Depression

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Prelude

Symptoms (Mahar et al. 2014)

Table 1
Symptoms of a depressive episode, at least five of which must persist for at least two weeks to meet diagnostic criteria, with depressed mood or anhedonia requisite (DSM-V; American Psychiatric Association, 2013).

Depressed mood most of the day, nearly every day
Compromised ability to experience pleasure (anhedonia) or interest in activities most of the day, nearly every day
Feelings of worthlessness or unreasonable guilt nearly every day
Sleep disturbance (insomnia or hypersomnia) nearly every day
Fluctuations in weight or appetite changes nearly every day
Psychomotor agitation or retardation nearly every day
Fatigue nearly every day
Diminished ability to think or concentrate nearly every day
Recurrent thoughts of death or suicidal ideation

Depression

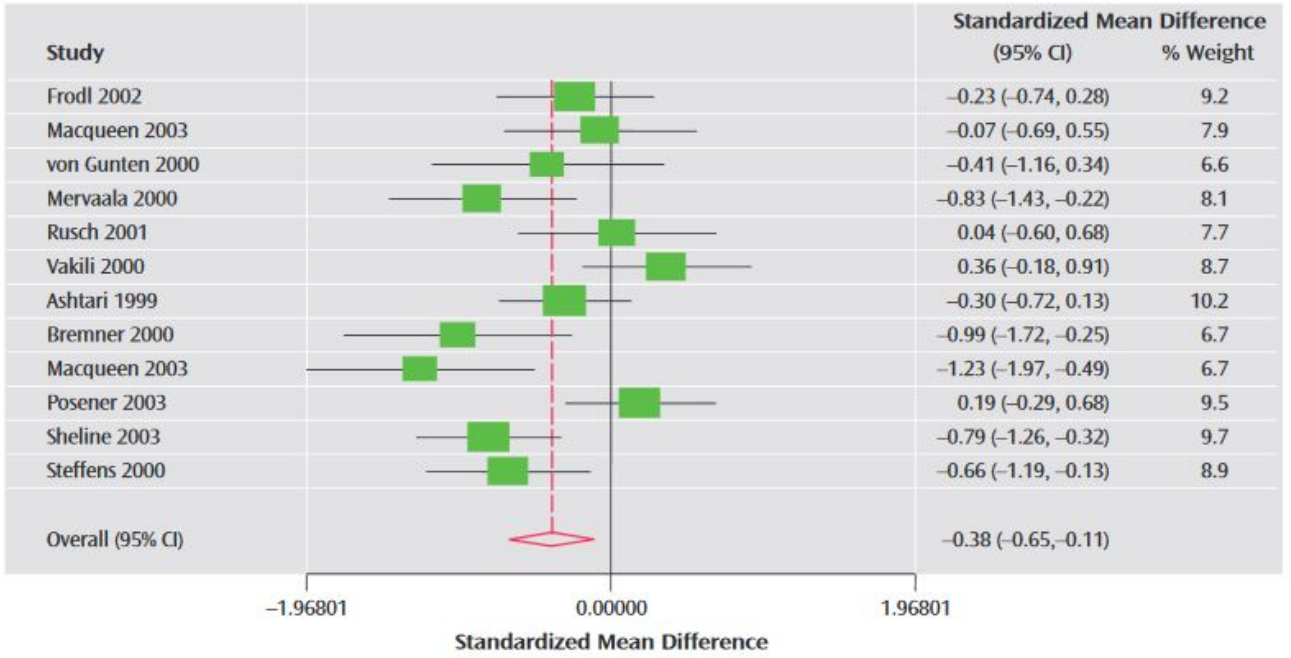
- Experienced by ~7% of Americans in any year
- Prevalence (up to ~20% lifetime)
- Females 2 – 3x males, higher 40+ years of age
- MZ concordance ~60% vs. DZ ~20% suggest genetic component

Neurological Factors

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

(Videbech and Ravnikilde 2004)

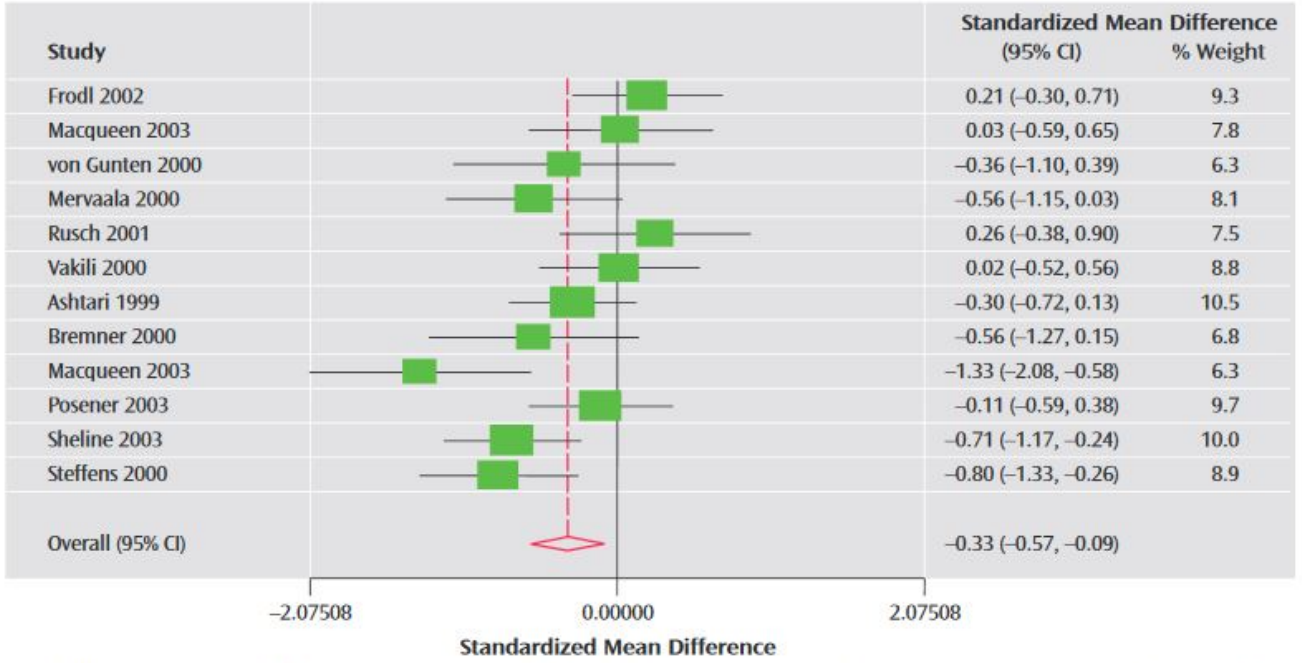
FIGURE 1. Standardized Mean Difference of Left Hippocampal Volume in Patients With Depression Relative to Comparison Subjects From a Meta-Analysis of 12 MRI Studies[a]



