

# Advances in Understanding the Anxiety Disorders: The Cognitive-Affective Neuroscience of ‘False Alarms’

DAN J. STEIN, MD, PhD

Department of Psychiatry, University of Cape Town, Cape Town, South Africa

**Background.** There have been significant advances in our understanding of the anxiety disorders; a range of data is now available on their epidemiology, nosology, psychobiology, and management. An integrative framework is required in order to conceptualize this data and to apply it in the clinic.

**Methods.** This is a nonsystematic review of literature on the psychobiology of some the major anxiety disorders, focused on the idea that each of these conditions can be conceptualized in terms of a different “false alarm,” mediated by specific neurocircuitry and with a particular evolutionary origin.

**Results.** The “false alarm” concept is able to integrate a range of data on the proximal mechanisms of anxiety disorders (including their mediating neurochemistry and neurogenetics), as well as hypotheses about the distal or evolutionary underpinnings of these conditions.

**Conclusion.** Fortunately, serotonergic antidepressants and cognitive-behavioral psychotherapy appear to be able to normalize the putative “false alarms” in anxiety disorders. A better understanding of the cognitive-affective neuroscience of anxiety disorders will hopefully lead to improved treatments.

**Keywords** Anxiety disorders, False alarms, Neurochemistry, Neurogenetics

## INTRODUCTION

Although anxiety has long held a central place in theories of psychopathology (1), it has only recently been appreciated that the anxiety disorders are amongst the most prevalent of the psychiatric disorders (2), and that they account for perhaps a third of all costs of mental illness (3). This recognition has given impetus to a growing range of studies on the nosology, epidemiology, psychobiology, and management of the anxiety disorders. Systematic reviews of interventions for anxiety disorders have helped to summarize the growing database of clinical trials research (4,5).

Nevertheless, an integrative theoretical framework may be useful for conceptualizing the full range of data on anxiety disorders, and for helping to apply it in the clinical setting. This is a nonsystematic review of literature on the psychobiology of

some of the major anxiety disorders (panic disorder, posttraumatic stress disorder, obsessive-compulsive disorder, social anxiety disorder), focused on the idea that each can be conceptualized in terms of a different “false alarm,” mediated by specific neurocircuitry and with a particular evolutionary origin (6).

## Background

Although the *Diagnostic and Statistical Manual: Mental Disorders* (DSM) originally included all anxiety disorders in one broad category known as ‘anxiety neurosis,’ the publication of the third edition of the DSM (DSM-III) represented a major advance in the anxiety disorders as it introduced a number of important methodological innovations, including explicit diagnostic criteria and a multiaxial system combined with a descriptive approach (7). The establishment of diagnostic criteria for a range of different anxiety disorders helped to propel work in this field forward, for example, encouraging systematic research on each of these conditions,

Address correspondence to Dan J. Stein, J-Block, Groote Schuur Hospital, Observatory 7925, Cape Town, South Africa. E-mail: dan.stein@uct.ac.za

including the development of standardized symptom severity rating scales.

At the same time, it is notable that classification systems for diagnosing anxiety disorders have received considerable criticism. Although the DSM system allows reliable diagnosis, there is far less evidence that its diagnostic constructs have validity. Thus, for example, the boundaries between normality and abnormality remain poorly defined (8), and the categorical nature of DSM constructs seems at odd with more dimensional clinical phenomena. More importantly, perhaps, there seems to be little overlap between clinical symptoms and biological dimensions (9). Thus there remains a need for additional conceptual and empirical work to address the nature of the anxiety disorders.

The introduction of diagnostic criteria for the anxiety disorders did, however, encourage their use in rigorous community studies of prevalence and sequelae (2,10). This work demonstrated that anxiety disorders were amongst the most prevalent, costly, and disabling of all psychiatric disorders. Thus, anxiety disorders account for approximately one-third of the cost of psychiatric illness, much of which is due to the indirect costs resulting from the associated disability and dysfunction (3,11). In a mortality and morbidity study conducted by the World Health Organization, OCD was found to be the tenth most disabling of all medical disorders (including cardiovascular disease and other general medical disorders) (12).

