

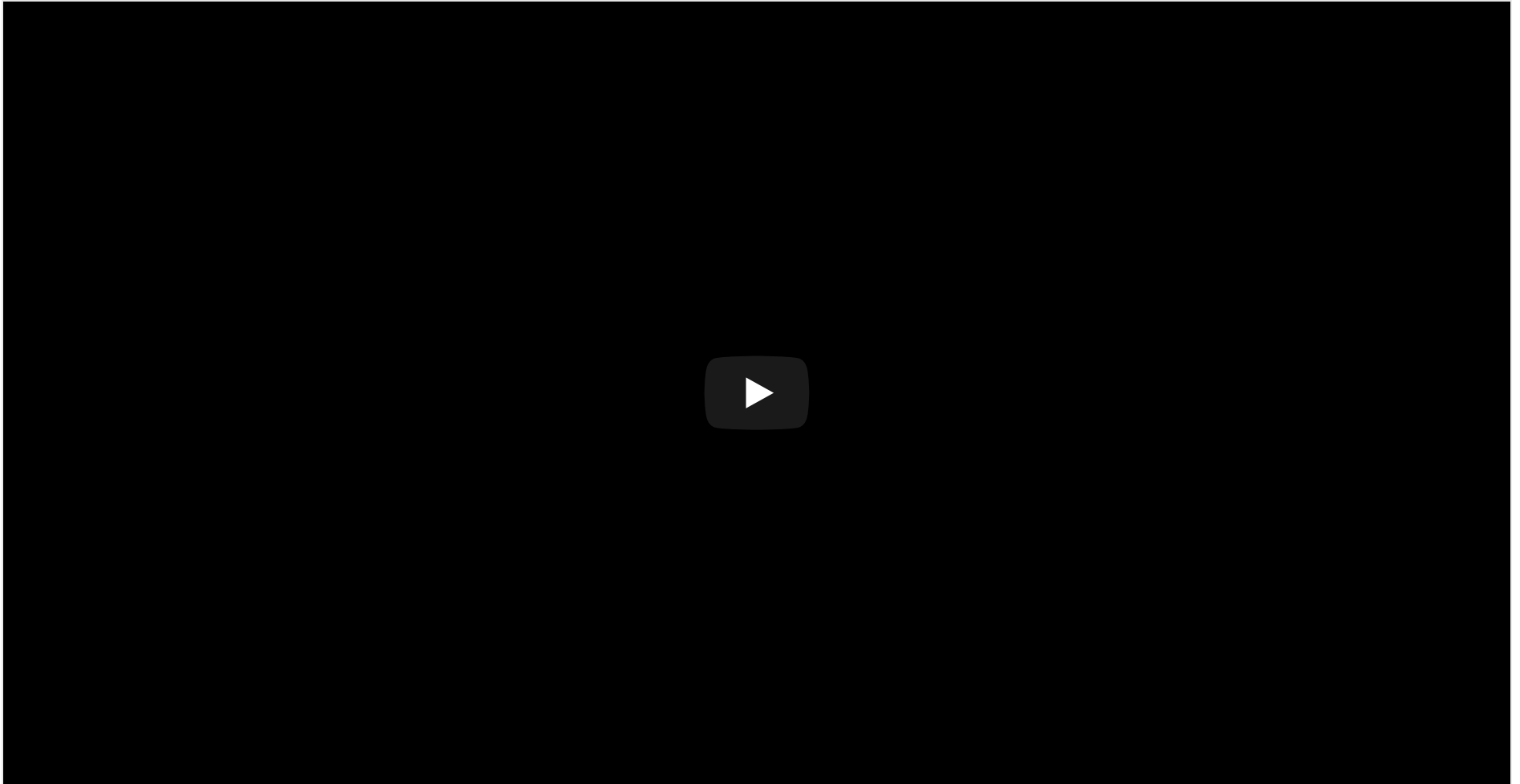
PSYCH 260/BBH 203

Depression and Bipolar Disorder

Rick O. Gilmore

2022-03-15 16:54:54

Prelude

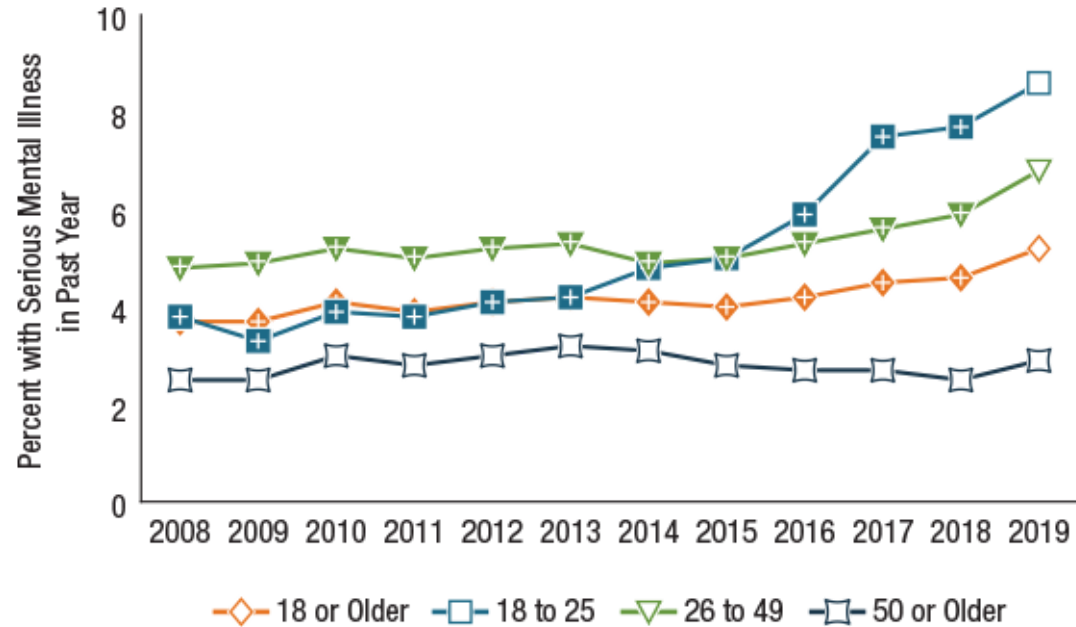


<https://www.youtube.com/embed/lioWzrpCtGQ>

Today's Topics

- The neuroscience of psychiatric disorders
- Major affective (mood) disorders
 - Major Depressive Disorder (depression)
 - Bipolar Disorder

Serious Mental Illness among Adults in the Past Year



<https://www.samhsa.gov/data/report/2019-nsduh-annual-national-report>

Neuroscience of psychiatric disorders

- Diagnosis via behavior & mood not specific “biomarker”
- Presume diseases of the mind are disorders of the brain
 - System-wide effects; no single or simple cause

Neuroscience of psychiatric disorders

- Heritability
 - *proportion of variance in trait accounted for by genetic factors*
 - Higher for psychiatric disorders than non-psychiatric diseases
 - Family member with mental illness highest known risk factor

Depression

Major Depressive Disorder

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

Symptoms

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

Table options ▼

[\(Mahar, Bambico, Mechawar, & Nobrega, 2014\)](#)

Depression

- Experienced by ~7% Americans in any year
- Prevalence (up to ~20% lifetime)
 - Females 2-3x males, higher 40+ years of age
- Heritability (large, 2.5 M Swedish population study)
 - Females 0.49 (twins); 0.51 (non-twin relatives)
 - Males 0.41 (twins); 0.36 (non-twin relatives)
 - [\(Kendler, Ohlsson, Lichtenstein, Sundquist, & Sundquist, 2018\)](#)

Neurobiology of Major Depressive Disorder (MDD)

