

Symptoms and Circuits, Part 1

Major Depressive Disorder

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Issue: *Major depressive disorder comprises multiple symptoms. Each symptom may be mediated by separate and distinct neuronal circuits.*

Constructing a Diagnosis of Major Depressive Disorder (MDD)

It is well known that a major depressive episode is defined as at least 5 symptoms out of a list of 9 possibilities, one of which must be depressed mood or loss of interest (Table 1).¹ Clinicians construct a diagnosis of MDD by compiling an inventory of all symptoms suffered by any individual patient during any specific period of time. Although constructing a diagnosis is important, the hierarchy of depressed mood and loss of interest over the other symptoms of MDD can distract treating clinicians from observing and monitoring these other symptoms associated with this disorder, particularly if mood improves but other symptoms remain after treatment.²

Each symptom may have a unique neurobiological mechanism mediated by different malfunctioning neurocircuits.² Certainly, not every patient with MDD has the same cluster of

symptoms, implying that different circuits may malfunction in different patients with the same disorder. Furthermore, not every patient with MDD who is given an antidepressant medication will experience improvement of all symptoms, implying that some but not all malfunctioning circuits may respond to a given drug in a given patient. Thus, individual patients with MDD can have a unique portfolio of symptoms not only before antidepressant treatment, but even after treatment.

Deconstructing the Symptoms of MDD

A novel strategy to reduce these residual symptoms and thus convert partial remitters to full remitters is to target the neurotransmitters in the circuits that potentially underlie those residual symptoms.² To do this, the clinician must deconstruct the syndrome of MDD into the specific symptoms still being experienced by each individual patient and then choose psychopharmacologic interventions to target those malfunctioning neuronal circuits that presumably mediate each residual symptom.²⁻⁴

The first step, therefore, is to match symptoms of MDD with their hypothetically malfunctioning circuits (see Table 1).² The next step is to choose a treatment that targets neurotransmitters in each symptomatic circuit be-

cause neurotransmitters and receptors interact with each other within pathways or circuits to regulate various functions of the brain, and dysfunction of certain distinct circuits theoretically can result in the symptoms of various psychiatric disorders.²⁻⁴

Neurotransmitters, Circuits, and Novel Treatment Strategies

The classical theory to explain depression is the “monoamine hypothesis,” which proposes that depression is related to a deficit of monoamines, particularly norepinephrine and serotonin, at critical synapses.⁵ Malfunctioning of monoamine pathways has been difficult to document in depression, but the antidepressant actions of currently available drugs and their ability to reduce or eliminate symptoms are definitely linked to boosting neurotransmission in monoamine pathways.² Therefore, the monoamine hypothesis may be a better theory for explaining the neurobiology of antidepressants than for explaining the neurobiology of the symptoms of depression.^{2,5}

A new paradigm is thus evolving for the role of monoamines in depression as regulators of many of the hypothetically malfunctioning circuits causing the symptoms associated with a major depressive episode. Each monoamine arises from a common site in the brainstem but is released in many projection areas throughout the brain.²⁻⁵

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Take-Home Points

- ◆ Recent advances in neuropharmacology and neuroimaging are mapping the topography of symptoms in major depressive disorder (MDD), demonstrating that different malfunctioning neuronal circuits apparently mediate different symptoms in MDD.
- ◆ Since all patients with MDD do not have the same symptoms, this implies that they do not all have the same malfunctioning circuits. Furthermore, since MDD patients treated with antidepressants commonly experience residual symptoms that prevent them from attaining complete remission, it implies that not all circuits are successfully targeted by treatment in such patients.
- ◆ A new neurobiologically informed treatment strategy for patients with MDD calls for targeting residual symptoms by selecting treatments capable of boosting specific neurotransmitters in the hypothetically malfunctioning circuits.

Table 1. Hypothetical Topography of Symptoms in Major Depressive Disorder

Symptom	Circuit
Depressed mood and sadness	Medial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex
Sleep disturbances	Hypothalamic sleep-wake switch, brainstem sleep centers
Problems concentrating	Dorsolateral prefrontal cortex
Change in weight or appetite	Hypothalamus
Fatigue and loss of energy	Physical fatigue: striatum, cerebellum, and spinal cord Mental fatigue: dorsolateral prefrontal cortex
Loss of interest and pleasure	Hypothalamus and limbic "pleasure centers" (nucleus accumbens)
Feelings of worthlessness or guilt and thoughts of suicide	Amygdala, anterior cingulate cortex, medial prefrontal cortex, orbitofrontal cortex
Psychomotor agitation or retardation	Striatum, cerebellum

Boosting monoamine actions with antidepressants in various specific sites of abnormal neuronal functioning could reduce the symptoms associated with that abnormal neuronal functioning. This paradigm would not necessarily require input from monoamine pathways to be deficient prior to treatment with an antidepressant. It could, however, explain how boosting just one or two monoamines could reduce a whole portfolio of symptoms, since the circuits mediating those symptoms may all receive innervation from monoamine neurons.

It is well known that some symptoms in some patients with depression can clearly be reduced or eliminated by antidepressants capable of boosting serotonin, norepinephrine, or both. On the other hand, many patients nevertheless still have residual symptoms

after treatment with such agents. A strategy to reduce these residual symptoms could be to target the pathways that are still presumably malfunctioning with a second agent capable of turning up the gain on serotonin, norepinephrine, or both, or by boosting the actions of other neurotransmitters known to be in the same circuit, which can include histamine, dopamine, acetylcholine, and many others. Such an approach gives rise to a rational, hypothesis-driven and testable action plan for selecting or combining pharmacologic agents tailored for the individual patient in order to eliminate whatever residual symptoms are unique to that patient and thereby attain complete remission of symptoms for that patient.²⁻⁴ Thus, the neurobiologically informed clinician can utilize the most recent scientific

advances to develop strategies for selecting treatments in MDD. ◆

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