BRAIN IMAGING

Key Words: imaging, pathophysiology, neural circuitry, anxiety, panic, phobia, obsessive-compulsive disorder

Neural Circuitry of Anxiety: Evidence from Structural and Functional Neuroimaging Studies

By Paul A. Cannistraro, MD and Scott L. Rauch, MD

ABSTRACT *~ Present understanding of the neural circuitry of anxiety has come from a variety of sources, including animal, clinical, and most recently, neuroimaging studies. Evidence from these sources has converged to form a translational bridge from animal models to human pathophysiology. In particular, the classical fear conditioning paradigm has served as a foundation for this bridge. Proposed models for the neural circuitry of normal anxiety as well as the anxiety disorders are discussed. A brief review of specific findings from neuroimaging studies of posttraumatic stress disorder, specific phobia, social phobia, obsessive-compulsive disorder, and generalized anxiety disorder is also provided.* Psychopharmacology Bulletin. *2003;37(4):8-25.*

Introduction: Fear and Anxiety

Anxiety can be distinguished from fear by the presence of subjective uncertainty with respect to the distress-inducing stimulus or situation. For example, the perceived possibility of the occurrence of negative consequences produces anxiety, whereas the immediate presence of an obviously harmful stimulus elicits fear. Pathological anxiety is greater than what would be expected for a given situation, thereby causing stress and impairing function.[1] Convergent evidence suggests that anxiety disorders arise out of some abnormality in cortical/subcortical interactions, resulting in an inappropriate expression of the fear response. We suggest that in order to better understand the pathophysiology of anxiety disorders, one should first examine the mechanism of normal fear.

Models of Fear and Anxiety

Fear conditioning provides one pragmatic model for understanding the physiological and behavioral characteristics of anxiety disorders.[2] It is possible that

Dr. Cannistraro is a post-doctoral fellow and Dr. Rauch is director of the Psychiatric Neuroimaging Research Group, Massachusetts General Hospital, Charlestown, MA.

To whom correspondence should be addressed: Scott L. Rauch, MD, Psychiatric Neuroimaging Research Group, Massachusetts General Hospital, Building149, Thirteenth Street, Charlestown, MA 02129; Tel: (617) 724-9553; Fax: (617) 726-4078; E-mail: rauch@psych.mgh.harvard.edu.

pathological anxiety in humans and conditioned fear in animals share similar brain mechanisms.[3] In the classical fear conditioning paradigm, the unconditioned stimulus (US) is an aversive sensory stimulus, an electric shock, which is paired with a neutral conditioned stimulus (CS) to produce a conditioned response (CR), namely fear. When the CS is subsequently repeatedly presented in the absence of the US, the CR eventually dissipates, in a process known as extinction. Aspects of this model may be relevant to all forms of pathological anxiety, though it is not necessarily the case that all anxiety disorders arise as a consequence of learned associations. In fact, it is only posttraumatic stress disorder (PTSD) that, by definition, is known to evolve in the aftermath of an emotionally traumatic event. Nonetheless, much has been learned about the neural circuitry of fear and anxiety from careful research in animals.

NEURAL CIRCUITRY OF ANXIETY

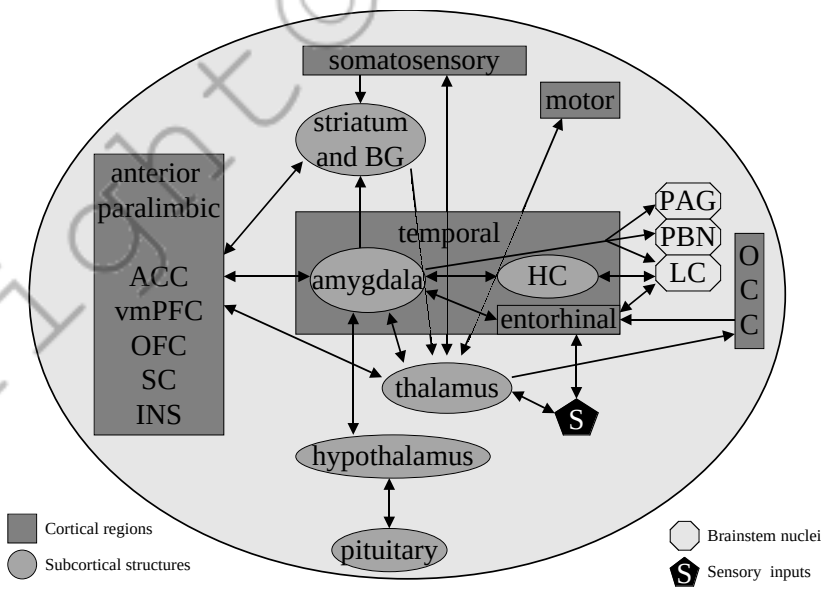
A very good starting point for the discussion of the neural circuitry of anxiety is the amygdala. This almond-shaped structure is actually a complex of numerous sub-nuclei lying within the anterior portion of the medial temporal lobe.[4] Convergent evidence suggests the amygdala mediates states of increased arousal, as well as the fear response. Sensory fibers from visual, auditory, olfactory, nociceptive and visceral pathways course through the anterior thalamus to the lateral nucleus of the amygdala (LNA), which relays the stimulus-related signal to the central nucleus of the amygdala (CNA). The CNA serves as the hub both for the integration of information and for the execution of autonomic and behavioral fear responses.[5,6] CNA efferents extend to the parabrachial nucleus, causing tachypnea,[7] to the lateral hypothalamus, which initiates the sympathetic response,[8] to the locus coeruleus, causing increases in blood pressure and heart rate as well as initiating the behavioral response to fear;[9] and to the paraventricular nucleus of the hypothalamus, resulting in activation of the hypothalamic-pituitary-adrenal (HPA) axis, which stimulates increases in adrenocorticoids.[10] The fundamental neural circuitry of anxiety is illustrated in Figure 1.

Reciprocal connections between the amygdala and sensory thalamus, prefrontal cortex, insular, and somatosensory cortex allow for two modes of fear responses which differ with respect to how finely-tuned they are to recognize threat-related information.[11] The rapid, less finely-tuned mode, needed for response to immediate threats, is activated via direct input from the sensory thalamus. The slower, more finely-tuned mode has the benefit of thalamo-cortico-amygdalo inputs which allow for valuable cortical assessments of threat-related information. Deficits in either or both of these pathways might prove to be the driving force behind pathological anxiety.

Convergent evidence points to two other potential sites of pathology in anxiety disorders. The hippocampus has been implicated in the processing of contextual information; information regarding safe versus potentially dangerous contexts can have a temporizing influence on the fear response.[12] Hippocampal dysfunction has therefore been implicated in pathological anxiety via overgeneralization, as a consequence of deficient appreciation for the contextual specificity of potentially threatening stimuli. Additionally, animal studies indicate that lesions in the medial prefrontal cortex significantly interfere with normal extinction.[13-15] Impaired extinction may likewise lead to pathological anxiety; individuals with such deficits would be unable to efficiently modify previously experienced associations between innocuous cues and genuinely threatening stimuli. In order to apply this information about neural circuitry and behavioral phenomena in animals for better understanding human conditions, it is important to thoughtfully consider the clinical features of the anxiety disorders.

