# Neuropsychology of Affective Disorders

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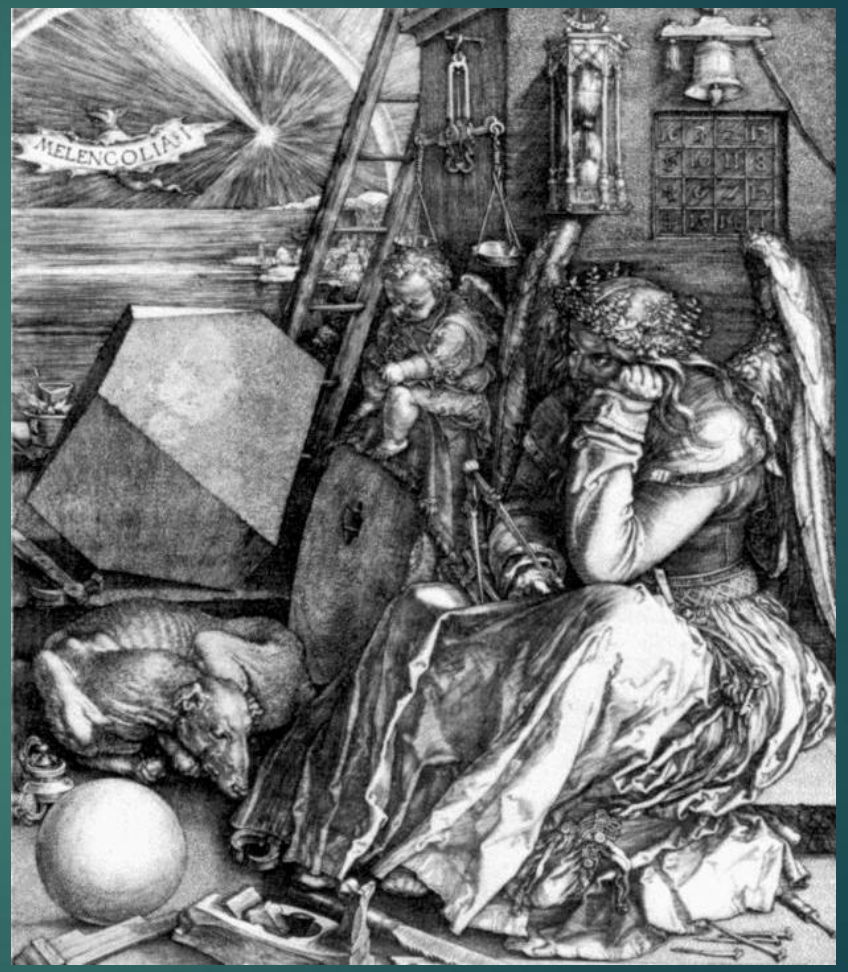
MARCH 11, 2015

# The Neuropsychology of Affective Disorders




'Hues of mania' - Natsaha Simon, 'Melancholia' - Durer

# DSM-5: Major Depressive Episode

- A. ≥ 5 sxs, same 2 week period, change in functioning
  - ≥ 1 = depressed mood, loss of interest/pleasure
  - Depressed Mood (kids = irritability), loss of interest/pleasure, weight loss (kids = failure to gain), sleep changes, agitation/retardation, fatigue, worthlessness/guilt, poor concentration, death/suicide thts

- B. Distress/impairment

# Anxious distress in MDD or Bipolar

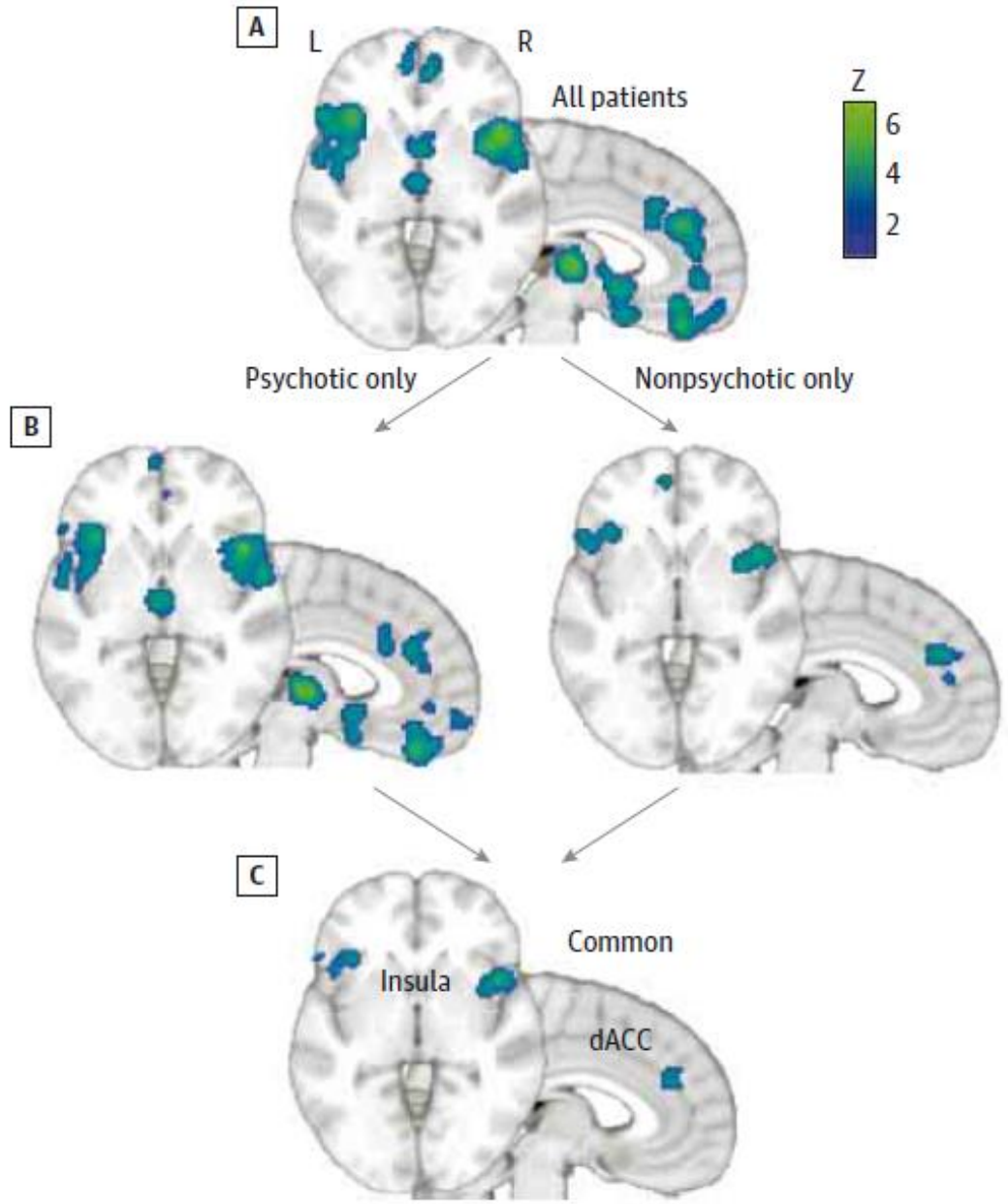
- An "anxious distress" modifier for bipolar disorder and depressive disorders added.
- Identifies pts with anxiety sxs that are not part of bipolar diagnostic criteria
- Research: Predicts outcome and suicide risk.

# Common Neurobiological Substrate for Mental Illness: EF network

- Major 2015 metaanalysis: tested for areas of common gray matter volume increase or decrease across Axis I diagnose
- 193 studies comprising15892 individuals across 6 diverse diagnostic groups (schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety)
- Results: Gray matter loss converged across diagnoses in 3 regions:
  - dorsal anterior cingulate
  - right insula,
  - and left insula.
- 3 independent healthy participant data sets: the common gray matter loss regions formed a tightly interconnected network during tasks and at resting
- Lower gray matter in this network was associated with poor executive functioning.
- Integrity of an anterior insula/dorsal anterior cingulate–based network, which relates to executive function deficits observed across diagnoses

Madeleine Goodkind, et al, 2015

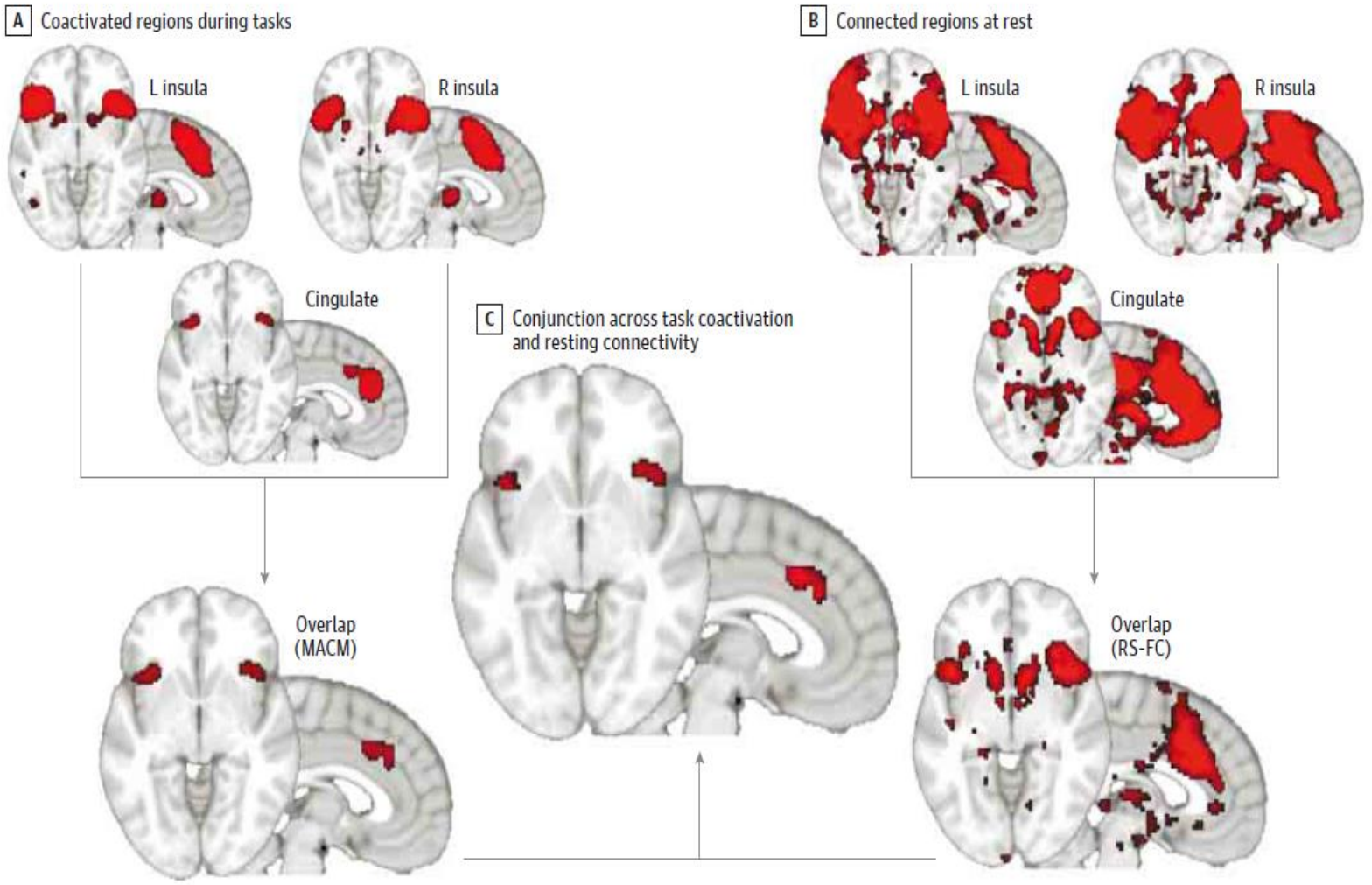
Figure 2. Shared Patterns of Decreased Gray Matter From the Voxel-Based Morphometry Meta-analysis




Results show common gray matter loss across diagnoses in the anterior insula and dorsal anterior cingulate (dACC).

Gray matter volume in the dorsolateral prefrontal cortex, a key region for working memory (a core impairment in schizophrenia and to a lesser extent, in major depression and non-psychotic bipolar disorder), was oddly unaffected in the meta-analysis.

Figure 5. Common Gray Matter Loss Regions From the Voxel-Based Morphometry Meta-analysis Are Part of An Interconnected Brain Network




A, Meta-analytic coactivation maps (MACMs) showing regions coactivated with each of the common gray matter loss regions in healthy participant task-based activation studies in the BrainMap database, as well as a conjunction across all 3 MACM maps. B, Resting-state (RS) functional connectivity (FC) in healthy individuals seeded by each of the common gray matter loss regions, as well as a conjunction across all RS-FC maps. C, Conjunction across all of the MACMs and RS-FC map demonstrates that each of the common gray matter loss regions shows both task-dependent and task-independent FC with the bilateral anterior insula and dorsal anterior cingulate (the regions showing consistent gray matter changes) as well as the thalamus. L indicates left; and R, right.

Gray matter loss regions are part of interconnected network: effect general executive functioning (task switching, interference, and working memory)

# Executive Function Groups

- This study reinforces need for all clinics to have a regular Executive Function group for Psychiatric patients.
- Need for teaching behavioral memory techniques, external prosthesis/reminder systems, problem solving strategies.
- Need to do routine MOCAs on psych pts.

# Neuropsychology of Major Depressive Disorder

# Depression is common

- United States: 19 million cases per year
- Prevalence: 13% of people in any 1 year
- Twice as many women (12%) vs. men (6%)
- Lifetime Risk: 10-25% women; 5-12% men
- 50% of all Psychiatry patients

# Major Depression: Prevalence

- Prevalence:
  - Independent from ethnicity, education, income, or marital status.
  - 1.5 –3X more common among first degree biological relatives

- Onset in the mid 20s but can begin at any age.

# Politics: Gun suicides outnumber gun homicides

- For every year since 1920, guns in U.S. are used more often for suicide than for homicides or home defense

- In 2011:
  - 31,672 Americans died by guns (Japan had 2 gun related deaths)
  - 11,000 were homicides (39%) (72% by handguns)
  - 19,392 were suicides (61%)

  - 200,000 nonfatal gunshot injuries;
  - 1382 murder-suicides in 2011 (27 per week)
  - 62 mass killings in US since 1982 (2 per year)

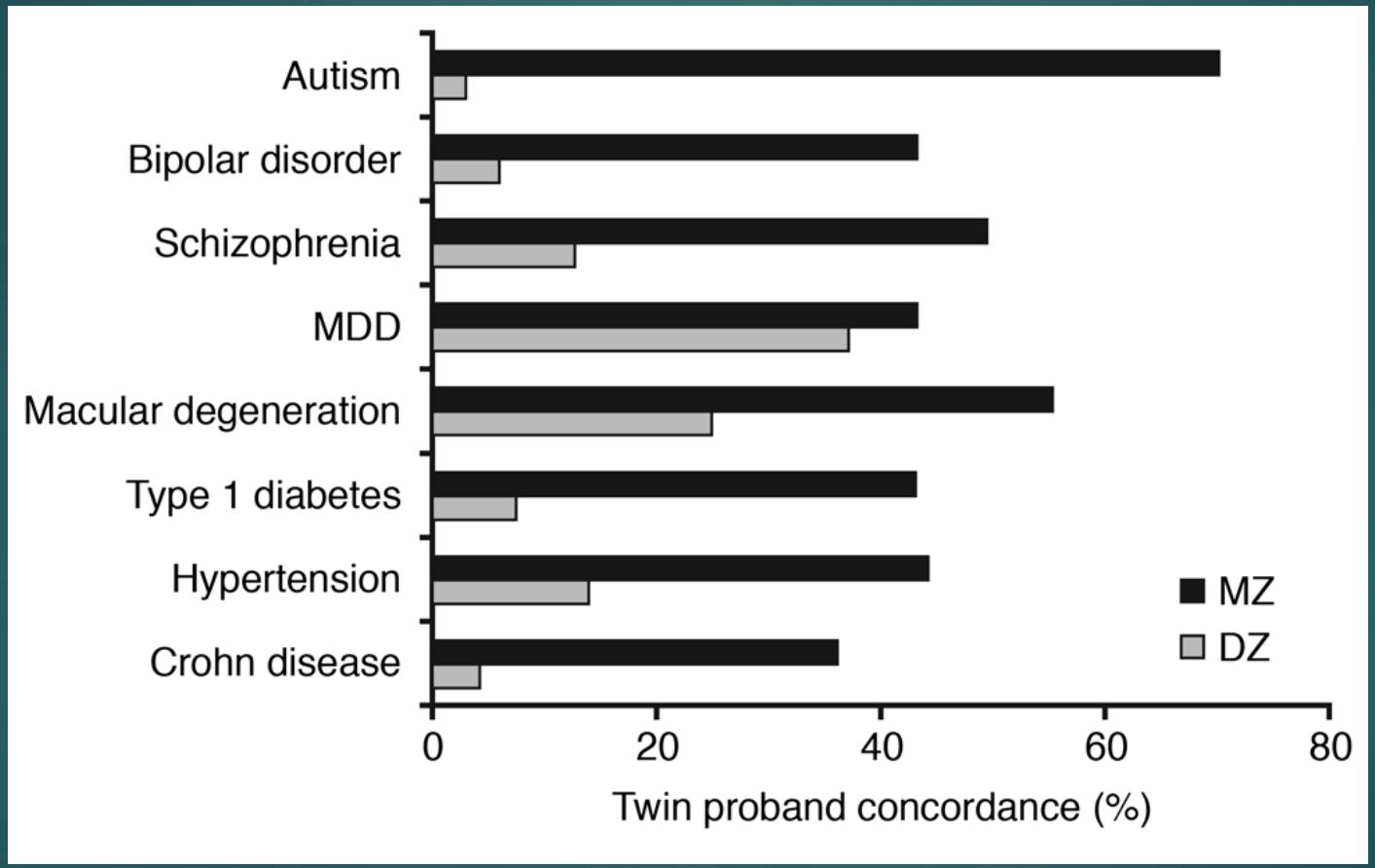
# Course

- Course of MDD is variable.
  - Some w/ discrete episodes with complete remission in between
  - Some w/ clusters of episodes,
  - Some w/ increasingly frequent episodes as they grow older.
  - Number of prior episodes predicts subsequent episodes.
  - At least 60% of individuals with MDD Single episode will have a second episode.

