511-2018-11-09-depression

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Today's topic(s)

- Depression
- Planning for student-led presentations

Depression

- Symptoms
  - Unhappy mood, 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, Bambico, Mechawar, & Nobrega, 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

Table options

Neurobiology of Major Depressive Disorder (MDD)

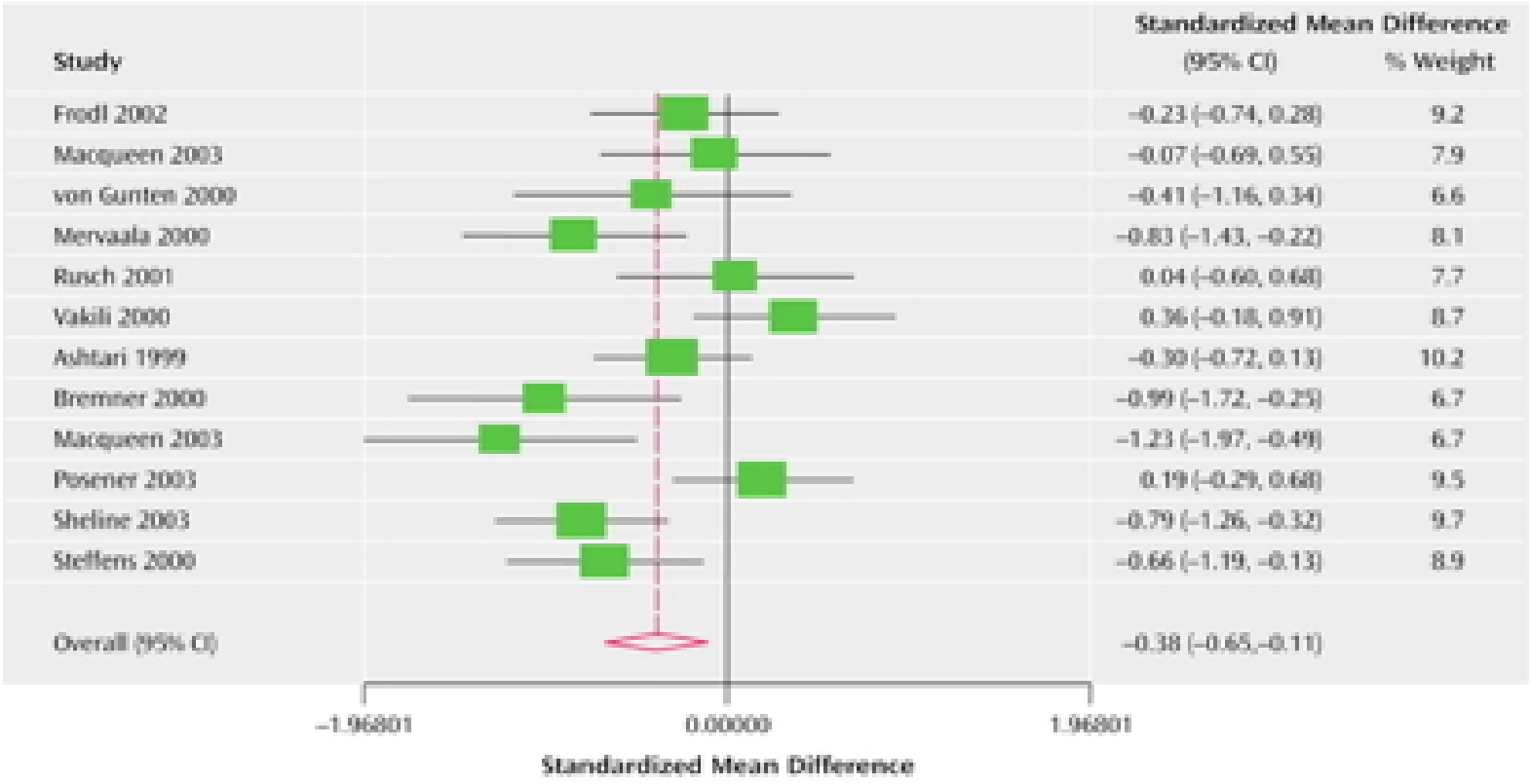
- Reduced sizes of brain regions
- Hypoactivity
- Pharmacological factors
- Synaptic neurotrophic dysfunction

Neurological factors

- Reduced hippocampal volumes
- (Videbech & Ravnkilde, 2004a) meta-analysis

(Videbech & Ravnkilde, 2004a)

Left Hippocampus



(Videbech & Ravnkilde, 2004b)

