CNS Spectrums (2015), **20**, 100–111.
doi:10.1017/S109285291400008X

REVIEW ARTICLE

Neurobiological correlates of social anxiety disorder: an update

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Social anxiety disorder (SAD) is a condition characterized by pervasiveness and impairment in social functioning, with a prevalence in the general population between 1.9% and 12.1%. The most consistent findings on its neurobiological underpinnings involve a wide range of neurotransmitters (serotonin, norepinephrine, glutamate, and GABA) and neuropeptides (oxytocin), but no comprehensive hypothesis is yet available. In particular, oxytocin is becoming increasingly established as a "prosocial neuropeptide" and, as such, is a major focus of current research, with a great range of therapeutic applications including SAD treatment. Specifically, the amygdala plays a pivotal role in conditioning and processing of fear, and exaggerated amygdala responses in SAD patients have been observed during various social-emotional stimuli. In addition to the amygdala, other brain areas of interest in SAD-related circuitry are represented by the medial prefrontal cortex, dorsal raphe, striatum, locus coeruleus, prefrontal cortex, insular cortex, and anterior cingulate cortex. The aim of this review is to provide an update on neurobiological correlates of SAD, with a special focus on neurotransmitters and brain areas possibly involved, and suggestions for future research that could lead to more specific therapeutic interventions.

Received 26 October 2013; Accepted 20 December 2013; First published online 26 February 2014

Key words: brain, neurobiology, neurotransmitters, oxytocin, social anxiety disorder.

Clinical Implications

- Social anxiety disorder (SAD) is a common, albeit underestimated, condition that is still poorly investigated in spite of its significant impact on social adjustment.
- The neurobiological bases of SAD are still largely unknown.
- The most consistent findings suggest that SAD may arise from dysfunctions of different brain areas, neurotransmitters and peptides, in particular oxytocin.
- A better understanding of the neurobiology of SAD should lead to more focused therapeutic interventions.

Introduction

Social anxiety disorder (SAD), previously known as social phobia (SP), according to Pierre Janet's definition at the dawn of the 20th century (1903),[1] is a condition poorly investigated to such an extent that the label of "the neglected anxiety disorder"[2] is still appropriate. It was proposed as a distinct nosological category in 1966,[3] while previously it had been classified among specific phobias, and was officially included in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) only in 1980.[4] In the third edition revised,[5] a generalized subtype of SP was also recognized, and finally in the fourth edition,[6] the term "social anxiety disorder" was first introduced. This term highlights the pervasiveness and impairment produced by SAD, while differentiating it more clearly from specific phobias.[7,8]

Social anxiety disorder is described as a persistent fear of 1 or more social situations or performances in which the person is exposed to unfamiliar people or to a possible judgment by others. As a result, feared social situations are avoided or faced with intense anxiety or distress. Usually SAD patients show low levels of self-esteem and are typically shy. Although they desire the company of others, they avoid social interactions and refrain from expressing opinions for the fear of being judged as unreliable or ridiculous.[9] Social anxiety

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disorder is characterized by an early onset, even in childhood, and about 50% of patients recall that they have always been that way.[9] As a result, educational and work functioning are greatly impaired.[10] The incidence of SAD is mildly high: recent studies, based on *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria, reported lifetime prevalence in the general population of between 1.9% and 12.1%.[11] The lowest rates have been observed in South Korea (0.53%) and Taiwan (0.60%), whereas the highest have been reported in Russia (45.6%) and Switzerland (16.0%). The prevalence in Europe ranges between 1.9% and 13.7%, and in the USA is around 5%.[11] When considering a general population sample, SAD is reported to be between 1.1 and 2.6 times more frequent in women than in men. Clinical population samples, on the other hand, have shown a relationship between genders close to 1.0.[11] This is probably due to social and cultural factors, since in some societies shyness and submissive behaviors are more accepted in women than in men, so that the women do not seek treatment as often as men.[11–14]

The generalized subtype of SAD (GSAD) is the most pervasive type of SAD, which interferes with individual functioning in the majority of social situations.[5,9,15] However, the rationale for this distinction is questionable, since some authors have reported that DSM operative criteria for GSAD would be of limited use in clinical settings. It has also been claimed that GSAD should be conceptualized more like a severe form of SAD, rather than a distinct subtype.[16,17] This notion has been accepted in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5)[18]; however, this is a controversial matter, as according to some authors, due to the low symptom threshold, it could include also avoidant personality disorder and healthy subjects.[19]