# Genetics

- Depression = 37% heritability in twins
- Early-onset, severe, and recurrent major depression have a higher heritability than other forms of depression
- Not a single gene
- Bipolar = 65% heritability in twins

# Genetics plays a major role in  psychiatric disorders




****Complex genetics at play in psychiatric disorders****

**(Tom Insel, Director NIMH, JCI, 2010)**

# Neurochemistry of Depression

- Classic theory of cause of depression: low serotonin
- All SSRIs (selective serotonin reuptake inhibitors): increase availability of Serotonin
- Serotonin important in TX, but not in causation
- Almost every compound that has been synthesized for the purpose of increasing serotonin or norepinephrine has been proved to be a clinically effective antidepressant

# Newer theory:
# Loss of new synapsis and neurons

- What causes depression is a shortage of serotonin due to:
  - lack of  new synapses
  - loss of neurogenesis (the generation and migration of new adult neurons, esp. in hippocampus)

- SSRIs  bolsters new synapses and new neurons, the loss of which causes depression.

# Neurochemical Aspects of Depression

- Interesting observation that patients taking reserpine for high blood pressure often became depressed.
  - reserpine depletes monoamines including norepinephrine, dopamine, and serotonin.

- Antidepressant action may be related to BDNF (Brain – Derived Neurotropic Factor (growth supporting factor)
  - Stress (cortisol) may be related to decrease in BDNF
  - Fluoxetine stimulates both BDNF and neurogenesis in the hippocampus

# Mood Disorders and Medical Conditions

- Cerebrovascular related Depression
  - 50% - 68% of CVA patients have depressive sxs
  - Depression predicts death in 6 months after MI

- The Depressed Medically Ill:
  - 3X more more likely to NOT follow treatment recommendations
  - Report more medical symptoms
  - When depression is ameliorated, report less medical sxs regardless if there is a change in medical condition.

# Biology of Depression

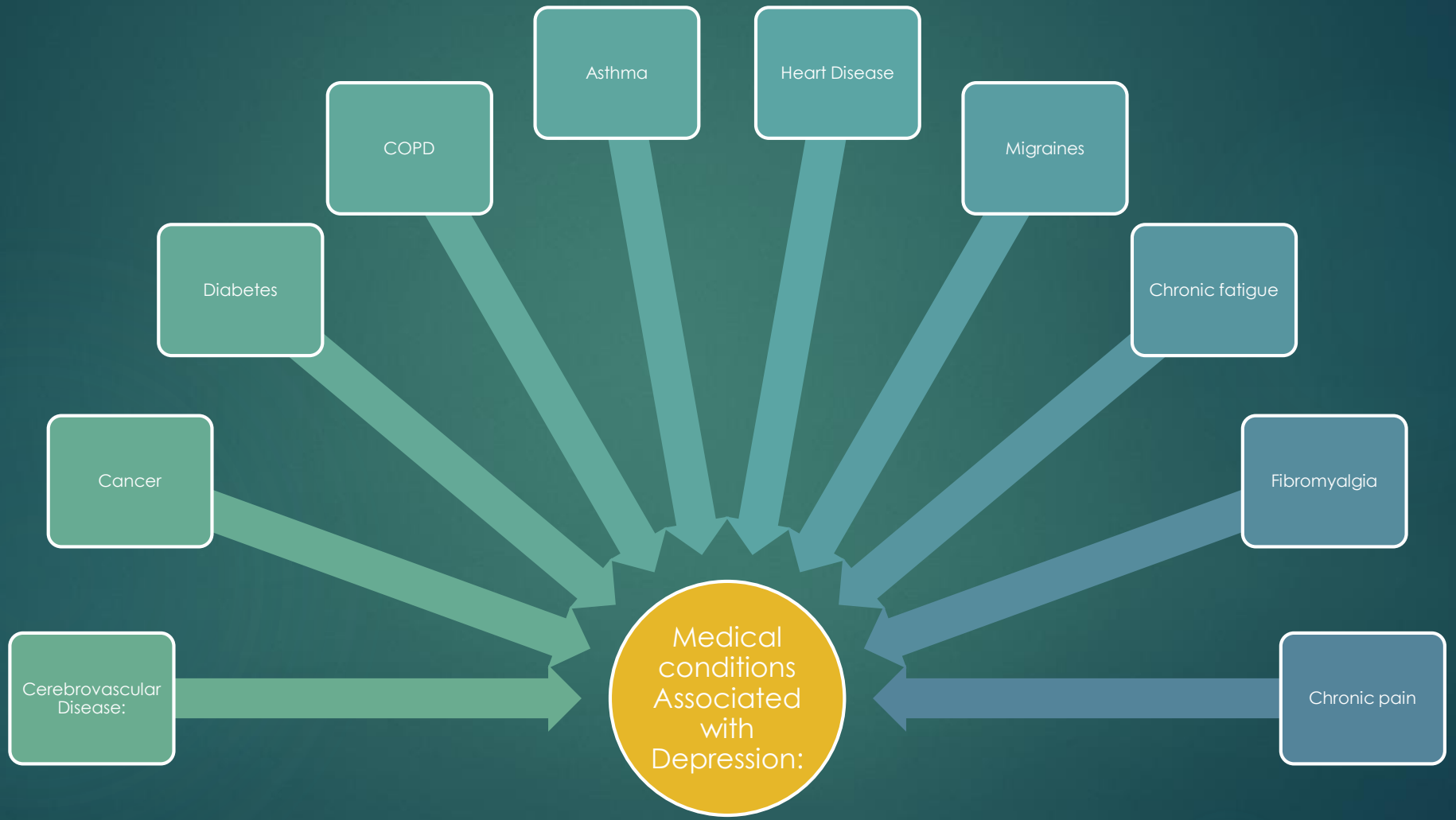
- Neuroendocrine: Depression causes an increase release of cortisol in 40-50% of pts

- Cortisol causes hippocampal atrophy

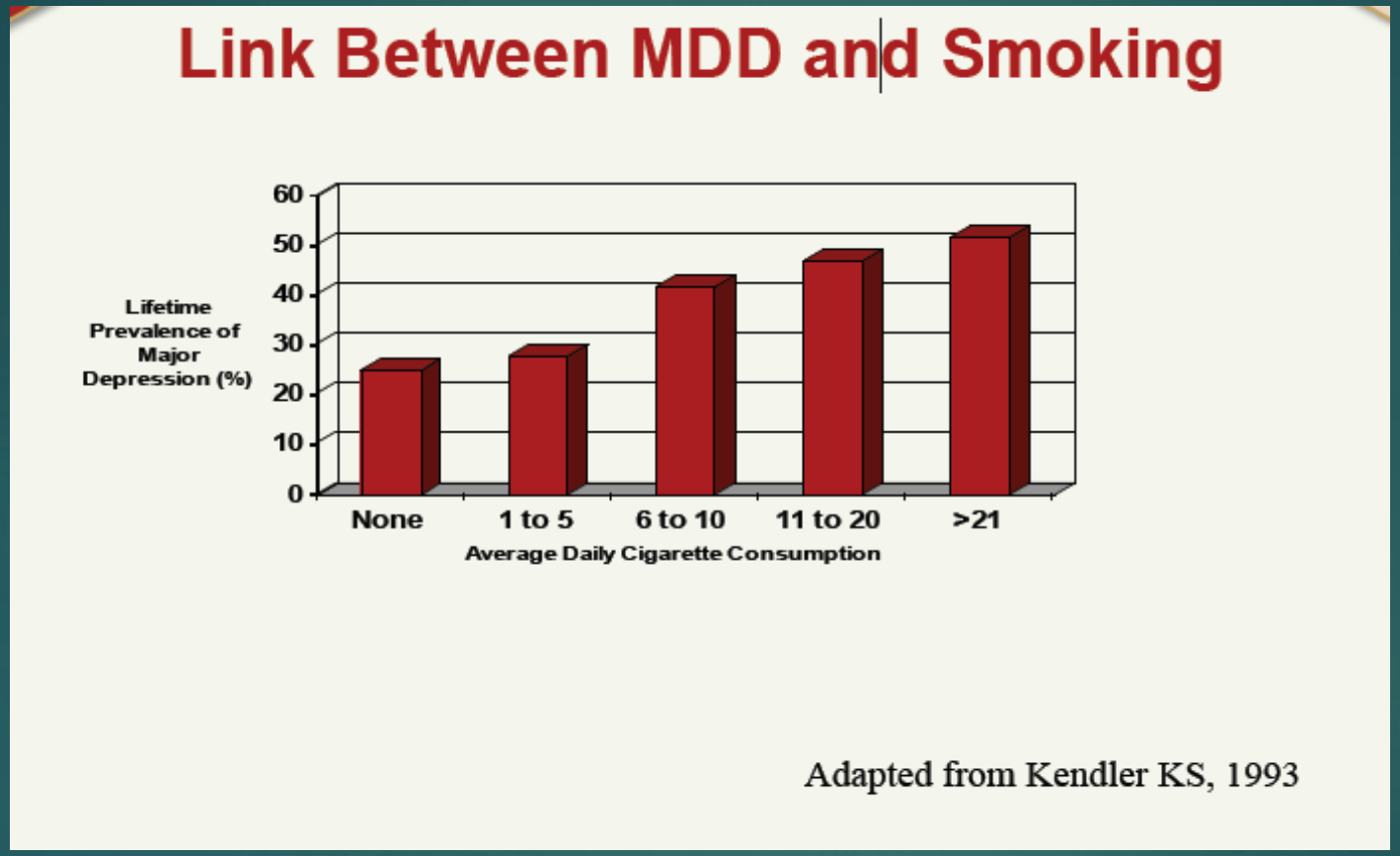
# Cushing's Disease & Depression: HyperCortisol

- Gluccocorticoid cascade hypothesis: Increased stress observed in mood disorders → Excessive release of CRF → Release of ACTH → Release of Cortisol
- Cushing's disease involves elevated cortisol levels and high cortisol associated with 60% prevalence of mood irregularities/depression.
- Cortisol kills hippocampal cells and causes hippocampal atrophy.
- Treatment of Cushing's disease typically resolves depressive sxs.
- Hypercortisolemia present in 50% of individuals with depression.

# Medical Conditions related to increased rates of Depression



# As Depression increases so does Smoking




~65% of people with bipolar disorder

# Neurocognitive Functions: Impaired Memory

- Study: An effect size analysis of neurocognitive function in patients with major depressive disorder
- 726 patients with depression and 795 healthy normal controls:
  - Depression had the largest effect on measures of encoding and retrieval from episodic memory (RAVLT).
  - Intermediate effect sizes: psychomotor speed and tests that require sustained attention.
  - Major depressive disorder is accompanied by dysfunction of effortful encoding of information along with an accompanying inefficiency of retrieving poorly encoded information from declarative memory.

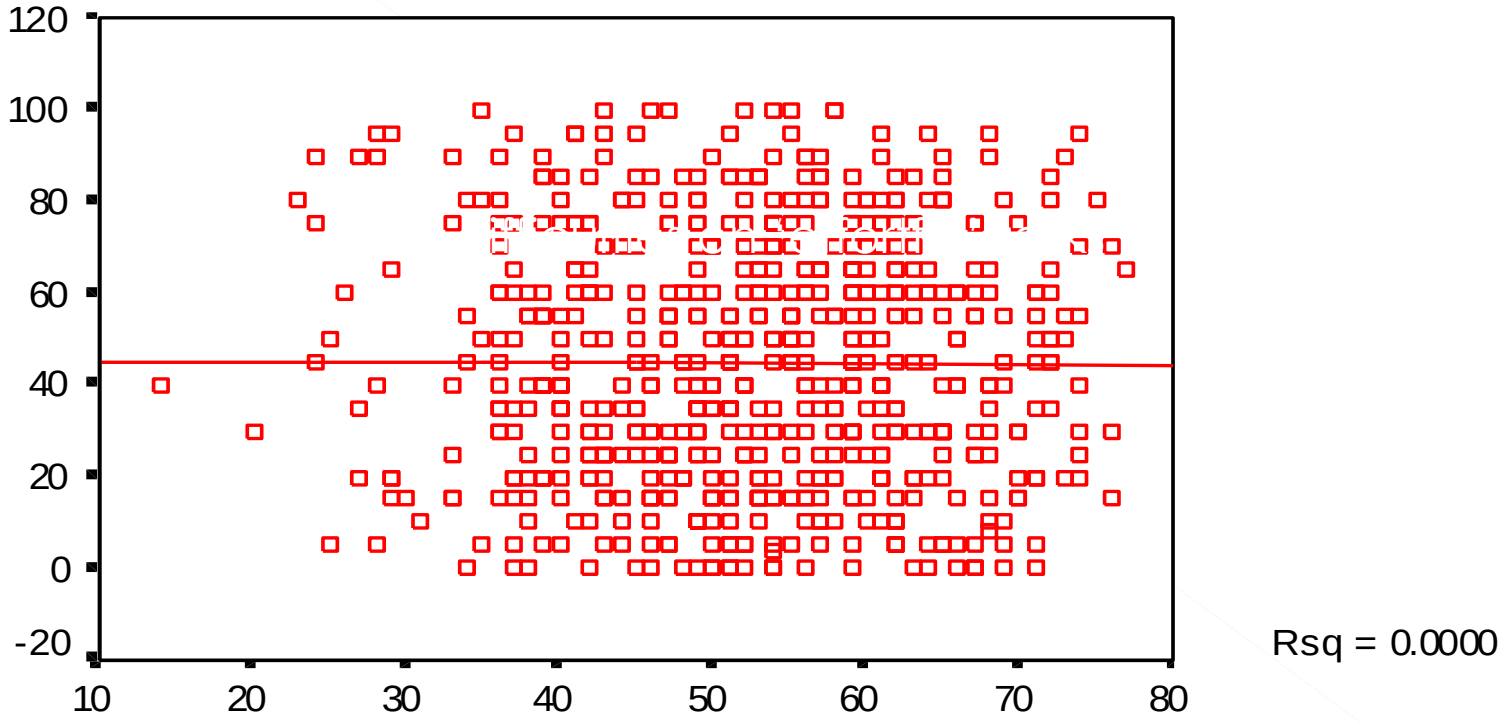
**On the Nature and Pattern of Neurocognitive Function in Major Depressive Disorder. Zakzanis, K. M.A.; Leach, Larry Ph.D.; Kaplan, Edith Ph.D., 1998**

# Depression: The Neuropsychological Evaluation:

- Include:
  - 1. Estimate of baseline functioning
  - 2. Effort measures
  - 3. Memory measures relying on REPEATED exposure to same stimuli such as a learning curve (CVLT, RAVLT)
  - 4. Processing Speed
  - 5. Working Memory
  - 6. Sustained attention
  - 7. Problem Solving
  - 8. Fine Motor Dexterity and Speed
  - 9. Emotion Perception and processing
  - 10. Objective Measure of Mood and Psychopathology

# Verbal memory complaints versus verbal memory test scores

Zero correlation in 995 cases




Green, 2003

# Effort in MDD

- Two disorders with poorest effort:
  - Pain pts
  - MDD pts

- Depressed Pts often complain about memory difficulties

- **Effort and Test Validity in MDD**
  - Issue of lack of effort, motivation, initiative, ability to make decisions.
  - Expected to pass SVT – not exaggerate impairment
  - However, may not perform to potential due to lower motivation, engagement, and ability to sustain effort when challenged.

