

# **Depression and Affective Neuroscience**

**Margaret R. Zellner, Ph.D., L.P.**

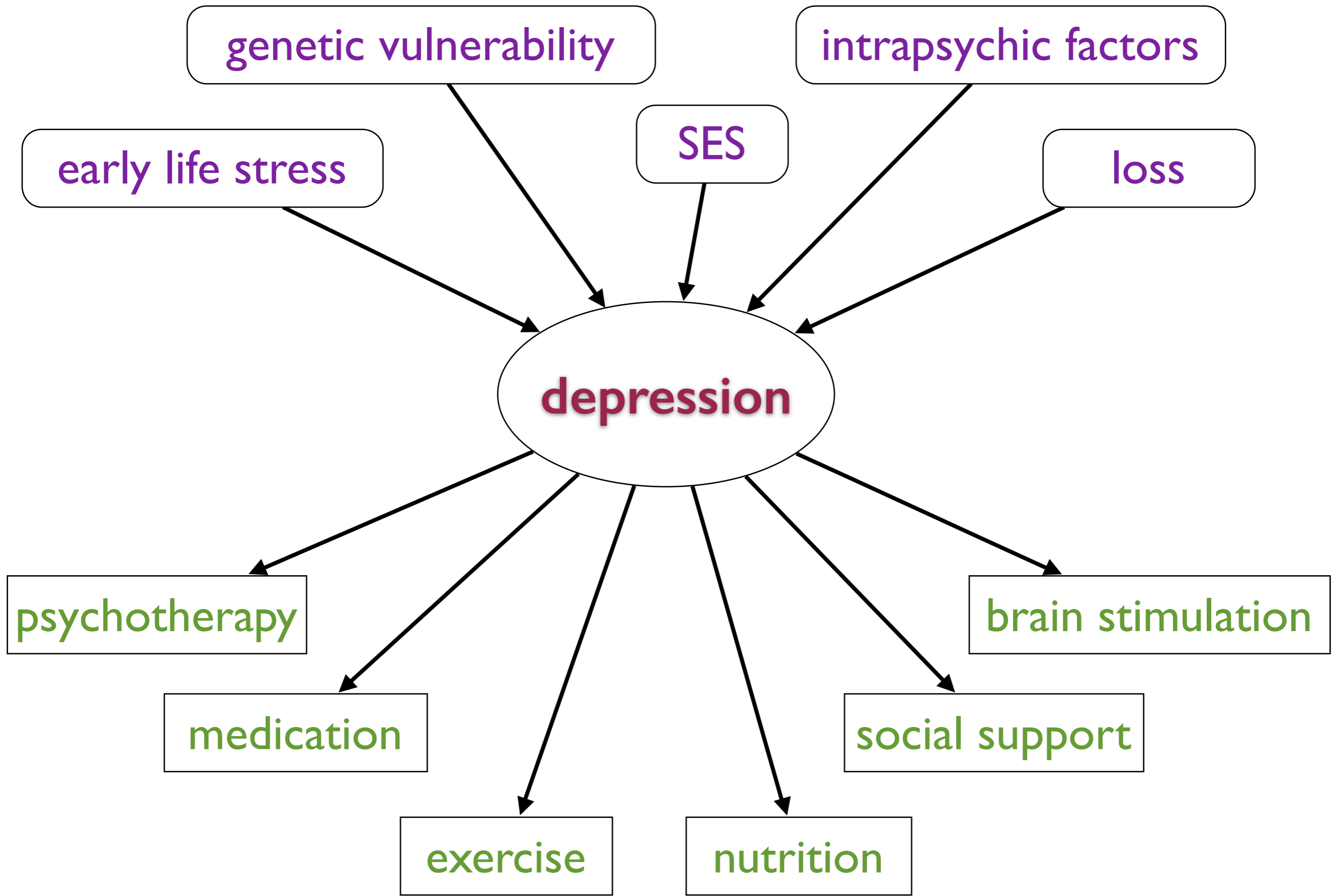
copies of presentations available at [mzellner.com](http://mzellner.com)

[mzellner@npsafoundation.org](mailto:mzellner@npsafoundation.org)

The National Psychological Association for Psychoanalysis (NPAP)

**The Neuropsychanalysis Foundation**

[www.npsafoundation.org](http://www.npsafoundation.org)

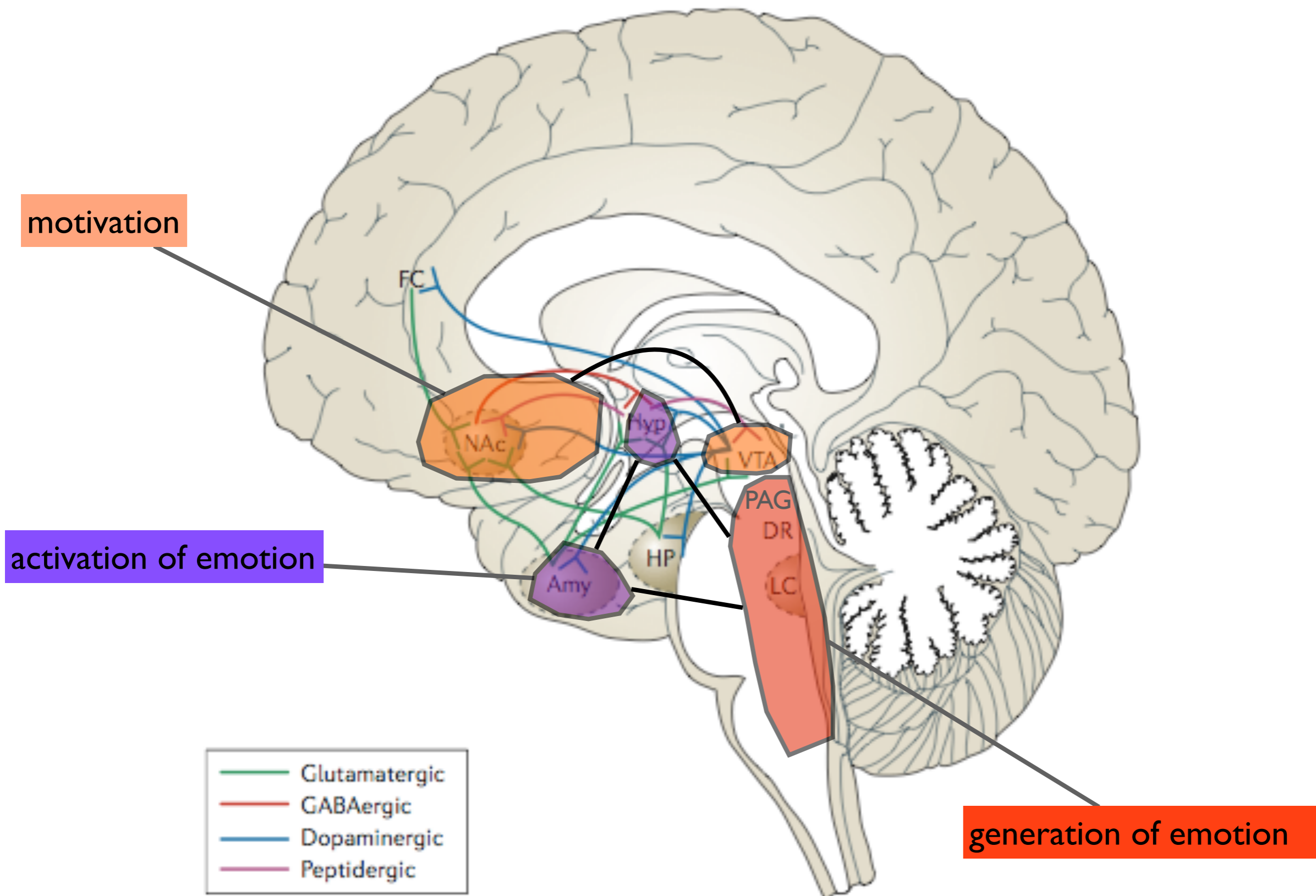


**action**

**perception**



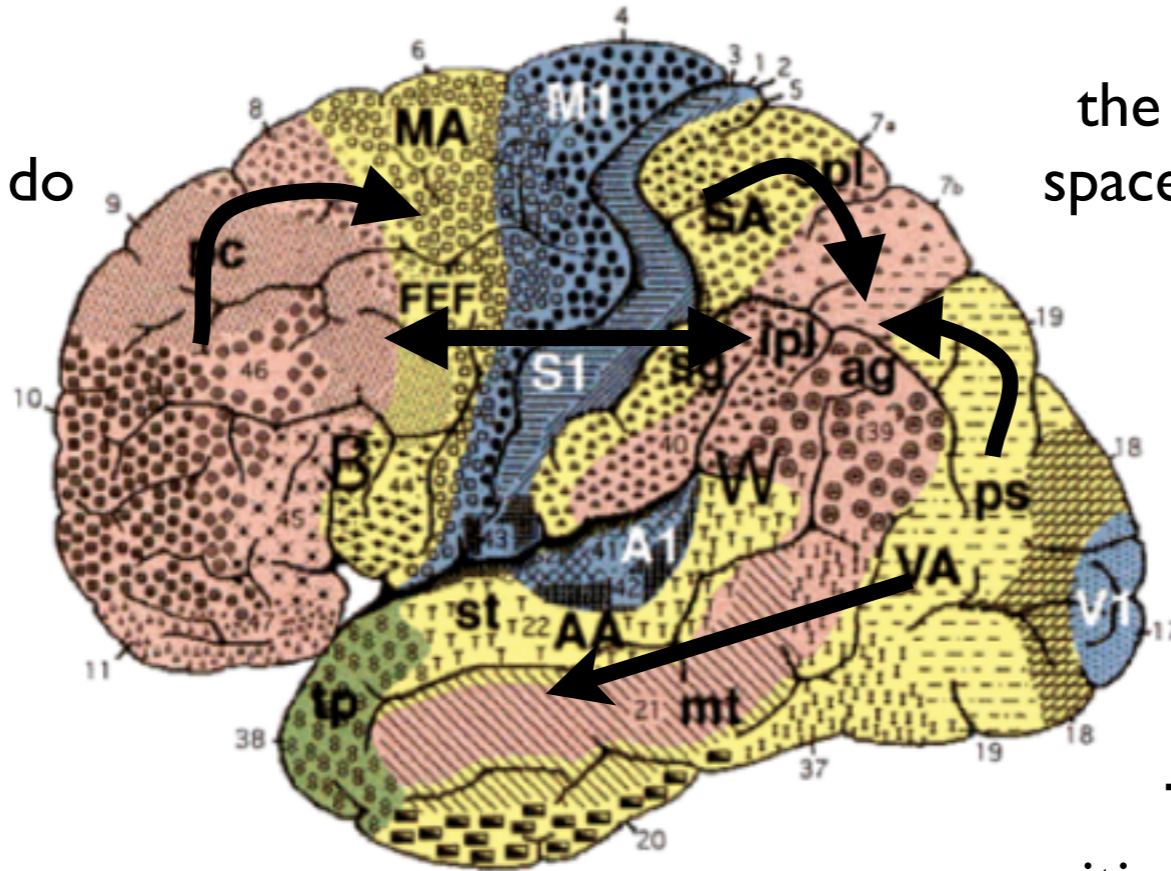
**emotion**



adapted from  
 Berton and Nestler 2006 Nat Rev Neurosci

## FRONTAL

planning  
- WHAT and HOW to do



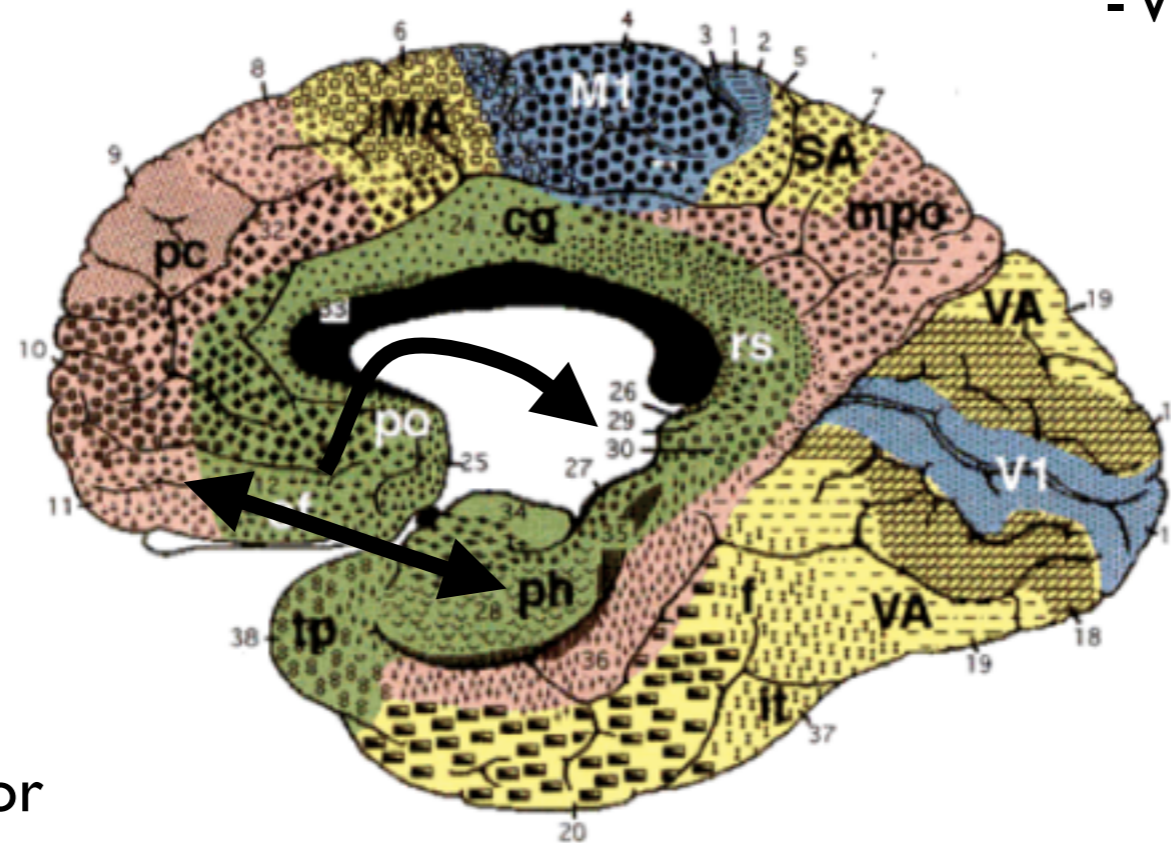
## PARIETAL

the body and objects in space - WHERE things are

## TEMPORAL

recognition of objects and people  
- WHO things are

**VMPFC,  
ANTERIOR TEMPORAL**  
memory, emotion, reward  
- meaning, or, WHY to do or  
not to do



Marcel Mesulam, 2000  
*Principles of Behaviora and  
Cognitive Neurology*

## A ATLAS BUNDLE LIST

Bundles in left and right hemispheres

### Arcuate fasciculus

- Direct Segment (red ■)
- Anterior Segment (green ■)
- Posterior Segment (yellow ■)

### Inferior Longitudinal fasciculus (purple ■)

### Inferior Fronto-Occipital fasciculus (violet ■)

### Uncinate fasciculus (cyan ■)

### Cingulum

- Cingulate long fibers (brown ■)
- Cingulate short fibers (light green ■)
- Temporal fibers (blue ■)

### Corticospinal tract (orange ■)

### Fornix (black ■)

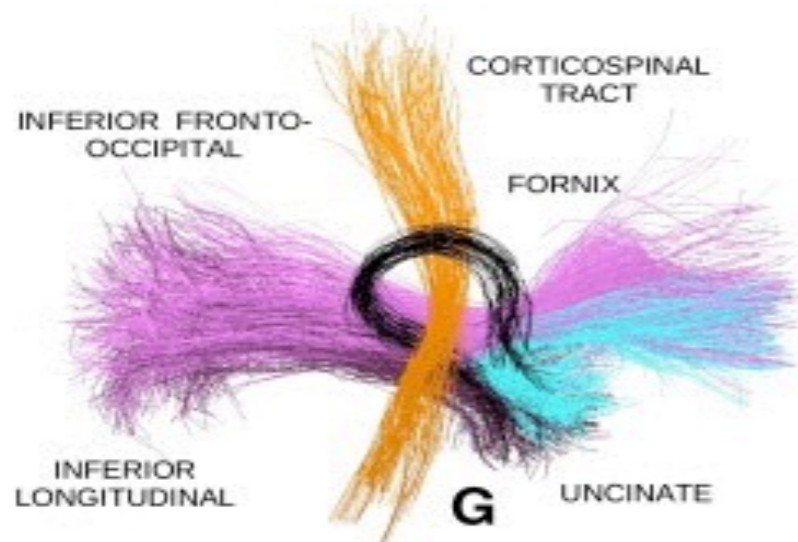
### Thalamic radiations

- Anterior radiations (gray ■)
- Superior motor radiations (teal ■)
- Superior parietal radiations (pink ■)
- Posterior radiations (light blue ■)
- Inferior radiations (ocre ■)

Interhemispheric bundles

### Corpus Callosum

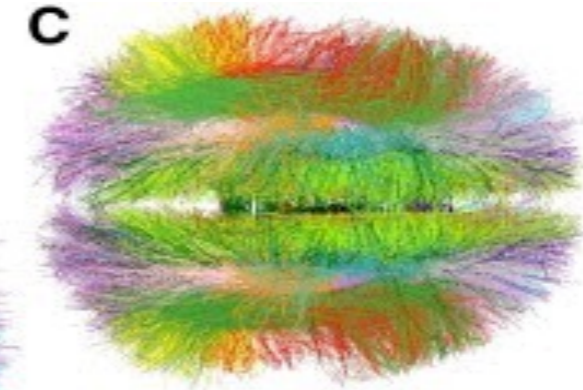
- Rostrum (fuchsia ■)
- Genu (dark blue ■)
- Body (dark green ■)
- Splenium (dark brown ■)