The epidemiological data also emphasized the early onset and high comorbidity of anxiety disorders; these conditions often begin during adolescence, and predispose to subsequent mood and substance use disorders. They are also a risk factor for various general medical disorders. Nevertheless, anxiety disorders remain underdiagnosed and misdiagnosed and only a small minority receive appropriate treatment (13). Despite this, sufferers frequently present to their physician with other complaints, such as somatic conditions or depression, and so are high utilizers of medical care. Continued attention to educating health care providers and the community about the anxiety disorders and their appropriate treatment remains necessary. A conceptual framework that destigmatizes the anxiety disorders, and provides a rationale for appropriate treatment, may be useful in proceeding with this work.

In addition to advances in diagnosis and epidemiology, progress in the fields of neuroanatomy, neurochemistry, neuroimmunology and neurogenetics has improved our understanding of the psychobiology of these disorders, and effective pharmacotherapeutic and psychotherapeutic interventions have been developed for their treatment. Indeed, there is a growing range of data addressing the relationships between biological and psychological aspects of the anxiety disorders; so that it has become possible to establish the initial framework for a cognitive-affective neuroscience of these conditions (6).

At the same time as this progress in understanding the proximal mechanisms underlying the anxiety disorders, there has been growing interest in the distal or evolutionary underpinnings of these conditions (14). It is important to know whether

any particular symptom arises from a defect (e.g., seizures), from a defense (e.g., pain), or from a dysregulation of a defense (e.g., dehydration from diarrhea). Evolutionary explanations of vulnerability to pathology rely on phenomena such as evolutionary trade-offs (different traits are adaptive in different environments), genome lag (evolved traits may be out of step with current environments), and historical constraints (how a trait has evolved may result in particular susceptibility to disease) (15,16).

The idea that anxiety represents an alarm with survival value is an old one, and is forcefully developed in Darwin's volume on the *Expression of Emotions in Man and Animals* (17). Darwin's volume was seminal in observing that human emotions have analogues in animal emotions, in hypothesizing that emotion has evolved because of its survival value, and in implying that human emotions are underpinned by specific but universal psychobiological mechanisms. Several authors have conceptualized the dysfunctions characteristic of anxiety disorders as "false alarms" (18). Such a notion would be consistent with psychobiological evidence for dysfunction in these conditions. We next consider some of the major anxiety disorders in terms of this framework.

### **Panic Disorder**

Panic disorder is present in approximately 2% of the population, with a somewhat higher incidence in females (2). While panic attacks may be present in all of the anxiety disorders, in panic disorder they are characteristically spontaneous. They are accompanied by a range of symptoms, including respiratory, cardiovascular, gastro-intestinal, and occulo-vestibular symptoms. Panic attacks vary, however, in their cueing, in their extent, and in the time of onset. Patients may go on to develop agoraphobia, or avoidance of situations which may precipitate panic attacks. This sequence of anxiety-avoidance immediately raises questions about the different neurocircuits involved in mediating these phenomena, and from a clinical perspective it emphasizes the importance of early exposure in preventing later avoidance.

Is there any evidence for a "false alarm" in panic disorder? Klein has argued that panic disorder is characterized by a false suffocation alarm (19). He suggests that the suffocation alarm is an evolved, adaptive response to a lack of oxygen (signaled by increasing  $PCO_2$  and brain lactate). He then goes on to hypothesize that the threshold for this alarm is lowered in panic disorder. Thus, the most prominent symptom of many panic attacks is dyspnea (indicating a specific emergency reaction to suffocation), and a range of studies document respiratory abnormalities in panic (such as increased sighing, perhaps indicating an attempt to avoid dyspnea by lowering  $PCO_2$ ). Panic attacks increase during a range of conditions characterized by increased  $PCO_2$  (e.g., premenstrual period) and decrease during conditions characterized by decreased  $PCO_2$  (e.g., pregnancy). Another possibility, however, is that panic

represents an acute danger alarm, that may be triggered by a range of stimuli including increased  $PCO_2$ .

An important advance in the cognitive-affective neuroscience of panic disorder and other anxiety disorders in which avoidance behavior develops, has been the delineation of brain circuits involved in fear conditioning. Nerve fibers from the central nucleus of the amygdala and the lateral bed nucleus of the stria terminalis (extended amygdala) innervate a number of brain structures that mediate responses to fear, such as the locus ceruleus (increased norepinephrine release), the periaqueductal grey (involved in defensive behaviors and postural freezing), the parabrachial nucleus (increased respiratory rate) and the nucleus pontine reticularis (startle response) in the brainstem, and the lateral nucleus (autonomic arousal and sympathetic discharge) and paraventricular nucleus (increased adrenocorticotrophin release) of the hypothalamus.

