al. atlas), and ↑ FC between DMPFC (DMN) and a subcortical network (amygdala, hippocampus, thalamus, caudate, putamen, pallidum)
[c]Ma 2020	DSM-IV criteria. MDD (N108, 26 ± 8, 68%), 40% taking medication, recruited amongst HC and patients with Sz and BD	88% first episode, HAMD/HAMA: Mean ± SD 21.2 ± 8.8 / 16.3 ± 9.5	Other Axis I disorders, lifetime substance abuse /dependence, history of "major medical or neurological conditions", head trauma LoC 5 + mins	6.7-minute 3 T eyes-closed rsfMRI. TR/TE 2 s/30 ms. Motion limits 3 mm/3°	FC between GM voxels. Included GN. Correlation matrices thresholded, voxels assigned to regions & 8 networks based on previous parcellation. Network FCs related to clinical variables, controlling for age/gender ($p < 0.05$ FDR corrected)	
Shi 2020	DSM-IV criteria. Treatment-naïve MDD (N23, 32 ± 7 y, 70%). HC (20)	HAMD/MADRS/HAMA:25.1 ± 1.3 / 31.7 ± 7.8 / 26.2 ± 8.0	Previous MDD episodes, antidepressant use or formal psychotherapy or ECT, age < 18 or > 55	6.7-minute 3 T eyes-closed rsfMRI. TR/TE 2 s/35 ms. Motion limits 1.5 mm/1.5°	Voxel-wise FC, then voxels assigned a single FC strength (FCS) by summing connectivity values between that voxel and all others. Included GN. FCS correlated with clinical variables ($p < 0.05$ uncorr)	Greater HAMA associated with ↓ FCS within left PCC and precuneus (−27, −75, 27, visual – precuneus is often considered both a DMN and extra-striate visual region)
Liu 2021	DSM-5 criteria. Medication-naïve MDD with (N35, 31 ± 7 y, 63%) and without (N17, 30 ± 8 y, 65%) GI symptoms. HC (28)	HAMD for MDD with/without GI symptoms: 22.7 ± 3.4 / 20.2 ± 2.7	Meeting DSM-5 criteria for other psychiatric disorders, history of brain injury or LoC, history of substance abuse, age < 18 or > 55	8.3-minute 3 T eyes-closed rsfMRI. TR/TE 2 s/30 ms. Motion limits 2 mm/2°. Analyses with and without GN.	VMHC differed between MDD groups in MFG/SFG. Excluded GN. These values examined for associations with HAMD sub-scores in all MDD patients ($p < 0.05$ B-H corrected)	Relationship between HAMD anxiety/somatisation sub-score and VMHC within MFG (± 42, 30, 39, ECN) / SFG (± 9, 36, 57, DMN) non-significant

3 T: 3-Tesla; BD: bipolar disorder; BDI: Beck Depression Inventory; B-H: Benjamini-Hochberg; dACC: dorsal anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; DMN: default mode network; DMPFC: dorsomedial prefrontal cortex; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Volume IV; EC: effective connectivity; ECN: executive control network; ECT: electroconvulsive therapy; FCS: functional connectivity strength; FDR: false discovery rate; GM: grey matter; GN: global normalisation; HAMA: Hamilton anxiety rating scale; HAMD: Hamilton depression rating scale; HC: healthy control participants; LoC: loss of consciousness; MADRS: Montgomery-Åsberg Depression Rating Scale; MFG: middle frontal gyrus; PCC: posterior cingulate cortex; rsfMRI: resting-state functional magnetic resonance imaging; ROI: region of interest; SFG: superior frontal gyrus; Sz: schizophrenia; TE: echo time; TR: repetition time; VMHC: voxel-mirrored homotopic connectivity. Superscript letters preceding author names identify studies contributing to relationships depicted in Fig. 2. MNI centroids are given where provided, with network labels assigned as per the nearest neighbour in the Power et al. atlas.

more common, biotype, was characterised by greater within-DMN (perigenual anterior cingulate – pgACC – to posterior cingulate cortex – PCC), and within-SN, connectivity.

Ma et al. (2020) calculated resting-state FC between individual brain voxels, then assigned voxels to resting-state networks using a previously-derived atlas before calculating mean connectivity differences within and between these networks. In a group of 108 patients with MDD, 43 of whom were taking medication for MDD, greater FC between dorsomedial prefrontal cortex ("DMPFC", an anterior DMN area) and a subcortical network (including amygdala and hippocampus) was associated with greater anxiety measured with the HAMA, as was FC between the left thalamus and a sensorimotor network. Shi et al. (2020) calculated FC between individual brain voxels, then assigned each voxel a single FC strength (FCS) by summing the connectivity values between that voxel and all other voxels. In 33 medication-naïve patients with MDD, they found that FCS within two DMN areas (left PCC and precuneus) was negatively correlated with anxiety measured with the HAMA. Finally, Liu et al. (2021) computed FC between homologous voxels in the left and right cortical hemispheres ("voxel-mirrored homotopic connectivity", VMHC). This can be deemed a measure of *within-network* FC. Voxels in middle frontal gyrus (ECN) and superior frontal gyrus (centroid within the DMN as per the Power atlas), exhibited differences in VMHC between controls and 35 medication-naïve patients with MDD. For the patients, correlations were examined between VMHC in these regions and an anxiety/somatization sub-score of the HAMD (including items 10 – psychic anxiety, 11 – somatic anxiety, 12 – gastrointestinal somatic symptoms, 15 – hypochondriasis, and 17 – insight). Both relationships were non-significant.