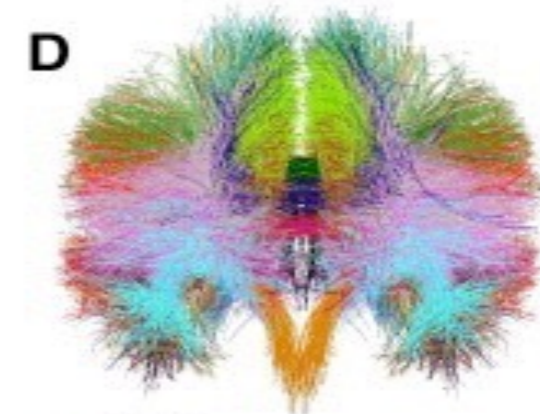
B



C

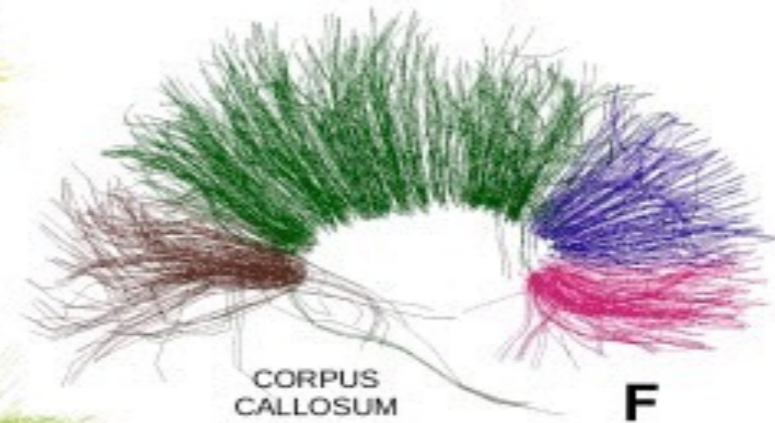
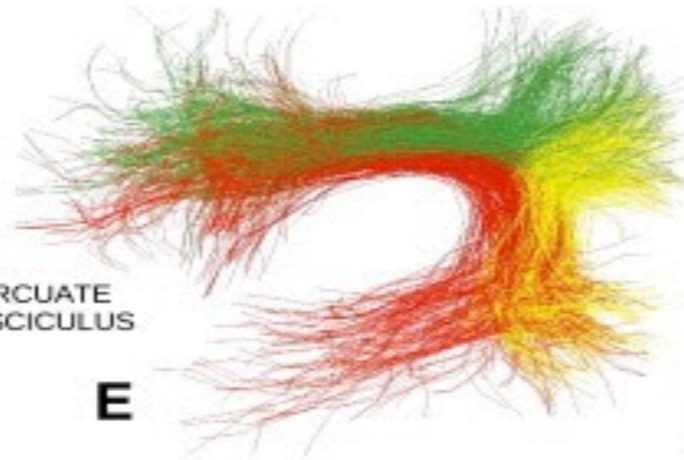


D



ARCUATE  
FASCICULUS

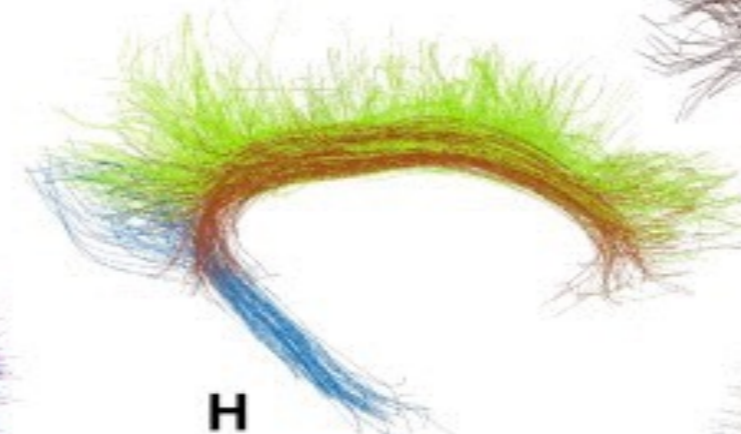
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CORPUS  
CALLOSUM

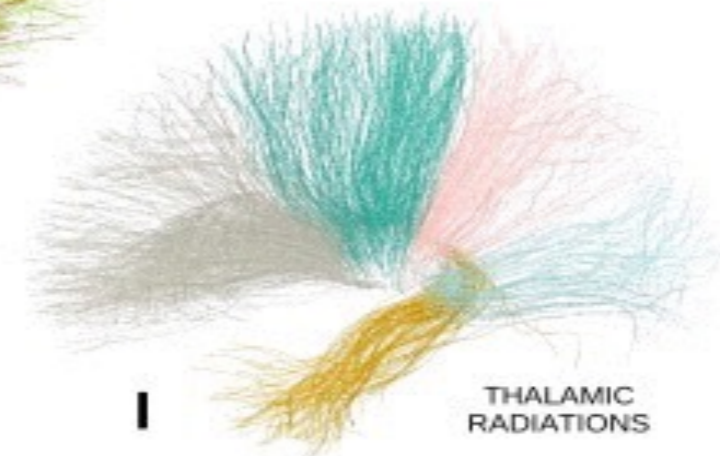
F

H

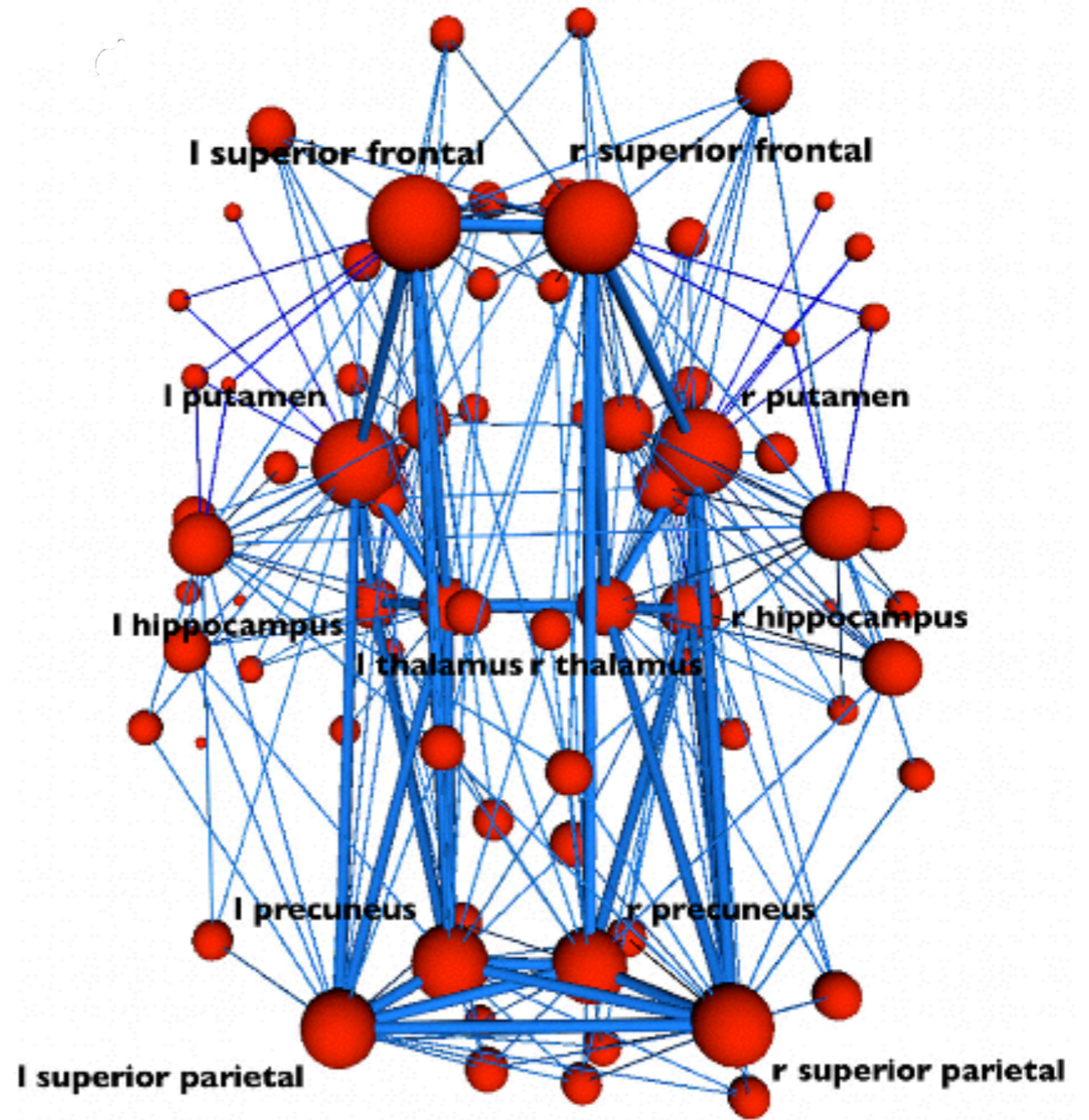
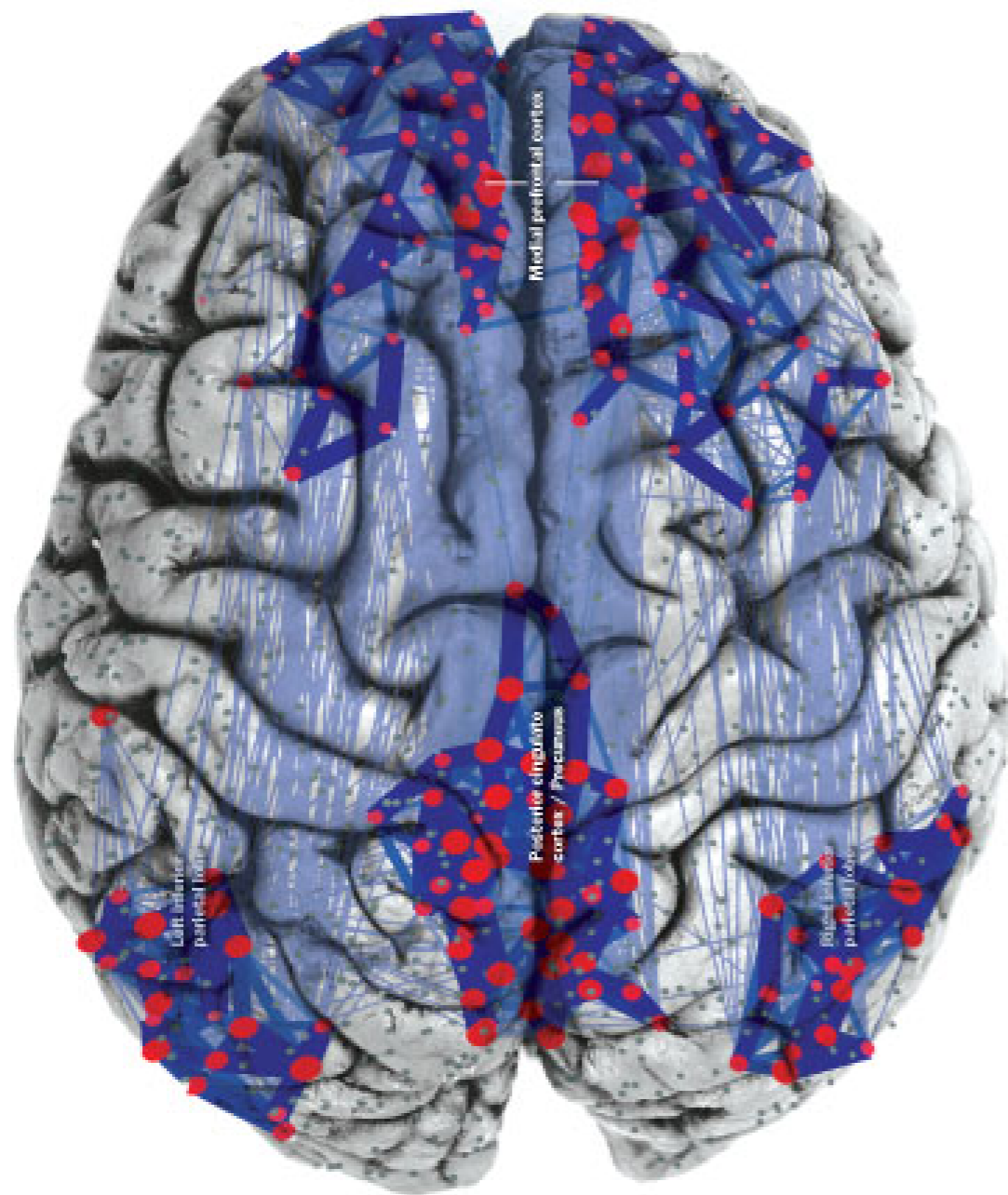


