Will the Real POTS Please Stand up? Patient Talk

Thomas Chelimsky, MD
Medical College of Wisconsin
Saturday, July 18, 2015

Outline

- Understanding POTS
  - What do the associated illnesses tell us?
  - The framework of autonomic disorders
- Defining POTS
  - Traditional Physiologic Perspective
  - Pain and POTS – What is going on in the brain?
- POTS Management
  - Non-pharmacologic (“I’m in charge”)
  - Pharmacologic (“Fix me”)

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POTS Definition

- "…sustained **heart rate increment of ≥ 30 beats/min within 10 min of standing or head-uptilt in the absence of orthostatic hypotensio**n.
- The standing heart rate for all subjects is often ≥120 beats/min.
- These criteria may not be applicable for individuals with low resting heart rates.
- For individuals aged 12 – 19 years the required increment is at least 40 beats/min.
- The orthostatic tachycardia may be accompanied by symptoms of cerebral hypoperfusion and autonomic overactivity that are relieved by recumbency."

- *2011 Consensus Statement*

Jenna: 24 years old and lightheaded with standing for 3 months

- An athlete, continued graduate school but reduced her daily running to 2/week, ¼ the distance.
- Fainted once when symptoms began, but learned to sit or lie down when symptoms become severe.
- Salt added by PCP helped a little. No other meds.
- Examination is normal except lying BP//HR 120/70//56 bpm, standing 110/80//95 bpm and she is lightheaded. Lytes, CBC, TSH, EKG normal.

Discussion

- Which organ systems are affected?
  - Just cardiovascular system?
- Is this a structural or functional disorder?
- Is this central or peripheral?

POTS other disorders

- Co-morbidities and family history
  - Migraine headaches since age 14, much worse since this started
  - Irritable bowel for 6 months
  - Frequent nausea – 5 pound involuntary weight loss
  - Unrefreshing sleep x 2 months and fatigue
- Organs affected:
  - Cardiovascular system
  - Upper and lower bowel
- *What will family history show?*

Family History

- Mother, sister, and 3 maternal aunts with migraine headaches
- Mother has IBS and fibromyalgia
- Sister, maternal aunt, 3 cousins with POTS
- One sister has pelvic pain (dx: endometriosis)
- One sister with generalized anxiety disorder.

Discussion

- Which organ systems are affected?
- Is this a structural or functional disorder?
- Is this central or peripheral?

Important Points - Presentation

- This is a functional autonomic disorder
  - Software much more damaged than hardware
  - Brain networks report many symptoms beyond just “POTS”
  - Few abnormalities on examination

Functional and Structural Contrast

	Structural - Hardware	Functional - Software
Patient Presentation	Minimizes Complaints – Family often argues patient is much worse than they admit	Complaints are overwhelming to patient and family
Examination Findings	Many	Few
Putative Pathology	Clearcut	Nebulous
Cardiovascular Autonomic Reflexes	Impaired	Preserved
Tilt Table Testing	Orthostatic Hypotension	Postural Tachycardia
Standing Norepinephrine Levels	Reduced	Increased
Theory of Fundamental Physiology	**Brainstem Pass-through Impaired – few sensations reach cortex**	**Brainstem Filter impaired – all sensations reach cortex**

