Adrenocortical and Catecholaminergic Systems Enable us to Cope with Stress

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Dr. Bowden has nothing to disclose with regard to commercial relationships.

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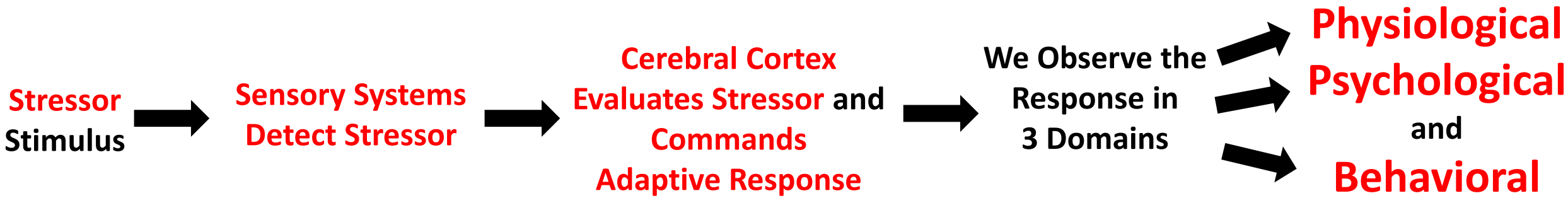
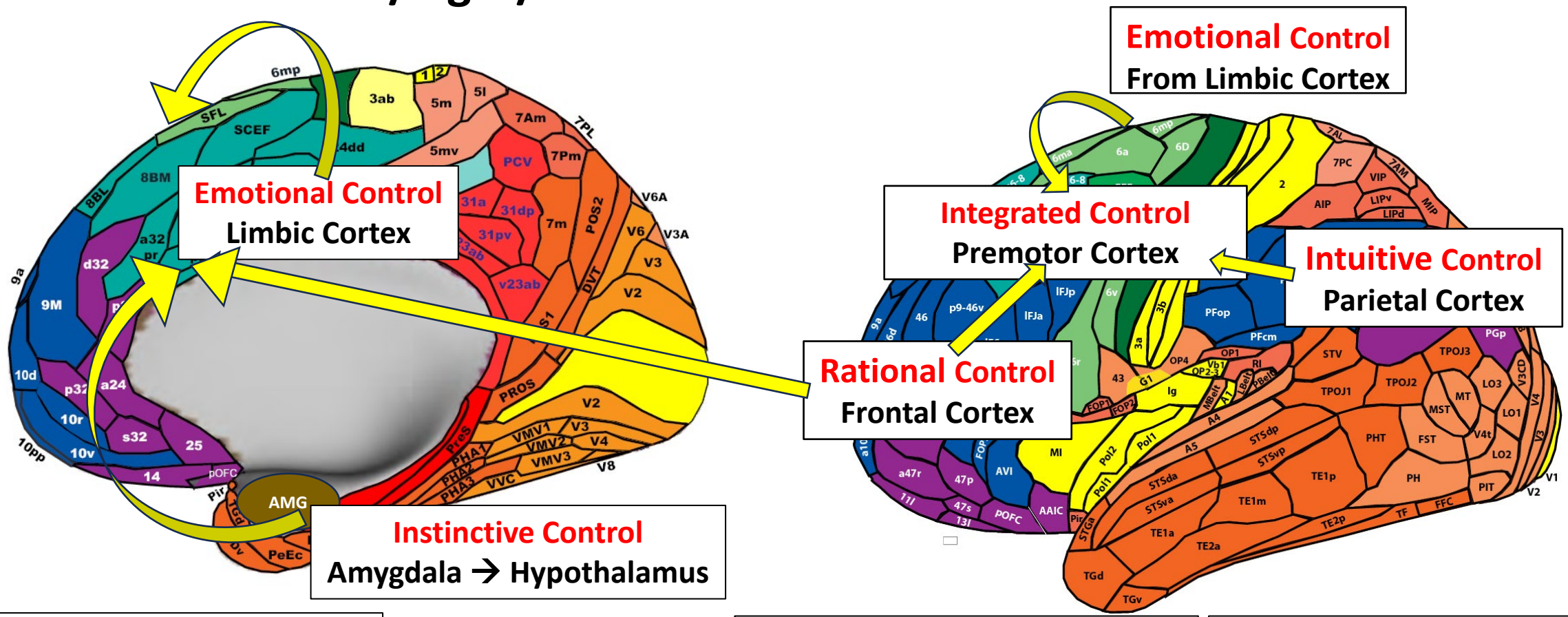
The General Model



The Nervous System controls responses in all three domains through three basic sensorimotor subsystems:

instinctive, intuitive, rational.

