

Neuropsychology of Anxiety

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Anxiety Disorders

Excessive fear & anxiety with related behavioral disturbance

DSM-5 Criteria for Diagnosis

Major Reshuffle: OCD & PTSD no longer anxiety disorders

- ▶ Both OCD & PTSD moved out of Anxiety Disorders into Trauma related Disorders
- ▶ DSM-IV Anxiety Disorders separated into three DSM-5 categorical groups:
 - ▶ *Anxiety Disorders*
 - ▶ *Obsessive Compulsive and Related Disorders*
 - ▶ *Trauma- and Stressor-Related Disorders (PTSD)*
 - ▶ Sequential ordering reflects close relationship among these disorders.
 - ▶ Chapters are arranged developmentally. **Sequenced by age of onset**

Changes

- ▶ Elimination of requirement that the patient (formerly, over 18 years old) "must recognize that their fear and anxiety are excessive or unreasonable".
- ▶ Instead anxiety must be "out of proportion to actual danger or threat"
- ▶ 6 month duration extended to all ages
- ▶ Panic attacks can now be added as a specifier to all other DSM-5 disorders:
 - ▶ Depressive
 - ▶ Bipolar
 - ▶ Eating
 - ▶ Psychotic
 - ▶ OCD

Specific Phobia

- ▣ Don't have to recognize that fear is excessive or unreasonable
- ▣ Criteria: A. marked fear or anxiety about specific object or situation
 - ▶ B. Fear, anxiety
 - ▶ C. Object or situation is actively avoided or endured with intense fear or anxiety
 - ▶ D. Out of proportion to actual danger
 - ▶ Chance of encountering phobic stimuli is no longer a determinant of dx
 - ▶ Impairing
 - ▶ Duration = 6 months for all ages
 - ▶ Specifier: object of fear, specific phobia types
 - ▶ Animal, natural environment, blood-injection-injury, situation, other

Social Anxiety Disorder (Social Phobia)

- ▶ Criteria: A. marked fear or anxiety about 1 or more social situations in which individual is exposed to scrutiny by others (kids with peers, not adults):
 - ▶ B. Fears he/she will act in a way or show anxiety sxs that will be negatively evaluated
 - ▶ D. Social situation is avoided or endured with fear or anxiety;
 - ▶ E. Fear and anxiety are out of proportion to actual danger
 - ▶ F. Persistent, 6 months
 - ▶ Recognition that fear is excessive no longer required.
- ▶ Specifier:
 - ▶ “Generalized” specifier has been deleted
 - ▶ Replaced with “performance only” specifier (“only in speaking or performing in public”)

Panic Disorder *

- ▶ Can now be specifier for any DSM disorder (rather than diagnose 2 separate disorders, just add specifier to the other disorder)
- ▶ But Panic Disorder and Agoraphobia have been delinked; if they co-occur, give two separate disorders.
- ▶ **No longer:**
 - ▶ Panic Disorder without agoraphobia or Panic Disorder with agoraphobia
- ▶ Criteria: A. Recurrent unexpected panic attacks
 - ▶ Panic: from calm or anxious state; abrupt surge of intense fear/discomfort, peak within minutes
 - ▶ A. 4 of 13 symptoms
 - ▶ B. 1 attack being followed by 1 month or more of persistent worry about additional attacks
 - ▶ B. And/or significant maladaptive behavior change related to attacks

Agoraphobia *

- ▶ Separated from panic disorder;
- ▶ **No longer:**
 - ▶ Panic Disorder with Agoraphobia
 - ▶ Agoraphobia without History of Panic Attack
- ▶ Criteria: A. Marked fear or anxiety about 2 or more of 5 situations:
 - ▶ Public transportation, open spaces, enclosed spaces, in line/crowd, outside of home alone
 - ▶ Individual fears or avoids those situations because escape might be difficult or help unavailable if panic-like or other incapacitating symptoms develop;
 - ▶ Clinician judgment that fears are out of proportion to actual danger
 - ▶ Persistent, 6 months
 - ▶ Impairment

Generalized Anxiety Disorder

- ▶ No change
- ▶ A. Excessive anxiety (across the board), more days than not, longer than 6 months
- ▶ B. Difficult to control worry
- ▶ C. Associated with ≥ 3 (child 1) more:
 - ▶ Restlessness, fatigue, difficulty concentrating, irritability, muscle tension, sleep disturbance
- ▶ D. Impairment
- ▶ Worst test-retest reliability (kappa .20) among clinicians

Substance/Medication-induced Anxiety Disorder *

- ▶ **No longer:** Substance-induced Anxiety Disorder

Anxiety Disorder Due to Another Medical Condition *

- ▶ **No longer:** Anxiety Disorder Due to a General Medical Condition
- ▶ Obsessions & compulsions removed from sxS

Obsessive-Compulsive and Related Disorders **

New chapter

OCD gets stand alone category

Major Changes

- ▶ Separated from DSM-IV Anxiety Disorders.
- ▶ Body Dysmorphic Disorder moved to this group from DSM-IV Somatoform Disorders.
- ▶ Trichotillomania Disorder moved here from DSM-IV Impulse Control Disorders.
- ▶ **New Diagnoses:**
 - ▶ Hoarding Disorder
 - ▶ Skin-Picking Disorder
 - ▶ Substance /Medication–induced OCD
 - ▶ OCD due to another medical condition

Obsessive-Compulsive Disorder

- ▶ A. Presence of obsessions, compulsions or both
- ▶ Clarification that obsessions are often urges, not impulses; they are intrusive and unwanted rather than merely inappropriate.
- ▶ Insight requirement removed (that obsessions & compulsions “are excessive or unreasonable”) for adults
- ▶ Specifiers (for more severe pathology)
 - ▶ with good or fair insight
 - ▶ with poor insight
 - ▶ with absent insight or delusional beliefs
 - ▶ Tic-related

Body Dysmorphic Disorder

▶ Criteria:

- ▶ A. Preoccupation with one or more perceived defects or flaws in physical appearance that are not observable or appear slight to others
- ▶ B. Performance of repetitive behaviors (mirror checking, etc.) or mental acts in response to appearance concerns

▶ Specifiers:

- ▶ 3 Levels of insight (delusional variant no longer coded as delusional disorder; just use “with absent insight/delusional beliefs” specifier)
- ▶ **With muscle dysmorphia** (feel not strong enough; serious sx: 50% SA; 80% are substance abusers; 25% anabolic steroid users)

Hoarding Disorder **

- ▶ New Diagnosis
- ▶ Hoarding:
 - ▶ not OCD,
 - ▶ more common than OCD,
 - ▶ genetically and neurologically distinct (ACC/Insula activation in hoarding)
- ▶ Criteria: A. Persistent difficulty parting with possessions regardless of actual value, resulting in accumulation of possessions that compromises use of living areas
- ▶ Distress/impairment
- ▶ Specify
 - ▶ Level of insight
 - ▶ With excessive acquisition

Trichotillomania (Hair-Pulling Disorder)

- ▶ moved from impulse control disorders
- ▶ A. Recurrent pulling out of hair/hair loss
- ▶ B. Repeated attempts to stop/decrease
- ▶ C. Distress/impairment

Excoriation ** (Skin-Picking Disorder)

- ▶ New Diagnosis
- ▶ A. Recurrent skin picking, cause skin lesions
- ▶ B. Repeated attempts to decrease/stop
- ▶ C. Distress/impairment

Other Specified & Unspecified OC and Related Disorders

- ▶ PANDAs (Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections)
- ▶ Can include conditions such as body-focused repetitive behavior disorder
 - ▶ Recurrent behaviors (not hair/skin)
 - ▶ Repeated attempts to decrease/stop
- ▶ Can include conditions such as obsessional jealousy
 - ▶ Nondelusional preoccupation with partner's perceived infidelity

Trauma- and Stressor-Related Disorders **

New Category

Exposure to a traumatic or stressful event

Specific Changes:

Trauma and Stressor Related Disorders

- ▶ Trauma related disorders are now a stand alone category
- ▶ Now listed here:
 - ▶ PTSD
 - ▶ Reactive Attachment Disorder
 - ▶ Acute Stress Disorder
 - ▶ Adjustment Disorders
- ▶ Added
 - ▶ Disinhibited Social Engagement Disorder
 - ▶ Added PSTD in Preschool Children

Changes

- ▶ For acute stress disorder and PTSD, the stressor criteria (Criterion A1 in DSM-IV) was modified:
- ▶ specify stressor as:
 - ▶ directly experienced,
 - ▶ witnessed,
 - ▶ or indirect experience (i.e. 9/11 events phone message transcriber).
- ▶ The subjective reaction (A2) requirement for specific subjective emotional reactions (“of intense fear, helplessness, or horror”) is eliminated.
 - ▶ Subjective response not required: Don't have to recognize you are in danger of dying.
 - ▶ Due to training, military personnel involved in combat, law enforcement officers and other first responders are trained not to react emotionally to traumatic events, but do have PTSD.

Posttraumatic Stress Disorder, **Adult** (≥ 6 years)

- ▶ A. Exposure to actual/threatened death, injury, serious violence; ≥ 1 SX
 - ▶ Sexual violence now specifically included as a trauma
 - ▶ Don't have to think you are in danger of dying
- ▶ A. Expansion to ≥ 1 of 4 Symptoms
- ▶ B. Presence ≥ 1 sx of 5, intrusion sxs
- ▶ C. Persistent avoidance of associated stimuli
- ▶ D. Persistent negative alterations in cognitions & mood
 - ▶ An additional category of negative mood, a persistent change in mood and thinking like dysphoria or anhedonia, has been added.

PTSD, Adult

- ▶ E. Marked alterations in arousal/reactivity
 - ▶ adds irritability, angry outbursts, reckless/self-destructive behavior
- ▶ F. Duration $\geq$ 1 month, distress/impairment
- ▶ Specify
 - ▶ With dissociative sx's (depersonalization, derealization)
 - ▶ With delayed expression

PTSD, ≤ 6 years

- ▶ More developmentally sensitive; Number of symptoms in each cluster - have been lowered
- ▶ Exposure to actual/threatened death, injury, serious violence; ≥ 1 of 3 sx
- ▶ Presence ≥ 1 sx, intrusion sxs
- ▶ Persistent avoidance of associated stimuli, ≥ 1 sx
- ▶ Negative alterations in cognitions & mood
- ▶ Marked alterations in arousal/reactivity
- ▶ Duration ≥ 1 month, distress/impairment
- ▶ Specify
 - ▶ With dissociative sxs (depersonalization, derealization)
 - ▶ With delayed expression

Acute Stress Disorder

- ▶ A. Exposure to actual/threatened death, injury, serious violence, ≥ 1 of 4 types of events
 - ▶ Experiencing, witnessing, learning about from close others, repeated/extreme exposures to aversive details
 - ▶ Not from watching TV (i.e. child & Challenger explosion)
- ▶ B. **Any 9 of 14 sx**s from 5 categories of intrusion, negative mood, dissociation, avoidance, arousal
- ▶ **Dissociative Sxs no longer required for dx**
- ▶ C. Duration, immediately after, **3 days to 1 mo**
- ▶ D. Distress/impairment
- ▶ **= brief version of PTSD**

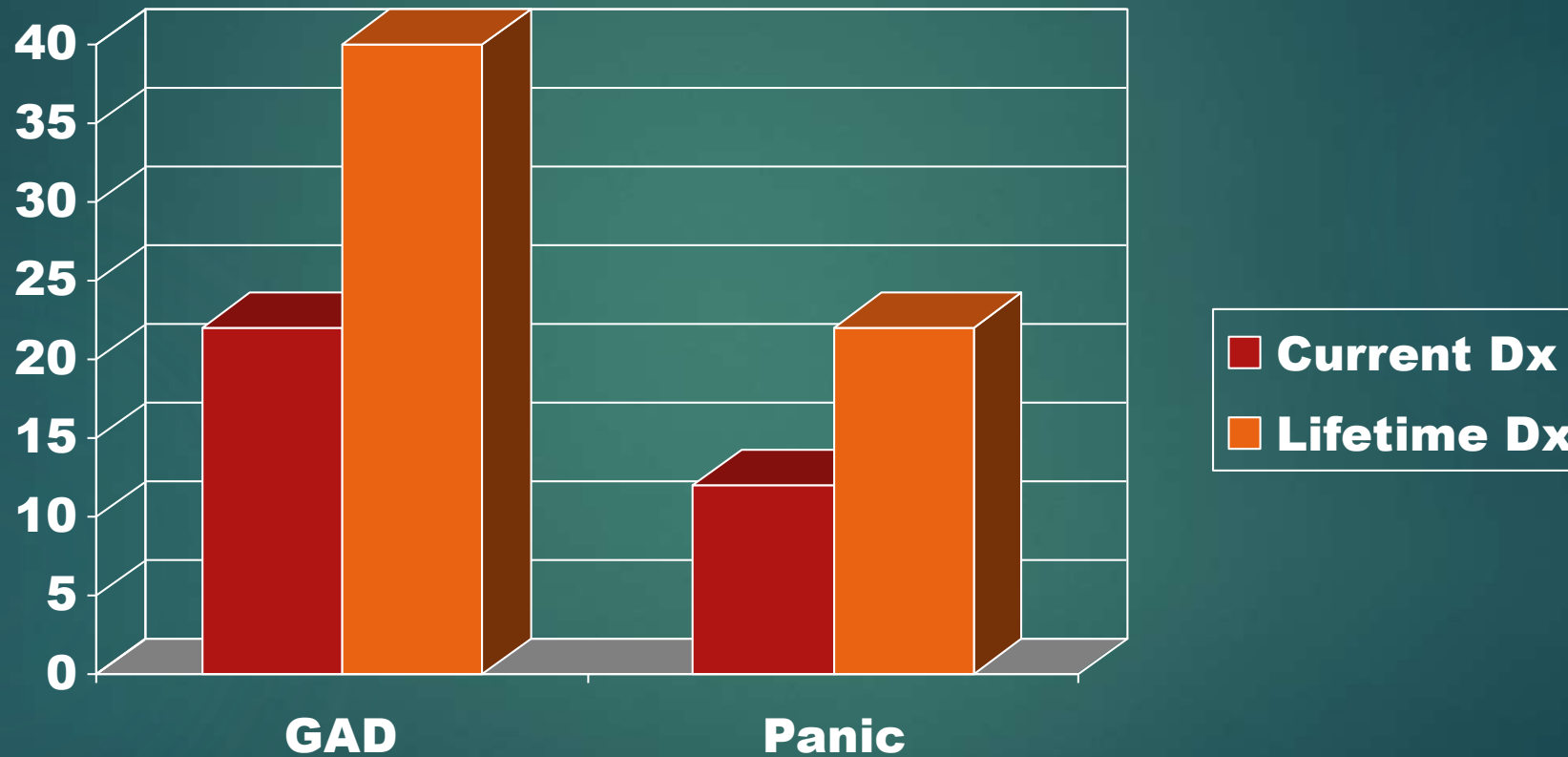
Adjustment Disorders

- ▶ No more separate chapter; No change in dx
- ▶ Reconceptualized as stress response syndrome: Having a stress and being unable to manage the stress
- ▶ A. Emotional/behavioral sx's in response to identifiable stressor, within 3 months
- ▶ B. Distress out of proportion
- ▶ B. Impairment
- ▶ **Exclusion: Not normal bereavement**
- ▶ Trumped by MDD or Panic Disorder

Prevalence Rates (Lifetime/Year)

- ▶ Any Psychiatric Disorder: 48% / 29.5%
- ▶ Any anxiety disorder: 24.9% / 17.2%
- ▶ SAD: 13.3% / 4.5%
- ▶ GAD: 5.1% / 3.1%
- ▶ Panic: 3.5% / 2.3%
- ▶ OCD: 2.5% / 1.3%

Anxiety disorders in High Utilizing Patients



They represent about 50% of healthcare utilization. There is an excessive amount of anxiety disorders in these thick chart patients.

Anxiety Disorders - General

- ▶ More similarities than differences, but some important differences
- ▶ F>M, except OCD
- ▶ Serotonergic drugs effective for most disorders
- ▶ Cognitive-Behavioral Therapy (CBT) likely effective for all

Anxiety Disorders - General

- ▶ Highly comorbid with Depression, Alcoholism, other Anxiety Disorders
- ▶ Often complicated by somatization
- ▶ Most treated in Primary Care
- ▶ Usually mismanaged

Anxiety Disorders and ETOH

- ▶ ETOH-use disorders are very prevalent
 - ▶ 4x general population in Panic Disorder
 - ▶ 3.5x in OCD
 - ▶ 2.5x in Phobias (Simple and Social)
- ▶ May relate to ETOH's GABA properties
- ▶ An attempt to self-medicate?
 - ▶ Can backfire, as withdrawal worsens anxiety
 - ▶ Difficult to treat the alcoholism without treating the anxiety disorder in these patients

Anxiety Disorders - Neurotransmitters

- ▶ Norepinephrine (NE)
 - ▶ Locus Ceruleus
 - ▶ stimulation leads to fear response
 - ▶ ablation inhibits fear response
 - ▶ beta agonists/alpha2 antagonists cause panic attacks in predisposed
- ▶ GABA
 - ▶ agonists ↓ anxiety/inverse agonists ↑ anxiety
- ▶ Serotonin (5-HT)
 - ▶ Chronic SSRI's, 5-HT 1a agonists ↓ anxiety

Anxiety Disorders - Neurotransmitters

- ▶ Many lines of evidence point to serotonin as an important mediator of anxiety states
 - ▶ some evidence is contradictory
 - ▶ the important aspect is probably serotonin's regulatory role in other neurotransmitter systems

Theories and Causes

► Early Theories

- Classical psychoanalytic theory: Anxieties and phobias seen as defenses against unconscious conflicts rooted in the child's early upbringing
- Behavioral and learning theories: Fears and anxieties learned through classical conditioning and maintained through operant conditioning (two-factor theory)
- Bowlby's attachment theory: Fearfulness is biologically rooted in the emotional attachment needed for survival; early insecure attachments lead children to view the environment as undependable, unavailable, hostile, and threatening

Theories and Causes 2

▶ Temperament

- ▶ Variations in behavioral reactions to novelty result in part from inherited differences in neurochemistry of brain structures
 - ▶ Amygdala: primary function to react to unfamiliar or unexpected events or threats
 - ▶ Projections of amygdala to motor system, anterior cingulate and frontal cortex, hypothalamus, and sympathetic nervous system
 - ▶ Children born with a low threshold for novel and unexpected stimuli are at greater risk for anxiety disorders; this type of temperament is called behavioral inhibition (BI)
 - ▶ Development of anxiety disorders in BI children depends on parental response; parents who set firm limits that teach children to cope with stress reduce the risk

Theories and Causes 3

▶ Family and Genetic Risk

- ▶ 33% of the variance in childhood anxiety symptoms is genetic, although identical twins do not necessarily have the same types of anxiety disorders
 - ▶ a general disposition to become anxious is what is inherited; the form of anxiety that takes place is a function of shared/non-shared environmental influences
 - ▶ highest genetic influence is for obsessive-compulsive behaviors and shyness/inhibition
- ▶ Serotonin and dopamine systems are related to normal anxiety
- ▶ Genes are linked to broad anxiety-related traits (e.g., behavioral inhibition); small contributions from multiple genes, not direct link with specific genes

Theories and Causes 4

► Neurobiological Factors

- No single structure/neurotransmitter controls the entire anxiety response system; several interrelated systems work together
 - Hypothalamic-pituitary-adrenal (HPA) axis, limbic system, prefrontal cortex, other cortical and subcortical structures, primitive brain stem
 - Overactive behavioral inhibition system (BIS) implicated; BIS may be shaped by early life stressors; esp. right prefrontal activation (25% variance)
 - Brain abnormalities such as more pronounced right > left asymmetries and an over-excitabile amygdala have been implicated in children who are anxious and/or behaviorally inhibited
 - One of primary neurotransmitter system implicated in anxiety disorders: γ -aminobutyric acidergic (GABA-ergic) system (inhibitory system)

Theories and Causes 5

▶ Family Factors

- ▶ Parenting practices (e.g., rejection, overcontrol, overprotection, modeling anxious behaviors) may be contributors to childhood anxiety disorders
- ▶ Parents of anxious children seen as overinvolved, intrusive, or limiting child's independence; critical and less positive interactions with their children
- ▶ Prolonged exposure to high doses of family dysfunction associated with extreme trajectories of anxious behavior
- ▶ Lower parental expectations for children's coping abilities
- ▶ Low SES
- ▶ Insecure early attachments (particularly ambivalent attachment)

Description of Anxiety Disorders

- ▶ Fear: reaction to present danger
- ▶ Anxiety: a mood state characterized by strong negative emotion and bodily symptoms of tension in anticipation of future danger or misfortune
- ▶ Anxiety disorders involve experiencing excessive and debilitating anxieties
- ▶ Experiencing Anxiety
 - ▶ Moderate amounts of anxiety are adaptive; we act more effectively and cope with potentially dangerous situations
 - ▶ Excessive, uncontrollable anxiety can be debilitating
 - ▶ The neurotic paradox is a self-defeating behavior pattern: despite knowing there is little to be afraid of, the person is terrified and does everything possible to escape/avoid the situation
 - ▶ Fight/flight response: immediate reaction to perceived danger or threat aimed at escaping potential harm

Description of Anxiety Disorders 2

▶ Experiencing Anxiety 2

▶ Three interrelated anxiety response systems:

- ▶ physical system: the brain sends messages to the sympathetic nervous system, which produces the fight/flight response and activates important chemicals; nonconscious
- ▶ Conscious cognitive/emotional system: activation often leads to subjective feelings of apprehension, nervousness, difficulty concentrating, and panic
- ▶ behavioral system: aggression and/or escape/avoidance

Description of Anxiety Disorders 3

▶ Anxiety versus Fear and Panic

- ▶ Anxiety: future-oriented mood state, which may occur in absence of realistic danger; characterized by feelings of apprehension and lack of control over upcoming events
- ▶ Fear: present-oriented emotional reaction to current danger, characterized by strong escape tendencies and surge in sympathetic nervous system
- ▶ Panic: group of physical symptoms of fight/flight response that unexpectedly occur in the absence of obvious danger or threat

Description of Anxiety Disorders 4

▶ Normal Fears, Anxieties, Worries, and Rituals

▶ Moderate fear and anxiety are adaptive, and emotions and rituals that increase feelings of control are common

▶ Normal fears

- ▶ what is normal at one age can be debilitating at an older age
- ▶ whether a fear is normal also depends on its effect and how long it lasts
- ▶ the number and type of fears change/decline over time

Description of Anxiety Disorders 5

▶ Normal Fears, Anxieties, Worries, and Rituals 2

▶ Normal anxieties

- ▶ Anxieties are common during childhood and adolescence
- ▶ The most common are: separation anxiety, test anxiety, excessive concern about competence, excessive need for reassurance, and anxiety about harm to a parent
- ▶ Girls display more anxiety than boys, but symptoms are similar
- ▶ Some specific anxieties decrease with age, but nervous and anxious symptoms often do not and may remain stable over time

Description of Anxiety Disorders 6

▶ Normal Fears, Anxieties, Worries, and Rituals 3

▶ Normal worries

- ▶ All children worry; moderate worry can help them prepare for the future
- ▶ Children with anxiety disorders worry more *often and more intensely* than other children

▶ Normal rituals and repetitive behavior

- ▶ Ritualistic and repetitive activity is common; it helps children gain control and mastery of their environment

NP of rituals

- ▶ Many common childhood routines involve repetitive behaviors and doing things “just right”: sucking thumb, covering ears, blankets certain way, fingering blanket, want sameness (repeating stories, bedtime rituals, book read exactly the same, food not touching, etc.)
 - ▶ Neuropsychological mechanism (development of &/or lack of Executive Functioning) underlies normal compulsive, ritualistic behavior as well as the ritualistic behaviors associated with OCD:
 - ▶ For younger children (< 6 years), set-shifting and response inhibition accounted for significant variance in their ritualistic, compulsive-like behaviors.
 - ▶ For older children (> 6 years), a combination of neuropsychological (response inhibition) and affective (animal fears and social anxiety) factors predict compulsive-like behaviors.

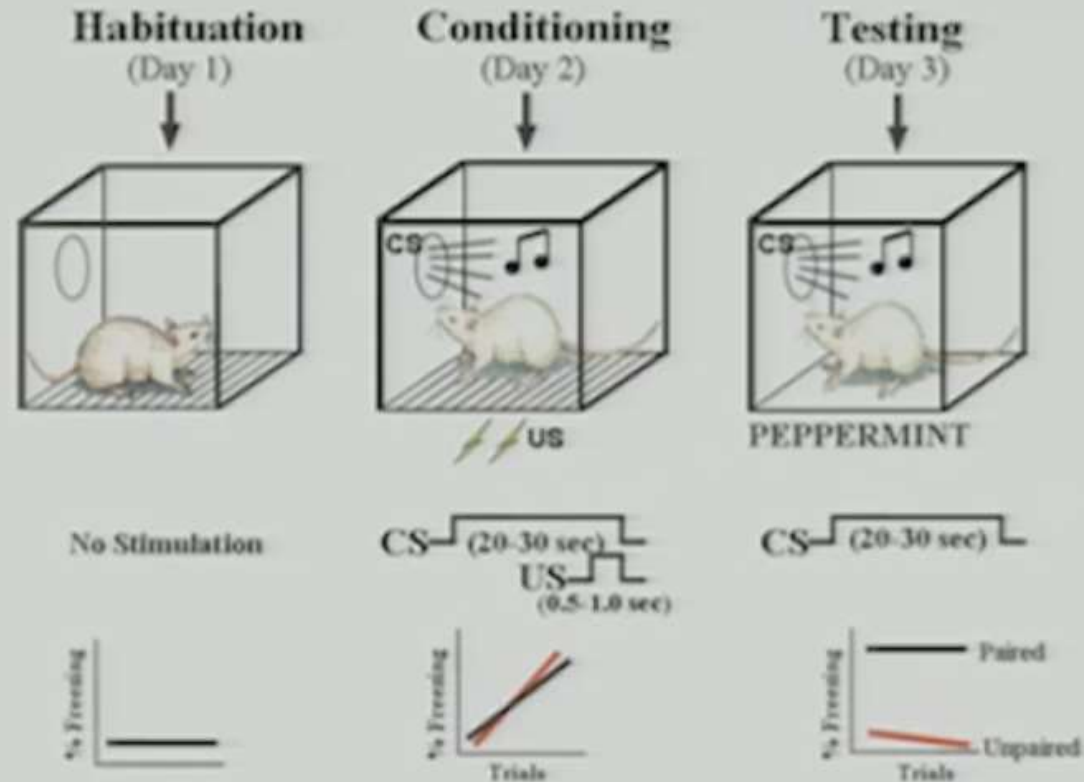
Fear Conditioning

- ▶ Over the past few decades, Pavlovian fear conditioning has become something of a gold standard in fear and anxiety research.
- ▶ Unlike Pavlov, who studied dogs and their reactions to rewards at mealtime, modern researchers place a rat in a cage and use a tone as a conditioned stimulus and a shock as an unconditioned stimulus, gauging success by whether the rat begins to display a conditioned response — often freezing behavior (essentially tensing up but in a particular crouching posture) — after simply hearing the tone without receiving the shock.



Pavlovian Fear Conditioning

Pavlovian Threat Conditioning Paradigm



Rat freezes after 1 time exposure to tone and shock

William James: Nature of feeling of fear

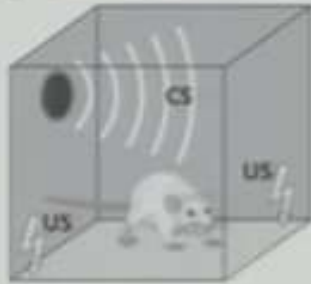
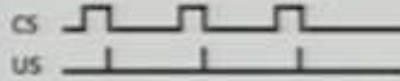


- ▶ What is the feeling of fear?: “Do we run from a bear because we are afraid, or are we afraid because we run?” James famously asked.
- ▶ Joe LeDoux: Asking two questions: Why do we run from danger, and what makes us feel fear?”
- ▶ Most research has addressed the first question, but focused on freezing rather than running. The conclusion has been that we freeze when in danger because the threatening event arouses a state of fear in the amygdala that initiates the response.
- ▶ But LeDoux points out that people can respond to threats without knowing the threat is present and without feeling fear.

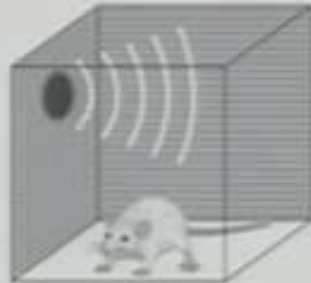
Research on Pavlovian Reactions Made Rapid Progress

BEHAVIOR

Acquisition: pairing of CS with US
(chamber constitutes CS)

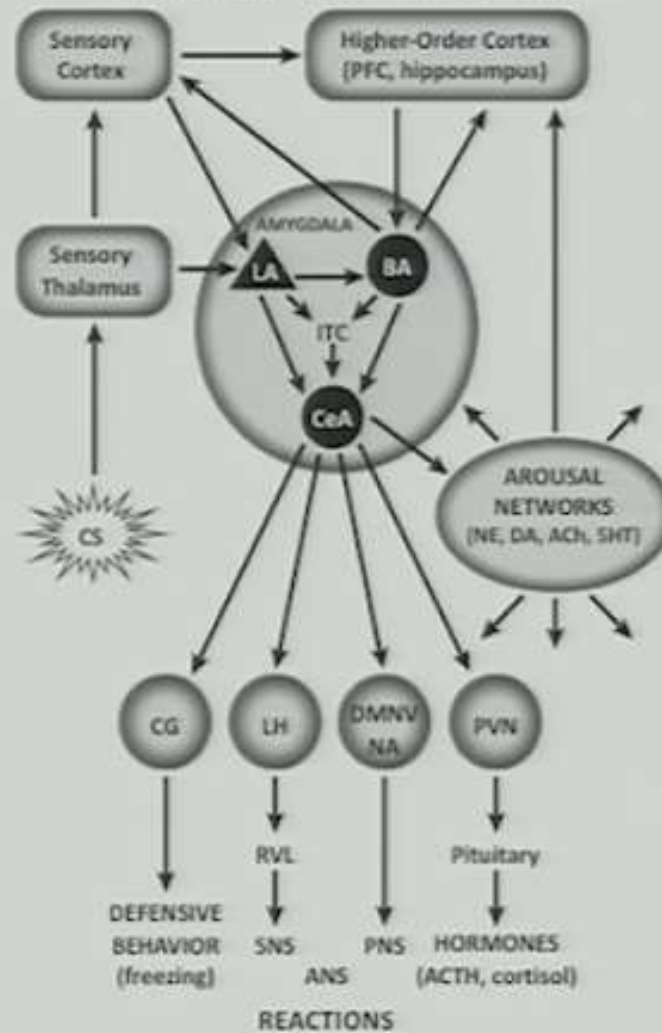


Cued CS Test: exposure to the CS alone

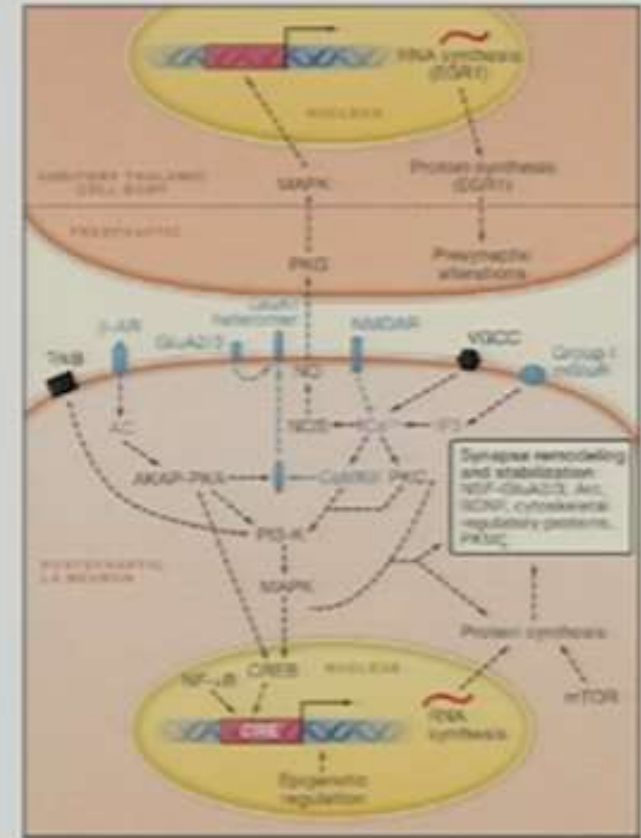


CIRCUITRY

Brain Processing of Conditioned Threats and Control of Conditioned Defense Reactions



CELLULAR AND MOLECULAR MECHAISMS



FEAR CONDITIONING AND PSYCHIATRY

trait anxiety	Indovina I, Robbins TW, Núñez-Elizalde AO, Dunn BD, Bishop SJ. Fear-conditioning mechanisms associated with trait vulnerability to anxiety in humans . <i>Neuron</i> . 2011 Feb 10;69(3):563-71.
panic disorder	Lissek S, Rabin SJ, McDowell DJ, Dvir S, Bradford DE, Geraci M, Pine DS, Grillon C. Impaired discriminative fear-conditioning resulting from elevated fear responding to learned safety cues among individuals with panic disorder . <i>Behav Res Ther</i> . 2009 Feb;47(2):111-8.
PTSD	Inslicht SS, Metzler TJ, Garcia NM, Pineles SL, Milad MR, Orr SP, Marmar CR, Neylan TC. Sex differences in fear conditioning in posttraumatic stress disorder . <i>J Psychiatr Res</i> . 2013 Jan;47(1):64-71.
psychopathy	Cohn MD, Popma A, van den Brink W, Pape LE, Kindt M, van Domburgh L, Doreleijers TA, Veltman DJ. Fear conditioning, persistence of disruptive behavior and psychopathic traits: an fMRI study . <i>Transl Psychiatry</i> . 2013 Oct 29;3:e319.
criminal behavior	Gao Y, Raine A, Venables PH, Dawson ME, Mednick SA. Association of poor childhood fear conditioning and adult crime . <i>Am J Psychiatry</i> . 2010 Jan;167(1):56-60.
psychiatric symptoms in active duty marines	Acheson DT, Geyer MA, Baker DG, Nievergelt CM, Yurgil K, Risbrough VB; MRS-II Team. Conditioned fear and extinction learning performance and its association with psychiatric symptoms in active duty Marines . <i>Psychoneuroendocrinology</i> . 2015 Jan;51:495-505.
early life Vulnerability to psychiatric problems	Lanius RA, Frewen PA, Vermetten E, Yehuda R. Fear conditioning and early life vulnerabilities: two distinct pathways of emotional dysregulation and brain dysfunction in PTSD . <i>Eur J Psychotraumatol</i> . 2010;1.

Finding:

Woman with amygdala damage can still feel fear.

Feinstein et al (2013) *Nature*

Headlines in Nature, Science, Scientific American, Wired, Discover:

"Humans Can Feel Terror Even if They
Lack the Brain's Fear Center,"

"Scaring the Fearless,"

"Evoking Fear in the Fearless,"

"Researchers Scare Fearless Patient,"

"What Scared the Fearless Woman?"