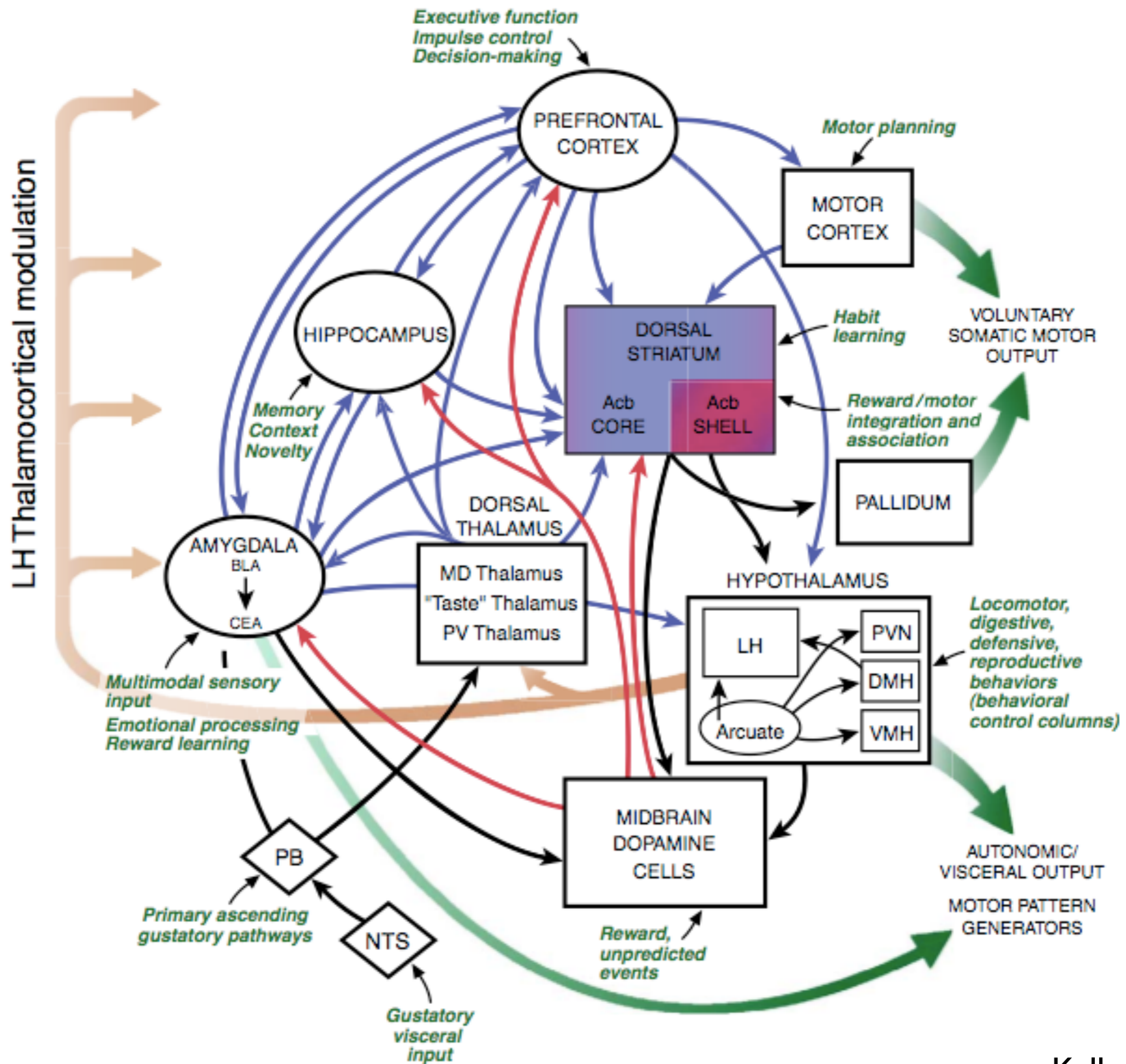
CINGULUM

I



THALAMIC  
RADIATIONS

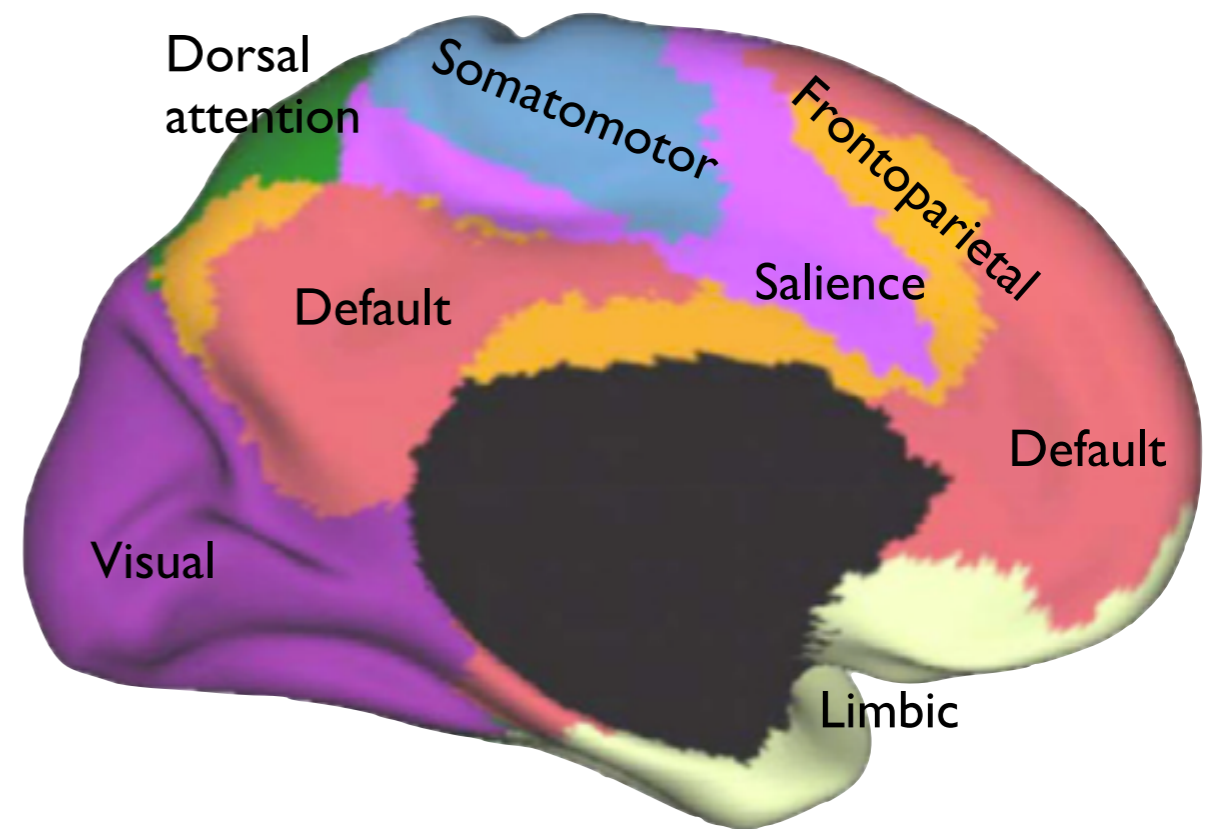
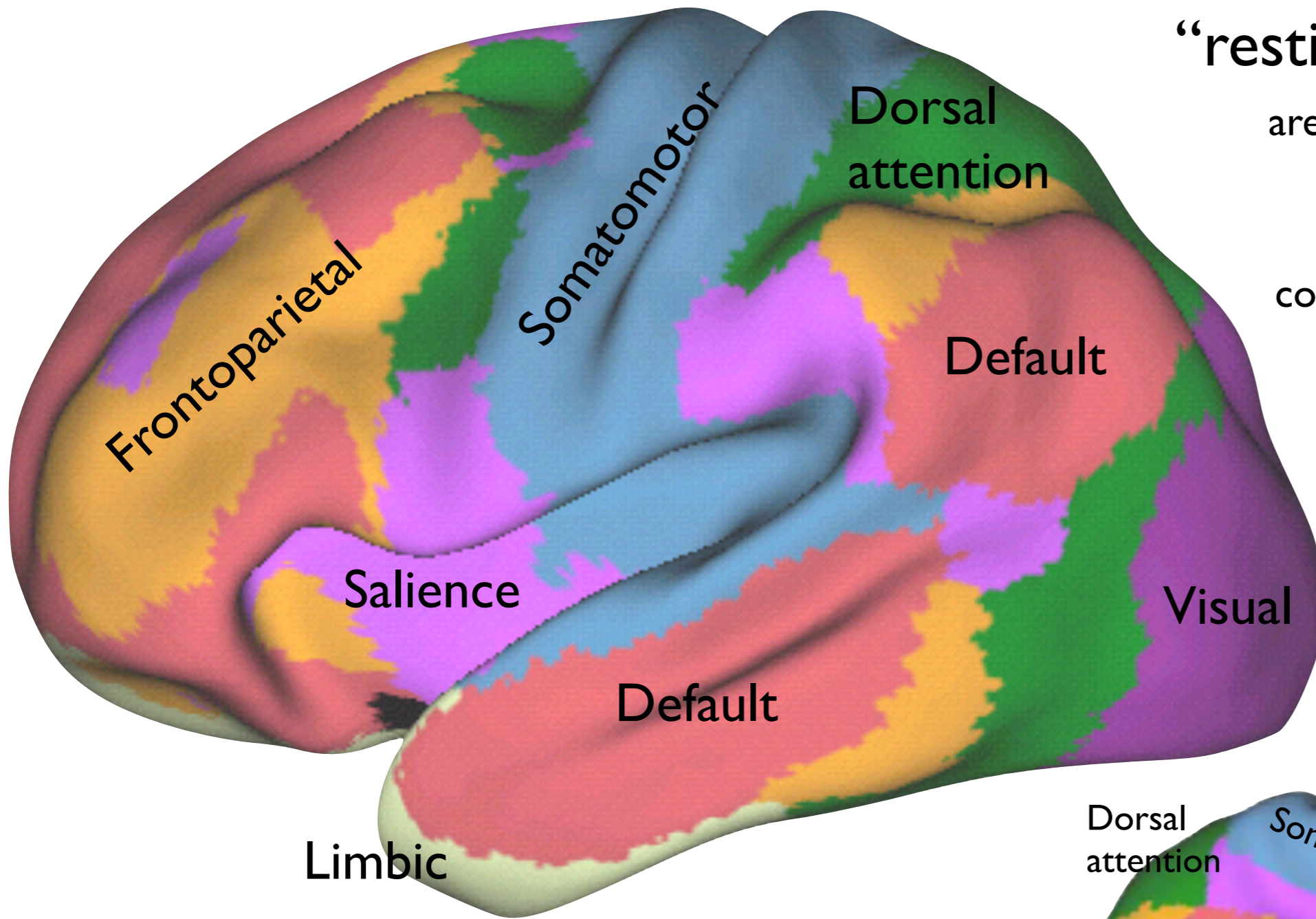






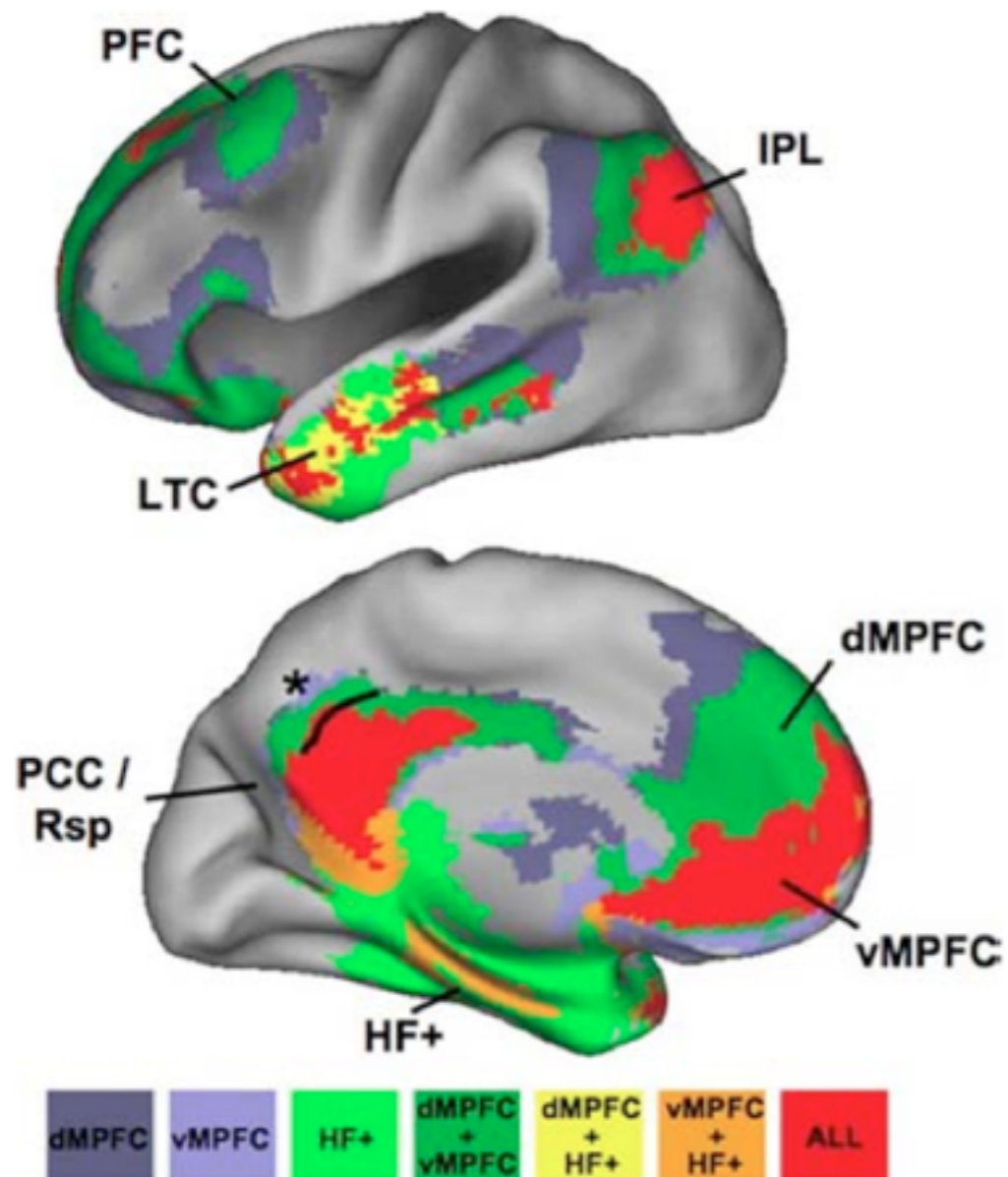
# “resting state” networks

areas presumed to be connected  
continuously active  
dynamically interactive  
correspond to functional studies

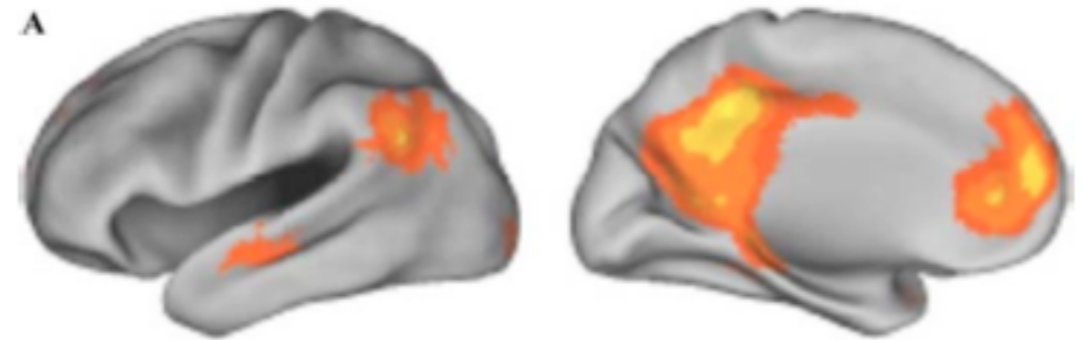


# default mode network

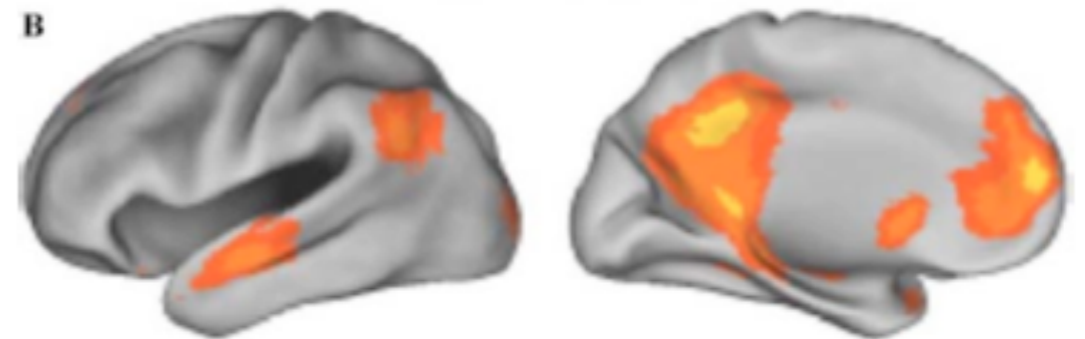
mind-wandering  
daydreaming  
stimulus-independent thought  
simulation  
episodic/autobiographical memory



