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Review

Neuroanatomical Correlates of Anxiety Disorders and Their Implications in Manifestations of Cognitive and Behavioral Symptoms

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Abstract: Developing an anxiety disorder can be the source of further cognitive, behavioral, and emotional struggles, impacting the quality of life of people experiencing such disorders and leading to a burden on health systems. Increased knowledge of the neurobiological events leading to the development of such disorders can be crucial for diagnostic procedures, as well as the selection and adaptation of therapeutic and preventive measures. Despite recent advances in this field, research is still at the initial steps when it comes to understanding the specific neurofunctional processes guiding these changes in the brains of people with an anxiety disorder. This narrative review gathered knowledge from previous studies, with the aim of evaluating the neuroanatomical changes observed in individuals experiencing social or generalized anxiety disorder (SAD, GAD), to further link these anxiety-related structural modifications with brain function abnormalities and the expression of symptoms in individuals experiencing anxiety disorders. In addition, contradictory results are discussed, leading to suggestions for future studies.

Keywords: biomarkers; cortical adaptation; neuroanatomical research; mental health; anxiety disorders

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1. Introduction

Disorders belonging to the anxiety spectrum are among the most common mental health issues stirring disability worldwide, affecting approximately 40 million European adults and 30 million Americans during their lifetime [1–3]. Divergency in prevalence across countries might likely be due to culturally influenced perspectives on mental health and associated disorders, or risk factors could actually be different between regions [4]. This implies that, although in some populations a high level of awareness on mental health issues may lead to over-diagnosis, in others many individuals might go through life without a condition being "officially" recognized. Nevertheless, current global prevalence of anxiety disorders has been established at 7.3%, with a range from 4.8 to 10.9% [4]. Anxiety is therefore more prevalent than mood disorders, including depression, in multiple countries [4], which explains the growing interest in researching its impacting effects on the brain.

As the sixth leading cause of disability in all countries, anxiety disorders can burden healthcare systems [4]. Their chronic nature can reduce quality of life and evolve to a more complex disability, as sole symptoms and consequent avoidant coping mechanisms and maladaptive behaviors significantly impair multiple aspects of functioning and cause distress in social, occupational or overall daily life [5,6]. Most disorders tend to persist, with patients still highly affected 6 to 12 years after diagnosis in some cases [7], and they are usually not treated until at least 10 years after onset [4].

The term "anxiety" derives from the Latin verb "ango", which translates as "to constrict", and the Latin word "angustus", which means "narrow" [8], reflecting the impairing nature of the condition in mental processing. According to the latest classification from the DSM-5-TR [6], anxiety is defined as "anticipation of future threat", whereas disorders of this spectrum are defined by their common features of excessive fear and anxiety related to atypical behavior [6]. In anxiety disorders, the anticipation of a possibly harmful context leads to heightened vigilance and avoidance behavior, generally accompanied by physical manifestations [6]. These maladaptive coping strategies often result in impairments of cognitive functions.

This increased vigilance people with an anxiety disorder will experience leads to a tendency to seek potential harmful stimuli, to the detriment of cognitive processes of sensory acquisition, attentional control, memory and higher executive functions [9]. Anxiety has been shown to have a negative impact on cognitive processes and executive functions [10]. Attentional control, in particular, is impaired in individuals with an anxiety disorder [11]. In the presence of a threatening stimulus, attention will be directed and maintained towards this internal (thoughts or feelings) or external distraction, increasing their detection and processing while decreasing their inhibition [10]. When there is no threatening stimulus, anxious individuals tend to direct their attention broadly in anticipation, decreasing the attention resources available for the performance of a task [10]. People with an anxiety disorder show biases in sustained attention towards threats and in selective attention for emotional stimuli, which interferes with the performance of tasks requiring attention [11]. This leads to an increased influence of the stimulus-driven attentional system and decreased influence of the goal-directed attentional system [10]. Biases in attention will lead to biases in the encoding and recalling functions of long-term memory [11]. Anxiety also negatively affects working memory resources [11]. People with an anxiety disorder will have more difficulty in dual tasking, decision making, spatial navigation and shifting function [9–11].

With the spectrum of anxiety disorders being relatively vast, only generalized anxiety disorder (GAD) and social anxiety disorder (SAD) will be discussed in this paper for the purpose of identifying structural abnormalities in the development of anxiety symptoms. With a lifetime prevalence and incidence rate of, respectively, 6% of the European population and 5 to 12% of the American population [5,12], GAD and SAD are among the most common subtypes of anxiety disorders. Even though these two are presented as separate disorders in DSM-IV and 5, the position that SAD cannot be separated from GAD has been previously discussed by Showraki et al. [13]. This paper suggests that SAD could be considered as a subtype of GAD. In their study, more than half (56%) of their GAD sample had a social-related anxiety, as opposed to performance-related anxiety, and almost half (49%) had anxiety in both social and performance situations [13]. It therefore makes it difficult to subtract SAD from GAD, and when investigating GAD, one should thus also include SAD.

In both GAD and SAD, there is a modified activity of brain function [5,12,14]. Functional activity abnormalities in the brains of people with GAD can be pointed out, especially in the amygdala (AM), anterior cingulate cortex (aCC) and prefontral cortex (PFC) [5]. There seems to be no consensus on whether activity of the AM increases or decreases, but disruption of intrinsic functional connectivity has been noticed [5]. In GAD, functional connectivity is lower in the prefrontal limbic and cingulate and increased in the prefrontal–hippocampal regions [5] These findings were correlated with the severity of clinical symptoms [5]. Connectivity between the aCC and the AM is impaired in GAD, and this may contribute to the emotional dysregulation manifested by patients [5]. Functional neuroimaging studies have shown that individuals experiencing SAD often present an increased activity in the autonomic nervous system, most likely instigated by alterations to the AM and the hypothalamus–pituitary–adrenal (HPA) axis [12]. Dysfunction to these systems, as well as other structures and areas involved in emotional processing and higher cognitive control, seems to be of crucial importance in understanding the origins of aberrant behavior in patients experiencing SAD [14]. Past research has put into focus that a

great number of psychiatric disorders emerge as a consequence of atypical brain development [15]. Although this is not a perfect match, function is also significantly correlated to structure in brain networks [16].