Examples

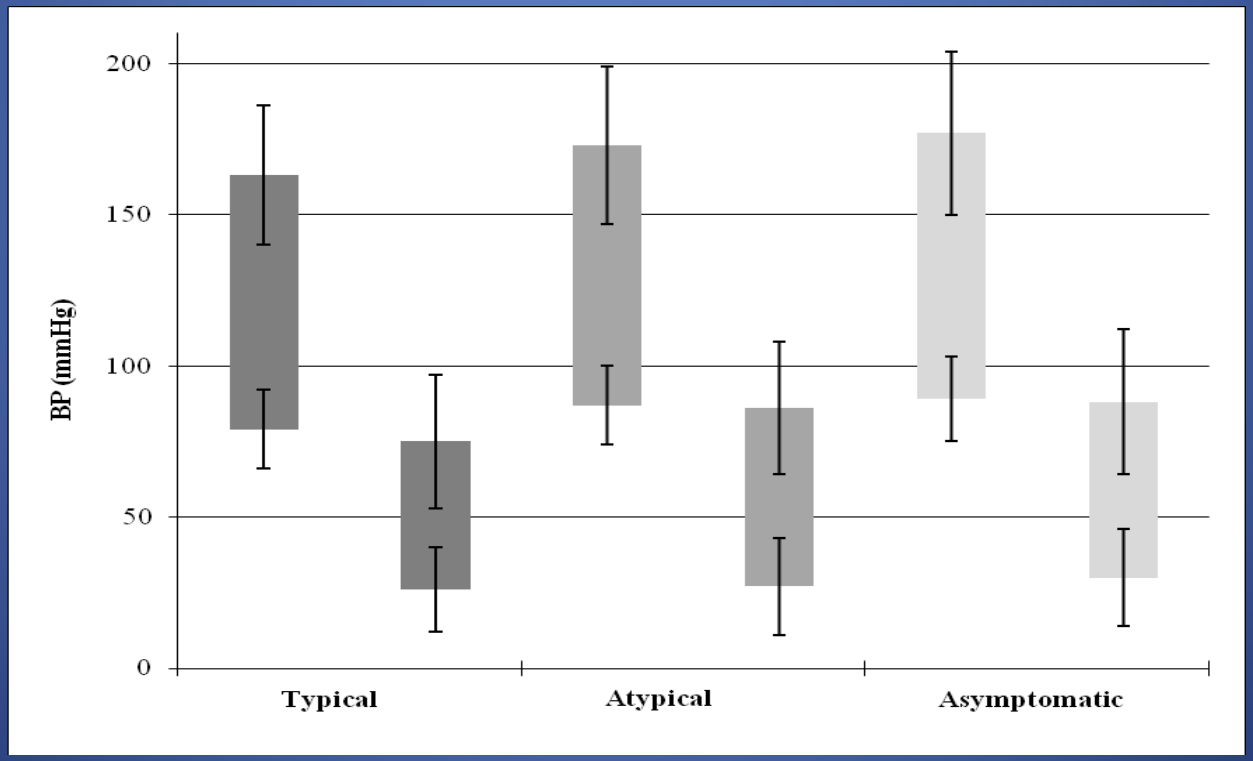
- **Structural: a well-defined change in ANS structure produces disease - examples:**
  - **Multiple system atrophy**
  - **Diabetic autonomic neuropathy**
  - **Baroreflex failure due to neck radiation**
  - **Hardware -> Solution is to fix hardware, replace parts (mostly we don't have them – factory is closed)**
- **Functional: a change in ANS function is involved in disease production, but is (1) less well-defined; (2) a link in a pathogenic chain, not primary:**
  - **Postural tachycardia syndrome**
  - **Irritable bowel syndrome**
  - **Syncope**
  - **Meaning of "Functional" NOT "non-organic"**
  - **Software -> Solution is to reprogram neural networks**

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Hypotension Unawareness in Profound Orthostatic Hypotension

Steven D. Arbogast, DO,[a] Amer Alshekhlee, MD, MS,[a] Zulfiqar Hussain, MD,[b] Kevin McNeeley,[a] Thomas C. Chelimsky, MD[a]



