

Neurobiological Aspects of Social Anxiety Disorder

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Abstract: Social anxiety disorder (SAD) has in recent years been widely recognized as a major public health concern. Neurobiologically oriented studies could provide important clues to the causes and cures of this disorder. The present article addresses important findings from neuroimaging and other biological examinations of SAD. Aberrant patterns of brain activity in the amygdala/medial temporal lobe region, insula and striatum are suggested. There is also evidence of abnormalities in the serotonergic and dopaminergic transmission systems. Brain imaging studies have reported reduced serotonin-_{1A} and dopamine D₂ receptor binding in certain regions. It is also suggested that serotonin-related gene polymorphisms are important for amygdala responsivity and treatment outcome in SAD.

Introduction

Social anxiety disorder (SAD), or social phobia, is a common and highly disabling condition that may follow a chronic course if left untreated (1). Understanding its underlying neurobiological mechanisms could ultimately have important implications for treatment and prevention.

Over the past two decades, numerous neurobiological methods have been used in studies of SAD including structural, functional and receptor brain imaging, pharmacological trials, candidate gene investigations and studies of psychophysiological, endocrine, biochemical and behavioral responses to stressful challenges. While an exhaustive discussion of all these methods is beyond the scope of the present article, important neurobiological findings will be reviewed with an emphasis on recent neuroimaging data.

Brain Circuits in Fear and Anxiety

Research in affective neuroscience points to several brain regions that may be malfunctioning in anxiety disorders. Studies on fear conditioning in animals and humans support a crucial role for the amygdala in the acquisition and expression of fear memories (2). There is also a vast literature demonstrating that the amygdala is important for attention and vigilance in aversive or ambiguous

situations (3) thus enabling rapid detection of environmental threat stimuli. Because SAD is characterized by exaggerated fear reactions (4), increased vigilance to potential danger signals (5) and possibly also increased fear conditionability (6), it can be assumed that the amygdala plays a prominent role in this disorder.

Anxiety, however, is a complex reaction engaging extensive neural networks. Briefly, the amygdala receives fast and crude sensory information about anxiety-inducing stimuli directly from the thalamus (2, 7), more thoroughly processed information from cortical association areas and contextual input from the hippocampus. The amygdala projects to structures such as the locus coeruleus, periaqueductal gray, hypothalamus and striatum, that subserve executive aspects of anxiety including autonomic, endocrine and skeletal-motor responses (7).

While the amygdala may be a trigger region predominantly responsible for eliciting certain emotions, the prefrontal cortex appears to be a modulatory region important for emotional control. Neuroimaging data imply that the prefrontal cortex, including the ventromedial and dorsolateral regions, exerts inhibitory top-down control of amygdala activation (8, 9) and a similar regulatory role has been proposed for the anterior cingulate cortex (10). The insula cortex is another important and often overlooked region in affective

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processing (11). Activation of the insula has been demonstrated in response to various negative emotional stimuli (12). It may be specifically involved in monitoring deviations in internal bodily states and interoceptive awareness (13). The insula may be a crucial node in the “internal” alarm system responding to excessive physiological arousal or interoceptive threat stimuli, while the amygdala is the corresponding key region for the “external” alarm system responding to environmental threat cues (14).

It could be hypothesized that affect regulation is compromised in individuals with SAD, either due to hyperactivity in emotion triggering areas like the amygdala and insula, or hypoactivity in modulatory regions like the anterior cingulate and prefrontal cortices.

Functional Neuroimaging Studies

In neuroimaging activation studies, the dynamic regulation of regional cerebral blood flow (rCBF) can be assessed with positron emission tomography (PET) and single photon emission computed tomography (SPECT), or functional magnetic resonance imaging (fMRI) can be used to measure blood oxygenation level dependent (BOLD) signal changes.