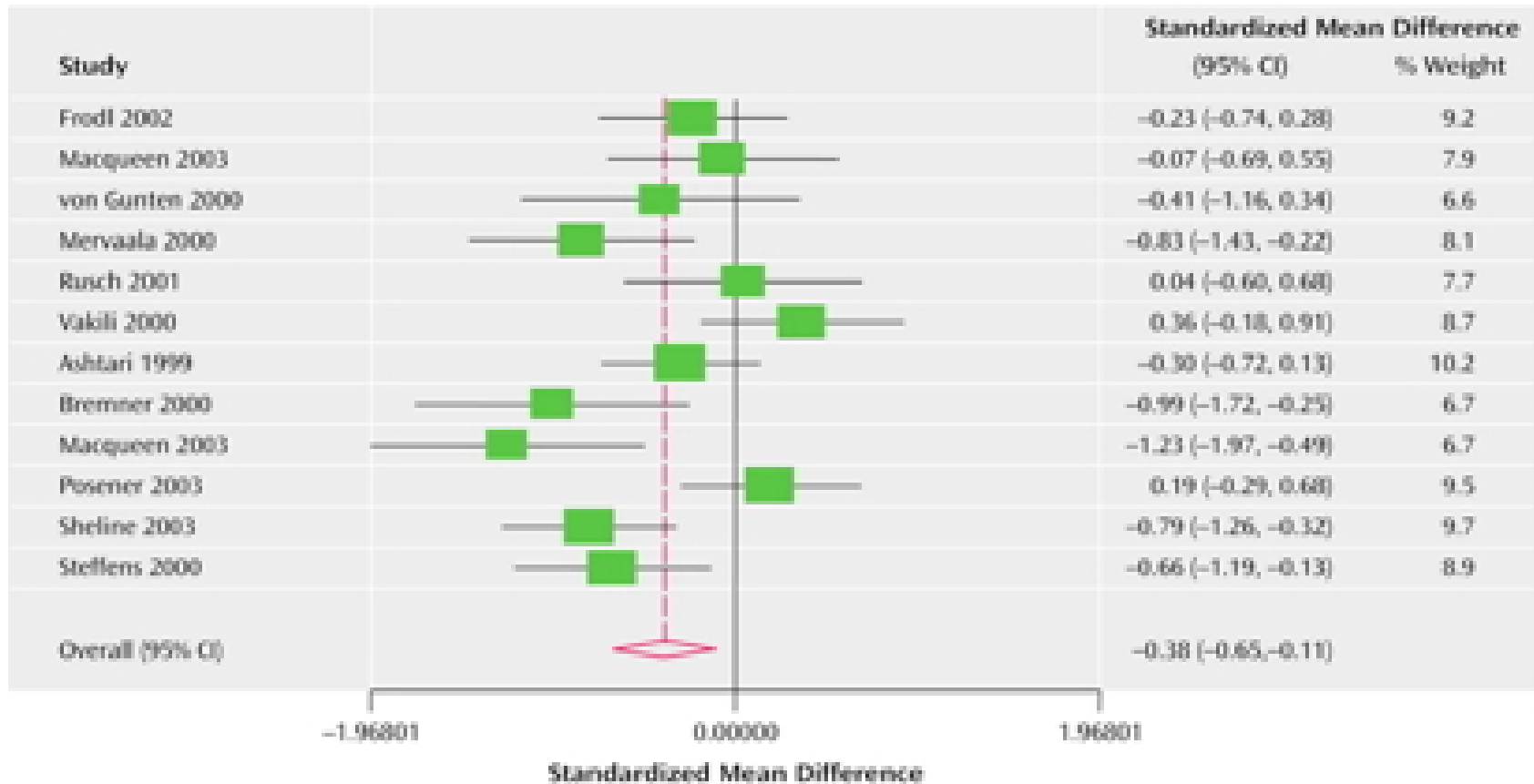
- Reduced sizes of brain regions
- Hypoactivity
- Pharmacological factors
- Synaptic dysfunction

MDD: Neurological factors

- Reduced hippocampal volumes
- [\(Videbech & Ravnkilde, 2004a\)](#) meta-analysis

(Videbech & Ravnkilde, 2004a)

Left Hippocampus



(Videbech & Ravnkilde, 2004b)

Right Hippocampus

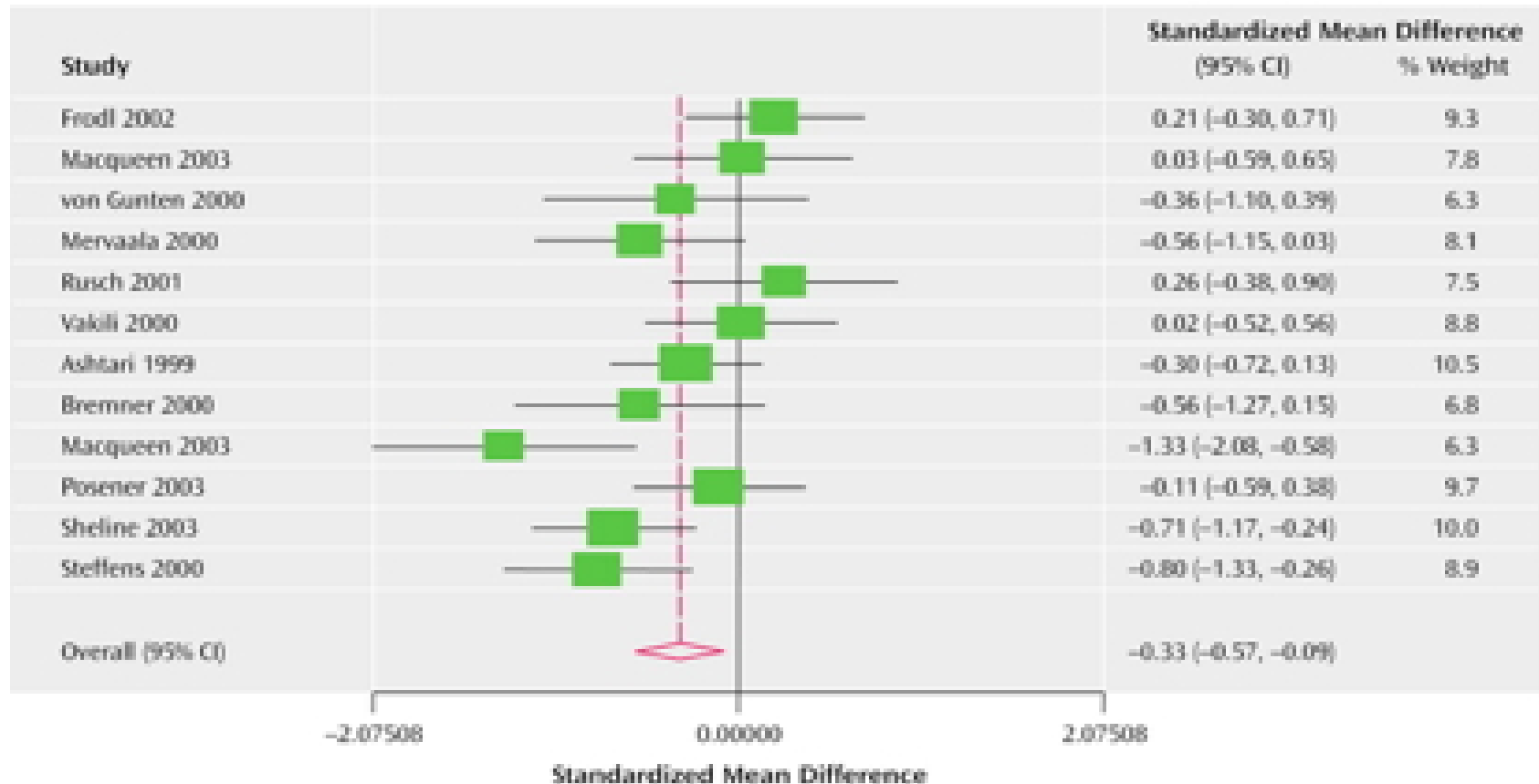


Table 1

Functional and structural changes in the limbic and PFC areas implicated in depression.