SM-046, is a female patient first described in 1994 who has had exclusive and complete bilateral amygdala destruction since late childhood as a consequence of an extremely rare genetic condition known as Urbach–Wiethe disease: little to no capacity to experience fear or anxiety; experience fear and panic attacks to suffocation via carbon dioxide inhalation; difficulty with negative social cues, fear in others; very outgoing; little negative feelings; she is very positive; hyper empathic; impaired declarative memory facilitation for emotional material; poor threat assessment; mother of 3

Finding:

Children rated as anxious by parents had bigger amygdala

Qin et al (2014) *Biological Psychiatry*

Headlines:

"Fear Center in Brain Larger Among Anxious Kids."

"Anxious Children have Bigger 'Fear Centers' in the Brain"

What's wrong with headlines:

1. Behavior was rated; anxiety was not measured
2. None of the children were clinically anxious
3. The amygdala is not the seat of fear, much less anxiety, if by fear and anxiety we mean conscious feelings

Amygdala Subregional Structure and Intrinsic Functional Connectivity Predicts Individual Differences in Anxiety During Early Childhood; ages 7 to 9, high childhood anxiety is associated with enlarged amygdala volume and this enlargement is localized specifically to the basolateral amygdala. Based on parental anxiety ratings of children. Not self reports

Finding:

Crayfish treated with a benzodiazepine were more exploratory (less inhibited) in chamber where they received electric shock

Fossat et al, 2014, *Science*

Headlines:

Science: Anxious Crayfish Can Be Treated Like Humans

NYT: Even Crayfish Get Anxious

BBC: Crayfish May Experience a Form of Anxiety

LeDoux conclusions about fear vs threat detection:

- Humans often experience a feeling of fear when exposed to stimuli associated with harm in the past.
- Humans can express so-called conditioned fear responses without being aware of the stimulus and without feeling anything
- We should not confuse the correlation of “fear” and threat-elicited responses in our own minds with causation
- We should not be invoking consciousness to explain things in animals that do not require conscious awareness in humans.

“Animals show emotions similar to those we describe in ourselves.” “...animals feel pleasure and sadness, excitement and resentment, depression, fear, and pain. They are far more aware and intelligent than we ever imagined...they are individuals in their own right.

-Jane Goodall

We're all anthropomorphic. It's natural, and may be related to our capacity for empathy.

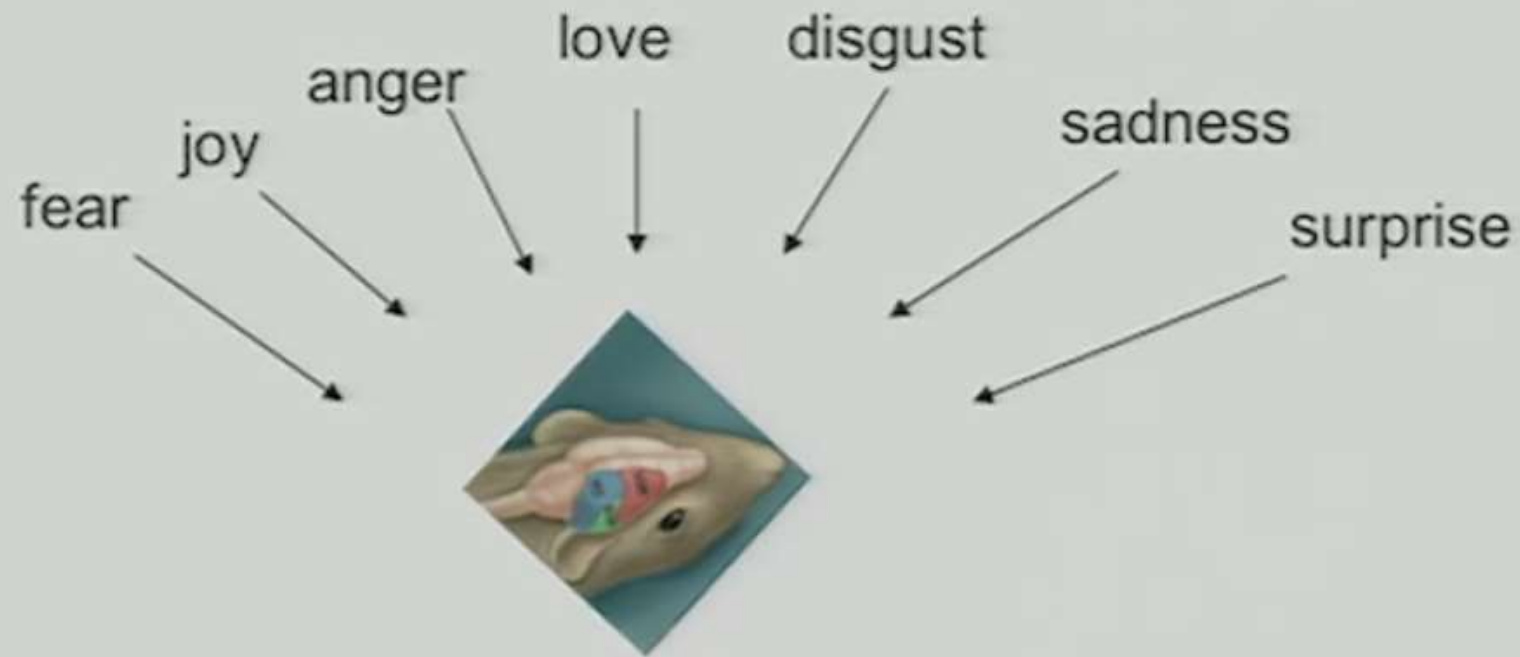
We assume that when if an animal responds in a way that resembles the way a human responds when in danger, and the human feels fear then the animal must feel fear

But just because it's natural doesn't mean that it's scientifically correct

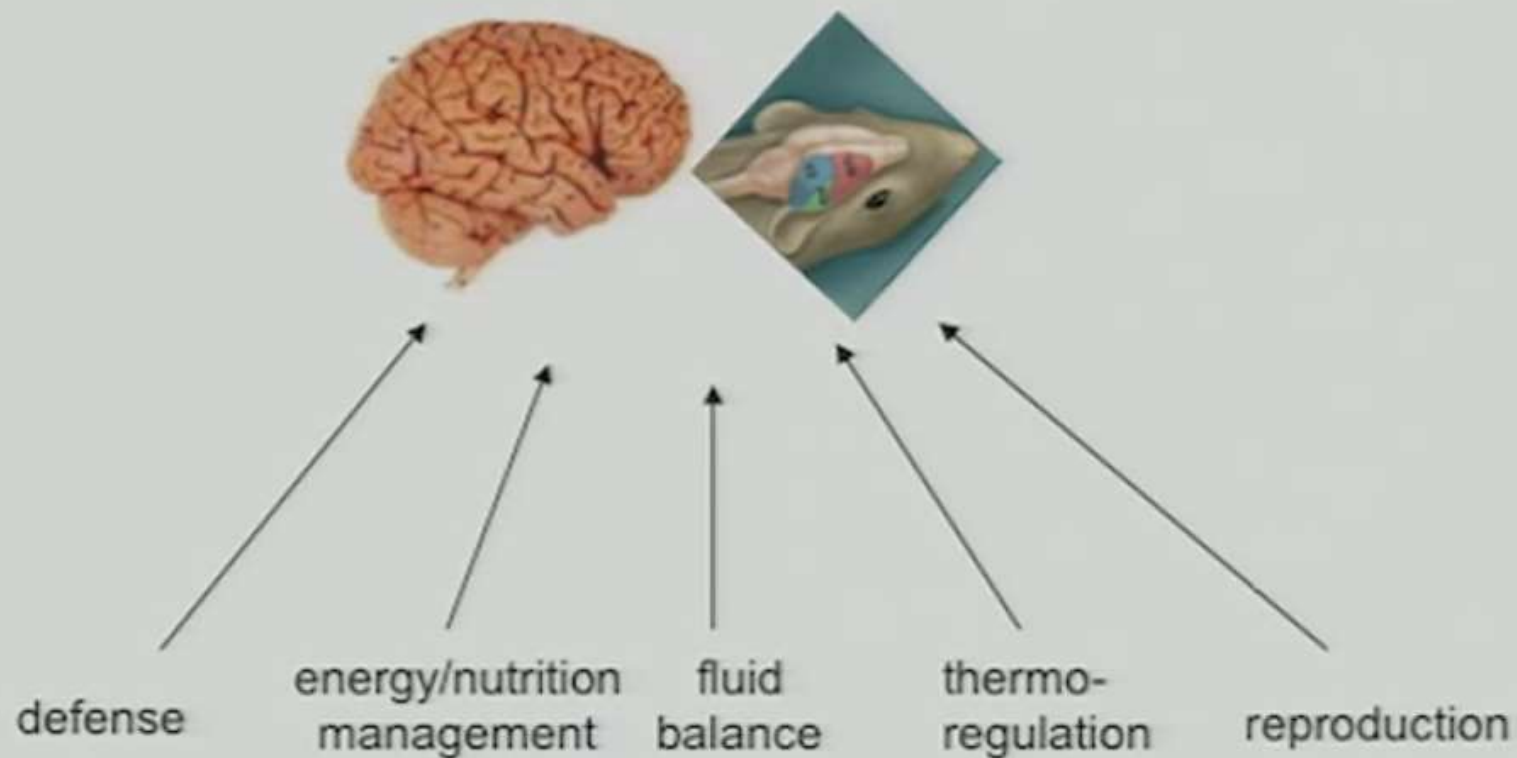
We have to wear different hats when being a scientist and a lay person

Francis Bacon– warned about the danger of using common language in science– we reify the referent of the word and give it a reality that it does not warrant

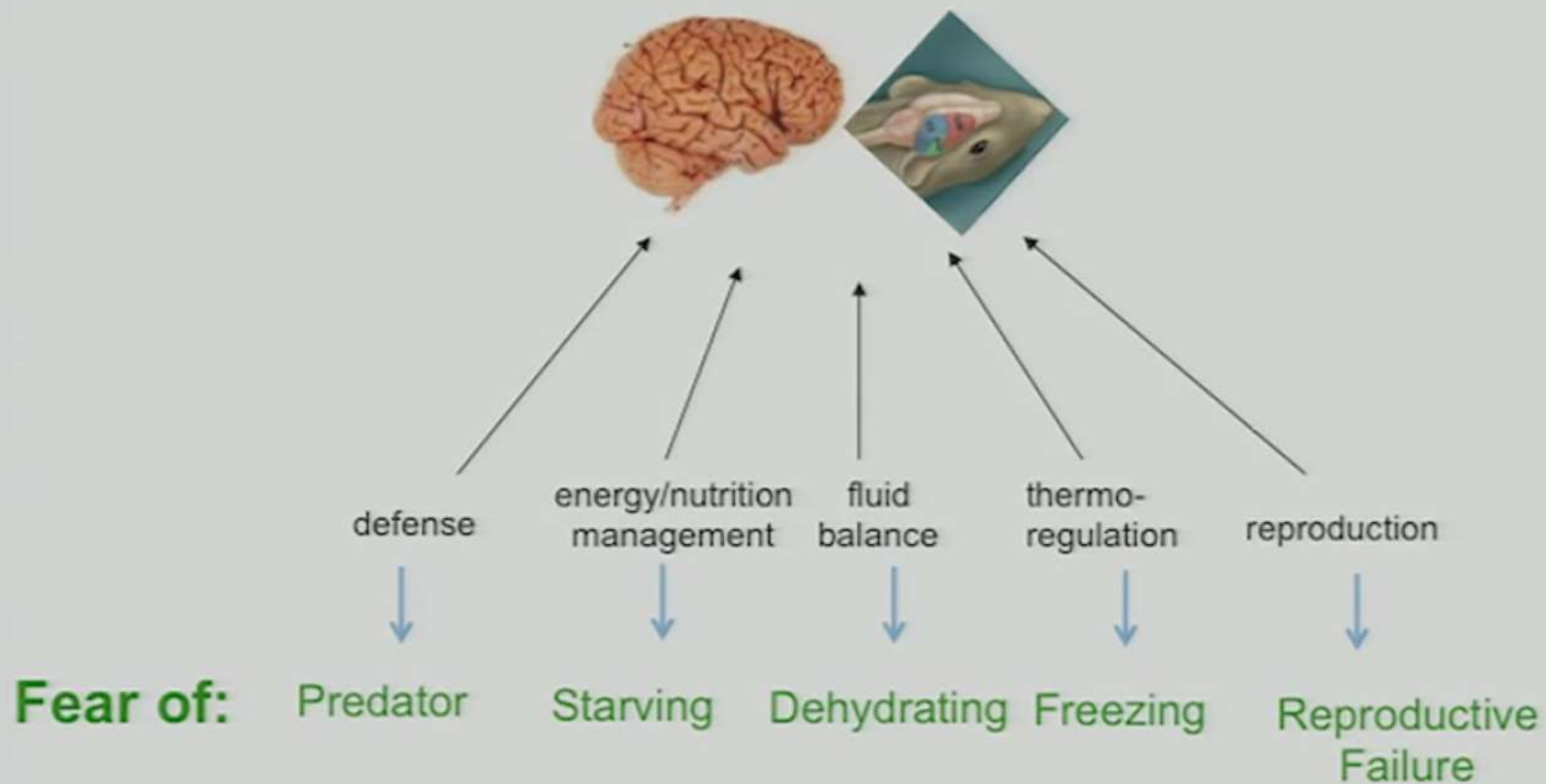
The Usual Approach to Animal Research on Emotion: start words related to human subjective experience



Fear Does Not Have an Exclusive Contract with Amygdala Defense Circuits



Fear Does Not Have an Exclusive Contract with Amygdala Defense Circuits



Fear is not threat detection

- Fear is the conscious awareness that you are in the presence of a threat (whether it is physical or existential)
- This is a cognitive process that depends on language, culture, and self-awareness
- While all organisms can detect and respond to threats, only organisms that know that threats are happening to them feel fear
- If other animals feel fear it is likely to be a very different experience from what a human calls fear
- Threat detection contributes to fear, but is not one and the same as fear

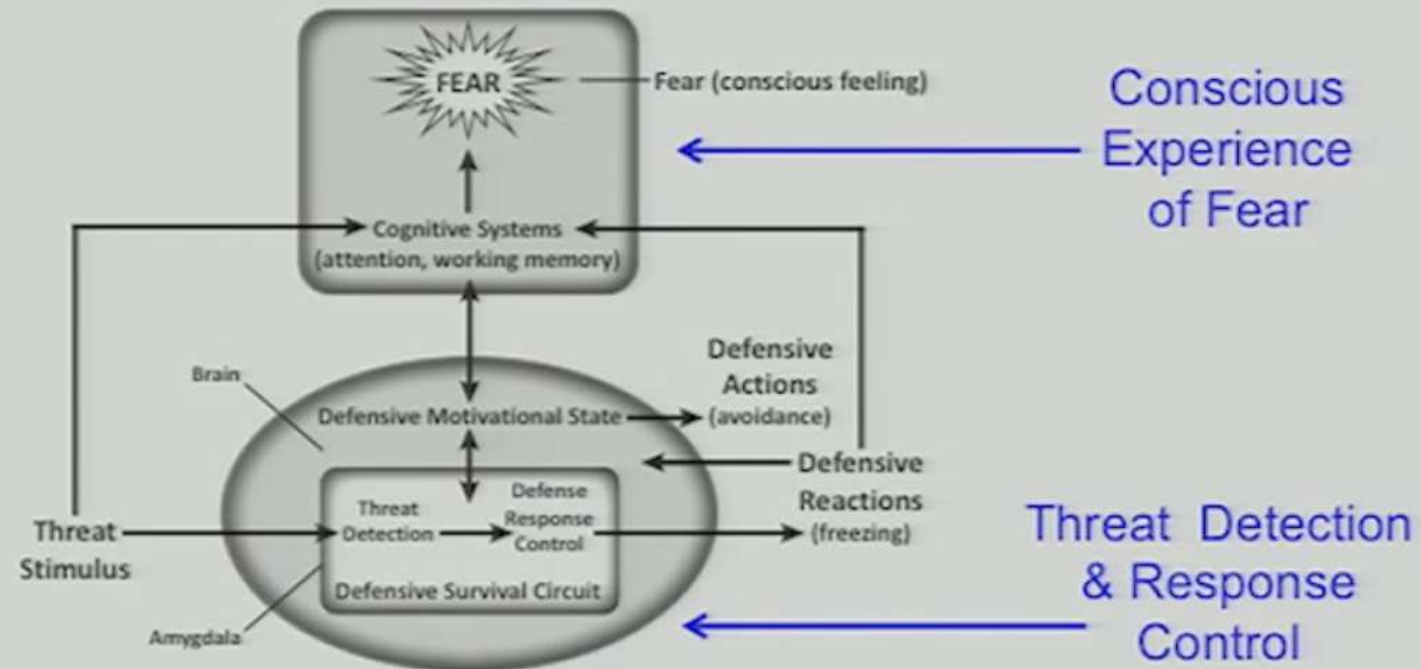
Split brain

- ▶ Right hemisphere reacted to and experiences negative valence, danger
- ▶ Only Left hemisphere says “fear”

Fear CS = Threat CS
Fear Response = Defensive Response
Fear State = Defensive Motivation State

Two Types of Defensive Responses
*reactions (freezing)
*actions (avoidance, PIT)

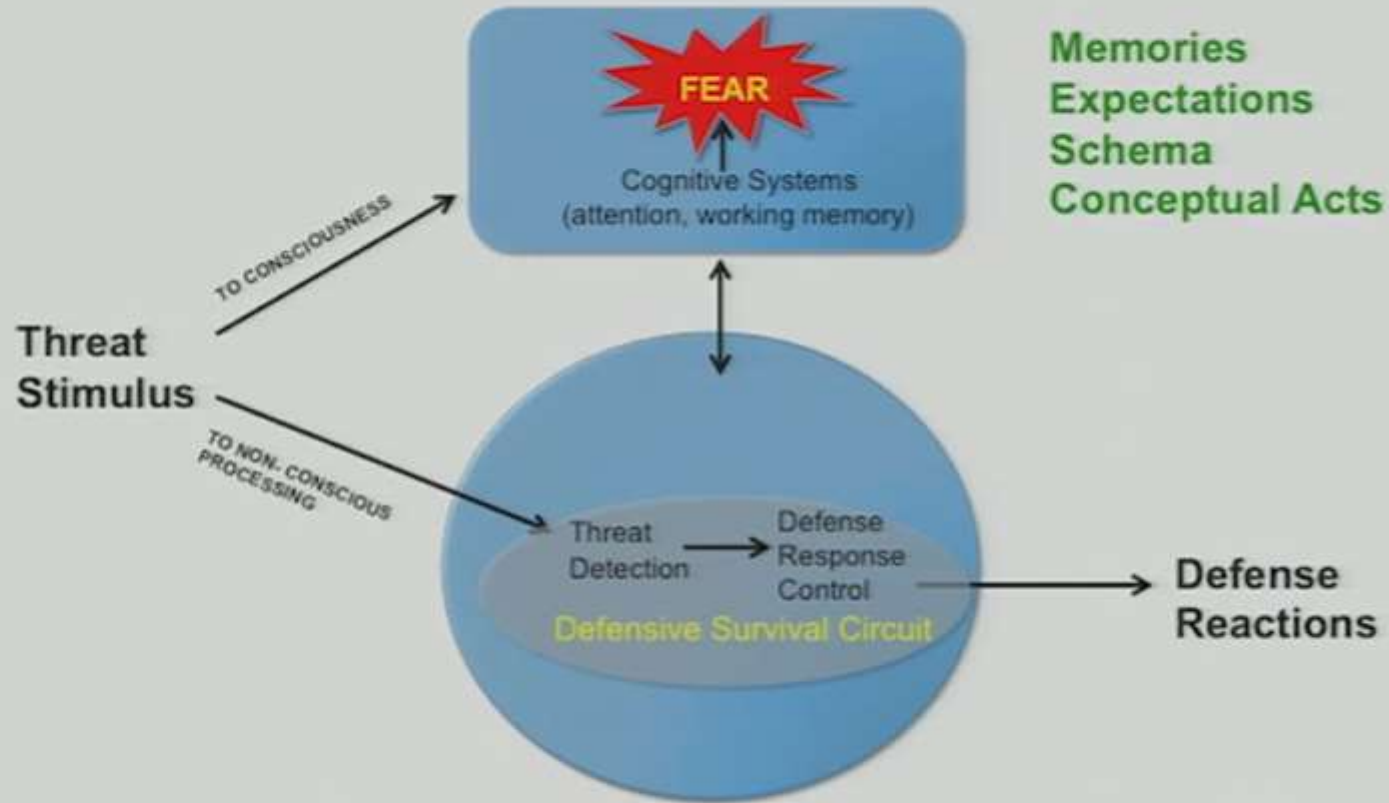
The Survival Circuit View of Fear and Defensive Motivation



Subcortical

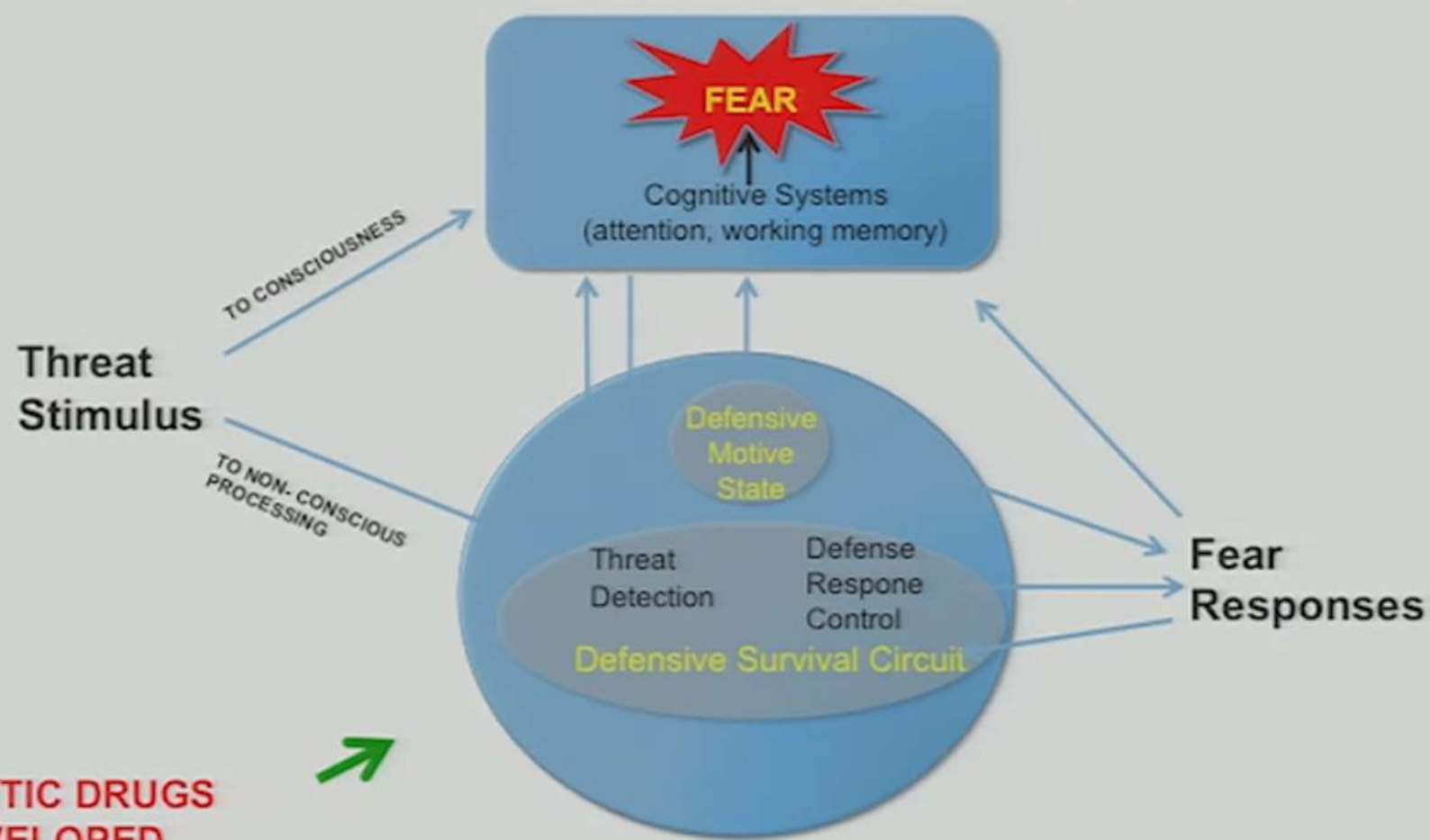
Cognitive Construction theory

**Fear is a Cognitive Event, *NOT* an Innate Feeling
Inherited from Animal Ancestors**



**Defensive Survival Circuits Have Been
Inherited from Animal Ancestors**

PATIENTS FEEL FEARFUL
AND ANXIOUS HERE

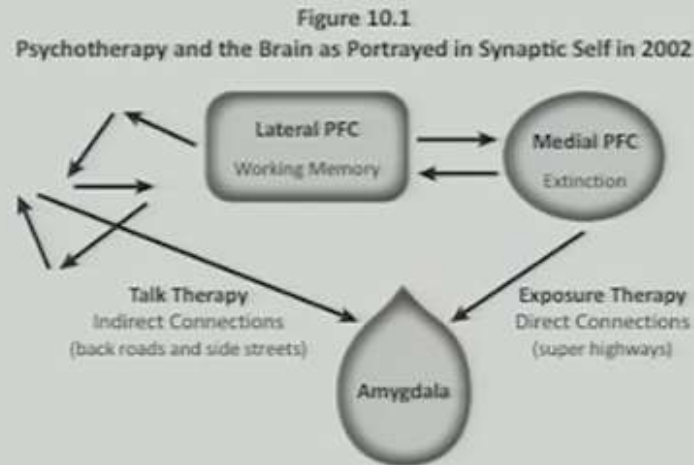


ANXIOLYTIC DRUGS
ARE DEVELOPED
ON BEHAVIORS THAT
ARE CONTROLLED HERE

CBT is not extinction

How Psychotherapy Might Be Improved By Neuroscience?

Exposure Therapy is often equated with extinction



But this was not accurate. Exposure therapy is much more than extinction

Extinction = stimulus repetition

Exposure therapy = talk therapy + instruction + cognitive coping skill training + relaxation training + stimulus repetition

INTERFERENCE— separate extinction from processes that depend on working memory and then optimize extinction

Fear vs Feeling of fear

- ▶ Studies using subliminal (nonconscious) presentations of threats in healthy subjects or in patients with blindsight (people who are cortically blind but able to respond to visual stimuli that they do not consciously see).
- ▶ In both cases, the subjects do not consciously “see” the stimulus and do not report feeling fear, but their amygdalae and bodies respond. Findings like these suggest that although threatening stimuli obviously can elicit feelings of fear, threats also can be processed nonconsciously to control bodily responses in the absence of any feeling.
- ▶ Different circuits control the nonconscious responses to threats (e.g., amygdala circuits) and the conscious feelings of fear elicited by the same stimuli (e.g., neocortical circuits).

LeDoux: threat conditioning, not fear, is innate & nonconscious

- ▶ We should stop using the word “fear” when discussing nonconscious threat processing and that “fear conditioning” should be called “threat conditioning.”
- ▶ This would allow scientists to use the procedure in humans, monkeys, rats, birds, fish, and invertebrates such as flies and slugs without having to struggle with the question of whether the animal feels fear, because fear is not the cause of conditioned responses studied in threat conditioning research.
- ▶ Fear may occur as well, but only in species that can be conscious of their own brains’ activities. Calling the procedure “fear conditioning” only confuses things.

Feeling of fear

- ▶ Fear is an experience that you have when you're threatened, and you can be threatened in a lot of different ways." Thus, LeDoux argued, categorizing "fear" as an emotion hardwired to the amygdala is inaccurate.
- ▶ Fear is a cognitive event, not an innate feeling inherited from animal ancestors. It depends on memories, expectations, schema, [and] conceptual acts ... we need to separate what fear is from the more basic defensive motivational processes.

Making Soup from Non-Soup Ingredients

Water
Onions
Garlic
Carrots
Celery
Salt
Pepper
Chicken

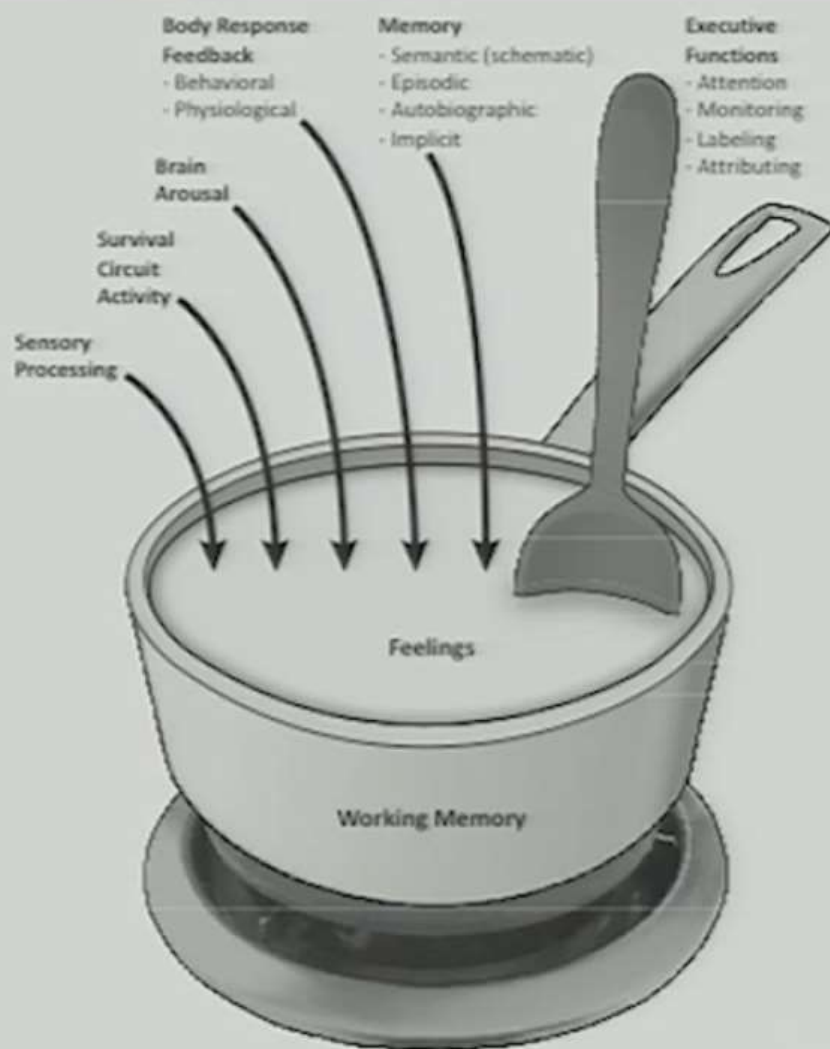


Making Fear from Non-Fear Ingredients

Sensory Processing of Threat
Survival Circuit Activity
Brain Arousal
Body Feedback
Attention
Semantic Memory
Episodic Memory
Implicit Fear Schema
Monitoring
Awareness that YOU are in danger
Interpretation



How Feelings are Made from Non-Emotional Ingredients



Emotions: like soup ingredients

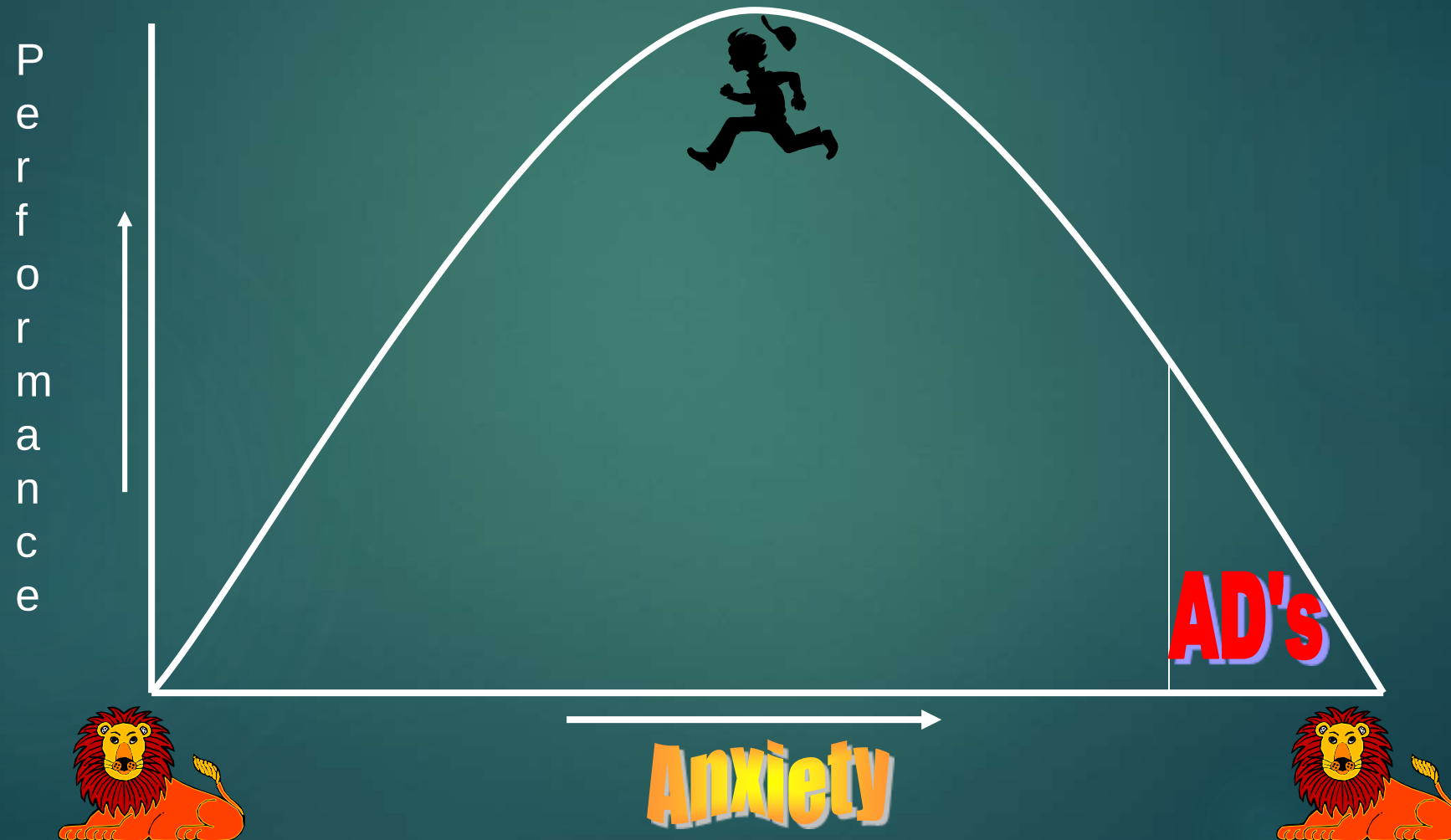
- ▶ Emotions like fear are comprised of several disparate components such as brain arousal, body feedback, attention, semantic and episodic memory, and schemas.
- ▶ The emotion we end up with depends on the kinds of “ingredients” and their amounts. To take the soup analogy further, the executive function of working memory is the “spoon” that stirs the ingredients to create feelings.
- ▶ Fear is not completely different in each of us. Something has to connect it all together to make it all homogenous.
- ▶ Although our conscious experiences of these may vary considerably, underneath are these universal survival circuits that operate implicitly, but similarly, in each of us.
- ▶ Fear based on survival circuits seems universal because it has these universal, nonconscious ingredients, not because it's innately formed as a conscious experience.

