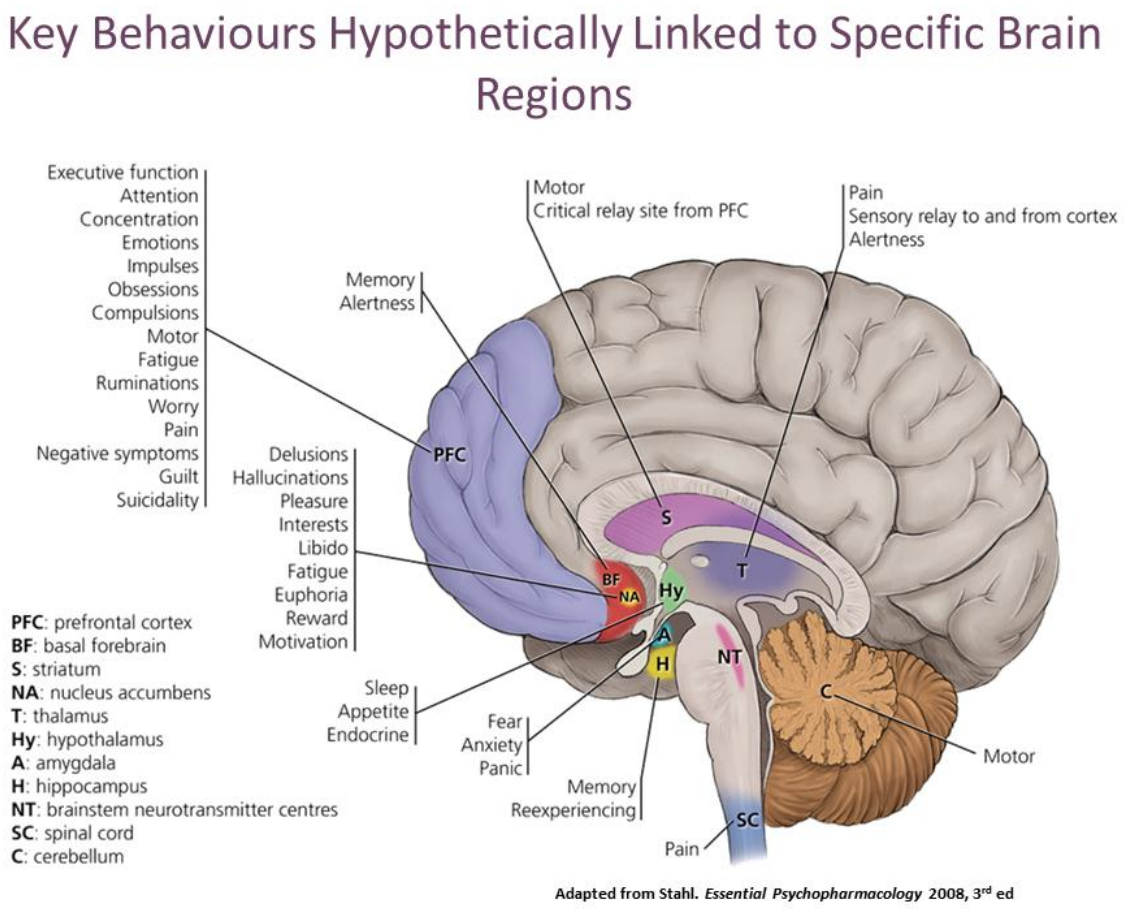
Specific areas of brain activity dysregulation

Key Behaviours Hypothetically Linked to Specific Brain Regions
Certain human behaviors are believed to be linked to various areas of the brain. These behaviors quite frequently represent symptoms of mental illness. Over the past several years we have gained an enormous amount of knowledge regarding the specific areas of the brain and the symptoms that seem to originate from these brain regions. Although this work is by no means complete, this information can be used clinically to help us select appropriate therapy for our patients who are suffering with mental illness.

