

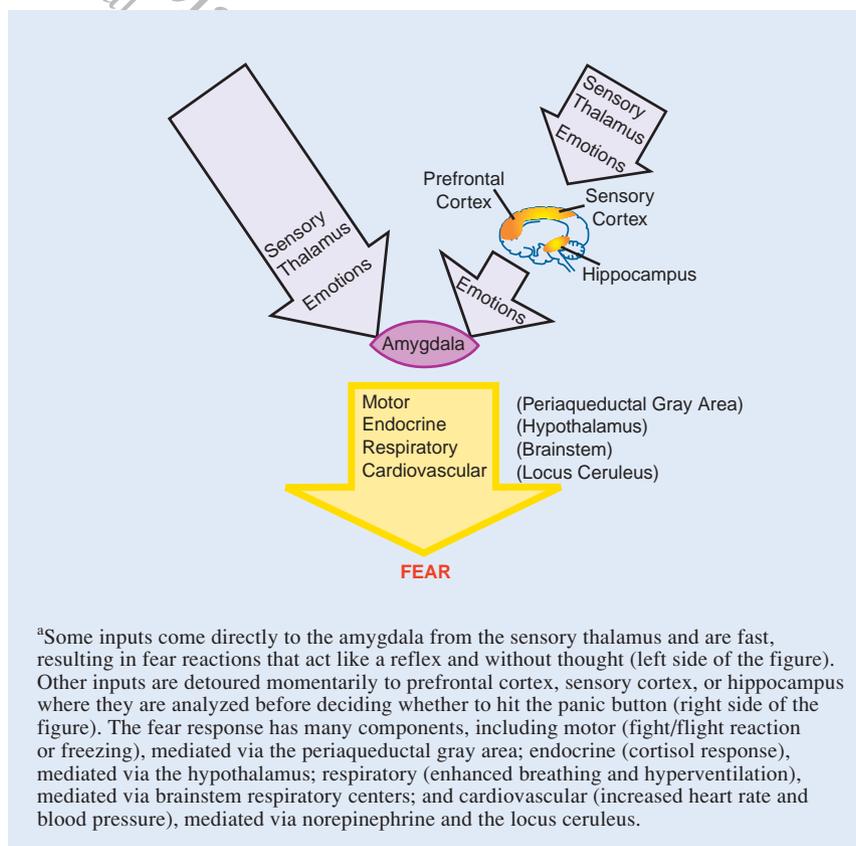
# Independent Actions on Fear Circuits May Lead to Therapeutic Synergy for Anxiety When Combining Serotonergic and GABAergic Agents

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**Issue:** Both serotonin and GABA powerfully regulate the neuroanatomical circuit that mediates fear in anxiety disorders. This suggests that use of pharmacotherapies acting on both systems may provide synergistic therapeutic actions.

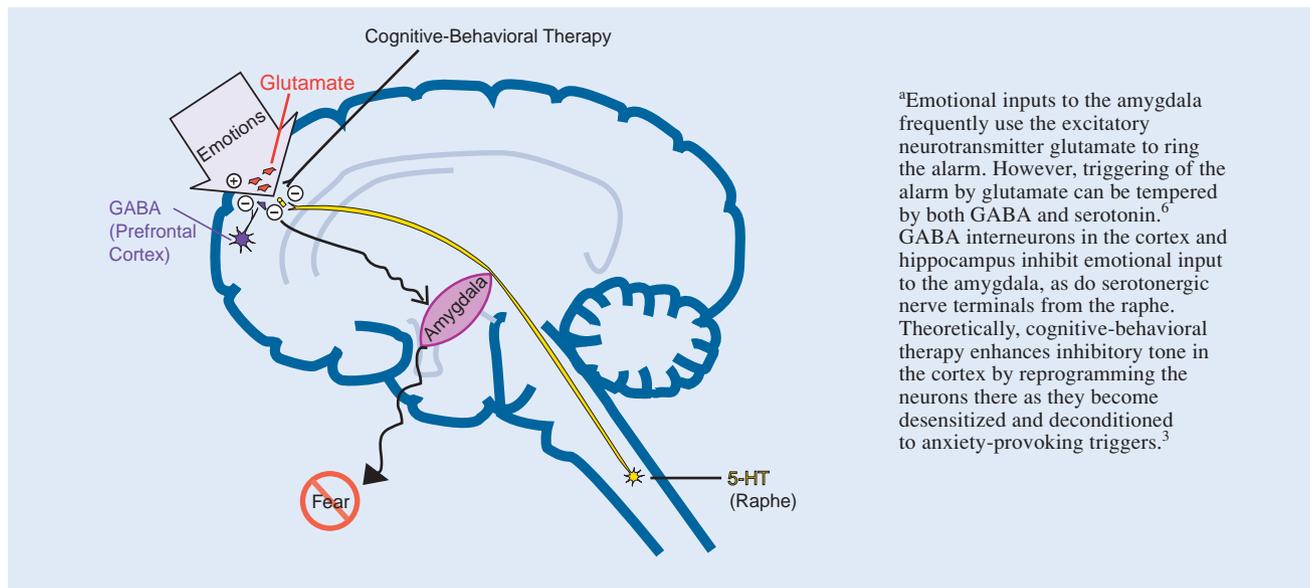
**I**n last month's BRAINSTORMS,<sup>1</sup> we discussed the fact that benzodiazepines are still the leading treatments for anxiety disorders, despite their limitations and being relegated to second-line use in modern treatment guidelines. Benzodiazepines act upon GABAergic neurotransmission to enhance neuronal inhibition<sup>2</sup> and are frequently used along with antidepressants that enhance serotonergic neurotransmission for the treatment of anxiety disorders today.<sup>1</sup> Here we illustrate the neuroanatomical substrate of fear, showing that both GABA and serotonin have inhibitory actions on the output of the fear response from the amygdala.<sup>3-5</sup>