3.4.2. *Analysis 2B (amygdala seed region connectivity studies)*

Four studies used amygdala seeds (Table 3). In 55 treatment-resistant patients with MDD not currently on medication, Ramasubbu et al. (2014) examined relationships between HAMA and FC between left amygdala and fourteen brain areas. They chose areas that had shown significant differences in amygdala FC between patients and healthy controls in a preceding analysis. They found a negative relationship between HAMA and FC between the left amygdala and the right temporal pole, part of the posterior DMN. Ramasubbu et al. focussed on left amygdala as it had shown a larger number of significant FC differences in the patients versus controls analysis. Yang et al. (2017) used a right amygdala seed in 35 unmedicated patients with MDD (right amygdala was chosen as its structural volume had shown relationships with HAMA in a preceding analysis; greater volume being associated with greater HAMA). Yang et al. found a negative relationship between HAMA and FC between the right amygdala and the left hippocampus as well as the left pallidus.

He et al. (2019), using multivariate linear regression to examine relationships between amygdala FC and HAMA scores in 75 medication

Table 3
Analysis 2B – amygdala seed region functional connectivity (FC) studies in major depressive disorder (MDD), with dimensional analysis of anxiety.

2b. Seed Amygdala	Sample	Severity	Exclusions	Scanning	ROIs/FC	Extracted results
[d]Ramasubbu 2014	DSM-IV criteria. MDD (N = 55, age 37 ± 10, 60% female), HC (N19, 33 ± 10, 58%)	MDD 2.7 ± 3.9 total episodes, HAMD/ HAMA total scores 21.4 ± 4.2 / 25.6 ± 5.2	Psychotropics in past 3 weeks. Other axis I disorders, substance abuse in last 6 months, personality disorder, nil response to 3 + antidepressants, age < 20 /> 55	7.7-minute 3 T eyes-open rsfMRI. TR/TE 2 s/30 ms. Excluded GN.	Left and right amygdala seeds using atlas. FC diffs between patients and controls examined for relationships with clinical variables in patients, focussing on left amygdala ($p < 0.05$ uncorr)	Greater HAMA associated with ↓ FC between left amygdala and right temporal pole (MNI centroid: 34, 12, −24, DMN)
[e]Yang 2017	DSM-IV criteria. MDD (N35, 45 ± 11, 100%), HC (N23, 39 ± 14, 100%)	MDD HAMD/HAMA: 28.3 ± 8.0 / 20.2 ± 7.2 Current episode duration 5.8 ± 8.2 months	Antidepressants /therapy last 6 mths, substance dep., neurological/endocrine disorders, brain injury, "major" psychiatric illness, age < 18 /> 60	8-minute 3 T eyes-open rsfMRI. TR/TE 2 s/25 ms. Excluded GN.	FC calculated with right amygdala seed from anatomical atlas. Significant FC differences between groups correlated with HAMA in patients ($p < 0.05$ uncorr)	Greater HAMA associated with ↓ FC between right amygdala and left hippocampus (−16, −16, −20, subcortical) or left pallidus (−14, 8, 2, subcortical)
[f]He 2019	DSM-IV criteria. MDD (N75, 40 ± 12, 50%) Medication naïve. HC (N42, 41 ± 12 45%)	MDD 2.8 ± 1.9 total episodes, HAMD/ HAMA: 21.3 ± 5.1 / 17.0 ± 6.5	Abuse of caffeine/ nicotine/ alcohol, hx of head trauma, LoC, some cardiac or pulmonary diseases, other "major" psychiatric disorders, neurodegenerative illnesses, age < 18 or > 59	8-minute 3 T eyes-closed rsfMRI. TR/TE 2 s/25 ms. Motion limits 2.5 mm/2.5°. Excluded GN.	Atlas amygdala seed region FC. FC relationships examined in patients using multivariate linear regression with HAMA and HAMD scores as covariates along with several potential confounders ($p < 0.05$, corr)	Greater HAMA associated with ↓ FC between amygdala and: DMPFC (12, 30, 51, DMN), PCC/ MCC, left MTG (−60, −39, −3, DMN), and right temporal pole (42, −3, −42, DMN)
[g]Qiao 2020	DSM-IV criteria. MDD divided into anxious (N83, 35 ± 11, 60%) & non-anxious (N70, 32 ± 10, 53%) subtypes based on HAMD subscore. HC (N62, 33 ± 10, 55%)	HAMD: 24.3 ± 4.2 / 19.4 ± 3.9 for anxious / non-anxious subgroups, respectively. HCs age, education, and gender-matched	Other psychiatric disorders, depression secondary to medical causes, substance abuse or dependence, "serious medical or neurological illness", age < 18 or > 55	4.3-minute 3 T eyes-closed rsfMRI. TR/TE 3 s/40 ms. Included GN.	Atlas amygdala seeds. FCs compared btwn groups controlling age, gender, and education. FCs showing sig. diffs. between groups examined for corrs. with dimensional anxiety /somatisation score ($p < 0.05$, Bonf.-corr.)	AD associated with ↓ FC btwn. right CM/LB amygdala & right MFG (42, 42, 9, ECN). In AD, anxiety/ somatisation score assoc. with ↓ FC in between right CM and right MFG

