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. 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. 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, Building 149, Thirteenth Street, Charlestown, MA 02129; Tel: (617) 724-9553; Fax: (617) 726-4078; E-mail: rauch@psych.mgh.harvard.edu.
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pathological anxiety in humans and conditioned fear in animals share similar brain mechanisms. 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. 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. CNA efferents extend to the parabrachial nucleus, causing tachypnea, to the lateral hypothalamus, which initiates the sympathetic response, to the locus coeruleus, causing increases in blood pressure and heart rate as well as initiating the behavioral response to fear, and to the paraventricular nucleus of the hypothalamus, resulting in activation of the hypothalamic–pituitary–adrenal (HPA) axis, which stimulates increases in adrenocorticoids. 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. 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.\textsuperscript{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.\textsuperscript{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.
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. Based on evidence from animal and clinical studies, Charney and Bremner have also reported a working model of PTSD, which in addition to amygdala, hippocampus, and prefrontal cortex, involves locus coeruleus, thalamus, hypothalamus, and periaqueductal 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. 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, decreased responses within medial frontal areas, and more pronounced deactivation within other heteromodal frontal cortical regions. 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, Rauch and colleagues found that subjects with PTSD exhibited greater amygdala reactivity than trauma-exposed subjects without PTSD. 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.

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, and during encoding of a narrative paragraph. Likewise, firefighters with PTSD compared to firefighters without PTSD were found to have decreased hippocampal activation during a word stem completion task. 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. Furthermore, investigators have reported correlations between hippocam-
pal volume and verbal memory as well as indices of trauma exposure and symptom severity. 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.

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...
many individuals with phobias cannot recall an initial conditioning event. Nonassociative models seek to address the observation that certain intense fears can exist without prior exposure to the phobic stimulus. Menzies and Clarke 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. 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. 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. In contrast to these reports, Rauch et al. 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.

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, models of social phobia have also focused on the amygdala. The model proposed by Amaral et al., 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, 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. 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. 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. 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).

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=periaqueductal gray; PBN=parabrachial nucleus; SC=subcallosal cortex.

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 or attribute PD to miscommunication between serotonergic and noradrenergic systems, previous models have pointed to abnormal brain stem responsiveness to carbon dioxide (ie, “false suffocation alarm”) as the primary pathology underlying PD.

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, the possibility remains that panic attacks are in fact triggered by implicit external cues (ie, cues of which the individual remains unaware).

The Neural Circuitry of Social Phobia

(Implanted sites of pathophysiology in white)
Numerous resting state studies of panic disorder have suggested abnormalities within the temporal lobe, including hippocampal and parahippocampal structures. Reiman et al., 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. 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. De Cristofaro et al. 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. 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 as well as anterior insula and ACC. In the setting of hypocapnia in lactate-sensitive PD subjects compared with healthy controls and non-lactate-sensitive PD subjects, Reiman et al. 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. found reduced temporal cortical volumes bilaterally (with no hippocampal volume differences), whereas Massana et al. 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
revealed increased activity in orbitofrontal cortex (OFC), ACC, and striatum in OCD subjects as compared to healthy controls. Furthermore, symptom provocation studies of OCD subjects have demonstrated OFC, ACC, and striatal activations in the symptomatic state versus the control neutral state. Treatment response studies have shown reduced hyperactivity in these same structures following behavioral and pharmacotherapy of OCD.

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. found a significant correlation between amygdala activation and increases in OCD symptom-related anxiety. Furthermore, exposure-based behavioral treatment of OCD 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

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**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=periaqueductal gray; PBN=parabrachial nucleus; SC=subcallosal cortex.

other disorders, such as MDD\textsuperscript{87} or panic disorder,\textsuperscript{88} or even a markedly anxious temperament.\textsuperscript{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.\textsuperscript{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,\textsuperscript{91} as well as cortex, limbic regions, and basal ganglia\textsuperscript{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.\textsuperscript{93} While it is premature to draw meaningful conclusions about the neural circuitry of GAD, it appears that serotonin, norepinephrine, and $\gamma$-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.
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