The Role of the Vagus in Esophageal Hypersensitivity – *A Potential Therapeutic Target*

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Sleep Disorders Related to Chronic GERD, February 2017

Gastro-oesophageal reflux disease

- Gastro-oesophageal reflux disease is a common and chronic condition

- At least 20% of adults in the United States report having heartburn once a week or more - *Drossman et al, Dig Dis Sci 1993*

- The symptoms of gastro-oesophageal reflux disease are variable but include heartburn and chest pain

Background 1 – Pain – the Ubiquitous Human Experience

Background 2 – One man's pain is another's...

Background 3 – Pain in the absence of injury...

Chest Pain – *As a Visceral Pain*

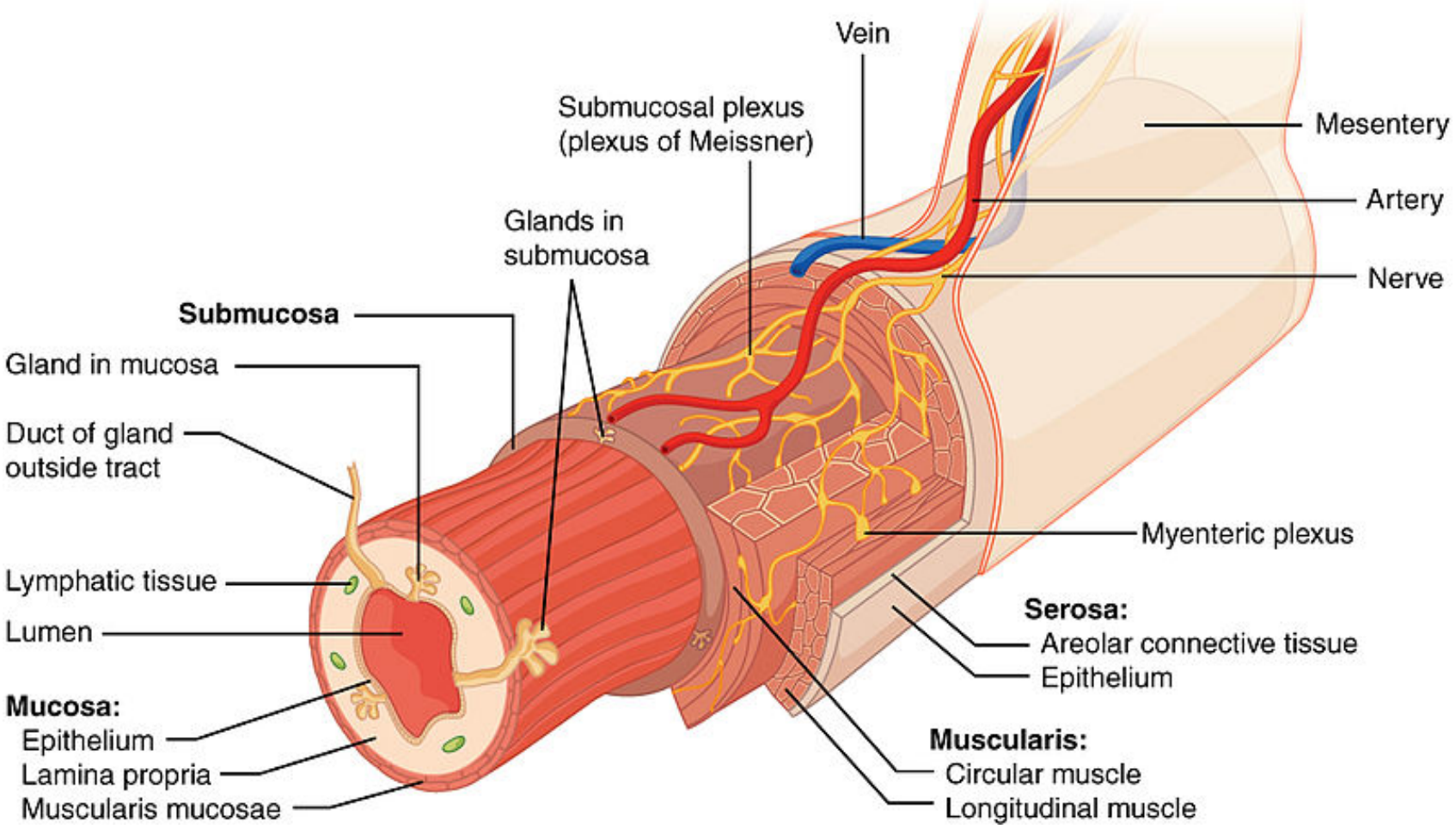
- The experience of oesophageal pain is highly individual, with a multitude of factors accounting for this variability - *Farmer et al, Pain 2013*

- Amongst these is dysfunction of the autonomic nervous system (ANS) – *Tougas et al, Gut 2007*

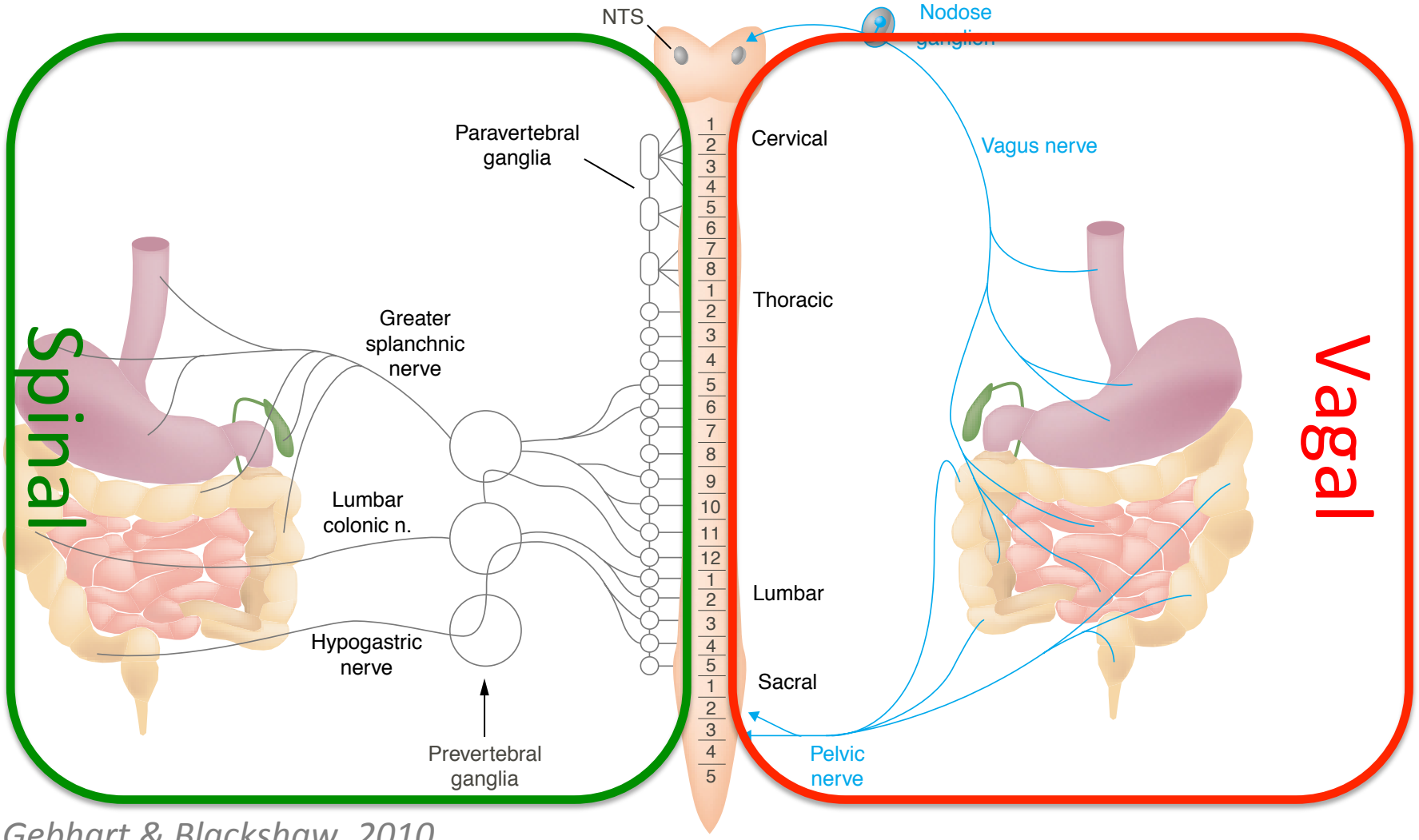
- ANS has a critical role in visceral pain perception through it multiple interactions at many levels of the brain gut axis *Farmer & Aziz, in Yamada's Textbook of Gastroenterology, 7th edition, ed. Podolsky et al.*

- Accumulating evidence that the parasympathetic nervous system (PNS) is anti-nociceptive – *Craig, Nat Rev Neuroscience 2002*