Affective Face Processing

Numerous activation studies of healthy volunteers have demonstrated amygdala hyperresponsivity to pictures of fearful, angry and even happy facial expressions contrasted with neutral faces (12). As individuals with SAD are agonized by being criticized or rejected, they are sensitive to facial expressions that may be interpreted as dislike or hostility. It could thus be hypothesized that SAD patients would show exaggerated amygdala responses to angry or threatening faces in comparison to healthy control subjects. Imaging studies suggest that this is indeed the case.

Stein and colleagues (15) measured fMRI BOLD signal changes while patients with generalized SAD and controls were exposed to harsh (angry, fearful and contemptuous) as well as accepting (happy) facial emotional expressions. Harsh faces induced

relatively increased neural activity in SAD patients compared to controls, in the left amygdala, rhinal and parahippocampal regions and also in frontal cortical areas bilaterally. Subsequent fMRI studies have confirmed elevated amygdala responses to harsh compared with happy faces (16), and to angry schematic or photographic faces compared with neutral expressions (17, 18) selectively in SAD patients. Intriguingly, two studies (16, 18) reported that the magnitude of the amygdala response correlated positively with symptom severity as measured by the Liebowitz Social Anxiety Scale (19).

These data suggest that the amygdala of SAD patients responds more to disorder-salient than to non-salient stimuli. However, one study did not observe differential amygdala activation to facial expressions of disgust in SAD patients compared with controls, even though disgust faces may be disorder-salient as they can be interpreted as social rejection (20). Another fMRI-trial reported elevated amygdala activation not only to angry faces but also to happy facial expressions in SAD patients (21), whereas two other studies failed to replicate this (16, 22). An early fMRI-study noted enhanced bilateral amygdala activation in response to neutral faces in SAD patients compared to healthy controls (23), a finding that was conceptually replicated, at least in the right amygdala, in a subsequent study (24). Also Cooney and colleagues (22) noted exaggerated right amygdala activation to neutral faces (relative to baseline) in SAD patients compared with controls. These data indicate that amygdala activity is exaggerated in SAD patients even when presumably neutral social cues are evaluated. Thus, it cannot be established that the amygdala is hyper-responsive to disorder-salient stimuli, even though this hypothesis has some support.

Fear conditioning

Fear conditioning is considered to be an amygdala-dependent type of learning (3) and a possible etiological mechanism through which SAD could evolve. Using fMRI, Schneider and co-workers (25) noted that patients with SAD had an increased activation, and healthy comparison subjects decreased activation, in the amygdala and the hippocampus when presented with neutral faces that had been previously paired with an aversive odor. It could

be hypothesized that amygdala hyperresponsivity is associated with enhanced fear conditionability in SAD. However, Veit and colleagues (24) failed to demonstrate increased amygdala activation during the acquisition of conditioned aversive reactions in SAD patients, and another experimental study could not demonstrate evidence for enhanced fear conditionability in subjects with generalized SAD compared with controls (26).

These negative findings might be explained by the choice of unconditioned stimulus as aversive odors or electric shocks may have little relevance for fear learning in naturalistic settings. A recent study found evidence for increased fear conditionability in SAD when using a novel conditioning paradigm with socially relevant unconditioned stimuli consisting of verbal insults with critical faces (6). Thus, while the evidence is mixed, it remains possible that SAD is characterized by enhanced capability for fear conditioning which in turn may be associated with an easily triggered subcortical network.

Anxiety Provocation

Symptom provocation is a powerful method to elicit strong emotional reactions in neuroimaging trials. For example, Tillfors and co-workers (4) used PET to measure rCBF during a stressful public speaking task, compared to a private speaking control condition, in patients with SAD and non-fearful comparison subjects. Heart rate and subjective anxiety ratings confirmed a more profound stress reaction in patients as compared to the healthy controls and this was associated with an exaggerated rCBF-response in the right amygdaloid complex. There was also a significant positive correlation between ratings of fear and increased activity in the right but not in the left amygdala (4).