Comorbidity with other psychiatric disorders is common in SAD, particularly with other anxiety disorders, such as obsessive-compulsive disorder (OCD),[20] generalized anxiety disorder (GAD),[21] panic disorder (PD),[22] and body dysmorphic disorder (BDD).[23] Patients with SAD may also fulfill the criteria for a diagnosis of major depression, dysthymia, or bipolar depression.[24,25] Alcohol abuse and dependence are similarly very common.[26]

The aim of this article is to review some of most recent findings on neurobiological underpinnings of SAD, with a particular emphasis on possible neurotransmitters and brain areas involved, and their therapeutic implications.

Neurotransmitters/Peptides

A wide range of neurotransmitters, in particular serotonin (5-HT), norepinephrine (NE), glutamate, GABA, and neuropetides, such as oxytocin (OT), have been hypothesized to be involved in the neurobiology of SAD and will be reviewed herein.

Serotonin

Serotonin is a neurotransmitter involved in the regulation of mood, sleep, appetite, anxiety, impulsivity, and sexuality, with these effects being mediated by at least 17 different 5-HT receptors. In particular, the serotonin-1A (5-HT1A) receptor seems to be important in the pathophysiology of anxiety disorders.[27–29] Animal studies have shown a modulatory effect of the 5-HT1A receptor activation on glutamatergic, GABAergic, and dopaminergic neurons, especially in the prefrontal cortex and limbic areas. However, studies in humans are very limited, apart from the findings of a PET study in SAD patients that showed lower 5-HT1A binding in the amygdala, anterior cingulate cortex, and insula.[28]

Evidence toward a pivotal role of 5-HT in SAD is represented by the evidence that depletion of tryptophan (TRP), the 5-HT precursor, which temporarily decreases serotonergic neurotransmission, can increase public speaking stress in patients with GSAD treated with selective serotonin reuptake inhibitors (SSRIs).[30] In a study that compared TRP depletion with a placebo condition, the subjects undergoing the TRP depletion showed a significant larger salivary alphaamylase (SAA) response to the public speaking task than the placebo group, with no differences in cortisol responses. These findings were interpreted as high vulnerability of the autonomic nervous system of GSAD patients, as compared with that of the hypothalamic–pituitary–adrenal (HPA) axis.[30]

Many studies in biological psychiatry have focused on the 5-HT transporter (SERT), a protein that represents the limiting factor of the intrasynaptic concentration of 5-HT.[31–34] The promoter gene that encodes the SERT is characterized by the presence of 2 alleles, which are labeled as short or long alleles.[35] The presence of 2 long alleles is associated with increased 5-HT reuptake.[36] Development of 2 SERT knock-out (KO) mice provided a unique mean to study the effect of SERT loss on anxiety-related behaviors under genetic and environmental conditions. Interestingly, SERT KO mice show increased anxiety-like behaviors on different tests validated for their sensitivity to drugs that affect anxiety in humans, such as the elevated plus-maze and light/dark exploration test.[31,32,37] In addition, recent data have shown that a third line of mutants that lack the C-terminus of the SERT exhibited also heightened anxiety-like behaviors. Loss of SERT gene function is involved not only in increased anxiety, but also in the ability to cope with stress. Along this line, a PET study of 18 patients with a DSM-IV diagnosis of SAD, which asked participants to

https://doi.org/10.1017/S109285291400008X Published online by Cambridge University Press

perform a stressful speaking task in front of an audience or alone, led to intriguing findings. Individuals with 1 or 2 copies of the short allele exhibited significantly increased levels of anxiety-related traits and enhanced right amygdala response to anxiety provocation, as compared with subjects who were homozygous for the long allele. In addition, patients with short alleles showed significantly higher Beck Depression Inventory depression and anxiety trait scores than those with long alleles. The amygdala's activity differed as a function of the SERT polymorphism only when passing from baseline to the provoked condition, while supporting the notion that the short allelic groups differed in neural responsiveness in parallel with the increased levels of anxiety related to the situational changes.[38] Further, individuals with the short allele were also emotions related to the situational changes.[38] Further, individuals with the short allele were also found to be more prone to develop major depression, but only if they had experienced multiple traumatic life events, such as childhood abuse or neglect, job loss, or divorce.[34] Other studies highlighted how the relationship between the short allele of the SERT promoter and stress reactivity was mediated by the level of functioning of the neural pathways that regulate emotion. The neural activation was assessed by functional magnetic resonance imaging (fMRI) in a relatively small (N = 14) number of short-allele individuals during perceptual processing of fearful and angry human facial expression.[39,40] During the task, short-allele individuals exhibited nearly 5-fold greater amygdala activity than long allele homozygotes. Genetically mediated changes in SERT function influence both structures and functions of the corticolimbic pathways that regulate the brain's ability for effectively dealing with stress. Some authors suggested that these neural changes contribute to the emergence of individual differences in affect and temperament that are associated with SERT gene variation.[34] Such findings, therefore, would suggest a genetically determined link between serotonergic functions and brain processing of emotions. In such a framework, it is possible to hypothesize a neuroanatomical system where anxiety proneness and brain regions that are fundamental for emotional processing are strictly intertwined in such a way that certain genetic assets could be relevant for the vulnerability of developing SAD after emotionally relevant events.