Review of anxiety disorders

Anxiety - symptom and disorder

- ▶ As a symptom accompanies many illnesses, both medical and psychiatric.
- ▶ As a disorder has specific features which indicate specific treatment options.
- ▶ Goal is to distinguish the disorders from anxiety as a symptom and then to identify the specific type of anxiety disorder.

Performance-Anxiety Curve



Toxic Stress

Toxic Stress in rats

- ▶ A period of early-life "psychological" stress (poor maternal care) causes late-onset, selective deterioration of both complex behavior and synaptic plasticity: two forms of memory involving the hippocampus, were severely but selectively impaired in middle-aged, but not young adult, rats exposed to fragmented maternal care during the early postnatal period.
- ▶ At the cellular level, disturbances to hippocampal long-term potentiation paralleled the behavioral changes and were accompanied by dendritic atrophy and mossy fiber expansion.
- ▶ These findings constitute the first evidence that a short period of stress early in life can lead to delayed, progressive impairments of synaptic and behavioral measures of hippocampal function, with potential implications to the basis of age-related cognitive disorders in humans.

Stress as the Body's Physiologic Response, Not the Event/Situation

- ▶ **Your physiologic response to events, situations, illnesses, physical perturbations, feelings etc.**
 - ▶ How you manage the challenge
 - ▶ This is what causes short and long term observable body changes and implications for health
- ▶ **Analogy: Your immune response to an infection**
 - ▶ Its how you manage the infection (fever, malaise, sickness behavior, swelling, activated lymph nodes etc.)
 - ▶ AND its what can be observed in your body as a reaction to the infection, and can be the way an illness takes a toll on you

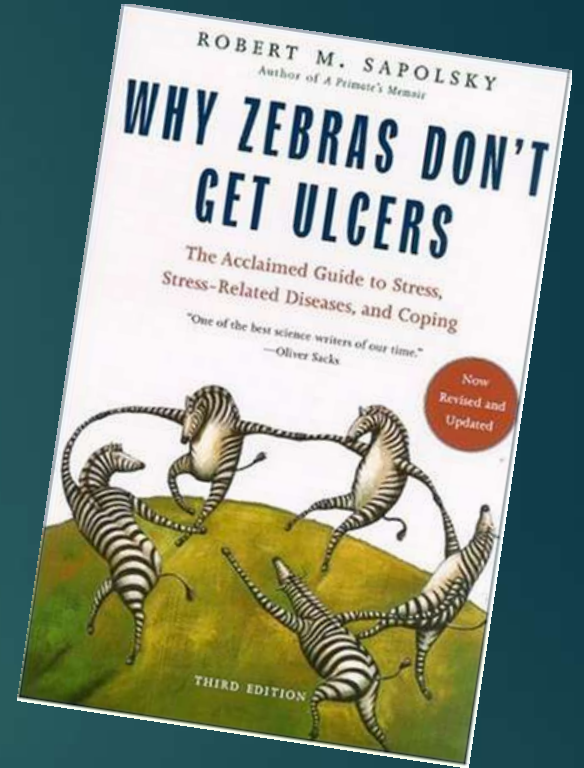
Physiologic Stress

How Does Stress Get “Under the Skin”?

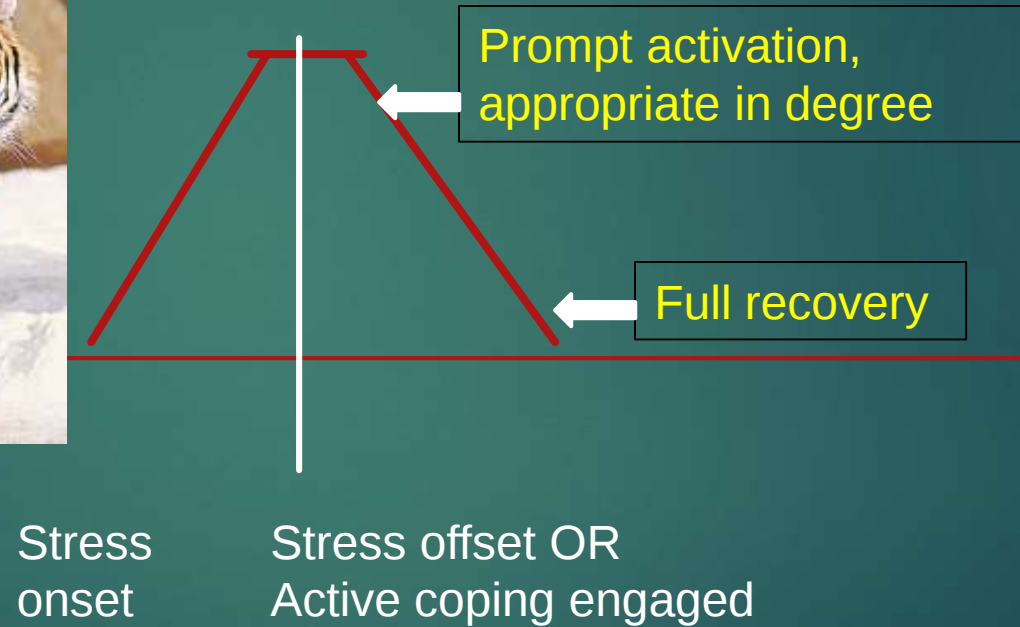


Physiologic Stress Response

- ▶ When the “tiger” enters the room, a cascade is initiated in the brain to manage the threat
- ▶ At least for humans, the tiger can be just thinking about having to do something threatening
 - ▶ imagining an anticipated or experienced conflict
 - ▶ preparing to perform in public
 - ▶ Preparing to enter a new environment



Ideal Stress Response



Function of the Stress Response

- ▶ Physiologic stress is largely about energy
 - Handling a threat is metabolically very costly, whether the response is to fight or to flee

Function of the Stress Response

- ▶ Our stress systems divert energy from long-term processes to the immediate threat

▶ **Away from**

- ▶ digestion
- ▶ reproduction
- ▶ growth
- ▶ repair
- ▶ long-term immune processes (making antibodies for a secondary infection)

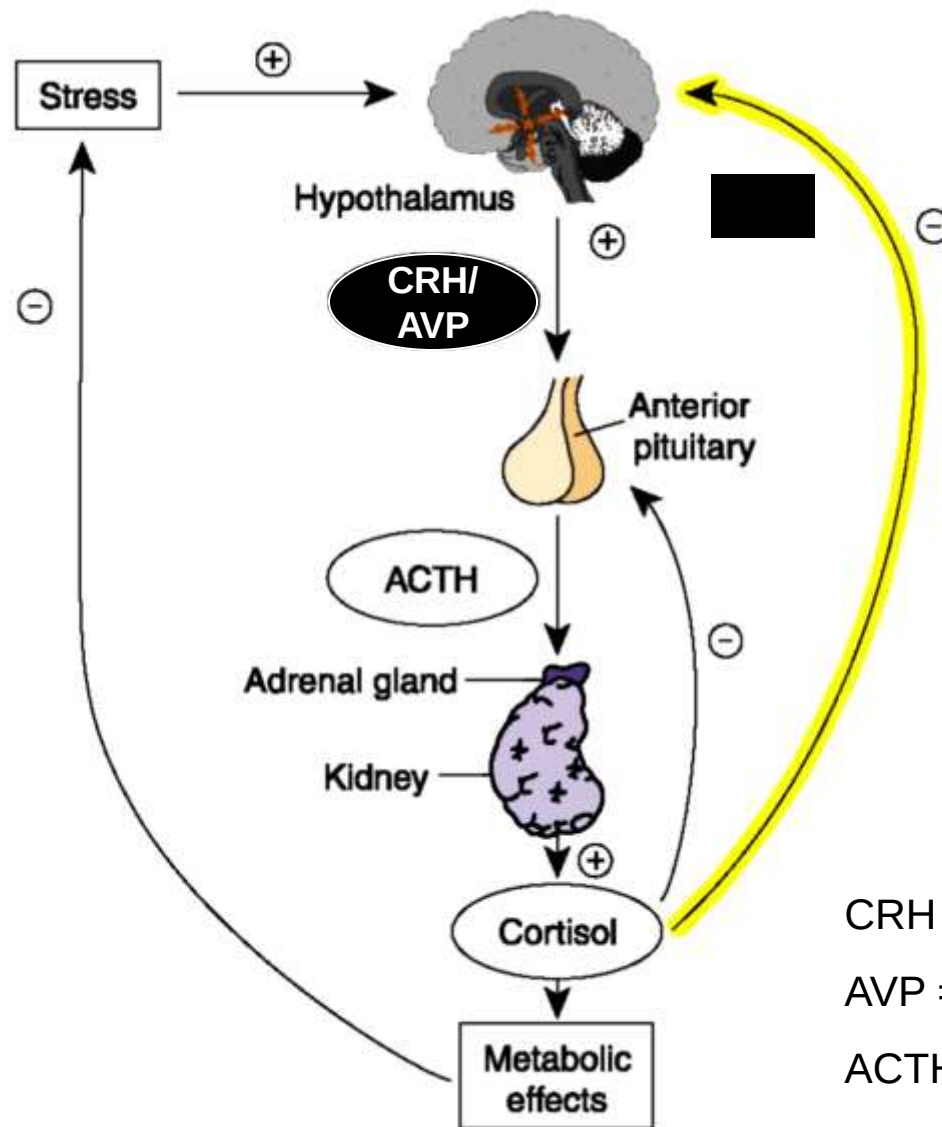
▶ **Toward**

- ▶ respiration
- ▶ glucose to burn
- ▶ increased heart rate to move energy to muscles
- ▶ short-term immune processes (trafficking white blood cells to the site of infection)

Two Stress-Response Systems

- ▶ Likely activated at the same time, the primary and secondary response help to manage threat
- ▶ First response: NE/SAM (brain-stem norepinephrine/ sympathetic-adrenomedullary)
 - ▶ Sympathetic nervous system
 - ▶ Parasympathetic nervous system
 - ▶ Burns through stored glucose to increase respiration, dilate pupils, increase heart rate etc.
- ▶ Second response: HPA
 - ▶ Hypothalamic-pituitary-adrenal (HPA) axis
 - ▶ Supports the first response by replenishing glucose stores and further suppressing long-term growth and restorative processes

HPA-Axis Response



CRH = corticotropin-releasing hormone

AVP = arginine vasopressin

ACTH = adrenocorticotrophic hormone

HPA-axis Cortisol

▶ **Highly Conserved System**

- ▶ HPA-axis shared with salmon (at least 400 million years old)

▶ **Cortisol**

- ▶ A potent steroid hormone that can cross the blood-brain barrier and the membranes of cells to exert wide-ranging effects
- ▶ Hydrocortisone cream, cortisone shots and steroid inhalants have clinical uses because they inhibit inflammation caused by the immune system

▶ **Functions of Cortisol**

- ▶ Mediates many bodily changes in response to stress & challenge
- ▶ Cortisol also has many other functions in the body, e.g. facilitates metabolism

When is physiologic stress good vs. bad?

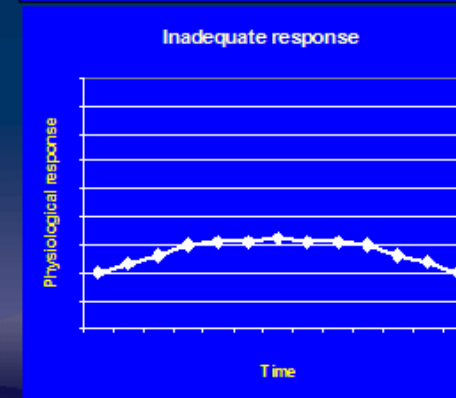
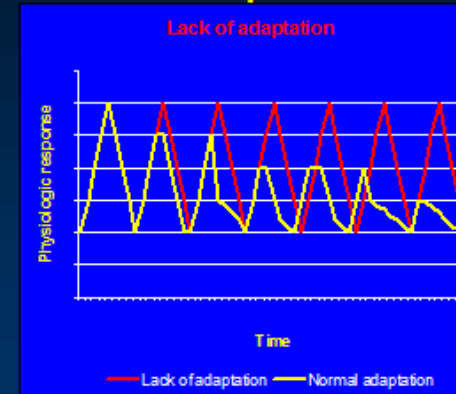
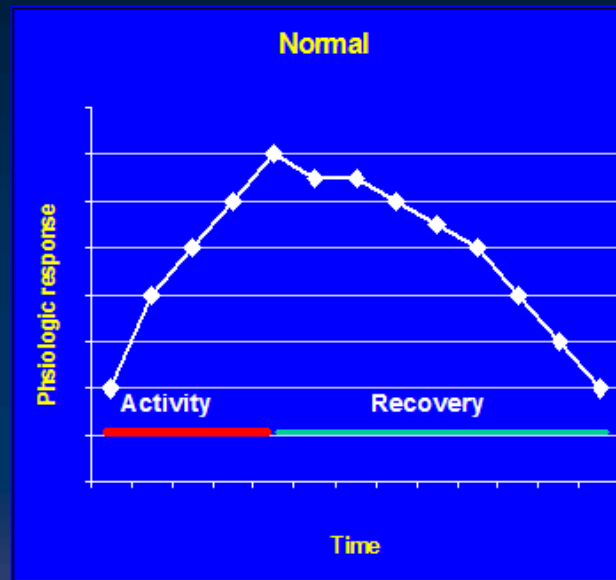
- ▶ When is it adaptive, helpful, necessary?
- ▶ When is it maladaptive, costly, and leading to physical and mental illness?

Stress as Allostasis & Allostatic Load

- ▶ Rather than referring to everything dealing with responses to environmental and psychosocial situations as "stress," we have provided a new formulation using two new terms, "allostasis" and "allostatic load." Allostasis, meaning literally "maintaining stability (or homeostasis) through change" was introduced by Sterling and Eyer (1988) to describe how the cardiovascular system adjusts to resting and active states of the body. **Developed and expanded by Bruce McEwen**
- ▶ **Reconceptualizes stress as an issue of balance**
- ▶ **Allostasis**
 - ▶ Maintaining homeostasis through change OR adaptation
- ▶ **“On” when you need it, “off” when you don’t**
 - ▶ Ideally, one would activate their stress systems infrequently, only for true threat situations, and they would quickly return to baseline once the threat was managed
- ▶ **Allostatic Load**
 - ▶ Wear and tear on stress systems over the life time; Occurs when the systems are activated chronically

Allostasis

physiological and behavioural response



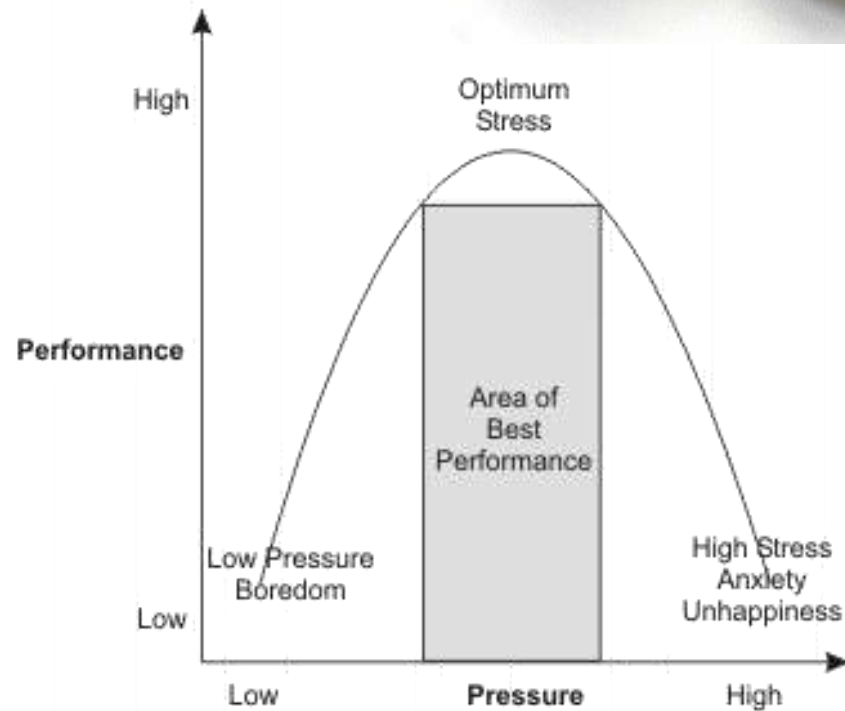
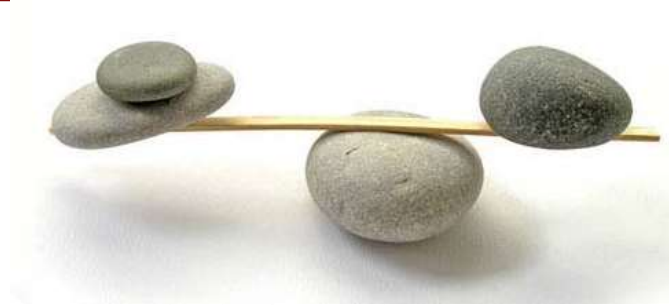
Behavioural

Rumination->magnification->learned helplessness

McEwen 1998, New Eng J Med, 338, 3, 171-179

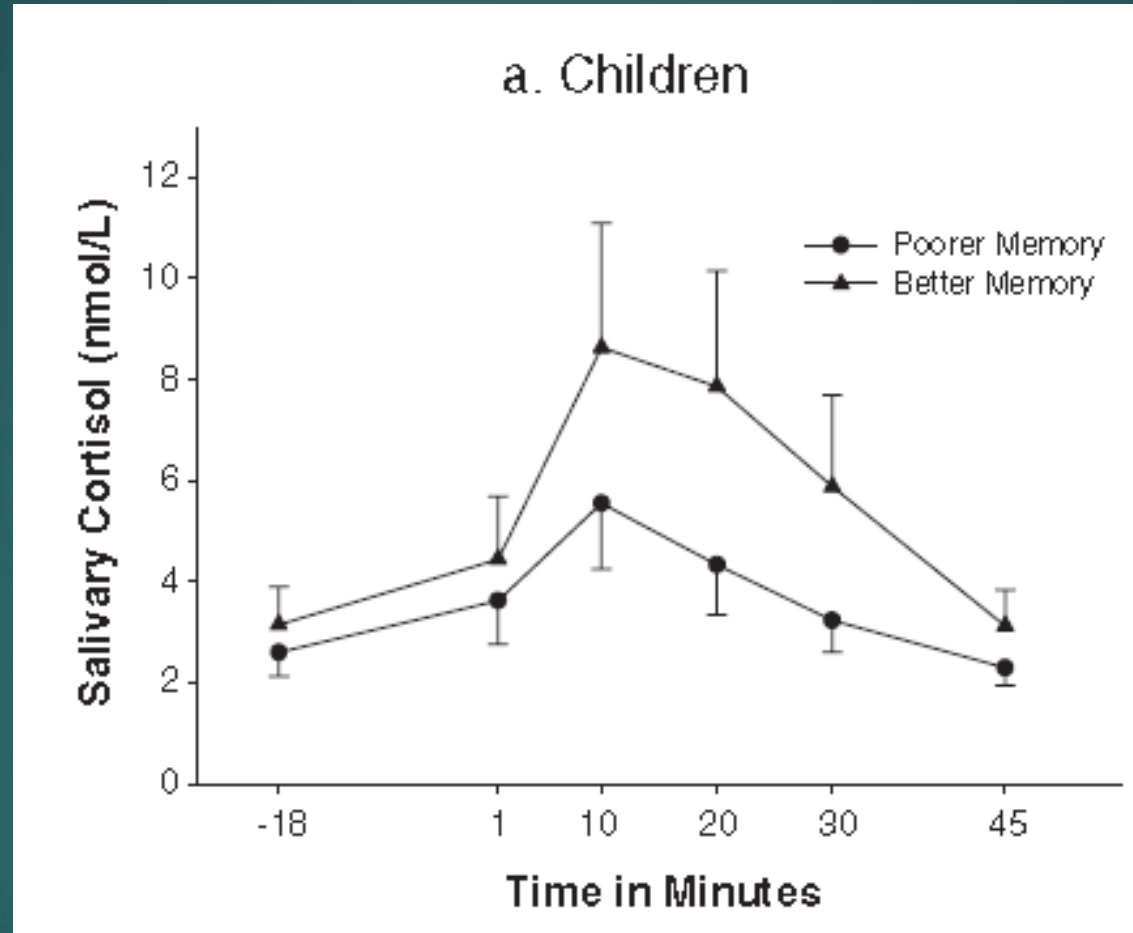
“Allostatic load” = cumulative negative effects, or the price the body pays for being forced to adapt to various psychosocial challenges and adverse environments) that is related to how inefficient the response is, or how many challenges an individual experiences (i.e., a lot of stressful events). Thus allostatic load is more than "chronic stress" and encompasses many aspects of an individual's life that affect the regulation and level of the mediators of allostasis.

A question of Balance



The Inverted-U relationship between pressure and performance

Enhanced Memory for the Details of a Mild Stressor



Quas, J. A., Yim, I. S., Edelstein, R. S., Cahill, L., & Rush, E. B. (2011). The role of cortisol reactivity in children's and adults' memory of a prior stressful experience. *Developmental psychobiology*, 53, 166-174.

A question of timing



Early in life



Long-term Effects of Chronic Stress

- ▶ Correlational and longitudinal studies suggest a strong link between stress across the lifetime and health
- ▶ This link is highly related to SES, so that low SES individuals are at a much greater risk for stress-related disease (Sapolsky, 2005)
 - ▶ This is not due simply to poorer health care access as it persists in countries with universal health care
 - ▶ It is also not due simply to lifestyle differences
 - ▶ Perceived low-status is in some cases most important
 - ▶ Stress-related illness is worse for people at the same income level who live in communities with higher disparities as compared with those who live in communities where their income status is more typical

Long-term Effects of Chronic Stress

▶ **Chronic stress:**

- ▶ influences susceptibility to or progression of a number of diseases including cardiovascular disease, diabetes, and infectious illness
- ▶ increases the risk for obesity, decreases immune function and can impair growth
- ▶ can impair cognitive functioning, including memory and attention
- ▶ increases risk for mental health problems including depression and anxiety

Long-term Effects of Chronic Stress

- ▶ **Effects of stress depend on many factors**

- ▶ the type of stressor
- ▶ the duration of the stress (acute vs. chronic)
- ▶ the unpredictability or uncontrollability of the stress
- ▶ the social environment of the stressed individual including caregiving in children and social support in adults
- ▶ The timing of the stress (early life stress may be most impactful)
- ▶ genetic risk factors

Stress & Challenge During Early Development

What is special about early life stress?



How might psychobiologic responses differ during development?

- ▶ Stress systems maturing
- ▶ Behavioral responses limited
- ▶ Dependence on caregivers

Physiologic Stress (& Normative Stress Physiology) Looks Different in Children



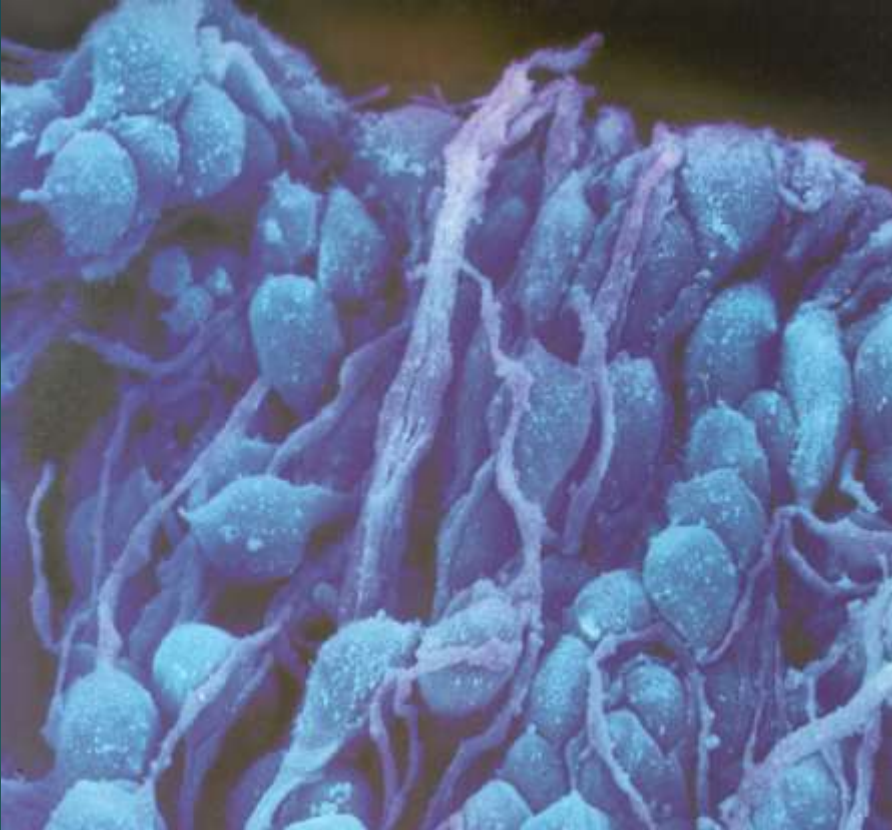
Programming

Susceptible to both organizing and disorganizing influences which can alter the fetal developmental trajectory with lasting influences on health.

These influences on the fetus have been described as “programming”.



The fetal brain is “under construction”

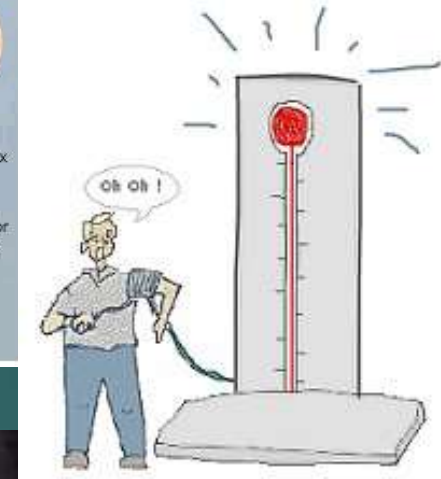
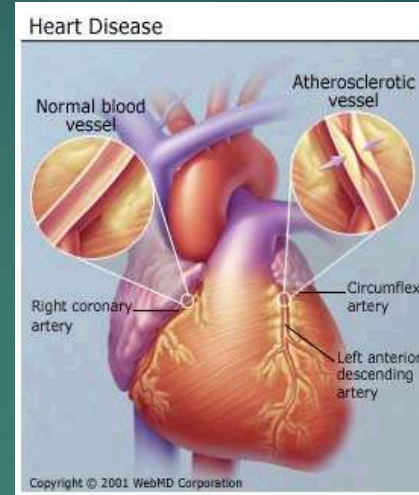


- By seven weeks nerve cells in brain have begun touching and forming primitive nerve paths
- Over 100,000 nerve cells/minute
- At birth the baby will have 100 billion nerve cells
- Proliferation, migration, differentiation, synaptogenesis, myelination continue

Birth Phenotype Predicts Disease in Adulthood



- Coronary artery disease
- Hypertension
- Diabetes
- Impaired pulmonary function/Asthma
- Endocrine cancers
- Osteoporosis
- Obesity



Birth Phenotype Predicts Child and Adult Psychopathology

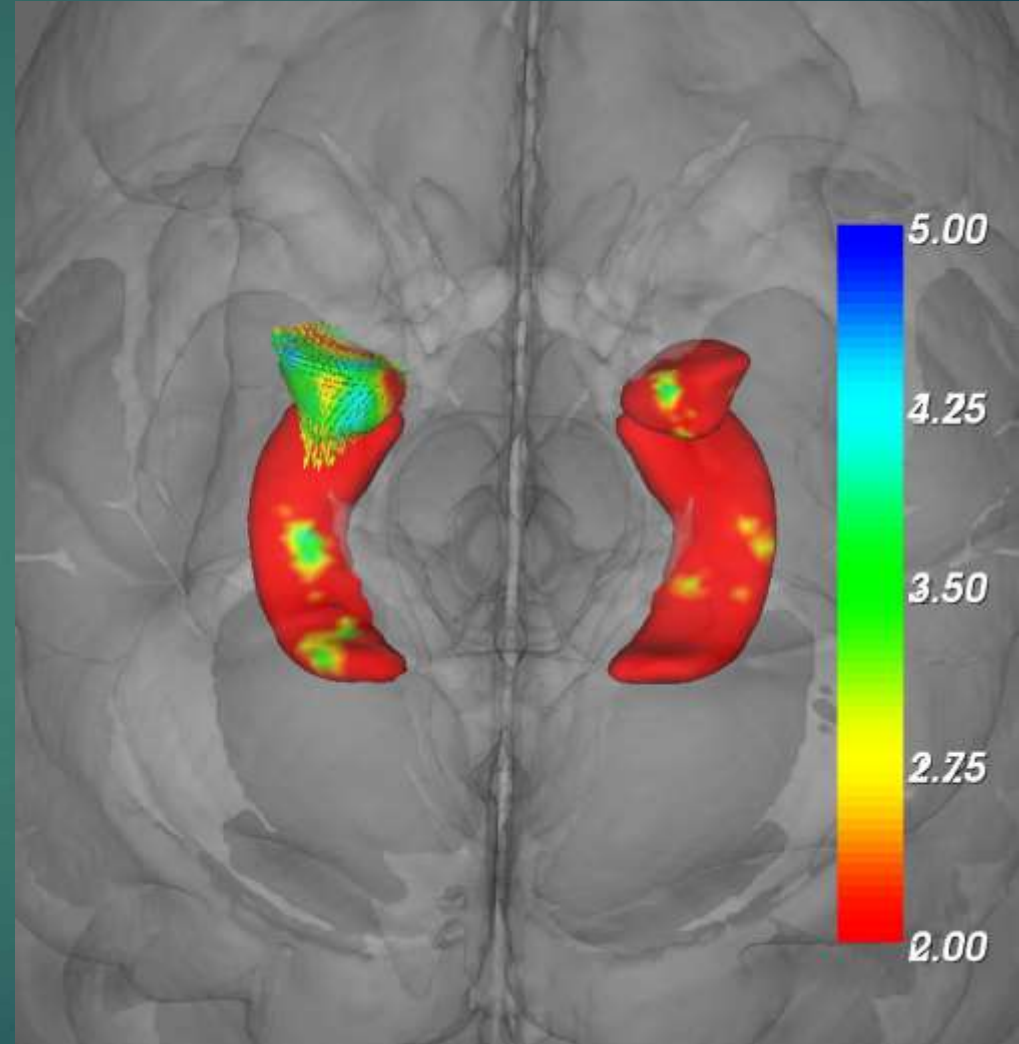


- Autism
- ADHD
- Affective disorders/Suicide
- Schizophrenia

Fetal exposure to maternal cortisol is associated with child brain development

Higher maternal cortisol concentrations in early gestation are associated with larger right amygdala volume and affective problems (CBCL) in girls at 6-9 years age.

The magnitude of the effect is substantial; a 1 standard deviation increase in maternal cortisol is associated with an a 6.4% increase in the size of the right amygdala



Bruce McEwen: Positive, Tolerable & Toxic Stress

SPECIAL COMMUNICATION

Neuroscience, Molecular Biology, and the Childhood Roots of Health Disparities Building a New Framework for Health Promotion and Disease Prevention

Jack P. Shonkoff, MD

W. Thomas Boyce, MD

Bruce S. McEwen, PhD

ADVANCES IN DEVELOPMENTAL biology are building an increasingly persuasive case for a new way of thinking about health promotion and disease prevention that focuses on the origins of persistent disparities in morbidity and mortality in the early years of life. Central to this framework is an increasing interest in the extent to which early experiences and exposures are biologically embedded and have lifelong consequences.

The following example illustrates how the translation of this evolving science base into innovative policy can generate new approaches to reducing the burden of preventable disease.

In 2008, the American Academy of Pediatrics issued a report to address a "new urgency given the current epidemic of childhood obesity with the subsequent increasing risk of type 2 diabetes mellitus, hypertension, and cardiovascular disease in older children and adults."¹ The report underscored the need for a more proactive approach in childhood to the prevention of cardiovascular disease through enhanced adherence to dietary guidelines, increasing physical activity, and consideration of pharmacologic treatment of dyslipidemia beginning as early as age 8 years. What the report did not consider is the idea, based on growing evidence of the cardiovascular sequelae of early life adversity, that new interventions to reduce significant stress

A scientific consensus is emerging that the origins of adult disease are often found among developmental and biological disruptions occurring during the early years of life. These early experiences can affect adult health in 2 ways—either by cumulative damage over time or by the biological embedding of adversities during sensitive developmental periods. In both cases, there can be a lag of many years, even decades, before early adverse experiences are expressed in the form of disease. From both basic research and policy perspectives, confronting the origins of disparities in physical and mental health early in life may produce greater effects than attempting to modify health-related behaviors or improve access to health care in adulthood.

JAMA. 2009;301(2):2252-2259

www.jama.com

in early childhood may be a more appropriate strategy for preventing adult heart disease than the off-label administration of statins to school-aged children. In this article, we explore the scientific validity of the proposition that reducing significant disadvantage early in life may be a powerful strategy for reducing the population-level burden of chronic morbidity and premature death.

Emergence of a New Scientific Approach for Health Policy

Differences in health outcomes related to social class and other markers of disadvantage have been well documented across a broad range of cultures, as well as in societies with a variety of health care systems.²⁻⁴ Despite the unassailable reliability of this robust association, the elucidation of precise causal mechanisms linking adversity to health status remains elusive, and effective policy remedies are not readily apparent.⁵

Notwithstanding the fundamental importance of high-quality medical care for those who are ill, the limited capacity of

high-quality care to reduce socioeconomic and racial disparities in health outcomes is clear. Central to this understanding is the persistence of social class gradients in disease prevalence and mortality rates in nations that provide universal access to health care services.⁶ Some critics have responded by suggesting greater focus on inequalities in service utilization and differential treatment by the health care system. Others have called for greater attention to the role of broader social and economic influences on health, although the task of translating this perspective into concrete policy initiatives has generated more rhetoric than action. While clinicians apply advances in the biomedical

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Corresponding Author: Jack P. Shonkoff, MD, Center on the Developing Child, Harvard University, 60 Church St, South Room, Cambridge, MA 02138 (jack_shonkoff@hs.nyu.edu).

Positive Stress

- ▶ **Moderate, short-lived increases in heart rate, blood pressure, and stress hormone levels.**
- ▶ **Precipitants:** include the challenges of dealing with frustration, receiving an injected immunization, and other normative experiences.
- ▶ **Key Features:**
 - ▶ an important aspect of healthy development
 - ▶ experienced in the context of stable and supportive relationships that facilitate adaptive responses
 - ▶ adaptive responses restore the stress response system to baseline status, and help the person handle future challenges

Tolerable Stress: not alone

- ▶ A physiological state that could potentially disrupt brain architecture (eg, through cortisol induced disruption of neural circuits or neuronal death in the hippocampus) but is buffered by supportive relationships that facilitate adaptive coping.
- ▶ **Precipitants:** include the death or serious illness of a loved one, homelessness, or a natural disaster
- ▶ **Key Features:**
 - ▶ Occurs within a time-limited period
 - ▶ Protective relationships help to bring the body's stress-response systems back to baseline, thereby giving the brain time to recover from potentially damaging effects.