FIGURE 1

THE NEURAL CIRCUITRY OF ANXIETY



ACC=anterior cingulate cortex; BG=basal ganglia; HC=hippocampus; INS=insular cortex; LC=locus coeruleus; vmPFC=ventral/medial prefrontal cortex; OCC=occipital cortex; OFC=orbital frontal cortex; PAG=periacqueductal gray; PBN=parabrachial nucleus; SC=subcallosal cortex.

Cannistraro PA, Rauch SL. *Psychopharmacology Bulletin*. Vol 37. No 4. 2003.

CLINICAL FEATURES OF THE ANXIETY DISORDERS

PTSD is defined as a syndrome which arises following exposure to an emotionally traumatic event. The response to the event must involve intense fear, helplessness, or horror. Characteristic symptoms include: increased physiological reactivity to reminders of the trauma, persistent avoidance of stimuli associated with the trauma, flashbacks and/or nightmares, and persistently increased arousal.

Specific phobia is characterized by a persistent, unreasonable fear of a circumscribed object or situation. Exposure to the phobic stimulus provokes an acute and severe fear response. Phobic situations are therefore avoided or endured with marked distress. The diagnosis is made only when the distress surrounding exposure (or avoidance) leads to significant interference with one's daily routine or one's occupational or social functioning.

The essential feature of social phobia is the presence of an acute anxiety response during social situations, related to the concern that one will be scrutinized or humiliated by others. As with specific phobia and PTSD, those with social phobia will either avoid the fear inducing stimulus, or endure it with considerable distress.

Panic disorder (PD) is defined by the presence of recurrent, unexpected panic attacks, accompanied by concern for future attacks, and avoidance of perceived environmental triggers. Panic attacks are characterized by the abrupt onset of intense fear or discomfort with associated somatic and/or cognitive symptoms. Somatic symptoms include stimulation of respiratory, cardiac, and gastrointestinal systems, whereas cognitive symptoms involve fears of dying, losing one's mind, or fainting. Thirty percent of patients with PD suffer from agoraphobia, or marked distress arising from being in places or situations which might trigger a panic attack, or in which assistance or escape might be difficult.

Obsessive-compulsive disorder is characterized by the presence of recurrent, intrusive, and distressing thoughts, impulses, or images (obsessions) and/or ritualized behaviors or mental acts (compulsions). Compulsions are typically performed in an attempt to reduce anxiety associated with obsessions. Sufferers of OCD can recognize that their obsessions are products of their own mind, and that both their obsessions and compulsions are excessive or unreasonable. To meet diagnostic criteria, obsessions and/or compulsions must be sufficiently time consuming or upsetting that they cause marked distress or significant impairment.

The essential feature of generalized anxiety disorder (GAD) is persistent (more days than not for at least six months) and excessive worry about several aspects of one's life (e.g. work or school performance) or the welfare of loved ones. While patients might not report the worry as excessive, they do complain of significant distress or impairment as a result. Patients with GAD must also have three associated symptoms from

among several, such as restlessness, fatigue, impaired concentration, irritability, muscle tension, and insomnia.

BRIDGING CLINICAL PHENOMENOLOGY AND PATHOPHYSIOLOGY

The anxiety disorders, like all psychiatric diagnoses, are in fact syndromes, defined by clusters of related signs and symptoms, rather than pathophysiology per se. The current nosological framework in psychiatry reflects the as yet unresolved challenge of bridging from clinical phenomenology to pathophysiology. Given that we have only begun to understand the neural circuitry of anxiety and psychiatric disorders, our current classification system is arguably the most effective tool available. That said, evidence from treatment and neuroimaging studies indicates that disorders in separate diagnostic categories may have overlapping pathology, and those within a given category may have very different mechanisms. Ongoing efforts in neuroimaging promise to elicit new insights into the commonalities and differences among the anxiety disorders and their respective neural circuitries, insights which may guide future approaches to both diagnosis and treatment. In the following sections, we review findings from structural and functional neuroimaging as they relate to evolving pathophysiological models of anxiety disorders.

NEUROIMAGING AND THE NEURAL CIRCUITRY OF ANXIETY DISORDERS

Neural Circuitry of Posttraumatic Stress Disorder

PTSD provides perhaps the best example of an anxiety disorder which appears to follow the classical fear conditioning model, in that the pathological symptoms form following exposure to a traumatic event. Rauch and colleagues[16] proposed a model of PTSD, emphasizing the amygdala and its interactions with limbic and paralimbic structures. According to this model, amygdala hyper-responsivity to threat-related stimuli is perhaps exacerbated or due to inadequate top-down modulation by ventral/medial prefrontal cortex and hippocampus. Alternatively, there might be a bottom-up progression of pathophysiology, whereby an intrinsically hyperactive amygdala over-stresses cortical regions and hippocampus, resulting in impairment in those areas—which in turn begets further amygdala hyperactivity.

Deficiencies in ventral/medial prefrontal cortex may interfere with impaired extinction of the fear response. In fact, PTSD and other anxiety disorders might involve abnormal sensitization (as opposed to habituation/extinction) of amygdala responses to threat-related stimuli. By this model, hippocampal dysfunction may underlie the overgeneralization of

fear responding, as well as concurrent impairment of explicit memory.[17] Based on evidence from animal and clinical studies, Charney and Bremner[18] have also reported a working model of PTSD, which in addition to amygdala, hippocampus, and prefrontal cortex, involves locus coeruleus, thalamus, hypothalamus, and periacqueductal gray. Functional imaging studies have supported an amygdalocentric model of PTSD, also implicating rostral anterior cingulate cortex (rACC; as one subterritory of ventral/medial prefrontal cortex) and hippocampus.

An initial PET symptom provocation study used script-driven imagery to elicit symptoms.[19] Increased rCBF was found within right orbitofrontal, insular, anterior temporal and visual cortex in the provoked versus control conditions. Subsequent symptom provocation studies have compared subjects with PTSD against trauma-exposed individuals without PTSD. Taken together, these findings have shown that in provoked versus control conditions, subjects with PTSD as compared with non-PTSD controls exhibit greater responses within the amygdala,[20-22] decreased responses within medial frontal areas,[23-26] and more pronounced deactivation within other heteromodal frontal cortical regions.[21,25] It bears mentioning that the interpretation and even replication of these findings has been in part limited by modest subject numbers, variation in experimental paradigms, and heterogeneity in subject samples.