Further understanding of the individual structures and biological circuits presenting divergent functioning in individuals experiencing anxiety disorders can improve comprehension of the manifestations of this condition, as well as possibly facilitate diagnostic and treatment methods. Hence, the purpose of this narrative review is to explore the congruencies in studies researching these systems, commenting on possible advantages this knowledge can bring to future research. For this, a literature review was performed on cortical and subcortical structural changes encountered in patients experiencing GAD and SAD. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [17], a systematic search of the PubMed and Cochrane Library databases was completed in January 2022 by the first author. Reflecting the relevant published literature, search and MeSH terms were identified that broadly focused on the topic. The final list of terms included neuroanatomy, brain anatomy, neuroanatomical structure, brain markers, neuromarkers, anxiety disorder, mental health disorder and emotional regulation. A manual search of these databases and of relevant gray literature was also completed, with an identical search of all literature performed in July 2023 to determine whether new studies had been published in the time during the construction of this paper. This second search provided no additional results.

The initial literature search aimed to select articles published in the last 5 years, so as to obtain the most up-to-date results. There, however, have been few studies published in the last 5 years on neuroanatomical modifications in patients with GAD or SAD, which resulted in our search being broadened to the last 10 years. Ultimately, studies were included if (a) they were case-controlled studies, (b) they were published in the last 10 years, (c) they were available in full text and in English, (d) they were investigating human adults of all ages, (e) the primary diagnosis of patients was SAD or GAD with a diagnosis matching either DSM-IV or -5 and (f) the outcome was structural magnetic resonance imaging (MRI), including gray matter volumes (GMV), white matter volumes (WMV), cortical thickness (CTh), whole brain volumes, structural connectivity or surface area. We excluded articles if (a) they did not have a healthy control group, (b) children, adolescents, pregnant women were the population of interest, (c) the aim was to test the effectiveness of a treatment, (d) the primary diagnosis of patients was any other disorder than SAD or GAD, (e) the population of interest was healthy subjects with anxious tendencies and (f) the outcome was genetics, chemical interaction and regulation or any functional imagery.

The database search generated 6979 articles (PubMed = 6807, Cochrane Library = 172), with a further 24 articles added via citation pearl growing. Following removal of duplicates, 854 articles were left for further screening based on the inclusion criteria. After abstract screening, 824 articles were excluded as these focused on other primary diagnoses than SAD or GAD, had no control group, had participant groups not of interest to this review or an unclear study design, leaving 30 articles for full text screening. These remaining articles were screened independently against the eligibility criteria, with 13 studies removed at this point. A final sample of 17 studies was agreed for inclusion in the review. Results of the selected studies were then discussed and compared with findings on functional activity abnormalities of similar populations.

Seventeen studies were selected for this review (Table 1). Eight mostly focused on GAD, while the other nine deepened the argumentation to include SAD. Ten of those had GMV as the main outcome measure, being coherent with the initial aims of this literature review, while four emphasized changes in WMV and four other studies described general changes observed in CTh. The different nomenclatures for investigated ROIs reported across the studies have been adapted in this paper for consistency.

Sample sizes of the selected studies ranged from 26 to 131 individuals, with a total of 876 individuals (SAD, n = 268; GAD, n = 158; controls, n = 437), ranging from late adolescence to late adulthood, with the lowest age range at late adolescence (18 years

old) and the highest range at late adulthood (58 years old), with children and the elderly being excluded due to developmental issues likely leading to biased results and loss of congruence. Only one study selected by sex, focusing exclusively on male patients [18]; one study omitted the sex distribution in the assessed population [19]; and female population ranged from 30.77 to 84.21% across all other papers. GAD or SAD was the primary confirmed diagnosis of patient groups in all studies. Six studies excluded patients with psychiatric comorbidities, while nine included patients with at least one past or current comorbid psychiatric disorder. Two studies did not mention comorbidities. Depression, across all ranges, was the most recurrent secondary diagnosis when included, present in 71 patients overall. Specific phobia were also present in sixteen patients, nine patients had comorbid panic disorder, four had comorbid obsessive-compulsive disorder, four had eating disorders, two had a substance use disorder and two SAD patients had secondary GAD. The lack of exclusion of psychiatric comorbidities upon participants' selection is to be expected in these populations, as anxiety disorders are very often comorbid with other subtypes of anxiety disorders or other mental disorders, the most common ones being depression and panic disorder [4,5]. The patient groups of all studies were diagnosed with GAD or SAD according to the DSM-IV or -5, with the addition of supplementary assessments. The selected studies used a total of 22 different scales to assess anxiety diagnosis and other specificities.

Table 1. Selected studies, indicating number of participants, patients' profiles and regions of interest.