The hippocampus, in contrast, is situated at the junction of two pathways that mediate spatial/perceptual memory and object/conceptual memory. It has been proposed that the amygdala paralimbic circuit is associated with the implicit processing involved in fear conditioning and hence mediates the positive symptoms of anxiety (such as hyperarousal), whereas the hippocampus paralimbic circuit is associated with the explicit memory of how and when the fear conditioning occurred and therefore mediates the negative symptoms of anxiety (such as avoidance behaviors). There is evidence to suggest that the implicit and explicit pathways have different evolutionary origins, with the implicit cognition being present earlier in development.

Is there any evidence that panic disorder involves dysregulation of amygdala-hippocampal fear systems? There is a literature demonstrating that panic disorder can be associated with a range of (especially right sided) temporal abnormalities including seizure disorder (20). Similarly, stimulation of the amygdala in preclinical and clinical studies (of seizure disorder patients) is associated with fear responses (21,22). Conversely, patients with amygdala lesions demonstrate selective impairment in the recognition of fearful facial expressions, and show an inability to be conditioned to fear—this is the classical Kluver-Bucy syndrome (23).

A structural imaging study suggested reduced temporal lobe volume in panic disorder (24). In addition, PET scanning during anxious anticipation in normals (25), and during lactate-induced panic attacks in panic disorder patients (26) both demonstrated increased activity in paralimbic regions (temporal poles). Activation of the amygdala is in turn associated with hyperactivity in its efferents (hippocampus, hypothalamus, brainstem). An early study suggested that only panic disorder patients susceptible to lactate-induced panic had abnormal asymmetry of a parahippocampal region at rest (27). Subsequent functional imaging studies have confirmed dysfunctions of hippocampus or parahippocampal regions in panic disorder, although the precise abnormalities documented have not always been consistent (28).

Serotonergic projections originating in the raphe extend to many of the neurocircuits involved in fear conditioning. Modulation of the serotonin system therefore has the potential to influence the major regions of the panic disorder circuit, so resulting in decreased noradrenergic activity, diminished release of corticotropin-release factor, and modification of defense/escape behaviors. Certainly, clinical studies have found evidence of serotonergic involvement in panic disorder; for example, exacerbation of panic symptoms is seen following administration of the serotonin agonist m-chlorophenylpiperazine (mCPP) or other agents that have serotonin agonistic effects (e.g., marijuana) (29). In addition, after administration of the serotonin releaser and reuptake inhibitor fenfluramine, panic disorder patients demonstrated increased parietal-temporal cortex activation (30). Most recently, panic disorder patients were found to have lower 5-HT<sub>1A</sub> receptor binding in the cingulate and raphe (31).

Conversely, there is now good evidence of the efficacy of SSRIs in panic disorder, so that these agents are generally considered to be a good first-line medication for the treatment of this condition (provided that relatively low doses are used at first, so as to avoid unnecessary agitation). Indeed, an early meta-analysis comparing SSRIs with imipramine and benzodiazepines suggested superiority of this class of agents over other medication (32). Although subsequent effect sizes in SSRI studies have not been as strong, SSRIs are presumably able to normalize functional abnormalities in panic disorder (33).

From a psychotherapy point of view, cognitive-behavioral principles may also be useful in decreasing the threshold for activation of the false alarm in panic disorder. Patients can be taught relaxation techniques in order to cope with the anxiety felt during panic attacks. Decreasing behavioral avoidance is another crucial goal. As patients become more confident in their ability to use CBT techniques, they can be gradually encouraged to bring on panic attacks (by hyperventilation or exercise), in order to practice their coping skills.

### *Posttraumatic Stress Disorder*

Posttraumatic stress disorder (PTSD) has long been considered a “normal” response to an “abnormal” traumatic event. However, it turns out that rates of trauma are extremely high, and that only a small percentage of people go on to develop chronic PTSD. Thus PTSD is increasingly seen as an abnormal response to a traumatic event (34). Certainly PTSD is a disorder that is characterized by considerable distress and functional impairment. DSM-IV attempts to define the traumatic event in both objective terms (there is physical danger) and subjective ones (there is horror, fear). Traumatic events classically associated with PTSD include interpersonal traumas such as combat (more common in men) and rape (more common in women), as well as natural disasters. The more severe the trauma, the more likely the subject is to develop PTSD.

