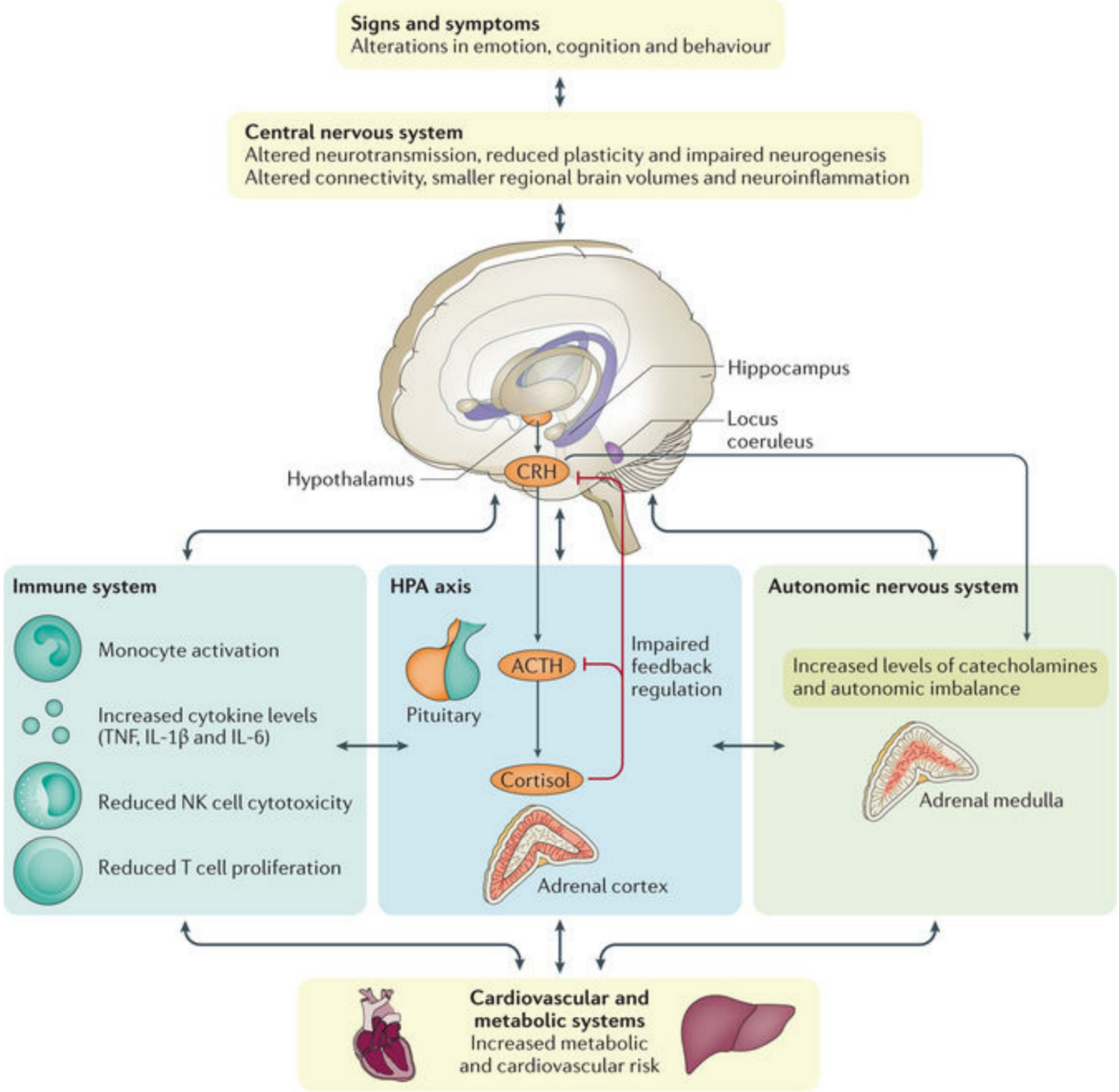
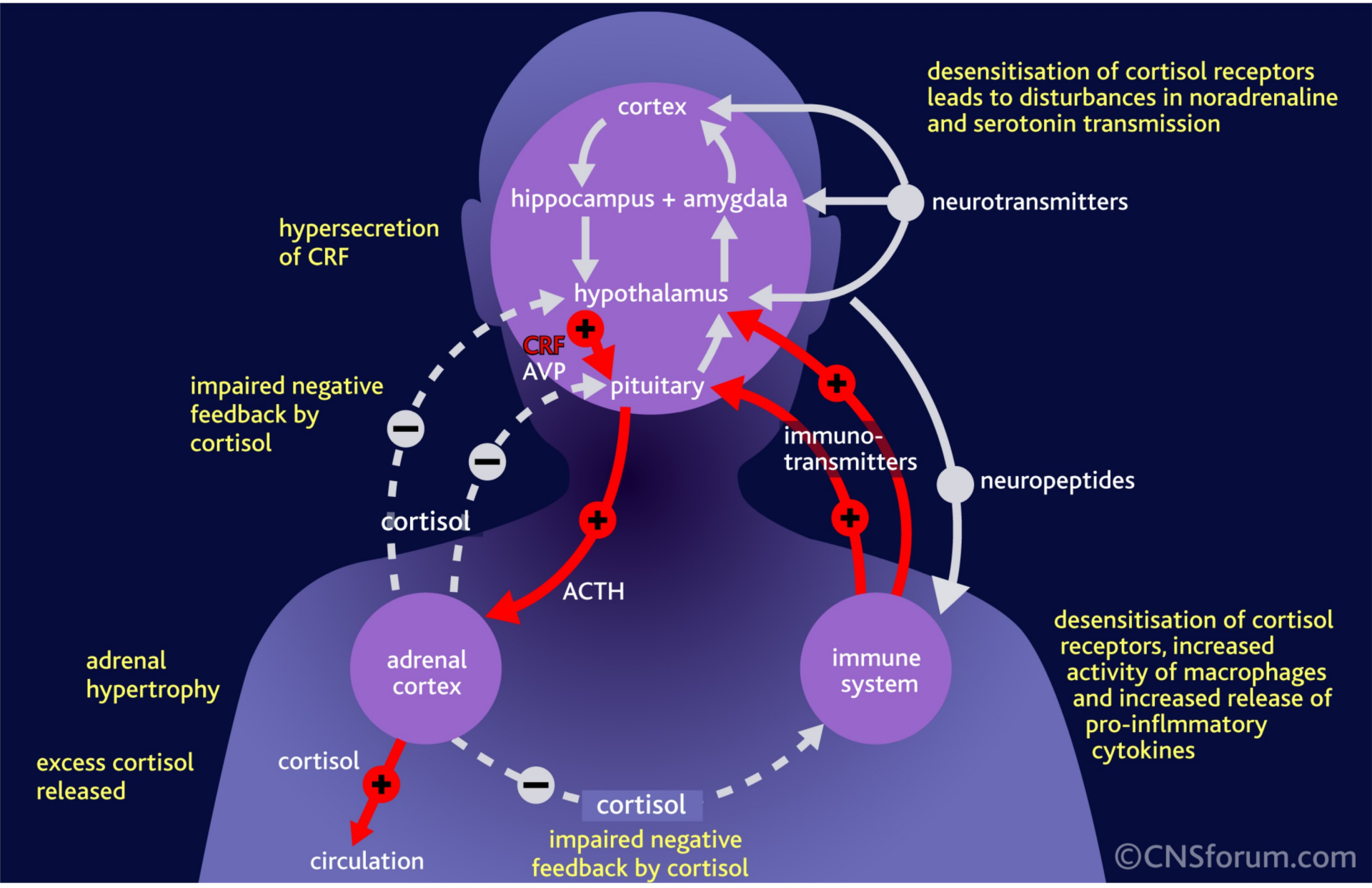
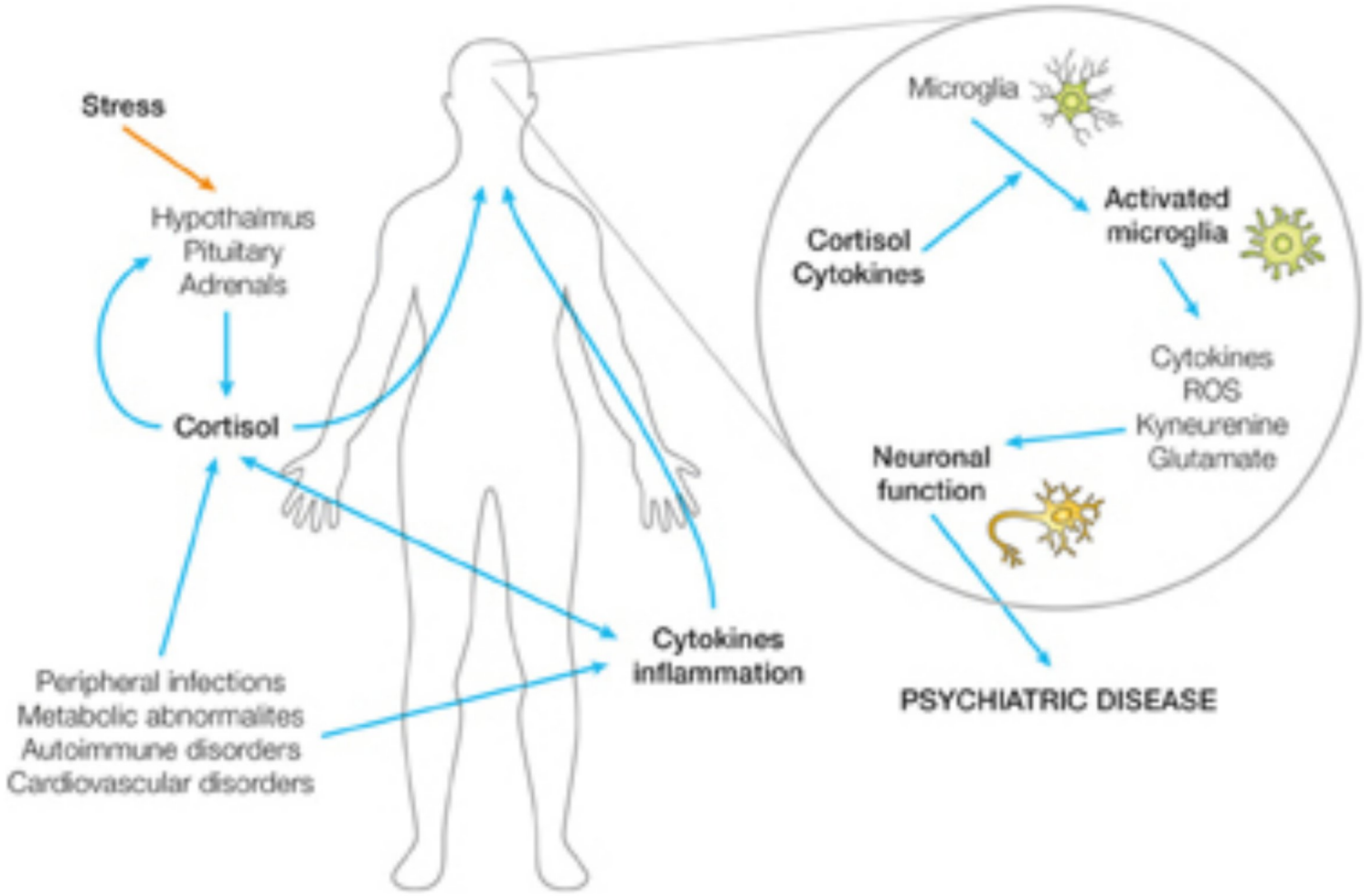
Psychophysiology of mental disease

Psychophysiological science is grounded on the premise that the mind is embodied: Mental processes influence the physiological state of the body while changes in the body's physiology influence thoughts, feelings and motivational behaviour.


Signs and symptoms
Alterations in emotion, cognition and behaviour
Central nervous system
Altered neurotransmission, reduced plasticity and impaired neurogenesis
Altered connectivity, smaller regional brain volumes and neuroinflammation
Hippocampus
Locus coeruleus
Hypothalamus
CRH
Immune system
Monocyte activation
Increased cytokine levels (TNF, IL-1β and IL-6)
Reduced NK cell cytotoxicity
Reduced T cell proliferation
HPA axis
Pituitary
ACTH
Impaired feedback regulation
Cortisol
Adrenal cortex
Autonomic nervous system
Increased levels of catecholamines and autonomic imbalance
Adrenal medulla
Cardiovascular and metabolic systems
Increased metabolic and cardiovascular risk


desensitisation of cortisol receptors leads to disturbances in noradrenaline and serotonin transmission
cortex
hippocampus + amygdala
neurotransmitters
hypersecretion of CRF
hypothalamus
CRF
AVP
pituitary
impaired negative feedback by cortisol
immuno-transmitters
neuropeptides
cortisol
ACTH
adrenal hypertrophy
adrenal cortex
immune system
desensitisation of cortisol receptors, increased activity of macrophages and increased release of pro-inflmmatory cytokines
excess cortisol released
cortisol
cortisol
circulation
impaired negative feedback by cortisol
©CNSforum.com


Stress
Hypothalmus
Pituitary
Adrenals
Cortisol
Peripheral infections
Metabolic abnormalites
Autoimmune disorders
Cardiovascular disorders
Cytokines
inflammation
Microglia
Activated
microglia
Cortisol
Cytokines
Cytokines
ROS
Kyneurenine
Glutamate
Neuronal
function
PSYCHIATRIC DISEASE

Depression is associated with small-to-moderate elevations in ACTH and cortisol and a reduction in CRH levels

There is significant overlap between the factors driving peripheral inflammatory disease and psychiatric disorders

Cardiovascular disease is closely linked with obesity, dyslipidemia, diabetes and metabolic disease…

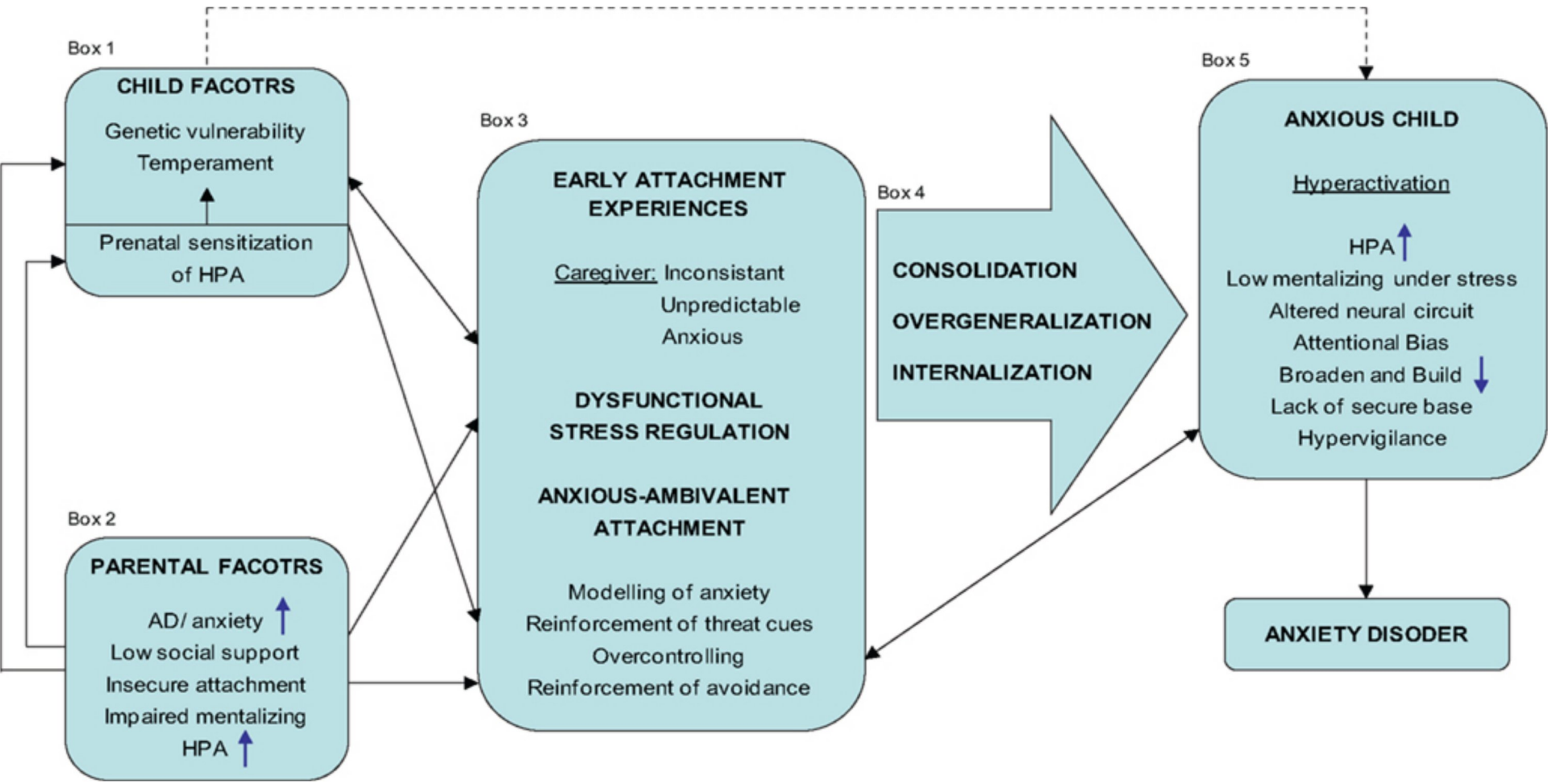
Obesity itself is considered to be a state of low-grade inflammation, and is linked with elevated depressive symptoms

Systemic inflammation activates Central Nervous System microglia (= macrofagi)

Activated microglia are a key source of reactive oxygen species, contributing to a status of inflammation-induced oxidative stress in the CNS