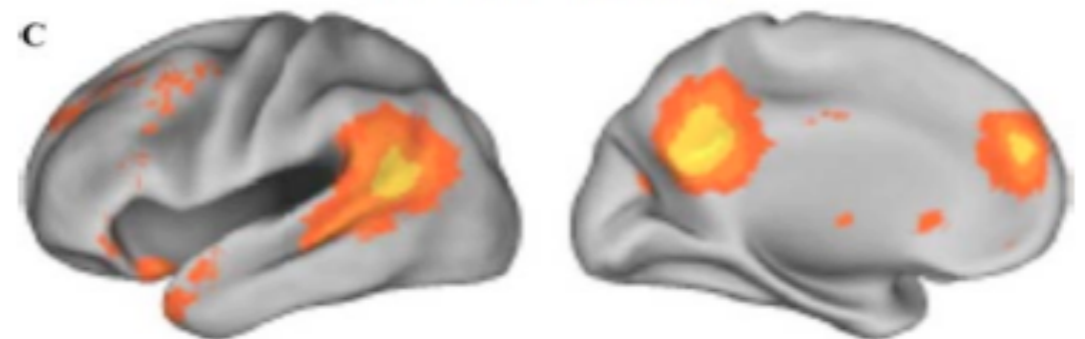
## AUTOBIOGRAPHICAL MEMORY



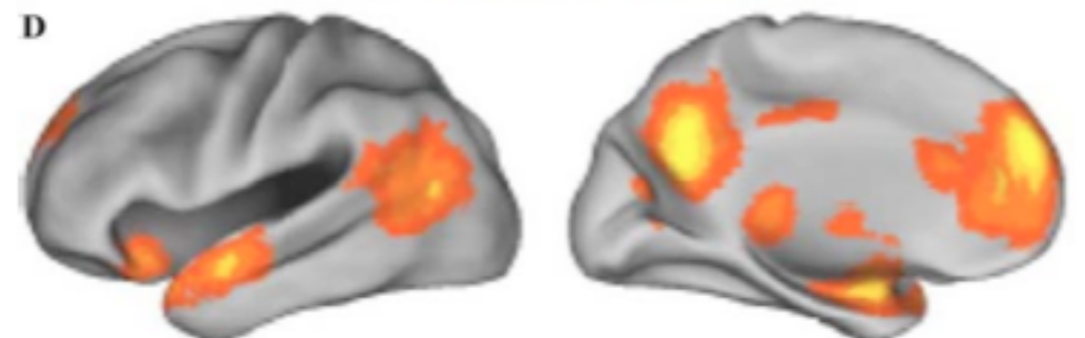
## ENVISIONING THE FUTURE



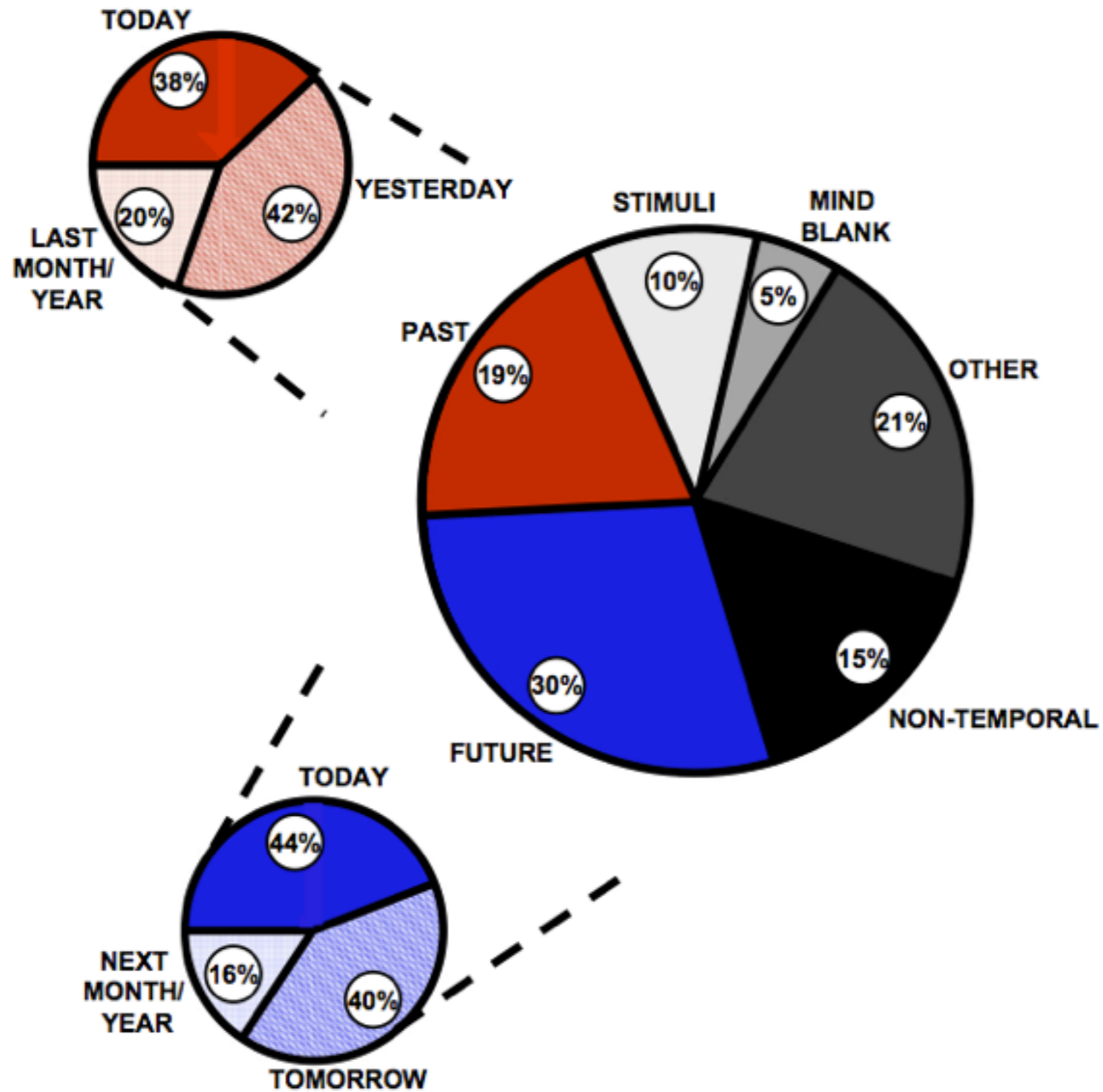
## THEORY OF MIND



## MORAL DECISION MAKING



# DMN correlated with spontaneous cognition



## attention network

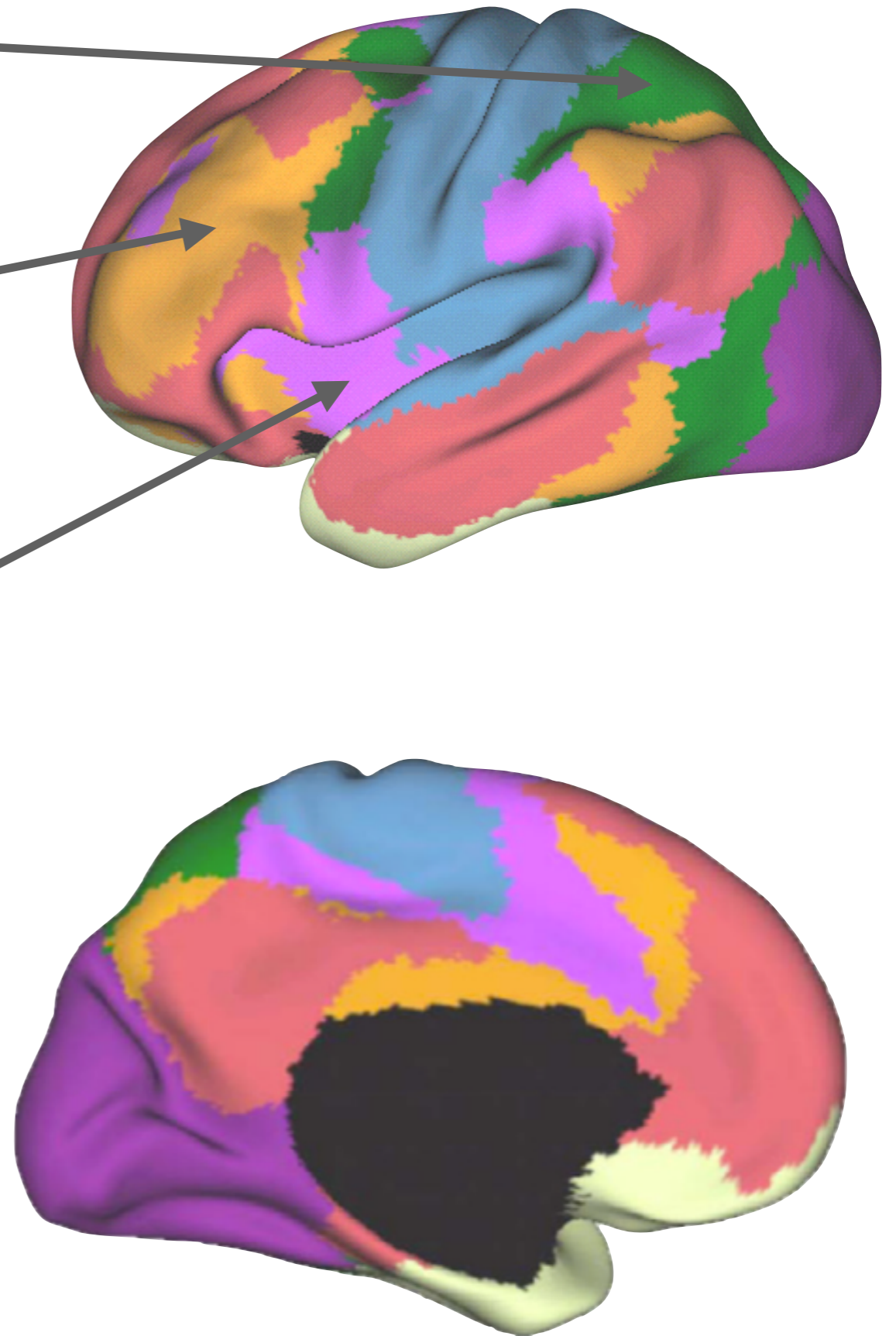
switching attention

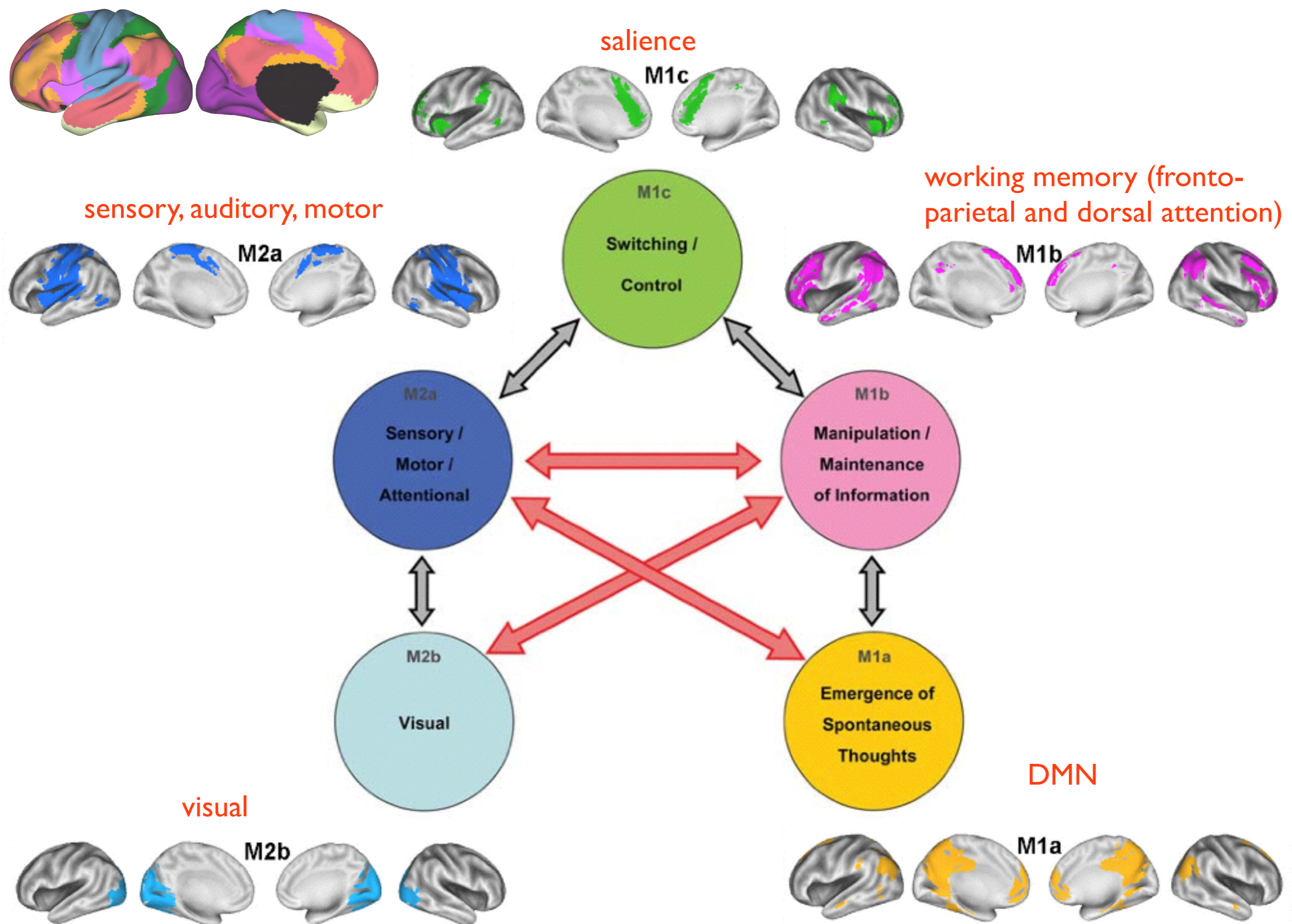
## executive control/ frontoparietal network

working memory  
staying on task  
maintaining focus

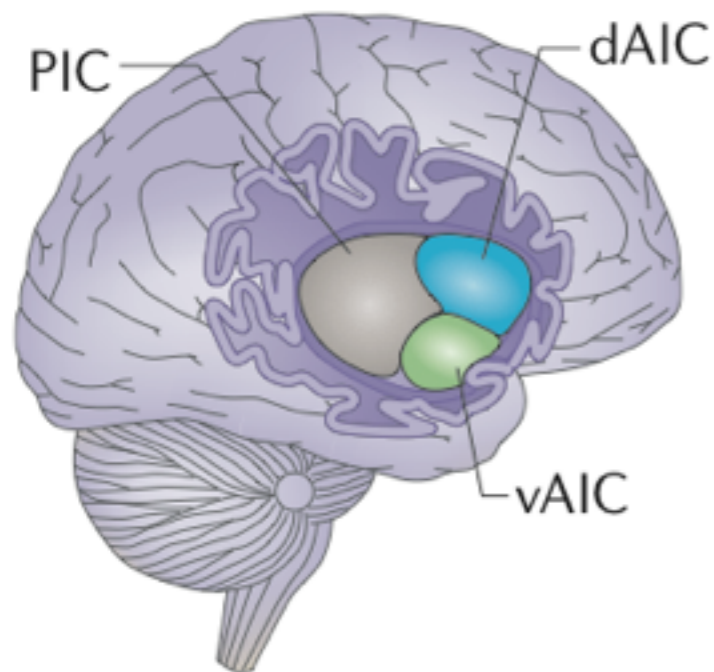
## salience network

encoding “value”  
monitoring errors  
subjective experience (“aha” moments, craving,  
and more)

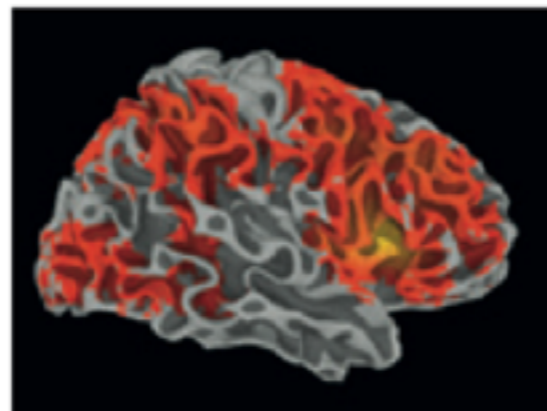




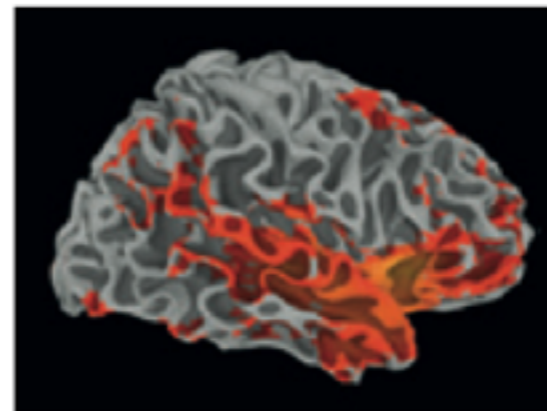
## Insula subdivisions



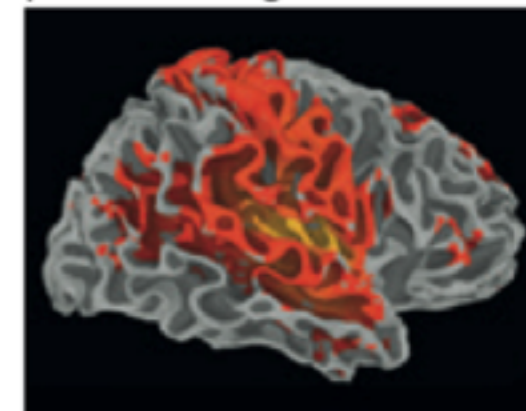
dAIC co-activation associated with cognitive processing areas



vAIC co-activation associated with affective processing areas



PIC co-activation associated with sensorimotor processing areas



Uddin 2015 NATURE REVIEWS | NEUROSCIENCE

## Posterior insula



Primary interoceptive representation



Homeostatic motor function (hypothalamus and amygdala)



Environmental conditions (entorhinal and temporal poles)



Hedonic conditions (nucleus accumbens, and orbitofrontal cortex)

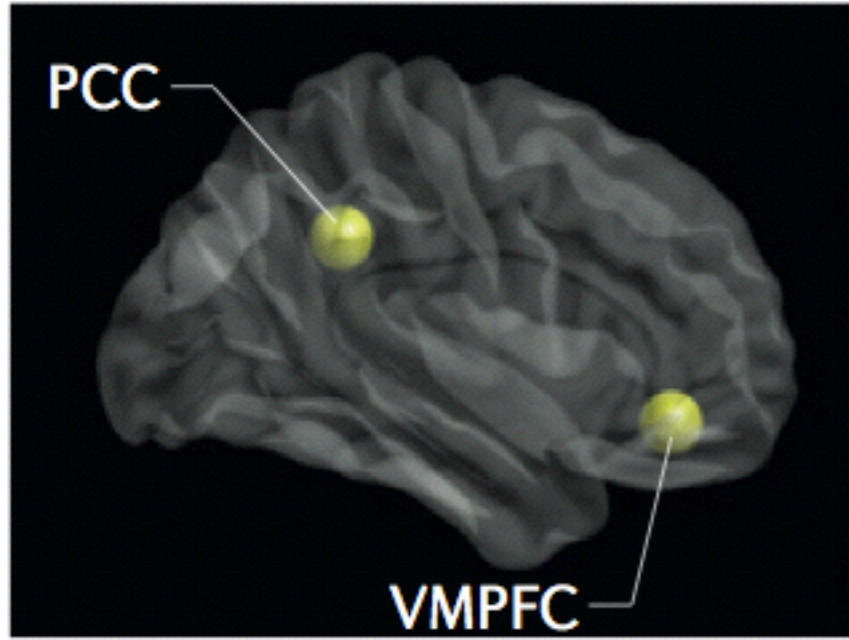


Motivational, social and cognitive conditions (ACC, VMPFC and DLPFC)