[a] Overall difference represents the Derimonian-Laird pooled effect size, calculated under the assumption of a random effects model. Studies are grouped by their RECUR variable, a value assigned on the basis of patient group type (1=first-episode patients, 2=mixed group, 3=patients with recurrent depression).

(Videbech and Ravnikilde 2004)

FIGURE 2. Standardized Mean Difference of Right Hippocampal Volume in Patients With Depression Relative to Comparison Subjects From a Meta-Analysis of 12 MRI Studies[a]



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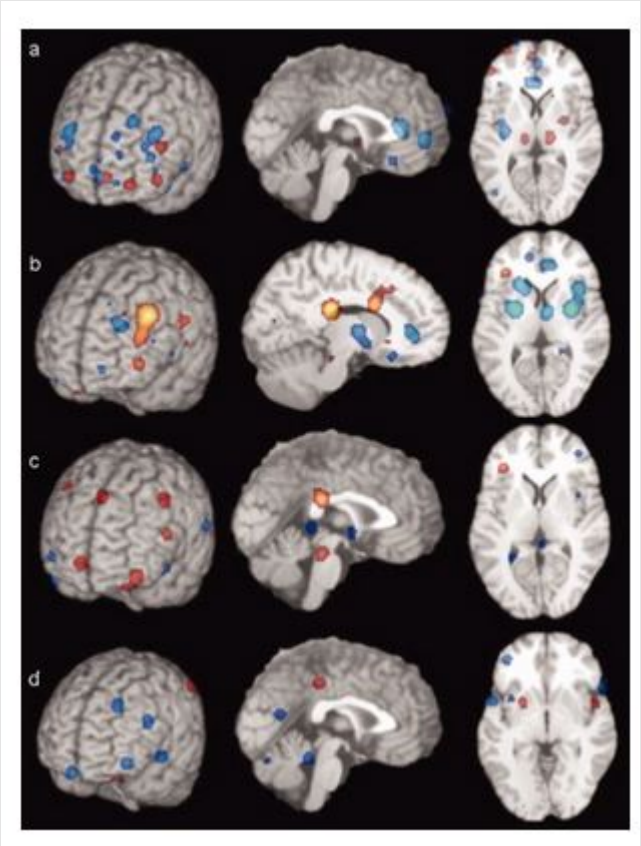
Neurological factors

- **(Fitzgerald et al. 2008)**
  - Hypoactivity in:
    - frontal and temporal cortex
    - anterior cingulate
    - insula
    - cerebellum
- (Siegle et al. 2002)
  - Persistent activation in amygdala

(Fitzgerald et al. 2008)

