Overview

Social anxiety disorder: a critical overview of neurocognitive research

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Social anxiety is a common disorder characterized by a persistent and excessive fear of one or more social or performance situations. Behavioral inhibition is one of the early indicators of social anxiety, which later in life may advance into a certain personality structure (low extraversion and high neuroticism) and the development of maladaptive cognitive biases. While there are several effective psycho- and pharmacotherapy options, a large number of patients benefit insufficiently from these therapies. Brain and neuroendocrine research can help uncover both the biological basis of social anxiety and potentially provide indicators, 'biomarkers,' that may be informative for early disease detection or treatment response, above and beyond self-report data. Several large-scale brain networks related to emotion, motivation, cognitive control, and self-referential processing have been identified, and are affected in social anxiety. Social anxiety is further characterized by increased cortisol response and lower testosterone levels. These neuroendocrine systems are also related to altered connectivity patterns, such as reduced amygdala–prefrontal coupling. Much work is needed however to further elucidate such interactions between neuroendocrine functioning and large-scale brain networks. Despite the great promise of brain research in uncovering the neurobiological basis of social anxiety, several methodological and conceptual issues also need to be considered.

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INTRODUCTION

Social anxiety disorder (SAD) is characterized by a persistent fear of one or more social or performance situations with exposure to unfamiliar people or to possible scrutiny by others.[1] A person with SAD fears that he or she will act in a way that will be humiliating or embarrassing, and exposure to the feared situations almost invariably provokes anxiety, which can take the form of panic attacks.[2] Social situations are either avoided or endured with intense anxiety or distress.[2] Imagine for instance being nervous, days in advance, about a meeting at work because of what colleagues think about how you look or what you say, and eventually calling in sick to avoid the meeting altogether. Such behavior, when repeated, will be unfavorable to *actual* performance reviews at work, and perhaps lead to gossiping, which in turn reinforces the social fears that led to the avoidance behavior to begin with. Here we will provide a critical overview of neurocognitive and neuroendocrine research on social anxiety. Our goal is to focus on a selection of important findings on the brain (focussing on functional Magnetic Resonance Imaging research) and neuroendocrine systems in adult SAD, rather than providing an exhaustive overview; for this, the interested reader is referred to references.[3–6] We will start by briefly covering

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developmental, cognitive and therapeutic perspectives, to first sketch a broader context, before we move to the brain and neuroendocrine research. We will also highlight several limitations of brain imaging studies.

DEVELOPMENT, COGNITION, AND TREATMENT

The diagnosis of SAD requires that the condition interferes substantially with the person's normal routine.[2] Hence, while almost everyone will get nervous when speaking in public, in order to 'qualify' as a disorder, this fear must be present in one or several different situations and lead to substantial distress. The lifetime prevalence rates are estimated between 5 and 12%.[7,8] A classical discussion on psychiatric disorders is whether they should be regarded as an extreme form of 'normal' behavior (i.e., simply a more extreme level of social anxiety) or as categorically different.[9] Work by Ruscio et al.[10] provided converging evidence for the dimensional nature of social anxiety. Hence we will incorporate both social anxiety (as an individual differences trait) and SAD (or social phobia; i.e., the set of symptoms that fulfill DSM criteria) in our discussion, since this distinction is unlikely to be respected by underlying brain mechanisms.

Research on personality traits and the development of social anxiety stresses the dimensional nature of social anxiety. Traits related to emotional processing, such as neuroticism (a temperamental sensitivity to painful or negative stimuli, and experiencing negative affect more frequently and/or intensely) and extraversion (a temperamental sensitivity to pleasurable stimuli (rewards) and experiencing positive effect, pride, and self-confidence more frequently and/or intensely)[11] are critical. Neuroticism is regarded as a 'vulnerability' marker, and extraversion a 'protective' factor[12,13] in the development of SAD. Moreover, it has been found that the heritability of social anxiety can, to a large extend, be explained by the heritability of these personality traits.[13] Note that this relation between personality factors and (social) anxiety development may be interpreted in a merely probabilistic manner: on average, someone who scores high on extraversion and low on neuroticism is less likely to develop social anxiety later in life. Personality traits may simply capture some aspects of (social) anxiety, such as a low stress threshold in the case of neuroticism, and therefore naturally show covariation, which makes such explanations somewhat circular.[14]

Another line of research aims to uncover the underlying or latent factors of social anxiety. Two independent studies found a similar three-factor solution for social anxiety, one consisting of social interaction fears, observation fears, and public speaking fears[15] and the other of public performance, close scrutiny, and social interaction.[16] This work on latent models of social anxiety may be helpful while dissecting 'subtypes' of social anxiety. When discussing the basic structure and personality characteristic of social anxiety in the population it is important to emphasize that such factors indeed just pertain to the population, not the individual.[17] That is, for any individual, the development and variation in social anxiety severity over time may be related to a single cognitive factor (e.g., the fear of negative evaluation) or to multiple factors. Research into such processes obviously requires longitudinal data. In the next section, we will briefly discuss the development and cognitive processes and treatment of social anxiety.

