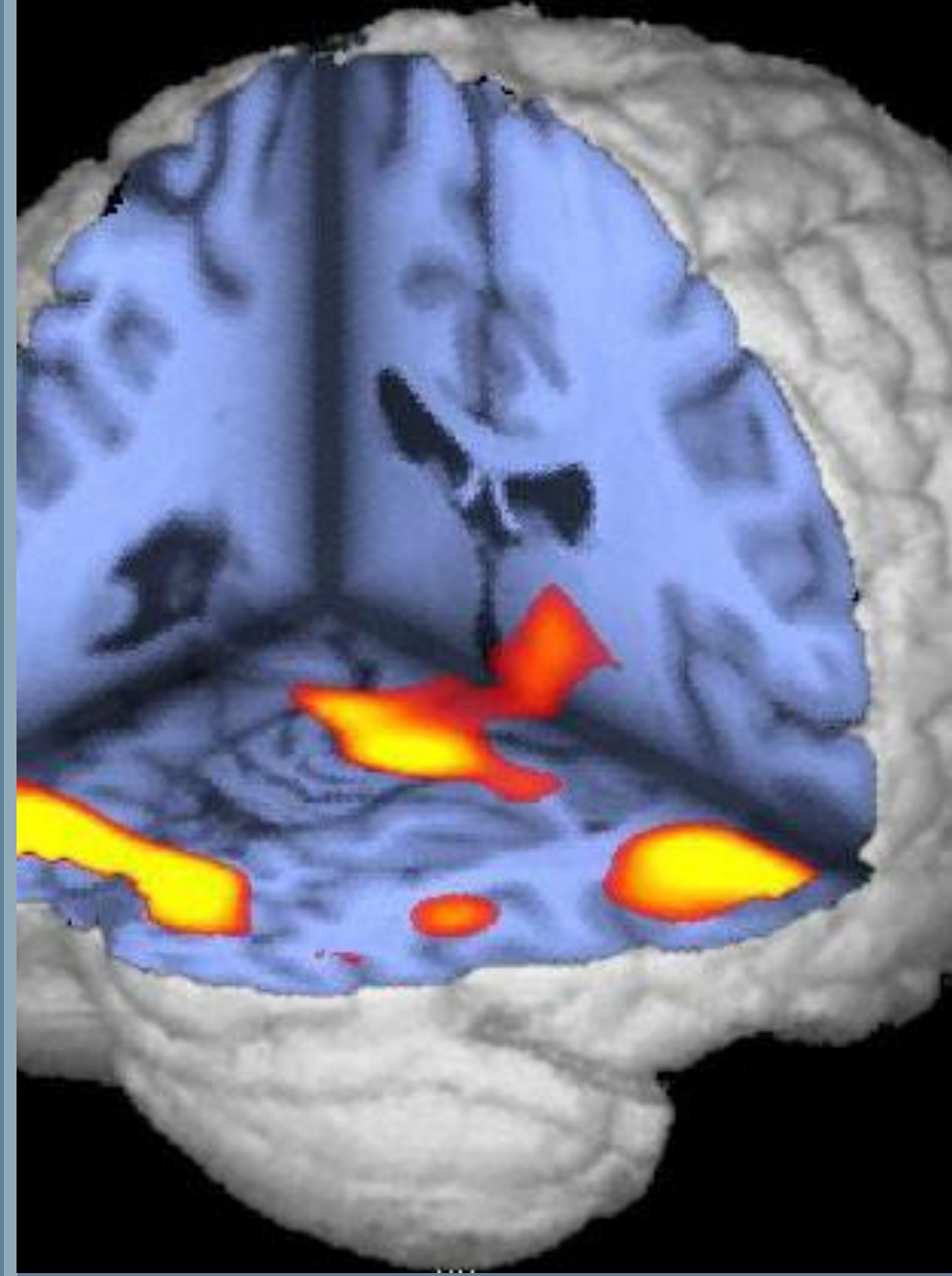




HARVARD
MEDICAL SCHOOL

Functional Neurocircuitry of Affective and Behavioral Processes and Neuropsychiatric Syndromes

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Brigham and Women's Hospital
Harvard Medical School



Disclosure

- Ceretype Neuromedicine; Co-Founder and SAB Chair; no overlapping products or services discussed
- No other related activities

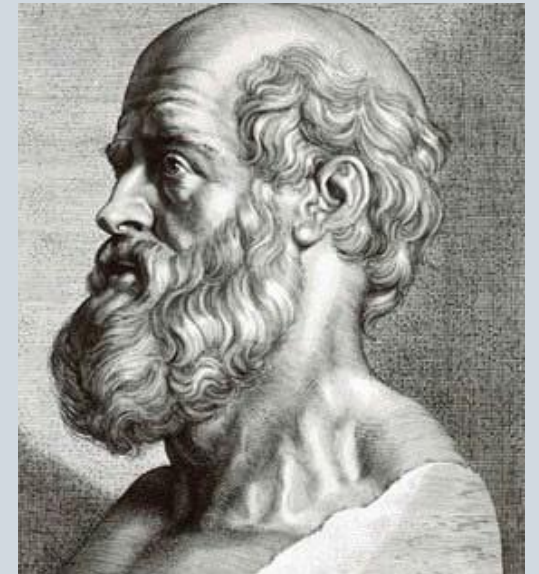
Outline

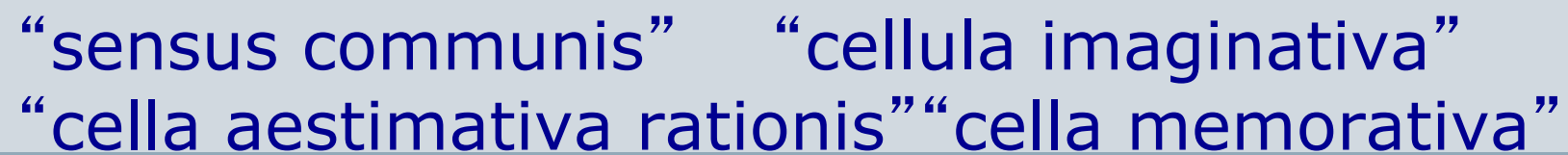
- Translational Functional Neuroimaging
- Neurocircuitry of Interest
- Selected Neuropsychiatric Disease Examples
- Synthesis: Integrated Brain Circuit Model of Emotion / Behavior

Hippocrates (460 – 377 BC)

“And men ought to know that from nothing else but thence [from the brain] come joys, delights, laughter and sports, and sorrows, griefs, despondency, and lamentations.

And by this... we acquire wisdom and knowledge, and see and hear and know what are foul and what are fair... And by the same organ we become mad and delirious, and fears and terrors assail us...”





Translational Methods

Basic Science

Clinical Systems Level Neuroscience



+ cognitive, affective, social neuroscience

Transcending the Mind-Brain, Psychiatry-Neurology Divide

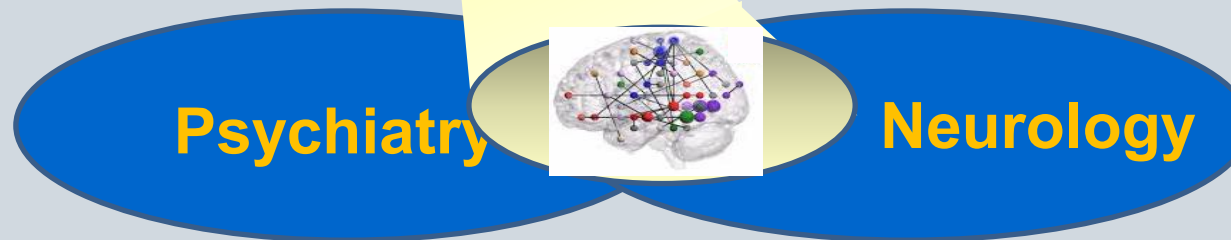


Neuroimaging in Psychiatry: A Quarter Century of Progress

David A Silbersweig¹, Scott L Rauch

Affiliations + expand

PMID: 28885277 DOI: [10.1097/HRP.0000000000000177](https://doi.org/10.1097/HRP.0000000000000177)

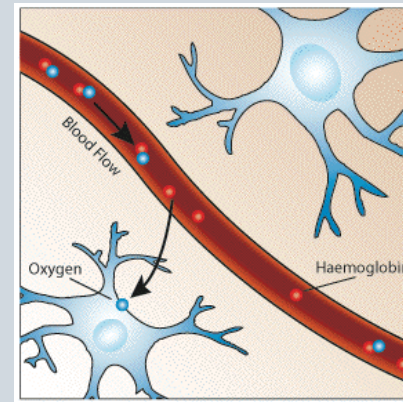


- From node to network (region to connectome)
- From correlation to causation to prediction
- From localization to targeted intervention

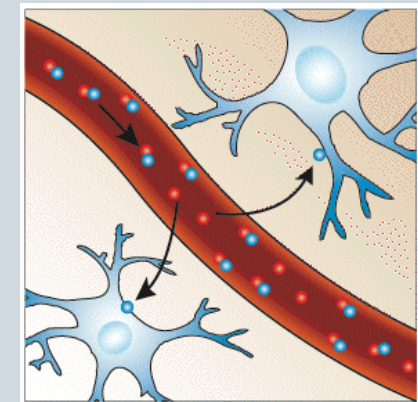
The Role of Neuroimaging



- mapping of brain states associated with mental states
- *in vivo*
- non-invasive

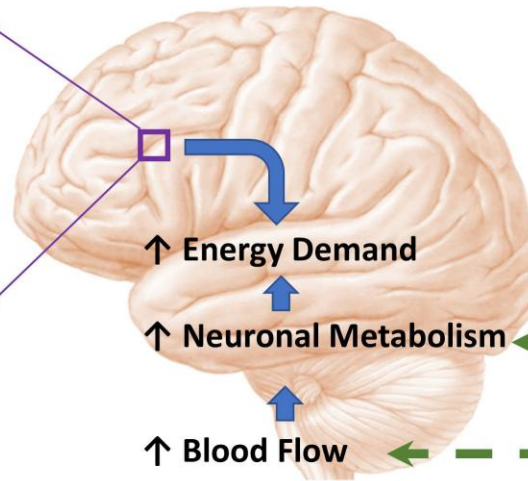
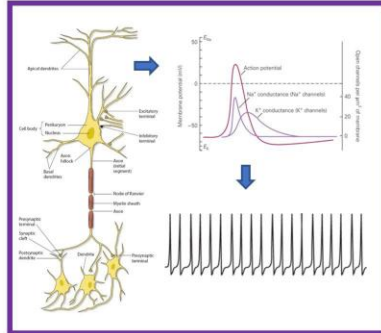


Resting



Activated

Region of focal brain activation



↑ Energy Demand

↑ Neuronal Metabolism

↑ Blood Flow

↑ Blood Volume

↑ Blood Oxygenation
(relative decrease in deoxyhemoglobin)

↑ Glucose, Oxygen

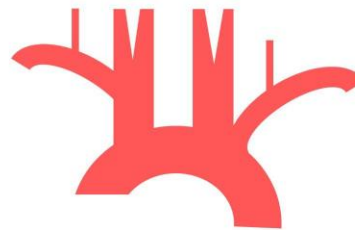
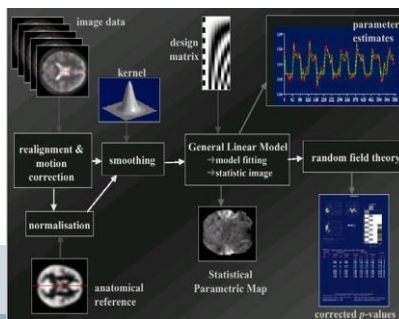
Functional Neuroimaging Method
(PET and fMRI)

← ^{18}F -FDG PET

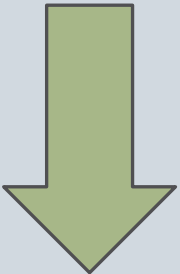
← H_2^{15}O PET; Arterial Spin Labeling fMRI

← ^{11}CO PET; Gadolinium DTPA fMRI

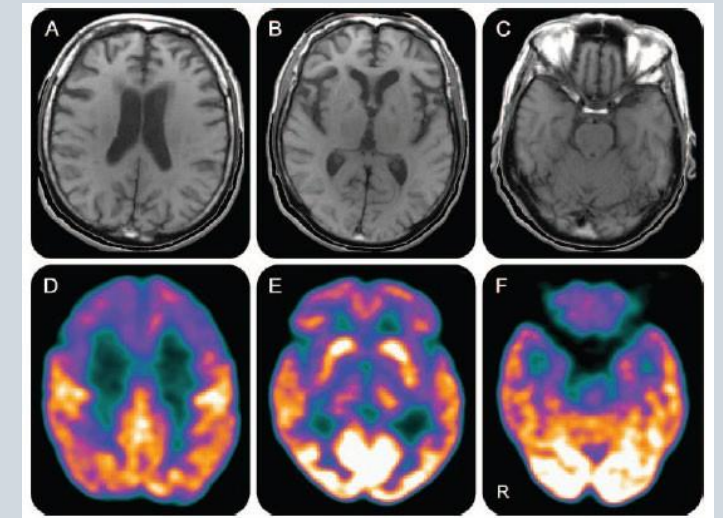
← BOLD fMRI



Functional neuroimaging applications

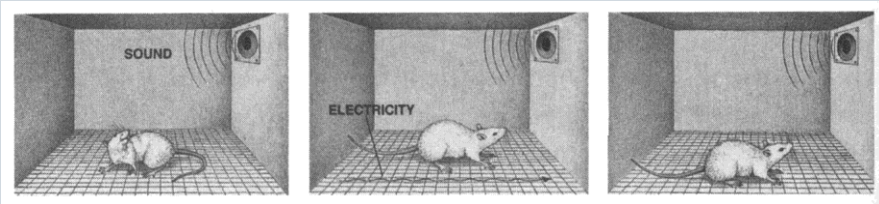
- Research
 - Normal brain function
 - Psychiatry
 - Neurology
 - Neurosurgery
- 

Clinical
Translational
- Clinical
 - Presurgical mapping (fMRI)
 - Post-RT change versus tumor recurrence (PET)
 - Neurodegenerative disorders, i.e. Alzheimer's, Parkinson's (PET)
 - Epilepsy (PET, fMRI)



Translational Approach

Example: Fear Conditioning and Threat Processing



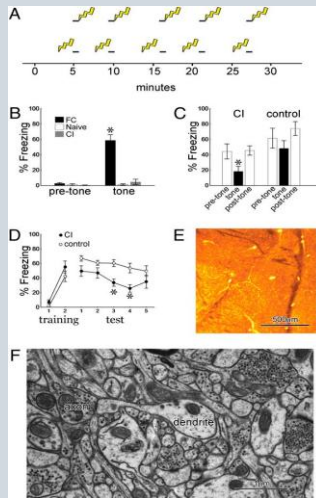
LeDoux et al

Animal Behavior

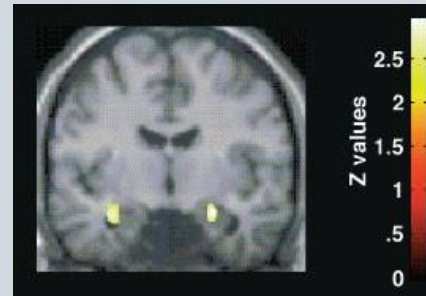
Cellular/Molecular

Healthy Humans

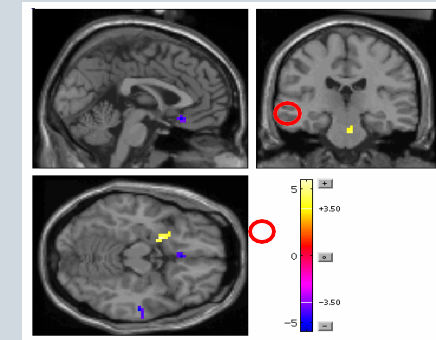
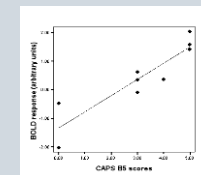
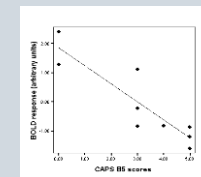
PTSD Patients