Three characteristic clusters of PTSD symptoms emerge after the trauma; re-experiencing, avoidance/numbing, and hyperarousal. Re-experiencing and hyperarousal symptoms are similar in some ways to the "positive" or panicky symptoms seen in various anxiety disorders, although they are distinguished by their focus on a traumatic event. Avoidance and numbing symptoms are redolent of the various "negative" or avoidance symptoms that also cut across the anxiety disorders, although loss of memory (of the traumatic event) is perhaps particularly distinguishing.

In PTSD, although current circumstances are safe, cues reminiscent of past trauma trigger an alarm reaction. In both disorders, conditioned fear may play an important role, with avoidance of those cues that trigger anxiety. What is remarkable about PTSD is the extent to which explicit cognition is taken "off-line", and to which memory can be thought of as stored in a "sensorimotor" form rather than in a "narrative" one. (Notably, PTSD can develop even when head trauma results in loss of explicit memories (35)). While such dissociation may be adaptive at the time of the trauma, it may interfere with processing of the traumatic event and subsequent adaptive responses (36). Maintenance of this dissociation in PTSD may reflect sensitization of neurochemical systems, perhaps after repeated exposure to traumatic events, and perhaps with consequent damage to the hippocampus.

A psychobiological conceptualization may emphasize that in humans, language and higher cognitive processes ordinarily play an important role. When these higher functions are taken "off-line", there is an inability to process traumatic events. In PTSD, this problem persists. Risk factors for PTSD can readily be conceptualized in terms of such a view. Thus patients with pre-trauma poor processing skills may be more prone to develop PTSD. Similarly, patients with peri-traumatic dissociation are more likely to have difficulty in verbalizing their responses. Finally, patients who experience guilt, shame, or lack of social support in the aftermath of traumatic events may have more difficulty in processing such experiences (37).

The animal literature suggests that fear conditioning can be extinguished by medial prefrontal cortex (anterior cingulate) (38), and there is some supportive human imaging data (39,40). From a different perspective, this "top-down" control can be understood in terms of the "processing" of the traumatic event. Implicit processes are integrated together with explicit ones, the traumatic event is articulated and integrated with the rest of the person's schemas, sensorimotor memory is augmented with narrative memory, and the person readjusts and adapts. A repeated traumatic event may however trigger the rapid amygdalo-thalamic fibers, overriding this frontal processing, and result in renewed symptoms. Indeed, there is a growing literature documenting the long-lasting psychobiological impact of early developmental trauma and of repeated exposure to stressors (41,42).

Brain imaging findings have provided some empirical evidence that such a model of PTSD is in fact at least partially correct. Structural findings have focused on decreased hippocampus volume

(43). Although not all studies have been consistent (44), in some work decreased hippocampus volume has correlated with trauma exposure or with cognitive impairment. It is possible that inherited variation in hippocampus volume may be a risk factor for subsequent PTSD (45), but more commonly such loss of volume is thought to represent atrophy (see below).

In healthy controls, imaging studies have demonstrated subcortical processing of masked emotional stimuli by the amygdala. Indeed, in an early study, PTSD patients exposed to audiotaped traumatic and neutral scripts during PET were found to have increases in normalized blood flow in right-sided limbic, paralimbic, and visual areas; with decreases in left inferior frontal and middle temporal cortex (46). Subsequent work has been more or less consistent (43). The authors of this research concluded that emotions associated with the PTSD symptomatic state are mediated by the limbic and paralimbic systems within the right hemisphere, with activation of visual cortex perhaps corresponded to visual reexperiencing. Decreased activity in Broca's area during exposure to trauma in PTSD, on the other hand, is consistent with patients' inability to verbally process traumatic memories (46).

Animal studies have demonstrated that serotonin is involved in regulation of the amygdala and connecting structures at a number of points (47); this may well be relevant to the mediation of PTSD symptoms. Clinical studies of abnormal paroxetine binding in PTSD, and exacerbation of PTSD symptoms in response to administration of mCPP are also consistent with a role for serotonin in this disorder (48).

