Neuroscience and Biobehavioral Reviews 96 (2019) 21–30

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Anxious brain networks: A coordinate-based activation likelihood estimation meta-analysis of resting-state functional connectivity studies in anxiety

Jie Xu[a], Nicholas T. Van Dam[b,c], Chunliang Feng[a,d], Yuejia Luo[a,e], Hui Ai[a,e,*], Ruolei Gu[f,g,**], Pengfei Xu[a,e,h,*]

[a] Shenzhen Key Laboratory of Affective and Social Neuroscience, Shenzhen University, Shenzhen, 518060, China
[b] School of Psychological Sciences, University of Melbourne, Victoria, 3010, Australia
[c] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, 10029, USA
[d] College of Information Science and Technology, Beijing Normal University, Beijing, 100875, China
[e] Center for Emotion and Brain, Shenzhen Institute of Neuroscience, Shenzhen, 518057, China
[f] Key Laboratory of Behavioral Science, Institute of Psychology, Chinese Academy of Sciences, Beijing, 100101, China
[g] Department of Psychology, University of Chinese Academy of Sciences, Beijing, 100049, China
[h] Department of Neuroscience, University Medical Center Groningen, University of Groningen, 9713, AW Groningen, the Netherlands

ARTICLE INFO

Keywords:
Anxiety
Anxiety disorders
Resting-state
Functional brain networks
Activation likelihood estimation
Meta-analysis

ABSTRACT

Anxiety and anxiety disorders are associated with specific alterations to functional brain networks, including intra-networks and inter-networks. Given the heterogeneity within anxiety disorders and inconsistencies in functional network differences across studies, identifying common patterns of altered brain networks in anxiety is imperative. Here, we conducted an activation likelihood estimation meta-analysis of resting-state functional connectivity studies in anxiety and anxiety disorders (including 835 individuals with different levels of anxiety or anxiety disorders and 508 controls). Results show that anxiety can be characterized by hypo-connectivity of the affective network with executive control network (ECN) and default mode network (DMN), as well as decoupling of the ECN with the DMN. The connectivity within the salience network and its connectivity with sensorimotor network are also attenuated. These results reveal consistent dysregulations of affective and cognitive control related networks over networks related to emotion processing in anxiety and anxiety disorders. The current findings provide an empirical foundation for an integrated model of brain network alterations that are common across anxiety and anxiety disorders.

1. Introduction

Anxiety, a common negative emotion in daily life, is characterized by sustained apprehension, vigilance, arousal, and avoidance behaviors (Tovote et al., 2015). Although anxiety has evolutionary adaptive value, it is often accompanied by unpleasant feelings and unwanted experiences, including worry, restlessness, irritability, and insomnia (Keedwell and Snaith, 1996). Pathological anxiety consumes mental resources limiting cognitive efficiency and impairs daily functioning and quality of life (Mathews and MacLeod, 2005; Rodriguez et al., 2005). The most common anxiety disorders include generalized anxiety disorder (GAD), social anxiety disorder (SAD), specific phobia (SP), and panic disorder (PD); high rates of comorbidity across these diagnoses suggest common vulnerabilities (Hamm et al., 2014). For instance, hypersensitivity to emotional stimuli has been broadly shown in individuals with GAD (Weinberg et al., 2010), SAD (Voegler et al., 2018), PD (Ludewig et al., 2003), and high trait anxiety (HTA; Hajcak et al., 2003). Individuals with GAD (Etkin et al., 2010), SAD (Mennin et al., 2009), PD (Ball et al., 2013), as well as HTA (Krug and Carter, 2010) have been shown to exhibit reduced regulation of emotion as well as decreased activation of the default mode network (DMN) during specific tasks. It has also been suggested that an imbalance between the affective network (AN) and executive control network (ECN) plays a crucial role in various anxiety disorders (Kim et al., 2011; Rauch et al.,

* Corresponding authors at: Shenzhen Key Laboratory of Affective and Social Neuroscience, Shenzhen University, 3688 Nanhai Ave., Nanshan District, Shenzhen, 518060, China.
** Corresponding author at: South Building, Courtyard 16, Lincui Road, Chaoyang District, Beijing, 100101, China.
E-mail addresses: h.ai@szu.edu.cn (H. Ai), gurl@psych.ac.cn (R. Gu), xupf@szu.edu.cn (P. Xu).

https://doi.org/10.1016/j.neubiorev.2018.11.005
Received 8 June 2018; Received in revised form 12 November 2018; Accepted 12 November 2018
Available online 17 November 2018
0149-7634/

2006). These findings suggest common neuropsychological components across most variants of anxiety and anxiety disorders. However, these neuropsychological components underlying the aforementioned common vulnerabilities are largely unknown.

Previous studies of anxiety mainly focus on syndrome-specific problems (e.g., fear in PD); findings reliably suggest that anxious individuals show an attentional bias to threat and heightened anticipatory feelings towards uncertain outcomes (Grupe and Nitschke, 2013). With the development of resting-state functional connectivity (rsFC) techniques, a network-based pathophysiology of anxiety has the potential to improve our understanding beyond syndrome-specific problems. This scheme links anxiety with atypical patterns of distinct functional brain networks associated with specific cognitive functions and could be detected during the resting state (Sylvester et al., 2012). For example, the ECN, consisting of the dorsolateral prefrontal cortex (dlPFC), inferior parietal lobule (IPL), and dorsomedial prefrontal cortex (dmPFC), is mainly involved in top-down cognitive regulation (Power et al., 2011; Seeley et al., 2007; Yeo et al., 2011) and has been shown to be altered in anxiety (Geiger et al., 2016). Similarly, the DMN, which is involved in emotion regulation and self-reference (Yeo et al., 2011), has been found to be altered in anxiety (Zhao et al., 2007).

Although abnormalities of intra- and inter-network functional connectivity have been observed in anxious individuals (e.g., Toazza et al., 2016; Yang et al., 2017), previous findings are heterogeneous and divergent. A predominant brain network model of anxiety focuses on the decreased connectivity between the AN (especially the amygdala) and ECN, such that anxiety reflects prefrontal dysregulation and exaggerated amygdala reactivity (Bishop et al., 2004; Bishop, 2007). This model has been supported by numerous studies (Clewett et al., 2014; Kim and Whalen, 2009; Prater et al., 2013), though other studies report increased connectivity between the AN and ECN in anxiety disorders relative to healthy controls (HC) (Etkin et al., 2009; Kim et al., 2014). Aside from extrinsic connectivity of the AN, some studies suggest that intrinsic connectivity of the AN should also be highlighted (e.g., Roy et al., 2013; Toazza et al., 2016). Other studies emphasize the importance of anterior insular (a part of the salience network, SN) hyperactivity in anxiety and anxiety disorders (Paulus and Stein, 2006, 2010), which has also received empirical evidence (e.g., Baur et al., 2013; Etkin and Wager, 2007). In an integrative network account, Sylvester et al. (2012) suggest that anxiety is associated with increased functioning of the ventral attention network (VAN) and SN, as well as decreased functioning of the DMN and ECN. In line with this account, Manning et al. (2015) have observed decreased connectivity between the nucleus accumbens and putamen (parts of the AN) in SAD. Shin et al. (2013) have reported increased functional connectivity between the anterior cingulate cortex (ACC) of the SN and the precuneus of the DMN in PD.

To ascertain the common brain networks that are fundamentally altered in anxiety and anxiety disorders, we conducted a functional connectivity-based meta-analysis of rsFC studies on anxiety and anxiety disorders. Meta-analysis is an increasingly popular method to overcome the heterogeneity and divergence of previous results and assess the strength of previous findings (Kotov et al., 2010; Müller et al., 2018). In addition, meta-analytic techniques may identify unexpected sources of heterogeneity and test for possible observer bias (e.g., researchers' predispositions to highlight the findings which confirm their hypotheses; see Hróbjartsson et al., 2013; Munafò et al., 2009). The aim of the current study was to test the consistency in anxiety-related hyper-/hypo-connectivity of a priori seed networks. According to previous findings about deficient brain networks of cognitive and affective regulation in anxiety and anxiety disorders (Bender et al., 2012; Orgeta, 2011), we predicted that seed regions of interest (ROIs) in the AN (especially the amygdala) would exhibit decreased connectivity with the ECN and/or DMN.

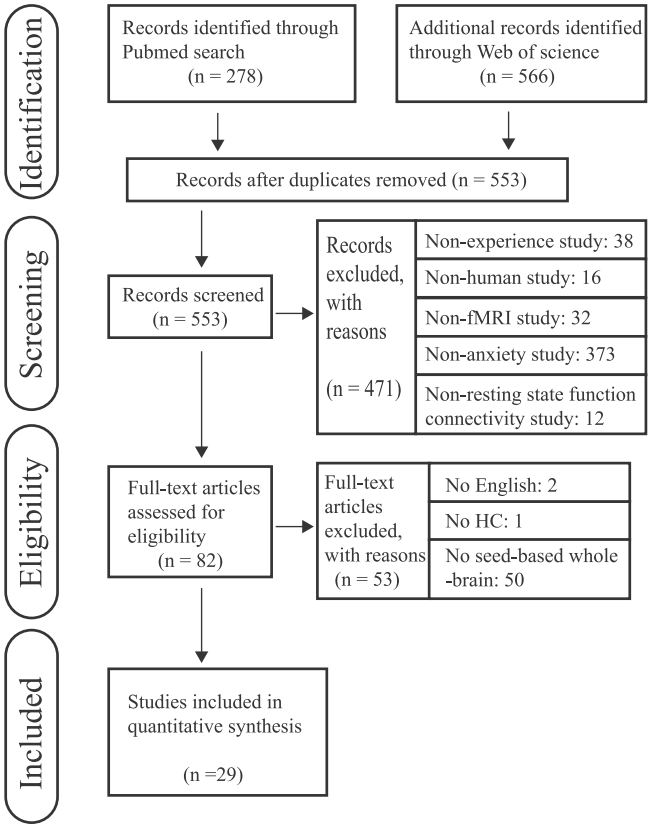

Fig. 1. Flow diagram of literature search and study selection.

