

# 260-2017-10-18-bipolar

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# Prelude

Love & Mercy Official Trailer #1 (2015) - Brian Wilson Biopic HD



# Today's Topics

- Wrap up on depression
- Bipolar disorder

# 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<sup>+</sup> channel or enhance GABA function) effects
  - Neurotrophic (stimulates neurogenesis) effects

# Patients speak

- Kitty Dukakis' (wife of former Governor/Presidential candidate Michael Dukakis) story:  
<http://www.nytimes.com/2016/12/31/us/kitty-dukakis-electroshock-therapy-evangelist.html>

# 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



# 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

# Major affective (emotional) disorders

- Types
  - Depression
  - Anxiety
  - Bipolar disorder
- Heritability
  - *proportion of variance in trait accounted for by genetic factors*
  - Monozygotic: .69
  - Dizygotic: .13

# 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, [\(Baldessarini, Pompili, and Tondo 2006\)](#)

# Symptoms

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

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

# Prevalence, subtypes

- 1-3% prevalence, subthreshold affects another 2%
- Subtypes
  - Bipolar I: manic episodes, possible depressive ones
  - Bipolar II: no manic episodes but hypomania (disinhibition, irritability/agitation) + depression

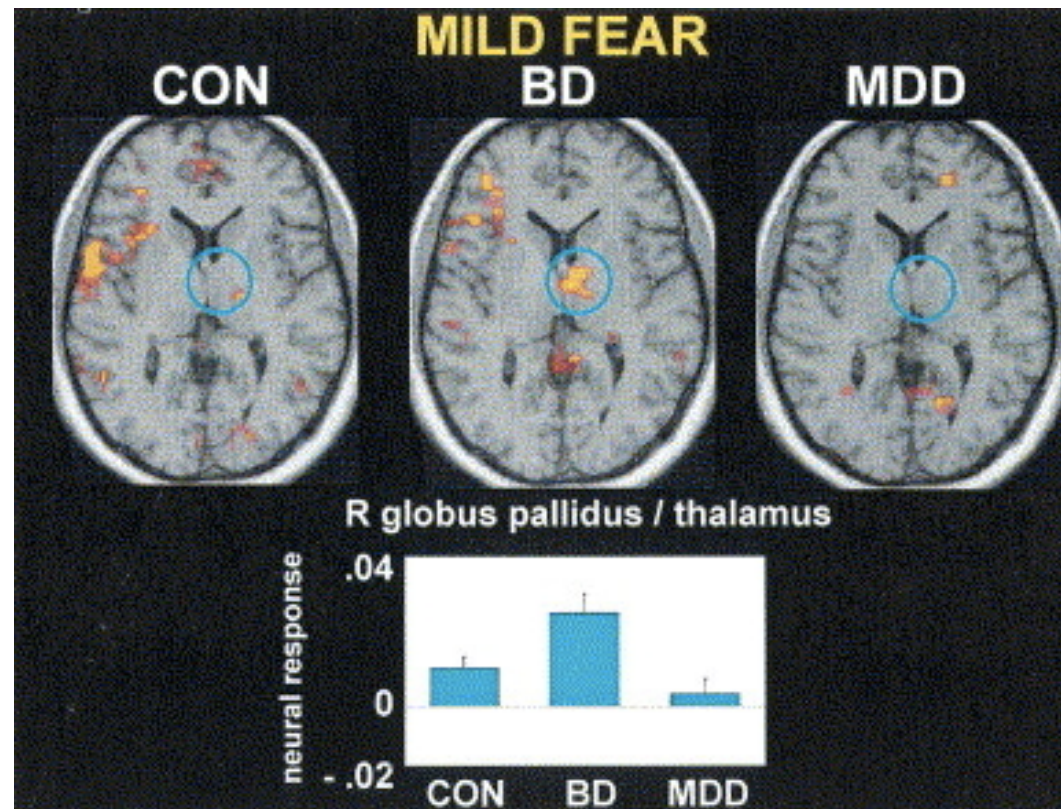
# Related symptoms

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

# Genetics

- Overlap between bipolar disorder and schizophrenia
- Genes for voltage-gated  $\text{Ca}^{++}$  channels
  - Regulate NT, hormone release
  - Gene expression, cell metabolism
- (Craddock and Sklar 2013)