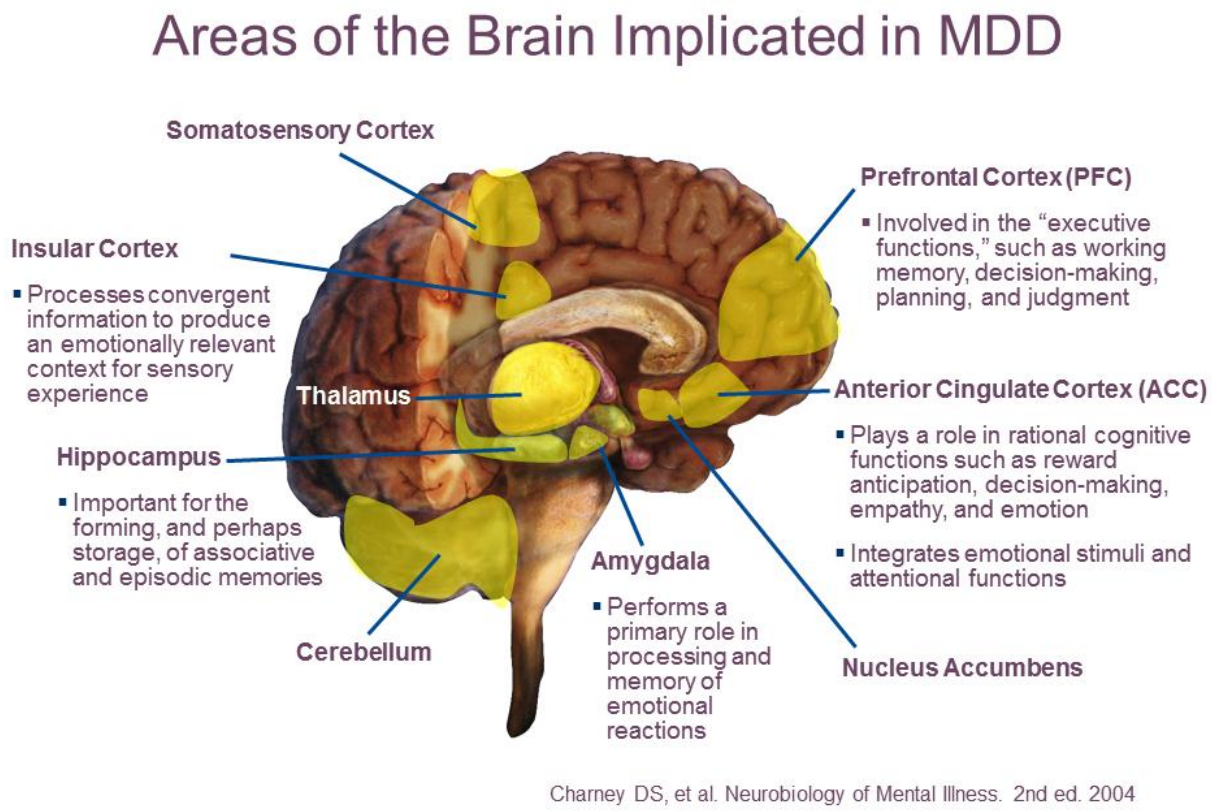
For example, executive functioning, attention and concentration have been linked to the prefrontal cortex. The neurons that innervate this area of the brain originate in the midbrain. These neurons may be serotonergic, dopaminergic or noradrenergic. In the case of executive functioning, attention and concentration, it appears that norepinephrine and dopamine play a critical role.



Adapted from Stahl. *Essential Psychopharmacology* 2008, 3rd ed

As we look at the symptoms of depression there is some evidence to support the fact that various brain regions and projections to these regions may be responsible for the symptoms.

Areas of the Brain Implicated in MDD



Some of the areas that may be involved in MDD are:

- prefrontal cortex (PFC)
- anterior cingulate cortex (ACC)
- insular cortex
- amygdale
- hippocampus
- primary and secondary somatosensory cortex
- posterior cerebellum
- thalamus
- nucleus accumbens.

In this CPD module, we will pay special attention to the PFC, ACC, insular cortex, hippocampus, and amygdala—all of whose key cognitive and emotional roles are briefly summarized here.

The nucleus accumbens is thought to play an important role in reward, pleasure, and addiction. It may be involved in the regulation of emotions, perhaps consequent to its role in mediating dopamine release.[2]

The thalamus relays all information received from the senses (except smell) to the various processing centers in the cerebral cortex. The thalamus regulates the electrical rhythms that parts of the brain use to communicate with each other.[2]

The somatosensory cortex deals with information from the various "touch" receptors, such as temperature, pressure, limb position, movement, pain, etc. It has been implicated in the processes by which memories (or some type of them) are consolidated during sleep.

The insular cortex may have an important role in a number of basic emotions, including anger, fear, disgust, happiness, and sadness.[2]

The cerebellum may be involved in some way in remembering strong emotions, in particular, in the consolidation of long-term memories of fear.[2]

The anterior cingulate cortex can be divided anatomically based on attributed functions into executive (anterior), evaluative (posterior), cognitive (dorsal), and emotional (ventral) components. The ACC seems to be especially involved when effort is needed to carry out a task such as in early learning and problem solving. It may also be involved in functions such as error detection, anticipation of tasks, motivation, modulation of emotional responses to the ACC, and for rendering new memories permanent.[2]