Norepinephrine

Norepinephrine (NE) is a neurotransmitter involved in the regulation of attention, concentration, memory, arousal, emotions, sleeping, dreaming, and learning.[41–43] The actions of NE are mediated by different adrenergic receptors, the so-called α (α1 and α2) and β. The current data on the possible role of NE in SAD are scant, were obtained in small samples of patients, are quite old, and have never been replicated, and, as such, are of limited value. Autonomic hyperarousal symptoms (blushing, tachycardia, tremors) are common symptoms in SAD, which suggest NE involvement. Higher NE plasma levels in patients with SAD or PD than in healthy control subjects or even in patients with PD after an orthostatic challenge test were reported more than 2 decades ago.[44] These findings are consistent with findings of 2 separate studies that reported that SAD patients share a greater increase in heart rate than control subjects.[45,46] These data are also supported by the heightened cortisol response to fenfluramine, which is also a 5-HT releasing agent, in SAD patients.[47] Limited data are also available on yohimbine, an α2 adrenergic antagonist, the administration of which increases anxiety levels in SAD patients, together with increased plasma concentrations of 3-methoxy-4-ydroxyphenylglycol, the main NE catabolite.[48] It is probable, although NE does not seem to play a pivotal role in the pathophysiology of SAD, that it is involved in the typical hyperarousal symptoms of this disorder.

Dopamine

Dopamine (DA) is a neurotransmitter that modulates motivation, pleasure, cognition, memory, learning, and fine motor control, as well as some neuroendocrine responses.[49] There are at least 5 major dopamine receptor subtypes, D1, D2, D3, D4, and D5, while other 2, the so-called D6 and D7, have yet to be clearly identified. The intrasynaptic concentration of DA is regulated by an active transporter (DAT), which is mainly found in the nigrostriatal, mesolimbic, and mesocortical pathways. Since DA is the key neurotransmitter in the striatum, neuroimaging studies using experimental tasks that activate striatal structures may be informative regarding its functioning. During a striatal-dependent learning task in a fMRI study, significantly lower BOLD response in the left caudate nucleus of GSAD patients was reported, as compared with control subjects.[50] Two independent SPECT studies confirmed this finding, and also showed reduced levels of striatal dopaminergic markers.[51,52]

The distribution and density of DAT were explored in 11 patients with SAD and in a control group by the radioligand ([123 I]β-CIT) with single photon emission computed tomography (SPECT). The results underlined that SAD patients had lower DAT striatal density than control subjects, and they suggested the presence of a lower number of dopaminergic synapses and neurons in the basal ganglia.[51] In another study, D2-receptor binding was measured by SPECT in SAD patients and a group of healthy control subjects during a constant infusion of the [123I]IBZM, a D2 tracer. The results demonstrated that

https://doi.org/10.1017/S109285291400008X Published online by Cambridge University Press