Developmental and Cognitive Models

Behavioral inhibition (BI), a temperamental trait referring to reactions of a child when confronted with novel situations or unfamiliar people,[18] is one of the earliest developmental indications of social anxiety. For example, research has shown a moderate relation between BI at 21 months, 31 months, and 4 years old,[19,20] and stable BI is a risk factor for social and other anxiety disorders.[18] During the course of a child's development, social anxiety may progress from such initial behavioral indicators, to increasing levels of self-consciousness and preoccupation with peer feedback and exclusion.[21] Several cognitive models have been proposed that describe this social information processing and, importantly, maintaining cognitive biases in social anxiety.[22,23] A detailed comparison of such models is beyond the scope of the article, but there are important overlapping elements including low perceived emotional control, post-event rumination, avoidance and the use of safety behaviors. Hofmann (2007) eloquently summarized a cascade of maladaptive cognition:

> When confronted with challenging social situations, individuals with SAD shift their attention toward their anxiety, view themselves negatively as a social object, overestimate the negative consequences of a social encounter, believe that they have little control over their emotional response, and view their social skills as inadequate to effectively cope with the social situation. In order to avoid social mishaps, individuals with SAD revert to maladaptive coping strategies, including avoidance and safety behaviors,

followed by post-event rumination, which leads to further social apprehension in the future.[24]

SAD is a heterogeneous condition, and naturally there are many different possible 'routes' to the development of similar social anxiety symptoms (principle of equifinality), while comparable predisposing factors (e.g., childhood trauma) may lead to very different symptom outcomes (principle of multifinality).[25] Moreover, distal factors (such as genes) and proximal ones (e.g., current stressors) create a complex interplay in the development of social anxiety.[26] Consider e.g., the relation between personality, life experience, and social support. Traumatic childhood experiences are well-known to increase the risk of anxiety disorders and heightened responsiveness of the stress system,[27,28] but adequate caregiving moderates this trauma–anxiety association.[28] Moreover, attachment security decreases the relation between BI and stress reactivity.[29] However, maternal overprotection combined with high BI is a risk factor for developing social anxiety[30] and another study showed that experiencing uncontrollable events increases the relation between BI and anxiety.[31] Moderately stressful events may thus be habituating (decreasing responsiveness over time) to one, but sensitizing (increasing responsiveness over time) to another, depending on such factors as maternal care, executive function, and gender.[26,32,33] This brief discussion only provides a sketch of the complexity in the development of social anxiety, and highlights that while BI is associated with the development of social anxiety, it does not constitute a determining factor for any particular individual.[32]

Treatment

Social anxiety can be treated relatively well, with both pharmaco- and psychotherapy.[2,34] A recent meta-analysis showed that individual cognitive behavioral therapy, compared to other psychological and pharmacological treatment had the largest symptom reduction effect.[35] Nonetheless, a considerable number of patients does not respond adequately to treatment.[24,36] One study estimated that about 40–50% of the patients do not show clinical improvement after cognitive behavioral treatment,[37] which underscores the need for the development of new treatments.[38] Insights into the mechanisms, neurobiological or otherwise, of a disorder are crucial in that respect, apart from the basic theoretical knowledge gain.[39] For example, research on attention biases and performance feedback has helped to improve standard cognitive behavioral therapy[40] and studies on the neurobiology of extinction learning resulted in pharmacological enhancement (D-cycloserine) of exposure training.[41]

NEUROBIOLOGY

There has been a steady increase of functional magnetic resonance imaging (fMRI) research into the neural mechanism underlying social anxiety (see Figure 1). Initial fMRI studies on SAD focused mainly on emotional face processing and the role of the amygdala. Several studies reported amygdala hyperactivation in response to socially threatening (angry/fearful/harsh) facial expressions,[4] putatively indicative of an increased fear response or attention toward socially fearful stimuli. Early positron emission tomography (PET) studies also showed exaggerated amygdala responses during speaking in public,[42,43] a prototypical example of a fearful situation in social anxiety. This is a popular and effective paradigm for studying SAD, inside or outside the scanner. Public speech (anticipation) paradigms have also been used to study activity in the major