3 T: 3-Tesla; CM: centromedial; DMN: default mode network; DMPFC: dorsomedial prefrontal cortex; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Volume IV; ECN: executive control network; FC: functional connectivity; GN: global normalisation; HAMA: Hamilton anxiety rating scale; HAMD: Hamilton rating scale for depression; HC: healthy control participants; LB: laterobasal; MDD: major depressive disorder; MFG: middle frontal gyrus; rsfMRI: resting-state functional magnetic resonance imaging; TR: repetition time; TE: echo time. Superscript letters preceding author names identify studies contributing to relationships depicted in Fig. 2. MNI centroids are given where provided, with network labels assigned as per the nearest neighbour in the Power et al. atlas.

naïve patients with MDD, also found negative relationships between HAMA and FC between the amygdala and several DMN regions, including both the anterior (DMPFC) and posterior (PCC, left middle temporal gyrus and right temporal pole) subdivisions. They considered left and right amygdala together in their results. The decreased amygdala FC association with greater anxiety may not be unique to DMN areas, however. Qiao et al. (2020) sub-divided the amygdala and compared FC for each subdivision between patients with MDD who scored higher (≥7, N = 83) or lower (<7, N = 70) on an anxiety/somatisation sub score of the HAMD, without classifying patients according to formal anxiety diagnoses. They did not report medication status. They found that FC between right centromedial and laterobasal amygdala and right MFG was lower in the anxious, than non-anxious, patient group.

3.4.3. Analysis 2 C (cingulate and insula seed region connectivity studies)

Five studies used cingulate or insula seed regions (Table 4). Three used seeds in anterior cingulate cortex, generally considered part of the SN (particularly the dACC) (Seeley et al., 2007). Wu et al. (2016) used a dACC seed and computed correlations with HAMA for a subset of dACC FC values in medication naïve, first episode MDD (N = 19). They found a positive correlation between HAMA and FC between dACC and right pallidum. Peng et al. (2020) used five ACC sub-regions as seeds – FC values differing between first episode medication naïve patients (N = 41) and controls were examined for relationships with clinical variables in patients. They found that HAMA was negatively associated with FC between the dACC and right superior parietal lobule (part of the ECN). Yang et al. (2019) used a seed region in middle cingulate cortex and found significant FC differences between patients (N = 73) and controls with insula (considered as a whole), but this FC was not significantly correlated with anxiety as measured with the Beck Anxiety Inventory (BAI) (Beck et al., 1988) in patients.

Yin et al. (2018) used sub-regions of insula as seeds and examined relationships between anxiety measured with the HAMA and FC relationships that had shown differences between patients (N = 40) and controls. They found a negative relationship between HAMA and FC between *posterior* insula and right postcentral gyrus. Posterior insula has been suggested to have a role in interoceptive awareness (Kuehn et al., 2016). Finally, Peng et al. (2018), utilising a similar approach with first episode MDD patients (N = 19), found positive relationships between HAMA and FC between the left anterior insula and left dACC (both salience network areas), and between anterior insula and angular gyrus (part of the DMN).

3.4.4. Analysis 2D (connectivity studies using other seed regions)

Six studies used other seed regions (Table 5). In 23 medication-free patients with MDD, Luo et al. (2018) found that greater FC between right inferior parietal cortex (an area regarded as containing both DMN and ECN sub-regions) and left medulla was associated with greater anxiety as measured with the HAMA (this FC relationship being chosen

Table 4
Analysis 2 C – cingulate and insular seed region functional connectivity (FC) studies in major depressive disorder (MDD), with dimensional analysis of anxiety.