Figure 1.  
The Amygdala Is the Brain's Panic Button<sup>a</sup>



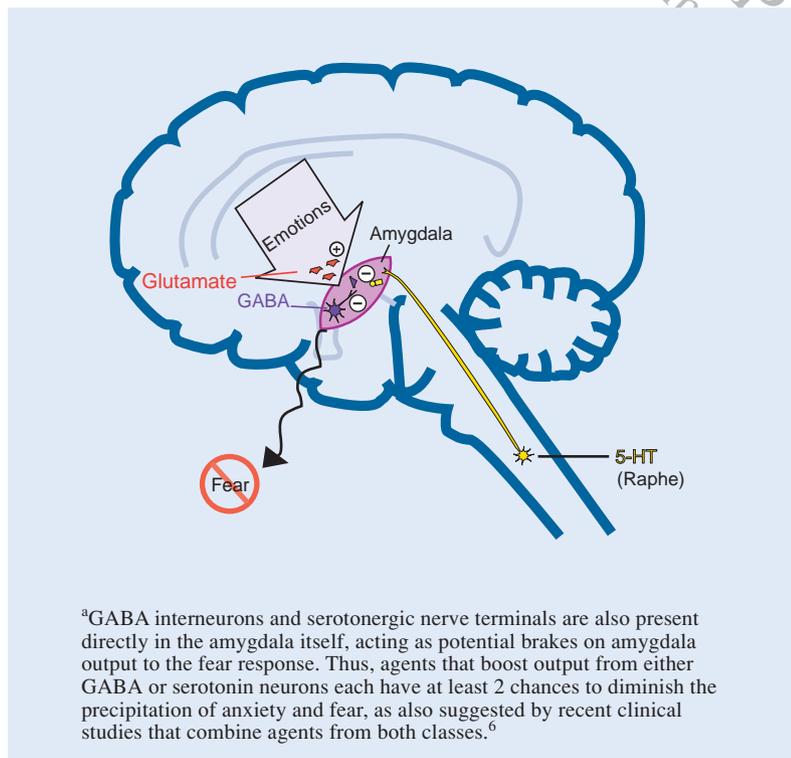
<sup>a</sup>Some inputs come directly to the amygdala from the sensory thalamus and are fast, resulting in fear reactions that act like a reflex and without thought (left side of the figure). Other inputs are detoured momentarily to prefrontal cortex, sensory cortex, or hippocampus where they are analyzed before deciding whether to hit the panic button (right side of the figure). The fear response has many components, including motor (fight/flight reaction or freezing), mediated via the periaqueductal gray area; endocrine (cortisol response), mediated via the hypothalamus; respiratory (enhanced breathing and hyperventilation), mediated via brainstem respiratory centers; and cardiovascular (increased heart rate and blood pressure), mediated via norepinephrine and the locus coeruleus.

Figure 2. GABA and Serotonin, and Presumably Successful Cognitive-Behavioral Therapy, From Brain Sources Outside the Amygdala Inhibit Amygdala Alarms<sup>a</sup>



<sup>a</sup>Emotional inputs to the amygdala frequently use the excitatory neurotransmitter glutamate to ring the alarm. However, triggering of the alarm by glutamate can be tempered by both GABA and serotonin.<sup>6</sup> GABA interneurons in the cortex and hippocampus inhibit emotional input to the amygdala, as do serotonergic nerve terminals from the raphe. Theoretically, cognitive-behavioral therapy enhances inhibitory tone in the cortex by reprogramming the neurons there as they become desensitized and deconditioned to anxiety-provoking triggers.<sup>3</sup>

Figure 3. GABA and Serotonin From Inside the Amygdala Inhibit Amygdala Alarms<sup>a</sup>



<sup>a</sup>GABA interneurons and serotonergic nerve terminals are also present directly in the amygdala itself, acting as potential brakes on amygdala output to the fear response. Thus, agents that boost output from either GABA or serotonin neurons each have at least 2 chances to diminish the precipitation of anxiety and fear, as also suggested by recent clinical studies that combine agents from both classes.<sup>6</sup>

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