The role of the central autonomic network in orthostatic tolerance and intolerance

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Off-Label Usage

None

Learning Objectives

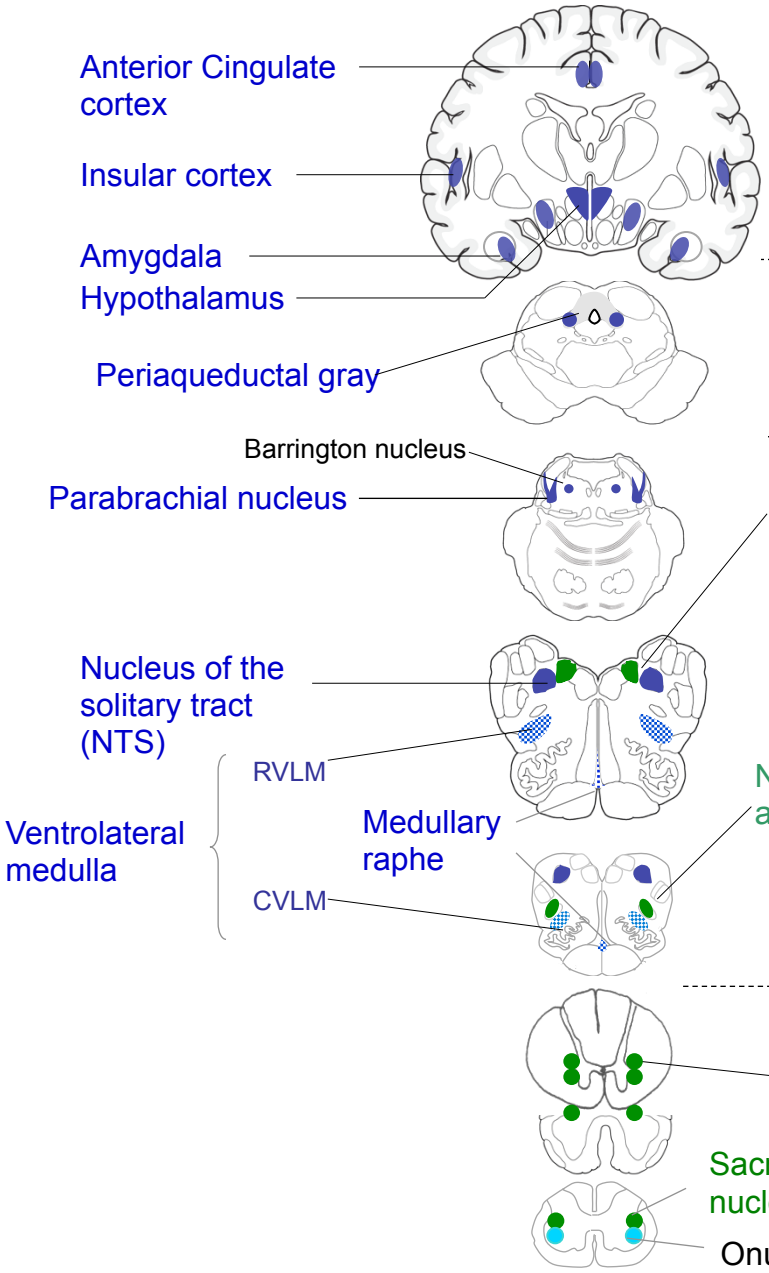
To define the components of the central autonomic network involved in orthostatic tolerance and orthostatic intolerance:

- arterial baroreflex (and vestibulo-sympathetic reflex)
- central causes of orthostatic intolerance
- the role of the interoceptive-emotional system in maintenance of orthostatic intolerance symptoms

Key Messages

- The baroreceptor reflex (baroreflex) is the key neural mechanism for maintenance of orthostatic tolerance
- Disorders of the central baroreflex arc manifest with neurogenic orthostatic hypotension
- Interoceptive sensitization, behavioral arousal; and conditioning contribute to persistence of symptoms of orthostatic intolerance in the absence of progressive autonomic failure

Central Autonomic Network (CAN)



