Francisco de Goya

The Sleep of Reason Produces Monsters

El sueno de la razon produce monstruos, 1799
Francisco de Goya

The Sleep of Reason Produces Monsters

El sueno de la razon produce monstruos, 1799

• Evolution & Organization of the Human Brain
• Biological underpinnings of PTSD (?)
Paul MacLean: The Triune Brain

Neo-Mammalian
- Cognition

Cold Light

Reflexes:
- Immediate
- Involuntary
- Inflexible
- Unconscious

Paleo-Mammalian
- Emotionality
- Species-Specific Social Behavior

Warm Light
Paul MacLean: The Triune Brain
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Paul MacLean: The Triune Brain
Man: More Lama Less Mule
Stimuli Entering the Brain: Evoke all 3 Response Propensities
The Well-Integrated Personality is a Well-Integrated Brain
The Amygdala is at the Apex of the Limbic System
All Three Brains can See
“Blindsight”
Learning, Extinction, & Relearning

Acquisition: Gradual
Extinction: Gradual
Re-Acquisition: Immediate
Is Extinction “Unlearning”

Visual Cortical Lesions
- Can *Still* acquire a Conditioned Emotional Response (Fear)
- Cannot Extinguish!
Is Extinction “Unlearning”

Disruption of Visual Cortical Connections to Frontal Cortex
- Can *Still* acquire a Conditioned Emotional Response (Fear)
- Cannot Extinguish!
Extinction is New Learning

1st: The Amygdala learns to fear a stimulus

2nd: The Frontal Cortex learns to ignore the stimulus (for now)

3rd: The Frontal Cortex Inhibits the Amygdala’s Fear Response
Neomammalian Brain regulates Paleomammalian Brain

Phase I:
- Extinction Acquired
- Ctx inhibits Amygdala
- No Fear Response

Phase II:
- Cortex Anesthetized
- Inhibition Failure
- Fear Response Returns

Phase III:
- Cortex Wakes up
- Inhibition Returns
- Fear Response Subsides
The Sleep of Reason Produces Monsters

Phase II:
• Cortex Anesthetized
• Inhibition Failure
• Fear Response Returns
PTSD: A Functional Disconnection Between Prefrontal Cortex & Amygdala?

Phase II:
- Cortex Anesthetized
- Inhibition Failure
- Fear Response Returns
Fear Potentiated Startle

Phase 1: Elevated Startle to Unexpected White Noise
Phase 2: Fear of shock Potentiates Startle in all Subjects
Phase 3: PTSD Patents do not respond to Safety Cue
PTSD: A Functional Disconnection Between Prefrontal Cortex & Amygdala?

Phase II:
- Cortex Anesthetized
- Inhibition Failure
- Fear Response Returns
Paul MacLean: The Triune Brain

Paul MacLean:
The Triune Brain

Neo-Mammalian
- Cognition
- Cold Light

Rene Descartes:
Cogito Ergo Sum

Blaise Pascal:
The Heart has it’s Reasons of which Reason Knows Not

Paleo-Mammalian
- Emotionality
- Species-Specific Social Behavior

Warm Light

Warm Light

Cold Light
The Heart has it’s Reasons of which Reason Knows Not

Fyodor Dostoevsky: *The Idiot*
“A sensation of existence in the most intense degree”

Patient R.A.: “Each time this happens, thoughts occur very clear and bright to me…as if this is what the world is all about…. [this is] the absolute truth.”
William James
The Peripheral Theory of Emotionality
Blasé Pascal & Solder’s Heart

Vagal Nerve Stimulation
For Intractable Depression

66-75% Ascending Sensory Fibers to the Amygdala
What is the Appropriate Intervention?

• Insight Therapy?
• Cognitive Therapy?
• Exposure Therapy?
Brain Stem Reflexes and the Knowledge of Good and Evil
Brain Stem Reflexes and the Knowledge of Good and Evil
Pre-Pulse Inhibition

An initial benign stimulus:

Inhibits startle reflex to a subsequent strong stimulus

Not due to:

• Anticipation
• Warning
• Experience
• Learning
PTSD: Hyper-Reactive to Benign Stimuli?