Cognitive activation studies have attempted to assess the functional capacity of the key elements in this model, namely rACC, amygdala, and hippocampus. With an fMRI masked-faces probe,[27] Rauch and colleagues found that subjects with PTSD exhibited greater amygdala reactivity than trauma-exposed subjects without PTSD.[28] Furthermore, amygdala reactivity, as measured by the magnitude of fMRI signal change, was shown to correlate with PTSD symptom severity. By virtue of an fMRI Emotional Counting Stroop paradigm, PTSD subjects, as compared with trauma-exposed subjects without PTSD, exhibited diminished recruitment of rACC.[29]

Using explicit learning probes and PET, investigators have found evidence of hippocampal dysfunction in PTSD. Diminished hippocampal activation has been reported during the performance of a verbal paired associates task in abuse survivors with PTSD,[30] and during encoding of a narrative paragraph.[31] Likewise, firefighters with PTSD compared to firefighters without PTSD were found to have decreased hippocampal activation during a word stem completion task.[32]

Complementary structural neuroimaging findings have focused mainly on modest differences in hippocampal volume between groups. In some cases, these findings remained significant after statistically controlling for potential confounders such as alcohol abuse or years of education.[17,33] Furthermore, investigators have reported correlations between hippocam-

pal volume and verbal memory[17] as well as indices of trauma exposure and symptom severity.[33] An initial cortical parcellation study found that Vietnam nurses with PTSD, as compared with those without PTSD, exhibited selectively decreased volumes in rACC and subcallosal cortex.[34]

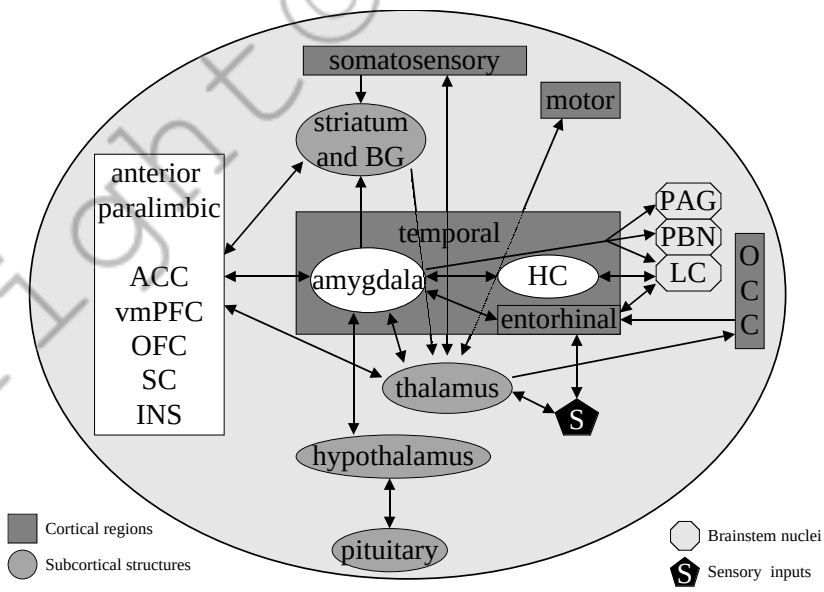
In summary, functional neuroimaging findings in PTSD suggest hyperresponsivity of the amygdala, and deficient activation of ventral/medial prefrontal cortex and hippocampus. Structural imaging studies indicate grossly smaller volumes of ventral/medial frontal cortex and the hippocampus. These data lend support to a model of PTSD (Figure 2) that parallels the established neurocircuitry of classical fear conditioning. However, the pathogenesis of these abnormalities in PTSD remains unclear.

Neural Circuitry of Specific Phobia

Leading theories of specific phobia are based on classical fear conditioning as well as nonassociative models. While the former do address the presence of a circumscribed phobic stimulus, they cannot explain why

FIGURE 2

THE NEURAL CIRCUITRY OF POSTTRAUMATIC STRESS DISORDER
(Implicated sites of pathophysiology in white)



ACC=anterior cingulate cortex; BG=basal ganglia; HC=hippocampus; INS=insular cortex; LC=locus coeruleus; vmPFC=ventral/medial prefrontal cortex; OCC=occipital cortex; OFC=orbital frontal cortex; PAG=periacqueductal gray; PBN=parabrachial nucleus; SC=subcallosal cortex.

Cannistraro PA, Rauch SL. *Psychopharmacology Bulletin*. Vol 37. No 4. 2003.

many individuals with phobias cannot recall an initial conditioning event.[35] Nonassociative models seek to address the observation that certain intense fears can exist without prior exposure to the phobic stimulus. Menzies and Clarke[36] speculate that specific phobias are the result of failed habituation of intrinsic developmental fears. While animal research has previously suggested an amygdalocentric model for specific phobia, human imaging studies appear to implicate a more central role for anterior paralimbic regions and sensory cortical regions which interact with amygdala.

Cognitive activation probes in conjunction with fMRI have recently yielded findings in specific phobia. Wright et al.[37] found indications of abnormal insular cortical function, but no significant differences in amygdala function in specific phobics versus controls while viewing emotionally valenced human faces. Using an implicit sequence learning task, Martis et al.[38] found no evidence of striatal dysfunction in specific phobics compared with healthy controls.

A series of symptom provocation paradigms have also been performed in specific phobics. PET studies have revealed increases in regional cerebral blood flow (rCBF) within secondary visual cortex, as well as rCBF decreases in prefrontal, posterior cingulate, anterior temporopolar cortex, and hippocampus.[39-41] In contrast to these reports, Rauch et al.[42] found significant rCBF increases in left somatosensory cortex, left thalamus, as well as several anterior paralimbic structures. Dominant-sided somatosensory cortical activation is seen in the context of subjects engaging in tactile imagery with eyes closed. Of note, the previous PET studies were conducted with subjects keeping their eyes open, providing one possible explanation for the discrepant findings by Rauch et al. An fMRI investigation of arachnophobics revealed activation in the right dorsolateral prefrontal cortex (BA 10), parahippocampal gyrus, and bilateral visual association cortex during viewing of films of spiders versus control scenes. Following successful cognitive-behavioral therapy the frontal and parahippocampal activations resolved.[43]

Given that theoretical models of specific phobia have focused on the amygdala, it is interesting to note that, taken together, these neuroimaging findings support a neurocircuitry model of specific phobia (Figure 3) that more directly implicates anterior paralimbic and sensory cortical regions—which interact with the amygdala—rather than the amygdala itself.