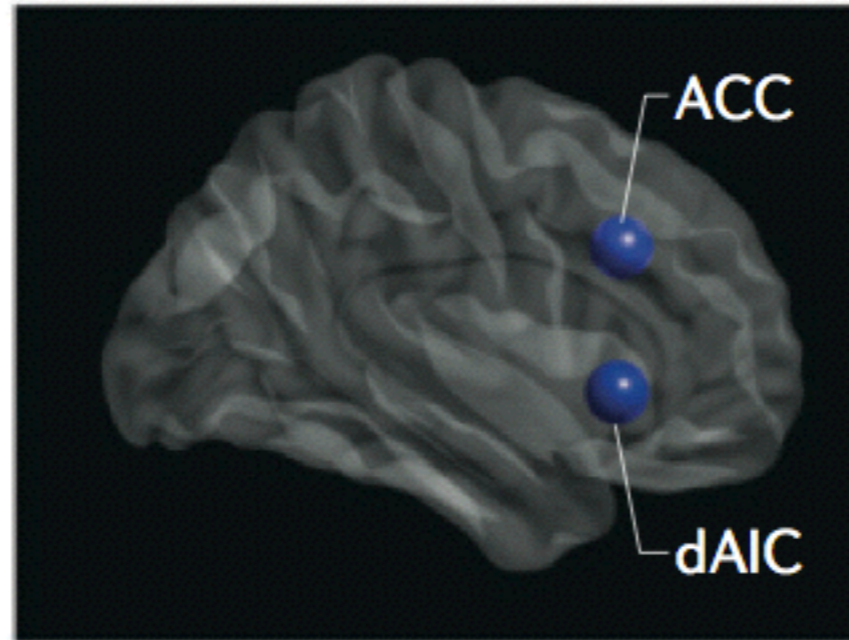
## Anterior insula

Craig 2009 NATURE REVIEWS | NEUROSCIENCE

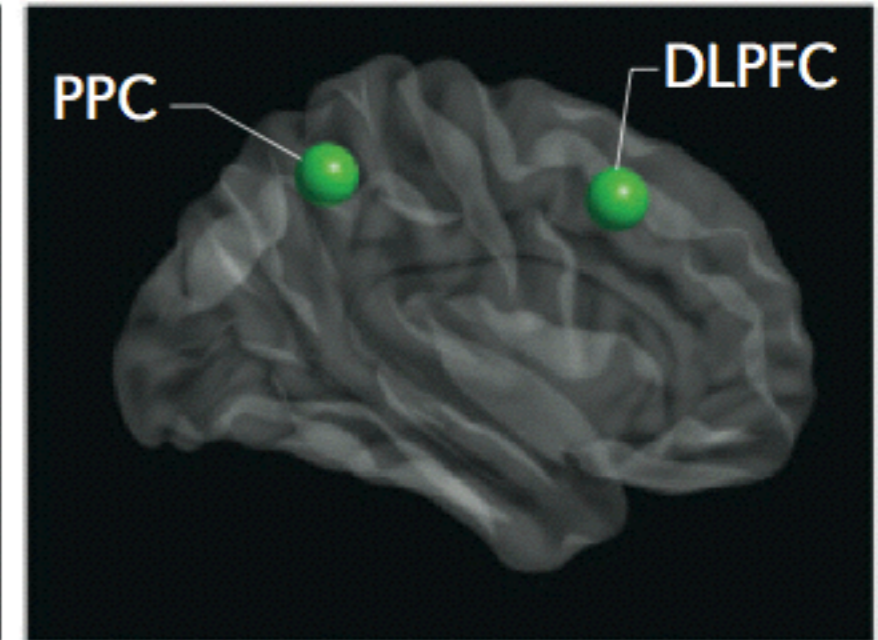
DMN



Salience network



CEN



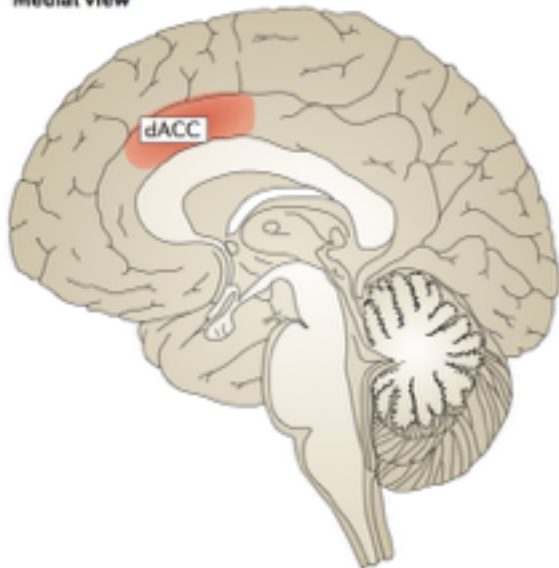
Dynamic switching

Internally directed action

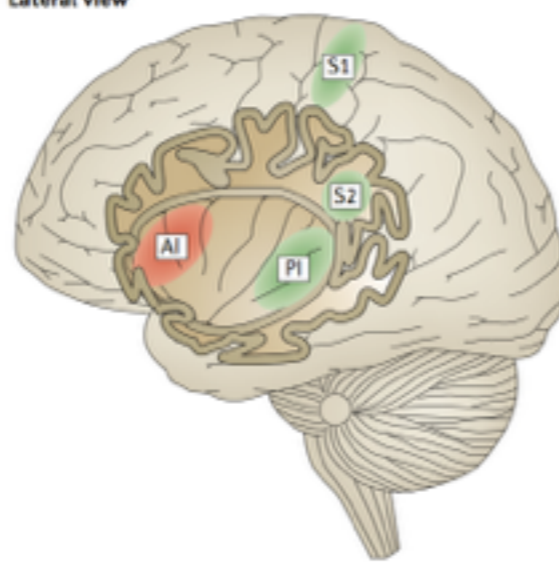
Externally directed action

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Medial view



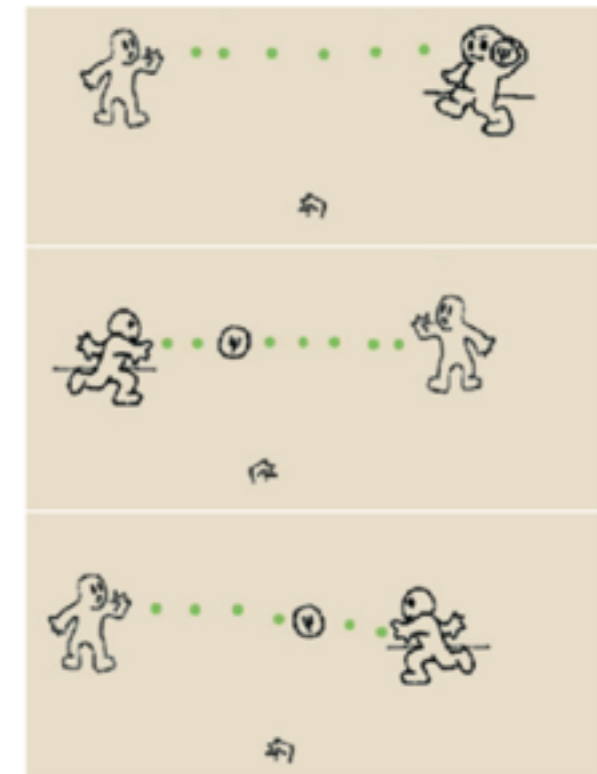
Lateral view



Social inclusion



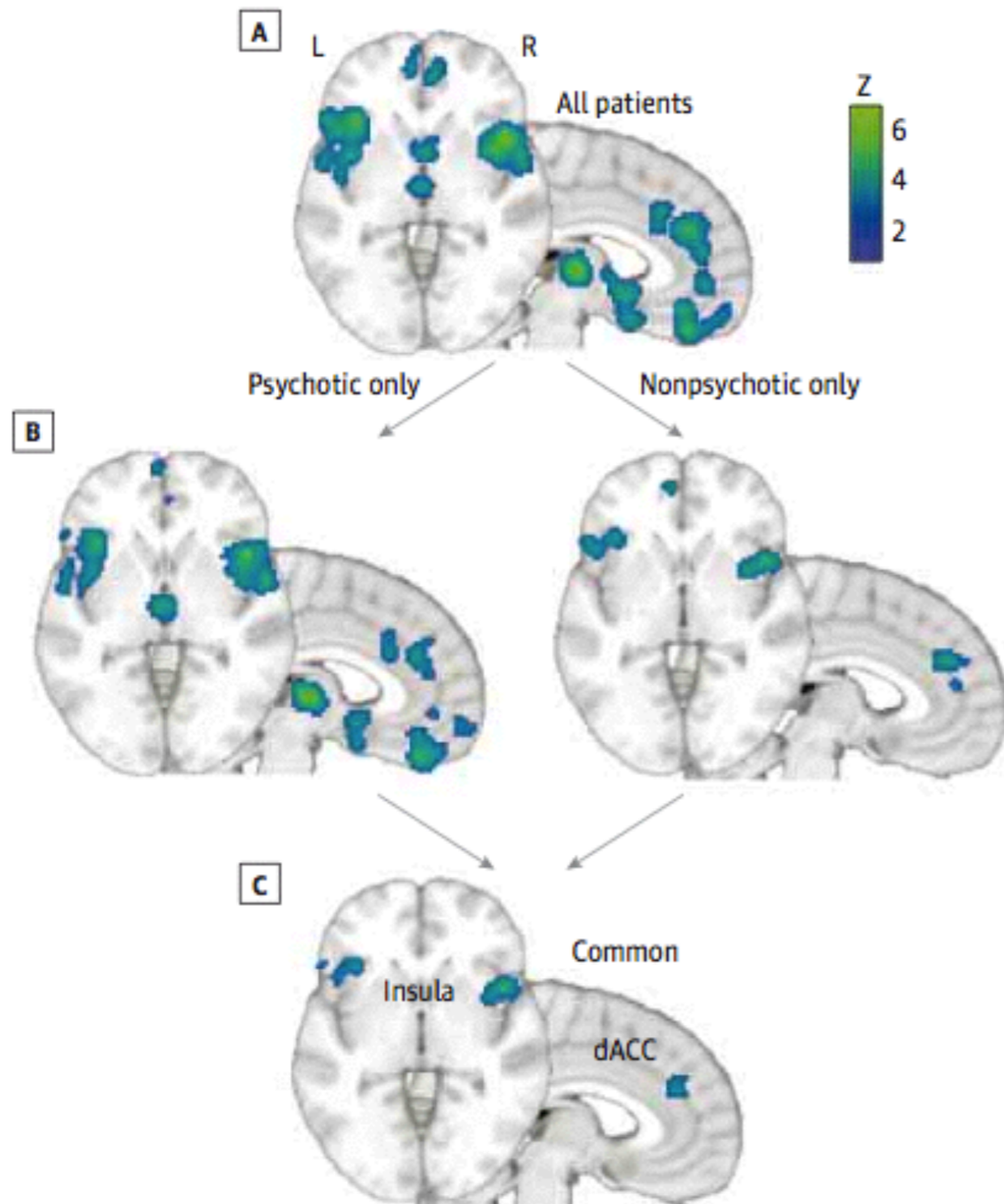
Social exclusion



Eisenberger 2012 Nat Rev Neurosci

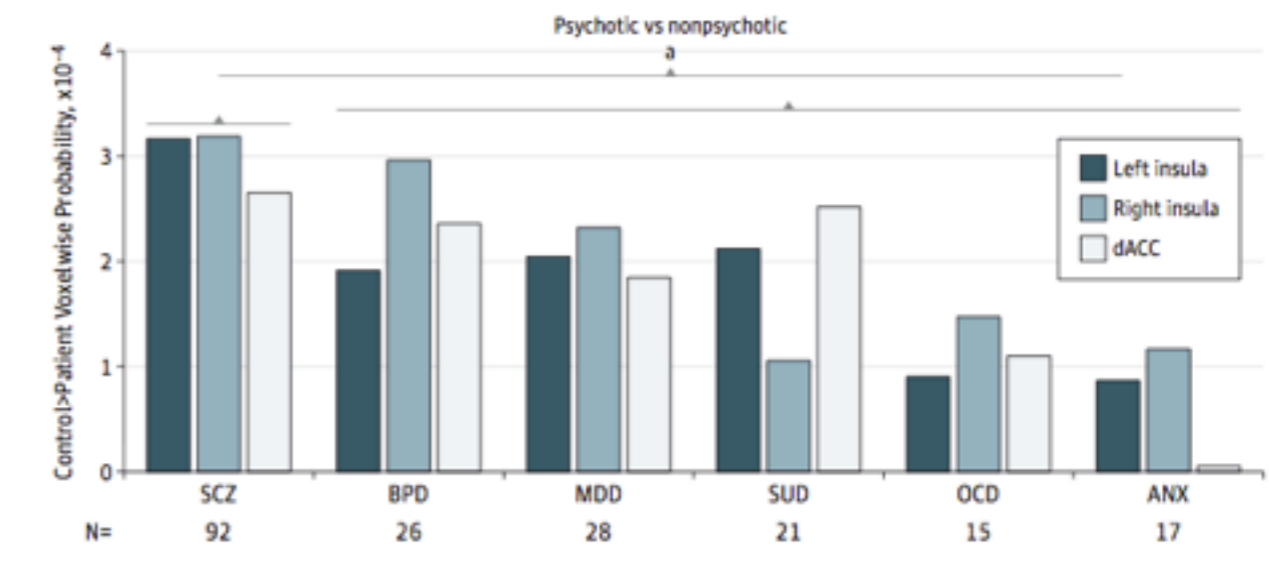
# Saliience network implicated across many psychiatric disorders

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



gray matter loss across 6 diagnoses (schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety) - the dorsal anterior cingulate, right insula, left insula

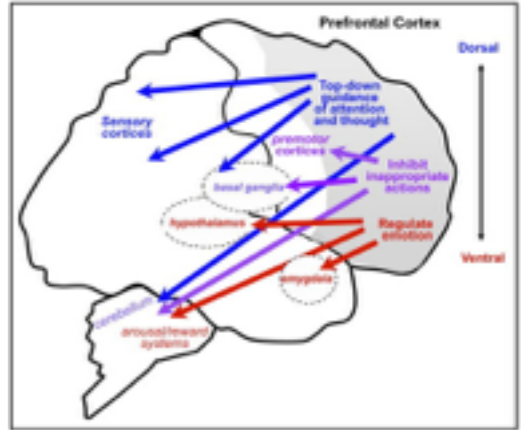
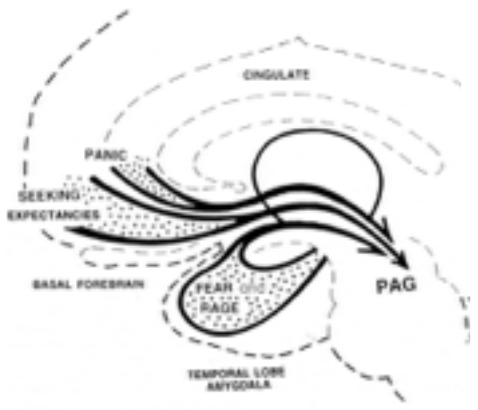
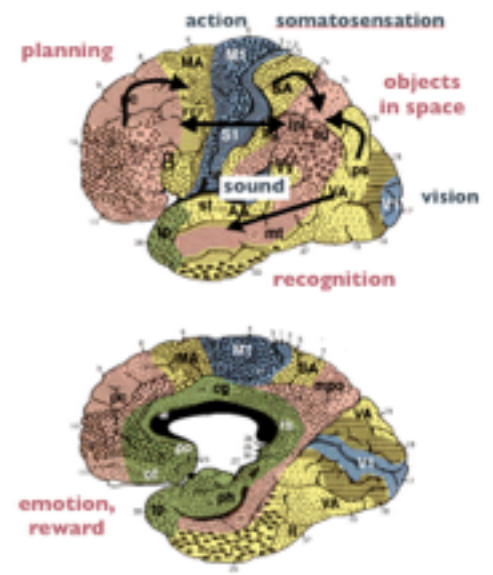
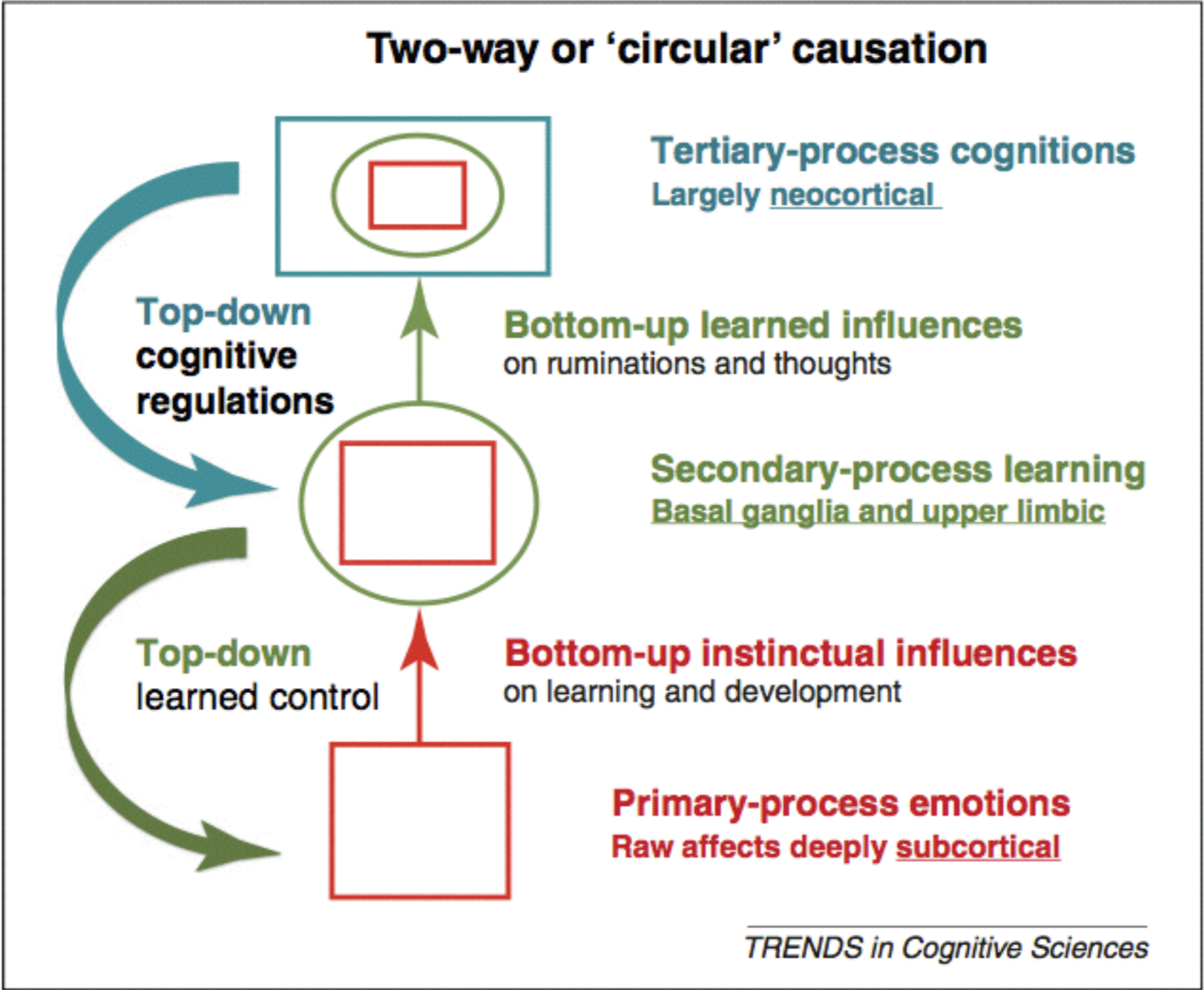
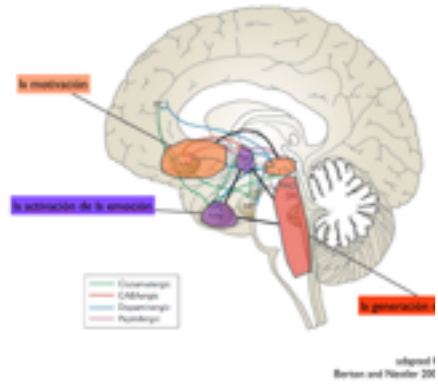
Figure 3. Extracted per-Voxel Probabilities of Decreased Gray Matter in the Voxel-Based Morphometry Meta-analysis, Separated by Individual Diagnosis and Common Gray Matter Loss Region (Left and Right Anterior Insula)