Furthermore, there is increasing evidence for the efficacy of SSRIs in the treatment of PTSD (5), with some hints that these agents may even be more effective than other classes of medication (49). Fluvoxamine was the first SSRI found effective in an open-label trial of PTSD, subsequent controlled trials with fluoxetine, paroxetine, and sertraline have all demonstrated efficacy. To date there are few studies of the effects of SSRIs on the functional neuroanatomy of PTSD, but they may exert an effect by normalizing temperolimbic activation (50).

A range of neurochemical findings in PTSD are consistent with sensitization of various neurotransmitter systems. In the prefrontal cortex of primates dopamine appears the most responsive system to stress; stress impairs prefrontal cognitive function, and this is ameliorated by pretreatment with low doses of dopamine blockers and other agents that reduce prefrontal dopamine turnover (clonidine, naloxone) (51). The authors of this study suggested that stress may take the prefrontal cortex "off-line" to allow more habitual responses mediated by subcortical structures to regulate behavior. The glutamatergic paths are also likely to be involved in the neuronal mechanisms that underly fear conditioning, as well as in the extinction of fear-associated memories, and indeed some anti-convulsants with glutamatergic effects may be useful for the treatment of PTSD (52).

The hypothalamic/pituitary/adrenal (HPA) axis is another important area in which there is growing integration of

neurochemical and neuroanatomical findings. Patients with PTSD have reduced plasma cortisol levels and increased glucocorticoid receptor sensitivity, as well as high concentrations of cortisol-releasing factor receptors in the amygdala. Such findings differ markedly from those found in chronic stress (where there is erosion of negative feedback and down-regulation of glucocorticoid receptors), in other anxiety disorders, and in depression. Notably, there are also prominent cortisol-releasing factor receptors in amygdala, particularly in the central nucleus. It has been proposed that dysfunction in the HPA system results in neuronal damage, especially in the hippocampus, with animal studies showing hippocampal damage following exposure to glucocorticoids or natural stressors.

While such findings have raised interest in the possibility that CRF antagonists may be useful in PTSD, in the interim there is strong evidence for the value of SSRIs and of cognitive-behavioral psychotherapy (CBT) in the management of this condition. Interestingly, there is a good deal of overlap between the principles of CBT and those of psychodynamic psychotherapy in the management of traumatized patients. Both encourage exploration of the traumatic event, with a gradual reduction in avoidance behaviors. The retelling of the trauma presumably allows an integration of implicit somatic and explicit verbal memories, and the articulation of new schemas that incorporate the traumatic experience into the patient's worldview. There is also a small but growing literature on the optimal use of both pharmacotherapy and psychotherapy (53).

### ***Obsessive-compulsive Disorder***

Obsessive-compulsive disorder (OCD) was the fourth most common psychiatric disorder in the United States Epidemiological Catchment Area (ECA) study (54), and has a lifetime prevalence of 2–3% in many parts of the globe (55). Furthermore, it was the 10th most disabling of all medical disorders in a landmark mortality and morbidity study (12). Indeed, OCD has been suggested to cost the economy of a country such as the United States several billion dollars each year (56). OCD is characterized by obsessions and compulsions. Obsessions are intrusive thoughts, ideas, or images that increase anxiety, whereas compulsions are repetitive rituals or mental actions performed in response to obsessions in order to decrease anxiety. While patients report a wide range of different kinds of obsessions and compulsions, there is an impressive consistency of themes between patients and across cultures.

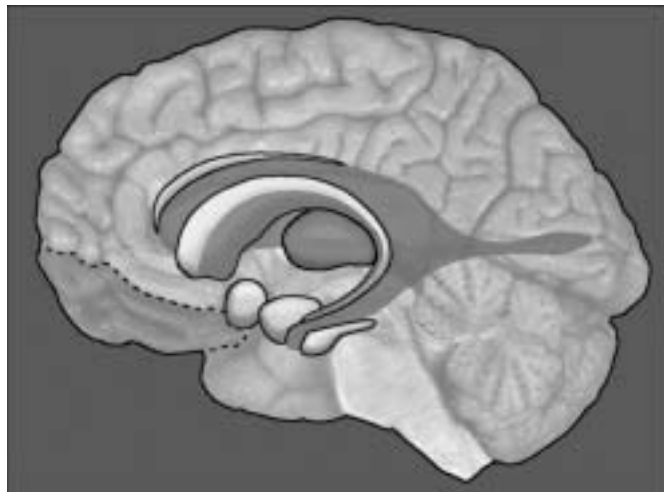
What is the false alarm in OCD? Although a number of different theories have been put forward, several authors have suggested that OCD can be characterized by inappropriate release of habit systems, or a failure to inhibit cortico-strially governed procedural strategies from intruding into consciousness. Such a view is consistent with 1) the limited number of symptom themes in OCD (e.g., washing, hoarding), and their apparent evolutionary importance; 2) dysfunction of CSTC circuits in a range of studies, with activation of