The Enteric Nervous System



The Peripheral Afferent Pathways…



Gebhart & Blackshaw, 2010

The Peripheral Afferent Pathways…

Spinal

PERCEPTION

PAIN

INHIBITION OF DIGESTIVE FUNCTION

Vagal

PHYSIOLOGICAL SENSATION

HUNGER, SATIETY etc

REFLEX CONTROL

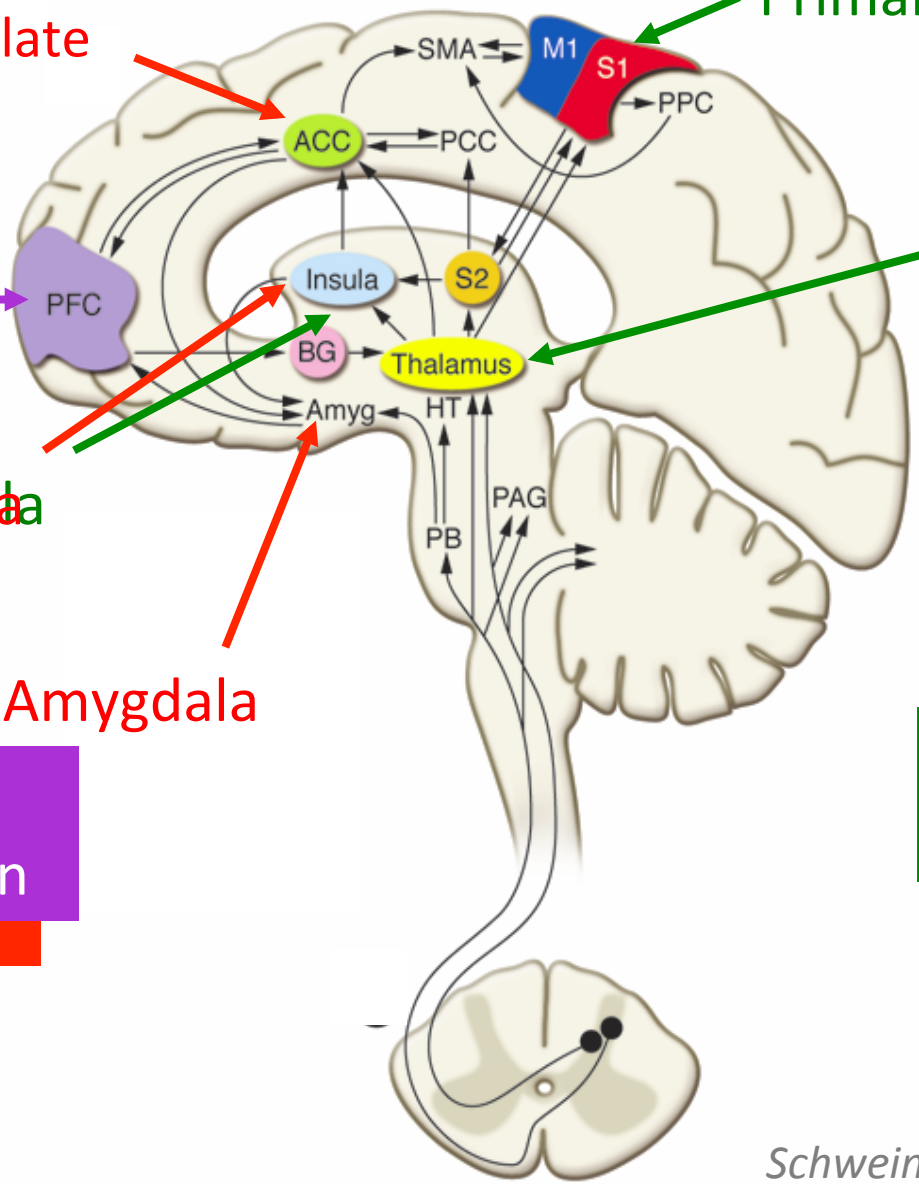
BEHAVIOUR

Anterior Cingulate Cortex (ACC)

Primary sensory area

Prefrontal Cortex

Thalamus



Anterior Insula

Amygdala

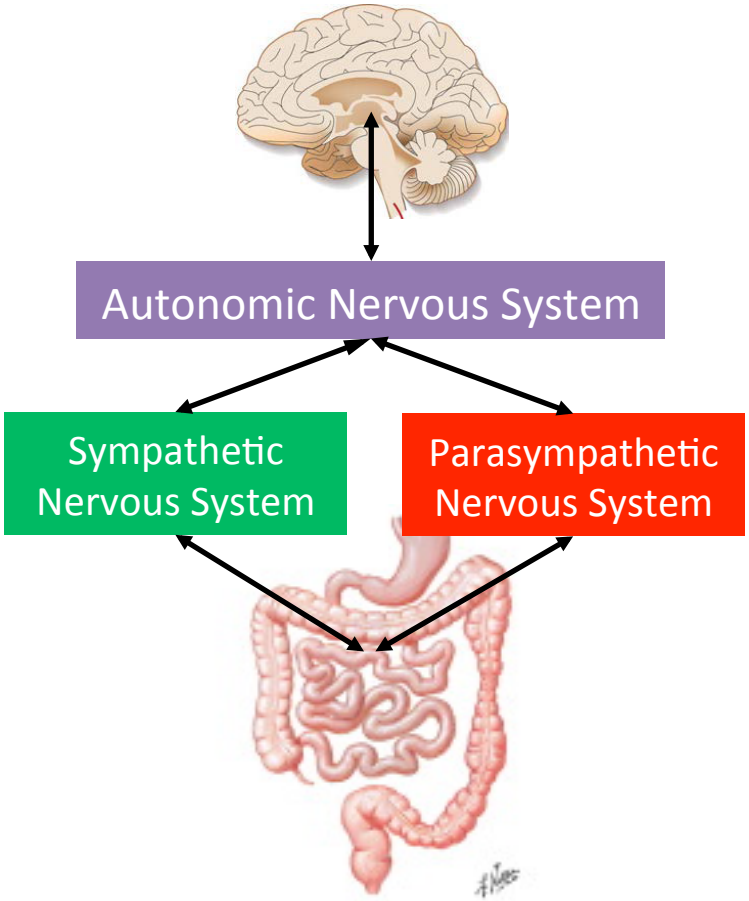
Cognitive Modulation

Affective

Sensory discrimination

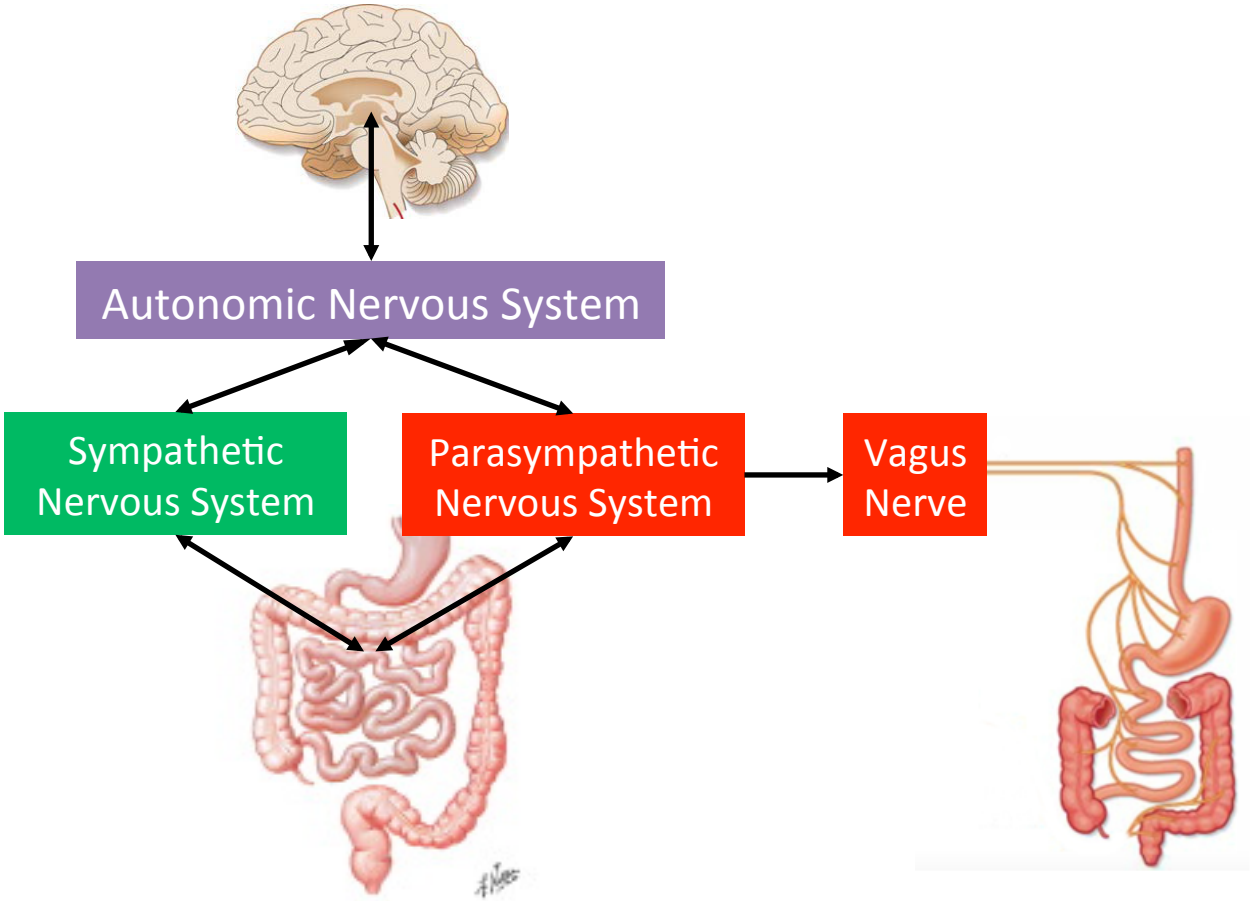
Schweinhardt and Bushnell, 2010

The Autonomic Nervous System



Adapted from Farmer & Aziz, Oxford Textbook of Medicine 2016

The Autonomic Nervous System



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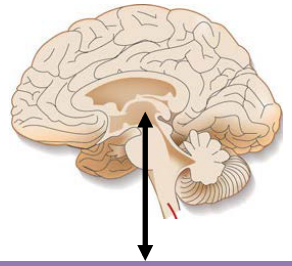
The Autonomic Nervous System