the mean D2-receptor binding potential in the striatum was significantly lower in SAD patients than in the control group.[52] These findings seem to be in agreement with preclinical studies that showed that animals with subordinate social status share behavioral features with human SAD, and may thus represent a useful model for understanding the brain function underlying human SAD.[53] The same findings were obtained in a PET study of female cynomolgus monkeys, which revealed lower striatal D2 binding in subordinate animals.[54] In humans, low D2 receptor binding seems to be strictly correlated with SAD, rather than representing a nonspecific correlate of stress and mental disorders.[52] It is, however, noteworthy that later the same authors did not replicate this finding in a larger group of GSAD patients.[55] Recently, lower levels of dopaminergic markers in frontal and limbic brain regions were noted in SAD patients than in control subjects.[56] In this study, 9 patients with SAD were recruited and examined by high-resolution PET and the high-affinity D2-receptor antagonist radioligand [11C] FLB457, before and after 15 weeks of cognitive behavioral therapy (CBT). The results showed a statistically significant reduction of social anxiety symptoms, as assessed by the anxiety subscale of Liebowitz Social Anxiety Scale (LSASanx), and negative correlations between the scale changes and those of the D2-receptor binding potential in dorsolateral prefrontal cortex, hippocampus. and medial prefrontal cortex. This last area seems to be involved also in monitoring the social evaluation and in fear extinction.[57–59] To summarize, these results would indicate that SAD may be associated with decreased central nervous system (CNS) dopaminergic transmission, although the available data are limited and need to be replicated in larger samples of patients.[55]

Oxytocin

Oxytocin (OT) is a neuropeptide that consists of 9 amino acids produced in the paraventricular and supraoptic nuclei of the hypothalamus. After synthesis, OT is carried through axonal transport to the neurohypophysis (posterior pituitary), where it is stored before being released into the bloodstream to exert its peripheral effect. This peptide is also released from the hypothalamus into the CNS in response to specific stimuli.[60] In humans, OT generally facilitates social interactions and feelings of attachment, and is becoming increasingly established as a "prosocial neuropeptide," with therapeutic potential in treatment of social, cognitive, and mood disorders.[61–67] A growing body of evidence implicates OT in mediation of complex social behaviors. In fact, in highly social species, OT has been shown to increase social approach behavior and pair bonding by reducing behavioral and neuroendocrine responses to social stress, and it is also been suggested to mediate the rewarding aspects of attachment.[68,69]

In mammals, the development of parent–child attachment is critical for the survival of the infant, and the establishment of a solid relationship will continue to provide regulatory emotional functions throughout adulthood. Some studies have previously demonstrated that as OT levels rise, animals increase their positive social interactions: they form social bonds, display selective infant–parent attachments, and form memories of these social interactions. The mother–infant interaction and other aspects of the early postnatal period may have profound and long-lasting behavioral and neurobiological effects. Early life experiences may alter response of adult neurogenesis to stress, and persistent changes in the corticotropin releasing hormone (CRF) systems due to early life stress have been demonstrated.[70,71] OT may be a candidate substrate for the transduction of early experiences into both short-term and long-term behavioral changes and other consequences, ranging from brain growth to later stress reactivity to ovarian disorders.[72] In humans there is evidence that the OT system is affected by early social experience. The failure to receive species-typical care disrupts the normal development of the OT and arginine vasopressin (AVP) systems in young children, while perturbations in these systems seem to interfere with the calming and comforting effects that typically emerge between young children and familiar adults who provide care and protection.[73] Indeed, OT and AVP levels are increased by socially pleasant sensory experiences, such as comforting touches and smells. In a recent study, OT cerebrospinal fluid (CSF) concentrations were measured in 22 healthy women. Exposure to maltreatment, in particular emotional abuse, was associated with decreased CSF OT concentrations. The amount, severity, and duration of the abuse, as well as current anxiety ratings, were inversely related to CSF OT concentrations, while suggesting that alterations in the OT system may be involved in the adverse outcomes of childhood trauma.[74] Furthermore, the neuroendocrine responses to intranasal OT administration in men with early parental separation (EPS) resulted in attenuated cortisol decreases, as compared to non-EPS control subjects, which indicated the presence of altered central sensitivity to the effects of OT after EPS.[75]

To date, one study only investigated the role of OT on behavior and physiology in human couple interaction. In this double-blind placebo-controlled study, 47 heterosexual couples received OT or placebo intranasally before a standard instructed couple conflict discussion. During the couple conflict, OT administration was significantly associated with increased positive communication in relation to a negative behavior. After the conflict, subjects treated with OT showed a reduction of salivary cortisol levels compared to those treated with

https://doi.org/10.1017/S109285291400008X Published online by Cambridge University Press

placebo. These results would support the hypothesis that, even in humans, OT would play a critical role in couple interaction and in the development of adult–adult pair bonds.[76]