In a follow-up report, it was noted that speech anticipatory anxiety was accompanied by exaggerated rCBF in the left amygdaloid-hippocampal region and the right dorsolateral prefrontal cortex (27). A similar cortical change pattern was noted in an EEG-study of anticipatory social anxiety (28) and a subsequent fMRI-study confirmed activation of the medial temporal lobe region including

the amygdala while patients with SAD anticipated making a public speech (29). However, all imaging studies of SAD have not verified exaggerated anxiety-related activity in the amygdala (30, 31). In fact, Kilts and colleagues (30) reported lower amygdala activity during anxiogenic tasks compared with an emotionally neutral condition.

Treatment response

In the SAD sample studied by Tillfors et al. (4), PET-assessments of rCBF during public speaking were repeated after nine weeks of treatment with cognitive-behavioral therapy (CBT) or the selective serotonin reuptake inhibitor (SSRI) citalopram. Neurofunctional changes were compared to a waiting-list control group. Both CBT and citalopram were successful in alleviating social anxiety and both types of treatment were accompanied by a decreased stress-related rCBF-response in the medial temporal lobe including the amygdala, hippocampus, and adjacent temporal cortical areas (32). Interestingly, patients showing the greatest initial decrease of activity in the amygdala and other subcortical regions were the most improved at follow-up a year later (32). Neural activity in the anterior cingulate and prefrontal cortices decreased with treatment which could mean that bottom-up processes dominate in social anxiety regulation. Moreover, many of the cortical regions in which activation differences between patients and controls were noted before treatment (4) were not affected by the treatments (32). Hence, treatment of SAD may involve normalization in some regions, compensatory metabolic changes in others, and some brain anomalies may persist after therapy even though symptoms improve.

A subsequent pharmacological PET-trial of SAD confirmed that short-term treatment with either citalopram or a neurokinin-1 receptor antagonist, but not placebo, attenuated the rCBF-response to public speaking in medial temporal regions including the amygdala (33). Reduced amygdala responsiveness following successful treatment has been noted also in other anxiety disorders (34) and depression (35). Also in healthy volunteers, drugs with anxiety-reducing properties like SSRIs (36) and benzodiazepines (37) attenuate amygdala responsiveness, suggesting that the amygdala is

a general target for several types of anti-anxiety treatment.

However, Kilts and colleagues (30) did not find an effect of nefazodone on amygdala activity although the drug was effective in reducing social anxiety and led to other rCBF-alterations including decreases in the medial prefrontal, dorsal anterior cingulate and insular cortices as well as increases in the hippocampus and occipital regions.

Insula cortex

Straube and colleagues (17) found strong support for involvement of the insula in the processing of socially threatening stimuli in SAD. Compatible findings have been reported also by others (e.g., 20, 29, 38), and a recent meta-analysis (39) concluded that hyperactivity in the insula region appears to be a common feature of many anxiety disorders including SAD. Decreased activity in the insula after treatment has also been reported (30). Thus, beside the amygdala, it seems likely that also the insula is involved in generating or mediating emotional reactions and that this region should be considered in pathophysiological models of SAD.

Frontocortical regions

As stated previously, increased amygdala excitability in SAD might imply a dysfunctional top-down inhibitory control from the prefrontal or anterior cingulate cortices. Consistent with this, Lorberbaum and co-workers (29) reported that anticipatory anxiety was associated with greater amygdala activity and lesser activity in dorsal anterior cingulate and prefrontal cortices in SAD patients relative to controls. Also, in the symptom provocation study by Tillfors et al. (4) differences in rCBF between patients and controls were noted in widespread cortical areas. Patients did not show the same pattern of increased rCBF as controls in the orbitofrontal, insular, perirhinal, retrosplenial, parietal and secondary visual cortices as well as in the temporal pole, which was interpreted as a fear-related shift from cortical to subcortical processing (4). In other words, while the amygdala region was activated by the stressful public speaking task, the failure to activate cortical areas could indicate that top-down inhibitory influences corresponding to cognitive evaluative or self-regulatory processes are compromised in SAD (4).