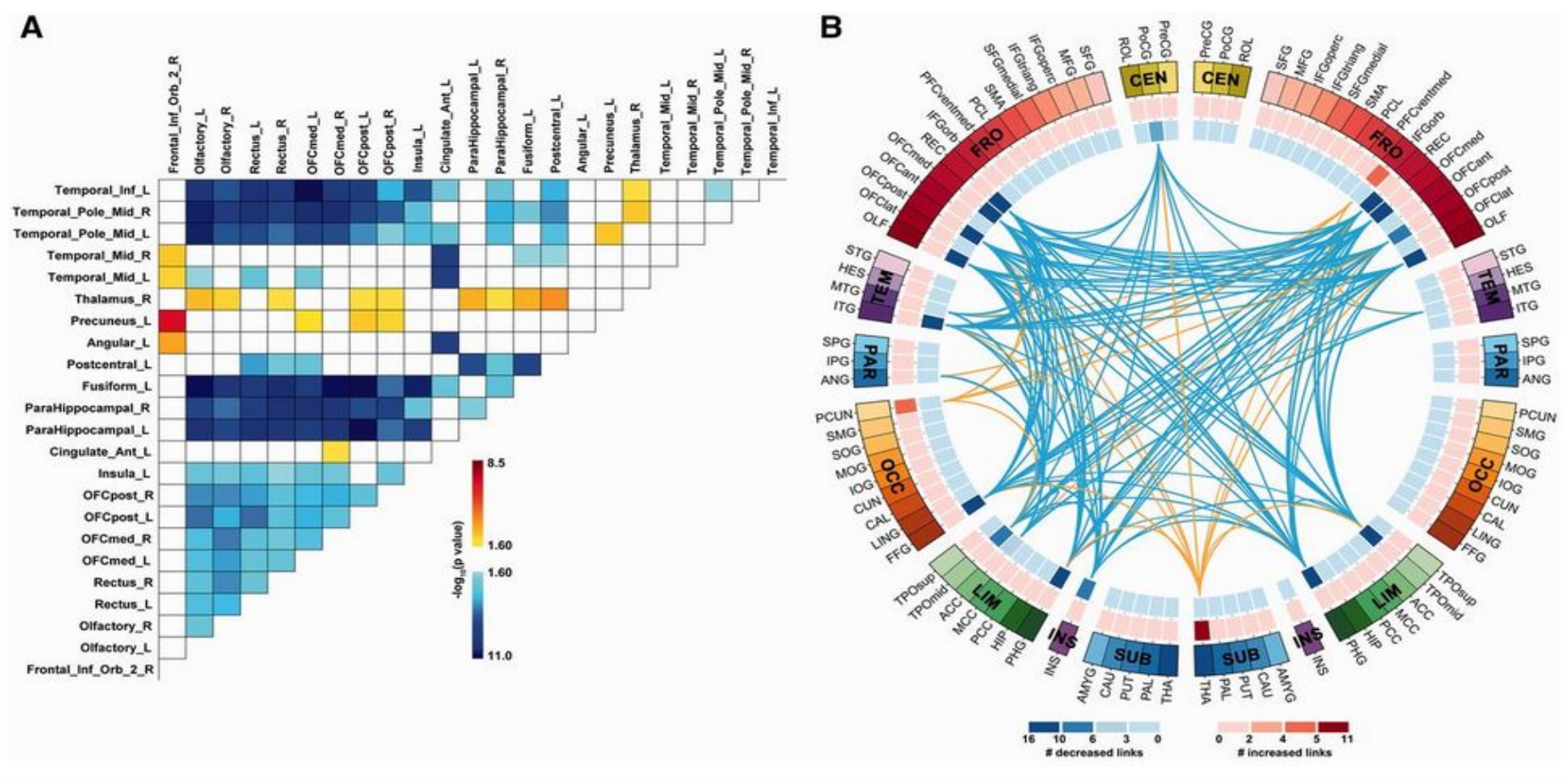


(a) patients v. controls
(b) patients on SSRI
(c) patients v. ctrls (happy stim)
(d) patients v. controls (sad stim)

Disruptive connectivity

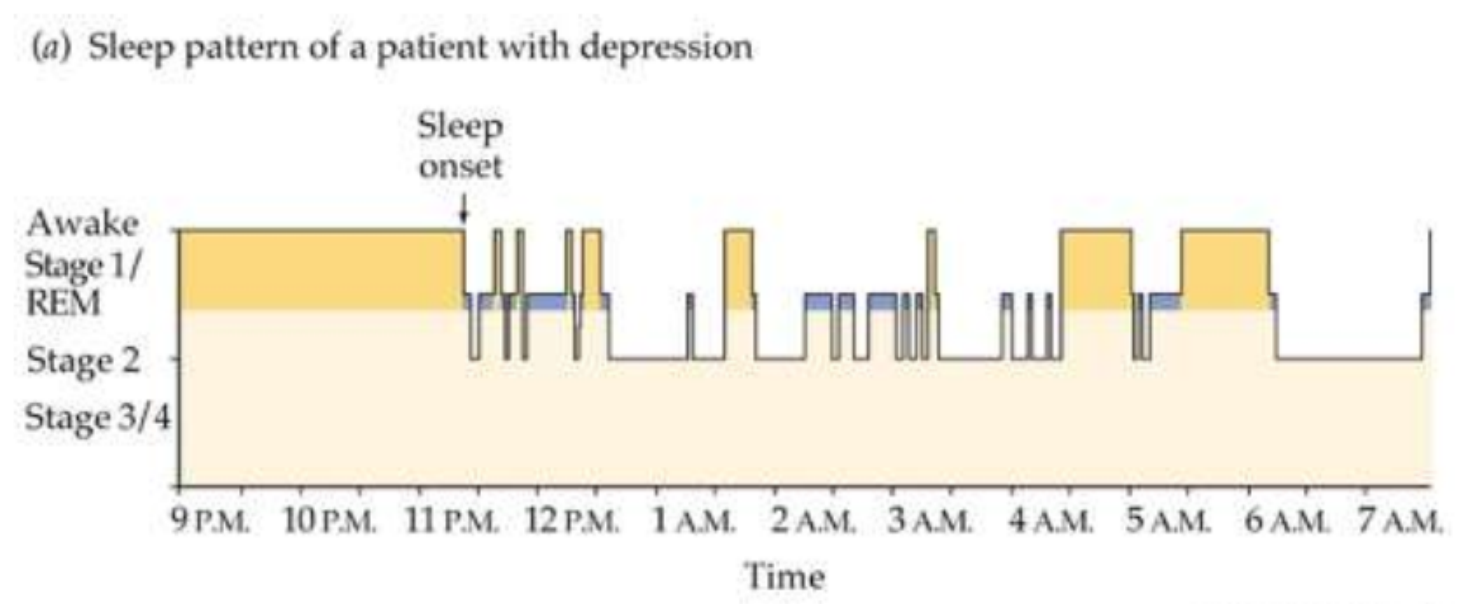
- Resting state fMRI (rsFMRI) in 421 patients with major depressive disorder and 488 control subjects
- Reduced connectivity between orbitofrontal cortex (OFC) and other areas of the brain
- Increased connectivity between lateral PFC and other brain areas
- (Cheng et al. 2016)

(Cheng et al. 2016)