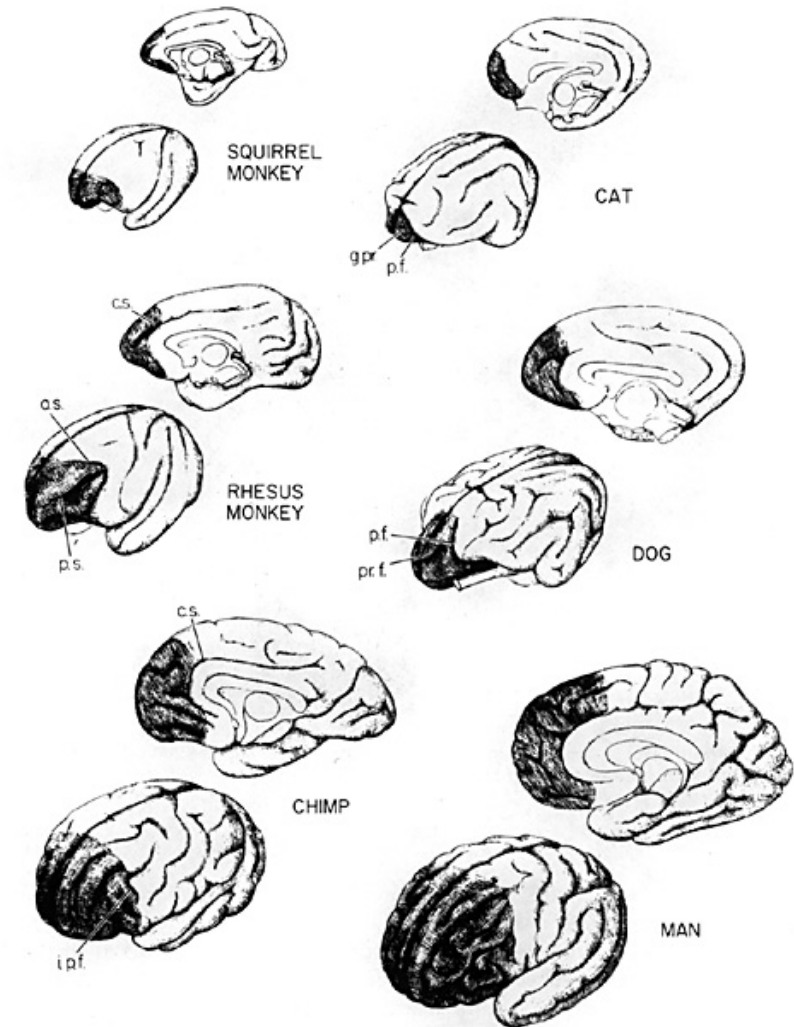
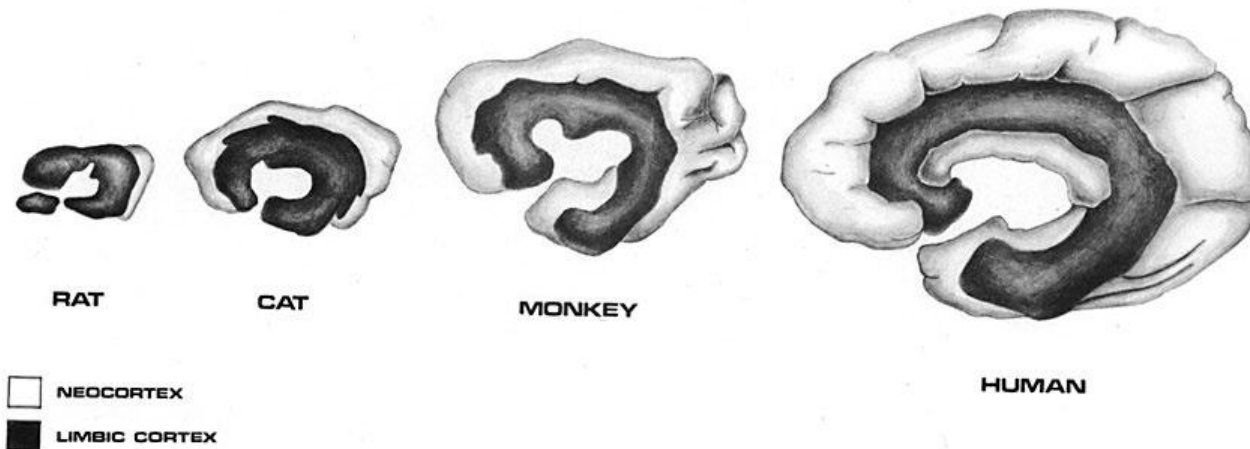
Ostroff et al, 2010



Isenberg et al, 1999



Evolutionary Context: Limbic and Prefrontal Cortex Across Species



Neurocircuitry of Interest

Functional Domains:

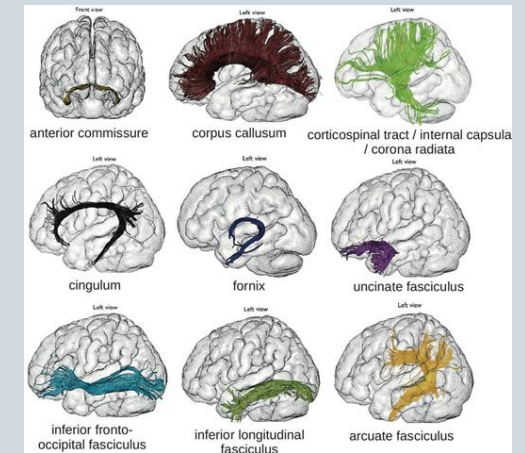
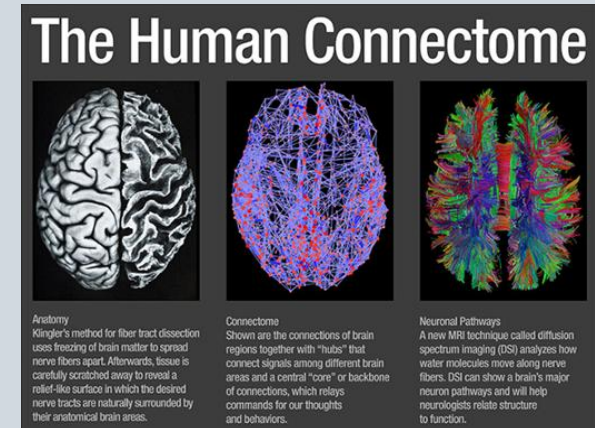
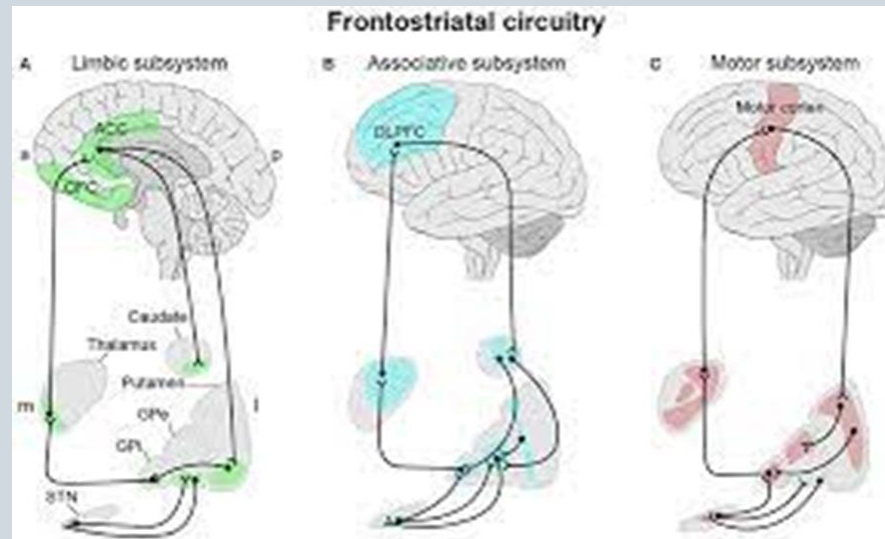
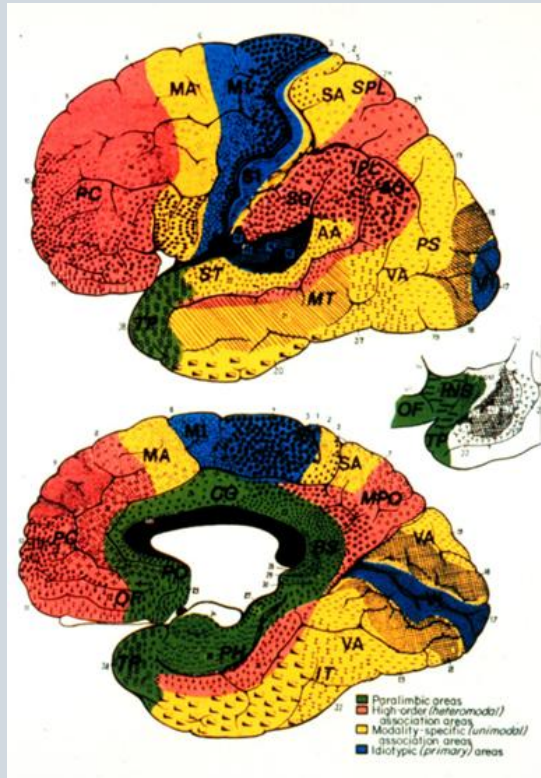
Threat Detection and
Defensive Responses
Limbic Circuitry

Reward and
Motivational Processing
Ventral Striatum, Associated Regions

Appraisal and
Top-Down Modulation
Prefrontal Regions

Systems Related to
Subjective Feeling,
Social Function
Insular Cortex, dmPFC, TPJ

Behavioral/Functional Neuroanatomy: Nodes and Circuits



Neurocircuitry of Interest

Functional Domains:

**Threat Detection and
Defensive Responses
Limbic Circuitry**

Reward and
Motivational Processing
Ventral Striatum, Associated Regions

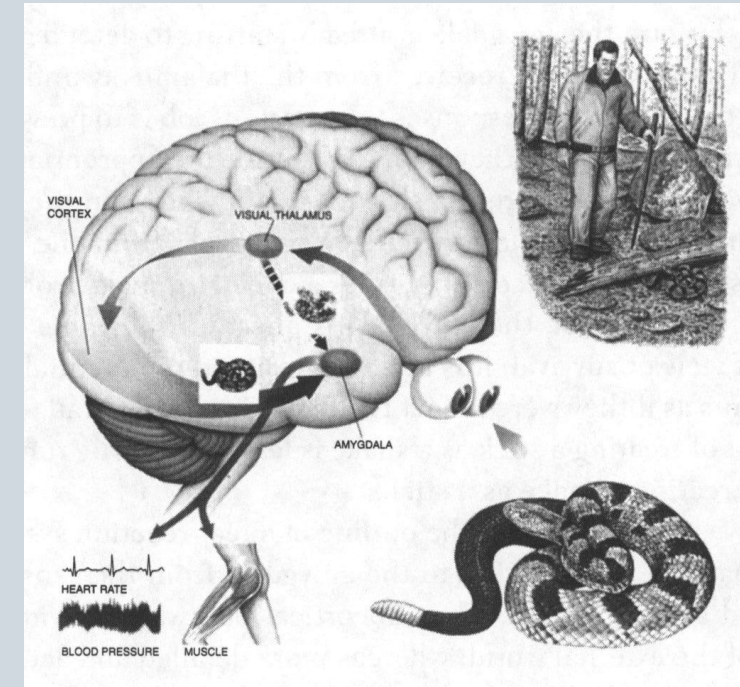
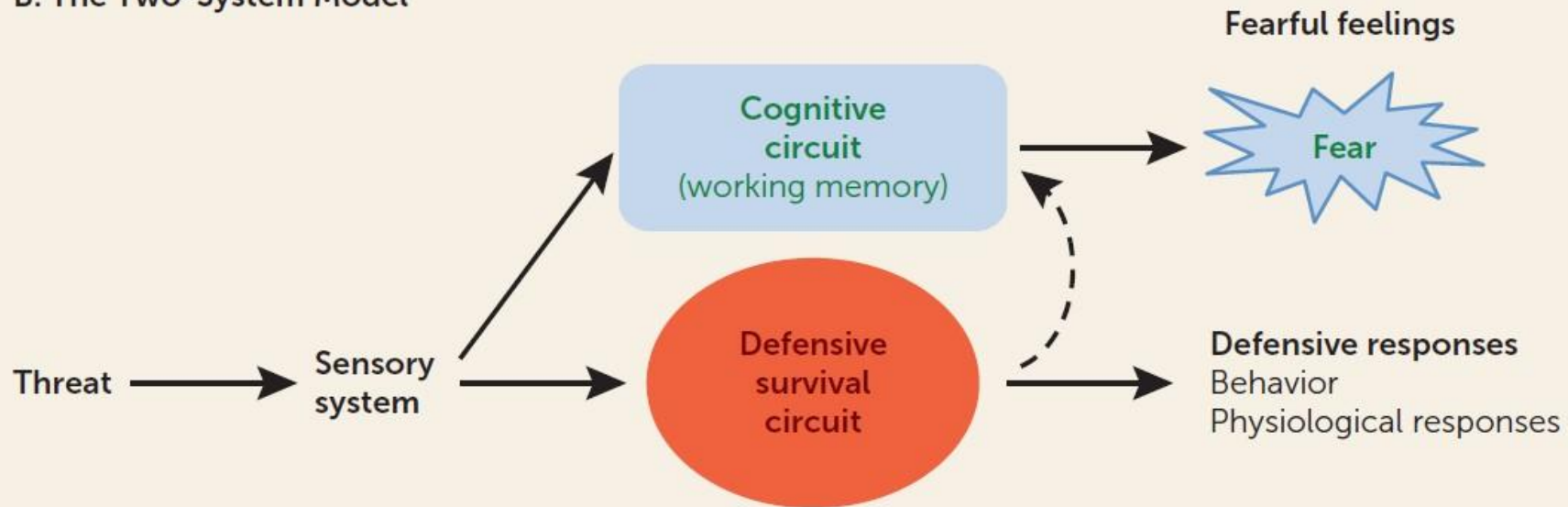
Appraisal and
Top-Down Modulation
Prefrontal Regions

Systems Related to
Subjective Feeling,
Social Function
Insular Cortex, dmPFC, TPJ

Threat Detection / Defensive Responses

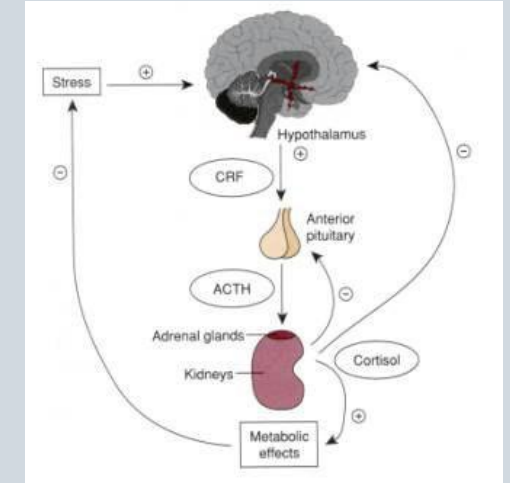
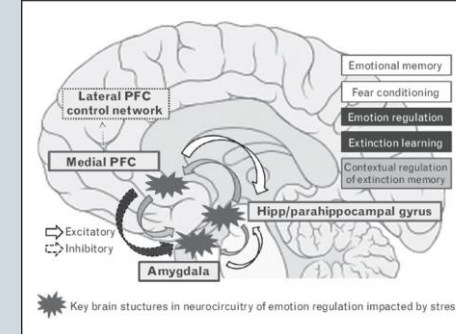
Reflexive behaviors (startle, freeze, flight, fight)
versus
Subjective experience and
Deliberate defensive actions (greater cortical involvement)

B. The Two-System Model

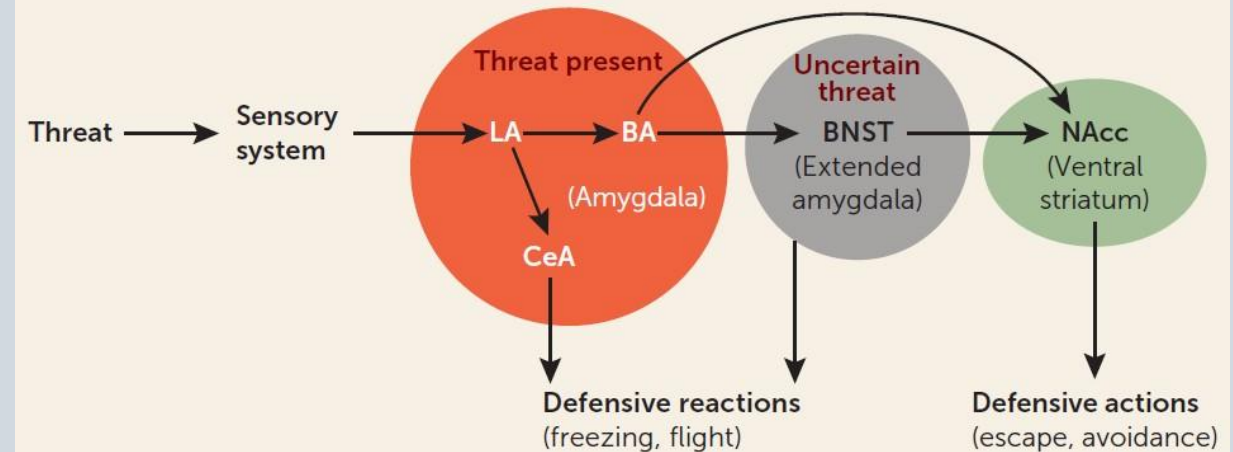


Threat Detection / Fear / Defensive Responses

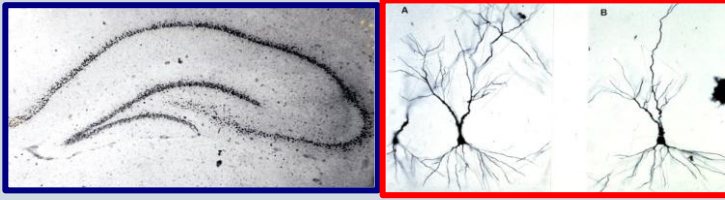
- Amygdala and bed nucleus of stria terminalis (BNST)
 - Lateral amygdala associated with sensory input
 - Central amygdala associated with reactions
 - Basal amygdala associated with defensive actions
- Immediate threat detected by sensory modalities is associated with amygdala
- Distant or uncertain threats are associated with BNST