Locations of Brain Areas that Transmit Defensive Freeze/Fight/Flee Commands to Premotor Cortex



Instinctive Response: e.g., one person slaps, other slaps back. Response is fast, automatic by simple innate genetically coded circuitry. Can be without awareness of action.

Emotional Response: may fight in anger, sob in fear, flee in panic…responses are with full awareness

Intuitive Response: slapped person may slap or back down. Fast, also genetically innate circuitry, more complex; one is aware of act as 'common sense' given relationship to slapper.

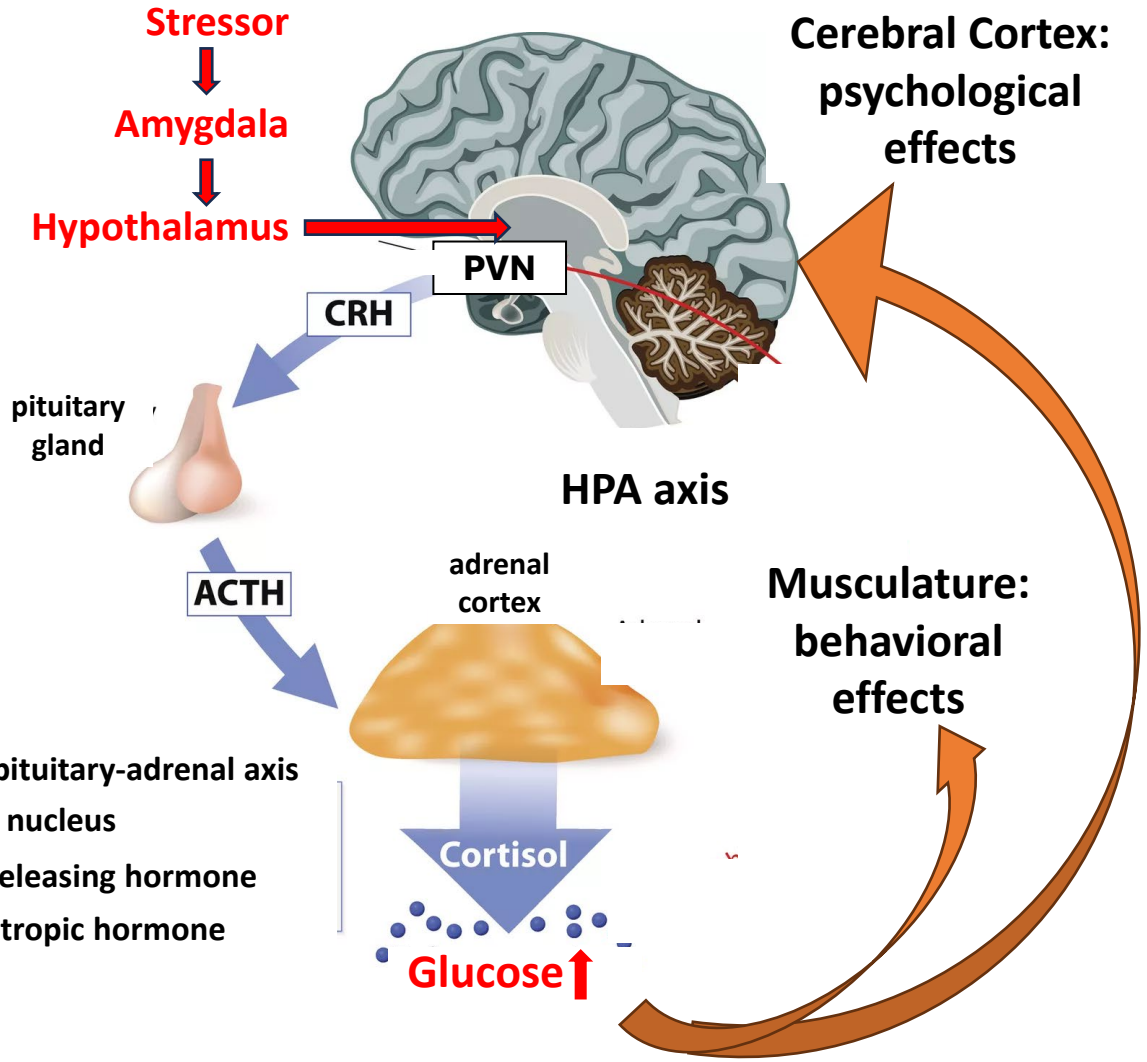
Rational Response: 'freeze', think, strategize before acting. Response slow by very complex continuously rewired circuitry; one is aware of the logic of the act based on multiple factors.