Grillon et al., 1996
PTSD: Hyper-Reactive to Benign Stimuli?

Grillon et al., *Biological Psychiatry*, 1998

<table>
<thead>
<tr>
<th></th>
<th>Session</th>
<th>Period</th>
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<tr>
<td></td>
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<td>PTSD veteransa</td>
<td>64.6 (6.1)</td>
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<td>92.5 (3.7)</td>
<td>93.2 (1.9)</td>
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S, safe; T, threat.

a$p < .007$ compared to non-PTSD civilians.
Does PTSD Change Personality?
or
Is There a Vulnerable Personality?

Grillon et al., 1996

Table 1:

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>State anxiety</th>
<th>Trait anxiety</th>
<th>Mississippi</th>
<th>Scale CES</th>
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<td>SD</td>
<td>Mean</td>
<td>SD</td>
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Grillon et al., 1998

Table 1. Mean (SD) Age and Psychometric Scores

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Mississippi</th>
<th>CES $^a$</th>
<th>Trait anxiety</th>
<th>Session 1</th>
<th>Session 2</th>
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<tr>
<td>PTSD veterans ($n = 34$)</td>
<td>(3.4)</td>
<td>(20.3)$^b$</td>
<td>(8.9)$^c$</td>
<td>(10.4)$^d$</td>
<td>50.8</td>
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<td>Combat controls ($n = 17$)</td>
<td>(4.8)</td>
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<td>(9.3)</td>
<td>(10.8)</td>
<td>(12.6)$^e$</td>
<td>(11.7)$^d$</td>
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<tr>
<td>Civilian controls ($n = 14$)</td>
<td>(3.9)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>27.7</td>
<td>29.2</td>
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$^a$Combat exposure scale.
$^b$p < .0009 relative to combat controls.
$^c$p < .03 relative to combat controls.
$^d$p < .0009 relative to combat veteran controls.
William James
The Peripheral Theory of Emotionality

Vegal Nerve Stimulation
For Intractable Depression

66-75% Ascending Sensory Fibers to the Amygdala
PTSD and the Triune Brain

The Paleo-Mammalian Brain:

- Too little inhibition from the Neo-Mammalian Brain (Limbic System)

- Too much excitation from the Reptilian Brain
How’s the Paleo-Mammalian Brain Doing?

The Paleo-Mammalian Brain regulates the release of stress hormones from the Adrenal Gland.

- Dopamine
- Nor-Epinephrine (Nor-Adrenalin)
- Epinephrine (Adrenalin)
- Cortisol – Increases expression of first three!!!!!

Stress Hormones produce visceral arousal for Fight-or-Flight (Think William James Peripheral Theory of Emotion)
How Does Cortisol Work?

Released by the adrenal gland in times of stress helps us deal with the stress (tiger)

The brain tells the adrenal gland:
   when and how much cortisol to release

The blood takes some of this cortisol to the brain
   For a hormone to work it must have a receptor
   to bind with.
Negative and Positive Feedback of Emotional Response

Positive Feedback Loop

Does the balance Between these two Loops determine Personality?

Negative Feedback Loop

Cortisol is Neurotoxic To the Hippocampus
Acute Tiger is Replaced by Chronic Boss

Positive Feedback Loop

Cortisol is Neurotoxic To the Hippocampus
The Furnace Melts the Thermostat

Does the balance Between these two Loops determine Personality?
The Melted Thermostat?
Combat Exposure & Hippocampal Volume

Closed Circles: PTSD

Gervits et al., *Biological Psychiatry*, 1996

Figure 2. Total hippocampal volume as a function of combat exposure scale score. Closed circles: PTSD subjects; open circles: non-PTSD subjects.
Exposure to threats (script) in sexually abused women with PTSD:

- 122% higher cortisol at exposure vs. abused women w/o PTSD
  ➢ Correlated with PTSD symptomology $r=0.70$
- 69% higher cortisol during recovery
- 60% higher cortisol at anticipation

- Greater Increase in sympathetic arousal: Elzinga, et. al.
  ➢ Heart rate
  ➢ Blood pressure (systole & diastole)
  ➢ Skin Conductance
  ➢ NOR-Epinephrine release
Elevated State Cortisol?