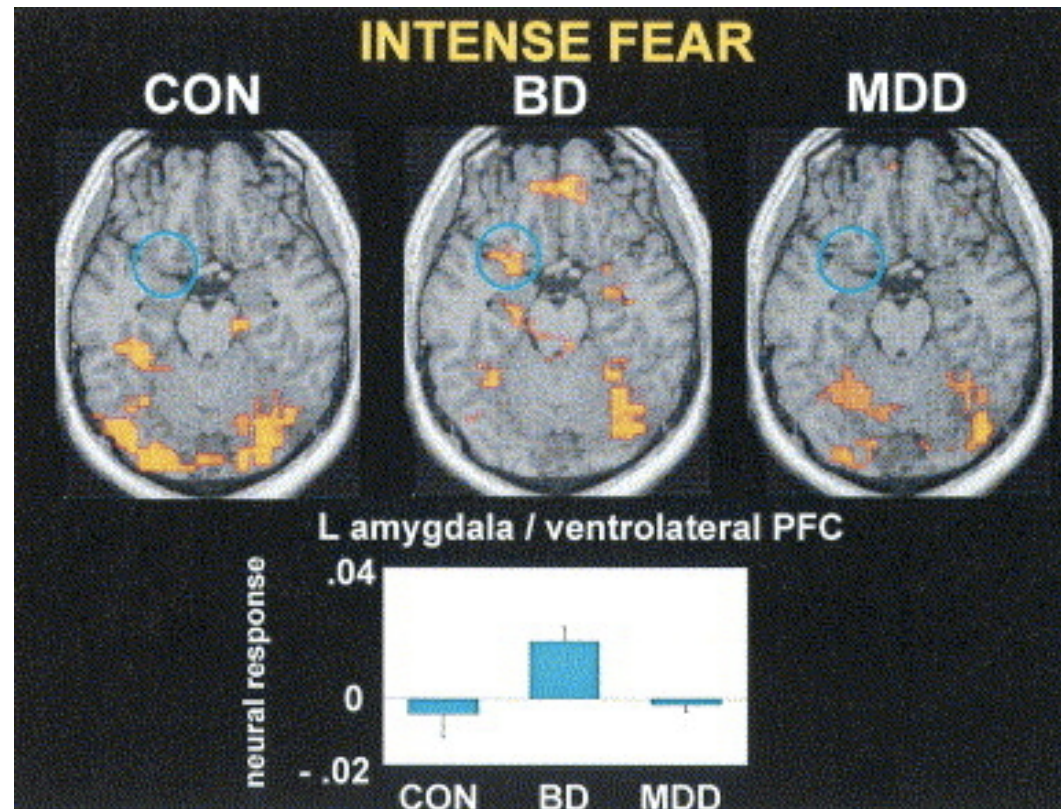
# Brain responses to emotional faces $\neq$ depression



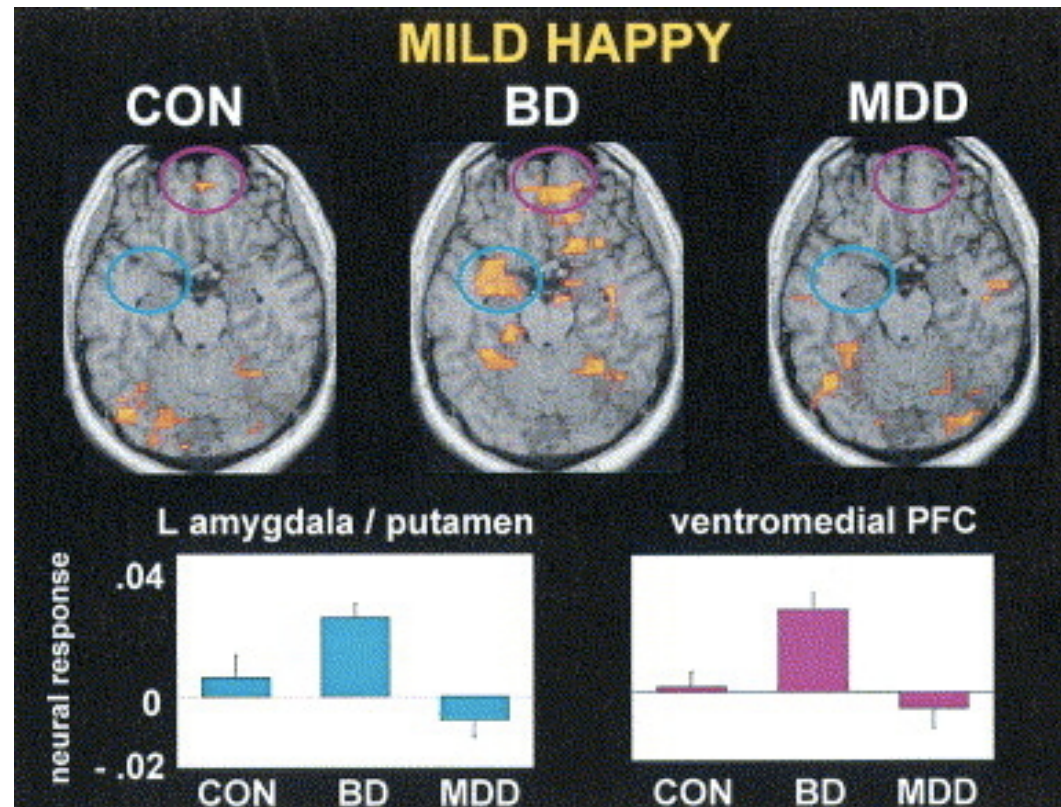
(Lawrence et al. 2004)



