The Brain Activation of Anxiety Disorders During Emotional Stimulations: A Coordinate-Based Activation Likelihood Estimation Meta-Analysis

Xia Liu

Qinghai Normal University

Xiuzhen Wang

Guangyuan Mental Health Center

Yongchao Li

Lanzhou University

Shanling Ji

Lanzhou University

Yu Zhang

Lanzhou University

Yinghui Zhang

Guangyuan Mental Health Center

Bin Hu (✉ bh@lzu.edu.cn)

Lanzhou University <https://orcid.org/0000-0003-3514-5413>

Research Article

Keywords: ALE, anxiety disorder, meta-analysis, fMRI, activation

Posted Date: November 8th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1027754/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Many studies have been analyzed the state of brain activation about anxiety under neuroimaging experiments with emotional stimuli. However, there is no meta-analysis to assess the commonality and specificity activation of different anxiety subtypes. Here, we used the activation likelihood estimation (ALE) to define the common and different activation between different subtypes of anxiety. A total of 29 functional magnetic resonance imaging (fMRI) studies revealed significantly increased bilateral amygdala, anterior cingulate gyrus, and parahippocampal gyrus activation in anxiety during emotional stimuli. Moreover, we observed the decreased activations in the posterior cingulate, lingual gyrus, and precuneus. In subanalyses of anxiety disorders, the increased activation of generalized anxiety and specific phobias are present in the left hippocampus and thalamus, respectively. Social anxiety and panic disorders showed increased activation in the parahippocampal gyrus, amygdala, thalamus, and insula. Social anxiety, generalized anxiety, and panic disorders displayed decreased activations in the fusiform gyrus, posterior cingulate, and specific phobias exhibited in the medial frontal gyrus. Although different anxiety showed dissimilar activations, the principal activations were observed in the limbic lobe, which might indicate the limbic circuit was a neural reflection of anxiety symptoms.

1. Introduction

Different subtypes of anxiety have common and specific clinical manifestations [1], we hypothesize that similarities and specificities of brain activation will be also observed among these patients when they were exposed to emotional stimuli. Facial expressions are the most direct visual emotional expression and transmission carrier in people's lives, and the brains of primates respond to them significantly [2]. Compared with the healthy controls (HCs), the response of anxiety disorders to negative emotional stimuli showed negative bias [3, 4]. Based on the negative bias, research on the activation of brain regions in anxiety disorders has attracted extensive attention during the processing of emotional pictures with fear, happiness, and neutral expressions. A previous study has shown that an individual's emotional state affects the processing of other's emotional faces [5]. People who have been in a state of anxiety or depression for a long time will affect their interactions with the outside world [6].

At present, there are great progress has been made in the brain region activation of anxiety via emotional stimulation. For example, generalized anxiety disorder (GAD) has abnormal activation arising from the amygdala [7, 8]. A previous study[9] found GAD showed significantly lower activities in the superior occipital gyrus, superior parietal gyrus, precuneus, fusiform gyrus, lingual gyrus, calcarine gyrus, cuneus, parahippocampal gyru, and cerebellar cortex. Recently, a fMRI study's [10] reported that GAD showed more activation in the insula but the amygdala was less activated.

Binelli et al. [11] found social anxiety disorders (SAD) were decreased prefrontal and fusiform activation when processing happy, fearful, and angry faces. Benedikt Figel et al [12] showed that SAD showed increased activation in the central nucleus.

In addition, the subtypes of panic disorders (PD) showed abnormal activation of the extended fear network comprising parts of the brainstem, insula, anterior and middle cingulate cortex, and lateral and medial prefrontal cortex [13]. Amygdala activation in PD appears to be less sensitive to decreasing intensities of fearful facial expressions [14]. During the masked fear versus neutral condition, PD and specific phobia (SP) showed greater activation in the left amygdala and reduced activation in the ventromedial prefrontal cortex (vmPFC) [15]. However, a study found that PD showed a sustained hyperactivation of the vmPFC under threat and safety conditions [16].

Although numerous studies have been conducted on the activation of different anxiety subtypes, there is still divergence in the commonness and characteristics of the activation of different anxiety subtypes. Therefore, we conducted a meta-analysis of fMRI studies for four types of anxiety to more fully describe brain activity in anxiety. We aim to analyze the co-activation and specific activation regions of different anxiety subtypes in response to emotional stimuli.

2. Methods And Materials

2.1 Literature search and exclusion criteria

We searched PubMed, Google Scholar, and Web of Science for studies published in English from 2000 to 2020, using the following terms and their derivatives: fMRI, emotion, facial stimuli, anxiety, panic disorder, PD, generalized anxiety disorder, GAD, social anxiety disorder, SAD, and specific phobias, SP. The inclusion criteria for our analyses are as follows:

- 1) Participants in these studies performed emotional picture stimulations during an MRI scan.
- 2) These studies compared the whole-brain activation of anxiety disorders of no medication and no comorbidities.
- 3) These studies reported the whole brain comparison of anxiety disorders and healthy controls in the Montreal Neurology Institute (MNI) or Talairach coordinates.
- 4) Participants in these studies were aged 18-60.
- 5) Psychiatrists using DSM-IV-TR to diagnose anxiety disorders.