Right Hippocampus

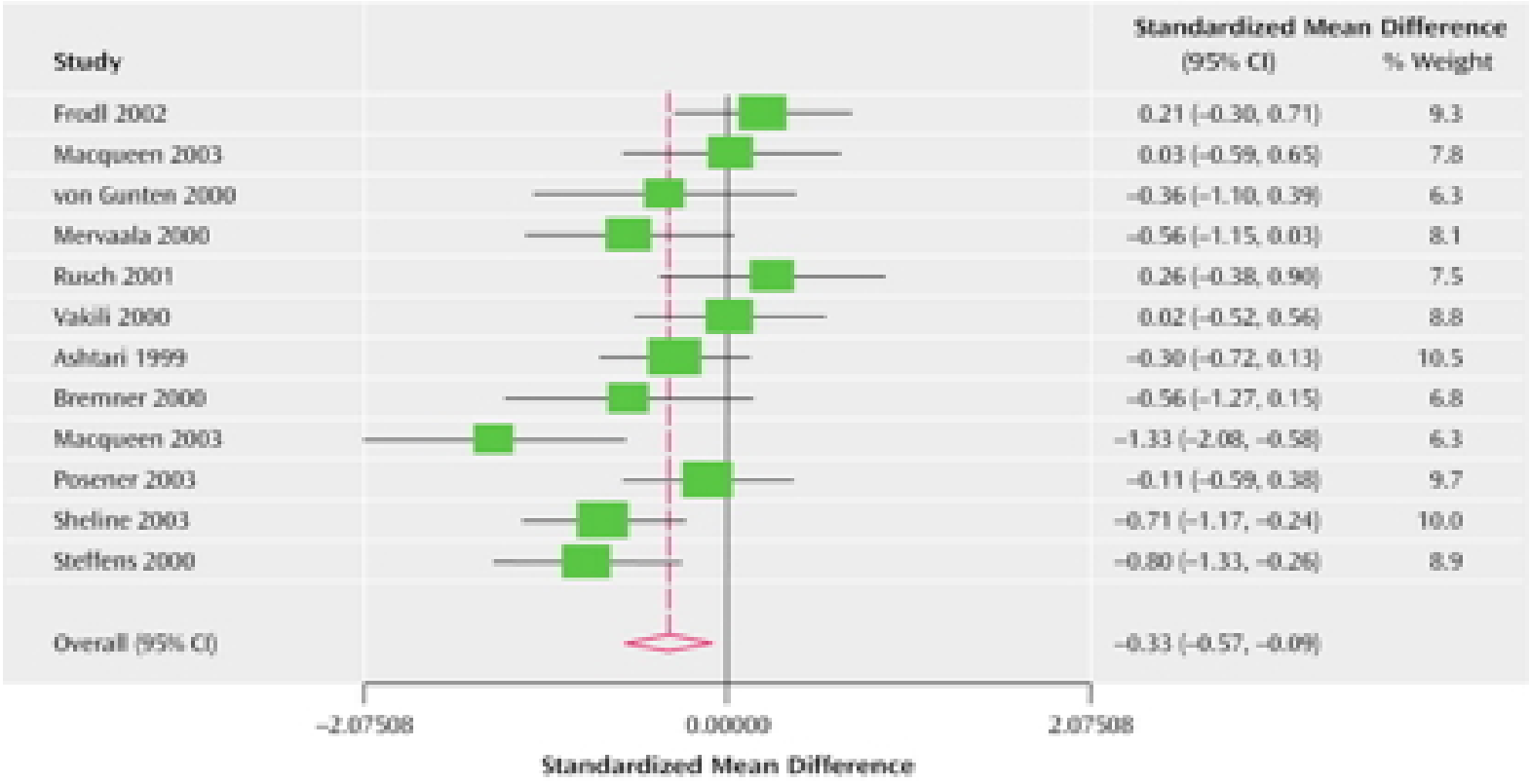


Table 1

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

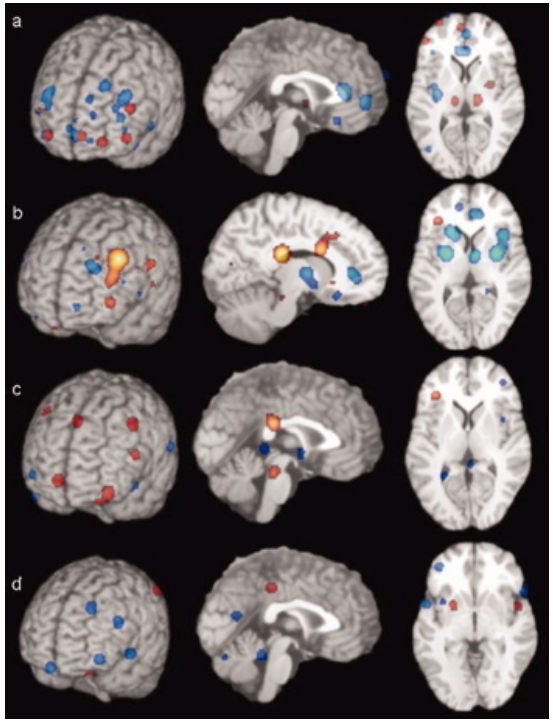
Substrate	Volume	Histological changes	Metabolic activity	Antidepressant effects
Orbital/VMPFC	↓	↓	↑	
Anterior cingulate cortex	↓			↓ Metabolic activity
Hippocampus	↓	↓		↑ Volume
Amygdala	↓?			↓ Metabolic activity
DLPFC	↓	↓	↓	