A recent double-blind study, using fMRI imaging to visualize amygdala activation by fear-inducing visual stimuli, showed that human amygdala function is strongly modulated by OT. As compared with placebo, OT potently reduced activation of the amygdala and reduced coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear.[77] It is of interest to note that OT administration did not affect self-report scales of psychological state. This agrees with the observations of Kosfeld et al,[78] who did not find an effect of OT on measured calmness and mood and showed that at the level of behavior, actual social interaction was necessary to bring out the OT effect. Namely, the neural effect of the neuropeptide on behavior is evident in the social context, but not when subjects rate themselves in isolation. Moreover, the reduction in amygdala activation was more significant for socially relevant stimuli (faces) than for the socially less relevant scenes; differential impairment of amygdala signaling related to the social relevance of the stimuli is in agreement with emerging primate lesion[79] and human data that indicate that social and non-social fear may depend on dissociable neural systems.[80]

Recently, we showed a significant and positive correlation between OT plasma levels and the anxiety scale of the experience in close relationships (ECR), a self-report questionnaire that measures adult romantic attachment, which showed that the higher the OT levels, the higher the score on the anxiety scale of the ECR.[81] In line with the majority of available findings,[82–85] we would suggest that OT might help to counteract anxiety. The role of OT would seem generally to be that of keeping anxiety levels under control to a point where they are no longer harmful, but may nevertheless lead to such strategies and behaviors as are best suited to ensuring a partner's continued proximity both during the first and subsequent stages of the romance. OT might thus be considered an essential element in securing the rewarding effects of a romantic relationship, as a result of its increasing a prospective sexual partner's willingness to accept the risk deriving from social contacts[78] through the modulation of anxiety mechanisms.

Just a few data suggest a direct role of OT in specific anxiety disorders including SAD. OT is positively related with sociality, calm, and tolerance and seems to decrease stress response and anxiety levels. Pregnancy, a period characterized by increased OT levels, is protective for some anxiety disorders, including panic disorder. In fact, OT is released during the stress response and seems to be an important modulator of anxiety and fear response, mainly with anxyolitic effect.[86–88] From a neurobiological point of view, dysfunctions of the amygdala, which is implicated in the biological response to danger signals in social interaction, have been detected in depression and anxiety disorders. As already mentioned, its function is strongly modulated by OT, as its intranasal administration may reduce amygdala activation and its output to the brain regions involved in the autonomic and behavioral response to fear.[77] Moreover, a down-regulation of OT receptors recently has been related to the pathophysiology of SAD, which might explain the cognitive misappraisals typical of the patients affected by this condition.[77] However, no significant differences in OT level were found in patients with SAD as compared with healthy control subjects; in the SAD patients, however, higher OT levels were associated with higher social anxiety symptom severity and dissatisfaction with social relationships.[89]

Taken together, these findings support the notion that OT is a prosocial hormone and, as such, it may influence the development of SAD and other disorders. However, research in this field in humans is just at its dawn, and there is a great need for data in clinical samples.

Peripheral Benzodiazepine Receptors and Neurosteroids

Some data suggest that peripheral benzodiazepine receptors (PBRs), now called translocator proteins,[90] which are located on mitochondrial outer membranes, may play a role in the pathophysiology of anxiety disorders and also SAD. Indeed, many functions are associated directly or indirectly with PBRs, including the regulation of cholesterol transport and the synthesis of steroid hormones, porphyrin transport, heme synthesis, apoptosis, cell proliferation, anion transport, regulation of mitochondrial functions, and immunomodulation. Several studies have demonstrated an up-regulation of PBRs during acute stress and a down-regulation with chronic stress.[91,92] Abnormally low numbers of platelet PBRs have been found in patients with PD,[93] posttraumatic stress disorder (PTSD),[94] and GAD,[95–97] while in contrast, OCD patients were found to show normal numbers of PBRs.[93] Johnson et al[98] evaluated the density (Bmax) and dissociation constant (Kd) of platelet PBRs for 53 medication-free GSAD patients compared with an equal number of control subjects. The GSAD group had lower PBR Bmax than the control group. This abnormality, which has been demonstrated in several anxiety disorders, could be linked pathophysiologically to a subset of chronic anxiety states. It has been underlined that plasma concentrations of pregnenolone sulfate, a neurosteroid that has been associated with increased dopamine-release in brain reward pathways, were lower in male patients with GSAD than in healthy control subjects.[99]

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Interestingly, some neurosteroids have been proposed as potential antianxiety agents,[100,101] as well as risk factors, related to gender, for bipolar disorder in adolescents.[102] These are all intriguing data, which, however, used to be supported by additional findings.