- **In a Healthy Individual and familiar Stable Environment, commands from the various control systems are usually compatible.**

- **Stress effects from all of the cortical sources are mediated by Adrenocortical (hormonal) and Catecholaminergic (neural) mechanisms.**

  - **Both mechanisms are controlled by the instinctive control system.**
    Amygdala → Hypothalamus

Hormonal Mechanism by which a Stressor Activates the Adrenal Cortex to Boost Glucose Energy Delivery to Muscles and Brain



HPA: hypothalamus-pituitary-adrenal axis
PVN: paraventricular nucleus
CRH: corticotropin-releasing hormone
ACTH: adrenocorticotropic hormone

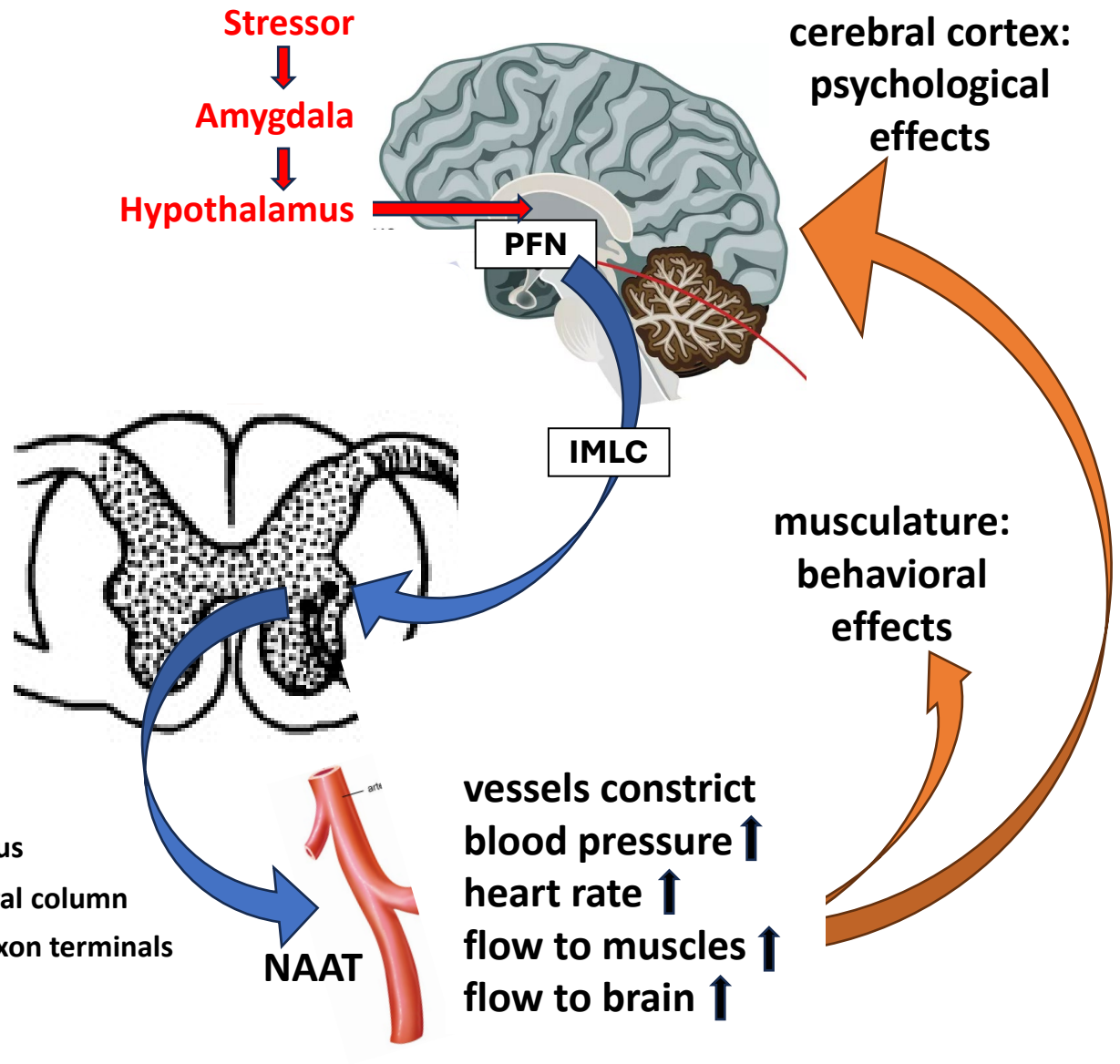
Example of Aging Effect

Aged primates that habitually exhibit depressed/anxious social behavior have a reduced adrenocorticoid response to acute stressors. Despite an elevated ACTH response, their corticosteroid response is low (Goncharova and Oganyan)[1]

Common Misconception

High dose cortisone treatment can damage the hippocampus and cause dementia in the elderly (Sapolsky). True in rodents, not in primates (Leverenz et al.)[2]

Neural Mechanisms by which a Stressor Activates Noradrenergic Cardiovascular Coping Circuitry



PFN: perifornical nucleus
IMLC: intermediolateral column
NAAT: noradrenergic axon terminals