2. Methods

2.1. Literature search

A comprehensive literature search was carried out using the Web of Science and PubMed databases on March 06, 2018 (including studies in-press), using the keywords "(anxiety OR anxious) AND (rest OR resting) AND (connect OR connectivity)." The search resulted in 553 potential references after elimination of duplicates (see Fig. 1; search method reported per PRISMA diagram, Moher et al., 2009).

We included original functional magnetic resonance imaging (fMRI) studies that used seed-based whole-brain rsFC 1) to compare anxiety disorders (GAD, SAD, SP, or PD) with healthy controls (HC), or 2) to correlate with individual level of anxiety (measured by State Trait Anxiety Inventory [STAI]; Beck Anxiety Inventory [BAI]; or Hamilton Anxiety Rating Scale [HAMA]). Studies focusing on posttraumatic stress disorder and obsessive-compulsive disorder were excluded, since they have been separated from anxiety disorders in the DSM-V (American Psychiatric Association, 2013).

In the first screening of the titles and abstracts, the following exclusion criteria were applied: 1) non-empirical studies, 2) non-human studies, 3) non-fMRI studies, 4) non-rsFC studies, 5) non-anxiety studies. Subsequently, full-text articles of the included studies were further evaluated for eligibility. Studies were also excluded due to: 1) not in English, 2) no HC group, 3) non-whole-brain functional connectivity analyses, 4) entirely overlapping sample and same seed Regions of Interest (ROIs) reported in another publication (Table S1). These searches and exclusion criteria yielded a sample of 29 studies, n = 1585 (Table 1). No identified publication reported on entirely overlapping samples and seed ROIs or using different anxiety disorders groups compared to a single HC group.

Table 1
Demographic Characteristics of Studies Included in Meta-analysis.

No.	Reference	HC N(M/F)	Age	Anxiety Symptoms	PAT N(M/F)	Age	Anxiety Types	Anxiety Symptoms
1	Andreescu et al., 2014	31(13/18)	58.8 ± 8.3	HAMA: 2.7 ± 1.8	24(5/19)	54.0 ± 7.9	GAD	HAMA: 20.6 ± 2.9
2	Arnold Anteraper et al., 2014	17(8/9)	25.0 ± 7.5	---	17(8/9)	24.7 ± 6.3	SAD	LSAS: 77.9 ± 14.1
3	Cha et al., 2014	25(0/25)	---	---	32(0/32)	---	GAD	---
4	Cui et al., 2017	20(14/6)	21.7 ± 3.6	LSAS: 20.0 ± 8.3 HAMA: 1.1 ± 1.7 STAI-T: 32.9 ± 4.9 STAI-S: 31.4 ± 4.8	21(15/6)	22.1 ± 3.9	SAD	LSAS: 53.9 ± 11.2 HAMA: 6.1 ± 4.6 STAI-T: 48.1 ± 6.9 STAI-S: 41.6 ± 8.2
5	Dorfman et al., 2016	36(15/21)	13.0 ± 2.7	SCARED-pc: 6.4 ± 5.2	35(14/21)	13.2 ± 2.7	AD	SCARED-pc: 32.7 ± 10.7
6	Geiger et al., 2016	15(7/8)	28.5 ± 8.2	LSAS: 22.3 ± 22.2	18(7/11)	29.6 ± 9.0	SAD	LSAS: 88.6 ± 24.8
7	Geng et al., 2016	60(35/25)	15.7 ± 1.0	STAI-T: 39.6 ± 6.1	---	---	---	---
8	Hahn et al., 2011	27(11/16)	27.7 ± 7.2	STAI-T: 29.0 ± 7.0 STAI-S: 30.3 ± 5.1	10(9/1)	28.6 ± 4.3	SAD, PD	STAI-T: 41.6 ± 11.5 STAI-S: 42.1 ± 9.0
9	Hamm et al., 2014	23(10/13)	14.6 ± 3.9	PARS: 2.0 ± 2.5	33(11/22)	13.9 ± 3.1	AD	PARS: 22.0 ± 3.9
10	He et al., 2016	280(99/181)	47.2 ± 17.9	STAI-T: 49.5 ± 10.0 STAI-S: 46.0 ± 8.7	---	---	---	---
11	Kim et al., 2014	29(8/21)	19.6 ± 0.9	STAI-S: 33.0 ± 7.8 STAI-T: 36.3 ± 8.1	---	---	---	---
12	Li et al., 2016	22(14/8)	38.1 ± 10.3	HAMA: 0.8 ± 0.9	21(13/7)	39.9 ± 12.2	GAD	HAMA: 0.9 ± 1.7
13	Liao et al., 2011	18(13/5)	21.9 ± 3.7	LSAS: 19.1 ± 7.9 HAMA: 0.9 ± 1.6 STAI-T: 32.7 ± 5.0 STAI-S: 31.3 ± 4.8	18(12/6)	22.7 ± 3.8	SAD	LSAS: 54.4 ± 12.0 HAMA: 6.4 ± 5.0 STAI-T: 48.3 ± 7.4 STAI-S: 41.1 ± 8.7
14	Liu et al., 2015	20(9/11)	15.6 ± 1.7	SCARED: 16.6 ± 8.2	26(10/16)	15.5 ± 1.5	GAD	SCARED: 37.1 ± 12.0
15	Makovac et al., 2016	21(13/8)	28.7 ± 9.5	PSWQ: 41.8 ± 7.3	19(2/17)	29.6 ± 6.9	GAD	PSWQ: 54.7 ± 5.7
16	Manning et al., 2015	53(36/17)	29.9 ± 8.3	SPAI: 36.7 ± 26.8 STAI: 30.0 ± 7.0	33(19/14)	29.4 ± 6.2	SAD	SPAI: 112.6 ± 22.3 STAI: 54.8 ± 10.5
17	Pace-Schott et al., 2017	13(2/11)	35.0 ± 15.0	STAI-S: 30.3 ± 5.1	12(2/10)	30.2 ± 10.3	GAD	STAI-S: 41.7
18	Pannekoek et al., 2013a	12(5/7)	34.0 ± 7.2	FQ: 20.8 ± 8.2	12(5/7)	34.8 ± 8.8	SAD	FQ: 4.5 ± 4.3
19	Pannekoek et al., 2013b	11(1/10)	35.0 ± 9.7	BAI: 1.9 ± 2.5	11(1/10)	34.5 ± 10.6	PD	BAI: 14.5 ± 5.6
20	Prater et al., 2013	17(7/10)	25.7 ± 7.2	LSAS: 7.9 ± 7.1 STAI-T: 26.0 ± 3.0	20(9/11)	26.0 ± 5.4	gSAD	LSAS: 79.4 ± 15.4 STAI-T: 46.5 ± 11.9
21	Roy et al., 2013	20(7/13)	14.8 ± 1.7	SCARED-pc: 5.6 ± 2.9	15(5/10)	14.9 ± 1.7	GAD	SCARED-pc: 30.3 ± 12.9
22	Yuan et al., 2018	43(26/17)	30.1 ± 8.6	LSAS: 20.0 ± 15.1 HAMA: 2.0 ± 2.3	43(27/16)	29.0 ± 7.6	SAD	LSAS: 69.2 ± 28.2 HAMA: 14.1 ± 7.2
23	Yuan et al., 2017	64(35/29)	23.8 ± 3.3	LSAS: 34.4 ± 21.3 STAI-T: 38.8 ± 8.4	46(28/18)	24.8 ± 6.1	SAD	LSAS: 64.8 ± 22.4 STAI-T: 32.0 ± 11.0
24[1]	Chen and Etkin, 2013	38(11/27)	34.0 ± 1.6	BAI: 3.5 ± 0.6 STAI-T: 29.8 ± 0.9	39(12/27)	32.4 ± 1.5	GAD	BAI: 24.3 ± 1.8 STAI-T: 58.5 ± 1.6
25[2]	Dodhia et al., 2014	18(18/0)	29.9 ± 10.2	LSAS: 13.9 ± 8.3 BAI: 2.2 ± 5.0 STAI-T: 27.4 ± 8.2 STAI-S: 23.4 ± 7.0	18(18/0)	29.4 ± 9.0	gSAD	LSAS: 81.7 ± 17.5 BAI: 16.9 ± 8.2 STAI-T: 50.4 ± 11.5 STAI-S: 38.8 ± 15.8
26[3]	Birn et al., 2014	14	10.2 ± 1.3	---	14	9.9 ± 1.2	AD	---
27[3]	Choi et al., 2016	20(12/8)	24.1 ± 1.8	LSAS: 17.4 ± 10.9 SIAS: 10.9 ± 4.4 SPS: 3.5 ± 3.7 HAMA: 0.9 ± 1.7	22(13/9)	24.1 ± 2.8	SAD	LSAS: 17.4 ± 10.9 SIAS: 10.9 ± 4.4 SPS: 3.5 ± 3.7 HAMA: 0.9 ± 1.7
28[3]	Shin et al., 2013	11(-/-)	38.2 ± 12.4	PDSS: 1.9 ± 2.5	11(-/-)	38.2 ± 12.8	PD	---
29[3]	Toazza et al., 2016	18(10/8)	16.7 ± 2.3	---	19(10/9)	17.9 ± 2.5	AD	---

Abbreviations: AD, Anxiety disorder; BAI, Beck Anxiety Inventory; FQ, Fear Questionnaire; GAD, Generalized Anxiety Disorder; gSAD, Generalized Social Anxiety Disorder; HAMA, Hamilton Anxiety Rating Scale; HC, Healthy Control; LSAS, Liebowitz Social Anxiety Scale; PARS, Pediatric Anxiety Rating Scale; PD, Panic Disorder; PDSS, Panic Disorder Severity Scale; PSWQ, Penn State Worry Questionnaire; SAD, Social Anxiety Disorder; SAS, Self-rating Anxiety Scale; SCARED-pc, Screen for Anxiety Related Disorders (SCARED) average of the child and parent responses; SIAS, Social Interaction Anxiety Scale; SPS, Social Phobia Scale; STAI, State-Trait Anxiety Inventory. Note: The following studies were not included in the meta-analysis because that:

[1] No significant results were found for GAD vs. HC.

