260-2017-03-17-depression

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Prelude

Today's topic(s)

- Depression

Depression

- Symptoms
  - Unhappy moode, insomnia, lethargy, loss of pleasure, interest, energy
- Agitation
- Lasting for several weeks or more

Depression

- Experienced by ~7% Americans in any year
- Prevalence (up to ~20% lifetime)
- Females 2-3x males, higher 40+ years of age
- MZ concordance ~60% vs. DZ ~20% suggests genetic component

Symptoms, (Mahar et al. 2014)

Neurological factors

- Reduced hippocampal volumes
- (Videbech and Ravnkilde 2004) meta-analysis
- Meta-analysis combines effects across many different studies

(Videbech and Ravnkilde 2004)

(Videbech and Ravnkilde 2004)

Neurological factors

- Hypoactivity in
  - Frontal and temporal cortex
  - Anterior cingulate
  - Insula
  - Cerebellum
- (Fitzgerald et al. 2008)

(Fitzgerald et al. 2008)

(a) patients v. controls, (b) patients on SSRIs, (c) patients v. ctrls (happy stim), (d) patients v. controls (sad stim)

Neurological Factors

- Persistent activation in amygdala
- Amygdala and dorsolateral prefrontal cortex (DLPFC) inversely related
- (Siegle et al. 2002)

Disrupted connectivity

- Resting state fMRI (rsFMRI) in 421 patients with major depressive disorder and 488 control subjects.
- Reduced connectivity between orbitofrontal cortex (OFC) and other areas of the brain
- Increased connectivity between lateral PFC and other brain areas

(Cheng et al. 2016)

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Disturbed sleep

- Less slow wave (stage 3 and 4)
- More REM earlier in night (typical is longer REM as night goes on)

Pharmacological factors

- Endocrine
  - Lowered thyroid function
  - High/chronic cortisol levels

Pharmacological factors

- Monoamine hypothesis
  - More: euphoria
  - Less: depression
  - Resperine (antagonist for NE & 5-HT) can cause depression
  - Low serotonin (5-HT) metabolite levels in CSF of suicidal depressives (Samuelsson et al. 2006)

(Samuelsson et al. 2006)

Treatments for depression

- Psychotherapy
  - Often effective when combined with drug treatment
- Drugs

- Exercise

Drugs

- Monoamine oxidase (MAO) inhibitors
  - MAO destroys excess monoamines in terminal buttons
  - MAO-I's boost monoamine levels
- Tricyclics
  - Inhibit NE, 5-HT reuptake
  - Upregulate monoamine levels, but non-selective = side effects

Drugs

- Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Fluoxetine (Prozac, Paxil, Zoloft)
  - Prolong duration 5-HT in synaptic cleft
  - Also increase brain steroid production
- Selective Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Cymbalta (SNRI)

How well do the drugs work?

- STAR*D trial
- On SSRI for 12-14 weeks. ~1/3 achieved remission; 10-15% showed symptom reduction.
- If SSRI didn't work, could switch drugs. ~25% became symptom free.
- 16% of participants dropped out due to tolerability issues
- Took 6-7 weeks to show response.

Who will benefit from drug therapy?

- Depends on
  - Early life stress
  - Brain (amygdala) response to emotional faces
- (Goldstein-Piekarski et al. 2016)
- Low-stress + low amyg reactivity -> > responding
- High stress + high amyg reactivity -> > responding

(Goldstein-Piekarski et al. 2016)

Problems with monoamine hypothesis

- Too simplistic
- NE, 5-HT interact
- Drugs fast acting (min), but improvement slow (weeks)

What do drugs do, then?

- Receptor sensitivity altered?
  - Serotonin presynaptic autoreceptors compensate
  - Postsynaptic upregulation of NE/5-HT effects
- Stimulate neurogenesis?
  - Link to neurotrophin, brain-derived nerve growth factor (BDNF)
  - BDNF boosts neurogenesis
  - SSRIs stimulate new neurons in hippocampus

Exercise as a treatment

(Babyak et al. 2000)

Drugs vs. therapy

(DeRubeis, Siegle, and Hollon 2008)

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Electroconvulsive Therapy (ECT)

- Last line of treatment for drug-resistant depression
- Electric current delivered to the brain causes 30-60s seizure.
- ECT usually done in a hospital's operating or recovery room under general anesthesia.
- Once every 2 - 5 days for a total of 6 - 12 sessions.

Electroconvulsive Therapy (ECT)

- Remission rates of up to 50.9% (Dierckx et al. 2012)
- Seems to work via
  - Anticonvulsant (block Na+ channel or enhance GABA function) effects
  - Neurotrophic (stimulates neurogenesis) effects

Patients speak

- Kitty Dukakis' story: http://www.nytimes.com/2016/12/31/us/kitty-dukakis-electroshock-therapy-evangelist.html

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www.ectreatment.org

Neurogenesis hypothesis, (Mahar et al. 2014)

- Chronic stress causes neural loss in hipp
- Chronic stress downregulates 5-HT sensitivity
- Depression ~ chronic stress
- Anti-depressants may upregulate neurogenesis via 5-HT modulation

Depression's widespread impact

- Widespread brain dysfunction
- Prefrontal cortex, amygdala, HPA axis, circadian rhythms
- Genetic + environmental factors
- Disturbance in 5-HT, NE systems, cortisol
- Many sufferers do not respond to available treatments

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