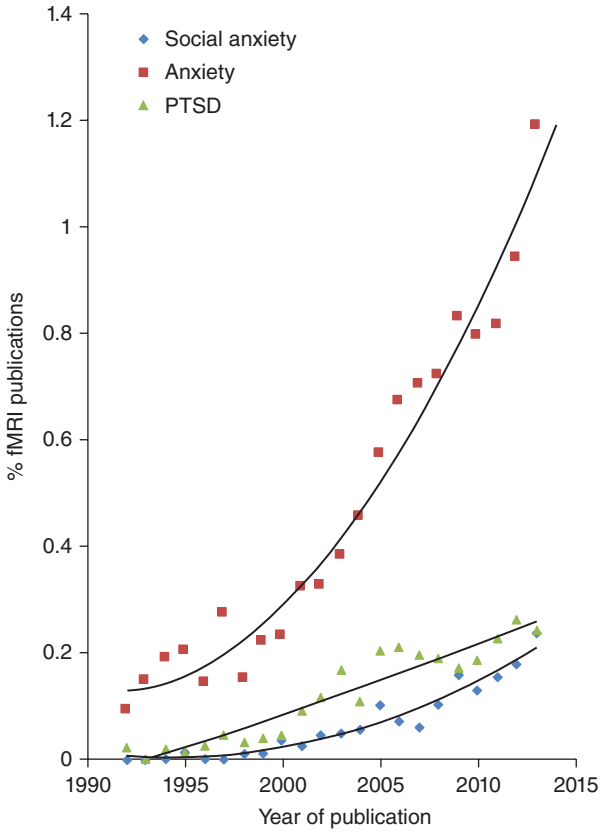


FIGURE 1 | Percentage of fMRI publications related to social anxiety, anxiety (in general), and Post Traumatic Stress Disorder (PTSD) per year since 1991, including (polynomial) trend line.

physiological stress systems: the autonomic nervous system (ANS) and the hypothalamus–pituitary–adrenal (HPA) axis. SAD patients show increased activity in these neuroendocrine systems during public speech.[44] Recent work increasingly utilizes other symptom-relevant task-designs to investigate processes like self-relevant praise or critique,[45] the reappraisal of negative self-belief[46] and social avoidance.[44,47]

Large-Scale Networks

Following early connectionist ideas concerning the brain basis of psychiatric disorders, fMRI studies are increasingly utilizing large-scale network approaches to delineate the neurobiology of psychiatric symptoms.[48] Brain network perspectives in psychiatry, and cognitive and affective functioning more generally (e.g., Refs 49 and 50) address the interplay and organizational principles of many, rather than a single brain region as the neurobiological foundation of complex psychological functions. Several distributed brain networks have robustly been identified,[51] and here we will discuss the neural systems critical for social anxiety: the emotion,[a] motivation,[a] cognitive control, and default mode networks (DMNs), see Box 1. These networks are relevant to particular symptoms of social anxiety (e.g., the emotion network and hyper attention to socially threatening stimuli) and are linked to resilience and vulnerability to adverse and stressful events.[53] Increasingly fMRI studies also focus on large-scale network organization during rest[54–58]; however, the plethora of analytic approaches renders that work challenging to compare and generalize at this point. Therefore, we would like to point out, that while below we will discuss fMRI research findings in terms of 'brain networks,' not all of these studies necessarily apply network or even connectivity analyses. The reason to nonetheless organize our discussion on research findings in such a way is pragmatic—to group results conveniently—as well as theoretical; to extrapolate a brain network model of social anxiety. This, in turn, may generate hypotheses for future research.

The investigation of the neuroendocrine systems is a second important line of research in the neurobiology of social anxiety. The hypothalamic–pituitary–gonadal (HPG) and hypothalamic–pituitary–adrenal (HPA) axes, and their respective end products, testosterone and cortisol, play an important role in regulation of social emotional behavior.[59] Whereas socially submissive and anxious behavior is associated with high cortisol and low testosterone levels, social dominance and aggression is typically associated with high testosterone and low cortisol levels.[59] Patients with SAD show alterations in these neuroendocrine systems consistent with the social submissiveness pattern: increased cortisol and decreased testosterone levels.[44,60,61] As will be discussed later, these hormones also interact with emotion- and motivational-related brain networks.