Authors and Year	*n*	Population of Interest (POI)	Comorbidities * in the POI	Regions of Interest
Brühl et al., 2014 [20]	92	33 SAD	1 MDD	right dlPFC, right parietal lobe, right TP, right aCC, left anterior INS, AM, HPC
Frick et al., 2013 [18]	26	14 SAD	1 SpPh, 2 OCD	left inferior TP
Frick et al., 2014 [21]	77	48 SAD	3 MDD, 2 PaD, 7 SpPh, 1 OCD	occipital lobe, FuG, LG
Hilbert et al., 2015 [22]	43	19 GAD	16 unspecified	right STR, right superior TP, left occipital lobe, left dlPFC, AM
Irle et al., 2014 [23]	131	67 SAD		superior FuG, SMA, left PRECUN, right ANG, right S1, right inferior PG
Kawaguchi et al., 2016 [24]	31	13 SAD	6 MDD, 2 PaD, 2 ED	left anterior INS, right posterior INS, AM, HPC
Makovac et al., 2016 [25]	38	19 GAD		SMG, M1, S1, AM
Meng et al., 2013 [26]	39	20 SAD		THA, right AM, right PRECUN
Molent et al., 2018 [27]	62	31 GAD	9 MDD, 4 PaD, 2 SpPH, 2 ED, 1 SUD	right caudal middle FuG
Moon et al., 2014 [28]	44	22 GAD	not reported	HPC, midbrain, THA, INS, superior TG, dlPFC
Moon and Jeong, 2015 [29]	44	22 GAD	22 mild depression	dlPFC, ALIC, midbrain, vmPFC
Moon and Jeong, 2016 [30]	26	13 GAD	13 mild depression	dlPFC, ALIC, midbrain, M1
Moon and Jeong, 2017 [31]	40	20 GAD	13 unspecified	dlPFC, ALIC, midbrain, THA, HPC, INS, superior TG

Table 1. *Cont.*

Authors and Year	*n*	Population of Interest (POI)	Comorbidities * in the POI	Regions of Interest
Syal et al., 2012 [19]	26	13 SAD		dlPFC, right INS, right TP, FuG, S1, right M1, right PCG, right SMG, right aCC
Talati et al., 2013 [32]	70	33 SAD	2 GAD, 11 MDD, 4 SpPh, 1 OCD, 1 SUD	CB, left PHG, left FuG, SMG, ANG, left middle occipital gyrus, TP, left inferior PFC, left inferior vmPFC, lower right AM, INS, left aCC
Terlevic et al., 2013 [33]	33 **	12 GAD		HPT
Tükel et al., 2015 [34]	54	27 SAD		left PRECUN, right middle TG, right inferior TG, left superior PG, right FuG

SAD: social anxiety disorder; GAD: generalized anxiety disorder; MDD: major depressive disorder; PaD: panic disorders; SpPh: specific phobia; SUD: substance use disorder; ED: eating disorder. AM: amygdala; TP: temporal pole; INS: insula; HPC: hippocampus; aCC: anterior cingulate cortex; HPT: hypothalamus; PFC: prefrontal cortex; vmPFC: ventromedial prefrontal cortex; THA: thalamus; M1: primary motor area/precentral gyrus; S1: primary somatosensory area/postcentral gyrus; SMA: supplementary motor area; PRECUN: precuneus; CB: cerebellum; STR: striatum; ALIC: anterior limb of the internal capsule; TG: temporal gyrus; ANG: angular gyrus; SMG: supramarginal gyrus; LG: lingual gyrus; FuG: fusiform gyrus; PG: parietal gyrus; PHG: parahippocampal gyrus; PCG: paracentral gyrus; OG: occipital gyrus. * past or current. ** the study also comprised 11 patients with PD; data from this group was not extracted.

2. Changes in Prefrontal Areas

The prefrontal cortex (PFC), with its adjacent functional areas, plays a crucial role in cognitive control and executive functions, acting on decision-making processes and in continuous development throughout life [35,36]. Among the different functional subdivisions of the PFC, the dorsolateral prefrontal cortex (dlPFC) seems to undergo stages of hyperactivation during emotional suppression in decision-making events, affecting attention and working memory [37]. Disturbances in these areas with an intricate relationship with the limbic system will unsurprisingly impact emotional regulation and therefore social behavior, as often reported in GAD [37,38]. In these patients, the activation of the left dlPFC is increased in comparison with controls, when participants are exposed to pleasurable (or positive emotional) stimulation [39], while it is decreased during exposure to a negative emotional context [40].

Another highly relevant prefrontal region that experiences maladaptive neuroplastic changes found here is the ventromedial prefrontal cortex (vmPFC). This region is well established in the literature for its role in social processing, as its links with the limbic system, here found acting oppositionally to the AM in emotionally charged responses [19,41]. In SAD, the balance between the vmPFC and AM appears to be disrupted, leading to aberrant inhibition of social threats processing by the latter, leading to deficits in the identification of social cues [19,42], which is another often-reported issue experienced by this population. A clear exemplification of this circuitry adaptation can be seen when patients experiencing GAD undertake face recognition tasks, and functional activity is disrupted in the medial prefrontal cortex (mPFC) [27]. These findings appear congruent in the literature, with abnormal functional activity also being reported in past reviews in the mPFC, vlPFC and dlPFC of patients experiencing GAD [5].

The dlPFC, mainly, of patients has been found to have structural adaptive changes in several studies [19,20,22,23,28–31]. Some reported an increase in GMV [28], others an increase in CTh on the right dlPFC [19,20], while others observed a decrease in WMV either bilaterally [28,30,31] or on the left side [22]. The vmPFC appears to also undergo structural transformation in patients in three studies, with a decrease in both GMV and WMV [25,28,32]. Functional connectivity was likewise altered in the rest of the PFC of patients in another study [32]. Other functional sites of the frontal cortex were subjected to

structural adaptations in patients with anxiety disorders, specifically the areas related to planification, such as the supplementary motor area (SMA), where authors observed an increase in GMV [23], and motor execution, represented by the precentral gyrus (M1) for which studies reported a decrease in both GMV and WMV [19,25,30].

Anatomical alterations occur in frontal regions involved in the modulation of the AM during emotion control, linked to executive functions such as attention, information processing and working memory. Social and emotional processes are impaired in patients with anxiety. Studies investigating patients post-acquired brain injury describe disorders of working memory that seem to be significantly related to the aberrant activation of the dlPFC in the right brain hemisphere [43].