# Emotion, instinct, drive

# Attention, perception, regulation



Panksepp and Solms 2012 Trends Cog Sci

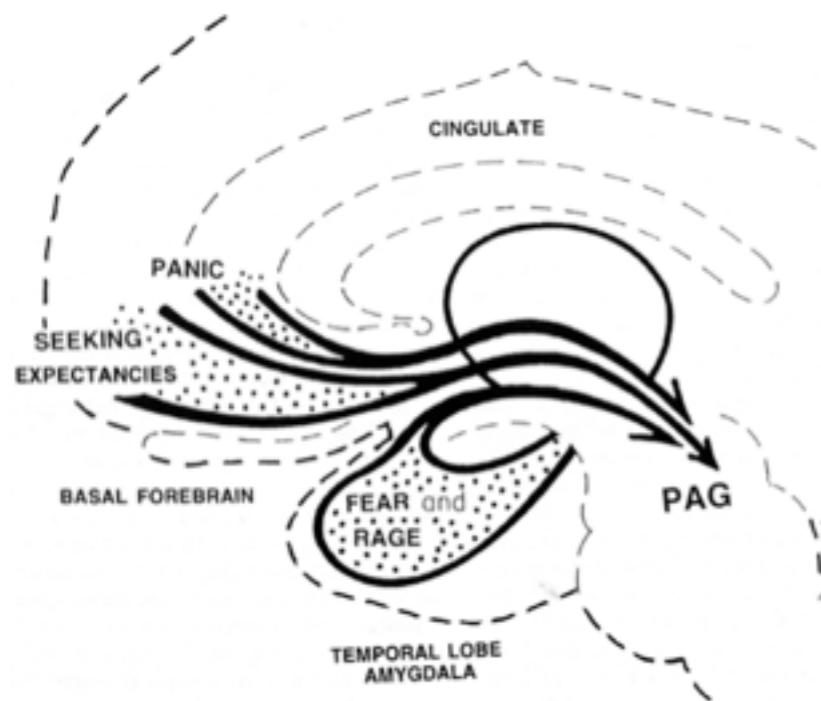
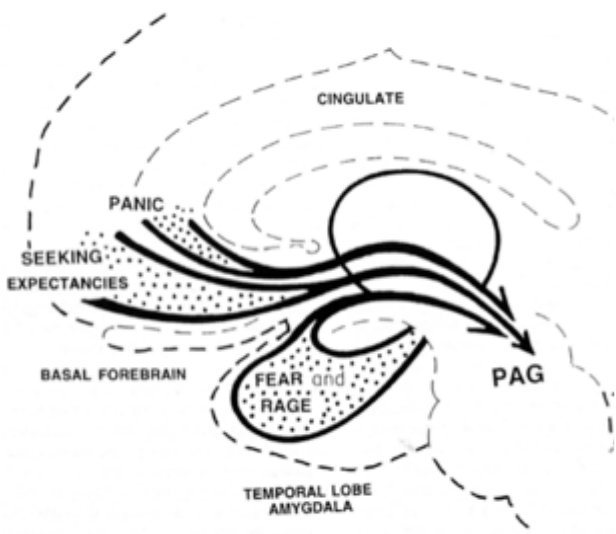


Table 1

Postulated relationships between basic emotional systems, common emotional processes, and major psychiatric disorders

Basic emotional system (Panksepp, 1998a)	Emergent emotions	Related emotional disorders
SEEKING (+ and -)	Interest Frustration Craving	Obsessive compulsive Paranoid schizophrenia Addictive personalities
RAGE (- and +)	Anger Irritability Contempt Hatred	Aggression Psychopathic tendencies Personality disorders
FEAR (-)	Simple anxiety Worry Psychic trauma	Generalized anxiety disorders Phobias PTSD variants
PANIC (-)	Separation distress Sadness Guilt/shame Shyness Embarrassment	Panic attacks Pathological grief Depression Agoraphobia Social phobias, autism
PLAY (+)	Joy and glee Happy playfulness	Mania ADHD
LUST (+ and -)	Erotic feelings Jealousy	Fetishes Sexual addictions
CARE (+)	Nurturance Love Attraction	Dependency disorders Autistic aloofness Attachment disorders

Basic Emotional Systems	Key Brain Areas	Key Neuromodulators
General Pos. Motivation <b>SEEKING/</b> Expectancy System	Nucleus Accumbens – VTA Mesolimbic and mesocortical outputs Lateral hypothalamus – <b>PAG</b>	DA (+), glutamate (+), opioids (+), <b>neurotensin (+)</b> , <b>orexin (+)</b> , Many other neuropeptides
<b>RAGE/</b> Anger	Medial amygdala to Bed Nucleus of Stria Terminalis (BNST). Medial and perifornical hypothalamic to <b>PAG</b>	<b>Substance P (+)</b> , Ach (+), glutamate (+)
<b>FEAR/</b> Anxiety	Central & lateral amygdala to medial hypothalamus and dorsal <b>PAG</b>	Glutamate (+), <b>DBI, CRF, CCK, alpha-MSH, NPY</b>
<b>LUST/</b> Sexuality	Cortico-medial amygdala, Bed nucleus of stria terminalis (BNST) Preoptic hypothalamus, VMH, <b>PAG</b>	Steroids (+), <b>vasopressin, &amp; oxytocin, LH-RH, CCK</b>
<b>CARE/</b> Nurturance	Anterior Cingulate, BNST Preoptic Area, VTA, <b>PAG</b>	<b>oxytocin (+), prolactin (+)</b> dopamine (+), <b>opioids (+/-)</b>
<b>PANIC/</b> Separation	Anterior Cingulate, BNST & Preoptic Area Dorsomedial Thalamus, <b>PAG</b>	<b>opioids (-), oxytocin (-)</b> <b>prolactin (-), CRF (+)</b> glutamate (+)
<b>PLAY/</b> Joy	Dorso-medial diencephalon Parafascicular Area, <b>PAG</b>	<b>opioids (+/-)</b> , glutamate (+) Ach (+), <b>cannabinoids,</b> TRH?



**SEEKING**

(↓ PLAY)

(↑ RAGE)

**RAGE**

↓ PLAY

↑ FEAR

**FEAR**

↓ PLAY, LUST, SEEKING

↑ RAGE

**LUST**

**CARE**

↓ GRIEF

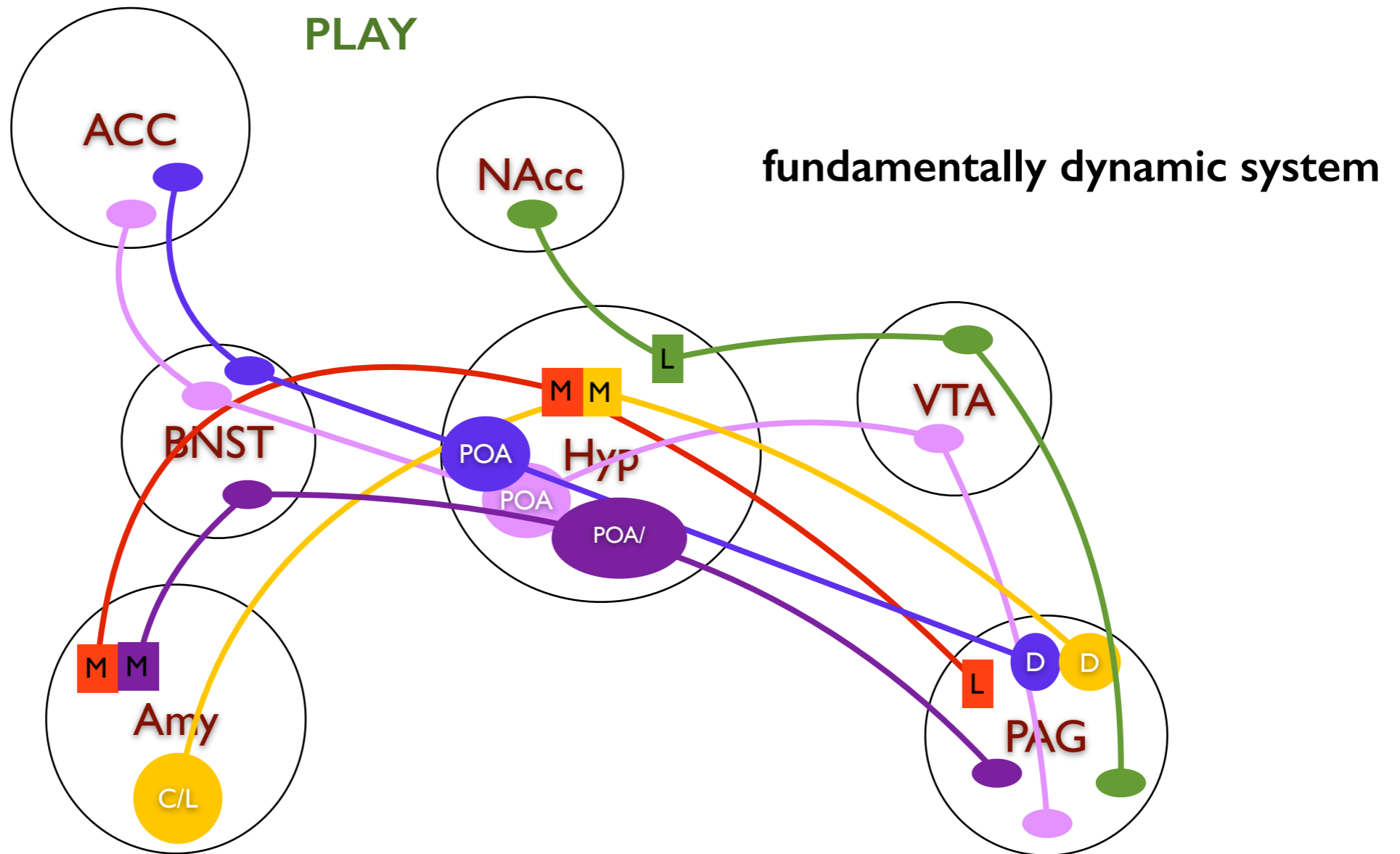
**PANIC/GRIEF**

↓ PLAY

↑↓ SEEKING

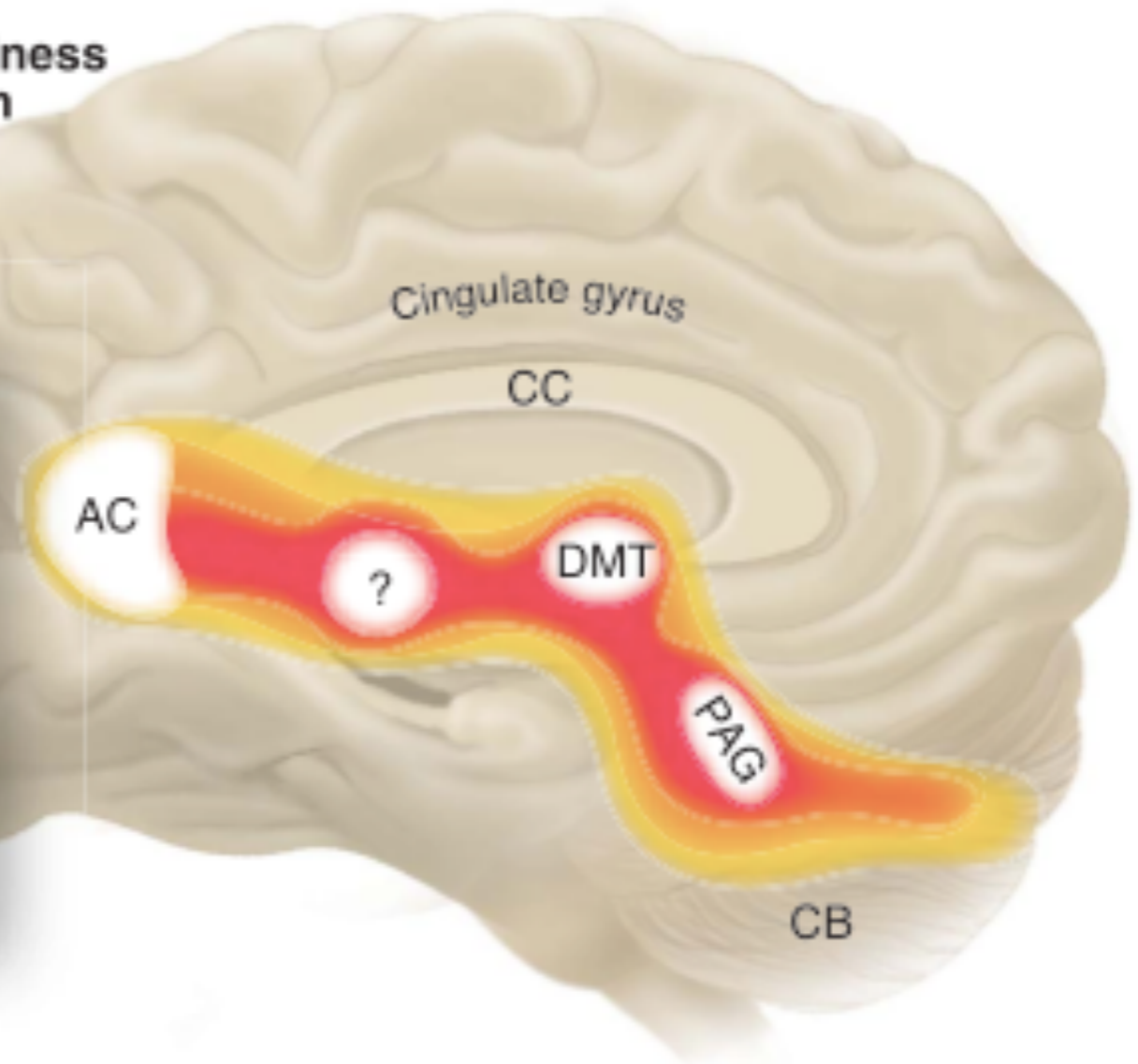
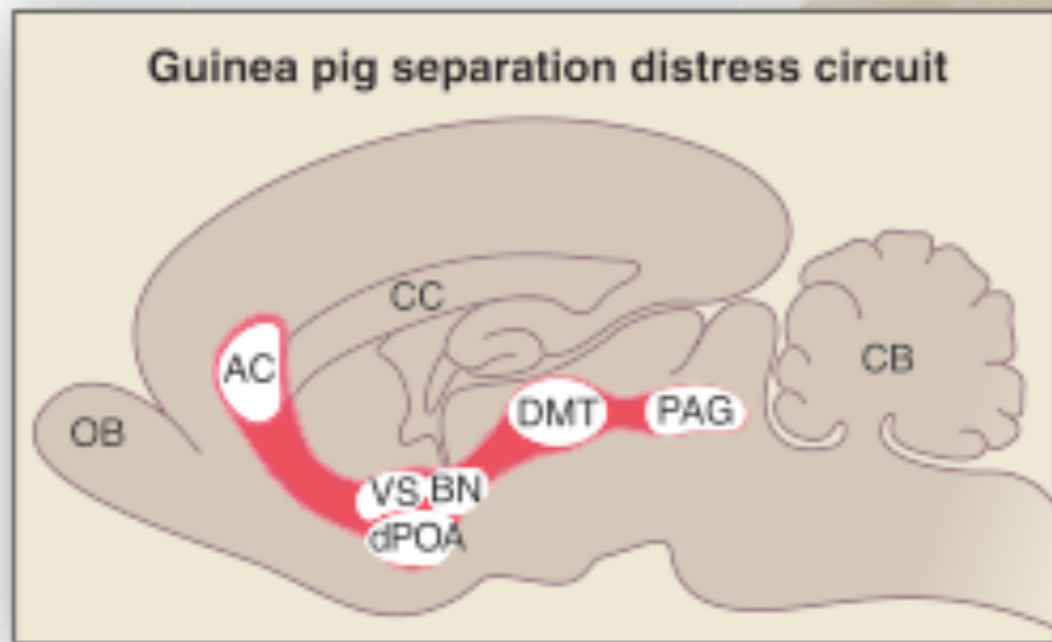
↑ FEAR