[2] Results were affected by acute oxytocin administration.

[3] The coordinates were not available.

2.2. Data extraction and coding

Coordinate extraction and coding were performed in three steps (Kaiser et al., 2015). First, the coordinate of each seed ROI was extracted and converted to Montreal Neurological Institute (MNI) space as needed (Lancaster et al., 2007). Second, according to the anatomical label and the coordinate, each seed ROI was assigned to one of eight previously defined seed-networks, identified by the integration across studies (Arnold Anteraper et al., 2014; Buckner et al., 2011; Choi et al., 2012; Geiger et al., 2016; Sang et al., 2012; Seeley et al., 2007; Sheline et al., 2010; Yeo et al., 2011; See Supplementary materials for details). Third, all peak coordinates of regions that connected to a seed ROI and showed significant differences between groups (defined as the effect network) were extracted. The coordinates reported in Talairach system were converted to MNI space (Lancaster et al., 2007). If the coordinates of whole-brain results were unavailable, the original authors were contacted for the information.

The contrasts were divided into “hyper-connectivity” and “hypo-connectivity” (Kaiser et al., 2015). Hyper-connectivity was defined as 1) increased positive or decreased negative rsFC in the anxious group or 2) positive correlations between rsFC and levels of anxiety. Hypo-connectivity was defined as 1) decreased positive or increased negative rsFC in the anxious group or 2) negative correlations between rsFC and levels of anxiety. Meta-analysis was conducted for each contrast of each network that included more than three independent studies.

2.3. ALE meta-analysis procedure

Meta-analysis was performed using GingerALE 2.3.6 (http://www.brainmap.org/ale/) to investigate brain connectivity differences between anxious individuals and controls in each seed-network with activation likelihood estimation (ALE; see Eickhoff et al., 2009, 2012). The steps of ALE were performed as follows. The clustering maps between experiments were calculated by modeling each focus of the study as the center of a three-dimensional Gaussian distribution with the full-width half-maximum (FWHM) weighted by the number of individuals and combining the probabilities of activation for each voxel. Non-parametric estimates for p values were derived for ALE scores by permuting 5000 times. The cluster determining threshold (CDT) was set at $p < 0.001$ using a minimum cluster extent of 200 mm^3 for hyper-connectivity and hypo-connectivity of each seed-network (Adler et al., 2005; Weng et al., 2014; Yang et al., 2012). All results were reported in MNI coordinates and overlaid onto the single-subject template “Colin's Brain” (Holmes et al., 1996) using MRIcron (http://people.cas.sc.edu/rorden/mricron/index.html) for presentation (Lancaster et al., 2007).

3. Results

Although 29 studies were initially selected after the two-step screening, the final analyses only included 23 studies. Six studies were excluded because they did not exhibit significant effects, involved acute drug effects, and/or did not provide coordinate information (details in Table 1). The final analyses included 20 comparative studies of 466 individuals with anxiety disorders (202 males, 27.3 ± 6.3 years) and 508 healthy controls (254 males, 26.2 ± 5.9 years), as well as three correlational studies of 369 healthy individuals (142 males, 39.9 ± 13.8 years).

The anxious group showed increased negative rsFC between the right amygdala and dmPFC of the ECN relative to HC (Fig. 2b and Table 2), indicating hypo-connectivity between different parts of the AN and ECN in anxious individuals. Anxiety and anxiety disorders also exhibited increased negative rsFC between the left amygdala and the ventromedial prefrontal cortex (vmPFC) of the DMN relative to HC (Fig. 2c), indicating hypo-connectivity between different parts of AN and DMN in anxious individuals. The anxious group also exhibited decreased positive rsFC between seeds of the DMN and dlPFC, suggesting hypo-connectivity between the DMN and ECN in anxiety (Fig. 3b and c). Decreased positive rsFC was found within seeds of the SN (Fig. 4b and c) and between seeds of the SN and postcentral gyrus (PTCG) (Fig. 4d), suggesting hypo-connectivity within the SN and between the SN and SMN in anxious individuals.

To avoid potential influences of including pediatric samples and/or differential connectivity among those without a clinical diagnosis, additional analyses without pediatric studies and without correlational studies were performed. The results were nearly identical, excepted that the rsFC in seed-network of SN was no longer significantly different between groups or in relation to anxiety (Table S4).

Given that the role of the amygdala in anxiety and anxiety disorders has been the focus of numerous studies (e.g., Rauch et al., 2006; Shin and Liberzon, 2010), we conducted an additional meta-analysis only including studies with the amygdala as the seed ROI. The result showed that anxiety and anxiety disorders could b characterized by hypo-connectivity between the right amygdala and the dmPFC of the ECN (Fig. 5b and Table 3). Anxiety and anxiety disorders were also associated with hypo-connectivity between the left amygdala and the vmPFC of the DMN (Fig. 5c and Table 3).

Because limited studies were available for the ECN (3 in total, including two contrasts of hyper-connectivity, two contrasts of hypo-connectivity), VAN (0), DAN (0), and VN (0), no meta-analysis was conducted for these networks (Table S2).

4. Discussion

The present meta-analysis revealed that anxiety and anxiety disorders were associated with altered functional connectivity within and/or between various brain networks, most notably the AN, SN, DMN, and ECN. Consistent alterations of connectivity across studies support the idea that there is a general pattern of altered functional brain networks across anxiety and anxiety disorders, highlighting their potential common vulnerabilities (Sylvester et al., 2012). Specifically, anxious individuals are characterized by hyper-arousal and worry states, as well as increased awareness of sensory processing, which may be underpinned by the hypo-connectivity between the SN and SMN (Bishop, 2007; Liao et al., 2010). Decreased intrinsic connectivity within the SN may reflect dysregulation between the AI and ACC, which may underpin alterations in attentional bias of negative information (Bishop et al., 2004; Geng et al., 2016). Decreased connectivity among the AN, DMN and ECN may be related to poor emotion regulation (indicating by hyperactivity of the amygdala), which has been proposed as a central feature in the neuropathophysiology of anxiety disorders (Kim et al., 2011; Rauch et al., 2006).

Hypo-connectivity between the AN and ECN (especially the dmPFC) was consistently observed in anxiety and anxiety disorders. This finding may reflect a deficit in top-down regulation of emotion, in which the dmPFC is known to play an important role (Kalisch, 2009). The finding may also be related to commonly observed hyperactivity of the amygdala in anxiety (e.g., Bishop, 2007); negative amygdalar connectivity with the dmPFC has been shown in tasks involving emotional appraisal/expression (Etkin et al., 2011). Although negative connectivity patterns are difficult to interpret (Fox et al., 2009; Murphy et al., 2009), one possible explanation is that a negative connectivity may reflect oppositional activity between two brain areas (i.e., competition for control over the other region). While a majority of neuropsychiatric research in anxiety typically focuses on connectivity between more lateral regions of the PFC and amygdala (e.g., Bishop, 2007), the dmPFC is believed to be critical emotional experience (Lindquist et al., 2012) and is known to be altered in function among individuals with anxiety (Etkin et al., 2011). Hence, altered connectivity between the AN and dmPFC likely reflects an increased sensitivity to fearful feelings and anxious experience, possibly as a manifestation of impaired automated emotion regulation.

Anxiety and anxiety disorders were also associated with hypo-

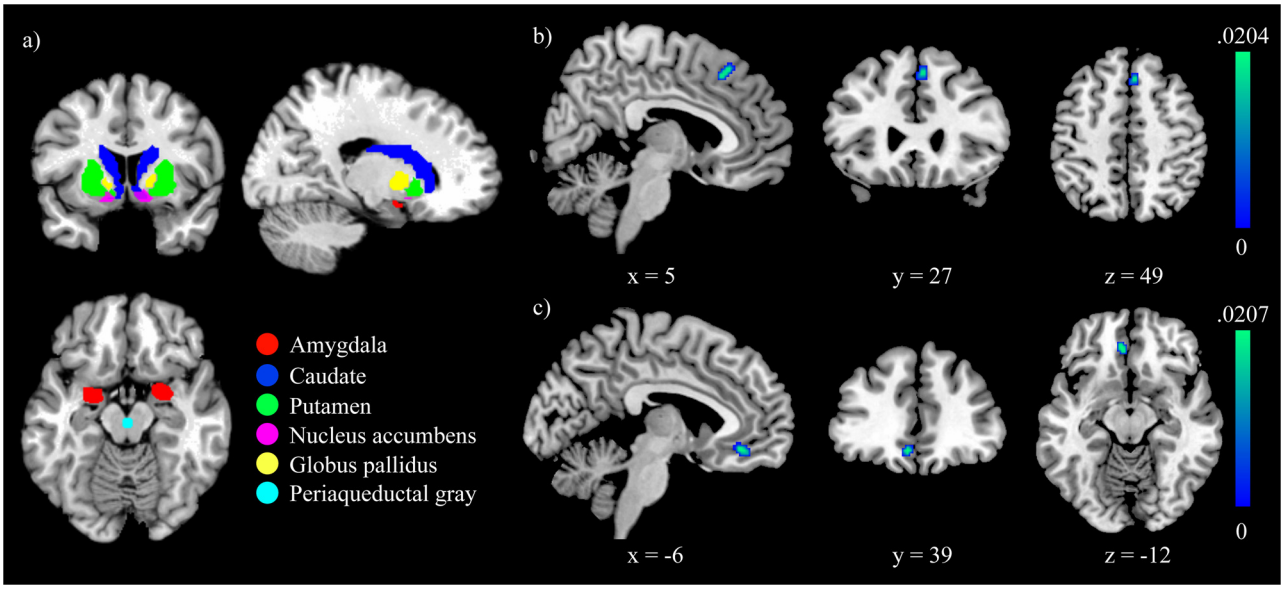

Fig. 2. Hypo-connectivity of the Affective Network. a) Seeds of the AN: amygdala, caudate, putamen, nucleus accumbens, globus pallidus, periaqueductal grey; Anxiety and anxiety disorders exhibited increased negative connectivity b) between the amygdala and the dmPFC of the ECN, c) between the amygdala and the vmPFC of the DMN. Color scale reflects *Maximum ALE score*. AbbreviationsALE, activation likelihood estimation; AN, affective network; DMN, default mode network; dmPFC, dorsomedial prefrontal cortex; ECN, executive control network; vmPFC, ventromedial prefrontal cortex.

connectivity between the AN and DMN (especially the vmPFC). The vmPFC has been shown to be critical to emotion regulation via modulating amygdala activity (Motzkin et al., 2015). This region also plays a pivotal role in value-based decision-making and social interaction (Hiser and Koenigs, 2018). Similar with the dmPFC, the vmPFC is believed to be part of the 'conceptualization' network, which is critical to emotional experience (Lindquist et al., 2012). Dodhia et al. (2014) found that the positive rsFC among individuals with generalized SAD (gSAD) decreased compared to HC, with higher social anxiety levels being correlated with lower amygdala-vmPFC connectivity. Hence, hypo-connectivity between the amygdala and vmPFC in anxiety and anxiety disorders may reflect impairments in the regulation of negative emotion, decision-making, and social processing. The consistent results between connectivity of the amygdala and AN suggest a dominant contribution of the amygdala to connectivity alterations of the AN in anxiety and anxiety disorders. Considering the oversampling of amygdala connectivity among studies of anxiety in the current meta-analysis, disentangling connectivity of the AN from that of the amygdala should be the focus of future research.