Disturbed sleep

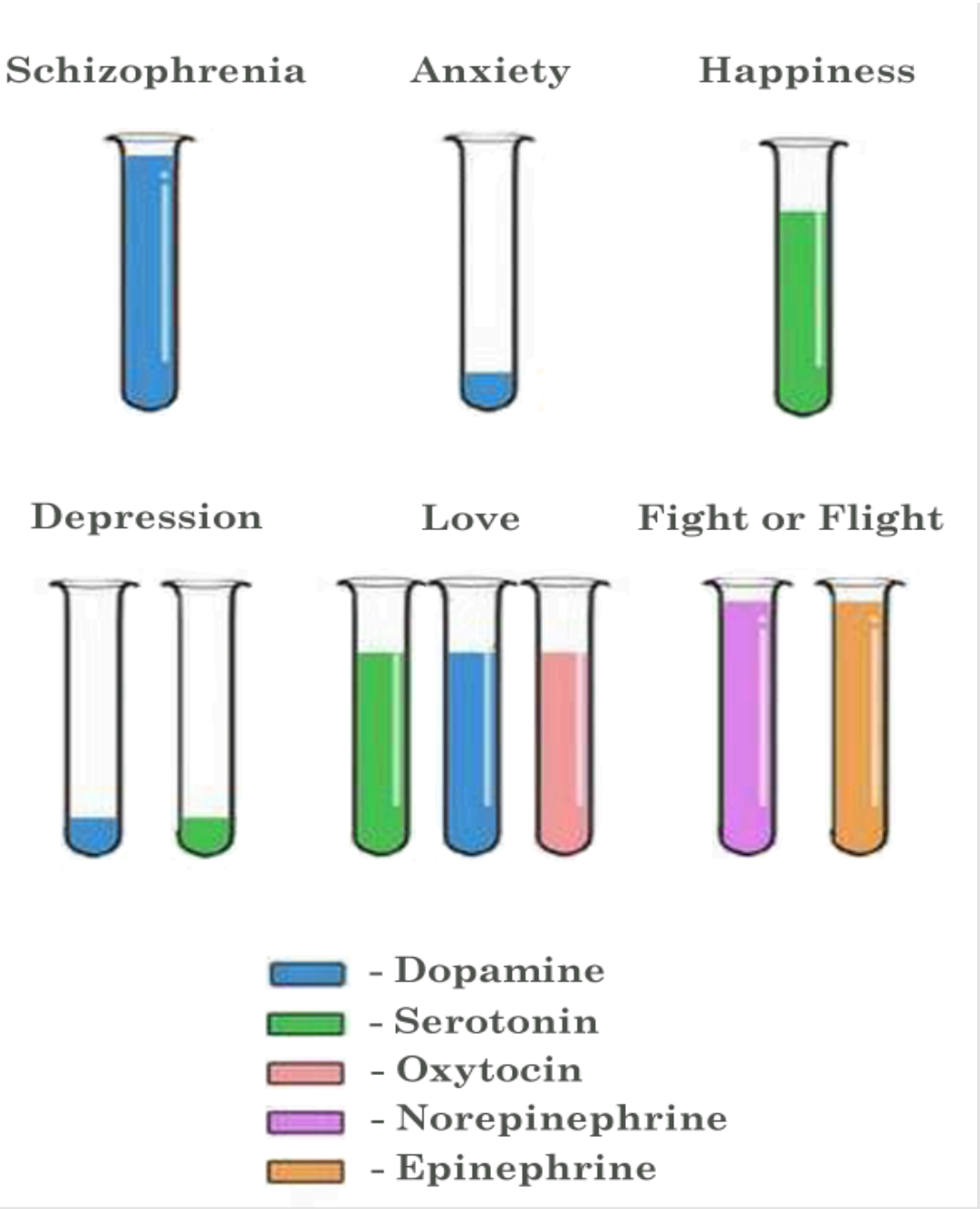
- Less slow wave (stage 3 and 4)
- More REM earlier in night (typical is longer REM as night goes on)