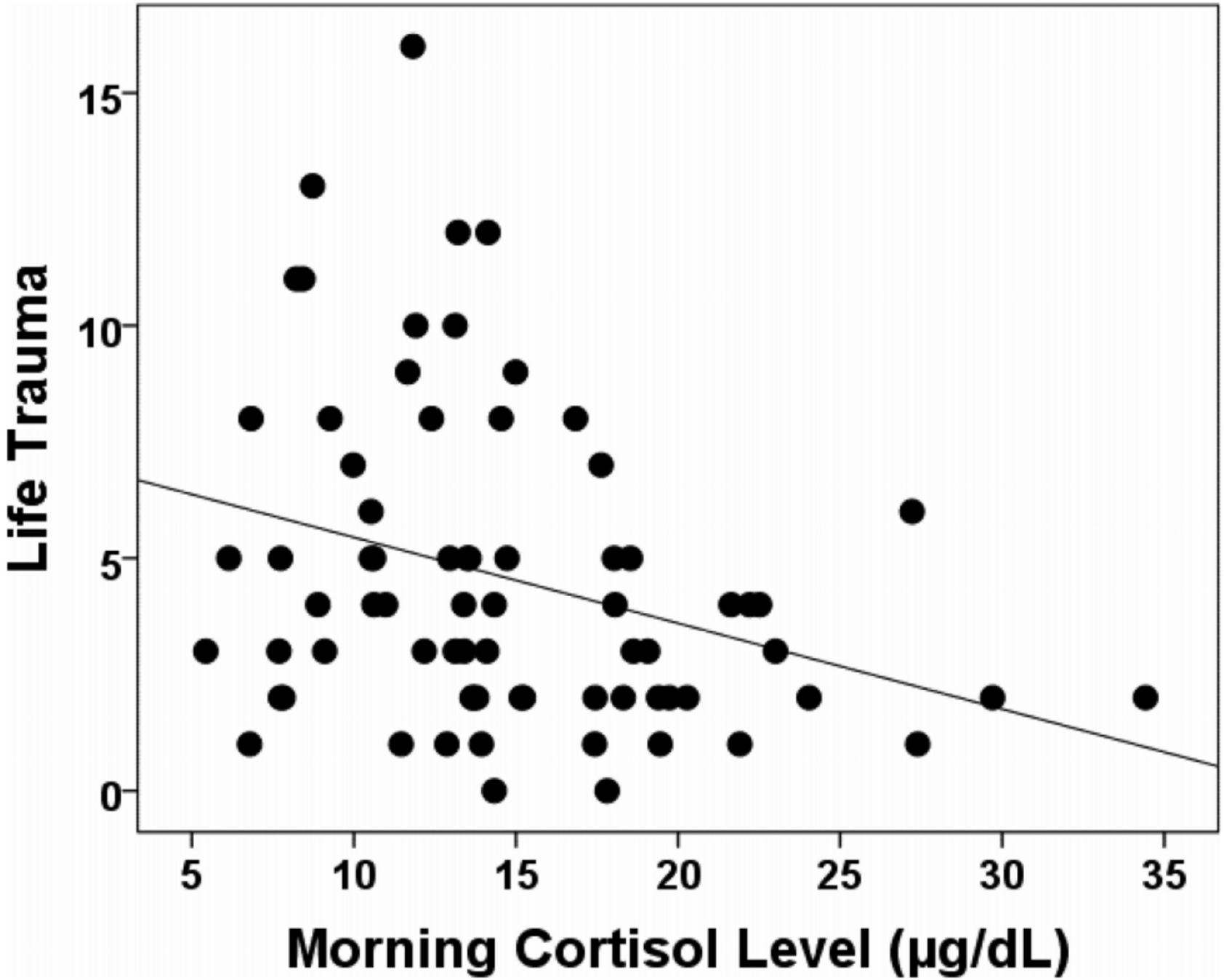
Oxidative stress, driven both peripherally and centrally, is strongly associated with psychiatric aetiology

These findings support the crosstalk between peripheral molecular processes to central effects related to cognitive and emotional function


Box 1
CHILD FACOTRS
Genetic vulnerability
Temperament
Prenatal sensitization of HPA
Box 2
PARENTAL FACOTRS
AD/ anxiety
Low social support
Insecure attachment
Impaired mentalizing
HPA
Box 3
EARLY ATTACHMENT EXPERIENCES
Caregiver: Inconsistant
Unpredictable
Anxious
DYSFUNCTIONAL STRESS REGULATION
ANXIOUS-AMBIVALENT ATTACHMENT
Modelling of anxiety
Reinforcement of threat cues
Overcontrolling
Reinforcement of avoidance
Box 4
CONSOLIDATION
OVERGENERALIZATION
INTERNALIZATION
Box 5
ANXIOUS CHILD
Hyperactivation
HPA
Low mentalizing under stress
Altered neural circuit
Attentional Bias
Broaden and Build
Lack of secure base
Hypervigilance
ANXIETY DISODER

Highlights

- Higher life trauma exposure was significantly associated with lower basal cortisol levels.
- Hyperactive response to stress in limbic-medial temporal lobe (MTL) regions was associated with both higher lifetime trauma scores and lower basal cortisol levels.
- Hyperactive response to stress in limbic-MTL regions mediated the relationship between trauma and low basal cortisol levels.

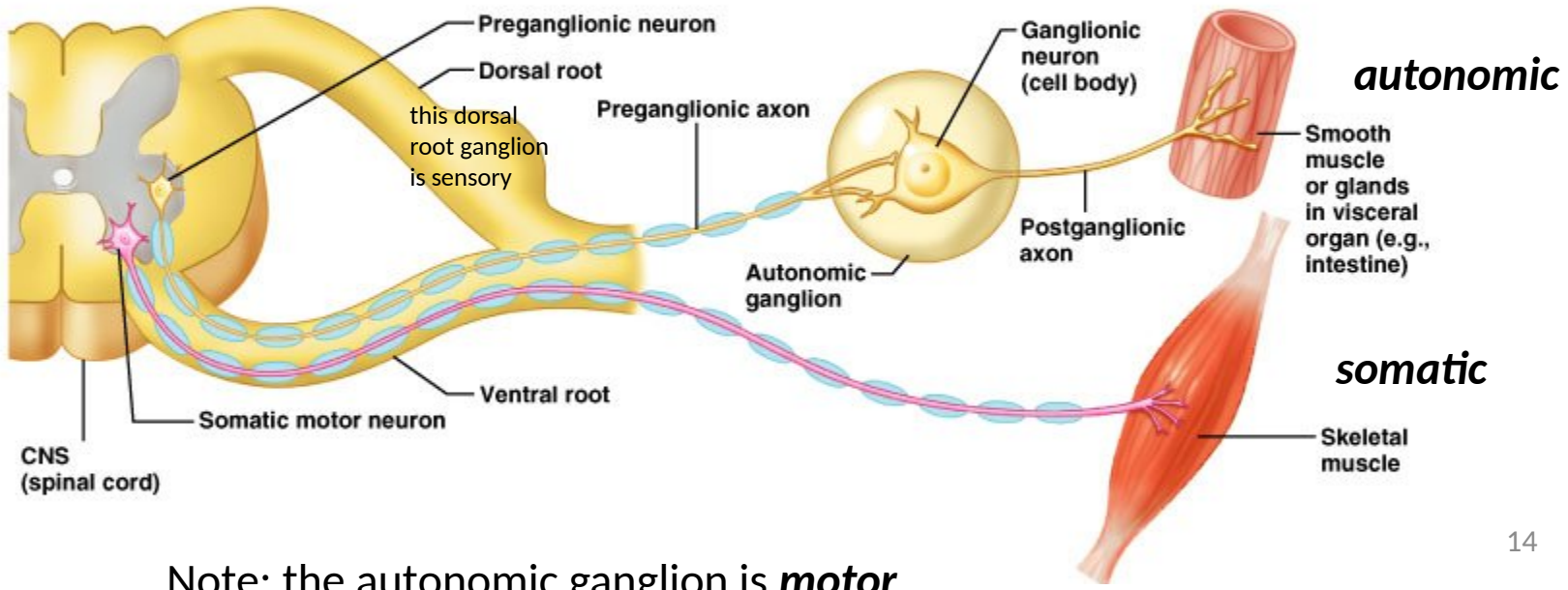

Life Trauma
15
10
5
0
5
10
15
20
25
30
35
Morning Cortisol Level (µg/dL)

Autonomic nervous system

- The autonomic nervous system is the subdivision of the peripheral nervous system that regulates body activities that are generally not under conscious control
- Visceral motor innervates non-skeletal (non-somatic) muscles

- Axon of 1st (*preganglionic*) neuron leaves CNS to synapse with the 2nd (*ganglionic*) neuron
- Axon of 2nd (*ganglionic*) neuron extends to the organ it serves

Diagram contrasts somatic (lower) and autonomic:



Note: the autonomic ganglion is ***motor***

Divisions of the autonomic nervous system

- Parasympathetic division
- Sympathetic division

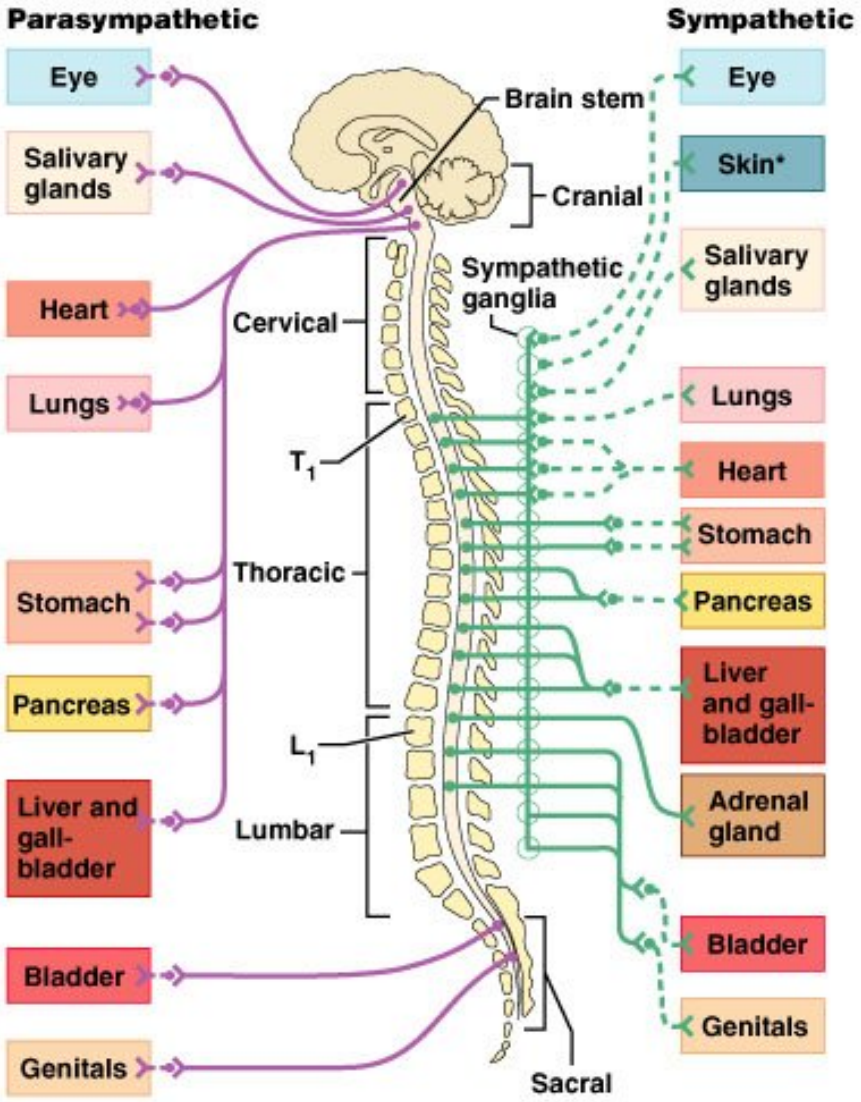
Serve most of the same organs but cause opposing or antagonistic effects

Parasysmpathetic: routine maintenance
"rest &digest"

Sympathetic: mobilization & increased metabolism
"fight, flight or fright" or "fight, flight or freeze"

Where they come from

Parasympathetic: craniosacral



Sympathetic: thoracolumbar

Parasympathetic nervous system

"rest & digest"

- Also called the ***craniosacral*** system because all its preganglionic neurons are in the brain stem or sacral levels of the spinal cord
  - Cranial nerves III,VII, IX and X
  - In lateral horn of gray matter from S2-S4
- Only innervate internal organs (not skin)
- ***Acetylcholine*** is neurotransmitter at end organ as well as at preganglionic synapse: "cholinergic"

- Cranial outflow
  - III - pupils constrict
  - VII - tears, nasal mucus, saliva
  - IX – parotid salivary gland
  - X (Vagus n) – visceral organs of thorax & abdomen:
    - Stimulates digestive glands
    - Increases motility of smooth muscle of digestive tract
    - Decreases heart rate
    - Causes bronchial constriction
- Sacral outflow (S2-4): form pelvic splanchnic nerves
  - Supply 2nd half of large intestine
  - Supply all the pelvic (genitourinary) organs

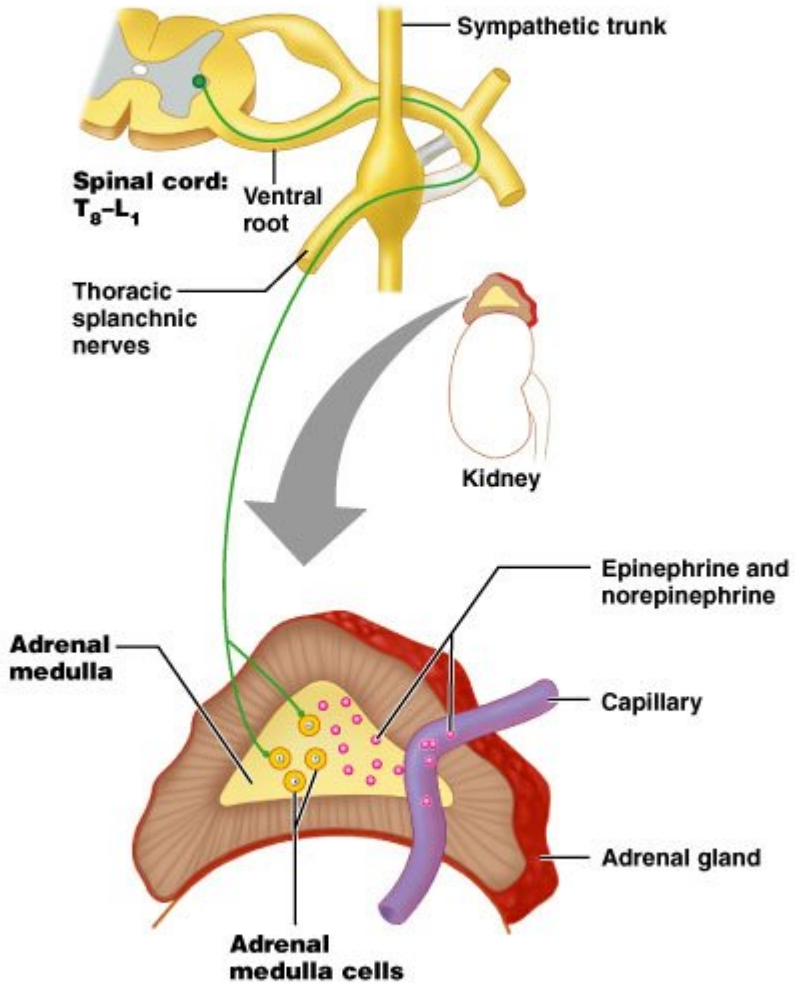
Sympathetic nervous system

"fight, flight or fright"

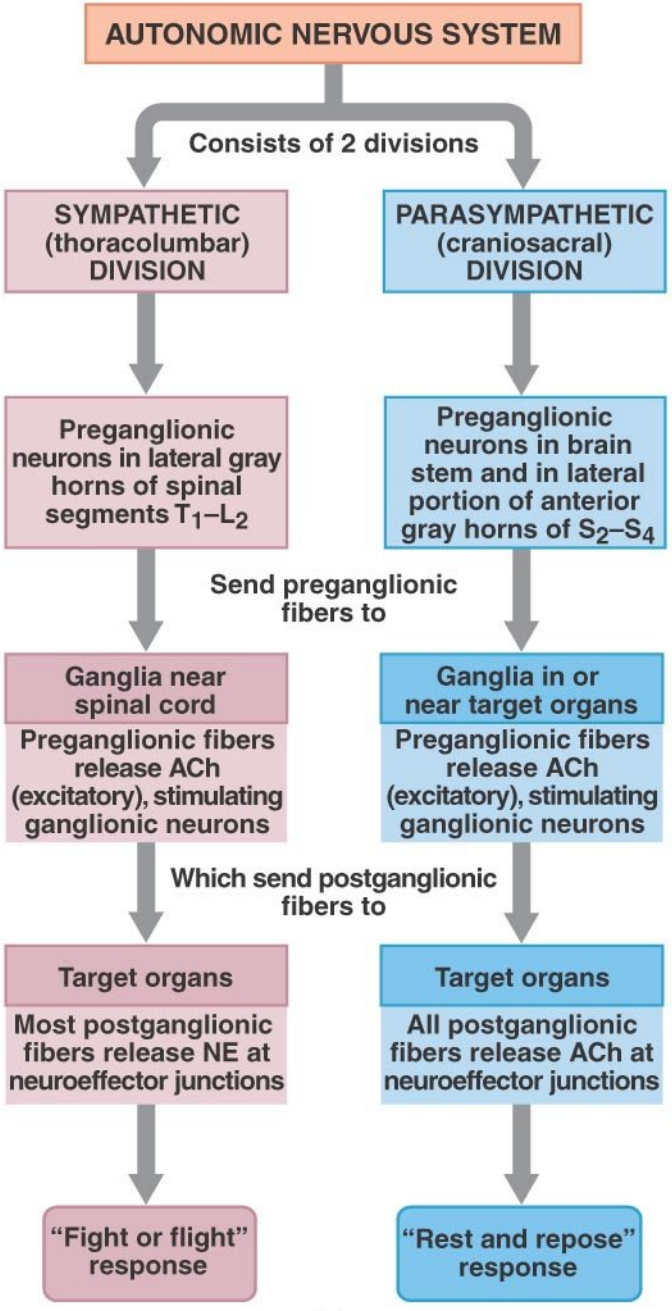
- Also called ***thoracolumbar*** system: all its neurons are in lateral horn of gray matter from T1-L2
- Lead to every part of the body (unlike parasymp.)
  - Easy to remember that when nervous, you sweat; when afraid, hair stands on end; when excited blood pressure rises (vasoconstriction): these sympathetic only
  - Also causes: dry mouth, pupils to dilate, increased heart & respiratory rates to increase O2 to skeletal muscles, and liver to release glucose
- ***Norepinephrine*** (aka noradrenaline) is neurotransmitter released by most postganglionic fibers (acetylcholine in preganglionic): "adrenergic"