Decreased positive connectivity was also observed in anxiety and anxiety disorders between the DMN and ECN, which are the primary, anti-correlated positive and negative networks of the brain (Fox et al., 2005; Power et al., 2011). As cognitive anxiety is common among individuals with anxiety, these results may reflect decreased executive control over processes related to mind-wandering (such as worry; Sylvester et al., 2012). It has been established that individuals with (cognitive) anxiety exhibit diminished executive control; thereby, such diminished control may reflect as worry symptom (Eysenck et al., 2007).

The present meta-analysis also revealed decreased connectivity within the SN (including the AI and ACC) in anxiety and anxiety disorders. Previous studies have highlighted a hyperactive AI in anxiety during the processing of negative emotion (Etkin et al., 2009; Etkin and Wager, 2007). Likewise, a hyperactive ACC in anxiety has been observed during error detection and conflict monitoring (Simons, 2010). Both the AI and ACC underpin hyperactive fear responses in anxiety and anxiety disorders (Etkin et al., 2009; Stein et al., 2007). Decreased within-network connectivity of the SN may underlie the dysregulation of AI and ACC activations (Bijsterbosch et al., 2014; Liao et al., 2011), which play critical roles in interoceptive processes (Paulus and Stein, 2010), information integration about reinforcers, and the implement of goal-directed behavior (Shackman et al., 2011), respectively. The combination of alterations to these regions may underpin heighted threat responsivity and intolerance of uncertainty that are commonly

Table 2
Results of the Meta-analysis of Resting-State Functional Connectivity in anxiety and AD*.

Seed Network	Seed Anatomy	Effect Network	Effect Anatomy	x	y	z	Volume (mm^3)	Max. ALE (×10^−2)
AD < HC								
AN	amygdala. R	ECN	dmPFC	5	27	49	216	2.04
	amygdala. L	DMN	vmPFC	−6	39	−12	208	2.07
DMN	cerebellum	ECN	dlPFC	−36	51	15	320	2.05
	PCC, cerebellum	ECN	dlPFC	−32	55	5	296	2.03
SN	AI, dACC	SN	ACC	12	27	27	496	1.79
	STG, AI, dACC	SMN	PTCG	52	−18	56	480	1.64
	STG, dACC	SN	AI	33	7	3	368	1.26

Abbreviations: ACC, anterior cingulate cortex; AD, anxiety disorder; AI, anterior insula; AN: affective network; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; dmPFC, dorsomedial prefrontal cortex; ECN, executive control network; HC, heathy control; L, left; PCC, posterior cingulate cortex; PTCG, postcentral gyrus; R, right; SMN, sensorimotor network; SN, salience network; STG, superior template gyrus; vmPFC, ventromedial prefrontal cortex.

* Coordinates are Montreal Neurological Institute standard stereotaxic spaces.

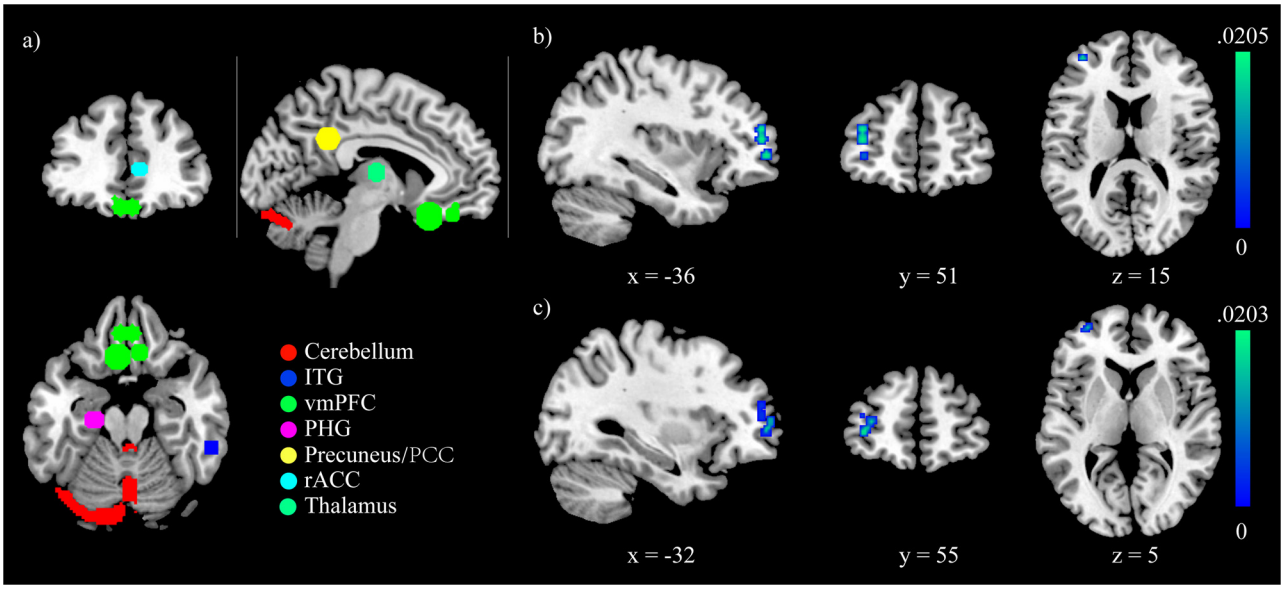

Fig. 3. Hypo-connectivity of the Default Mode Network. a) Seeds of DMN; Anxiety and anxiety disorders exhibited decreased positive connectivity between the DMN and the dlPFC of the ECN, b and c). Color scale reflects *Maximum ALE score*. Abbreviations: ALE, activation likelihood estimation; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; ECN, executive control network.

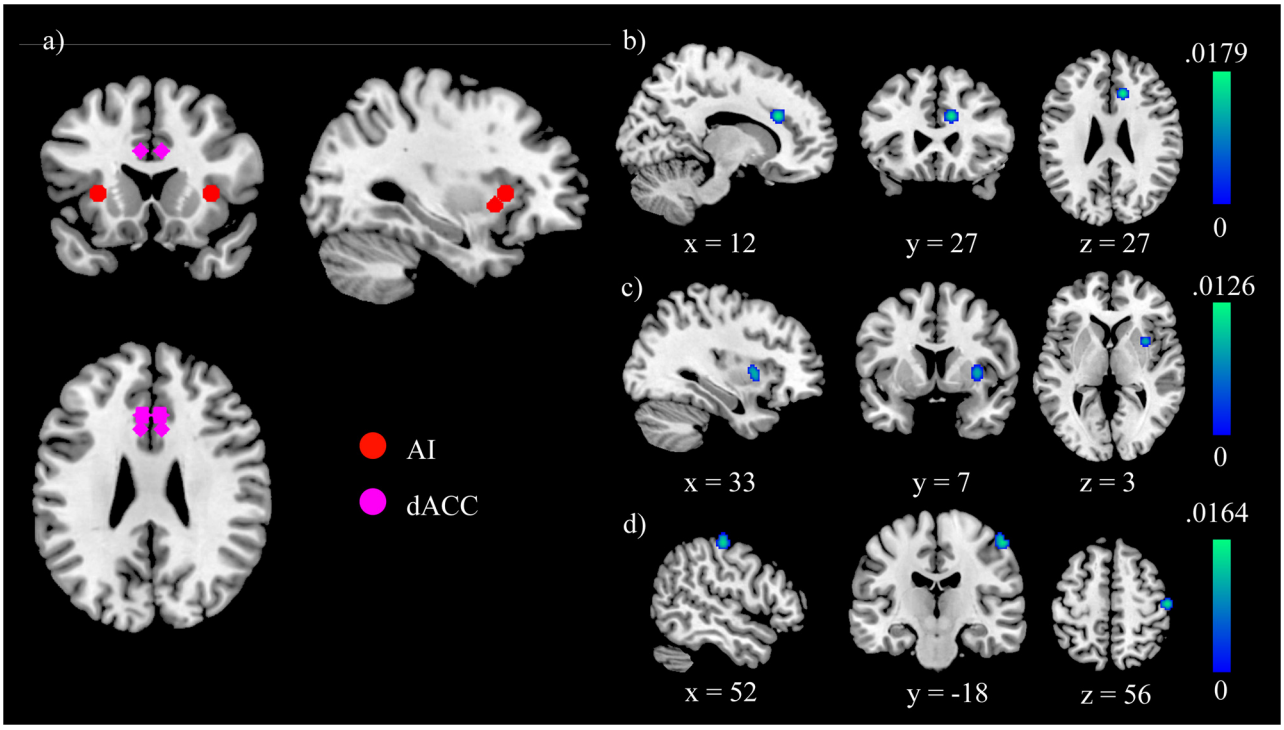

Fig. 4. Hypo-connectivity of the Salience Network. a) Seeds of SN: AI and ACC; Anxiety and anxiety disorders exhibited decreased positive connectivity b and c) within the SN, and d) between the SN and the PTCG of the SMN. Color scale reflects *Maximum ALE score*. Abbreviations: ACC, anterior cingulate cortex; ALE, activation likelihood estimation; AI, anterior insula; PTCG, postcentral gyrus; SN, salience network; SMN, sensorimotor network.

related to anxiety (Grupe and Nitschke, 2013).