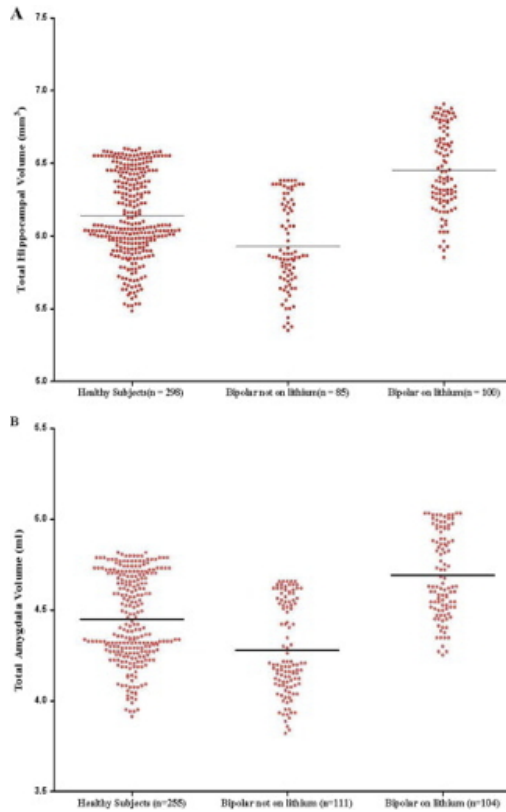
## (Lawrence et al. 2004)



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# Amyg, Hip volume reduced



(Hallahan et al. 2011)

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## 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

- Mood stabilizers
  - Lithium (Li)
  - Valproate (Depakote)
- Anticonvulsants
  - GABA agonists
  - Usually to treat epilepsy
  - e.g. lamotrigine (Lamictal)
- Atypical antipsychotics

# Lithium "discovered" accidentally

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

# Effects of Lithium

- Reduces mania, minimal effects on depressive states
- Preserves PFC, hip, amygdala volume
- downregulates DA, glu; upregulates GABA
- modulates 5-HT, NE
- [\(Malhi et al. 2013\)](#)

# Other treatment options

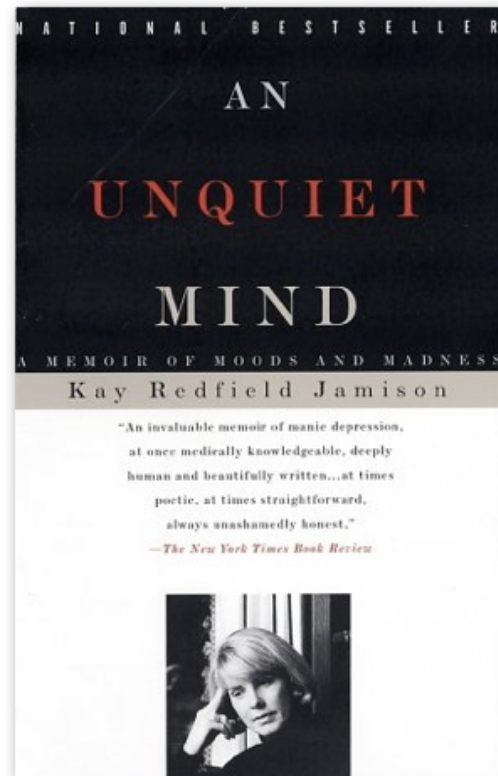
- Psychotherapy
- Electroconvulsive Therapy (ECT)
- Sleep medications



# Prospects

- STEP-BD cohort (n=1469)
  - 58% achieved recovery
  - 49% had recurrences within 2 years
  - Residual depressive symptoms can persist
- (Geddes and 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

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