(Palazidou, 2012)

Hypoactivity in

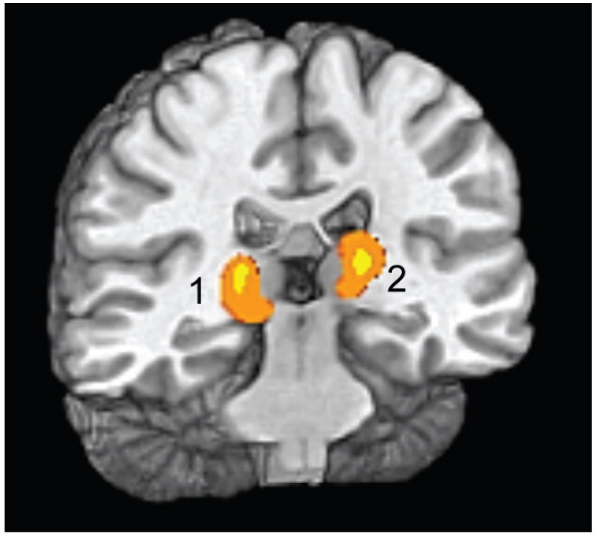
- Frontal and temporal cortex
- Anterior cingulate
- Insula
- Cerebellum
- (Fitzgerald, Laird, Maller, & Daskalakis, 2008)

(Fitzgerald et al., 2008)



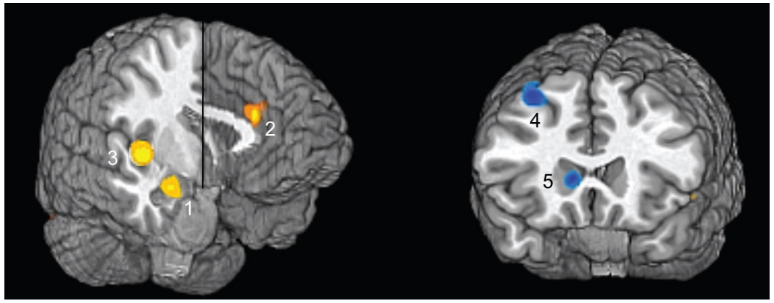
[a] patients v. ctrls, [b] patients on SSRIs, [c] patients v. ctrls (happy stim), [d] patients v. controls (sad stim)

Baseline hyperactivity (Hamilton et al., 2012)



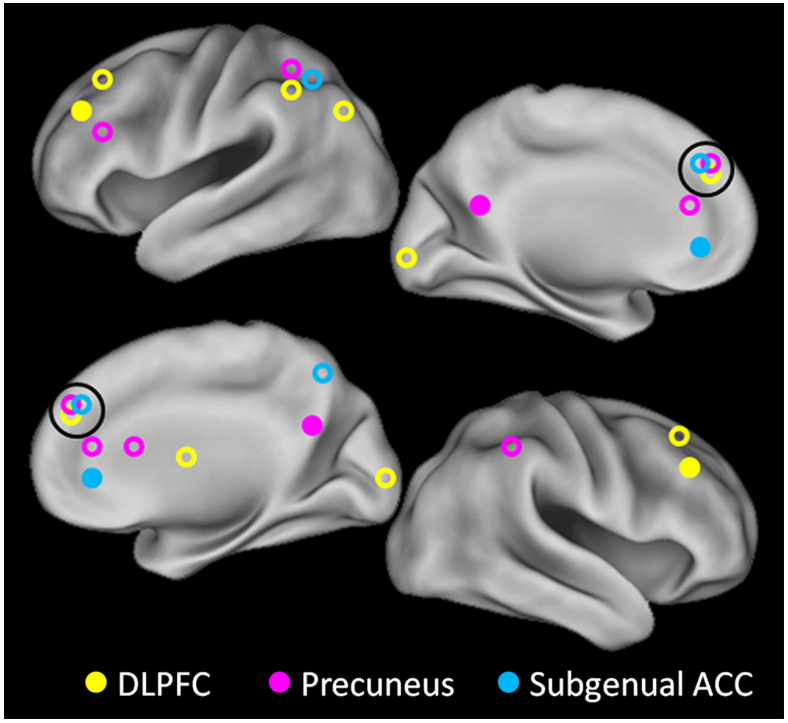
Structure	Direction of Effect	Talairach Coordinates	Cluster Size (mm^3)	Number
Pulvinar nucleus	Depressed > Comparison	–15, –24, 8	3,054	1
Pulvinar nucleus	Depressed > Comparison	17, –25, 4	2,514	2

Valence-specific hyperactivity (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

Increased connectivity between resting state network regions and dorsal PFC (Sheline, Price, Yan, & Mintun, 2010)