Ultimately, we selected 29 studies (Fig. 1, Table 1) that satisfied these criteria. These 29 studies included 517 anxiety disorders and 497 HCs. Subject demographics are summarized in Table1. In these 29 studies, we included all coordinate values that were clearly explained by the author. If the coordinates of the research report are in Talairach space, we use the algorithm [17] in the Ginger Activation Likelihood Estimation (ALE) software [18] to convert them into MNI space.

Table1. Characteristics of included studies.

Study	Subject	M/F	Age(SD)	Type of stimulation
Ball.T et al,[52]	23GAD	11/11	27.0(9)	Emotional images
	18PD	6/17	35.0(11)	
	22HC	15/3	29.0(7)	
Moon et al,[9]	18GAD	9/9	37.1(11)	Emotional images
	18HC	9/9	36.5(7.7)	
Maddock et al, [53]	6PD	2/4	34.0(-)	Emotional words
	8HC	3/5	35.0(-)	
Chechko et al, [54]	18PD	8/10	34.4(8)	Emotional faces/words
	18HC	8/10	30.0(6.4)	
Killgore et al, [55]	15SAD	4/11	35.6(8.7)	Emotional faces
	14PD	4/10	28.3(8.1)	
	22HC	8/14	30.7(9.2)	
Kaldewaij et al, [14]	18PD	4/14	36.5(13.8)	Emotional faces
	17HC	3/14	34.1(11.7)	
Evans et al,[56]	11SAD	4/7	29.0(7.5)	Emotional faces
	11HC	4/7	27.9(10.6)	
Goldin et al, [57]	15SAD	6/9	31.6(9.7)	Harsh facial expressions and violent scenes
	17HC	8/9	32.1(9.3)	
Bruhl et al,[58]	14SAD	7/7	33.0(12)	General emotional pictures
	16HC	6/10	31.0(7.2)	
Hahn et al,[59]	10Anxiety	9/1	28.6(4.3)	Emotional faces
	27HC	11/16	27.7(7.2)	
Nakao et al, [60]	6SAD	4/2	31.7(7.9)	Photographs of social situation task
	9HC	6/3	32.8(5.0)	
Klumpp et al, [29]	29gSAD	12/17	24.7(5.9)	Emotional faces
	26HC	10/16	26.2(6.3)	
Frick et al,[61]	14SAD	14/0	32.4(8.8)	Emotional faces
	12HC	12/0	28.0(8.2)	
Heide et al,[62]	29gSAD	11/18	24.9(6.3)	Emotional faces

	27HC	12/15	24.9(5.9)	
Michal et al, [63]	27SAD	15/12	31.1(7.6)	Emotional faces
	27HC	14/13	32.6(9.5)	
Michael et al, [64]	21SAD	5/16	30.5(7.17)	General emotional pictures
	23HC	5/18	30.0(7.99)	
Binelli et al,[11]	20SAD	6/14	25.05(5.25)	Emotional faces
	20HC	8/12	25.65(6.31)	
Heitmann et al, [65]	30SAD	11/19	27.5(7.74)	Emotional images
	30HC	11/19	27.07(5.35)	
Jung et al,[30]	36SAD	17/19	25.4 (3.1)	Emotional faces
	42HC	19/23	24.7 (3.1)	
Murray et al, [66]	15gSAD	5/10	39.1(14.3)	Emotional faces
	15HC	5/10	39.3(12.3)	
Amir et al,[67]		3/8	24.1(5.2)	Emotional faces
	11gSAD	3/8	23.9(5.7)	
	11HC			
Phan et al,[24]	10gSAD	5/5	26.7(6.8)	Emotional faces
	10HC	5/5	26.6(6.8)	
Goossens et al,[68]	15 SP	2/13	24.0(2)	Emotional images
	14HC	2/12	23.0(1)	
Yoon et al,[31]	11gSAD	5/6	27.0(6.07)	Emotional faces
	11HC	5/6	26.9(6.16)	
Gentili et al, [26]	8SAD	4/4	39.0(7)	Emotional faces
	7HC	4/3	30.0(7)	
Caseras et al, [69]	14SP	3/11	22.71(2.89)	Emotional images
	14HC	3/11	23.0(2.66)	
Caseras et al, [70]	14SP	2/12	21.5(2.73)	Emotional images
	17HC	2/15	21.76(2.88)	
Klupp et al,[27]	12gSAD	-	28.2(8.6)	Emotional faces
	12HC	-	33.6(9.6)	

Blair et al,[28]		8/7	30.3(8.49)	Response to own/other opinions
	15gSAD	9/6	31.1(6.37)	
	15HC			

Abbreviations: MNI, Montreal Neurological Institute; PD, panic disorder; GAD, generalized anxiety disorder; SAD, social anxiety disorder; SP, specific phobias.