B. Processing Present Versus Uncertain Threats

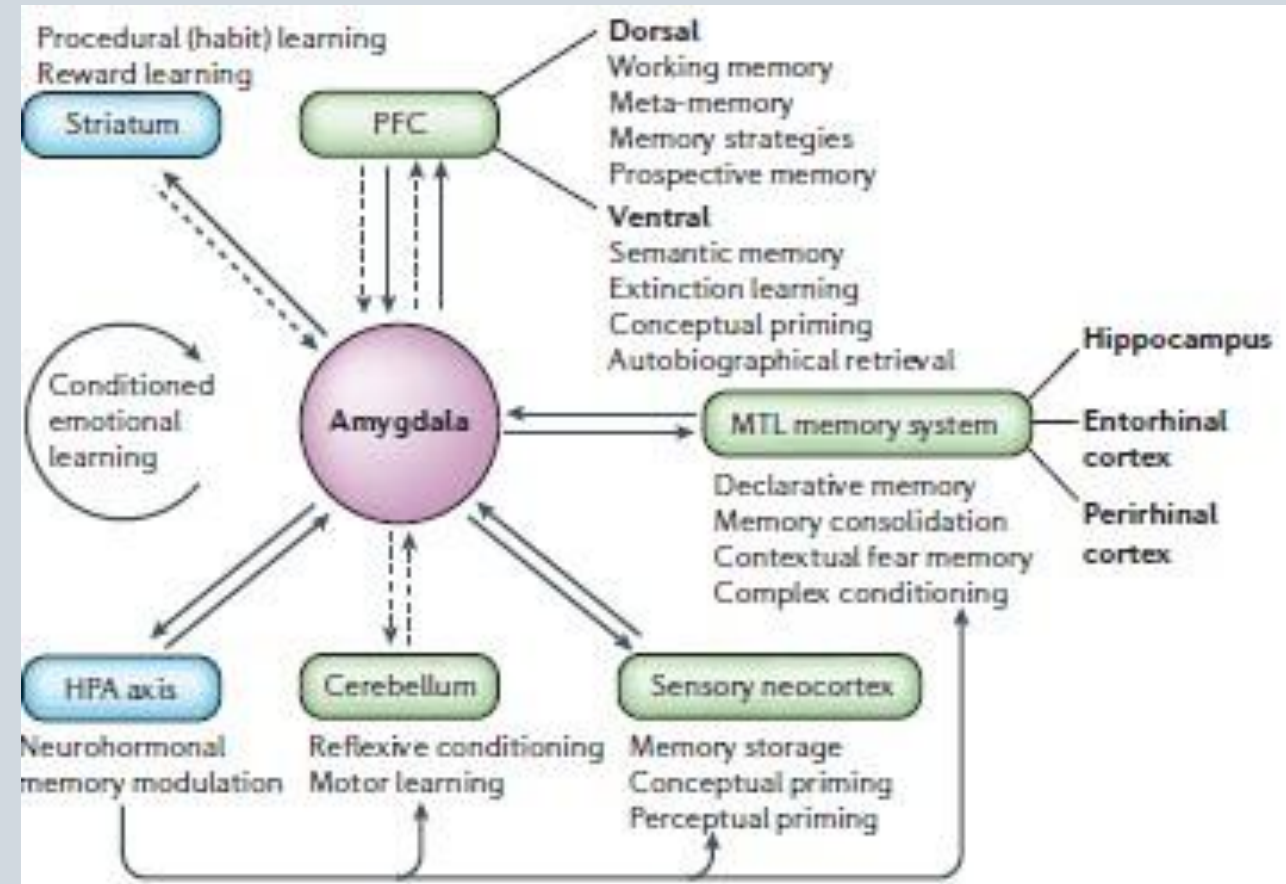


LeDoux & Pine, 2016



Stress

- Early life stress (i.e. physical abuse, neglect) has been associated with increased amygdala and decreased hippocampal and vmPFC volumes
 - May make the system hyperresponsive to cues associated w/ potential threat
- Neuromodulatory effect of stress hormones on hippocampus leads to greater long-term memory for emotionally charged events compared to neutral ones



Potential mechanisms by which the amygdala mediates the influence of emotional arousal on memory – Lebar and Cabeza 2006

Neurocircuitry of Interest

Functional Domains:

Threat Detection and
Defensive Responses
Limbic Circuitry

**Reward and
Motivational Processing**
Ventral Striatum, Assc. Regions

Appraisal and
Top-Down Modulation
Prefrontal Regions

Systems Related to
Subjective Feeling,
Social Function
Insular Cortex, dmPFC, TPJ

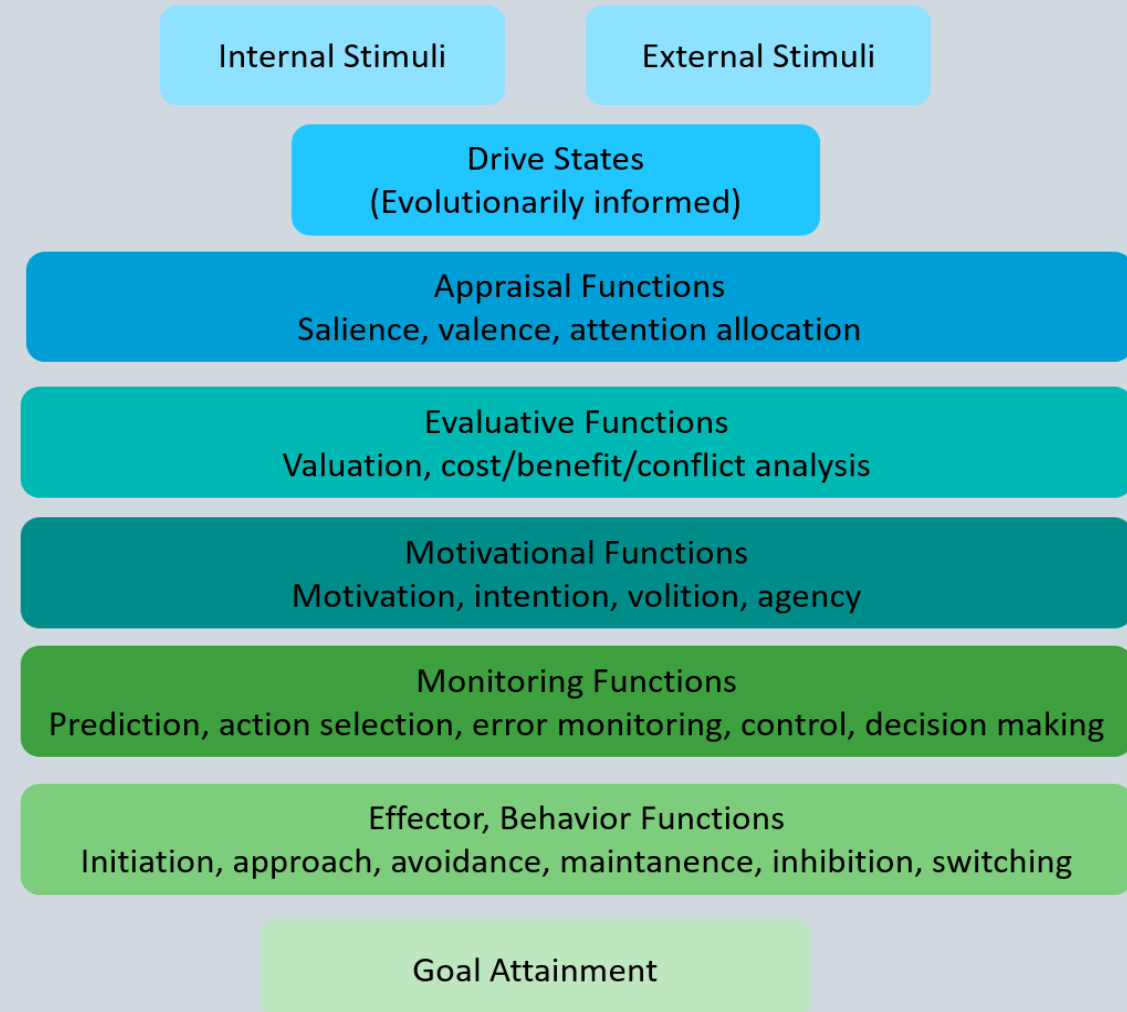
From Perception to Evaluation, Reward and Motivation

Nucleus accumbens

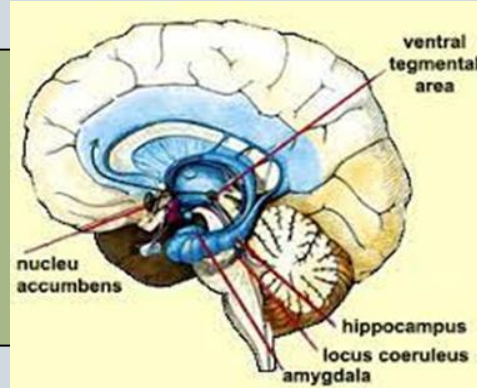
- Detects salient stimuli
- Assigns value
- Assists in balancing approach motivation with threat detection networks

Input

Output



Reward and Motivation



Nucleus accumbens

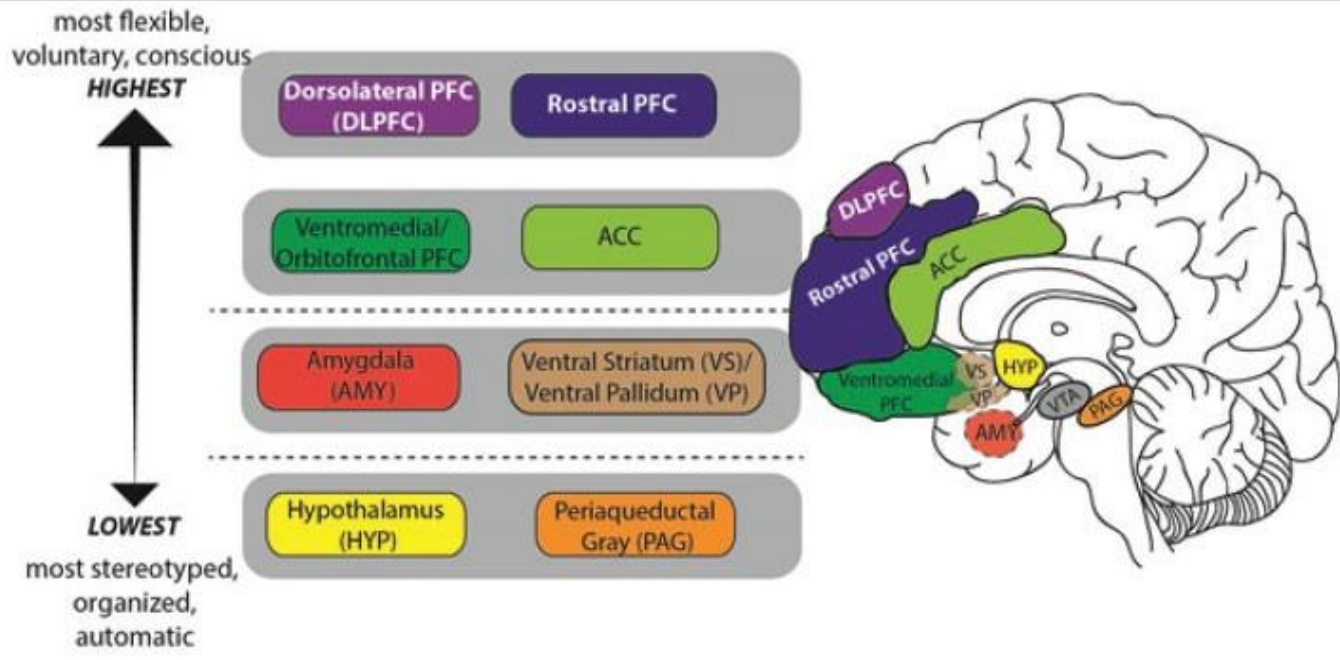
- Core
 - Related to approach behavior
 - Associated with dorsal striatum
- Shell
 - Related to aversion and nonrewarding stimuli
 - Associated with limbic structures

Hypothalamus

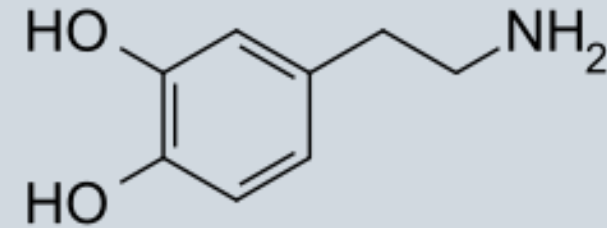
- Mediates basic drives (thirst, hunger)
- Influences salience of objects needed for survival

Prefrontal cortex (particularly orbitofrontal, ventromedial, and anterior cingulate)

- Assists in appraisal of potential rewards / outcomes



Reward and Motivation



Dopamine (DA) reward processing model:

1. Initial broad assessment of all sensory input identifying:
 - Stimuli similar to previous rewards
 - Involvement in reward-related contexts
 - Novel stimuli
2. Next step involves identifying specific value and utility
 - Balance reward, risk, delay
 - Compare to outcome, allowing for learning and updating value predictions

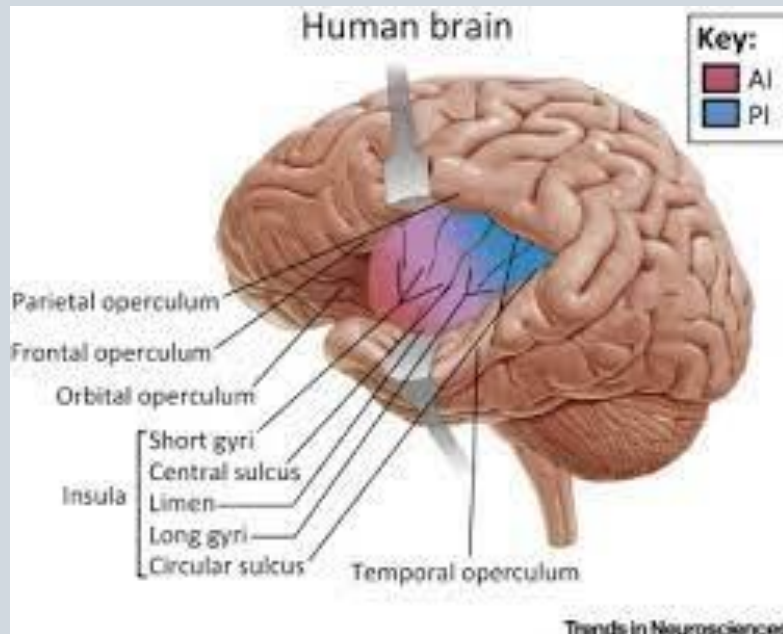
Reward and Motivation

versus

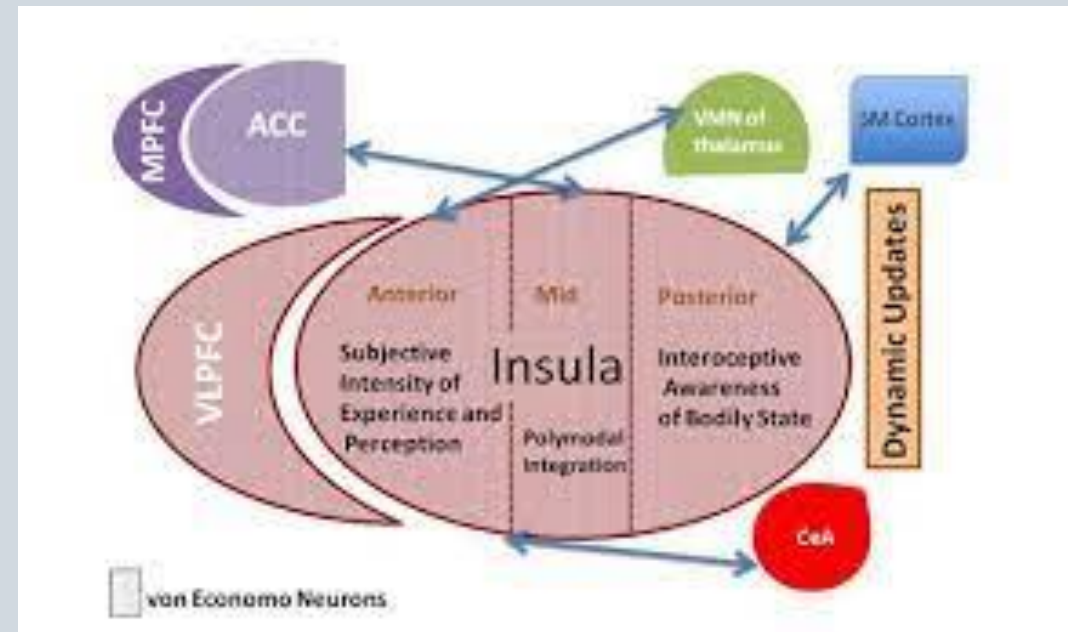
Threat Detection / Defensive Responses

- Balance of aversive / avoidant systems and approach systems
- Individual variations affect ultimate emotional experience and behavioral outcomes:
 - Genetic variation leading to baseline trait levels
 - Trauma history (especially early life)
 - External environmental reinforcers
 - Priming, inhibition, habituation, reinforcement/extinction learning
 - Pharmacologic mediation
 - Energy stores

Insula: Integration of Emotional, Social, Interoceptive, Sensory- Motor and Cognitive Information

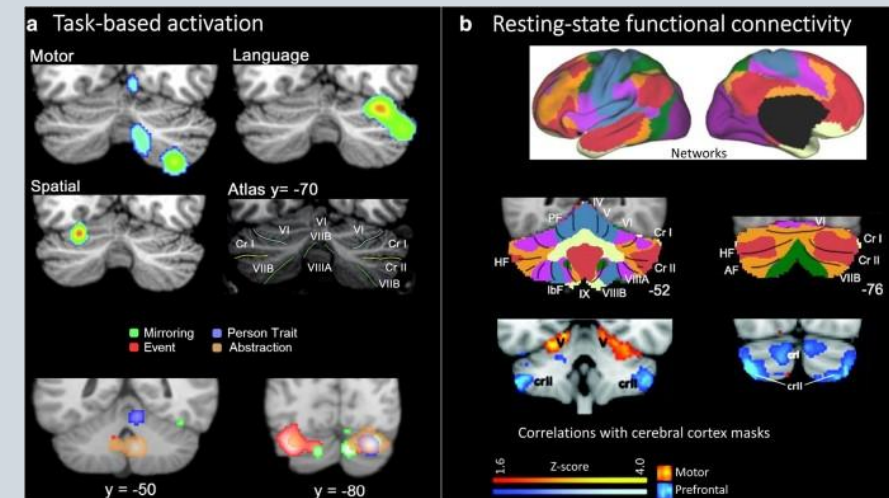
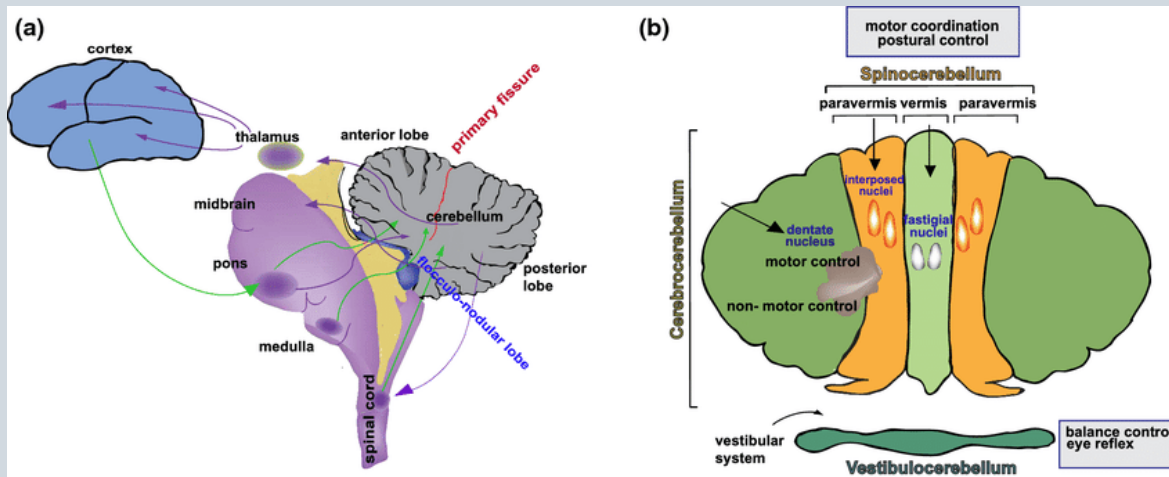