The Emotion Network

The amygdala is a core region involved in emotion processing[62] and considered to be a hub region in the emotion network.[63] Initially, the function of the amygdala was mainly linked to fear processing because of its evident importance in fear conditioning.[62] Currently however, the amygdala is argued to detect relevant information in the surroundings more broadly and is therefore essential in the processing of salient or ambiguous stimuli.[64] Along these lines there is an abundance of evidence for the importance of the amygdala in the processing of social cues such as faces,[65,66] regardless of a specific valence such as only to fear or anger.[67] Social anxiety studies, however, have recurrently shown amygdala hyperactivation especially in response to socially threatening facial expression.[3,4] The bed nucleus of the stria terminalis (BNST) is part of the so-called 'extended amygdala' and is critical in sustained threat responses[68,69] and has also been related to anxious temperament.[70] In addition, several brainstem nuclei are important for neuroendocrine and neurotransmitter control and release. Serotonin is a key neurotransmitter of the emotion network[71] and a target for pharmacological and genetic research.[72] The insula and the fusiform gyrus also show hyperactivation in social anxiety[3] and can be considered other central parts of the emotion network. Some studies suggest that pharmacological and behavioral treatments normalize the aberrant fusiform activity[3] and one report suggested that fusiform activity is predictive for treatment response.[73]

While evidence thus exists for hyperactivation of the emotion circuit, and particularly of the amygdala, it is important to emphasize that considerable work remains to be done both regarding the clinical significance as wells as the basic functional roles of the emotion network in humans.[68] For example, it is well known from animal literature that the amygdala consists of several anatomically and functionally separable nuclei with distinctive connectivity patterns (see e.g., Ref 74). Delineating the specific contributions of these subnuclei is far from trivial with standard fMRI protocols (due to the highly correlated time-series of neighboring structures) although attempts have been made.[75] Moreover, several

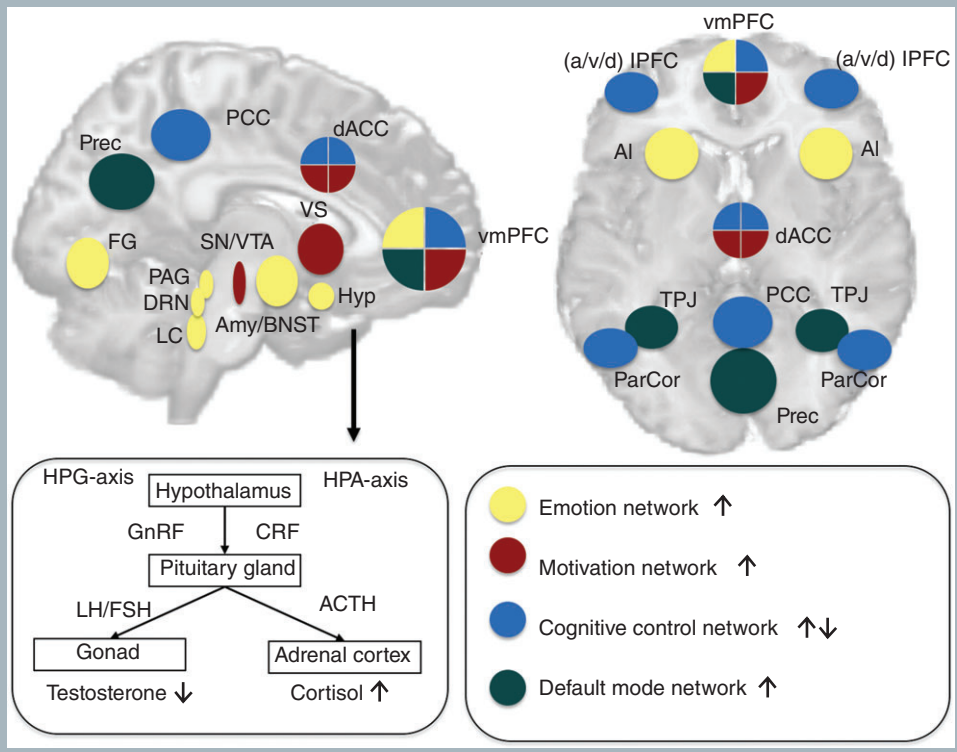
BOX 1

BRAIN NETWORKS AND NEUROENDOCRINE SYSTEMS RELATED TO SOCIAL ANXIETY

Schematic overview of brain networks altered in social anxiety grouped in four broad brain networks. *The emotion network:* salient sensory information is relayed from the visual cortex (Fusiform Cortex) and the thalamus (not shown) to the amygdala. Moreover, the amygdala is connected to regions involved in the autonomic (locus coeruleus, release of norepinephrine) and hormonal (hypothalamus, release of corticotrophin-releasing hormone) responses to stress. The hypothalamus is the critical region involved for the *HPG and HPA axis*, related to the release of testosterone and cortisol, respectively. *The motivation circuit:* The ventral striatum receives dopaminergic input from the VTA, in response to impeding or obtained incentives. Both networks are influenced by *The Cognitive Control Network*, consisting of prefrontal and parietal cortex regions, which is thought to exert 'top–down' control and as such 'downregulate' subcortical hyperactivity. The DMN consist of the ventral medial PFC, precuneus, and temporal–parietal junction that show increased synchronization at rest, and are also important for self-referential processes.