About Structural Dysautonomias

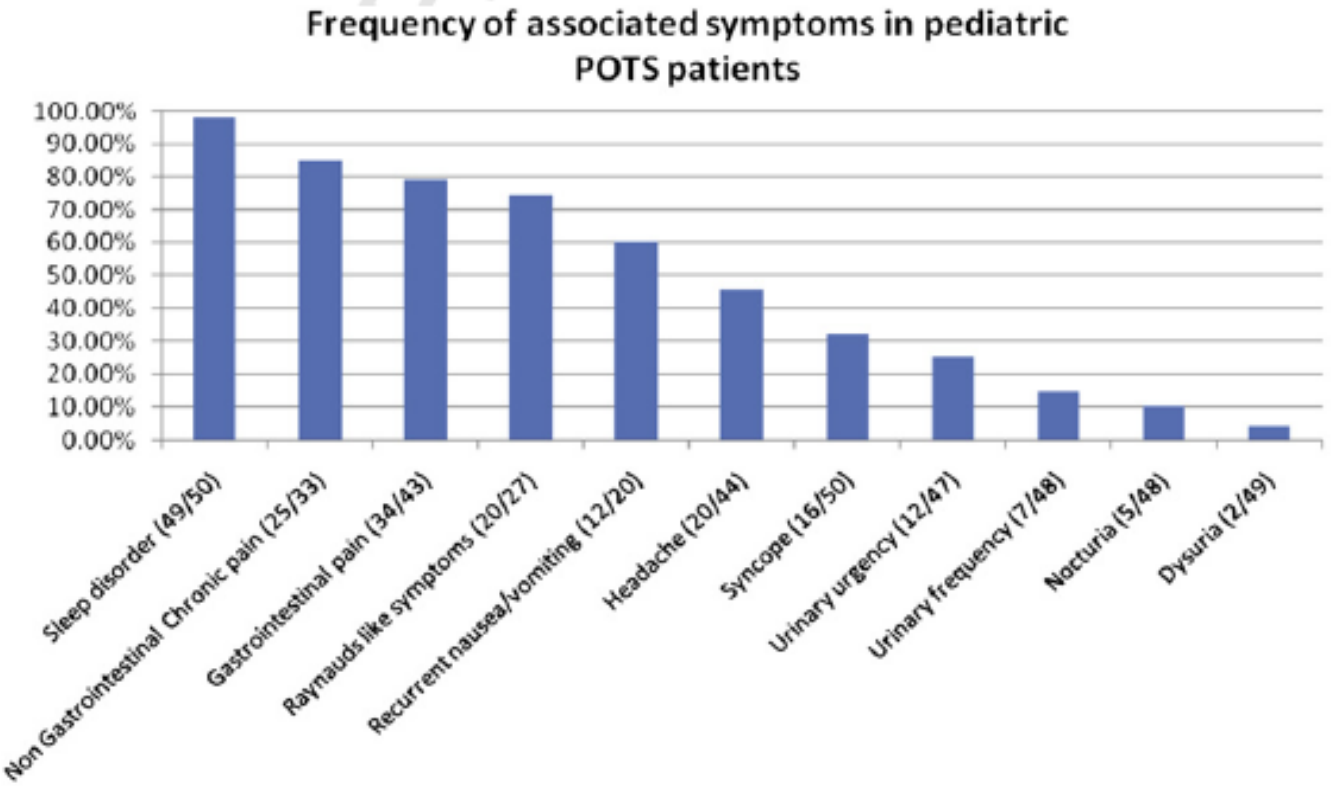
- Classification: conceptual framework only
  - Not absolute: a minority overlap
  - Diabetes or immunologic issues can be associated with what looks like a functional disorder
  - As insight grows: Functional (software) -> Structural (hardware)
- Structural classification
  - Central Nervous System
    - Parkinsonian Disorders: MSA; PD- Lewy body spectrum
    - Spinal Cord Disorders, traumatic & demyelinating
  - Peripheral Nervous System
    - Pure autonomic failure (ganglionic degeneration)
    - Autonomic neuropathies (Diabetes, Immune, etc.)

Some Functional Disorders

- Non-painful
  - Syncope
  - Postural Tachycardia Syndrome (POTS)
  - Chronic Fatigue Syndrome
  - Cyclic Vomiting Syndrome
- Painful
  - Functional Dyspepsia
  - Functional Abdominal Pain
  - Abdominal Migraine
  - Migraine Headache
  - Irritable Bowel Syndrome (IBS)
  - Interstitial Cystitis
  - Complex Regional Pain Syndrome (CRPS)
  - Raynaud's Syndrome
  - Fibromyalgia