Level-Specific Function

Behavioral Arousal
Interoceptive awareness
Emotion
Stress responses
Homeostasis

Integration of autonomic function with arousal and pain modulation,

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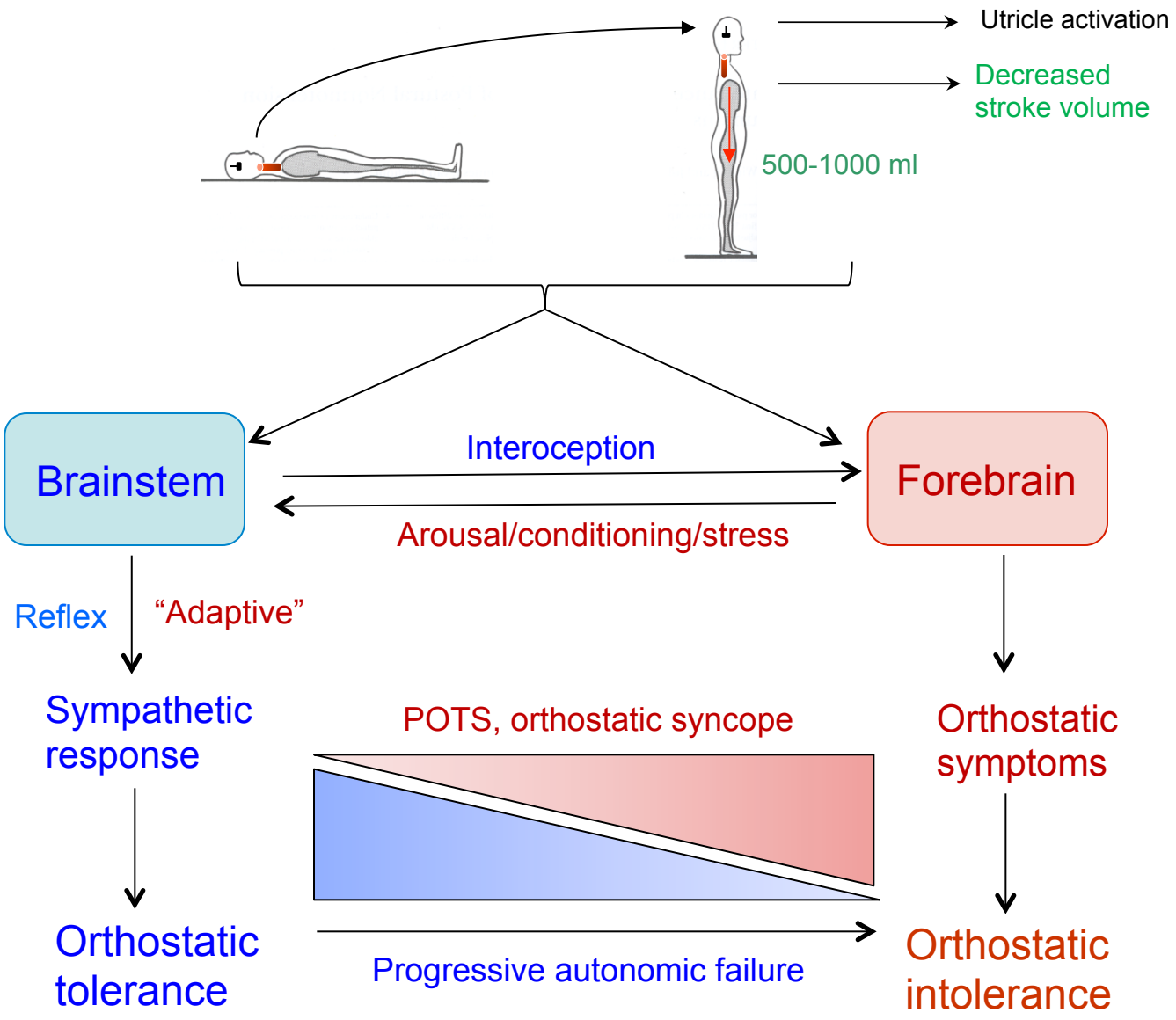
-Tonic control of blood pressure
-Respiratory rhythms
-Autonomic reflexes
- circulation,
- respiration
- micturition
- gastrointestinal

Segmental sympathetic and sacral (micturition, defecation, erection) reflexes

Role of the CAN in Orthostatic Tolerance and Intolerance: Basic Principles

- Interconnected regions of the CAN control the two variables that determine arterial blood pressure (ABP) :
  - cardiac output (stroke volume and heart rate-HR)
  - total peripheral resistance
- The medullary baroreflex sympathetic output to skeletal muscle and splanchnic blood vessels is critical to prevent orthostatic hypotension (OH)
- Impairment of the central sympathetic output of the baroreflex manifest with neurogenic OH
- Interoceptive inputs to forebrain areas involved in emotion are the basis of symptoms of orthostatic intolerance (dizziness, fatigue)

Responses to Orthostatic Stress



Mechanisms for Orthostatic Tolerance

- A series of regulatory mechanisms are activated to prevent orthostatic hypotension (OH) In chronological order of activation, these include

  - neural mechanisms: baroreflex and other medullary reflexes (eg, vestibulosympathetic)

  - humoral mechanisms: arginine vasopressin (AVP) and renin-angiotensin-aldosterone

  - capillary- fluid-shit system

  - renal-body fluid control system.

- The baroreflex provides a powerful moment-to-moment negative feedback regulation that minimizes fluctuations of arterial pressure during standing, exercise and emotion

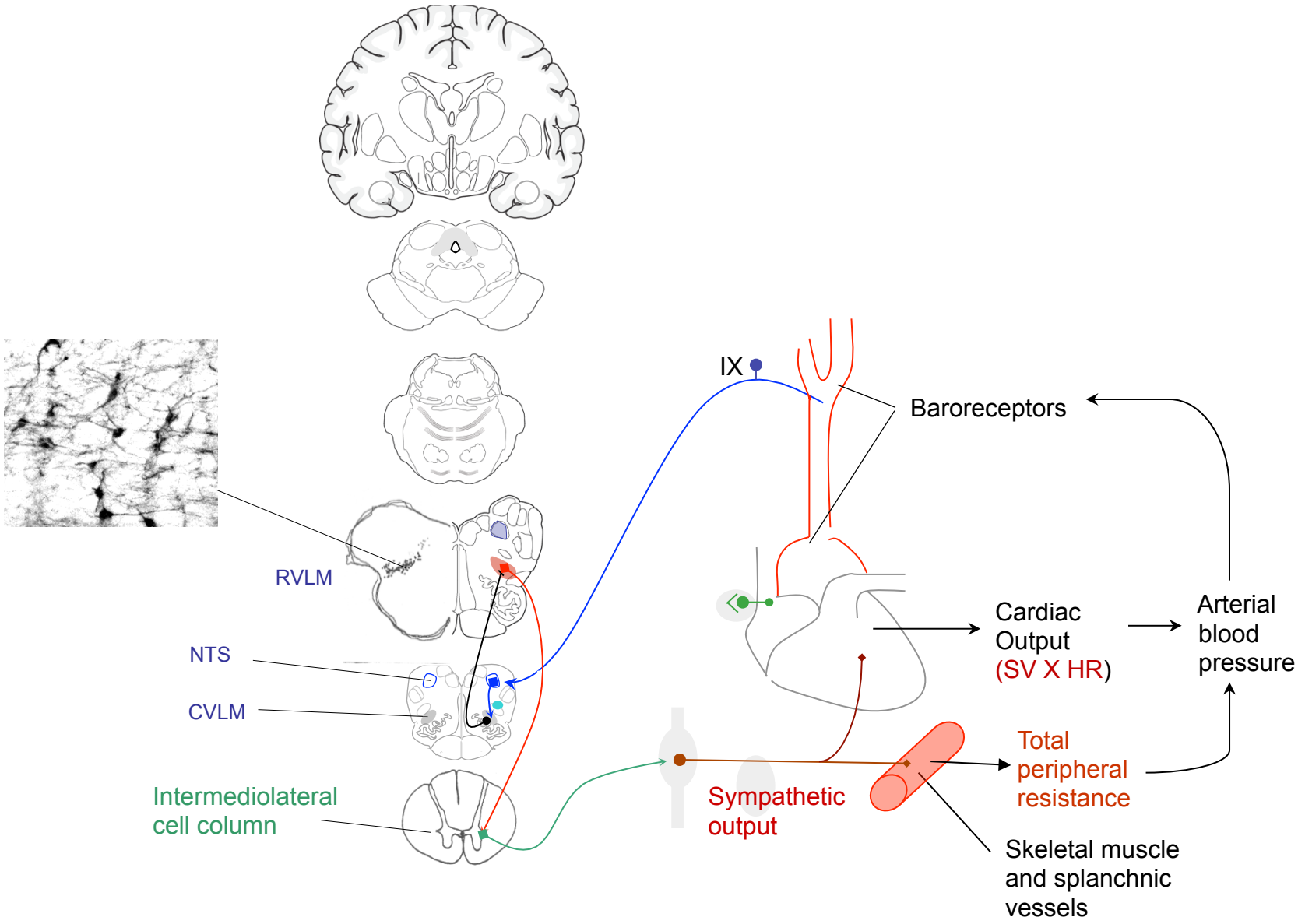
- The central baroreflex arc includes neurons of the nucleus of the solitary tract (NTS) that elicit (1) inhibition sympathoexcitatory neurons of the rostral ventrolateral medulla (RVL) via the caudal ventrolateral medulla; and (2) activation of cardiovagal neurons of the nucleus ambiguus; and (3) tonic inhibition of AVP release