Neural Circuitry of Social Phobia

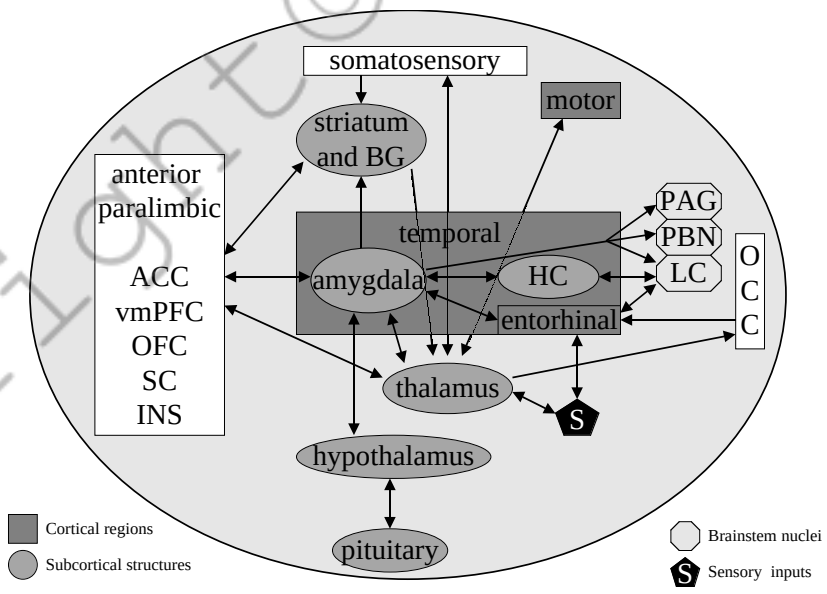
Recognizing the amygdala's role in the mediation of social behavior,[44] models of social phobia have also focused on the amygdala. The model proposed by Amaral et al.,[45] based on lesion studies in Macaques, portrays the amygdala as playing a protective role, allowing the organism to detect and avoid danger. Together with the involvement of the amygdala in the

appraisal of human facial expressions,[46] these two functions provide a rationale for theories of amygdala involvement in the pathophysiology of social phobia.

Findings from fMRI studies of social phobia lend empirical support to the involvement of amygdala as well as hippocampus in this disorder. Birbaumer and colleagues reported that subjects with social phobia, but not healthy controls, exhibited amygdala activation while viewing neutral facial expressions.[47] Schneider and colleagues found that while social phobics experienced increased amygdala and hippocampal activation when neutral faces were paired with an aversive stimulus, healthy controls had decreased activation in these same regions.[48] Stein and colleagues reported that when viewing contemptuous versus happy or angry versus happy faces subjects with generalized social phobia exhibited increased amygdala, uncus, and parahippocampal gyrus activation as compared with healthy controls.[49] Interestingly, the current evidence from neuroimaging indicates fundamental differences between the neural circuitry of specific phobia and that of social phobia, with the latter appearing to be predominantly amygdala-focused (Figure 4).

FIGURE 3

THE NEURAL CIRCUITRY OF SPECIFIC PHOBIA
(Implicated sites of pathophysiology in white)



ACC=anterior cingulate cortex; BG=basal ganglia; HC=hippocampus; INS=insular cortex; LC=locus coeruleus; vmPFC=ventral/medial prefrontal cortex; OCC=occipital cortex; OFC=orbital frontal cortex; PAG=periacqueductal gray; PBN=parabrachial nucleus; SC=subcallosal cortex.

Cannistraro PA, Rauch SL. *Psychopharmacology Bulletin*. Vol 37. No 4. 2003.

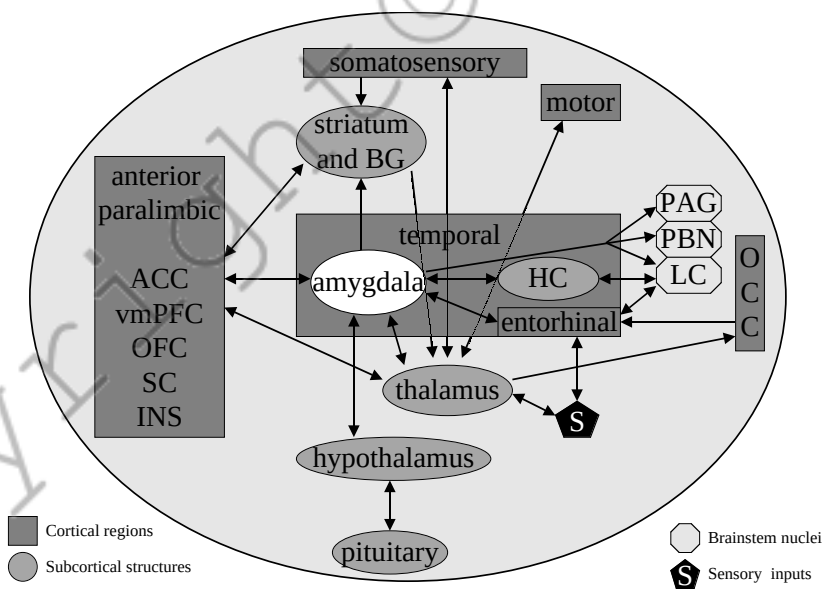
Neural Circuitry of Panic Disorder

The variety of neurocircuitry models of PD reflect both the complexity of the panic response system and the limited degree to which we understand it at this time. While more recent models resemble those of PTSD[50] or attribute PD to miscommunication between serotonergic and noradrenergic systems,[51] previous models have pointed to abnormal brain stem responsiveness to carbon dioxide (ie, "false suffocation alarm") as the primary pathology underlying PD.[52-54]

The existing models are all consistent with the idea that a normal anxiety response is inappropriately and spontaneously set in motion due to some homeostatic imbalance. Another possibility would be that panic attacks are actually manifestations of minor anxiety episodes, initiated in response to explicit external cues, that have been allowed to progress due to deficits in those systems that are in place to terminate the fear response. Finally, given reports of amygdala activation in response to visual stimuli below the level of awareness,[27] the possibility remains that panic attacks are in fact triggered by implicit external cues (ie, cues of which the individual remains unaware).

FIGURE 4

THE NEURAL CIRCUITRY OF SOCIAL PHOBIA
(Implicated sites of pathophysiology in white)



ACC=anterior cingulate cortex; BG=basal ganglia; HC=hippocampus; INS=insular cortex; LC=locus coeruleus; vmPFC=ventral/medial prefrontal cortex; OCC=occipital cortex; OFC=orbital frontal cortex; PAG=periacqueductal gray; PBN=parabrachial nucleus; SC=subcallosal cortex.

Cannistraro PA, Rauch SL. *Psychopharmacology Bulletin*. Vol 37. No 4. 2003.

Numerous resting state studies of panic disorder have suggested abnormalities within the temporal lobe, including hippocampal and parahippocampal structures. Reiman et al.,[55] using PET, reported that lactate-sensitive PD subjects exhibited lower left/right ratios of parahippocampal rCBF during a neutral state. In another PET study, Nordahl et al. described lower left/right hippocampal ratios of rCMRglu in PD subjects compared with healthy controls during a neutral state PET-FDG study.[56] A more recent PET-FDG investigation by Bisaga et al. found that PD subjects had elevated rCMRglu in the left hippocampus and parahippocampal area, with reduced rCMRglu in right superior temporal regions, as compared with healthy controls.[57] De Cristofaro et al.[58] employed a resting state SPECT paradigm which indicated that PD subjects exhibited increased rCBF in left occipital cortex, and reduced rCBF in bilateral hippocampus as compared with healthy controls.