Toxic Stress

- ▶ Strong, frequent, and/or prolonged activation of the body's stress-response systems in the absence of the buffering protection of adult support.
- ▶ **Precipitants/Major risk factors:** extreme poverty, recurrent physical and/or emotional abuse, chronic neglect, severe maternal depression, parental substance abuse, and family violence
- ▶ **Key Features:**
 - ▶ Disrupts brain architecture
 - ▶ Affects other organ systems
 - ▶ Sets stress-management systems to relatively lower (or higher) thresholds for responsiveness that persist throughout life
 - ▶ These changes increase the risk of stress related disease and cognitive impairment well into the adult years

What we have

- ▶ A body of longitudinal association studies linking early experiences to later health and well-being
- ▶ Compelling animal models of the full pathway from a presented challenge to modifications of maternal and offspring behavior to supporting changes in stress physiology and concomitant changes in gene expression
 - ▶ Including some models of remediation
- ▶ Short-term process/linkage studies in human children
- ▶ Promising Interventions

Example Longitudinal Study: ACES Study

- ▶ Collaboration between the CDC and Kaiser
- ▶ 17,000 Participants
- ▶ Compute an ACE score to calculate early life adversity
- ▶ 6 or more associated with a 20-year reduction in life span
- ▶ 4 or more with a number of health conditions

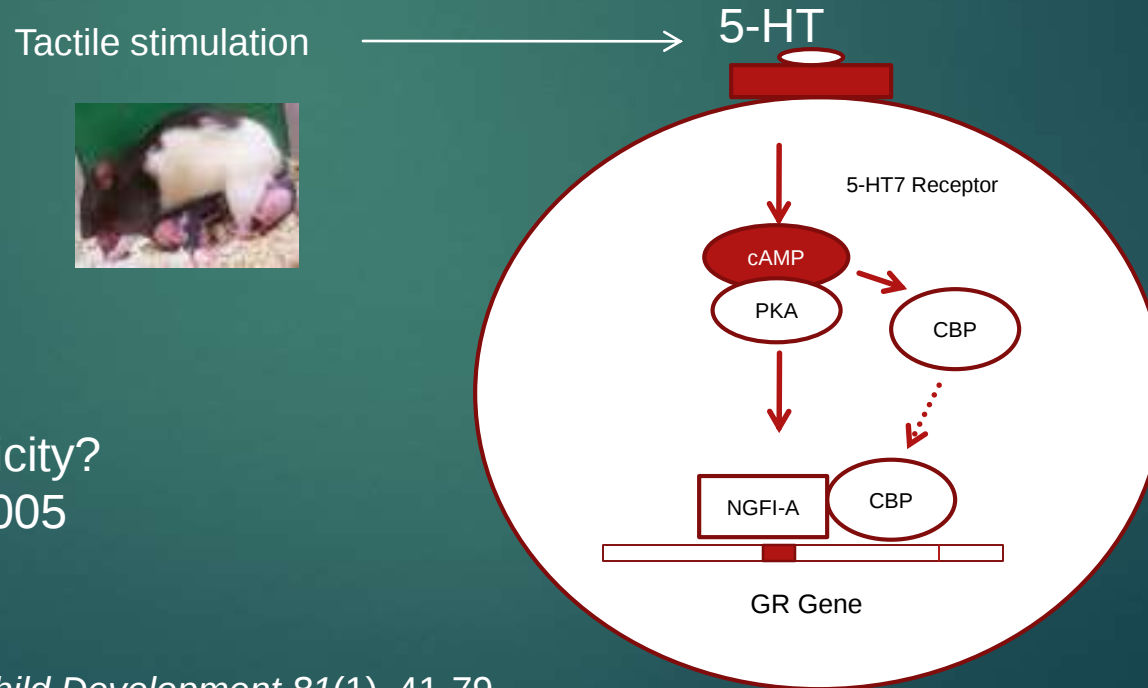


For more information: <http://www.cdc.gov/ace/>

Example Compelling Animal Model

Handling Stress: Epigenetic Transmission

- ▶ Pups with high Licking & Grooming mother rats have increased GC receptor transmission due to acetylation of both NGFI-A and CREB-binding protein



Maternal care as a model for
experience-dependent chromatin plasticity?
Michael J. Meaney and Moshe Szyf, 2005

From Meaney (2010). *Child Development*, 81(1), 41-79.

Handling Stress Paradigm

- ▶ First studies (Levine, et al., 1957) showed that rat pups subjected to early handling stress have better outcomes as adults
 - ▶ They respond with a milder stress response through adulthood, are less fearful, and have better functioning
- ▶ Initial interpretation: stress inoculation
 - ▶ Mild early stress helps set the system to handle stress later in life

***Note that in effect this is Meaney's current working model – but with an evo-devo reframe for the human analog of the low LG pups

Handling Stress: Maternal Response

- ▶ How stress exposure has its effects: maternal behavior is changed by the brief separations
 - ▶ Dams increased their natural caregiving behaviors, including licking, grooming and arched-back nursing
- ▶ Rat pups who experienced handling stress followed by high rates of LG especially showed the better adult outcomes
- ▶ importance of maternal care in modifying the expression of genes that regulate behavioral and neuroendocrine responses to stress, as well as hippocampal synaptic development" in animal studies.†



Handling Stress: High vs. Low LG-ABN Rats

- ▶ Bred dams who differed in their base rates of these behaviors
 - ▶ (high LG-ABN rats and low LG-ABN rats)
- ▶ Offspring of high and low LG-ABN rats differed
 - ▶ Offspring of high LG-ABN dams showed the benefits previously attributed to early stress inoculation
 - ▶ Offspring of low LG-ABN dams did not
- ▶ Genetic transmission vs. effects of rearing?
 - ▶ Low LG dams also more fearful
 - ▶ Were offspring of high LG-ABN dams inheriting protective genes, or was it the caregiving that mattered most?

Handling Stress: Caregiving

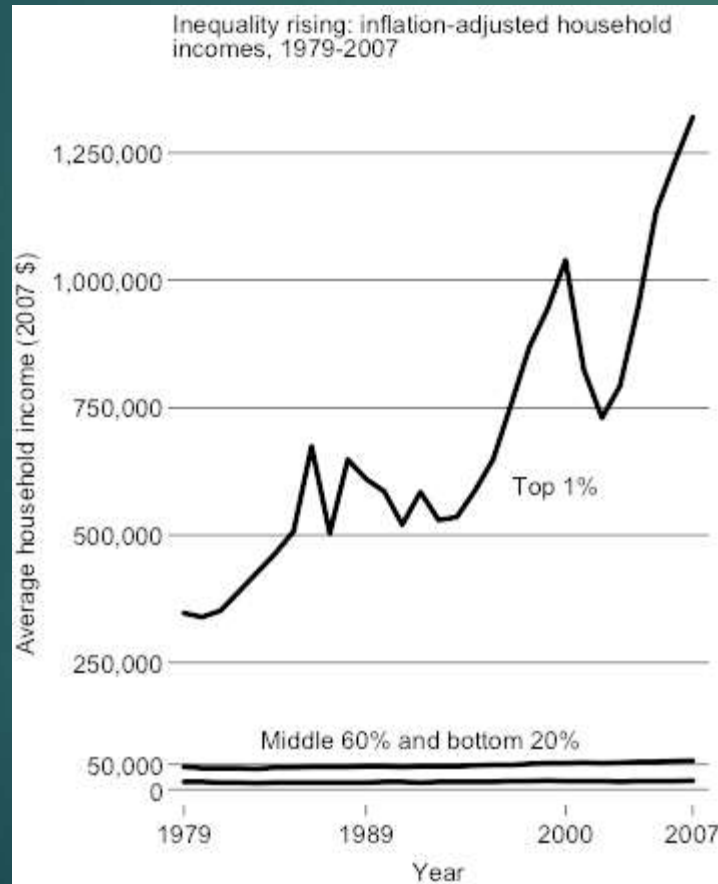
- ▶ Cross-fostering the pups
 - ▶ Pups of high LG-ABN dams were switched to low LG-ABN dams and vice versa
- ▶ Caregiving was the important variable
 - ▶ the pups fostered with the high LG-ABN dams showed the positive outcomes even though they were the offspring of low LG-ABN dams
 - ▶ AND, they grew up to be high LG-ABN dams themselves

Risk and Resilience

- ▶ **Social and biological risk is not deterministic**
 - ▶ Some individuals with fewer risk factors may develop stress-related illness
 - ▶ Some individuals with many risk factors may appear relatively unaffected
- ▶ **Risk factors and resilience factors are often each others' opposites**
 - ▶ Easy temperament/difficult temperament; high IQ/low IQ; maternal psychopathology/good maternal health
- ▶ **Note that with sufficient strain to the system in the absence of support, no one is immune**
- ▶ **Note that across decades of research, one of the most powerful resilience factors is one, consistent, supportive adult**

How are Negative Life Events and their Consequences Perpetuated Generation to Generation?

► Socio-culturally



Epigenetically



Epigenetically

- ▶ We inherit our genes, or our DNA from our two biological parents, arranged in a novel configuration. But DNA does not equal behavior, disease etc.
- ▶ Genes must be copied and activated (or deactivated) in every cell of the body and across the lifespan
 - ▶ If this wasn't true, how would heart cells differ from brain cells etc.?
- ▶ A number of processes mark genes for activation or inactivation, collectively epigenetic processes (on top of the genome)
- ▶ These markers are controlled/sensitive to illness, stress and toxin exposure, environmental supports etc.

Panic Disorder

Panic Disorder

▶ Old:

- ▶ Panic Disorder without agoraphobia
- ▶ Panic Disorder with agoraphobia

▶ Criteria: Recurrent unexpected panic attacks

- ▶ Panic: from calm or anxious state; abrupt surge of intense fear/discomfort, peak within minutes
- ▶ 4 of 13 symptoms
- ▶ 1 attack being followed by 1 month or more of persistent worry about additional attacks
- ▶ And/or significant maladaptive behavior change related to attacks

Panic Disorder

- ▶ Prevalence and Comorbidity
 - ▶ Panic attacks common (3-4% of teens)
 - ▶ Panic disorder less common (about 1% of teens)
 - ▶ Panic attacks are more common in females (2 to 1) than males and are related to stressful life events
 - ▶ Comorbidity: most commonly other anxiety disorders or depression
 - ▶ may be at risk for suicidal behavior or alcohol/drug abuse
- ▶ Onset, Course, and Outcome
 - ▶ Age of onset for first panic attack: 15-19 years; 95% of PD adolescents are postpubertal
 - ▶ Worst prognosis of all anxiety disorders

Panic Disorder - Epidemiology

- ▶ Concordance
 - ▶ MZ twins-80 to 90%
 - ▶ DZ-10-15%
- ▶ 1st degree relatives have 4-18x rate of Panic Disorder

Panic Disorder

- ▶ Patient with panic account for
 - ▶ 20-30% of ER visits
 - ▶ 15% of total medical visits
 - ▶ average 19.8 medical visits per year (7x the base rate)
- ▶ Lower quality of life
- ▶ Increased risk for hypertension, MI, and stroke
- ▶ Poor work performance
 - ▶ less than 1/2 can work fulltime
 - ▶ 4 x the unemployment rate

Panic Disorder - Pathophysiology

- ▶ Biological
 - ▶ Overactive autonomic responses
 - ▶ Neurotransmitters implicated
 - ▶ GABA
 - ▶ NE
 - ▶ 5HT
 - ▶ Pharmacologic challenges
 - ▶ Yohimbine
 - ▶ Lactate
 - ▶ CO₂

Panic Disorder - Diagnosis

- ▶ Recurrent unexpected panic attacks
- ▶ At least one attack has been followed by 1 month or more of:
 - ▶ persistent concern about having more attacks
 - ▶ worry about the implications of the attack
 - ▶ (eg. losing control, having an MI, “going crazy”)
 - ▶ significant change in behavior related to attacks

Panic Attacks

4 or more of below symptoms, develop abruptly & peak within 10 minutes

- ▶ Palpitations
- ▶ Chest pain
- ▶ Sweating
- ▶ Trembling
- ▶ SOB
- ▶ Nausea
- ▶ Feeling dizzy/faint
- ▶ Derealization/ depersonalization
- ▶ Fear of going crazy/dying
- ▶ Numbness/tingling (perioral/acral)
- ▶ Chills/hot flushes

Differential dx of Panic

- ▶ Cardiovascular diagnosis
- ▶ Pulmonary
- ▶ Neurological
- ▶ Endocrine
- ▶ Other Psychiatric
- ▶ Drug Intoxications
 - ▶ stimulants
 - ▶ caffeine
 - ▶ cocaine
- ▶ Drug Withdrawal
 - ▶ alcohol/sedatives/hypnotics

Panic Disorder: Abnormal Fear System

- ▶ Irregularly sensitive fear system involving:
 - ▶ Overactive amygdala (fear conditioning)
 - ▶ Underactive PFC (does not suppress attentional bias)
 - ▶ Deficient hippocampal function (contextual fear misinterpretation)
 - ▶ Reduced ACC (reduced conflict monitoring)
 - ▶ Insula
 - ▶ Brain stem and hypothalamus
 - ▶ Putamen atrophy
 - ▶ Lower GABA levels in basal ganglia

Panic Disorder

- ▶ Panic attack: sudden, overwhelming period of intense fear or discomfort accompanied by characteristics of the fight/flight response
 - ▶ Rare in young children, common in adolescents; related to pubertal development, not age
- ▶ Panic disorder: recurrent unexpected panic attacks followed by at least one month of persistent concern about having another attack, constant worry about the consequences, or a significant change in behavior related to the attacks (anticipatory anxiety)
- ▶ High anticipatory anxiety and situation avoidance may lead to agoraphobia:
 - ▶ fear of being alone in/avoiding certain places or situations
 - ▶ fear of having a panic attack in situations where escape would be difficult or help is unavailable

Agoraphobia

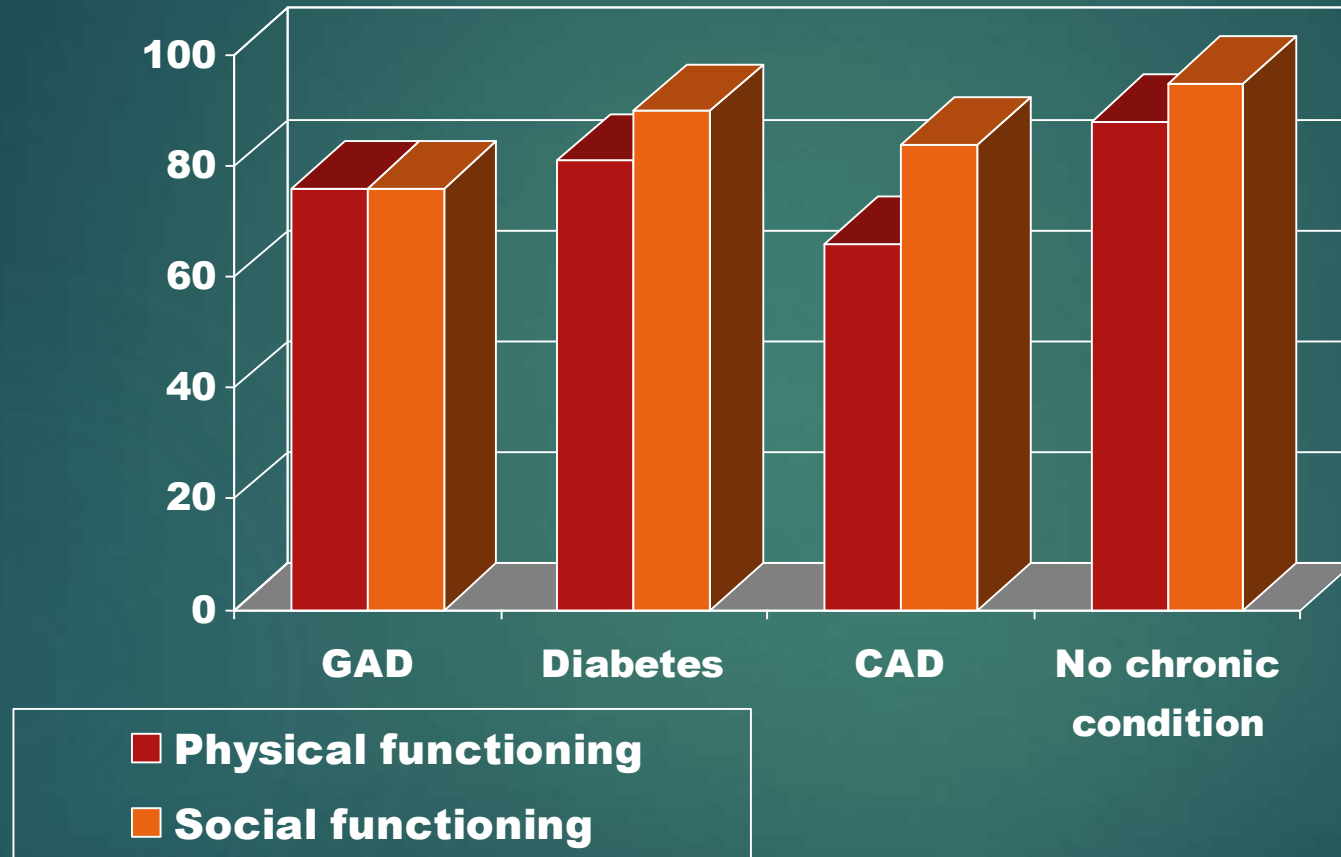
- ▶ Fear of leaving the “house”
- ▶ >95% have Panic Disorder
- ▶ If present, prognosis is worse

Generalized Anxiety Disorder (GAD)

Generalized Anxiety Disorder

- ▶ Excessive, uncontrollable anxiety and worry about many events and activities on most days
- ▶ Worry excessively about minor everyday occurrences, even when they see they are making themselves and others unhappy
- ▶ Accompanied by at least one somatic symptom (e.g., headaches, stomach aches, muscle tension, trembling)
- ▶ Prevalence and Comorbidity
 - ▶ 3% to 6% of children (equal rates in boys and girls)
 - ▶ High rates of other anxiety disorders and depression
- ▶ Onset, Course, and Outcome
 - ▶ Average age of onset: 10-14 years
 - ▶ Older children have more symptoms that may diminish with age
 - ▶ Symptoms persist over time

GAD - Comparison with other medical conditions



GAD actually has more disability and dysfunction in social terms than either diabetes, coronary artery disease. Only coronary artery disease has a worse physical functioning.

GAD - Genetics

- ▶ High concordance in twin studies
 - ▶ 50% for MZ
 - ▶ 15% for DZ
- ▶ 25% of 1st degree relatives have GAD

GAD - Diagnosis

- ▶ Excessive anxiety and worry, more days than not for at least 6 months
- ▶ 3 or more of:
 - ▶ restlessness/keyed up/on edge
 - ▶ easily fatigued
 - ▶ difficulty concentrating/mind going blank
 - ▶ irritability
 - ▶ muscle tension
 - ▶ sleep disturbance

GAD-Anxiety symptoms

▶ Psychic

- ▶ Anxious or irritable mood
- ▶ Tension/inability to relax
- ▶ Fears
- ▶ Difficulty concentrating
- ▶ Insomnia (usually initial)

▶ Somatic

- ▶ GI disturbance
- ▶ Headaches
- ▶ Insomnia
- ▶ Palpitations
- ▶ Muscle tension and aches
- ▶ SOB/ dyspnea
- ▶ Loss of libido

SWICKIR is QUICKER

- ▶ S--somatic complaints
 - ▶ W--worry
 - ▶ I--insomnia
 - ▶ C--concentration is poor
 - ▶ K--keyed up and tense
 - ▶ I--irritable
 - ▶ R--restless
-
- ▶ Worry + 3 for 6 months= GAD

Obsessive-Compulsive Disorder (OCD)

Obsessive-Compulsive Disorder

- ▶ Obsessive-Compulsive Disorder: Recurrent, time-consuming, disturbing obsessions (persistent and intrusive thoughts, ideas, impulses, or images) and compulsions (repetitive, purposeful, and intentional behaviors) performed to relieve the anxiety
 - ▶ OCD is extremely resistant to reason
 - ▶ OCD children often involve family members in rituals
 - ▶ Rituals fail to provide long-term relief from anxiety, resulting in time-consuming, never-ending cycle of obsessions and compulsions
 - ▶ Often leads to severe disruptions in normal activities, health, social and family relations, and school functioning

Obsessive-Compulsive Disorder 2

- ▶ Prevalence and Comorbidity
 - ▶ 2-3% of children
 - ▶ Clinic-based studies find it twice as common in boys; community samples don't find a gender difference
 - ▶ Comorbidities: Most common are other anxiety disorders, depressive disorders, disruptive behavior disorders
 - ▶ Also, substance-use, learning and eating disorders, as well as vocal and motor tics
- ▶ Onset, Course, and Outcome
 - ▶ Average age of onset: 9-12 years with peaks in early childhood and early adolescence
 - ▶ Family history for those with early onset
 - ▶ Chronic disorder; as many as two-thirds continue to have OCD 2-14 years after initial diagnosis

OCD

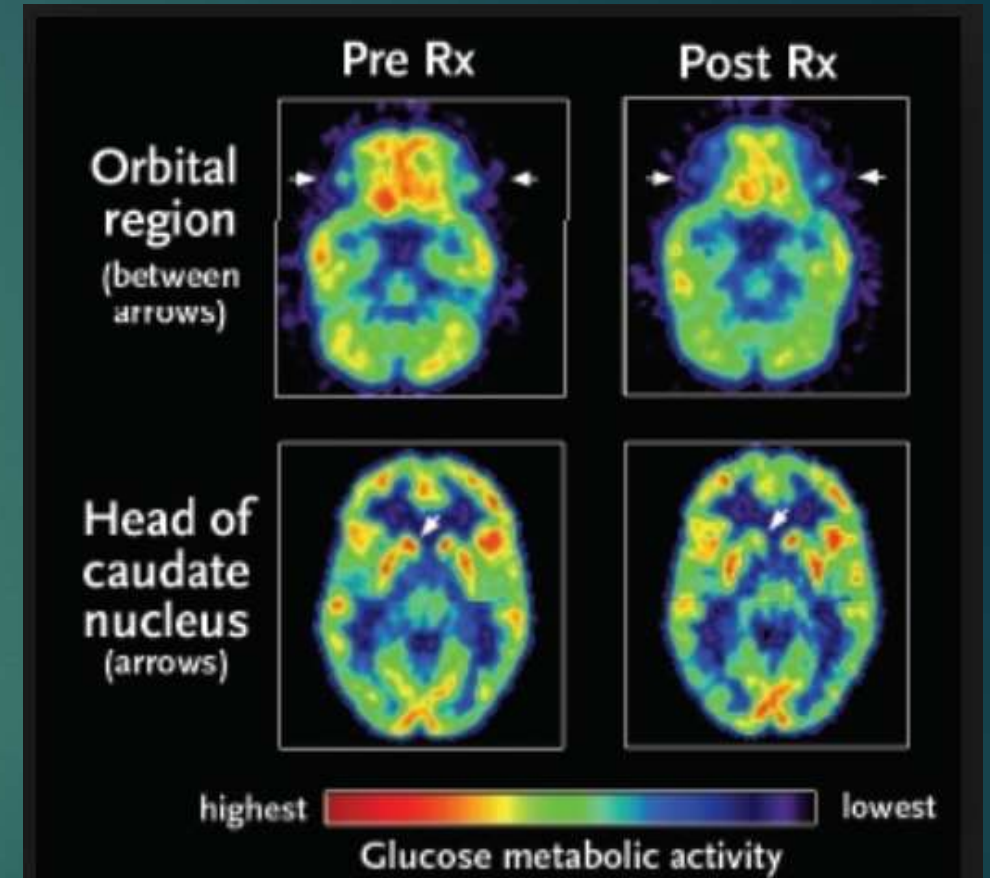
- ▶ Higher prevalence than earlier thought
- ▶ Rarely present to a psychiatrist
- ▶ Comorbidity is common
 - ▶ Major Depression , Social Phobia, and Tourette's
- ▶ Many remain ill after treatment
- ▶ OCD is not OC Personality Disorder
 - ▶ Only 15-35% of OCD pt's had any premorbid obsessional traits

OCD

- ▶ Only AD with $F=M$ rates
 - ▶ except in adolescents ($M>F$)
- ▶ Genetic factors
 - ▶ $MZ>DZ$
 - ▶ 35% of 1st degree relatives have OCD
- ▶ Relation to Tourette's Disorder
 - ▶ 90% of TD have compulsions
 - ▶ Up to 66% meet criteria for OCD

OCD - Pathophysiology

- ▶ Orbitofrontal cortex, anterior cingulate cortex, and caudate nuclei exhibit increased metabolism on PET scans
- ▶ Effective tx with either SSRI or behavioral therapy reduces hypermetabolism of right caudate
- ▶ Effective tx with SSRI reduces hypermetabolism in orbitofrontal cortex



OCD - Role of Serotonin

- ▶ Potent SRI's are effective in OCD
- ▶ m-chlorophenylpiperazine (m-CPP), a serotonin agonist exacerbates obsessions and rituals in about 1/2 of patients with OCD
- ▶ m-CPP effect can be blocked by clomipramine and fluoxetine
- ▶ *Norepinephrine Reuptake Inhibitors (NRIs)* are ineffective in OCD

OCD - Diagnosis

- ▶ Presence of either obsessions or compulsions
- ▶ In adults, at some point recognized as excessive
- ▶ Cause distress or are disabling
- ▶ Can specify, *with poor insight*

Obsessions/Compulsions

▶ Obsessions:

- ▶ Recurrent or persistent thoughts, impulses, or images seen as intrusive or inappropriate that cause marked anxiety/distress
- ▶ Not simply excessive worries
- ▶ Attempts are made to suppress or neutralize obsessions
- ▶ Obsessions recognized as product of one's own mind (not delusional)

▶ Compulsions:

- ▶ Repetitive behaviors or mental acts driven to perform in response to obsession, or according to rules rigidly applied
- ▶ Behaviors or mental acts are aimed at preventing or reducing distress or preventing dreaded event or situation
- ▶ Are admitted as 'silly' by most patients

Common Symptom Patterns

- ▶ Contamination (washing)
- ▶ Pathological doubt (checking)
- ▶ Intrusive thoughts (sexual/aggressive)
- ▶ Symmetry ("obsessional slowness")
- ▶ Hoarding
- ▶ Counting

OCD - Delay in Diagnosis/Treatment

- ▶ 10yr lag between onset of symptoms and seeking professional help
- ▶ 6yr lag before correct diagnosis is made
- ▶ 1.5 yrs before appropriate treatment
- ▶ total of 17 yrs between onset of symptoms (age 14.5) and appropriate treatment (age 31.5)

OCD-Present to...

- ▶ Dermatologist-chapped hands, eczemoid appearance
- ▶ ID/Internist-persistent fear of HIV/AIDS
- ▶ FP/Internist-may mention excessive washing, counting, or checking
- ▶ Dentist-gum lesions
- ▶ Pediatrician-parent concerns about excessive washing, counting, etc.
- ▶ Pediatric cardiologist-OCD secondary to Sydenham's chorea and other PANDA's

SOCIAL ANXIETY DISORDER (SAD)

Specific Phobia

- ▶ Phobia: age-inappropriate persistent, irrational, or exaggerated fear that leads to avoidance of the feared object or event and causes impairment in normal routine; lasts at least 6 months
- ▶ Specific phobia: an extreme and disabling fear of objects or situations that in reality pose little or no danger or threat
 - ▶ Child goes to great lengths to avoid the object/situation
 - ▶ Beliefs persist despite evidence no danger exists
 - ▶ If feared object/situation is encountered often it can become a serious problem
- ▶ Evolutionary theory: infants are biologically predisposed to learn certain fears
- ▶ 5 DSM-IV subtypes: animal, natural environment, blood-injection-injury, situational, “other”

Specific Phobia (cont.)

▶ Prevalence and Comorbidity

- ▶ About 4-10% of children at some point in their lives, although few are referred for treatment
 - ▶ more common in girls
 - ▶ most common co-occurring disorder is another anxiety disorder, although comorbidity is lower than for other anxiety disorders

▶ Onset, Course, and Outcome

- ▶ Phobias involving animals, darkness, insects, blood, and injury: 7-9 years of age
 - ▶ although consistent with normal development, clinical phobias are more likely than normal fears to persist over time
- ▶ Specific phobias occur at any age; peak between 10-13

Social Phobia

- ▶ Social anxiety/social phobia: A marked, persistent fear of social or performance requirements that expose the child to scrutiny and possible embarrassment
 - ▶ anxiety over mundane activities
 - ▶ most common fear is doing something in front of others
 - ▶ more likely than other children to be highly emotional, socially fearful and inhibited, sad, and lonely
- ▶ Generalized social phobia: the most severe form involves fear of most social situations

Social Phobia (cont.)

- ▶ Prevalence, Comorbidity, and Course
 - ▶ 1-3% of children
 - ▶ More common in girls, who are more concerned with social competence and interpersonal relationships than are boys
 - ▶ Two-thirds also have another anxiety disorder
 - ▶ Most common comorbid disorders: specific phobia or panic disorder; 20% of social phobic adolescents suffer from major depression and may self-medicate with alcohol and other drugs
 - ▶ Common age of onset: early to mid-adolescence; rare under age 10
 - ▶ Prevalence increases with age and may be predicted by early rejection by peers
- ▶ Selective mutism--failure to talk in specific social situations--may be a form of social phobia; seen in 0.5% of children

Social Anxiety Disorder

- ▶ AKA Social Phobia
- ▶ Very prevalent
- ▶ Fear of humiliation or embarrassment
- ▶ Leads to avoidance
- ▶ Most severe form is Avoidant PD

Specific Phobias

- ▶ Most common psychiatric disorder
- ▶ Irrational fear that produces avoidance
- ▶ 5 Types: animal, natural environment, blood-injection-injury, situational, other
- ▶ Specific phobias may be comorbid with panic disorder. May respond to SSRI.
- ▶ Best evidence is for CBT
 - ▶ “Systematic desensitization”

Shared neuropathology

Neural Circuits as substrates of Mental Illness

- ▶ 1987 introduction of AZT and Prozac
- ▶ 2015: HIV has potential cure, but still no process physiology understanding of mental illnesses
- ▶ By 2030, \$6 trillion cost for MI

Mental Illness: psychopathology vs nosology

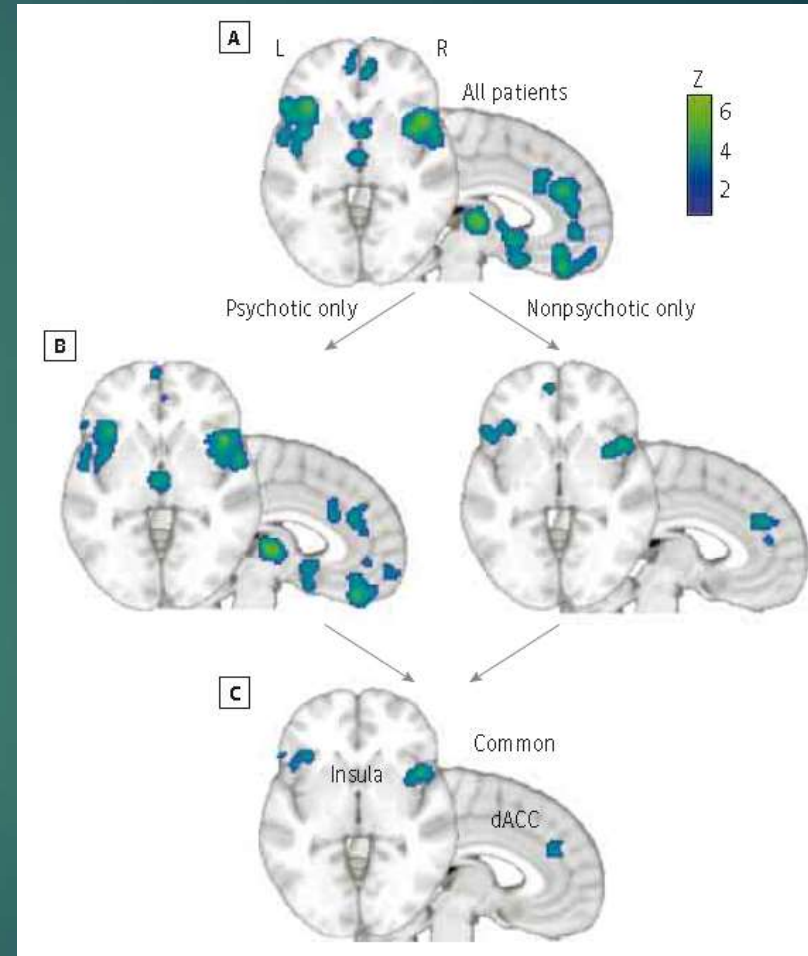
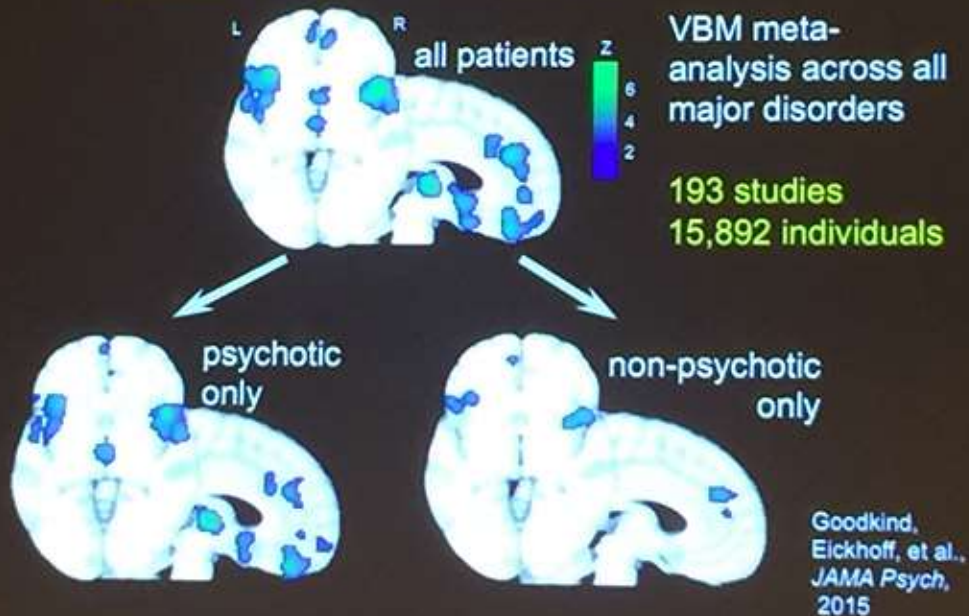
- ▶ MI is plagued with unscientific assertions
- ▶ DSM-5: a symptom list, not neural circuitry of MI
- ▶ NIMH: Rdoc (research domain criteria), brain systems
- ▶ Need to look at MI in a dimensional and transdiagnostic framework based on neuroscience; symptoms are an expression of dysfunction in neural circuits

Identification of a Common Neurobiological Substrate for Mental Illness: Metaanalysis

- ▶ Meta-analysis of 193 studies comprising 15 892 individuals across 6 diverse diagnostic groups (schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety)
- ▶ Gray matter loss converged across diagnoses in 3 regions: the dorsal anterior cingulate, right insula, and left insula.
- ▶ By contrast, there were few diagnosis-specific effects, distinguishing only schizophrenia and depression from other diagnoses.
- ▶ In the parallel follow-up analyses of the 3 independent healthy participant data sets, we found that the common gray matter loss regions formed a tightly interconnected network during tasks and at resting and that lower gray matter in this network was associated with poor executive functioning.