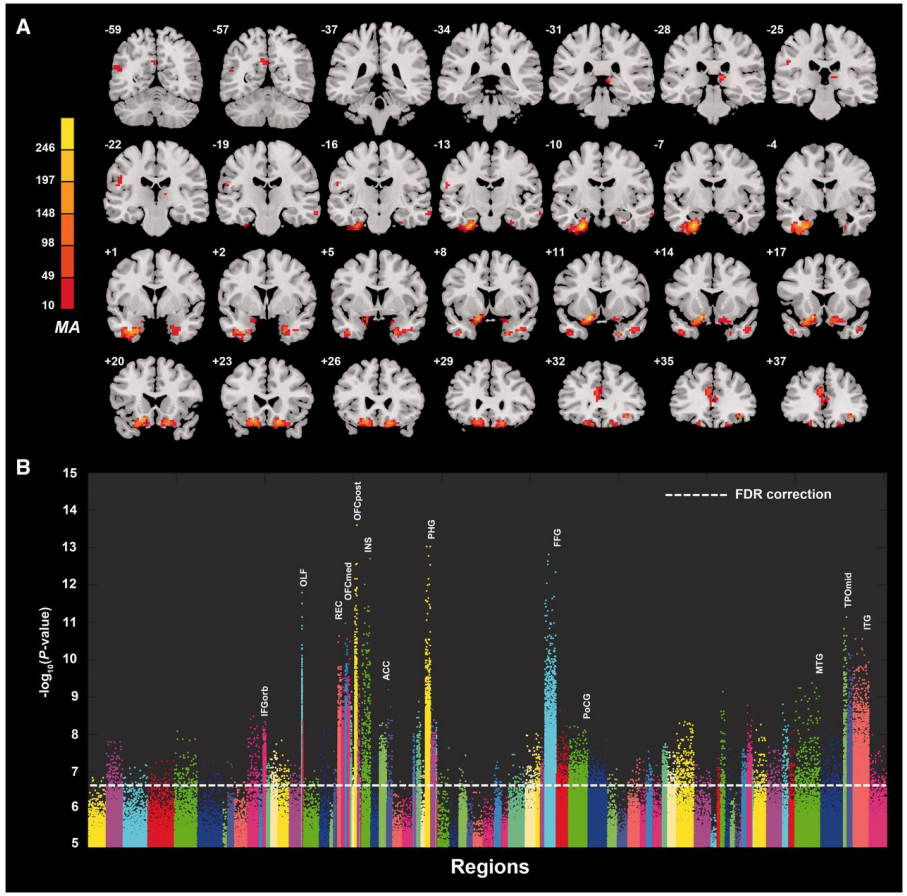


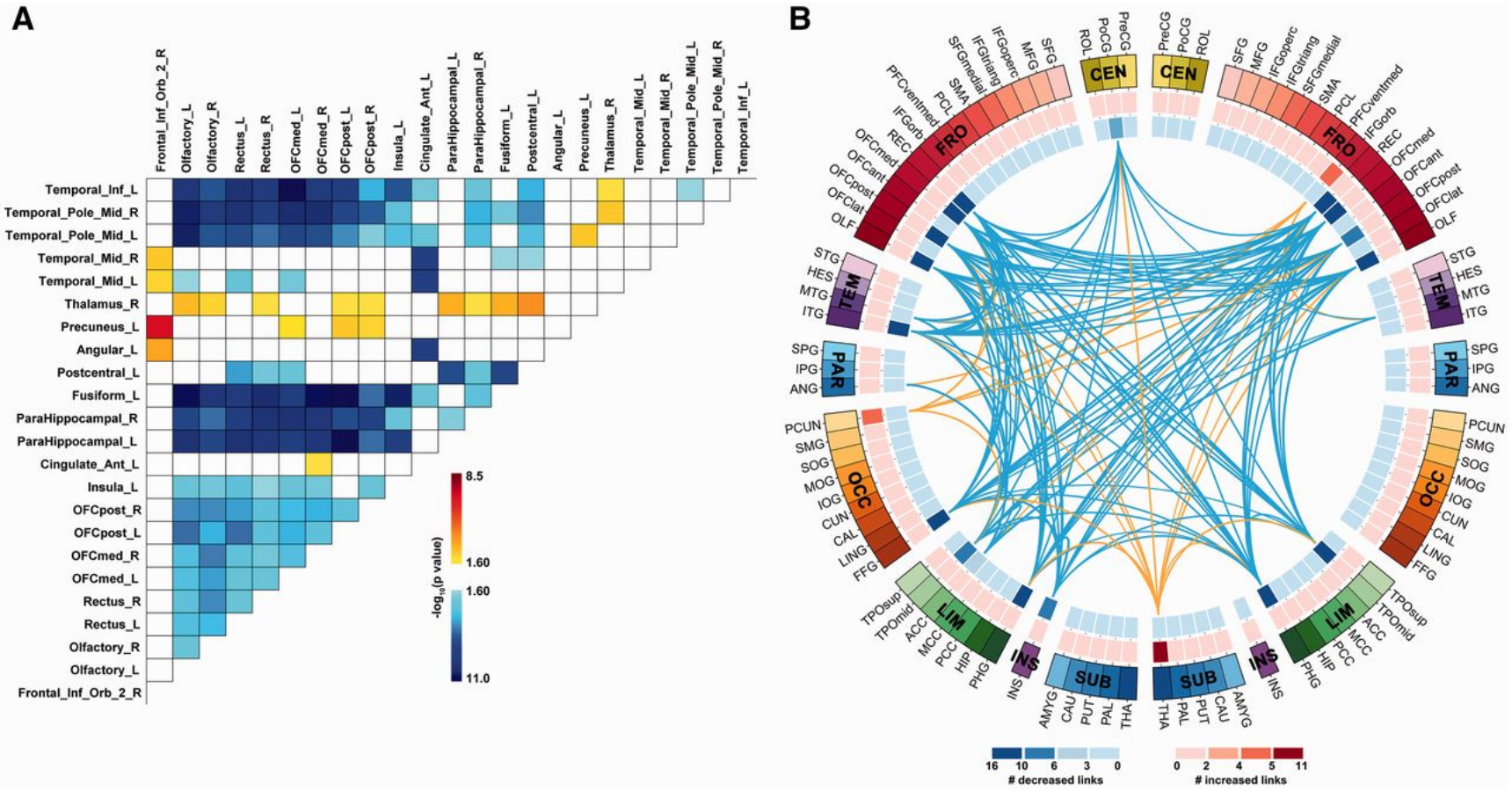
CCN (yellow); precuneus, part of DMN (pink); and affective division of the ACC (turquoise)

