Neurobiology and Etiology of Panic Disorder

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Panic disorder entered the psychiatric nomenclature a quarter-century ago, and an explosion of studies followed. Defining the core phenomenology of panic disorder can be advanced by an understanding of its pathophysiology and exploration of its etiology. The lessons learned can guide the delivery of treatments to enhance the likelihood of achieving remission and the discovery of novel treatments for panic disorder. *(J Clin Psychiatry 2005;66[suppl 4]:3–7)*

Advancing our understanding of a mental illness like panic disorder requires the recursive relating of knowledge gained in one area to information in another and progressively repeating the exercise. Wisdom is the ability to emphasize the knowledge that would provide the critical wedge. This article attempts to explore selectively the neurobiology of panic disorder using such a technique, and review genetic contributions.

THE PANIC DISORDER PHENOTYPE

As currently defined, panic attacks lie at the core of panic disorder. A panic attack requires a rapid crescendo of emotionally intense anxiety (expressed as fear/discomfort as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [DSM-IV] criteria) that peaks within 10 minutes. Additionally, at least 4 of 13 associated symptoms must co-occur for the event to qualify as a panic attack. These symptoms can be broadly (and somewhat arbitrarily) divided into psychic and somatic ones. Psychic symptoms include fear of dying, dissociation (derealization/depersonalization), and social concerns of behaving inappropriately (losing control or "going crazy"). Somatic symptoms include cardiac (palpitations, chest pain, dizziness), respiratory (shortness of breath, choking, paresthesias, and dizziness from hyperventilating), gastrointestinal (nausea), motor (trembling), and autonomic (sweating, chills) symptoms. The most common symptoms in a panic attack involve autonomic, cardiac, and (especially in women) respiratory ones.[1]

The phenotype of panic disorder, however, needs clarification.[2] Panic attacks were historically perceived as a severe expression of anxiety. Recognition of panic disorder as a separate entity from generalized anxiety disorder (GAD) occurred in 1978 with the publication of DSM-III. However, the *International Classification of Diseases*, 9th Revision (ICD-9), also published in 1978 by the World Health Organization, disagreed. It continued to define "anxiety states" as "occurring either in attacks or as a persisting state," and stated that "anxiety is usually diffuse and may extend to panic."[3(p553)] Panic disorder included panic attacks and its consequences—the anticipation with anxiety of another panic attack (symptomatically similar to general anxiety) and the potential for avoidance behaviors. Depression is also a common derivative of panic attacks, although given its independent diagnostic label, its presence is considered a comorbidity.

An apparent driver behind the DSM-III distinction was the dissociation of pharmacologic responsivity. Anxiety disorders as a group were differentiated from the depressive disorders partly because the classes of medications effective for them were different. Thus "minor tranquilizers" such as benzodiazepines were effective for anxiety, whereas "antidepressants" like the tricyclic antidepressants (TCAs, e.g., imipramine) were effective in major depression. However, the seminal work of Klein[4] demonstrated that panic disorder responded to TCAs. At that time, the belief was that general anxiety was not TCA responsive, and thus began the effort to separate panic from general anxiety. Clinical studies soon questioned the assumption that TCAs were ineffective in general anxiety, as a controlled trial demonstrated the efficacy of a TCA in GAD.[5] Thus, the panic disorder/GAD diagnostic separation did not reflect pharmacologic specificity. Is there neurobiological evidence supporting partition of panic disorder from GAD?

Affective neuroscience has demonstrated that the anxiety/fear response is a protective, evolutionarily main-

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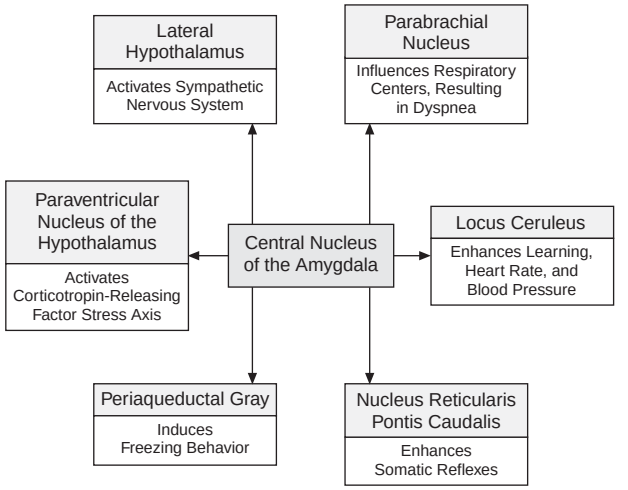
Figure 1. Anxiety Responses Emanating From the Central Nucleus of the Amygdala via Output Pathways