2.2 ALE

The method of ALE was proposed by E. G. et al, [19]. This method integrates many brain imaging results and obtains stable activated functional brain areas through automated statistical analysis. We used cluster-level Family-wise error (FWE) to correct for multiple comparisons, with significance set as $p \leq 0.1$. We applied 1000 permutations and used $p = 0.1$ as the cluster construction threshold and the statistical threshold for cluster-based comparison. Import the threshold map of the ALE value into the mango (<http://ric.uthscsa.edu/mango>). The coordinates were extracted from studies and subsequently referred to as foci.

3. Results

3.1 Co-activation of anxiety disorders

We explored the co-activation of the brain in response to stimuli in the anxiety included in this study. The higher activations were located in the two parahippocampal gyrus, subcallosal gyrus, lentiform nucleus, thalamus, ventral posterior lateral nucleus, bilateral amygdala, postcentral gyrus, medial dorsal nucleus, anterior nucleus, insula, and precentral gyrus (red). The lower activations were located in the posterior cingulate, precuneus, and posterior cingulate, lingual gyrus, and fusiform gyrus (blue). (Fig. 2 and Table 2).

Table 2
ALE cluster significant after cluster-level FWE correction for multiple comparisons

Cluster No.	MNI coordinates			ALE($\times 10^{-3}$)	Hemisphere	BA or anatomical location
	X	Y	Z			
Anxiety>HC						
1	-22	2	-22	29.12	L	34
	14	2	-18	21.26	R	34
	14	-8	-22	15.71	R	34
	-16	8	-8	13.03	L	lentiform nucleus. putamen
	24	-8	-10	12.99	R	lentiform nucleus. lateral globus pallidus
	-28	-14	10	12.08	L	lentiform nucleus. putamen
	-22	-18	8	11.98	L	thalamus. the ventral posterior lateral nucleus
	30	-8	-24	11.11	R	parahippocampal. amygdala
	-22	-12	-12	10.00	L	amygdala
	-52	-22	36	9.83	L	2
	-4	-12	-4	9.74	L	thalamus
	-22	0	-2	9.58	L	lentiform nucleus. Putamen
	4	-14	8	9.51	R	thalamus. medial dorsal nucleus
	-4	0	10	9.18	L	thalamus. anterior nucleus
	-42	-14	20	7.69	L	13
	-42	-10	38	7.59	L	6
	14	-8	-4	7.30	R	thalamus.
	-14	-6	-2	7.25	L	lentiform nucleus. medial globus pallidus
	-40	-2	16	7.01	L	13
Anxiety<HC						
1	-24	-64	-14	12.67	L	posterior lobe. declive.
BA, Brodmann area; L, left; R, right; x, y, z coordinates provided in MNI space; Anatomical labeling according to MNI atlas (nearest grey matter) associated with the peak coordinates; Maximum ALE value observed in the cluster.						

Cluster No.	MNI coordinates			ALE($\times 10^{-3}$)		Hemisphere	BA or anatomical location
	-8	-46	18	12.31	L		29
	-24	-50	-24	9.42	L		anterior lobe. culmen.
	-6	-48	34	9.06	L		31
	-4	-68	42	8.88	L		7
	12	-66	12	8.78	R		30
	-28	-74	-10	8.52	L		posterior lobe. declive
	-16	56	-16	8.39	L		30
	14	-58	12	8.39	R		30
	-36	-56	-22	8.25	L		anterior lobe. culmen
	-12	-66	4	8.24	L		19
	-8	-80	20	8.24	L		7
	-12	-80	48	8.17	L		19
	-8	-80	48	8.15	L		18
	-20	-94	24	7.94	L		18
	-8	-86	24	7.90	L		18
	12	-56	6	7.72	R		anterior lobe. Culmen
	4	-56	30	7.56	R		31
	-20	-58	0	7.54	L		19
	-44	-78	-8	6.63	L		19
	-10	-64	34	5.29	L		31
	8	-44	24	5.11	R		30
	2	-64	22	5.00	L		23
	-14	-42	-18	5.00	L		anterior lobe. culmen
BA, Brodmann area; L, left; R, right; x, y, z coordinates provided in MNI space; Anatomical labeling according to MNI atlas (nearest grey matter) associated with the peak coordinates; Maximum ALE value observed in the cluster.							

3.2 Diverse activations of different anxiety subtypes

In groups, we also have discussed the diverse brain activations in different anxiety subtypes under emotional stimulations (Fig. 3). GAD showed hyperactivity in the left hippocampus (red) as well as

hypoactivity in the posterior cingulate, fusiform gyrus, middle temporal gyrus, cuneus, and lingual gyrus (blue). SAD showed hyperactivity in the lentiform nucleus, medial globus pallidus, insula, amygdala, and thalamus (red) as well as hypoactivity in the precuneus, parahippocampal gyrus, and fusiform gyrus (blue). PD exhibited hyperactivity in the lateral globus pallidus, subcallosal gyrus, putamen, parahippocampal gyrus, amygdala, thalamus, medial dorsal nucleus, anterior nucleus, medial globus pallidus, and insula (red) as well as hypoactivity in the fusiform gyrus, posterior cingulate, middle temporal gyrus, superior temporal gyrus, precuneus and inferior parietal lobule (blue). SP showed hyperactivity in the fusiform gyrus, lingual gyrus, cingulate gyrus, anterior cingulate, thalamus, and inferior occipital gyrus (red) as well as hypoactivity in the medial frontal gyrus (blue).