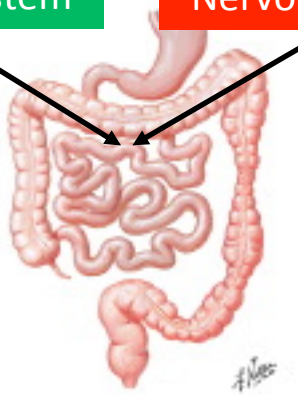


Autonomic Nervous System

Sympathetic Nervous System

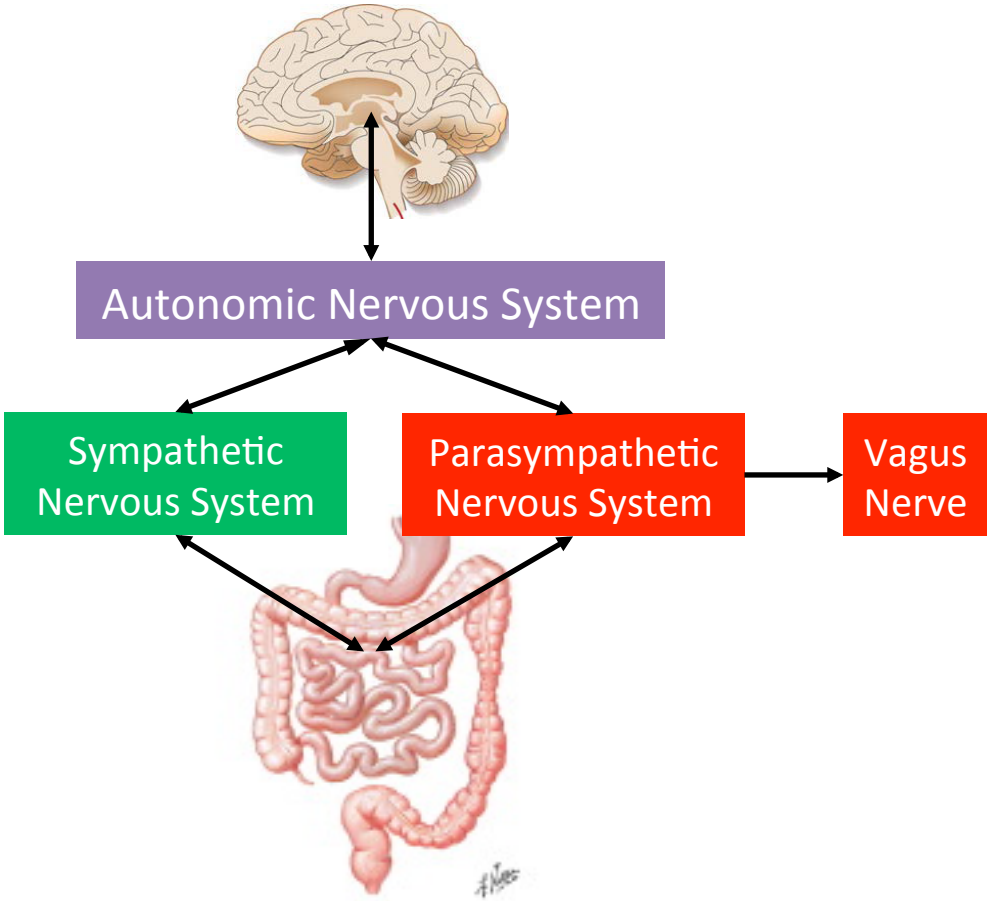
Parasympathetic Nervous System

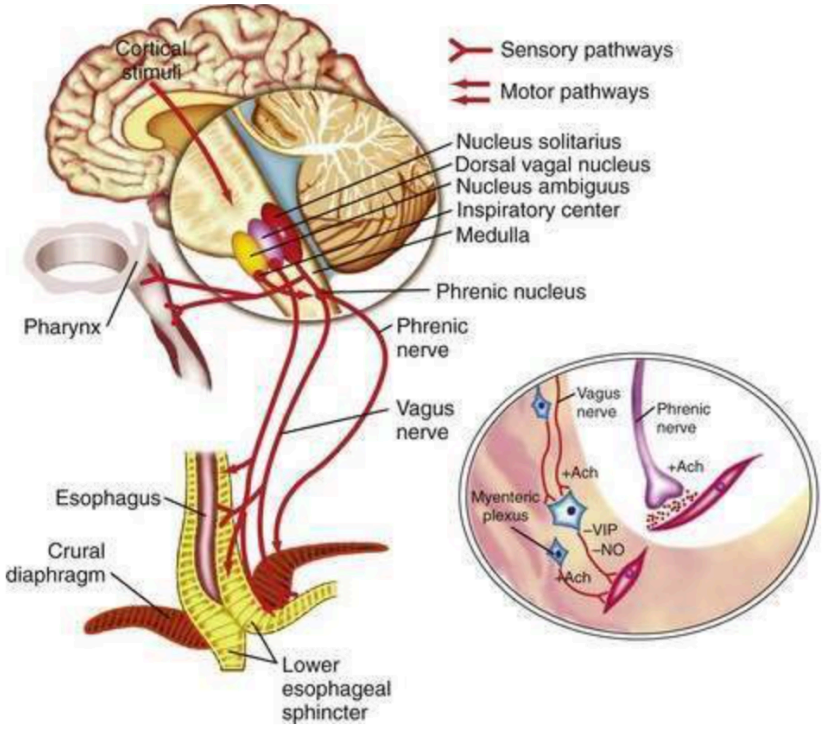
Vagus Nerve



Adapted from Farmer & Aziz, Oxford Textbook of Medicine 2016

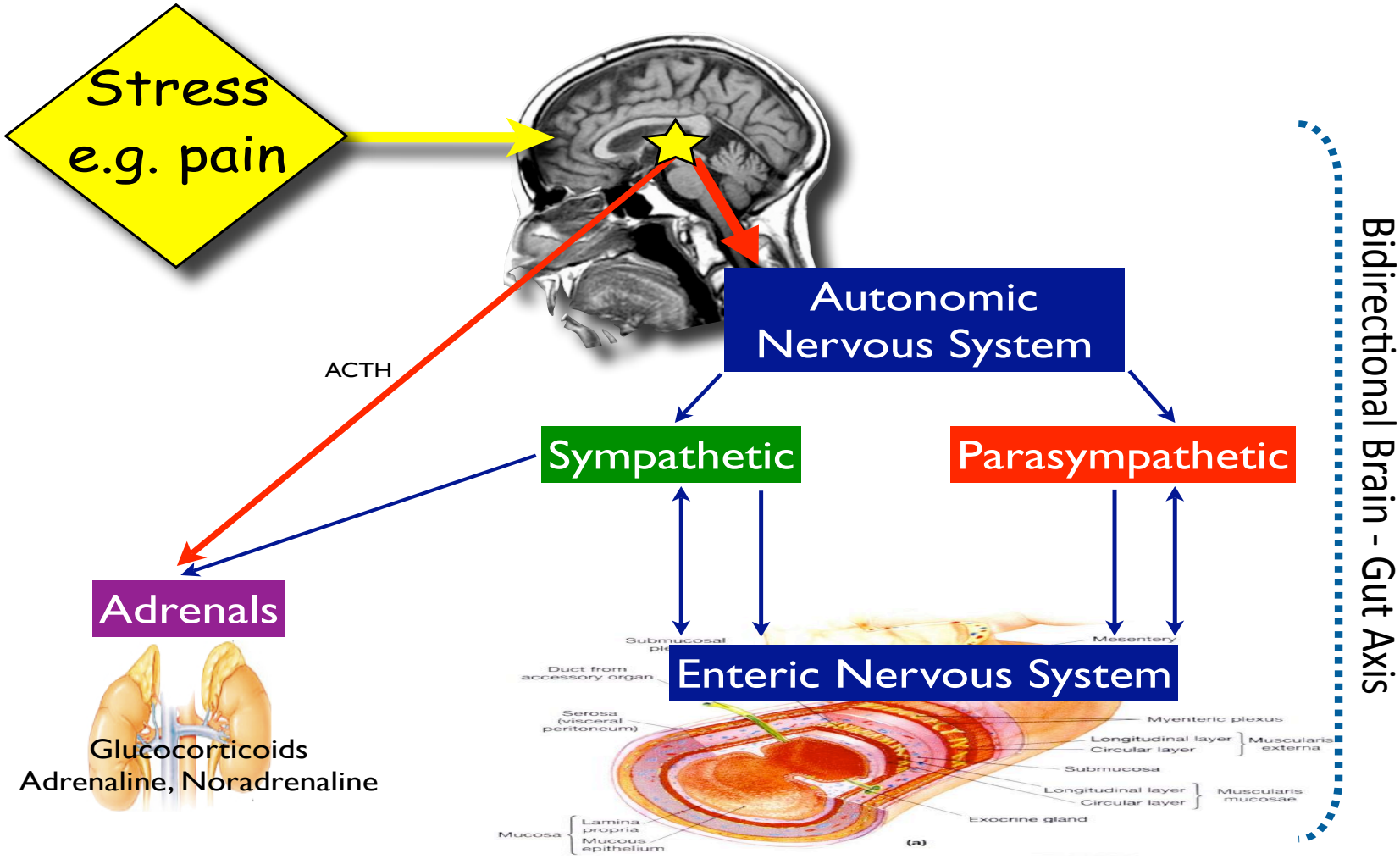
The Vagus and the Lower Oesophageal Sphincter





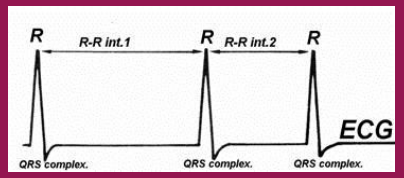
Adapted from Farmer & Aziz, Oxford Textbook of Medicine 2016

Brain Gut Axis



Current Widely Utilised Measures of Autonomic "Tone"

Time Domain Anaylsis

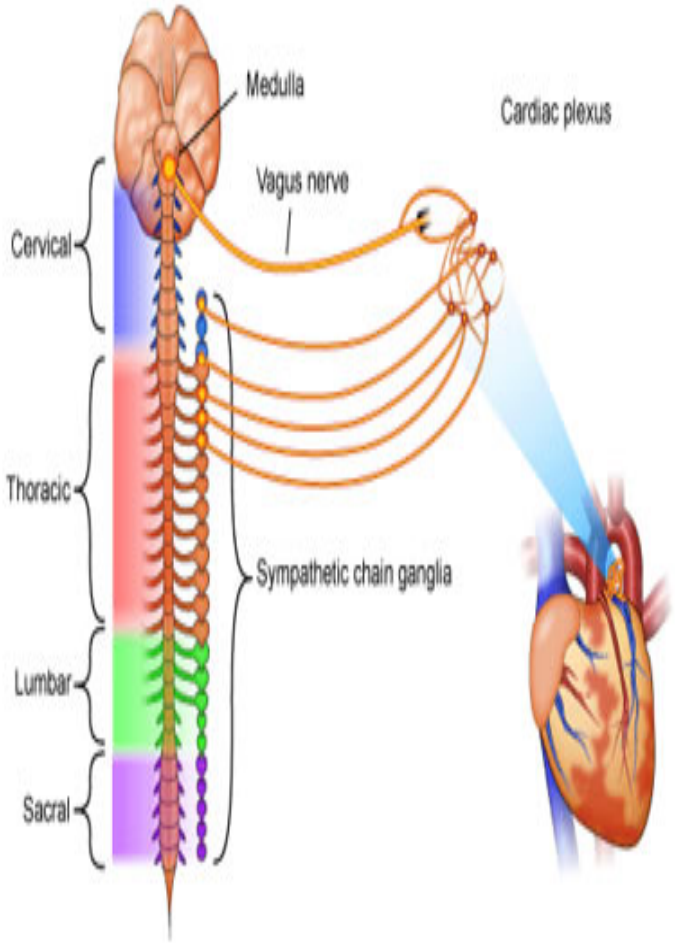


Examples

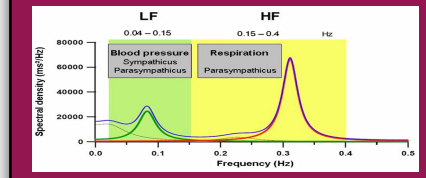
SDNN (ms)
SDANN (ms)
pNN50 (%)
Triangular Index (ms)
RMSSD (m/s)

Challenges

Limited statistical power for the evaluation of short-term recordings of less than five minutes.