temporal rather than striatal areas during implicit cognition (57); and 3) abnormalities in serotonergic systems which innervate cortico-striatal circuits and which may be associated with disinhibition.

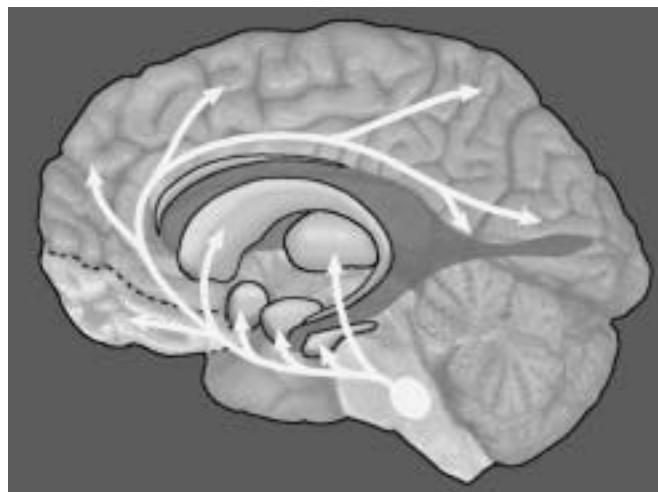
A limited number of different procedural strategies may be relevant to OCD. Much of the literature has focused on contamination and increased grooming. Some animal models appear highly relevant to such a formulation, demonstrating a remarkably similar pharmacotherapy response profile with OCD (58,59). Indeed, some OCD spectrum disorders can perhaps be conceptualized as grooming disorders (60). However, other procedural strategies may be highly relevant; these include hoarding (61) and symmetry behavior (which again appears to be mediated by specific evolutionary mechanisms, and which may be particularly relevant to body dysmorphic disorder). Notably, the primary emotion in OCD does not appear to be fear; and some authors have begun to suggest rather that the emotion that is particularly relevant to OCD is that of disgust (62). Interestingly, the neurobiology of fear and disgust can be dissociated on neurobiological studies; whereas fear involves the amygdala (see section on panic disorder), disgust is mediated by CSTC circuits.

Basic research shows that cortical-striatal-thalamic-cortical (CSTC) circuits also play a central role in the control of procedural strategies (63). Furthermore, there is considerable evidence to suggest that these circuits are involved in OCD. Initially this was based on neurological and neuropsychological data showing that conditions with basal ganglia involvement, such as Sydenham's chorea and Huntington's disease may be associated with OCD symptoms. More recent work on paediatric autoimmune neuropsychiatric disorders associated with Streptococcus, or PANDAS, has suggested that autoimmune reactions may result in basal ganglia damage and hence lead to OCD (64). OCD is occasionally treated neurosurgically by disruption of the cortical-striatal circuits; the apparent efficacy of this treatment provides further support for their role in mediating OCD. Most recently, structural and functional imaging studies have revealed abnormalities in basal ganglia volume, and hyperactivity in the orbitofrontal cortex, anterior cingulate and caudate nucleus (which is made worse by exposure to feared situations) (65) (Figure 1).

Turning to neurochemistry, a number of factors support the role of serotonin in OCD. Cerebrospinal fluid levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) decrease during treatment with a serotonin reuptake inhibitor (66), whilst challenge with the serotonergic agonist mCPP worsens OCD symptoms (67). There are also a number of interesting animal models of specific serotonin subtypes. Particular focus has been placed on the 5-HT<sub>1D</sub> receptor in the orbitofrontal cortex, which is desensitized by high doses of SSRIs over several weeks, thus following the same time course and dose-response seen clinically in OCD patients who respond to SSRI treatment (68). Pharmacological challenge and genetic studies provide additional evidence supporting the role of this subreceptor in OCD (69,70).