Altered connectivity

(Cheng et al., 2016)

- 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


A
-59
-57
-37
-34
-31
-28
-25
-22
-19
-16
-13
-10
-7
-4
+1
+2
+5
+8
+11
+14
+17
+20
+23
+26
+29
+32
+35
+37
246
197
148
98
49
10
MA
B
FDR correction
-log10(P-value)
15
14
13
12
11
10
9
8
7
6
5
IFGorb
OLF
REC
OFCmed
OFCpost
INS
ACC
PHG
FFG
PoCG
MTG
TPOmid
ITG
Regions


A
Frontal_Inf_Orb_2_R
Olfactory_L
Olfactory_R
Rectus_L
Rectus_R
OFCmed_L
OFCmed_R
OFCpost_L
OFCpost_R
Insula_L
Cingulate_Ant_L
ParaHippocampal_L
ParaHippocampal_R
Fusiform_L
Postcentral_L
Angular_L
Precuneus_L
Thalamus_R
Temporal_Mid_L
Temporal_Mid_R
Temporal_Pole_Mid_L
Temporal_Pole_Mid_R
Temporal_Inf_L
-log10(p value)
8.5
1.60
1.60
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B
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FRO
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PAR
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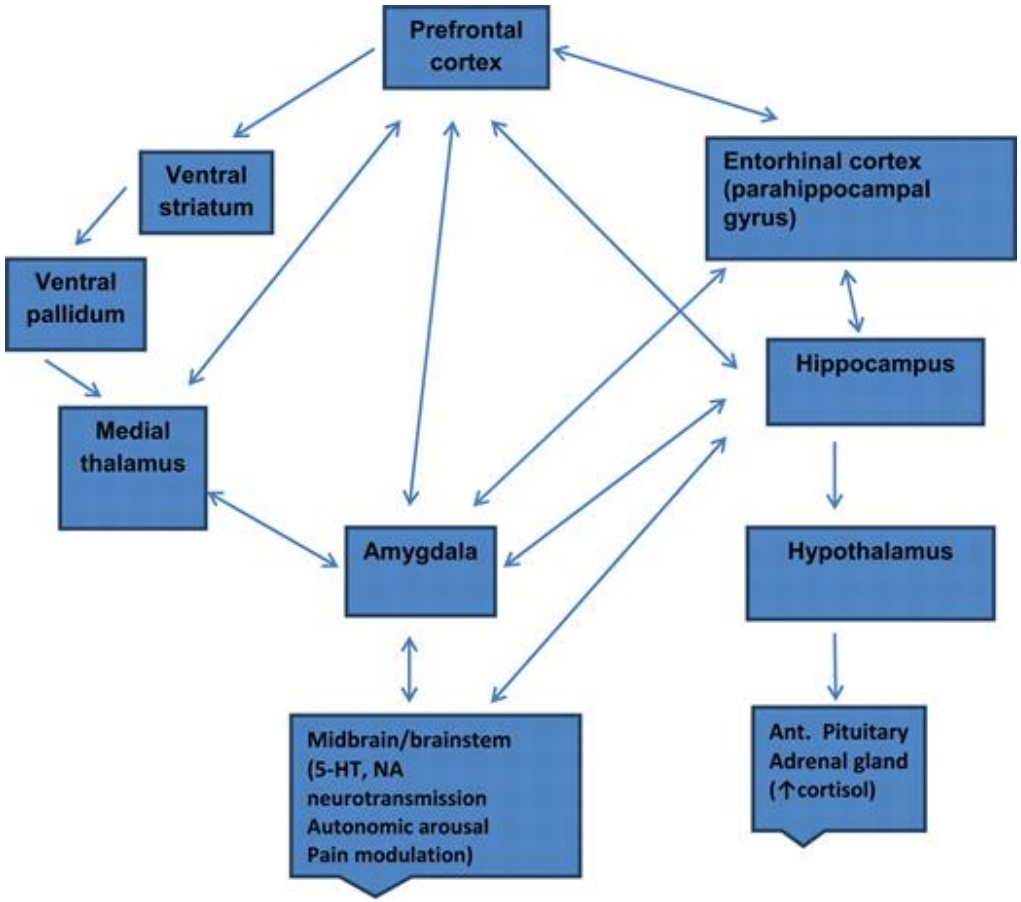
decreased links
16 10 6 3 0
increased links
0 2 4 5 11