# Cognitive Functioning and Effort:

- Issues that come up with depression are: lack of effort, motivation, initiative, ability to make decisions.
- Theory: Cognitive decrement due to less effort
  - e.g. spontaneous recall harder than memory recognition
- Theory: Cognitive decrement due to decreased resource availability, increased distractibility due to inefficient inhibitory processes, mood congruent memory biases.
- Effort Measures
  - Amotivation may result in failed effort measures
  - Problem compounded if/when primary or secondary gain is involved

# NP testing in Depression

- Effort often abnormal: Fail effort measures; NP is normal if they pass effort measures
- Processing speed, attention↓↓
- Subcortical Memory Pattern: Recognition memory normal
- Normal confrontation naming and fluency; conversation fluid
- Can have variable and inconsistent performance
- Tearfulness & affect; not apathy
- Frequent “I don’t know”, “why are you torturing me”

# Age Interactions

- Greater cognitive impairment is seen in depressed patients ≥60 than those <60 years old (Christensen et al, 1997)
- Fewer studies have considered age of illness onset
- Late-onset (LOD) vs. early-onset (EOD) depression:
  - LOD has lower rate of family history, higher rate of dementia, and more white matter hyperintensities than EOD
  - EOD patients have greater hippocampal volume loss than LOD, possibly due to effects of excess glucocorticoid effects

# The cognitive neuropsychology of depression in the elderly

LUCIE L. HERRMANN, GUY M. GOODWIN AND KLAUS P. EBMEIER*

*Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, UK*

(2007)

| Cognitive function | Number of studies | *n* | Effect size (95% CI) | Comment |
|---|---|---|---|---|
| Executive function | | | | |
| LOD/controls | 7 | 266/413 | 0·56 (0·30–0·82) | Both LOD and EOD significantly worse than controls, and LOD worse than EOD |
| LOD/EOD | 6 | 150/149 | 0·39 (0·16–0·63) | |
| EOD/controls | 3 | 100/101 | 0·42 (0·13–0·71) | |
| Processing speed | | | | |
| LOD/controls | 3 | 89/98 | 0·58 (0·28–0·88) | LOD and EOD significantly worse than controls, but EOD significantly (although marginally) better than LOD |
| LOD/EOD | 6 | 156/155 | 0·28 (0·05–0·51) | |
| EOD/controls | 3 | 103/98 | 0·37 (0·08–0·66) | |
| Episodic memory | | | | |
| LOD/controls | 6 | 268/413 | 0·44 (0·24–0·64) | LOD and EOD perform significantly worse than controls, but no difference between LOD and EOD |
| LOD/EOD | 5 | 130/134 | 0·04 (−0·25 to 0·32) | |
| EOD/controls | 3 | 103/101 | 0·48 (0·20–0·77) | |

Meta-analysis of 10 studies of 351 LOD, 174 EOD, and 413 elderly NCs

- Executive deficits are typical of LOD
- Memory and psychomotor speed deficits are common to both

# Cognitive Functioning and Age of Onset:

## Early Onset

- More resistant to treatment
- More persistent

## Adult Onset

- Decreased attention on effortful tasks
- Decreased initial acquisition of stimuli
- Decreased retrieval of information encoded
- Subcortical symptoms
- Cognitive sxs improve when severity of depression lessens

## Older Adults

- Probable underlying neurological changes
- Likely secondary depression
- Less familial factors
- Associated with cerebral atrophy, deep white matter changes, cognitive impairments
- Depression treatable by conventional pharmacotherapies
- Cognitive sxs persist.

# Cognitive Functioning and Severity

- With increasing severity of depression →
  - processing speed and executive skills ↓ ↓
  - poorer treatment prognosis

- Memory and executive functions declines correlate with:
  - History of inpatient hospitalizations
  - Number of prior depressive episodes

# Reversible Cognitive Deficits in MDD

- Old idea of pseudodementia
  - Real cognitive dysfunction
  - Implication that it is not real is wrong
- Older research studies were inconsistent; did not use effort measures
- For many, if not most, cognitive deficits in MDD are both real & reversible when depression is under control.

# Depression and Cognition

- Depression can cause cognitive impairment (must test effort level)
- Presence of depression:
  - visual memory and nonverbal intelligence ↓ (processing speed ↓)
- Depressed patients with EF deficits appear to have a slow or poor response to antidepressant Tx

# Depression and Cognitive Disorders

- Cognitive Impairment (MMSE<24) increases with age:
  - 15% age 65-74; 25% age 75-84; 45% in 85+

- Chronic Depression increases stress related cortisol levels; high cortisol levels reduce hippocampal volume, decrease neurogenesis

- 20-40% of Alzheimer's exhibit "depressive" sxs: part of prodrome, apathy, or consequence of vascular condition

Alexopoulos, Lancet, 2005; Sneed et al., AJGP, 2010

# Cognitive Profile of MDD

- Cognitive disorder associated with MDD is "potentially" reversible.
- 
- Most Prominent Domains Affected:

  Attention

  Processing Speed

  Executive Functioning

  Memory

# Cognitive Profile for Depression

- ATTENTION:
  - More difficulties on 'effortful' tasks as opposed to simple, automatic processing e.g. Forward DS grossly intact
  - Sustained attention (CPT) – errors of omission and commission
    - CPT difficulties often noted in euthymic/remitted states

- PSYCHOMOTOR SPEED:
  - Psychomotor Slowing may be specific to Melancholic Depression and/or older adults with depression
  - Slowing may be more evident on more effortful tasks

# Cognitive Profile for Depression

- MEMORY:
  - Acquisition process more impacted than retrieval – likely related to attention interfering with encoding
  - Level of impairment correlated with number of depressive episodes

- **The Good News –** memory decrements subside in remission

# 1997 Meta-analysis (pre-effort measure era)

- 13 studies; N = 377
- Fair degree of variability in cognition
- 50% exhibited substantial cognitive deficits (2 SDs)
  - Verbal Fluency (FAS; 11%)
  - Motor scanning (TMT A; Digit Symbol; 18%)
  - Visual spatial (Rey, Block Design; 15%)
  - Learning (RAVLT, CVLT; 15%)

Veiel, 1997

# Cognition in MDD Overview

| | |
|---|---|
| Intelligence | • Generally intact |
| Attention | • Acute: diminished Sustained, Working Memory<br>• Milder deficits may persist |
| Processing Speed | • Depression – reduced urgency and motivation ➔ slower |
| Sensorimotor | • Depression – slow as w/ processing speed |

# Cognition in MDD Overview 2

| | |
|---|---|
| Language | • No language deficits<br>• Severe depression – may lack engagement |
| Effort | • Must always be assessed in MDD<br>• More difficulties on 'effortful' tasks |
| Executive Functioning | • Diminished in symptomatic patients |

# Cognition in MDD Overview 3

| | |
|---|---|
| Memory | • Slow learning<br>• Weak recall, relatively intact recognition<br>• Expected to be relatively mild (if effort adequate) |
| Memory – Depressed | • Weak spontaneous recall |
| Visual Memory | • Normal |

# The Neuroanatomy of Depression

- Cerebral Cortex: Global  decreased activity, particularly in the frontal lobes

- The most common PET finding in depression is a decrease in the basal activity of the dorsolateral prefrontal cortex.

- Less consistently reported is increased activity in the ventrolateral prefrontal cortex.

# Blood Flow and Metabolic Abnormalities in Depression

- Decreased blood flow and metabolism: dorsolateral and medial prefrontal areas.
- Increased blood flow and metabolism: orbital regions, amygdala, and medial thalamus
  - Increased amygdala action.
    - Amygdala associated with assigning emotional significance to stimuli.
    - Amygdala activity stimulates cortisol release
  - Effective antidepressant treatment: orbital cortex and amygdala decreased metabolism to normal.

# Functional Neuroimaging (PET, SPECT) in MDD

Demonstrates decreased metabolic activity in:

- Dorsal prefrontal cortex
  - Orbital prefrontal cortex
  - Cingulate (regulation of mood and affect)

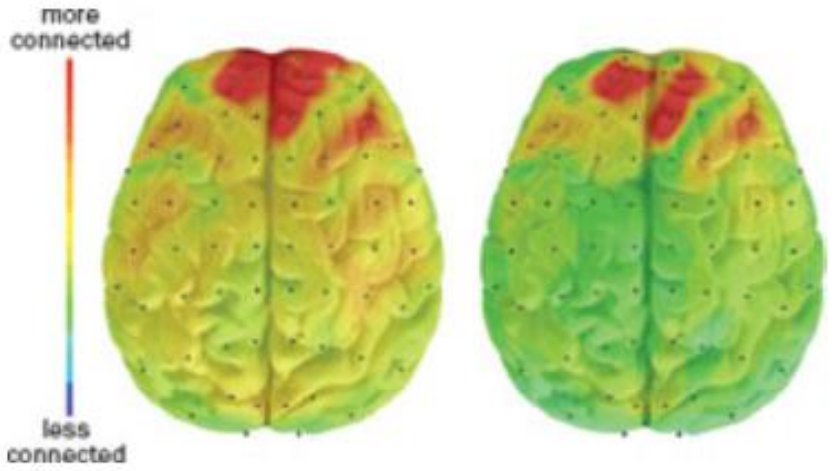
- Subcortical
  - Caudate (psychomotor changes)
  - Reduced Hippocampus

- IN SUM: Morphological and functional imaging studies note involvement of frontal, limbic and subcortical regions.

# Depression and Task-Positive Network over-activation

- TPN = dACC, left and right insula, and superior parietal lobule
- Depressed individuals experience difficulties in removing negative thoughts and memories from Working Memory once they are no longer relevant; leads to the sustained negative affect
- Process of removing no-longer-relevant negative material from WM is associated in depression with abnormal over-activation of the TPN; normals have overactive TPN for positive thts
- TPN activates when DMN deactivates & vice versa

# Depression Linked with Hyperconnected Brain Areas

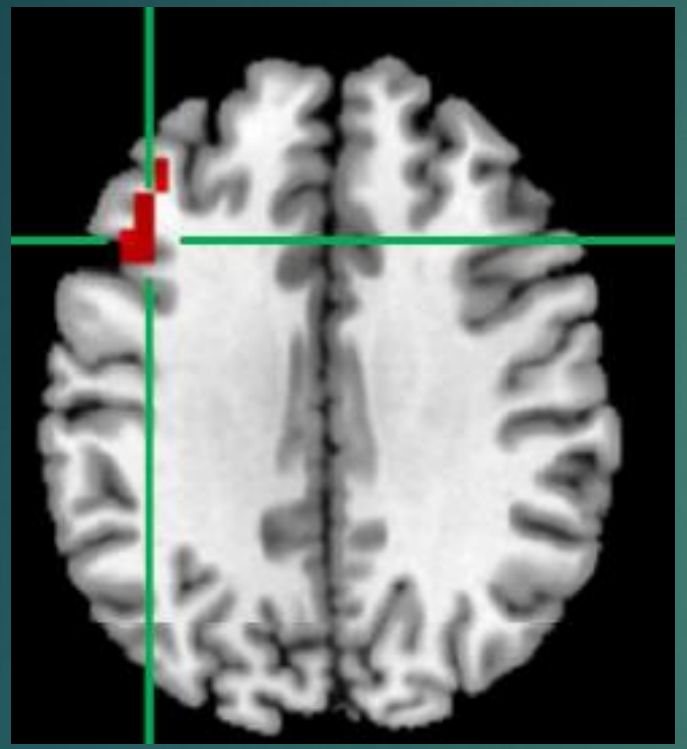



EEG data reveal how tightly connected the frontal cortex (*red*) is to the rest of the brain in depression (*left*) and health (*right*).

- Stronger links among certain frontal corticolimbic circuits are seen in patients more prone to rumination, the act of continuously replaying negative thoughts.
- Reduced with ECT
- Cause or effect?

ANDREW F. LEUCHTER ET AL., IN *PLOS ONE*,, 2012

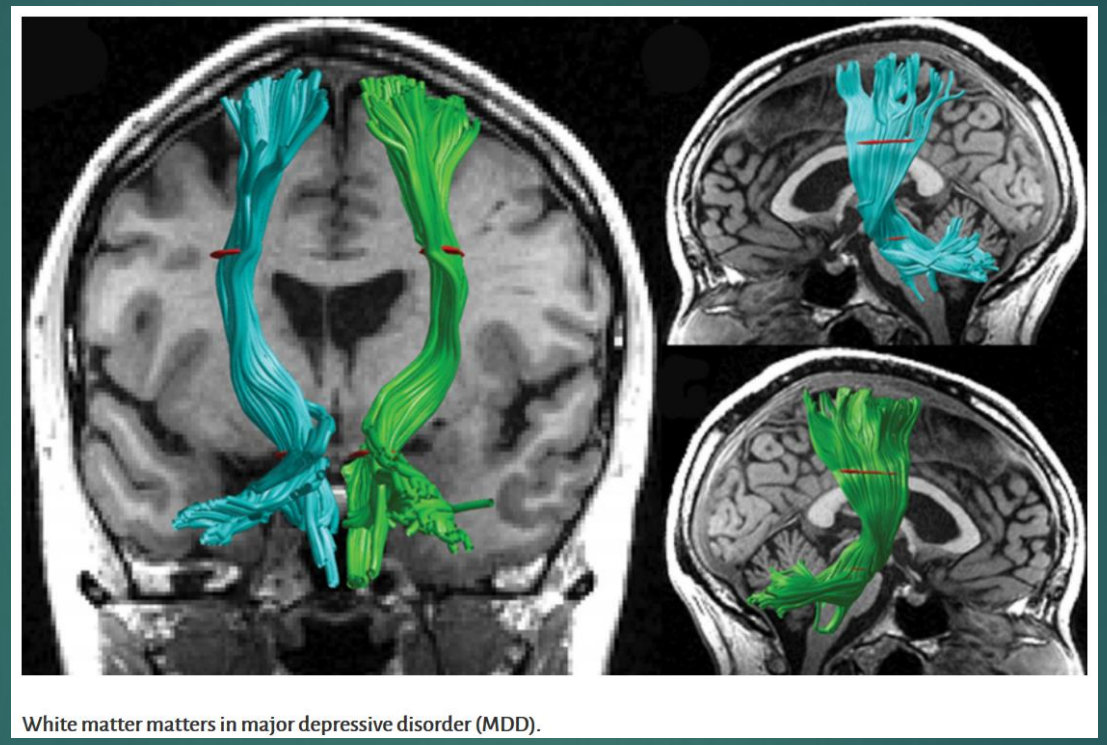
# Brain Center for Depression: DL PFC Overconnectivity



Left DLPFC (shown in red): a significant reduction in functional connectivity was observed after ECT treatment.

Accompanied by a significant decrease in depressive symptoms

# White Matter deficits in Depression: psychomotor sxs

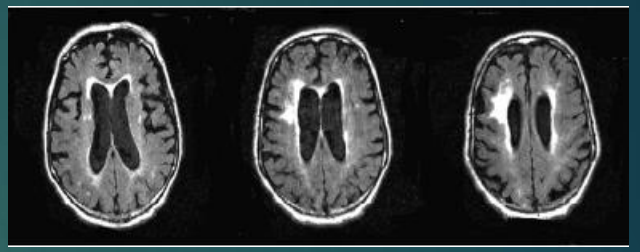


White matter matters in major depressive disorder (MDD).