- Upon standing, unloading of the baroreceptors reduces NTS input, resulting in

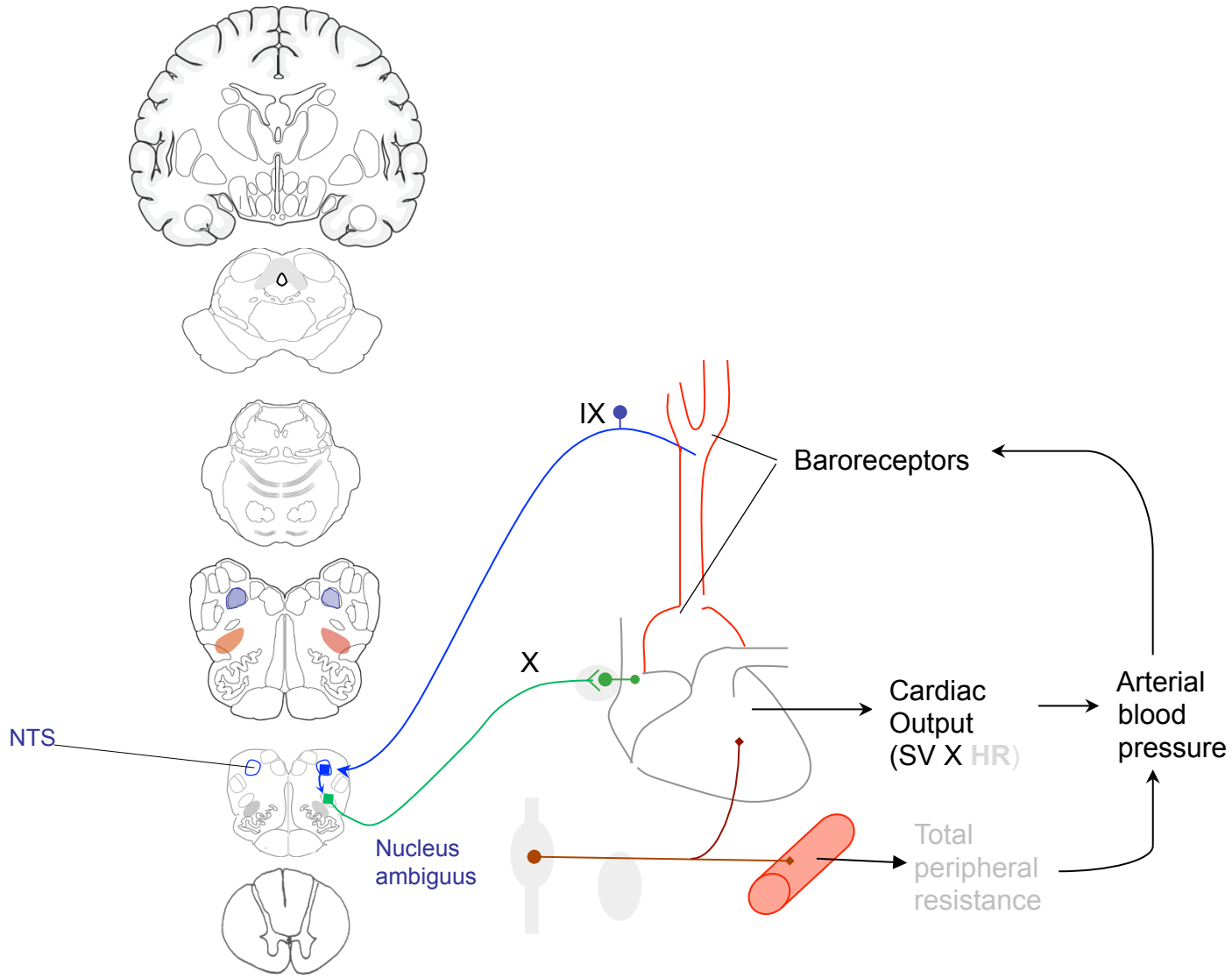
  - RVL triggered-sympathetically mediated vasoconstriction (critical)

  - Inhibition of cardiovagal output (tachycardia)