GAD and PD showed more regular hypoactivity in the anterior lobe (culmen of vermis), limbic lobe (posterior cingulate) and temporal lobe (fusiform gyrus, middle temporal gyrus), and SAD showed noteworthy hypoactivity in the parietal lobe (precuneus) and anterior lobe (culmen) (see Fig. 4A). SAD and SP showed more frequent hyperactivity in the sub-lobar (thalamus, lentiform nucleus putamen, insula) and limbic lobe (parahippocampal gyrus, posterior cingulate, anterior cingulate), and PD showed significant hyperactivity in the frontal lobe (inferior frontal gyrus, subcallosal gyrus, medial frontal gyrus) and limbic lobe (posterior cingulate, parahippocampal gyrus) (see Fig. 4B). The integration of activation for different anxiety disorders on the brain were showed in Fig. 5.

4. Discussion

We have demonstrated a meta-analysis of the activation states of anxiety under emotional stimulations by the ALE method to compare the brain activation in different subtypes of anxiety.

We found that anxiety disorders displayed increased activation in the bilateral amygdala, anterior cingulate gyrus, parahippocampal gyrus, and common decreased activation mainly in the posterior cingulate, lingual gyrus, and precuneus. These conclusions are consistent with the previous studies [14, 20–30].

Although activations in the amygdala always appear in anxiety disorders involving emotional stimulations, there was a divergence in the activation of the left and right amygdala. For instance, some studies have highlighted the hyperactivity of the two-sided amygdala in anxiety disorders [23, 24, 27, 29, 31–33], while other studies have only found it in the unilateral amygdala. This may be related to the different functions of the left and right amygdala [34]. The right amygdala is related to sensory-driven, bottom-up processing [35]. And the left amygdala is associated with the cognitive evaluation of emotional stimulations [36, 37]. Our meta-analysis showed the activation of the bilateral amygdala increases when anxiety were stimulated by emotional facial pictures.

We also detected more activation in the parahippocampal gyrus (BA 34) in anxiety, this is consistent with the structure in Pavlov fear conditioning in animals and humans [38]. An earlier review and meta-analysis of fMRI data in anxiety disorders also pointed out that the activation of the parahippocampal gyrus was significantly increased [39, 40].

Additionally, we also found that under the stimulative tasks, the activation of the cingulate cortex of anxiety disorders was significantly different from HCs. As previous studies [41–44] reported that the cingulate cortex is related to emotional processing and participates in emotional regulation in depression and anxiety. Our results have once again verified this theory.

We also found that anxiety disorders showed markedly increased activations in the anterior cingulate cortex. As reported that the anterior cingulate cortex plays a key role in regulating mood in individuals, especially anxiety [45]. In the insula (BA 13) of anxiety, we found an increased activation. This also confirms the evidence from studies [46] and [47] that the insula has an impact on facial emotional processing. We also found a decreased activation in the anterior wedge (BA 7) and the visual associative cortex (BA 19) of anxiety disorders. This may be related to the inherent functional structure of the front wedge in humans [48], [49]. The size of the anterior right wedge is positively correlated with the individuals' linguistic creativity [50]. This also reflects the remarkable characteristics of anxiety disorders' avoidance behavioral response and impaired cognition, speech, and various related physiological reactions.

However, our meta-analysis has some limitations that must be considered. Primarily, due to the timing of selecting studies, some related publications may be missed. Moreover, the age of the participants included in the meta-analysis was not divided in detail. Because anxiety problems, particularly negative cognitions problems, increased with age, and are significantly higher among females [51].

5. Conclusions

In summary, our meta-analysis confirmed that anxiety disorders exhibit common increased activation mainly in the bilateral amygdala, anterior cingulate gyrus, and parahippocampal gyrus, and common decreased activation mainly in the posterior cingulate gyrus, and precuneus. Although there are differences in the activation of the four anxiety subtypes, they all show an increased or decreased activation in the limbic lobes. This may be related to the fact that the limbic lobe is composed of the cingulate gyrus, hippocampal gyrus, hippocampus, and other ingredients that affect memory and emotion. Therefore, the activation difference of the limbic circuit may be a neural reflection of anxiety symptoms, which may become the target of clinical intervention and future research.

Declarations

Acknowledgements

Not applicable.

Funding Sources

This work was supported in part by the National Key Research and Development Program of China (Grant No. 2019YFA0706200), in part by the National Natural Science Foundation of China (Grant No.61632014, No.61627808), in part by the Natural Science Foundation of Gansu Province of China (Grant No.20JR5RA292)

Conflict of interest

The authors declare no potential conflict of interest.

