Neuroanatomical Correlates of Anxiety Disorders

Subjects: Neurosciences

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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.

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

1. 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 [1][2]. 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 [3]. 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 [3][4]. 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 [5], while it is decreased during exposure to a negative emotional context [6].

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 [7][8]. 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 [7][9], 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) [10]. 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 [11].

The dlPFC, mainly, of patients has been found to have structural adaptive changes in several studies [7][12][13][14][15][16][17][18]. Some reported an increase in GMV [15], others an increase in CTh on the right dlPFC [7][12], while others observed a decrease in WMV either bilaterally [15][17][18] or on the left side [13]. The vmPFC appears to also undergo structural transformation in patients in three studies, with a decrease in both GMV and WMV [15][19][20]. Functional connectivity was likewise altered in the rest of the PFC of patients in another study [20]. 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 [14], and motor execution, represented by the precentral gyrus (M1) for which studies reported a decrease in both GMV and WMV [7][17][19].

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 [21].

2. Abnormalities in the Parietal Lobe

The parietal lobe is involved in sensory processing and associative loops serving spatial orientation and perceptual events [14][22]. 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 [14][23]. In SAD, functional activity of the parietal lobe is increased [24], disrupting PRECUN activity [25]. In GAD, functional connectivity in the supramarginal and posterior superior parietal lobe is likewise aberrant during the processing of emotions [10][26].

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 [7][12], while others observe an increase in GMV in the left PRECUN [14][27] or a decrease in GMV in the right PRECUN [25]. Authors from another study reported a decrease in WMV in the SMG and in S1 [19], while others observed GMV anomalies in the SMG [19][20] and decreased GMV in S1 [14][19]. Finally, an increase in the GMV of structures of the psPC and piPC were pointed out across studies [14][19][20][27].

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 [14]. Rapid information processing is also impaired in anxiety [28]. 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.

3. 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 [7][29]. 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 [7][20][30]. This explains the link between structural abnormalities of the TP area and changes in emotional regulation, affecting social behavior [29].

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 [7][31]. 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 [32]. Together with the middle TG, the left inferior TG plays an important role in language processing, semantic memory, visual perception and integrating sensory input [27]. The fusiform gyrus (FuG), a neighboring region, is linked to social information processing [7], particularly facial expression recognition with the lingual gyrus (LG) [27][31]. 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) [31].

A number of the selected studies considered also reported structural changes in the TP in individuals experiencing forms of anxiety [7][12][13][20]. Some studies reported a decrease in GMV in this region bilaterally [20], others an increase in GMV [13] or an increase in CTh [7][12] 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 [31] and the other an increase in GMV [33]. Some of the selected studies also investigated structural alterations in the FuG of people with an anxiety disorder. One reported an increase in CTh [31], while others observed increased GMV uni- or bilaterally [20][27][33]. Some studies described increased GMV in the inferior and middle TG [27], and decreased GMV in the superior TG [15][18] 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 [20]. 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.

4. The Insular Cortex and Interoception

The insular cortex (INS) plays a pivotal role in evaluating, experiencing and expressing internal sensations [34], and consequently, in the modulation of interoceptive thoughts [30]. Patients experiencing anxiety disorders with aberrant interoception over-identify potential social threats. They seem to present INS hyperactivation when presented with a stressor [35], 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 [7][12][15][18][20][35], which in part explains the chronic aspect of anxiety disorders.

5. 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 [12][31][36][37]. 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 [15][38]. 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 [18].

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 [12][13][19][35], as has been replicated with voxel-based morphometry in another study [39]. Nonetheless, other studies still reported increased CTh in the right aCC [7][12], decreased total volume of the HPT [40], and decreased GMV in the left aCC [20], THA [15][18][25], right AM [20][25] and HPC [15][18], 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. [7], regions that report a loss of CTh are directly interconnected with the AM [7]. Decreased connectivity between the AM and the inferior TG, which, as seen before, undergoes structural changes [27], is linked to the aberrant processing of negative social information in SAD patients [7]. Moreover, circuitry abnormalities have been reported in the limbic system in patients with GAD [11][15], in the occipital cortex [41] and the TP [7][12][13][20]. 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 [42].

6. Conclusions

The link between changes in the neuroanatomy of brain regions and the related impairments manifested in people with an anxiety disorder are highlighted. Deficits in emotional processing affecting social behaviour in patients with an anxiety disorder were related to the structural modifications encountered in the dlPFC, TP, SMG, inferior TG, aCC and HPC of patients with an anxiety disorder. The dlPFC, the parietal cortex and the aCC, involved in attention impairments in people going through an anxiety disorder, can be linked with neuroanatomical changes in patients with an anxiety disorder. Deficits in self-awareness and self-evaluation experienced by people with an anxiety disorder have been put into relation with structural abnormalities in the PCUN, TP, INS and aCC in patients with anxiety disorders. In addition, structural changes found in the vmPFC, TP, inferior TG, FuG, LG and PHG of patients experiencing an anxiety disorder can be linked with their function in social cognition and behaviour, impaired in people with an anxiety disorder. Finally, structures involved in decision-making and planning, such as the dlPFC, SMA, PCUN, TP and aCC, were showing structural adaptations in patients with an anxiety disorder, highlighting the impairments those people experience with this function.

Some of the subcortical structures and cortical areas that sustained changes in patients experiencing mental health issues in the anxiety spectrum — 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 are in turn playing a role in the expression of social behaviour. Therefore, in addition to investigating separate structures and circuits, this paper raised the need for future research to assess neuroanatomical changes in more global networks to better comprehend interactions.

Further research focusing on neuroanatomical adaptations in people experiencing anxiety disorders could facilitate diagnosis, and evaluation of treatments efficacy. The development of a 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.

References

1. Kolk, S.M.; Rakic, P. Development of Prefrontal Cortex. Neuropsychopharmacology 2022, 47, 41–57.
2. Friedman, N.P.; Robbins, T.W. The Role of Prefrontal Cortex in Cognitive Control and Executive Function. Neuropsychopharmacology 2022, 47, 72–89.

3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. Milad, M.R.; Rauch, S.L. The Role of the Orbitofrontal Cortex in Anxiety Disorders. Ann. N. Y. Acad. Sci. 2007, 1121, 546–561.
9. 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.
10. 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.
11. Maron, E.; Nutt, D. Biological Markers of Generalized Anxiety Disorder. Transl. Res. 2017, 19, 12.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.
21. Azouvi, P.; Arnould, A.; Dromer, E.; Vallat-Azouvi, C. Neuropsychology of Traumatic Brain Injury: An Expert Overview. Rev. Neurol. 2017, 173, 461–472.
22. 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.
23. 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.
24. 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.
25. 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.

26. 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.
27. 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.
28. Miskovic, V.; Schmidt, L.A. Early Information Processing Biases in Social Anxiety. Cogn. Emot. 2012, 26, 176–185.
29. 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.
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.
35. 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.
36. Rajmohan, V.; Mohandas, E. The Limbic System. Indian J. Psychiatry 2007, 49, 132–139.
37. 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.
38. 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.
39. 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.
40. 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.
41. 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.
42. 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.