Adrenal gland is exception

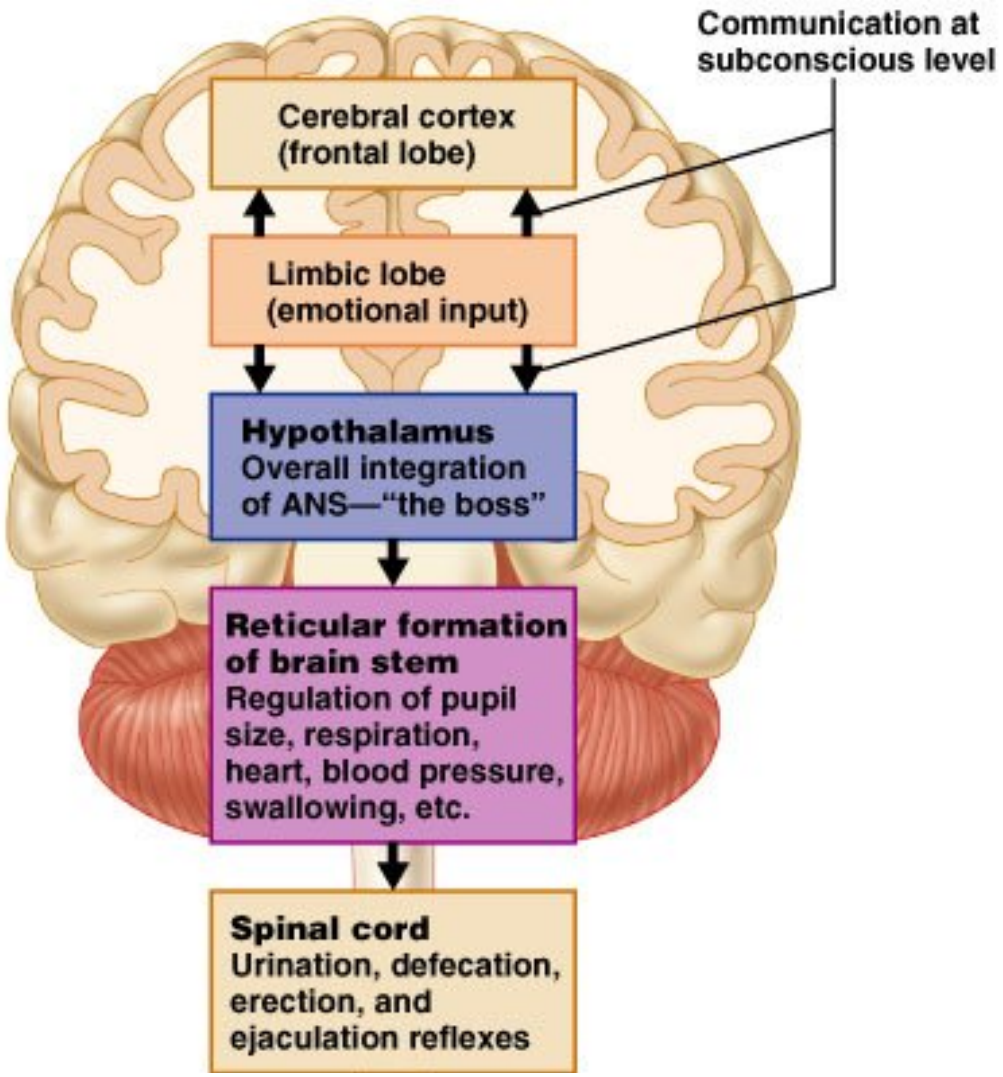
- Synapse in gland
- Can cause body-wide release of epinephrine aka adrenaline and norepinephrine in an extreme emergency (adrenaline “rush” or surge)



Summary



Central control of the Autonomic NS



Amygdala: **main limbic region for emotions**

-Stimulates sympathetic activity, especially previously learned fear-related behavior

-Can be voluntary when decide to recall frightful experience - cerebral cortex acts through amygdala

-Some people can regulate some autonomic activities by gaining extraordinary control over their emotions

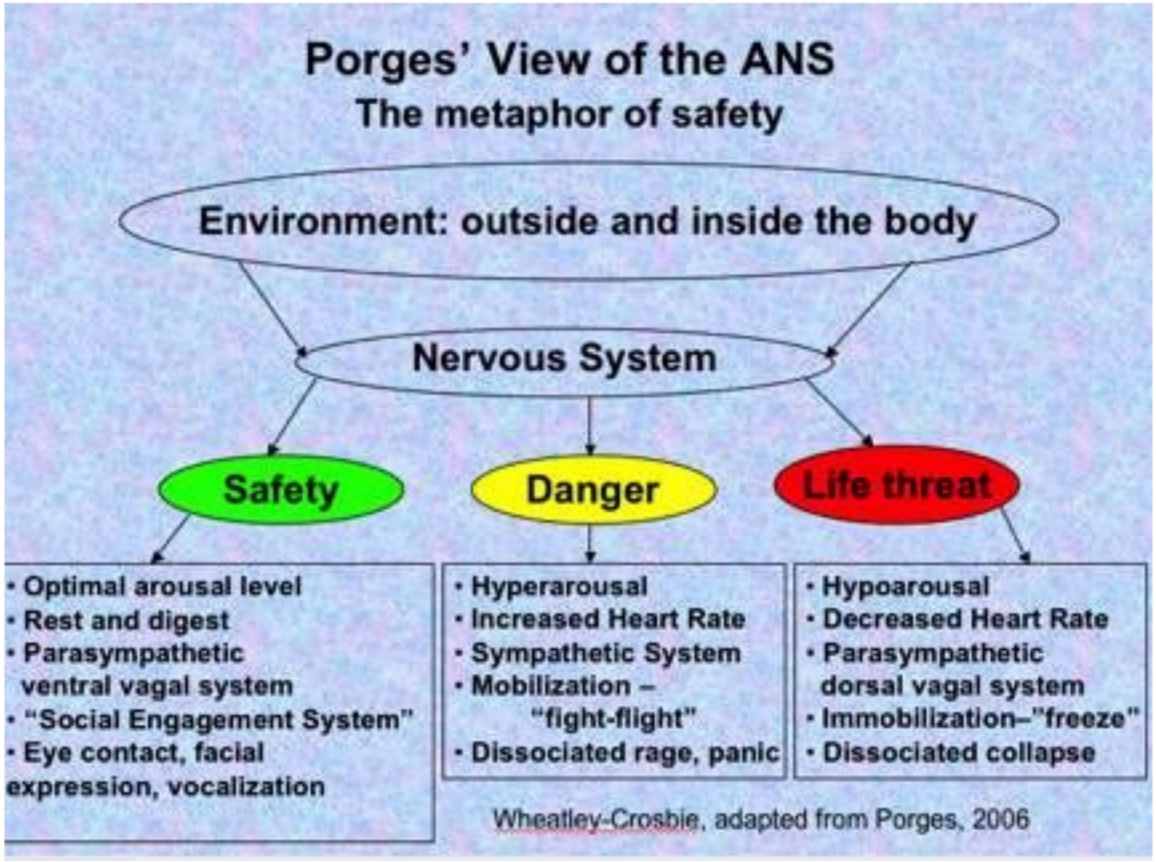
Hypothalamus**: main integration center**

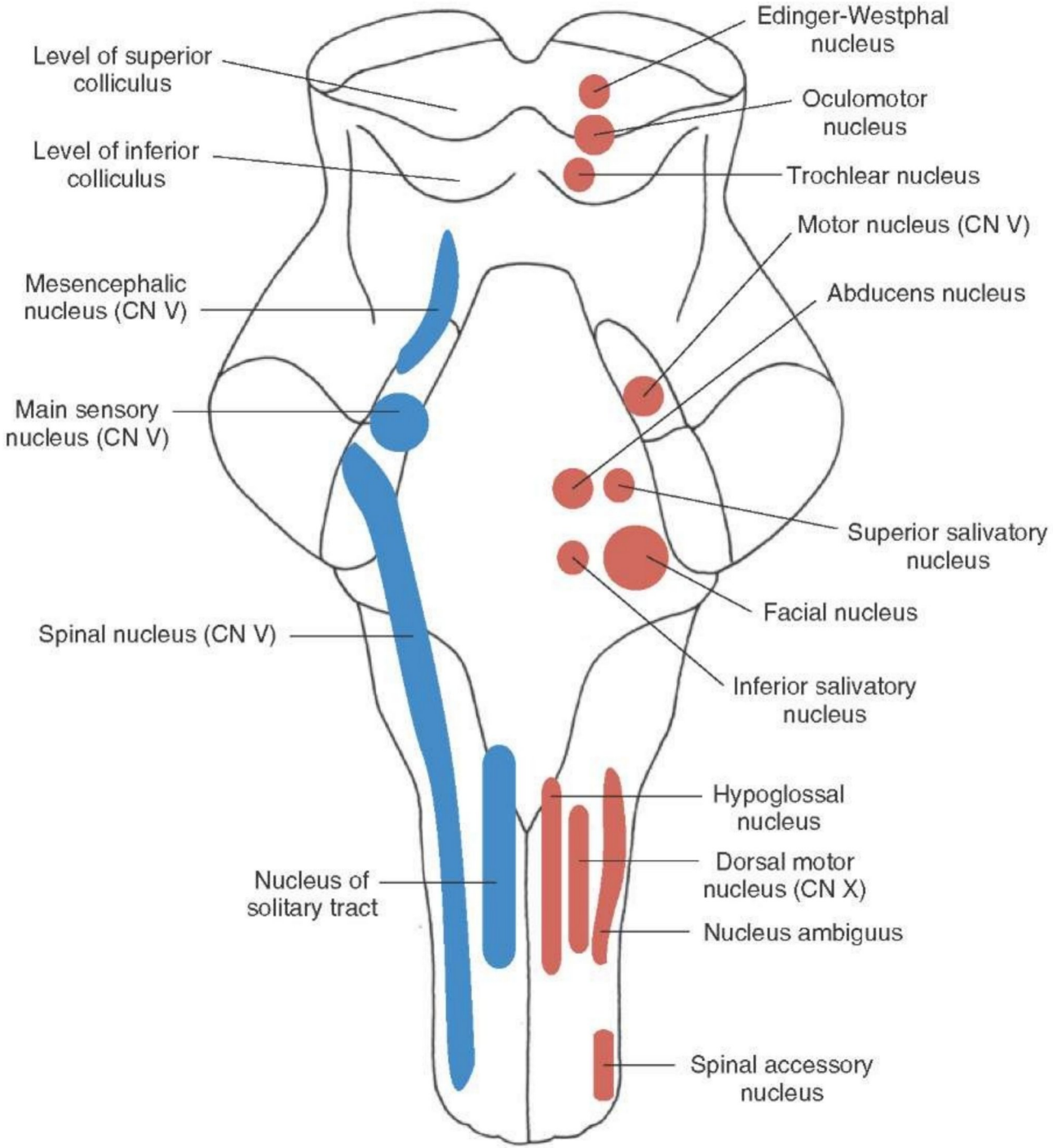
Reticular formation: **most direct influence over autonomic function**

. . .when the heart is affected it reacts on the brain; and the state of the brain again reacts through the pneumo-gastric [vagus] nerve on the heart; so that under any excitement there will be much mutual action and reaction between these, the two most important organs of the body

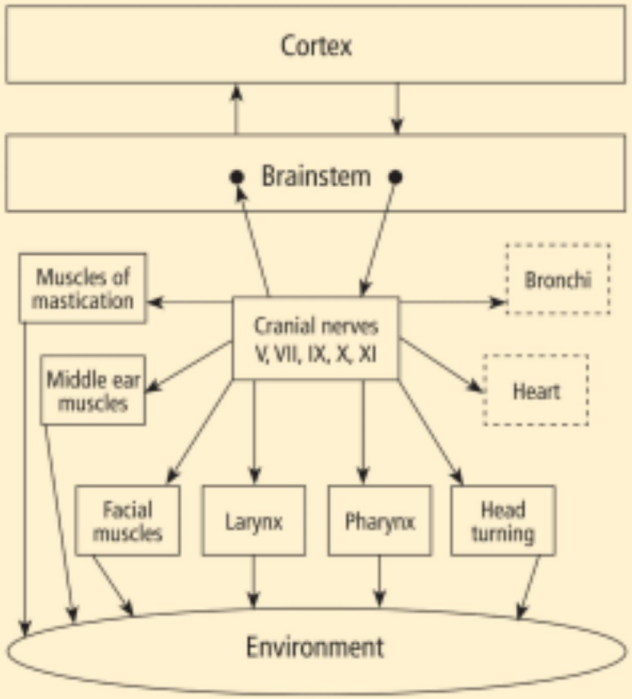
C. Darwin

3 phylogenetic stages in the development of the vertebrate ANS




Edinger-Westphal nucleus
Level of superior colliculus
Oculomotor nucleus
Level of inferior colliculus
Trochlear nucleus
Motor nucleus (CN V)
Mesencephalic nucleus (CN V)
Abducens nucleus
Main sensory nucleus (CN V)
Superior salivatory nucleus
Facial nucleus
Spinal nucleus (CN V)
Inferior salivatory nucleus
Hypoglossal nucleus
Dorsal motor nucleus (CN X)
Nucleus of solitary tract
Nucleus ambiguus
Spinal accessory nucleus

The social engagement system



1) There is a phylogenetic shift in the regulation of the heart from endocrine communication to unmyelinated nerves and finally to myelinated nerves;

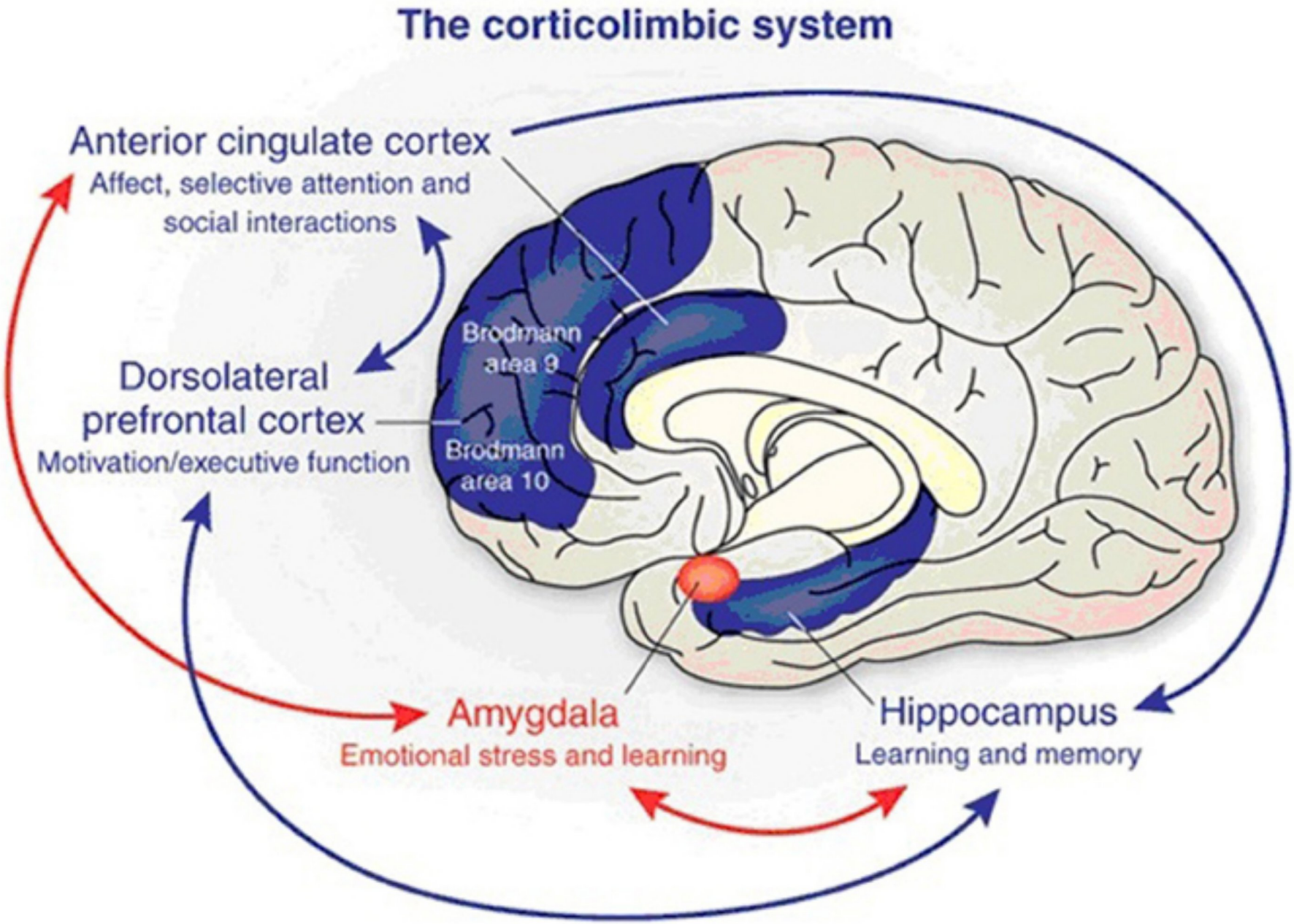
2) A face–heart connection evolved as source nuclei of vagal pathways shifted ventrally from the older dorsal motor nucleus to the nucleus ambiguus. This resulted in an anatomical and neurophysiological linkage between neural regulation of the heart via the myelinated vagus and the special visceral efferent pathways that regulate the striated muscles of the face and head, forming an integrated social engagement system;

