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Review

Neural structures, functioning and connectivity in Generalized Anxiety Disorder and interaction with neuroendocrine systems: A systematic review

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ABSTRACT

Background: Research on the neurobiological basis of Generalized Anxiety Disorder (GAD) has considerably expanded in recent years. However, many studies investigated different domains and used different methods and paradigms. Therefore, this review aims to integrate the findings to date and to identify the core correlates of neurobiological underpinnings of GAD discovered so far.
Methods: We conducted a systematic review of original papers investigating neural correlates, connectivity, or structural changes as well as reporting changes in the serotonergic system, noradrenergic system and cortisol levels in DSM-IV-defined GAD samples until December 2013.
Results: Studies have identified abnormal amygdala and prefrontal cortex activation in patients and decreased functional connectivity between these areas. Furthermore, studies showed increased gray matter volume and decreased structural connectivity between these structures. Neuroendocrine findings are less consistent, but increased reactivity of the noradrenergic system and perpetuations in the cortisol secretion have been reported.
Limitations: Only studies on DSM-IV defined Generalized Anxiety Disorder which employed a group comparison were included.
Conclusions: Current research suggests a distinct set of neurobiological alterations in Generalized Anxiety Disorder. However, future research on the interaction between these structures and systems and on the specificity of these findings in relation to other mental disorders is urgently needed.

Contents

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1. Introduction

Generalized Anxiety Disorder (GAD) is a chronic condition characterized by excessive and uncontrollable worry and anxiety about a variety of events and situations, accompanied by physical symptoms such as restlessness, muscle tension, irritability, and difficulties in concentration or sleep (American Psychiatric Association, 2000). It is prevalent in the general population (lifetime prevalence 4–6%; Beesdo et al., 2010; Kessler et al., 2012), in primary care (point prevalence 5–7%; Wittchen et al., 2002b), and in clinical treatment settings (point prevalence $>$ 10%; Brown and Barlow, 2002) and is associated with significant personal and economic burden (Wittchen et al., 2002a; Hoffman et al., 2008). Nevertheless, few studies on the neurobiology of GAD are available to date. Most of this research has focused on relatively small samples and selected paradigms, allowing for some initial insights on neurobiological alterations in GAD. However, as we learn more about the neurobiology of a range of mood and anxiety disorders, we understand that these disorders are characterized by overlapping, but also disorder-specific structural, functional and endocrine alterations. Identifying these neurobiological underpinnings of mental disorders may not only prove critical for understanding the development and maintenance of these disorders, but also for establishing a validator-based classification of mental disorders and various clinical applications in the future (Regier et al., 2009; Insel et al., 2010).

Therefore, our aim was to conduct a systematic review on the neurobiology of DSM-IV-defined GAD across different domains and different methods. Here, we focus on results of structural and functional neuroimaging studies (including structural and functional connectivity, respectively) as these results may inform us about fundamental changes in brain organization and functioning in GAD patients. Furthermore, we included results on three neuroendocrine systems based on their important role in mood regulation, arousal and stress, all of them areas that seem critical for understanding the etiopathogenesis of GAD. As far as currently possible, we attempt to point out how findings in the neuroimaging and neuroendocrine studies may be linked to one another. As comorbidity is common in GAD (Wittchen et al., 2002a; Beesdo et al., 2010), with other anxiety disorders and depression being the most closely linked conditions, we also shortly review studies that directly investigated commonalities and distinctions of GAD neurobiology with depression (mostly major depression) and/or other anxiety disorders (mostly post-traumatic stress disorder and phobias). Finally, we point out perspectives for clinical practice and suggest future research directions that may help to facilitate the transfer from fundamental research to the clinic.

2. Methods

Based on the scope of our review, the following inclusion criteria were used: original papers in English or German; comparison of a DSM-IV-defined GAD sample (or subgroup from a bigger sample) with a healthy control group; functional or structural investigation of brain areas or connectivity or investigation of serotonergic system, noradrenergic system or the Hypothalamic–Pituitary–Adrenal (HPA) axis or cortisol. Articles from January 1994 until December 2013 were included.

As our review focuses on pathological changes found in GAD samples, we did not consider pharmacological studies here, although these may be valuable for the understanding of neuroendocrine alterations in GAD as well (see already available reviews on this topic, e.g. Martin et al., 2010; Strawn et al., 2012b). As we took only DSM-IV defined GAD into account, endocrine findings based on earlier definitions had to be omitted as we cannot be sure whether these findings are still valid given the considerable criteria changes from DSM-III-R to DSM-IV. Also, many of these early studies were never replicated for DSM-IV GAD (for an overview on this issue: Connor and Davidson, 1998).

In order to include all studies within the scope of this review, broadly defined search terms were used in PubMed and Web of Science literature searches:
(((“generalized anxiety disorder”) OR (“generalised anxiety disorder”) OR GAD) AND (neurobiology OR neuroimaging OR Imaging OR MRI OR PET OR CT OR endocrinology OR neuroendocrinology OR serotonin OR noradrenalin OR cortisol OR HPA)).

Additionally, we screened references of the selected articles for further relevant articles. All studies which presented a group comparison between subjects with GAD and healthy controls were included in this review. Furthermore, we screened these articles for additional direct group comparisons between GAD and other mental disorders, which we present for areas consistently implied in GAD as well.

3. Results

In both databases combined, a total of 1765 different studies were found. Of these, 1718 studies were dismissed as irrelevant (e.g. as GAD is also the abbreviation of an antibody; see Fig. 1 for a flow chart on included and excluded studies). From the 38 neuroimaging-articles selected for this study, 15 and 24 investigated structural and functional changes in brain areas in GAD, respectively. From the 9 neuroendocrine articles selected for this study, 4 and 1 investigated changes in the serotonergic and noradrenergic system in GAD, respectively, and 7 investigated the HPA axis or cortisol. Some studies did match several domains (i.e. both structural and functional neuroimaging); however, no study investigated both neural correlates and neuroendocrinology. Among the selected articles, 8 presented an additional comparison to another mental disorder.

3.1. GAD versus healthy samples

3.1.1. Neuroimaging

3.1.1.1. Structural neuroimaging. Structural neuroimaging studies have identified several alterations in GAD compared to controls