Brain Circuits in SAD

The amygdala and medial prefrontal cortex have been often considered as target regions for SAD research. The amygdala indeed plays a key role in arousal and emotional response, in particular in fear response. The amygdala is also connected to the locus coeruleus, which released NE in response to stress, and to the paraventricular nucleus of the hypothalamus, which results in activation of the HPA axis. There exist reciprocal connections between the amygdala and the sensory thalamus and prefrontal, insular, and somatosensory cortexes. The amygdala receives crude sensory information about anxiety-inducing stimuli directly from the thalamus, and, additionally, it receives more processed information from cortical association areas and contextual input from the hippocampus.[103,104]

The amygdala projects further to the periaqueductal gray and striatum, which subserve executive aspects of anxiety including autonomic, endocrine, and skeletal-motor responses. In this framework, there is a rapid, less finely tuned pathway that responds to immediate threats, which is activated via direct input from the sensory thalamus. Moreover, there is a slower, more finely tuned mode that benefits from thalamo–cortico–amygdala inputs allowing valuable cortical assessments of threat-related information.[103]

Amygdala

For some decades, several findings have supported the pivotal role of the amygdala in conditioning and processing of fear.[104] Sensory fibers from visual, auditory, olfactory, nociceptive, and visceral pathways through the anterior thalamus arrive to the lateral nucleus of the amygdala (LNA), which is connected to the central nucleus of the amygdala (CNA). The CNA serves as a central processing hub for both information and execution of autonomic and behavioral fear responses. CNA efferents extend to the parabrachial nucleus and to the lateral hypothalamus.[103] Exaggerated amygdala responses in SAD have been observed during public speaking or the anticipation of public speaking[105,106] and negative comments,[56] and also in response to neutral, angry, contemptuous, happy, and schematic angry facial expressions.[107] The anterior cingulate cortex and neighboring prefrontal areas control the attention to threat-related stimuli and inhibit amygdala activity by top-down regulation. While the amygdala may be a trigger region predominantly responsible for eliciting certain emotions, the prefrontal cortex appears to be a modulatory region that is important for emotional control. Neuroimaging data may imply that the prefrontal cortex, including the ventromedial and dorsolateral regions, exerts inhibitory top-down control of amygdala activation, and a similar regulatory role has been proposed for the anterior cingulate cortex.[108] Patients with GSAD and a control group were exposed to hostile vs happy facial emotion[109] or to neutral faces during fMRI.[110] Interestingly, the SAD patients showed an exaggerated right amygdala activation compared with control subjects. These findings emphasized modifications particularly in the amygdala/medial temporal lobe region, insula, and striatum of patients with SAD, and they stressed the alterations of serotonergic and dopaminergic neurotransmission. Therefore, activation studies in SAD patients, with a few exceptions, have demonstrated amygdala hyper-responsivity to different social–emotional stimuli, including anticipatory and situationally elicited speech anxiety.[109,110] However, it is unclear whether the amygdala is generally hyper-responsive or reacts exclusively to disorder-specific stimuli. An increased activity of the amygdala is associated with a decreased activation of the mesiofrontal cortex in patients with anxiety disorders.[101]

Dorsal raphe

Another area of interest in SAD-related circuitry is the dorsal raphe nuclei, where 5-HT is produced. While projections from the prefrontal cortex and locus coeruleus inhibit the activity of the raphe nucleus,[111,112] the raphe nucleus projections seem to inhibit the locus coeruleus and, interestingly, the hypothalamus and the amygdala.[113,114]

Dorsal raphe nuclei exhibit CRF receptor-binding sites.[115] CRF administration into dorsal raphe nuclei reduces the release of 5-HT levels in the lateral septum, which can be attenuated by pretreatment with a CRF receptor antagonist.[116] The dorsal raphe nucleus neurons innervate basal ganglia, while median neurons innervate the limbic structures.[117] It should be pointed out that projections from the prefrontal cortex and locus coeruleus inhibit the activity of the raphe nucleus.[111,112] At the same time, the raphe nucleus projections inhibit locus coeruleus and, interestingly, the hypothalamus and the amygdala, the latter in an indirect way.[101,102] Two main pathways project from the dorsal raphe nuclei to the periaqueductal gray and also to the amygdala and frontal cortex, which mediate avoidance behavior to potential threats. Interestingly, D-fenfluramine, a 5-HT releasing agent, seemed to decrease the rise of anxiety levels experienced in nonclinical subjects who were speaking in front of a video camera.[118]

https://doi.org/10.1017/S109285291400008X Published online by Cambridge University Press