There are, however, some problems with the prefrontal inhibitory control hypothesis. Many cognitive representations of social anxiety, such as negative self-appraisal and post-event rumination, may be associated with excessive activity in frontocortical regions. These processes may result in top-down excitation rather than inhibition of the amygdala. Kilts and colleagues (30) noted that anxiety-related activity in the left ventrolateral prefrontal cortex was inversely correlated with the right amygdala response although higher anxiety was associated with higher prefrontal and lower amygdala activity. Several studies also report that neural activity in the amygdala and putative frontal control regions change in the same direction in response to emotional challenges (15, 24, 27, 38) and treatments (32) which is difficult to reconcile with a top-down pathophysiological model.

Neurotransmitter Abnormalities

A range of neurotransmitters may be important in SAD including the monoamines, glutamate, GABA, and several neuropeptides, but to date, the serotonergic and dopaminergic transmission systems have received most of the attention.

The serotonergic system

Serotonin has been implicated in animal models of fear and anxiety (40). The therapeutic efficacy of SSRIs (41) strongly suggests that serotonin has a crucial role in SAD. As outlined previously, patients with SAD exhibit hyperresponsiveness in the amygdala, which is densely innervated by serotonergic fibers (42), and this hyperresponsivity is attenuated by SSRI-treatment (32, 33). Allelic variation in serotonin-related genes modulate amygdala responsivity both in healthy volunteers (43) and in patients with SAD (44). Serotonergic involvement is also supported by neuroendocrine challenges studies. For example, patients with SAD show exaggerated cortisol response to the serotonin-releasing compound fenfluramine, indicating supersensitivity of the post-synaptic serotonin receptors (45).

Using PET and the [¹¹C]WAY 100635 radiotracer, Lanzenberger and co-workers (46) demonstrated a significantly lower serotonin-_{1A} receptor

binding potential in SAD patients relative to controls in the amygdala, anterior cingulate cortex, insula, and dorsal raphe nuclei. These results are in turn consistent with reports on elevated anxiety in serotonin- $1A$ receptor knock-out mice and with previous PET studies of panic disorder and state anxiety in healthy volunteers (46). Another PET-study evaluated the occupancy of the serotonin reuptake transporter after treatment with paroxetine in a small sample of SAD patients (47). After 3–6 months of continuous treatment, occupancy of the serotonin reuptake transporter was high (> 80%) in all patients and regions measured. There have also been attempts to image presynaptic serotonin synthesis in SAD by means of PET (48). Future studies of this kind could help to unravel the molecular mechanisms involved in the development and treatment of social anxiety.

The dopaminergic system

Dopamine plays a central role in motivation and reward-seeking behaviors and several lines of evidence point to a dysfunction of this transmitter system in SAD. Patients with Parkinson's Disease, which is associated with dopamine hypofunction, appear to have enhanced risk for developing SAD (49). One study noted that plasma concentrations of pregnenolone sulphate, a neurosteroid that has been associated with increased dopamine-release in brain reward pathways, were lower in male subjects with generalized SAD compared to healthy volunteers (50). Pharmacological trials have reported that monoamine oxidase (MAO) inhibitors, a potentially dopamine-enhancing class of drugs, are effective in treating SAD (41). Abnormal central dopaminergic neurotransmission has also been reported in animal trials relevant to SAD, such as studies of social subordination in primates (51).

Because dopamine is the key neurotransmitter in the striatum, neuroimaging studies using experimental tasks that activate striatal structures may be informative regarding dopaminergic functioning. In line with this, a recent fMRI-trial reported a significantly lower fMRI BOLD response in the left caudate nucleus of SAD patients as compared to controls during a striatal-dependent learning task (52). Two independent SPECT studies also point directly to an altered dopamine system activity in

SAD. Tiihonen and co-workers (53) reported that the striatal dopamine reuptake site density was markedly lower in patients with SAD than in age and gender matched comparison subjects, presumably reflecting a smaller number of dopaminergic synapses and neurons in the basal ganglia. Another group of investigators observed that striatal dopamine D_2 receptor binding was significantly lower in subjects with SAD than in comparison subjects (54).