Arrows indicate whether the social anxiety literature broadly points to hyper- or hypo-activation and connectivity patterns. Note that this is a highly simplified model; many other important regions exist which are not shown, and in addition, many of the presented regions consist of several subregions characterized by specific patterns of connectivity and functioning (particularly the amygdala, see Ref 74). Moreover, while these four networks are partly separable anatomically and functionally, they also clearly overlap and interact, for instance in the connections between the amygdala and ventral striatum.

AI; Anterior Insula, Amy; Amygdala, BNST; Bed Nucleus Stria Terminalis, dACC; dorsal Anterior Cingulate Cortex, DRN; Dorsal Raphe Nucleus, FG; Fusiform Gyrus, Hyp; Hypothalamus, LC; locus coeruleus. PAG; periaqueductal grey, ParCor; Parietal Cortex, PCC; Posterior Cingulate Cortex. PFC; Prefrontal Cortex (a; anterior, d; dorsal, l; lateral, m; medial, v; ventral), Prec; Precuneus, SN/VTA Substancia Nigra/Ventral Tegmental Area, TPJ; Temporal Parietal Junction, VS; Ventral Striatum. ACTH; Adrenocorticotropic hormone. CRF; Corticotropin-releasing factor, GnRF; Gonadotropin-releasing hormone, LH/FSH; Luteinizing hormone/Follicle-stimulating hormone.



important brainstem regions that are part of the emotion network (see Box 1) are both smaller than the standard spatial resolution in fMRI, and highly susceptible to physiological artifacts in functional imaging and therefore difficult to reliably detect.[76] Functionally, the exact role of the amygdala in prolonged states of social stress—as opposed to short-lasting salience responses—is still topic of debate. For example, amygdala deactivation during social stress has been found.[77,78] We recently observed disrupted cortical-amygdala connectivity in SAD during the anticipation of social threat,[79] and suggested that the role of the amygdala during prolonged states of social threat may be better understood in terms of a shift in connectivity patterns rather than in a decrease of activity (see also Refs 49 and 50). However, to date this largely remains an open question. The complex relation between social anxiety and avoidance is further illustrated by recent notions that increased amygdala reactivity and threat hypervigilance is related to *reduced* inhibition,[71] or so-called 'aversive disinhibition.' Accordingly, persistent tendencies to avoid social situations in SAD might reflect a secondary strategy to cope with this aversive disinhibition, a notion compatible with the vigilance–avoidance theory.[80] Ly and colleagues indeed found that a social avoidant coping style is accompanied by disinhibition of action and striatal activity in the context of social threat.[81]

The amygdala thus undoubtedly plays a critical role in salience, vigilance-avoidance and stress processing, and amygdala activity constitutes a potential biomarker for social anxiety, e.g., Ref 82. However, future research also needs to address some the concerns raised above (and other ones, see Ref 83) regarding the role of the amygdala and the emotion network in social anxiety.

The Motivation Network

The motivation network comprises of a relatively well-described set of brain regions in the brainstem, striatum, and medial prefrontal cortex (mPFC) integral to mesolimbic dopaminergic activity.[84] The ventral tegmental area (VTA) is the main brainstem source of dopamine and is connected to regions of the ventral striatum. The ventral striatum encompasses the nucleus accumbens, and ventral parts of the putamen and caudate nucleus. Functionally, the ventral and dorsal striatum are argued to be best distinguished by their mPFC connectivity to the medial orbitofrontal cortex/anterior cingulate cortex and dorsolateral PFC, respectively.[84] Despite the extensive amount of research, considerable debate is still going on about the type of functions related to the motivation network.[85] Dopamine serves to promote complex functions such as reinforcement learning[86] and reward anticipation. Hence, the 'motivation network' is often referred to as the 'reward network.'[87] However, an accumulating amount of studies have now shown that the selective focus on rewards renders an incomplete picture. Several recent studies indicate that different dopaminergic neurons are involved in motivational valence (DA neurons that are responsive only to impeding rewards) and motivational salience (DA neurons which respond to both impeding reward and punishment, as far as they can actively be avoided.[88] These findings complement previous notions of the importance of the striatum in aversive motivation.[85,89] Studies in humans have further highlighted this broader view of striatal (dopaminergic) activity. For example, the striatum was shown to be involved in fear conditioning and avoidance learning.[90] Such developments in the understanding of dopaminergic striatal functioning are clearly relevant to the etiology of social anxiety, specifically in relation to avoidance motivation.[91]