Structure of corticospinal tracts was more likely to possess abnormalities in those with MDD, including bilateral posterior limbs of the internal capsule, right superior *corona radiata*, and the left external capsule. Given the role of the CSTs in motor processes, it is possible that our findings of anomalous FA in these structures are related to psychomotor symptoms that often characterize MDD

# Late Onset Depression

- 1st onset at or after age 60



- Presence of HTN, TIA, vascular surgery, CVAs

- MRI = LF, Left putamen, deep WM lesions

- Late life onset of depression is associated with an increased risk for vascular dementia and Alzheimer's disease
-
- Greater overall cognitive impairment and disability:
  - reduced depressive ideation: less guilt feelings and greater lack of insight

- The more Executive Dysfunction, poorer response to meds

Alexopoulos et al, AGP, 1997; robinson, Biol Psych, 2003; Sheline et al 2010

# Depression

- Somatize distress
- No decline in structure/ content of speech
- OK incidental learning and Temporal Orientation
- Constructional / copy tasks: careless, but able to perform adequately
- ** More likely to give "I don't know" responses
- Identifiable precipitant
- ** Aware and disturbed by cognitive difficulties

# Dementia

- Vegetative sxs less common
- Presence of aphasias, apraxias, agnosias
- ** Greater memory Impairment
- Deficits in construction/copy and perseveration
- More likely to give wrong responses
- Deterioration is typically slow with insidious onset
- Less concern over cognitive changes

# Late Life Depression + elevated Beta Amyloid = higher AD

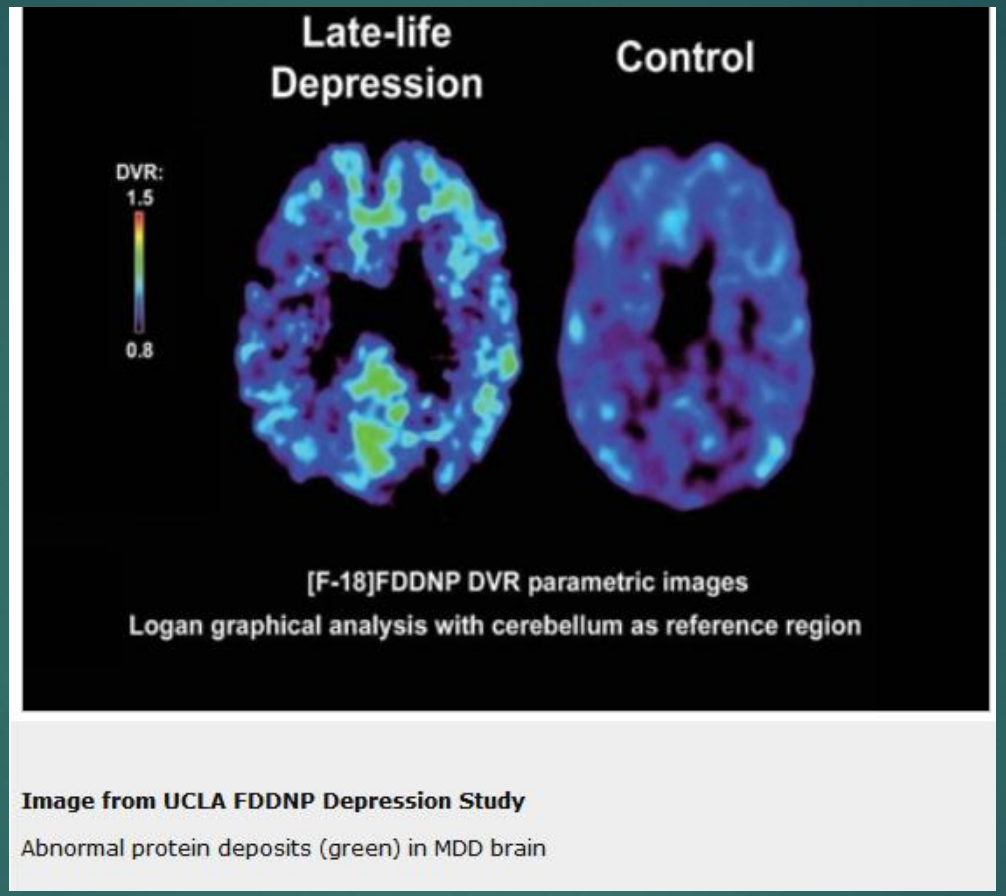
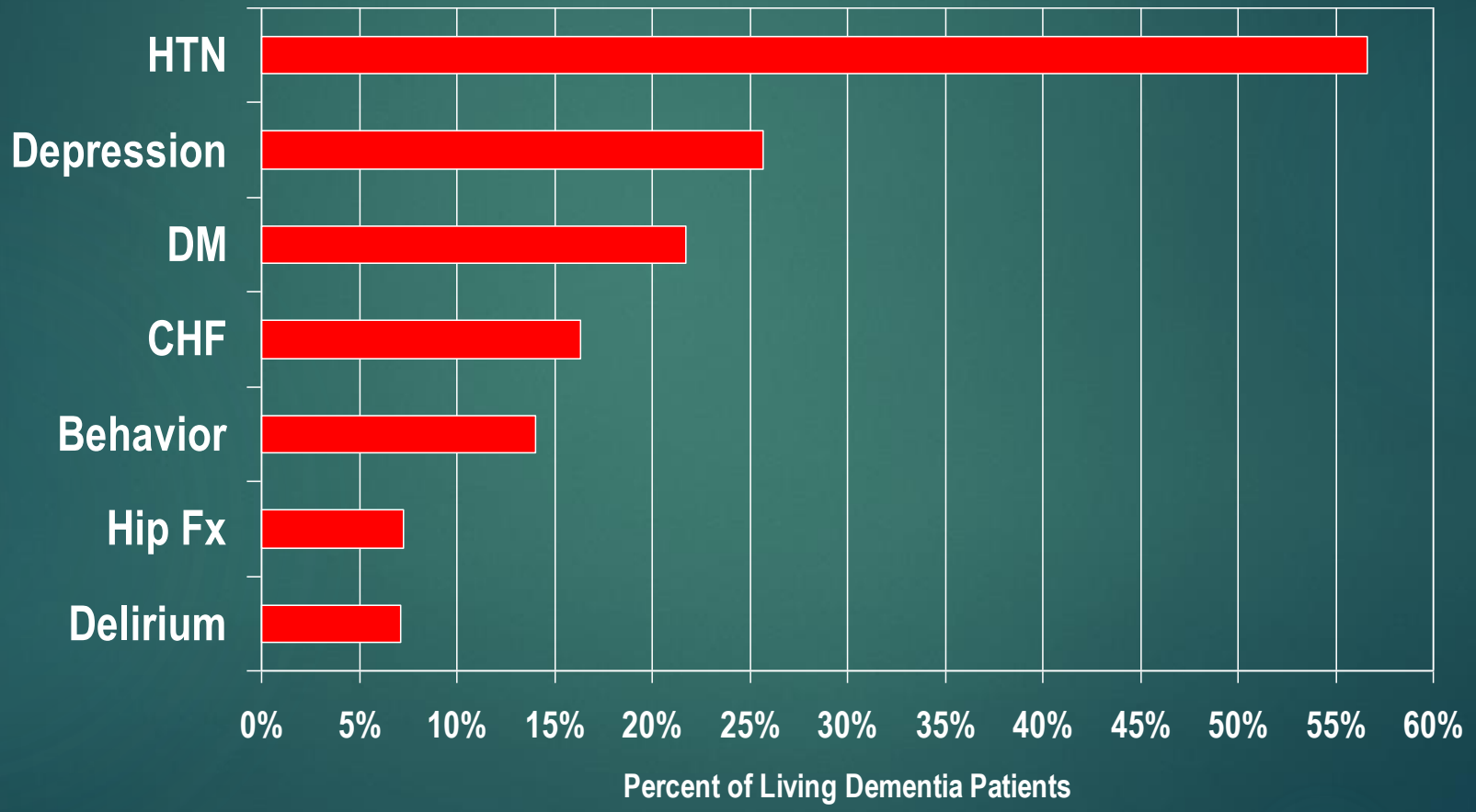



**Image from UCLA FDDNP Depression Study**

Abnormal protein deposits (green) in MDD brain

Combination of elevated amyloid-levels and coexisting depressive symptoms puts you at a higher risk for faster progression to Alzheimer's disease.

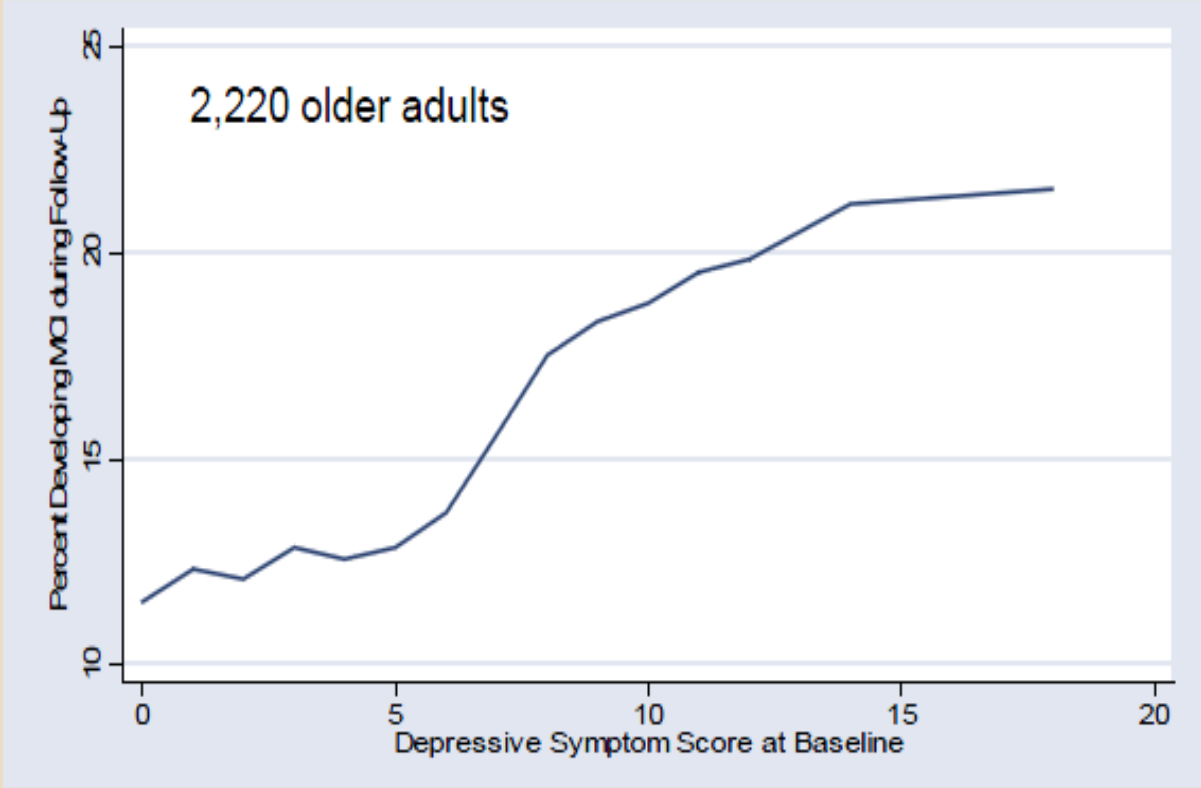
# Co-Morbidities of NorCal Dementia Pts



# Depression & NCD/dementia

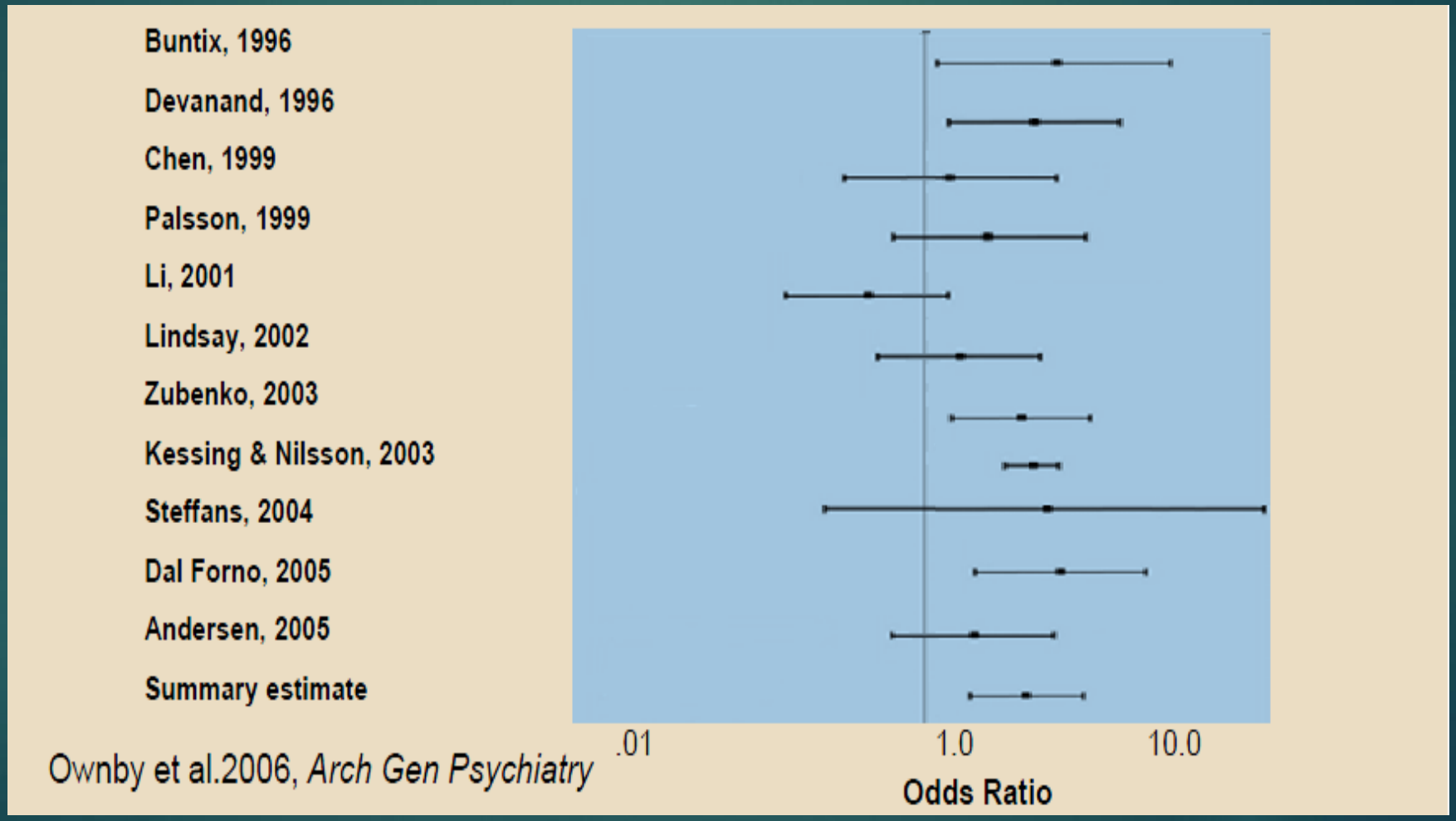
- Ongoing Major Depression is a risk factor for dementia
- Depression turns off neurogenesis
- All anti-depression TX (either medication or Cognitive Behavioral Therapy or ECT) turns on neurogenesis and reduces risk of NCD/dementia in cognitively normal
- Use of Aricept temporarily improves cognition, but increases recurrence of depression in cognitively impaired

# Risk of MCI increases with Depressive Symptoms




*Barnes et al., Archives of General Psychiatry, 2006*

# Depression Associated with a Doubling in Risk of Dementia




Ownby et al.2006, *Arch Gen Psychiatry*

# Depression and NCD/dementia

- Depression after age 50: higher risk for NCD/dementia
- Depression at hospital admission is an independent risk factor for poorer post hospitalization cognitive function

# Neurogenesis and Depression

- Cortisol is released in response to stressful experiences and serves many beneficial functions.
- Increased Cortisol release is associated with cognitive impairments and depressive illness.
- In the hippocampus, stress and cortisol strongly inhibit adult neurogenesis.
- Decreased neurogenesis has been implicated in the origin of anxiety and depression.
- Increased hippocampal atrophy in MDD; Increased risk for Alzheimer's

# Reduced Neuroplasticity in Schizophrenia, MDD, Bipolar Disorder, Stress Disorders: AD risk

- Stress Disorders, Depression, Bipolar Disorder & Schizophrenia are associated with:
  - **reduced neurogenesis**
  - **reduced nerve growth factor (NGF) and BDNF**
  - **hippocampal atrophy**
- Risk of dementia correlates with increase in the number of episodes in depressive and bipolar affective disorders.
- All 4 increase risk for Alzheimer's Disease.

# AD risk of affective disorders; risk increases with every episode

- Danish Study: All hospital admissions with primary affective disorder in Denmark during 1970–99; 18,726 MDD and 4248 BP patients

- **Results:** rate of Major Neurocognitive Disorder tended to increase:
  - 13% with every episode leading to admission for patients with depressive disorder
  - 6% with every episode leading to admission for patients with bipolar disorder.

- **Conclusion:** Risk of major NCD increases with the number of episodes in depressive and bipolar affective disorders.

# BDNF: You want more

- Brain-derived neurotrophic factor (BDNF) is critical for axonal growth, neuronal survival, and synaptic plasticity, and its levels are affected by stress and cortisol.

- Antidepressant drugs and electroconvulsive therapy increase BDNF levels

- BDNF is the link among stress, neurogenesis, and hippocampal atrophy in depression.

- Physical exercise increases BDNF

# Antidepressants:  Increase Hippocampal Volume

# Medications and Neurogenesis

- Psychotropic medications used in treating those disorders are neuroprotective and induce neurogenesis
- All antidepressant drugs and ECT increase  neurogenesis & BDNF.
- Mood stabilizers such as lithium and valproate increase neurogenesis.

H. Nasrallah, Medscape Psych., 2008; Reif, et. al., Molecular Psych. 2006

# Anti-depressants reduce Beta Amyloid

- People who have taken an antidepressant in the last five years have about half the BA load in their brains as the people who hadn't taken an antidepressant.
- The longer the antidepressant dose, the less BA plaque.
- Antidepressants appear to be neuroprotective.

# Alcohol and Depression:
# Know if your patient drinks

2 Negative consequences of Alcohol:

- **1 – It is a Depressant**
- **2 – It produces Frontal Lobe Disinhibition (no brakes)**

50% of completed suicides are done under the influence of alcohol

# Antidepressant use correlated with stroke

Antidepressant use is correlated with a 48% greater risk of stroke and that the magnitude of associations was greater in high-potency SSRIs (Paxil, Prozac).

