

Symptoms and Circuits, Part 2

Anxiety Disorders

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Issue: *Numerous anxiety disorders may have malfunctioning neuronal circuits in common, which may account for the overlapping symptoms and frequent comorbidity of many anxiety disorders with one another.*

A paradigm shift is occurring in conceptualizing the biological basis of psychiatric disorders, namely the notion of “symptoms and circuits.”^{1,2} Psychiatric syndromes are being deconstructed into their symptoms and then matched to hypothetically malfunctioning neuronal circuits that can potentially not only explain the genesis of these symptoms but also provide a target for therapeutic agents to relieve these symptoms. We have already discussed this idea in relationship to major depressive disorder (MDD).³ Here we discuss how symptoms and circuits are relevant to a modern formulation of anxiety disorders (Table 1). Next month we will discuss how symptoms and circuits apply to schizophrenia.

Overlapping Symptoms, Overlapping Circuits

Many different anxiety disorder subtypes have been defined as distinct diagnostic entities based upon unique

symptom profiles.⁴ Constructing a diagnosis of one anxiety disorder versus another thus requires taking an inventory of current symptoms and making a certain diagnosis only when specified diagnostic criteria are satisfied. Recently, the usefulness of this approach both for clinical practice and for biological research has been questioned, since most patients exhibit different symptoms over time and thus metamorphose from one disorder to another or add a second anxiety disorder or MDD to their original anxiety disorder as their symptoms evolve.^{1,2,5,6} Furthermore, treatments for one anxiety disorder are often the same as for another, and the same malfunctioning circuits are implicated in symptoms of fear and worry across many anxiety disorders.⁵⁻⁹ Thus, the emphasis now is on deconstructing anxiety disorders into their individual symptoms.^{7,9,10}

Different Types of Fear in Different Anxiety Disorders?

The amygdala becomes activated whenever fear is provoked, not only in patients with an anxiety disorder, but also in normal controls.^{5,7} This is not surprising, because fear can be a normal emotion and can even be useful when it leads to adaptive behaviors. Fear can also be abnormal and interfere with a person’s normal functioning if it is present all the time, is

unpredictable, or occurs at inappropriate times. These variations of fear suggest that the often helpful emotion of normal fear may be mediated by the same circuit that mediates abnormal fear in anxiety disorders. In anxiety disorders, however, the fear circuit seems to discharge when it should not. For example, catastrophic output from the amygdala could mediate the unpredictable panic attacks of panic disorder, the situationally triggered panic attacks of social anxiety disorder, and the reexperiencing of post-traumatic stress disorder (PTSD) triggered by emotional or sensory memories. Chronically overactive output from the amygdala could mediate generalized anxiety disorder’s unremitting symptoms of anxiety, restlessness, irritability, and feeling “keyed up” and “on edge.”

Does Anxious Misery Differ in Various Anxiety Disorders?

Thinking about one’s misery can be appropriate, especially if it leads to corrective action. Thus, worry can often serve a purpose. However, when it is excessive or inappropriate, it can interfere with normal functioning and become a symptom of an anxiety disorder. A reverberating circuit from orbitofrontal cortex to striatum to thalamus and back to prefrontal cortex may mediate the thoughtful contemplation of planning and

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organizing as well as the symptoms of worry and obsessing.^{10,11} Overactivity of this circuit is one hypothetical explanation of the worry of generalized anxiety disorder, the obsessions of obsessive-compulsive disorder, and the worry about having more symptoms in panic disorder, social anxiety disorder, and PTSD.

Neurotransmitters, Circuits, and Novel Treatment Strategies

Clinicians are always interested in finding therapeutic options for patients with inadequate responses to therapeutic agents, and the notion of symptoms and circuits suggests a therapeutic rationale for combining agents that have independent actions on whatever circuit is conceptualized as mediating the residual symptoms. Thus, combining serotonergic agents with GABAergic agents is already widely recognized to improve symptoms in numerous anxiety disorders.⁹ Adding agents with novel mechanisms of action to serotonergic and GABAergic agents may provide even greater symptom relief in the future. The concept of symptoms and circuits in anxiety may have implications beyond helping to explain the biological basis of symptoms in anxiety disorders; it may also give clinicians a therapeutic strategy for selecting and combining current and future agents to achieve remission of all symptoms and improve patient outcomes.

Take-Home Points

- ◆ On the one hand, malfunctioning within an amygdala-centered circuit may be a common neurobiological substrate for fear-related symptoms in many anxiety disorders.
- ◆ On the other hand, malfunctioning within a cortico-striato-thalamic-cortical circuit may be a common neurobiological substrate for “anxious misery” and worry-related symptoms in many anxiety disorders.
- ◆ Since these circuits can manifest a diverse range of abnormal activating responses, they may generate a whole portfolio of fear- and worry-related symptoms across numerous anxiety disorders.
- ◆ A neurobiologically informed treatment strategy to attain remission of symptoms and thus an improved outcome for patients with a wide range of anxiety disorders calls for targeting the neurotransmitters and receptors that regulate hypothetically malfunctioning neuronal circuits mediating the portfolio of symptoms being experienced by each individual patient.

Table 1. Hypothetical Topography of Some Key Symptoms in Anxiety Disorders

Symptom	Circuit
Fear (panic, phobia)	Episodic but catastrophic output from the amygdala and from projections to and from medial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex
Worry (anxious misery, apprehensive expectation, obsessions)	Continuously excessive activity in orbitofrontal projections to striatum, striatum to thalamus, and thalamus back to prefrontal cortex
Reexperiencing	Hippocampal memories triggering catastrophic emotional output via the amygdala
Restlessness (feeling “keyed up” or “on edge,” increased arousal, irritability)	Surges of increased output from elevated baseline activity within projections to and from the amygdala as well as within projections to and from medial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex
Anxious avoidance	Periaqueductal gray matter and motor output
Compulsions	Corticostriatal outputs
Muscle tension	Motor output to spinal cord
Fatigue	Physical fatigue: striatum and cerebellum and spinal cord Mental fatigue: dorsolateral prefrontal cortex
Sleep disturbances	Hypothalamic sleep-wake switch, brainstem sleep centers
Problems concentrating	Dorsolateral prefrontal cortex

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