Symptoms provocation studies of PD appear to more directly implicate cortical regions in the manifestation of PD symptoms. In an fMRI study using script-driven imagery, Bystritsky et al.[59] reported that relative to healthy controls, PD subjects exhibited increased activation in inferior frontal, cingulate, and orbitofrontal cortex as well as hippocampus. Other symptom provocation studies have used pharmacological challenges; in comparison with healthy controls, PD subjects exhibited decreased rCBF in cortical regions including bilateral frontal cortex[60] as well as anterior insula and ACC.[61] In the setting of hypocapnia in lactate-sensitive PD subjects compared with healthy controls and non-lactate-sensitive PD subjects, Reiman et al.[62] found rCBF increases in bilateral temporopolar cortex and bilateral insular cortex/claustrum/putamen.

With regard to structural imaging, two morphometric MRI studies have found abnormalities in temporal cortex of PD versus control subjects. Vythilingam et al.[63] found reduced temporal cortical volumes bilaterally (with no hippocampal volume differences), whereas Massana et al.[64] found decreased gray matter density in parahippocampal cortex.

Taken together, these findings from human imaging studies implicate temporal lobe structures, prefrontal cortex, insula, and motor striatal regions in the neural circuitry of PD (Figure 5). Reduced activity in prefrontal cortex during the symptomatic state might possibly reflect a deficiency in top-down control of the fear response, theoretically allowing for the cascade of neural events that is experienced as a panic attack. Temporal cortical abnormalities may mitigate explicit information processing as well as modulation of amygdala responses.

Neural Circuitry of OCD

In contrast to neurocircuitry models for the other anxiety disorders, leading theories of OCD do not emphasize a central role for the amygdala.

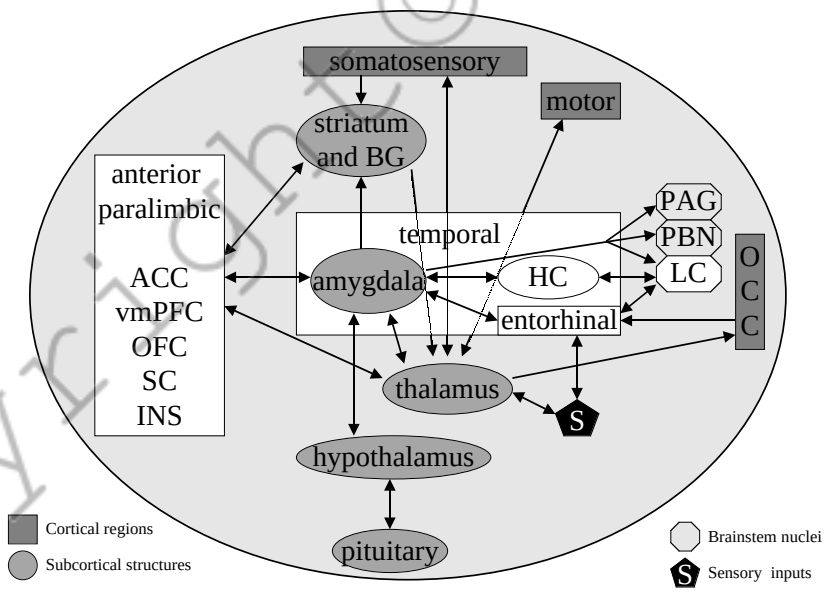
Rather, considerable evidence implicates cortico-striatal circuitry in the pathophysiology of OCD (Figure 6). In addition to mediating motor activities, the striatum has been implicated in a variety of cognitive and affective functions. Specifically, it is believed to mediate repetitive, stereotyped cognitive processes on an implicit level.[65-67]

The striatum, through its influence at the level of the thalamus, is believed to influence reciprocal thalamo-cortical interactions.[68,69] Obsessions maybe mediated by overactivity within frontal cortex while stemming from impaired thalamic gating fundamentally attributable to deficient striatal function. In addition, the repetitive ritualized behaviors or compulsions might be the expression of aberrant or compensatory striatal activity.[70] Given the intimate connections between amygdala and striatum, their anatomical proximity, and respective roles, it has been suggested that activation of the amygdala during a state of fear or anxiety could readily induce stereotyped behaviors observed during striatal activation.[71]

Data from neuroimaging studies lend further support to the relevance of the above model to OCD. Resting state PET and SPECT studies have

FIGURE 5

THE NEURAL CIRCUITRY OF PANIC DISORDER
(Implicated sites of pathophysiology in white)



ACC=anterior cingulate cortex; BG=basal ganglia; HC=hippocampus; INS=insular cortex; LC=locus coeruleus; vmPFC=ventral/medial prefrontal cortex; OCC=occipital cortex; OFC=orbital frontal cortex; PAG=periacqueductal gray; PBN=parabrachial nucleus; SC=subcallosal cortex.

Cannistraro PA, Rauch SL. *Psychopharmacology Bulletin*. Vol 37. No 4. 2003.

revealed increased activity in orbitofrontal cortex (OFC), ACC, and striatum in OCD subjects as compared to healthy controls.[72-77] Furthermore, symptom provocation studies of OCD subjects have demonstrated OFC, ACC, and striatal activations in the symptomatic state versus the control neutral state.[78-80] Treatment response studies have shown reduced hyperactivity in these same structures following behavioral and pharmacotherapy of OCD.[77,81-84]

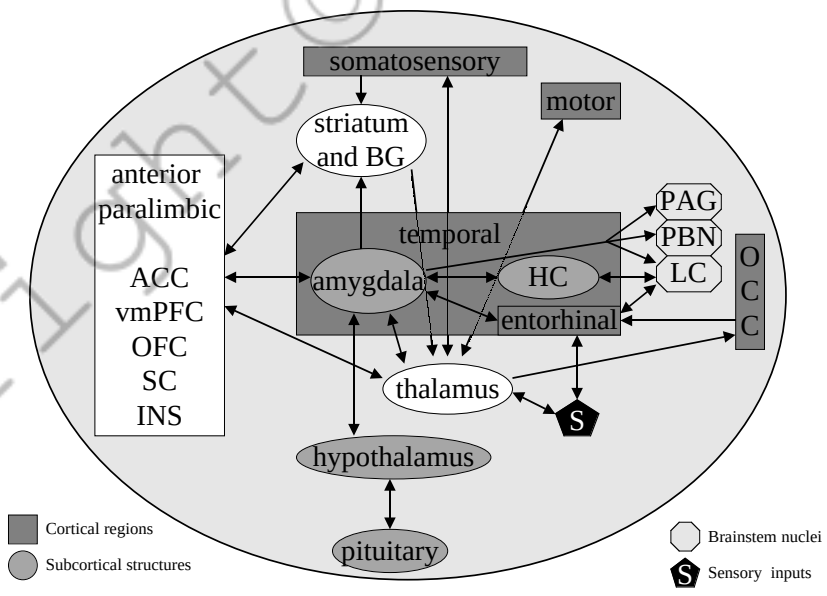
With regard to a role for the amygdala in the neural circuitry of OCD, the current evidence is limited. However, a recent fMRI study by Mataix-Cols et al.[85] found a significant correlation between amygdala activation and increases in OCD symptom-related anxiety. Furthermore, exposure-based behavioral treatment of OCD[86] can be likened to the process of extinction in the classical fear conditioning paradigm.