Identification of a Common Neurobiological Substrate for Mental Illness: Metaanalysis

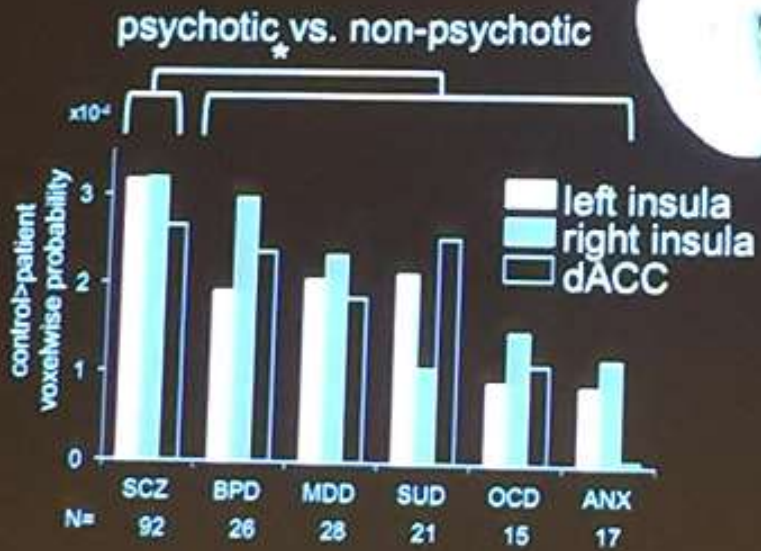
Is there a common neurobiological substrate for mental illness?



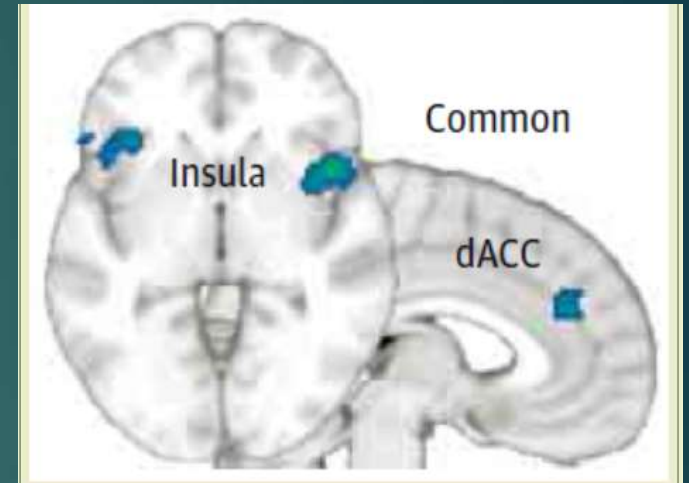
An anterior insula/dorsal anterior cingulate–based network, which may relate to executive function deficits

Anterior insula/dorsal anterior cingulate-based network

Common gray matter loss network

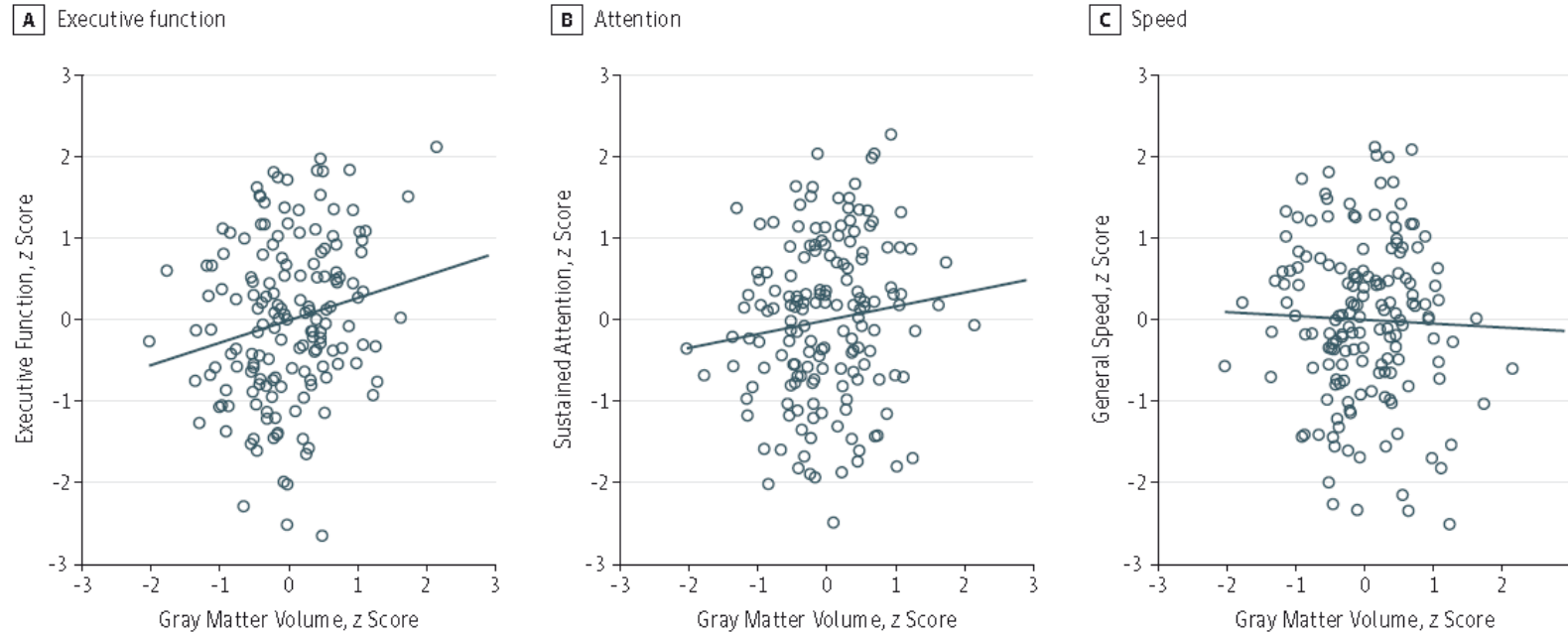


Goodkind,
Eickhoff, et al.,
JAMA Psych,
2015



Functional consequences: Salience Network deficit

Figure 6. Relationship Between Gray Matter Volume in the Common Gray Matter Loss Regions and Performance on a Computerized Battery of Behavioral Cognitive Tests

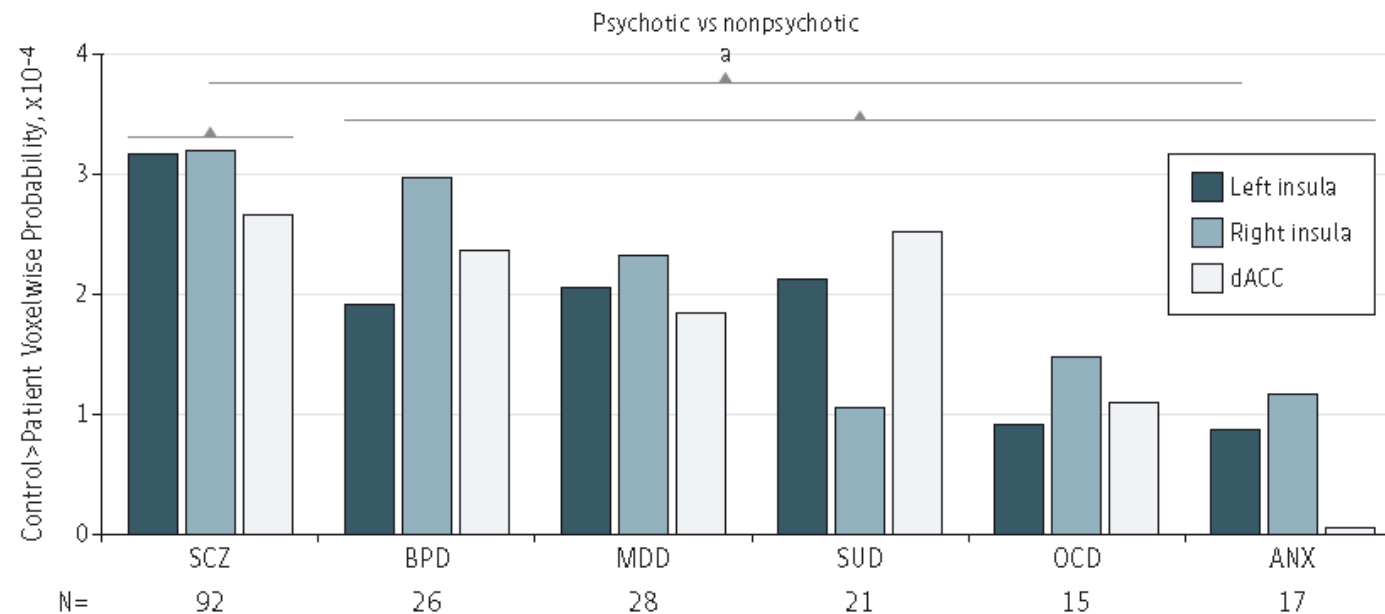


Based on a principal components analysis, cognitive test performance was reduced to 3 components: general executive function, the specific domain of sustained attention, and general cognitive performance and performance speed. Lower voxel-based morphometry-measured gray matter volume in these regions is associated with worse executive functioning (A) and a trend for worse sustained attention (B) but not general performance and speed (C).

Common network that deals with negative emotional material & cognitive control to deal with it;
Grey matter decrease in healthy is associated with EF & Attention decrease

Common grey matter loss (Insula/ACC) network in multiple MI

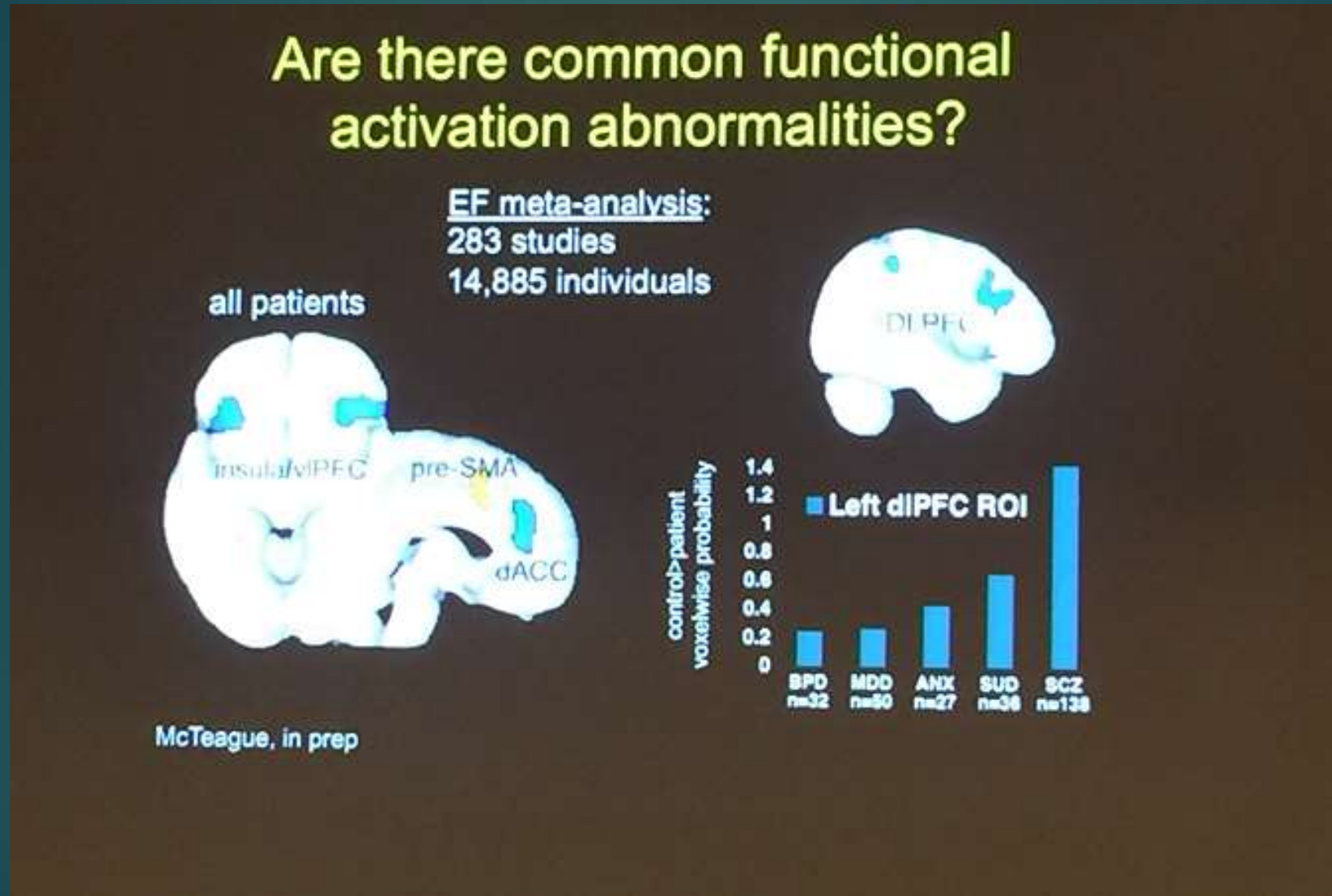
Figure 3. Extracted per-Voxel Probabilities of Decreased Gray Matter in the Voxel-Based Morphometry Meta-analysis, Separated by Individual Diagnosis and Common Gray Matter Loss Region (Left and Right Anterior Insula)



Values represent the probability of identifying a gray matter abnormality for an average voxel within the region of interest, derived from the modeled activation maps. ANX indicates anxiety disorders; BPD, bipolar disorder; dACC, dorsal anterior cingulate; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SCZ, schizophrenia; and SUD, substance use disorder.

^a $P < .05$ for comparison of the psychotic with the nonpsychotic disorders.

Functional activation abnormalities: Left dIPFC

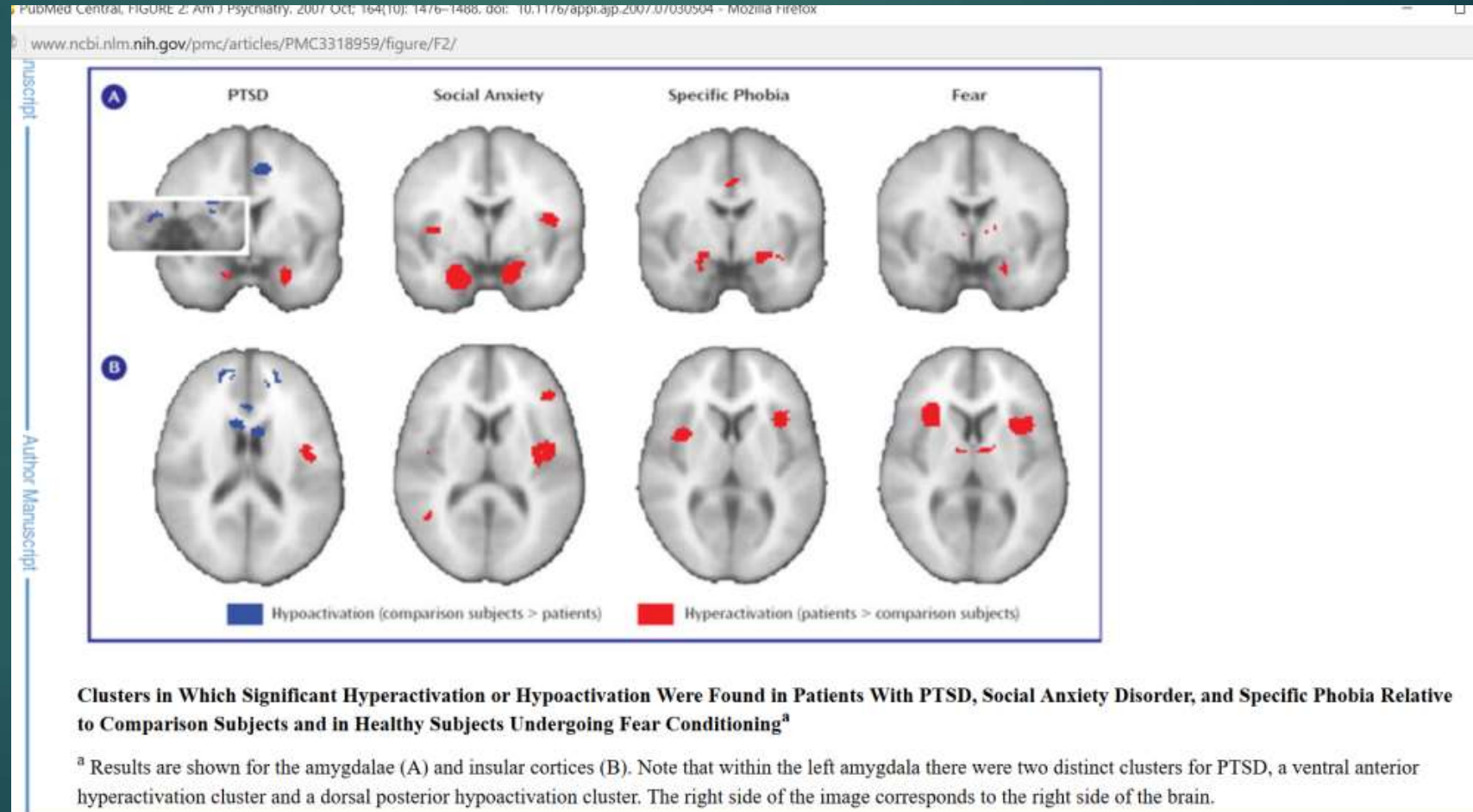


Transdiagnostic dimensional structure of PTSD, MDD, & GAD symptoms

- ▶ Three of the most common trauma-related mental disorders—posttraumatic stress disorder (PTSD), major depressive disorder (MDD), and generalized anxiety disorder (GAD)—are highly comorbid and share common transdiagnostic symptom dimensions of threat (i.e., fear) and loss (i.e., dysphoria) symptomatology.
- ▶ Exploratory factor analysis revealed that a 3-factor transdiagnostic model comprised of:
 - ▶ loss (i.e., dysphoria),
 - ▶ threat (i.e., anxious arousal, re-experiencing, and avoidance symptoms),
 - ▶ somatic anxiety (i.e., physiological manifestations of anxiety) symptoms provided the best representation of trauma-related PTSD, MDD, and GAD symptoms.

Functional Neuroimaging of Anxiety: A Meta-Analysis of Emotional Processing in PTSD, Social Anxiety Disorder, and Specific Phobia

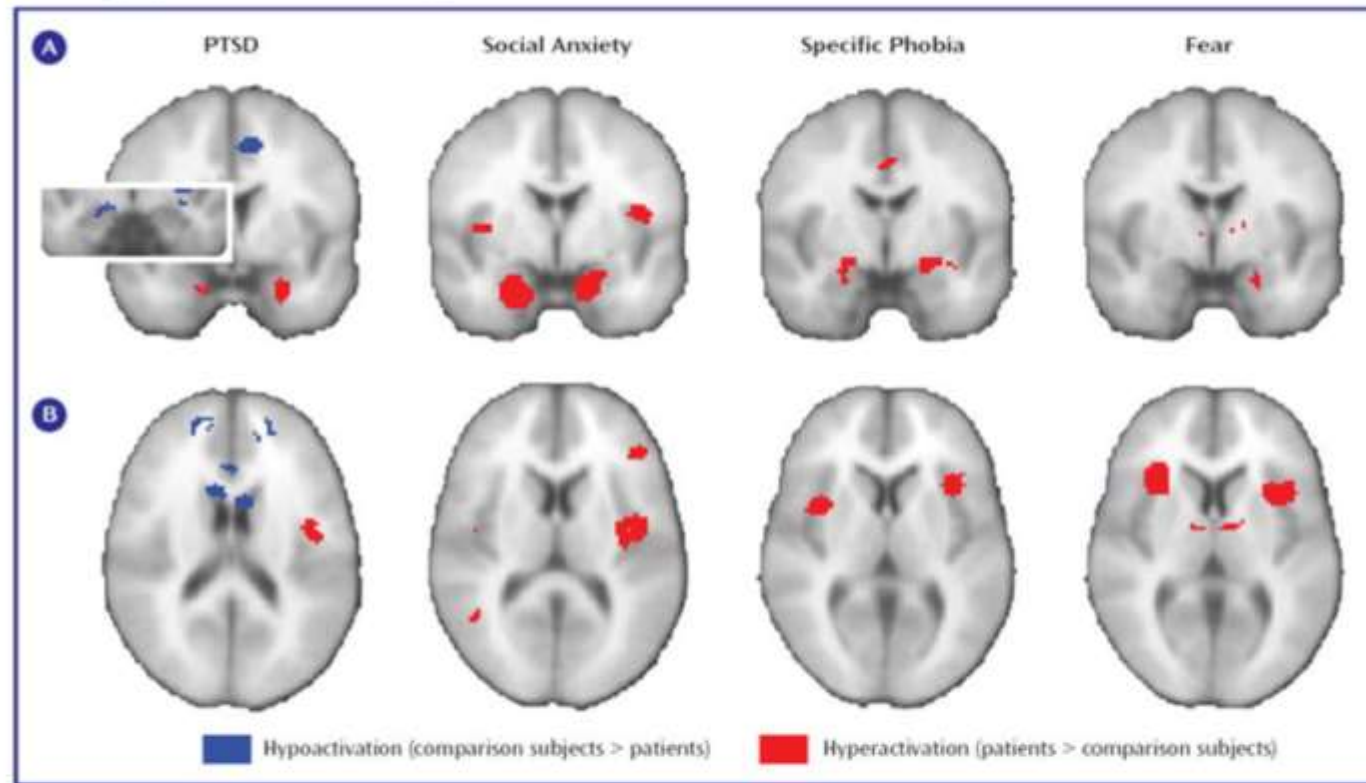
Red =
Hyperactive
Amygdala &
Insula



Etkin and Wager, 2007:

PTSD, Social Anxiety Disorder, and Phobias

- ▶ Patients with any of the three disorders consistently showed greater activity than matched comparison subjects in the amygdala and insula, structures linked to negative emotional responses.
- ▶ A similar pattern was observed during fear conditioning in healthy subjects. Hyperactivation in the amygdala and insula were more frequently observed in social anxiety disorder and specific phobia than in PTSD.
- ▶ By contrast, only patients with PTSD showed hypoactivation in the dorsal and rostral anterior cingulate cortices and the ventromedial prefrontal cortex-
structures linked to the experience and regulation of emotion.
- ▶ Provided neuroimaging evidence for common brain mechanisms in anxiety disorders and normal fear. Effects unique to PTSD furthermore suggested a mechanism for the emotional dysregulation symptoms in PTSD that extend beyond an exaggerated fear response.



Clusters in Which Significant Hyperactivation or Hypoactivation Were Found in Patients With PTSD, Social Anxiety Disorder, and Specific Phobia Relative to Comparison Subjects and in Healthy Subjects Undergoing Fear Conditioning^a

^a Results are shown for the amygdalae (A) and insular cortices (B). Note that within the left amygdala there were two distinct clusters for PTSD, a ventral anterior hyperactivation cluster and a dorsal posterior hypoactivation cluster. The right side of the image corresponds to the right side of the brain.

Fear and avoidance

- ▶ Fear and avoidance of trigger cues are common to many anxiety disorders and resemble the arousal and avoidance responses shown by normal subjects to conditioned fear cues.
- ▶ Thus, a common element of anxiety disorders may be an abnormally elevated fear response.
- ▶ Based on animal models of fear learning, this hypothesis leads to the prediction that amygdalar dysfunction is common to a variety of anxiety disorders. Indeed, amygdalar hyperactivity has been observed during symptom provocation or negative emotional processing in patients with posttraumatic stress disorder (PTSD), social anxiety disorder, specific phobia, panic disorder, and obsessive-compulsive disorder (OCD).

Amygdala & Insula activation

- ▶ A similar pattern was observed during fear conditioning in healthy subjects.
- ▶ Hyperactivation in the amygdala and insula were, of interest, more frequently observed in social anxiety disorder and specific phobia than in PTSD.
- ▶ By contrast, only patients with PTSD showed hypoactivation in the dorsal and rostral anterior cingulate cortices and the ventromedial prefrontal cortex—structures linked to the experience and regulation of emotion; a mechanism for the emotional dysregulation symptoms in PTSD that extend beyond an exaggerated fear response.

Shared amygdalar and insula hyperactivation

- ▶ Meta-analysis revealed consistent amygdalar hyperactivity in all three disorders.
- ▶ Amygdalar hyperactivation in PTSD, social anxiety disorder, and specific phobia reflects a common exaggerated engagement of fear circuitry, which results in shared symptoms among the disorders.
- ▶ Amygdala and insula hyperactivation may be key components of a common neurobiological pathway for at least the three anxiety disorders studied, which may reflect overactivation of a core fear system

Top-down inhibition

- ▶ Monitoring of emotional conflict was associated with dorsomedial prefrontal activation, whereas resolution of emotional conflict was associated with rostral anterior cingulate cortex increases and amygdala decreases, consistent with its top-down inhibition.
- ▶ Extinction of conditioned fear: increased activity in the rostral anterior cingulate cortex and ventromedial prefrontal cortex and decreased activity in the amygdala.
- ▶ Rostral anterior cingulate cortex activation and amygdala decreases have been observed during placebo anxiolysis,
- ▶ Placebo-induced increases in mu-opioid activity have been found in the rostral anterior cingulate cortex, the ventromedial prefrontal cortex, and the amygdala while the subject was experiencing pain.
- ▶ Emotional control processes mediated by the rostral anterior cingulate cortex/ventromedial prefrontal cortex may reflect an individual's emotional coping or resilience mechanisms,

PTSD: hypoactivations in vmPFC

- ▶ Rostral anterior cingulate cortex/ventromedial prefrontal cortex dysfunction in PTSD
- ▶ Stress inoculation may inform approaches at enhancing medial prefrontal emotion regulation systems.
- ▶ Only PTSD featured prominent hypoactivations (comparison subjects > patients), which were seen in the ventromedial prefrontal cortex, rostral and dorsal anterior cingulate cortex, and thalamus, regions associated with the experience or regulation of emotion.

Emotional Processing

- ▶ Conflict regulation, a test of implicit regulation of emotional processing.
- ▶ Behavioral data indicated that only patients with generalized anxiety (i.e., the anxiety-only and comorbid groups) failed to implicitly regulate emotional conflict. By contrast, deficits in activation and connectivity of the ventral anterior cingulate and amygdala, areas previously implicated in regulating emotional conflict, were found in all patient groups.
- ▶ Depression-only patients, however, compensated for this deficit by also activating the left and right anterior lateral prefrontal cortices, in which activity was correlated with behavioral evidence of successful implicit regulation, thus mediating the disorder-specificity of the behavioral phenotype.
- ▶ These data support the existence of a common abnormality in anxiety and depression in the ventral cingulate and the amygdala, which may be related to a shared genetic etiology.

GAD: poor ACC and mPFC control

- ▶ Patients with GAD were completely unable to regulate emotional conflict and failed to engage the pregenual anterior cingulate in ways that would dampen amygdalar activity.
- ▶ Patients with GAD show significant deficits in regulation of emotional processing.
- ▶ Conceptualization of anxiety as importantly involving abnormalities in emotion regulation, particularly a type occurring outside of awareness, may open up avenues for novel treatments, such as by targeting the medial prefrontal cortex.

GAD: decreased connectivity in insula & ACC salience network

- ▶ Across the subregions, GAD patients had increased connectivity with a previously characterized frontoparietal executive control network and decreased connectivity with an insula- and cingulate-based salience network.
- ▶ In GAD, we find evidence of an intra-amygdalar abnormality and engagement of a compensatory frontoparietal executive control network, consistent with cognitive theories of GAD.

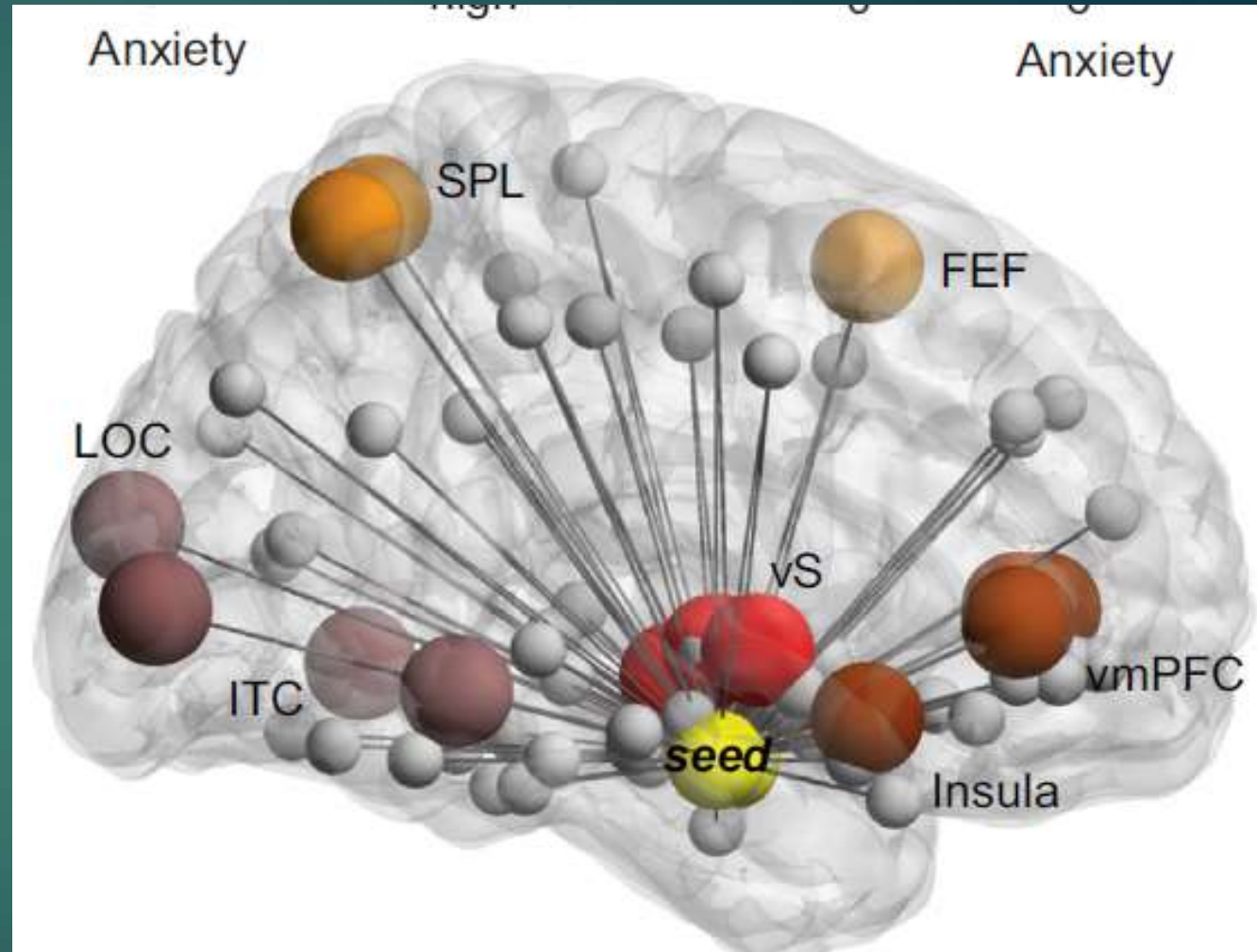
Qin 2014: stress and larger amygdala

- ▶ Stress and anxiety in early life are associated with greater dendritic arborization and aberrant pruning of synapses over development, leading into an increased rate of growth in amygdala linked to prolonged activation of stress hormones, such as cortisol,
- ▶ A high childhood anxiety is predicted by increased connectivity of the amygdala, and the BLA in particular, with multiple distributed brain regions involved in emotion.

Hyper connectivity of Basolateral Amygdala to 4 systems

4 areas:

- 1) sensory and perceptual system (lateral occipital and inferior temporal cortices);
- 2) Frontoparietal attentional system (frontal eye field and superior parietal lobe);
- 3) Striatal reward and motivational system (ventral striatum);
- 4) Saliency and emotion regulation system (anterior insula and vmPFC).



Evidence for serotonergic dissociation between anxiety, fear

- ▶ Confirmed Deakin and Graeff's Theory: acute reductions in serotonergic levels would cause important worsening of symptoms in patients with a subgroup of disorders more related to fear, but not in those with psychiatric disorders more related to anxiety
- ▶ Serotonin is critical to prevent fear (panic) but not anxiety.

NP of anxiety disorders

- ▶ Overall, the total anxiety disorder group exhibited significant impairments in episodic memory and executive functioning.
- ▶ Panic disorder and OCD were related to impairments in both episodic memory and executive functioning.
- ▶ Social phobia was associated with episodic memory dysfunction.
- ▶ Verbal fluency and psychomotor speed were not affected by anxiety.
- ▶ Specific phobia and GAD: no NP deficits.