3. Abnormalities in the Parietal Lobe

The parietal lobe is involved in sensory processing and associative loops serving spatial orientation and perceptual events [23,44]. The precuneus (PRECUN), as well as more lateral portions of the superior parietal lobe, (i.e., posterior superior parietal cortex), are activated during visualization of prospective actions, introspection and self-reflection and risk avoidance behavior, assisting in multifactorial decision-making processes [23,45]. In SAD, functional activity of the parietal lobe is increased [46], disrupting PRECUN activity [26]. In GAD, functional connectivity in the supramarginal and posterior superior parietal lobe is likewise aberrant during the processing of emotions [27,47].

Some congruent structural changes were reported in many of the selected studies in the parietal lobe of patients with an anxiety disorder. More precisely, some studies report an increase in CTh in the right parietal lobe [19,20], while others observe an increase in GMV in the left PRECUN [23,34] or a decrease in GMV in the right PRECUN [26]. Authors from another study reported a decrease in WMV in the SMG and in S1 [25], while others observed GMV anomalies in the SMG [25,32] and decreased GMV in S1 [23,25]. Finally, an increase in the GMV of structures of the psPC and piPC were pointed out across studies [23,25,32,34].

The regions of the parietal lobe that experience functional and structural changes seem to be linked with the difficulties in sensorimotor integration, attention, anticipation of others' intentions, introspection, decision making, and emotional faces processing observed in patients experiencing anxiety disorders. In individuals experiencing anxiety disorders, delayed anticipation has been proposed in relationship with functional impairment of the parietal cortex [23]. Rapid information processing is also impaired in anxiety [48]. Aberrant self-evaluation in the context of social situations and performances, a common symptom in this population, can also be related to the abovementioned regions.

4. Changes in the Temporal Lobe

The temporal lobe, in particular the right temporal pole (TP), has been shown to be involved in social and emotional processing, through the recruitment of socially relevant autobiographical memory influencing decision-making processes, imperative for social behavior [19,49]. Over direct and indirect connections between the TP (bilaterally) with the vmPFC and AM, this region seems to be implicated in the processing of abstract social concepts, while also assisting in processes of empathy, understanding others' emotional state, interoception and adaptive behavior [19,32,50]. This explains the link between structural abnormalities of the TP area and changes in emotional regulation, affecting social behavior [49].

The processing of negatively charged emotional information has been shown to be related to changes in the inferior temporal gyrus (TG), likely due to the impact of visual responses in social stimuli and emotional faces processing [18,19]. A pattern of inferior TG hyperactivity has been observed in imaging studies, with participants experiencing SAD when submitted to a trigger such as public speaking [51]. Together with the middle TG, the left inferior TG plays an important role in language processing, semantic memory, visual perception and integrating sensory input [34]. The fusiform gyrus (FuG), a neighboring region, is linked to social information processing [19], particularly facial expression recog-

nition with the lingual gyrus (LG) [18,34]. In SAD, emotional face processing is impaired, showing the link between anxiety disorders and structural and/or functional alterations in the FuG, as well as the parahippocampal gyrus (PHG) [18].

A number of the selected studies considered for this review also reported structural changes in the TP in individuals experiencing forms of anxiety [19,20,22,32]. Some studies reported a decrease in GMV in this region bilaterally [32], others an increase in GMV [22] or an increase in CTh [19,20] on the right side only. Authors of two studies also reported structural adaptations in the LG of SAD patients, with one reporting an increase in CTh [18] and the other an increase in GMV [21]. Some of the selected studies also investigated structural alterations in the FuG of people with an anxiety disorder. One reported an increase in CTh [18], while others observed increased GMV uni- or bilaterally [21,32,34]. Some studies described increased GMV in the inferior and middle TG [34], and decreased GMV in the superior TG [28,31] of patients experiencing forms of anxiety. Finally, authors of another study found that the left PHG gyrus of SAD patients had an increase in GMV compared to healthy controls [32]. The structural changes described above can be seen in ROIs with a role in social behavior, emotional processing and interoception. Likewise, these regions have been linked to empathy and the integration of language and visual processing. This relationship between functional regions and the anatomical adaptations they undergo in anxiety disorders helps us to understand the origin of aberrant social and emotional processing in these populations.

5. The Insular Cortex and Interoception

The insular cortex (INS) plays a pivotal role in evaluating, experiencing and expressing internal sensations [52], and consequently, in the modulation of interoceptive thoughts [50]. Patients experiencing anxiety disorders with aberrant interoception over-identify potential social threats. They seem to present INS hyperactivation when presented with a stressor [24], thus reinforcing their initial anxiety response and initiating a vicious circle. This pattern of hyperactivation seems to contribute to further structural changes, such as the loss of CTh [19,20,24,28,31,32], which in part explains the chronic aspect of anxiety disorders.

6. Amygdala and Related Circuits

The AM and the pregenual portion of the aCC are implicated in the modulation of intrinsic and extrinsic emotional processing, directly affecting the perception of self, others and decision-making events related to social interaction, through a process of reciprocal inhibition [18,20,53,54]. In addition, the right AM—hippocampus (HPC) circuit seems to be imperative for the representation of conditioned fear, modulating behavioral responses to perceived threats, playing a crucial role in the modulation of the HPA axis [28,55]. In individuals experiencing disorders of the anxiety spectrum, a hyperactivation of this system is associated with exacerbated systemic responses to perceived threats, leading to an elevated release of cortisol and consequent structural degradation [31].