Spectral Analysis



Examples

Ultra-low frequencies (<0.003 Hz)
Very-low LF (0.003-0.05 Hz) Mid-LF (0.05-0.15 Hz)
HF (0.15-0.4 Hz).
LF:HF Balance

Challenges

Stationarity assumptions regarding respiratory frequency

Limited temporal resolution

Controversy as to what the measures mean

BRAINSTEM

Sympathetic Sudomotor
Skin Conductance Responses

Parasympathetic Afferent
Cardiac Sensitivity to the Baroreflex

Parasympathetic Efferent
Cardiac Vagal Tone

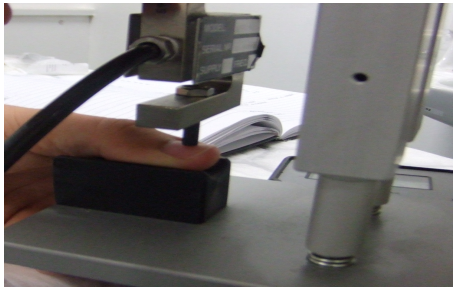
Sympathetic Cardiomotor
Cardiac Sympathetic Index

Mixed Measures
Heart rate
Blood pressure

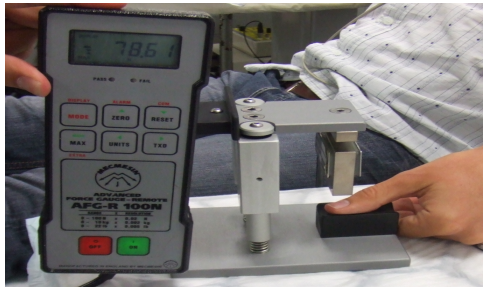
Baroreceptors
Pulmonary Stretch Receptors
Arterial chemoreceptors

Functional Chest Pain

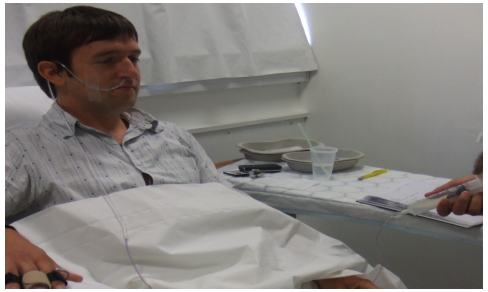
- Case control study of patients with functional chest pain – *Farmer et al, Neurogastro and Motility 2014*



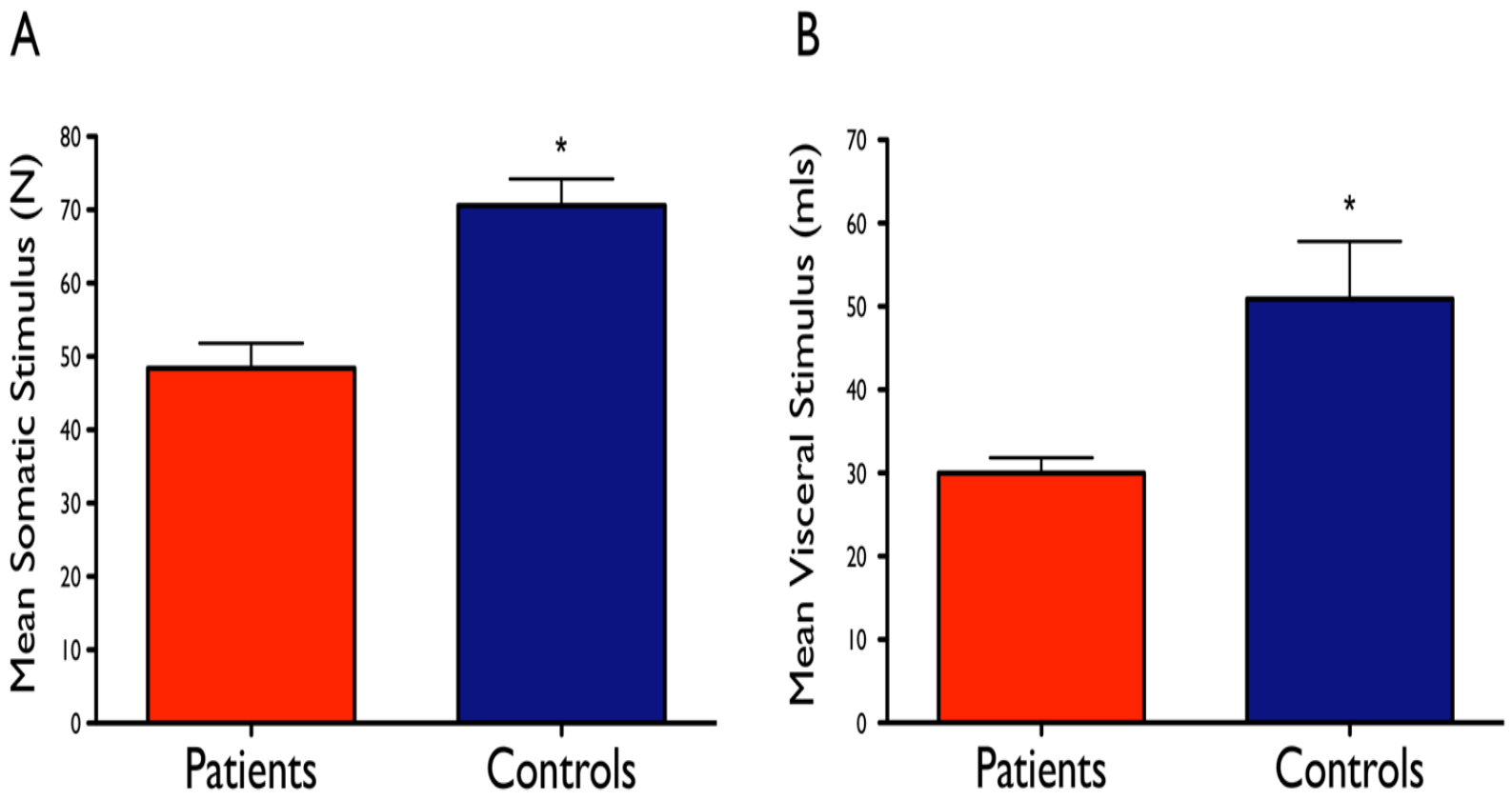
Somatic Pain



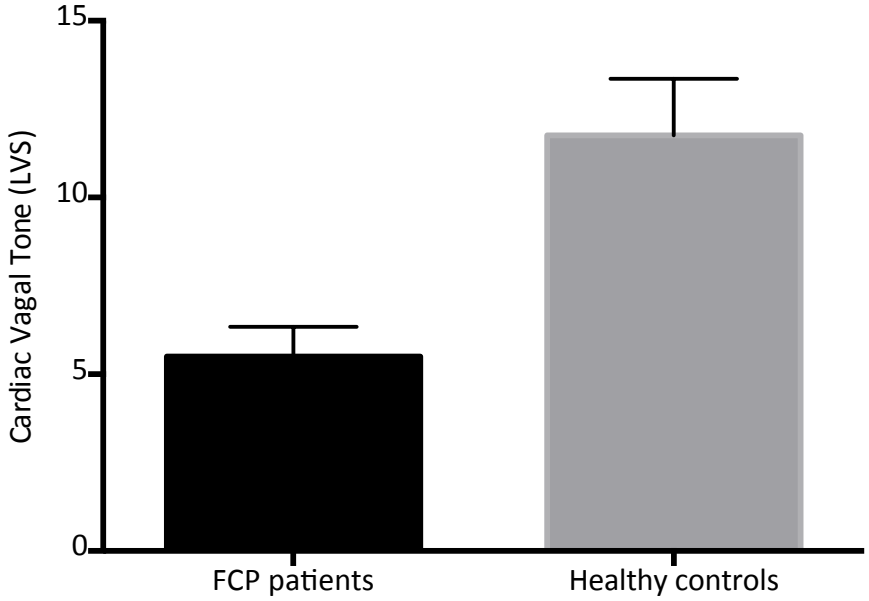
Visceral Pain

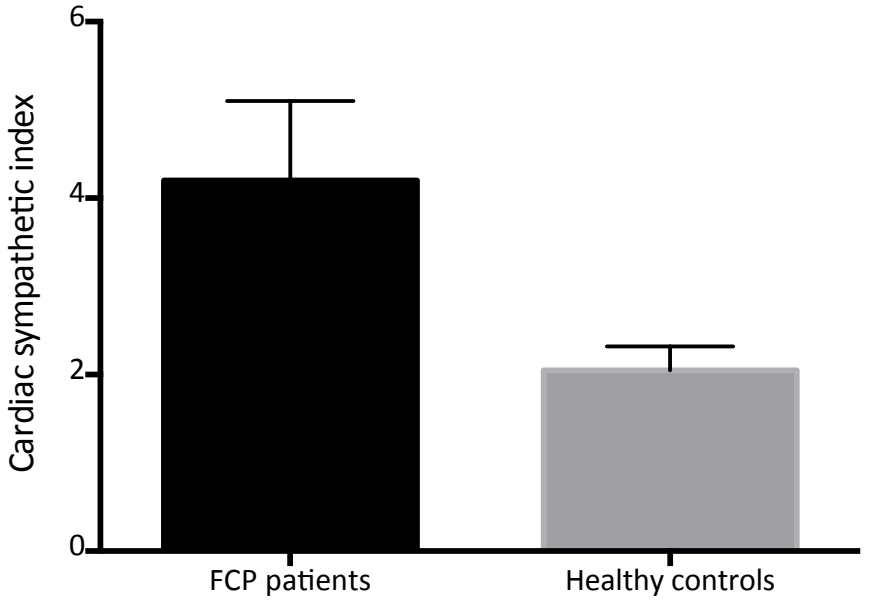


Behavioural Responses to Pain in FCP



Baseline “Autonomic Tone” in FCP





Other Evidence for Autonomic Dysfunction

- NCCP – higher baseline HR and lower vagal activity & in response to acid infusion vagal outflow increases in acid sensitive patients – *Tougas et al, Gut 2001*

- GORD - heightened sensitivity to oesophageal acid infusion associated with reduced vagal tone during the infusion – *Chen & Orr, J Gastro Hep 2004*

- EE vs. NERD - lower resting vagal tone in patients with EE vs. NERD – *Cunningham et al, Gut 1999*

Modulating Vagal Tone…

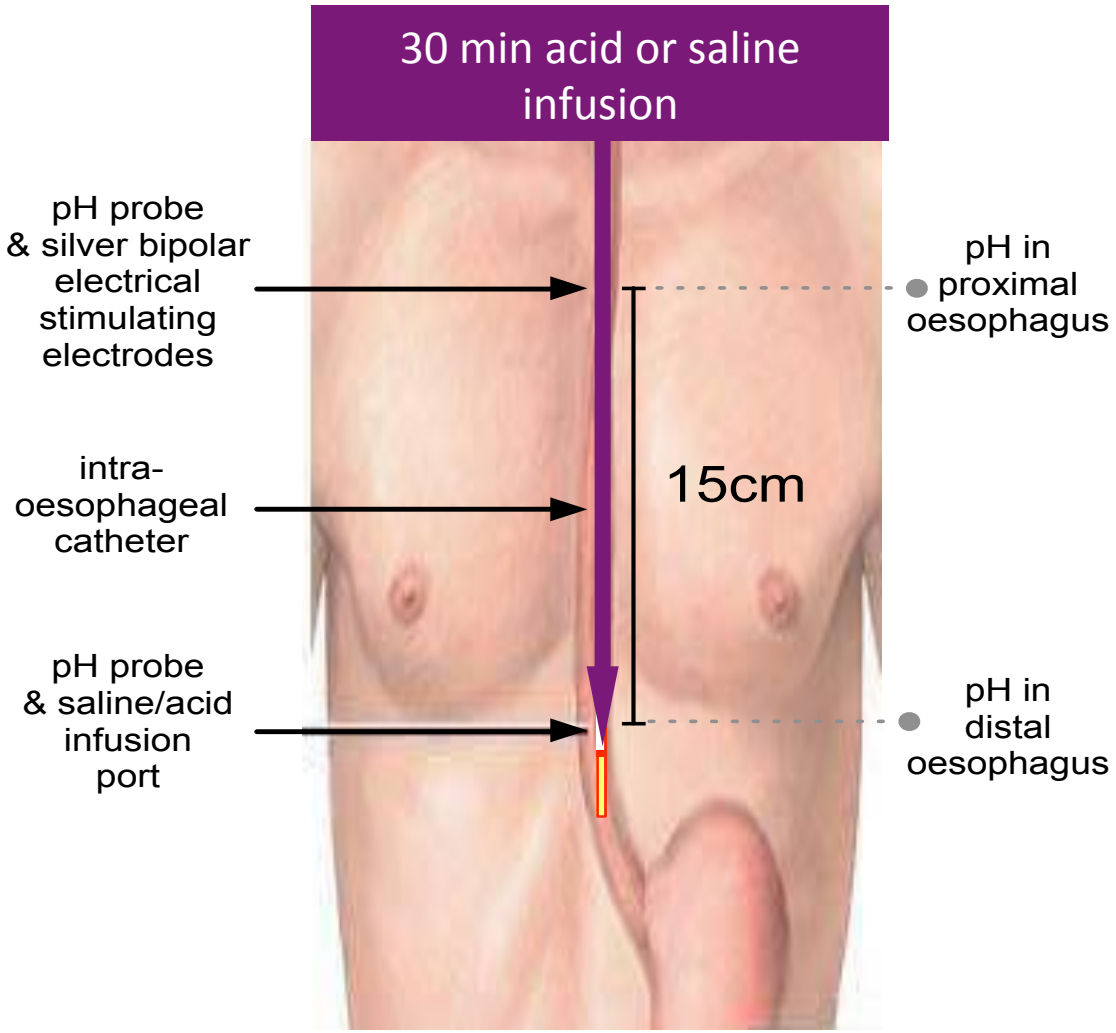
- Vagal nerve activity can be enhanced:-
  - Physiologically - through slow deep breathing
  - Electrically – using vagal nerve stimulation