2c. Seed Cing/ Ins	Sample	Severity	Exclusions	Scanning	ROIs/FC	Extracted results
[h]Wu 2016	DSM-IV criteria. MDD (N = 19, 34 ± 9, 53%), medication naïve. HC (N19, matched for age, sex, education, handedness). As in Peng 2018; partial overlap with Peng 2020	First episode. HAMD/HAMA scores: 24.9 ± 3.8 / 17.8 ± 4.6	Head injury with LoC, history of cortisol medication use or ECT, alcohol/ substance abuse, neurological disease, other psychiatric diagnoses, age < 18 or > 45	6.3-minute 1.5 T eyes-closed rsfMRI. TR/TE 2.5 s/35 ms Included GN.	Dorsal ACC seed from previous study. FC within dorsal ACC & between dorsal ACC and PCC/right pallidum examined for relationships with clinical measures ($p < 0.05$ uncorr)	Greater HAMA associated with ↑ FC between dorsal ACC (MNI centroid: 0, 17, 37, SN) and right pallidum (18, −10, 6, subcortical)
[i]Peng 2018	As in Wu 2016; partial overlap with Peng 2020	As in Wu 2016	As in Wu 2016	As in Wu 2016	Six insula ROIs centred on co-ordinates from a previous study. FCs involving angular gyrus and dorsal ACC examined for correlations with HAMA in patients ($p < 0.05$ uncorr)	Greater HAMA associated with ↑ FC between left dAI (−38, 6, 2, SN) and bilateral AG (Nm-atlas: −43, −64, 37/48, −58, 36, DMN), between right dAI (35, 7, 3, SN) and left AG, and between bilateral dAI /left dorsal ACC
Yin 2018	DSM-IV criteria. MDD (N40, 30 ± 10, 63%), 53% taking antidepressant. HC (N70, 29 ± 8, 56%), alongside BD patients	93% first episode. HAMD/HAMA scores: 22.4 ± 9.6 / 17.5 ± 10.3	Other Axis 1 / personality disorders, substance abuse /dependence past 3 mths, neurological disorders, head trauma 5 + mins. LoC, ages < 16 /> 48	6.7-minute 3 T eyes-closed rsfMRI. TR/TE 2 s/30 ms. Motion limit 2.5 mm/2.5°. Included GN	Three insular sub-regions used as seeds. FC values showing significant differences between groups then correlated with clinical variables ($p < 0.05$ uncorrected)	Greater HAMA associated with ↓ FC between posterior insula and right postcentral gyrus
Yang 2019	DSM-IV criteria. MDD (N73, 33 ± 9, 63%), 85% taking antidepressant. HC (93, 30 ± 7, 51%), alongside Sz and BD groups	51% first episode. BDI / BAI scores: 21.9 ± 7.1 / 32.6 ± 15.0	"Organic causes of depression including heart, liver, or kidney disease" and "other mental disorders"	6.7-minute 3 T rsfMRI. TR/TE 2 s/30 ms. Motion limits 2 mm/ 2°. Included GN.	FC between MCG and insula showed consistent group differences – this FC was correlated with clinical measures ($p < 0.05$ uncorr)	No significant relationships between BAI and FC between the MCG and left/right insula FC
[j]Peng 2020	DSM-IV criteria. MDD (N41, 33 ± 9, 61%), medication naïve. HC (N43, 32 ± 9, 53%). Partial overlap with Peng 2018	First episode. HAMD / HAMA scores: 23.7 ± 3.7 / 18.2 ± 4.4	Head injury + LoC, history of cortisol medication use or ECT, alcohol/ substance abuse, neurological disease, other psychiatric diagnoses, age < 18 or > 45	6.3-minute 1.5 T eyes-closed rsfMRI. TR/TE/ FA 2.5 s/35 ms/90°. Included GN.	Five ACC sub-region seeds. FCs with significant differences between MDD and HC examined for relationships with clinical features, controlling for age ($p < 0.05$, FDR-corrected)	Greater HAMA associated with ↓ FC between left caudal ACC (± 5, −10, 37, SN) and right superior parietal lobule (Nm-atlas: 26, −55, 57, ECN)

1.5 T: 1.5-Tesla; 3 T: 3-Tesla; ACC: anterior cingulate cortex; AG: angular gyrus; BAI: Beck Anxiety Inventory; BD: bipolar disorder; BDI: Beck Depression Inventory; dAI: dorsal anterior insula; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Volume IV; ECT: electro-convulsive therapy; FDR: false discovery rate; GN: global normalisation; HAMA: Hamilton anxiety rating scale; HAMD: Hamilton depression rating scale; HC: healthy control participants; LoC: loss of consciousness; MCG: middle cingulate gyrus; PCC: posterior cingulate cortex; ROI: region of interest; rsfMRI: resting-state functional magnetic resonance imaging; Sz: schizophrenia; TR: repetition time; TE: echo time. Superscript letters preceding author names identify studies contributing to relationships depicted in Fig. 2. For these studies, MNI centroids are given where provided, with network labels assigned as per the nearest neighbour in the Power et al. atlas. Where centroids were not provided, centroids of corresponding regions in the Neuromorphometrics atlas (Nm-atlas) in SPM are used where possible.

Table 5
Analysis 2D – other region functional connectivity (FC) studies in major depressive disorder (MDD), with dimensional analysis of anxiety.