Anxiety and anxiety disorders also showed reduced connectivity between the dACC of the SN and the PTCG of the SMN, the later of which acts as a primary sensory receptive area (Corkin et al., 1970; Nelson and Chen, 2008). Prior work has suggested that decreased connectivity in the SMN contributes to sensory processing alterations in anxiety disorders, such as heighted awareness of bodily physiology (Liao et al., 2010). Therefore, the altered connectivity between the dACC and PTGG may reflect increased awareness of bodily physiology, which underlies the underlying vulnerability of anxiety sensitivity.

The network-level alterations described in the present meta-analysis provide potential treatment targets via noninvasive brain stimulation (e.g. Fox et al., 2014), such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), for individuals with anxiety disorders. There has been some evidence that tDCS (e.g. Ironside et al., 2018) and TMS (e.g., Diefenbach et al., 2016; Zwanzger et al., 2009) may facilitate symptom reduction in anxiety, though the findings are inconclusive (Paes et al., 2011). One potential reason that brain stimulation has not been widely applied for the treatment of anxiety disorders is that these disorders are often characterized by

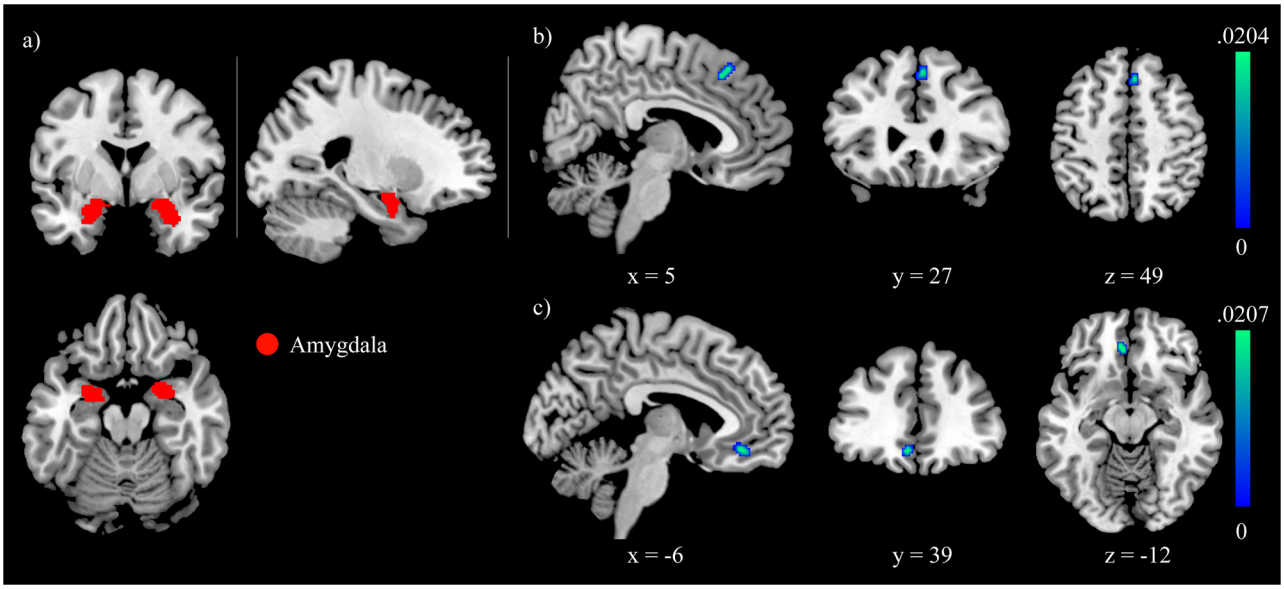

Fig. 5. Hypo-connectivity of the amygdala. a) Seed of amygdala; Anxiety and anxiety disorders exhibited increased negative connectivity b) between the amygdala and dmPFC of the ECN, c) between the amygdala and the vmPFC of the DMN. Color scale reflects Maximum ALE score. Abbreviations: ALE, activation likelihood estimation; DMN, default mode network; dmPFC, dorsomedial prefrontal cortex; ECN, executive control network; vmPFC, ventromedial prefrontal cortex.

Table 3
Results of the Meta-analysis of Resting-State Functional Connectivity of the amygdala seed in anxiety and AD*.

Seed Network	Seed Region	Effect Network	Effect Region	x	y	z	Volume (mm^3)	Max. ALE (×10^−2)
AD < HC								
AN	amygdala. R	ECN	dmPFC	5	27	49	240	2.04
	amygdala. L	DMN	vmPFC	−6	39	−12	208	2.07

Abbreviations: ADanxiety disorder; AN: affective network; DMNdefault mode network; dmPFCdorsomedial prefrontal cortex; ECNexecutive control network; HChealthy control; Lleft; Rright; vmPFCventromedial prefrontal cortex.

* Coordinates are Montreal Neurological Institute standard stereotaxic spaces.

neural alterations that are distant from the scalp (e.g. Etkin and Wager, 2007) and therefore could not be easily targeted by brain stimulation (Ressler and Mayberg, 2007). However, recent work has shown that functional connectivity of subcortical structures (especially the hippocampus and amygdala) can be modulated through TMS/tDCS by targeting the cortical-subcortical circuit (see e.g., Wang et al., 2014; Ironside et al., 2018). In this way, network-based noninvasive brain stimulation has been shown to be clinically effective for various neuropsychiatric diseases including chronic pain, addiction, depression, obsessive-compulsive disorder, Parkinson's disease, and Alzheimer's disease (Fox et al., 2014). For instance, it has been shown that TMS targeting the dlPFC improves emotion regulation (Diefenbach et al., 2016) and reduces anxiety symptoms in GAD (Bystritsky et al., 2009; Dilkov et al., 2017; Mantovani et al., 2013). Thus, our network-based model of anxiety and anxiety disorders may lead to effective use of noninvasive brain stimulation combining with neuroimaging techniques for the treatment of clinical anxiety.

5. Limitations and future directions

Allocation of brain regions to networks is complex, and numerous parcellations exist based on anatomy, cytoarchitecture, connectivity, and other perspectives. The plethora of parcellations posits a challenge to network assignment. Fox example, the MTG could be assigned to the DMN or VAN (Fox et al., 2005, 2006; Yeo et al., 2011); the IPS could be assigned to the ECN or DAN (Corbetta and Shulman, 2002; Dosenbach et al., 2013; Fox et al., 2006); likewise, the IPL could be assigned to ECN and VAN (Corbetta and Shulman, 2002; Dosenbach et al., 2013). In this study, we have chosen multiple classification systems that have been widely used (e.g., Yeo et al., 2011). Whether this classification scheme is robust remains to be determined; alternative network allocations cannot be ruled out due to the complex nature of brain networks. Moreover, it is unclear to what extent anxiety-related abnormal connectivity in the resting state is associated with structural abnormalities, although some studies have explored their relationship in anxiety and anxiety disorders. For example, reduced (para-) limbic volume has been associated with increased resting-state functional connectivity in SAD (Liao et al., 2011). It should be noted that the current meta-analysis was only conducted for resting-state rather than task-based neuroimaging studies. While there are phasic shifts in connectivity related to specific cognitive-affective activity (see e.g., Prater et al., 2013), our results suggest that abnormal intrinsic connectivity patterns in anxiety and anxiety disorders may be, at least partially, tonic. For example, the amygdala coupling to the dlPFC may be a phasic abnormality specific for social threat task, whereas the amygdala coupling to the rostral ACC may reflect both phasic and tonic abnormalities (Prater et al., 2013). Future studies are needed to examine task-specific and task-general modulations of intrinsic connectivity patterns in anxiety and anxiety disorders.

While anxiety and anxiety disorders are different concepts, they are highly overlapped with one another; thus, the neural contributions to trait anxiety and anxiety disorders are likely to have general features. For example, it has been shown that both healthy individuals with high levels of trait anxiety and patients with anxiety disorders exhibit decreased connectivity between the amygdala and mPFC (Kim et al., 2011). Unfortunately, there are very few studies of healthy individuals with high levels of anxiety (n = 3). Thus, there was insufficient data to conduct a separate meta-analysis of brain network alterations in anxiety

or in its comparison with anxiety disorders. Another important issue is different network-level deficits across various anxiety disorders. As proposed by Sylvester et al., (2012), anxiety disorders may share a common network abnormality while specific network differences are likely attributable to the unique presentation of a given diagnosis and/or individual presentation of psychopathology. For example, there are common aberrant couplings of the lateral parietal cortex with the ACC and of the amygdala with the PCC among between individuals with GAD and SAD, whereas connectivity between the PCC and vmPFC in SAD increases relative to GAD (Rabany et al., 2017). Future studies are needed to clarify specific and general distinct network alterations across variants of anxiety and anxiety disorders across individuals, trait anxiety, and anxiety disorders.

6. Concluding remarks

The current meta-analysis provides a comprehensive overview of altered brain networks in anxiety and anxiety disorders. Our findings highlight the critical role of the within- and between-network connectivity of the AN in anxiety, indicating the importance of emotion processing (AN) and top-down cognitive and affective regulation (ECN and DMN). We also found hypo-connectivity among a broad range of networks in anxiety and anxiety disorders, including those responsible for the processing of perception, salience, and uncertainty. These findings support the hypothesis that anxiety is related to multiple neural network abnormalities and have important implications for network-based pathophysiology and brain-stimulation-based treatment of anxiety.