- Deep slow breathing is common to many complimentary therapies which have been shown to efficacious in treating chronic visceral pain syndromes – *Palsson & Whitehead, CGH 2013*

- The biological mechanism of action of these therapies is largely unexplored – *Matteoli et al, Gut 2013*

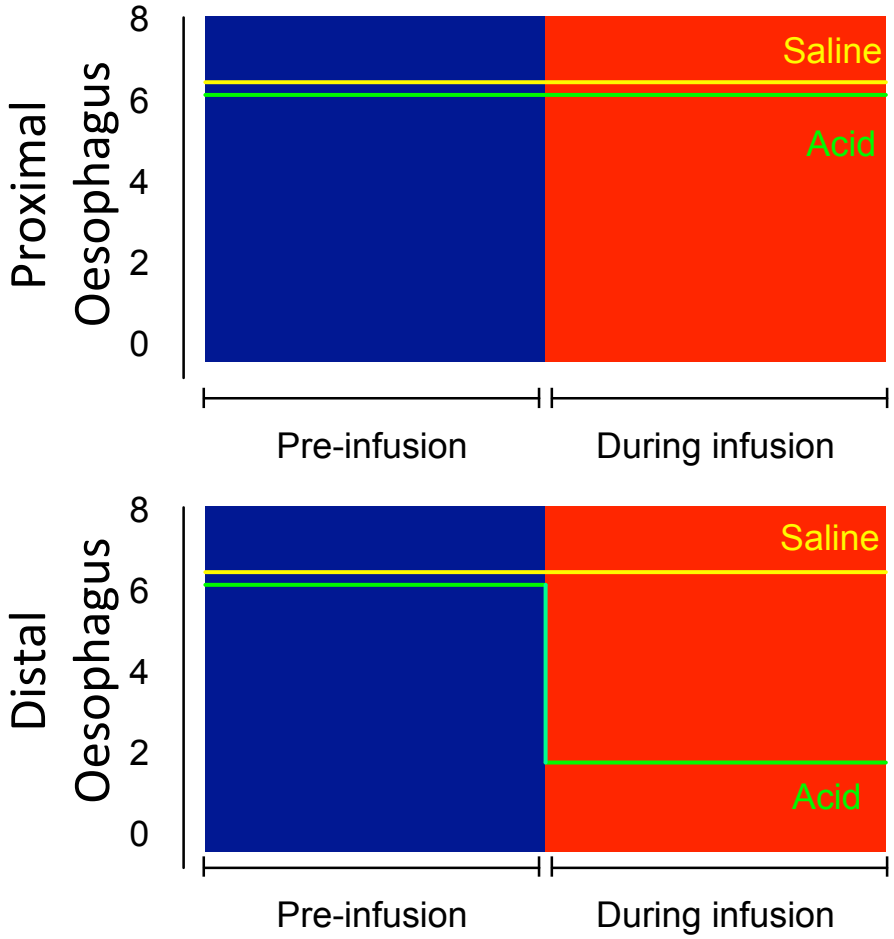
Oesophageal Pain Hypersensitivity Model

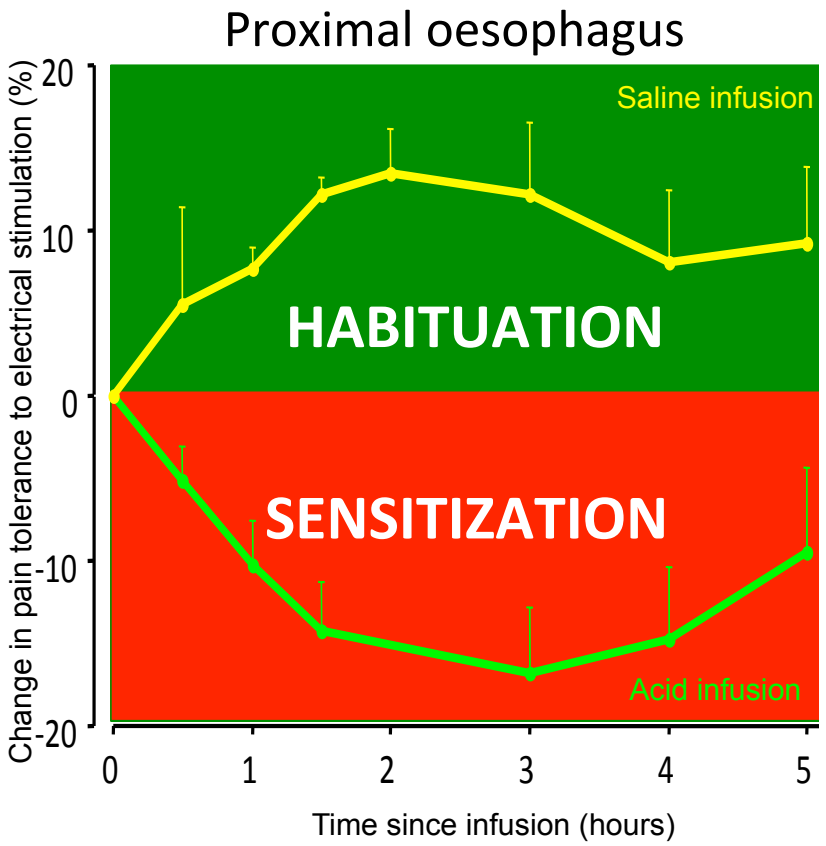
Pain tolerance levels to electrical stimulation measured in the proximal oesophagus at baseline



Pain tolerance levels to electrical stimulation measured in the proximal oesophagus at 30 minutes intervals post infusion

Oesophageal Pain Hypersensitivity Model

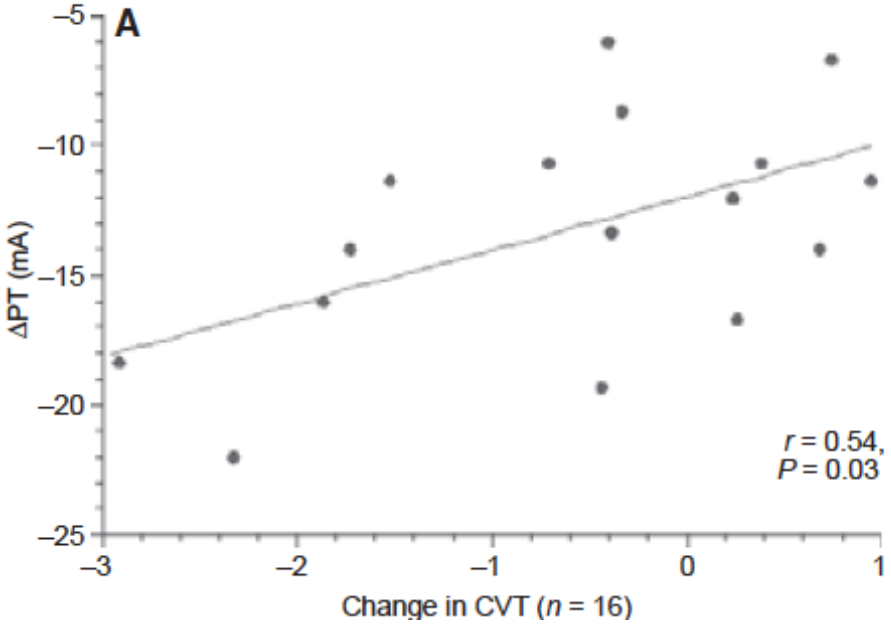




Sarkar et al, Lancet 2000

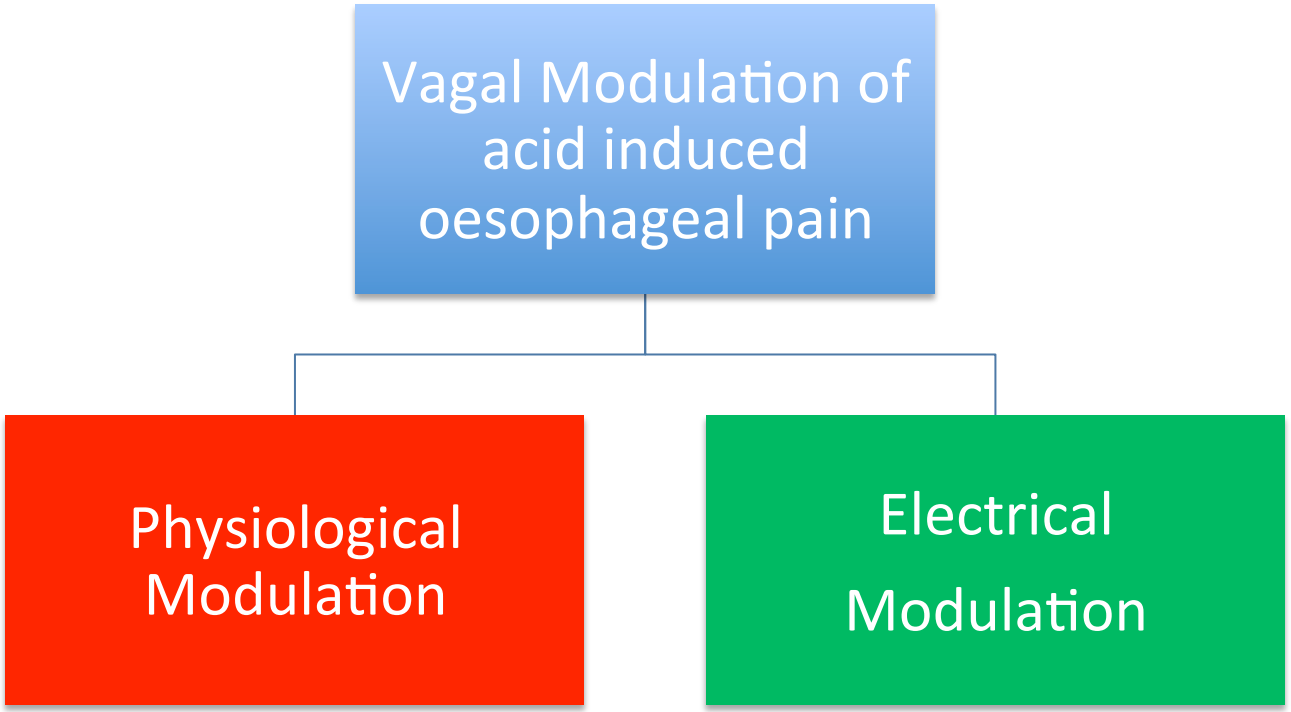
Autonomic Effect of Distal Oesophageal Acidification