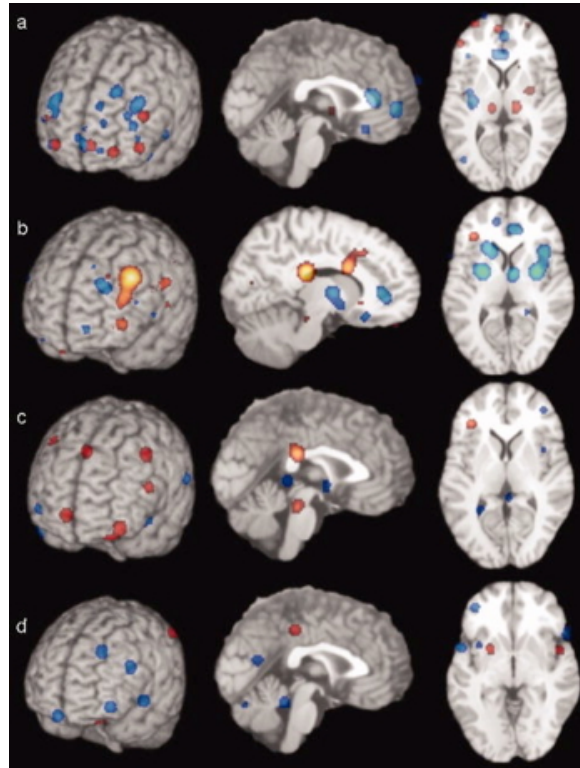
Substrate	Volume	Histological changes	Metabolic activity	Antidepressant effects
Orbital/VMPFC	↓	↓	↑	
Anterior cingulate cortex	↓			↓ Metabolic activity
Hippocampus	↓	↓		↑ Volume
Amygdala	↓?			↓ Metabolic activity
DLPFC	↓	↓	↓	

(Palazidou, 2012)

MDD: Neurological factors

- *Hypoactivity* ([Fitzgerald, Laird, Maller, & Daskalakis, 2008](#)) in
 - Frontal and temporal cortex
 - Anterior cingulate
 - Insula
 - Cerebellum

(Fitzgerald et al., 2008)

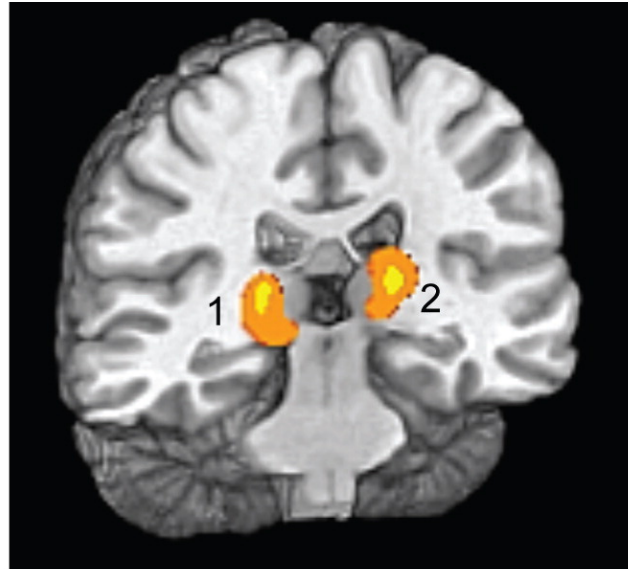


Row (a) patients v. controls, (b) patients on SSRIs, (c) patients v. ctrl (happy stim), (d) patients v. controls (sad stim)

Neurological factors

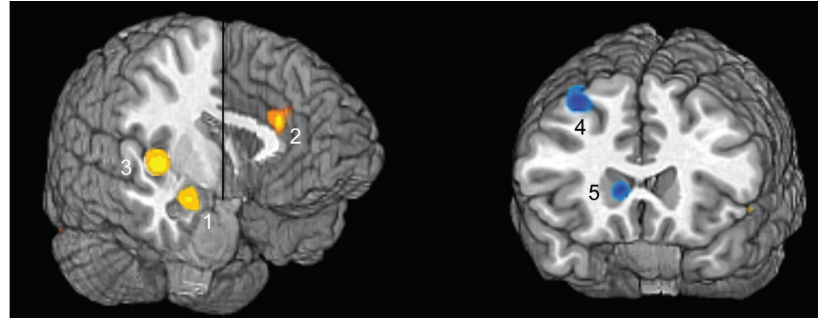
- *Hyperactivity* ([Hamilton et al., 2012](#))
 - At baseline: in pulvinar nucleus of thalamus
 - In response to negative stimuli: amygdala, insula, anterior cingulate
- *Hypoactivity*
 - In response to negative stimuli: prefrontal cortex, striatum of basal ganglia

Baseline hyperactivity [\(Hamilton et al., 2012\)](#)



Structure	Direction of Effect	Talairach Coordinates	Cluster Size (mm ³)	Number
Pulvinar nucleus	Depressed > Comparison	-15, -24, 8	3,054	1
Pulvinar nucleus	Depressed > Comparison	17, -25, 4	2,514	2

Hyper/hypo-activity specific to emotional valence (Hamilton et al., 2012)