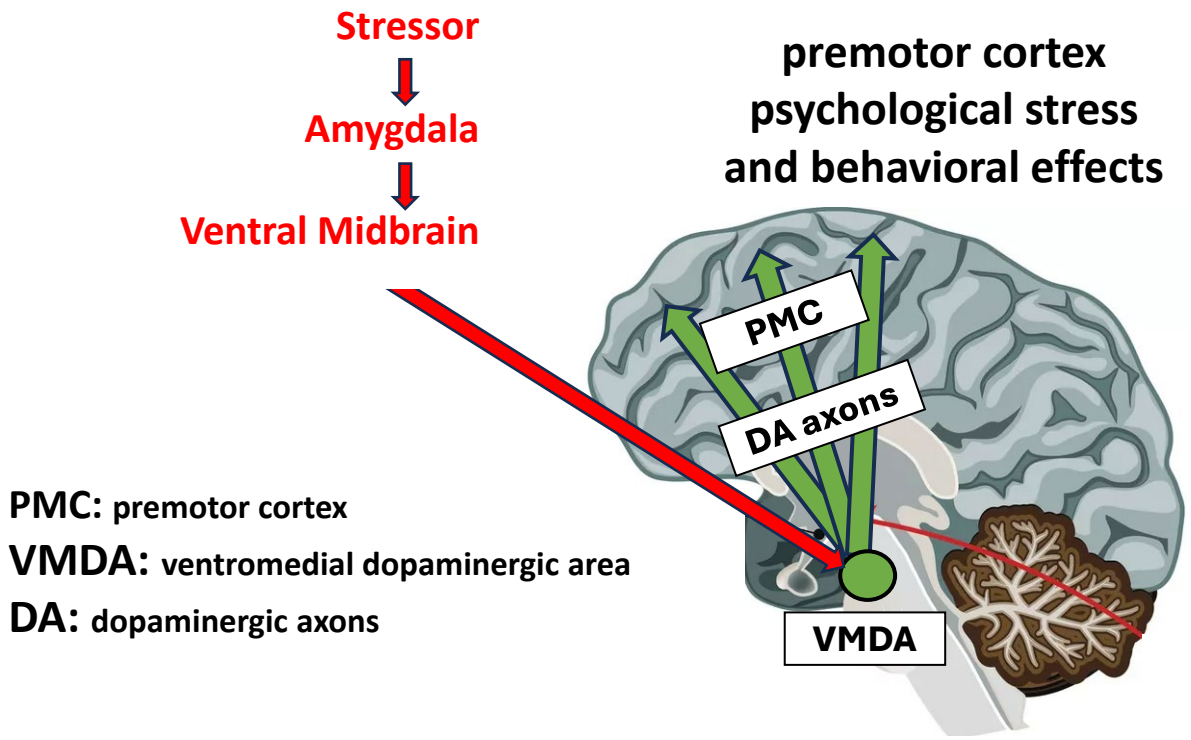
Example of Aging Effect

Norepinephrine and epinephrine responses to the cold pressor test increase with age into one's eighties (Raskind et al.)[3]

Common Misconception

Hypothalamic control of the cardiovascular system is mediated by the paraventricular nucleus (PVN). True in rodent, not In primates where the perifornical nucleus (PFN) controls (Smith et al.)[4]