(Palazidou, 2012)

Pharmacological factors

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

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, Jokinen, Nordström, & Nordström, 2006)

Measuring 5-HT

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

Table 2

Neurochemical/hormonal abnormalities in depression.

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

(Palazidou, 2012)

Drug treatments

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

Drug treatments

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

Cymbalta (SNRI)

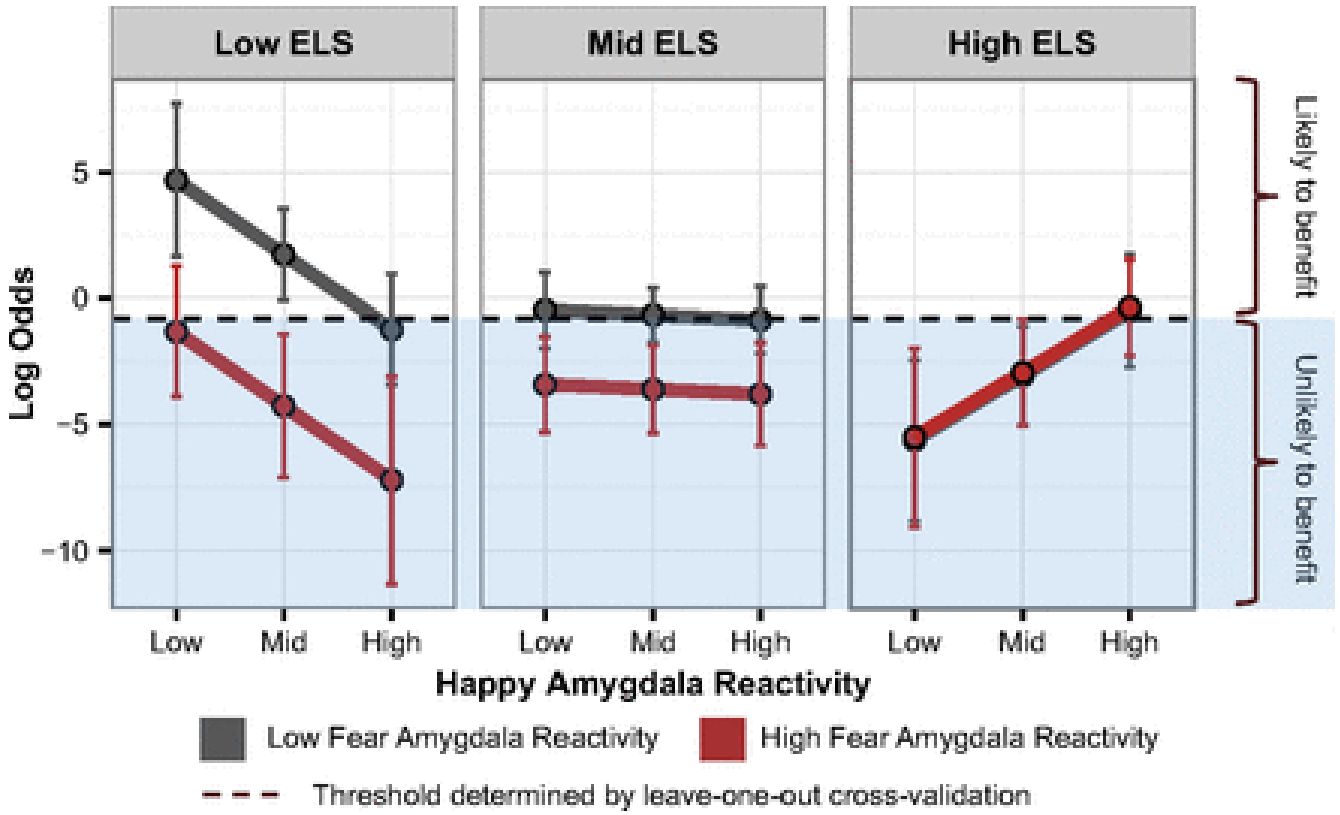
Cymbalta Commercial (real one)

How well do 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 benefits 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)
- "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)

"

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(Ruhé, Mason, & Schene, 2007)

What do drugs do, then?