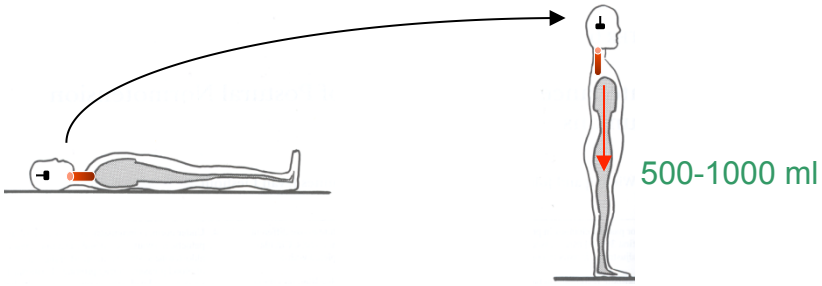
Baroreflex: Sympathetic Vasomotor Arc



Baroreflex: Cardiovagal Arc



Normal Baroreflex Control of Arterial Pressure and Heart Rate

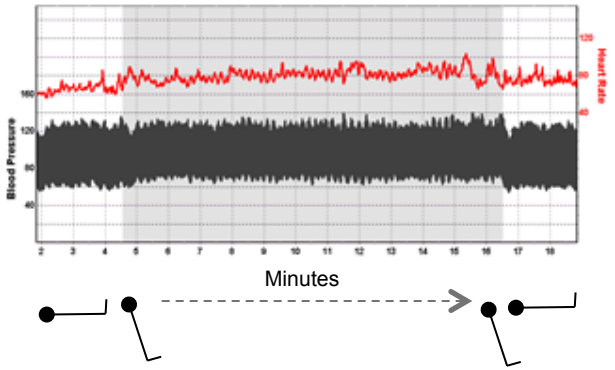


Muscle SNA

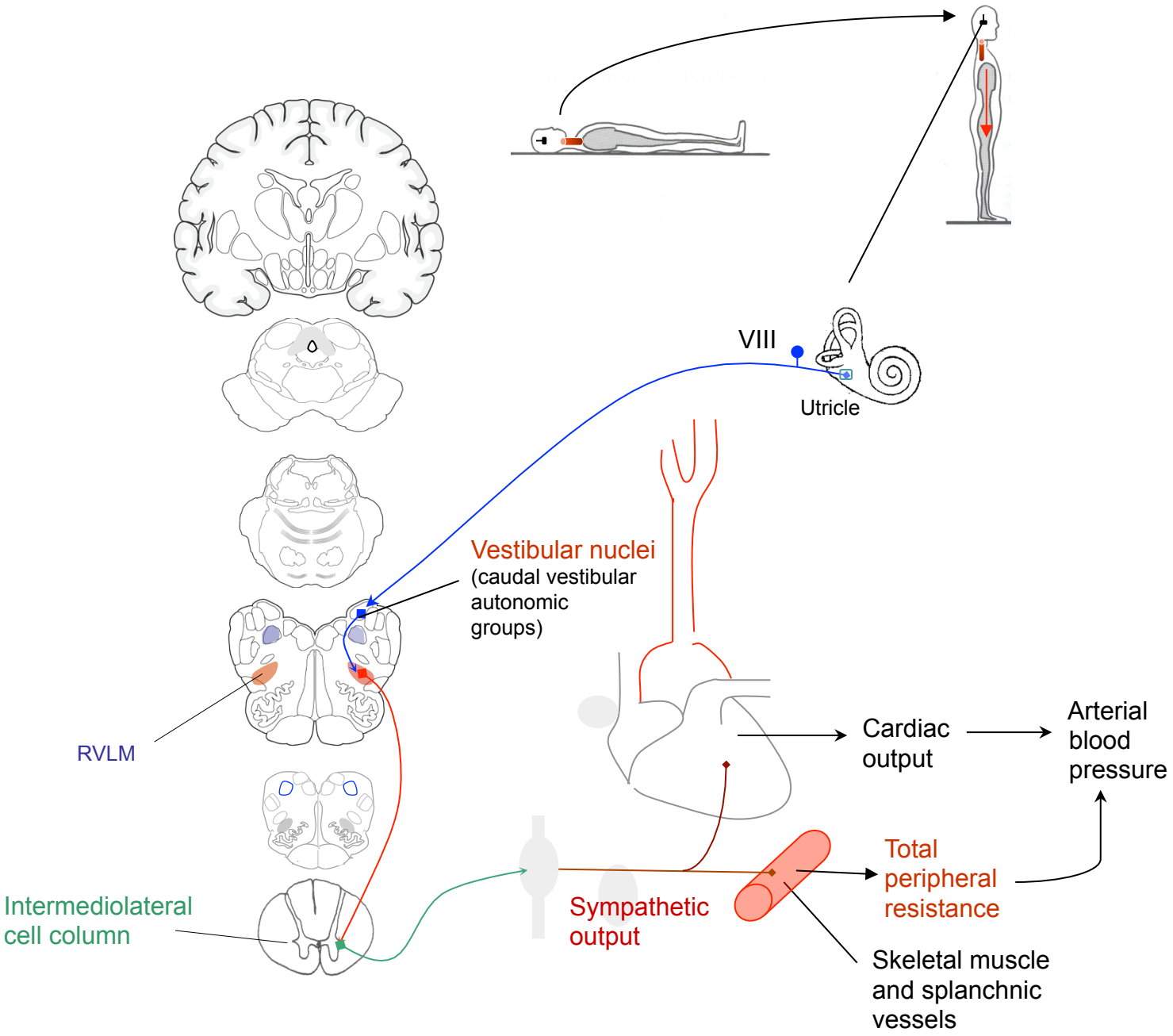
Forearm venous plasma NE (pg/ml)