Namkung



Pavuluri

Cerebellum—Not Just Motor. Cognitive Affective Syndromes



Schmahmann

Neurocircuitry of Interest

Functional Domains:

Threat Detection and
Defensive Responses
Limbic Circuitry

Reward and
Motivational Processing
Ventral Striatum, Associated Regions

**Appraisal and
Top-Down Modulation
Prefrontal Regions**

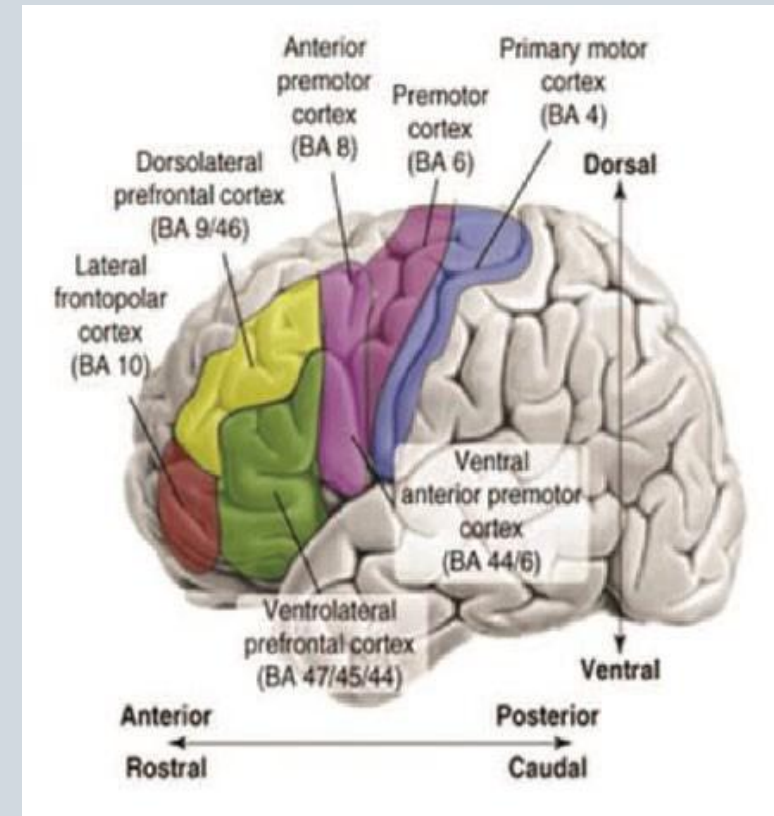
Systems Related to
Subjective Feeling,
Social Function
Insular Cortex, dmPFC, TPJ

Appraisal and Top-Down Modulation

Prefrontal cortices allow for:

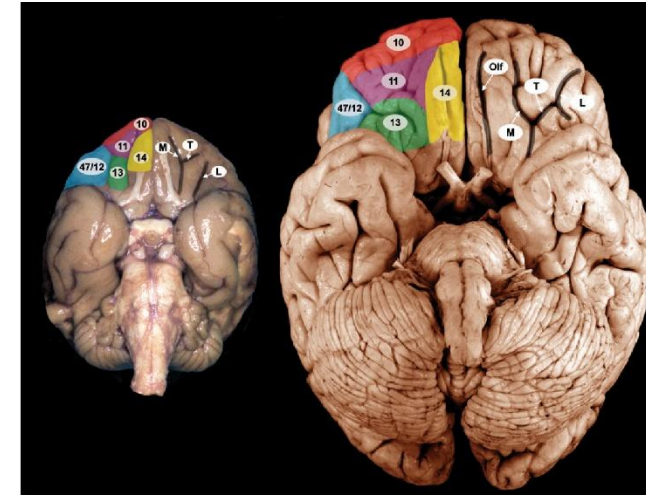
- Monitoring
- Planning
- Sustaining goal-directed activity
- Modifying behavior based on feedback / changing contingencies

*Higher order brain regions allow for flexibility in responses depending on environmental context.

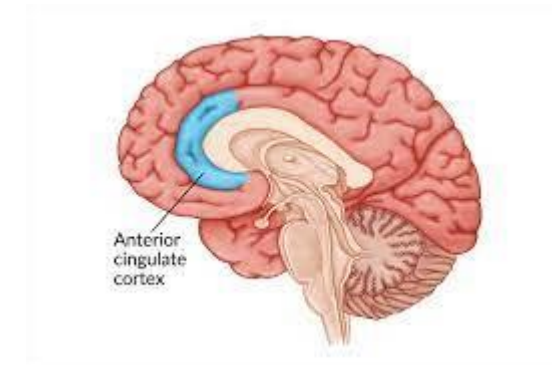
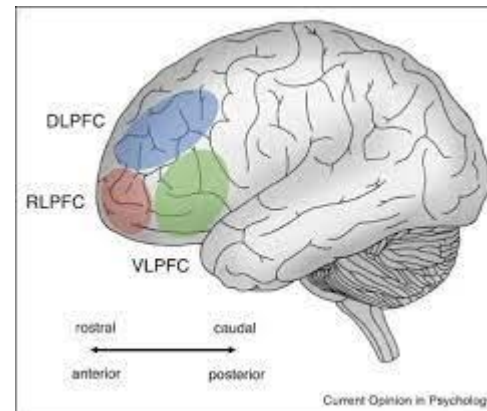
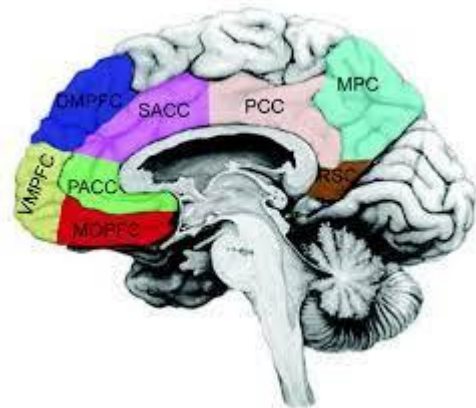


Prefrontal Cortices

Prefrontal Subsystems: Functions and Syndromes



Wallis



**Orbital, Medial, Dorsolateral, Dorsomedial,
Rostral**

Dixon et al, 2017

Appraisal and Top-Down Modulation

Lateral OFC

- Direct input from sensory modalities and limbic system
- Contributes to evaluation of **external** stimuli in context of current goals

Orbitofrontal Cortex (OFC)

Medial OFC

- Coactivated with limbic and default mode network
- Appraisal of **internal** stimuli (i.e. imagined future events and episodic memories)

Appraisal and Top-Down Modulation

Medial Prefrontal Cortex (mPFC)

Dorsomedial PFC (dmPFC)

- Appraisal of others' mental states
- Intuiting others' anticipated mental states to guide choices

Rostral medial PFC

- Appraisal of one's own mental state
- Appraisal of self-related information

Ventromedial PFC (vmPFC)

- Emotion regulation
- Altering behavior in response to environmental changes

Appraisal and Top-Down Modulation

Lateral Prefrontal Cortex

Dorsolateral PFC

- Frontoparietal attention networks
- Defer gratification / value future opportunities

Nonspecified lateral PFC

- Reappraisal of initial negative reactions

Ventrolateral PFC

Response inhibition

Goal appropriate response selection

Appraisal and Top-Down Modulation

Cingulate Cortex

Subgenual / Pregenual ACC

- Involved more in emotional processing
- Anticipates future physiological needs
- Assist in appraisal of interoceptive sensation

Dorsal ACC

- Involved more in cognitive processing (error/conflict monitoring)

Anterior MCC

- appraisal of actions and behaviors and their potential future outcomes

Neurocircuitry of Interest

Functional Domains:

Threat Detection and
Defensive Responses
Limbic Circuitry

Reward and
Motivational Processing
Ventral Striatum, Associated Regions

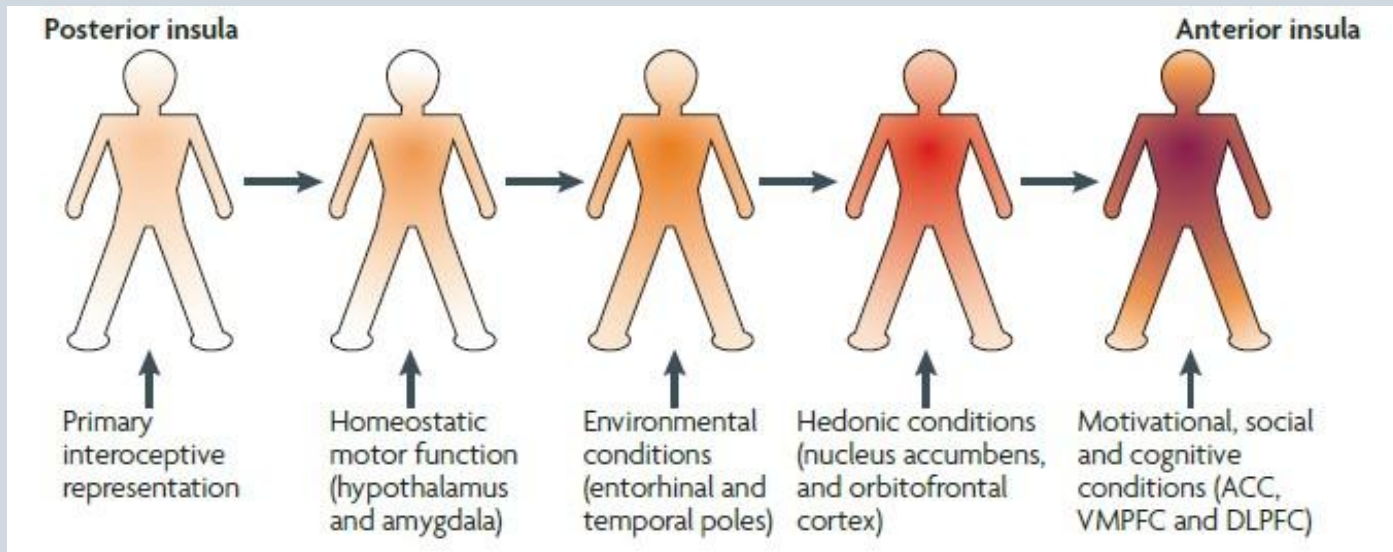
Appraisal and
Top-Down Modulation
Prefrontal Regions

**Systems Related
to Subjective
Feeling, Social
Function**
Insular Cortex, dmPFC, TPJ

Awareness of Self

Insular Cortex

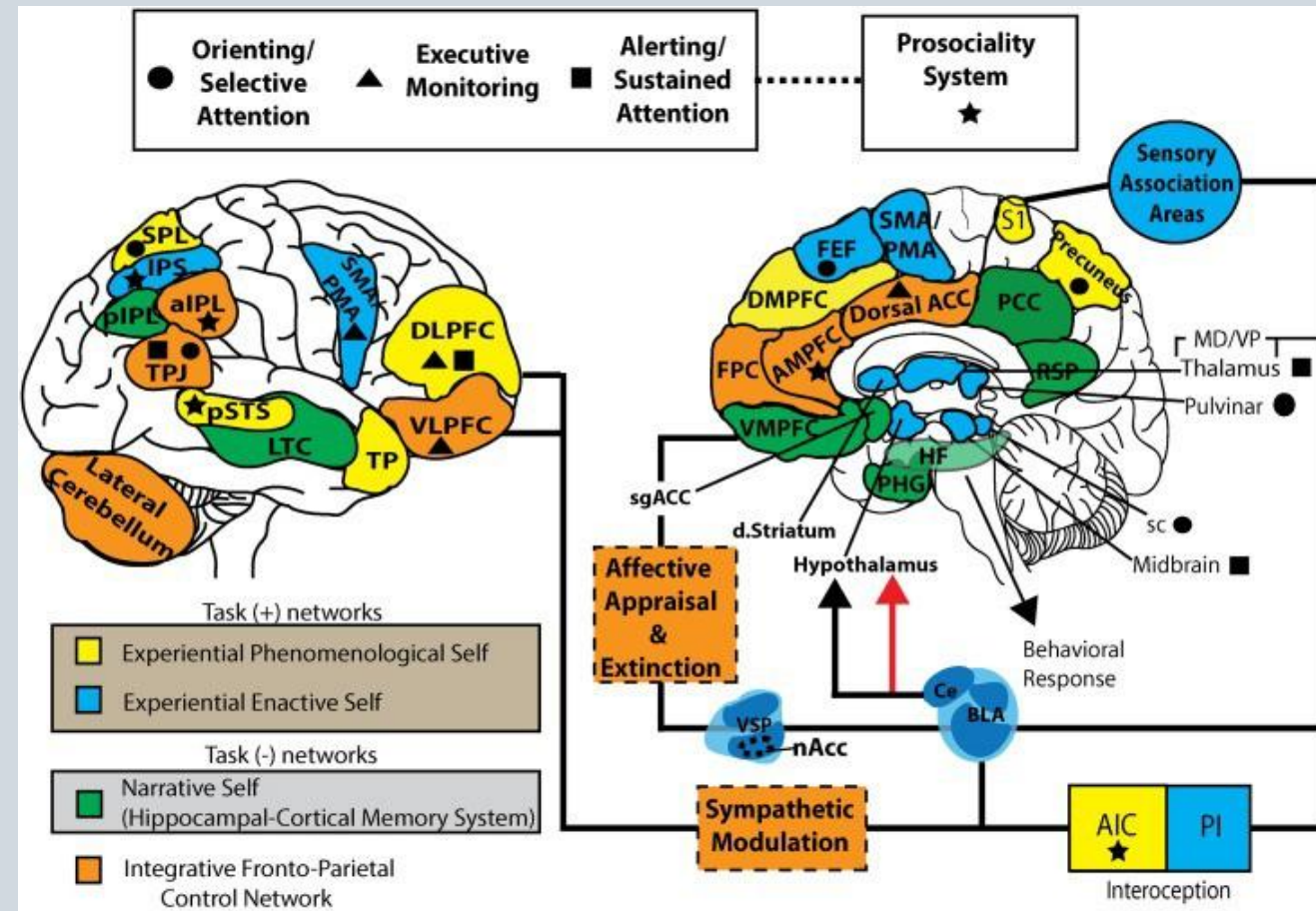
- Representation of interoceptive information
 - Posterior to anterior gradient
 - Primary interoceptive states
- ↓
- 'Global emotional moment'



Awareness of Self

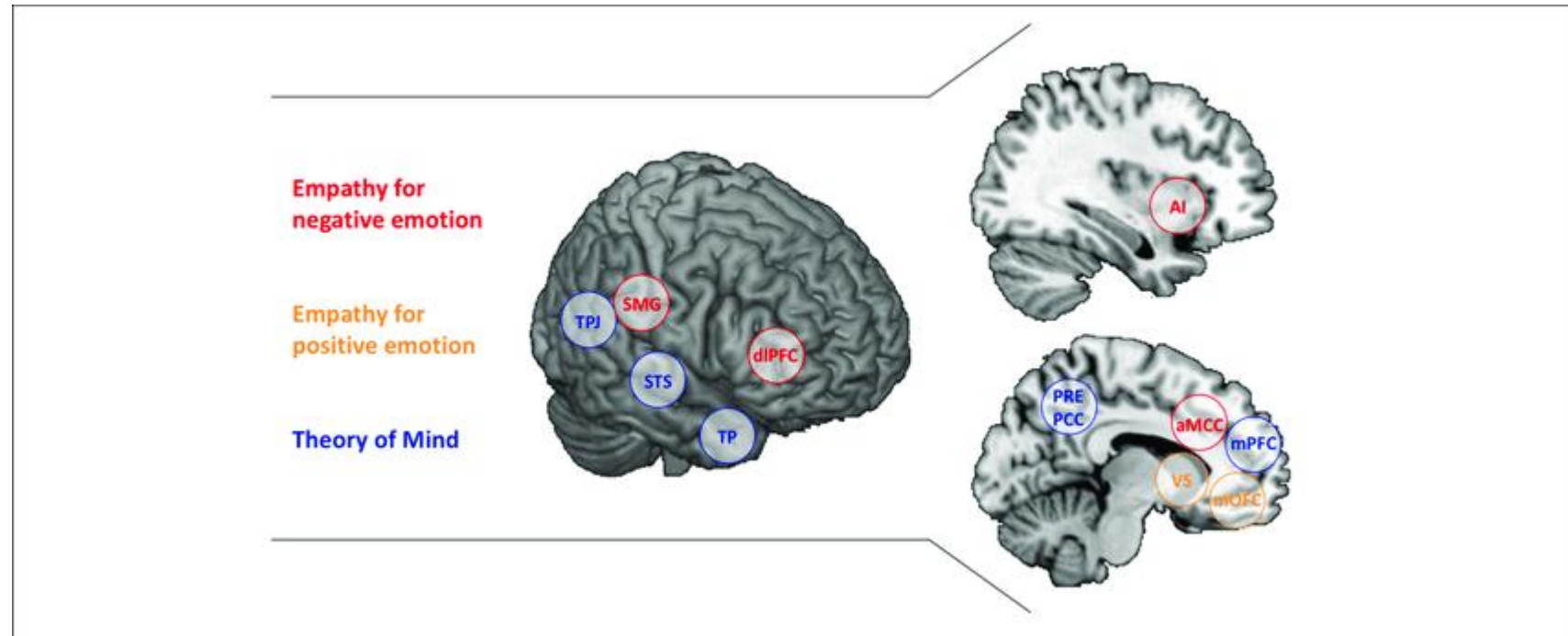
Different experiences of self:

- Task (+) experiential phenomenological self / experiential enactive self
- Task (-) narrative self