Several studies have shown alterations in dopaminergic activity in SAD, however, both increases and decreases are found.[92,93] fMRI studies revealed that adolescents with a history of BI[94] and adolescents with SAD[95] exhibited increased activation in the ventral striatum, not only for impending monetary rewards, but also for punishments. Another study found that social anxiety patients, in contrast to controls, showed increased striatal responses to partner reciprocation in a trust game, irrespective of (among others) uncooperative behavior of the partner.[96] These findings point at overall increased striatal responsiveness in social anxiety. Interestingly, a study comparing *social and nonsocial* rewards in SAD found that social anxiety was associated with stronger striatal activation for monetary rewards, but weaker activation for social rewards.[97] This could perhaps reflect a dissociation between these two types of incentives. Our recent work showed reduced putamen (part of the striatum) activation in SAD during social reward anticipation, suggesting that the natural preference to obtain a social reward is weakened in SAD.[47] The motivational drives and preferences in social anxiety and particularly comparing the anticipation of social and nonsocial rewards and punishments, are exciting lines of research. Moreover, it may be a fruitful avenue to differentiate social anxiety from other affective disorders such as depression, which has been associated with reduced reward sensitivity.[53]

The Cognitive Control Network

The PFC is involved in several higher-order cognitive functions (working memory, executive control, and task-switching) generally referred to as cognitive control, including control of social emotional action.[98,99] Additionally, the PFC is crucial for modifying emotional responses.[100] Recent meta-analytic work has identified a large number of prefrontal, as well as parietal regions involved in such emotion regulatory processes.[46,101] The PFC has many connections to regions that are part of the emotion and motivation networks and can hence exert a regulatory role over various processes in these areas. For example, the amygdala has major cortical connections, and the connections with the ventromedial PFC (vmPFC) are imperative for amygdala inhibition during fear extinction.[102] Research in humans has shown similarities between cortical regulation of the amygdala during fear extinction and instructed emotion regulation.[103] This observation may suggest that the human capacity to voluntarily regulate emotional responses is mediated by phylogenetically older fear networks. Extending these ideas to psychopathology, a reduction of this prefrontal emotion regulatory capacity may form the basis of various (other) anxiety disorders.[104,105]

Deficiencies in emotion regulatory capacities are certainly another hallmark feature of social (and many other) anxiety disorders.[106] Reappraisal studies in SAD[107,108] showed reduced regulatory-related activity and connectivity,[108] which can be reversed with CBT.[109] Other treatment research is less consistent regarding treatment-related changes in cognitive-control associated prefrontal functioning,[3] which may point at the complexity and heterogeneity of prefrontal functioning across subjects. Reduced spontaneous regulatory processes could be particularly pronounced during public speech anticipation and may relate to an increased stress or anxiety response.[110] In a recent study, we indeed showed that SAD patients displayed diminished cortical-amygdala connectivity during the anticipation of giving a public speech.[79] These studies point toward a decreased, cognitive-control network mediated, emotion regulatory capacity in social anxiety. Interestingly, SAD patients show *increased* prefrontal activity during salient face processing, which has been argued to reflect a compensatory mechanism to regulate overactive subcortical regions, or simply reveal increased attention for such salient stimuli.[3]

The Default Mode Network

The observation that the brain uses most of its energy at rest and shows a pattern of large-scale network organization is perhaps one of the bigger contributions of brain imaging to the fundamental understanding of brain functioning. The DMN traditionally encompassing the posterior cingulate and medial prefrontal regions[111] forms a particular circuit, which is more active during rest than during cognitive performance. Functionally, the DMN is also related to processes like mind-wandering and self-referential processing[111] and the DMN is strongly connected to social-affective areas.[112] The DMN has been implicated in a wide variety of psychiatric disorders[113] including social anxiety,[114] which fits with cognitive models emphasizing disturbed self-evaluative and referential processes.

Several research paradigms have been developed that tap into such self-referential processes in social anxiety. For instance, Blair and colleagues demonstrated that SAD patients showed enhanced processing in medial prefrontal regions, specifically during negative comments directed at them.[45,115] This finding has been extended to subclinical social-anxiety.[116] Another study found increased DMN activity during the anticipation of monetary reward.[117] The DMN has typically been established in resting-state fMRI studies, and several aberrant functional connectivity patterns with or within the DMN have been found[57,118] although not consistently.[56] The role of the vmPFC is again of specific interest since it plays such an integral role in all four networks, including the DMN. One may speculate that in social anxiety the balance in vmPFC functioning is shifted toward default-mode related self-referential processing and away from cognitive control functions, like amygdala regulation.