It seems realistic to expect structural changes in the AM and HPC in patients experiencing a chronic state of anxiety. Still, case-control studies report no significant anatomical changes in these structures in patients diagnosed with anxiety disorders, compared to healthy controls [20,22,24,25], as has been replicated with voxel-based morphometry in another study [56]. Nonetheless, other studies still reported increased CTh in the right aCC [19,20], decreased total volume of the HPT [33], and decreased GMV in the left aCC [32], THA [26,28,31], right AM [26,32] and HPC [28,31], likely indicating that cortical systems involved in threat consolidation, perception and response are more prone to neuroanatomical changes than the AM itself.

In the case-controlled study by Syal et al. [19], regions that report a loss of CTh are directly interconnected with the AM [19]. Decreased connectivity between the AM and the inferior TG, which, as seen before, undergoes structural changes [34], is linked to the aberrant processing of negative social information in SAD patients [19]. Moreover, circuitry abnormalities have been reported in the limbic system in patients with GAD [5,28], in

the occipital cortex [57] and the TP [19,20,22,32]. This presumably implies that a greater fronto-temporal circuit is involved in these behavioral responses, with the AM contributing to processing but also acting as a "hub" for this system. Nodal centrality in networks involving the AM seems to be abnormal in patients experiencing SAD, contributing to this hypothesis [58].

7. Limits and Future Perspectives

The limitations of some of the selected articles may have affected the outcomes of the present review, since the number of papers on this specific field is limited, resulting in a liberal criterion for selection. Despite how hormonal changes in the elderly might have an impact on neurocircuitry, the exclusion of studies of this population was not considered a viable option for this review, thus contributing to possible bias [59]. Studies with patients with comorbidities were not excluded, even though this could create a bias due to overlaps between diagnoses interfering in the neuroanatomy of structures. There were inconsistencies in the selection of participants in these papers, with some authors out-selecting comorbidities, while others allowed them to a certain extent, likely to accommodate for the available population of voluntary participants. As mentioned above, the selected studies applied in summary 22 additional scales to aid the diagnostic of anxiety, which could likely raise discrepancies in the selection of patients. This paper does not account for the impact of medication on eventual neuroplastic processes affecting structural development, since the great majority of papers used here did not report on pharmacological treatment. Finally, we could not restrict the diagnosis to DSM-5-TR, which is the best available diagnosis criteria, because this manual was developed in 2013 and revised in 2022, and we included articles beyond this timeframe. No major changes were made between the two manuals to definitions of SAD or GAD [13,14].

There is high variation between the selected studies in the observed neuroanatomical areas that sustained changes, which might be due to both GAD and SAD disorders being included. Even though the study by Showraki [13] has highlighted the intertwining of GAD and SAD, further studies comparing the functional and structural presentation of these disorders is needed [13]. A re-evaluation of the separation or unification of the two disorders might therefore emerge.

Inconsistencies in the selection of participants based on sex could also explain the variation between studies in the observed modified brain areas. Brain structures and connectivity have been shown to be significantly different between healthy male and female participants [60,61]. These differences could in turn have a potential impact on the structural modifications observed in people experiencing anxiety disorders. Studies investigating neuroanatomical changes correlated with sex would be needed to explore this hypothesis.

The question of structural adaptation of the AM—volumetric and/or linked to functional connectivity—might in turn be due to the inclusion of studies with participants presenting psychiatric comorbidities. Although consensus on the presence of functional and structural disruption seems to occur in the literature, the exact nature of this disruption might require further investigation. Samples without comorbidities should be prioritized, whenever possible, as their presence may lead to confounders in both diagnostic criteria and the advent of symptoms.

At last, considering equipment limitations (most studies applied three Tesla scans at best) in the selected papers, studies evaluating structural adaptations with higher precise and more specific behavioral measurements would be helpful to further comprehend the extent of those adaptations. A recurrent issue in this line of investigation is that imaging measures are mostly applied for clinical practice, to then later be processed further and finally used in research. The discrepancy in symptom perception across different cultures is also an issue that seems to lead to great variability of results, impeding coherence.

8. Conclusions

This review highlighted macroscopic presentations of neurological adaptation processes and the most common behavioral presentation in people experiencing disorders of the anxiety. Deficits in emotional processing affecting social behavior in this population were related to structural adaptations mostly found around the dlPFC, TP, SMG, inferior TG, aCC and HPC. The dlPFC, the parietal cortex and the aCC appear as prominent regions of interest related to executive deficits. Deficits in self-awareness and self-evaluation have been linked to adaptations in the PRECUN, TP, INS and aCC, confirming the participation of these areas. In addition, structural changes found in the vmPFC, TP, inferior TG, FuG, LG and PHG of patients experiencing an anxiety disorder appear to be linked with difficulties in social cognition and social behavior.

Some of the regions that undergo adaptive processes in patients experiencing an anxiety disorder—such as the lateral and posterior parietal cortices, PFC, inferior TG and superior FG—are involved in more complex networks (i.e., the Default Mode and Fronto-Parietal Networks), which in turn play a role in the expression of social behavior. Further comprehension of maladaptive structural brain adaptations in people experiencing anxiety disorders could facilitate diagnosis and the evaluation of treatments' efficacy. The development of screening based on structural neuroimaging of targeted ROIs could also, to a certain extent, lead to the implementation of prevention measures for people experiencing trait anxiety.