Neural Circuitry of GAD

Controversy has surrounded the diagnosis of GAD; some have questioned whether GAD is a discrete disorder or rather a manifestation of

FIGURE 6

THE NEURAL CIRCUITRY OF OBSESSIVE COMPULSIVE DISORDER
(Implicated sites of pathophysiology in white)



ACC=anterior cingulate cortex; BG=basal ganglia; HC=hippocampus; INS=insular cortex; LC=locus coeruleus; vmPFC=ventral/medial prefrontal cortex; OCC=occipital cortex; OFC=orbital frontal cortex; PAG=periacqueductal gray; PBN=parabrachial nucleus; SC=subcallosal cortex.

Cannistraro PA, Rauch SL. *Psychopharmacology Bulletin*. Vol 37. No 4. 2003.

other disorders, such as MDD[87] or panic disorder,[88] or even a markedly anxious temperament.[89] Consequently, the development of a model for the neural circuitry of GAD is understandably in the early stages, with limited empirical data yet available.

Insight into possible neurotransmitter systems involved in GAD might be derived from a double-blind placebo-controlled study by Montgomery et al. indicating that venlafaxine, a serotonin and norepinephrine reuptake inhibitor, exhibited superior efficacy over placebo in the treatment of GAD.[90] Additionally, a small number of neuroimaging studies have begun to gather preliminary evidence with regard to the pathophysiology of GAD. PET studies have found metabolic differences in occipital lobe,[91] as well as cortex, limbic regions, and basal ganglia[92] following benzodiazepine treatment in GAD subjects versus normal controls. Another imaging study has found significant changes in cerebral benzodiazepine receptor distribution in GAD subjects compared with healthy controls.[93] While it is premature to draw meaningful conclusions about the neural circuitry of GAD, it appears that serotonin, norephinephrine, and γ-aminobutyric acid neurotransmitter systems may be involved in its pathophysiology.

CONCLUSION

While the neural circuitry of anxiety and anxiety disorders has not yet been fully established, progress continues. Data from animal studies, human treatment studies, and observed clinical phenomena inspire models of fear and anxiety. These models in turn generate hypotheses that can be tested with functional and structural neuroimaging techniques.

In addition to a phenomenological framework for conceptualizing anxiety disorders, it is useful to consider how they compare with regard to localization of findings from neuroimaging. From this perspective, one might group anxiety disorders on the basis of predominant amygdala involvement (social phobia), predominant cortical involvement (specific phobia), or a combination of cortical and amygdala involvement (PTSD). At this stage, the data suggest PD should fall in the second or third category; however, an abundance of convergent evidence points to cortico-striatal systems in the pathophysiology of OCD. Finally, there is insufficient evidence to categorize GAD by this scheme at this time. By further illuminating the neurobiological commonalities and differences between the anxiety disorders, neuroimaging should continue to serve as a valuable tool for psychiatric neuroscience. Ultimately we should hope for a diagnostic scheme that reflects diseases of known pathophysiology, rather than syndromes described by lists of signs or symptoms. Hopefully, such an eventuality will provide for not only improved diagnosis, but also enhanced treatment for those who suffer from these maladies. ⌘

ACKNOWLEDGMENTS

Dr. Rauch is supported in part by NIMH grant MH60219; Dr. Cannistraro is supported in part by the Ethel Dupont-Warren Fellowship from Harvard Medical School. The authors wish to acknowledge Drs. Lisa Shin, Paul Whalen, and Chris Wright for conceptual contributions to past reviews from their laboratory on similar topics.

REFERENCES

1. *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition. Washington, DC: American Psychiatric Association, 1994.
2. Kent JM, Sullivan GM, Rauch SL. *Neural Circuitry and Signaling in Anxiety*. In: Kaplan GB, Hammer RP, eds. Brain Circuitry and Signaling in Psychiatry: Basic Science and Clinical Applications. Arlington, VA: American Psychiatric Publishing, 2002.
3. LeDoux JE. *The Emotional Brain*. New York: Simon and Schuster, 1996.
4. Amaral DG, Price JL, Pitkanen A, Carmichael ST. *Anatomical organization of the primate amygdaloid complex*. In: Aggleton. JP, ed. The Amygdala: Neurobiological Aspects of Emotion, Memory and Mental Dysfunction. New York, NY: Wiley-Liss, 1992:1-66.
5. Davis M. The role of the amygdala in fear and anxiety. *Annu Rev Neurosci.* 1992;15:353-75.
6. LeDoux JE, Iwata J, Cicchetti P, Reis DJ. Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. *J Neurosci.* 1988;8:2517-29.
7. Takeuchi Y, McLean JH, Hopkins DA. Reciprocal connections between the amygdala and parabrachial nuclei: ultrastructural demonstration by degeneration and axonal transport of horseradish peroxidase in the cat. *Brain Res.* 1982;239:583-8.
8. Price JL, Amaral DG. An autoradiographic study of the projections of the central nucleus of the monkey amygdala. *J Neurosci.* 1981;1:1242-59.
9. Cedarbaum JM, Aghajanian GK. Afferent projections to the rat locus coeruleus as determined by a retrograde tracing technique. *J Comp Neurol.* 1978;178:1-16.
10. Dunn JD, Whitener J. Plasma corticosterone responses to electrical stimulation of the amygdaloid complex: cytoarchitectural specificity. *Neuroendocrinol.* 1986;42:211-7.
11. de Olmos JS. *Amygdaloid nuclear gray complex*. In: Paxinos GT, ed. The Human Nervous System. San Diego, CA: Academic Press, 1990:583-710.
12. LeDoux J. Fear and the brain: where have we been, and where are we going? *Biol Psychiatry.* 1998;44:1229-38.
13. Morgan MA, LeDoux JE. Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Behav Neurosci.* 1995;109:681-8.
14. Morgan MA, Romanski LM, LeDoux JE. Extinction of emotional learning: contribution of medial prefrontal cortex. *Neurosci Lett.* 1993;163:109-13.
15. Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature.* 2002;420:70-4.
16. Rauch SL, Shin LM, Whalen PJ, Pitman, RK. Neuroimaging and the neuroanatomy of PTSD. *CNS Spectrums*. 1998;3(suppl 2):30-41.
17. Bremner JD, Randall P, Scott TM, et al. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry.* 1995;152:973-81.
18. Charney DS, Bremner JD. *Psychobiology of Posttraumatic Stress Disorder*. In: Bunney S NE, Charney DS, ed. Neurobiology of psychiatric disorders. New York: Oxford University Press, 1999:494-517.
19. Rauch SL, van der Kolk BA, Fisler RE, et al. A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch Gen Psychiatry.* 1996;53:380-7.
20. Liberzon I, Taylor SF, Amdur R, et al. Brain activation in PTSD in response to trauma-related stimuli. *Biol Psychiatry.* 1999;45:817-826.
21. Shin LM, McNally RJ, Kosslyn SM, et al. A positron emission tomographic study of symptom provocation in PTSD. *Ann N Y Acad Sci.* 1997;821:521-3.
22. Pissiota A, Frans O, Fernandez M, von Knorring L, Fischer H, Fredrikson M. Neurofunctional correlates of posttraumatic stress disorder: a PET symptom provocation study. *Eur Arch Psychiatry Clin Neurosci.* 2002;252:68-75.
23. Bremner JD, Narayan M, Staib LH, Southwick SM, McGlashum T, Charney DS. Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *Am J Psychiatry.* 1999;156:1787-1795.