- This model does not induce oesophageal hyperalgesia in all subjects – i.e. there is considerable inter-individual variability
- Using this model cardiac vagal tone was measured and compared to the change in pain tolerance thresholds (sensitization)
- Relationship demonstrated between the change in vagal tone and the degree of sensitization



Sharma et al, NGM 2012

Studies Exploring the Effect of Vagal Modulation



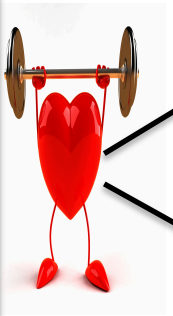
Hypothesis & Aims

- We hypothesized that physiologically elevating vagal tone may have anti-hyperalgesic and analgesic properties in the human oesophagus

- We aimed to test this hypothesis by performing physiological and pharmacological modulation of vagal tone in the oesophageal pain hypersensitivity model

- Encompassed two studies:-
  - *Physiological Modulation - Study 1 – evaluating the effect of a deep breathing protocol vs. sham breathing – London, UK*
  - *Pharmacological Modulation Study 2 – evaluating the effect of atropine vs. placebo during deep breathing – Aalborg, Denmark*

Methods –*Effect of Deep Breathing*

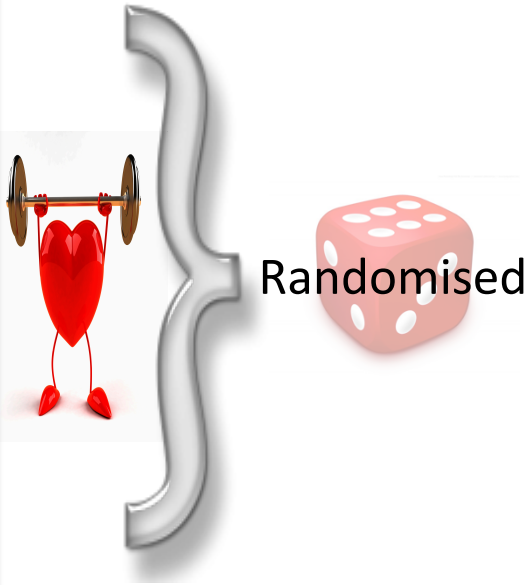


Sympathetic → Skin conductance responses

Parasympathetic → Cardiac vagal tone

Subjects were intubated with the catheter and baseline electrical thresholds measured in the proximal oesophagus

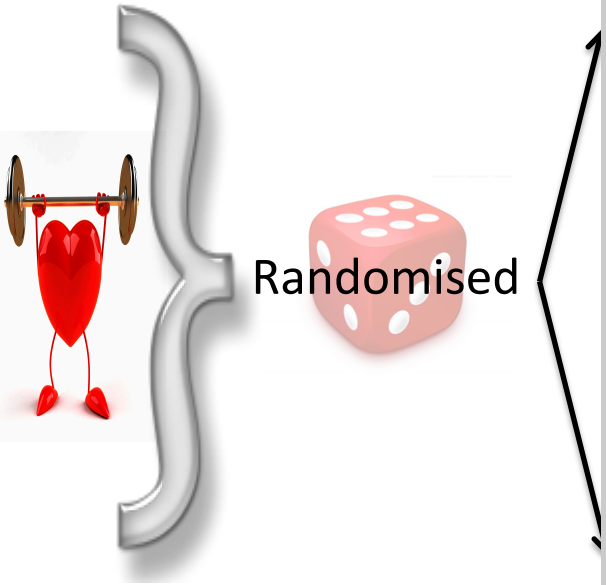
Methods –*Effect of Deep Breathing*



Randomised

Subjects crossed over to alternate intervention >6 weeks to prevent any carryover effect

Methods – *Effect of Atropine*

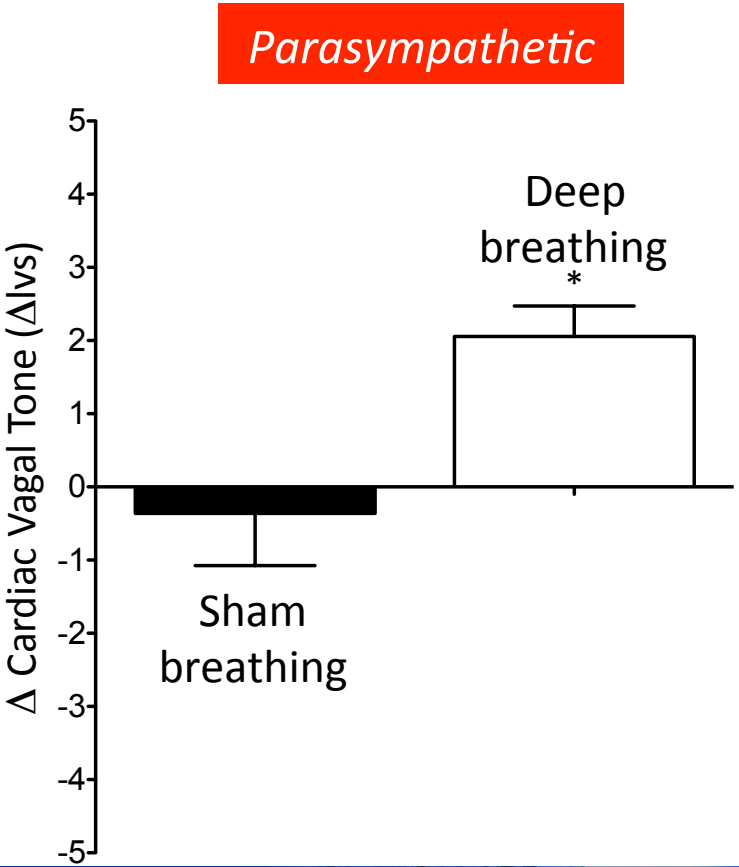


Subjects crossed over to alternate intervention >6 weeks to prevent any carryover effect

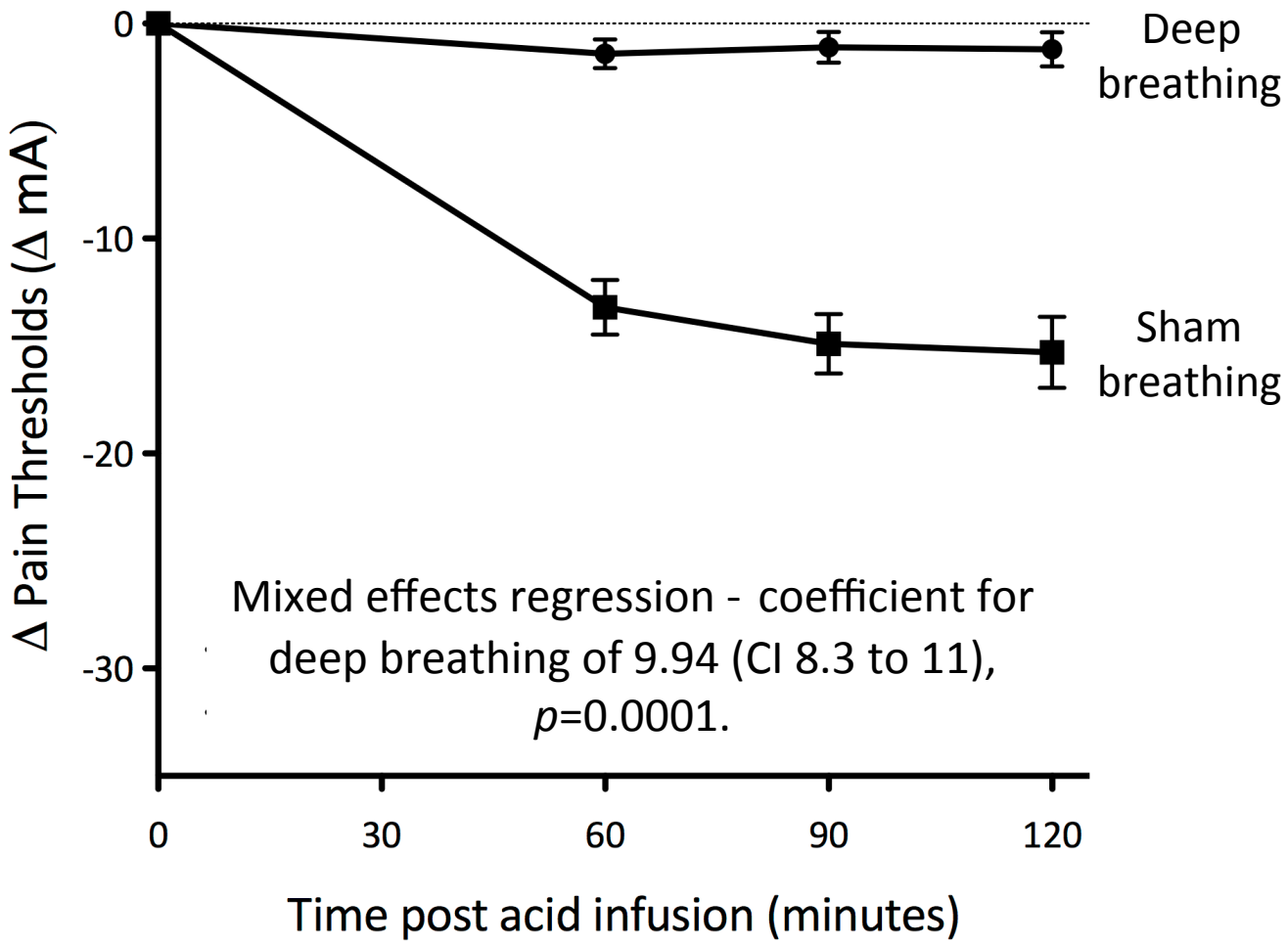
IB: Atropine is an anti-cholingeric (thus blocks PNS tone)
nd 0.5mg was administered as an infusion over 30 minutes
s. placebo infusion of saline