- Why?
- Anti-depressant medication use may be an indicator of depression severity
- Correlative: The medications themselves may not be the primary cause of the risk.

# Depression increases Stroke Risk

- Depression is a risk factor for stroke
- LF Stroke often produces depression
- Risk is higher if have past hx of depression
- Treatment can improve both depression and cognitive effects.

# STAR*D Study

- STAR*D study:
  - 37% respond to 1st drug
  - 19% to 2nd drug;
  - total of 67% effectiveness rate
  - At 1 year, most need 2nd drug
  - Half of those who recovered relapsed within a year
  - No placebos used; CBT not paid for

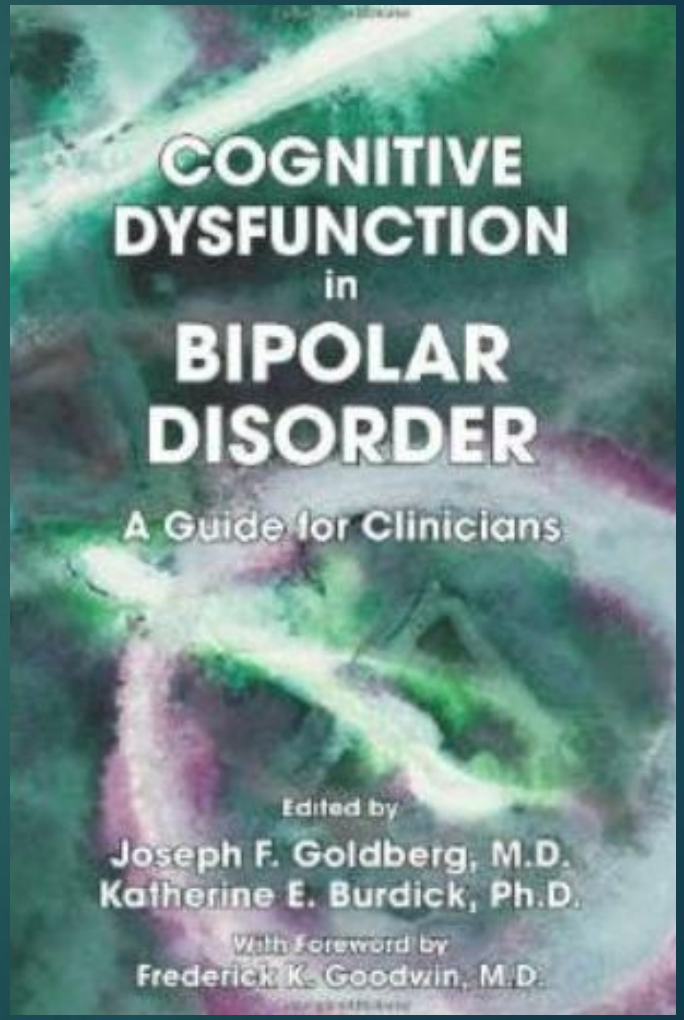
# Listening to Prozac  but Hearing Placebo.

- I. Kirsch + 2 other studies: antidepressant meta-analyses:
  - drugs alleviated depression no better than a placebo
  - both anti-depressants & placebos were both 82% effective
  - the worse side effects a patient experiences, the more effective the drug; 80% guess right about being on real drug, and have stronger placebo effect
  - lion's share of the drugs' effect comes from the fact that patients expect to be helped by them
  - Not placebo only in patients with very severe symptoms
- Power of Placebos: holy trinity of "belief, expectation, and hope"

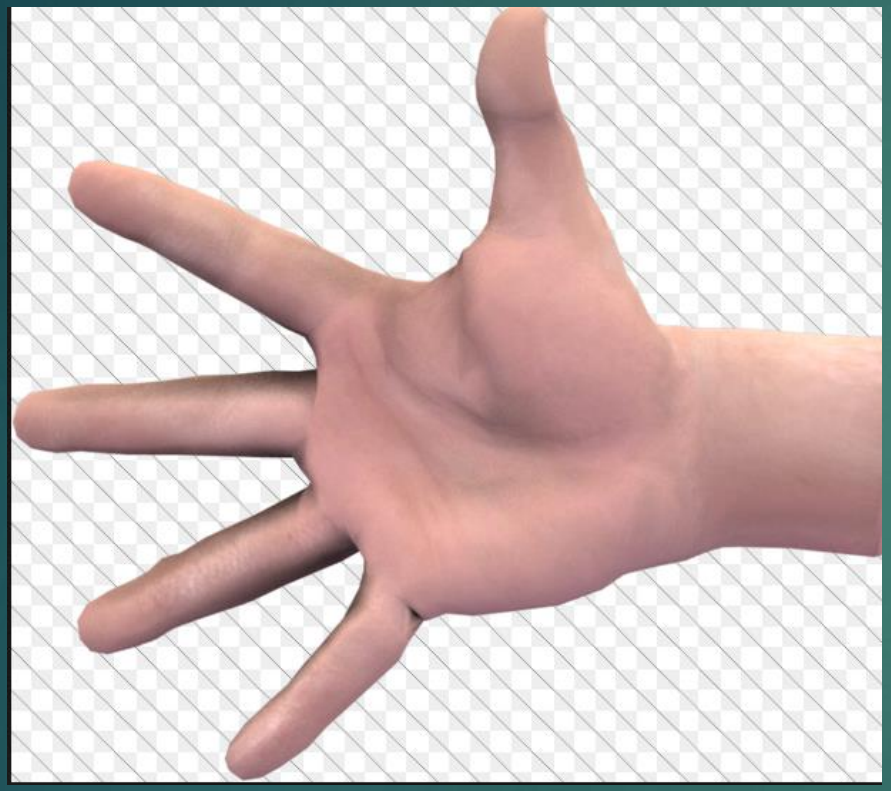
# Neuropsychology of Bipolar Disorder

# Bipolar Disorder: The Book

- **Cognitive Dysfunction in Bipolar Disorder: A Guide for Clinicians by** Joseph F. Goldberg & Katherine E. Burdick, 2008



# Prefrontal inhibitory circuits (fingers) vs Amygdala (thumb)



Out of control amygdala

Normal prefrontal control of amygdala overreaction

# Manic Episode

- Criterion A: Hallmark, primary criterion for mania and hypomania changed: is "persistently increased energy and activity" as well as altered elevated mood.

- Abnormal Mood: Distinct period of abnormal & persistently elevated, expansive or irritable mood

- A. Increased energy & activity: Abnormally & persistently increased goal directed activity
- A. ≥ 1 week, most of the day, nearly every day (any duration if hospitalized)

- B. ≥ 3 sxs (4 if irritable)
  - Grandiosity, less sleep, talkative, racing thoughts, distractibility, goal directed behavior, high risk behavior
- C. Impairment

# Hypomanic Episode

- A. Increased energy & activity: Abnormally & persistently increased goal directed activity
- A. Abnormal Mood: Distinct period of abnormal & persistently elevated, expansive or irritable mood
- A. ≥ 4 days, most of the day, nearly every day (any duration if hospitalized)
- B. ≥ 3 sxs (4 if irritable)
  - Grandiosity, less sleep, talkative, racing thoughts, distractibility, goal directed behavior, high risk behavior
- C. Change in function, but not severe, observable by others

# DSM-5: Bipolar Disorder

- 1. Manic Episode: abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy lasting at least 1 week; present most of the day, nearly every day. MDD common, but not required.
- 2. Three or more of the following (four if mood is only irritable)
  - Inflated self-esteem or grandiosity
  - Decreased need for sleep
  - More talkative or pressured speech
  - Flight of ideas or racing thoughts
  - Distractibility
  - Increase in goal-directed activity
  - Excessive involvement in pleasurable activities that have a high potential for painful consequences (buying, sex, etc.)
- 3. Causes marked impairment in social or occupational functioning; or need for hospitalization
- 4. All typical exclusions apply (not due to other psych, medical, substance D/O, etc.)

# Bipolar I, II & Cyclothymia

- 1. Bipolar I Disorder – Presence of full manic episode and depression
- 2. Bipolar II Disorder – Presence of depression and hypomania x 4 days; (no history of manic episodes)
- 3. Cyclothymia – Two years of mood cycles, but events don't meet criteria of depression or mania (less severe with shorter swings)
- **A manic or hypomanic episode due to antidepressant medication is sufficient for Bipolar diagnosis.**

# Bipolar Disorder

- Bipolar disorder is a mood disorder, characterized by long-term episodic, cyclical patterns involving extreme fluctuations of mood that cause significant disruptions in one's social, interpersonal, and occupational life.
- 1.2% of population
- Typically bipolar disorder emerges in the teen years or early adulthood. In some cases, it appears in childhood.
- Approximately 50% of people have their first episode of bipolar disorder before the age of 20.
- This onset of bipolar disorder is about 10 years younger than the onset of unipolar depression.

(Reiser and Thompson, 2005)

# Bipolar - manic/depression

- Alternating periods of despondency and elation
- Effects men and women in equal numbers
- Elation may be characterized by delusions and grandiosity
- Average age onset is 30
- Depression can last for 6 months
- Mania 2 months on average
- Cycle rate varies; average is 8 months without medication

# Three times more days depressed than manic or hypomanic

- Depression represents the predominant abnormal mood state for treated outpatients with bipolar I and II disorder.
- The depression/mania ratio was 2.9 in the bipolar I and 3.8 in bipolar II sub-groups.
- Percentages of time spent ill for bipolar I versus II patients were:
  - euthymia 48% versus 50%;
  - depression 36% versus 37%;
  - hypomania 12% versus 10%;
  - mania 1% versus 0.2%;
  - cycling 4% versus 3%.

- A 13 year study found that people with bipolar disorder spend an average of one-third of the weeks of their lives in states of depression (Judd et al. 2002.)

Kupka RW, et al. 2007

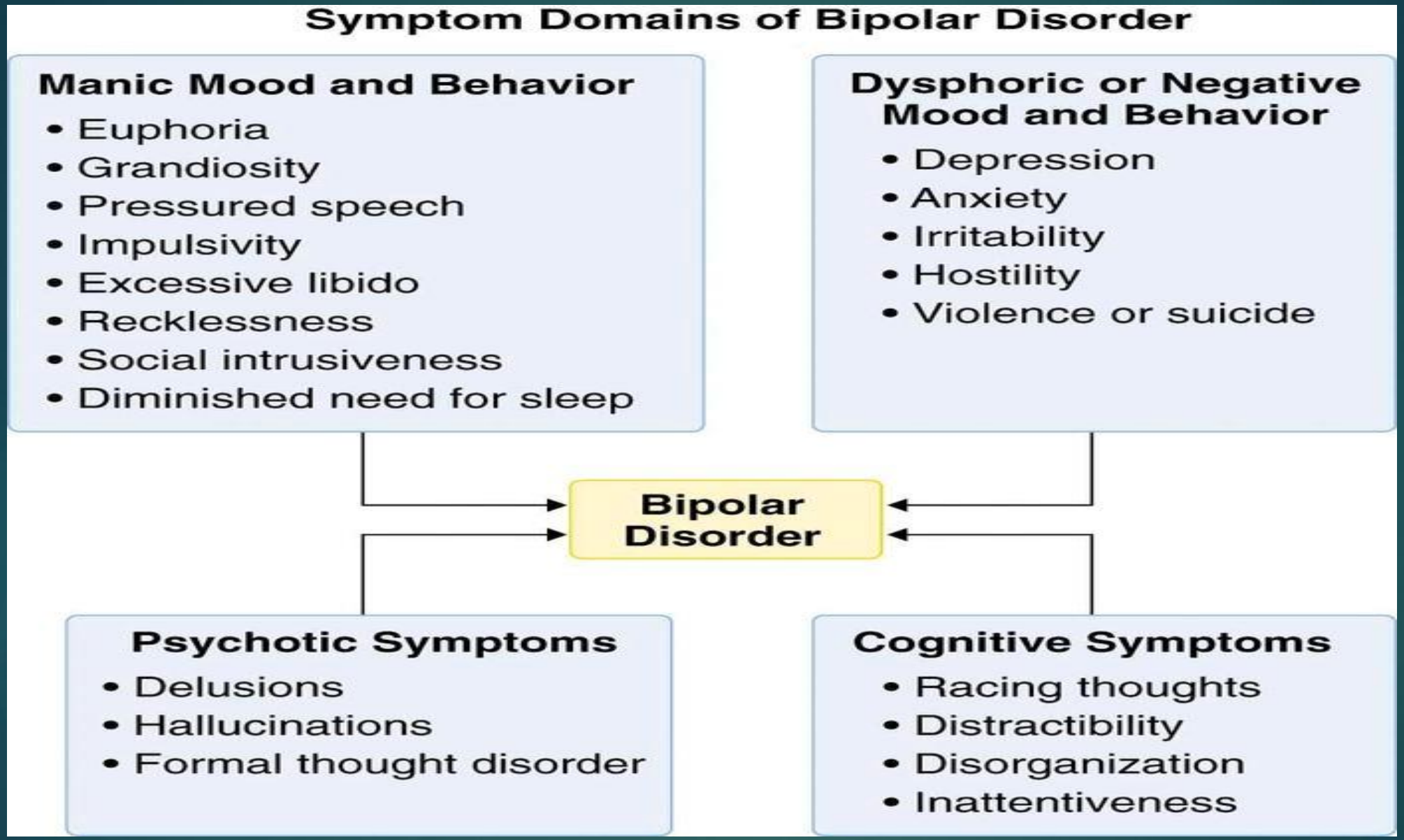
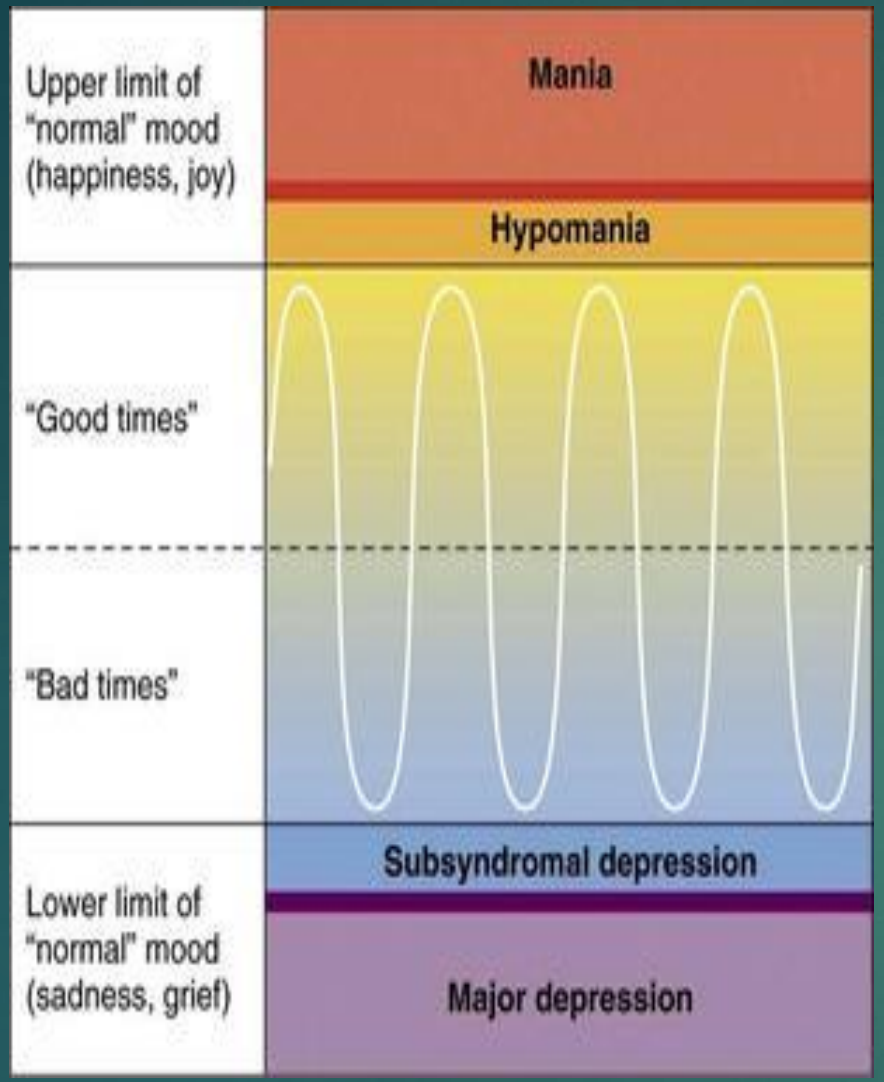



IMAGE SOURCE
http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/psychiatry-psychology/bipolar-disorder/images/bipolar-disorder-fig2_large.jpg