Spectral analysis of R-R interval

Normal

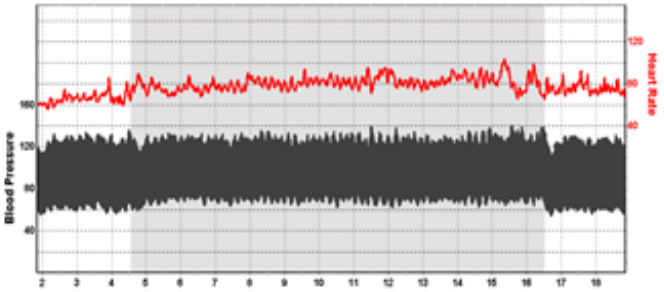


Vestibulo-sympathetic Reflex

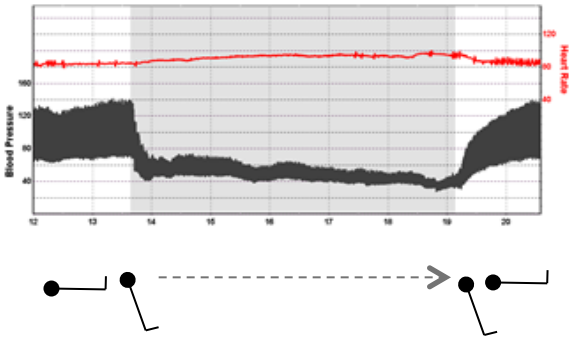


Syndromes of Orthostatic Intolerance as Defined by Head-up Tilt Responses

Normal

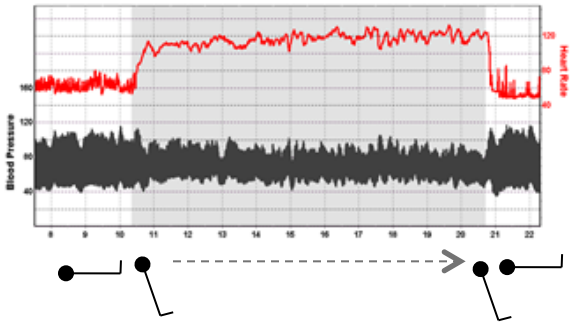


Neurogenic orthostatic hypotension



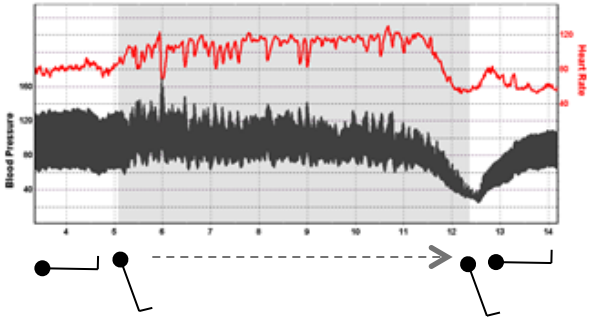
Autonomic failure

Postural tachycardia syndrome (POTS)



Hypovolemia
Deconditioning
Venous pooling
Limited autonomic neuropathy
Anxiety

Reflex (neurally mediated) syncope



Constitutional
Hypovolemia
Deconditioning
Venous pooling
Anxiety

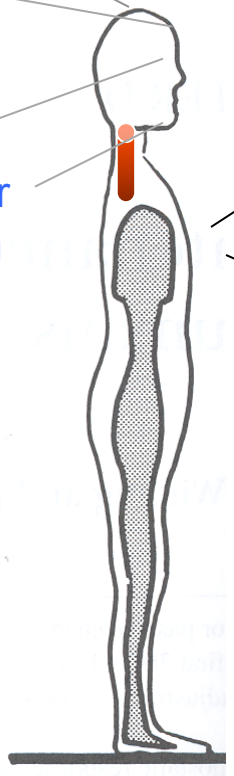
Orthostatic Intolerance

Lightheadedness
Presyncope-syncope

Confusion

Blurred vision

Neck and shoulder
(coat-hanger) pain



No evidence
of sympathetic
activation

→ Autonomic failure

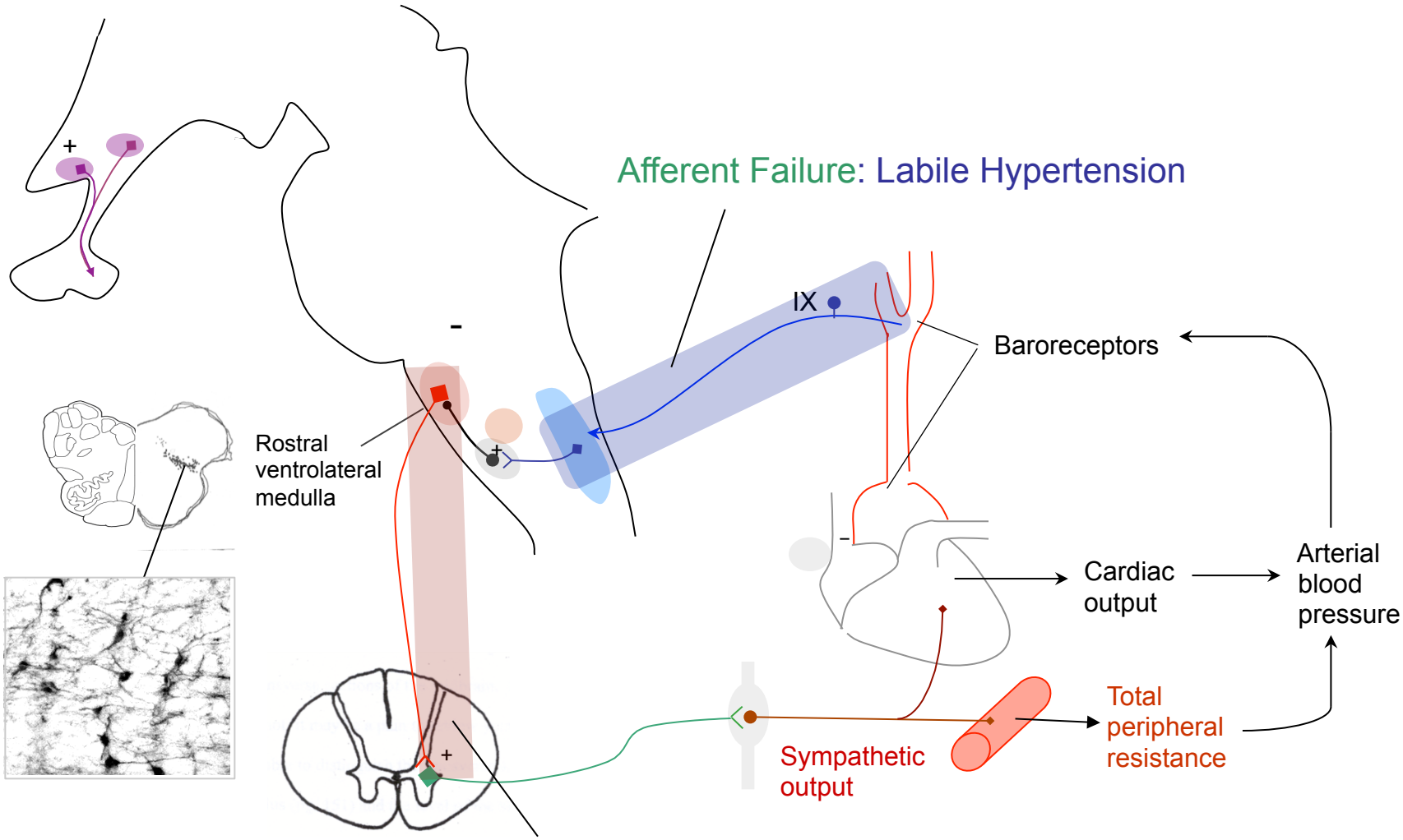
Sympathetic activation
-Palpitations
- Pallor
- Sweating
- Tremor
- Hyperventilation