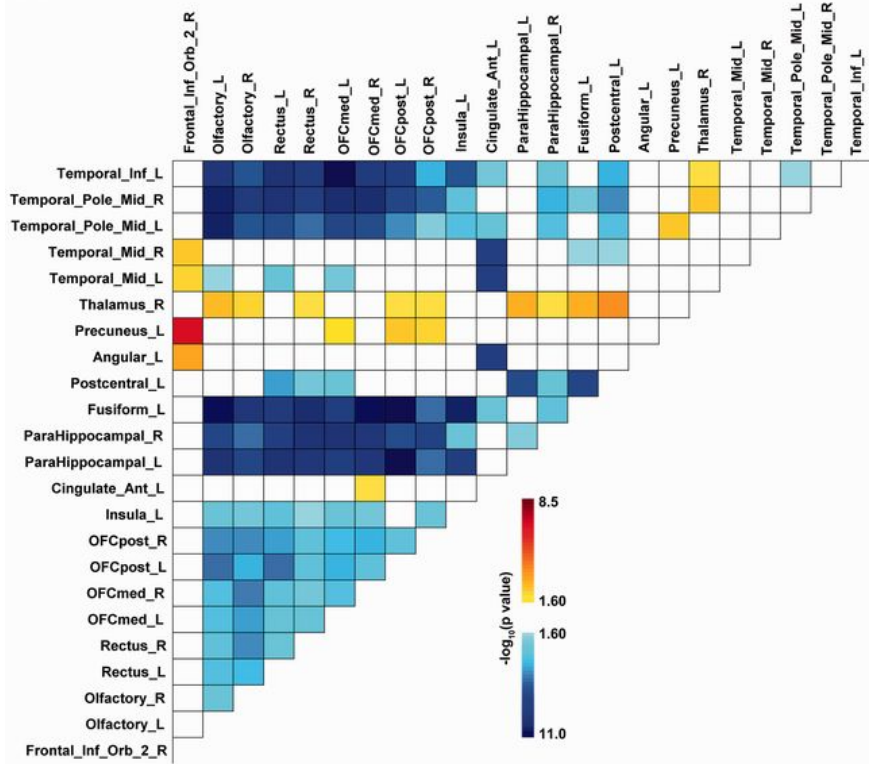
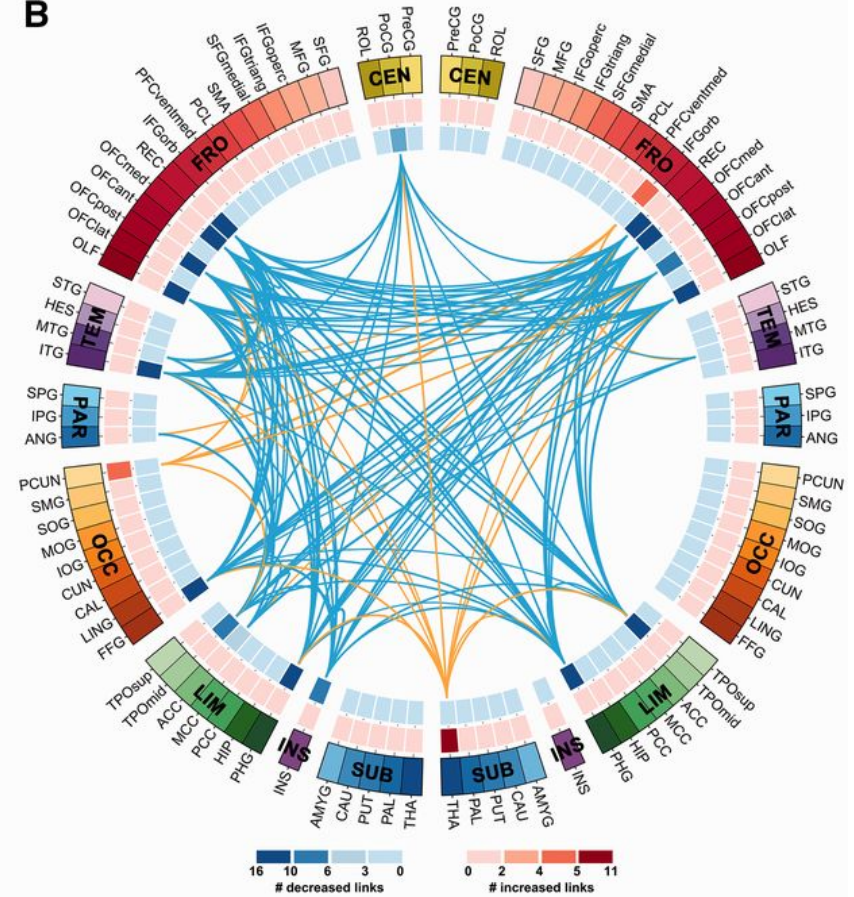


Structure	Direction of Effect	Valence Specific Effect?	Talairach Coordinates	Cluster Size (mm ³)	Number
Amygdala	Depressed > Comparison	Yes	24, -4, -13	318	1
Dorsal anterior cingulate cortex	Depressed > Comparison	Yes	-2, 30, 20	196	2
Insula and superior temporal gyrus	Depressed > Comparison	Yes	-38, -6, -8	834	3
Precentral gyrus	Depressed > Comparison	Yes	-30, -15, 44	621	-
Middle temporal gyrus	Depressed > Comparison	Yes	-39, -64, 17	440	-
Dorsolateral prefrontal cortex	Comparison > Depressed	Yes	30, 13, 47	1,380	4
Dorsolateral prefrontal cortex	Comparison > Depressed	No	-22, 27, 42	949	-
Caudate body	Comparison > Depressed	No	10, 20, 6	382	5

Disrupted connectivity

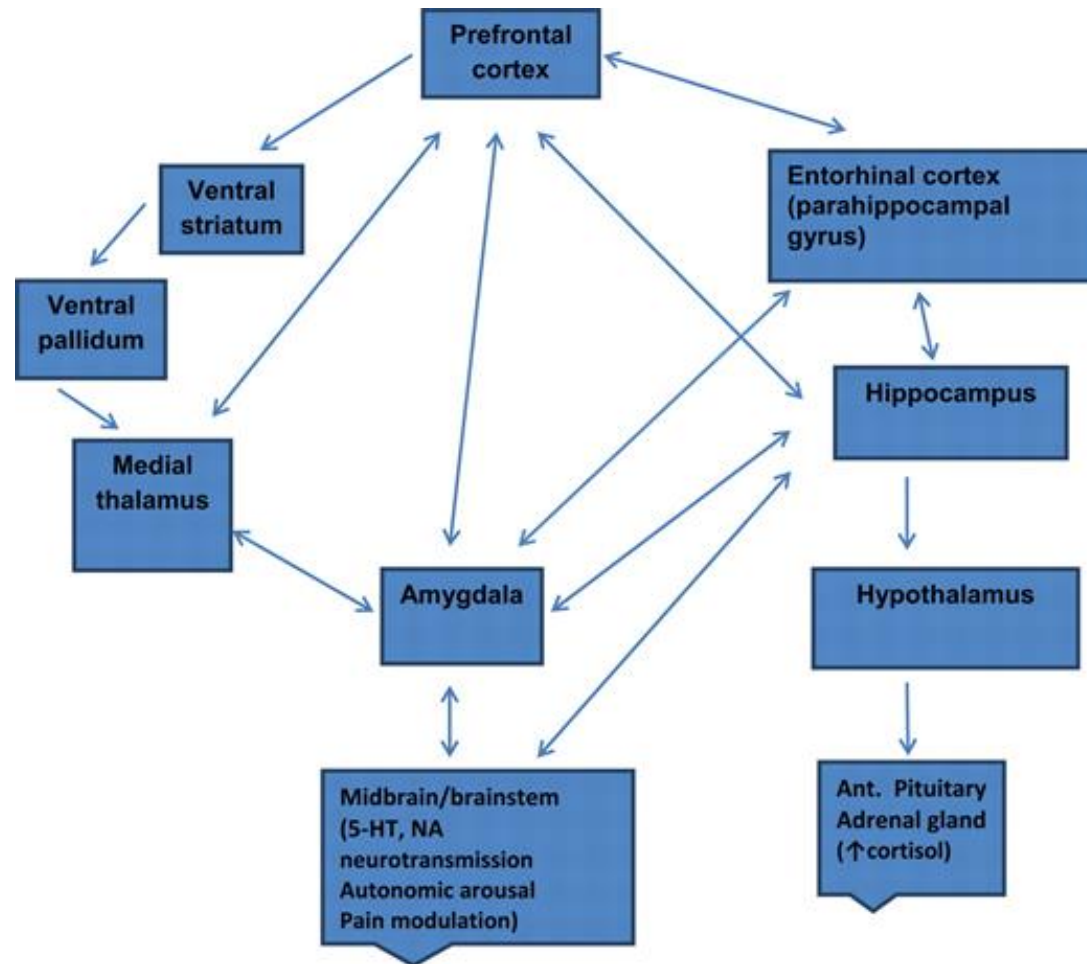
- Resting state fMRI (rsfMRI) in $n = 421$ patients with major depressive disorder and $n = 488$ control subjects.
- *Reduced* connectivity between orbitofrontal cortex (OFC) and other areas of the brain
- *Increased* connectivity between lateral PFC and other brain areas

[\(Cheng et al., 2016\)](#)

A**B**

(Cheng et al., 2016)

MDD: Network of areas implicated



(Palazidou, 2012)

Pharmacological factors

- Endocrine
 - Thyroid dysfunction ([Medici et al., 2014](#))
 - Altered cortisol reactivity ([Burke, Davis, Otte, & Mohr, 2005](#))

MDD: Pharmacological factors

- Monoamine hypothesis
 - More: euphoria
 - Less: depression
 - Reserpine (antagonist for NE & 5-HT) can cause depression
 - Low serotonin (5-HT) metabolite levels in CSF of suicidal depressives ([Samuelsson, Jokinen, Nordström, & Nordström, 2006](#))

Measuring 5-HT

- CSF, platelets, plasma, urine, saliva
- CSF & platelets correlate highly ([Audhya, Adams, & Johansen, 2012](#))
- But, salivary 5-HT does not correlate with mood symptoms ([Leung et al., 2018](#))

MDD: Pharmacological factor summary

Table 2

Neurochemical/hormonal abnormalities in depression.