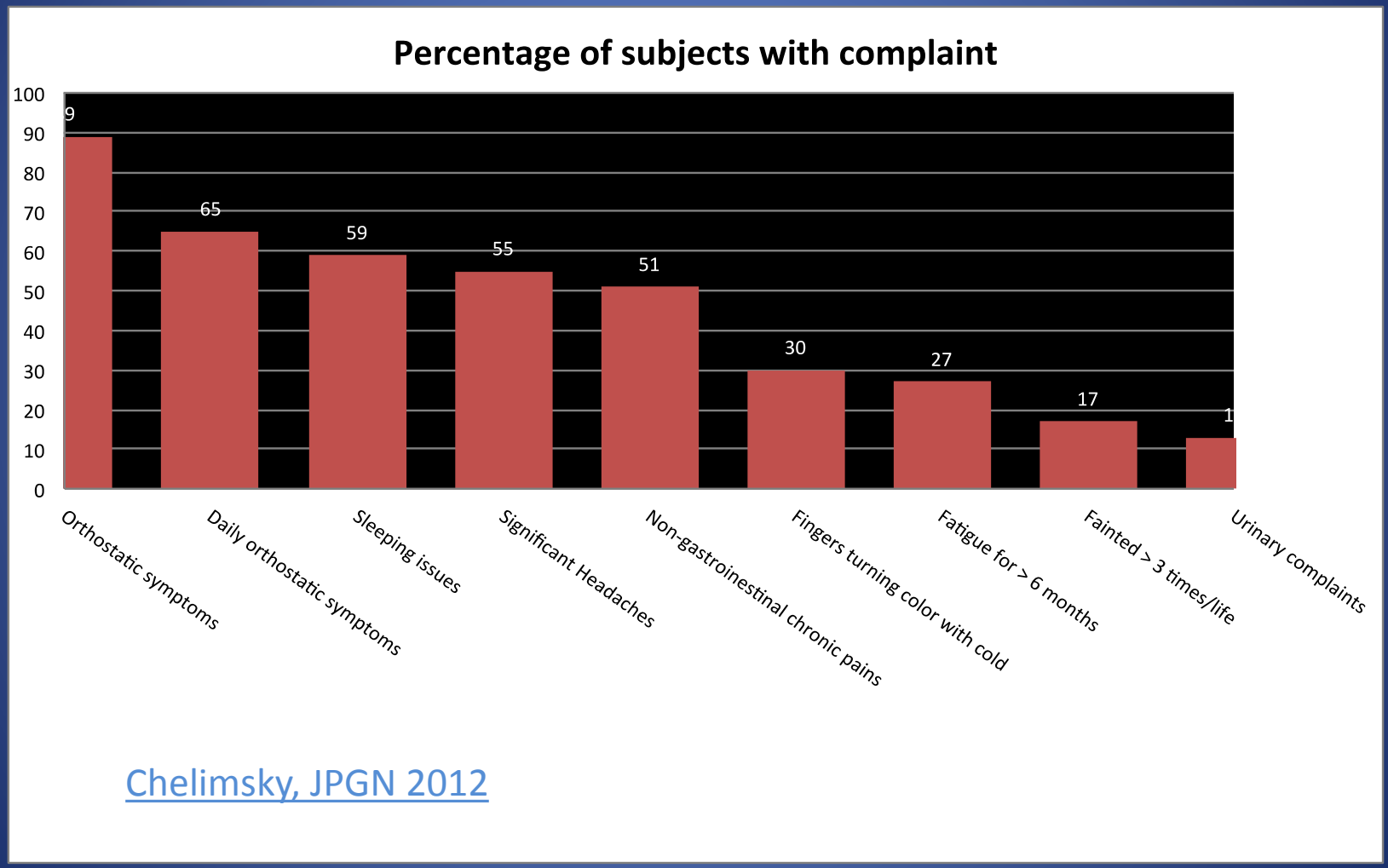
Comorbidities in Pediatric Patients with Postural Orthostatic Tachycardia Syndrome

Ajitesh Ojha, Thomas C. Chelimsky, MD, and Gisela Chelimsky, MD



THE JOURNAL OF PEDIATRICS

Co-morbidities of Functional abdominal pain



Chelimsky, JPGN 2012

Association between FGID and orthostasis

- 24 pediatric patients with FGID
- Only tilt
- Presenting symptoms:
  - Abdominal pain 71%
  - Nausea 56%
  - Vomiting 50%
- Results: (NMH=neurally mediated hypotension)
  - POTS 4
  - POTS + NMH 8
  - NMH 12

Sullivan, S et al. JPGN 2005

Association between FGID and orthostasis

- Patients were treated for orthostatic intolerance
- Follow up 18/24
- Resolution of symptoms with fludrocortisone: 4
- Improvement in symptoms:
  - Fludrocortisone: 4
  - Fludrocortisone + sertaline: 4
  - Midodrine: 1