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References

1. Wittchen, H.-U.; Jacobi, F. Size and Burden of Mental Disorders in Europe—A Critical Review and Appraisal of 27 Studies. *Eur. Neuropsychopharmacol.* **2005**, *15*, 357–376. [CrossRef] [PubMed]
2. Shah, A.A.; Han, J.Y. Anxiety. *Continuum* **2015**, *21*, 772–782. [CrossRef] [PubMed]
3. Bandelow, B.; Michaelis, S. Epidemiology of Anxiety Disorders in the 21st Century. *Dialogues Clin. Neurosci.* **2015**, *17*, 327–335. [CrossRef] [PubMed]
4. Stein, D.J.; Scott, K.M.; de Jonge, P.; Kessler, R.C. Epidemiology of Anxiety Disorders: From Surveys to Nosology and Back. *Dialogues Clin. Neurosci.* **2017**, *19*, 127–136. [CrossRef] [PubMed]
5. Maron, E.; Nutt, D. Biological Markers of Generalized Anxiety Disorder. *Transl. Res.* **2017**, *19*, 12. [CrossRef] [PubMed]
6. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; American Psychiatric Association: Washington, DC, USA, 2022.
7. Generalised Anxiety Disorder—The Lancet. Available online: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(06)69865-6/fulltext (accessed on 4 December 2023).
8. Crocq, M.-A. A History of Anxiety: From Hippocrates to DSM. *Dialogues Clin. Neurosci.* **2015**, *17*, 319–325. [CrossRef]
9. Robinson, O.J.; Vytal, K.; Cornwell, B.R.; Grillon, C. The Impact of Anxiety upon Cognition: Perspectives from Human Threat of Shock Studies. *Front. Hum. Neurosci.* **2013**, *7*, 203. [CrossRef] [PubMed]
10. Eysenck, M.W.; Derakshan, N.; Santos, R.; Calvo, M.G. Anxiety and Cognitive Performance: Attentional Control Theory. *Emotion* **2007**, *7*, 336–353. [CrossRef]
11. Grant, D.M.; White, E.J. Influence of Anxiety on Cognitive Control Processes. In *Oxford Research Encyclopedia of Psychology*; Oxford University Press: Oxford, UK, 2016; ISBN 978-0-19-023655-7.
12. Cremers, H.R.; Roelofs, K. Social Anxiety Disorder: A Critical Overview of Neurocognitive Research: Social Anxiety Disorder. *WIREs Cogn. Sci.* **2016**, *7*, 218–232. [CrossRef]
13. Showraki, M.; Showraki, T.; Brown, K. Generalized Anxiety Disorder: Revisited. *Psychiatr. Q* **2020**, *91*, 905–914. [CrossRef]