tained, unconditioned response that is "hardwired" into the brain.[6] The anxiety response includes, among others, a set of defensive behaviors, autonomic arousal, and potentiation of somatic reflexes. The functional anatomy of the anxiety response has an amygdala-centered neurocircuit.[7] Its output pathways emanate from the central nucleus of the amygdala, and their activation can potentially explain the various symptoms that comprise anxiety (Figure 1). Thus, output to the lateral hypothalamus activates the sympathetic nervous system; output to the parabrachial nucleus influences the respiratory centers, resulting in dyspnea; output to the periaqueductal gray induces freezing behavior; output to the nucleus reticularis pontis caudalis enhances somatic reflexes; output to the locus ceruleus enhances learning, heart rate, and blood pressure; and output to the paraventricular nucleus of the hypothalamus activates the corticotropin-releasing factor stress axis. These responses are intrinsic and do not have to be learned. What are learned are the associations of the aversive threats with the triggering of the anxiety response—the "conditioning" of anxiety.

How is the amygdala differentially involved in GAD from panic disorder? The symptom criteria for panic attacks versus GAD overlap because of the common core of emotional anxiety, which includes excessive threat assessment and arousal—functions largely mediated by the amygdala.[8] A component of the extended amygdala, the bed nucleus of the stria terminalis (BNST), may mediate the more diffuse symptoms of GAD.[9] Muscle tension seems to be differentially prominent in GAD, while cardiac, respiratory, and autonomic symptoms abound in panic disorder.[10] Are these differences derived from the episodic/continuous nature of panic disorder/GAD, or are they a reflection of differential emphasis in the input/output of the amygdala/BNST? Since the anxiety response is triggered by threat, the nature of the threat will influence the response. Thus, for example, if the heart stops beating, brain functions end shortly thereafter. Similarly, if respiration is acutely impeded (e.g., in choking), the time period for continued brain functioning is limited to a few minutes. Hence, the anxiety response will be initiated quickly and peak rapidly. Are the symptoms most commonly experienced in panic attacks the result of the threat being perceived in the cardiac and respiratory systems with a parallel or consequent arousal of the autonomic nervous system? Would this be the basis for the DSM-IV panic attack criteria requiring abrupt development and a peak reached within 10 minutes?

Evidence of a respiratory trigger for panic is supported by laboratory challenges that can reliably induce panic attacks. Thus, lactate infusions and breathing 35% carbon dioxide[11] induce panic attacks in individuals with a current or past history of panic attacks. This respiratory triggering of panic attacks occurs more frequently in panic disorder than in other anxiety (e.g., GAD) and mood disorders. In the cardiac arena, paroxysmal supraventricular tachycardia (PSVT) mimics panic disorder. In a study of 107 consecutive patients with PSVT, 67% met criteria for panic disorder.[12] Following successful treatment of the PSVT (largely, ablation of the triggering site), 96% of the patients were free of panic disorder at follow-up. Dysautonomia has also been associated with panic disorder.[13,14]

Hence, the argument can be made that the sudden triggering of the anxiety response is the key difference between panic disorder and GAD. A treatment that reduces the amygdala-mediated activation of the anxiety response (e.g., benzodiazepines and most antidepressants) would therefore be effective for both panic disorder and GAD. A corollary hypothesis is that for subtypes of panic disorder with triggers emanating from the cardiac, respiratory, and autonomic nervous systems, treatments specifically inhibiting or preventing their end-organ activation will be effective, even if they do not directly affect the amygdala. Such treatments should not be effective for GAD.