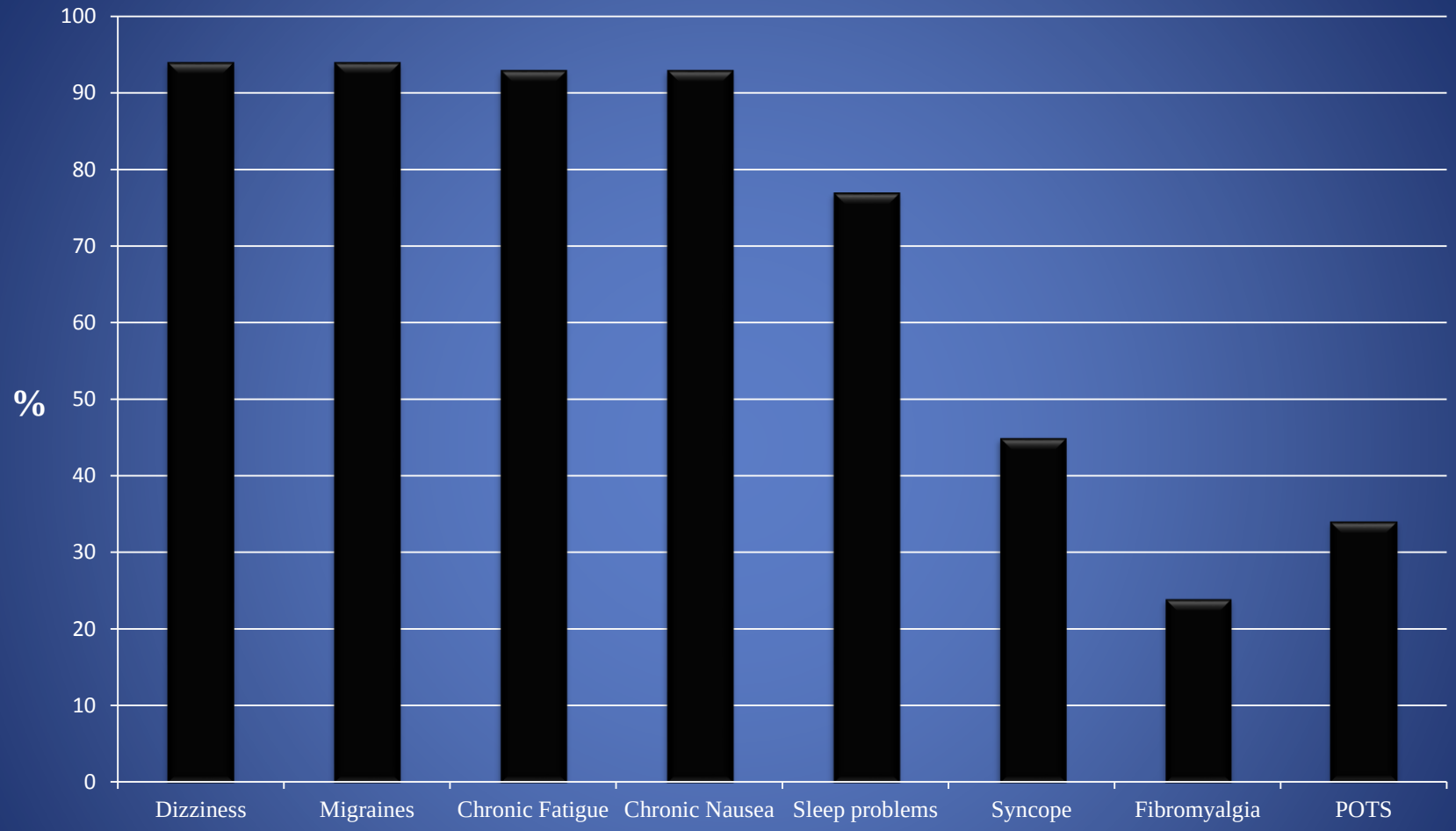
Sullivan, S et al. JPGN 2005

POTS and FGID: different aspects of the same problem?