Neurobiology of GAD

- ▶ Overactive ACC
- ▶ Elevated Norepinephrine levels
- ▶ Overactive basal ganglia
- ▶ Serotonin deficits affecting limbic system & PFC
- ▶ Insufficiency of GABA receptors &/or HPA overactivity

GAD & DTI of Uncinate fasciculus

- ▶ Reduced integrity of the uncinate fasciculus, a crucial white matter pathway linking ventral PFC and ACC to limbic regions, in patients with GAD.
- ▶ Suggest weak top-down control of amygdala reactivity.
- ▶ Worry, the hallmark feature of GAD may actually sensitize amygdala activity, resulting in a generalized state of heightened anxiety

NP deficits in GAD

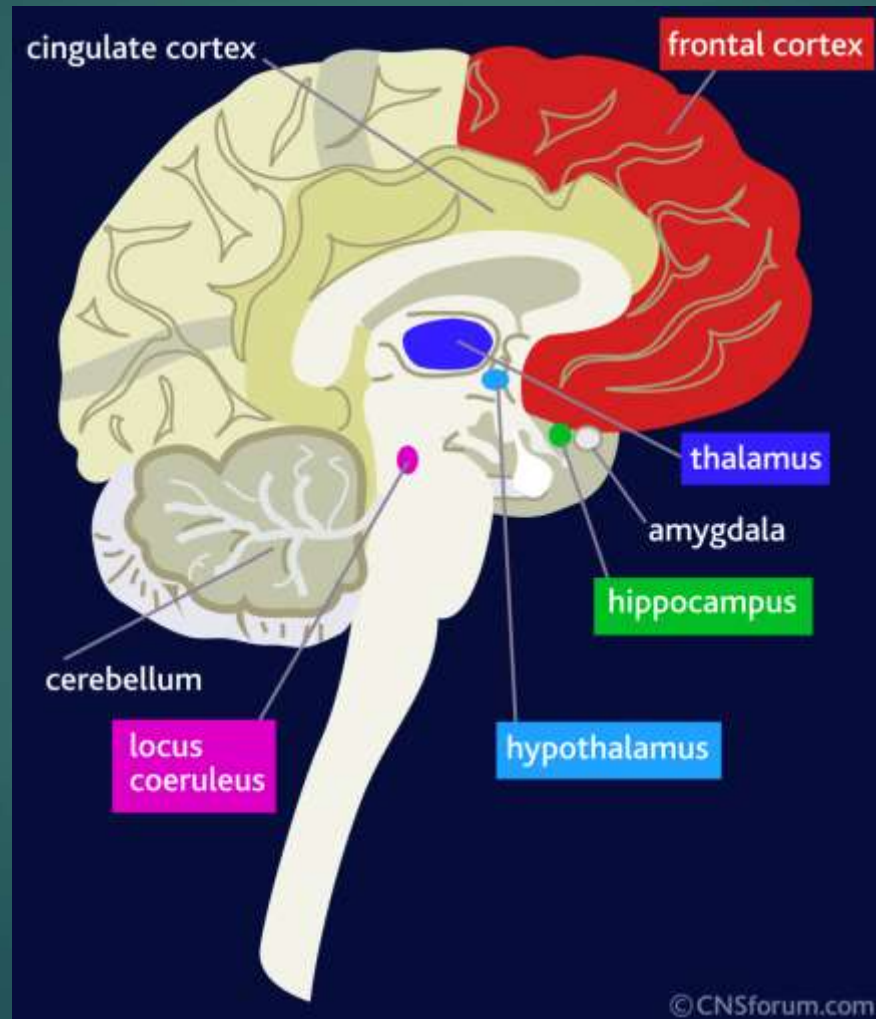
- ▶ GAD pts: Anxiety effects
 - ▶ Strong effect on:
 - ▶ working memory
 - ▶ processing speed
 - ▶ RT
 - ▶ attention,
 - ▶ cognitive flexibility
 - ▶ Test effects: Stroop, CPT, Shifting Attention Test, CVLT
 - ▶ Attentional bias for wide range of negative external stimuli

The Neuropsychology Of PTSD

Stuck information Processing

After two clinical rotations at the Salpetriere, Sigmund Freud, with Joseph Breuer, reported that in case of traumatic stress: “The . . . *memory of the trauma . . . acts like a foreign body which long after its entry must be regarded as an agent that is still at work. . . . If a [motor] reaction is suppressed [the affect] stays attached to the memory. It may therefore be said that the ideas which have become pathological have persisted with such freshness and affective strength because they have been denied the normal wearing-away processes by means of abreaction and reproduction in states of uninhibited association*” (Breuer and Freud, 1893, pp. 7–11).

Neuropsychology of PTSD



Post-traumatic and Acute Stress Disorders

- ▶ PTSD: Persistent anxiety following an overwhelming traumatic event that occurs outside the range of usual human experience
 - ▶ Three core features of PTSD are:
 - ▶ persistent re-experiencing of the event
 - ▶ persistent avoidance of associated stimuli and numbing of general responsiveness
 - ▶ persistent symptoms of extreme arousal
- ▶ Acute stress disorder: Development of at least three dissociative symptoms within one month after a traumatic experience, lasting at least two days but not longer than a month (short-lived)

Post-traumatic and Acute Stress Disorders 2

▶ Prevalence and Comorbidity

- ▶ Although at least 2/3 of children experience at least one potentially traumatic event by age 16, most do not develop PTSD
- ▶ A large national sample: Six-month prevalence for adolescents ages 12-17 was 3.7% for boys, 6.3% for girls
 - ▶ Comorbidity: depression and/or substance abuse

▶ Onset, Course, and Outcome

- ▶ Onset and course depend on age of child when trauma occurs and nature of the trauma; onset may be delayed for months or years
- ▶ In some cases may persist for a lifetime
- ▶ Many factors affect recovery, like nature of the traumatic event, child characteristics, social support

Childhood trauma Sequelae

- ▶ Severe and prolonged childhood trauma has dire consequences:
Compared with normals
- ▶ 4 to 12 times greater risk to develop alcoholism, depression, drug abuse and suicide attempts.
- ▶ 2 to 4 times greater risk for smoking, having had ≥ 50 sex partners, leading to increased incidence of sexually transmitted disease
- ▶ 1.4 to 1.6 times greater risk for physical inactivity and obesity
- ▶ 1.6 to 2.9 times greater risk for ischemic heart disease, cancer, chronic lung disease, skeletal fractures, hepatitis, stroke, diabetes, and liver disease (Felletti et al., 1998)

PTSD DSM-5 criteria

- ▶ Note: The following criteria apply to adults, adolescents, and children older than six. There is a Pre-school Subtype for children age six and younger (see below).
- ▶ A. Exposure to actual or threatened a) death, b) serious injury, or c) sexual violation, in one or more of the following ways:
 - ▶ 1. directly experiencing the traumatic event(s)
 - ▶ 2. witnessing, in person, the traumatic event(s) as they occurred to others
 - ▶ 3. learning that the traumatic event(s) occurred to a close family member or close friend; cases of actual or threatened death must have been violent or accidental
 - ▶ 4. experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse); this does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work-related.

DSM-5 PTSD Continued

- ▶ Criterion A.2 requiring fear, helplessness or horror in DSM-IV-TR has been removed.
- ▶ Both A.1 and A.2 are required.
- ▶ DSM-IV-TR required that the “person's response involved intense fear, helplessness, or horror.” DSM-5 has eliminated this requirement that the individual have an active awareness of the experience.

PTSD Continued

- ▶ The individual must
- ▶ 1. directly experiencing the traumatic event(s)
- ▶ 2. witnessing, in person, the traumatic event(s) as they occurred to others
- ▶ 3. learning that the traumatic event(s) occurred to a close family member or close friend; cases of actual or threatened death must have been violent or accidental
- ▶ 4. experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse); this does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work-related.

PTSD Criteria

- ▶ Duration is more than one month.
- ▶ Re-experiencing:
 - ▶ Recurrent and intrusive distressing recollections of the event.
 - ▶ Recurrent distressing dreams
 - ▶ Re-experiencing (dreams, flashbacks, hallucinations).
- ▶ Distress at exposure to traumatic stimuli
- ▶ Physiological reactivity to traumatic stimuli

Ptsd Criteria

- ▶ Avoidance:
- ▶ Of thoughts, feelings, conversations, activities, places or people.
- ▶ Inability to recall an aspect of the trauma.
- ▶ Diminished interest in significant activities
- ▶ Feeling detached or estranged from others
- ▶ Restricted range of affect
- ▶ Sense of foreshortened future.
- ▶ Increased arousal:
- ▶ Difficulty falling or staying asleep, irritability, anger, difficulty concentrating, hypervigilance, exaggerated startle response.

PTSD Overview

- ▶ Posttraumatic stress disorder (PTSD) is an anxiety disorder that a person may develop after experiencing or witnessing an extreme, overwhelming traumatic event during which they felt intense fear, helplessness, or horror.
- ▶ The dominant features of PTSD are
 - ▶ emotional numbing (i.e., emotional nonresponsiveness),
 - ▶ hyperarousal (e.g., irritability, on constant alert for danger),
 - ▶ reexperiencing of the trauma (e.g., flashbacks, intrusive emotions).

Complex vs Single Incident PTSD

- ▶ Lenore Terr originally distinguished Type 1 vs Type 2 PTSD.
- ▶ Type 1 is Single traumatic incident.
- ▶ Type 2 is repeated, long-term, ongoing trauma. Type 2 often presents as dissociative symptoms, numbing, avoidance and emotional instability.
- ▶ Typically in Type 2, Complex PTSD, stabilization must occur before treating the trauma with exposure, and treatment is more lengthy.

Prevalence

- ▶ The National Comorbidity Survey Replication (NCS-R), conducted between February 2001 and April 2003, comprised interviews of a nationally representative sample of 9,282 Americans aged 18 years and older. PTSD was assessed among 5,692 participants, using DSM-IV criteria.
- ▶ Lifetime prevalence of PTSD among adult Americans to be 6.8%
- ▶ Current past year PTSD prevalence was estimated at 3.5%
- ▶ The lifetime prevalence of PTSD among men was 3.6% and among women was 9.7%.
- ▶ The twelve month prevalence was 1.8% among men and 5.2% among women (3).

Prevalence in special populations

- ▶ Medical Patients: An examination of the records of the 384,000 Medicaid recipients in Massachusetts in 1997/98 (Macy et al., 2002) revealed that PTSD had the same prevalence as depression.
- ▶ The estimated lifetime prevalence of PTSD among these Veterans was 30.9% for men and 26.9% for women.
- ▶ Of Vietnam theater Veterans, 15.2% of males and 8.1% of females were currently diagnosed with PTSD. (Kulka et al 1990)

PTSD Overview

Some of the disorders that must be ruled out when diagnosing PTSD include the following:

- ▶ Acute stress disorder (duration of up to 4 weeks)
- ▶ Adjustment disorder (less severe stressor or different symptom pattern)
- ▶ Mood disorder or other anxiety disorder (symptoms of avoidance, numbing, or hyperarousal are present before exposure to the stressor)
- ▶ Other disorders with intrusive thoughts or perceptual disturbances (obsessive compulsive disorder, schizophrenia, other psychotic disorder)
- ▶ Substance abuse or dependence disorder
- ▶ Furthermore, malingerers — that is, people who falsely claim to be traumatized—sometimes feign PTSD symptoms in order to win money in a court case as compensation for "emotional suffering."

Criterion for PTSD

The person has been exposed to a traumatic event in which both of the following have been present:

1. The person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others.
2. The person's response involved intense fear, helplessness, or horror.
Note: in children, it may be expressed instead by disorganized or agitated behavior.

Symptoms of PTSD are grouped into 3 Categories

1 - Intrusive elements:

- ▶ Recurrent and intrusive distressing recollections of the event.
- ▶ Recurrent dreams of the event
- ▶ Sudden acting or feeling as if the traumatic event were recurring
- ▶ Intense psychological distress at exposure to things that symbolizes or resembles an aspect of the trauma, including anniversaries thereof.
- ▶ Physiological reactivity when exposed to internal or external cues of the event.
- ▶ At least one of these symptoms to be diagnosed with PTSD

2 - Avoidance Features

- ▶ Efforts to avoid the thought or feelings associated with the trauma
- ▶ Efforts to avoid activities, places, people or situations that arouse recollection of the trauma.
- ▶ Inability to recall an important aspect of the trauma (psychological amnesia)
- ▶ Markedly diminish interest in significant activities
- ▶ Feelings of detachment or estrangement from others
- ▶ Restricted range of affect-unable to have loving feelings
- ▶ Sense of foreshortened future- does not expect to have career, marriage, children or normal life span.

At least three of these symptoms to be diagnosed with PTSD

3 - Persistent symptoms of increased arousal (not present before trauma)

- ▶ Difficulty falling asleep or staying asleep
- ▶ Irritability or outburst of anger-irritability can progress to rage
- ▶ Difficulty concentrating
- ▶ Hypervigilance- resembles frank paranoia
- ▶ Exaggerated startled response

At least two of these symptoms to be diagnosed with PTSD

Recap...

- ▶ 1 or more Re-experiencing symptom
- ▶ 3 or more Avoidance symptoms
- ▶ 2 or more Increased arousal symptoms
- ▶ All of which must be present for a duration of more than 1 month and causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Types of PTSD

- ▶ Acute PTSD - symptoms less than three months
- ▶ Chronic PTSD - symptoms more than three months
- ▶ Although symptoms usually begin within 3 months of exposure, a delayed onset is possible months or even years after the event has occurred.

[Can J Psychiatry, Vol 51, Suppl 2, July 2006]

Diagnosis of PTSD

- ▶ There are no laboratory tests to detect PTSD.
- ▶ To diagnose PTSD, a healthcare provider will consider the above symptoms together with history of trauma. He or she will likely also use psychological assessment tools to confirm the diagnosis and involve an appropriately trained specialist
- ▶ Although it may be tempting to diagnosis yourself, the diagnosis should be made by a mental health professional. This usually involves a a formal evaluation.

Associated Characteristics

▶ Cognitive Disturbances:

- ▶ Disturbance in how information is perceived and processed
- ▶ Intelligence and Academic Achievement: Despite normal intelligence, deficits are seen in memory, attention, and speech or language
 - ▶ High levels of anxiety can interfere with academic performance; those with generalized social anxiety may drop out of school prematurely
- ▶ Threat-Related Attentional Biases: selective attention to potentially threatening/dangerous information
 - ▶ Anxious vigilance or hypervigilance permits the child to avoid potentially threatening events
- ▶ Cognitive Errors and Biases
 - ▶ Perceptions of threats activate danger-confirming thoughts
 - ▶ See themselves as having less control over anxiety-related events than other children

Associated Characteristics

▶ Physical Symptoms

- ▶ Somatic complaints such as stomachaches or headaches, more common in children with PD and SAD than those with specific phobia
- ▶ More frequent in adolescents than in younger children and in children who display school refusal
- ▶ 90% have sleep-related problems, including nocturnal panic (abrupt waking in a state of extreme anxiety similar to daytime panic attack)

Associated Characteristics

- ▶ Social and Emotional Deficits
 - ▶ Low social performance/high social anxiety
 - ▶ Social withdrawal, loneliness, low self-esteem, difficulty initiating and maintaining friendships
 - ▶ Deficits in understanding emotion/differentiating between thoughts and feelings
- ▶ Anxiety and Depression: Social phobia, GAD, SAD, and multiple anxiety disorders (not specific phobia) commonly associated with depression
 - ▶ May reflect pathways from anxiety to depression
 - ▶ genetically mediated for GAD and phobic symptoms
 - ▶ shared environment for persistent SAD and later GAD
 - ▶ Negative affectivity is related to anxiety and depression

Gender, Ethnicity, and Culture

- ▶ Higher incidence in girls likely due to genetic vulnerabilities and gender role orientations
- ▶ Cultural differences in patterns of referral, help-seeking behaviors, diagnoses, and treatment may be related to parental education
- ▶ The experience of anxiety is pervasive across cultures
- ▶ Ethnicity and culture may affect the expression, developmental course, and interpretation of anxiety symptoms
- ▶ Cultural differences in traditions, beliefs, and practices affect occurrence and symptoms of anxiety
- ▶ Behavior lens principle: Child psychopathology reflects a mix of actual child behavior and the lens through which others view it in a child's culture

Age of Onset and Cultural Features

- ▶ Can occur at any age, including childhood, and can affect anyone.
- ▶ Individuals who have recently immigrated from areas of considerable social unrest and civil conflict may have elevated rates of PTSD.
- ▶ No clear evidence that members of different ethnic or minority groups are more or less susceptible than others.

Onset

- ▶ Symptoms usually begin within the first 3 months after the trauma, although there may be a delay of months, or even years, before symptoms appear.

Immediate Onset

- ▶ Better response to treatment
- ▶ Better prognosis (i.e., less severe symptoms)
- ▶ Fewer associated symptoms or complications
- ▶ Symptoms are resolved within 6 months

Delayed Onset

- ▶ Characterized by an onset of symptoms at least 6 months after the stressor
- ▶ Associated symptoms and conditions develop
- ▶ Condition more likely to become chronic
- ▶ Possible repressed memories
- ▶ Worse prognosis

Course

- ▶ The symptoms and the relative predominance of re-experiencing, avoidance, and increased arousal symptoms may vary over time.
- ▶ Duration of symptoms also varies: Complete recovery occurs within 3 months after the trauma in approximately half of the cases. Others can have persisting symptoms for longer than 12 months after the trauma.
- ▶ Symptom reactivation may occur in response to reminders of the original trauma, life stressors, or new traumatic events.

Course 2

- ▶ The severity, duration, and proximity of an individual's exposure to a traumatic event are the most important factors affecting the likelihood of developing PTSD.
- ▶ Social supports, family history, childhood experiences, personality variables, and pre-existing mental disorders may influence the development of PTSD.
- ▶ PTSD can also develop in individuals without any predisposing conditions, particularly if the stressor is extreme.
- ▶ The disorder may be especially severe or long lasting when the stressor is of human design (torture, rape).

Possible Causes

A person develops PTSD in response to exposure to an extreme traumatic stressor involving direct personal experience of an event.

This includes:

- ▶ actual or threatened death or serious injury
- ▶ threat to one's physical integrity
- ▶ witnessing an event that involves death, injury, or a threat to the physical integrity of another person
- ▶ learning about unexpected or violent death, serious harm, or threat of death or injury experienced by a family member or other close associate

Examples of Traumatic Events Experienced Directly

- ▶ Military combat
- ▶ Violent personal assault (sexual assault, physical attack, robbery, mugging)
- ▶ Being kidnapped
- ▶ Being taken hostage
- ▶ Terrorist attack
- ▶ Torture
- ▶ Incarceration as a prisoner of war or in a concentration camp
- ▶ Natural or manmade disasters
- ▶ Severe automobile accidents
- ▶ Being diagnosed with a life-threatening illness

Examples of Witnessed Traumatic Events

- ▶ Observing the serious injury or unnatural death of another person due to violent assault, accident, war, or disaster
- ▶ Unexpectedly witnessing a dead body or body parts

Examples of Events Experienced by Others that are Learned About

- ▶ Learning of a violent personal assault, serious accident, or serious injury experienced by a family member or a close friend
- ▶ Learning of a sudden, unexpected death of a family member or a close friend
- ▶ Learning that one's child has a life-threatening disease

Chance of Developing PTSD

- ▶ Likelihood of developing this disorder may increase as the intensity of and physical proximity to the stressors increase.
- ▶ There is evidence of a heritable component to the transmission of PTSD
 - A history of depression in relatives has been related to an increased vulnerability to developing PTSD.

Prevalence

- ▶ Approximately 70% of adults in the United States have experienced a traumatic event at least once in their lifetime. Up to 20% of these people will go on to develop PTSD.
- ▶ An estimated 5.2 million American adults ages 18-54 have PTSD (or approximately 3.6%).
- ▶ Women are about twice as likely as men to develop PTSD.
- ▶ Approximately 30% of Vietnam veterans developed PTSD at some point after the war and 8% after the Persian Gulf War.

Estimated Risk for Developing PTSD Based on Event

- ▶ Rape (49%)
- ▶ Severe beating or physical assault (31.9%)
- ▶ Other sexual assault (23.7%)
- ▶ Serious accident or injury (i.e. car or train accident) (16.8%)
- ▶ Shooting or stabbing (15.4%)
- ▶ Sudden, unexpected death of family member or friend (14.3%)
- ▶ Child's life-threatening illness (10.4%)
- ▶ Witness to killing of serious injury (7.3%)
- ▶ Natural Disaster (3.8%)

www.ptsdalliance.org

www.nimh.nih.gov/publicat/reliving.cfm

The Evaluation

- ▶ The nature of the evaluation for PTSD can vary widely depending on how the evaluation will be used and the training of the professional evaluator.
- ▶ An interview may take anywhere from 15 minutes to eight or more 1 hour sessions when the information is needed for legal or disability claims.
- ▶ Regardless of the length of the evaluation, it will include in-depth questioning of the traumatic event and symptoms being experienced as a result of these experiences.

Evaluation

More thorough assessments are likely to include:

- ▶ Detailed structured interviews and psychological tests
- ▶ Close family member may be asked to provide more information
- ▶ Client may undergo a procedure that examines your physiological reactions (heart rate, blood pressure, plasma NE measurements) to mild reminders of your trauma.

Assessment Tools

- ▶ Two main categories of PTSD evaluations are structured interviews and self report questionnaires.
- ▶ Interviews
- ▶ Clinician Administered PTSD Scale (CAPS) developed by National Center for PTSD
- ▶ It has a format that requests information about the frequency and intensity of the core PTSD symptoms and common associated symptoms which may have implications on treatment and recovery. The CAPS-1 yields both continuous and dichotomous scores for current and lifetime PTSD symptoms.

Treatment Outcome PTSD Scale (TOP-8)

- ▶ It is shorter, is easier to use, and is highly correlated with the CAPS, which is more time-consuming and less practical for use in clinical practice
- ▶ Scores:
 - 5 or less reflects no or minimal PTSD symptoms
 - 7 equals mild symptoms
 - 15 moderate symptoms
 - 21 indicates severe symptoms
- ▶ Remission in PTSD should be defined as no longer meeting the diagnostic criteria for the disorder, full functionality, and no or minimal anxiety and depression symptoms.

Other Interviews

- ▶ Structured Clinical interview for DSM (SCID) used in assessment of a range of psychiatric disorder including PTSD
- ▶ Anxiety Disorder Interview Schedule revised (ADIS)
- ▶ Structured Interview for PTSD (SI-PTSD)
- ▶ PTSD Symptom Scale Interview (PSS-I)
- ▶ Each has unique features

Self Report Questionnaires

- ▶ Several self-report measures have been developed as a cost and time efficient way of obtaining information about PTSD distress.
- ▶ These measures provide a single score representing the amount of distress an individual is experiencing.
- ▶ PTSD Checklist-- This measure comes in two versions. One is for civilians and another specifically designed for military personnel and veterans.
- ▶ Impact of Event Scale-Revised (IES-R)
- ▶ Kean PTSD Scale of the MMPI-2
- ▶ Mississippi Scale for Combat Related PTSD and the Mississippi Scale for Civilians
- ▶ The Post traumatic Diagnostic Scale (PDS)
- ▶ And many more...

Symptoms in Preadolescents and Adolescents

- ▶ With age, symptoms become increasingly similar to adult manifestations (*Cohen et al., 2000*).
- ▶ However, for adolescents, abstract conceptions of identity, future, safety, and connection are vulnerable to alterations. (*Cook-Cottone, 2000; Johnson, 1998*)
- ▶ For example—a sense of foreshortened future (e.g., diminished expectations of getting married, establishing a career, and experiencing a normal life span).
- ▶ Those with chronic PTSD may present with self-injurious behaviors, suicidal ideation, conduct problems, dissociation, derealization, depersonalization, and/or substance abuse, which can mask the posttraumatic etiology of the disorder. (*Cohen et al., 2000; Johnson, 1998*)

Childhood Posttraumatic Stress Disorder: Diagnosis, Treatment, and School Reintegration., By: Cook-Cottone, Catherine,
School Psychology Review, 02796015, 2004, Vol. 33, Issue 1

PTSD and General Symptom Measures

- ▶ Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA)
- ▶ The Child PTSD Symptom Scale (CPSS)
- ▶ The CPTS-RI Revision 2
- ▶ Trauma Symptom Checklist for Children (TSCC)
- ▶ Trauma Symptom Checklist for Young Children (TSCYC)
- ▶ Child Posttraumatic Stress Reaction Index (CPTS-RI)
- ▶ Children's Impact of Traumatic Events Scale-Revised (CITES-2)
- ▶ Parent Report of Child's Reaction to Stress

Differential Diagnosis

Differential diagnosis of the disorder or problem; that is, what other disorders or problems may account for some or all of the symptoms or features.

PTSD is frequently co-morbid with other psychiatric disorders including:

- ▶ Anxiety disorders
- ▶ Acute Stress Disorder
- ▶ Obsessive compulsive disorder
- ▶ Adjustment disorder
- ▶ Depressive disorders
- ▶ Substance Abuse disorders

PTSD Compared to Other Disorders

While the symptoms of posttraumatic stress disorder (PTSD) may seem similar to those of other disorders, there are differences.

- ▶ Acute stress disorder
- ▶ Obsessive-compulsive disorder
- ▶ Adjustment disorder

Differences between Acute Stress Disorder

- ▶ In general, the symptoms of acute stress disorder must occur within four weeks of a traumatic event and come to an end within that four-week time period.
- ▶ If symptoms last longer than one month and follow other patterns common to PTSD, a person's diagnosis may change from acute stress disorder to PTSD.

Differences between PTSD and Obsessive-Compulsive Disorder

- ▶ Both have recurrent, intrusive thoughts as a symptom, but the types of thoughts are one way to distinguish these disorders.
- ▶ Thoughts present in obsessive-compulsive disorder do not usually relate to a past traumatic event. With PTSD, the thoughts are invariably connected to a past traumatic event.

Differences Between PTSD and Adjustment Disorder

- ▶ PTSD symptoms can also seem similar to adjustment disorder because both are linked with anxiety that develops after exposure to a stressor.
- ▶ With PTSD, this stressor is a traumatic event. With adjustment disorder, the stressor does not have to be severe or outside the “normal” human experience.

Differences Between PTSD and Depression

- ▶ Depression after trauma and PTSD both may present numbing and avoidance features, but depression would not induce hyperarousal or intrusive symptoms

PTSD Information

- ▶ It is important to ask all patients with mental health symptoms about trauma, particularly women suffering from treatment – resistant depression and those with general medical complaints, since patients with PTSD often present with somatic symptoms.

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NOTE:

- ▶ Although many who experience severe trauma will develop symptoms of PTSD, most individuals exposed to a traumatic event do not develop a psychiatric illness.

J Clin Psychiatry. Volume: 67Suppl2, Issue: 2006,

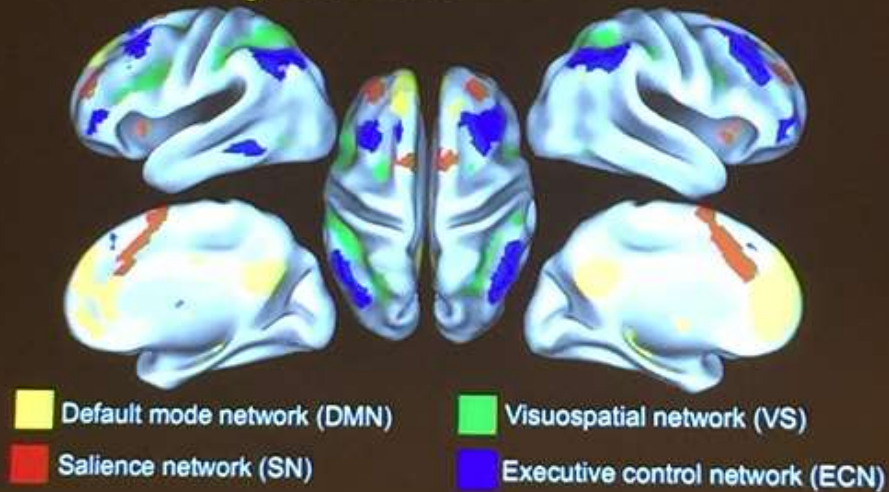
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Why PTSD Victims Might Be Resistant to Getting Help

- ▶ Sometimes hard because people expect to be able to handle a traumatic event on their own
- ▶ People may blame themselves
- ▶ Traumatic experience might be too painful to discuss
- ▶ Some people avoid the event all together
- ▶ PTSD can make some people feel isolated making it hard for them to get help
- ▶ People don't always make the connection between the traumatic event and the symptoms; anxiety, anger, and possible physical symptoms
- ▶ People often have more than one anxiety disorder or may suffer from depression or substance abuse

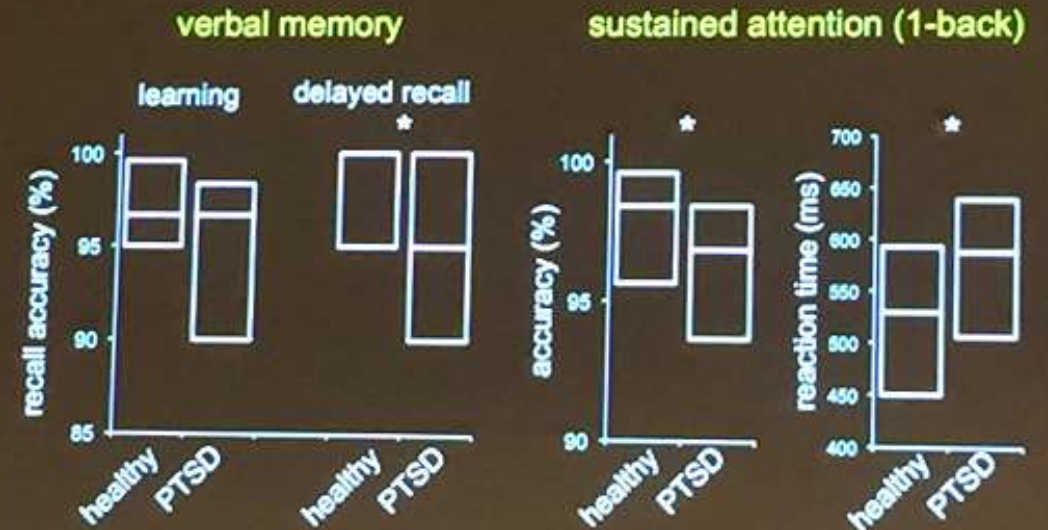
Cognitive Deficits in PTSD: Verbal memory & Sustained attention

Network basis of cognitive dysfunction: PTSD



Huemer, Patenaude et al (in prep)

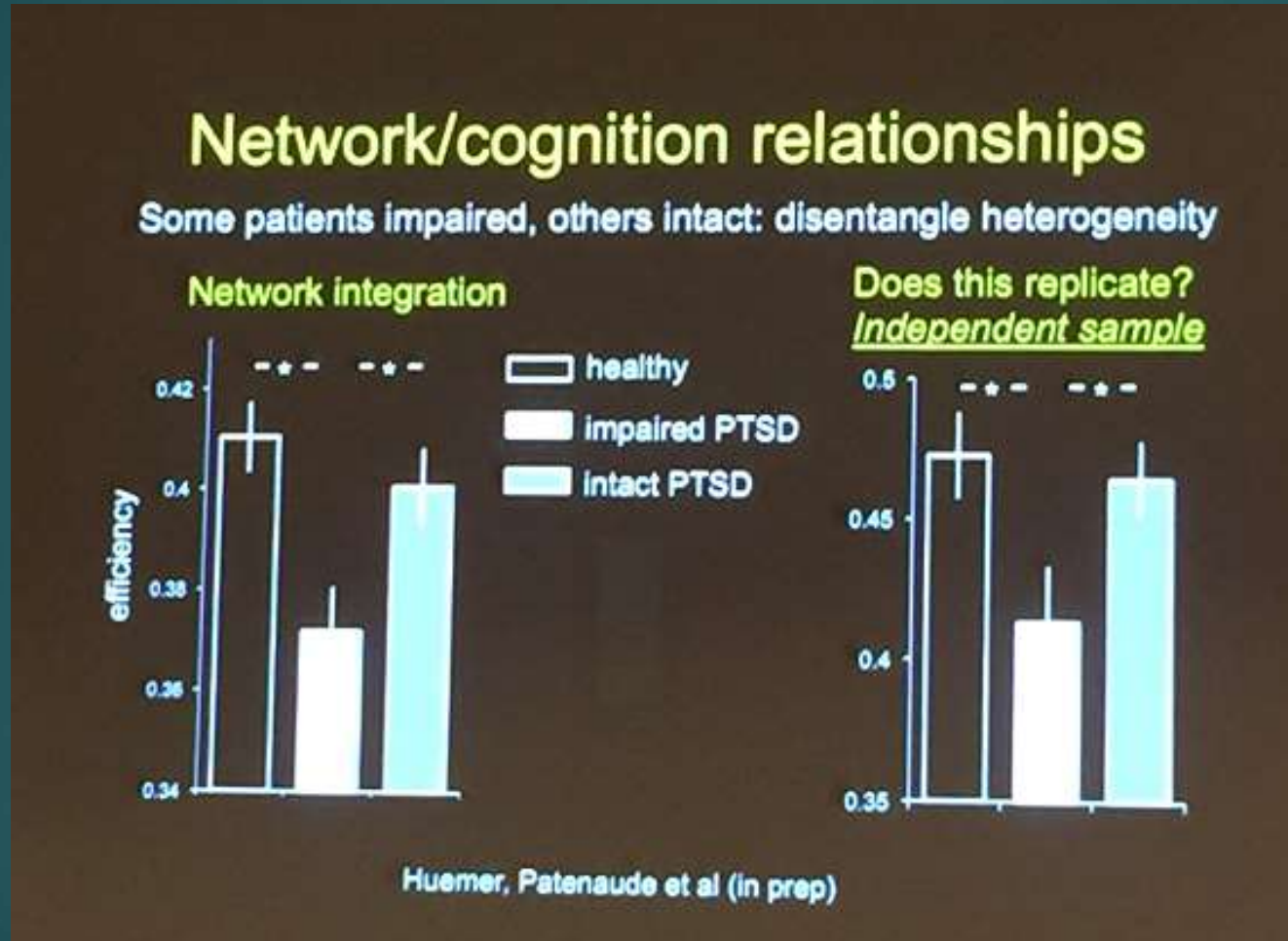
Cognitive deficits in PTSD



★ Related to integration or segregation?

Huemer, Patenaude et al (in prep)

PTSD is heterogeneous: some impaired, some not;
network integrity efficiency deficit only in impaired PTDS



Less network global efficiency in impaired PTSD

- ▶ The most effective treatments for PTSD are psychotherapies. These psychotherapies have primarily been trauma focused, involving imaginal or in-person exposure to traumatic reminders and other triggers.
- ▶ More cognitively focused psychotherapies also exist. Yet despite the efficacy of psychotherapy as a first-line treatment for PTSD, large individual differences in outcomes exist, with roughly only half of patients responding to treatment and fewer than that fully remitting.

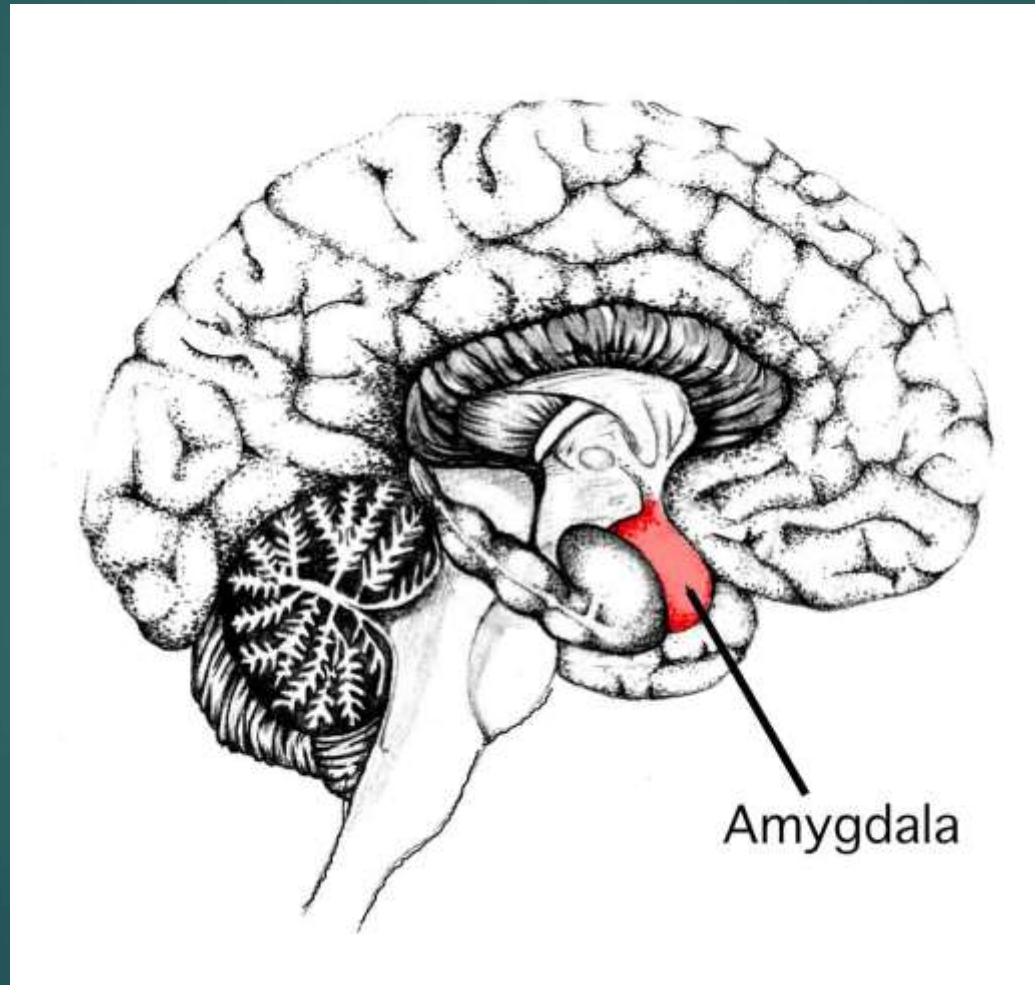
PTSD meta-analysis

- ▶ Meta-analyses of brain structure, brain function, and neuropsychological functioning in PTSD have demonstrated consistent impairments in systems important in emotion (including fear), memory, and executive functions.
- ▶ At the neuropsychological level, moderate effect size (i.e., Cohen $d \sim 0.5$) impairments have been observed in learning and memory and executive functions such as sustained attention. These functions involve overlapping neural circuitry in frontoparietal regions, with verbal memory additionally requiring frontal-hippocampal interactions.
- ▶ Impaired baseline verbal memory, measured during encoding and short- and long-term retrieval, predicted worse treatment outcome.