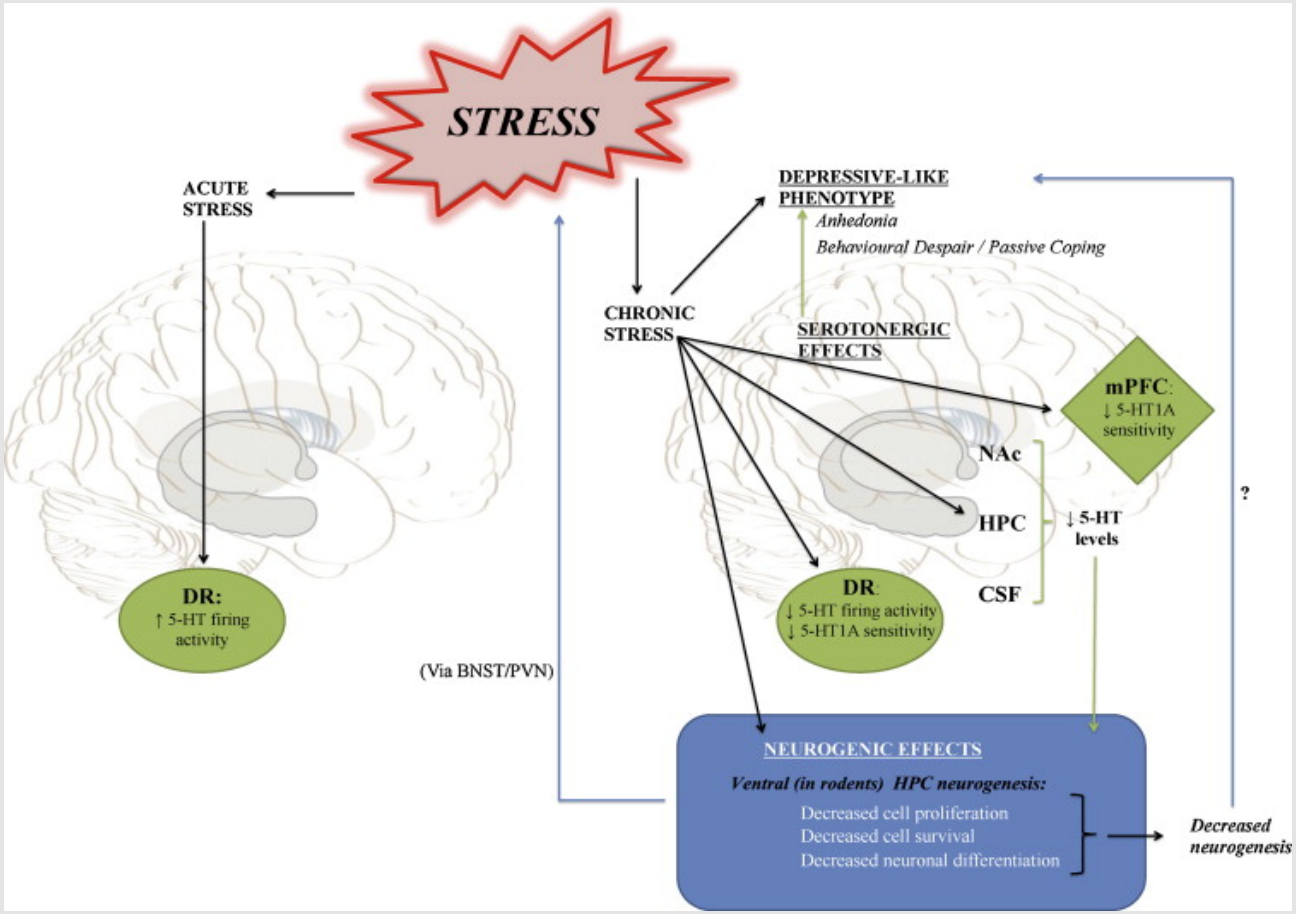
Pharmacological factors

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

- 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)


Schizophrenia
Anxiety
Happiness
Depression
Love
Fight or Flight
- Dopamine
- Serotonin
- Oxytocin
- Norepinephrine
- Epinephrine

(Mahar et al. 2006)



Problems with monoamine hypothesis

- Too simplistic
- NE, 5-HT interact
- Treatments targeting monoamines can act fairly quickly (min), but overall improvement slow (weeks)

Treatments for depression

- Psychotherapy
  - Often most effective when combined with drug treatment
- Drugs (only the legal kind)
- Exercise

Exercise as treatment (Babyak et al. 2000)

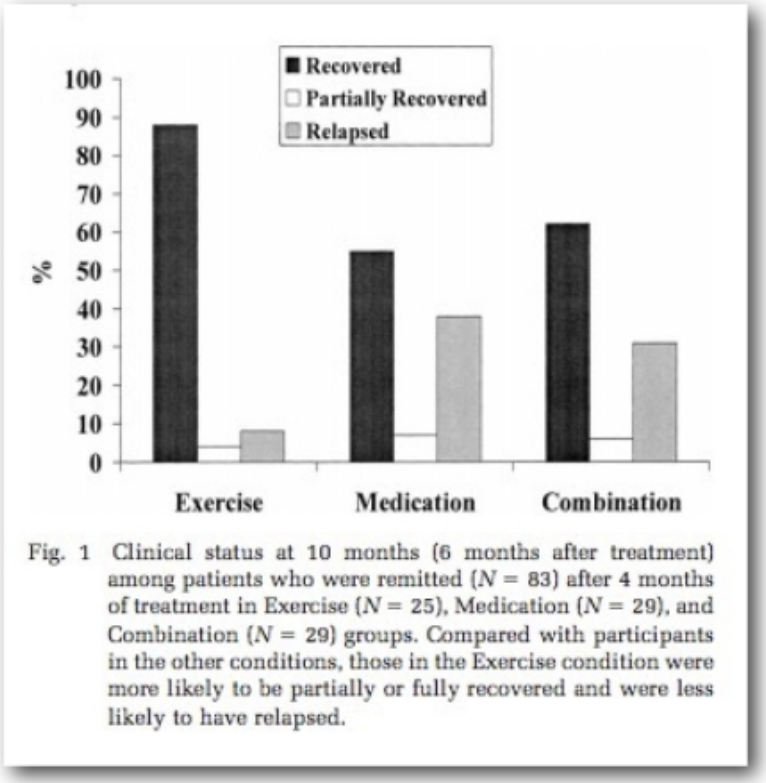


Fig. 1 Clinical status at 10 months (6 months after treatment) among patients who were remitted ($N = 83$) after 4 months of treatment in Exercise ($N = 25$), Medication ($N = 29$), and Combination ($N = 29$) groups. Compared with participants in the other conditions, those in the Exercise condition were more likely to be partially or fully recovered and were less likely to have relapsed.