When Instinctive and Intuitive Responses are Not Adaptive, The Frontal Dopaminergic, Positive Emotion System Can Override Them



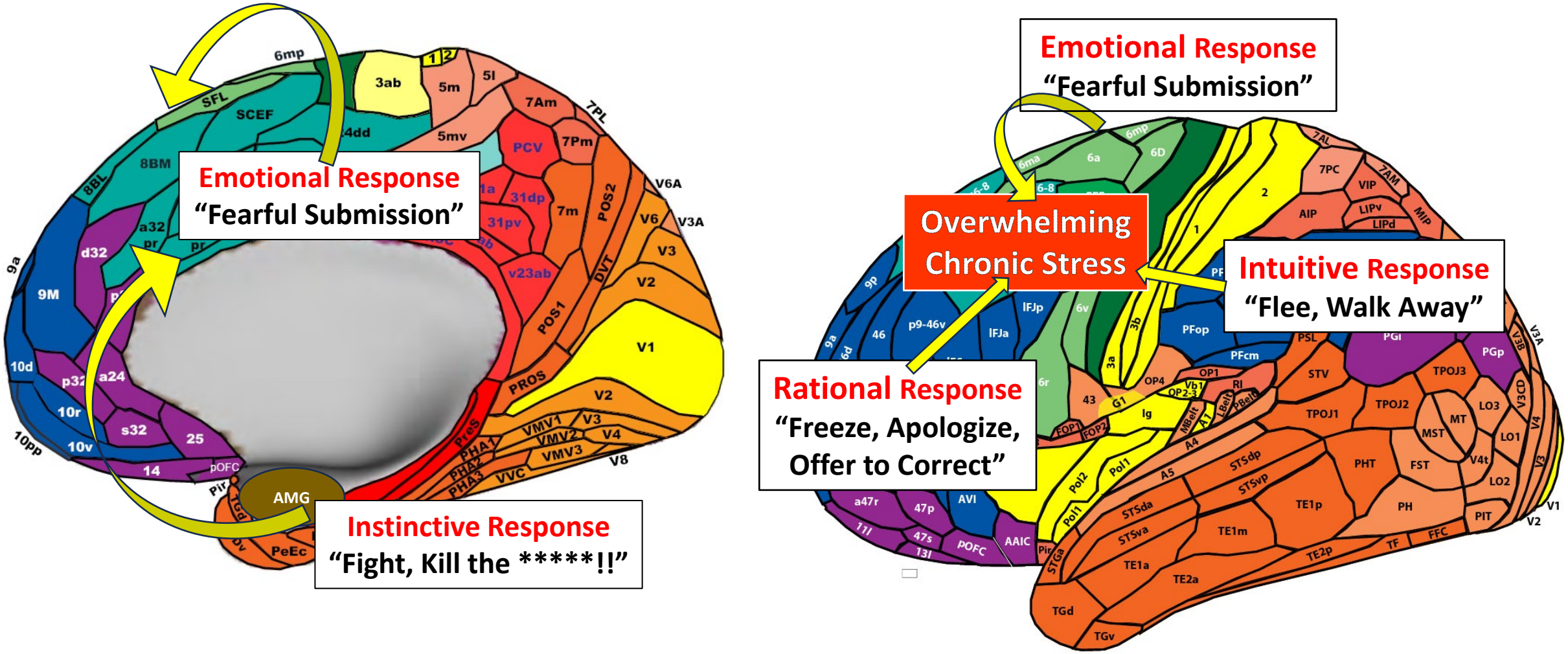
Example of Aging Effect

"Dopamine levels decrease by 10% per decade from early adulthood, and in accordance with this change, cognitive and motor performance decline" (Rieckmann et al., 2011).

