Overview of the Neurobiology of Major Depressive Disorder

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Psychiatric diagnoses

- “Symptoms and behaviors are the output of brain function, whereas syndromes are man-made constructions.”

- Preskorn S, 2014

Research Domain Criteria (RDoC) initiative

- Negative Valence Systems
- Positive Valence Systems
- Cognitive Systems
- Systems for Social Processes
- Arousal/Regulatory Systems
Current Treatment Practices in MDD

STAR*D Study Design Overview

Acute Outcome Worsens with Increasing Number of Prior Treatment Failures

Antidepressant Effects of the NMDA Antagonist
CPT-101 (50mg) versus Placebo

Trivedi et al. (Am J Psychiatry, 2004); Rush et al. (Neuropsychopharmacology, 2004); Peña et al. (Am J Psychiatry, 2004); McGrath et al. (Am J Psychiatry, 2004)
Affective Cortical-Striatal Circuits

Evaluation of Emotionally Salient Information

The amygdala evaluates the emotional salience of sensory stimuli through a network of cortical and subcortical structures.

1) Sensory thalamus, superior colliculus & pulvinar
2) Pathway projecting to higher-order cortical processing areas involving conscious perception
3-4) Subcortical sensory pathways that allow for rapid, automatic assessment of stimulus features below the level of explicit conscious awareness


Gating Neural Processing through the Basal Ganglia: Grace, 2003

Neural Model of Mood Disorders

Dysfunction of PFC-striatal modulation of limbic circuitry alters emotional processing, behavior

Dysfunction of orbital & medial PFC, striatal, & monoaminergic systems that modulate limbic circuits

Increased activity of limbic & brainstem systems that mediate emotional behavior

 polarity - e.g., lesions of orbital C & striatum; degenerative diseases of basal ganglia; dendritic reshaping

polarity - e.g., putative sensitization associated with TLE, CRF/CORT hypersecretion, repeated stress
Altered Extended Visceral Motor Network Function and Disinhibition of Emotional Expression

Regional blood flow abnormalities in patients with depression

Comparison of Patients With Depression, Well-Posed Family History (n=12) and Healthy Controls (n=12)

- Patients with depression had increased blood flow in amygdala and left medial and lateral orbitobasal areas, consistent with ventromedial PFC.

Summary: Structural and Functional Changes in MDD

MDD = Major depressive disorder.
**Areas of the brain implicated in MDD**

- Insular Cortex
- Hippocampus
- Amygdala

Charney DS, Nestler EJ. *Neurobiology of Mental Illness*; 2004.

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**Some key areas of the brain that may play a role in both MDD and pain**

- Insular Cortex
- Prefrontal Cortex
- Hippocampus
- Anterior Cingulate Cortex
- Amygdala

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**In MDD, the amygdala may facilitate painful symptoms (hypothetical model)**

- Negative Emotion (fear, stress)
- Negative Emotion (depression, anxiety disorders)
- Positive Emotion (happiness, pleasant states, etc.)

Inhibits amygdala activity

Facilitates amygdala activity


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**Areas of prefrontal cortex (PFC) involved in MDD**

A. Ventromedial prefrontal cortex (VMPFC)^4
   - Modulates pain, aggression, and sexual and eating behaviors^4

B. Lateral orbitofrontal cortex (LOPFC)^4
   - Connects and inhibits maladaptive and perseverative emotional responses

C. Dorsolateral prefrontal cortex (DLPFC)^4
   - Maintains cognitive control, solving of complex tasks, and manipulation of information in working memory

Key brain areas involved in regulation of mood

- **A. Ventromedial prefrontal cortex (VMPFC)**
  - Mediates pain and aggression, and sexual and eating behaviors.
  - Regulates salience and emotional response.

- **B. Lateral orbitofrontal cortex (LOFC)**
  - Activity is increased in depression, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and panic disorder.
  - Corrects and inhibits maladaptive, perseverative, and emotional responses.