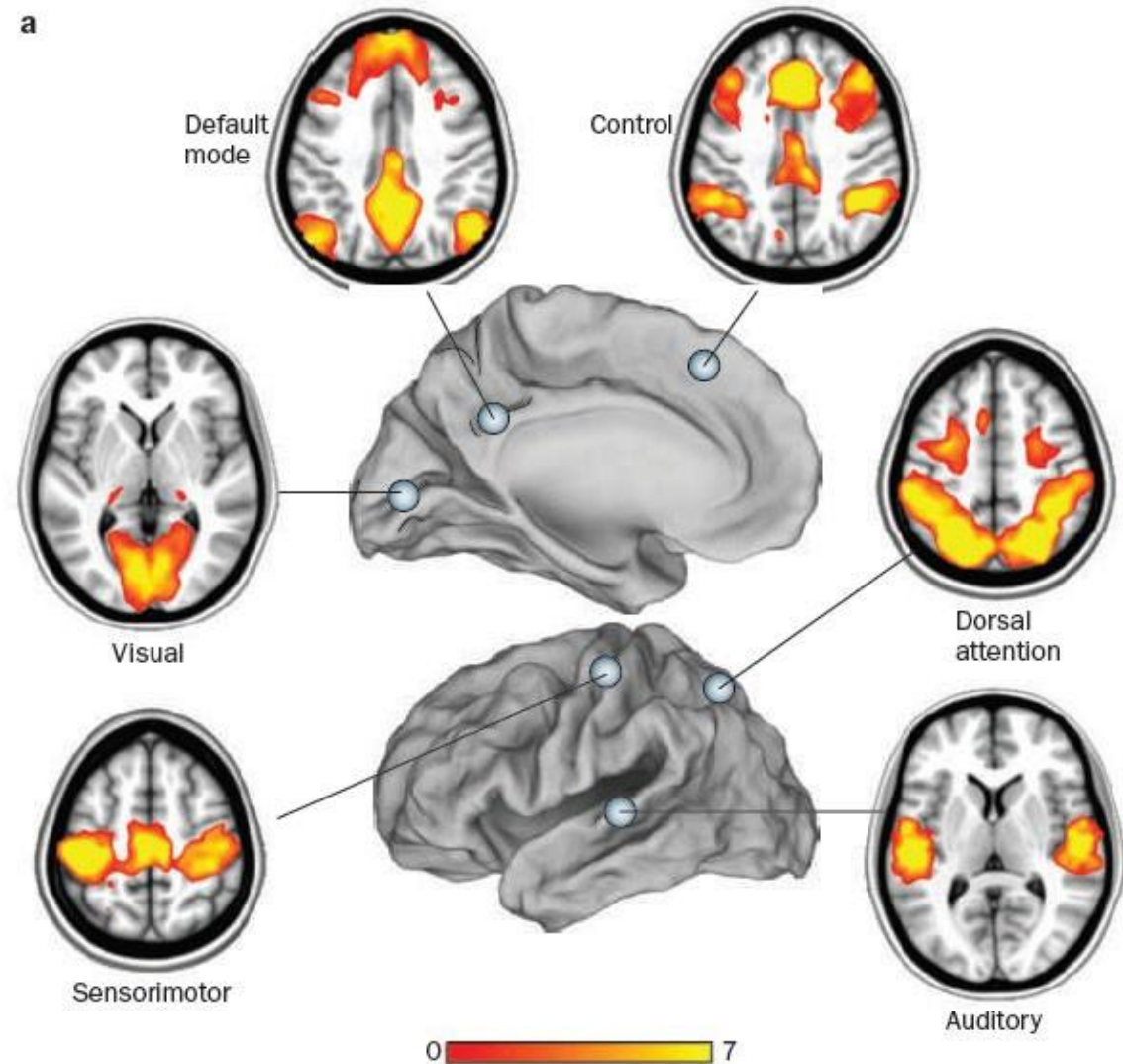
Vago and Silbersweig, 2012

Awareness of Others



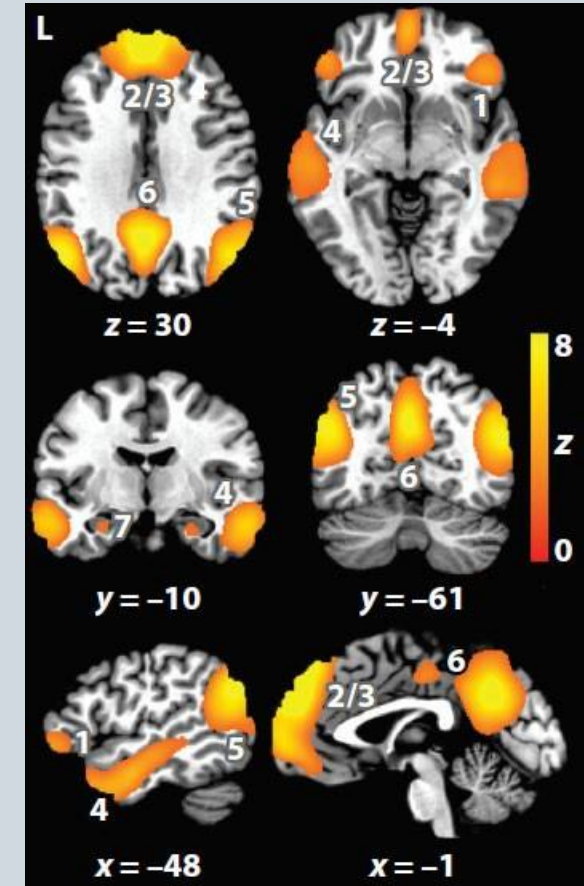
Large-Scale Networks

- Default mode network (DMN)
- Central executive network (CEN)
- Salience network



Default mode network

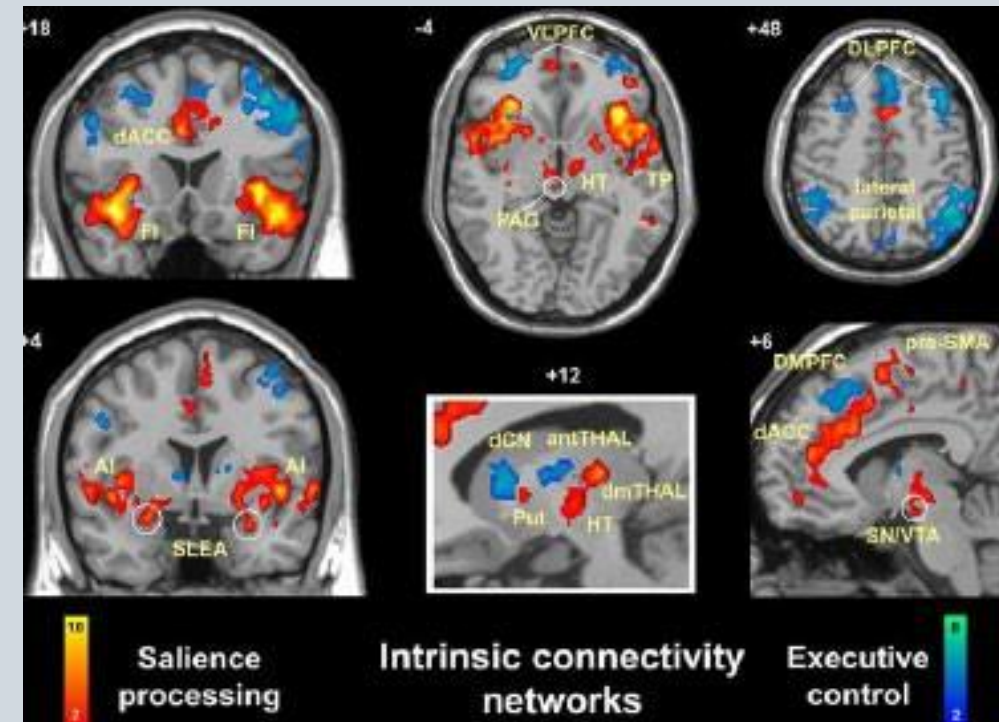
- “Task-negative” network
- Involved in self-referential thoughts (reflecting on past experiences, envisioning the future) and contributes to emotional processing
- Three main subdivisions
 - Ventromedial prefrontal
 - Dorsomedial prefrontal
 - Posterior cingulate and adjacent precuneus
- Anterior component involved in self-reflection and emotion
- Posterior component involved in episodic memory and perceptual processing



Raichle, 2015

Central executive and salience networks

- Central executive network, or “task-positive” network
 - Nodes in dorsolateral prefrontal and posterior parietal cortices
 - Involved in attention to and manipulation of information and decision making
 - Anti-correlated to default mode network
- Salience network
 - Key nodes in anterior insular cortex, dorsal ACC, subcortical regions
 - Assists in detecting behaviorally relevant internal and external stimuli
 - Assists in toggling between DMN and CEN

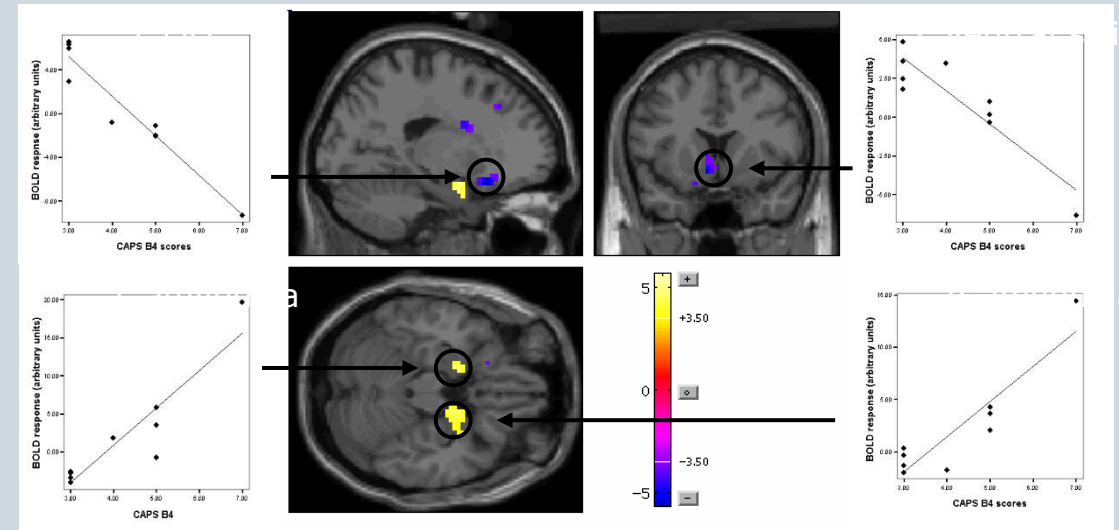
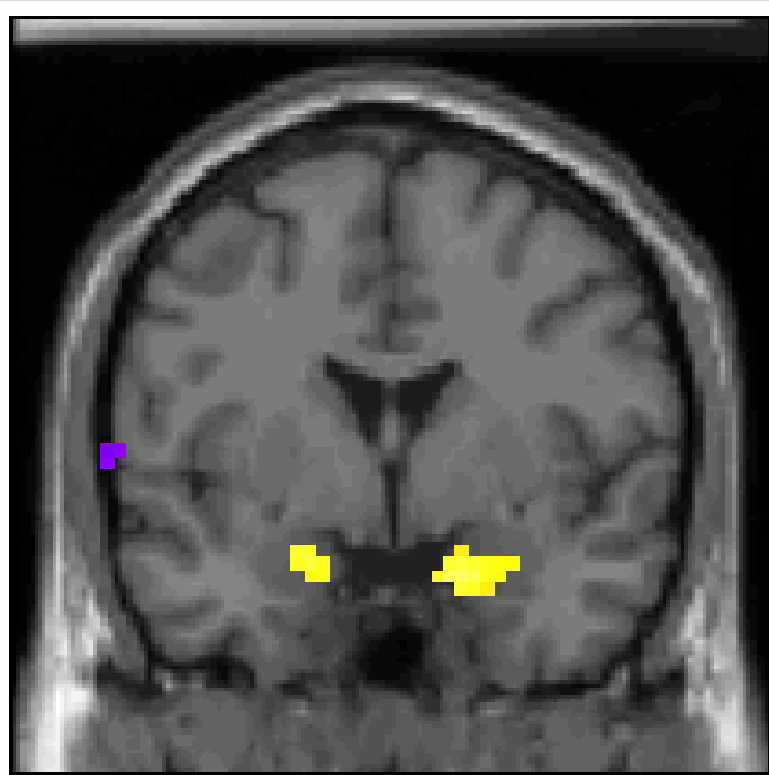


Seeley et al, 2007

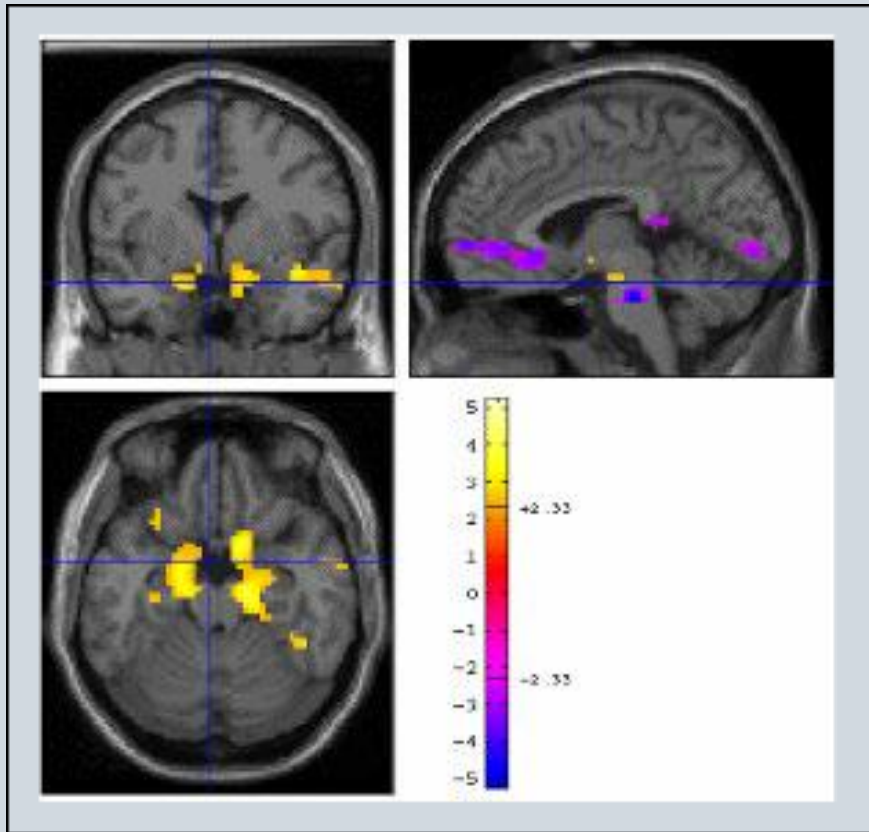


Selected Examples of Convergent Neural Circuitry of Psychiatric Symptoms Across the Neuropsychiatric Spectrum

PTSD: Brain activations associated with degree of psychological, physiological distress in trauma (vs neutral) word condition



*Selected examples:
Convergent symptoms and brain circuit
abnormalities across psychiatry and neurology*

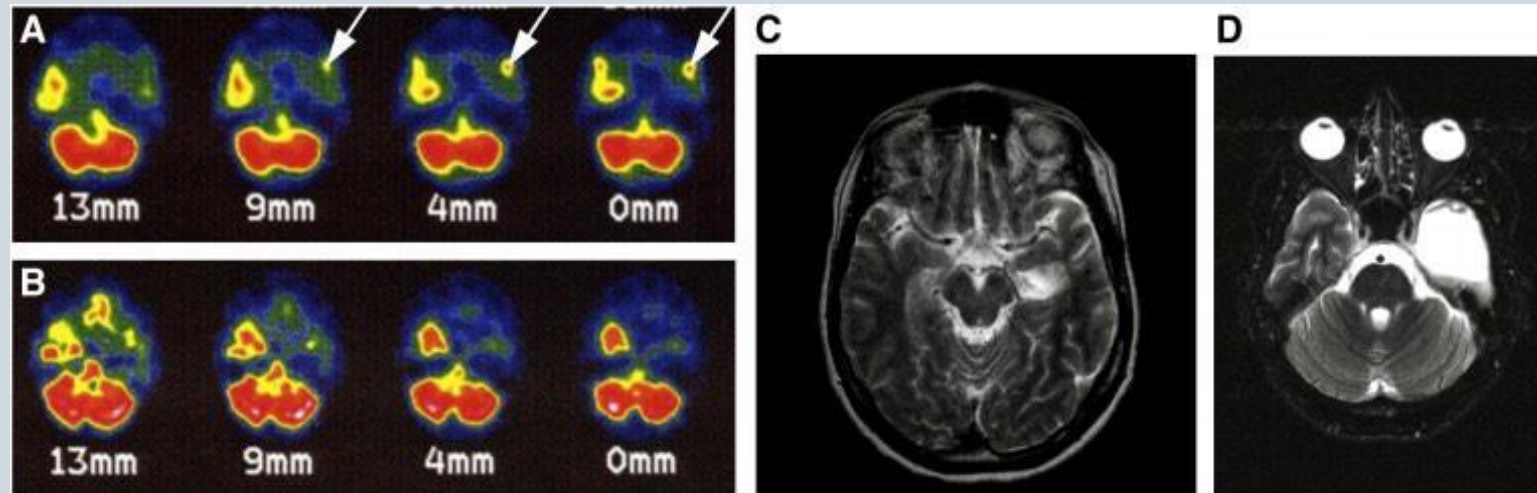


Schizophrenia pts with paranoid delusions have greater and inappropriate amygdala activation

Fear/threat circuitry involved in paranoid delusions in schizophrenia

Selected examples: Convergent symptoms and brain circuit abnormalities across psychiatry and neurology

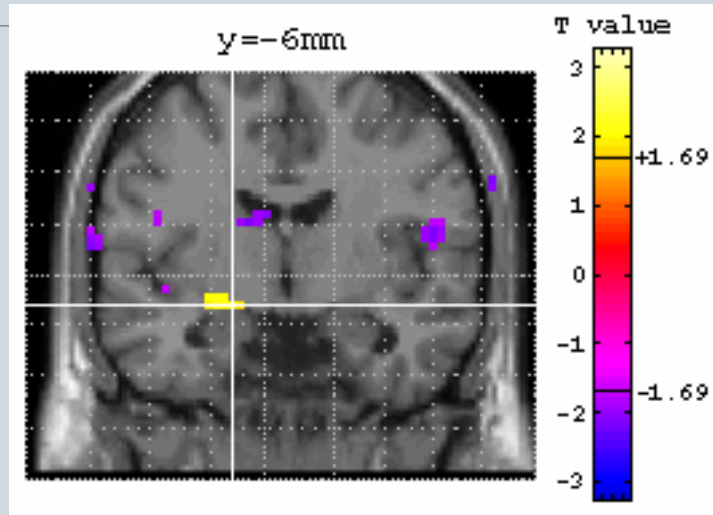
SPerception of fear and autonomic features of mesial temporal epilepsy



Persistent fear auras with anterior medial temporal seizure focus, before and after two surgeries.