→ POTS
Reflex syncope

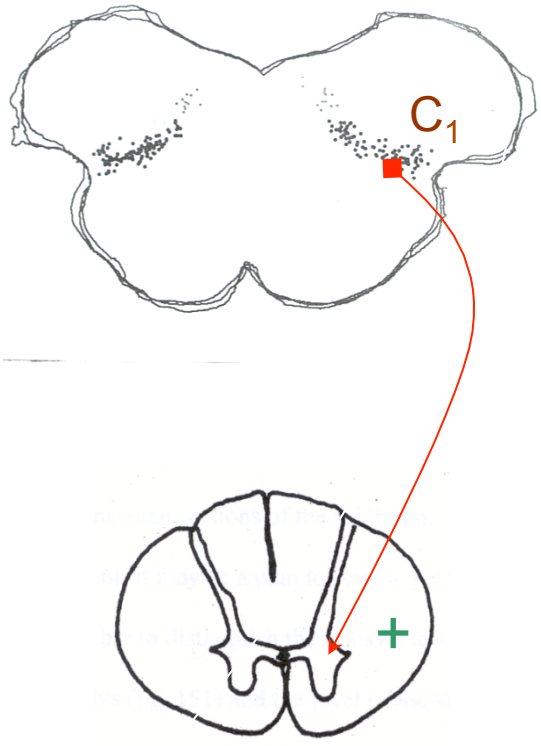
Generalized fatigue

Exercise intolerance

Central Baroreflex Disorders as Cause of Orthostatic Intolerance



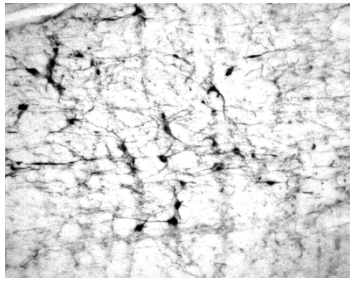
Involvement of the Baroreflex Sympathetic Pathway in MSA