Acknowledgements

This study was supported by National Natural Science Foundation of China (31530031, 31500920, 31871137, 31571124, 81471376, 31700959 and 31671133), National Basic Research Program of China (973 Program, 2014CB744600 and 2011CB711000), Zhujiang Talent Project for Postdoctoral researchers, Guangdong young Innovative Talent Project (2016KQNCX149), Natural Science Foundation of Shenzhen University (85303[HYPHEN]00000275), Shenzhen Science and Technology Research Funding Program (JCYJ20170412164413575) and Shenzhen Peacock Program (827[HYPHEN]000235 and KQTD2015033016104926).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2018.11.005.

References

Adler, C.M., Levine, A.D., DelBello, M.P., Strakowski, S.M., 2005. Changes in gray matter volume in patients with bipolar disorder. Biol. Psychiatry 58 (2), 151–157. https://doi.org/10.1016/j.biopsych.2005.03.022.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth edition. American Psychiatric Association, Arlington,VA. https://doi.org/10.1176/appi.books.9780890425596.744053.

Andreescu, C., Sheu, L.K., Tudorascu, D., Walker, S., Aizenstein, H., 2014. The ages of anxiety-differences across the lifespan in the default mode network functional connectivity in generalized anxiety disorder. Int. J. Geriatr. Psychiatry 29 (7), 704–712. https://doi.org/10.1002/gps.4051.

Arnold Anteraper, S., Triantafyllou, C., Sawyer, A.T., Hofmann, S.G., Gabrieli, J.D., Whitfield-Gabrieli, S., 2014. Hyper-Connectivity of Subcortical Resting-State Networks in Social Anxiety Disorder. Brain Connect. 4 (2), 81–90. https://doi.org/10.1089/brain.2013.0180.

Ball, T., Ramsawh, H., Campbell-Sills, L., Paulus, M., Stein, M., 2013. Prefrontal dysfunction during emotion regulation in generalized anxiety and panic disorder. Psychol. Med. 43, 1475–1486.

Baur, V., Hänggi, J., Langer, N., Jäncke, L., 2013. Resting-state functional and structural connectivity within an insula-amygdala route specifically index state and trait anxiety. Biol. Psychiatry 73 (1), 85–92. https://doi.org/10.1016/j.biopsych.2012.06.003.

Bender, P.K., Reinholdt-Dunne, M.L., Esbjørn, B.H., Pons, F., 2012. Emotion dysregulation and anxiety in children and adolescents: gender differences. Pers. Individ. Dif. 53 (3), 284–288. https://doi.org/10.1016/j.paid.2012.03.027.

Bijsterbosch, J., Smith, S., Forster, S., John, O.P., Bishop, S.J., 2014. Resting state correlates of subdimensions of anxious affect. J. Cogn. Neurosci. 26 (4), 914–926. https://doi.org/10.1162/jocn_a_00512.

Birn, R.M., Shackman, A.J., Oler, J.A., Williams, L.E., McFarlin, D.R., Rogers, G.M., Kalin, N.H., 2014. Evolutionarily conserved prefrontal-amygdalar dysfunction in early-life anxiety. Mol. Psychiatry 19 (8), 915–922. https://doi.org/10.1038/mp.2014.46.

Bishop, S.J., 2007. Neurocognitive mechanisms of anxiety: an integrative account. Trends Cogn. Sci. (Regul. Ed.) 11 (7), 307–316. https://doi.org/10.1016/j.tics.2007.05.008.

Bishop, S., Duncan, J., Brett, M., Lawrence, A.D., 2004. Prefrontal cortical function and anxiety: Controlling attention to threat-related stimuli. Nat. Neurosci. 7 (2), 184–188. https://doi.org/10.1038/nn1173.

Buckner, R.L., Krienen, F.M., Castellanos, A., Diaz, J.C., Yeo, B.T.T., 2011. The organization of the human cerebellum estimated by intrinsic functional connectivity. J. Neurophysiol. 106 (5), 2322–2345. https://doi.org/10.1152/jn.00339.2011.

Bystritsky, A., Kerwin, L.E., Feusner, J.D., 2009. A preliminary study of fMRI-Guided rTMS in the Treatment of generalized anxiety disorder. J. Clin. Psychiatry 70, 431–432.

Cha, J., Greenberg, T., Carlson, J.M., Dedora, D.J., Hajcak, G., Mujica-Parodi, L.R., 2014. Circuit-wide structural and functional measures predict ventromedial prefrontal cortex fear generalization: implications for generalized anxiety disorder. J. Neurosci. 34 (11), 4043–4053. https://doi.org/10.1523/JNEUROSCI.3372-13.2014.

Chen, A.C., Etkin, A., 2013. Hippocampal network connectivity and activation differentiates post-traumatic stress disorder from generalized anxiety disorder. Neuropsychopharmacology 38 (10), 1889–1898. https://doi.org/10.1038/npp.2013.122.

Choi, E.Y., Yeo, B.T.T., Buckner, R.L., 2012. The organization of the human striatum estimated by intrinsic functional connectivity. J. Neurophysiol. 108 (8), 2242–2263. https://doi.org/10.1152/jn.00270.2012.

Choi, S.H., Shin, J.E., Ku, J., Kim, J.J., 2016. Looking at the self in front of others: Neural correlates of attentional bias in social anxiety. J. Psychiatr. Res. 75, 31–40. https://doi.org/10.1016/j.jpsychires.2016.01.001.

Clewett, D., Bachman, S., Mather, M., 2014. Age-related reduced prefrontal-amygdala structural connectivity is associated with lower trait anxiety. Neuropsychology 28 (4), 631–642. https://doi.org/10.1037/neu0000060.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3 (3), 201–215. https://doi.org/10.1038/nrn755.

Corkin, S., Milner, B., Rasmussen, T., 1970. Somatosensory thresholds. Arch. Neurol. 23 (1), 41. https://doi.org/10.1001/archneur.1970.00480250045007.

Cui, Q., Vanman, E.J., Long, Z., Pang, Y., Chen, Y., Wang, Y., Duan, X., Chen, H., Gong, Q., Zhang, W., Chen, H., 2017. Social anxiety disorder exhibit impaired networks involved in self and theory of mind processing. Soc. Cogn. Affect. Neurosci 12, 1284–1295.

Diefenbach, G.J., Assaf, M., Goethe, J.W., Gueorguieva, R., Tolin, D.F., 2016. Improvements in emotion regulation following repetitive transcranial magnetic stimulation for generalized anxiety disorder. J. Anxiety Disord. 43, 1–7. https://doi.org/10.1016/j.janxdis.2016.07.002.

Dilkov, D., Hawken, E.R., Kaludiev, E., Milev, R., 2017. Repetitive transcranial magnetic stimulation of the right dorsal lateral prefrontal cortex in the treatment of generalized anxiety disorder: A randomized, double-blind sham controlled clinical trial. Prog. Neuropsychopharmacol. Biol. Psychiatry 78 (May), 61–65. https://doi.org/10.1016/j.pnpbp.2017.05.018.

Dodhia, S., Hosanagar, A., Fitzgerald, D.A., Labuschagne, I., Wood, A.G., Nathan, P.J., Phan, K.L., 2014. Modulation of resting-state amygdala-frontal functional connectivity by oxytocin in generalized social anxiety disorder. Neuropsychopharmacology 39 (9), 2061–2069. https://doi.org/10.1038/npp.2014.53.

Dorfman, J., Benson, B., Farber, M., Pine, D., Ernst, M., 2016. Altered striatal intrinsic functional connectivity in pediatric anxiety. Neuropsychologia 85, 159–168. https://doi.org/10.1016/j.neuropsychologia.2016.03.019.

Dosenbach, N.U.F., Fair, Da, Cohen, A.L., Schlaggar, B.L., Petersen, S.E., 2013. NIH Public Access 12 (3), 99–105. https://doi.org/10.1016/j.tics.2008.01.001.

Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., Fox, P.T., 2009. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Hum. Brain Mapp. 30 (9), 2907–2926. https://doi.org/10.1002/hbm.20718.

Eickhoff, S.B., Bzdok, D., Laird, A.R., Kurth, F., Fox, P.T., 2012. Activation likelihood estimation meta-analysis revisited. NeuroImage 59 (3), 2349–2361. https://doi.org/10.1016/j.neuroimage.2011.09.017.

Etkin, A., Wager, T.D., 2007. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am. J. Psychiatry 164 (10), 1476–1488. https://doi.org/10.1176/appi.ajp.2007.07030504.

Etkin, A., Prater, K.E., Schatzberg, A.F., Menon, V., Greicius, M.D., 2009. Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. Arch. Gen. Psychiatry 66 (12), 1361–1372. https://doi.org/10.1001/archgenpsychiatry.2009.104.

Etkin, A., Prater, K.E., Hoeft, F., Menon, V., Schatzberg, A.F., 2010. Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. Am. J. Psychiatry 167, 545–554.

Etkin, A., Egner, T., Kalisch, R., 2011. Emotional processing in anterior cingulate and medial prefrontal. Trends Cogn. Sci. 15 (2), 85–93. https://doi.org/10.1016/j.tics.2010.11.004.Emotional.