Ethical Approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to Participate

Not applicable.

Consent to Publish

All authors consent to publish.

Availability of data and materials

The data underlying the findings of this study is available upon request.

Code availability

Not applicable.

Author Contributions

The idea of this work was conceived by Xia Liu. The literature selection and ALE meta-analysis was conducted by Xia Liu via the supervision of Yinghui Zhang and Bin Hu. The manuscript was drafted by Xia Liu. Xiuzhen Wang, Yongchao Li, Shanling Ji, Yu Zhang, Yinghui Zhang, and Bin Hu provided valuable suggestions to revise the manuscript.

References

1. Öhman, A. (1993). "Fear and anxiety as emotional phenomena: Clinical phenomenology, evolutionary perspectives, and information-processing mechanisms," *In M. Lewis & J. M. Haviland (Eds.),* pp. 511-536,
2. Yovel, G. (2016). "Neural and cognitive face-selective markers: An integrative review," *Neuropsychologia*, vol. 83, pp. 5-13,
3. Gotlib, J. J. (2010). Cognition and depression: Current status and future directions,. *Annu. Rev. Clin. Psychol*, 6, 285–312
4. Mathews, M. C. (2005). "Cognitive vulnerability to emotional disorders,". *Annu. Rev. Clin. Psychol*, 1, 167–195
5. Mokhtari, B. H. (2015). "The effect of observers' mood on the local processing of emotional faces: evidence from short-lived and prolonged mood States,". *Adv Cogn Psychol*, 11(1), 14–21
6. Saris, A. M., van der Werff, I. M. J., van der Wee, S. J. A., & Penninx, N. J. A. (2017). Social functioning in patients with depressive and anxiety disorders,. *Acta Psychiatr Scand*, 136(4), 352–361
7. Etkin, A., Prater, K. E., F, S. A., & Greicius, M. D., Menon.V., and. (2009). Disrupted amygdalar subregion functional connecivity and evidence of a compensatory network in generalized anxiety disorder. *Arch Gen Psychiatry* vol, 66, 1361–1372
8. e. a. Tye. K. M., "Amygdala circuitry mediating reversible and bidirectional control of anxiety,"*Nature*, vol. 471, pp.358–362,
9. Moon., J. G. W. (Oct 2015). Functional neuroanatomy on the working memory under emotional distraction in patients with generalized anxiety disorder. *Psychiatry Clin Neurosci*, 69(10), 609–19
10. Li Jian, Z. Y., & Ma, Z. (2020)., "Emotion reactivity-related brain network analysis in generalized anxiety disorder: a task fMRI study,"*BMC Psychiatry*, vol. 20, no. 1,
11. Binelli., M. A., C, S. S., Blanco-Hinojo, N. R., Perez-Garcia, L., Perez-Jurado, D. C. J. F. M., & Martin-Santos, P. J. L, (Apr 2016). R, "Facial emotion processing in patients with social anxiety disorder and Williams-Beuren syndrome: an fMRI study," *J Psychiatry Neurosci*, vol. 41, no. 3, pp. 182-91,
12. Benedikt Figel, L. B., Buff, C., Carina, Y., Heitmann, D., Hofmann, M., Bruchmann, M. P. I. ... Herrmann (2019). Thomas Straube, "Phasic amygdala and BNST activation during the anticipation of temporally unpredictable social observation in social anxiety disorder patients,"*NeuroImage: Clinical*, vol. 22,
13. Sobanski, W. G. (2017). "Functional neuroanatomy in panic disorder: Status quo of the research,". *World J Psychiatry*, 7(1), 12–33
14. Kaldewaij, R. A., Reinoud, H., & Catherine, J. (2019). "A lack of differentiation in amygdala responses to fearful expression intensity in panic disorder patients," *Psychiatry Research-Neuroimaging*, vol. 291, pp. 18-25, Sep 30
15. Killgore, B. J., Schwab, W. D., Price, Z. J., Weiner, L. M., Gold, M. R., Rosso, A. L. ... Rauch, M. H. (2014). Cortico-limbic responses to masked affective faces across ptsd, panic disorder, and specific phobia,. *Depress Anxiety*, 31(2), 150–9