- **C. Dorsolateral prefrontal cortex (DLPFC)**
  - Cognitive control, solving complex tasks, and manipulation of information in working memory.
  - Hypoactivity of DLPFC in depression has been associated with an endocrinological and immunological manifestations of depression.

Patients with MDD have 32% smaller medial orbitofrontal cortices (MOFC) (VMPFC) than controls

Anterior cingulate cortex (ACC) function: emotional and cognitive integration

- **A. Dorsal ACC (dACC)**
  - Part of cognitive/executive function network; involved in sustained attention, decision making, and effortful control of behavior; altered activity in MDD and pain.

- **B. Retrol ACC**
  - Interface between dorsal (cognitive) and ventral (unconscious/affective) divisions of ACC.

- **C. Ventral ACC (subcallosal and subgenual)**
  - Assesses the salience of emotional and motivational information and consequently makes adjustments in the behavior; modulates sympathetic and immunological responses in depression, anxiety, and pain.

Decreased activity in DLPFC & dACC in MDD patients

- Areas of increased activation in patients with MDD at rest (red) and decreased activation.
- **Increased activity:** LOFC, VMPC, amygdala, thalamus, caudate.
- **Decreased activity:** DLPFC, insula, pregenual and dACC, Sup Temp gyr.

MDD may impact function and structure of the subgenual anterior cingulate

- Metabolism in the subgenual ACC increased compared to a control group.
- Increases in subgenual ACC metabolism corresponded to increased depression severity.

Brain atrophy in depression?

**Correlation between hippocampal volume and duration of untreated depression**

- There was a significant inverse relationship between total hippocampal volume and the length of time depression went untreated.


Task Design

Backward Masking Task Design

Neutral Target Faces

Depressed Patients Had an Attenuated Ventral Striatal (Nucleus Accumbens) Response to Positive Stimuli

Increased Amygdala Activity in MDD

*MRI Study of Patients With MDD (n=11) and Healthy Controls (n=11)
Domains influenced by orexin 2 receptor antagonism: Potential benefits in MDD

"Orexins primarily mediate behavior under situations of high motivational relevance, such as during physiological need states, exposure to threats or reward opportunities." Mehlman, Ahne-Jensen, et al. Neuropeptides, 2014

**Anxiety/ Stress-Related Circadian Rhythm**

- Reduction in insomnia, daytime arousal
- Prevention of physiological sleep (arousal, sleep depth)
- Overall benefits of sleep: deep sleep and its immunomodulatory effects, prevention of sleep deprivation, maintenance of adaptive hippocampal network, reduction in cardiovascular disease

**Endocrine/Neuroendocrine/ Endothelial Function**

- Attenuation of leptin ("hormone") component of central insensitivity
- Normalization of leptin sensitivity, depression-like behaviors increase chronic stress model

**Reward Processing/ Motivated Behavior/ Addictive**

- Persistent insomnics, GLI insomniacs, addictive/insensitive reward system

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**Neurocircuitry of Mood Disorders, Neurosurgical Sites for Tx refractory MDD**

**Anterior Cingulotomy:**
- Prefrontal
- Lateralization
- DBS in LP

**Ventral, rostral pallidum**
- Medial prefrontal network
- MDM, Thalamus

**Sub-caudate Tractotomy:**
- DBS in WM
- Adjacent to Aac Nu; Med. caudate

**Hypothalamus & Brainstem**
- Paraventricular hypothalamus & Habenula

Modified from Price J, Drevets W; TCS, 2012

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**Elevated limbic drive on orexin & cortisol release amplifies stress response, induces hyperarousal and core depressive/anxiety/somatic Sx of MDD**

**Gold, Drevets & Charney, 2006**

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**Hippocampal dysfunction contributes to neuroendocrine dysregulation**

- Hypothalamus
- Hippocampus
- CRF
- Glucocorticoids
- Dexamethasone
- ACTH
- Adrenal cortex

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