Substrate	Concentration/activity
Cortisol, CRH	↑
Proinflammatory cytokines	↑
BDNF	↓
5-HT neurotransmission	↓
NA neurotransmission	↓

[\(Palazidou, 2012\)](#)

Treatments for depression

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

Drugs

- Monoamine oxidase (MAO) inhibitors
 - MAO destroys excess monoamines in terminal buttons & glia
 - 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 of 5-HT in synaptic cleft
 - Also increase brain steroid production
- Selective Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Cymbalta (SNRI)

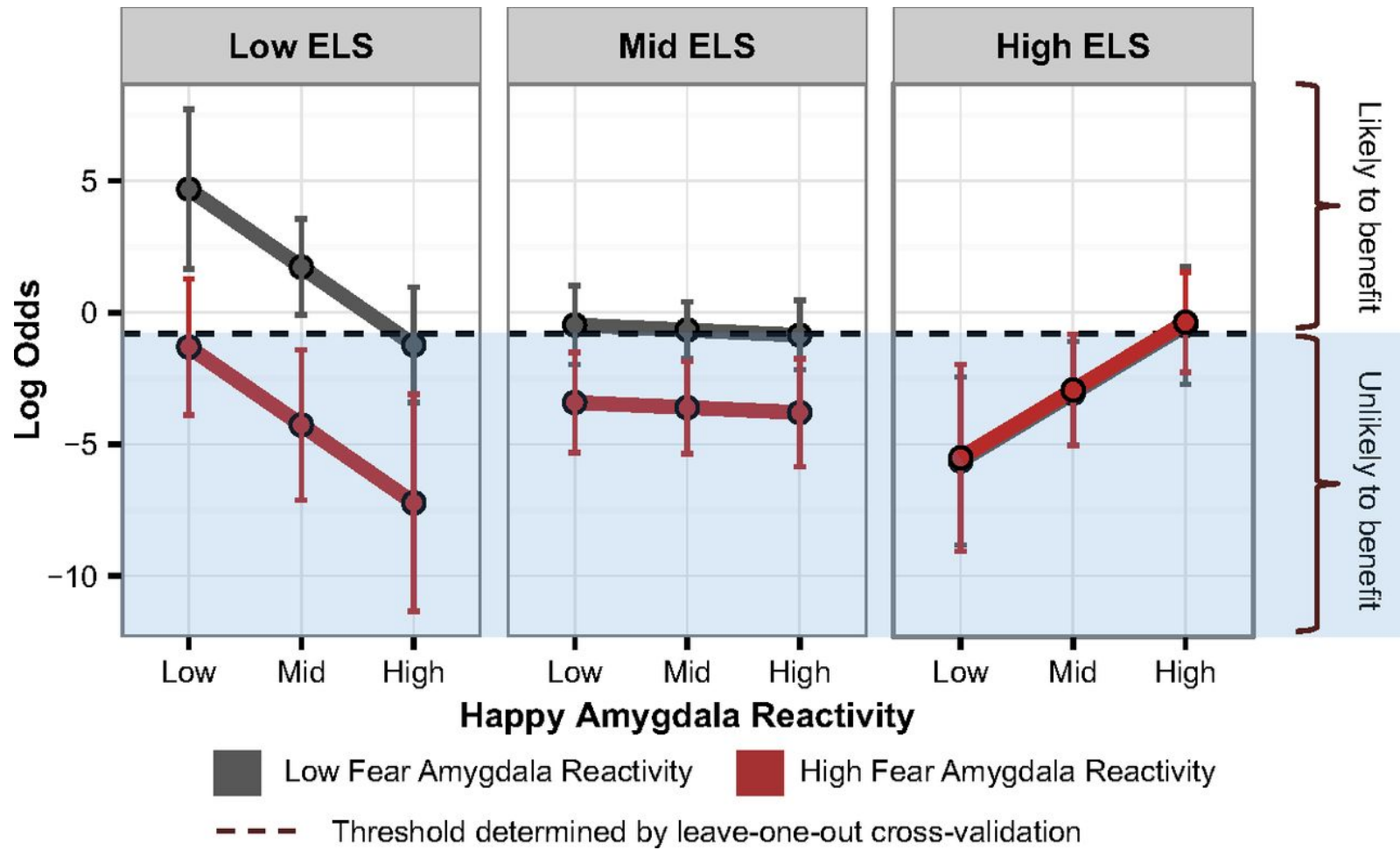


How well do the drugs work?

- [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
- 6-7 weeks to show response

Who benefits from drug therapy?

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



(Goldstein-Piekarski et al., 2016)

Monoamine hypothesis of depression

- Disrupted (lowered) levels of monoamines (especially NE & 5-HT) result in depression

Problems with monoamine hypothesis

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

"No correlation between serotonin and its metabolite 5-HIAA in the cerebrospinal fluid and [11C]AZ10419369 binding measured with PET in healthy volunteers." ([Tiger et al., 2015](#))

"...we performed the first meta-analysis of the mood effects in [acute tryptophan depletion] ATD and [alpha-methyl-para-tyrosine] APTD studies. The depletion of monoamine systems (both 5-HT and NE/DA) does not decrease mood in healthy controls. However, in healthy controls with a family history of MDD the results suggest that mood is slightly decreased...by [monoamine depletion]..."

(Ruhé, Mason, & Schene, 2007)

What do drugs do, then?

- Alter receptor sensitivity?
 - 5-HT presynaptic autoreceptors compensate
 - Postsynaptic upregulation of NE/5-HT effects

What do drugs do, then?

- Stimulate neurogenesis?
 - Link to neurotrophin, brain-derived nerve growth factor (BDNF)
 - BDNF boosts neurogenesis
 - SSRIs stimulate growth of new neurons in hippocampus

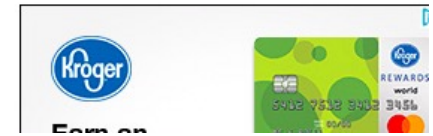
Neurogenesis hypothesis, ([Mahar et al., 2014](#))

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

Health

In biggest advance for depression in years, FDA approves novel treatment for hardest cases

The nasal spray works in a new way and is based on an old anesthetic, ketamine, that has been used as a party drug.



[Washington Post, 2019-03-06](#)

Ketamine

- Selective antagonist of the NMDA receptor, an ionotropic glutamate receptor
- Relieves depressive symptoms relatively quickly ([Berman et al., 2000](#)) and ([Zarate et al., 2006](#))
- Boosts synaptic spine formation ([Li et al., 2010](#)) and reverses effects of induced stress

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, Heijnen, Broek, & Birkenhäger, 2012](#))
- Seems to work via
 - Anticonvulsant (block Na⁺ channel or enhance GABA function) effects
 - Neurotrophic (stimulates neurogenesis) effects

ECT more effective than Ketamine?