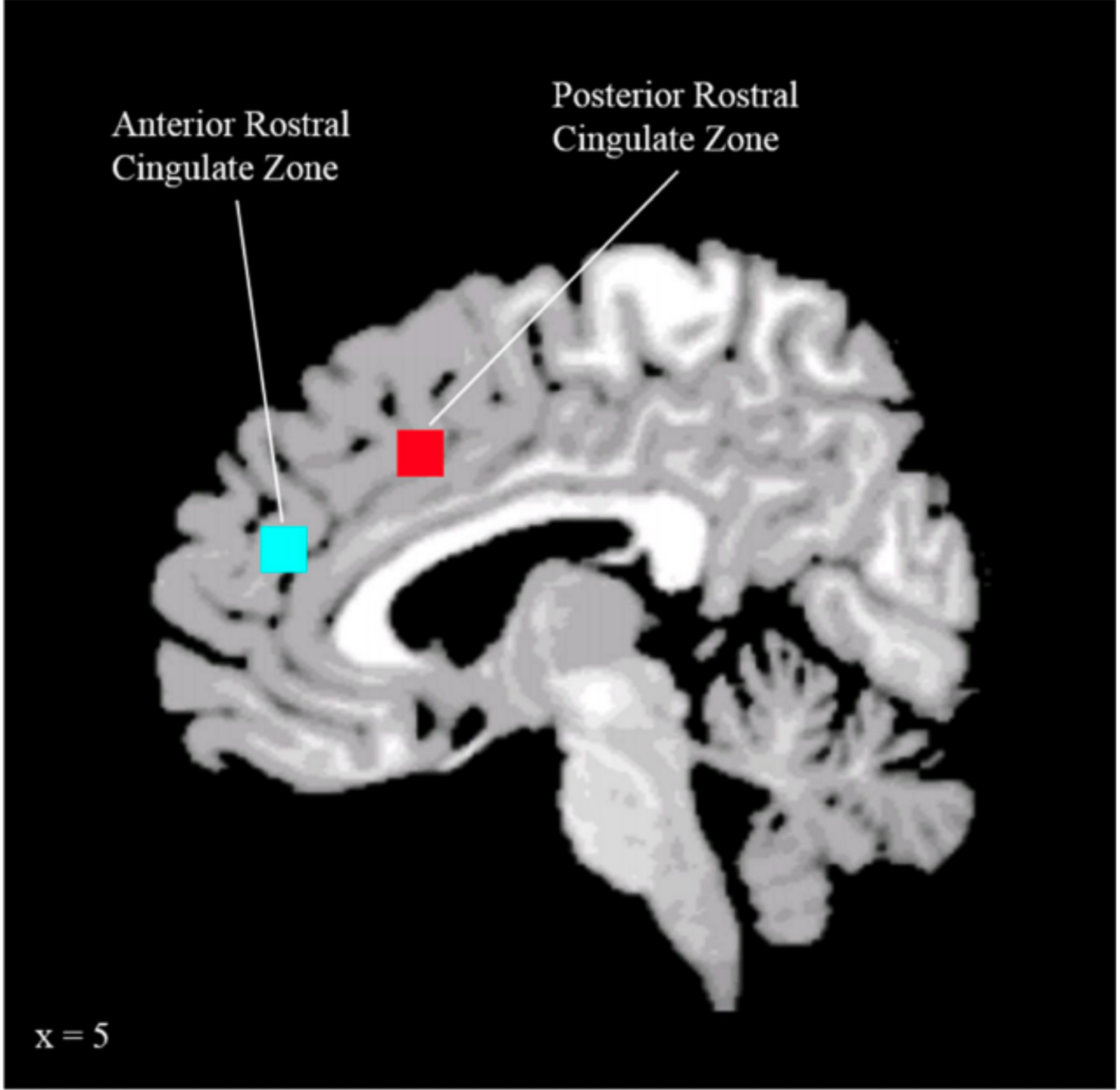
3) With increased cortical development, the cortex exhibits greater control over the brainstem via direct (eg, corticobulbar) and indirect (eg, corticoreticular) neural pathways originating in motor cortex and terminating in the source nuclei of the myelinated motor nerves emerging from the brainstem

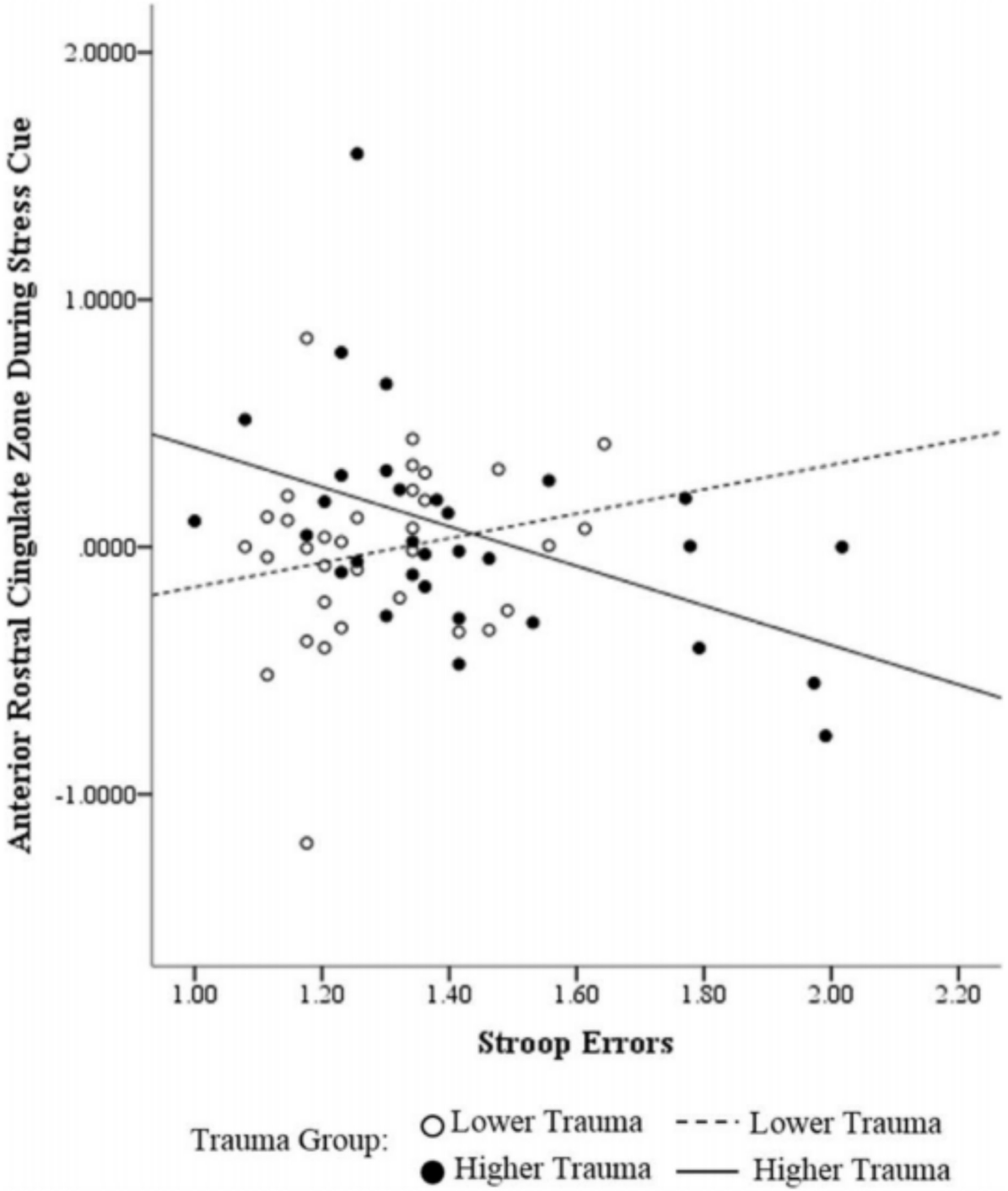
To effectively switch from defensive to social engagement strategies, the mammalian nervous system needs to perform two important adaptive tasks:
(1)assess risk, and
(2) if the environment is perceived as safe, **inhibit** the more primitive limbic structures that control fight, flight, or freeze behaviors.

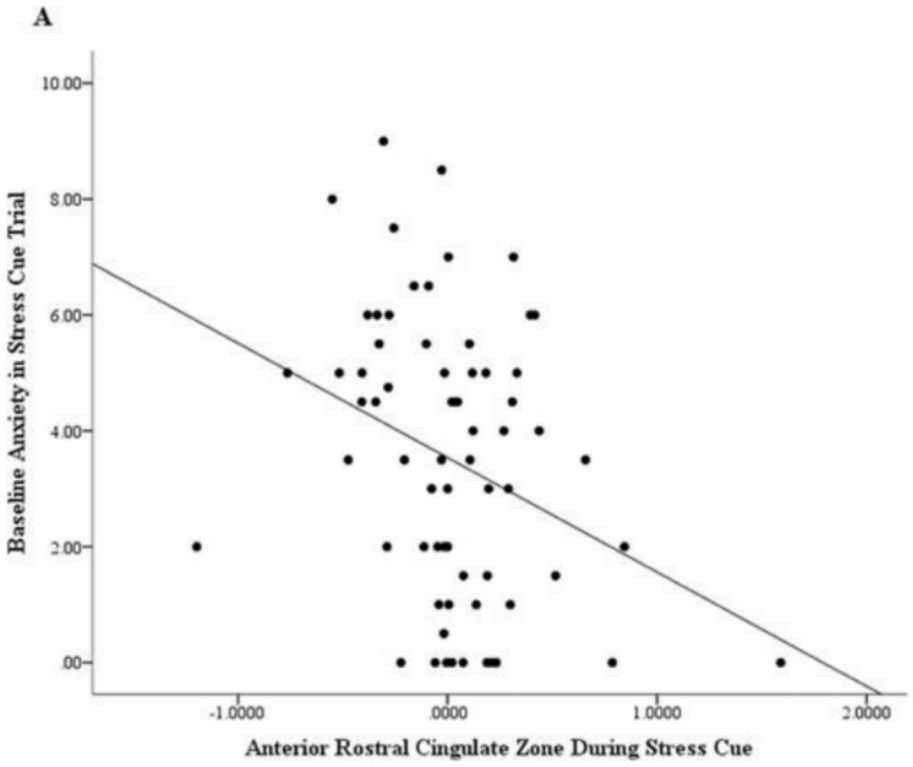
The ‘fight or flight’ pattern of bodily response is produced stereotypically to a range of perceived environmental threats that as a minimum capture attention….

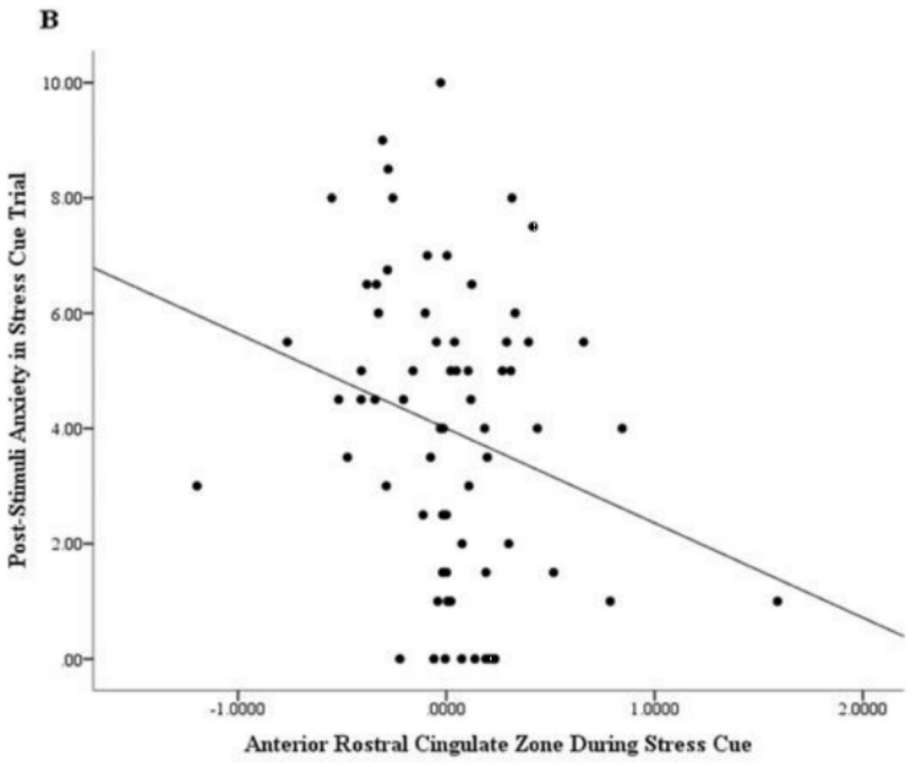
… the same pattern accompanies shifts in attention and cognitive evaluations with negative behavioural connotations.

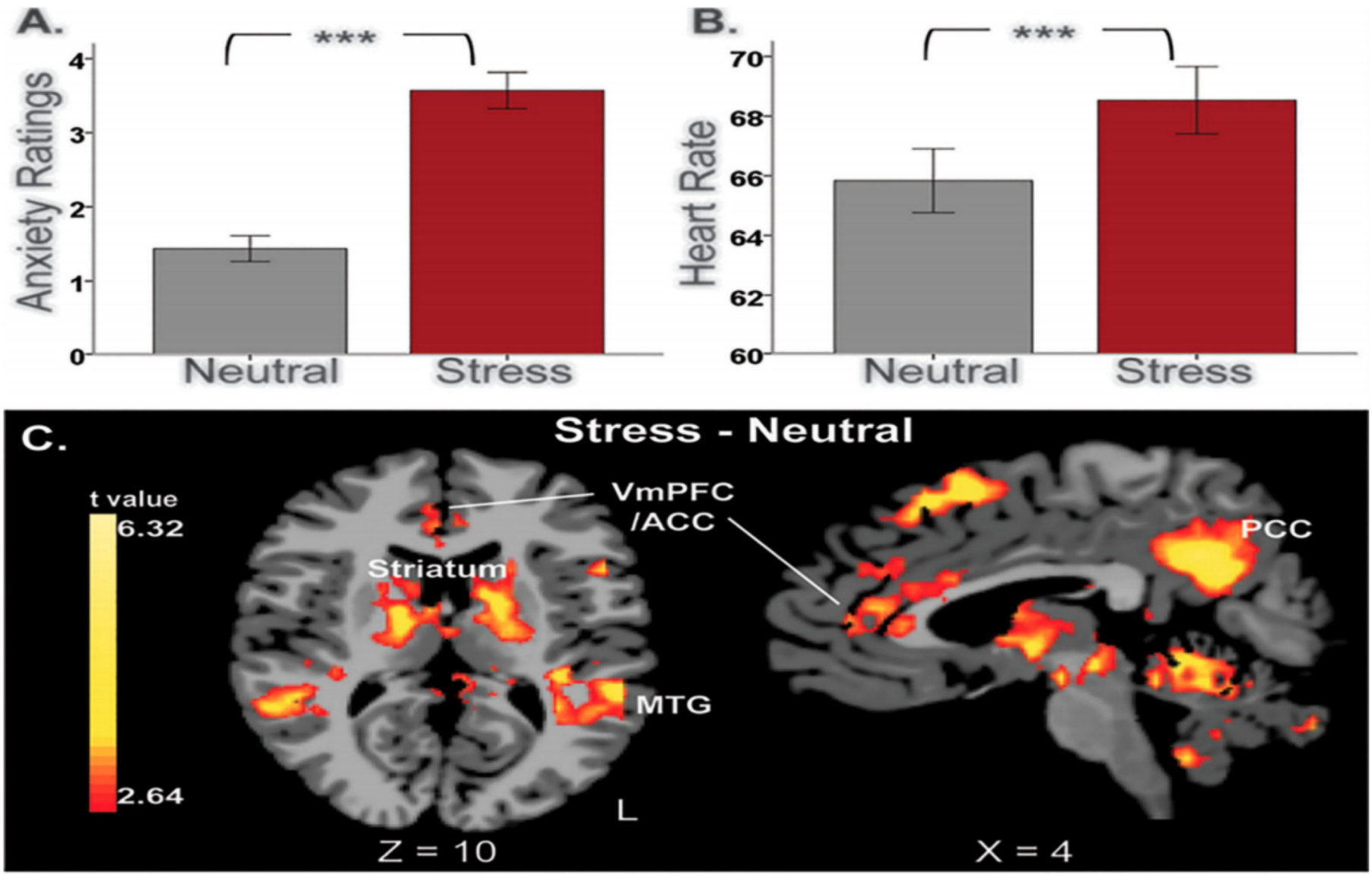

The corticolimbic system
Anterior cingulate cortex
Affect, selective attention and social interactions
Dorsolateral prefrontal cortex
Motivation/executive function
Brodmann area 9
Brodmann area 10
Amygdala
Emotional stress and learning
Hippocampus
Learning and memory