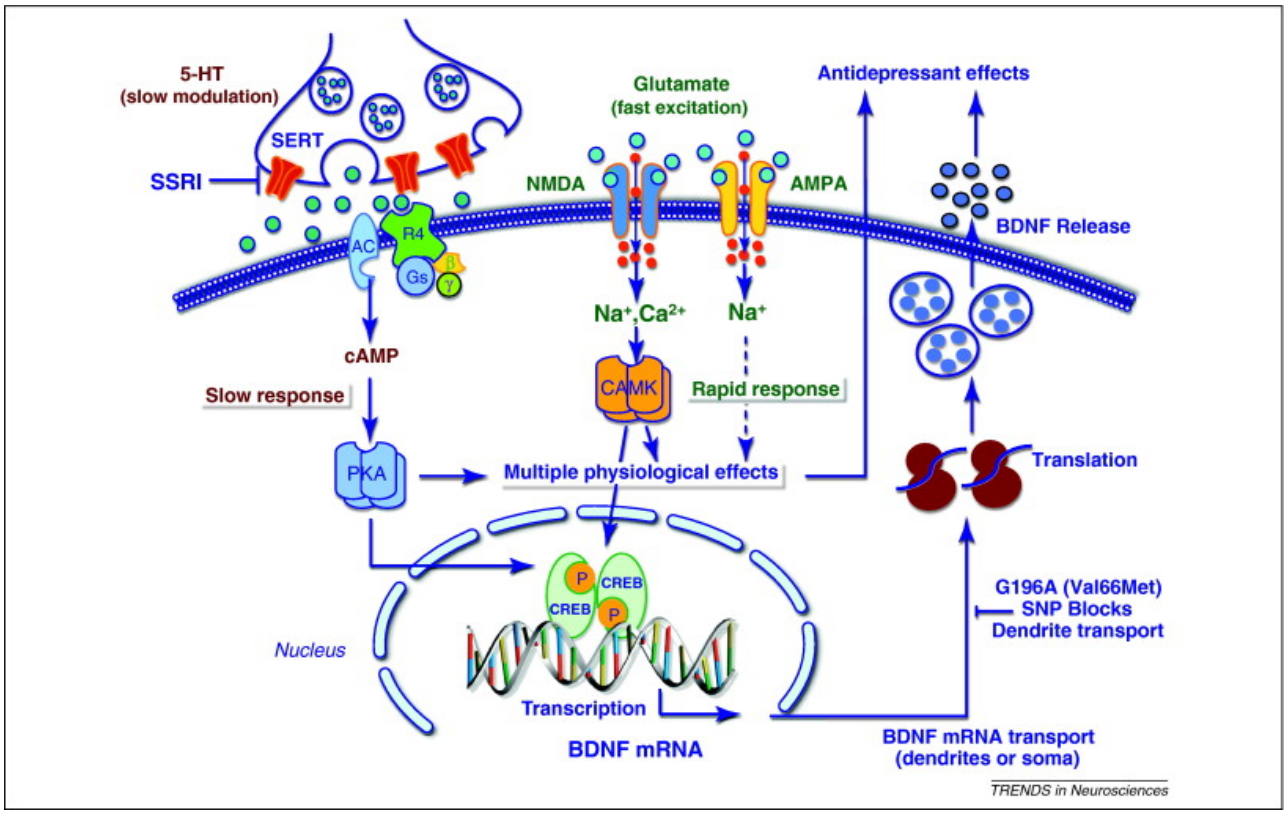
Ketamine again

- Relieves depressive symptoms relatively quickly (Berman et al., 2000) and (Zarate et al., 2006)
- Boosts synaptic spine formation (N. Li et al., 2010) and reverses effects of induced stress