IMAGE SOURCE: http://withoutalabel.me/page/2/



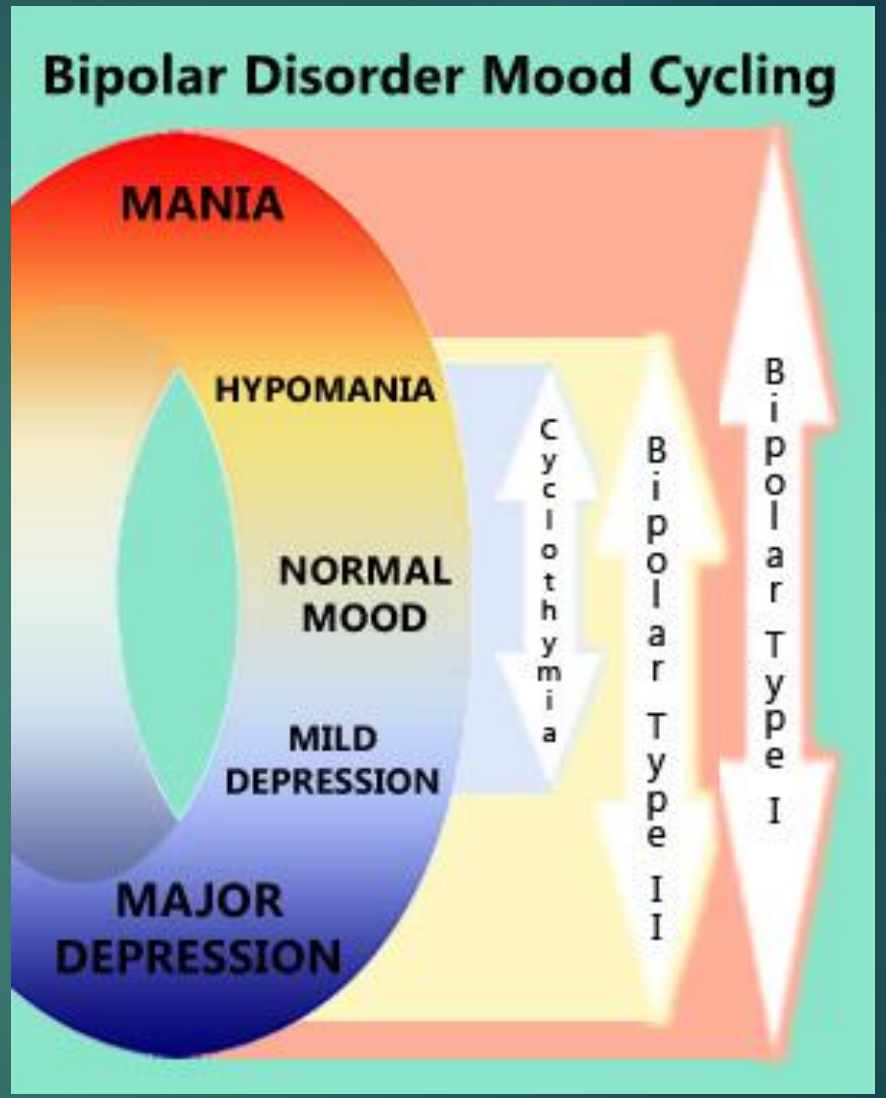




IMAGE SOURCE
# 1 = http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/psychiatry-psychology/bipolar-disorder/
#2 = https://www.imhro.org/education/about-bipolar-disorder/bipolar-disorder-symptoms

- How bipolar pts present for TX:
  - Depressed
  - Anxious
  - Experiencing mood swings
  - Unable to sleep
  - Irritable
  - Low energy/fatigued
  - Unable to focus
  - Drinking too much
  - In trouble with the law or drug use
  - Relationship problems
  - Impulse control problems
  - Person says they are fine; family and friends see it differently

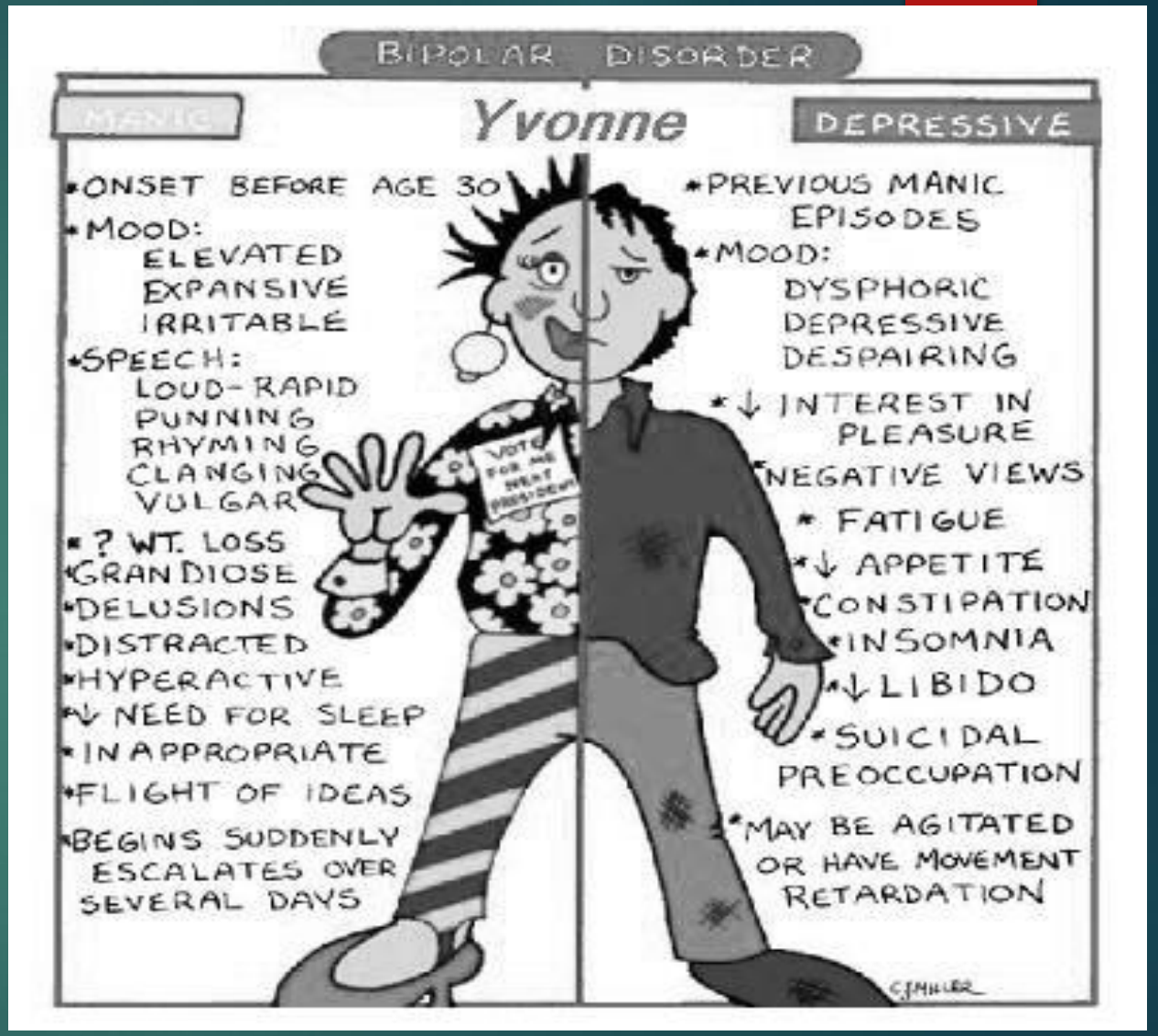



IMAGE SOURCE http://neurowiki2012.wikispaces.com/Signs+and+Symptoms+of+Bipolar+Disorder

# Bipolar Disorder:

- A recurrent d/o: >90% will have a second manic episode
- 20-30% will display mood lability/mood sxs between episodes
- A first manic episode after age 40 is likely caused by a medical condition.

# Early Onset Bipolar

- Patients with early-onset bipolar disorder are at risk for a host of poor outcomes:
  - notably rapid cycling,
  - lengthy episodes,
  - polarity switches,
  - and deteriorations in functioning.
- There are neurotoxic effects of repeated episodes on the developing juvenile brain,
- Introducing psychosocial interventions early in the course of the disorder (even during the preonset period) may decrease long-term chronicity, psychosocial impairment, and caregiver burden.

# Genetics

- Genetic factor
  - 10 times more like to have it if you have a close relative that does
  - Concordance rate is 69% in identical twins and 13% in fraternal twins
    - Same if reared together as if reared apart
  - Evidence of minor EF deficits in first degree relatives

# Bipolar Course: Mania is bad for your brain

- No cognitive deficit prior to illness onset of BPD
- Evidence of minor EF deficits in first degree relatives
- Toxic to Brain: Deleterious effects of repeated manic episodes and psychotropic medication on cognitive performance
- Lithium therapy status may be a protective confounder in inconsistent studies of hippocampal volume .

G. Goodwin, et al., Europ Neuropharm, 2007

# Functional recovery

- More than 97% of bipolar patients appear to recover clinically within 2 years
- But only 37% recover functionally during the same time period.
- A significant contributor to the substantial difference is residual cognitive dysfunction.

# Statistics of Bipolar Disorder

- Only 25% of bipolar I patients achieve full recovery of function
- Up to 50% of Bipolar I patients do not recover from acute manic episodes within 1 year
- Rates of recurrence average 40%-60% in 1-2 years even when patients undergo pharmacotherapy.

David J. Miklowitz, Amer J Psy, 2008

# Statistics 2

- Patients spend as much as 47% of their lives in symptomatic states, especially depressive states.
- During symptomatic periods in bipolar outpatients undergoing treatment, depressive symptoms are three times as likely as manic symptoms to be present.
- This is notable both because
  - most mood stabilizers are not as effective in treating the depressive phase of illness (they are for acute mania only)
  - Many bipolar patients are treated with conventional antidepressants (40-50%) with or without the recommended mood stabilizers or atypical antipsychotics.

# Statistics 3

- Only about 40% of patients are fully adherent with medication regimens in the year following an episode.
- While antidepressants may be effective in some individuals with bipolar disorder, they can precipitate a rapid mood switch from depression to mania, a phenomenon also known as treatment-emergent mania(5-20%).

- Bipolar disorder linked to risk of early death from natural causes

- Most common conditions leading to premature death were heart disease, respiratory disease, diabetes and stroke

# Statistics 4

- Stressful life events and high levels of familial expressed emotion are robust predictors of mood recurrences and delayed episode recovery in bipolar illness.

- Individual, family, group, and systematic care treatments are effective in combination with pharmacotherapy in delaying relapses, stabilizing episodes, and reducing episode length.

# Cognitive Deficits

- Neurocognitive deficits in bipolar illness are fundamental to the disorder, representing a more direct biological consequence of genes

- Changes in the fluency of thought and speech, learning and memory impairment, and disturbances in associational patterns and attentional processes are as fundamental to depression and mania as are changes in mood and behavior.

- A significant number of bipolar patients show persistent cognitive deficits during remission from affective symptoms.

( Hasler, Drevets, Gould, Gottesman, & Manji, 2006).

# Neurocognitive Deficits in Bipolar Disorder

- There is growing evidence that individuals with bipolar affective disorder have cognitive impairments, even during periods of symptom remission (euthymic state).
- While these cognitive impairments are typically less pronounced than those found in other psychiatric (e.g. schizophrenia) or neurological (e.g. Alzheimer's dementia) illnesses,
- Reduced neuropsychological ability significantly affects bipolar patients' psychosocial functioning
- Acute manic phases have most impaired NP deficits

# Neurocognitive Deficits in Bipolar Disorder

- Even during periods of symptom remission, bipolar pts exhibit:
  - **Marked deficits in executive-function and verbal learning**
  - **The more intense the disease process, the worse the cognitive deficits**
  - **Deficits are persistent, despite psychiatric symptom reduction**
- Significantly affect psychosocial functioning

# Euthymia: normal non-depressed, reasonably positive mood

- BP patients routinely complain of neuropsychological difficulties.

- Euthymia (neutral mood in absence of a depressive or manic cycle) does not equate with normal NP function

- Each phase has a characteristic pattern of deficits with disturbance in attention and memory being common across all phases of the illness:
  - bipolar depression - psychomotor slowing and impairment of memory;
  - hypomania by frontal-executive deficits
  - Euthymia = a milder disturbance of attention, memory and executive function.

# Euthymia 2

- 75% of asymptomatic patients scored:
  - more than one standard deviation below healthy comparison subjects
  - on at least four cognitive measures,
  - suggesting widespread, but relatively mild, neuropsychological dysfunction in bipolar disorder.

Glahn et al., 2007

# Anosognosia: Neurological Unawareness of Deficits

- 50% of Bipolars have neurologically based anosognosia
- Anosognosia = unawareness of deficits
- Severity of poor insight strongly correlated with degree of frontal lobe dysfunction and executive dysfunction (WCST, verbal fluency, Trails)
- Basis of not seeking treatment or medication noncompliance
- Reason why closing state mental hospitals is a disaster; strong cause of homelessness

# Blind to deficits: No correlation between NP deficits and self-Report

- Patient mood ratings for mania and depression are not significantly correlated with self-report inventories or objective neuropsychological variables.
- The findings suggest that most bipolar patients:
  - Have NP deficits
  - Unable to report them accurately
- Such discrepancies could relate to impaired insight/ansognosia, efforts to conceal deficits, or to subthreshold affective symptoms.

# Need for NP screening or testing

- Given the known NP deficits in Bipolar disorder, clinicians should routinely do mental status testing (MOCAs) with newly stabilized Bipolar pts.

- Those that have more serious deficits (esp. EF), should receive NP evaluation.

# Meta-Analysis of Bipolar Disorder

- 42 studies of 1,197 patients in euthymia, 13 studies consisting of 314 patients in a manic/mixed phase of illness, and 5 studies of 96 patients in a depressed state
- For euthymia, results revealed generalized moderate level of impairment across all neuropsychological domains, esp. verbal learning and delayed verbal and nonverbal memory
- During a manic/mixed or depressed phase: exaggerated impairment of verbal learning,
- During a depressed phase: phonemic fluency deficit.

M. Kurtz & R. Gerraty, Neuropsychology, 2009

# Another Meta-analysis of euthymic BD: Executive & Verbal Memory Deficits



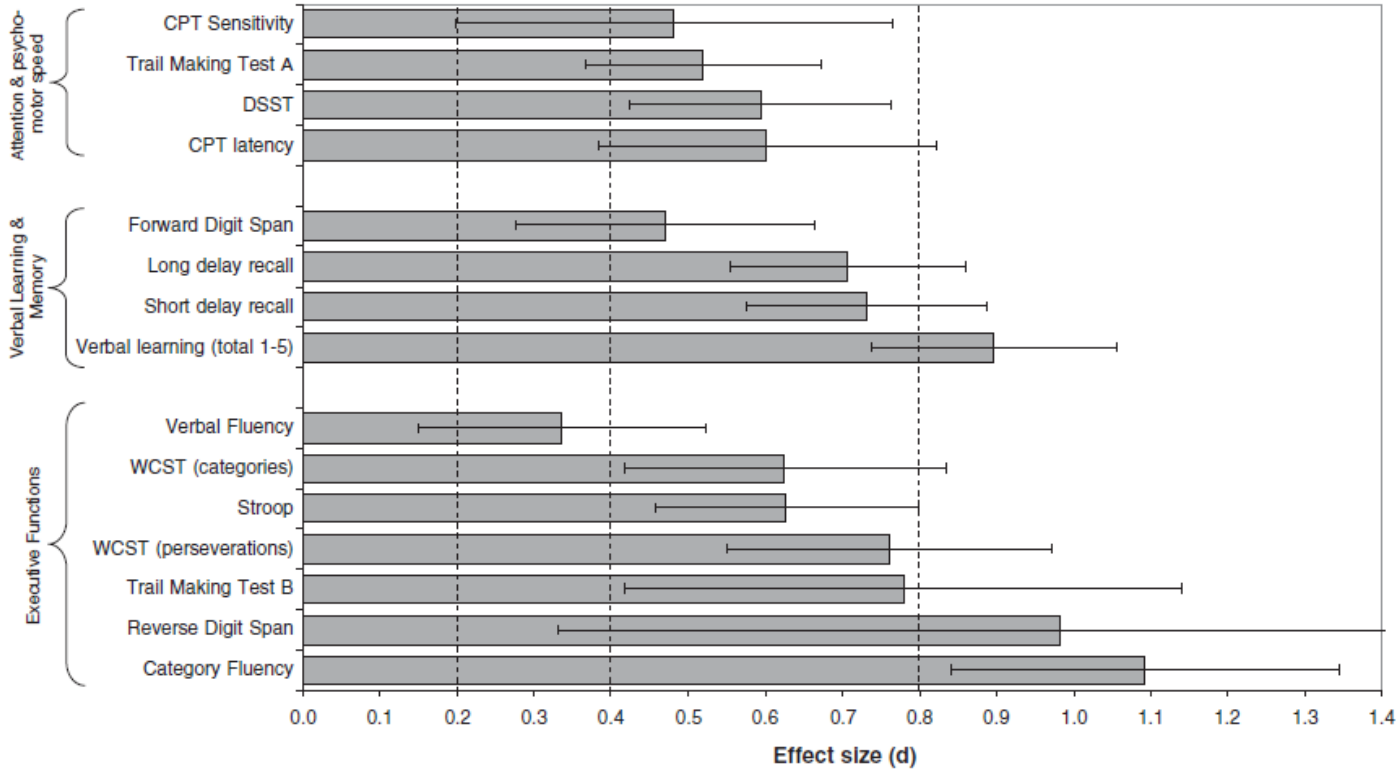



Fig. 1. Results of the meta-analyses (effect sizes plus 95% confidence limits). DSST, Digit Symbol Substitution Test; CPT, Continuous Performance Test; WCST, Wisconsin Card Sorting Test.