16. Klahn, K. I., & Lueken, A. L. (2017). "Commonalities and differences in the neural substrates of threat predictability in panic disorder and specific phobia,". *Neuroimage Clin*, 14, 530–537
17. Lancaster, T. G., Martinez, J. L. D., Salinas, M., Evans, F., Zilles, A., Mazziotta, K., & Fox, P. T., J.C. and. (2007). "Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template,". *Hum. Brain Mapp*, 28, 1194–1205
18. Eickhoff, L. A., Grefkes, S. B., Wang, C., Zilles, L. E., & Fox, K. (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
19. Turkeltaub, E. G., Jones, P. E., & Zeffiro, K. M. (2002). TA., "Meta-analysis of the functional neuroanatomy of single-word reading: method and validation," *Neuroimage*, vol. 16, no. 3, pp. 765–780,
20. Klumpp, P. D., Angstadt, H., Fitzgerald, M., & Phan, D. A. (2013). KL., "Anterior cingulate cortex and insula response during indirect and direct processing of emotional faces in generalized social anxiety disorder," *Biology of Mood & Anxiety Disorders*, vol. 3, no. 7,
21. Gaebler, D. J., Lamke, M., Fydrich, J. P., & Walter, T. (2014). "Behavioural and neural correlates of self-focused emotion regulation in social anxiety disorder,". *J Psychiatry Neurosci*, 39(4), 249–258
22. Thomas Straube, I. T. K., Glauer, M., Mentzel, H. J., Wolfgang, H. R., & Miltner (2004). Effect of task conditions on brain responses to threatening faces in social phobics_an event-related functional magnetic resonance imaging study,. *Biological Psychiatry*, 56(12), 921–930
23. Stein, G. P., Sareen, M. B., Zorrilla, J., & Brown, L. T. E. (2002). "Increased amygdala activation to angry and contemptuous faces in generalized social phobia,". *Arch Gen Psychiatry*, 59(11), 1027–1034
24. Phan, F. D. A., L, K., Nathan, P., & J, Tancer, M. E. (Mar 1 2006). Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biol Psychiatry*, 59(5), 424–9
25. Campbell, S. J., W, D., Paulus., M., P, Goldin, P., R, Stein., M., & B, Reiss, J. P. (2007). "Time-varying amygdala response to emotional faces in generalized social phobia," *Biol Psychiatry*, vol. 62, no. 5, pp. 455-63, Sep 1
26. Gentili., G. M. I., C, Ricciardi. E, Vanello. N, Pietrini., P, V, H. J., & Guazzelli. M, "Differential modulation of neural activity throughout the distributed neural system for face perception in patients with Social Phobia and healthy subjects," *Brain Res Bull*, vol. 77, no. 5, pp.286–92, Nov 25 2008.
27. Klumpp., A. M., Phan, H., & L, K., "Amygdala reactivity to faces at varying intensities of threat in generalized social phobia: an event-related functional MRI study," *Psychiatry Res*, vol. 183, no. 2, pp.167–9, Aug 30 2010.
28. Blair, G. M., Otero, K. S., Majestic., M., C, Odenheimer., S., Blair., J. M., & Pine, D. (2011). S, "Atypical modulation of medial prefrontal cortex to self-referential comments in generalized social phobia," *Psychiatry Res*, vol. 193, no. 1, pp. 38-45, Jul 30

29. Klumpp, A. M., Phan, H., & L, K. (Jan 2012). Insula reactivity and connectivity to anterior cingulate cortex when processing threat in generalized social anxiety disorder. *Biol Psychol*, 89(1), 273–6
30. Jung, S. J. E., Ye-Ha, L. Y. I., Jang. Joon, H., Jo. Hang, J., & Choi. Soo-Hee, "Altered Amygdala Resting-State Functional Connectivity and Hemispheric Asymmetry in Patients With Social Anxiety Disorder," *Frontiers in Psychiatry*, vol. 9, Apr 26 2018, Art. no. 164.
31. Yoon., F. D. A., & L, K., "Amygdala reactivity to emotional faces at high and low intensity in generalized social phobia: a 4-Tesla functional MRI study," *Psychiatry Res*, vol. 154, no. 1, pp.93–8, Jan 15 2007.
32. Blair., S. J., Smith, K., W, B., Rhodes., R, & Geraci. (2008). M, "Response to emotional expressions in generalized social phobia and generalized anxiety disorder: evidence for separate disorders," *Am J Psychiatry*, vol. 165, no. 9, pp. 1193-202, Sep
33. Blair., G. M., S, K., Korelitz. K, Otero., M., Towbin., K., Blair, E. M. L. E., J, R., & Pine, D. (Nov 2011). The pathology of social phobia is independent of developmental changes in face processing,. *Am J Psychiatry*, 168(11), 1202–9
34. Holtmann, O., Schlossmacher, I., Moenig, C., et al. (2018). "Amygdala enlargement and emotional responses in (autoimmune) temporal lobe epilepsy," *Sci Rep* vol. 8, no. 9561,
35. Z. DH., "The human amygdala and the emotional evaluation of sensory stimuli," *Brain Res Brain Res Rev*, vol. 41, no. 1, pp.88–123,
36. Gläscher, A. R. (2003). Processing of the arousal of subliminal and supraliminal emotional stimuli by the human amygdala,. *J Neurosci*, 12(32), 10274–82
37. Wright, L. Y. (2006). P, "Neutral faces activate the amygdala during identity matching," *Neuroimage*, vol. 29, no. 2, pp. 628-36,
38. Alvarez., B. A., P, R., Chen., G., Pine, D. S., & Grillon, C. (2008). "Contextual Fear Conditioning in Humans: Cortical-Hippocampal and Amygdala Contributions,". *Journal of Neuroscience*, 28(24), 6211–6219
39. Etkin, A., & Wager, T. D. (2007). "Functional Neuroimaging of Anxiety: A Meta-Analysis of Emotional Processing in PTSD, Social Anxiety Disorder, and Specific Phobia,". *American Journal of Psychiatry*, 164(10), 1476–1488
40. Freitas-Ferrari, H. J., & Trzesniak, M. C. (2010). "Neuroimaging in social anxiety disorder: a systematic review of the literature,". *Prog Neuropsychopharmacol Biol Psychiatry*, 34(4), 565–580
41. Mohamed, L. C., & Lee, A. Z. (2014). Facial Bell's palsy affects default mode network connectivity,. *Chin J Magn Reson Imaging* vol, 5, 408–15
42. Schaefer, P. K. M., & Benca., H. S. (2006). "Event-Related Functional Magnetic Resonance Imaging Measures of Neural Activity to Positive Social Stimuli in Pre- and Post-Treatment Depression,". *Biological Psychiatry*, 60(9), 974–986
43. Drevets, S. J., & Trimble, W. C. (2008). The subgenual anterior cingulate cortex in mood disorders. , " *CNS Spectrums*, 13(8), 663–681

