

The Physical Realm of Depression

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Major Depressive Disorder

- MOD can be a chronic, recurrent, and progressive condition
- MOD is associated with alteration in functional and structural changes in the brain
- MOD, stress, and pain are all associated with similar suppression of neurotrophic factors and compromised neuroplasticity
- Remission not response is the ultimate goal of treatment

Key brain areas in regulation of mood

Ventromedial prefrontal cortex-VMPFC

- Pain and aggression, sexual and eating
- Autonomic and neuroendocrine response
- i Lateral orbital prefrontal cortex-LOPFC
- Activity increases in depression, OCD, PTSD, panic disorder

Serotonin(S-HT) and norepinephrine(NE) pathways in the brain

Hippocampus: The "weak link"?

- 5-HT and NE influence the balance between excitatory (glutamnergic) and inhibitory (GABAergic) activity in the prefrontal cortex and limbic system
- Excitatory (glutamnergic) neurons from the prefrontal cortex have regulatory influence on the locus coeruleus (LC-NE) and the dorsal nuclei raphe (DNR-5-HT)

Hippocampus: The "weak link"?

- A combination of excessive excitatory input from the VMPFC and increased levels of glucocorticoids may have a "toxic" effect on the hippocampus
- Hippocampal dysfunction may contribute to the cognitive impairment and emotional and neuroendocrine dysregulation often observed in MOD

Major Depression may have systemic consequences

- Hypothalamus stimulates the pituitary to release ACTH which then drives the adrenal gland
- Adrenal gland releases too much adrenaline and cortisol
- Increased adrenaline lead to heart attacks, diminished heart rate variability, arrhythmias platelet aggregation which increases strokes and

BDNF Brain-derived neurotrophic factor

Neurogenesis is now thought to be possible
in the brain

BDNF associated with production of NEW
neurons

Neurotrophins modify synaptic transmission
in an activity dependent manner
BDNF is downregulated with stress

Beyond synapse: Serotonin and norepinephrine aid BDNF synthesis

- BDNF, depression and antidepressants
- BDNF is downregulated in MOD and increased with antidepressant treatment
- BDNF influences regulation of mood and perception of pain
- BDNF promotes neuroplasticity, neurogenesis, and neuroprotection

Major depressive disorder: The ~ consequences

- affects emotional, cognitive, behavioral, and physical manifestations
- changes metabolism in the prefrontal cortex and limbic system
- changes the size of the hippocampus and prefrontal cortex
- affects the immunity system'--
- diminishes neurotrophic activity
- affects the parts of the brain that have noradrenergic and serotonin innervation

Restoring homostasis and harmony

- Continuous antidepressant use associated with increase serotonin and norepinephrine in the prefrontal cortex and limbic system
- Effective antidepressant tx assoc with decreased activity in the VMPFC, hippocampus and amygdala and increased activity in the DLPFC
- These changes likely are part of the improvements: decrease sadness, anxiety, body slowdown, fatigue, improved cognition
- Activation of 5-HT and NE may help also with neuroplasticity, neurogenesis, and cellular resilience

Importance of choosing an effective treatment first

- Rapid remission is the most important predictor for long term outcome
- Longer duration of previous episode reduces likelihood of recovery
- Pain reduces chance of outcome
- Lack of response to first antidepressant is a predictor of future treatment resistance