14. Spence, S.H.; Rapee, R.M. The Etiology of Social Anxiety Disorder: An Evidence-Based Model. *Behav. Res. Ther.* **2016**, *86*, 50–67. [CrossRef] [PubMed]
15. Sylvester, C.M. Editorial: Several Roads Lead to Anxiety. *J. Am. Acad. Child Adolesc. Psychiatry* **2020**, *59*, 703–704. [CrossRef] [PubMed]
16. Suárez, L.E.; Markello, R.D.; Betzel, R.F.; Misic, B. Linking Structure and Function in Macroscale Brain Networks. *Trends Cogn. Sci.* **2020**, *24*, 302–315. [CrossRef] [PubMed]
17. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gotzsche, P.C.; Ioannidis, J.P.A.; Clarke, M.; Devereaux, P.J.; Kleijnen, J.; Moher, D. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Healthcare Interventions: Explanation and Elaboration. *BMJ* **2009**, *339*, b2700. [CrossRef] [PubMed]
18. Frick, A.; Howner, K.; Fischer, H.; Eskildsen, S.F.; Kristiansson, M.; Furmark, T. Cortical Thickness Alterations in Social Anxiety Disorder. *Neurosci. Lett.* **2013**, *536*, 52–55. [CrossRef]
19. Syal, S.; Hattingh, C.J.; Fouché, J.-P.; Spottiswoode, B.; Carey, P.D.; Lochner, C.; Stein, D.J. Grey Matter Abnormalities in Social Anxiety Disorder: A Pilot Study. *Metab. Brain Dis.* **2012**, *27*, 299–309. [CrossRef]
20. Brühl, A.B.; Hänggi, J.; Baur, V.; Rufer, M.; Delsignore, A.; Weidt, S.; Jäncke, L.; Herwig, U. Increased Cortical Thickness in a Frontoparietal Network in Social Anxiety Disorder: Increased Cortical Thickness in SAD. *Hum. Brain Mapp.* **2014**, *35*, 2966–2977. [CrossRef]
21. Frick, A.; Engman, J.; Alaie, I.; Björkstrand, J.; Faria, V.; Gingnell, M.; Wallenquist, U.; Agren, T.; Wahlstedt, K.; Larsson, E.-M.; et al. Enlargement of Visual Processing Regions in Social Anxiety Disorder Is Related to Symptom Severity. *Neurosci. Lett.* **2014**, *583*, 114–119. [CrossRef]
22. Hilbert, K.; Pine, D.S.; Muehlhan, M.; Lueken, U.; Steudte-Schmiedgen, S.; Beesdo-Baum, K. Gray and White Matter Volume Abnormalities in Generalized Anxiety Disorder by Categorical and Dimensional Characterization. *Psychiatry Res. Neuroimaging* **2015**, *234*, 314–320. [CrossRef]
23. Irle, E.; Barke, A.; Lange, C.; Ruhleder, M. Parietal Abnormalities Are Related to Avoidance in Social Anxiety Disorder: A Study Using Voxel-Based Morphometry and Manual Volumetry. *Psychiatry Res. Neuroimaging* **2014**, *224*, 175–183. [CrossRef]
24. Kawaguchi, A.; Nemoto, K.; Nakaaki, S.; Kawaguchi, T.; Kan, H.; Arai, N.; Shiraishi, N.; Hashimoto, N.; Akechi, T. Insular Volume Reduction in Patients with Social Anxiety Disorder. *Front. Psychiatry* **2016**, *7*, 3. [CrossRef] [PubMed]
25. Makovac, E.; Meeten, F.; Watson, D.R.; Garfinkel, S.N.; Critchley, H.D.; Ottaviani, C. Neurostructural Abnormalities Associated with Axes of Emotion Dysregulation in Generalized Anxiety. *NeuroImage Clin.* **2016**, *10*, 172–181. [CrossRef] [PubMed]
26. Meng, Y.; Lui, S.; Qiu, C.; Qiu, L.; Lama, S.; Huang, X.; Feng, Y.; Zhu, C.; Gong, Q.; Zhang, W. Neuroanatomical Deficits in Drug-Naïve Adult Patients with Generalized Social Anxiety Disorder: A Voxel-Based Morphometry Study. *Psychiatry Res. Neuroimaging* **2013**, *214*, 9–15. [CrossRef] [PubMed]
27. Molent, C.; Maggioni, E.; Cecchetto, F.; Garzitto, M.; Piccin, S.; Bonivento, C.; Maieron, M.; D'Agostini, S.; Balestrieri, M.; Perna, G.; et al. Reduced Cortical Thickness and Increased Gyrification in Generalized Anxiety Disorder: A 3 T MRI Study. *Psychol. Med.* **2018**, *48*, 2001–2010. [CrossRef] [PubMed]
28. Moon, C.-M.; Kim, G.-W.; Jeong, G.-W. Whole-Brain Gray Matter Volume Abnormalities in Patients with Generalized Anxiety Disorder: Voxel-Based Morphometry. *NeuroReport* **2014**, *25*, 184–189. [CrossRef] [PubMed]
29. Moon, C.-M.; Jeong, G.-W. Alterations in White Matter Volume and Its Correlation with Clinical Characteristics in Patients with Generalized Anxiety Disorder. *Neuroradiology* **2015**, *57*, 1127–1134. [CrossRef]
30. Moon, C.-M.; Jeong, G.-W. Brain Morphological Alterations and Cellular Metabolic Changes in Patients with Generalized Anxiety Disorder: A Combined DARTEL-Based VBM and 1H-MRS Study. *Magn. Reson. Imaging* **2016**, *34*, 429–436. [CrossRef]
31. Moon, C.-M.; Jeong, G.-W. Abnormalities in Gray and White Matter Volumes Associated with Explicit Memory Dysfunction in Patients with Generalized Anxiety Disorder. *Acta Radiol.* **2017**, *58*, 353–361. [CrossRef]
32. Talati, A.; Pantazatos, S.P.; Schneier, F.R.; Weissman, M.M.; Hirsch, J. Gray Matter Abnormalities in Social Anxiety Disorder: Primary, Replication, and Specificity Studies. *Biol. Psychiatry* **2013**, *73*, 75–84. [CrossRef]
33. Terlevic, R.; Isola, M.; Ragogna, M.; Meduri, M.; Canalaz, F.; Perini, L.; Rambaldelli, G.; Travan, L.; Crivellato, E.; Tognin, S.; et al. Decreased Hypothalamus Volumes in Generalized Anxiety Disorder but Not in Panic Disorder. *J. Affect. Disord.* **2013**, *146*, 390–394. [CrossRef]
34. Tükel, R.; Aydın, K.; Yüksel, Ç.; Ertekin, E.; Koyuncu, A.; Taş, C. Gray Matter Abnormalities in Patients with Social Anxiety Disorder: A Voxel-Based Morphometry Study. *Psychiatry Res. Neuroimaging* **2015**, *234*, 106–112. [CrossRef] [PubMed]
35. Kolk, S.M.; Rakic, P. Development of Prefrontal Cortex. *Neuropsychopharmacology* **2022**, *47*, 41–57. [CrossRef] [PubMed]
36. Friedman, N.P.; Robbins, T.W. The Role of Prefrontal Cortex in Cognitive Control and Executive Function. *Neuropsychopharmacology* **2022**, *47*, 72–89. [CrossRef] [PubMed]
37. Gray, J.R.; Braver, T.S.; Raichle, M.E. Integration of Emotion and Cognition in the Lateral Prefrontal Cortex. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4115–4120. [CrossRef]
38. Monk, C.S.; Telzer, E.H.; Mogg, K.; Bradley, B.P.; Mai, X.; Louro, H.M.C.; Chen, G.; McClure-Tone, E.B.; Ernst, M.; Pine, D.S. Amygdala and Ventrolateral Prefrontal Cortex Activation to Masked Angry Faces in Children and Adolescents with Generalized Anxiety Disorder. *Arch. Gen. Psychiatry* **2008**, *65*, 568–576. [CrossRef]