**Figure 1** Increased activity in orbitofrontal cortex and striatum in patients with obsessive-compulsive disorders. Reproduced with permission from the University of Stellenbosch.



**Figure 2** Normalization of activity in cortico-striatal-thalamic-cortical circuits by either pharmacotherapy or psychotherapy in obsessive-compulsive disorder. Reproduced with permission from the University of Stellenbosch.

Finally, it is notable that OCD has a selective response to SRIs compared with NRIs. Early work demonstrated that clomipramine, a serotonergic tricyclic, and then fluvoxamine, a SSRI, were more effective than desipramine, a noradrenergic tricyclic (71). Indeed, after treatment of OCD patients with either SSRIs there is normalization of activity in the CSTC circuitry (72). In refractory cases, augmentation of SSRIs with low doses of a dopamine blocker may be useful in altering the underlying abnormal functional neuroanatomy of OCD, changing the processing of the cues that falsely trigger OCD symptoms, and so decreasing symptoms (73).

Similarly, the first-line psychotherapy of OCD is cognitive-behavioral therapy (CBT). Patients with OCD often anticipate that exposure will be difficult if not impossible. Work demonstrating the ability of both pharmacotherapy and psychotherapy to normalize brain activity (72) provides a useful rationale for persuading them to at least attempt to apply the principles of CBT (Figure 2). Over time, they often become increasingly confident in their ability to fight against the symptoms of OCD. In extremely refractory patients, more invasive interventions (e.g., deep brain stimulation or neurosurgery) can be considered.

### ***Social Anxiety Disorder***

Social anxiety disorder (SAD; social phobia or SP) is, apart from specific phobia, the most common of the anxiety disorders, with prevalence ranging from 3 to 16% in various studies (2,10). It is more common in women in community studies, but in clinical studies the ratio of men with the disorder increases considerably. Cross-national community studies show similarities in demographic and clinical features in different parts of the world (74). SAD is characterized by fear of embarrassment

or humiliation in social situations. Patients with generalized social anxiety disorder fear most social situations and have higher co-morbidity; this subtype is also more disabling and has a stronger genetic component.

Again, a number of authors have attempted to characterize social anxiety disorder in terms of a false alarm. One possibility is that social anxiety disorder represents a false appeasement display (18). In the animal world, dominant and submissive status are signaled by a range of mechanisms. Appeasement displays play an important role in indicating acceptance of the status quo to a dominant conspecific (75). An embarrassed blush accompanied by lowering of the gaze and a silly grin may be reminiscent of certain appeasement displays. Further, empirical studies show that displays of embarrassment do mitigate the negative reactions of others (76), and that SAD patients misperceive the need for social appeasement; for example, by having an exaggerated opinion of their low status or by overestimating the threat from their social surroundings.

Evolutionary hypotheses about false alarms are strengthened when cases of the pathological absence of a particular alarm are noted. Are there some conditions in which there is insufficient social anxiety? Apart from Kluver-Bucy syndrome (in which there is a loss of fear), it turns out that people with a hereditary condition known as William's disorder may be characterized by hypersociability (77). Such hypersociability can of course potentially land patients in all sorts of trouble, and it is notable that there is increasing evidence of disturbances in face and gaze processing, and in their underlying structural and functional neuroanatomy in this condition (with some evidence of increased volume in limbic and cortical areas) (78,79).

Indeed, there is a growing body of knowledge about the neurocircuitry involved in recognizing and processing the faces, emotions, and gaze of others (80). A range of structures have been suggested to mediate social cognition, including the

amygdala and temporal regions, the striatum, and prefrontal and cingulate cortex (81). Similarly in SAD, both limbic (amygdala-hippocampal) and cortico-striatal circuits have been implicated. Thus SAD patients demonstrate selective activation of the amygdala when exposed to fear-relevant stimuli (82) or tasks (83), or show abnormal patterns of amygdala activation during aversive conditioning (84). In addition, SAD patients have a greater reduction in putamen volume with aging (85), reduced choline and creatinine signal:noise ratios in subcortical, thalamic, and caudate areas (86), and decreased N-acetyl-aspartate (NAA) levels and a lower ratio of NAA to other metabolites in cortical and subcortical regions (86,87).