**PLAY**



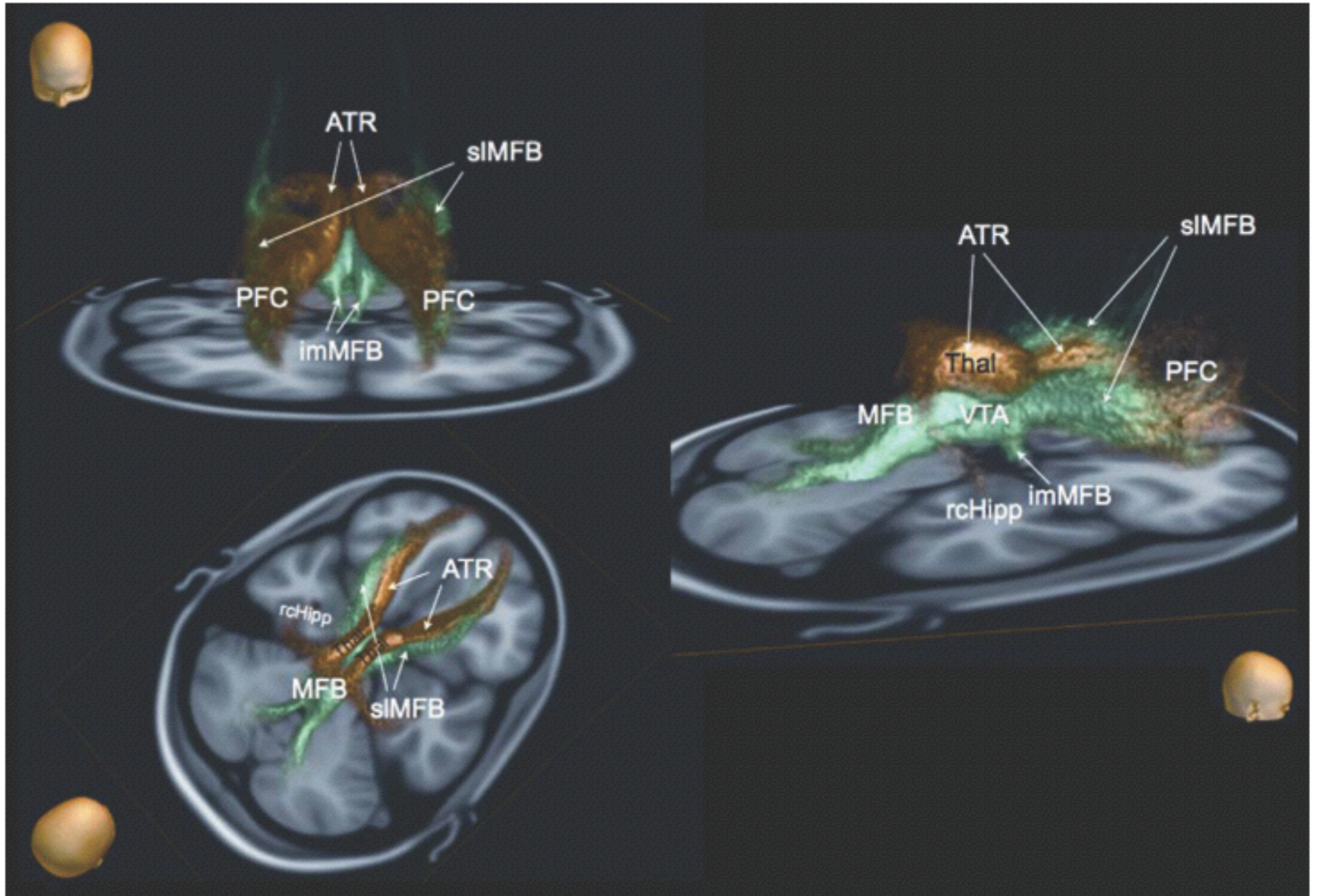
# PANIC/GRIEF System

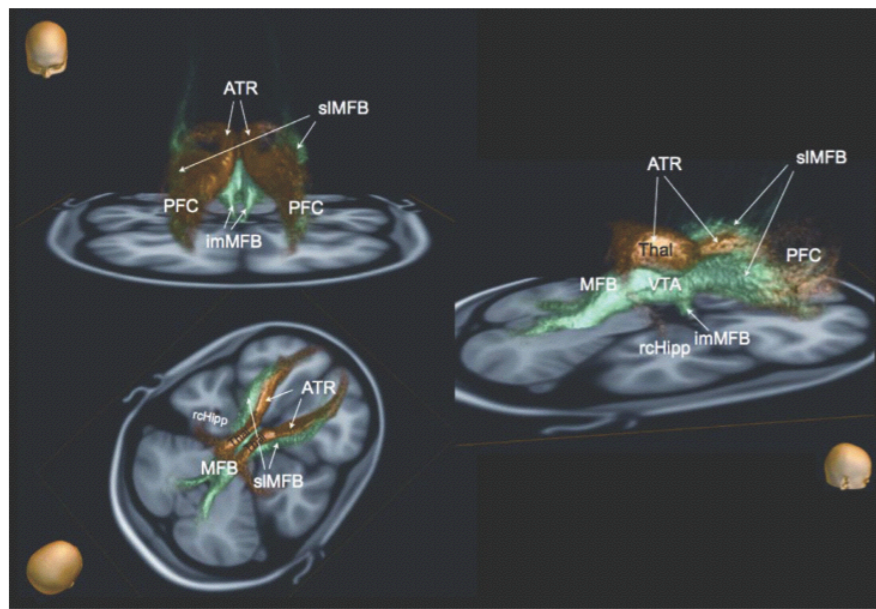
Human sadness system



## PANIC/GRIEF System

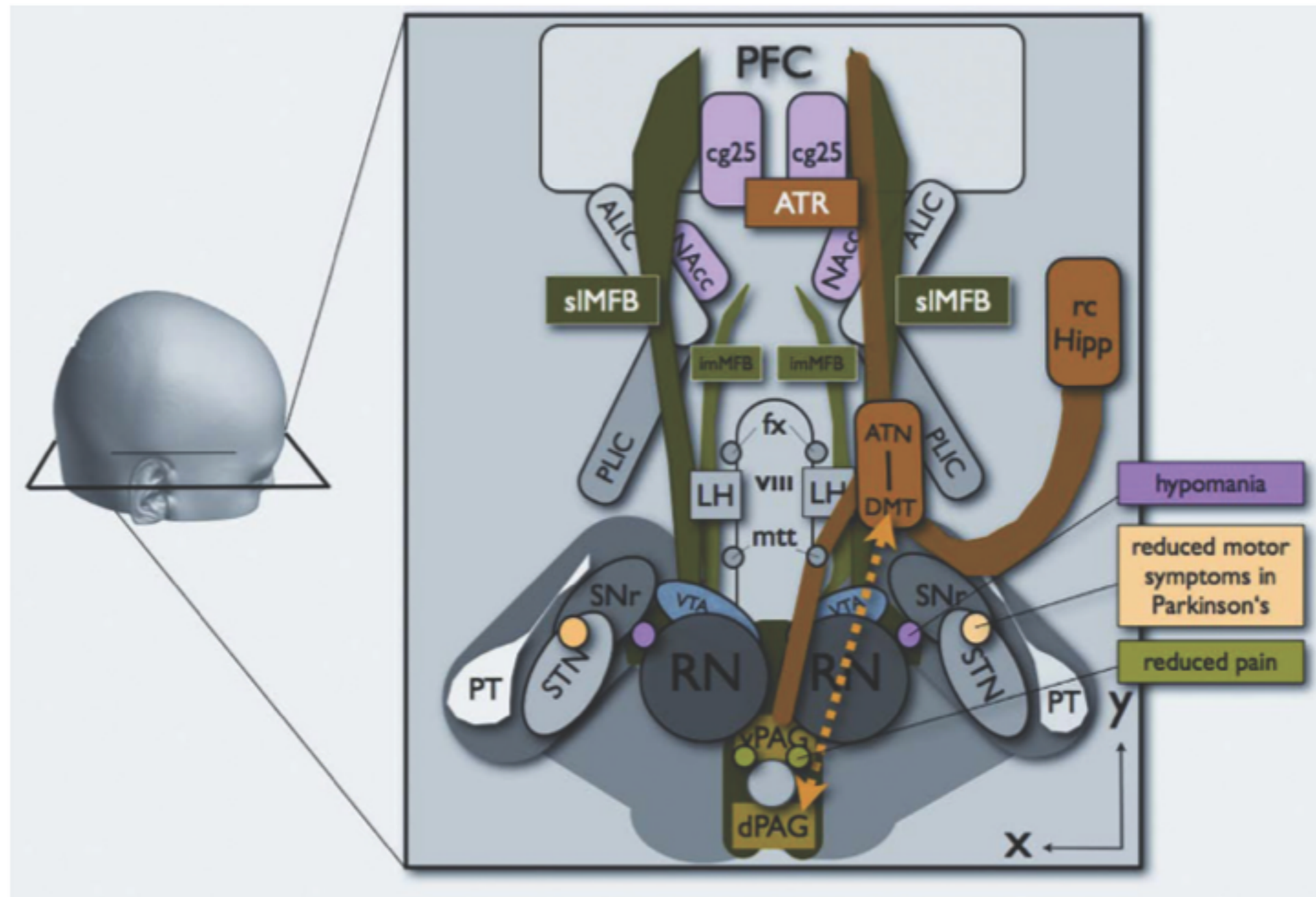
## SEEKING System



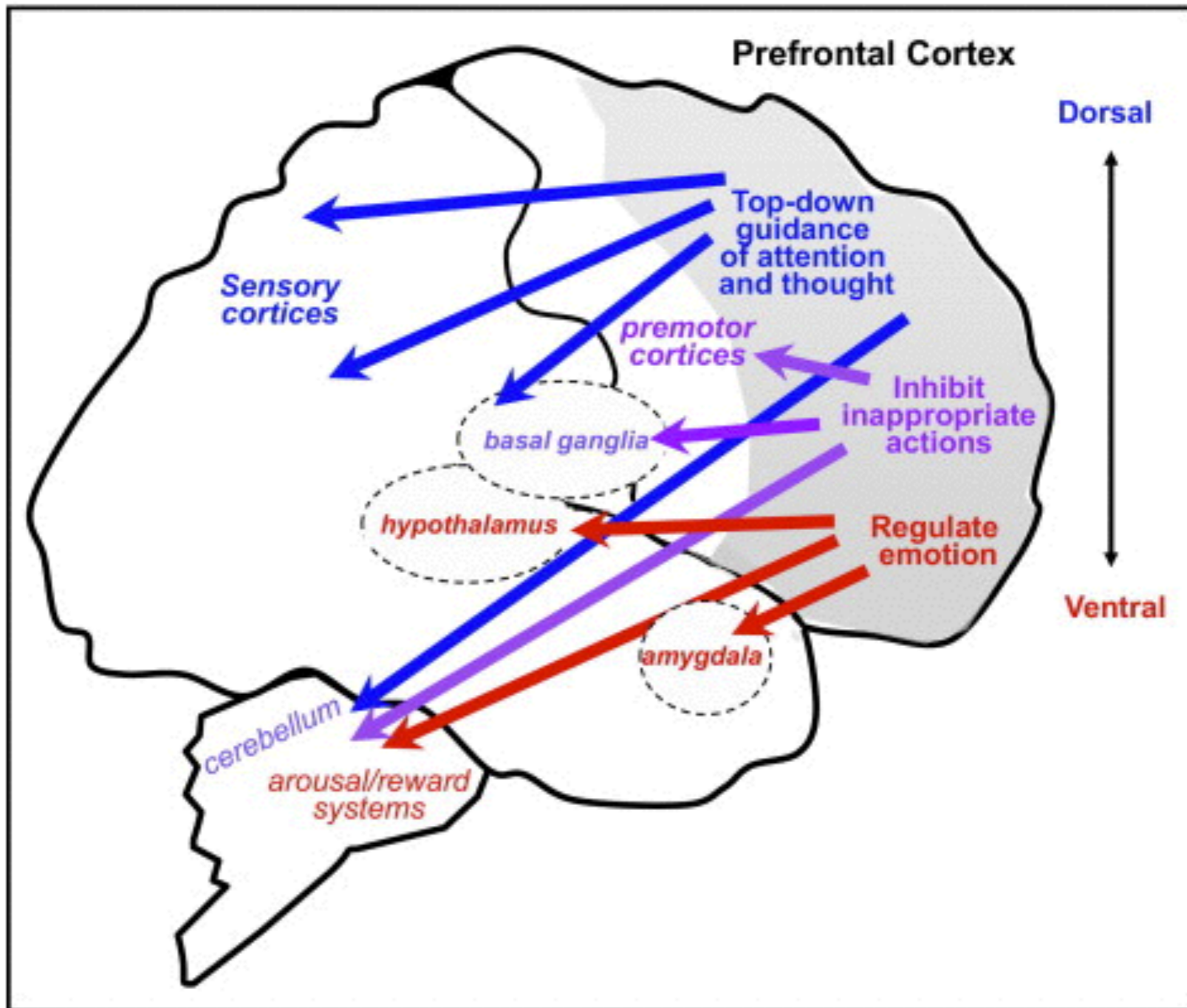


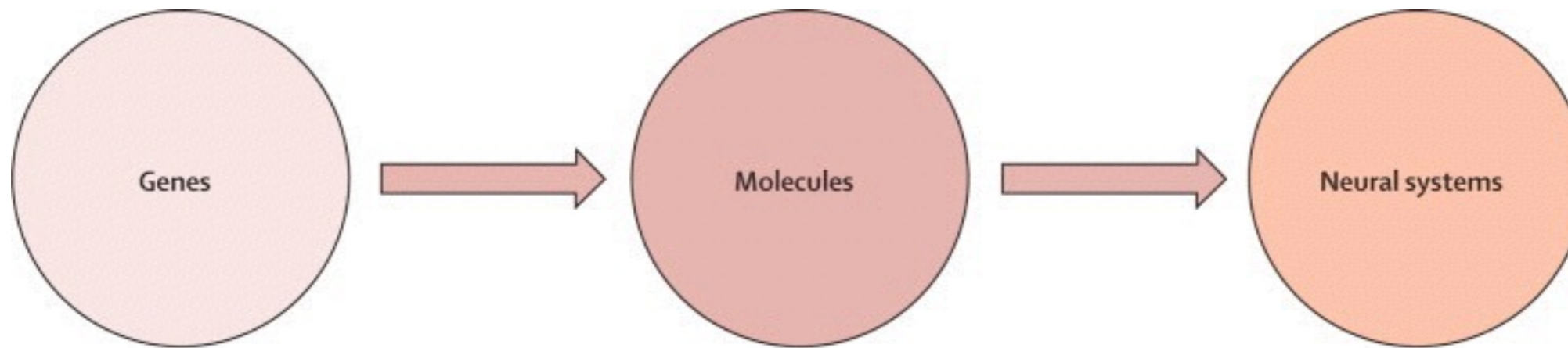
# PANIC/GRIEF System

# SEEKING System



# Affect Regulation





#### Genetic measures

- Candidate genes associated with MDD (ie, beyond the conventional monoamine focus)
- Candidate genes associated with biological mechanisms and metabolic pathways for antidepressant medications
- Serotonergic mechanisms
- Other mechanisms
- Genome-wide association studies

#### Molecular measures

- Neurotrophic factors and other growth factors
- Proinflammatory cytokines
- Impaired regulation of the hypothalamic-pituitary-adrenocortical axis

#### Neuroimaging measures

##### Abnormalities in anatomically-defined neural systems

- Subcortical neural systems for emotion and reward processing
- Medial prefrontal regions involved in processing and implicit regulation of emotion
- Lateral prefrontal cortical systems involved in cognitive control and voluntary or effortful regulation of emotion

##### Abnormalities in neurotransmitter-defined neural systems

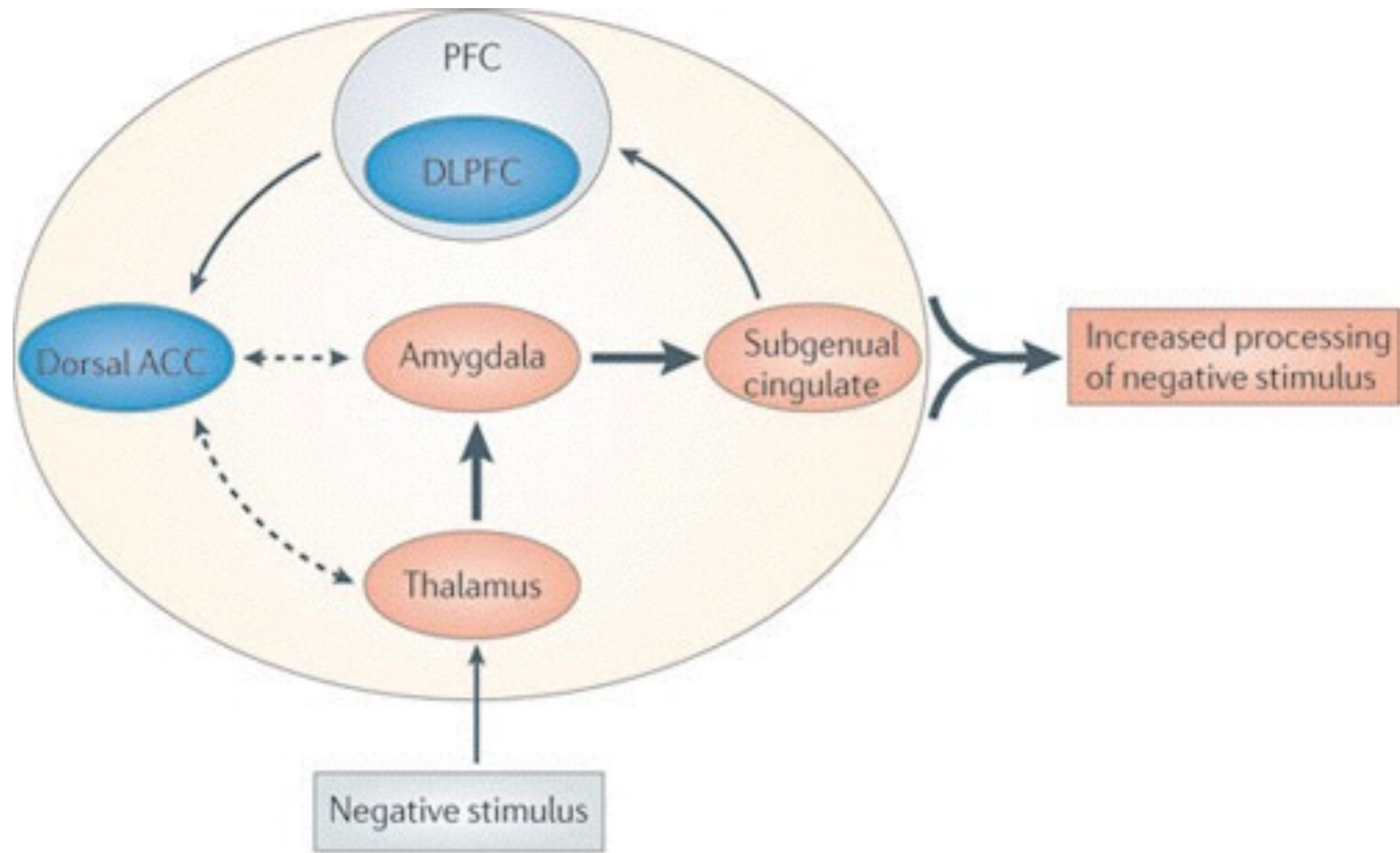
- Medial prefrontal-limbic network, modulated by serotonin
- Reward network, centred on ventral striatum and medial prefrontal cortices, modulated by dopamine