44. Ahrens, S. D., Wallace, A., & Cheung, M. (1999). "Rapid simultaneous comparison system for subjective grading scales for facial paralysis,". *Am J Otol*, 20(5), 667–671
45. Zeng, L. S., Zhang, J., Huang, C., & Yu, G. (2018). "The Mechanism of Hyperalgesia and Anxiety Induced by Remifentanyl: Phosphorylation of GluR1 Receptors in the Anterior Cingulate Cortex,". *J Mol Neurosci*, 65(1), 93–101
46. Etkin, W. T. (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
47. Mennella, L. R., Taylor, R., & Dunkley, M. J. (2017). BT., "Disconnection from others in autism is more than just a feeling: whole-brain neural synchrony in adults during implicit processing of emotional faces,"*Mol Autism*, vol. 8, no. 7,
48. Margulies, V. J., & Kelly, D. S. (2009). "Precuneus shares intrinsic functional architecture in humans and monkeys,". *Proc Natl Acad Sci USA*, 106(47), 20069–20074
49. Cattoni, T. G., Uccioli, F., Manazza, R., Gastaldi, F., & Perani, G. (2020). D., "An fMRI Study on Self-Perception of Patients after Aesthetic Implant-Prosthetic Rehabilitation,"*Int J Environ Res Public Health*, vol. 17, no. 2,
50. Wu, Y. Q., & Li, Y. Y. (2019). "Altered spontaneous brain activity patterns in patients with retinal vein occlusion indicated by the amplitude of low-frequency fluctuation: A functional magnetic resonance imaging study,". *Exp Ther Med*, 18(3), 2063–2071
51. Thabet., V. P. (1998). Social adversities and anxiety disorders in the Gaza Strip,. *Archives of disease in childhood*, 78(5), 439–442
52. Ball, R. H. J., Paulus, L., P, M., Stein, M., & B (Jul 2013). Prefrontal dysfunction during emotion regulation in generalized anxiety and panic disorders,. *Psychol Med*, 43(7), 1475–86
53. Maddock., B. M., RJ, Kile., SJ, & Garrett (2003). AS, "Brain regions showing increased activation by threat-related words in panic disorder," *Neuroreport*, vol. 14, no. 3, pp. 325-328,
54. Chechko., W. R., N, E. A., Holsboer. F, Czisch., M., & Samann, P. G. (2009). "Unstable prefrontal response to emotional conflict and activation of lower limbic structures and brainstem in remitted panic disorder," *PLoS One*, vol. 4, no. 5, p. e5537, May 20
55. Killgore, W. D. S., Jennifer, B., Schwab, C., Zachary, J., Price. Lauren, M., Weiner. Melissa, R. ... Pollack. Mark, H. (Feb 2014). Rauch. Scott L., "CORTICO-LIMBIC RESPONSES TO MASKED AFFECTIVE FACES ACROSS PTSD, PANIC DISORDER, AND SPECIFIC PHOBIA,". *Depression and Anxiety*, 31(2), 150–159
56. Evans., W. C. I., C, K., Wedig., M. M., Gold, A., L, Pollack, M., H, Rauch, S., & L (2008). "A functional MRI study of amygdala responses to angry schematic faces in social anxiety disorder,". *Depress Anxiety*, 25(6), 496–505
57. Goldin, M. T., R, P., Hakimi., S., & Canli., T. (Feb 2009). "Neural bases of social anxiety disorder: emotional reactivity and cognitive regulation during social and physical threat,". *Arch Gen Psychiatry*, 66(2), 170–80
58. Bruhl, R. M., B, A., Delsignore., A., Kaffenberger., T., Jancke., & Herwig L, (U, "Neural correlates of altered general emotion processing in social anxiety disorder," *Brain Res*, vol. 1378, pp. 72-83, Mar 10