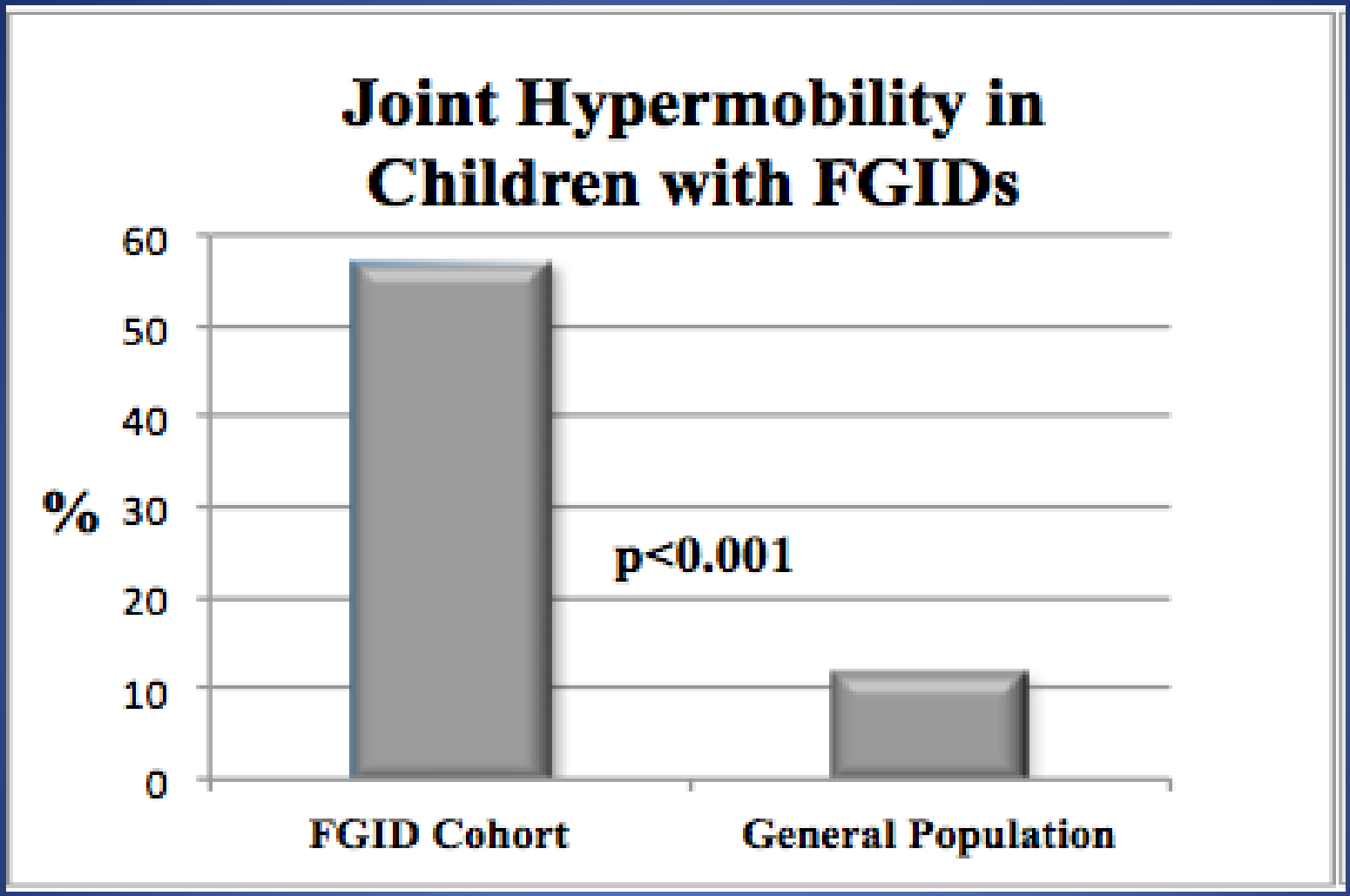
- Chief complaints of patients with POTS: dizziness, lightheadedness, lower extremities weakness
- GI complaints of patients with POTS: nausea, bloating, early satiety, abdominal pain