##### Newer neuroimaging methodologies to study MDD

- Measurement of brain activity during rest

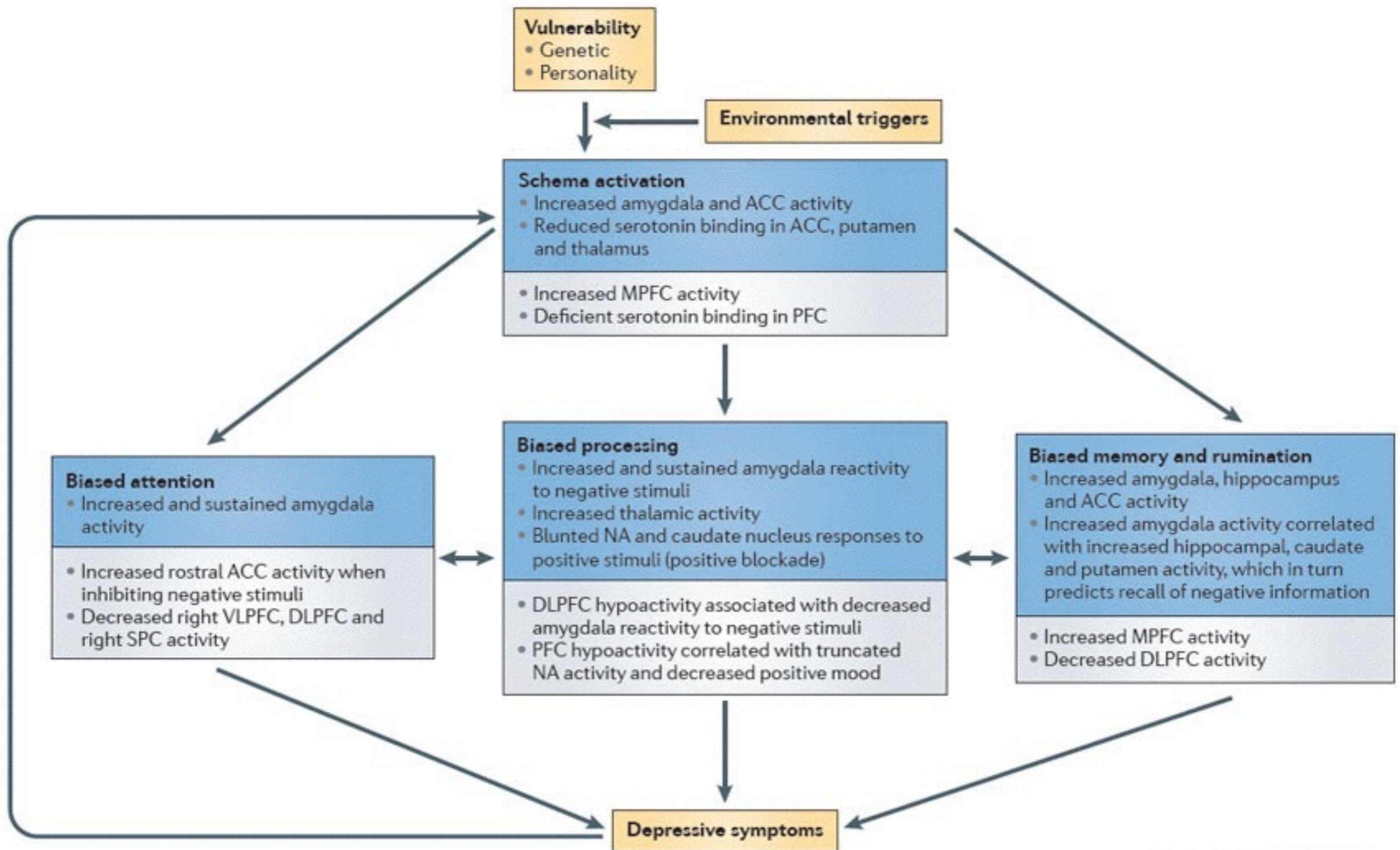
##### Neuroimaging and antidepressant treatment response





Nature Reviews | Neuroscience

Disner, S. G., Beevers, C. G., Haigh, E. A. P., & Beck, A. T. (2011). Neural mechanisms of the cognitive model of depression. *Nature Reviews Neuroscience*, 12(8), 467–477. doi:10.1038/nrn3027



# PANIC-shutdown model of depression

(Panksepp & Watt 2009)

**euthymia**

or

**depressive vulnerability**

- baseline opioid and oxytocin tone (social contact, good internal objects)
- responsive DA system
- appropriate levels of other global neuromodulators (NE, ACh, 5-HT)

- impaired infrastructure due to history
- impaired infrastructure due to genes
- depressive intrapsychic factors:  
intrapsychic conflict/defenses around grieving ("the shadow of the object" / relating to negative internal objects)

**loss:  
separation distress**

- ↑ HPA activation
- ↑ DA release, NE, ACh
- ↓ opioids
- ↑ dynorphin

*Bowlby: protest*

**termination of  
separation distress:**

**reunion**

- ↑ opioids, oxytocin
- ↓ HPA activation
- ↑ DA tone

**sadness**

- ↓ opioids, oxytocin
- ↓ HPA activation
- ↓ DA tone
- ↑ PNS activation

**shut down**

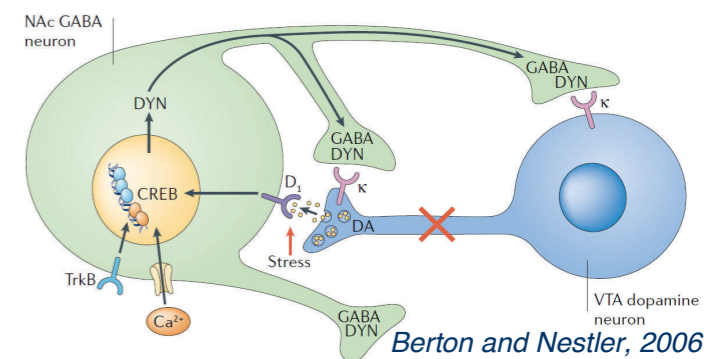


} *despair*

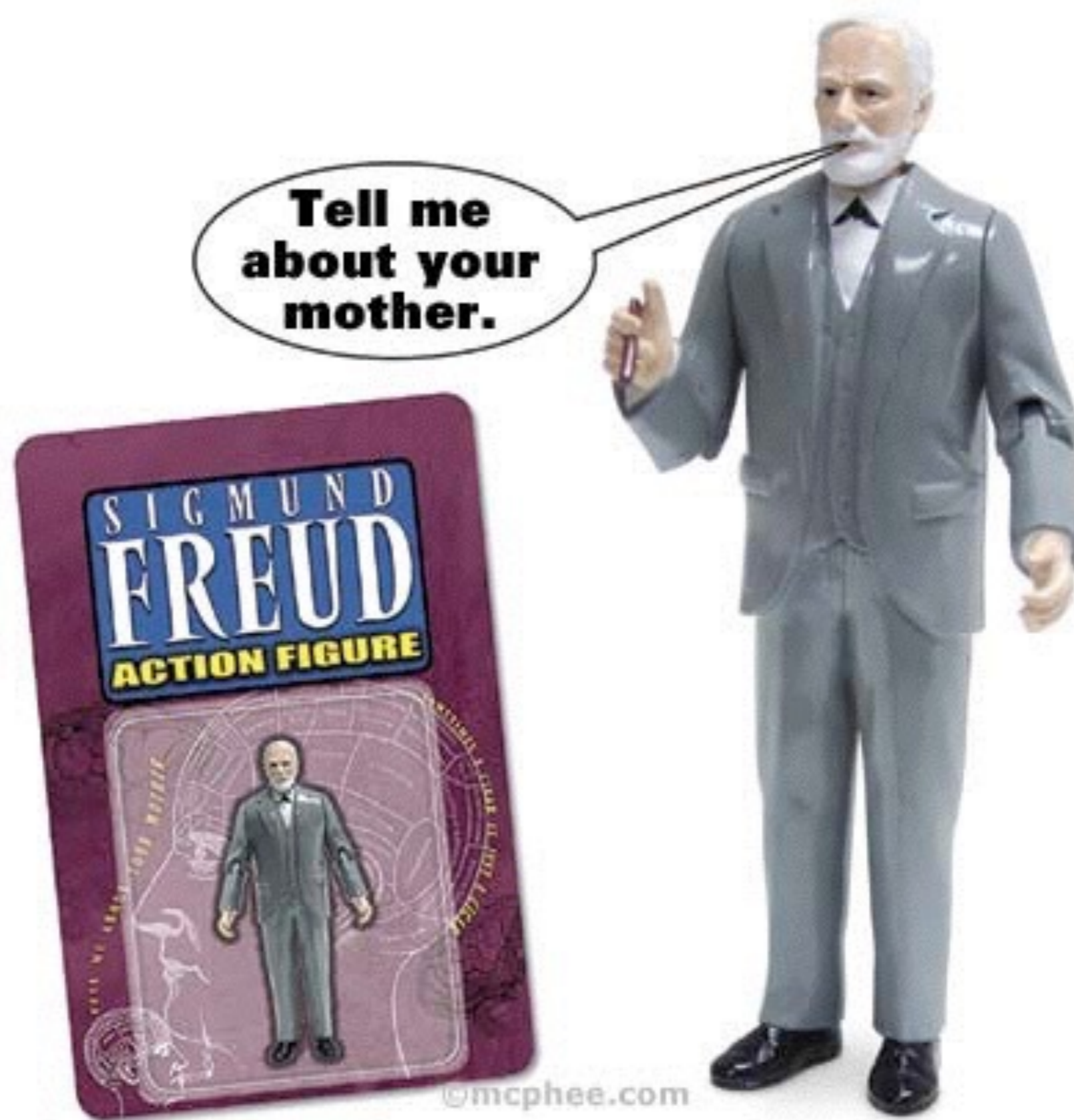
**depression**

- circadian disruption
- immune system - "sickness behavior"
- continued dynorphin activation?
- chronic HPA activation, leading to cognitive and immune problems, hypersensitive amygdala, other...

**decathexis**

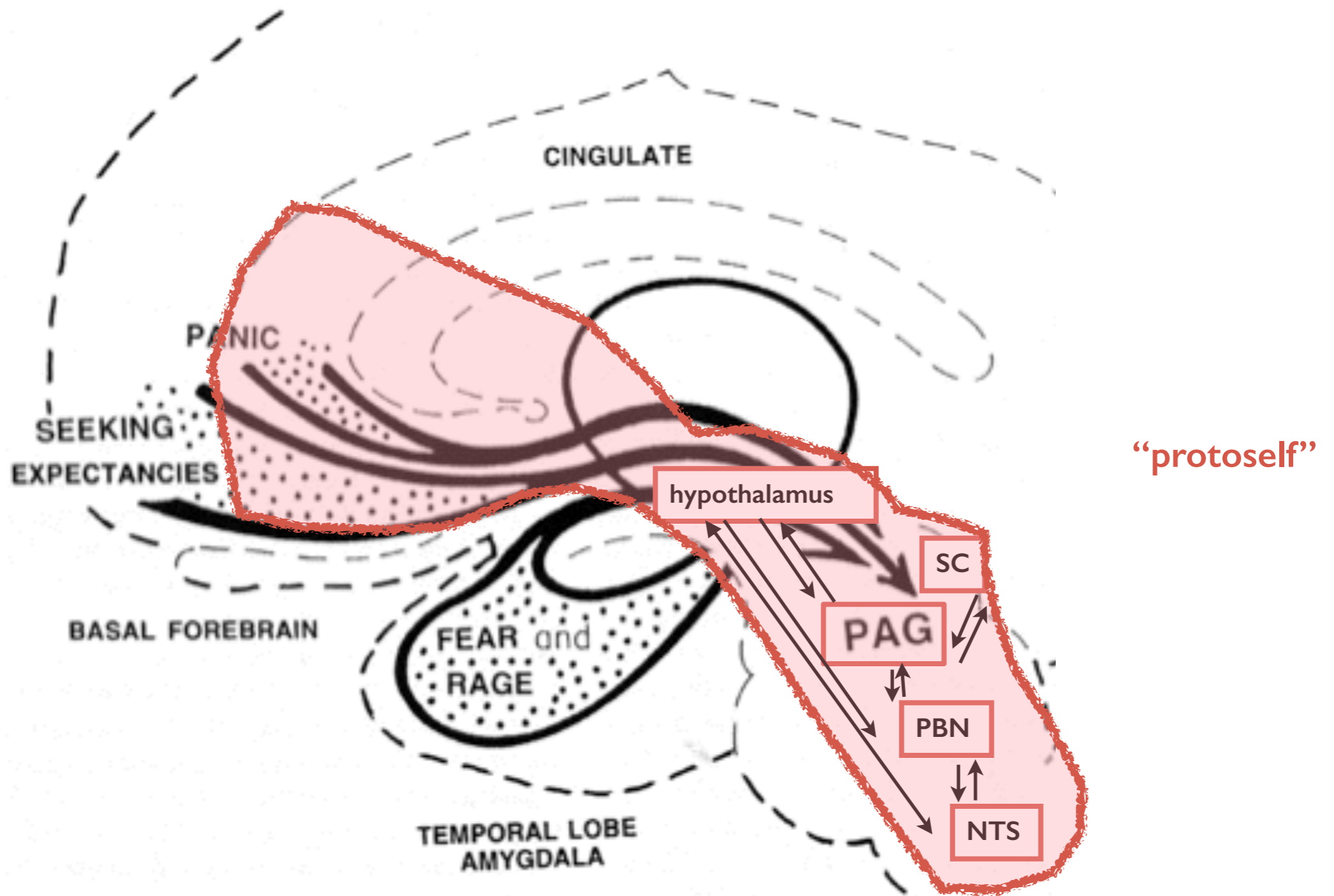


# Questions and discussion?



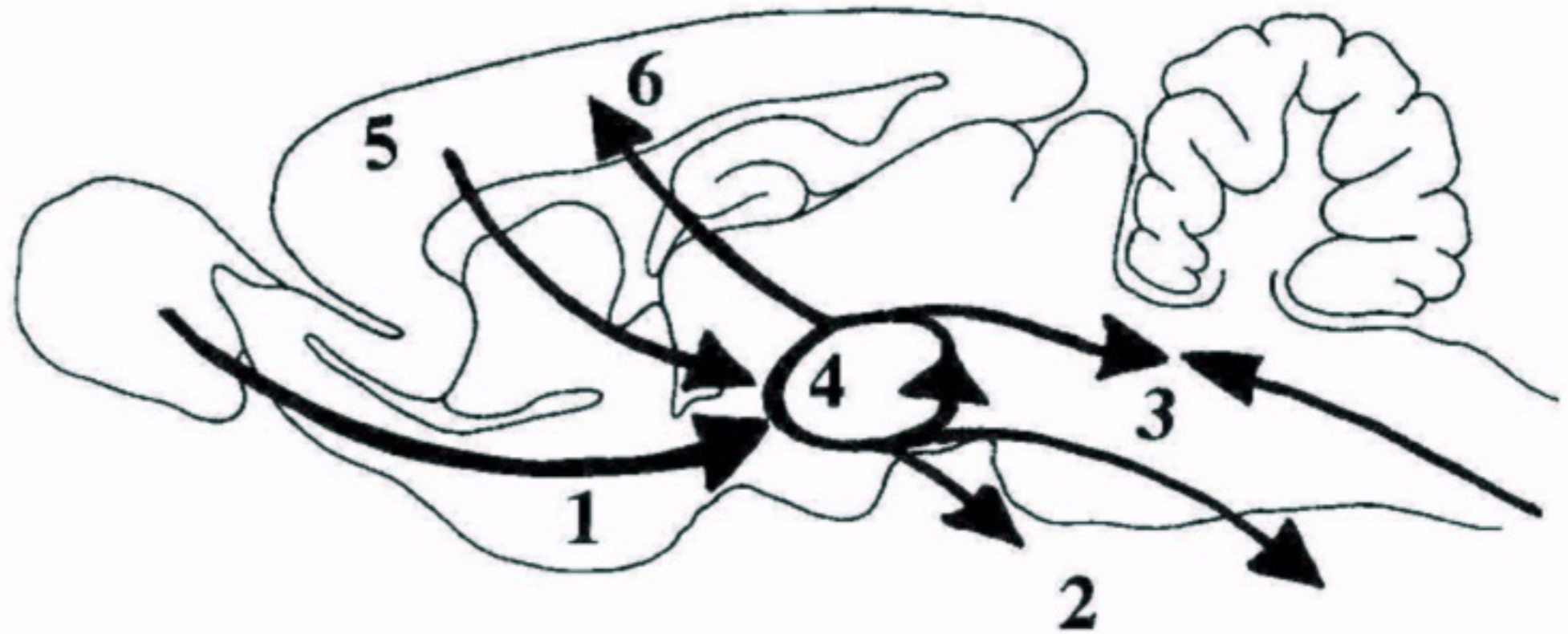
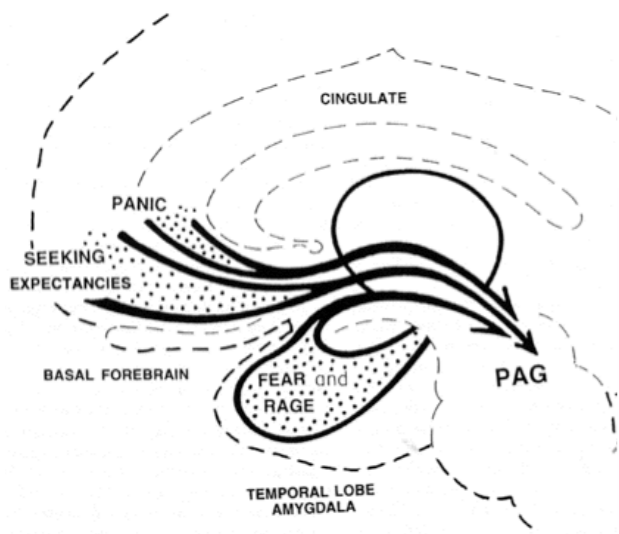
# Additional slides

# basic emotion systems



Antonio Damasio  
*Self Comes to Mind* (2012)

Jaak Panksepp  
*Affective Neuroscience* (1998)  
*Archeology of Mind* (2012)



**Neural interactions characteristics of brain emotional systems:**

- 1) Various sensory stimuli can unconditionally access emotional systems;
- 2) Emotional systems generate instinctual motor outputs &
- 3) Modulate sensory inputs.
- 4) Emotional systems have positive feedback components which can sustain emotional arousal after precipitating events have passed.
- 5) These systems can be modulated by cognitive inputs, &
- 6) These systems can modify/channel cognitive activities.