Eysenck, M.W., Derakshan, N., Santos, R., Calvo, M.G., 2007. Anxiety and cognitive performance: attentional control theory. Emotion 7 (2), 336–353. https://doi.org/10.1037/1528-3542.7.2.336.
Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. From the Cover: the human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. 102 (27), 9673–9678. https://doi.org/10.1073/pnas.0504136102.
Fox, M.D., Corbetta, M., Snyder, A.Z., Vincent, J.L., Raichle, M.E., 2006. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc. Natl. Acad. Sci. 103 (26), 10046–10051. https://doi.org/10.1073/pnas.0604187103.
Fox, M.D., Zhang, D., Snyder, A.Z., Raichle, M.E., 2009. The global signal and observed anticorrelated resting state brain networks. J. Neurophysiol. 101 (6), 3270–3283. https://doi.org/10.1152/jn.90777.2008.
Fox, M.D., Buckner, R.L., Liu, H., Chakravarty, M.M., Lozano, A.M., Pascual-Leone, A., 2014. Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. Proc. Natl. Acad. Sci. 111 (41), E4367–E4375. https://doi.org/10.1073/pnas.1405003111.
Geiger, M.J., Domschke, K., Ipser, J., Hattingh, C., Baldwin, D.S., Lochner, C., Stein, D.J., 2016. Altered executive control network resting-state connectivity in social anxiety disorder. World J. Biol. Psychiatry 17 (1), 47–57. https://doi.org/10.3109/15622975.2015.1083613.
Geng, H., Li, X., Chen, J., Li, X., Gu, R., 2016. Decreased intra- and inter-salience network functional connectivity is related to trait anxiety in adolescents. Front. Behav. Neurosci. 9 (January), 1–10. https://doi.org/10.3389/fnbeh.2015.00350.
Grupe, D.W., Nitschke, J.B., 2013. Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. Nat. Rev. Neurosci. 14 (7), 488–501. https://doi.org/10.1038/nrn3524.
Hahn, A., Stein, P., Windischberger, C., Weissenbacher, A., Spindelegger, C., Moser, E., Lanzenberger, R., 2011. Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. NeuroImage 56 (3), 881–889. https://doi.org/10.1016/j.neuroimage.2011.02.064.
Hajcak, G., McDonald, N., Simons, R.F., 2003. Anxiety and error-related brain activity. Biol. Psychol. 64, 77–90.
Hamm, L.L., Jacobs, R.H., Johnson, M.W., Fitzgerald, D.A., Fitzgerald, K.D., Langenecker, S.A., Phan, K.L., 2014. Aberrant amygdala functional connectivity at rest in pediatric anxiety disorders. Biol. Mood Anxiety Disord. 4 (1), 15. https://doi.org/10.1186/s13587-014-0015-4.
He, Y., Xu, T., Zhang, W., Zuo, X.N., 2016. Lifespan anxiety is reflected in human amygdala cortical connectivity. Hum. Brain Mapp. 37 (3), 1178–1193. https://doi.org/10.1002/hbm.23094.
Hiser, J., Koenigs, M., 2018. The multifaceted role of the ventromedial prefrontal cortex in emotion, decision making, social cognition, and psychopathology. Biol. Psychiatry 83 (8), 638–647. https://doi.org/10.1016/j.biopsych.2017.10.030.
Holmes, C.J., Hoge, R., Collins, L., Evans, A.C., 1996. Enhancement of T1 MR Images Using Registration for Signal Averaging. NeuroImage 3 (3), S28. https://doi.org/10.1016/S1053-8119(96)80030-9.
Hróbjartsson, A., Thomsen, A.S.S., Emanuelsson, F., Tendal, B., Hilden, J., Boutron, I., Brorson, S., 2013. Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. Cmaj 185 (4), 201–211. https://doi.org/10.1503/cmaj.120744.
Ironside, M., Browning, M., Ansari, T.L., Harvey, C.J., Sekyi-Djan, M.N., Bishop, S.J., Harmer, C.J., O'Shea, J., 2018. Effect of prefrontal cortex stimulation on regulation of amygdala response to threat in individuals with trait anxiety. JAMA Psychiatry. https://doi.org/10.1001/jamapsychiatry.2018.2172. Published online October 17, 2018.
Kaiser, R.H., Andrews-Hanna, J.R., Wager, T.D., Pizzagalli, D.A., 2015. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatry 72 (6), 603–611. https://doi.org/10.1001/jamapsychiatry.2015.0071.
Kalisch, R., 2009. The functional neuroanatomy of reappraisal: time matters. Neurosci. Biobehav. Rev. 33 (8), 1215–1226. https://doi.org/10.1016/j.neubiorev.2009.06.003.
Keedwell, P., Snaith, R.P., 1996. What do anxiety scales measure? Acta Psychiatr. Scand. 93, 177–180. https://doi.org/10.1111/j.1600-0447.1996.tb10627.x.
Kim, M.J., Whalen, P.J., 2009. The structural integrity of an amygdala-prefrontal pathway predicts trait anxiety. J. Neurosci. 29 (37), 11614–11618. https://doi.org/10.1523/JNEUROSCI.2335-09.2009.
Kim, M.J., Loucks, R.A., Palmer, A.L., Brown, A.C., Solomon, K.M., Marchante, A.N., Whalen, P.J., 2011. The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. Behav. Brain Res. 223 (2), 403–410. https://doi.org/10.1016/j.bbr.2011.04.025.
Kim, J., Yoon, H., Park, S., Shin, Y., Kim, J., 2014. Characteristics of intrinsic functional connectivity of amygdalar subregions in social anxiety disorder. Anxiety and Mood 10 (1), 44–51.
Kotov, R., Gamez, W., Schmidt, F., Watson, D., 2010. Linking "Big" personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. Psychol. Bull. 136 (5), 768–821. https://doi.org/10.1037/a0020327.
Krug, M.K., Carter, C.S., 2010. Adding fear to conflict: a general purpose cognitive control network is modulated by trait anxiety. Cogn. Affect. Behav. Neurosci. 10, 357–371.
Lancaster, J.L., Tordesillas-Gutiérrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., Fox, P.T., 2007. Bias between MNI and talairach coordinates analyzed using the ICBM-152 brain template. Hum. Brain Mapp. 28 (11), 1194–1205. https://doi.org/10.1002/hbm.20345.
Li, W., Cui, H., Zhu, Z., Kong, L., Guo, Q., Zhu, Y., Li, C., 2016. Aberrant functional connectivity between the Amygdala and the temporal pole in drug-free generalized anxiety disorder. Front. Hum. Neurosci. 10, 549. https://doi.org/10.3389/fnhum.2016.00549.
Liao, W., Chen, H., Feng, Y., Mantini, D., Gentili, C., Pan, Z., Zhang, W., 2010. Resting State Correlates of Subdimensions of Anxious Affect. NeuroImage 52 (4), 1549–1558. https://doi.org/10.1162/jocn_a_00512.
Liao, W., Xu, Q., Mantini, D., Ding, J., MacHado-De-Sousa, J.P., Hallak, J.E.C., Chen, H., 2011. Altered gray matter morphometry and resting-state functional and structural connectivity in social anxiety disorder. Brain Res. 1388, 167–177. https://doi.org/10.1016/j.brainres.2011.03.018.
Lindquist, Kristen A., Wager, Tor D., Kober, Hedy, Bliss-Moreau, Eliza, Barrett, Lisa Feldman, 2012. The brain basis of emotion: A meta-analytic review. Behavior Brain Science 35 (3), 121–143. https://doi.org/10.1017/S0140525X11000446.
Liu, W., Yin, D., Cheng, W., Fan, M., You, M., Men, W., Zhang, F., 2015. Abnormal functional connectivity of the amygdala-based network in resting-state FMRI in adolescents with generalized anxiety disorder. Med. Sci. Monit. 21, 459–467. https://doi.org/10.12659/MSM.893373.
Ludewig, S., Paulus, M.P., Ludewig, K., Vollenweider, F.X., 2003. Decision-making strategies by panic disorder subjects are more sensitive to errors. J. Affect. Disord. 76, 183–189.
Makovac, E., Meeten, F., Watson, D.R., Herman, A., Garfinkel, S.N.D., Critchley, H., Ottaviani, C., 2016. Alterations in amygdala-prefrontal functional connectivity account for excessive worry and autonomic dysregulation in generalized anxiety disorder. Biol. Psychiatry 80 (10), 786–795. https://doi.org/10.1016/j.biopsych.2015.10.013.
Manning, J., Reynolds, G., Saygin, Z.M., Hofmann, S.G., Pollack, M., Gabrieli, J.D.E., Whitfield-Gabrieli, S., 2015. Altered resting-state functional connectivity of the frontal-striatal reward system in social anxiety disorder. PLoS One 10 (4), 1–15. https://doi.org/10.1371/journal.pone.0125286.
Mantovani, A., Aly, M., Dagan, Y., Allart, A., Lisanby, S.H., 2013. Randomized sham controlled trial of repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex for the treatment of panic disorder with comorbid major depression $. J. Affect. Disord. 144 (1–2), 153–159. https://doi.org/10.1016/j.jad.2012.05.038.
Mathews, A., MacLeod, C., 2005. Cognitive vulnerability to emotional disorders. Annu. Rev. Clin. Psychol. 1 (1), 167–195. https://doi.org/10.1146/annurev.clinpsy.1.102803.143916.
Mennin, D.S., McLaughlin, K.A., Flanagan, T.J., 2009. Emotion regulation deficits in generalized anxiety disorder, social anxiety disorder, and their co-occurrence. J. Anxiety Disord. 23, 866–871.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Academia and clinic annals of internal medicine preferred reporting items for systematic reviews and meta-analyses. Ann. Intern. Med. 151 (4), 264–269. https://doi.org/10.7326/0003-4819-151-4-200908180-00135.
Motzkin, J.C., Philippi, C.L., Wolf, R.C., Baskaya, M.K., Koenigs, M., 2015. Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. Biol. Psychiatry 77 (3), 276–284. https://doi.org/10.1016/j.biopsych.2014.02.014.
Müller, V.I., Cieslik, E.C., Laird, A.R., Fox, P.T., Radua, J., Mataix-Cols, D., Eickhoff, S.B., 2018. Ten simple rules for neuroimaging meta-analysis. Neurosci. Biobehav. Rev. 84 (April 2017), 151–161. https://doi.org/10.1016/j.neubiorev.2017.11.012.
Munafò, M.R., Freimer, N.B., Ng, W., Ophoff, R., Veijola, J., Miettunen, J., Flint, J., 2009. 5-HTTLPR genotype and anxiety-related personality traits: a meta-analysis and new data. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. 150 (2), 271–281. https://doi.org/10.1002/ajmg.b.30808.
Murphy, K., Birn, R.M., Handwerker, D.A., Jones, T.B., Bandettini, P.A., 2009. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? NeuroImage 44 (3), 893–905. https://doi.org/10.1016/j.neuroimage.2008.09.036.
Nelson, A.J., Chen, R., 2008. Digit somatotopy within cortical areas of the postcentral gyrus in humans. Cereb. Cortex 18 (10), 2341–2351. https://doi.org/10.1093/cercor/bhm257.
Orgeta, V., 2011. Emotion dysregulation and anxiety in late adulthood. J. Anxiety Disord. 25 (8), 1019–1023. https://doi.org/10.1016/j.janxdis.2011.06.010.
Pace-Schott, E.F., Zimmerman, J.P., Bottary, R.M., Lee, E.G., Milad, M.R., Camprodon, J.A., 2017. Resting state functional connectivity in primary insomnia, generalized anxiety disorder and controls. Psychiatry Res. 265, 26–34. https://doi.org/10.1016/j.pscychresns.2017.05.003.
Paes, F., Machado, S., Arias-Carrion, O., Velasques, B., Teixeira, S., Budde, H., Nardi, A.E., 2011. The value of repetitive transcranial magnetic stimulation (rTMS) for the treatment of anxiety disorders: an integrative review. CNS Neurol. Disord. Drug Targets 10 (5), 610–620. https://doi.org/10.2174/187152711796234943.
Pannekoek, J.N., Veer, I.M., Van Tol, M.J., Van der Werff, S.J.A., Demenescu, L.R., Aleman, A., Van der Wee, N.J.A., 2013a. Resting-state functional connectivity abnormalities in limbic and salience networks in social anxiety disorder without comorbidity. Eur. Neuropsychopharmacol. 23 (3), 186–195. https://doi.org/10.1016/j.euroneuro.2012.04.018.
Pannekoek, J.N., Veer, I.M., Van Tol, M.J., Van Der Werff, S.J.A., Demenescu, L.R., Aleman, A., Van Der Wee, N.J.A., 2013b. Aberrant limbic and salience network resting-state functional connectivity in panic disorder without comorbidity. J. Affect. Disord. 145 (1), 29–35. https://doi.org/10.1016/j.jad.2012.07.006.
Paulus, M.P., Stein, M.B., 2006. An insular view of anxiety. Biol. Psychiatry 60 (4), 383–387. https://doi.org/10.1016/j.biopsych.2006.03.042.
Paulus, M.P., Stein, M.B., 2010. Interoception in anxiety and depression. Brain Struct. Funct. 214 (5–6), 451–463. https://doi.org/10.1007/s00429-010-0258-9.
Power, J.D., Cohen, A.L., Nelson, S.M., Wig, G.S., Barnes, K.A., Church, J.A., Petersen, S.E., 2011. Functional network organization of the human brain. Neuron 72 (4), 665–678. https://doi.org/10.1016/j.neuron.2011.09.006.
Prater, K.E., Hosanagar, A., Klumpp, H., Angstadt, M., Phan, K.L., 2013. Aberrant amygdala-frontal cortex connectivity during perception of fearful faces and at rest in