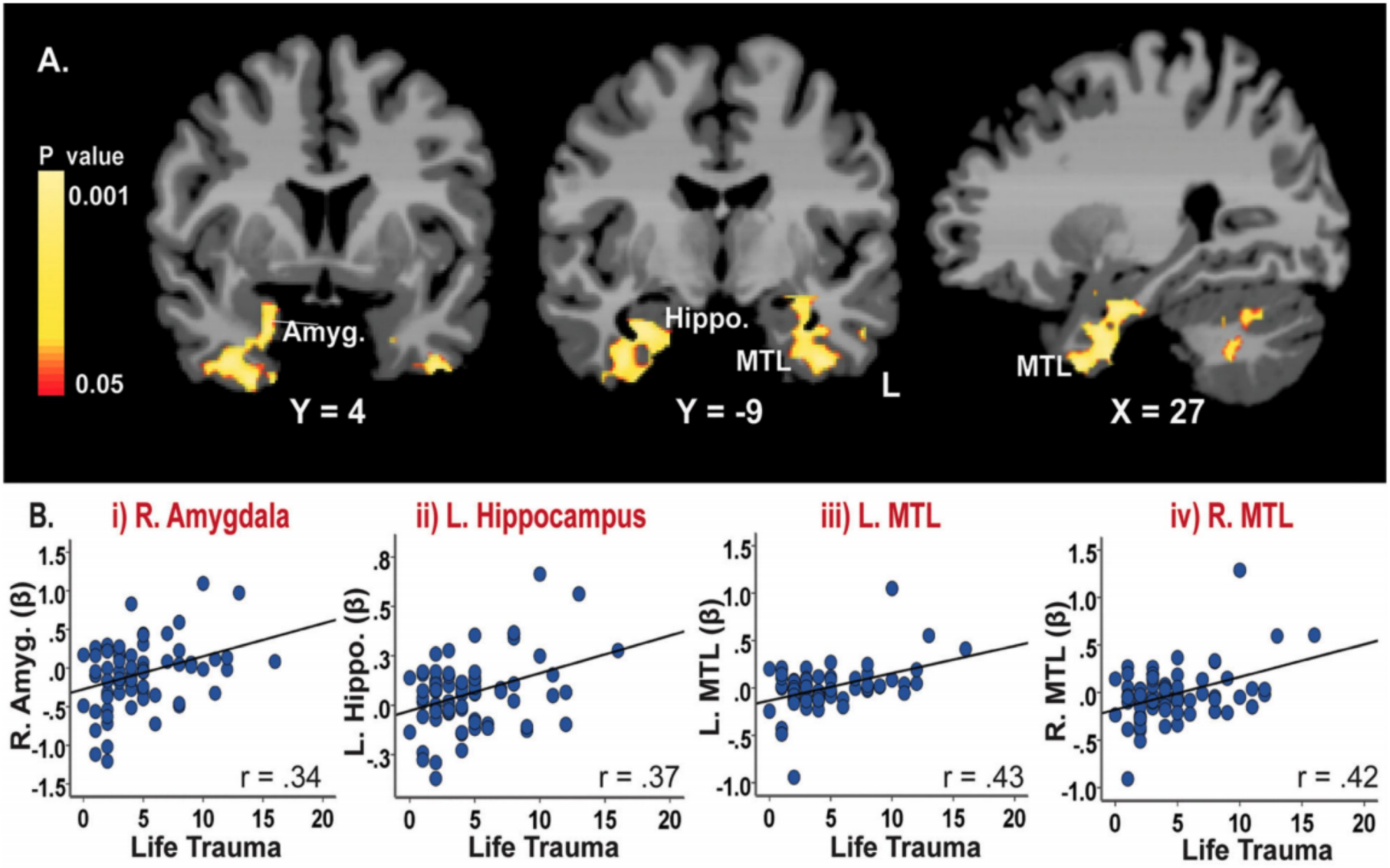

Anterior Rostral
Cingulate Zone
Posterior Rostral
Cingulate Zone
x = 5

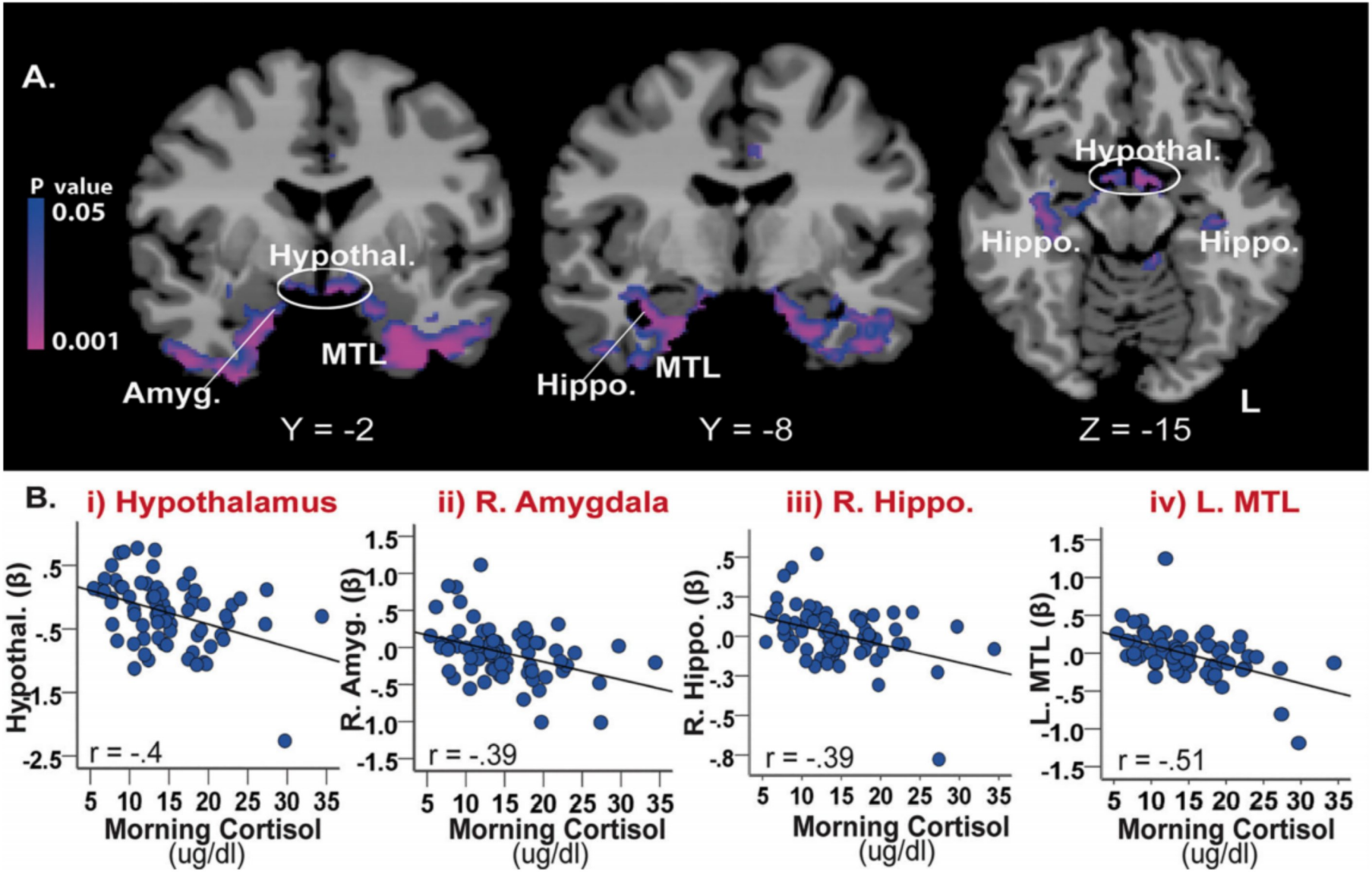

Anterior Rostral Cingulate Zone During Stress Cue
2.0000
1.0000
.0000
-1.0000
1.00
1.20
1.40
1.60
1.80
2.00
2.20
Stroop Errors
Trauma Group:
Lower Trauma
Higher Trauma
Lower Trauma
Higher Trauma


A
Baseline Anxiety in Stress Cue Trial
10.00
8.00
6.00
4.00
2.00
.00
-1.0000
.0000
1.0000
2.0000
Anterior Rostral Cingulate Zone During Stress Cue


B
Post-Stimuli Anxiety in Stress Cue Trial
10.00
8.00
6.00
4.00
2.00
.00
-1.0000
.0000
1.0000
2.0000
Anterior Rostral Cingulate Zone During Stress Cue


A.
***
Anxiety Ratings
4
3
2
1
0
Neutral
Stress
B.
***
Heart Rate
70
68
66
64
62
60
Neutral
Stress
C.
Stress - Neutral
t value
6.32
2.64
VmPFC
/ACC
Striatum
MTG
PCC
L
Z = 10
X = 4


A.
P value
0.001
0.05
Amyg.
Y = 4
Hippo.
MTL
L
Y = -9
MTL
X = 27
B.
i) R. Amygdala
R. Amyg. (β)
r = .34
Life Trauma
ii) L. Hippocampus
L. Hippo. (β)
r = .37
Life Trauma
iii) L. MTL
L. MTL (β)
r = .43
Life Trauma
iv) R. MTL
R. MTL (β)
r = .42
Life Trauma


A.
P value
0.05
0.001
Hypothal.
MTL
Amyg.
Y = -2
Hippo.
MTL
Y = -8
Hypothal.
Hippo.
Hippo.
L
Z = -15
B.
i) Hypothalamus
Hypothal. (β)
r = -.4
Morning Cortisol
(ug/dl)
ii) R. Amygdala
R. Amyg. (β)
r = -.39
Morning Cortisol
(ug/dl)
iii) R. Hippo.
R. Hippo. (β)
r = -.39
Morning Cortisol
(ug/dl)
iv) L. MTL
L. MTL (β)
r = -.51
Morning Cortisol
(ug/dl)

Trauma Group Demographic Information and Group Comparison

	Low CTQ (SD)	High CTQ (SD)	t/x2
Age at MRI scanning (Years)	14.7 (.81)	14.97 (1.05)	−1.16
Gender (Male/Female)	19/14	21/10	.71
Race (AA:C:O)	25:03:05	25:04:02	1.24
Stroop Error Score	1.29 (.15)	1.43 (.26)	−2.5 *
Prenatal Drug Exposure (Cn:CnS:S:NS)	4:15:4:10	4:21:1:5	4.41
Maternal Education (High-School Diploma)	22/11	22/9	.14
KABC mental processing	92.84 (15.13)	95.46 (10.91)	−.79

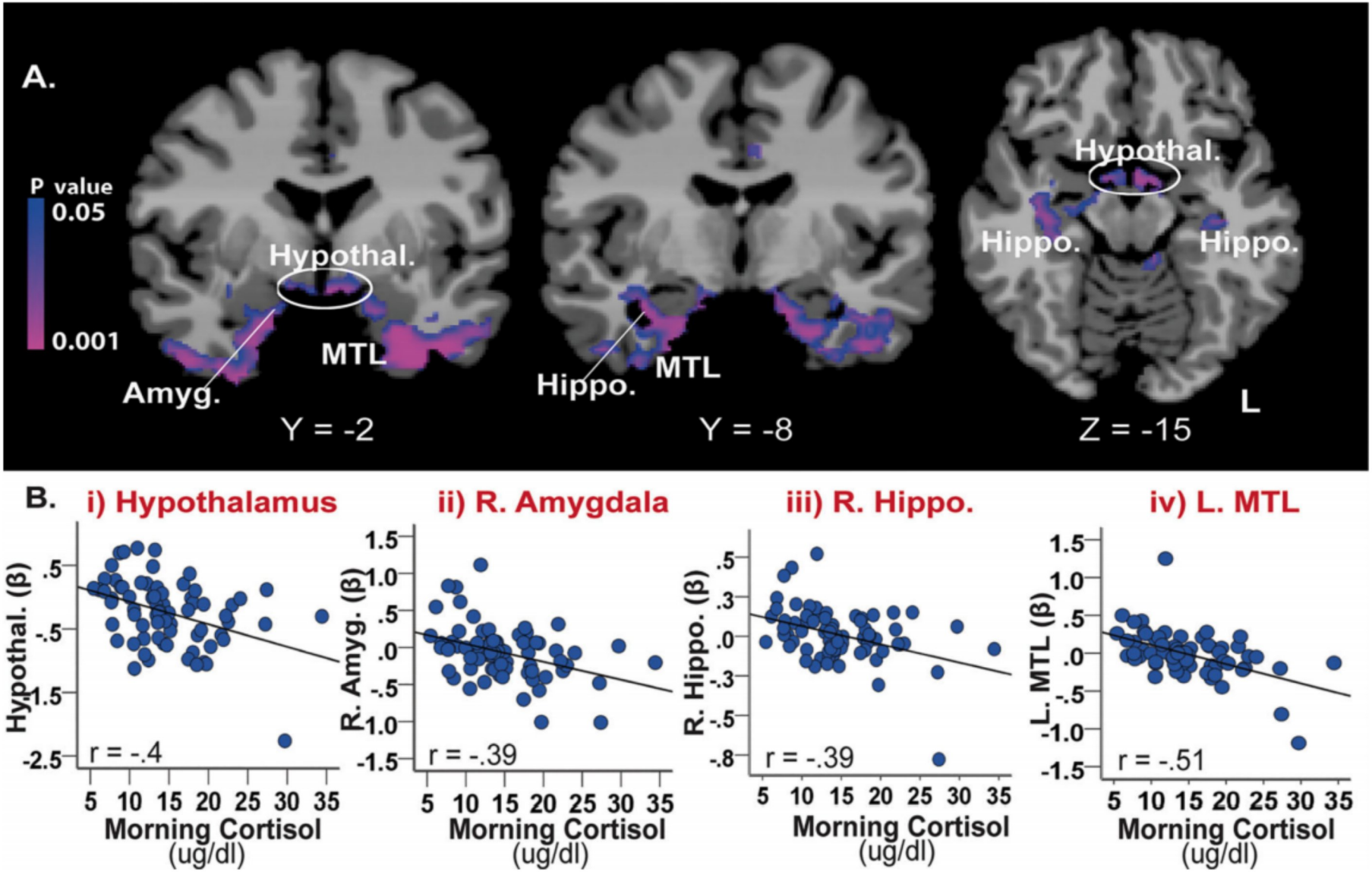
Abbreviations: Childhood Trauma Questionnaire (CTQ), African-American (AA), Caucasian (C), Other (O), Kaufman assessment battery for children (KABC); Cocaine only (Cn), Cocaine and other substances (CnS), Other substances only (S), No substance use (NC).

* $p \leq .05$

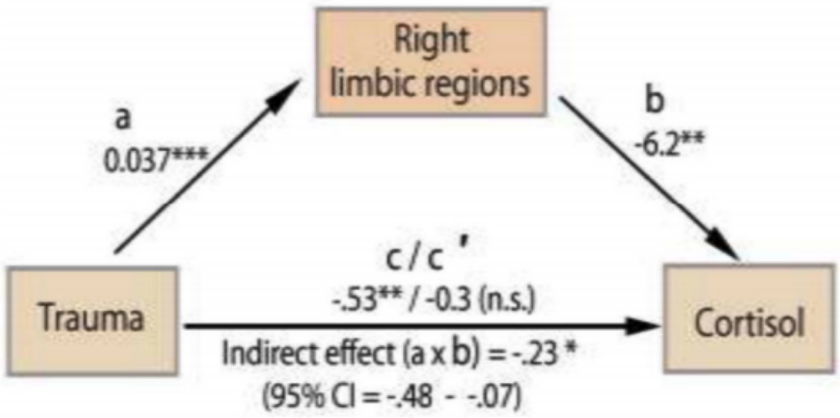
Correlations Between Stroop Error, Trauma Group and ROI Activation During Stress Condition

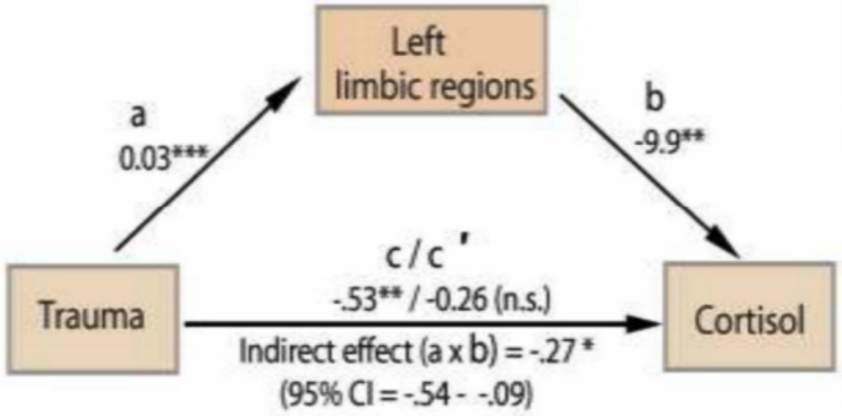
Variables	1	2	3
1. Stroop Error			
2. Trauma Group	.32**		
3. Anterior Rostral Cingulate Zone	−.23*	.14	
4. Posterior Rostral Cingulate Zone	−.05	.21	.76***

* p≤.05

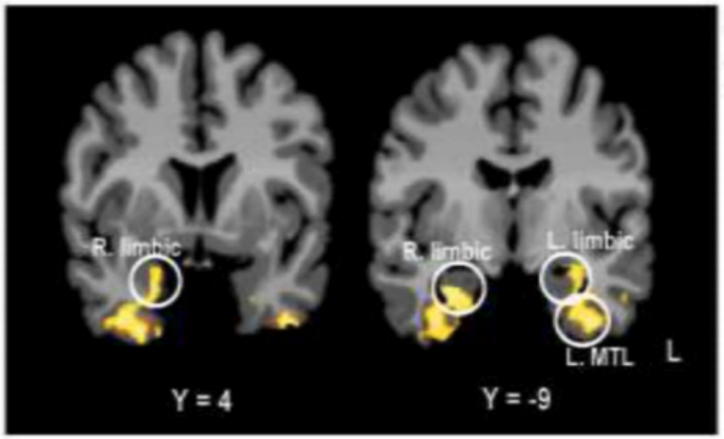

A.
P value
0.05
0.001
Hypothal.
MTL
Amyg.
Y = -2
Hippo.
MTL
Y = -8
Hypothal.
Hippo.
Hippo.
L
Z = -15
B.
i) Hypothalamus
Hypothal. (β)
r = -.4
Morning Cortisol
(ug/dl)
ii) R. Amygdala
R. Amyg. (β)
r = -.39
Morning Cortisol
(ug/dl)
iii) R. Hippo.
R. Hippo. (β)
r = -.39
Morning Cortisol
(ug/dl)
iv) L. MTL
L. MTL (β)
r = -.51
Morning Cortisol
(ug/dl)

A. Limbic regions

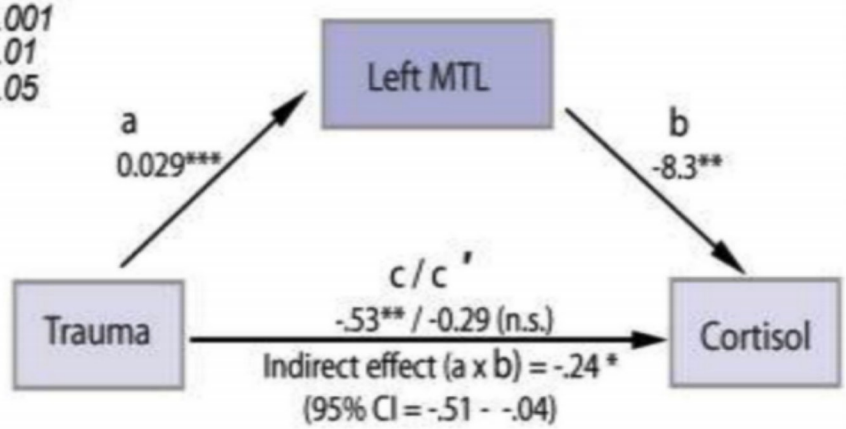




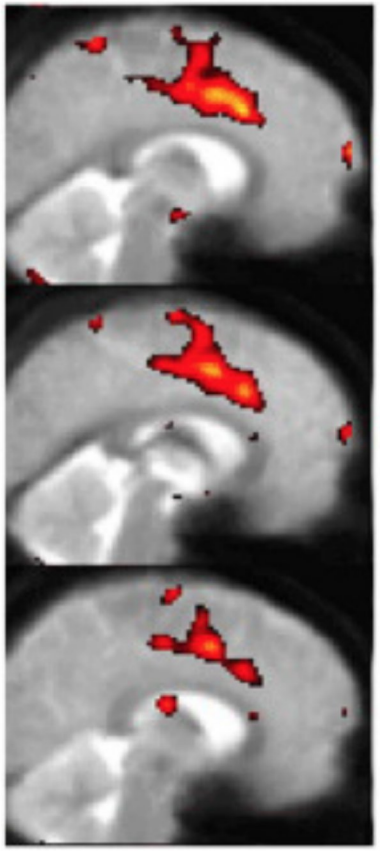
B. Medial temporal lobe



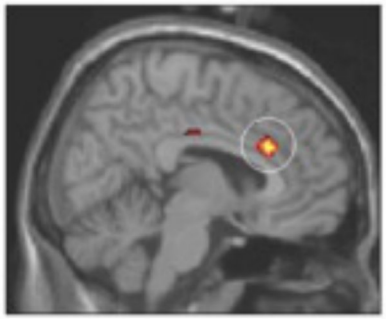
*** p<0.001
** p<0.01
* p<0.05

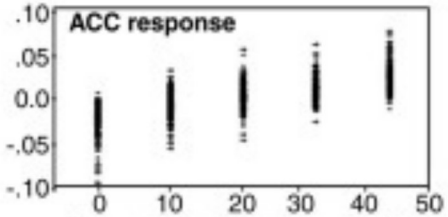


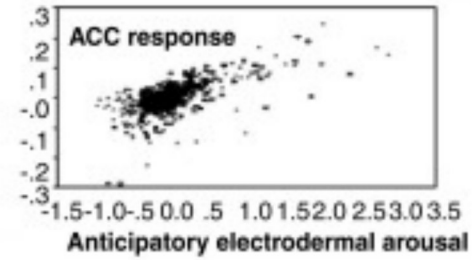
A Sympathetic influences on heart



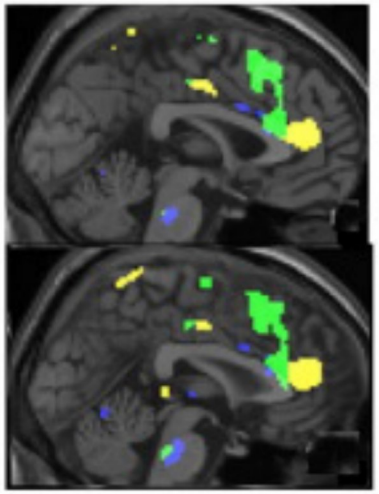
B Risk and anticipatory electrodermal arousal