Locus coeruleus

The activity of the locus coeruleus is implicated in the increased attention in response to threat, while the paragigantocellularis and prepositus hypoglossi nuclei are the primary modulators of NE release by the locus coeruleus. In particular, the prepositus hypoglossi nucleius shows CRF receptors that improve the release of NE in response to stress.[119,120]

Prefrontal cortex

As reported above, alterations of the serotonergic system have been widely described in mesiofrontal areas during an exaggerated amygdala responsiveness in SAD patients.[104,105,106] Several functional studies have reported increased or altered amygdala activation to facial stimuli in SAD patients, and have also confirmed a specific association of augmented responsiveness to anxious or angry faces in these patients.[108,109]

Recently, hypoactive dorsolateral prefrontal cortex (dlPFC) response was described in pediatric patients with OCD and those with other anxiety disorders, including SAD. These findings suggest that insufficient error-related engagement of the dlPFC are associated with anxiety across traditional diagnostic boundaries and appears during the early stages of illness.[121] In a clinical trial, regional electroencephalography (EEG) activity was recorded in 23 SAD patients before and after CBT. The results showed that patients shifted significantly from greater relative right to greater relative left resting frontal brain activity from pre- to posttreatment. Greater left frontal EEG activity at pretreatment predicted greater reduction in social anxiety from pre- to posttreatment and lower posttreatment social anxiety after accounting for pretreatment symptoms. These relationships were specific to the frontal alpha EEG asymmetry. These findings suggest that resting frontal EEG asymmetry may be a predictor of symptom change and end-state functioning in SAD patients who undergo effective psychological treatment.[122]

To summarize, these are scattered, albeit interesting, data that require further support in larger and different clinical samples.

Anterior cingulate cortex

Facial expressions of fear and disgust led to an exaggerated activation response of rostral cingulate cortex (rACC) in SAD patients.[56,123] One study reported increased orbitofrontal cortex activation to angry prosody.[124] In contrast, other studies described decreased activation[125] and glucose metabolic rates in the ventromedial prefrontal cortex, which both increased following treatment with tiagabine.[126] Glutamate/creatine and N-Acetylaspartate (NAA)/creatine ratios appeared to be elevated in the rACC and related to symptom severity.[127] Studies of dorsal anterior cingulate cortex (dACC) function in SAD have been somewhat controversial. Greater dACC activation has been reported in response to negative comments[56] and harsh or disgusted facial expressions,[123] while treatment with nefazodone decreased activation in the dACC.[128] In contrast, other studies have reported decreased dACC activation in anticipation of public speaking,[105,106] as well as decreased glucose metabolism at rest.[13] One possible explanation of these controversies is that medial prefrontal cortex/dACC responses to faces in SP are temporally delayed.[129] Finally, one study reported reduced 5-HT1A receptor binding in the anterior cingulate cortex in patients with SAD, although it was not specified whether this finding occurred in the dACC or rACC.[28]

Insular cortex

Insular cortex activation appears to be elevated in SAD patients during the anticipation of public speaking[105,106] and in response to emotional facial expressions, including schematic facial expressions.[107]

Striatum

One study showed reduced caudate activation during an implicit sequence-learning task in GSAD[50] patients, and another suggested that D2 receptor binding and DAT densities are reduced in the striatum of SAD patients.[51]

Conclusion

In spite of its nosological dignity and great impact on individual's adjustment, SAD is a condition that is still poorly diagnosed and investigated. For this reason, available data on its possible neurobiology are scant, are often derived from findings obtained in other anxiety disorders, and are mainly hypothetical. In any case, while keeping in mind all these limitations, there exist preliminary data of involvement of some neurotransmitters and brain areas, so that a general and preliminary framework can be drawn (Figures 1 and 2). Serotonin seems to play a major role in SAD, and not surprisingly represents the major target of currently approved medications, that is to say, SSRIs.[130,131]

However, undoubtedly, NE and DA are also important in SAD and may well become some of the targets of future specific drugs, as they are neurosteroids. This is particularly relevant for OT, which seems to be a core element in the neural processes that promote human sociality. SAD may be the result of excessive negative attribution given to social stimuli, and/or deficit of prosocial mechanisms. Interestingly, there are some intriguing data showing that intranasal OT has anxiolytic