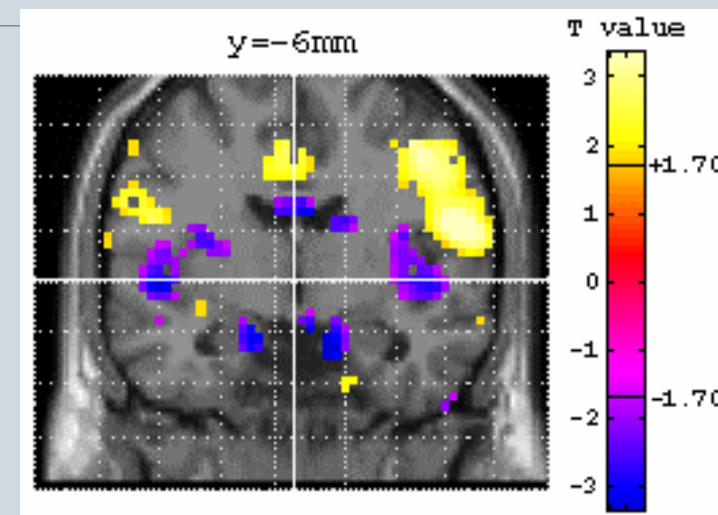
Urbanic et al, 2011

Neuromodulation by Psychotherapy: Schizophrenia and Paranoid Delusions Before and After Group CBT



BEFORE
(P6 score =4)

↑ Extended amygdala



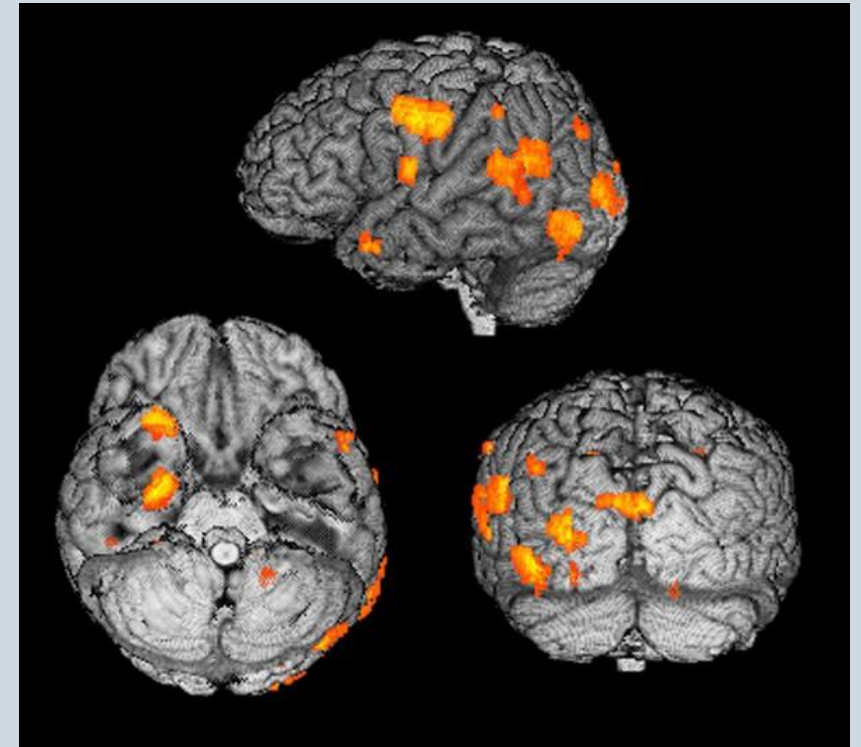
AFTER
(P6 score =2)

↓ Amygdala
↑ Dorsal AC
↑ DLPFC

Selected examples: Convergent symptoms and brain circuit abnormalities across psychiatry and neurology

Psychosis

- Schizophrenia pts with hyperdopaminergic state leading to dysregulation of salience networks
 - Misattribution of assigned salience of experiences (delusions) or internal representations (hallucinations)
 - Additional failure of prefrontal monitoring leads to lack of insight
- Corollary discharge (reafferent signaling)
 - Disruption of this mechanism in psychosis leads to disconnection between anterior (initiation of a thought) and posterior (reception of sensory consequence) region
 - Produces misinterpretation of agency



Selected examples: Convergent symptoms and brain circuit abnormalities across psychiatry and neurology

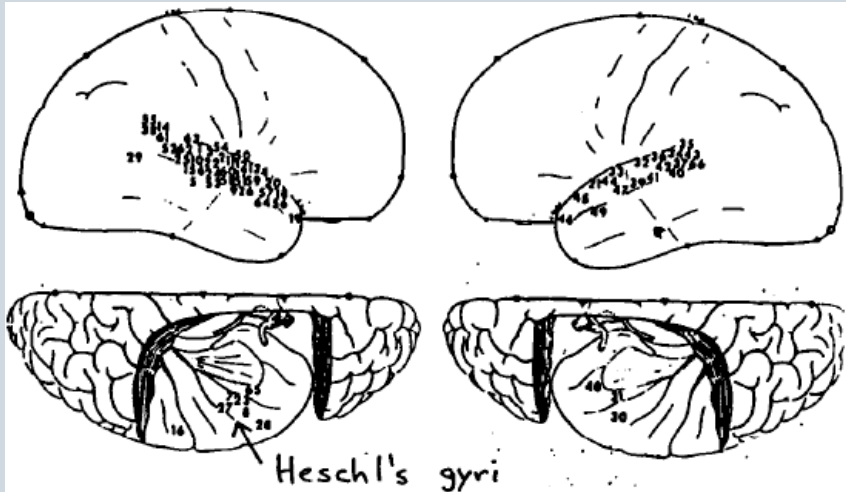


FIG. 9.—AUDITORY EXPERIENTIAL RESPONSES TO STIMULATION. 1. a voice (14); Case 28. 2. voices (14), 3. a voice (15), 4. a familiar voice (17), 5. a familiar voice (21), 6. a voice (23), 7. a voice (24), 8. a voice (25), 9. a voice (28); Case 29. 10. familiar music (15), 11. a voice (16), 12. a familiar voice (17), 13. a familiar voice (18), 14. familiar music (19), 15. voices (23), 16. voices (27); Case 4. 17. familiar music (14), 18. familiar music (17), 19. familiar music (24), 20. familiar music (25); Case 30. 21. familiar music (23); Case 31. 22. familiar voice (16); Case 32. 23. familiar music (23); Case 5. 24. familiar music (Y), 25. sound of feet walking (1); Case 6. 26. familiar voice (14), 27. voices (22); Case 8. 28. music (15); Case 9. 29. voices (14); Case 36. 30. familiar sound (16); Case 35. 31. a voice (16a); Case 23. 32. a voice (26), 33. voices (25), 34. voices (27), 35. a voice (28), 36. a voice (33); Case 12. 37. music (12); Case 11. 38. a voice (17d); Case 24. 39. familiar voice (14), 40. familiar voices (15), 41. dog barking (17), 42. music (18), 43. a voice (20); Case 13. 44. familiar voice (11), 45. a voice (12), 46. familiar voice (13), 47. familiar voice (14), 48. familiar music (15), 49. a voice (16); Case 14. 50. voices (2), 51. voices (3), 52. voices (5), 53. voices (6), 54. voices (10), 55. voices (11); Case 15. 56. familiar voice (15), 57. familiar voice (16), 58. familiar voice (22); Case 16. 59. music (10); Case 17. 60. familiar voice (30), 61. familiar voice (31), 62. familiar voice (32); Case 3. 63. familiar music (8), 64. familiar music (10), 65. familiar music (D2); Case 10. 66. voices (11); Case 7.

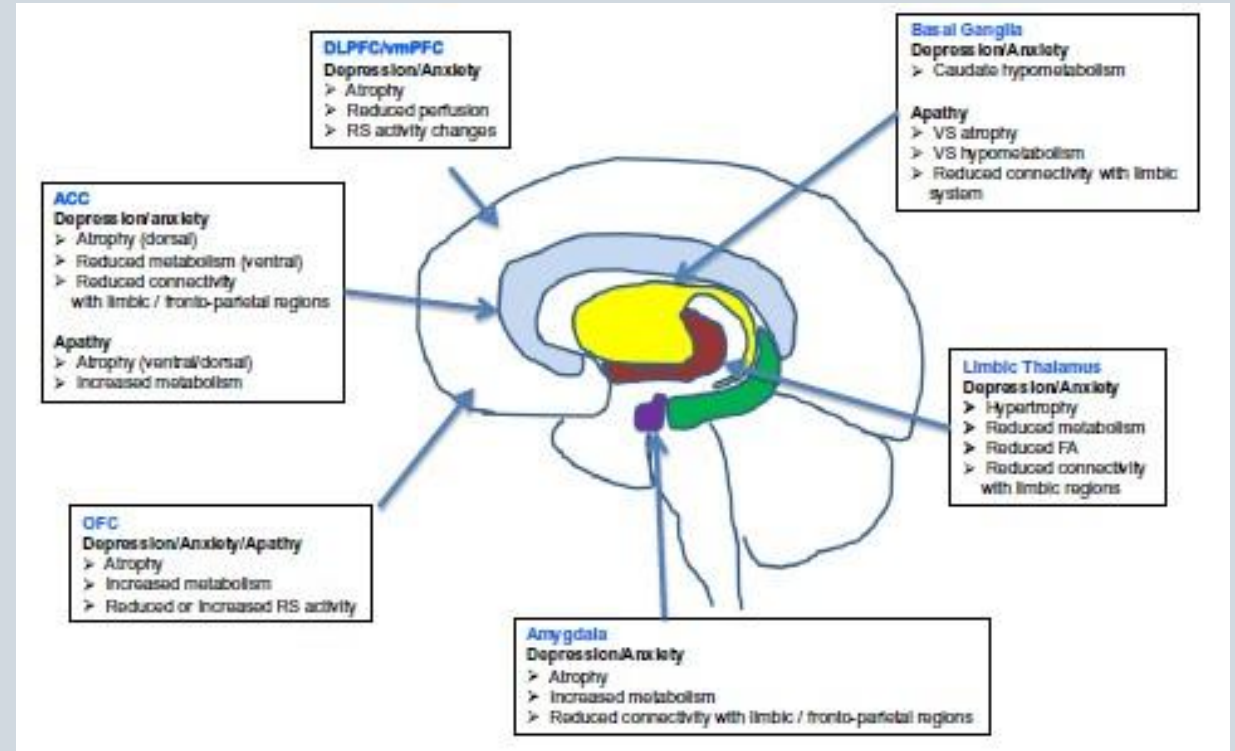
Psychosis

- Auditory hallucinations invoked by stimulating aspects of temporal lobe
- Crude/simple hallucinations moving to more experiential response (voice, music) as electrode moved from primary auditory cortex toward first transverse temporal gyrus
- Subjects typically retained insight, like a dream state, “like I go into a daze”

Selected examples: Convergent symptoms and brain circuit abnormalities across psychiatry and neurology

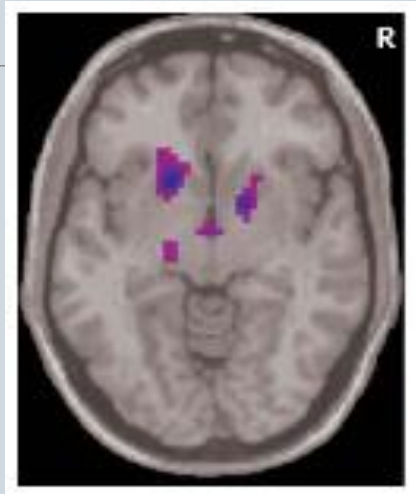
Affect and Motivation

- Depressed patients with significantly less activation in ventral striatal regions in anticipation of reward
- Parkinson's disease patients depression and apathy inversely correlated to DA transporter binding in ventral striatum

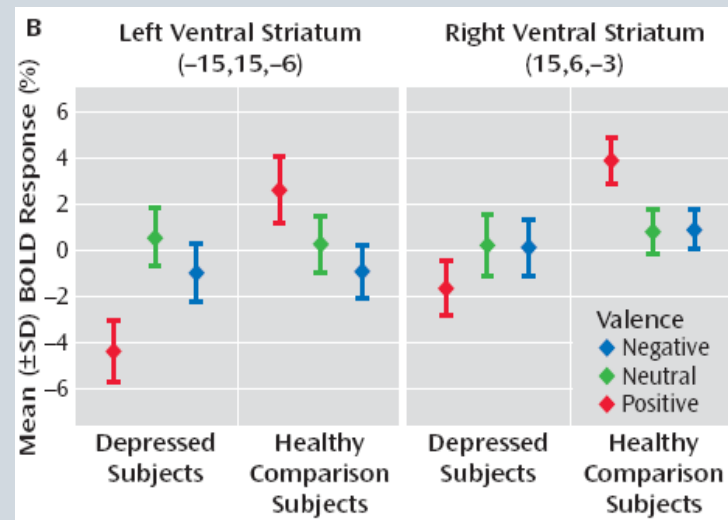


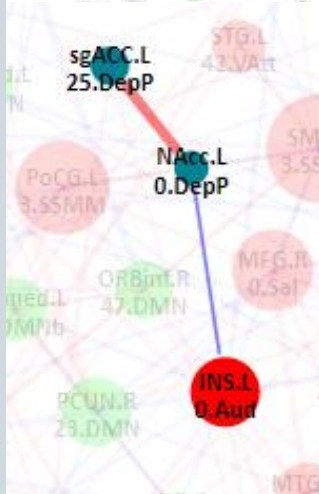
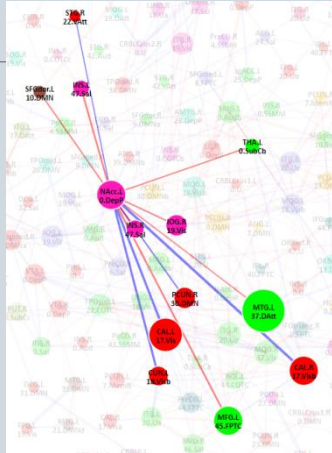
Anatomic / metabolic abnormalities in depression / apathy / anxiety in Parkinson's disease – Thobois et al, 2017

Anhedonia in Major Depression

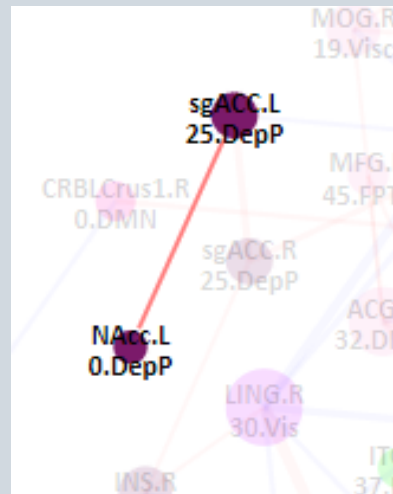
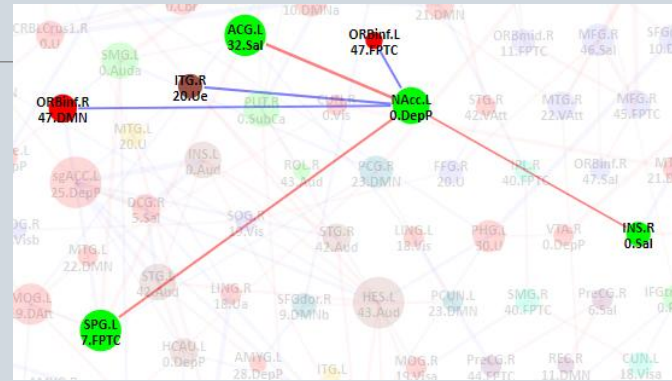


Epstein et al

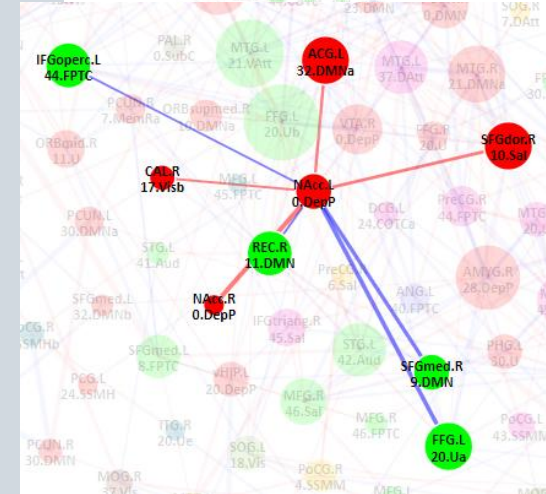
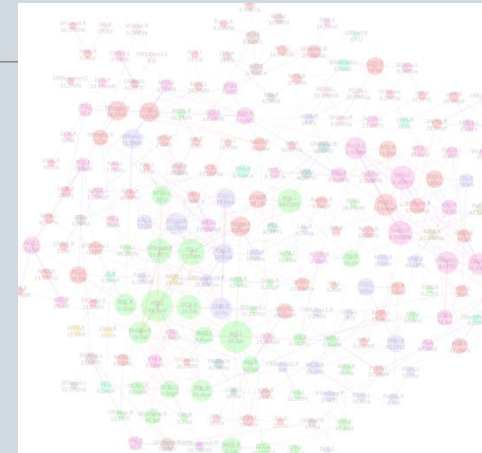