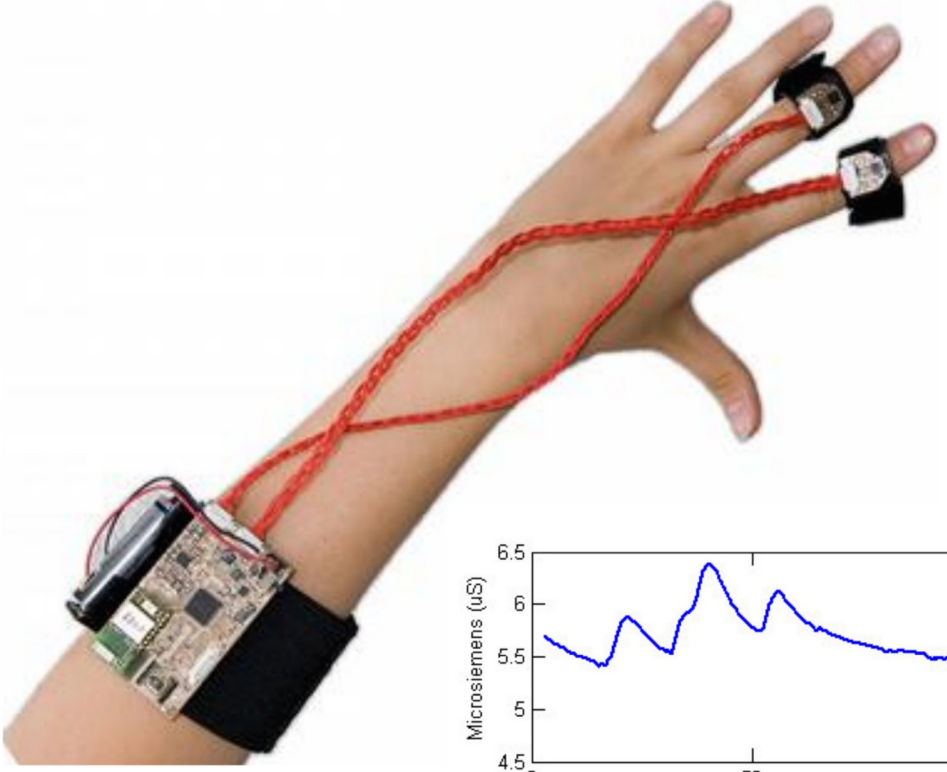
C Error and evoked pupillary response

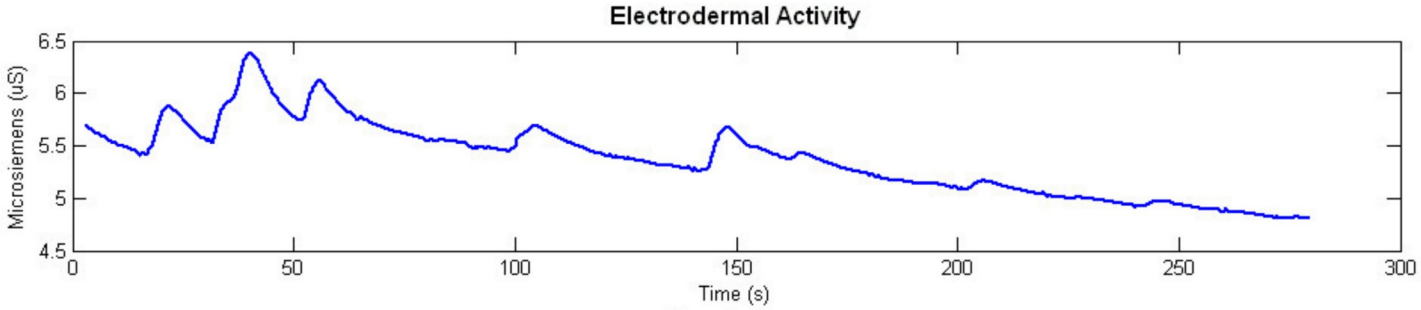


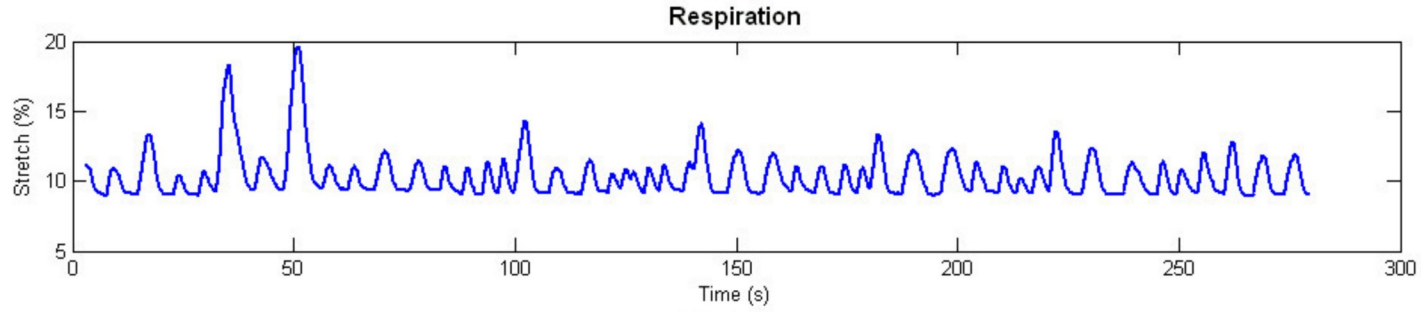
Activity relating to pupillary response alone

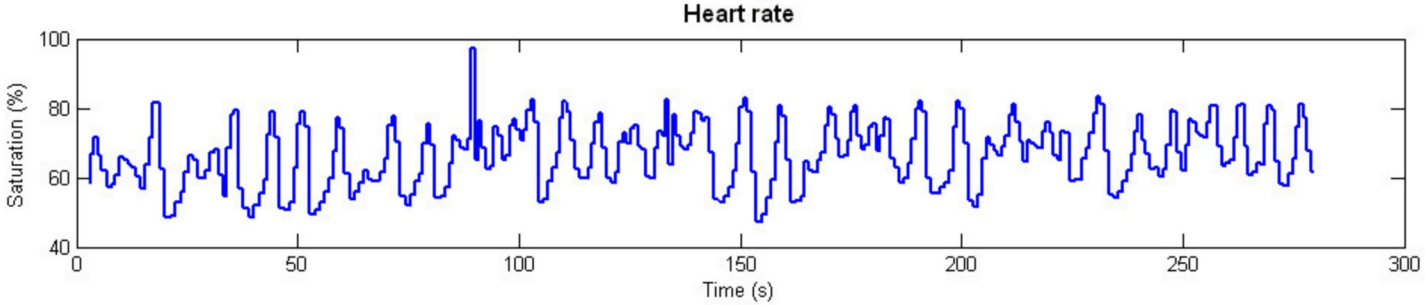
Activity relating to pupillary response & error processing

Activity relating to error processing alone




Electrodermal Activity
Microsiemens (uS)
6.5
6
5.5
5
4.5
0
50
100
150
200
250
300
Time (s)


Respiration
Stretch (%)
20
15
10
5
0
50
100
150
200
250
300
Time (s)


Heart rate
Saturation (%)
100
80
60
40
0
50
100
150
200
250
300
Time (s)

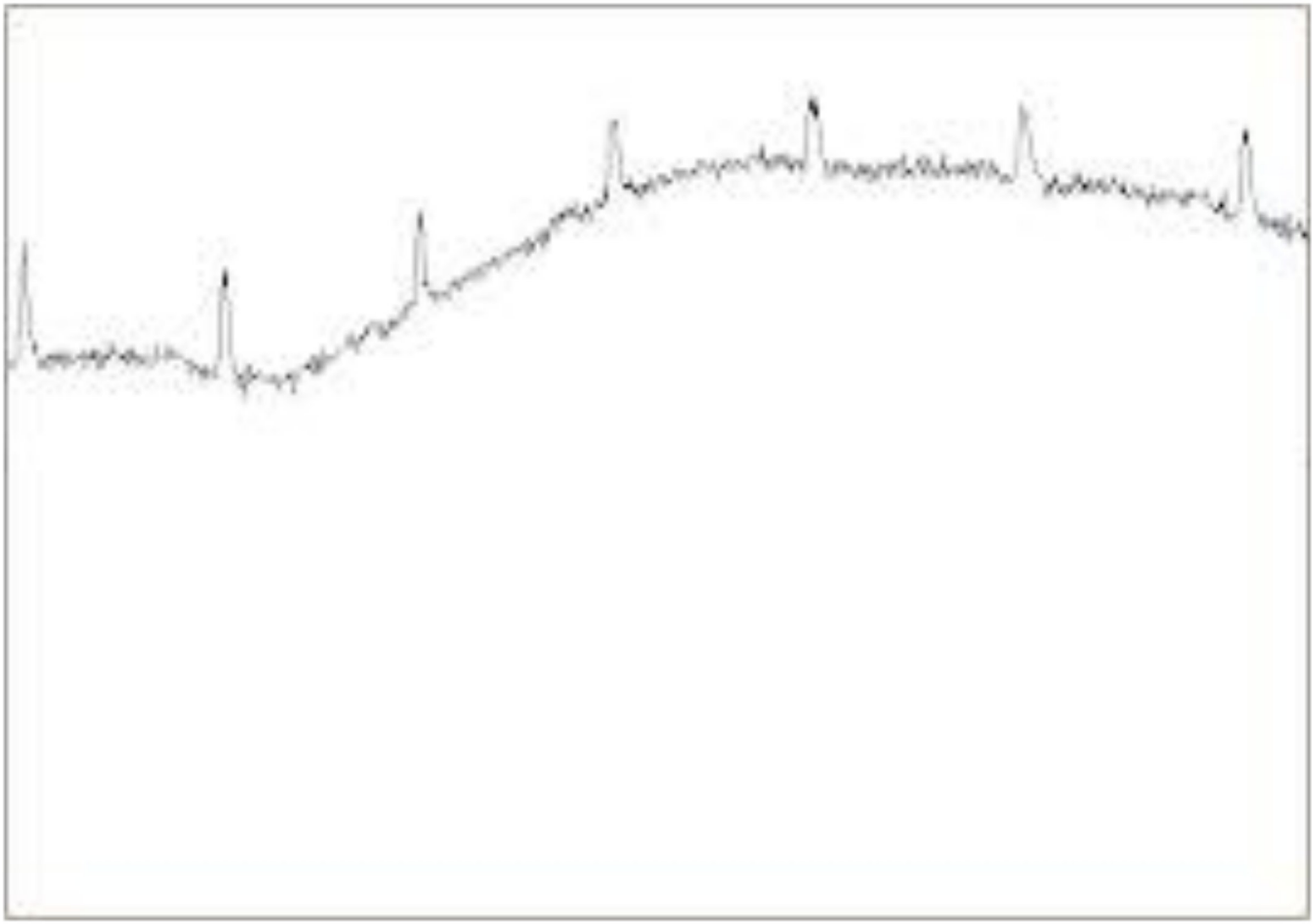
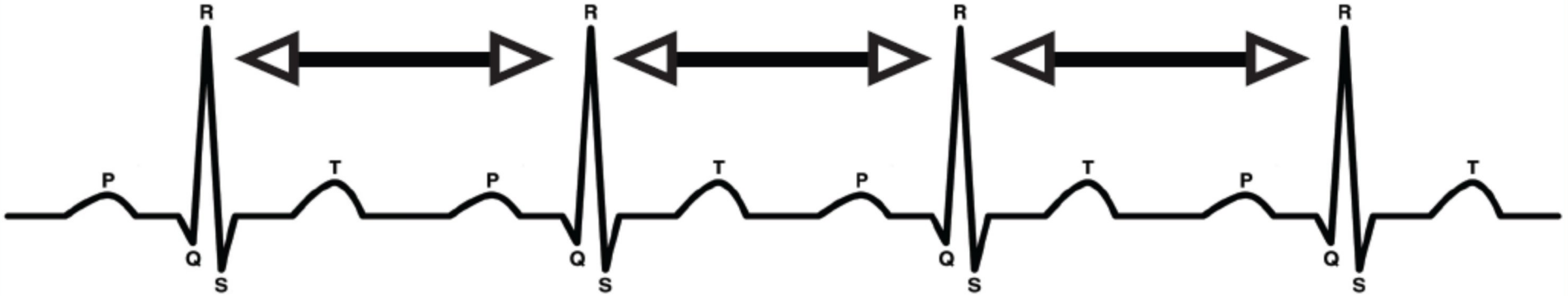
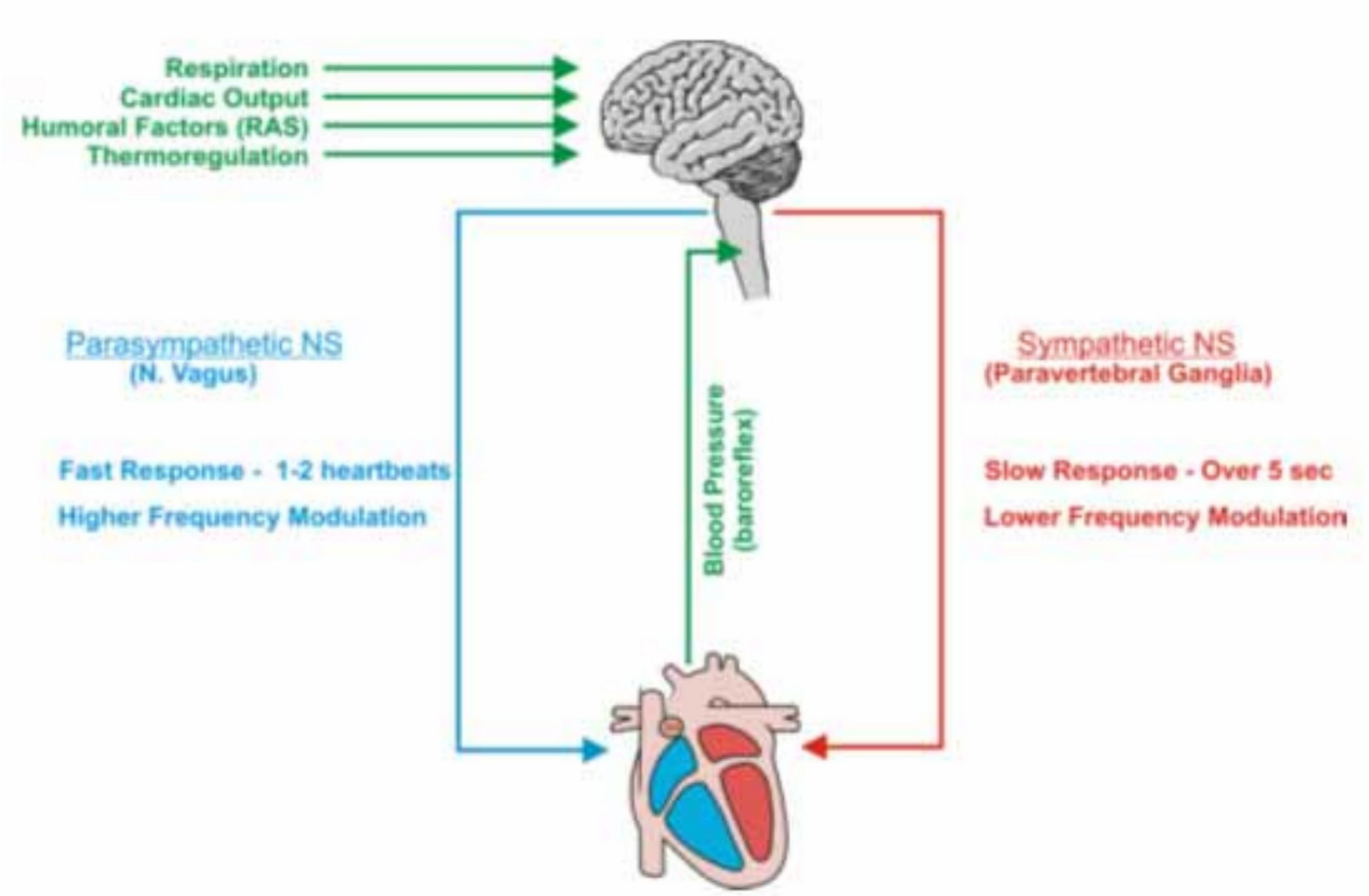
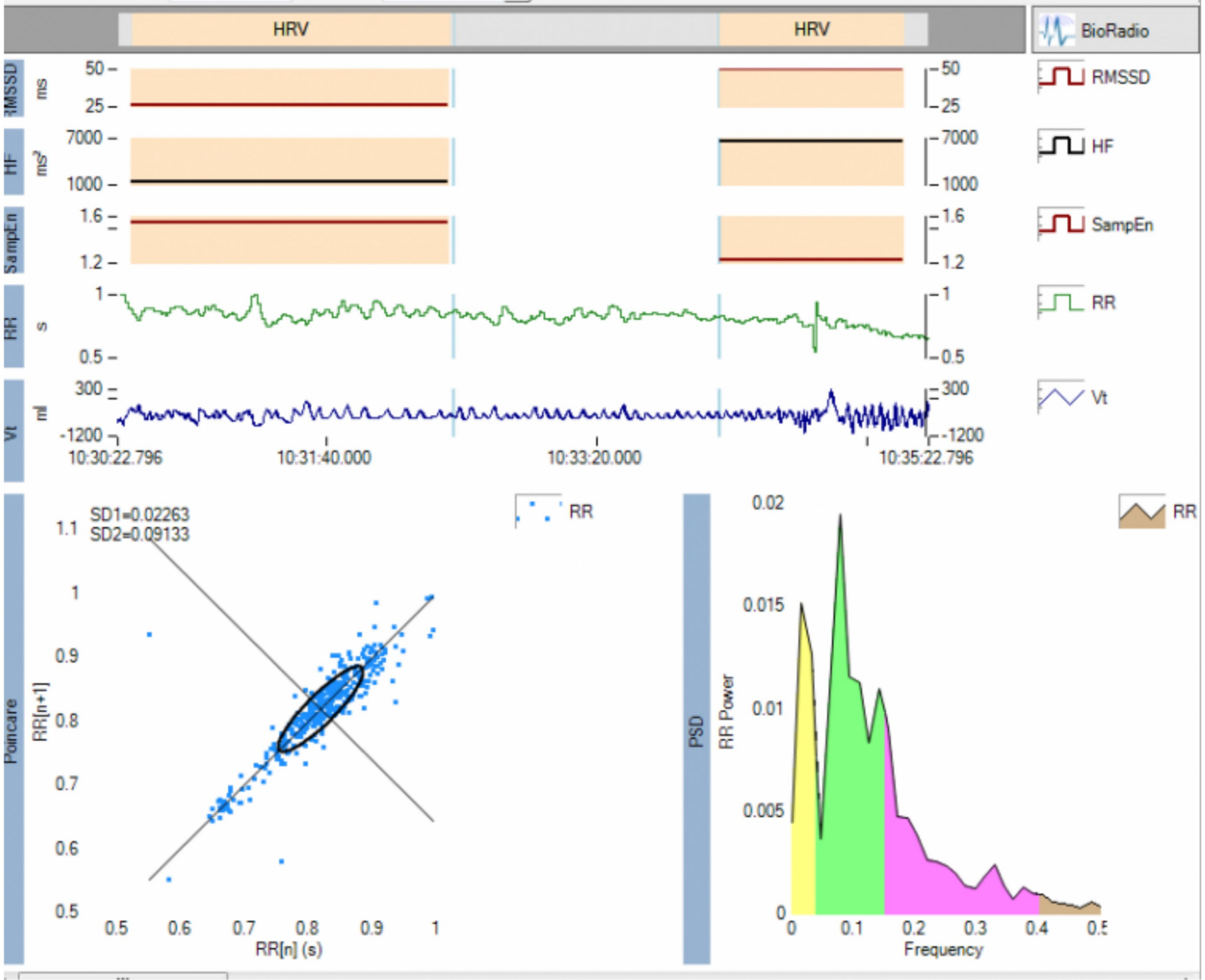
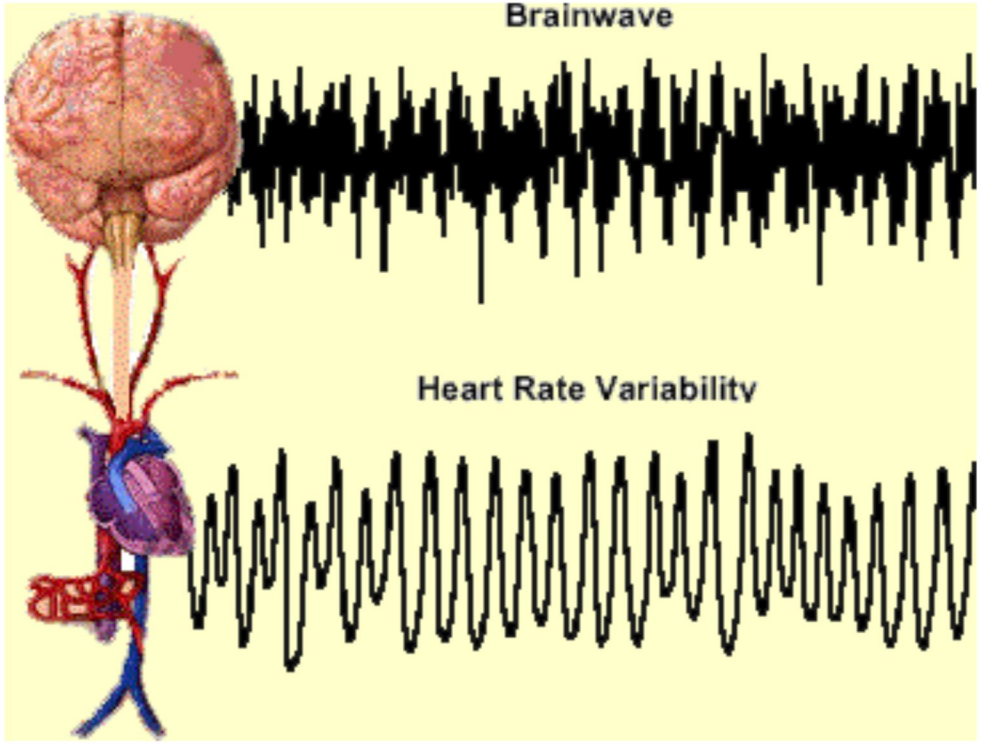