Sandroni P, et al. *Mayo Clin Proc*; 74:1106-10 1999

Co-morbid Symptoms & FGIDs



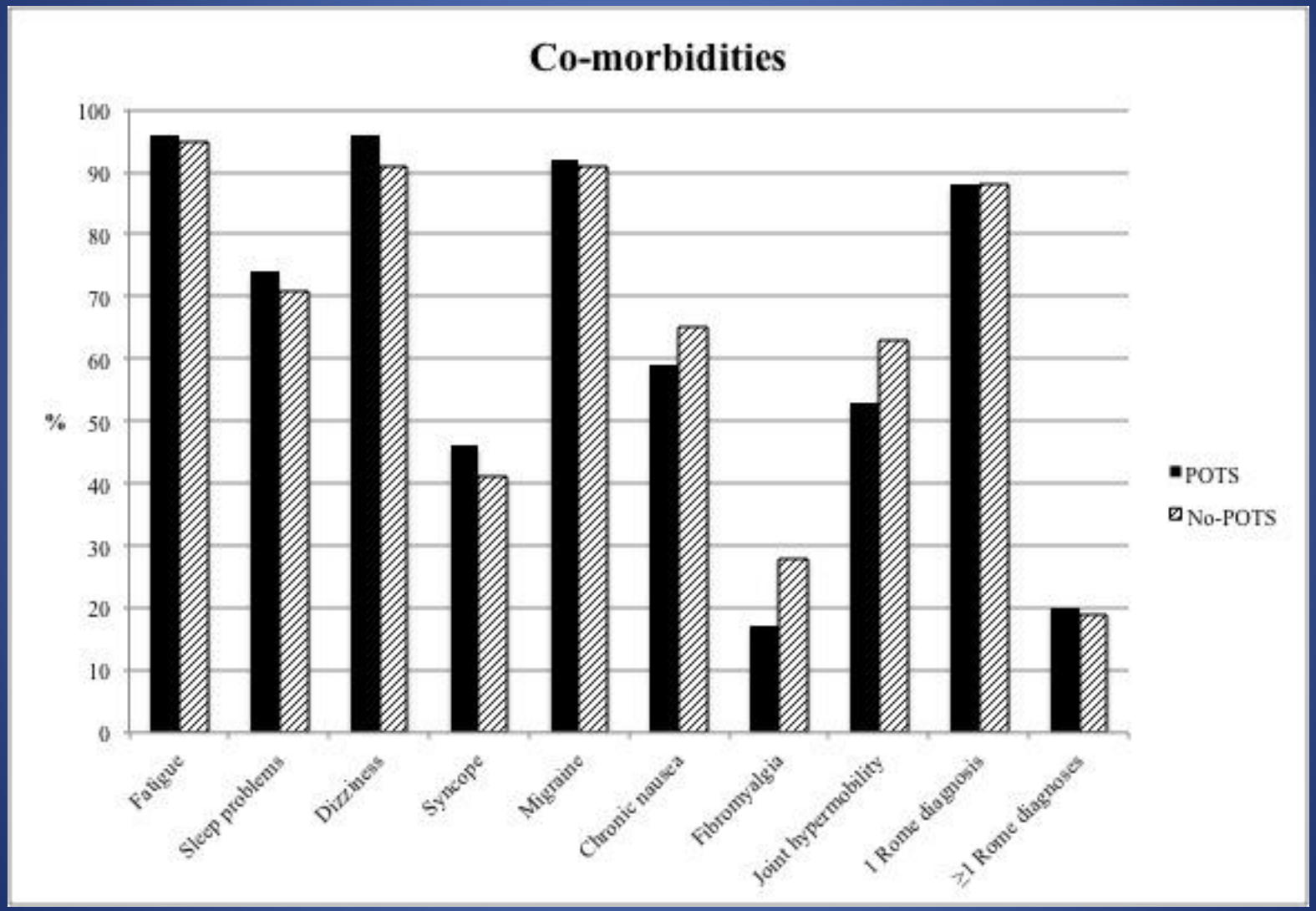
Kovacic, et al. J Peds 2014



Kovacic, et al. J Peds 2014

Is POTS a “cause”?
Is POTS just part of the picture?

Co-morbidities and POTS



Chelimsky, G et al. J Peds 2015

Questions for the audience

- How many have a lightheadedness and rise in heart rate when they stand NOW?
  - For whom is this the MAJOR problem?
  - For whom is this minor compared to other issues?
- How many have migraine?
- How many have bowel issues?
- How many are hypermobile (very flexible)?