Robinson, et. al., J of Affect Disorders, 2006

# Neuropsychological Profile of Bipolar disorder

**Table 1 The neuropsychological profile of bipolar disorder**

| Cognitive domain | Bipolardepression | Euthymia | Mania |
|---|---|---|---|
| Set-shifting and (or) concept formation | ↓ | ↓↓ | ↓↓ |
| Verbal fluency | ↓ | ↓• | ↓ |
| Decision making | — | ↓• | ↓ |
| Planning and (or) problem solving | ↓ | ↓ | ↓↓ |
| Nonverbal intelligence | ↓ | ••• | ↓ |
| Sustained attention | ↓ | ↓↓↓ | ↓↓ |
| Verbal memory–delayed recall | ↓ | ↓ | ↓ |
| Visual memory | ↓ | ↓• | ↓ |

↓ = Re duced and (or) im paired, com pared with healthy con trol sub jects; • = no change, com pared with healthy con trol sub jects. Each sym bol de notes the find ing from one study.

Each ↓ = 1 study

Malhi, et al, 2004

# Meta-analytic Study of Manic vs. Euthymic States

- Manic BP: moderate impairments were evident across a variety of neurocognitive measures, including:
  - attention,
  - working memory,
  - language,
  - psychomotor speed,
  - executive function.

- Euthymic Bipolar disorder characterized by generalized moderate level of NP impairment with marked deficits in verbal learning and memory.

Matthew M. Kurtz & Raphael T. Gerraty, 2009

# Meta-analyis 2

- Patients in a manic or depressed state had significantly greater effect-size impairment in verbal learning than patients in a euthymic state.
- Patients with depression also showed greater phonemic fluency deficits relative to euthymic patients.

# NP deficits predict Social & Vocational Functioning

- Verbal memory impairments and/or executive dysfunction are associated with:
  - reduced social and vocational functioning in patients with bipolar disorder,
  - even in the absence of manic or depressive symptoms

Martinez-Aran et al., 2004; Dickerson et at., 2004

# Lithium reduces AD Risk

- Bipolar disorder is associated with increased risk for dementia.
- Prevalence of Alzheimer's disease between 66 elderly euthymic patients with bipolar disorder who were on chronic lithium therapy and 48 similar patients without recent lithium therapy.
- Lithium treatment reduces the prevalence of Alzheimer's disease in patients with bipolar disorder to levels in the general elderly population.
- But note that very high doses of Lithium can produce cognitive deficits

# Localization in Bipolar Disorder

Mood Disorders: Network of prefrontal-striatum-amygdala

- Prefrontal cortex in the pathogenesis of BD
  - Glucose metabolism: hyperactive in manic period; hypoactive in depressed period
  - Cerebral blood flow: hypoactive in both
- OFC and ACC dysfunction and atrophy
- Cortical-subcortical-limbic disruption in recovered euthymic patients that manifests as cognitive dysfunction.

# Enlarged Amygdala in BD

- Decreased volume and increased response to emotional stimuli in the amygdala in adolescents with BD
- In adults, chronic BD I may enlarge the amygdala over time due to # of episodes & medication effects.
- An inverse association between volume and response to emotional stimuli.
- Increased amygdala volume is prototypical of BD I

# Fatal Illness More Likely in Bipolar Patients

- A review of 17 studies involving more than 331,000 patients:
- Mortality in bipolar patients ranges from 35 % to 200 % higher than in comparison groups.

- Almost every cause of death was higher among bipolar patients: cardiovascular, respiratory, cerebrovascular (including strokes), and endocrine (like diabetes).

- The chronic stress of bipolar illness may lead to metabolic syndrome and atherosclerosis, or to insulin resistance, which increase the risk for sudden cardiac death.

- Psychiatric medications, because many lead to weight gain, may increase the risk for diabetes and cardiovascular disorders.

Katon, 2009

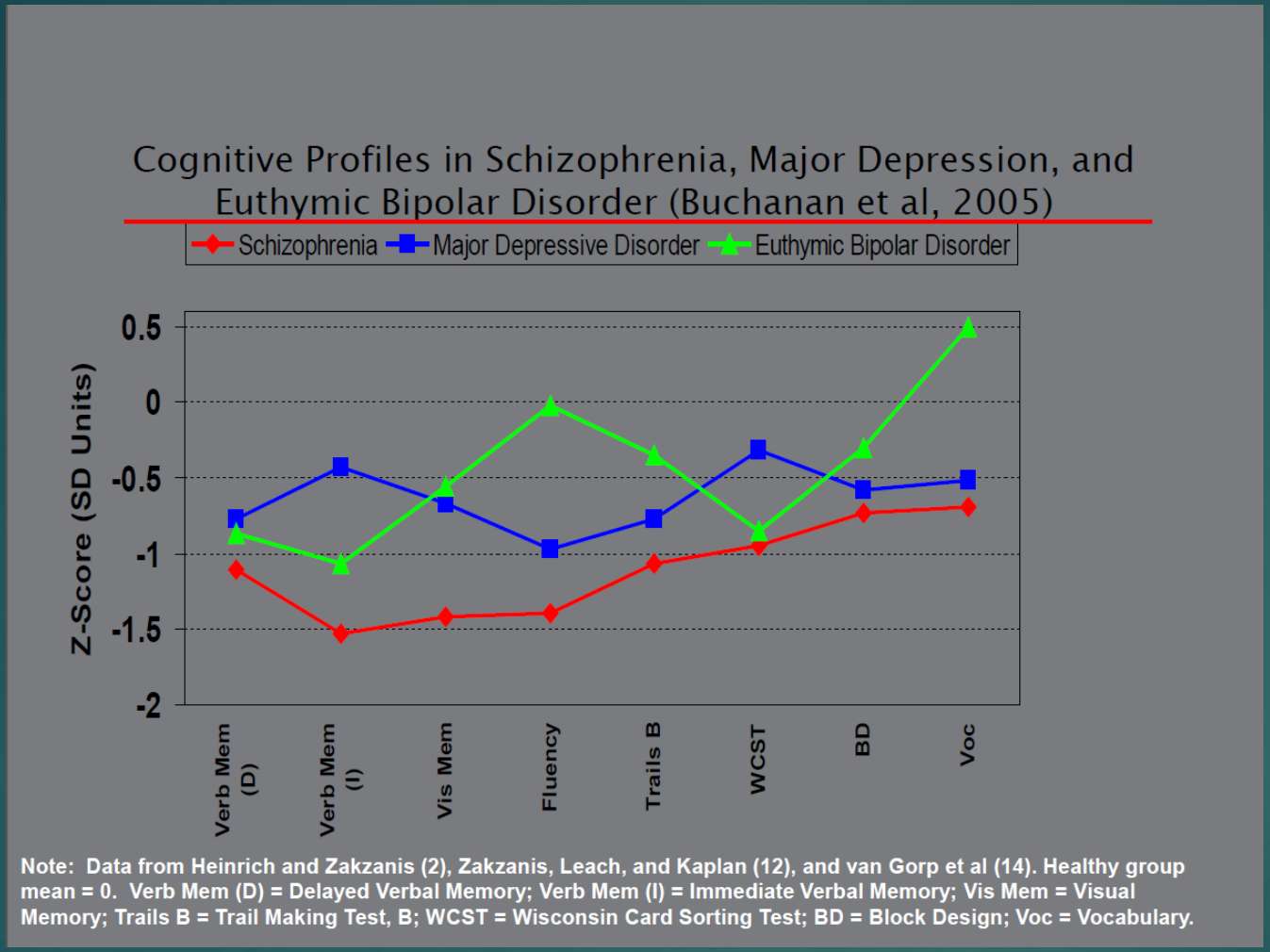
# Cognition in Bipolar

- Poorer learning and memory, executive functions, psychomotor speed
- Similar to MDD pattern, but worse
- Manic state – greatest deficits
- Euthymic State – least deficits
  - Greater deficits on measures of executive function and memory than on measures of attention and speed
- Negative correlation between number of manic episodes and verbal memory, memory retention, and executive functions.

# Cognitive Deficits 2

- Diffuse cognitive dysfunction during the acute phases of bipolar illness.
- Deficit levels seem to remit during periods of euthymia
- Some deficits may persist in approximately one third of bipolar patients.

# Cognition in Schizophrenia, MDD, & Euthymic Bipolar




Note: Data from Heinrich and Zakzanis (2), Zakzanis, Leach, and Kaplan (12), and van Gorp et al (14). Healthy group mean = 0. Verb Mem (D) = Delayed Verbal Memory; Verb Mem (I) = Immediate Verbal Memory; Vis Mem = Visual Memory; Trails B = Trail Making Test, B; WCST = Wisconsin Card Sorting Test; BD = Block Design; Voc = Vocabulary.

Lower scores = worse
Euthymic = Green
Depression = Blue
Schizophrenia = red

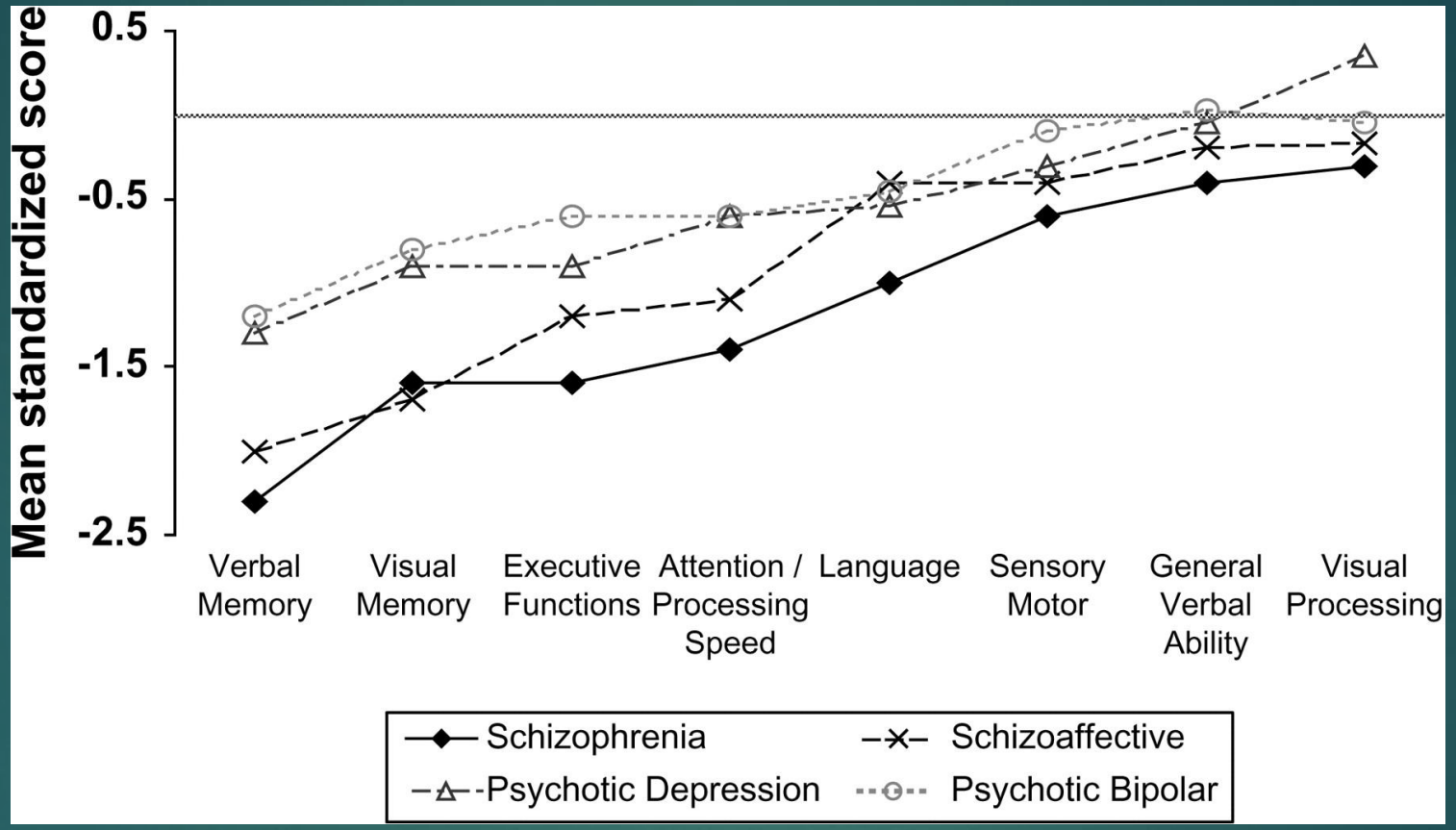
Similar deficits in Schiz & euthymic Bipolar: Verbal memory & WCST

# 2010 Metaanalysis of affective psychosis

- 27 studies, 763 patients with affective psychosis (550 BD and 213 major depressive disorder) and 1823 healthy controls.
- Patients with AP were impaired in all 15 cognitive tasks with large effect sizes for most measures.
- No significant differences between the magnitude of impairments between the BD and major depressive disorder groups.
- The largest effect size was found for symbol coding, Stroop task, verbal learning, and category fluency ( = attentional processing & learning and memory)
- In general, the pattern of cognitive impairments in AP was similar to reported findings in euthymic patients with BD, but relatively more pronounced.

Emre Bora, et al., 2010

# 4 psychotic groups vary minimally; Schizophrenia most severe




4 psychotic groups vary only minimally in their NP performance profiles. This may further suggest similar pathophysiology, involving frontal lobe circuits, underlying the NP deficits in different psychotic disorders.

Reichenberg A et al. Schizophr Bull 2008;35:1022-1029

# Schizophrenia and Bipolar Disorder

- More and more epidemiological, genetic and neuroimaging studies show similarities between bipolar disorder (BD) and schizophrenia (SZ).
- Patients with BD disorder suffer from cognitive deficits that are milder but qualitatively similar to those of patients with schizophrenia.
- Remitted BD patients out-performed stable schizophrenia pts. on most cognitive measures but this advantage disappeared when they were acutely symptomatic.
- SZ and BD disorder show greater similarity in terms of the nature than in severity of their neuropsychological deficits.

# Language and IQ

- There is very little evidence of language or IQ deficits in bipolar disorder.
- General intellectual function: this was largely preserved in BD. Impairments when present were limited to acute episodes and to performance scores.
- Those euthymic bipolar patients with cognitive difficulties tend to have attentional, executive, and long-term memory impairments

Quraishi & Frangou, 2002

# Cognitive Impact of Medications

- Few studies
- While lithium has a negative effect on memory and speed of information processing, patients were often unaware of these deficits.
- Mean memory test scores remained stable over a six-year interval in lithium–treated bipolar patients.
- This suggests that long-term lithium usage is unlikely to cause progressive cognitive decline

Honig et al 1999; Engelsmann et al, 1988

# Core feature of BPD: Executive Dysfunction

- All aspects of executive function (planning, abstract concept formation, set shifting) are impaired in symptomatic BD patients.
- Executive dysfunction is the main long-term neuropsychological deficit of bipolar disorder.
- Performance on executive function tests was sensitive to the presence of even residual symptoms but it may be normal in fully recovered patients with uncomplicated BD.
- Most sensitive measures: WCST PE errors, TMT B, Fluency, Digit Span backwards
- EF & memory deficits present in first degree relatives
- EF dysfunction as endophenotype candidate

Quraishi S, Frangou S, 2002; Arts et al., 2008

# Core Cognitive Feature: Sustained Attention Deficit

- Attention: attentional abnormalities were seen in symptomatic BD patients and persisted in remission in measures of sustained attention and inhibitory control.

- This deficit was related to progression of illness, but was none the less present in a subgroup of patients near illness onset.

- **Conclusions:** Sustained attention deficit may represent a neuropsychological vulnerability marker for bipolar disorder.