Adult sexual abuse is associated with elevated neuro-hormones in women with PTSD due to childhood sexual abuse. Friedman et al., *Journal of Traumatic Stress*, 2007

<table>
<thead>
<tr>
<th>Urine variables</th>
<th>Group</th>
<th>M</th>
<th>SD</th>
<th>t(67)</th>
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<td>Cortisol (μg/day)</td>
<td>No ASA</td>
<td>36.2</td>
<td>9.9</td>
<td>4.34***</td>
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<td>Norepinephrine (μg/day)</td>
<td>No ASA</td>
<td>31.1</td>
<td>9.7</td>
<td>3.14**</td>
<td>0.76</td>
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<td>Epinephrine (μg/day)</td>
<td>No ASA</td>
<td>4.9</td>
<td>2.6</td>
<td>1.17</td>
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<tr>
<td></td>
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<td>249.3</td>
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*Note. PTSD = posttraumatic stress disorder; ASA = adult sexual abuse.

**p < .01. ***p < .001.
Cause or Effect?

Does a stressful personality $\rightarrow \downarrow$ Hippocampus $\rightarrow \uparrow$ Vulnerability to PTSD?

Gilbertson et al., *Nature Neuroscience*, 2002
PTSD: High Co-Morbidity for Depression

**Major Depression:**

- Elevated, unregulated cortisol levels
  - Dexamethasone Suppression Test
  - Metyrapone reverses Tx-resistant MD
- Atrophy of Hippocampus
- Deficits of Cognition & Long-Term Memory
- Anhedonia

- All AD Tx stimulate BDNF production in Hippocampus
  (Brain-Derived Neurotrophic Factor)
  - Serotonergics
  - NOR-Adrenergics
  - ECT (Most potent Tx & Inducer of BDNF)
  - Exercise
  - Estrogen & DHEA
BDNF effects on Hippocampus

↑ Dendritic Arborization
↑ Synaptogenesis
↑ Neogenesis

Currently Depressed patients:
• ↓ L & R Hippocampus vs. Remitted Patients
• Negative correlation between Hippocampal size & Duration of MD
• Negative correlation between Hippocampal size & # of Episodes

(Does smaller Hippocampus lead to more severe illness?)

Caetano et al., *Psychiatric Research: Neuroimaging*, 2004
A Model of PTSD

Lack of Inhibition of fear response

Atrophy & Depression

Hyper-Reactivity
What about Impact of Families?
Early Life Trauma

• Increased risk of PTSD in adulthood from other traumas
  Reduced capacity to cope with subsequent Stress?

• Increased risk of Alcoholism in adulthood from early traumas
How does Nurturance lead to Permanent Changes in Adult Personality?

Licking & Grooming in infancy leads to a Permanent Increase in:

- Cortisol receptors in the Hippocampus
- The Negative Feedback Pathway
- Thus, tighter regulation of the stress response
- Even with cross-fostering
- Critical Period!
How does Nurturance result in more Hippocampal Cortisol Receptors?

• Nurturance removes a Methyl Group (CH₃) from the gene that codes for the Cortisol Receptor in Hippocampal neurons

• Methylation inhibits gene expression

• Demethylation promotes gene expression
Nurturance does it Again!

- DNA is wrapped around a protein skeleton called Histone.
- The tighter the wrap, the less gene expression.
- Attaching an Acetyl group loosens the wrapping, thus increasing gene expression.
- Nurturance acetylates histones, thus increasing gene expression.
Summing Up

Mothering Style Permanently Alters:

• Genetic expression (De-Methylation, Acetylation)

• Brain biochemistry (Cortisol Receptors)

• Endocrine (hormone) physiology (cortisol expression)

• Personality & Behavior (Fear, Exploration, Stress Response)

• Loss of Memory & Cognition with Age

• Risk of Psychopathology (Learned Helplessness – Depression)
But Wait! – There’s More!

High nurturance results in:

More benzodiazepine receptors in the Amygdala

- The emotion center of the brain
- Change is permanent
- What’s a benzodiazepine?
  Valium
  There may be natural valium substances in the brain