2d. Other seeds	Sample	Severity	Exclusions	Scanning	ROIs/FC	Extracted results
[k]Bai 2018	DSM-IV criteria. MDD (N = 50, age ± SD 39 ± 11, 66% females), HC (N57, 37 ± 9, 61%)	MDD HAMD/HAMA scores: 22.8 ± 4.0 / 15.1 ± 6.8	Substance misuse, schizoaffective disorder or schizophrenia, ECT in last 3 months, history of neurological illness, age < 18 or > 65	8-minute 3 T-eyes-closed rsfMRI. TR/TE 2 s/22.5 ms. Included GN.	Atlas NAcc & mOFC ROIs seed regions. Signif. FC differences between patients & controls tested for relationships with clinical measures in patients (p < 0.05 uncorrected)	Greater HAMA associated with ↓ FC between right NAcc (MNI centroid: 8, 10, −10, subcortical) and right temporal pole (33, 6, −36, DMN)
Luo 2018	DSM-IV criteria. MDD (N23, 30 ± 7, 61%), HC (N34, 30 ± 7, 56%) matched for age, gender, and education level	74% first episode. HAMD/HAMA scores: 34.3 ± 7.6 / 24.4 ± 8.6	History of head injury, seizures, substance abuse, "serious medical or surgical illness"	8-minute 3 T eyes-closed rsfMRI. TR/TE 2 s/30 ms. Motion limits 1.5 mm/ 1.5°. Excluded GN.	Six brainstem subregion seeds. Signif. diff. in FC between left medulla and right IPC between MDD and HC – examined relationships between this FC and clinical variables in MDD	Greater HAMA associated with ↑ FC between left medulla and right IPC (p < 0.05 uncorrected)
Yan 2019	DSM-IV criteria. MDD split into 35 "AD" (33 ± 9 y, 46%), 25 non-AD (33 ± 8 y, 56%) based on HAMD sub-score, HC (N27) matched age, education, gender	100% first episode. HAMD total – AD: 26.2 ± 4.2, non-AD: 22.1 ± 4.4	History of head injury "somatic disease", "other psychiatric disease". SD patients: 3 + of a set of somatic symptoms, non-SD: < 3. Age < 20 or > 45	6.7-minute 3 T eyes-closed rsfMRI. TR/TE 3 s/40 ms. Motion limits 2 mm/2°. Included GN.	Voxels with signif. activity diffs. between AD & non-AD used as seed regions. FCs with signif. diffs. btwn groups then correlated with clinical variables (p < 0.05, Bonf. corr.)	No association between a HAMD anxiety/ somatisation sub-score and FC between the orbital part of the right IFG and left IPC within the AD group
Zhao 2020	DSM-IV. MDD split into 60 "AD" (34 ± 9 y, 53%), 38 non-AD (32 ± 9 y, 100%) based on HAMD sub-score. HC (N60, 33.6 ± 9.2, 43%). Overlap with Yan 2019	100% first episode. HAMD total – AD: 26.4 ± 4.8, non-AD: 20.9 ± 3.2	History of antidepressant use or psychotherapy, "other major psychiatric or neurological illness", age < 18 or > 55	6.7-minute 3 T eyes-closed rsfMRI. TR/TE 3 s/40 ms. Motion limits 2 mm/2°. Included GN.	Voxels with signif. activity diffs. between AD & non-AD used as seed regions. Age, gender, years of education used as covariates (p < 0.001)	No differences between AD or non-AD using seed in the right orbital part of MFG
Zhu 2020	ICD-10 criteria. MDD split into 42 "NSE" (43 ± 10, 67%) and 54 "LSE" (45 ± 12, 57%). 69%/ 26%/5% taking SSRI/ SNRI/NaSSA	HAMD total – NSE: 26.7 ± 12.6, LSE: 27.6 ± 12.4.	Other psych. disorders (Sz, BD, anx. dis., substance abuse /dependence), head injury with LoC, "signif. neuro./physical diseases"	6.2-minute 3 T eyes-closed rsfMRI. TR/TE 2 s/30 ms. Motion limits 2.5 mm/ 2.5°. Excluded GN.	Voxels with signif. activity diffs. between NSE /LSE used as seed regions. FCs with signif. diffs btwn groups corr. with clinical variables (p < 0.05, uncorr)	Greater HAMA associated with ↓ FC between right cuneus and right LTC
Hu 2021	DSM-IV criteria. MDD (N114, 39 ± 13, 64%), HC (N112, 37 ± 13, 64%) matched for age, sex, education	44% taking an antidepressant. HAMD total 20.7 ± 4.3	Bipolar disorder, cardiovascular disease or diabetes, age < 18 or > 75	8-min 3 T eyes-closed rsfMRI. TR/TE 2 s/30 ms. Excluded GN.	Left /right anterior, middle, posterior hippocampal seeds. FCs with signif. diffs btwn groups corr. with clinical variables, controlling for age and sex (FDR p < 0.05)	Greater HAMD anxiety/ somatization sub-score associated with ↓ FC between right anterior hippocampus and posterior insula (MNI 36, −12, 9, sensory/somatomotor)