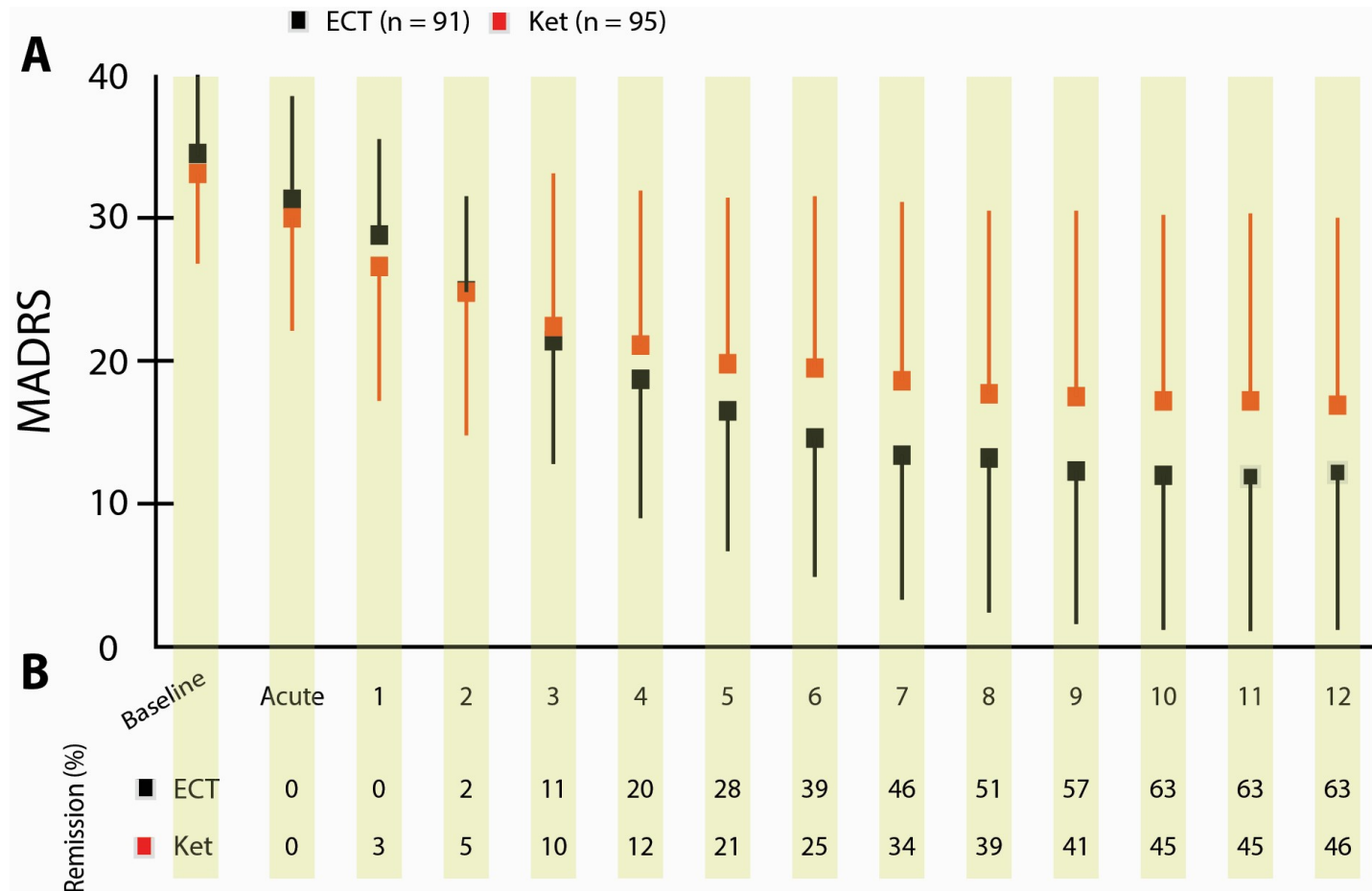


Fig 3: [\(Ekstrand et al., 2021\)](#)

The promise of deep brain stimulation



Depression's impact

- Widespread brain dysfunction
- Prefrontal cortex, amygdala, HPA axis, circadian rhythms
- Genetic + environmental factors
- Disturbance in 5-HT, NE systems, cortisol
- Metabolic pathways ([Pu et al., 2020](#))
- Many sufferers do not respond to available treatments

Points on depression

- Drug treatments affect neuromodulator NT systems, but
 - Can't effectively measure NT levels
 - Neuromodulators interact, so many side-effects
- 'Monoamine hypothesis' of depression is at-best incomplete

- 'Talk' therapies can change behavior/mood by creating new/strengthened circuits
- Emerging therapies (ketamine, deep brain stimulation) show promise, but...

“Leading biological hypotheses propose that biological changes may underlie major depressive disorder onset and relapse/recurrence. Here, we investigate if there is prospective evidence for biomarkers derived from leading theories. We focus on neuroimaging, gastrointestinal factors, immunology, neurotrophic factors, neurotransmitters, hormones, and oxidative stress....Our search resulted in 67,464 articles”

[\(Kennis et al., 2020\)](#)

"...Only cortisol (N=19, OR=1.294, p=0.024) showed a predictive effect on onset/relapse/recurrence of MDD, but not on time until MDD onset/relapse/recurrence."

"However, this effect disappeared when studies including participants with a baseline clinical diagnosis were removed from the analyses..."

[\(Kennis et al., 2020\)](#)

"...there is a lack of evidence for leading biological theories for onset and maintenance of depression. Only cortisol was identified as potential predictor for MDD, but results are influenced by the disease state. High-quality (prospective) studies on MDD are needed to disentangle the etiology and maintenance of MDD."

[\(Kennis et al., 2020\)](#)

Bipolar disorder

Bipolar disorder

- Formerly “manic depression” or “manic depressive disorder”
- Alternating mood states
 - Mania or hypomania (milder form)
 - Depression
- Cycles 3-6 mos in length, but
 - Rapid cycling (weeks or days)
- Suicide risk 20-60x normal population, [\(Baldessarini, Pompili, & Tondo, 2006\)](#)

Symptoms

Symptoms of mania or a manic episode include:	Symptoms of depression or a depressive episode include:
<p>Mood Changes</p> <ul style="list-style-type: none">▶ A long period of feeling "high," or an overly happy or outgoing mood▶ Extreme irritability <p>Behavioral Changes</p> <ul style="list-style-type: none">▶ Talking very fast, jumping from one idea to another, having racing thoughts▶ Being easily distracted▶ Increasing activities, such as taking on new projects▶ Being overly restless▶ Sleeping little or not being tired▶ Having an unrealistic belief in one's abilities▶ Behaving impulsively and engaging in pleasurable, high-risk behaviors	<p>Mood Changes</p> <ul style="list-style-type: none">▶ An overly long period of feeling sad or hopeless▶ Loss of interest in activities once enjoyed, including sex. <p>Behavioral Changes</p> <ul style="list-style-type: none">▶ Feeling tired or "slowed down"▶ Having problems concentrating, remembering, and making decisions▶ Being restless or irritable▶ Changing eating, sleeping, or other habits▶ Thinking of death or suicide, or attempting suicide.