24. Bremner JD, Staib LH, Kaloupek D, Southwick SM, Soufer R, Charney DS. Neural correlates of exposure to traumatic pictures and sound in vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. *Biol Psychiatry.* 1999;45:806-816.
25. Shin LM, McNally RJ, Kosslyn SM, et al. Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: A PET investigation. *Am J Psychiatry.* 1999;156:575-84.
26. Lanius RA, Williamson PC, Densmore M, et al. Neural correaltes of traumatic memories in posttraumatic stress disorder: a functional MRI investigation. *Am J Psychiatry.* 2001;158:1920-1922.
27. Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci.* 1998;18:411-8.
28. Rauch SL, Whalen PJ, Shin LM, et al. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biol Psychiatry.* 2000;47:769-76.
29. Shin LM, Whalen PJ, Pitman RK, et al. An fMRI study of anterior cingulate function in posttraumatic stress disorder. *Biol Psychiatry.* 2001;50:932-42.
30. Bremner JD, Vythilingam M, Vermetten E, et al. Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. *Biol Psychiatry.* 2003;53:879-89.
31. Bremner JD, Vythilingam M, Vermetten E, et al. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *Am J Psychiatry.* 2003;160:924-932.
32. Shin LM, Shin PS, Heckers S, et al. Explicit memory and hippocampal function in posttraumatic stress disorder. *Hippocampus.* (in press).
33. Gurvits TV, Shenton ME, Hokama H, et al. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biol Psychiatry.* 1996;40:1091-1099.
34. Rauch SL, Shin LM, Segal E, et al. Selectively reduced regional cortical volumes in posttraumatic stress disorder. *Neuroreport.* (in press).
35. Fyer AJ. Current approaches to etiology and pathophysiology of specific phobia. *Biol Psychiatry.* 1998;44:1295-304.
36. Menzies RG, Clarke JC. The etiology of phobias: a non-associative account. *Clin Psychol Rev.* 1995;15:23-48.
37. Wright CI, Martis B, McMullin K, Shin LM, Rauch SL. Amygdala and insular responses to emotionally valenced human faces in small animal specific phobia. *Biol Psychiatry.* 2003;54:1067-76.
38. Martis B, Wright CI, McMullin KG, Shin LM, Rauch SL. Functional MRI evidence for lack of striatal dysfunction during implicit sequence learning in individuals with animal phobia. *Am J Psychiatry.* (in press).
39. Wik G, Fredrikson M, Ericson K, Eriksson L, Stone-Elander S, Greitz T. A functional cerebral response to frightening visual stimulation. *Psychiatry Res Neuroimaging.* 1993;50:15-24.
40. Fredrikson M, Wik G, Greitz T, et al. Regional cerebral blood flow during experimental fear. *Psychophysiol.* 1993;30:126-130.
41. Fredrikson M, Wik G, Annas P, Ericson K, Stone-Elander S. Functional neuroanatomy of visually elicited simple phobic fear: additional data and theoretical analysis. *Psychophysiol.* 1995;32:43-48.
42. Rauch SL, Savage CR, Alpert NM, et al. A positron emission tomographic study of simple phobic symptom provocation. *Arch Gen Psychiatry.* 1995;52:20-8.
43. Paquette V, Levesque J, Mensour B, et al. "Change the mind and you change the brain": effects of cognitive-behavioral therapy on the neural correlates of spider phobia. *Neuroimage* 2003;18:401-9.
44. Adolphs R, Tranel D, Damasio AR. The human amygdala in social judgment. *Nature.* 1998;393:470-4.
45. Amaral DG. The primate amygdala and the neurobiology of social behavior: implications for understanding social anxiety. *Biol Psychiatry.* 2002;51:11-7.
46. Adolphs R, Tranel D, Damasio H, Damasio A. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature.* 1994;372:669-72.
47. Birbaumer N, Grodd W, Diedrich O, et al. fMRI reveals amygdala activation to human faces in social phobics. *Neuroreport.* 1998;9:1223-6.
48. Schneider F, Weiss U, Kessler C, et al. Subcortical correlates of differential classical conditioning of aversive emotional reactions in social phobia. *Biol Psychiatry.* 2000;45:863-871.
49. Stein MB, Goldin PR, Sareen J, Zorrilla LT, Brown GG. Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Arch Gen Psychiatry.* 2002;59:1027-34.
50. Gorman JM, Kent JM, Sullivan GM, Coplan JD. Neuroanatomical hypothesis of panic disorder, revised. *Am J Psychiatry.* 2000;157:493-505.
51. Coplan JD, Lydiard RB. Brain circuits in panic disorder. *Biol Psychiatry.* 1998;44:1264-76.
52. Papp LA, Klein DF, Gorman JM. Carbon dioxide hypersensitivity, hyperventilation, and panic disorder. *Am J Psychiatry.* 1993;150:1149-57.