Negative Words



Neutral Words

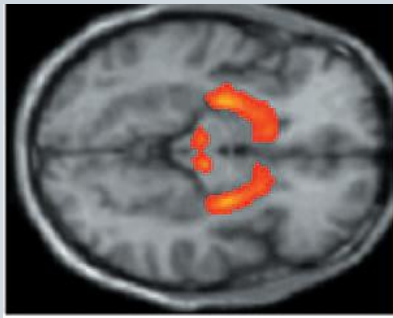


Positive Words

Major
Depression
Patients

Healthy
Normal
Subjects

Anhedonia in Parkinson's Disease

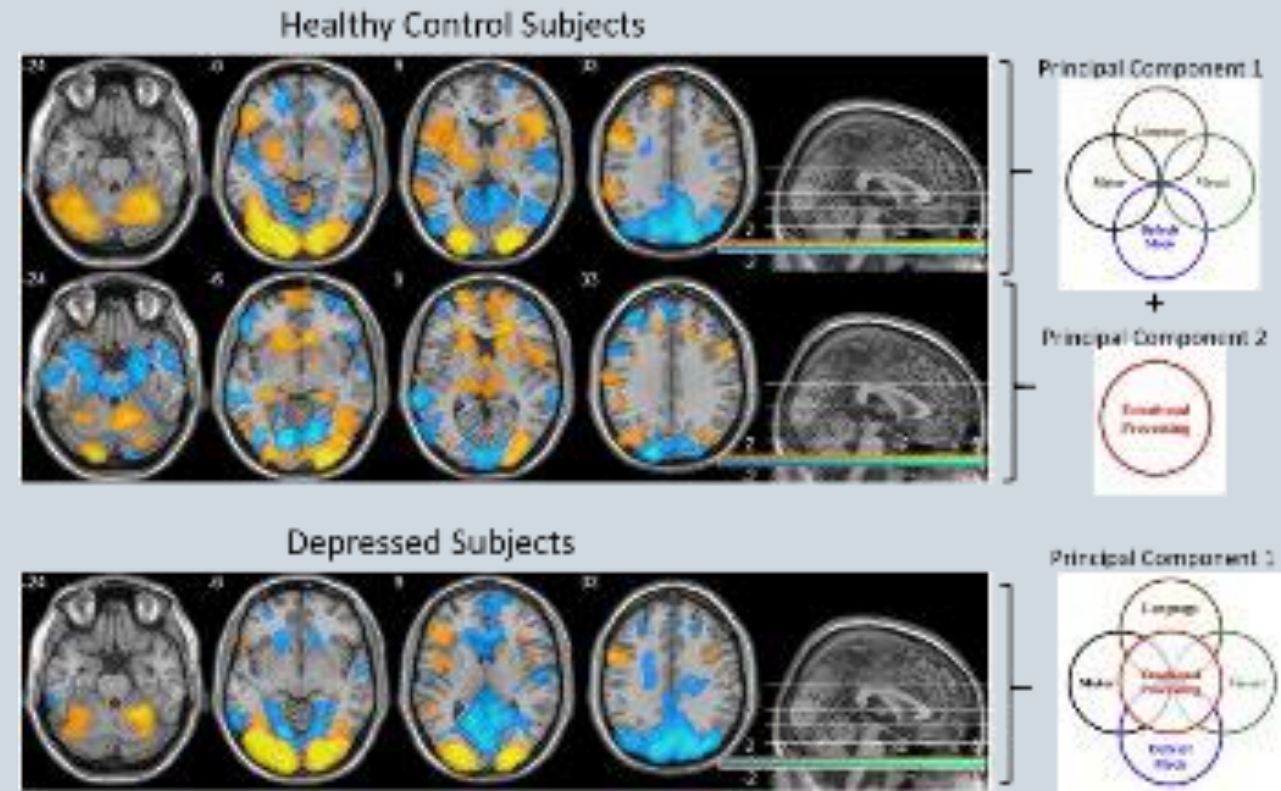


Remy et al

Selected examples: Convergent symptoms and brain circuit abnormalities across psychiatry and neurology

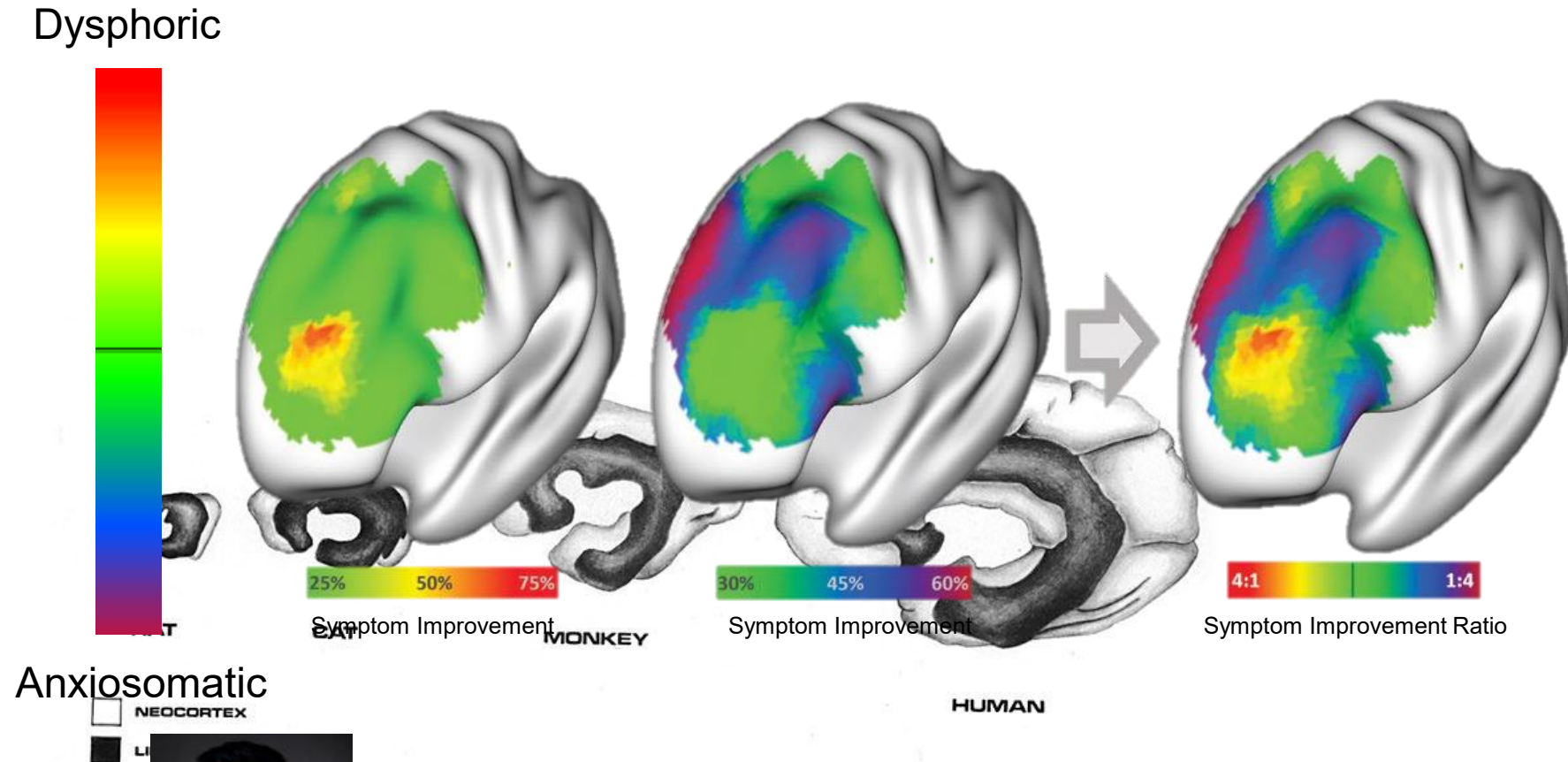
Affect and Motivation

- Patients with major depression have greater confluence of activation between emotional processing regions (ventral striatum, ACC, insula) and sensory, linguistic, and motor areas
- Reflective of affective disturbance coloring one's cognition and behavior (i.e. psychomotor slowing).



Epstein et al, 2011

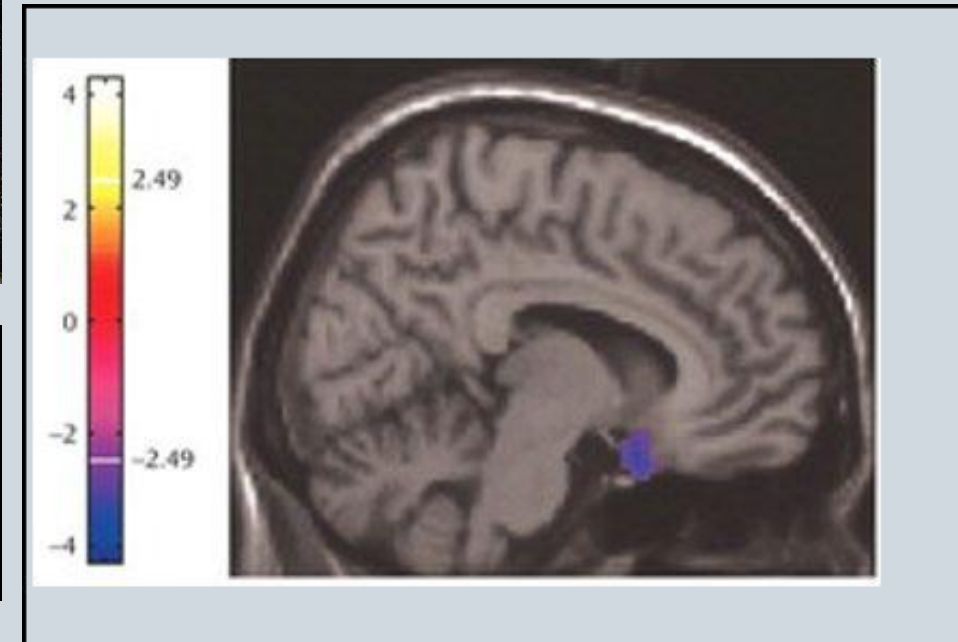
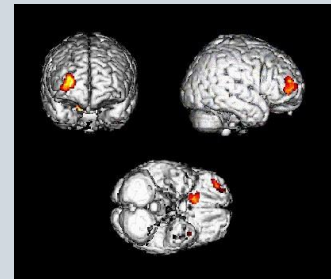
rsfMRI Connectomics: Symptom/Pt-Specific Targets



Selected examples: Convergent symptoms and brain circuit abnormalities across psychiatry and neurology

Impulsivity

- Phineas Gage demonstrated profound disinhibition following injury involving right and left prefrontal cortex (including oFC)
- Borderline personality disorder with decreased constraint on go/no go task correlated to decreased vmPFC
- Manic patients with hyperactivity of approach motivation, great effort expended in reward pursuit
 - Greater activation of ventral striatum and oFC in anticipation of reward
- oFC AVM pt with disinhibition

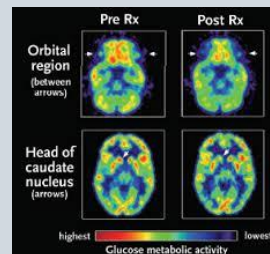


Decreased activation of mOFC in borderline personality disorder patient compared to healthy control

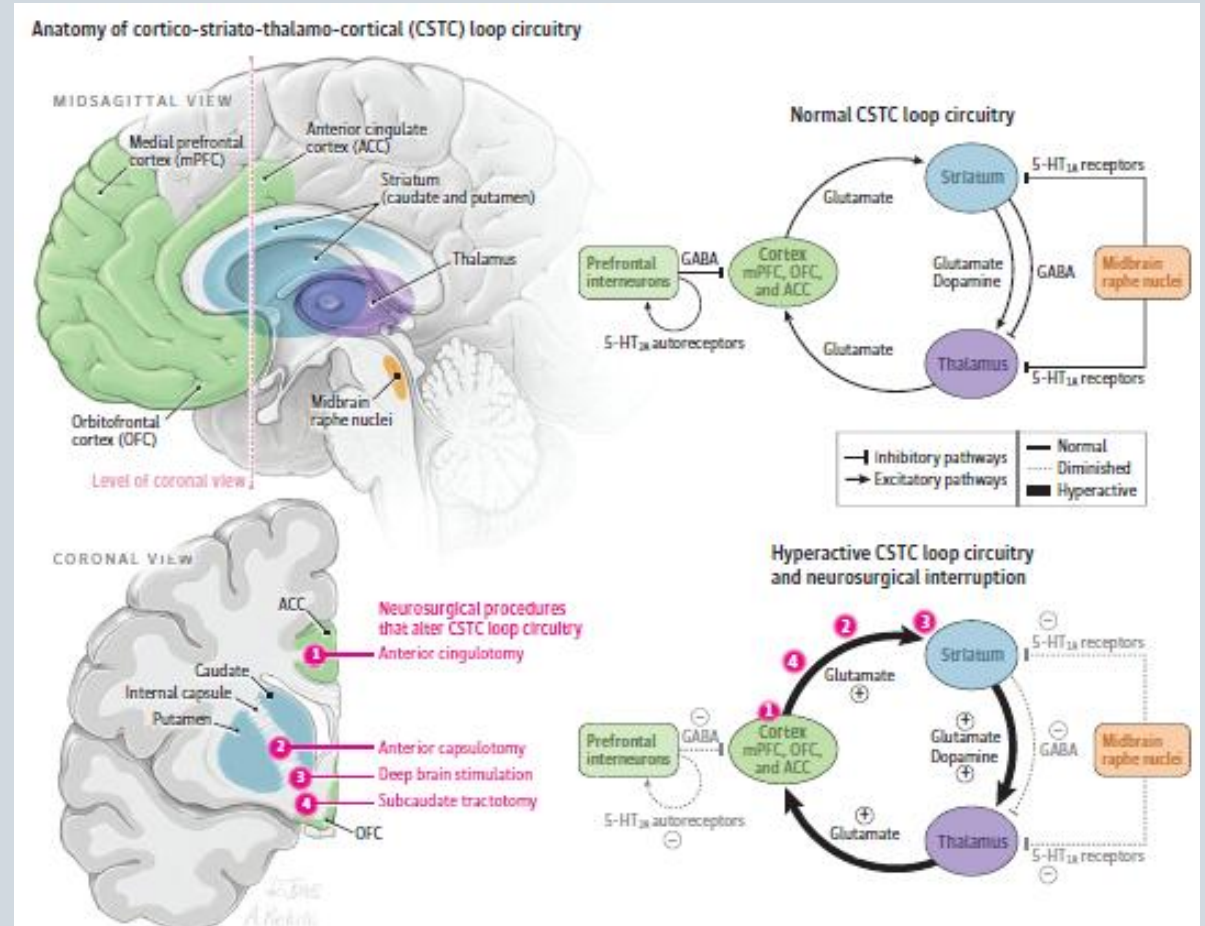
Obsessive and Compulsive Symptoms

Obsession/rigid thought pattern and compulsion are seen across many disorders
Dysfunction within specific cortico-striatal-thalamic-cortical loops

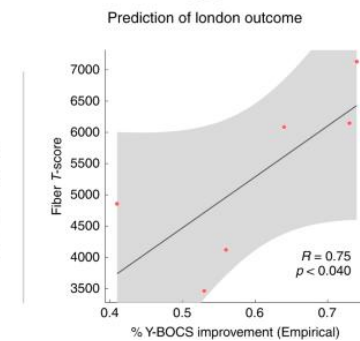
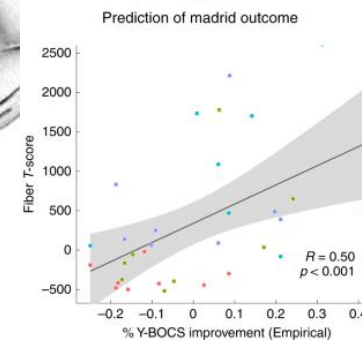
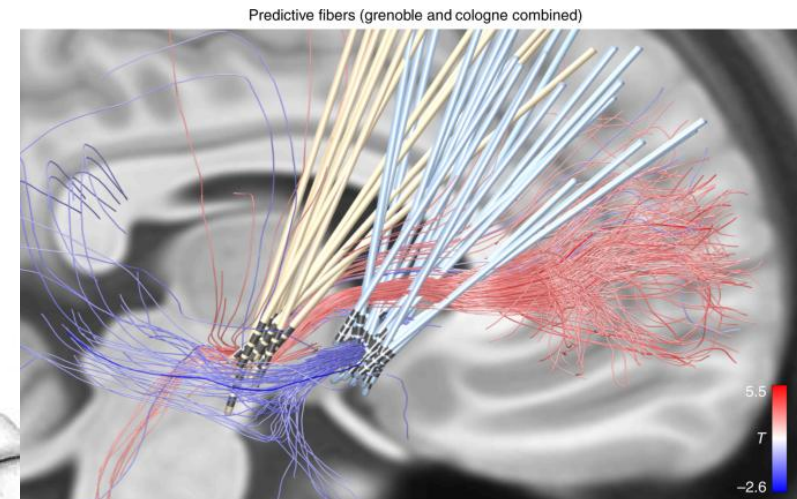
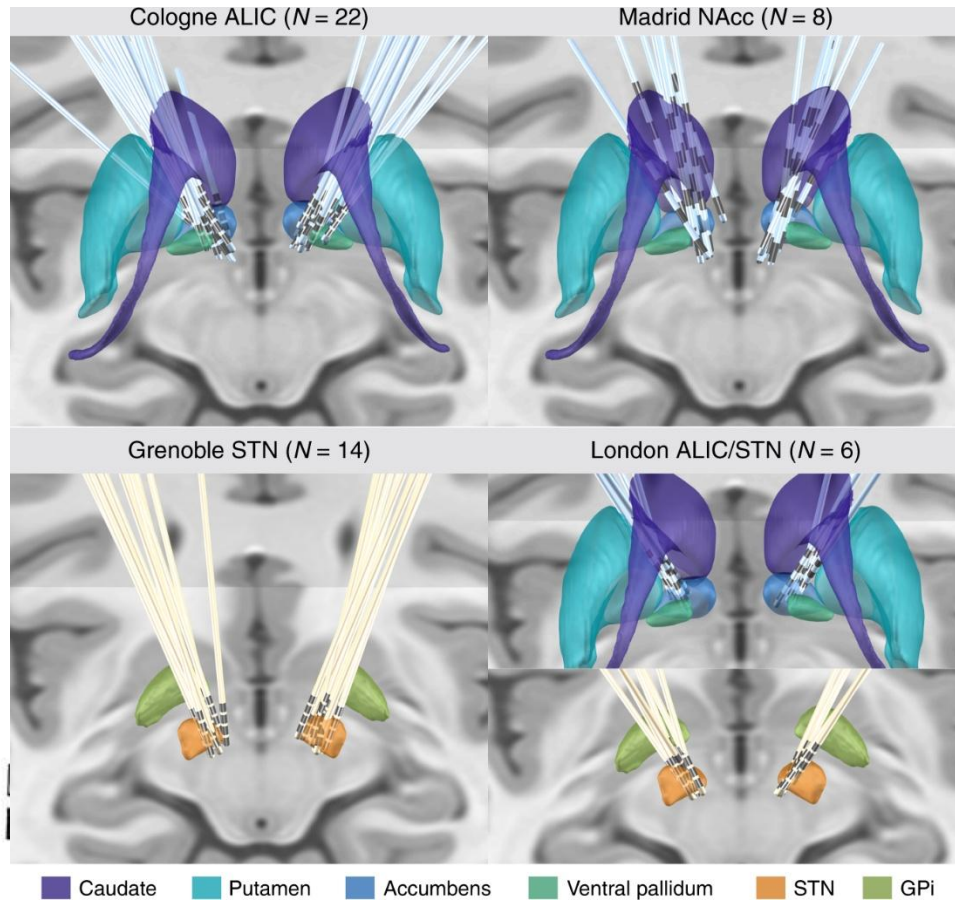
- Greater urge to engage in compulsive behaviors
- Reward/motivation/reinforcement learning, habit formation
- Decreased top-down prefrontal control