NEUROBIOLOGY OF PANIC DISORDER

The sequence of events in a prototypical panic attack and what follows can be matched with the potential neurobiological alterations derived from neuroscientific knowledge. For example: a young lady driving on an interstate experiences an unexpected panic attack. Some confluence of events triggers the amygdala, the central command switch, which activates a fixed action pattern of responses in her brain and the body, as though she is under life-threatening attack. She pulls over to the side of the road, paralyzed with fear. After a few minutes, the worst is over, and she gathers up her courage and slowly drives to the safety of her home. The experience is terrifying and leaves

an emotional memory—a strengthening of synapses in the lateral nucleus of the amygdala that represent the experience.[15] Subsequent experiences, either actual or anticipated, that match components of that emotional memory, now trigger the anxiety response—her anxiety has become "conditioned."

The conventional or "explicit" memory system also remembers the panic attack. Explicit memory involves the hippocampus as its hub and is crucial for the autobiographical memory of the attack. However, it is in the role of recording the *context* in which the panic attack occurs that the hippocampus has greatest relevance to the anxiety response. Contextual conditioning serves to anticipate potentially threatening situations. Thus the interstate, for example, is now associated with the panic attack, and driving on one may elevate the potential for another panic attack. Although not previously connected with fear, driving is now associated with a heightened sense of vigilance and anxiety, the result of contextual conditioning. The anticipation of interstate driving may become dysphoric, and the situation may therefore be avoided. The functional anatomy of such avoidance involves the medial/orbital prefrontal cortex and its reciprocal connections with the amygdala. Excessive activation of the amygdala decreases prefrontal activity, which in turn reduces its inhibitory control of the amygdala.[16,17] Thus the learning of new information that may counter the initial association (a process called *extinction*) is impaired—the conditioned avoidance becomes lasting.

The amygdala, hippocampus, and prefrontal cortex are the critical "joints" that connect the components of the experience of anxiety. Since there is a separate anatomy and neurochemistry to these hubs, they can each have variable thresholds for their activation. Pretreatment with a β-blocker prior to a trauma may prevent the emotional imprinting of the traumatic experience.[18] The development of conditioned anxiety is mediated by dopamine receptors in the amygdala, leading to facilitation of the declarative memory associations through the hippocampus.[19] LeDoux[6] suggests that avoidance conditioning is mediated through the prefrontal cortex and also involves dopamine receptors. Agonism at the dopamine D_1 receptor can suppress the ability of the prefrontal cortex to inhibit amygdala activity, and dopamine D_2 agonism enhances the excitability of lateral amygdala neurons.[16]

If one matches the components of panic attacks, anticipatory/general anxiety, and phobic avoidance with the previously described functional anatomy, one can potentially explain the varying presentations of panic disorder and the dilemmas with diagnostic boundaries. If the baseline activity of the amygdala is set tonally high (from, for example, high anticipatory anxiety or temperament) the likelihood that another stimulus will trigger a panic attack increases. If the hippocampally mediated explicit memory is constantly triggered by conscious associations to the panic attack (including struggling hard to "forget" the experience), it increases the likelihood of another panic attack. If there is a history of behavioral inhibition in childhood, there may be a temperamental skewing toward avoidance, increasing the likelihood of developing a phobia of driving on the interstate or driving per se. The permutations and combinations of possibilities are numerous.

Why do some individuals and not others develop avoidance after a panic attack? There are well-characterized premorbid differences between individuals (e.g., personality, temperament, genetic disposition) that lead some toward avoidance behaviors, independent of a panic attack. A set of behaviors in the toddler years, labeled *behavioral inhibition* by Kagan et al.,[20] appears to enhance the potential for avoidance. The central characteristic of these behaviors is the inhibition of spontaneous behavior in the face of novelty (neophobia). New situations are perceived as more unpredictable compared to familiar situations. Follow-up studies of adults who displayed behavioral inhibition as children demonstrate an enhanced likelihood of social avoidance.[21]

Could the characteristics of the panic attack also play a role in the potential for developing avoidance? Animal studies demonstrate that if an aversive event (e.g., a panic attack) is immediately preceded by a specific stimulus (e.g., the freeway on-ramp), the stimulus will be avoided, as approaching it has been "punished" by the aversive event. On the other hand, if the aversive event has longer aftereffects (i.e., the panic attack is of extensive duration), a stimulus associated with its termination may be reinforced and behaviorally lead to approach, not avoidance.[22] Bidirectional plasticity (synaptic depression or potentiation) in circuits is driven by such nuances of timing. Behavior therapists have argued that sustained voluntary exposure to an anxiety trigger overcomes the associated negative reinforcement that had previously led to avoidance.