39. Blair, K.; Shaywitz, J.; Smith, B.W.; Rhodes, R.; Geraci, M.; Jones, M.; McCaffrey, D.; Vythilingam, M.; Finger, E.; Mondillo, K.; et al. Response to Emotional Expressions in Generalized Social Phobia and Generalized Anxiety Disorder: Evidence for Separate Disorders. *Am. J. Psychiatry* **2008**, *165*, 1193–1202. [CrossRef]
40. Price, R.B.; Eldreth, D.A.; Mohlman, J. Deficient Prefrontal Attentional Control in Late-Life Generalized Anxiety Disorder: An fMRI Investigation. *Transl. Psychiatry* **2011**, *1*, e46. [CrossRef]
41. Milad, M.R.; Rauch, S.L. The Role of the Orbitofrontal Cortex in Anxiety Disorders. *Ann. N. Y. Acad. Sci.* **2007**, *1121*, 546–561. [CrossRef]
42. Beer, J.S.; Heerey, E.A.; Keltner, D.; Scabini, D.; Knight, R.T. The Regulatory Function of Self-Conscious Emotion: Insights from Patients with Orbitofrontal Damage. *J. Pers. Soc. Psychol.* **2003**, *85*, 594–604. [CrossRef]
43. Azouvi, P.; Arnould, A.; Dromer, E.; Vallat-Azouvi, C. Neuropsychology of Traumatic Brain Injury: An Expert Overview. *Rev. Neurol.* **2017**, *173*, 461–472. [CrossRef]
44. Fogassi, L.; Ferrari, P.F.; Gesierich, B.; Rozzi, S.; Chersi, F.; Rizzolatti, G. Parietal Lobe: From Action Organization to Intention Understanding. *Science* **2005**, *308*, 662–667. [CrossRef] [PubMed]
45. Paulus, M.P.; Rogalsky, C.; Simmons, A.; Feinstein, J.S.; Stein, M.B. Increased Activation in the Right Insula during Risk-Taking Decision Making Is Related to Harm Avoidance and Neuroticism. *Neuroimage* **2003**, *19*, 1439–1448. [CrossRef] [PubMed]
46. Brühl, A.B.; Rufer, M.; Delsignore, A.; Kaffenberger, T.; Jäncke, L.; Herwig, U. Neural Correlates of Altered General Emotion Processing in Social Anxiety Disorder. *Brain Res.* **2011**, *1378*, 72–83. [CrossRef] [PubMed]
47. Kropf, E.; Syan, S.K.; Minuzzi, L.; Frey, B.N. From Anatomy to Function: The Role of the Somatosensory Cortex in Emotional Regulation. *Braz. J. Psychiatry* **2018**, *41*, 261–269. [CrossRef] [PubMed]
48. Miskovic, V.; Schmidt, L.A. Early Information Processing Biases in Social Anxiety. *Cogn. Emot.* **2012**, *26*, 176–185. [CrossRef] [PubMed]
49. Olson, I.R.; Plotzker, A.; Ezzyat, Y. The Enigmatic Temporal Pole: A Review of Findings on Social and Emotional Processing. *Brain* **2007**, *130*, 1718–1731. [CrossRef]
50. Hatton, S.N.; Lagopoulos, J.; Hermens, D.F.; Naismith, S.L.; Bennett, M.R.; Hickie, I.B. Correlating Anterior Insula Gray Matter Volume Changes in Young People with Clinical and Neurocognitive Outcomes: An MRI Study. *BMC Psychiatry* **2012**, *12*, 45. [CrossRef]
51. Tillfors, M.; Furmark, T.; Marteinsdottir, I.; Fredrikson, M. Cerebral Blood Flow during Anticipation of Public Speaking in Social Phobia: A PET Study. *Biol. Psychiatry* **2002**, *52*, 1113–1119. [CrossRef]
52. Phan, K.L.; Wager, T.; Taylor, S.F.; Liberzon, I. Functional Neuroanatomy of Emotion: A Meta-Analysis of Emotion Activation Studies in PET and fMRI. *Neuroimage* **2002**, *16*, 331–348. [CrossRef]
53. Rajmohan, V.; Mohandas, E. The Limbic System. *Indian J. Psychiatry* **2007**, *49*, 132–139. [CrossRef]
54. Zhao, Y.; Sallie, S.N.; Cui, H.; Zeng, N.; Du, J.; Yuan, T.; Li, D.; De Ridder, D.; Zhang, C. Anterior Cingulate Cortex in Addiction: New Insights for Neuromodulation. *Neuromodulation* **2020**, *24*, 187–196. [CrossRef] [PubMed]
55. Femenía, T.; Gómez-Galán, M.; Lindskog, M.; Magara, S. Dysfunctional Hippocampal Activity Affects Emotion and Cognition in Mood Disorders. *Brain Res.* **2012**, *1476*, 58–70. [CrossRef] [PubMed]
56. Bas-Hoogendam, J.M.; van Steenbergen, H.; Nienke Pannekoek, J.; Fouche, J.-P.; Lochner, C.; Hattingh, C.J.; Cremers, H.R.; Furmark, T.; Månsson, K.N.T.; Frick, A.; et al. Voxel-Based Morphometry Multi-Center Mega-Analysis of Brain Structure in Social Anxiety Disorder. *Neuroimage Clin.* **2017**, *16*, 678–688. [CrossRef] [PubMed]
57. Pannekoek, J.N.; Veer, I.M.; van Tol, M.-J.; van der Werff, S.J.A.; Demenescu, L.R.; Aleman, A.; Veltman, D.J.; Zitman, F.G.; Rombouts, S.A.R.B.; van der Wee, N.J.A. Resting-State Functional Connectivity Abnormalities in Limbic and Salience Networks in Social Anxiety Disorder without Comorbidity. *Eur. Neuropsychopharmacol.* **2013**, *23*, 186–195. [CrossRef] [PubMed]
58. Zhang, X.; Lai, H.; Li, Q.; Yang, X.; Pan, N.; He, M.; Kemp, G.J.; Wang, S.; Gong, Q. Disrupted Brain Gray Matter Connectome in Social Anxiety Disorder: A Novel Individualized Structural Covariance Network Analysis. *Cereb. Cortex* **2023**, *33*, 9627–9638. [CrossRef] [PubMed]
59. van den Beld, A.W.; Kaufman, J.-M.; Zillikens, M.C.; Lamberts, S.W.J.; Egan, J.M.; van der Lely, A.J. The Physiology of Endocrine Systems with Ageing. *Lancet Diabetes Endocrinol.* **2018**, *6*, 647–658. [CrossRef]
60. Luders, E.; Gaser, C.; Narr, K.L.; Toga, A.W. Why Sex Matters: Brain Size Independent Differences in Gray Matter Distributions between Men and Women. *J. Neurosci.* **2009**, *29*, 14265–14270. [CrossRef]
61. Ingalhalikar, M.; Smith, A.; Parker, D.; Satterthwaite, T.D.; Elliott, M.A.; Ruparel, K.; Hakonarson, H.; Gur, R.E.; Gur, R.C.; Verma, R. Sex Differences in the Structural Connectome of the Human Brain. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 823–828. [CrossRef]