The PFC is divided into the lateral, orbitofrontal, and medial prefrontal areas and is involved in "executive functions," such as working memory, decision-making, planning and judgment. It is thought that the reduced ability to recall the context of memories that occurs with advancing age is evidence that the prefrontal cortex is also critical for context processing.[2] The ventromedial PFC receives integrated sensory information from the orbital PFC as well as fear- and reward-related input from the amygdala, medial temporal lobe, and nucleus accumbens. The VMPFC projects to the hippocampus, diencephalon, and brainstem, where it regulates autonomic and neuroendocrine response and pain modulation.[3] The orbital PFC plays a role in correcting and inhibiting maladaptive, perseverative, and emotional responses.[3] Hyperactivation of the orbital PFC is not seen in patients with mania. Finally, hypoactivity of the dorsolateral PFC in depression has been associated with psychomotor retardation and anhedonia.[5]

The hippocampus is important for the forming, and perhaps long-term storage, of associative and episodic memories. Specifically, the hippocampus has been implicated in the encoding of face-name associations, the retrieval of face-name associations, the encoding of events, and the recall of personal memories in response to smells. The hippocampus is one of several limbic structures that have been implicated in mood disorders. Included in the

functions of hippocampal circuitry are control of learning and memory and regulation of the hypothalamic-pituitary-adrenal (HPA) axis, both of which are altered in depression. The hippocampus has connections with the amygdala and PFC, regions that are more directly involved in emotion and cognition and thereby contribute to other major symptoms of depression.[2]

The amygdala performs primary roles in the formation and storage of memories associated with emotional events. The amygdala also is involved in the modulation of memory consolidation.[2]

Broadmann's areas: VMPFC = 10, 11, 12, 25 and 325; DLPFC = 9, 464

The "Anatomy" of Depression: Linking Symptoms to the Brain
Numerous symptoms are required to make a diagnosis of depression. Each symptom is hypothetically associated with inefficient information processing in various brain circuits, with different symptoms topographically localized in specific brain regions.[1]

The "Anatomy" of Depression: Linking Symptoms to the Brain

	Linking Symptoms to Neurotransmitters → 5HT, NE, DA	Potential Brain Regions Involved	Continued Research Involving Brain Regions
	Depressed mood → **5HT, NE, DA**	ii, xii	i. Prefrontal Cortex (PFC) ii. VentroMedial (VMPFC) iii. DorsoLateral (DLPFC) iv. Orbital (OFC) v. Basal Forebrain (BF) vi. Hypothalmus (Hy) vii. Thalmus (Th) viii. Spinal Cord (SC) ix. Nucleus Accumbens (NA) x. Striatum (S) xi. Cerebellum (C) xii. Amygdala (A)
S	Sleep → **5HT, NE, DA**	i, v, vi, vii	
I	interest, apathy → **NE, DA**	i, vi, ix	
G	guilt, worthlessness → **5HT**	ii, xii	
E	energy → **NE, DA**	i, vii, ix	
C	concentration, function → **NE, DA**	iii	
A	appetite, weight → **5HT**	vi	
P	psychomotor → **5HT, NE, DA**	i, ix, x, xi	
S	suicide → **5HT**	ii, iv, xii	

Main Clinical Point: There is some evidence to support the fact that various brain regions and neurotransmitters may be responsible for the symptoms of depression.

Stahl. *Essential Psychopharmacology* 2008, 3rd ed

Historically the selection of antidepressants for our patients has been guided by various factors including: Cost of medication, previous response to medication, agitated or retarded symptoms, comorbid symptoms or disorders (i.e., anxiety), etc. There has been little attention paid to the specific symptoms that patients present with. Our current naturalistic

approach to depression has resulted in remission in less than 40% of our patients. Considering the specific initial presenting symptoms, and selecting a strategy directed to address these symptoms, may have significant impact on the number of patients who enjoy a full functional recovery from their depression.

The recent appreciation of the inhibitory effect of serotonin on the neurotransmission of both norepinephrine (NE) and dopamine from their respective nuclei in the mid brain may explain why patients who complain of apathy at baseline do not see resolution of this symptom with a predominantly serotonergic strategy. As was previously mentioned, serotonin, norepinephrine and dopamine do not function independently of one another. Recent research has identified the fact that serotonin can exhibit an inhibitory affect on the neurotransmission of both dopamine and norepinephrine. This information may help explain why some of our patients who are treated with a predominantly serotonergic strategy may notice a worsening of noradrenergic and dopaminergic mediated symptoms. Consider the patient t who has exhibited improvement in mood and a decrease in thoughts of worthlessness and suicidality but is still suffering with symptoms of depression. A common residual symptom is that apathy, a symptom of depression mediated through pathways innervated by norepinephrine and dopamine.

Consider a patient with a childhood diagnosis of ADHD who is now 25 and presenting with MDD. Although this patient is not taking any medications for ADHD as an adult, one must assume that he still has some impairment of dopaminergic and noradrenergic transmission to the prefrontal cortex (PFC) as an adult. Treating such an individual with a predominantly serotonergic strategy may in fact lead to a worsening of his symptoms of ADHD. Medications which address dopamine and norepinephrine as well as serotonin may be more useful for this type of patient.

References

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