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

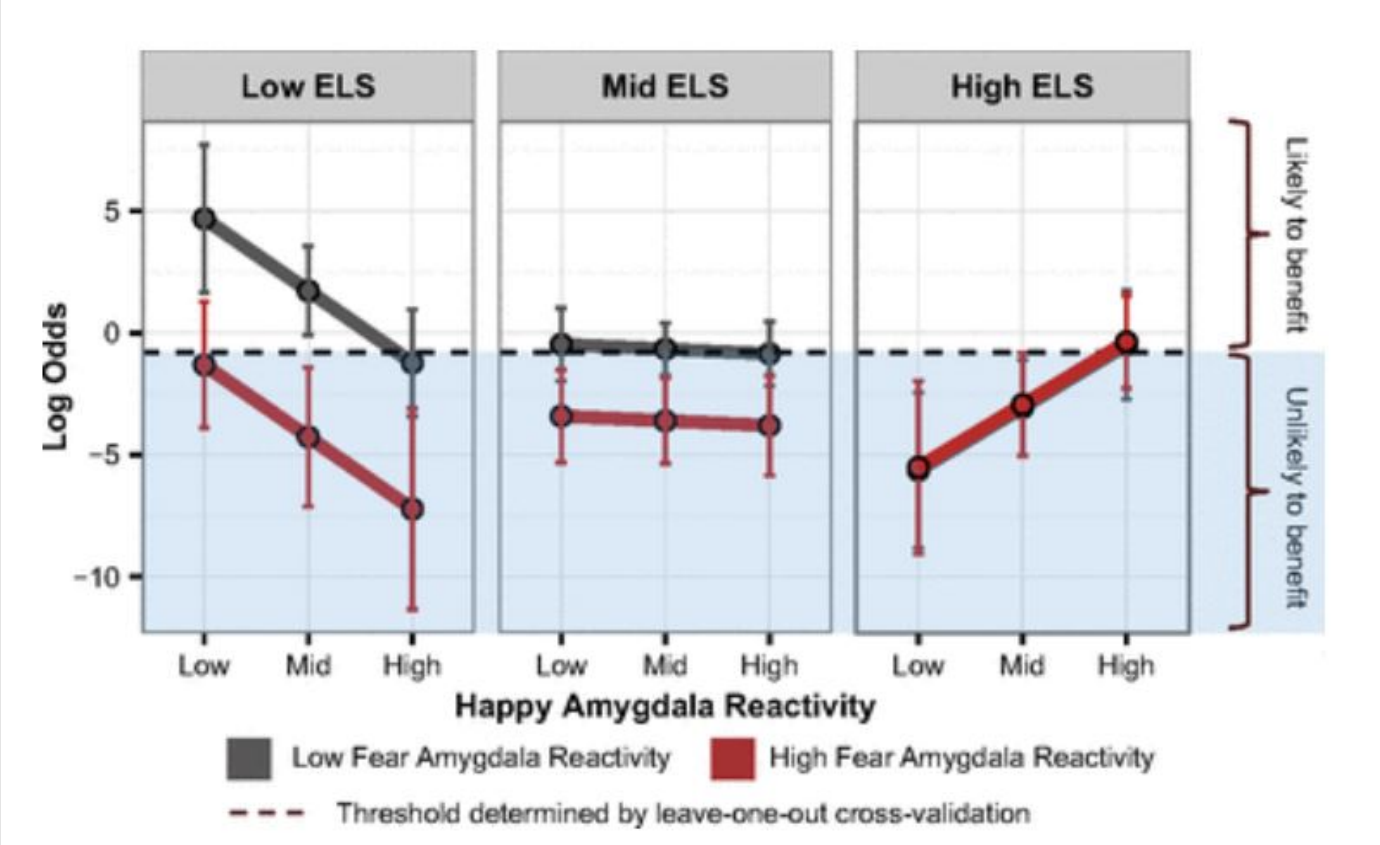
How well do the drugs work?

- 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)



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

Drugs vs. therapy

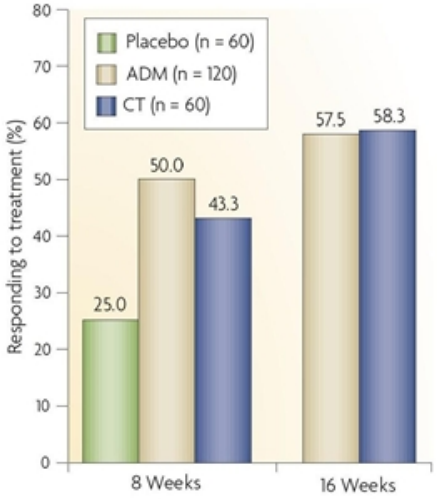


Figure 1 | **Cognitive therapy and antidepressant medication have comparable short-term effects.** This graph shows the response of outpatients who had moderate-to-severe depression to cognitive therapy (CT), antidepressant medication (ADM) or placebo. Patients who were assigned to ADM or to CT showed a significantly higher response rate after 8 weeks of treatment than those who were assigned to placebo. After 16 weeks of treatment the response rates of ADM and CT were almost identical[35].

(DeRubeis, Siegle, and Hollon 2008)