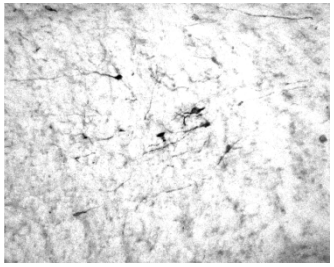


Control

MSA

RVL





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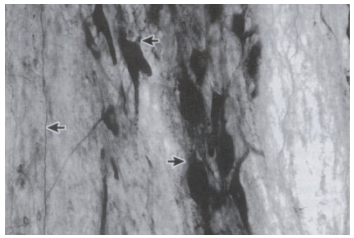
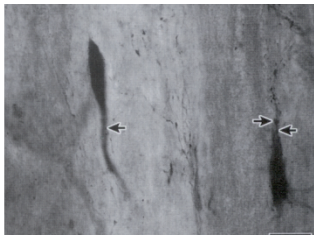
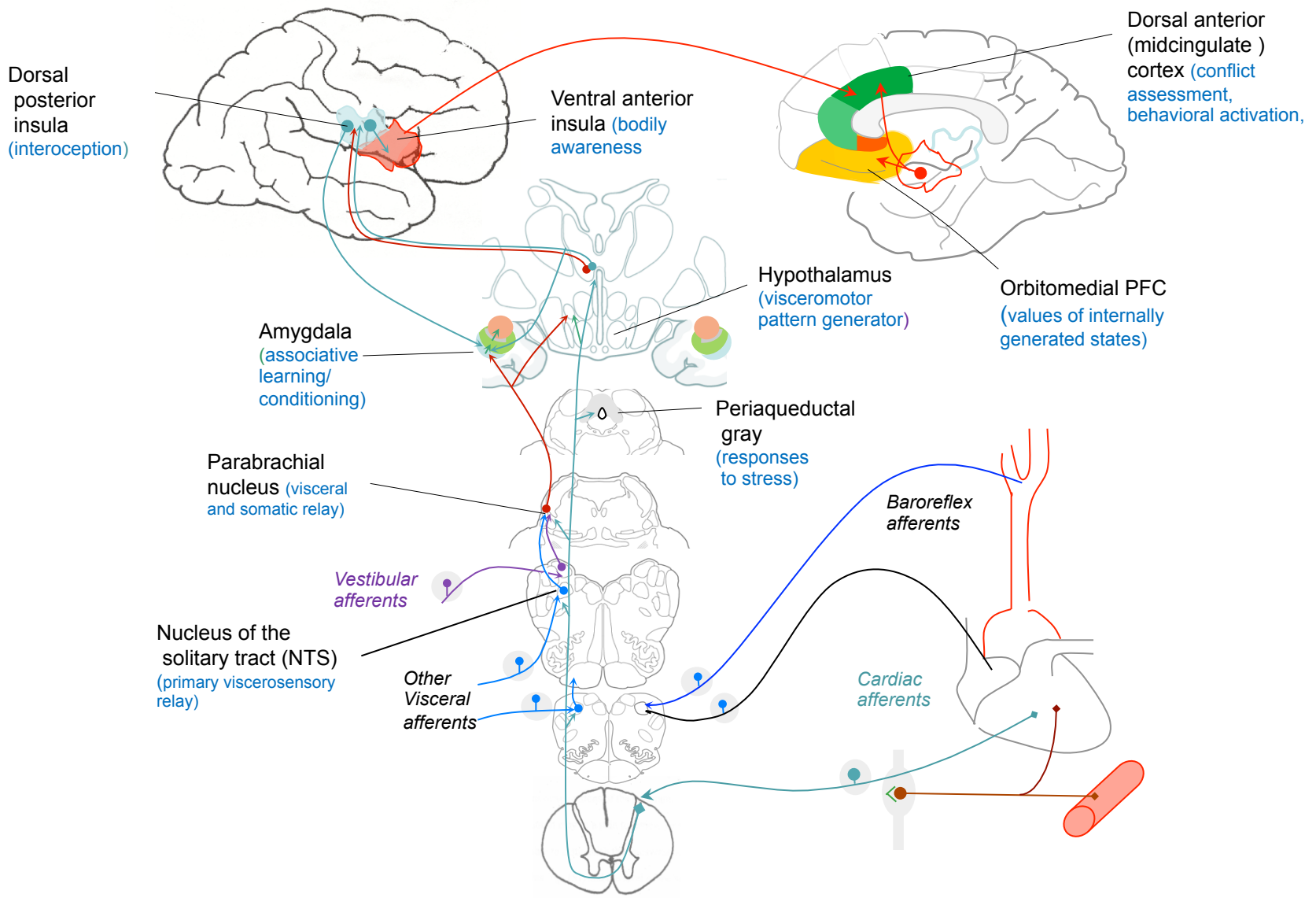




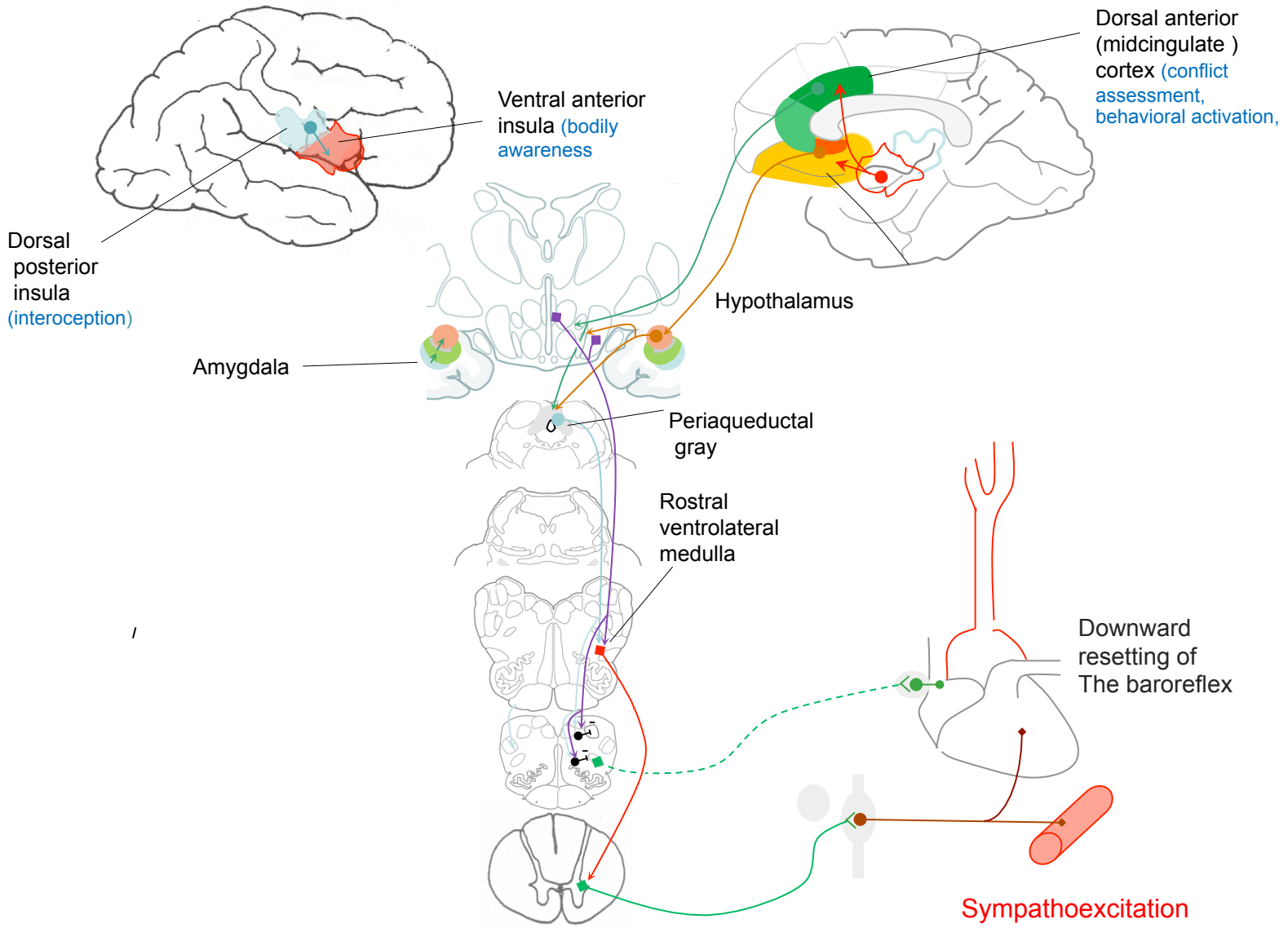
Central Mechanisms for Orthostatic Intolerance