generalized social anxiety disorder. Depress. Anxiety 30 (3), 234–241. https://doi.org/10.1002/da.22014.
Rabany, L., Diefenbach, G.J., Bragdon, L.B., Pittman, B.P., Zertuche, L., Tolin, D.F., Assaf, M., 2017. Resting-state functional connectivity in generalized anxiety disorder and social anxiety disorder: evidence for a dimensional approach. Brain Connect. 7 (5), 289–298. https://doi.org/10.1089/brain.2017.0497.
Rauch, S.L., Shin, L.M., Wright, C.I., 2006. Neuroimaging studies of amygdala function in anxiety disorders. Ann. N. Y. Acad. Sci. 985 (1), 389–410. https://doi.org/10.1111/j.1749-6632.2003.tb07096.x.
Ressler, K.J., Mayberg, H.S., 2007. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nat. Neurosci. 10, 1116–1124.
Rodriguez, B.F., Bruce, S.E., Pagano, M.E., Keller, M.B., 2005. Relationships among psychosocial functioning, diagnostic comorbidity, and the recurrence of generalized anxiety disorder, panic disorder, and major depression. J. Anxiety Disord. 19 (7), 752–766. https://doi.org/10.1016/j.janxdis.2004.10.002.
Roy, A.K., Fudge, J.L., Kelly, C., Perry, J.S.A., Daniele, T., Carlisi, C., Ernst, M., 2013. Intrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. J. Am. Acad. Child Adolesc. Psychiatry 52 (3), 290–299. https://doi.org/10.1016/j.jaac.2012.12.010. e2.
Sang, L., Qin, W., Liu, Y., Han, W., Zhang, Y., Jiang, T., Yu, C., 2012. Resting-state functional connectivity of the vermal and hemispheric subregions of the cerebellum with both the cerebral cortical networks and subcortical structures. NeuroImage 61 (4), 1213–1225. https://doi.org/10.1016/j.neuroimage.2012.04.011.
Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27 (9), 2349–2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007.
Shackman, A.J., Salomons, T.V., Slagter, H.A., Andrew, S., Winter, J.J., Davidson, R.J., 2011. The integration of negative affect, pain, and cognitive control in the cingulate cortex. Nat. Rev. Neurosci. 12 (3), 154–167. https://doi.org/10.1038/nrn2994.
Sheline, Y.I., Price, J.L., Yan, Z., Mintun, M.A., 2010. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc. Natl. Acad. Sci. 107 (24), 11020–11025. https://doi.org/10.1073/pnas.1000446107.
Shin, L.M., Liberzon, I., 2010. The neurocircuitry of fear, stress and anxiety disorders. Neuropsychopharmacology 35, 169–191.
Shin, Y.-W., Dzemidzic, M., Jo, H.J., Long, Z., Medlock, C., Dydak, U., Goddard, A.W., 2013. Increased resting-state functional connectivity between the anterior cingulate cortex and the precuneus in panic disorder. J. Affect. Disord. 150 (3), 1091–1095. https://doi.org/10.1016/j.jad.2013.04.026.
Simons, R.F., 2010. The way of our errors: theme and variations. Psychophysiology 47 (1), 1–14. https://doi.org/10.1111/j.1469-8986.2009.00929.x.
Stein, M.B., Simmons, A.N., Feinstein, J.S., Paulus, M.P., 2007. Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. Am. J. Psychiatry 164 (2), 318–327. https://doi.org/10.1176/appi.ajp.164.2.318.
Sylvester, C.M., Corbetta, M., Raichle, M.E., Rodebaugh, T.L., Schlaggar, B.L., Sheline, Y.I., Lenze, E.J., 2012. Functional network dysfunction in anxiety and anxiety disorders. Trends Neurosci. 35 (9), 527–535. https://doi.org/10.1016/j.tins.2012.04.012.
Toazza, R., Franco, A.R., Buchweitz, A., Molle, R.D., Rodrigues, D.M., Reis, R.S., Manfro, G.G., 2016. Amygdala-based intrinsic functional connectivity and anxiety disorders in adolescents and young adults. Psychiatry Research - Neuroimaging 257 (September), 11–16. https://doi.org/10.1016/j.pscychresns.2016.09.010.
Tovote, P., Fadok, J.P., Lüthi, A., 2015. Neuronal circuits for fear and anxiety. Nat. Rev. Neurosci. 16 (6), 317–331. https://doi.org/10.1038/nrn3945.
Voegler, R., Peterburs, J., Lemke, H., Ocklenburg, S., Liepelt, R., Straube, T., 2018. Electrophysiological correlates of performance monitoring under social observation in patients with social anxiety disorder and healthy controls. Biol. Psychol. 132, 71–80.
Wang, J.X., Rogers, L.M., Gross, E.Z., Ryals, A.J., Dokucu, M.E., Brandstatt, K.L., Voss, J.L., 2014. Memory Enhancement: targeted enhancement of cortical-hippocampal brain networks and associative memory. Science 345 (6200), 1054–1057. https://doi.org/10.1126/science.1252900.
Weinberg, A., Olvet, D.M., Hajcak, G., 2010. Increased error-related brain activity in generalized anxiety disorder. Biol. Psychol. 85, 472–480.
Weng, H.-H., Tsai, Y.-H., Chen, C.-F., Lin, Y.-C., Yang, C.-T., Tsai, Y.-H., Yang, C.-Y., 2014. Mapping gray matter reductions in obstructive sleep apnea: an activation likelihood estimation meta-analysis. Sleep 37 (1), 167–175. https://doi.org/10.5665/sleep.3330.
Yang, J., Pan, P., Song, W., Huang, R., Li, J., Chen, K., Shang, H., 2012. Voxelwise meta-analysis of gray matter anomalies in Alzheimer's disease and mild cognitive impairment using anatomic likelihood estimation. J. Neurol. Sci. 316 (1–2), 21–29. https://doi.org/10.1016/j.jns.2012.02.010.
Yang, X., Liu, J., Meng, Y., Xia, M., Cui, Z., Wu, X., He, Y., 2017. Network analysis reveals disrupted functional brain circuitry in drug-naive social anxiety disorder. NeuroImage. https://doi.org/10.1016/j.neuroimage.2017.12.011.
Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Buckner, R.L., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. 106 (3), 1125–1165. https://doi.org/10.1152/jn.00338.2011.
Yuan, Minlan, Meng, Y., Zhang, Y., Nie, X., Ren, Z., Zhu, H., Zhang, W., 2017. Cerebellar neural circuits involving executive control network predict response to group cognitive behavior therapy in social anxiety disorder. Cerebellum 16 (3), 673–682. https://doi.org/10.1007/s12311-017-0845-x.
Yuan, C., Zhu, H., Ren, Z., Yuan, M., Gao, M., Zhang, Y., Zhang, W., 2018. Precuneus-related regional and network functional deficits in social anxiety disorder: a resting-state functional MRI study. Compr. Psychiatry 82, 22–29. https://doi.org/10.1016/j.comppsych.2017.12.002.
Zhao, X.H., Wang, P.J., Li, C.B., Hu, Z.H., Xi, Q., Wu, W.Y., Tang, X.W., 2007. Altered default mode network activity in patient with anxiety disorders: An fMRI study. Eur. J. Radiol. 63 (3), 373–378. https://doi.org/10.1016/j.ejrad.2007.02.006.
Zwanzger, P., Fallgatter, A.J., Zavorotnyy, M., Padberg, F., 2009. Anxiolytic effects of transcranial magnetic stimulation-an alternative treatment option in anxiety disorders? J. Neural. Transm. 116, 767–775.