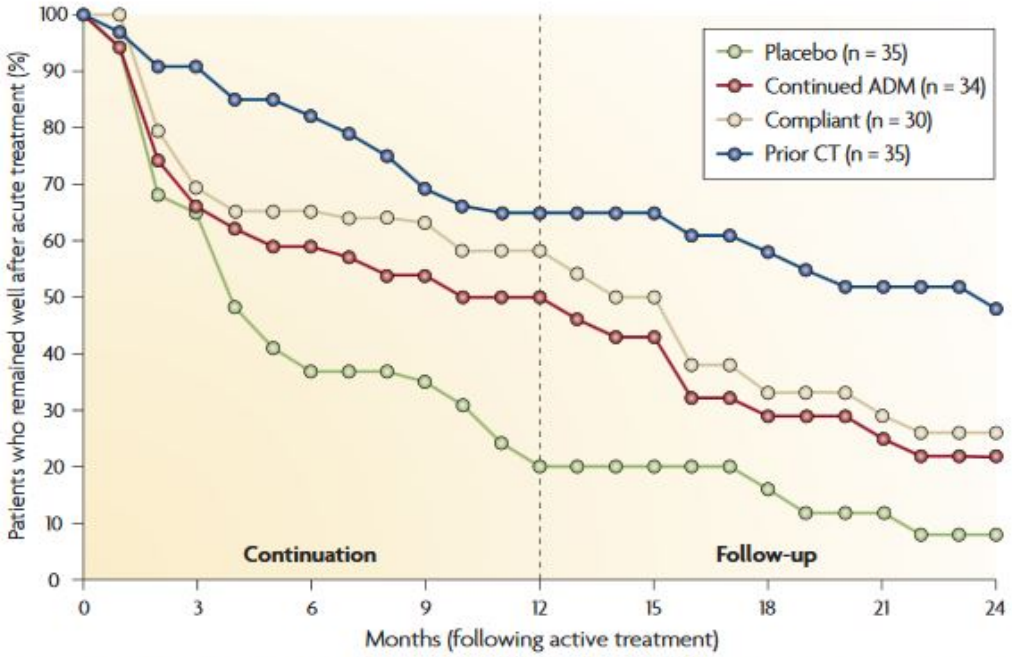


Figure 2 | **Less relapse after cognitive therapy compared with antidepressant medication.** The second phase of the parent antidepressant medication (ADM) versus cognitive therapy (CT) study[35] followed patients who had responded to ADM or to CT[38]. Patients who had responded to ADM were randomly assigned to either continue ADM treatment for one year (beige and red lines) or to change to placebo treatment for 1 year (green line). Patients who responded to CT were allowed three sessions of CT during the 1-year continuation period. In the follow-up period, none of the patients received any treatment. The figure shows that prior treatment with CT protected against relapse of depression at least as well as the continued provision of ADM, and better than ADM treatment that was subsequently discontinued. Note that the patient group that was given ADM in the continuation year contained a number of patients who did not adhere to the medication regimen. The red line indicates the response of the ADM-continuation group including these non-compliant patients, whereas the beige line shows the response of the patients in this group after the non-compliant patients had been removed from the analysis. Figure modified, with permission, from REF. 38 © (2005) American Medical Association.

(DeRubeis, Siegle, and Hollon 2008)

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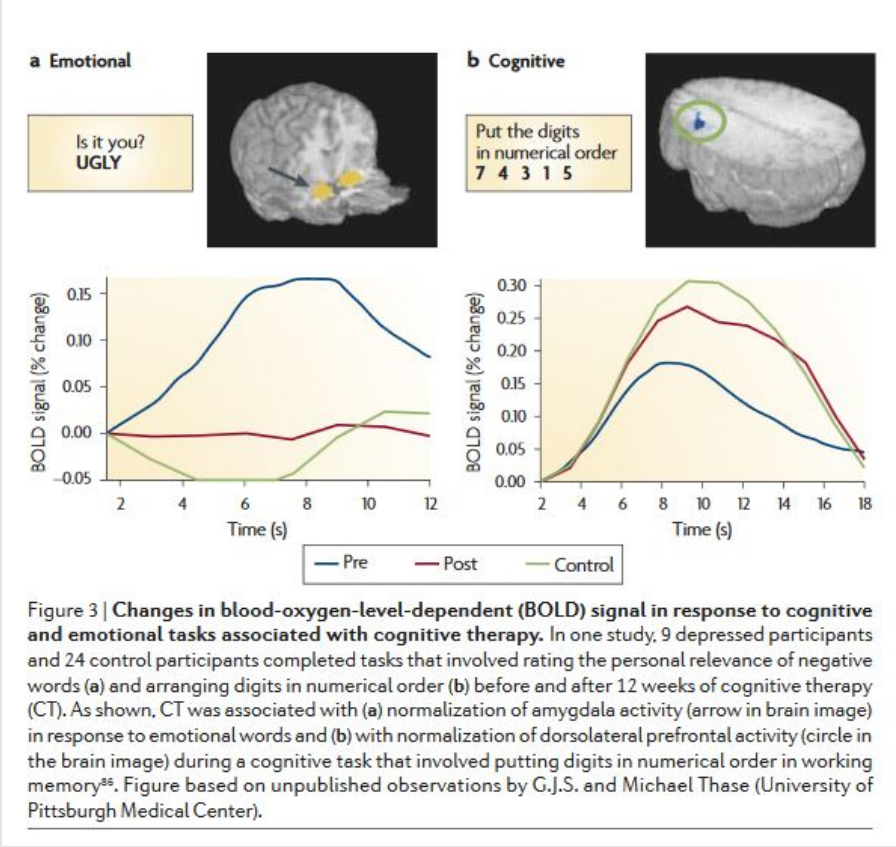


Figure 3 | **Changes in blood-oxygen-level-dependent (BOLD) signal in response to cognitive and emotional tasks associated with cognitive therapy.** In one study, 9 depressed participants and 24 control participants completed tasks that involved rating the personal relevance of negative words (**a**) and arranging digits in numerical order (**b**) before and after 12 weeks of cognitive therapy (CT). As shown, CT was associated with (**a**) normalization of amygdala activity (arrow in brain image) in response to emotional words and (**b**) with normalization of dorsolateral prefrontal activity (circle in the brain image) during a cognitive task that involved putting digits in numerical order in working memory[85]. Figure based on unpublished observations by G.J.S. and Michael Thase (University of Pittsburgh Medical Center).

(DeRubeis, Siegle, and Hollon 2008)