53. Klein DF. False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis. *Arch Gen Psychiatry.* 1993;50:306-17.
54. Papp LA, Martinez JM, Klein DF, et al. Respiratory psychophysiology of panic disorder: three respiratory challenges in 98 subjects. *Am J Psychiatry.* 1997;154:1557-65.
55. Reiman EM, Raichle ME, Robins E, et al. The application of positron emission tomography to the study of panic disorder. *Am J Psychiatry.* 1986;143:469-477.
56. Nordahl TE, Semple WE, Gross M, et al. Cerebral glucose metabolic differences in patients with panic disorder. *Neuropsychopharmacology.* 1990;3:261-272.
57. Bisaga A, Katz JL, Antonini A, et al. Cerebral glucose metabolism in women with panic disorder. *Am J Psychiatry.* 1998;155:1178-1183.
58. De Cristofaro MT, Sessarego A, Pupi A, Biondi F, Faravelli C. Brain perfusion abnormalities in drug-naive, lactate-sensitive panic patients: a SPECT study. *Biol Psychiatry.* 1993;33:505-12.
59. Bystritsky A, Pontillo D, Powers M, Sabb FW, Craske MG, Bookheimer SY. Functional MRI changes during panic anticipation and imagery exposure. *Neuroreport.* 2001;12:3953-7.
60. Woods SW, Koster K, Krystal JK, et al. Yohimbine alters regional cerebral blood flow in panic disorder. *The Lancet.* 1988;2:678.
61. Boshuisen ML, G.J. TH, Paans AM, Reinders AA, den Boer JA. rCBF differences between panic disorder patients and control subjects during anticipatory anxiety and rest. *Biol Psychiatry.* 2002;52:126-35.
62. Reiman EM, Raichle ME, Robins E, et al. Neuroanatomical correlates of a lactate-induced anxiety attack. *Arch Gen Psychiatry.* 1989;46:493-500.
63. Vythilingam M, Anderson ER, Goddard A, et al. Temporal lobe volume in panic disorder—a quantitative magnetic resonance imaging study. *Psychiatry Res.* 2000;99:75-82.
64. Massana G, Serra-Grabulosa JM, Salgado-Pineda P, et al. Parahippocampal gray matter density in panic disorder: a voxel-based morphometric study. *Am J Psychiatry.* 2003;160:566-568.
65. Rauch SL, Savage CR, Brown HD, et al. A PET investigation of implicit and explicit sequence learning. *Hum Brain Mapping.* 1995;3:271-286.
66. Rauch SL, Savage CR, Alpert NM, et al. Probing striatal function in obsessive-compulsive disorder: a PET study of implicit sequence learning. *J Neuropsychiatry Clin Neurosci.* 1997;9:568-73.
67. Houk JC, Davis JL, Beiser DG. *Models of Information Processing in the Basal Ganglia*. Cambridge: MIT Press, 1995:1-382.
68. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci.* 1986;9:357-81.
69. Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res.* 1990;85:119-46.
70. Rauch SL, Jenike MA. Neurobiological models of obsessive-compulsive disorder. *Psychosomatics.* 1993;34:20-32.
71. Rauch SL, Whalen PJ, Dougherty DD, Jenike MA. Neurobiological Models of Obsessive-Compulsive Disorders. In: Jenike M, ed. *Obsessive-Compulsive Disorders: Theory and Management*. Philadelphia: Mosby Year Book, Inc., 1997.
72. Jenike MA, Breiter HC, Baer L, et al. Cerebral structural abnormalities in obsessive-compulsive disorder. A quantitative morphometric magnetic resonance imaging study. *Arch Gen Psychiatry.* 1996;53:625-32.
73. Baxter LR, Jr., Schwartz JM, Mazziotta JC, et al. Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. *Am J Psychiatry.* 1988;145:1560-3.
74. Swedo SE, Schapiro MB, Grady CL, et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. *Arch Gen Psychiatry.* 1989;46:518-23.
75. Nordahl TE, Benkelfat C, Semple WE, Gross M, King AC, Cohen RM. Cerebral glucose metabolic rates in obsessive compulsive disorder. *Neuropsychopharmacology.* 1989;2:23-8.
76. Machlin SR, Harris GJ, Pearlson GD, Hoehn-Saric R, Jeffery P, Camargo EE. Elevated medial-frontal cerebral blood flow in obsessive-compulsive patients: a SPECT study. *Am J Psychiatry.* 1991;148:1240-2.
77. Perani D, Colombo C, Bressi S, et al. [18F]FDG PET study in obsessive-compulsive disorder. A clinical/metabolic correlation study after treatment. *Br J Psychiatry.* 1995;166:244-50.
78. Rauch SL, Jenike MA, Alpert NM, et al. Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. *Arch Gen Psychiatry.* 1994;51:62-70.
79. Breiter HC, Rauch SL, Kwong KK, et al. Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. *Arch Gen Psychiatry.* 1996;53:595-606.
80. McGuire PK, Bench CJ, Frith CD, Marks IM, Frackowiak RS, Dolan RJ. Functional anatomy of obsessive-compulsive phenomena. *Br J Psychiatry.* 1994;164:459-68.
81. Benkelfat C, Nordahl TE, Semple WE, King AC, Murphy DL, Cohen RM. Local cerebral glucose metabolic rates in obsessive-compulsive disorder. Patients treated with clomipramine. *Arch Gen Psychiatry.* 1990;47:840-8.

82. Baxter LR, Jr., Schwartz JM, Bergman KS, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. *Arch Gen Psychiatry.* 1992;49:681-9.
83. Swedo SE, Pietrini P, Leonard HL, et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Revisualization during pharmacotherapy. *Arch Gen Psychiatry.* 1992;49:690-4.
84. Schwartz JM, Stoessel PW, Baxter LR, Jr., Martin KM, Phelps ME. Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry.* 1996;53:109-13.
85. Mataix-Cols D, Cullen S, Lange K, et al. Neural correlates of anxiety associated with obsessive-compulsive symptom dimensions in normal volunteers. *Biol Psychiatry.* 2003;53:482-93.
86. Franklin ME, Abramowitz JS, Kozak MJ, Levitt JT, Foa EB. Effectiveness of exposure and ritual prevention for obsessive-compulsive disorder: randomized compared with nonrandomized samples. *J Consult Clin Psychol.* 2000;68:594-602.
87. Piccinelli M. Comorbidity of depression and generalized anxiety: is there any distinct boundary? *Curr Opin Psychiatry.* 1998;11:57-60.
88. Uhde TW, Boulenger JP, Roy-Byrne PP, Geraci MF, Vittone BJ, Post RM. Longitudinal course of panic disorder: clinical and biological considerations. *Prog Neuropsychopharmacol Biol Psychiatry.* 1985;9:39-51.
89. Akiskal HS. Toward a definition of generalized anxiety disorder as an anxious temperament type. *Acta Psychiatr Scand Suppl.* 1998;393:66-73.
90. Montgomery SA, Mahe V, Haudiquet V, Hackett D. Effectiveness of venlafaxine, extended release formulation, in the short-term and long-term treatment of generalized anxiety disorder: results of a survival analysis. *J Clin Psychopharmacol.* 2002;22:561-7.
91. Buchsbaum MS, Wu J, Haier R, et al. Positron emission tomography assessment of effects of benzodiazepines on regional glucose metabolic rate in patients with anxiety disorder. *Life Sci.* 1987;40:2393-400.
92. Wu JC, Buchsbaum MS, Hershey TG, Hazlett E, Sicotte N, Johnson JC. PET in generalized anxiety disorder. *Biol Psychiatry.* 1991;29:1181-99.
93. Tiihonen J, Kuikka J, Rasanen P, et al. Cerebral benzodiazepine receptor binding and distribution in generalized anxiety disorder: a fractal analysis. *Mol Psychiatry.* 1997;2:463-71.