3 T: 3-Tesla; AD: anxious depression; BD: bipolar disorder; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Volume IV; ECT: electro-convulsive therapy; GN: global normalisation; HAMA: Hamilton anxiety rating scale; HAMD: Hamilton rating scale for depression; HC: healthy control participants; IFG: inferior frontal gyrus; IPC: inferior parietal cortex; LoC: loss of consciousness; LSE: low sleep efficiency; LTC: lateral temporal cortex; MFG: middle frontal gyrus; mOFC: medial orbitofrontal cortex; NAcc: nucleus accumbens; NaSSA: noradrenergic and specific serotonergic antidepressant; NSE: normal sleep efficiency; ROI: region of interest; rsfMRI: resting-state functional magnetic resonance imaging; Sz: schizophrenia; SNRI: serotonin and noradrenaline reuptake inhibitor; SSRI: selective serotonin re-uptake inhibitor; TE: echo time; TR: repetition time. Superscript letters preceding author names identify studies contributing to relationships depicted in Fig. 2. For these studies, MNI centroids are given where provided, with network labels assigned as per the nearest neighbour in the Power et al. atlas.

as it showed significant differences between patients and controls in a preceding analysis using medullary sub-regions as seeds). In patients with "somatic" depression (i.e., depression accompanied by prominent somatic symptoms such as fatigue and disturbances in appetite and sleep (Silverstein, 1999)), Yan et al. (2019) found no correlation between an anxiety sub-score on the HAMD and FC between left inferior parietal cortex and the orbital part of the right inferior frontal gyrus (they examined this particular FC as it showed differences between patients with somatic versus "non-somatic" depression). Dividing medication-naïve MDD patients according to anxiety/somatisation HAMD sub-score into lower (<7, N = 38) and higher (≥ 7, N = 60) anxiety groups, Zhao et al. (2020) found no differences between patient groups in FC values using a seed region in the orbital aspect of MFG (chosen as this area showed activation differences between the low and high anxiety groups). Bai et al. (2018), using seeds in nucleus accumbens and medial orbitofrontal cortex, then examining relationships with HAMA for FC values that had shown significant differences between patients (N = 50) and controls, found a negative relationship with FC between HAMA and FC between right nucleus accumbens and right temporal pole (DMN). Zhu et al. (2020) found that FC between the right cuneus and right lateral temporal cortex was negatively correlated with HAMA (this relationship being examined as it had shown differences between two groups of patients with MDD, one with high, and one with low, "sleep efficiency"). Finally, Hu et al. (2021) divided the hippocampus into left and right anterior, middle, and poster subdivisions and compared seed-region FC for each subdivision between a large sample (N = 114) of patients with MDD (44% of whom were taking an antidepressant) and age-, sex-, and education-matched controls. Of those FC relationships showing significant between-group differences, FC between right anterior hippocampus and posterior insula was negatively correlated with an anxiety/somatisation sub-score of the HAMD in patients.

4. Discussion

We identified two studies that compared functional connectivity between MDD alone and MDD with a co-morbid anxiety disorder. There

were nineteen studies that examined relationships between connectivity and a dimensional measure of anxiety in a single-disorder MDD group. Of the latter studies, most quantified anxiety using total score on the HAMA, this was followed by use of an anxiety sub-score based on the HAMD. There was marked heterogeneity in reported relationships between connectivity and anxiety, partly due to a focus on small sets of connectivity relationships within individual studies, as well as due to differences in region of interest definitions. Most studies reported associations with the amygdala – consistent with the known role for this area in processing fear and threat (Davis, 1992), followed by the DMN, then the SN and ECN, and thus these relationships will form the focus of this discussion.

With regards to amygdala FC, there was an apparent discrepancy between associations with anxiety in two studies that used whole brain analyses and three studies that used amygdala seed region analyses. Considering whole brain analyses, Pannekoek et al. (2015) found increased FC between a limbic network (including amygdala and hippocampus) and posterior DMN and ECN in their co-morbid MDD and anxiety disorder group, and Ma et al. (2020) found greater dimensional anxiety to be associated with greater subcortical (including amygdala, hippocampus, globus pallidus) FC with the anterior DMN in MDD patients. Considering amygdala seed region analyses, however, both Ramasubbu et al. (2014) and He et al. (2019) found *reduced* FC between amygdala and DMN regions with greater dimensional anxiety, and Qiao et al. (2020) found *reduced* FC between amygdala and ECN with greater anxiety. The findings of Yang et al. (2017) suggest a solution to this apparent discrepancy. Yang et al. found reduced FC between the amygdala and other limbic (hippocampus) and subcortical (globus pallidus) structures with greater dimensional anxiety.