Results –*Effects of Deep Breathing*

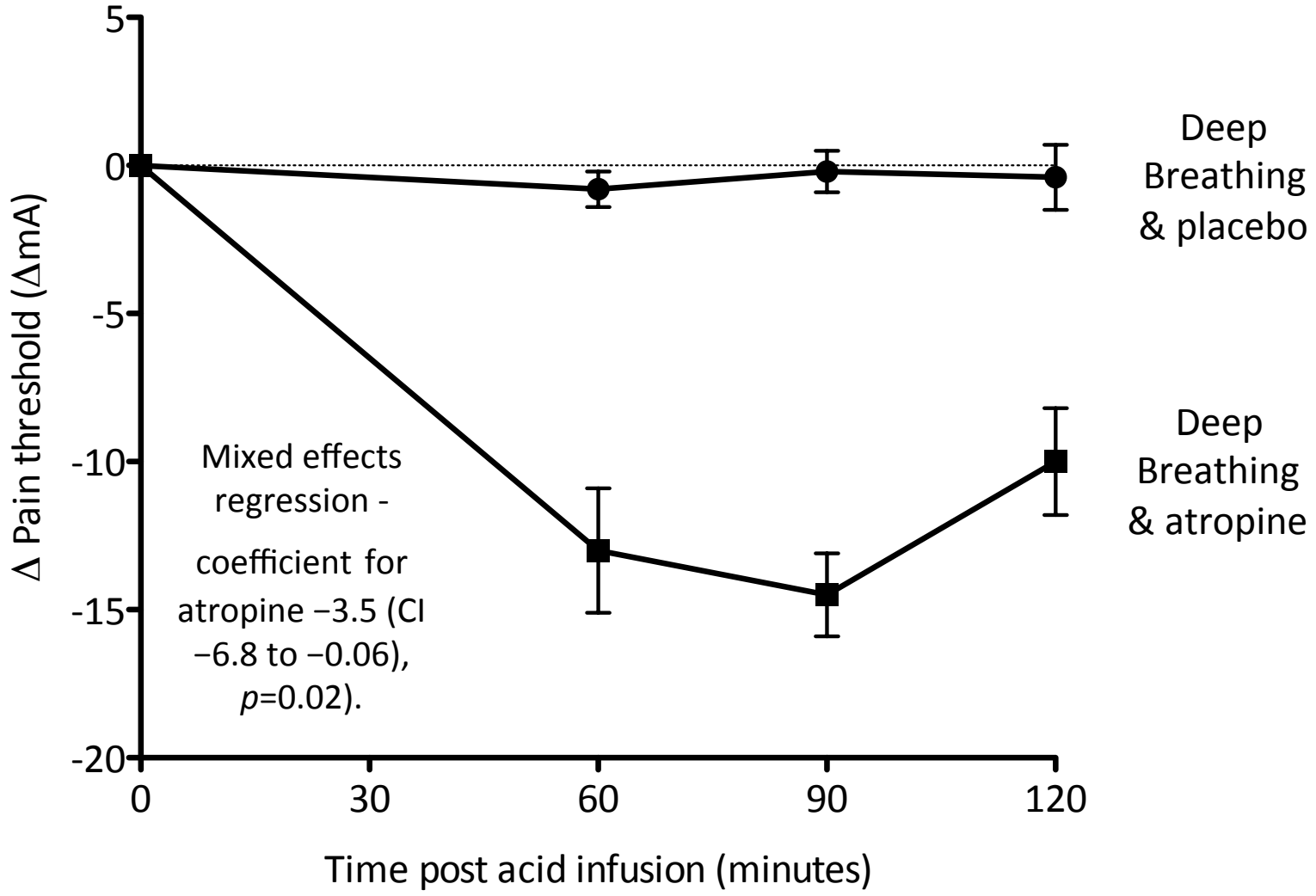
- 55 healthy subjects (31 men, mean age 26 years, range 18–48 years)



Results –*Effects of Deep Breathing*



Results — *Effects of Atropine/Placebo*



Conclusions – *Physiological Modulation*

- *Physiologically* elevating parasympathetic nervous system tone, using deep breathing, prevents the development of oesophageal pain hypersensitivity in a validated human model

- *Pharmacologically* this anti-hyperalgesic effect of deep breathing is ameliorated by antagonizing the rise in PNS tone with atropine

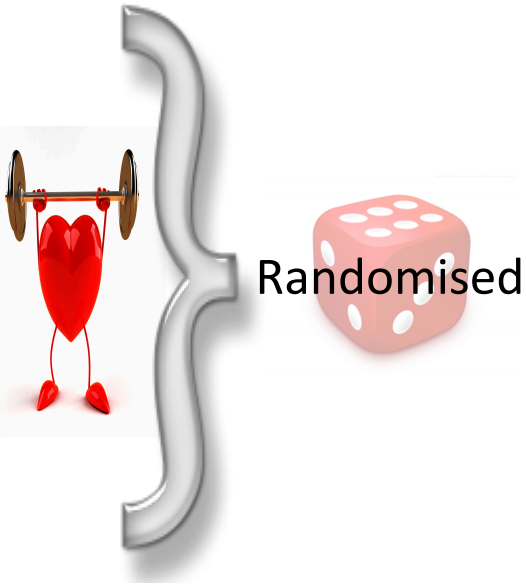
Hypothesis, Aims & Design

- We hypothesized that the anti-hyperalgesic properties of the vagus in the oesophagus could be exploited using transcutaneous stimulation of the auricular branch of the vagus nerve

- We aimed to test this hypothesis by performing electrical modulation of PNS tone in a validated model of oesophageal pain hypersensitivity

- Double blind, randomized, placebo controlled crossover study in healthy subjects

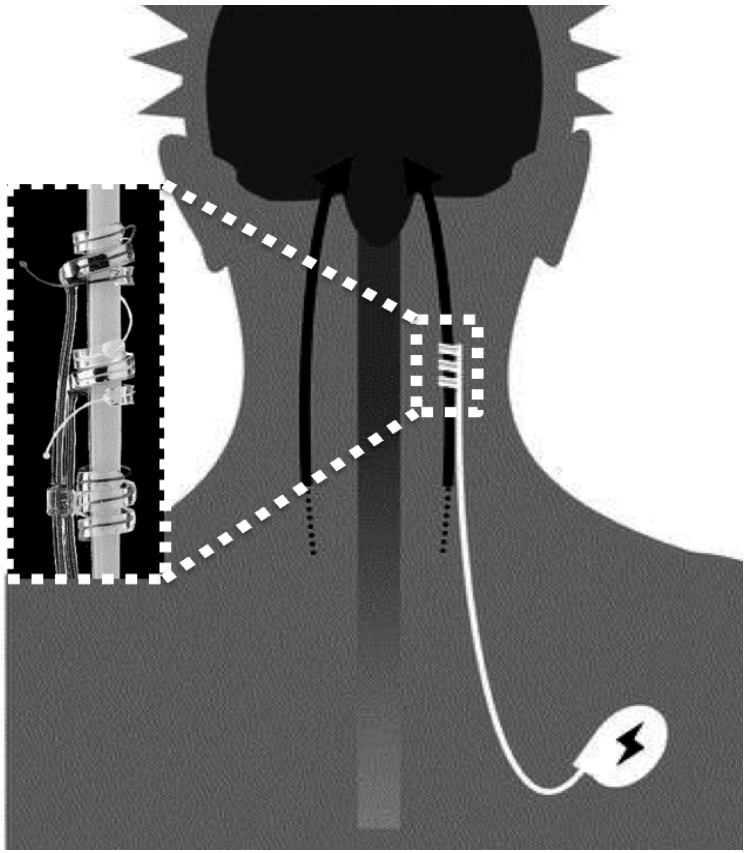
Methods



Subjects crossed over to alternate intervention >6 weeks to prevent any carryover effect