Neuroendocrine Circuitries

In line with animal models of social submissiveness,[59] recent studies in SAD patients have demonstrated increased cortisol stress responses in SAD compared to healthy and PTSD controls.[44] However, basal testosterone levels were found to be decreased in female patients with SAD.[61] Also, in relation to personality constructs relevant to social anxiety, testosterone was associated with higher extraversion, and lower neuroticism.[119] Interestingly, in patients with SAD, high cortisol responses to the Trier Social Stress Test were associated with increased social avoidance tendencies on a social approach-avoidance (AA) task when people make approaching and avoiding movements (often by pulling or pushing a joystick) in response to angry and happy faces. This finding was replicated using cortisol administration in patients with SAD.[120] Whereas cortisol facilitates threat avoidance, studies in healthy participants have shown that

testosterone administration results in a shift from avoidance to approach on an AA task.[121] This effect has recently been replicated in patients with SAD[122,123] suggesting that single dose testosterone administration can alleviate avoidance tendencies even in patients with SAD. A recent fMRI study using the same social AA task confirmed that testosterone may exert its effects by biasing the amygdala specifically to social threat approach; testosterone increased amygdala responses to angry faces when participants pulled the joystick toward them and decreased it pushing the joystick away.[124] Testosterone furthermore exerts its effects by acting on dopaminergic projections form the amygdala to the striatum.[125] In addition, it typically reduces HPA axis activity previously found to be related to social avoidance in patients with SAD.[120] These findings indicate that the HPA and HPG axis may be disregulated in SAD, and have effects on brain networks relevant for SAD. Several other hormones and peptides are also related to social submissiveness and avoidance in SAD, such as oxytocin,[126] progesterone[127] and vasopressin.[128] A recent oxytocin administration study, e.g., showed a normalization of reduced frontal-amygdala resting state connectivity in SAD.[129]

DISCUSSION

Based on several fMRI findings we reviewed, one may attempt draw a general picture of the large-scale network underpinnings of social anxiety: (1) hyperresponsive emotion network, both in response to social threatening stimuli and at rest; (2) a perhaps surprisingly active motivational system; particularly in obtaining nonsocial rewards and avoiding social punishment, reflective of a distinctive pattern of motivational drives in social anxiety; (3) a diminished cognitive control and emotion regulation network, both during instructed (e.g., reappraisal) and unprompted socially stressful situations, but yet a heightened prefrontal threat attention system; and (4) a strongly active and extensively connected 'default-mode' or self-referential network both at rest and during self-referential critique. The neuroendocrine findings on social anxiety suggest higher cortisol and lower testosterone responses. Integrating these brain imaging and neuroendocrine social anxiety findings, one observes that the testosterone/cortisol ratio is related to PFC-amygdala decoupling, higher amygdala activity, higher striatal activity, and amygdala-striatal projections (and the opposite is the case for impulsive aggression[130]). It is important to point out that this is a tentative model and, as mentioned before, much work is needed to delineate the integration of brain networks and neuroendocrine systems in social anxiety, and other mood and affective disorders.

As we noted, we infer our 'network-model' largely on studies that not necessarily employ network analysis, and we believe that herein rests one of the great opportunities for future research, in addition to the further integration of brain networks and neuroendocrine approaches. A particularly powerful method that is on the rise is the use of whole-brain connectivity analyses, e.g., applying graph theory,[131] potentially in combination with machine-learning (see Ref 57 for such a method in social anxiety). These approaches explicitly address network functioning with the appropriate analytic tools, and for example, establish the clustering or information-processing efficiency of networks.[131] Several studies are already moving in that direction[57,58] but due to the heterogeneity in analyses we regard these results difficult to generalize at this point. When contemplating a brain-network model for social anxiety, It is important to consider the principle of equifinality again: individuals may vary in the brain mechanism underlying similar social anxiety symptoms. For instance, it is possible, and perhaps very likely that in some individuals severe anxiety during public speech is related to exaggerated attention to social threat and a hyperactive amygdala and emotion circuitry. Others might show social anxiety symptoms in relation to an exaggerated striatal response underlying a strong avoidance motivation of social evaluation. It may even be more likely that such processes and underlying brain networks interact in different ways for different individuals. One may speculate that it is possible, by means of clustering analyses,[48] to define subgroups of social anxiety based on brain network interactions and properties. Such work could move beyond homogenous biological explanatory models (e.g., social anxiety is 'caused' by a hyperactive amygdala)—which may not apply to a large amount of socially anxious individuals.