- In addition to central autonomic failure, central mechanisms also provide the basis for symptoms in patients with other forms of orthostatic intolerance, including POTS and orthostatically-induced reflex syncope
- The mechanisms involved include
  - interoception (body feeling)
  - behavioral conditioning
  - behavioral arousal
  - stress response
- Interoceptive inputs are relayed via the dorsal horn and NTS to the parabrachial nucleus which conveys these inputs to the
  - hypothalamus (stress response),
  - amygdala (conditioned responses) and, via the thalamus,
  - insular cortex (awareness of body feelings) and
  - dorsal anterior cingulate cortex (behavioral arousal)
- Both directly and via the periaqueductal gray, these CAN areas
  - trigger sympathoexcitation
  - reduce baroreflex gain

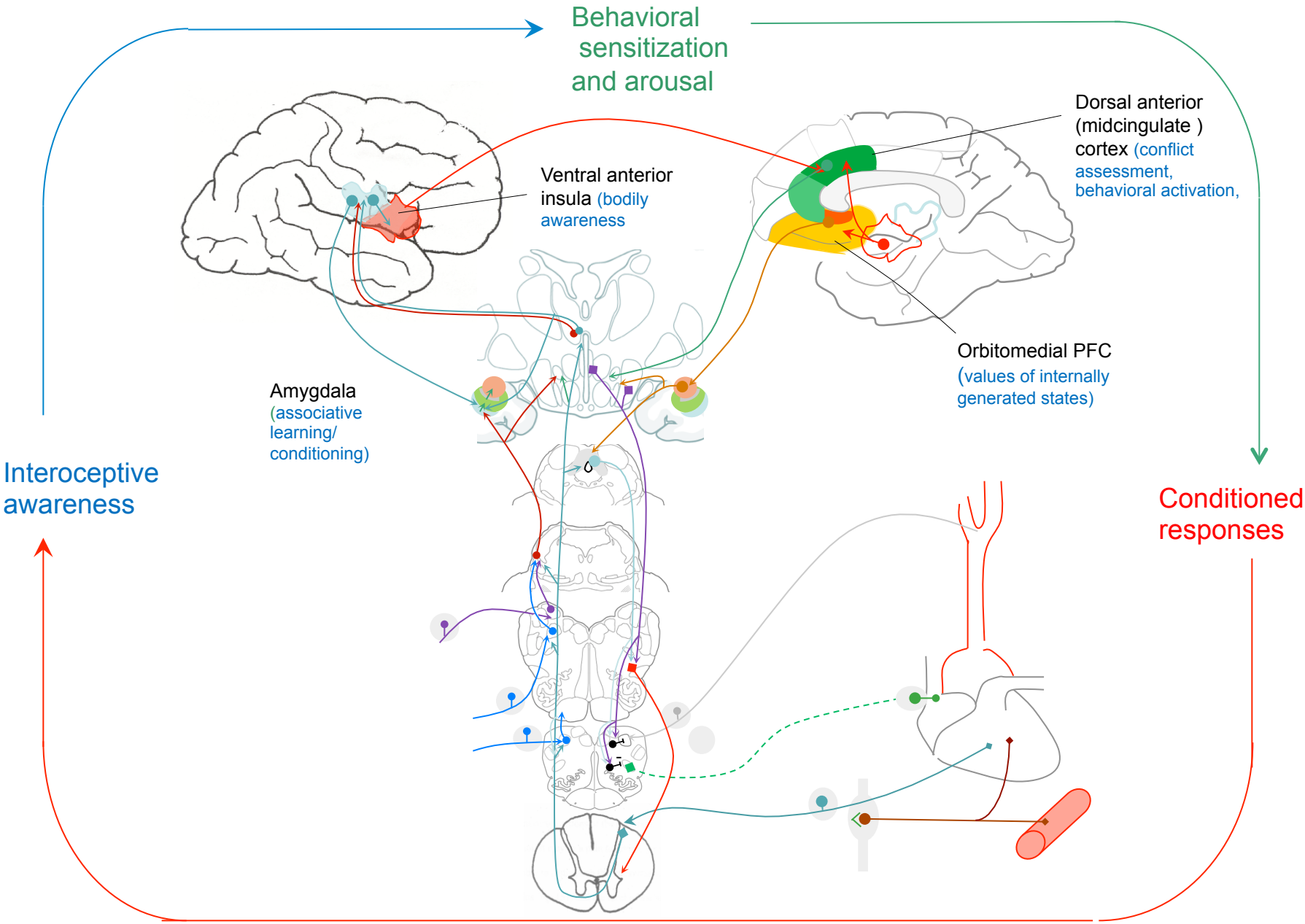
Interoceptive System



Hemodynamic Response to Emotion and Stress



Mechanisms of Chronic Orthostatic Intolerance



References

Wieling W and Shepherd JT. Initial and delayed circulatory responses to orthostatic stress in normal humans and in subjects with orthostatic intolerance *Int Angiol*. 1992, 11:69

Benarroch EE. The arterial baroreflex: functional organization and involvement in neurologic disease. *Neurology* 2008; 71:1733

Carter JR, Ray CA. Sympathetic responses to vestibular activation in humans. *Am J Physiol Regul Integr Comp Physiol.* 2008;294(3):R681

Saper CB. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *Annu Rev Neurosci.* 2002;25:433-469.

Craig AD. Interoception: the sense of the physiological condition of the body. *Curr Opin Neurobiol.* Aug 2003;13(4):500-505.

Critchley HD. Neural mechanisms of autonomic, affective, and cognitive integration. *J Comp Neurol.* Dec 5 2005;493(1):154-166.

Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. *Mayo Clin Proc* 2012, 87:1214