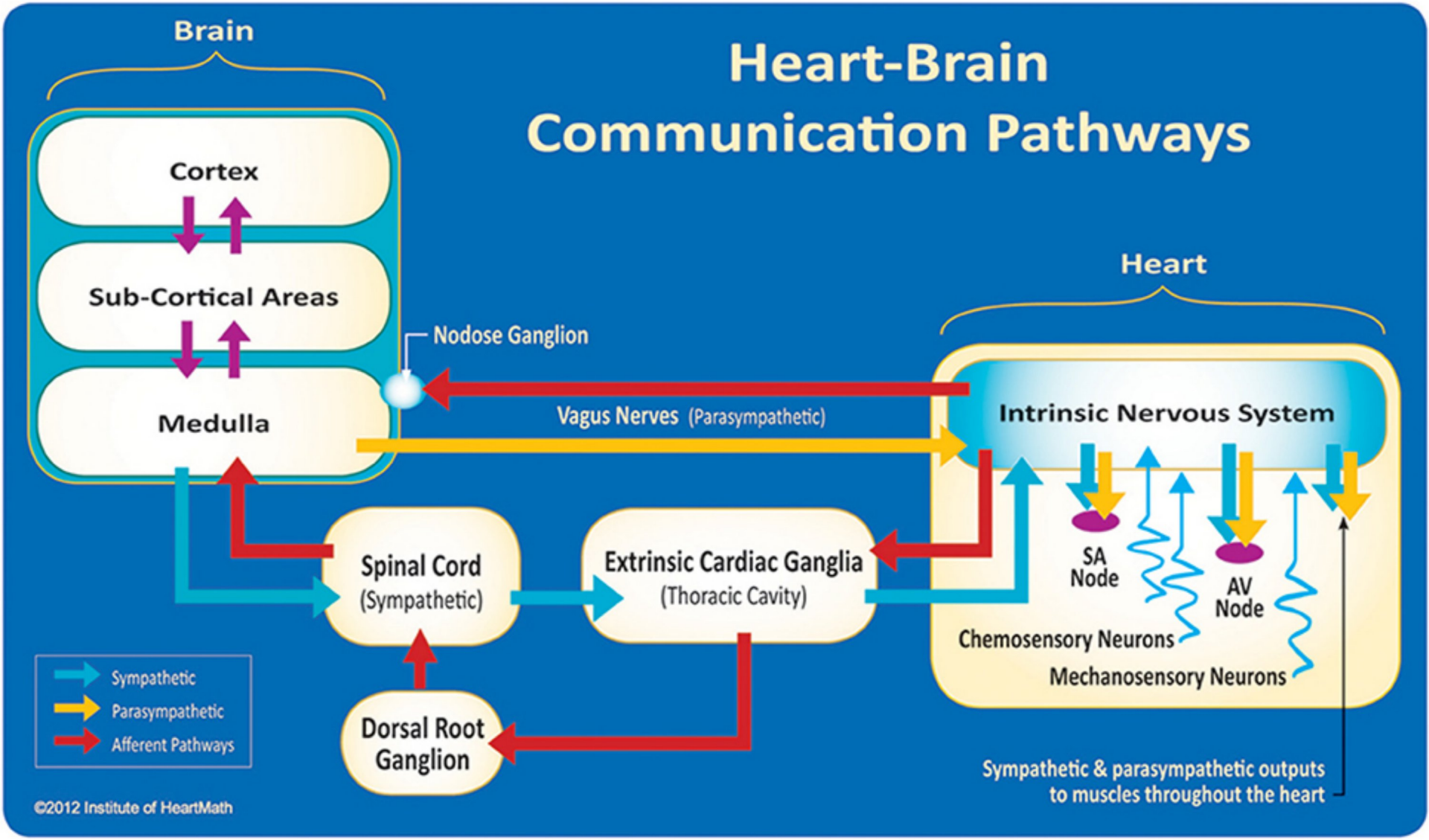
Figure 1: Heart rate variability is measured by calculating the time between R spikes on an ECG trace

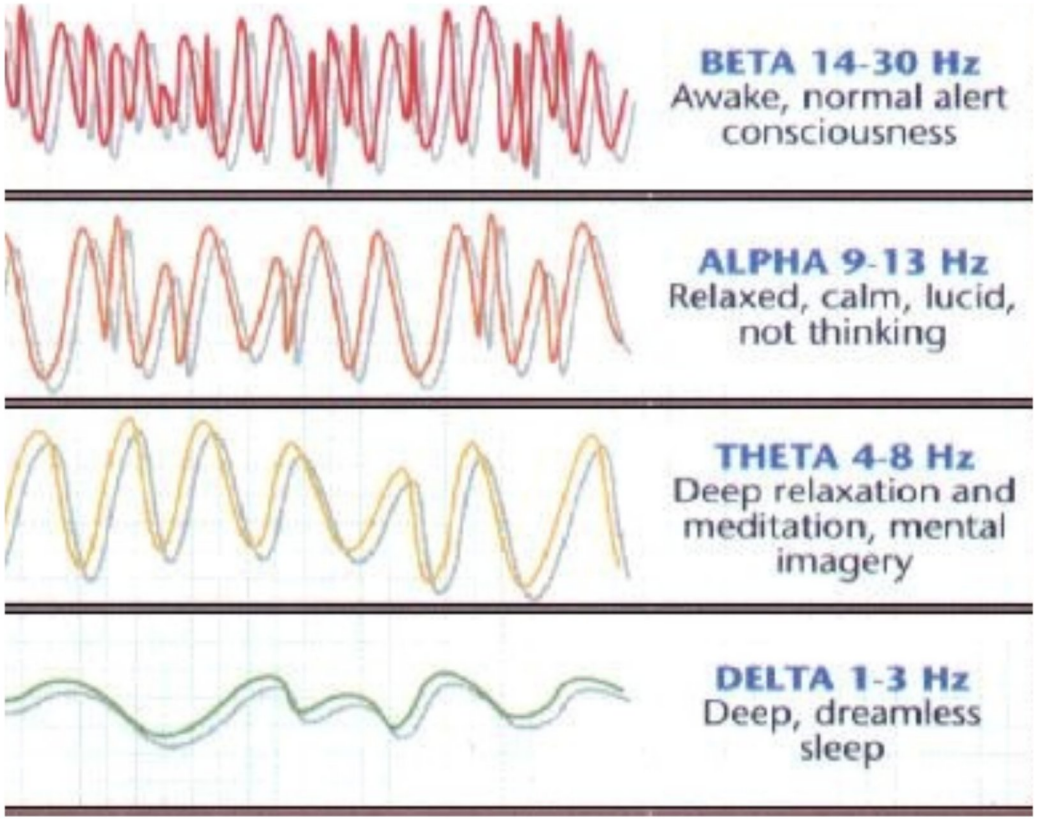



Respiration
Cardiac Output
Humoral Factors (RAS)
Thermoregulation
Parasympathetic NS
(N. Vagus)
Fast Response - 1-2 heartbeats
Higher Frequency Modulation
Blood Pressure
(baroreflex)
Sympathetic NS
(Paravertebral Ganglia)
Slow Response - Over 5 sec
Lower Frequency Modulation


HRV
HRV
BioRadio
RMSSD
ms
50
25
HF
ms²
7000
1000
SampEn
1.6
1.2
RR
s
1
0.5
Vt
ml
300
-1200
10:30:22.796
10:31:40.000
10:33:20.000
10:35:22.796
Poincare
SD1=0.02263
SD2=0.09133
RR
RR[n+1]
RR[n] (s)
PSD
RR Power
Frequency

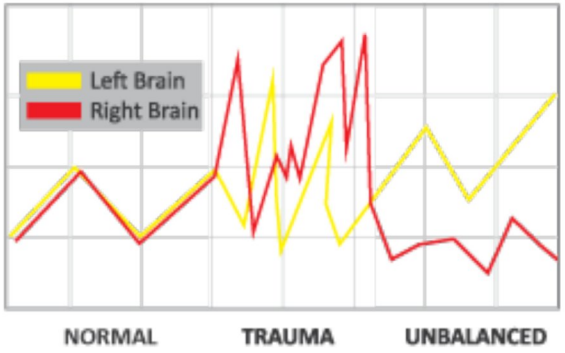

Brainwave
Heart Rate Variability


Brain
Heart-Brain
Communication Pathways
Cortex
Sub-Cortical Areas
Medulla
Nodose Ganglion
Vagus Nerves (Parasympathetic)
Heart
Intrinsic Nervous System
SA
Node
AV
Node
Chemosensory Neurons
Mechanosensory Neurons
Spinal Cord
(Sympathetic)
Extrinsic Cardiac Ganglia
(Thoracic Cavity)
Dorsal Root
Ganglion
Sympathetic
Parasympathetic
Afferent Pathways
Sympathetic & parasympathetic outputs
to muscles throughout the heart
©2012 Institute of HeartMath

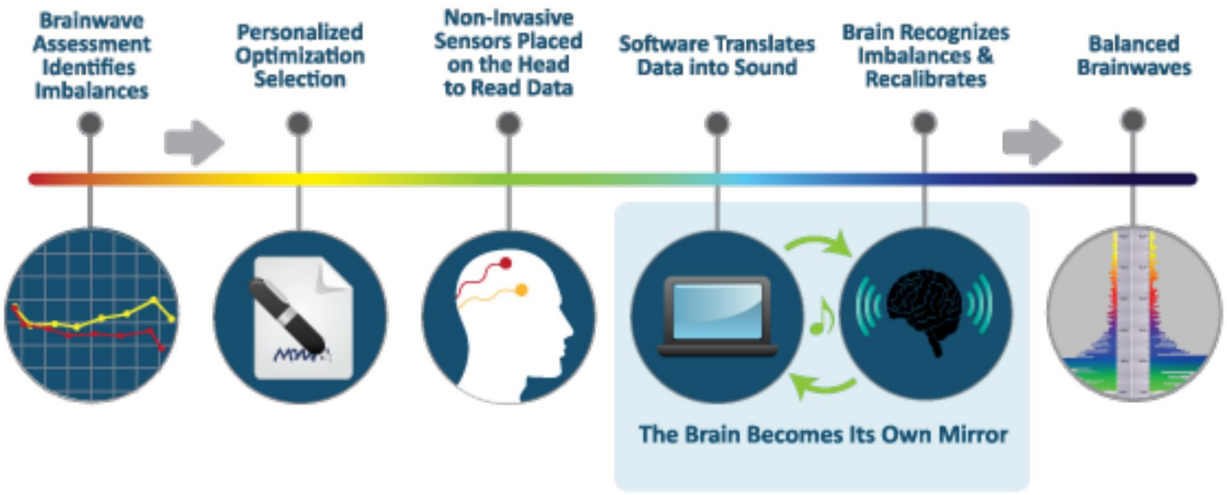

BETA 14-30 Hz
Awake, normal alert consciousness
ALPHA 9-13 Hz
Relaxed, calm, lucid, not thinking
THETA 4-8 Hz
Deep relaxation and meditation, mental imagery
DELTA 1-3 Hz
Deep, dreamless sleep

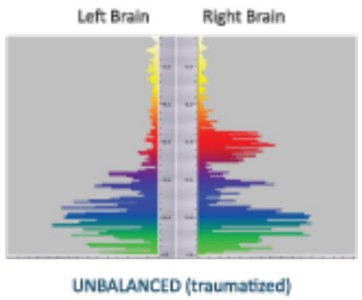
Trauma Impacts the Brain Physical & Emotional

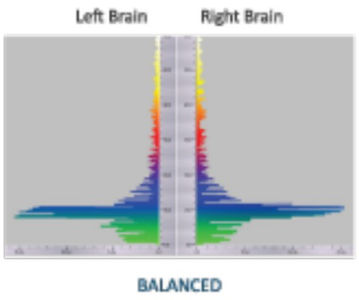
Traumas – both physical and emotional – can knock brain functions out of balance. The resulting imbalance is often exacerbated as ailments and disorders. In turn, most of these consequences are eased when the brain is back in a state of harmony.