Together, the above results suggest that greater anxiety is associated with greater dysconnectivity of the amygdala – that is, with reduced connectivity between not only the amygdala and the DMN and ECN, but also between the amygdala and other limbic and subcortical areas. Conceivably, the lower connectivity between the amygdala and the DMN and ECN may represent loss of top-down regulation of amygdala reactivity to perceived threat. Such a role might most readily be expected of the ECN (Xu et al., 2019). Interestingly, Qiao et al. (2020) found that the ECN region implicated in anxiety-related reductions in FC with the amygdala was the right DLPFC. This is consistent with early work showing that stimulation of right DLPFC prior to traditional stimulation of left DLPFC is associated with greater reduction in anxiety measures in people with treatment resistant depression (Griffiths et al., 2019).

A role for the DMN in regulating amygdala reactivity is also plausible. In their review, Kim et al. (2011) propose that anterior DMN (medial prefrontal cortex) regulates amygdala reactivity to ensure effective threat processing. Consistent with this, Gonzalez-Escamilla et al. (2018) found that inhibitory TMS to DMPFC enhanced neural responses to threat stimuli recorded with electroencephalography. Threat responses were predicted by the volume of both the DMPFC and the amygdala. Further support for DMN targeting for anxiety symptoms in people with MDD comes from a recent study by Siddiqi et al. (2020), who examined the relationship between improvement in "dysphoric" and "anxiosomatic" symptoms and TMS site in people with treatment-resistant depression. Whilst TMS was targeted at left DLPFC in all their patients, this targeting was based on scalp measurements, so the actual stimulated cortical location, which could be retrospectively determined from MRI scans that the patient had received, differed based on brain anatomy. Siddiqi et al. found that the peak targets for reducing anxiosomatic symptoms lay within the DMN, including the DMPFC. The findings of our review provide support for further studies into targeting DMN regions for MDD with co-morbid anxiety.

The ECN and DMN have been described as externally- (ECN) versus internally- (DMN) oriented in their scope (Menon, 2011). Thus, speculatively, the ECN and DMN may regulate amygdala responses to threat provoked by external (e.g., social, environmental) and internal (e.g., ruminative, bodily symptom) stimuli, respectively. With regards to the DMN, the anterior DMPFC would be most expected to exert top-down regulation of the amygdala. However, included studies indicated that associations between anxiety and amygdala-DMN connectivity were not limited to the DMPFC and included temporal and posterior DMN structures in addition. The functional significance of these associations remains to be determined. They may be secondary to amygdala-DMPFC and within-DMN connectivity, they could reflect modulatory roles of other DMN regions on the amygdala, or they could reflect reductions, or dysfunctions, in exchange of information between amygdala and, for example, memory structures in the temporal cortex.

The relationship between amygdala-ECN and amygdala-DMN connectivity warrants further exploration. One of the most consistent findings in a meta-analysis of FC changes associated with MDD alone was an increase in positive connectivity between the ECN and DMN – these networks are anticorrelated or uncorrelated in health (Kaiser et al., 2015). It may be that lower amygdala FC with the DMN and ECN in people with MDD reflects primary dysfunctions in both the DMN and ECN, or it may reflect a primary dysfunction in one of these networks that is then readily propagated to the other network due to increased positive connectivity between the DMN and ECN. Speculatively, the latter may provide a basis for the high levels of co-morbid anxiety disorder in MDD (Kaufman and Charney, 2000). The findings of Shi et al. (2020), that anxiety was particularly associated with the average FC of DMN regions, along with associations between anxiety and FC between DMN and basal ganglia (Bai et al., 2018), suggest that the DMN deficits may be primary under this scenario.

Finally, it is known that the SN can regulate the interaction between the DMN and ECN (Goulden et al., 2014; Sridharan et al., 2008). Indeed, disruptions of co-ordination between the DMN and ECN by the SN have been implicated in a range of psychiatric disorders beyond MDD (Menon, 2011). It may be that the specific dysfunction in anxiety is impairments of communication between these networks and the amygdala. To this end, it is plausible that deficits in the SN represent a more proximal cause of anxiety-related abnormalities in connectivity between the amygdala and the DMN or ECN in people with MDD. Price et al. (2017) found greater effective (directed) connectivity from the SN to the amygdala and the ECN in their group with higher levels of co-morbid anxiety disorders, suggesting that the SN drove up amygdala activity and potentially contributed to ECN dysregulation, and implying that ECN dysregulation may be primary to DMN dysregulation. However, Peng et al. (2020) found anxiety-related *reductions* in FC between the SN and ECN and, in a subsequent study, Peng et al. (2018) identified anxiety-related increases in FC between the SN and DMN. In any case, these findings suggest that areas of the SN may be useful targets for treating anxiety co-morbidity in MDD, potentially with the goal of restoring normal regulatory control of the amygdala from both the DMN and ECN. However, the SN involves deeper brain areas (dACC and anterior insula) that are more difficult to target with neuromodulation methods than areas such as the DMPFC.