Baxter

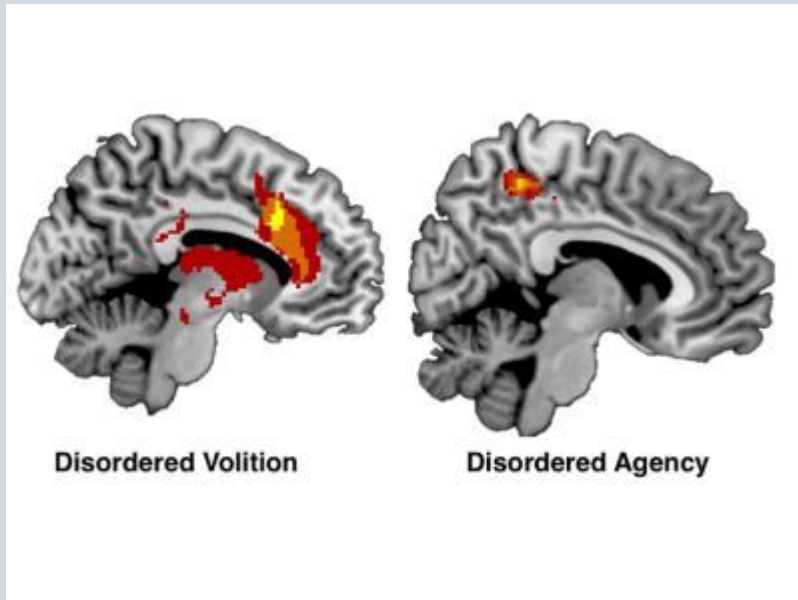


Unified Connectomic Target for DBS in OCD

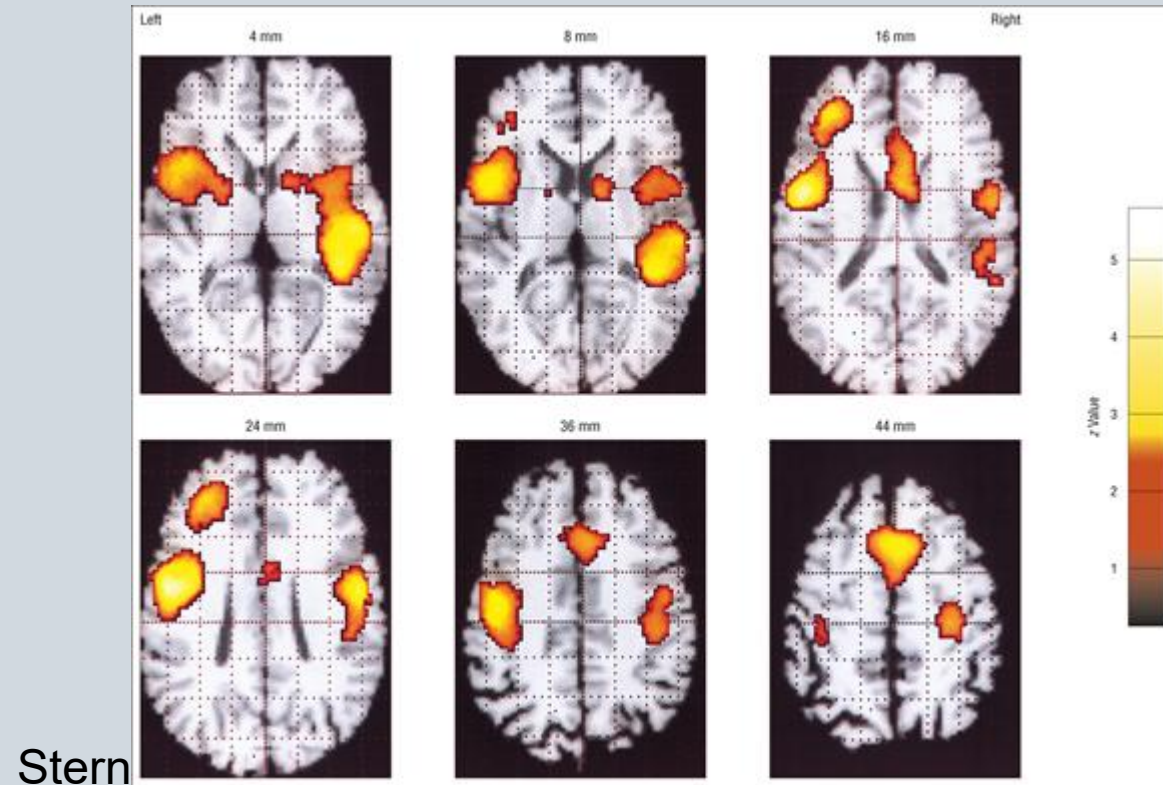


Li et al, 2020

Volition and Agency: Lesion network mapping of Akinetic Mutism, Alien Limb, and Functional Neuroimaging of Tourette Syndrome



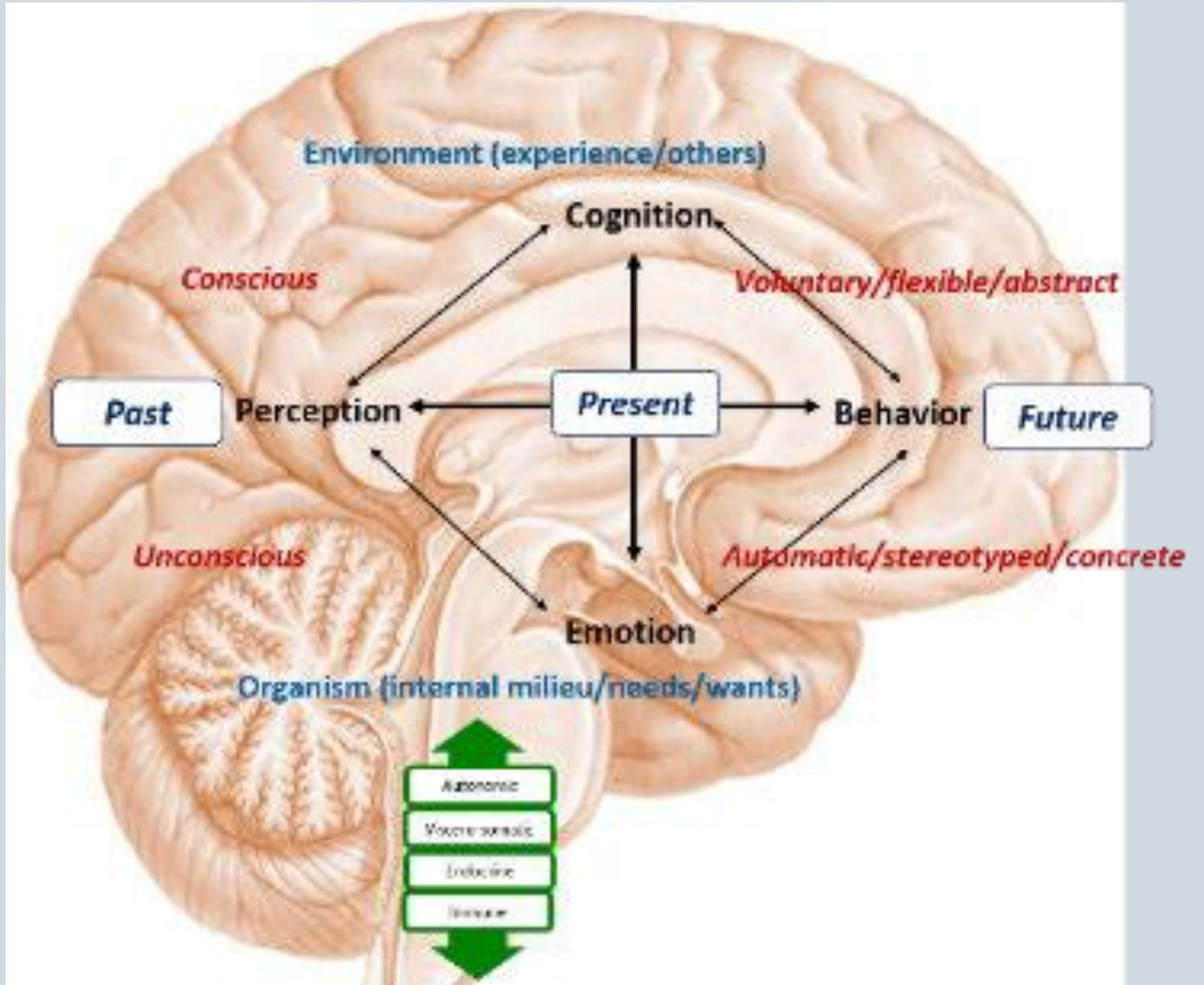
Darby et al
et al



Stern

SYNTHESIS: *Integrated brain circuit model of emotion & behavior*

Core processes and functions:
mapping gradients onto brain
circuits

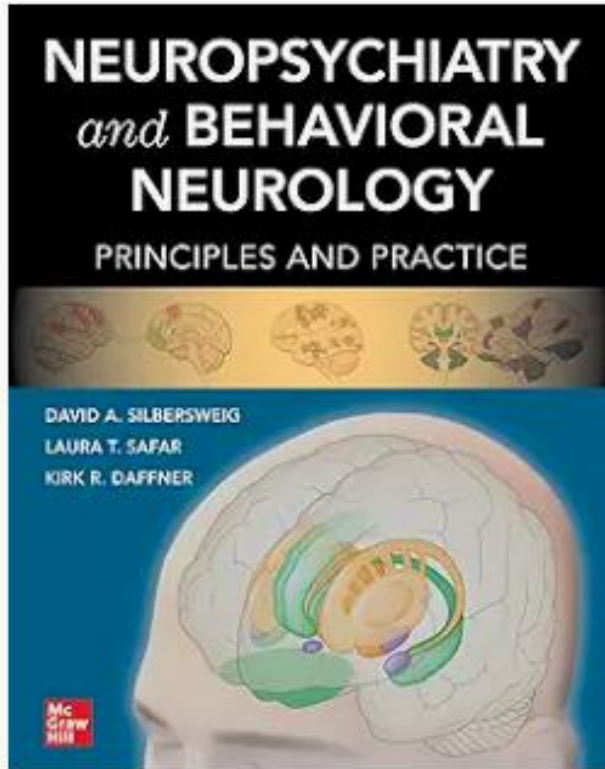


Convergent Principle

Perceptual, cognitive, emotional, behavioral, social and executive functions and interactions can be

localized and characterized in the context of neural nodes, circuits and connectivity which can be impacted by a range of etiopathologies, resulting in circuitopathies--specific clinical presentations and responses

within and across a spectrum of neurologic and psychiatric brain/mind disorders



COMMENTARY

Toward a Unified Classification System for Brain–Mind Disorders: Putting Calls for Integrated Clinical Neuroscience Into Action

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SYNTHESIS: Integrated brain circuit model of emotion & behavior

Gradients and Balances

- **VENTRAL-MEDIAL systems:** brainstem, hypothalamus, amygdala, ventral hippocampus, ventral striatum, medial OFC, sgACC
 - Past / self / internal world / stereotyped / simple-concrete representations / unconscious / involuntary
- Reciprocal interaction with **DORSAL-LATERAL** (executive / cognitive / language) neocortical systems (e.g. dorsomedial PFC, DLPFC, temporoparietal association cortex)
 - Future / others / external world / flexible / complex-abstract representations / conscious / volitional control
- Emotional / behavioral balance
 - Positive / approach: drive, urge, motivation, volition, planning
 - Negative / avoidance: fear, anxiety, threat, frustration, inhibition, ruminations, concerns
 - Salience / meaning
 - Self / other awareness



SYNTHESIS: Integrated brain circuit model of emotion & behavior

Spatio-Temporal Networks of Brain Activity

- **EMOTION AND BEHAVIOR** associated with dynamic modulation in hierarchical, bidirectional systems
 - **Cortical / limbic / subcortical; paralimbic** (mediating interaction between internal world and external environment)
 - Competing responses, selection for action, conflict, changing contingencies
 - In context of genes, neurodevelopment, experience, disease
- **DISORDERS** associated with distinct patterns of abnormal activity and connectivity in fronto-limbic neocortical and subcortical regions, consistent with clinical phenomenology and behavioral neuroanatomy
 - **Nodes:** local neuronal circuits
 - **Circuits:** large scale, distributed
 - Modulation, compensation, plasticity
- May include fronto-limbic dysregulation of **dynamic** emotional / behavioral responses
 - Specificity; accuracy; valence; salience; bias; set point; threshold; extent; timing; flexibility; stability; appropriate context; awareness; monitoring; top down control



SYNTHESIS: Integrated brain circuit model of emotion & behavior

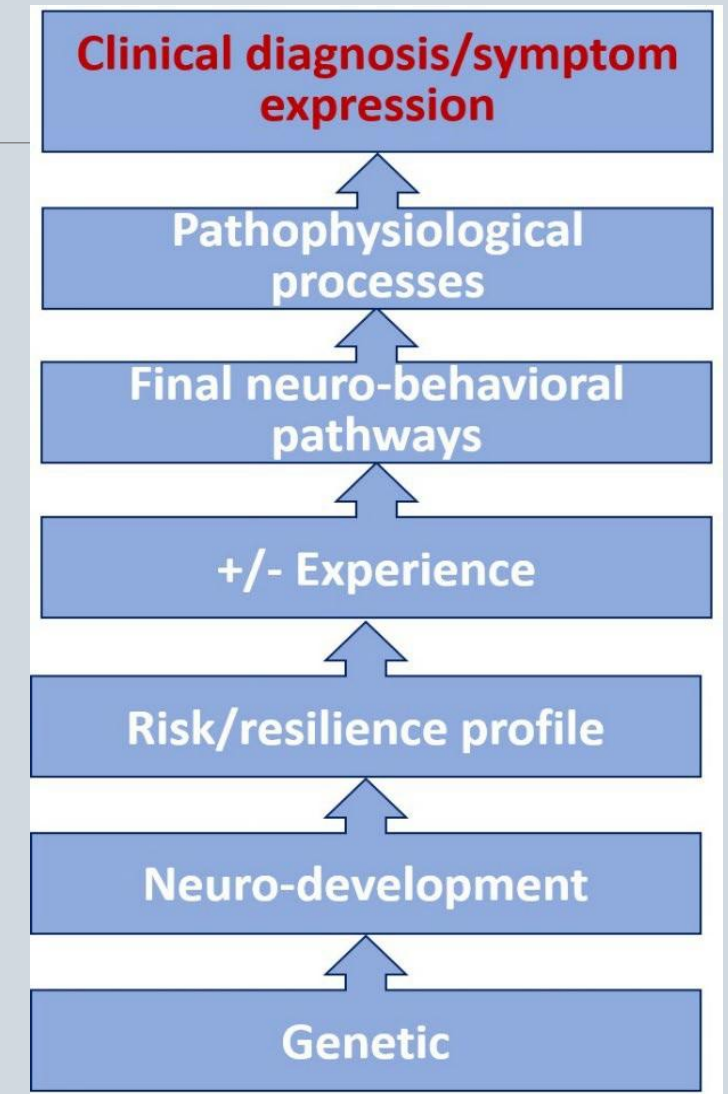
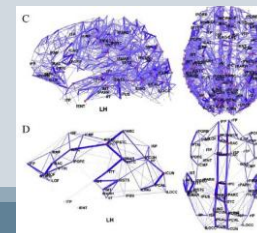
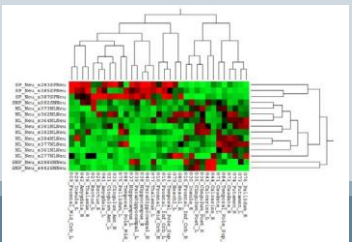
Psychiatric and Neurologic Disorders / Symptoms, Functions, Regions / Circuits

- Anhedonia in **depression**; depression / apathy in **Parkinson's Disease**
 - Abnormal motivation / reward with pleasurable activities
 - Ventral striatum
- **Schizophrenia** and **anxiety d/o** (paranoia, panic, PTSD); **temporal lobe epilepsy, frontal lesions**
 - Abnormal fear assessment, response, modulation
 - Amygdala, ventromedial PFC
- Hallucinations in **schizophrenia**; hallucinations in **brain stimulation**
 - Involuntary, salient auto-percepts without insight
 - Modality-specific cortices in context of mesolimbic and prefrontal
- Impulsivity in **borderline personality disorder**; impulsivity in **traumatic brain injury**
 - Abnormal emotional behavioral control
 - Orbitofrontal cortex

SYNTHESIS: Integrated brain circuit model of emotion & behavior

Final common pathways of neuropsychiatric disease and treatment

- Pathophysiology vs etiology
- Role of translational functional neuroimaging: possibilities and limitations
 - Multi-modal biomarkers
 - Targeted therapeutics
- Clinical implications
 - Dx (neurologic / psychiatric)
 - Tx (individualized treatment, psychopharmacology, brain stimulation)
 - Px (early intervention, prevention)





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