Brainwave Optimization How It Works

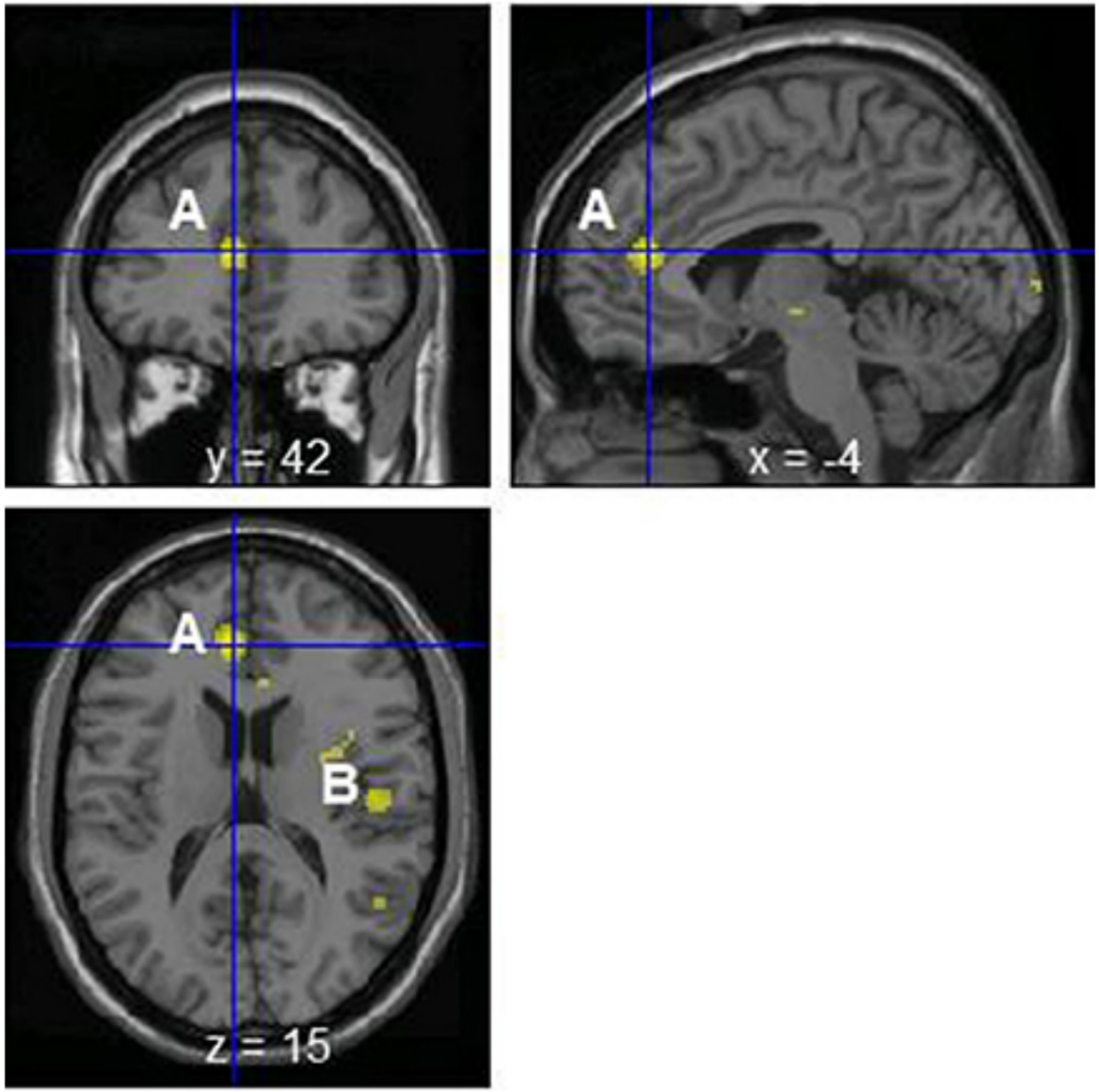




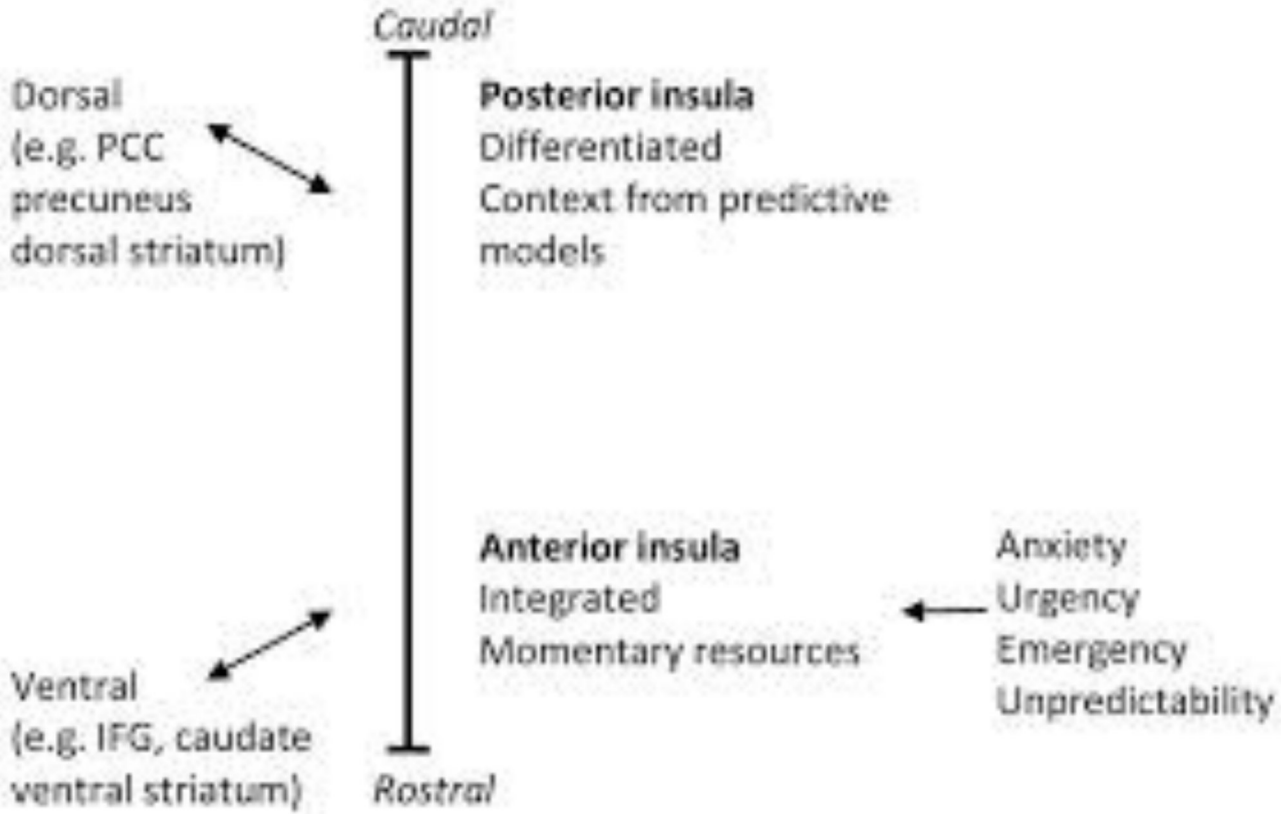


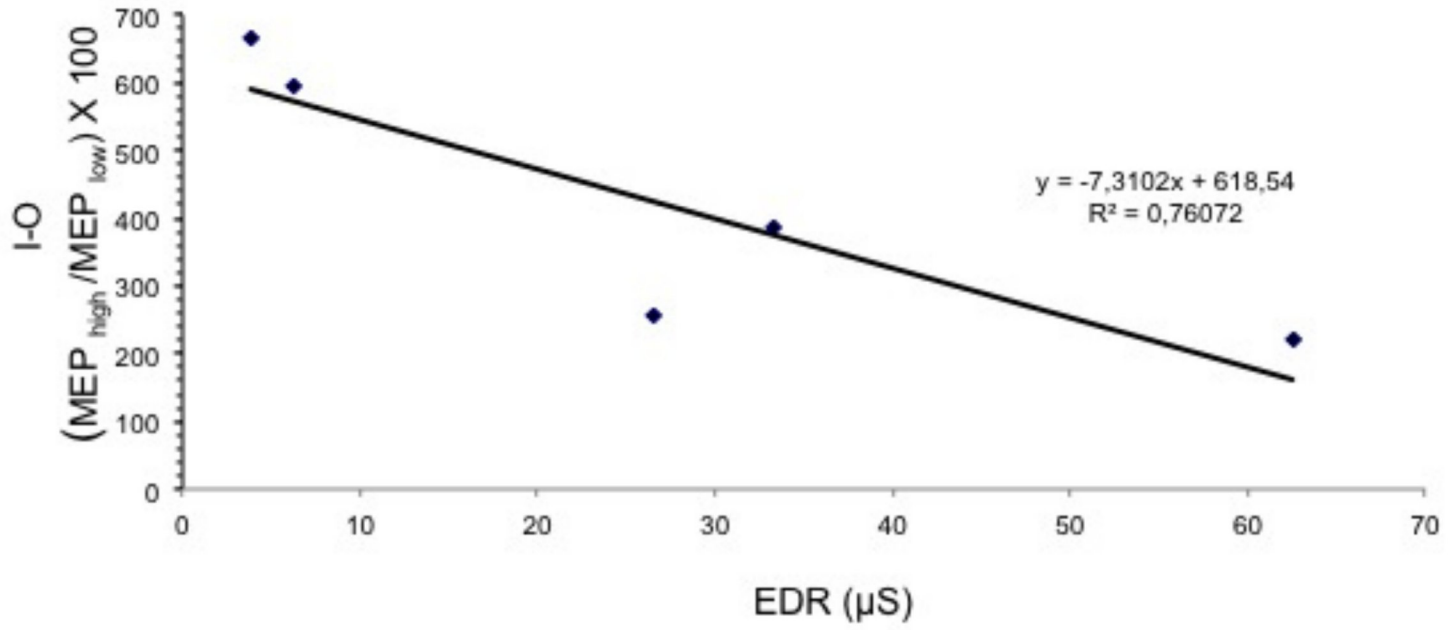
Unbalanced vs. Balanced Brain

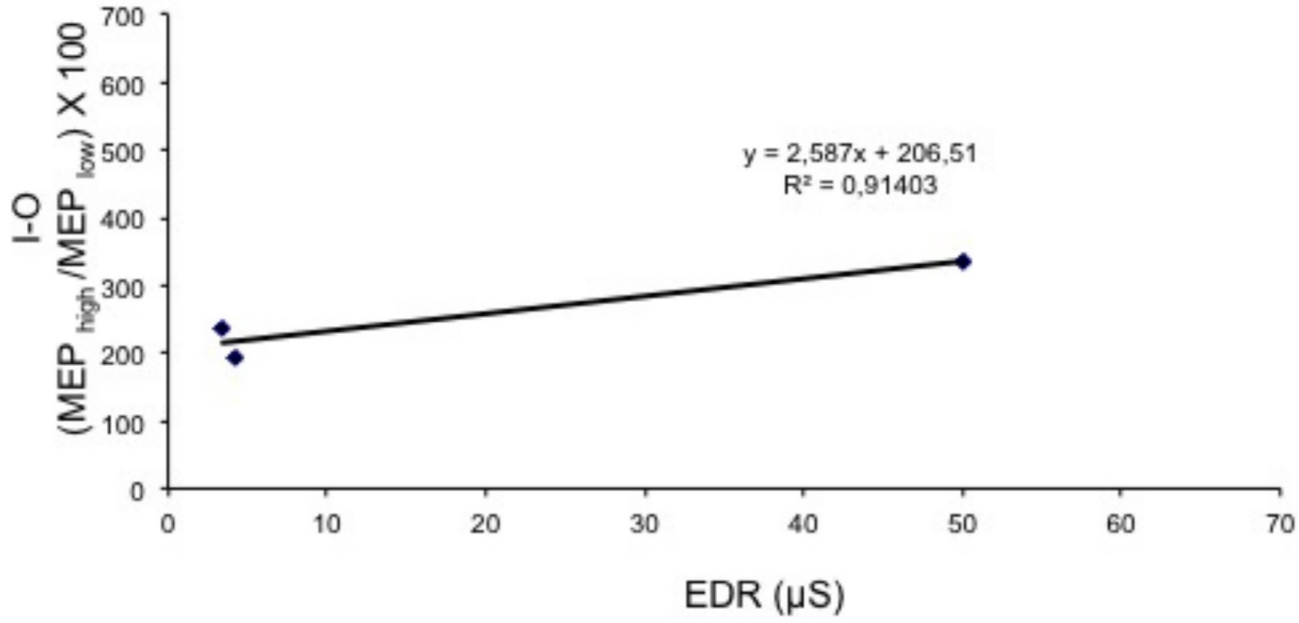
The brain controls the entire body. Balance is essential and the key to overall well-being and performance. Once the brain is balanced, the body follows. Brainwave Optimization™ is all about optimizing the brain, and hence optimizing all brain and bodily functions.

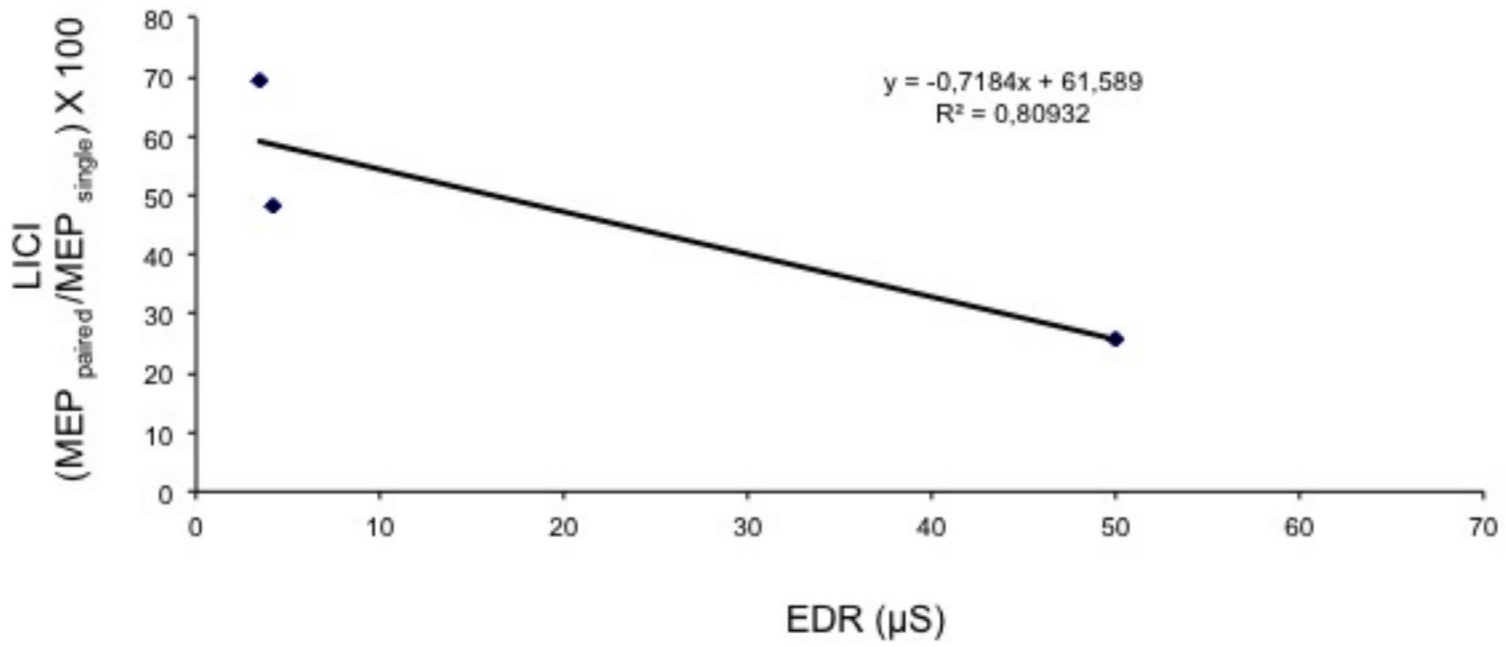

A
y = 42
A
x = -4
A
B
z = 15

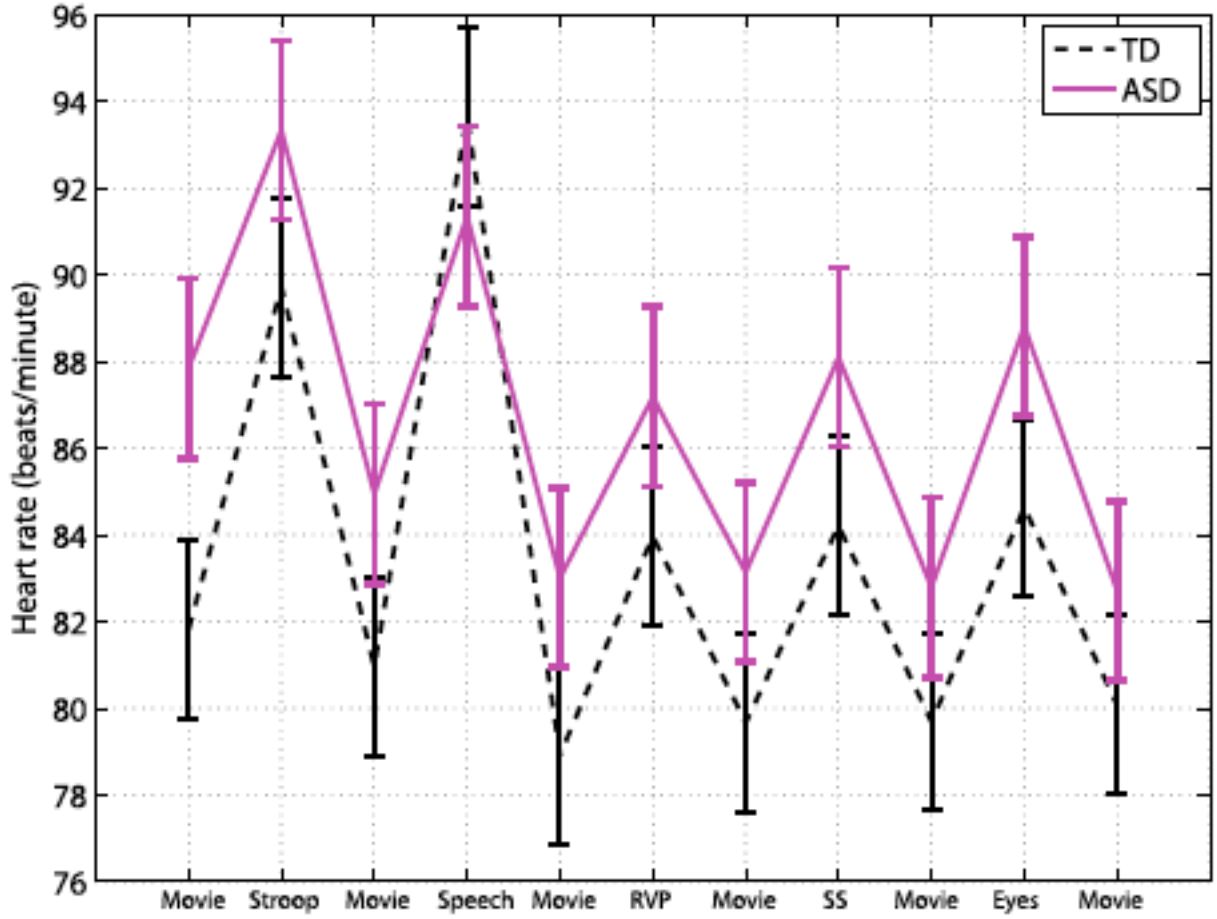
greater parasympathetic and perhaps less sympathetic activation associated with happiness and disgust and a shift toward sympathetic dominance with sadness and anger


Caudal
Dorsal
(e.g. PCC
precuneus
dorsal striatum)
Posterior insula
Differentiated
Context from predictive
models
Anterior insula
Integrated
Momentary resources
Anxiety
Urgency
Emergency
Unpredictability
Ventral
(e.g. IFG, caudate
ventral striatum)
Rostral


I-O
(MEP high/MEP low) X 100
700
600
500
400
300
200
100
0
0
10
20
30
40
50
60
70
EDR (µS)
y = -7,3102x + 618,54
R² = 0,76072


I-O
(MEP high /MEP low) X 100
700
600
500
400
300
200
100
0
y = 2,587x + 206,51
R² = 0,91403
0
10
20
30
40
50
60
70
EDR (µS)


LICI
(MEP paired/MEP single) X 100
y = -0,7184x + 61,589
R² = 0,80932
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
EDR (µS)


96
94
92
90
88
86
84
82
80
78
76
Heart rate (beats/minute)
TD
ASD
Movie
Stroop
Movie
Speech
Movie
RVP
Movie
SS
Movie
Eyes
Movie