Dopamine Contributes to Resilience

The DA System supports Resilient Behavior in an unexpected way…namely by strengthening frontal lobe circuitry that inhibits cortical structures that would ordinarily protect against risky actions, e.g., to allow risky defense of one's child or other oved one (Bowden and German, 2021)[5]

In Hostile Social Environments the Defensive Sympthetic Nervous System is Constantly Mobilized for Violent Fights and Vigorous Flights that Never Come



Chronic hyperactivation of neurons by 'conflicting drives' (Freud) or 'clash of neural processes' (Pavlov) disables Premotor Cortex causing a variety of physiological, psychological and behavioral disorders, such as hypertension, panic disorder, hysteria, depression, suicide .

How Could Hyperactivation of Neurons in Premotor Cortex Cause the Physiological Brain Dysfunction Underlying Psychological and Behavioral Stress Disorders?

THE LACTATE HYPOTHESIS

Assume That…

- ~1/3 of neurons in Premotor Cortex (PMC) are in the circuitry of the Defensive Repertoire: Freeze or Fight or Flee
- ~1/3 of those are dedicated to 1 of the 4 control systems
- under healthy conditions, all control systems command the same response, so 1/9 = ~10% of PMC neurons are normally activated
- when 4 systems command incompatible responses ~40% active
- PMC can meet energy requirements of 1 command aerobically
- Activation of 40% entails shift to anaerobic (hypoxic) metabolism

THE LACTATE HYPOTHESIS

We Know That…

- **Aerobic metabolism generates energy by a process that requires oxygen**
- **When oxygen supplied by blood flow is inadequate, neurons shift to an anaerobic process involving lactate.**
- **Lactate is metabolized to generate energy, but that process also creates acidity.**
- **The burning feeling sensed in extreme muscular exercise is attributed to the anaerobic build up of lactic acid in muscles.**
- **Intravenous lactate triggers panic in patients with panic disorder, presumably by a similar mechanism in the brain**
- **Extreme acidity deactivates the enzymes required for lactate production.**

THE LACTATE HYPOTHESIS

We Propose That…

- When extreme stress-induced acidity deactivates enzymes that mediate lactate production, energy creation stops. PMT is disabled.
- The panic induced by lactate in those predisposed to panic disorder is the psychological correlate of the physiological loss of response control by PMC.
- Psychological and behavioral disorders are caused by inability of aerobic and anaerobic sources of energy to support neuronal signalling, the flow of action potentials through neuronal circuitry that is essential for effective neural control.

CONCLUSIONS

- When premotor cortex is disabled, strategic control of emotional behavior by the intuitive and rational cortical systems reverts to explosive instinctive fight (to the extreme of homicide) and flight (to the extreme of suicide) mediated by the amygdala and hypothalamus.

- A society that does not protect its population from chronic overwhelming psychosocial stress will develop a subset of individuals whose premotor cortex is disabled and who exhibit passionate antisocial and self-destructive behavior.

- Dopamine-like drugs that suppress psychological stress might be expected to enhance resilience. Possible, but not probable. Amphetamine, cocaine, morphine, heroin, etc., indeed, substitute pleasure for stress initially, but used repeatedly lose the psychological benefit and produce behavioral addiction (Bowden and German).[5]

- More likely than a drug cure in the long run: The primary contribution of the medical profession to dealing with disorders due to overwhelming psychological stress will be made by Public Health Officials who focus societal efforts on meeting vital needs…for physical security, habitation, nutrition, income and medical care for self and family…than by Medical and Psychiatric interventions.

KNOWLEDGE GAP

- **The Lactate Hypothesis needs to be tested in an animal model of physiological and behavioral responses to overwhelming stress.**

- **Do changes of lactate metabolism in Premotor Cortex correlate with changes in behavioral state as an animal develops a disorder and exhibits resilience in recovery.**