PTSD & GAD

- ▶ Anxiety and fear also functionally associate with different subdivisions of the hippocampus along its longitudinal axis:
 - ▶ the human posterior hippocampus is involved in memory, through connectivity with the medial prefrontal-medial parietal default-mode network,
 - ▶ while the anterior hippocampus is involved in anxiety, through connectivity with limbic-prefrontal circuits.
- ▶ As predicted, in healthy subjects resting-state connectivity dissociated between posterior hippocampal connectivity with the default-mode network, and anterior hippocampal connectivity to limbic-prefrontal circuitry.
- ▶ The posterior hippocampus and the associated default-mode network, across both resting-state connectivity and task-based measures, were perturbed in PTSD relative to each of the other groups.
- ▶ By contrast, we found only modest support for similarly blunted anterior hippocampal connectivity across both patient groups.

Amygdala



Amygdala

It initiates the activation of the neurochemical and neuroanatomical threat circuitries (LeDoux,1992).

This can happened in several milliseconds.

Projections from the amygdala to the reticularis pontis caudalis potentiate the startle response and initiate defensive behaviors that do not require direct action of the sympathetic nervous system.

Projections from the amygdala to the lateral hypothalamus and to the rostral ventral medulla initiate sympathetic nervous system (and catecholamine) responses.

Amygdala

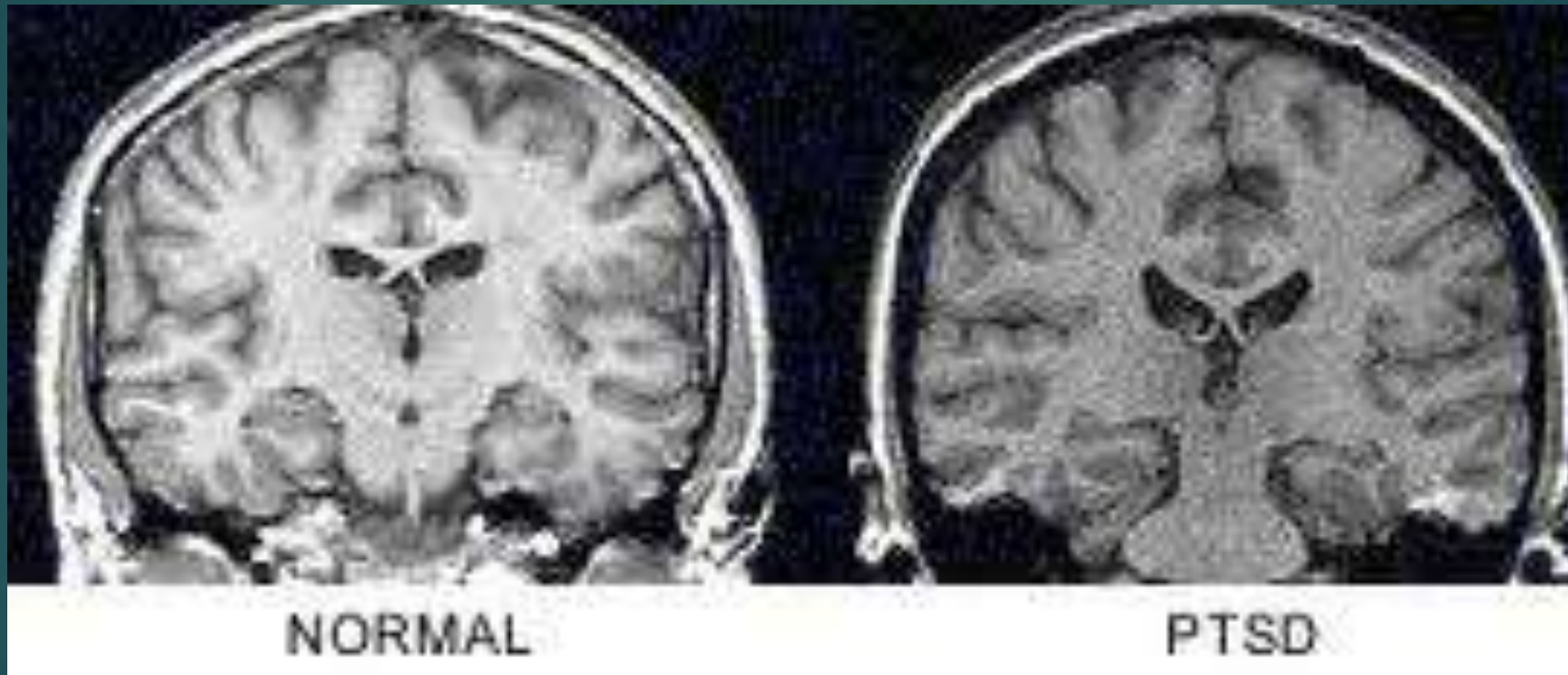
An immediate response to stress is the coordinated sympathetic discharge that causes increases in heart rate and blood pressure (fight-or-flight response).

Exposure to traumatic reminders provokes autonomic activation in about two-thirds of patients with PTSD (e.g., Pitman et al., 1987), which is likely mediated by activation of the amygdala and related structures.

Amygdala

- ▶ Projections from the amygdala initiate the parasympathetic responses that bring on autonomic arousal although they operate independently of the sympathetic nervous system.
- ▶ Projections from the central amygdala to the bed nucleus of the stria terminalis initiate the HPA axis response.
- ▶ Amygdala transforms sensory stimuli into emotional and hormonal signals, and
- ▶ Initiates and controls emotional responses.

Hippocampus in PTSD



Hippocampal Involvement

- ▶ The hippocampus plays an important role in memory, hippocampal circuits are involved in mediating explicit memories of traumatic events and in mediating learned responses to a constellation of feared cues.
- ▶ Death of hippocampal neurons and hippocampal shrinkage is seen after exposure of animals to chronic stress. This reaction may be mediated in part by hippocampal glucocorticoid receptors (Charney et al., 1993).

Hippocampus

- ▶ The high density of glucocorticoid receptors in the hippocampus indicates that it may play an important role in emotion regulation.
- ▶ Glucocorticoids have been shown to have a strong impact on hippocampal neurons (Cahill and McGaugh, 1998; McEwen, 1998).
- ▶ Gurvits and her colleagues found both significantly smaller left and right hippocampi in combat veterans with PTSD. High levels of cortisol caused hippocampal cell death.

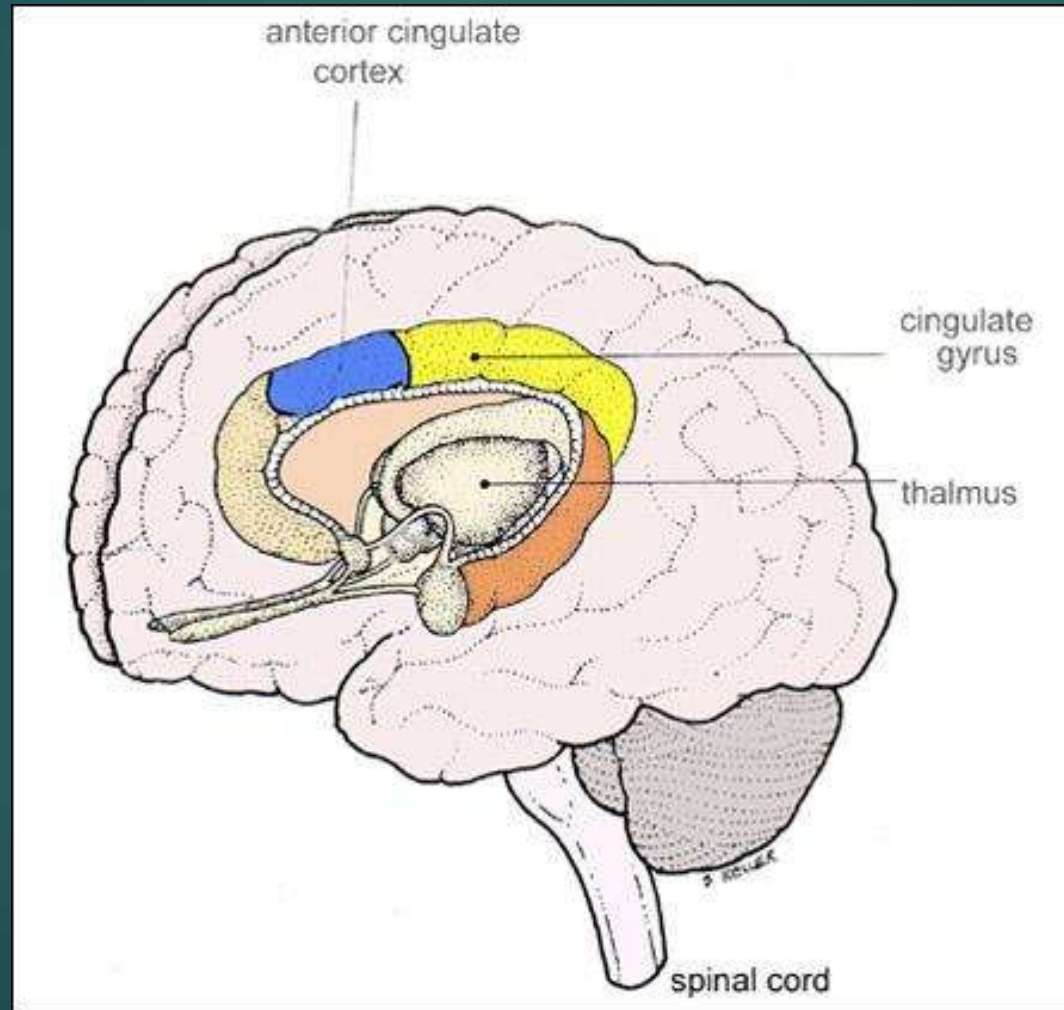
Hippocampus and emotional expression in PTSD.

- ▶ Davidson et al. (2000) suggested hippocampal involvement in psychopathology is most apparent in the processing of emotional information.
- ▶ In individuals with compromised hippocampal function, the normal contextual regulatory role would be impaired.
- ▶ We would expect individuals with damage to the hippocampus to be prone to display emotional behavior in inappropriate contexts. In PTSD we don't see a display of abnormal emotions, but the presentation of normal emotions in inappropriate contexts.

Hippocampus

- ▶ Patients with PTSD behave in ways that are reminiscent of animals with hippocampal lesions, in being unable to modulate emotional responses in a context-appropriate manner.
- ▶ e.g. the Vietnam Vet who dives to the floor when a helicopter goes over head.

Anterior Cingulate Cortex



Anterior Cingulate cortex

- ▶ The Anterior Cingulate Cortex activates in response to emotion.
- ▶ Research is beginning to distinguish between cognitive and affective divisions of the ACC, according to the location of activation in response to cognitive versus emotional tasks.
- ▶ Dorsal ACC activation is consistently found in response to the classical Stroop task (cognitive).
- ▶ More anterior activation is seen in response to an emotional Stroop task (response time of the participant to name colors of negative emotional words). (Bush et al., 2000; Whalen et al., 1998)

Anterior Cingulate Cortex

- ▶ Some PTSD studies find increased activation (Bremner, 1999b, 1999a; Shin et al., 2001; Lanius et al., 2001) in the ACC
- ▶ Some find decreased activation. (Sachinvala, 2000)
- ▶ Carter et al. (1999) suggest that ACC activation results in a call for further processing by other brain circuits to address the conflict that has been detected. In people with PTSD the automatic mechanisms of emotion regulation are likely unable dampen the strong emotion that may be activated in the laboratory.

ACC Continued

- ▶ PTSD neuroimaging studies suggest that many traumatized subjects are less capable of activating the ACC in response to emotionally arousing stimuli.
- ▶ Levin et al., 1999 found increased ACC activation after effective PTSD treatment.

PTSD Responses

- ▶ Responses to stimuli related to trauma
- ▶ Responses to neutral but strong stimuli such as loud noises (acoustic startle), which does not habituate when PTSD resolves. Ornitz and Pynoos, 1989
- ▶ Significant conditioned autonomic reactions, such as heart rate, skin conductance and blood pressure

PTSD Responses

- ▶ Kolb proposed that excessive stimulation of the CNS at the time of the trauma may result in permanent neuronal changes that have a negative effect on learning, habituation, and stimulus discrimination. These neuronal changes would not depend on actual exposure to reminders of the trauma for expression. The abnormal startle response characteristic of PTSD exemplifies such neuronal changes.
- ▶ Perhaps this is why the use of beta blockers within 72 hours of the trauma can stop the development of PTSD

Brain Stem Dysregulation

- ▶ PTSD sufferers have dysregulation at the brain stem level (Sahar et al., 2001).
- ▶ The regulatory processes of the brainstem involve the reticular activating system, Porges et al., 1996.

Attentional systems

- ▶ Activation of the ascending reticular activating system stimulates attentional systems, the thalamus and cerebral cortex.
- ▶ The hyper- and hypoarousal seen in traumatized individuals likely involve excesses of sympathetic and parasympathetic activity, leading to a breakdown of attentional systems commonly seen in traumatized people who develop PTSD.

Hormonal Response in PTSD

- ▶ Instead of returning to baseline, there is a progressive kindling of the individual's stress response.
- ▶ At first only intense stress is accompanied by the release of endogenous, stress-responsive neurohormones, such as cortisol, epinephrine, norepinephrine (NE), vasopressin, oxytocin, and endogenous opioids.
- ▶ When the individual has full blown PTSD even minor reminders of the trauma may bring on a full-blown neuroendocrine stress reaction.
- ▶ It permanently alters how an organism deals with its environment on a day-to-day basis and it interferes with how it copes with subsequent acute stress.



Cortisol and PTSD

- ▶ Two studies of trauma survivors show that individuals with a low initial cortisol response to stress are most vulnerable to developing PTSD.
- ▶ McFarlane et al., 1993 measured the cortisol response immediately after the a motor vehicle accident. At six months individuals who developed PTSD has a significantly lower cortisol response right after the motor vehicle accident than those who developed major depression.

Cortisol

- ▶ Resnick et al. (1997) collected blood samples from 20 acute rape victims and measured their cortisol response in the emergency room. Three months later, they took a trauma history and evaluated for PTSD. Victims who had a prior history of sexual abuse were significantly more likely to have PTSD. Lower cortisol levels shortly after the rapes were correlated with histories of prior assaults.
- ▶ These findings can be interpreted to mean either that prior exposure to traumatic events results in a blunted cortisol response to subsequent trauma or in a quicker return of cortisol to baseline following stress.

Medically Unexplained Symptoms:

- ▶ Fibromyalgia
- ▶ Chronic Fatigue Syndrome
- ▶ Rheumatoid Arthritis
- ▶ Reflex Sympathetic Dystrophy.
- ▶ Hypothyroidism
- ▶ Hashimoto's Thyroiditis
- ▶ Grave's Disease
- ▶ Systemic Lupus Erythematosus
- ▶ Sjogren's Syndrome
- ▶ Crohn's Disease
- ▶ Type I Diabetes
- ▶ Multiple Sclerosis

Other symptoms of hypocortisolemia

- ▶ Diarrhea with stress
- ▶ Irritable bowel inflammation
- ▶ Sore throat
- ▶ Flu-like symptoms
- ▶ Achy skin
- ▶ Headaches
- ▶ Trouble staying hydrated
- ▶ Fatigue, more in afternoon
- ▶ Autoimmune disorders
- ▶ Bergman, 2011

Brain Structures involved in integration of experience

- ▶ In PTSD the brain's ability to integrate experience and information does not function properly.
- ▶ CNS Structures thought to be involved in processes of integration:
- ▶ The parietal lobes integrate information between different cortical association areas (Damasio, 1999).
- ▶ The hippocampus creates a cognitive map that allows for the categorization of experience, connecting it with other autobiographical information (O'Keefe and Nadel, 1978)
- ▶ The corpus callosum allows for the transfer of information by both hemispheres (Joseph, 1988) which allows us to integrate emotional and cognitive aspects of experience.

Brain structures

- ▶ The cingulate gyrus, acts as an amplifier and filter and helps integrate the emotional and cognitive elements of the mind of the mind (Devinsky et al., 1995)
- ▶ Various prefrontal areas, where sensations and impulses are “held in mind” and compared with previous information to plan appropriate actions.
- ▶ Recent neuroimaging studies of patients with PTSD have suggested a role for all of these structures in the neurobiology of PTSD.

MRI Studies

- ▶ MRI studies show that both male combat veterans and women survivors of childhood sexual abuse with PTSD have decreased hippocampal volumes. In some of these studies, decreased volume of the hippocampus correlated with trauma exposure or memory deficits.
- ▶ MRI Studies also showed nonspecific white matter lesions and decreased hippocampal volume.

Neurotransmitters

- ▶ Several neurotransmitters systems are involved in PTSD. These include the noradrenaline, dopamine, opioid and serotonin systems.
- ▶ In addition, it is likely that the hypothalamic-pituitary-adrenal (HPA) axis is important in this disorder. An emerging theme in the literature is that sensitization of neurochemical systems is a crucial characteristic of PTSD (Charney et al., 1993; Yehuda, 1998).

Opioids

- ▶ The opioid system may also be involved in PTSD, with endogenous opioids being released during trauma in order to act as "internal pain-killers".
- ▶ There is evidence for sensitization of this system, with less intense shock required for subsequent analgesia.
- ▶ PTSD patients often prefer opioid substances for abuse.
- ▶ In the research setting, the opioid antagonist naloxone has been reported to reverse the analgesia induced by exposure to combat films.

Medial Prefrontal Cortex

- ▶ The medial prefrontal cortex (mPFC), amygdala, sublenticular extended amygdala (SLEA), and hippocampus, are involved in mediating symptom formation in PTSD.
- ▶ These symptoms include fear conditioning, habituation, extinction, cognitive-emotional interactions, self-related and social emotional processing.

Basolateral Amygdala

- ▶ Exposure to early acute stressors creates spine synapse formation in the basolateral amygdala. Mitra et al 2005; Mitra et al 2002.
- ▶ There is increased dendritic growth in the basolateral amygdala greater increases in spine density, dendritic retraction in the hippocampus with exposure to chronic/repeated stressors. McEwen 2005; Mitra et al 2005.

Reaction to 9/11 attacks

- ▶ With fMRI imaging, bilateral amygdala activity in response to viewing fearful faces was higher in individuals not suffering from PTSD who were within 1.5 miles of ground zero three years after the attacks.
- ▶ This suggests that the amygdala and closely related structures are more active after exposure to traumatic stressors. Ganiel et al 2007

The Neuropsychology of PTSD

PTSD & NP Deficits

- ▶ No clear PTSD typical NP profile
- ▶ Individuals with PTSD show signs of cognitive impairment when tested with NP instruments, more so than individuals exposed to trauma who do not have PTSD.
- ▶ Correlated with:
 - ▶ lower educational level,
 - ▶ smaller hippocampal volume,
 - ▶ dysfunction of frontal regions
 - ▶ NP deficits effect occupational and social function

Anxiety-produced NP deficits

- ▶ Increased anxiety levels produce deficits in measurement of attention and EF
- ▶ Anxiety can increase NP performance; high levels impair performance
- ▶ WM effects: worry consumes limited attentional resources in WM (largest Stroop effect in anxious pts)
- ▶ Anxiety leads to attentional bias: more attention to threat-related stimuli which interferes with EF goal directedness

PTSD & Hippocampus

- ▶ MRI studies show that both male combat veterans and women survivors of childhood sexual abuse with PTSD have decreased hippocampal volumes
- ▶ Verbal memory - increased intrusion errors



AND YET THE QUESTION REMAINED:
"WHO CAME FIRST?"

Chicken or the Egg?: Prior vulnerability

- ▶ Differences in cognitive functioning prior to trauma: unaffected twins of veterans with PTSD also showed reduced hippocampus volume
- ▶ Lower cognitive capacity risk factor for PTSD?
- ▶ Premorbid dysexecutive functioning

Gilbertson, M.W., et al. (2006). Neurocognitive function in monozygotic twins discordant for combat exposure. *Journal of Abnormal Psychology*, 115, 484-495.

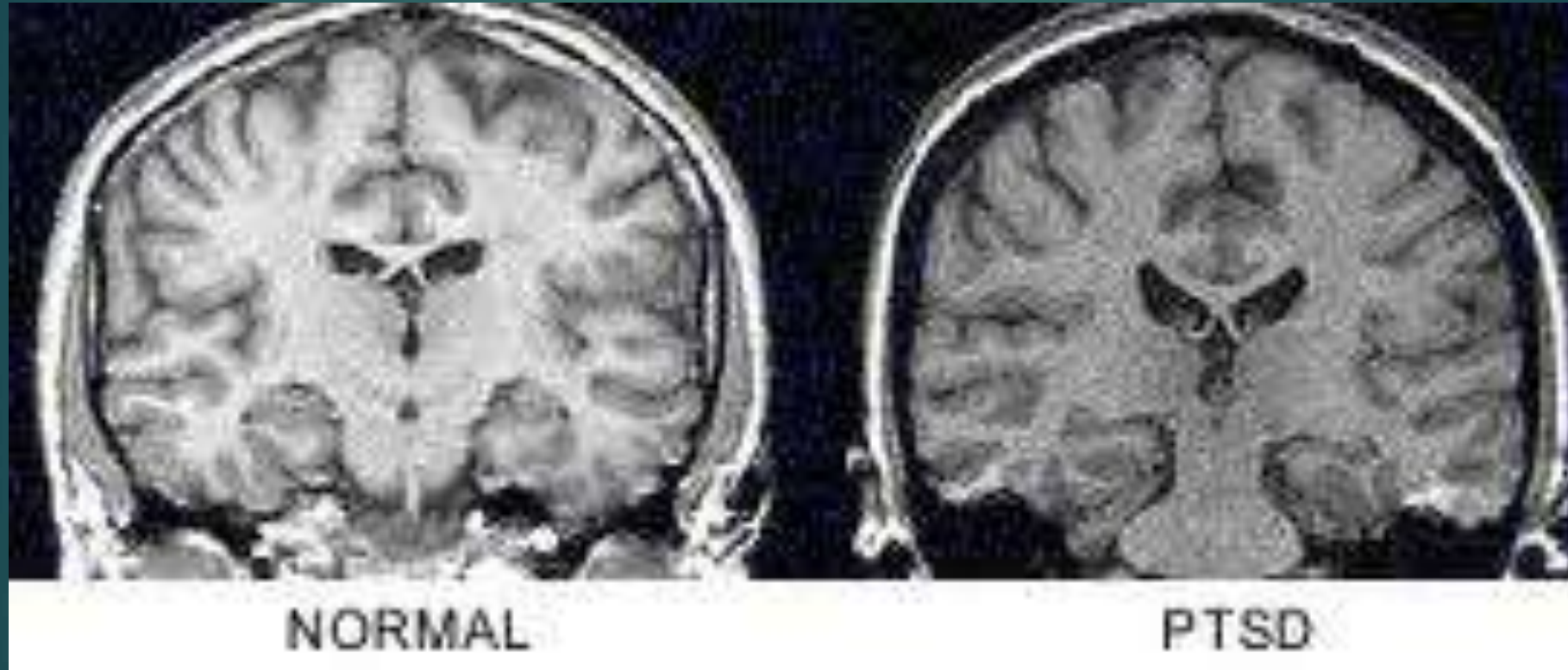
PTSD: "resting" brain activity

- ▶ What happens in the brains of combat veterans with PTSD in the absence of external triggers:
- ▶ Amygdala activation was significantly higher in the 52 combat veterans with PTSD than in the 52 combat veterans without PTSD.
- ▶ Elevated brain activity in the anterior insula
- ▶ PTSD group had lower activity in the precuneus. Correlates with more severe "re-experiencing" symptoms

Childhood trauma & Amygdala

- ▶ All the ACE data and predictions apply to PTSD
- ▶ Amygdala involvement: Exposure to traumatic reminders provokes autonomic activation in about two-thirds of patients with PTSD
- ▶ Mediated by activation of the amygdala and related structures.
- ▶ S-allele (of serotonin) carriers or hx of child abuse have higher amygdala activation and more PTSD (opposite for resilience)

Hippocampus in PTSD



Hippocampal Involvement

- ▶ Hippocampus:
 - ▶ involved in mediating explicit memories of traumatic events
 - ▶ fear conditioning.
- ▶ Hippocampal atrophy is seen after exposure of animals to chronic stress.

Charney et al., 1993

Hippocampus 2

- ▶ Glucocorticoids have been shown to have a strong impact on hippocampal neurons.
- ▶ Gurvits and her colleagues found both significantly smaller left and right hippocampi in combat veterans with PTSD.
- ▶ It is believed that high levels of cortisol caused hippocampal cell death.

Hippocampus and emotional expression in PTSD

- ▶ Hippocampal involvement in psychopathology is most apparent in the processing of emotional information.
- ▶ Expect individuals with damage to the hippocampus tend to be prone to display emotional behavior in inappropriate contexts.
- ▶ In PTSD:
 - ▶ we don't see a display of abnormal emotions
 - ▶ presentation of normal emotions in inappropriate contexts.
 - ▶ unable to modulate emotional responses in a context-appropriate manner.

Need to activate Anterior Cingulate

- ▶ ACC activation results in a call for further processing by other brain circuits to address a detected conflict.
- ▶ PTSD neuroimaging studies suggest that many traumatized subjects are less capable of activating the ACC in response to emotionally arousing stimuli.
- ▶ Levin et al., 1999 found increased ACC activation after effective PTSD treatment.



Medial Prefrontal Cortex

- ▶ PTSD involves:
 - ▶ medial prefrontal cortex (mPFC): underactive
 - ▶ amygdala: overactive
 - ▶ Hippocampus: impaired
- ▶ These areas include fear conditioning, habituation, extinction, cognitive-emotional interactions, self-related and social emotional processing.
- ▶ mPFC plays a role in the "contextualization" of stimuli, and dysregulation of contextualization processes for PTSD symptoms.

PTSD & Medial Prefrontal Cortex

- ▶ Medial prefrontal is underactive in PTSD
- ▶ Greater pretreatment gray matter density in the medial prefrontal cortex predicts better response to cognitive behavioral therapy of PTSD

Flashbulb Memories

- ▶ The hippocampus normally creates a cognitive map that allows for the categorization of experience,
- ▶ When PTSD patients have their flashbacks, the trauma is relived as isolated sensory, emotional, and motoric imprints, without much of a storyline.
- ▶ This has been shown in victims of childhood abuse, assaults, accidents in adulthood and in patients who gained awareness during surgery, (van der Kolk et al., 1997; van der Kolk and Fisler, 1995; van der Kolk et al., 2000).
- ▶ This supports the idea that traumatic memories result from a failure of the CNS to synthesize sensations related to the event into an integrated semantic memory.

van der Kolk et al., 1997; van der Kolk and Fisler, 1995; van der Kolk et al., 2000.

Pet Scan Studies

- ▶ Positron emission tomography (PET) studies show that veterans with PTSD demonstrate increased right amygdala activity when exposed to combat movies. Rauch et al., 1998.
- ▶ PTSD subjects exposed to detailed narratives of their own trauma demonstrated *increased metabolic* activity in the right hemisphere: in the amygdala, the insula, and the medial temporal lobe (areas related to emotional appraisal).
- ▶ There was a significant *decrease in activation* of the left inferior frontal area—Broca's area. (Speechless terror?)
- ▶ Most neuroimaging studies have found activation of the cingulate cortex (which possibly plays an inhibitory role) in response to trauma-related stimuli in individuals with PTSD, but others have found decreases, even while using similar activation strategies.

Pet scan and EMDR

- ▶ Van der Kolk found a reversal of the above with increased frontal lobe and Broca's area activation on PET Scan while reading a vivid account of the their trauma post EMDR.

PTSD and Cognition

- ▶ Attention and Memory common complaints
- ▶ Samuelson, et al. (2009) – lower scores on working memory and verbal memory (Contextually based)

Does PTSD Impair Cognition Beyond the Effect of Trauma?

TABLE 3. Summary of Positive and Negative Findings for Association of Cognitive Domains, by Type of Sample Subject

Cognitive Impairment	Sample	Positive	Negative
Attention	Veterans	5	1
	Abused individuals	1	1
	Refugees/war victims	2	0
	Undergraduates	0	2
	Disaster survivors	1	0
	Other	0	0
	Total	9	4
Learning	Veterans	5	2
	Abused individuals	1	1
	Refugees/war victims	1	1
	Undergraduates	0	0
	Disaster survivors	0	1
	Other	0	1
	Total	7	6
Memory	Veterans	3	5
	Abused individuals	2	2
	Refugees/war victims	0	3
	Undergraduates	0	0
	Disaster survivors	1	1
	Other	0	1
	Total	6	12
Executive Function	Veterans	4	3
	Abused individuals	1	1
	Refugees/war victims	1	1
	Undergraduates	1	1
	Disaster survivors	2	0
	Other	0	1
	Total	9	7
Visuospatial Function	Veterans	0	7
	Abused individuals	0	1
	Refugees/war victims	1	0
	Undergraduates	0	0
	Disaster survivors	0	1
	Other	0	0
	Total	1	9

Date of download:
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PTSD Meta-analysis

- ▶ 21 studies: Most studies were of veterans, and most studies found significant cognitive deficits.
- ▶ Individuals with PTSD have poorer attention capability
- ▶ Memory results have not been consistent, but there seems to be Impaired learning in PTSD due to:
 - ▶ prefrontal changes,
 - ▶ reduction in hippocampus,
 - ▶ and increased glucocorticoid levels can all be implicated

Memory

- ▶ Memory: 12 of 18 studies were negative. Related to deficits in attention and learning? Lack of effort testing?
- ▶ Other studies have found verbal learning difficulties due to inefficient encoding processing

Meta-analysis 2

- ▣ Evidence for visuospatial impairment is negative.
- ▣ Executive function: results are conflicting: 9 of 16 studies were positive.
- ▶ Low intelligence and low premorbid cognitive functioning have been suggested to increase vulnerability to PTSD
- ▶ Growing research suggest that some of structural & functional abnormalities may be present prior to trauma & may reflect pre-trauma vulnerabilities.

During a Traumatic Event

- ▶ Norepinephrine- Mobilizing fear, the flight response, sympathetic activation, consolidating memory
- ▶ Too much = hypervigilance, autonomic arousal, flashbacks, and intrusive memories
- ▶ Serotonin- self- defense, rage and attenuation of fear
- ▶ Too little = aggression, violence, impulsivity, depression, anxiety
- ▶ PTSD victims – switch is stuck on

Causal Attributions

- ▶ “PTSD is typified by both automatic, involuntary symptoms, (e.g. flashbacks, intrusive thoughts, autonomic hyperarousal) and consciously mediated attempts to make meaning of the trauma experience. The automatic and involuntary symptoms appear to represent conditioned responding to environmental triggers associated with the trauma.”
- ▶ However, much less is known about the origins and consequences of victims’ efforts to understand their traumas or about how best to treat the symptoms associated with personal beliefs about traumas. The most comprehensive and widely cited guidelines for treating PTSD include using variants of cognitive therapy (including attribution retraining and cognitive restructuring).”

Massas., Phillip M and Hulsey, Timothy L. (2006) Causal Attributions in Posttraumatic Stress Disorder: Implications for Clinical Research and Practice, *Psychotherapy: Theory, Research, Practice, Training* 43, 201-215.

Anxiety Disorders and Risk for NCDs

Glucocorticoids

- Glucocorticoids belong to a class of hormones that are released in response to stress
- This release is part of the systemic arousal of the HPA axis.
- Cortisol is the primary glucocorticoid measured in humans and primates.

Glucocorticoids

- ❑ Released in response to stress

- ❑ If release prolonged:

 - Can damage the hippocampus

 - Can result in memory decline

Glucocorticoids /Animal Studies



In rats, an increase in glucocorticoids leads to changes in the hippocampus:

- Dendritic atrophy
- Decrease in hippocampal neurons
- McEwen and Sapolsky (1995)

Prolonged exposure to glucocorticoids increases the severity of neurologic insults (e.g. hypoxia, seizures) to the hippocampus.

Sapolsky, 1985, 1986; Morse & Davis, 1989

Cortisol, Hippocampus, and Memory in Humans

Glucocorticoids administered to young normal adults impaired memory.

Wolkowitz et al., 1990; Newcomer et al., 1998

Increased plasma cortisol predicts reduced hippocampal volume and impaired memory in non-demented elderly.