Genetic Factors

Genetically-oriented studies of SAD and related constructs such as behavioral inhibition, neuroticism, introversion and harm-avoidance suggest that genetic factors play at least a moderate role in the etiology of excessive social anxiety (55). Recently, polymorphisms in monoaminergic genes have attracted considerable interest in studies combining neuroimaging and molecular genetic techniques. The short (s) allele of the promoter polymorphism of the human serotonin transporter gene (the 5-HTT-linked polymorphic region; 5-HTTLPR) has been associated with anxiety-related personality traits, increased fear conditionability, and life-stress-induced affective disorder (56). Several imaging studies in healthy volunteers have shown that carriers of the s allele exhibit increased amygdala reactivity to emotional tasks in comparison to subjects who are homozygous for the long (l) allele (43). Consistently, SAD patients carrying the 5-HTTLPR s allele showed elevated right amygdala activity in comparison to ll homozygotes during a stressful public speaking task compared with a private speech control condition (44). Thus, emotion-triggering areas in the brain seem to activate more in carriers of the s variant. The 5-HTTLPR has also been demonstrated to influence an amygdala – anterior cingulate cortex feedback circuit putatively involved in emotion regulation (10).

Interestingly, Stein and colleagues (57) noted that the 5-HTTLPR s allele was associated with poorer SSRI response in SAD patients. Thus, it is possible that treatment modulates amygdala activity differentially in s carriers relative to ll homozygotes. However, the s variant is very common in the general population and it is not necessarily etiologically relevant for SAD. Several other

genotypes influence amygdala responsivity and could thus be considered in future studies of SAD, for example the tryptophan hydroxylase-2 gene (G-703T polymorphism) (58) and the catechol-O-methyltransferase gene (COMT Val158Met) (59). As allelic variations in these and other genes might underlie interindividual variability in amygdala responsivity, gene polymorphisms are important to account for when comparing amygdala reactivity in SAD patients and controls.

Summary and Concluding Remarks

Neuroimaging studies point to deviations particularly in the amygdala/medial temporal lobe region, insula and striatum of patients with SAD, and there is also evidence of compromised serotonergic and dopaminergic neurotransmission. Activation studies of SAD have with a few exceptions demonstrated amygdala hyperresponsivity to various social-emotional stimuli, including anticipatory and situationally-elicited speech anxiety but it is not clear whether the amygdala is generally hyperresponsive or reacts to disorder-specific stimuli only. Amygdala responsivity is also strongly associated with certain gene polymorphisms like the 5-HTTLPR that may or may not be etiologically relevant for SAD. While the amygdala and insula may represent hyperactive emotion-triggering areas, there is no clear evidence supporting dysfunctional emotion regulation pathways from anterior cingulate or prefrontal sectors to subcortical regions. Amygdala activity is attenuated by successful pharmacological and cognitive-behavioral treatments while activity in higher-level cortical regions appears to change in the same direction, supporting the importance of bottom-up processes.

Although experimental and clinical researchers have made important progress toward understanding the neurobiology of SAD we still have an incomplete picture of the specific biological abnormalities involved. Also, with exception of the genetic factors, it is unclear whether the biological dysfunctions precede the onset of SAD or develop as a consequence of the disorder. Imaging techniques and other neurobiological methods could perhaps be used in longitudinal research to address this topic. Neurotransmitter and receptor

dynamics need to be further studied and functional connectivity analyses could be used to evaluate top-down and bottom-up processes in social anxiety and its treatment. The predictive value of relevant gene polymorphisms for treatment outcome and concomitant neurofunctional changes needs to be examined. In the near future we could also hope for clinical evaluation of novel pharmacological agents such as Corticotropin-releasing factor (CRF) antagonists and continued testing of putative cognitive enhancers like d-cycloserine that may augment the effects of exposure-based therapy.

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