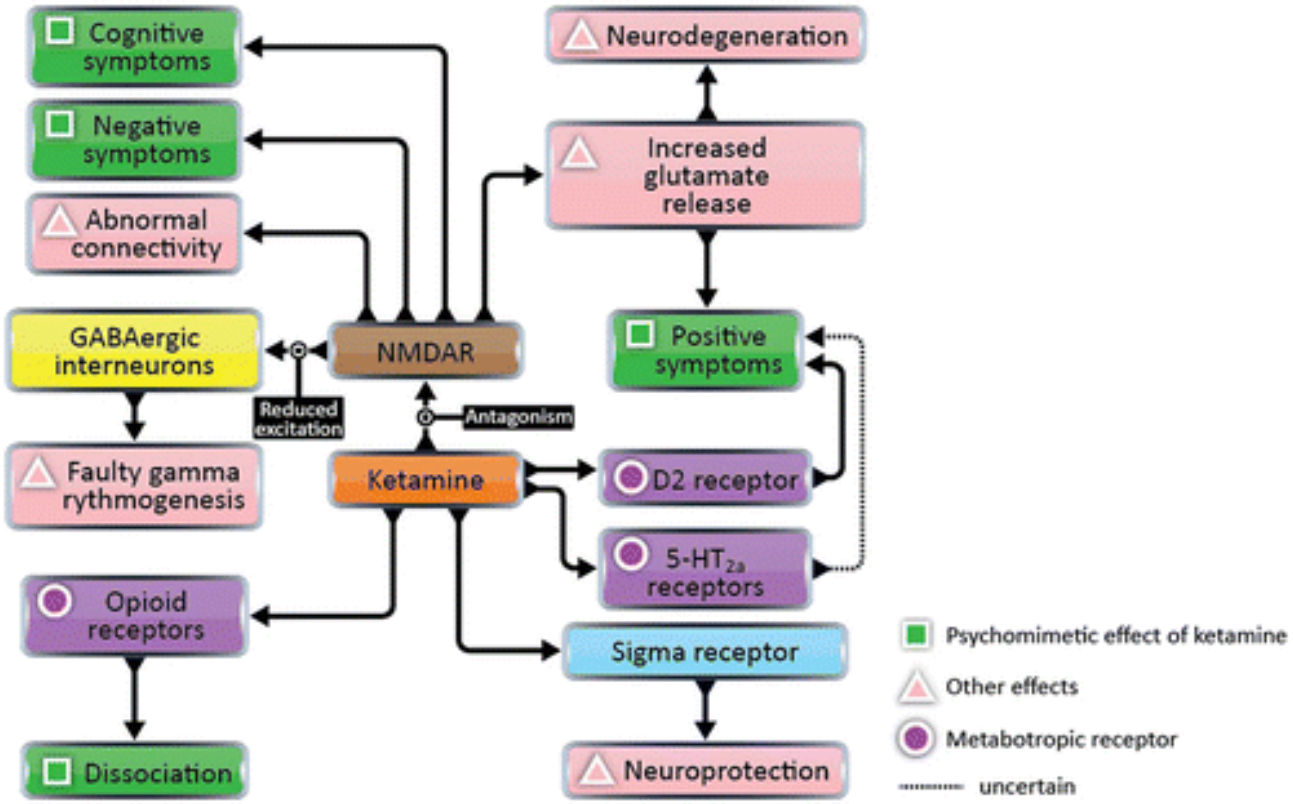
Pathway of pathology (Duman & Aghajanian, 2012)

- Depression ~ chronic stress (Mahar et al., 2014)
- Stress -> chronic HPA axis activity
- Chronic HPA activity -> neuronal atrophy in hipp & PFC
- Stress & cortisol decrease expression of brain-derived neurotrophic factor (BDNF)
- BDNF boosts neurogenesis
- SSRIs act via BDNF, as do NMDA receptor antagonists (e.g., ketamine)

(Duman & Voleti, 2012)



(Frohlich & Van Horn, 2014)



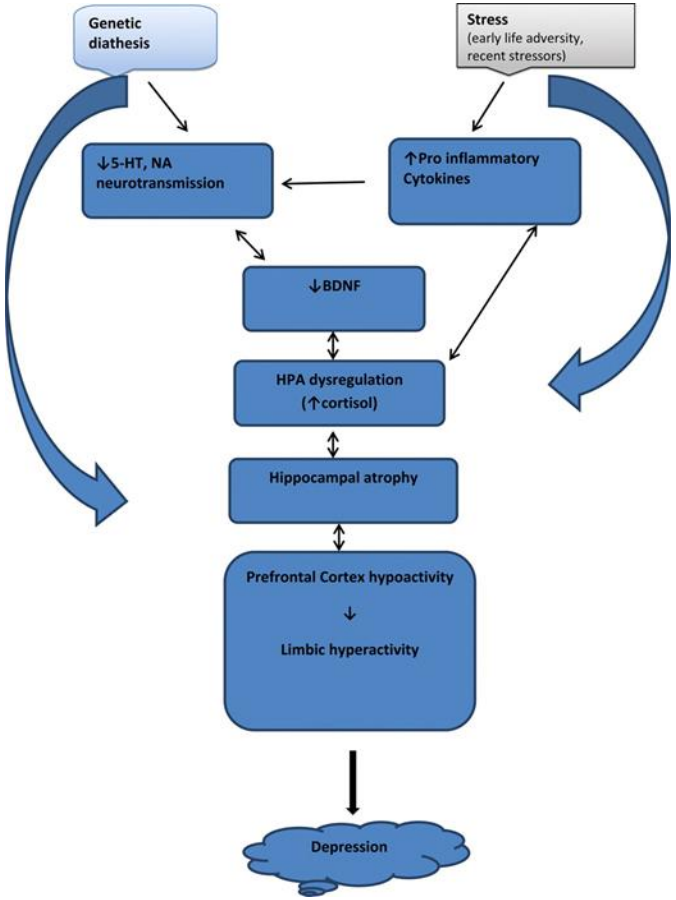
Electroconvulsive Therapy (ECT)

- 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

Putting the pieces together



(Palazidou, 2012)

The disordered mind: Take home messages

- Multi-level, multi-method, multi-variate approaches essential to understanding mental illness
- Developmental processes across the life span
- Networks all the way down…

References

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