5. Limitations

There were only two studies that compared people meeting diagnostic criteria for a co-morbid anxiety disorder alongside MDD with a non-co-morbid group. Thus, most of the review relied on studies that included a dimensional measure of anxiety. Such studies mostly used total score on the HAMA, or an anxiety sub-score of the HAMD, and did not distinguish different types of anxiety pathology, which may be associated with different FC alterations. Moreover, whilst the HAMA has items covering both the cognitive and physiological aspects of anxiety, it does not address the core psychopathology of specific anxiety disorders (such as worry for GAD). Critically, whilst the HAMA is regarded as a valid measure of anxiety severity in people with depression, it has been criticised for having poor discriminability between anxiety and depressive disorders (Zimmerman et al., 2017). Moreover, HAMD

anxiety sub-scores are based on a small number of items, and there is criticism around the use of HAMD sub-scores given evidence for unstable factor structure (Goldberger et al., 2011). Future work with a wider range of anxiety measures, covering the psychological symptoms of anxiety including worry and fear, are needed. It is also unclear whether the co-morbid state of MDD and a suprathreshold anxiety disorder is qualitatively different to MDD with high dimensional anxiety, or whether the diagnosed co-morbid state represents the high end of dimensional anxiety.

A further limitation concerns the nature of correlations between anxiety and FC. A positive correlation, for example, could be due to: negative FC (i.e., anti-correlated activities) at low levels of anxiety and positive FC at high levels of anxiety; negative FC at low levels of anxiety and zero FC (uncorrelated activities) at high levels of anxiety; or zero FC at low levels of anxiety and positive FC at high levels. Some studies did not provide sufficient information to distinguish these possibilities. Of those that did provide information, many used global normalisation (a pre-processing step involving subtracting out activity modulations common across the whole brain), which can serve to re-centre connectivity values, making uncorrelated brain areas appear anti-correlated in their activities, for example (Anderson et al., 2011).

Few studies reported details of imaging quality assessment or pre-processing pipeline validation, and only one study reported pre-specification of the extracted analyses.

Most of the included studies restricted their analyses of relationships with anxiety to a small set of FC values. Whilst this reduces concerns around multiple comparisons, the specificity of the relationships reported in such studies is unclear (it may be that equal, or stronger, relationships would be present with other, non-examined, FC values). Thus, further studies that look at relationships between co-morbid anxiety and a wider range of FC values across the brain are needed to fully understand differences in brain networks in the co-morbid state.

The focus on small sets of FC values, and the lack of common regions of interest and analysis pipelines, contributed to the heterogeneity observed in the findings, and precluded conducting a formal meta-analysis in this review. This is reflected in the model in Fig. 2 in that each specific link is supported by only one or two studies. For these reasons, the model presented in Fig. 2 should be regarded as preliminary. Future work should also move beyond FC to explore effective connectivity, which captures the influence of one brain area upon another. Only one of the included studies examined effective connectivity. Treating aberrant connectivity patterns will likely require stimulating the drivers of the aberrant connectivity, which can only be confidently determined through effective connectivity analyses. With further effective connectivity studies, the model in Fig. 2 could be refined to specify the directions of influence, thus improving its ability to guide neuromodulation target selection. Additional advances will likely come from incorporating into the model the effects of tasks on connectivity relationships. Whilst resting-state paradigms have provided a large amount of information on brain networks (Power et al., 2011; Yeo et al., 2011), and on network abnormalities in disease (Fox et al., 2014; Woodward and Cascio, 2015), they may be inherently limited in the level of detail that they can provide (Finn, 2021). Whilst task-based studies have so far used a range of different tasks, limiting comparability (and have often not performed connectivity analyses), "rest" itself is not an entirely homogeneous state. Moreover, understanding abnormalities in the engagement or disengagement of connectivity pathways will be important in understanding disease. Finn (2021) suggests that future studies utilise paradigms incorporating participant reports of thoughts or images experienced during scanning (to enable examination of correlates of different brain states), the use of engaging, "naturalistic", stimuli such as films or stories, and the integration of rest with task periods.

6. Conclusion

As noted, there are several limitations to the included studies that make any model of the connectivity correlates of anxiety in MDD preliminary. Our model thus awaits confirmation, and it will be well-suited to exploration in future open, large-scale, well-characterised, FC datasets. Amidst significant heterogeneity in the findings, there is initial evidence that anxiety in MDD is associated with dysconnectivity of the amygdala from other brain networks, including the DMN and ECN (which conceivably could serve a regulatory function over the amygdala) as well as from the activities of other limbic and subcortical areas. The ECN, in the form of the DLPFC, is already used as a TMS treatment target for depression, with some evidence of benefit of right DLPFC stimulation in addressing anxiety (as opposed to traditional left DLPFC stimulation for addressing mood). The results of this review suggest that DMN areas may represent potential under-researched treatment targets for MDD with co-morbid anxiety, conceivably with the goal of re-establishing another aspect of amygdala regulation. Further work is needed incorporating patients with MDD and suprathreshold co-morbid anxiety disorder diagnoses, as well as dimensional anxiety measurement focussing on the psychological symptoms of anxiety, to confirm these findings, and examination of effective, as opposed to solely functional, connectivity, is needed to help untangle the interactions between brain networks and identify the optimal treatment targets for the co-morbid state.

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Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104701.

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