While we have largely focused on neural and neuroendocrine mechanism of social anxiety in the current review, we would like to emphasize that this reflects our research background, not a ranking of importance. With respect to the relation between these approaches (cognitive, developmental, and biological), it may be relevant to address some of issues outlined in Ref 132 with relation to social anxiety research. We regard it imperative for instance not to conflate 'biological' with either 'determinism' or 'objective.' For example, suppose one observes that

someone is socially anxious, grew up in a high-pressure society or family and has a hyperactive amygdala when viewing angry facial expressions. This hyperactive amygdala could be regarded as 'merely' a mediator of societal influences and social anxious thoughts, feelings or behavior, but should not necessarily be considered deterministically: being predisposed to social anxiety because of a hyperactive amygdala. Data on amygdala activity, in and on itself does not favor for instance a genetic, environmental, or gene × environment interacting explanation. Brain and neuroendocrine systems are part of an intricate set of mechanisms underlying social anxiety, and understanding the process of developing social anxiety will ultimately require a multidisciplinary integration of large amounts of data (i.e., explanatory pluralism[132]). Another point we would like to make, regards the relation between biological information, clinical information, and an 'objective/subjective distinction.' Biological research data have the intuitive appeal to be more objective than for instance self-report, because biological measures cannot be 'controlled' in a way that self-report measures can (i.e., 'someone may say he is not socially anxious, but his amygdala activity shows us he is'). While it is indeed easier to control the answer you give on a questionnaire than direct your amygdala activity, imaging research suffers from distinct methodological concerns that affect the reliability of findings (see Box 2). Moreover, it is perhaps underappreciated that many biological systems, including the brain, are intrinsically complex, variable, and highly noisy systems[133] which makes rendering simple, robust and generalizable biomarkers highly unlikely. With respect to diagnosing social anxiety, so far the cheapest and most effective way to identify social anxiety remains to ask whether someone is socially anxious.

BOX 2

DON'T BELIEVE THE HYPE: A QUICK CHECKLIST FOR EVALUATING fMRI RESEARCH FINDINGS

The problem of low statistical power in clinical studies has been pointed out decades ago,[134] and the issue is amplified in clinical neuroscience, and fMRI particularly.[135] A very large number of dependent variables (tens of thousands of voxels), but generally a small number of observations (i.e., number of subjects, 15–25 per group) creates a statistical very unfavorable situation.[136] In order to correct for multiple comparisons, the significance threshold needs to be lowered to a level were only very large effects can be detected. If one applies this correction stringently (e.g., whole-brain family wise error correction), almost no effect will survive, in particular between-group differences. If one takes a more liberal approach this greatly increases the likelihood of false positive; noise may get mistaken for important brain findings. The flexibility in data analyses further complicates some of the problems, which makes the status of fMRI-research findings difficult to asses.[137] When interpreting fMRI-research results, any combination of some of the methods below may serve as a flag for above-mentioned issues:

- *The number of subjects per group*. This is often in the 15–25 range[92] which is only sufficient to detect very large effects.
- *The type of multiple comparison correction method(s)*. In particular, it is worthwhile to see whether an uncorrected threshold (e.g., $p < 0.001$ or 0.005) is used which renders the false positive rate uncertain and variable across studies.[138] In addition, the use of the program AlphaSim to determine a cluster-level threshold may generate lenient thresholds if the spread (smoothness) of the data is underestimated.[139]
- *Region of interest analysis*. The multiple comparison correction problem can be addressed by focussing on one or more so-called regions of interest instead.[140] Unfortunately, it is unclear whether regions of interest are truly established beforehand,[141] which compromises the meaning of the statistical significance level.

It is critical to stress that none of these methods are incorrect per se, but the status of individual research findings may be less robust than is often assumed because of it. Meta-analyses are therefore invaluable, but we have to bear in mind the potential publication biases of the studies that form the input.

CONCLUSION

Social anxiety is a common disorder with deleterious effects on daily functioning, despite the efforts in therapy development, a substantial number of patients do not respond to treatment. Brain imaging and neuroendocrine research can help uncover the biological basis of social anxiety, yet methodological concerns and theoretical limitations need to be considered. Future research should aim to integrate different levels of analysis within the biological domain (large-scale networks and neuroendocrine research), and across developmental, cognitive and therapeutic approaches.

NOTE

[a] Note that several regions of these two networks are often jointly referred to as the 'salience network', especially in resting-state fMRI studies.[52]

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