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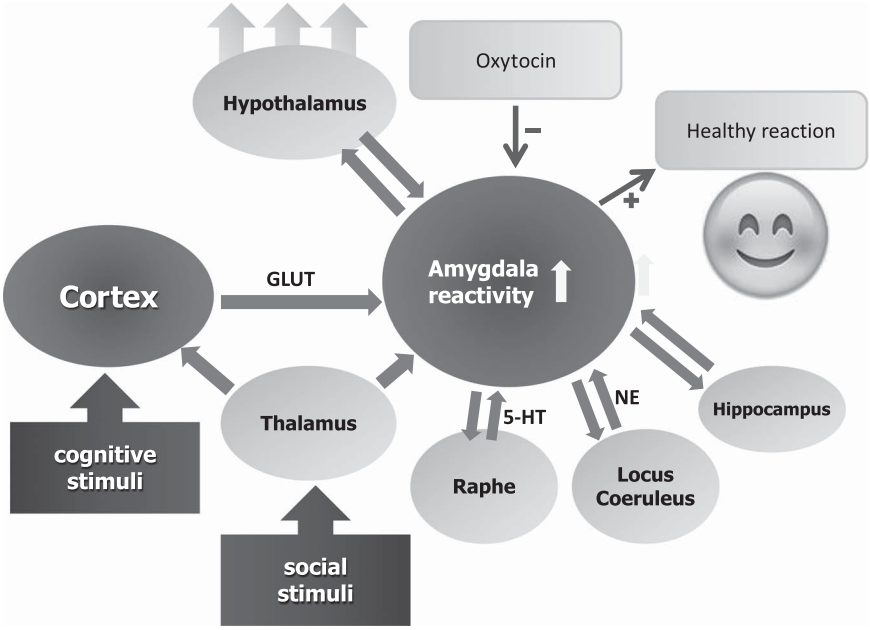

FIGURE 1. Normal processing of social stimuli (brain circuits and neurotransmitters possibly involved). Glut = glutamate, 5-HT = serotonin, NE = norepinephrine.

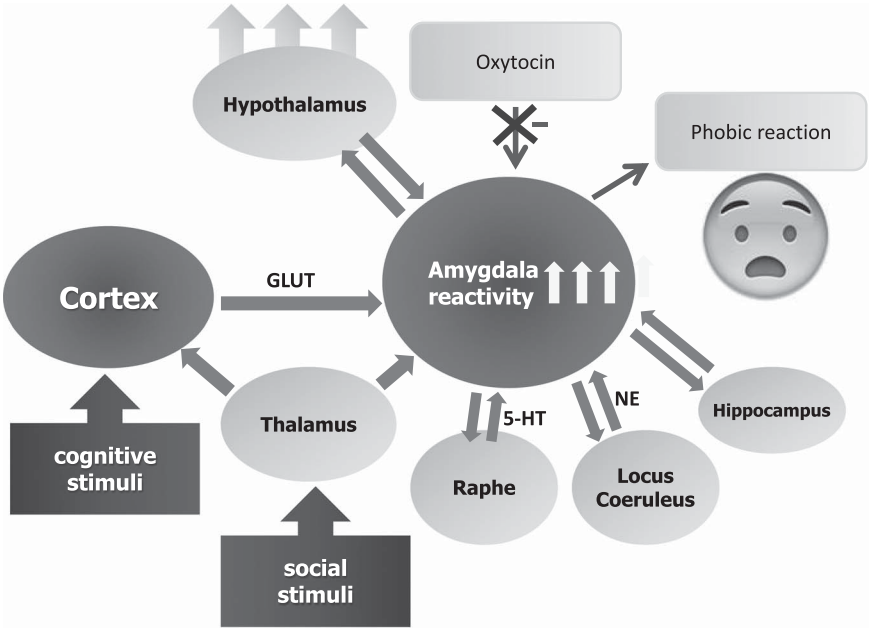

FIGURE 2. Abnormal processing of social stimuli (brain circuits and neurotransmitters possibly involved). Glut = glutamate, 5-HT = serotonin, NE = norepinephrine.

and prosocial properties, so the modulation of this peptide and the development of agonist/antagonists acting at the level of its receptors seem to constitute a real step toward the discovery of "natural" drugs.

Disclosures

The authors do not have any disclosures, and the authors do not have any affiliation with or financial interest in any organization that might pose a conflict of interest.

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