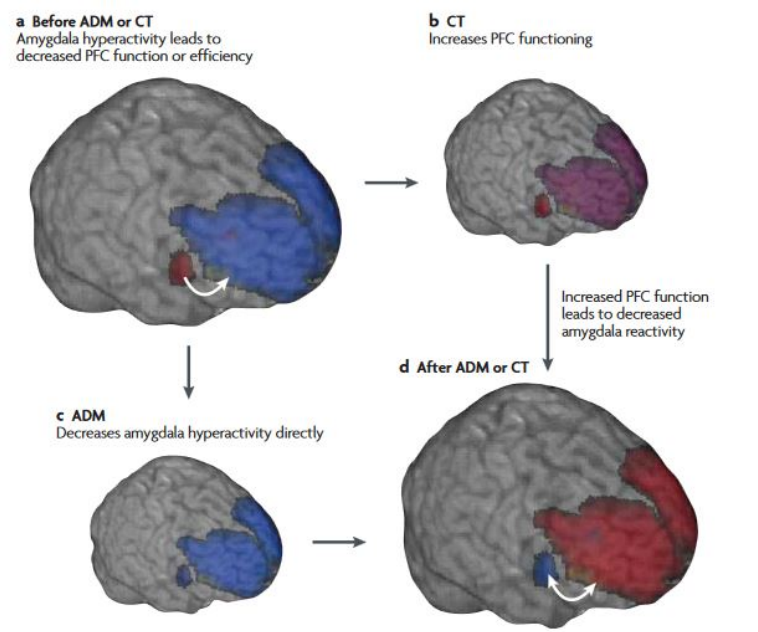
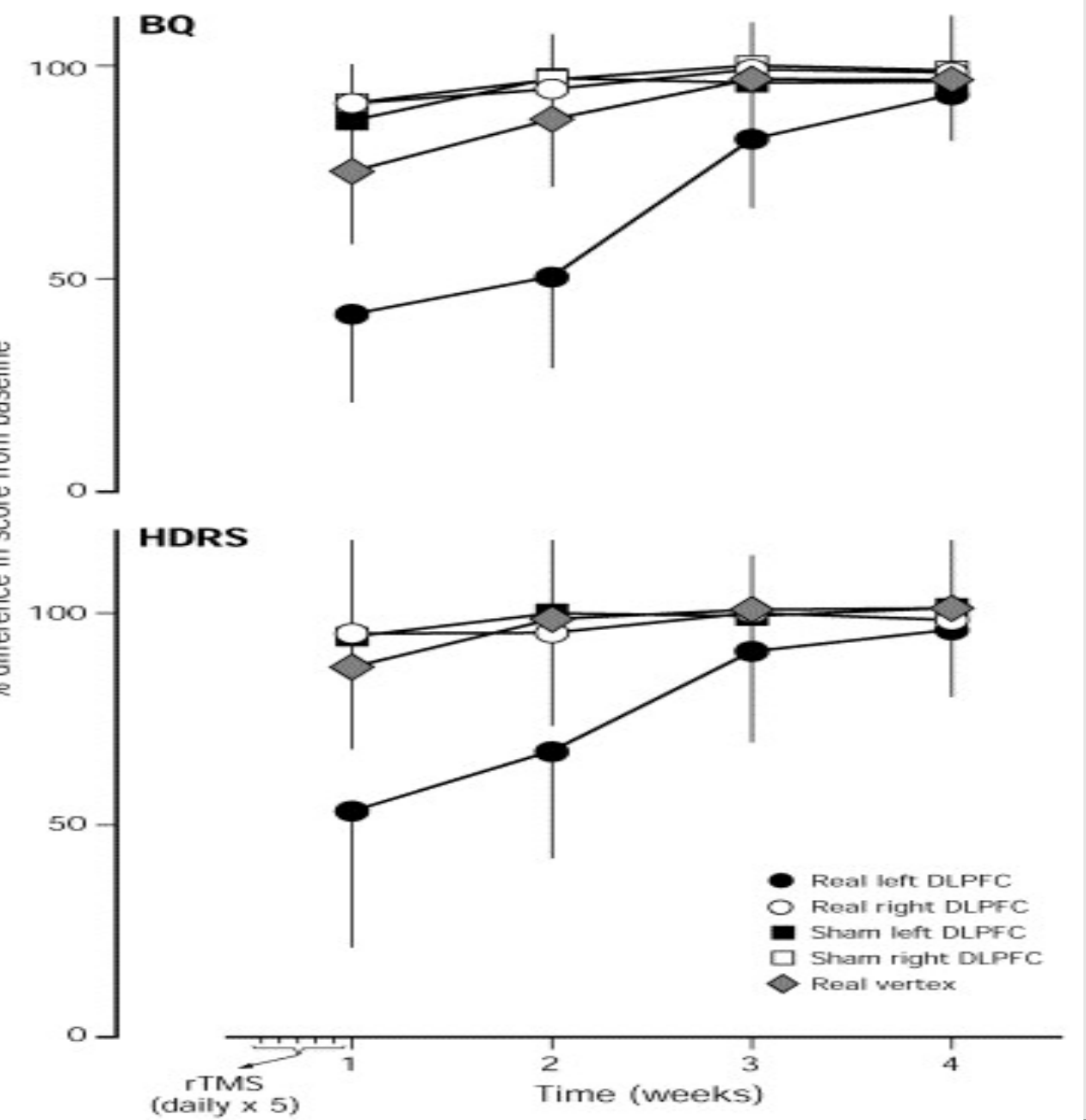


Figure 4 | **Hypothetical time course of the changes to amygdala and prefrontal function that are associated with antidepressant medication and cognitive therapy. a** | During acute depression, amygdala activity is increased (red) and prefrontal activity is decreased (blue) relative to activity in these regions in healthy individuals. **b** | Cognitive therapy (CT) effectively exercises the prefrontal cortex (PFC), yielding increased inhibitory function of this region. **c** | Antidepressant medication (ADM) targets amygdala function more directly, decreasing its activity. **d** | After ADM or CT, amygdala function is decreased and prefrontal function is increased. The double-headed arrow between the amygdala and the PFC represents the bidirectional homeostatic influences that are believed to operate in healthy individuals.

Rapid Rate Transcranial Magnetic Stimulation (rTMS)

- Lesion/neuroimaging studies link depression to left dorsolateral prefrontal lobe dysfunction
- Copper coil emits series of magnetic pulses that can inhibit or excite specific cortical structures; in this case, goal is an excitatory effect of PFC
- Actual mechanisms not well understood
- Noninvasive, but slightly painful to some individuals depending on their tolerance



Pascual-Leone, Rubio, Pallardo, & Cata

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

eurogenesis hypothesis, (Mahar et al. 201

- 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

epression'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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