L. Clark, *The British Journal of Psychiatry* (2002)

# Memory

- Verbal memory is impaired, even in euthymic patients
- May be linked to duration of illness and number of episodes
- Visuo-spatial memory deficits were variable depending on the tasks used.
- Meta-analysis: Verbal learning and Memory are markers of BD 1
  - 65 studies
  - Verbal Learning and Memory had largest effect sizes over all 3 mood states in BD

**Quraishi S, Frangou S,** 2002; Kurtz & Gerraty, 2009

# Adolescent Bipolar TX & Brain

- At baseline the patient group had hypoactivation in the dorsolateral prefrontal cortex (DLPFC) and hyperactivation in the posterior cingulate cortex.
- Between pre- and post-treatment activation increased in the DLPFC and decreased in the amygdala.
- Increases in DLPFC activation were significantly correlated with improvement in mania symptoms.
- Enhancement of frontal executive control brain regions may underlie improvement in mood dysregulation in pediatric patients at familial risk for bipolar disorder.

Amy S. Garretta, et al., 2014

# Meta-Analysis: More episodes, more deficits, more HBOs

- Toxic disease process: Significant cognitive impairment may be present in bipolar illness, particularly in a subgroup of chronic, elderly or multiple-episode patients

- Negative relation between number of manic episodes and performance on tasks of verbal memory and executive functions.

- Number of manic episodes correlated to decrease in memory retention
- Underlying functional correlate of these cognitive deficits may be white matter lesions ('signal hyperintensities') in the frontal lobes and basal ganglia
- Frontal and subcortical hypometabolism in bipolar illness

Bearden et al., Bipolar Disorders, 2002

# More MDD or Bipolar episodes, greater risk of Dementia

- Danish Study: All hospital admissions with primary affective disorder in Denmark during 1970–99. n = 18,726 MDD; 4348 Bipolar

- Rate of dementia tended to increase:
  - 13% with every episode leading to admission for patients with depressive disorder
  - 6% with every episode leading to admission for patients with bipolar disorder.
- **Conclusion:** On average, the risk of dementia seems to increase with the number of episodes in depressive and bipolar affective disorders.

# Neuropsychological functioning in Bipolar Disorder and Mania

Neuropsychological Functioning:

- 1. IQ generally well preserved.
    - Impairments (when present) limited to acute episodes
- 2. Diminished attention during manic episode and may persist in remission
    - Sustained attention and inhibitory control
- 3. Verbal memory often impaired in symptomatic and euthymic patients
- 4. Executive functioning impaired in symptomatic patients and euthymic patients.

# Social Cognitive Deficits in BD

- BD 1 pts have significant impairments in:
  - Identification of primary facial emotions
  - Social perception
  - Mirror neuron firings

# Neuroanatomy of Affective Disorders

Areas of Focus:

**FRONTAL**

**Prefrontal Cortex**

**LIMBIC**

**Hippocampus**

**Cingulate Gyrus**

**SUBCORTICAL**

**Basal Ganglia**

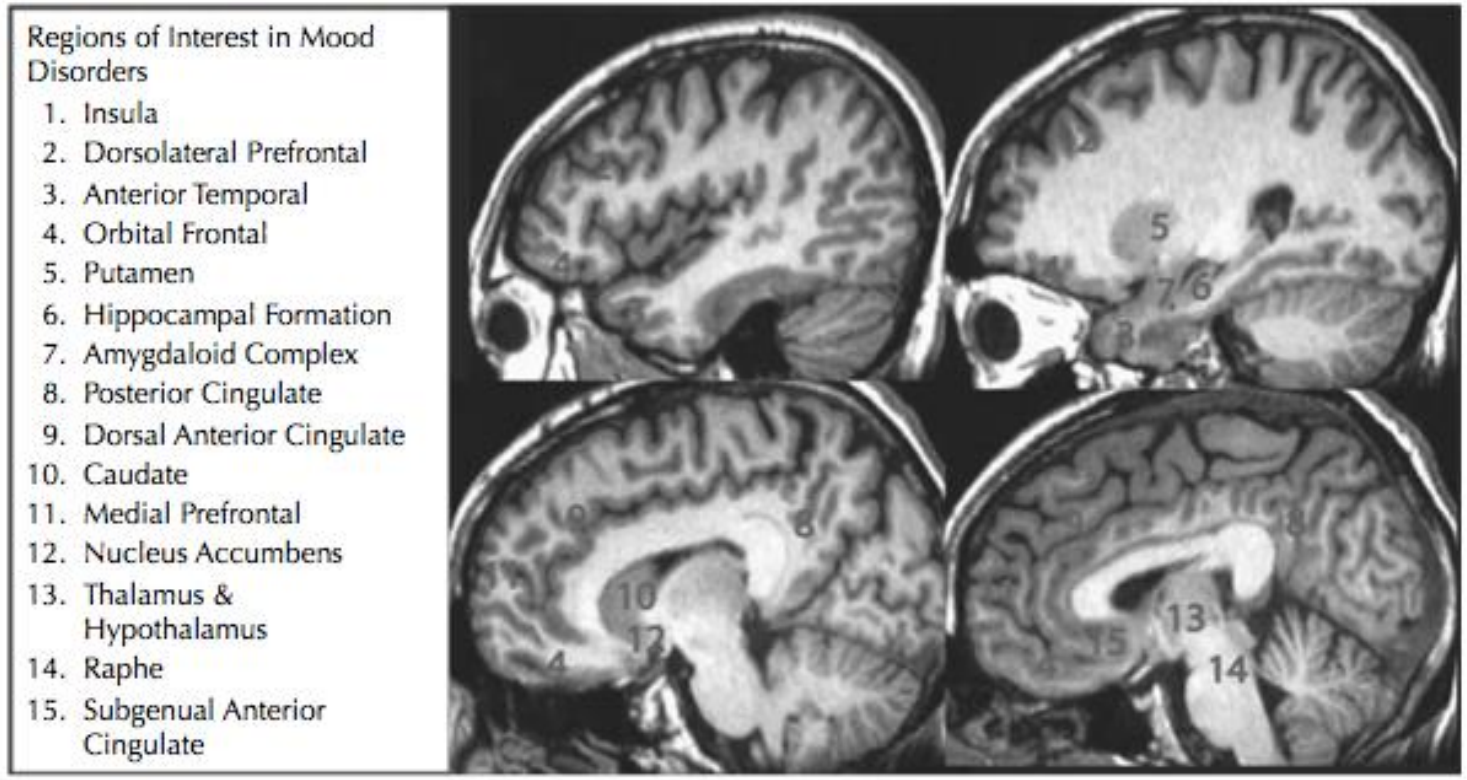



**Figure 22–1.** Frequent Regions of Interest Reported in Structural and Imaging Studies Relevant to Understanding Depression and Related Psychiatric Disorders. Numbers indicate center of foci, although some foci are collapsed across the left-right axis to reduce the number of images necessary to display these foci.

# Neuroanatomy- Mood Disorders

- Hippocampus studies: Relationship between hippocampal volume/integrity and depression (causality direction unclear)
- Frontal lobes: Studies focusing on frontal lobe and cingulate gyrus; Differences noted between remitted and unremitted depression.
- Basal Ganglia: May be reduced in volume in unipolar and increased in bipolar
- Subcortical and periventricular hyperintensities: increased subcortical intensities with depression.

# Meta-Analysis of BD I

- N = 98 MRI studies
- Increase size in bilateral ventricles
- Increased WM hyperintensities (most replicated BD1 finding) – mostly in frontal & parietal in deep white
- Abnormalities in cerebellum
  - Reduced frontal glial cell count

Kempton, et al., 2008

# Cognitive deficits not due to psychotropic medications

- Data from neurocognitive performance in unmedicated bipolar patients:
  - Cognitive deficits and underlying abnormalities in neuronal activation in patients with bipolar illness are not primarily attributable to the use of psychotropic medications

Bearden et al 2006

# BPD and ADHD overlap in children

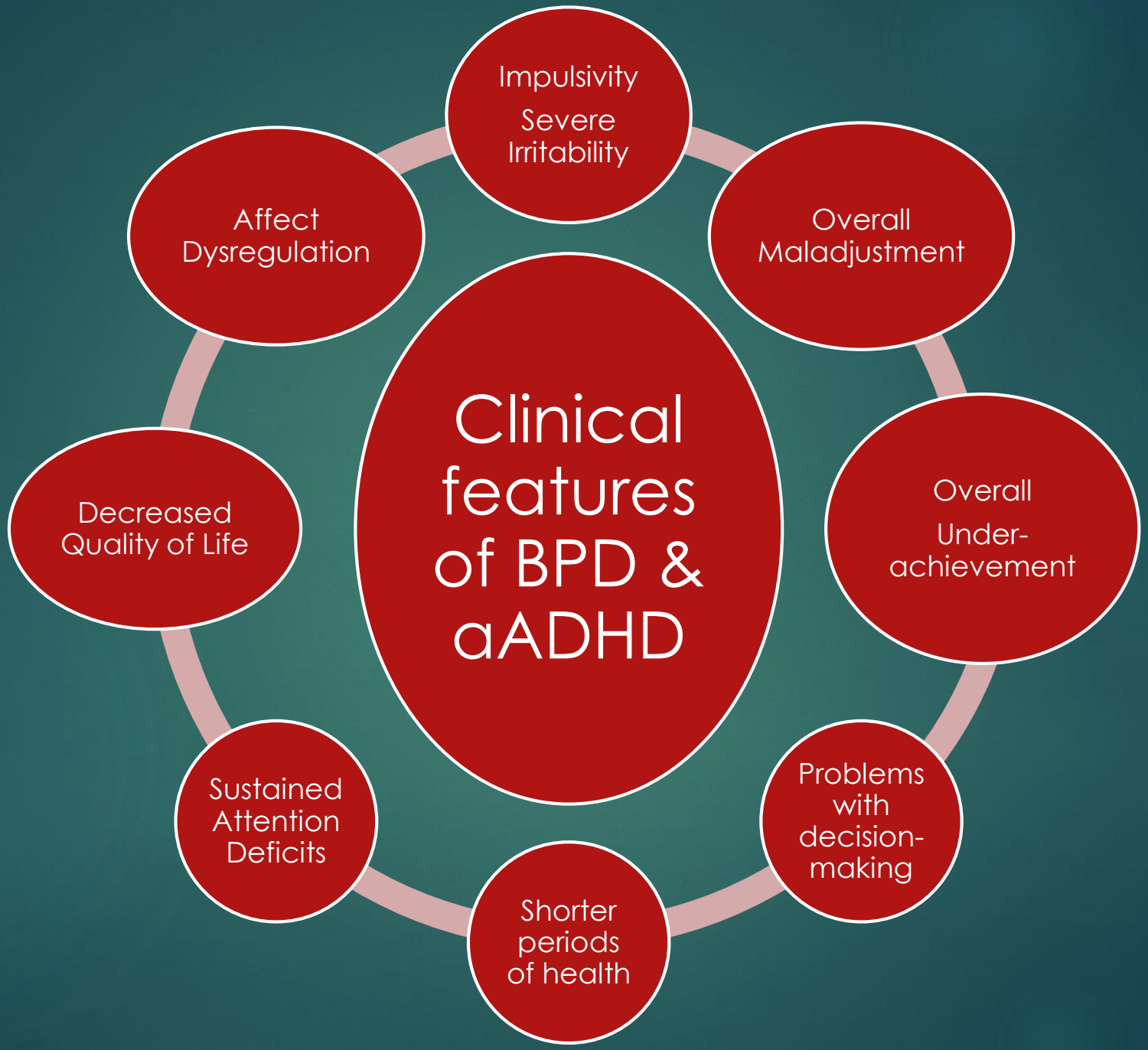
- Across all of the measures of neuropsychological functioning, the only difference observed between youths with BPD + ADHD and youths with ADHD was that youths with BPD + ADHD performed more **poorly on processing speed.**

- Comorbidity with ADHD may account for many of the NP deficits observed in children with bipolar disorder.

Henin, Consulting and Clinical Psych, 2007

# Co-Morbidity: Diagnostic Challenges

- Mount Sinai study (Bernardi, et al., 2010, with an n=100) found that patients with both adult ADHD and BPD:
  - Reported significantly earlier onset of mood disorder,
  - A higher number of previous mood episodes
  - Significantly higher impulsivity
  - Decreased reactive control
  - Higher 'Negative Emotionality' temperamental scores


Clinical features of BPD & aADHD
Impulsivity
Severe Irritability
Overall Maladjustment
Overall Under-achievement
Problems with decision-making
Shorter periods of health
Sustained Attention Deficits
Decreased Quality of Life
Affect Dysregulation

# Neuropsychological Assessment

- BPD demonstrated poorer performance on immediate verbal memory tasks.
- Both groups demonstrated lower scores on the recognition phase of verbal and nonverbal memory tasks, as well as on the executive functioning tasks with a high working memory component.
- Individuals with ADHD performed better than BPD individuals on a recognition phase of Rey list memory task and Rey Figure.
- This suggests a crucial role of the executive component on memory deficits of BPD patients.

(Torralva, et al. 2011)

# Treatment of Bipolar Disorder

- Psychoeducation is the active ingredient in most forms of psychotherapy for bipolar illness: a didactic, information-oriented approach to the illness.

- Some psychosocial modalities emphasize early recognition of mood symptoms, whereas others emphasize interpersonal relationships, communication skills, and stress management.

# Treatments 2

- Good Treatments are associated with 30% to 40% reductions in relapse rates over 12- to 30-month periods.
- Patients who receive intensive psychosocial treatment have better functional outcomes than those who receive routine pharmacological care over 1-2 year periods.
- Across studies, treatment models containing 12 or more sessions consistently perform better than comparison treatments of 3 or fewer sessions

# Cognitive Rehabilitation

- CR improves multiple domains of cognitive functioning. These improvements are not limited to cognitive progress but encompass a range of outcomes including:
  - improved independent living skills,
  - increased hours worked
  - money earned in vocational rehabilitation,
  - and improved social adjustment
- Effect sizes for improvements in specific training exercises have generally been large, with more moderate effect sizes for other cognitive outcomes and improvements in community functioning.

Velligan et al.2000, 2002; 2006,2007; Medalia & Richarson, 2005.

# Bibliography


- Cognitive Dysfunction in Bipolar Disorder: J. Goldberg & K Burdick
- Kay Redfield Jamison: *An Unquiet Mind*
- William Styron: *Darkness Visible*
- Mimi Baird: *He Wanted the Moon: The Madness and Medical Genius of Dr. Perry Baird, and His Daughter's Quest to Know Him*

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- All of my lectures in PDF files

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  - Logon: Kaiser
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  - Logon: test
  - Password: P@ssW

# Bipolar vs. ADHD in Adults

# Bipolar Disorder & ADHD

"In distinguishing bipolar disorder from other disorders, the single most useful differential feature is the course of the illness.

# Pediatric-onset of BPD comorbid with ADHD, a distinct subtype

- Biederman, et al. (2012) study provided evidence to suggest a familial risk, as well as a distinct familial subtype of the disorders.

- Pediatric BPD comorbid with ADHD bred true in families, stressing the importance of a structured clinical interview which addresses family history of mental illness, specifically BPD.

# BPD & adult ADHD & Cortical Thickness

- 2012 study (n=31) addressed the lack of neuroimaging research regarding comorbidity and neuroanatomical differences associated with the two disorders (Makris et al., 2012).
- BPD was associated with significantly thicker cortices in 13 regions.
- aADHD was associated with significantly thinner neocortical gray matter in 28 regions, independent of BPD.
- This study supports the hypothesis that each disorder contributes to cortical variability in distinct brain regions. "The comorbid state represents a combinatory effect of the two."

# Neuroanatomical Correlates of BPD & aADHD

Beiderman, et al. (2008) hypothesized that ADHD/BPD independently contribute to volumetric alterations and their study revealed neuroanatomical deficits co-occurred with ADHD/BPD.

| BPD | ADHD |
|---|---|
| Smaller orbital prefrontal cortex | Less neocortical gray matter |
| Larger right thalamus | Less overall frontal lobe volume |
| | Less overall superior prefrontal cortex volume |
| | Smaller right anterior cingulate cortex |
| | Less cerebellar gray matter |
| | Valera et al.,(2007) found 5 brain regions<br>▪ the dorsolateral and orbital frontal regions, mainly on the right side,<br>▪ the anterior cingulate cortex,<br>▪ the basal ganglia, especially its striatum-specifically controlling movement/behavior<br>▪ the cerebellum (principally the vermis on the right side), and the anterior portion of the corpus callosum (the splenium) |

# Co-Morbidity: Diagnostic Challenges

- Norwegian study from 1997 to 2007 suggests a "close relationship between some symptoms" of BPD and ADHD in adults (Halmøy, et al., 2010).
- **Screening for underlying or co-existing ADHD or BPD, vice versa, should be conducted**.

- Concurrent diagnosis is controversial. A study was completed to look at the phenomenology, course or illness, heredity, biological markers and treatment response was investigated.
- Proposed comorbidity was apparent in 47% of ADHD patients and 21 % of BPD patients.

# Neuropsychological Assessment: CPTs

- Sustained attention deficits, in Bipolar disorder patients, euthymic versus manic patients.
- Euthymic patients demonstrated decreased target sensitivity, or omission errors, and response time inconsistency.
- While manic patients demonstrated increased false responding (commission errors), perseveration and vigilance deficits (Bora, et. al. 2006).