Finally, frontal areas may play a role in social anxiety. Although not all work is consistent, there is a report of increased dorso-lateral prefrontal cortex activity during symptom provocation in a PET study of SAD (88), and of cortical grey matter abnormalities in SAD in particular (87). Anterior cingulate, which is involved in performance monitoring (89), may play a crucial role in a number of anxiety disorders, including SAD. In addition, imaging studies that have pooled or compared findings across different anxiety disorders suggest the importance of increased activation of inferior frontal cortex in mediating anxiety symptoms (90).

Serotonin plays a central role in mediating social behavior in animal models. In nonhuman primate models, increased serotonergic function is seen in dominant animals, while a reduction in serotonergic function is associated with avoidance of social interaction (91). A change in status results in a corresponding change in serotonergic function, so that a clear reduction in serotonin levels is seen when a dominant animal is removed from its social group. Other neurotransmitter systems also play a role in mediating social behavior, for example, striatal D<sub>2</sub> binding is decreased in lower social status monkeys (92).

Some analogous findings are apparent in human patients with SAD (93). Thus pharmacological challenge with mCPP result in increased anxiety in SAD, while increased cortisol levels are seen after fenfluramine challenge, suggesting a role for serotonin in this disorder. Notably, SAD individuals with one or two copies of the short allele of a functional polymorphism in the promoter region of the human serotonin transporter gene had increased right amygdala response to anxiety provocation (94). Several lines of evidence also suggest dopaminergic mediation of SAD, including molecular imaging studies that have found decreased striatal dopamine reuptake site densities (95), and lower striatal D<sub>2</sub> receptor binding (96).

Furthermore, trials with citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, and venlafaxine have been positive in SAD (97). Although open-label fluoxetine was useful, a controlled trial was unable to demonstrate efficacy. CBT has also been demonstrated effective for the treatment of SAD. Patients are encouraged to expose themselves to anxiety-inducing situations, and to reduce gradually their avoidance behaviors. Over time, patients can learn to overcome their social anxiety, with consequent improvements in social and occupational

dysfunction. Growing understanding of the psychobiology of behavioral inhibition (98,99), a risk factor for SAD, supports interest in early intervention, and perhaps even prevention of SAD. Finally, the recent finding that both pharmacotherapy and psychotherapy are able to normalize the functional neuroanatomy of SAD supports an integrative approach, using different modalities to decrease the threshold of the underlying false alarm, as needed.

## CONCLUSION

There have been considerable advances in our knowledge of the proximal neuroanatomy and neurochemistry of the anxiety disorders, largely due to the development of appropriate animal models, and advances in methods including imaging and genetics. We have a growing ability to translate basic findings from bench to bedside, and to integrate findings across multiple levels (e.g., genetics and imaging (94)). At the same time there is growing interest in the distal, evolutionary bases of anxiety disorders, with the possibility that each anxiety disorder is characterised by a particular false alarm. Although evolutionary constructs are not yet fully validated, the notion of false alarms does appear to have clinical utility (6).

A perennial question in the study of the anxiety disorders is the extent to which a splitting or lumping approach should be taken towards the diagnosis and assessment of different conditions. Advances in the psychobiology of different anxiety disorders suggest that it is important to be aware of each of these conditions as a unique entity. In some cases, the differences are subtle; for example, the distinctive disruptions of the HPA in PTSD. In other cases, the evidence suggests that a particular condition may be so different as to even fall outside the category of anxiety disorders (100). At the same time, there are often overlaps in the underlying neurocircuitry of different anxiety disorders, and so a response to the same or similar interventions (101).

Current treatments with serotonergic antidepressants are fortunately effective in the anxiety disorders; they may act to normalize the neurocircuitry that underlies the false alarms that are characteristic of these disorders. There is also growing evidence that effective psychotherapies are also able to exert such effects, albeit via different mechanisms (102,103). Here again, research on anxiety disorders has allowed an elegant integration of different arenas of investigation. Further advances in our understanding of the basic psychobiology of fear conditioning and extinction may lead to additional improvements in the way in which we combine or sequence different treatment modalities (104), and so to improved effectiveness.

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