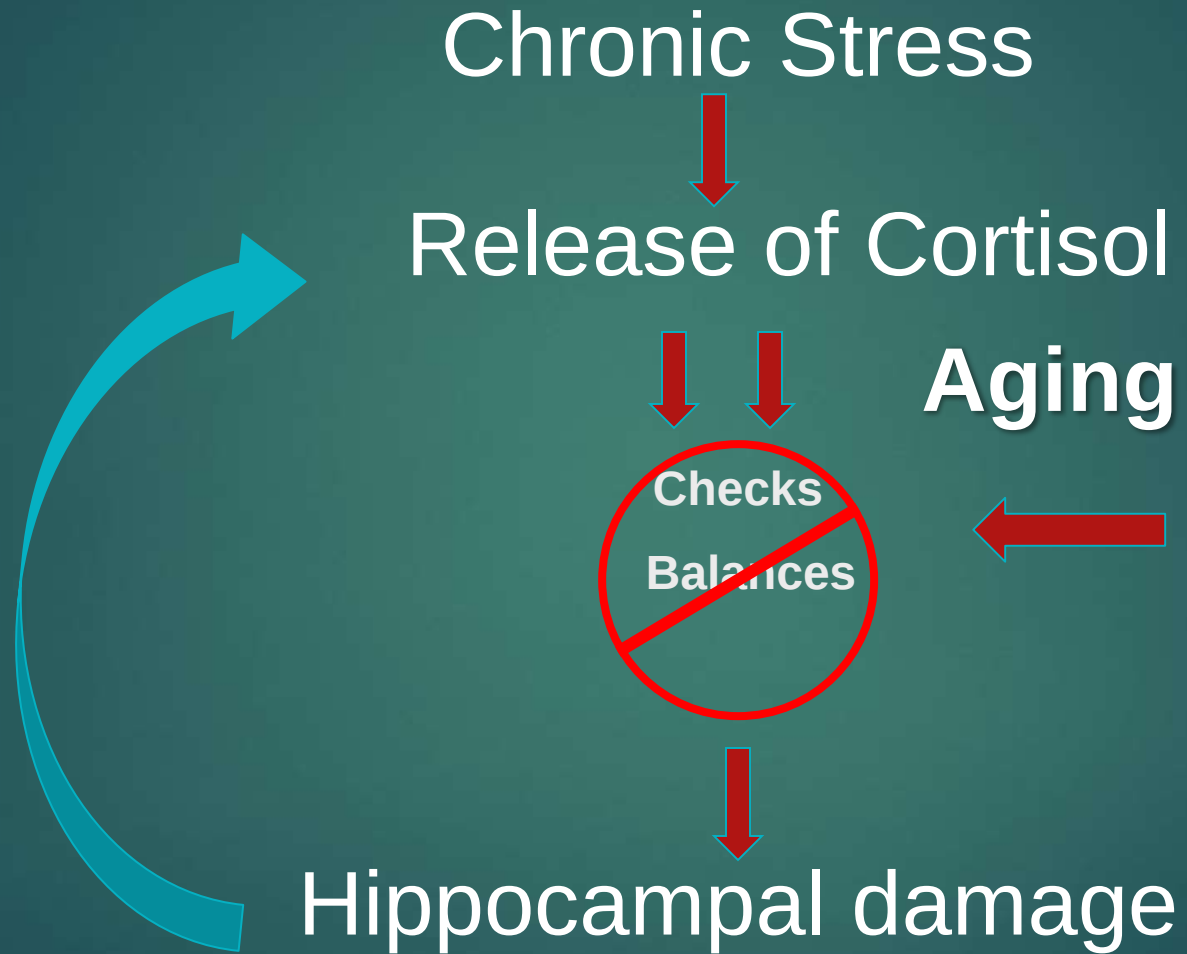
Lupien et al., 1998

Vulnerability Assumption

Anything that adds to the vulnerability of the hippocampus and related structures has the potential to hasten the onset of dementia.

The aging brain is particularly vulnerable to prolonged exposure to stress.

“Glucocorticoid Cascade Hypothesis”



Sapolsky et al., 1986

Stress and Neuropathology of Alzheimer's Disease

In rodent studies, glucocorticoids:

- ❑ Increase A β formation
- ❑ Augment tau accumulation
- ❑ May play a central role development and progression of AD.

Green et al., 2006

Genetic risk factor for AD: Apolipoprotein E (APOE)

- Besides age, APOE-e4 allele is major risk factor for late onset AD
- A cholesterol transport protein with three isoforms: e2, e3, and e4.
- Mechanism for increased risk unknown.



APOE & Stress in Humans

- ❑ Subjects: Non-demented, female caregivers of patients with AD
- ❑ Increased level of self-reported stress was associated with an increased level of depression - only in those caregivers with at least one APOE- e4 allele.

Gallagher-Thompson et al., 2001

APOE and Stress - Animal Studies



Postulate:

The effects of stress mediated by glucocorticoids depend on the presence of APOE.

APOE-deficient mice showed greater elevations in glucocorticoids compared to controls after repeated restraint stress.

Zhou and colleagues (1998, 1999)

Repeated stress



APOE-deficient

APOE (Controls)



Glucocorticoids ↑

Glucocorticoids

Zhou and colleagues (1998, 1999)

APOE, Cortisol, and AD

- ❑ APOE inhibits glucocorticoid production. APOE-e4 may be less effective in inhibiting than APOE-e3 and APOE-e2.
- ❑ APOE-e4 might be less effective than the e3 and e2 alleles in repairing neuronal damage or providing neuronal protection in response to CNS injury.

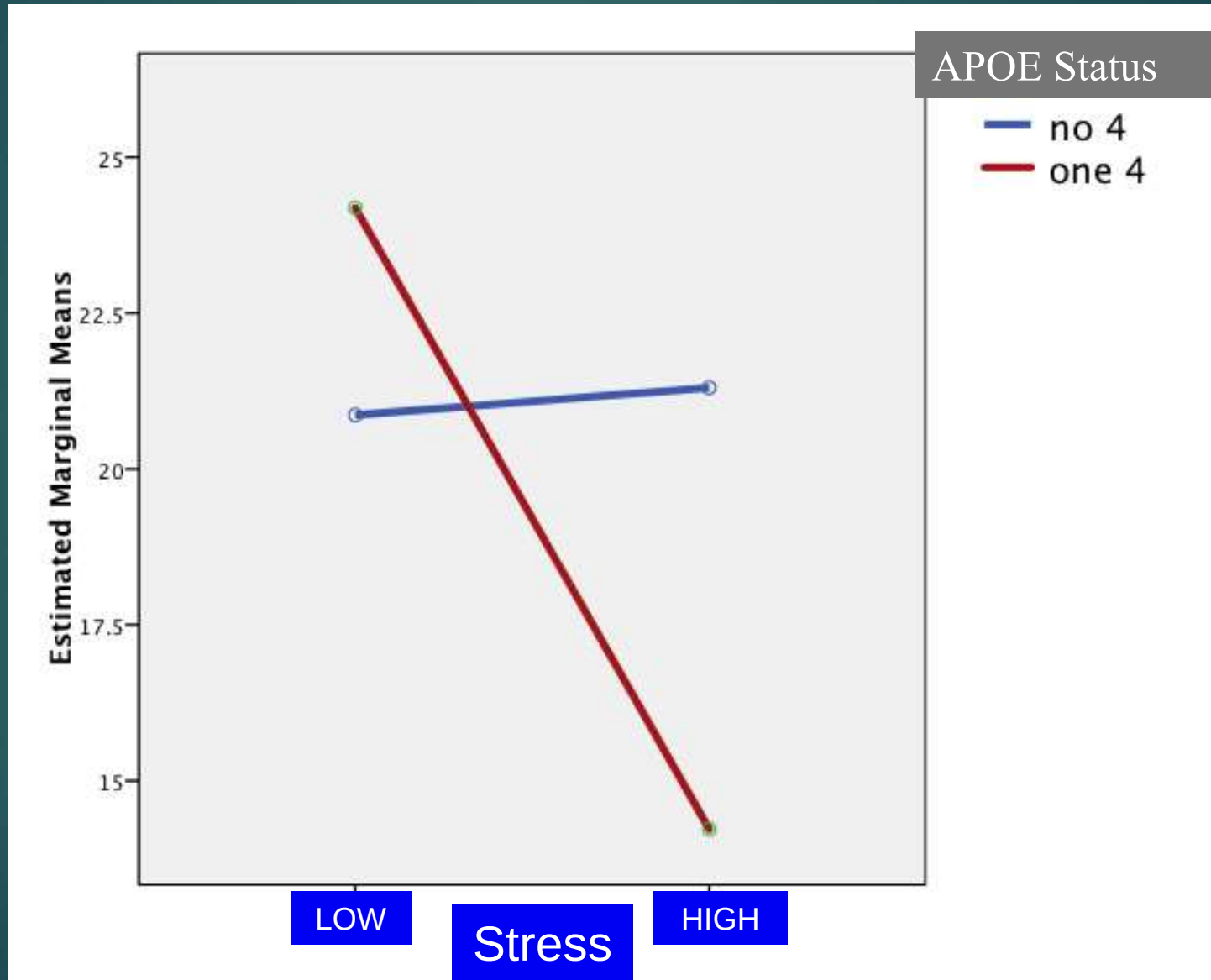
Huang, 2006

Baseline Hypotheses:

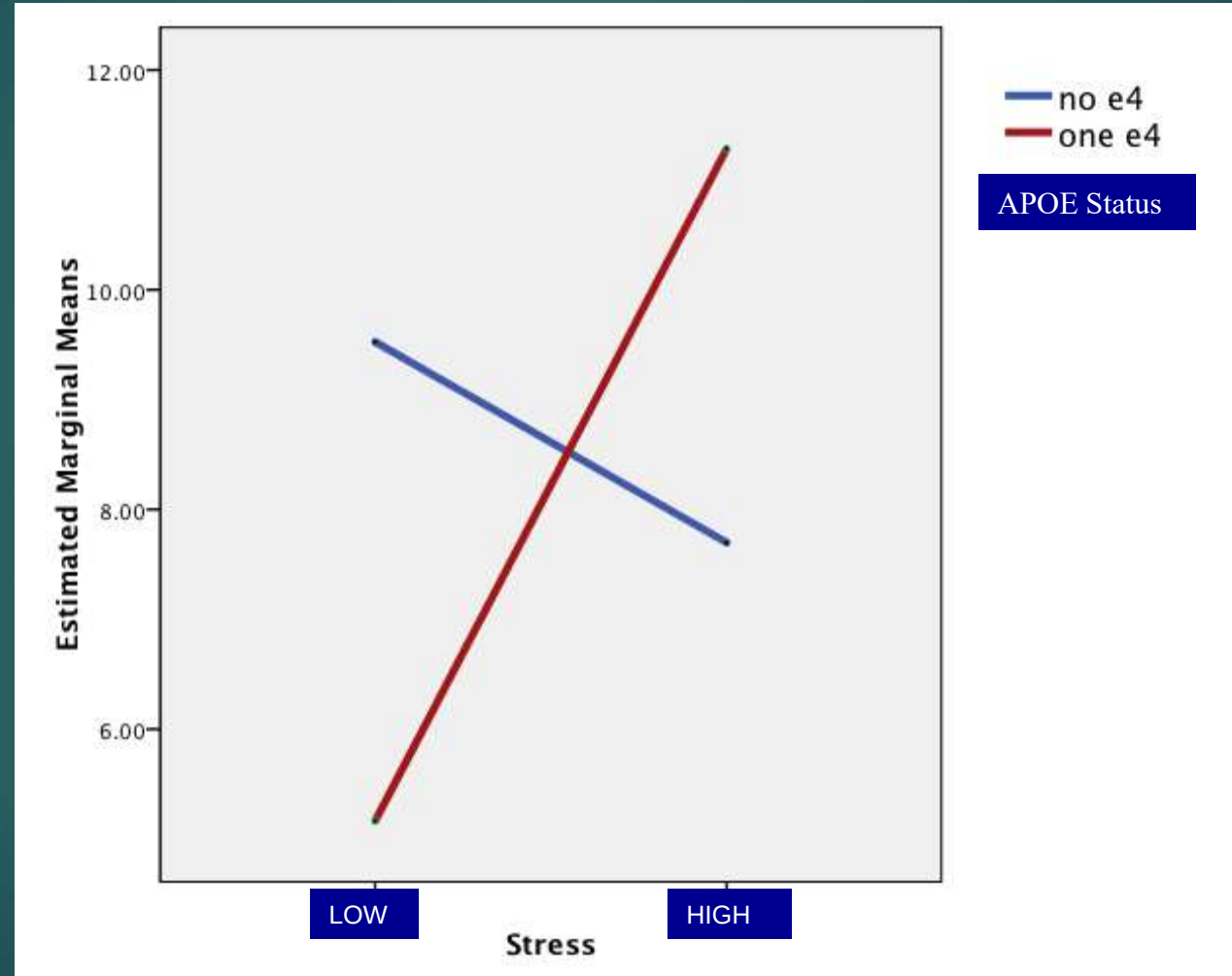
Both age and APOE-e4 are risk factors for Alzheimer's disease and it has been shown that sustained levels of cortisol are associated with the neuropathology of Alzheimer's disease.

- I. Older individuals experiencing prolonged stress will show worse memory performance than those without significant stress.
- II. The relationship between stress and memory will be more robust in those with at least one APOE-e4 allele.

Story Recall – Delay Condition – lower in APOE-4



Cortisol – 30 minutes after awakening – higher in APOE-4



Summary - Study I

Prolonged exposure of older, non-demented individuals to significant stress in the presence of an e4 allele is associated with:

- ❑ memory decline
- ❑ elevated level of peak cortisol
- ❑ The greater the measure of stressful life events averaged over time, the greater the decline (slope) of specific memory measures.

Summary Study 2

- ❑ Exposure of older individuals to stressful events over approximately two years was associated with poor performance on selected memory tests.
- ❑ Higher cortisol levels averaged over time did not predict decline on any of the memory measures.

Conclusions

- ❑ Older, non-demented individuals who possess at least one APOE-e4 allele are more vulnerable to memory decline associated with chronic stress than those without an e4 allele.
- ❑ A measure of stressful life events measured over time is associated with memory decline in older adults.
- ❑ Higher cortisol is associated with more rapid progression to MCI and dementia associated with AD

Treatment of Anxiety Disorders

Treatment

- ▶ Individual Therapy
- ▶ Group Support (especially for Chronic PTSD)
- ▶ Medication

Treatment

- ▶ Acute PTSD - Stress debriefing? and psychotherapy
- ▶ Severe Acute PTSD - Stress debriefing?, medication, group and individual psychotherapy
- ▶ Chronic PTSD - Stress debriefing?, medication, group and individual psychotherapy
- ▶ For PTSD in children, adolescents, and geriatrics the preferred treatment is psychotherapy

Treatment

- ▶ Exposure Therapy - Education about common reactions to trauma, breathing retraining, and repeated exposure to the past trauma in graduated doses. The goal is for the traumatic event to be remembered without anxiety or panic resulting.
- ▶ Cognitive Therapy - Separating the intrusive thoughts from the associated anxiety that they produce.
- ▶ Stress inoculation training - variant of exposure training teaches client to relax. Helps the client relax when thinking about traumatic event exposure by providing client a script.

Treatment

- ▶ Cognitive-behavioral therapy (CBT)
 - ▶ The most effective procedure for treating most anxiety disorders
 - ▶ Teaches
 - ▶ to understand how thinking contributes to anxiety
 - ▶ how to modify their maladaptive thoughts to decrease symptoms (most effective for most anxiety disorders)
 - ▶ Skills training and exposure combat problematic thinking

Cognitive-Behavioral Therapy (CBT)

- ▶ Treatment of choice
- ▶ As effective as meds for many AD's
- ▶ Few side effects
- ▶ Protects against relapse
- ▶ Use when less than optimal response to meds or when patient requests

Cognitive-Behavioral Therapy (CBT)

- ▶ Cognitive
 - ▶ Works on faulty/distorted thought patterns
 - ▶ Overestimation, catastrophizing frequent in anxiety disorders
- ▶ Behavioral
 - ▶ Breathing and relaxation techniques
 - ▶ Graduated exposure targeted at avoidant behaviors

CBT

- ▶ Cognitive behavioral therapy (CBT), typically helps only half of the patients who try it.
- ▶ In 2008 Richard Bryant, a professor of psychology at the University of New South Wales in Australia, and his colleagues attempted to identify that half up front. Before CBT they took brain scans using functional MRI of 14 subjects while showing them photographs of frightening faces.
- ▶ Seven people—the same who later failed to improve—showed greater than normal activity in brain regions associated with experiencing fear: the amygdala and the ventral anterior cingulate cortex.
- ▶ In another study Bryant found that the people who did benefit from CBT began treatment with larger rostral anterior cingulate cortices. Both animal and human studies have linked this brain area to “extinction”

Treatment

- ▶ “Cognitive Restructuring involved teaching and reinforcing self-monitoring of thoughts and emotions, identifying automatic thoughts that accompany distressing emotions, learning about different types of cognitive distortions, and working to dispute the distress-enhancing cognitions, with a particular focus on abuse-related cognitions, for which the therapist remained alert during the personal experience work.”
- ▶ “In summary for women who did not drop out, CBT treatment was highly effective for achieving remission of PTSD diagnosis, ameliorating PTSD symptom severity, and reducing trauma-related cognitive distortions, compared with a WL control Group.”

(McDonagh, A., McHugo, G., Sengupta, A., Demment C.C., et al., (2005) Randomized Trial of Cognitive-Behavioral Therapy for Chronic Posttraumatic Stress Disorder in Adult Female Survivors of Childhood Sexual Abuse. *Journal of Consulting and Clinical Psychology*, 73, 515-524.)

Exposure Treatment

- ▶ Overview: Main line of attack for treating anxiety disorders is exposing children to anxiety producing situations/objects/occasions
- ▶ Behavior therapy: Exposure to feared stimulus while providing ways of coping other than escape and avoidance
 - ▶ Graded exposure: gradual exposure using Subjective Units of Distress Scale and beginning with least distressing stimulus
 - ▶ Systematic desensitization
 - ▶ Flooding
 - ▶ Response prevention
 - ▶ Modeling and reinforced practice; in vivo exposure works best

How Extinction Might Be Improved By Neuroscience

- 1. Subliminal extinction.** Present the stimuli non-consciously to prevent working Memory from being involved
- 2. Space out the extinction process.** Like all forms of learning extinction is more effective if the learning occurs gradually. Just as cramming for an exam is inefficient, so is extinction cramming.
- 3. Reduce interference after the session.** *Keep the patient isolated and engaged in tasks that will not interfere with the formation of the extinction memory.*
- 4. Allow the patient to sleep after therapy.** Persistent long-term memory is facilitated by sleep.
- 5. Combine extinction with memory enhancing drugs.** This is not drug treatment in the conventional sense since the drug is only given during extinction. The stronger extinction learning then reduces responses to the extinguished threats.
- 6. Erase the memory of the threat.** Make memory of trigger stimuli inaccessible using reconsolidation procedures that target specific triggers, or achieve the same goal by adjustment of the timing of stimulus exposure during extinction. The latter approach is very powerful and has been shown to reduce drug craving in addicts.

NS based therapies

- ▶ Subliminal visual exposure of spiders to spider phobics lead to less avoidance later: subcortical exposure implicitly
- ▶ Psychotherapy is mass training (cramming) which is not as good as extended training; gene transcription factor CREB, required for memory, gets depleted by mass effect (takes an hour to replenish)
- ▶ Avoid reinforcement of phobia between sessions; interference with new learning (no internet spider searches)
- ▶ Need sleep after session to consolidate training
- ▶ Combine extinction and reconsolidation: separate extinction trials by 10 minutes to 4 hours (eliminates relapse cues in cocaine addicts); 10+ minutes reengages reconsolidation process which lasts for 4 hours

LeDoux: Separate processes to be dealt with independently

Psychiatric problems that fall under the general rubric of fear/anxiety disorders can result from pathophysiological changes in

- survival circuits
- motivational circuits
- cognitive circuits that construct conscious feelings

These interact but are also somewhat separate and should probably be treated separately to maximize therapeutic benefits

Implicit functions have to be altered through processes that work implicitly while conscious experiences (thoughts and feelings) have to be dealt with in their own terms

Panic Disorder - Treatment

- ▶ Try not to start meds first
- ▶ SSRI's mainstay of treatment
 - ▶ “start low, go slow”
- ▶ Imipramine, MAOI's also effective
- ▶ Benzodiazepines work, but be careful
- ▶ Cognitive-Behavioral Therapy
 - ▶ emphasis on breathing techniques and graduated exposure

Panic Disorder - Treatment

- ▶ The idea is to stimulate the presynaptic 5HT_{1a} receptor to tell the cell it is making too much 5HT
- ▶ The neuron responds with a decrease in 5HT production and release
- ▶ Other effects include downstream inhibition of locus ceruleus activity
 - ▶ 'fight or flight' center

GAD - Treatment

- ▶ Cognitive-Behavioral Therapy
 - ▶ more cognitive, less behavioral than other Anxiety Disorders
- ▶ Buspirone 10-20mg po tid
 - ▶ as effective at 6 wks as benzos
 - ▶ No addiction
 - ▶ No sedation or behavioral disinhibition
- ▶ SSRI's/venlafaxine- start low and go slow
- ▶ Benzodiazepines as last resort due to addiction and behavioral disinhibition

OCD - Treatments

- ▶ Cognitive Behavioral Therapy
 - ▶ Exposure-Response Prevention
- ▶ SSRI or clomipramine
- ▶ Add neuroleptic if comorbid Tourette's
- ▶ Psychosurgery for treatment resistant OCD (as few as 1 in 400 OCD patients)
 - ▶ include cingulotomy, capsulotomy, limbic leukotomy, subcaudate tractotomy
 - ▶ may see more use with gamma knife

SAD-Treatment

- ▶ Cognitive-Behavioral Therapy
- ▶ SSRI's have best evidence
- ▶ MAOI's also work
- ▶ Benzodiazepines may work
- ▶ Beta-blockers only for situational type

2015 PTSD Treatment Metaanalysis of 64 studies

- ▶ Evidence supports efficacy of exposure therapy including the manualized version Prolonged Exposure (PE); cognitive therapy (CT), cognitive processing therapy (CPT), cognitive behavioral therapy (CBT)-mixed therapies (moderate effect); eye movement desensitization and reprocessing (EMDR) and narrative exposure therapy (low–moderate effect). Effect sizes for reducing PTSD symptoms were large.
- ▶ Several psychological treatments are effective for adults with PTSD. Support highest for exposure.
- ▶ Head-to-head evidence was insufficient to determine these treatments' comparative effectiveness, and data regarding adverse events was absent from most studies.

Medications

- ▶ SSRIs – Sertraline (Zoloft), Paroxetine (Paxil), Escitalopram (Lexapro), Fluvoxamine (Luvox), Fluoxetine (Prozac)
- ▶ Affects the concentration and activity of the neurotransmitter serotonin
- ▶ May reduce depression, intrusive and avoidant symptoms, anger, explosive outbursts, hyperarousal symptoms, and numbing
- ▶ FDA approved for the treatment of Anxiety Disorders including PTSD

Medications

- ▶ Tricyclic Antidepressants- Clomiprimine (Anafranil), Doxepin (Sinequan) Nortriptyline (Aventyl), Amitriptyline (Elavil), Maprotiline (Ludiomil) Desipramine (Norpramin)
- ▶ Affects concentration and activity of neurotransmitters serotonin and norepinephrine
- ▶ Have been shown to reduce insomnia, dream disturbance, anxiety, guilt, flashbacks, and depression

Treatment

- ▶ With treatment, symptoms should improve after 3 months
- ▶ In Chronic PTSD cases, 1-2 years

Future Direction of Treatment Continued

- ▶ “Early Diagnosis and intervention- either psychotherapeutic or pharmacological- following trauma may some day reduce symptoms of posttraumatic stress disorder.”
- ▶ “Cognitive models- how the victim understands and appraises the stressful experience- are influential, and cognitive style also helps predict the occurrence of PTSD.”

(Levin, Aaron, Experts Seek Best Way To Treat Trauma Reactions, *Psychiatric News*, 2006, 41)

Depression treatment with rTMS (10 Hz) to the left dorsolateral prefrontal cortex

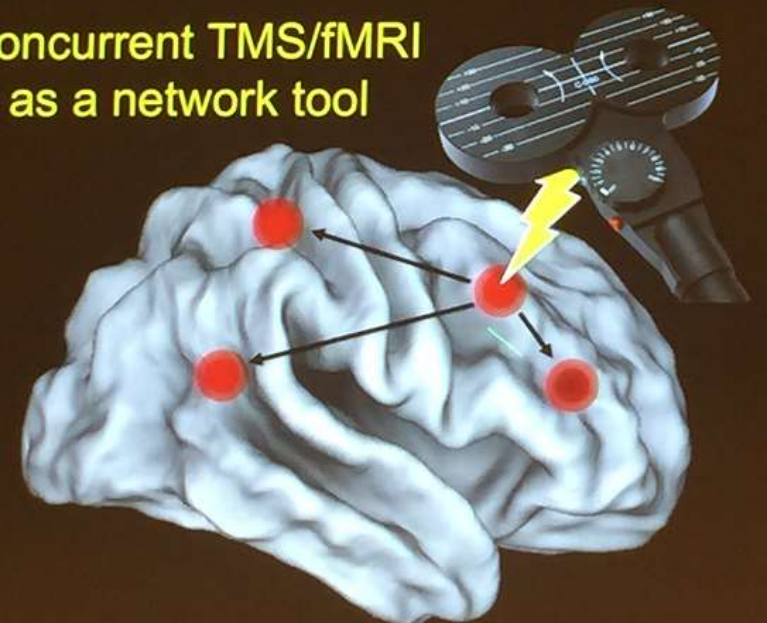
Combining TMS and neuroimaging to test causal circuit mechanisms

Concurrent TMS/fMRI:



Chen, PNAS 2013

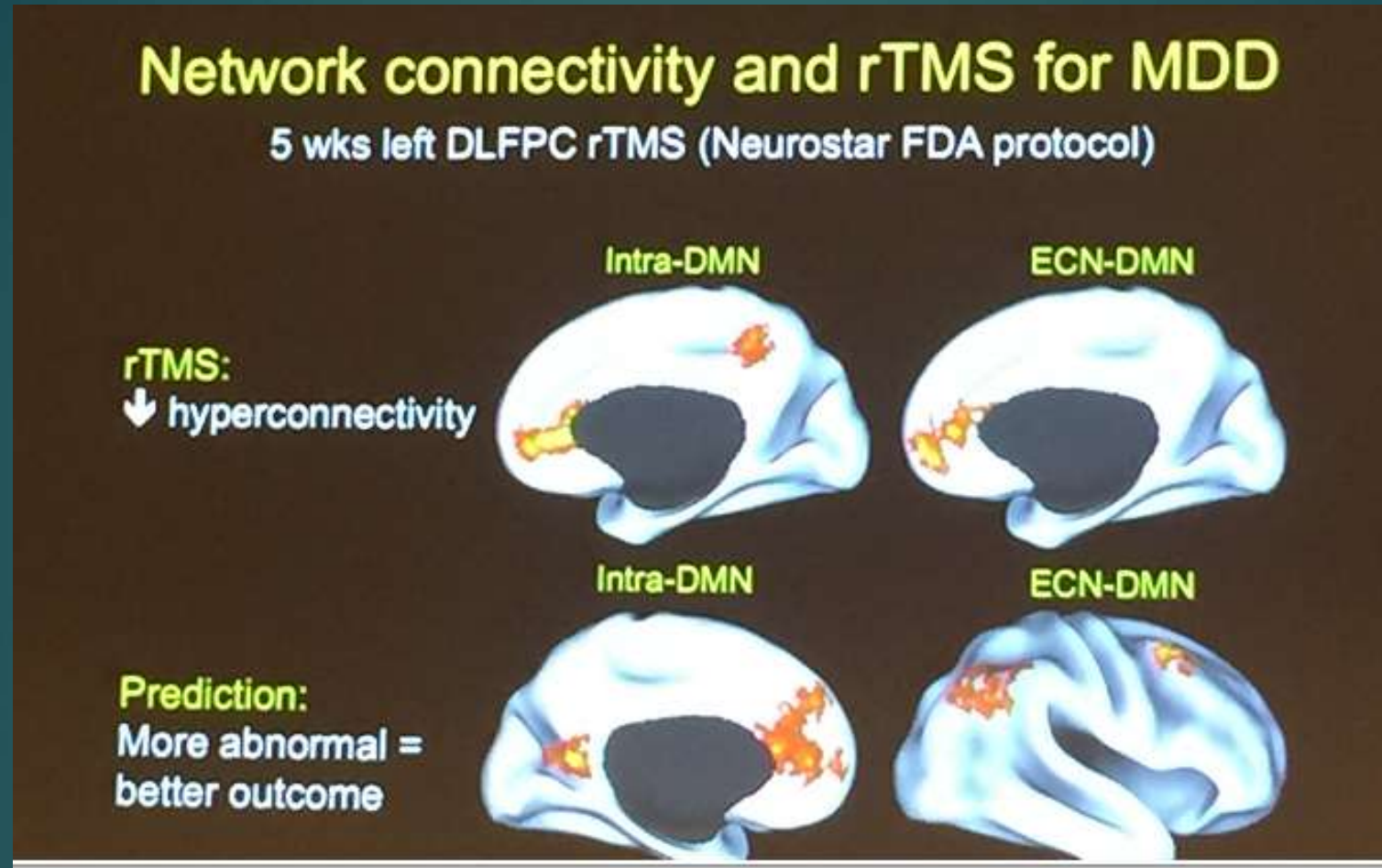
Concurrent TMS/fMRI
as a network tool



Tx implications

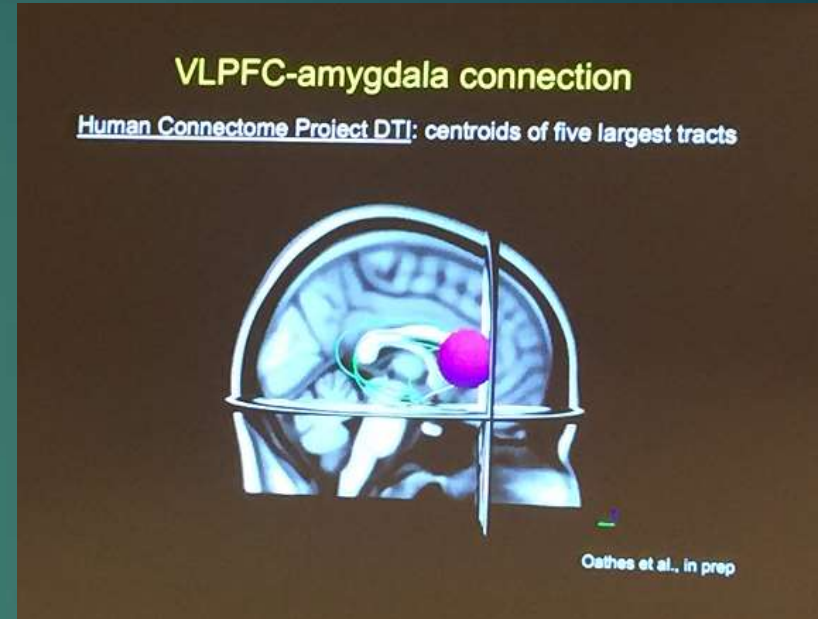
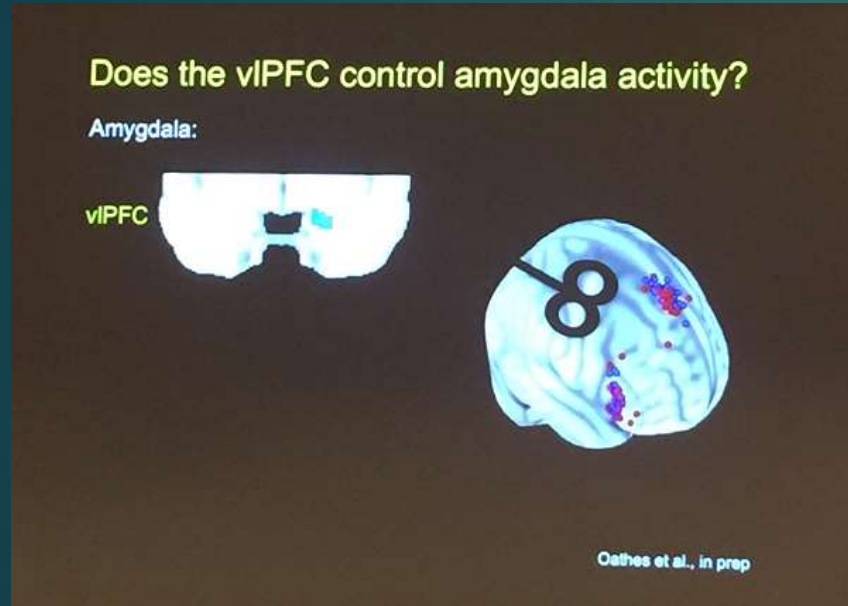
- ▶ The DMN shows various abnormalities in a range of neuropsychiatric disorders, including depression, posttraumatic stress disorder, schizophrenia, Alzheimer's disease, and autism.
- ▶ We also note in particular that the MPFC, which is one key part of the DMN, has been postulated to be critical for the antidepressant effects of medications and rTMS.
- ▶ It is therefore intriguing that the MPFC-regulating CEN node (pMFG) was located 5–6 cm anterior of primary motor cortex, consistent with current methods for localizing the clinical rTMS stimulation site.
- ▶ Thus, because connectivity-guided modulation of this node selectively regulates the MPFC/DMN, our results may serve as a unique platform for circuit-driven interventions in humans, including for depression.

rTMS treatment of MDD



Repetitive transcranial magnetic stimulation (TMS) of the dorsolateral prefrontal cortex (DLPFC) is an established treatment for depression. Abnormalities in two large-scale neuronal networks—the frontoparietal central executive network (CEN) and the medial prefrontal-medial parietal default mode network (DMN)—are consistent findings in depression and potential therapeutic targets for TMS.

vIPFC controls Amygdala



rTMS to the right side of the vl frontal gyrus increased connectivity between the amygdala and the ventral anterior cingulate cortex more than stimulation to the left side. Stimulation of the posterior portion of the medial frontal gyrus increased connectivity more than stimulation of the anterior portion.

rTMS Implications per Etkin at Stanford

- ▶ Brain processes drive sx's, i.e. reward circuits & anhedonia
- ▶ Use of deep rTMS predicted to be available in 1 year, ultrasound: induce neuroplasticity, not just mood change
- ▶ Hope there will be no DSM6
- ▶ Concept of specific symptoms is suspect given transdiagnostic data
- ▶ Goal: fmri for normal vs abnormal circuits; dx is irrelevant
- ▶ Goal of Tx: enhance neural circuit compensation

References

- ▶ American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (Revised 4th ed.). Washington, DC: Author.
- ▶ The functional neuroanatomy of PTSD: a critical review. Liberzon, I. Sripada, C.S. 2008

References

- ▶ Prog Brain Res, 2008; 167 151-69
- ▶ Charney DS, Deutsch AY, Krystal JH, Southwick SM, Davis M. Psychobiologic mechanisms of post-traumatic stress disorder. Arch Gen Psychiatry 1993; 50: 295–305.
- ▶ Kulka, R.A., Schlenger, W.A., Fairbanks, J.A., Hough, R.L., Jordan, B.K., Marmar, C.R.,... Cranston, A.S. (1990). *Trauma and the Vietnam War generation: Report of findings from the National Vietnam Veterans Readjustment Study*. New York: Brunner/Mazel.
- ▶ Rauch SL, Shin LM, Whalen PJ, Pitman RK. Neuroimaging and the neuroanatomy of post-traumatic stress disorder. CNS Spectrums 1998; 7S: 30–41.
- ▶ van der Kolk, B. A. (1994, January). The body keeps the score: Memory and the evolving psychobiology of posttraumatic stress by Bessel van der Kolk. Harvard Review of Psychiatry, 1(5): 253-265, Prog Brain Res. 2008;167:151-69.
- ▶ van der Kolk BA. The psychobiology of post-traumatic stress disorder. J Clin Psychiatry 1997; 58S: 16–24.
- ▶ van der Kolk BA. The psychobiology of post-traumatic stress disorder. In *The Textbook of Biological Psychiatry. Edited by Jaak Panksepp* Copyright © 2004 by Wiley-Liss, Inc. ISBN: 0-471-43478-7
- ▶ Yehuda R. Recent developments in the neuroendocrinology of post-traumatic stress disorder. CNS Spectrums 1998; 7S: 22–29.