<http://www.nimh.nih.gov/health/topics/bipolar-disorder/index.shtml>

Prevalence, subtypes

- 1-3% lifetime prevalence, subthreshold affects another ~2% ([Merikangas et al., 2007](#))
- Subtypes
 - **Bipolar I:** manic episodes, possible depressive ones
 - **Bipolar II:** no manic episodes but hypomania (disinhibition, irritability/agitation) + depression

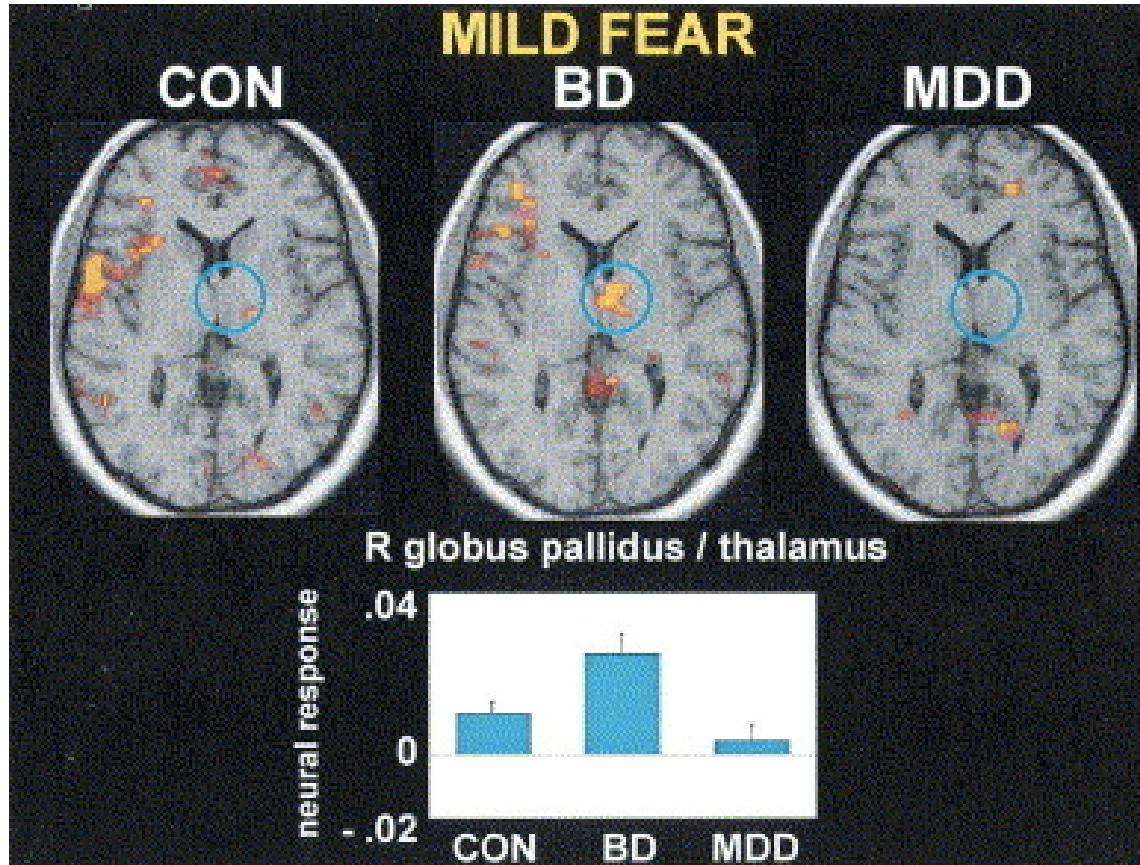
Related symptoms

- Psychosis (hallucinations or delusions)
- Anxiety, attention-deficit hyperactivity disorder (ADHD)
- Substance abuse

Genetics

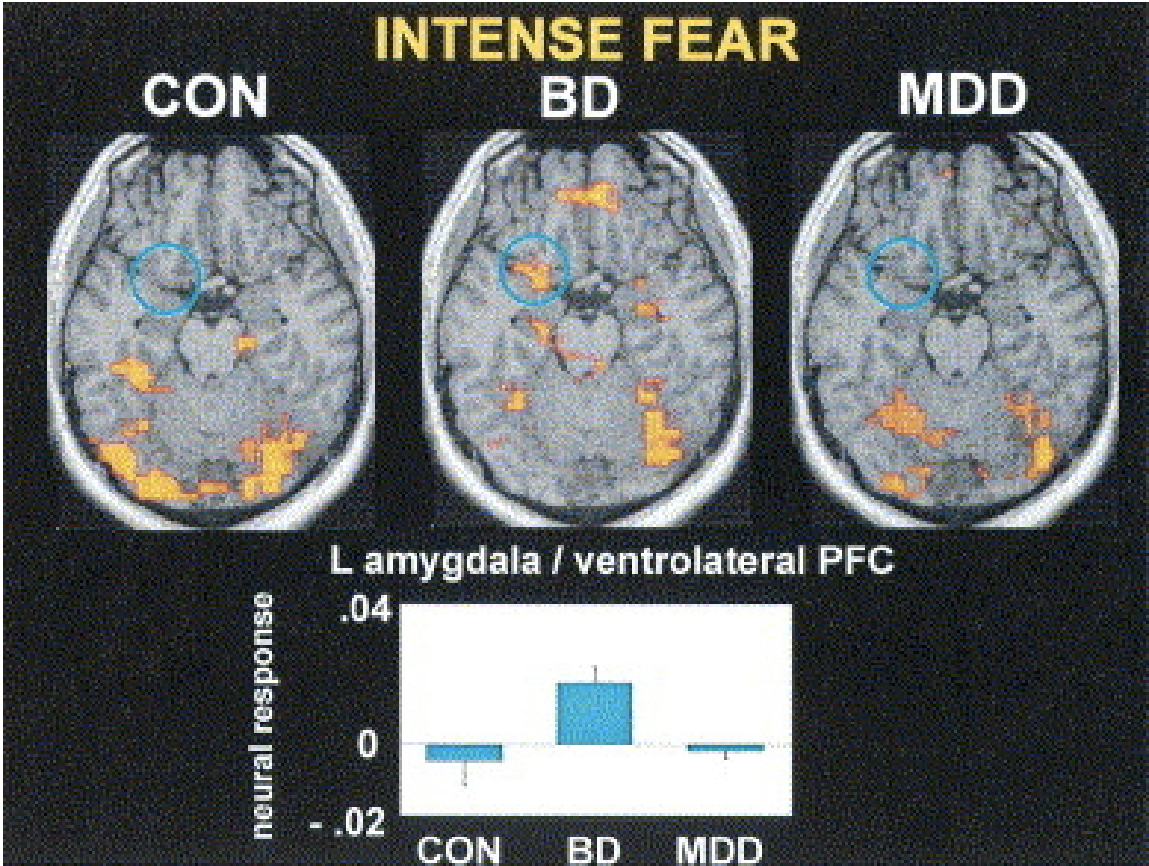
- Overlap between bipolar disorder and schizophrenia
- Genes for voltage-gated Ca⁺⁺ channels
 - Regulate NT, hormone release
 - Gene expression, cell metabolism
- [\(Craddock & Sklar, 2013\)](#)