- 2011).
59. S. P. Hahn. Andreas, Windischberger. Christian, Weissenbacher. Andreas, Spindelegger. Christoph, Moser. Ewald, Kasper. Siegfried, Lanzenberger. Rupert, "Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder," *Neuroimage*, vol. 56, no. 3, pp. 881-889, Jun 1
 60. S. H. Nakao. Tomohiro, Yoshiura. Takashi, Togao. Osamu, Murayama. Keitaro, Tomita. Mayumi, Masuda. Yusuke, Kanba. Shigenobu, "fMRI of patients with social anxiety disorder during a social situation task," *Neuroscience Research*, vol. 69, no. 1, pp.67–72,
 61. Frick., H. K., Fischer. H, A., Kristiansson., M., & Furmark. (Oct 2013). T, "Altered fusiform connectivity during processing of fearful faces in social anxiety disorder," *Translational Psychiatry*, vol. 3, Art. no. e312.
 62. Heide Klumpp, D. P., Angstadt, M., Daniel, A., Fitzgerald¹, & Luan Phan, K. (2013). "Anterior cingulate cortex and insula response during indirect and direct processing of emotional faces in generalized social anxiety disorder," *Biology of Mood & Anxiety Disorders*, vol. 3, no. 7,
 63. Michal, P. R. G., Ziv, H., Jazaieri, K. S., Hahn, James, J., & Gross, &. (2013). Emotion regulation in social anxiety disorder_ Behavioral and neural responses to three socio-emotional tasks,. *Biology of Mood & Anxiety Disorders*, 3, no. 20
 64. Gaebler, J. K. D. M., Lamke, J. P., & Fydrich, T. (2014). Henrik Walter, "Behavioural and neural correlates of self-focused emotion regulation in social anxiety disorder,". *J Psychiatry Neurosci*, 39, 249–58
 65. Heitmann., F. K., Y, C., Neumeister., P., Zepp, B., M, P. J., Zwitterlood, P., & Straube (Apr 2016). T, "Abnormal brain activation and connectivity to standardized disorder-related visual scenes in social anxiety disorder," *Hum Brain Mapp*, vol. 37, no. 4, pp. 1559-72,
 66. Murray, M. P. R. G., Stein, B., Jitender Sareen, M. S., Lisa, M. D., Eyler, T., Zorrilla, P. D. ... Brown, P. D. (2002). "Increased Amygdala Activation to Angry and Contemptuous Faces in Generalized Social Phobia,"
 67. Amir. N, K. H., L, A. M. P. K., & Miller, E. J. B. J. S. (L. S., "Increased activation of the anterior cingulate cortex during processing of disgust faces in individuals with social phobia," *Biol Psychiatry*, vol. 57, no. 9, pp. 975-81, May 1 2005).
 68. Goossens., S. K., Peeters., L., R, Griez., E., & Sunaert. S, "Visual presentation of phobic stimuli: amygdala activation via an extrageniculostriate pathway?," *Psychiatry Res*, vol. 155, no. 2, pp.113–20, Jul 15 2007.
 69. Caseras., G. V, X, L. A., Brammer., M., Vilarroya. O, C. S., & Mataix-Cols, R. M. T. R. (Jan 2010). D, "The functional neuroanatomy of blood-injection-injury phobia: a comparison with spider phobics and healthy controls,". *Psychol Med*, 40(1), 125–34
 70. Caseras., G. V, X, L. A., Brammer., M., Vilarroya. O, C. S., & Mataix-Cols, R. M. T. R. (Oct 2010). D, "Dynamics of brain responses to phobic-related stimulation in specific phobia subtypes," *Eur J Neurosci*, vol. 32, no. 8, pp. 1414-22,

Figures

Figure 1

Paper selection strategy flow chart.

Figure 2

Brain maps of hyperactivity and hypoactivity in anxiety disorders compared to HCs determined by meta-analysis: anxiety disorders > HCs (red) and anxiety disorders < HCs (blue). Results are displayed at $p < 0.1$. The bar illustrates z-scored ALE activation: all coordinates are given as MNI.

Figure 3

Brain maps of hyperactivity (red) and hypoactivity (blue) in GAD, SAD, PD and SP, respectively. Results are displayed at $p < 0.1$. The bar illustrates z-scored ALE activation: all coordinates are given as MNI. GAD, generalized anxiety disorder; SAD, social anxiety disorder; PD, panic disorder; SP, specific phobias.

Figure 4

Anxiety disorders showed the increase and decrease activations in the diferent lobes. The vertical axis represents the weighted percentage.

Figure 5

The integration of activation for different subtypes of anxiety on the brain. (A) represents decreased activation, (B) represents increased activation. The colorbar: red represents generalized anxiety disorder

(GAD), yellow represents panic disorder (PD), blue represents social anxiety disorders (SAD), green represents specific phobia (SP). L:left, R:right.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [1657317173667707BIBChecklist.docx](#)