Nomenclature craves clear boundaries for categories. The neurobiology underlying panic disorder with its highly interrelated components (panic attacks, anticipatory/general anxiety, phobia) is reflective of neurocircuits that may be separate but not independent. Hence, pathologies can exist in each domain separately, or pathologies in one domain can derail others. The fundamental question is, at what point should a symptom or a symptom profile be worthy of a separate diagnostic label? The DSM iterations made these choices, often arbitrarily or with little data. Agoraphobia was a separate diagnosis from panic disorder in DSM-III; it became a subtype of panic disorder in DSM-III-R (the ICD-10 made the opposite choice, giving agoraphobia priority over panic disorder when they were comorbid). Should the presence of consistent anticipatory anxiety result in the additional diagnosis of GAD? In the presence of a few panic attacks, should the anxiety and avoidance of a gathering be considered social phobia or

agoraphobia? Should avoidance of interstates alone following panic attacks be diagnosed as panic disorder or a specific phobia? Does it matter? Probably, given that some components respond better to certain treatments. Thus antidepressants appear to be best at controlling the panic attacks and anticipatory anxiety, with secondary benefit for avoidance. Behavior therapy (a form of psychotherapy), on the other hand, directly targets avoidance. Thus, intelligent combinations of treatments enhance the potential for the achievement of remission in all domains of symptoms.

ETIOLOGY OF PANIC DISORDER

Examining the etiology of a complex illness like panic disorder is daunting, given that genes can function only within the environmental context.[23] On the basis of studies of panic disorder in families and twins,[24] the heritable contribution of genes to the development of the disorder is estimated as 0.48, using a summary odds ratio by means of the Mantel-Haenszel method, with the remaining proportion derived largely from the individual's environment. Nongenetic factors such as life events,[25] or other factors such as cigarette smoking,[26] have been linked to panic attacks/disorder. Thus, suggestive evidence from genetic studies supports the diagnostic distinction of panic disorder, although the diagnostic characterizations in these studies are by and large static labels, whereas the clinical illness is dynamic, with evolving symptoms and comorbidities.

The genetic contribution to the risk for panic disorder/panic attacks may be general or specific. The genetic contribution may play a role in some component of the vulnerability for panic attacks. Thus, the concordant induction of panic attacks by 35% carbon dioxide breathing is greater in monozygous compared to dizygous twins.[27]

Genome-wide scans have reported significant association of broadly defined panic disorder (inclusive of other anxiety disorders) with chromosomes 9,[28] 13,[29] and 22.[29] Gelernter and colleagues[30] reported suggestive linkage to chromosomes 1 and 11 for panic disorder and chromosome 3 for agoraphobia. Comorbidity of panic disorder in a subtype of bipolar disorder has been linked to chromosome 18.[31] Candidate gene studies report association with the cholecystokinin B receptor allele 7[32] and the L/L genotype of the catecholamine *O*-methyltransferase (COMT) polymorphism with panic disorder.[33]

Chromosomal linkage information still requires the identification of the specific gene, its gene product, the mechanisms controlling its expression, its role in triggering or modifying the expression of the disorder, etc. There is a need for a conceptual model of how a gene may code for the vulnerability of the components of panic disorder along the lines of COMT, frontal lobe function, and risk for schizophrenia.[34] Etiology of panic disorder will then be tied to pathophysiology, phenomenology, and the mechanism of treatment response. The efforts to discover novel treatments will also have new targets. Combining treatments, if necessary, will be based on knowledge rather than random decisions, and a larger proportion of individuals with panic disorder can achieve remission of their illness.

CONCLUSION

Panic disorder is a common and complex anxiety disorder whose diagnostic boundaries are still fluid. However, examining its clinical phenomenology from the perspective of its underlying neurobiology, and ultimately etiology, adds new dimensions to our understanding of it. Such advances will allow the clinician to prescribe treatments in the contexts of pathophysiology and evidence-based knowledge to help patients achieve remission.

Drug name: imipramine (Tofranil and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, imipramine is not approved by the U.S. Food and Drug Administration for the treatment of panic disorder.

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