Methods

Invasive

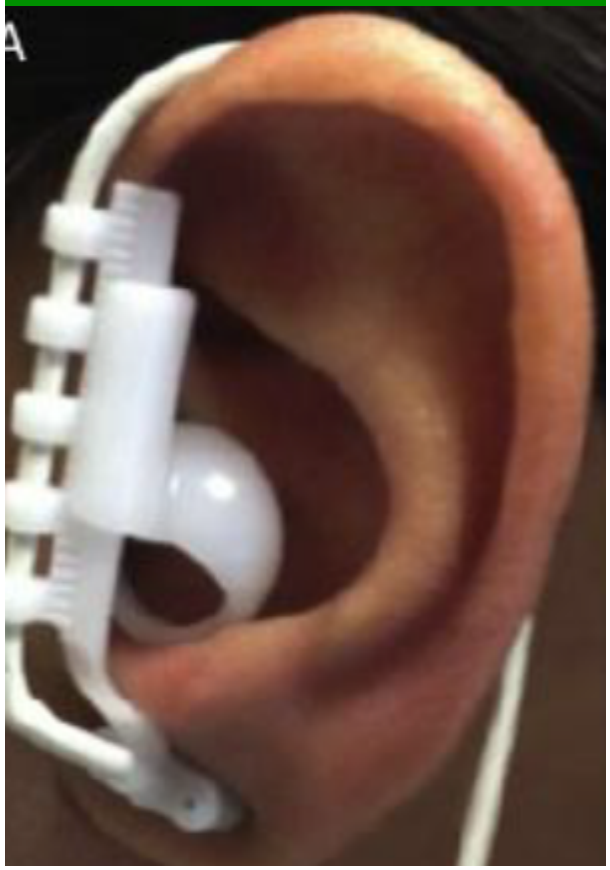


Non-invasive

Methods

Electrical vagal nerve stimulation

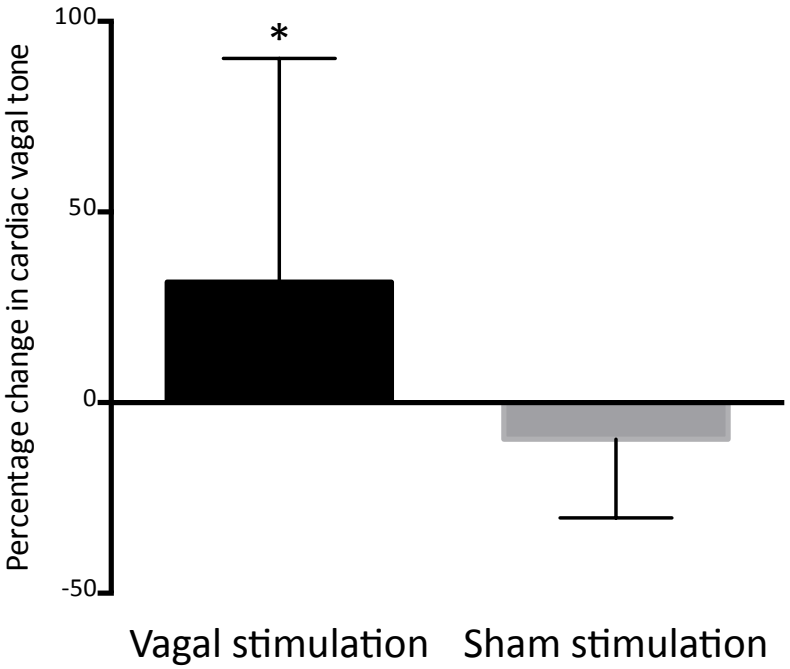
Sham stimulation



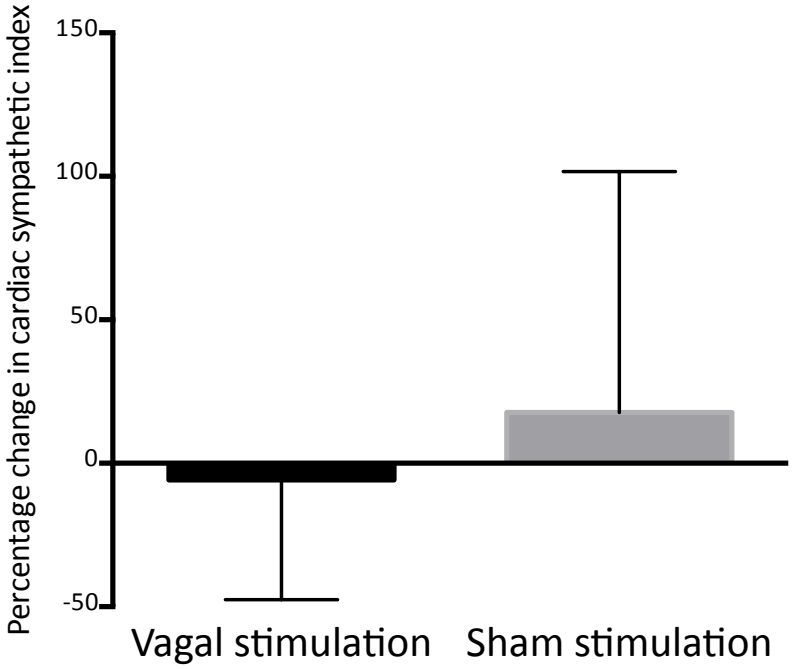
Results 1

- 15 healthy subjects (11 male, mean age 30 years, range 21-42)

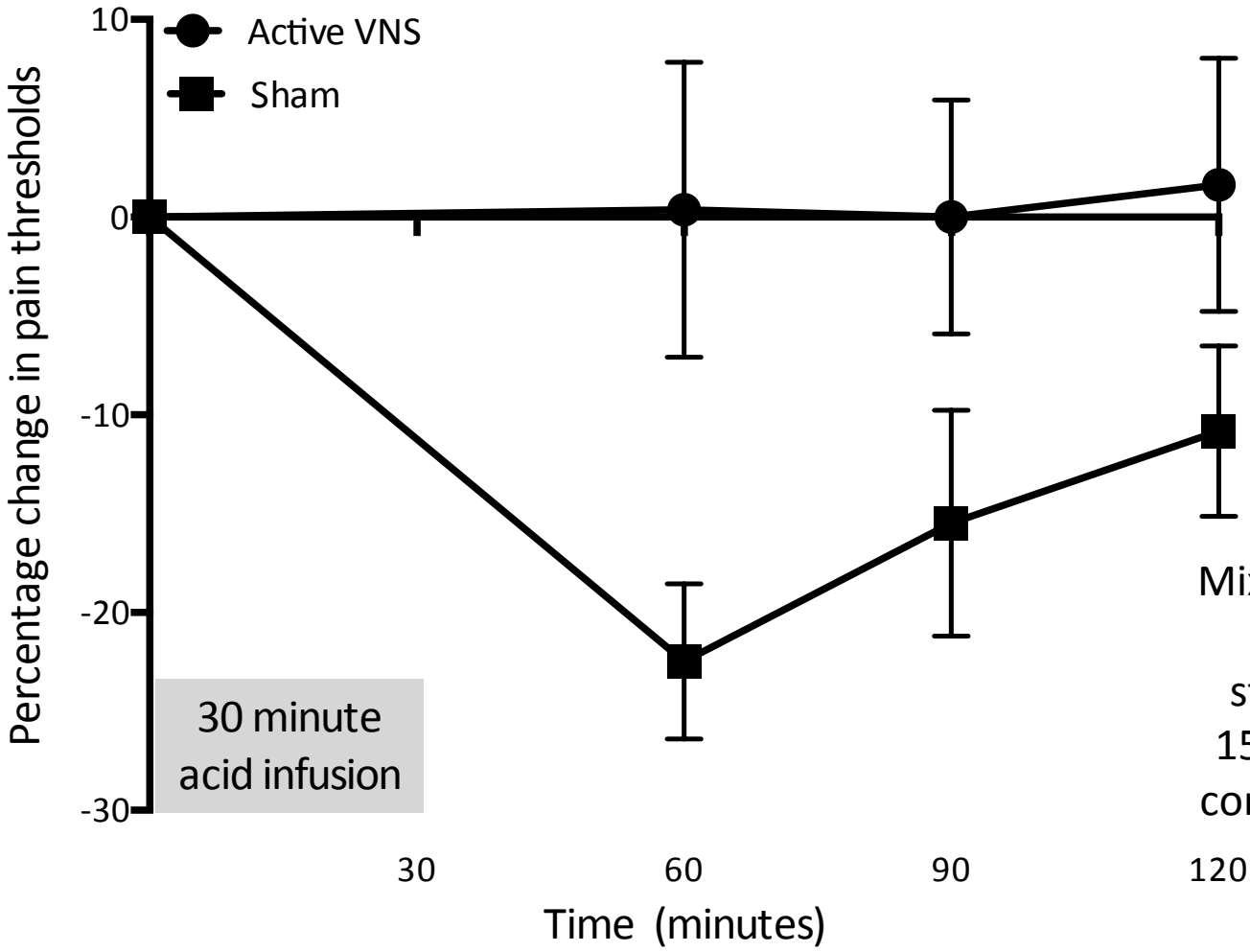
Parasympathetic



Sympathetic



Results 2 – *Effect of Vagal Stimulation on Pain*



Mixed effects regression - coefficient for vagal stimulation coefficient 15.4mA /unit time (95% confidence interval 8.8 to 22.2), p=0.001

Conclusions – *Electrical Modulation*

- *Electrically* elevating vagal tone, using transcutaneous stimulation, prevents the development of oesophageal pain hypersensitivity in a validated human model

- These findings may facilitate the development of a novel area of therapeutics in chronic oesophageal and visceral pain syndromes

- Further work is warranted in patients groups to ascertain whether a similar effect is demonstrable – such as those with gastro-oesophageal reflux disease

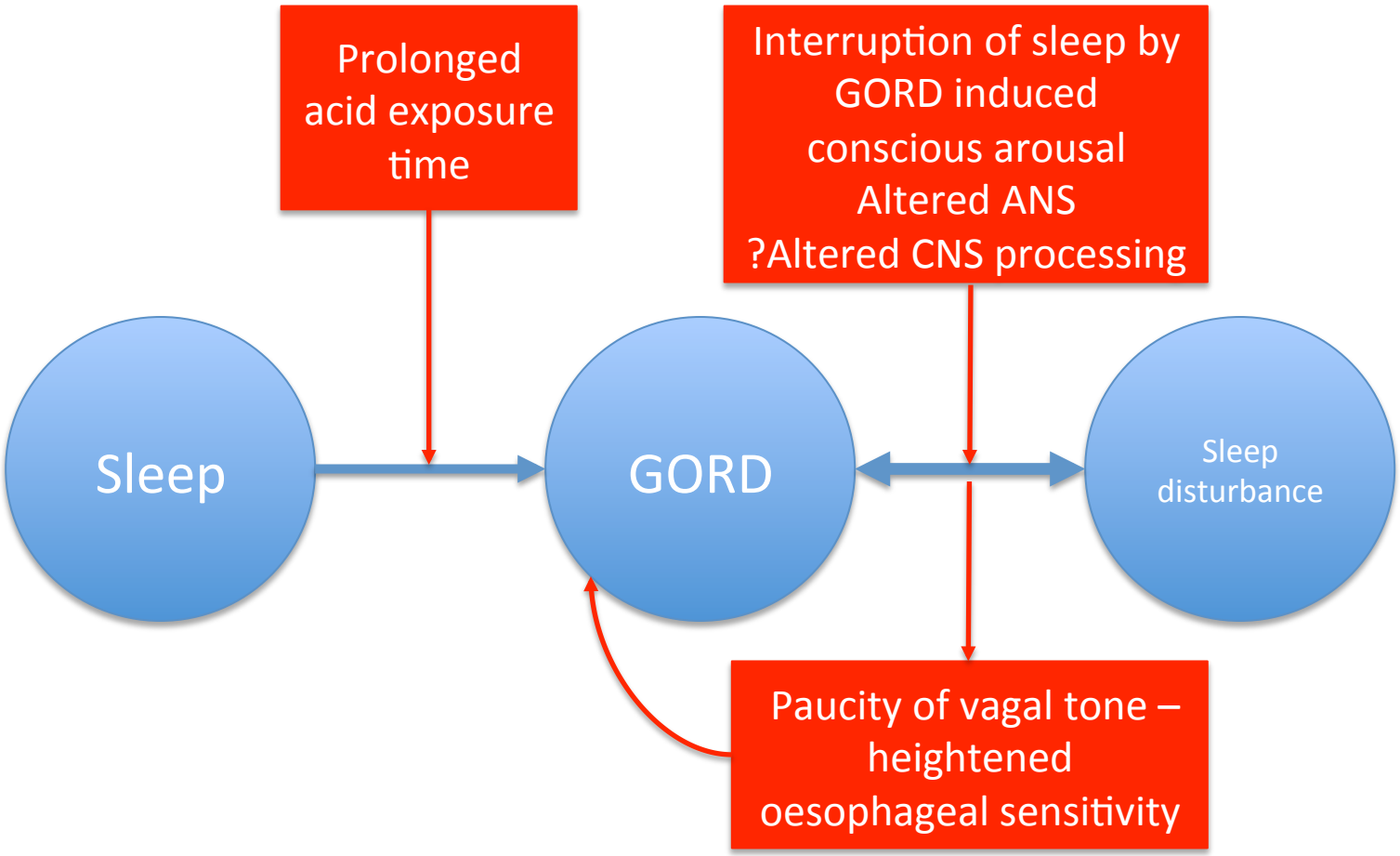
Autonomic Effects of Sleep Deprivation

- Cardiovascular events, especially sudden cardiac death, are affected by prolonged mental stress and chronic fatigue – *Rozanski et al. Circulation 2003*

- It is postulated that alterations in the stress responsive physiological systems may account for this change

- In a study of 30 male college students, chronic sleep deprivation was associated with a reduction in vagal activity – *Takase et al. Biomedicine and Pharmacotherapy 2004*

The Vagus – The Missing Link?



Conclusions

- Vagal nerve activity can be enhanced:-
  - Physiologically - through slow deep breathing
  - Electrically – using vagal nerve stimulation

- Vagus nerve stimulation has the potential to treat acid induced pain

- This warrants further exploration in patient groups

- May facilitate improved sleep in GORD patients


VIVA
LAS VAGUS