Brain responses to emotional faces \neq depression

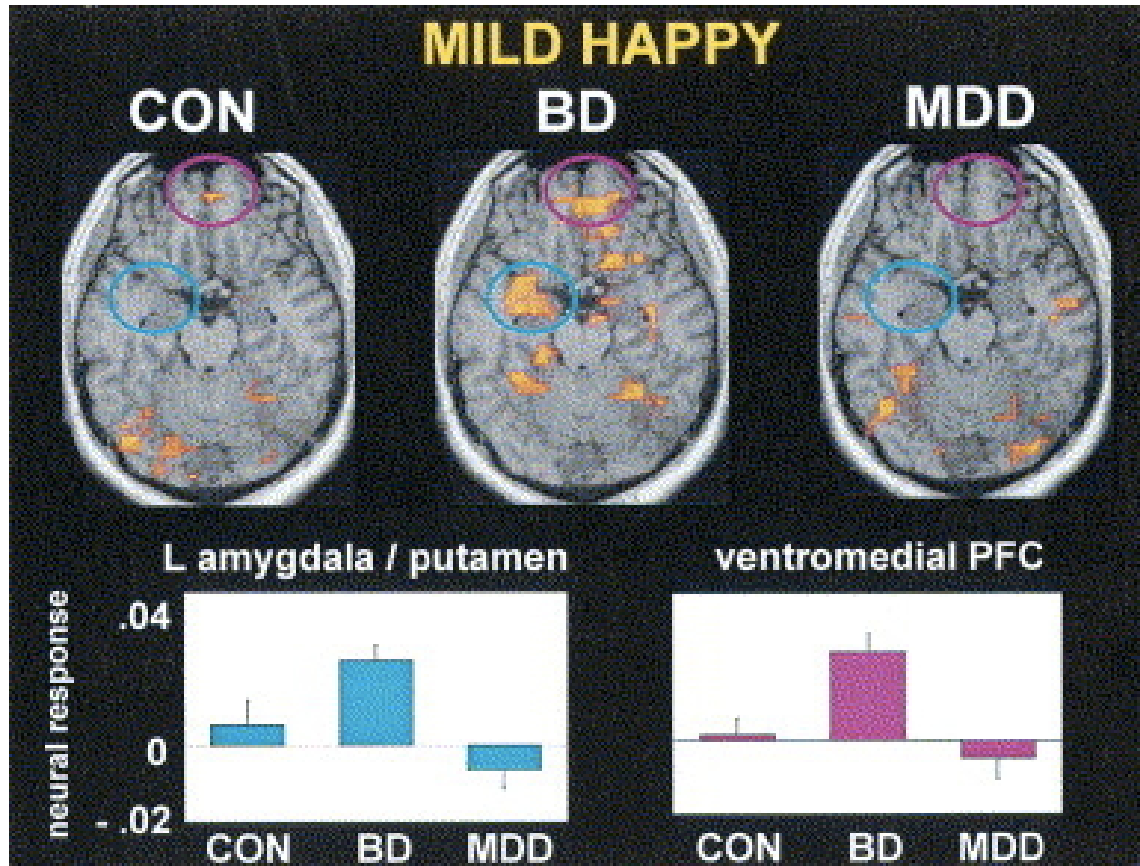


(Lawrence et al., 2004)

(Lawrence et al., 2004)



(Lawrence et al., 2004)



**Amygdala, hippocampus volume reduced;
ventricles larger**

(Hallahan et al., 2011)

Results

Individuals with bipolar disorder had increased right lateral ventricular, left temporal lobe, and right putamen volumes. Bipolar patients taking lithium displayed significantly increased hippocampal and amygdala volume compared with patients not treated with lithium and healthy comparison subjects. Cerebral volume reduction was significantly associated with illness duration in bipolar individuals.

Conclusions

The application of mega-analysis to bipolar disorder imaging identified lithium use and illness duration as substantial and consistent sources of heterogeneity, with lithium use associated with regionally specific increased brain volume.

Drug treatments

- Anti-depressants not especially effective ([Sidor & MacQueen, 2012](#))
- Mood stabilizers
 - Lithium (Li)
 - Valproate (Depakote)

- Anticonvulsants
 - Usually to treat epilepsy
 - GABA agonists
 - e.g. lamotrigine (Lamictal)
- Atypical antipsychotics

Lithium “discovered” accidentally

- [John Cade](#) discovered in 1948
- Injections of manic patients' urine with a lithium compound (chemical stabilizer) into guinea pig test animals
- Had calming effect
- Earliest effective medications for treating mental illness

Effects of lithium

- Reduces mania, minimal effects on depressive states
- Preserves PFC, hipp, amyg volumes
- Has other 'neuroprotective' effects ([Machado-Vieira, Manji, & Zarate, 2009](#))

Effects of lithium

- downregulates DA, glutamate; upregulates GABA
- modulates 5-HT, NE
- *levels can be tested/monitored via blood test*
- [\(Malhi, Tanious, Das, Coulston, & Berk, 2013\)](#)

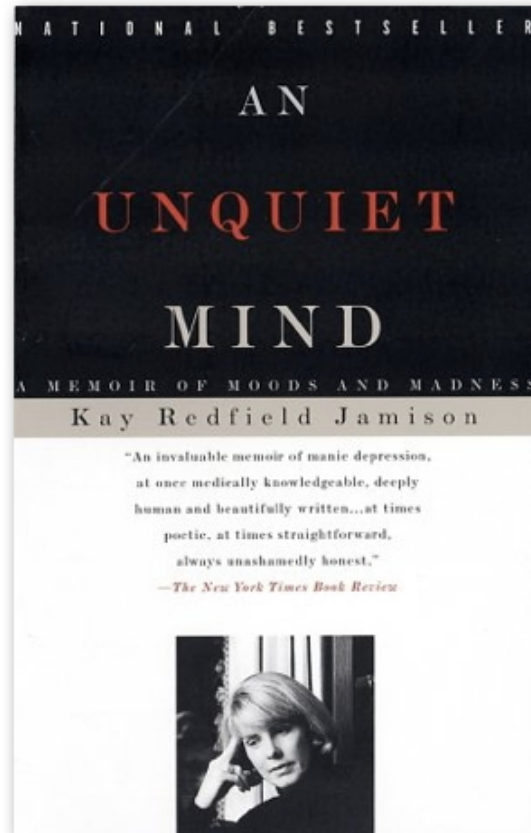
Other treatment options

- Psychotherapy
- Electroconvulsive Therapy (ECT)
- Sleep medications

Prospects

- STEP-BD cohort ($n = 1,469$)
 - 58% achieved recovery
 - 49% (of recovered) had recurrences within 2 years
 - Residual depressive symptoms can persist
- [\(Geddes & Miklowitz, 2013\)](#)

An Unquiet Mind



BP summed-up

- Changes in mood, but \neq depression
- Genetic + environmental risk
- Changes in emotion processing network activity, size of hippocampus
- Heterogeneous
- No simple link to a specific NT system

Next time...

- Schizophrenia

References

- Audhya, T., Adams, J. B., & Johansen, L. (2012). Correlation of serotonin levels in CSF, platelets, plasma, and urine. *Biochimica Et Biophysica Acta*, 1820(10), 1496–1501. <https://doi.org/10.1016/j.bbagen.2012.05.012>
- Baldessarini, R. J., Pompili, M., & Tondo, L. (2006). Suicide in Bipolar Disorder: Risks and Management. *CNS Spectrums*, 11(06), 465–471. <https://doi.org/10.1017/S1092852900014681>
- Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., & Krystal, J. H. (2000). Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry*, 47(4), 351–354. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/10686270>
- Burke, H. M., Davis, M. C., Otte, C., & Mohr, D. C. (2005). Depression and cortisol responses to psychological stress: A meta-analysis. *Psychoneuroendocrinology*, 30(9), 846–856. <https://doi.org/10.1016/j.psyneuen.2005.02.010>
- Cheng, W., Rolls, E. T., Qiu, J., Liu, W., Tang, Y., Huang, C.-C., ... Feng, J. (2016). Medial reward and lateral non-reward orbitofrontal cortex circuits change in opposite directions in depression. *Brain*, aww255. <https://doi.org/10.1093/brain/aww255>
- Craddock, N., & Sklar, P. (2013). Genetics of bipolar disorder. *The Lancet*, 381(9878), 1654–1662. [https://doi.org/10.1016/S0140-6736\(13\)60855-7](https://doi.org/10.1016/S0140-6736(13)60855-7)
- Dierckx, B., Heijnen, W. T., Broek, W. W. van den, & Birkenhäger, T. K. (2012). Efficacy of electroconvulsive therapy in bipolar versus unipolar major depression: A meta-analysis. *Bipolar Disorders*, 14(2), 146–150. <https://doi.org/10.1111/j.1399-5618.2012.00997.x>
- Ekstrand, J., Fattah, C., Persson, M., Cheng, T., Nordanskog, P., Åkeson, J., ... Movahed Rad, P. (2021). Racemic ketamine as an alternative to electroconvulsive therapy for unipolar depression: A randomized, Open-Label, Non-Inferiority trial (KetECT). *The International Journal of*