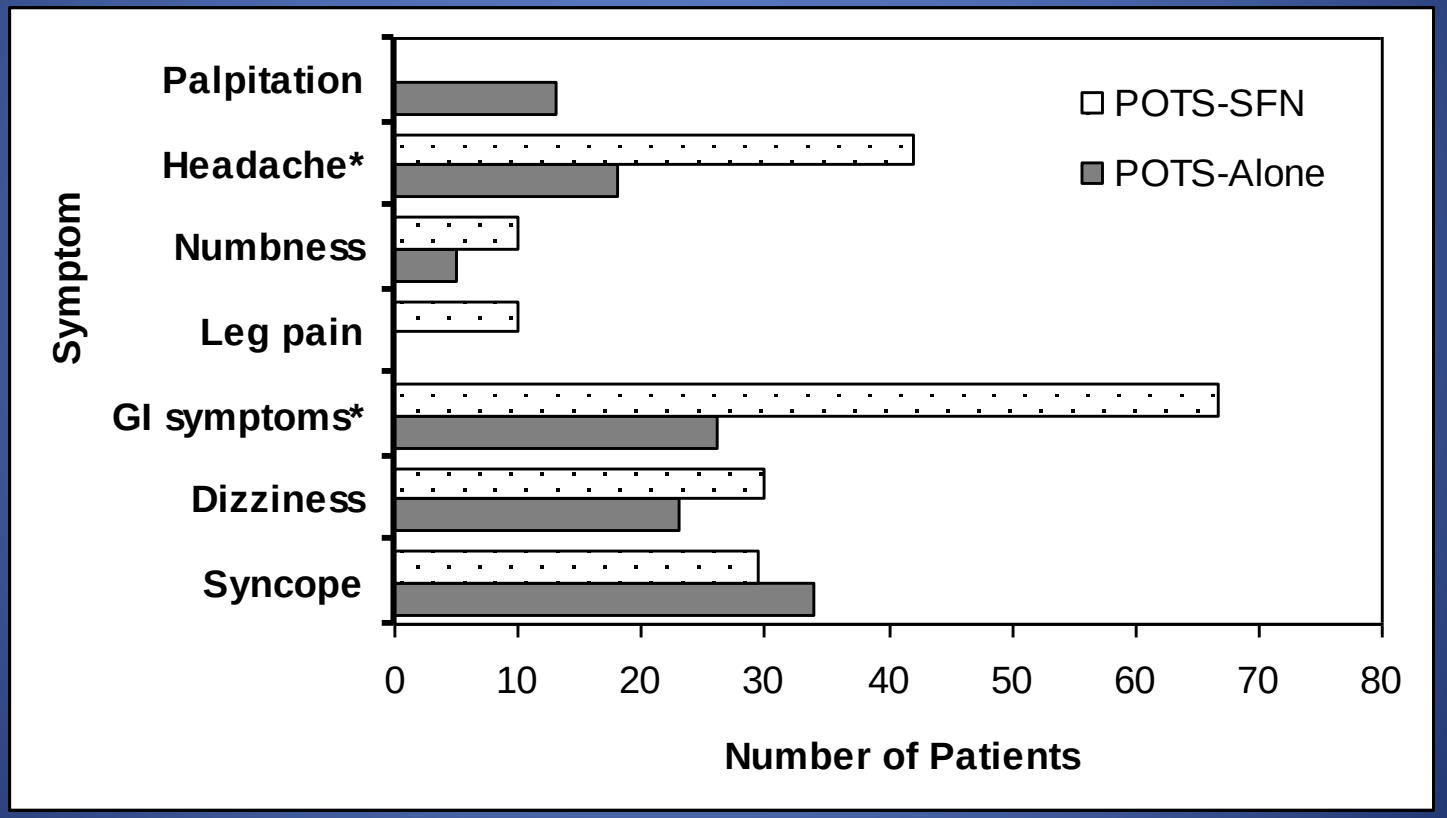
Other Co-morbidities

- Fibromyalgia
- Hypermobility (double jointed)
- Chronic vomiting or nausea
- Constipation or Irritable Bowel Syndrome
- Chronic fatigue
- Pelvic pain and interstitial cystitis
- Anxiety, PTSD
- Depression

POTS Types (Not a classification)

- Neuropathic
- Immunologic
- Hyperadrenergic
- Associated with Hypermobility
- High flow/low flow

Neuropathic POTS



Alshekhlee et al, 2005

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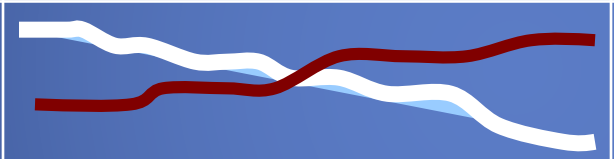
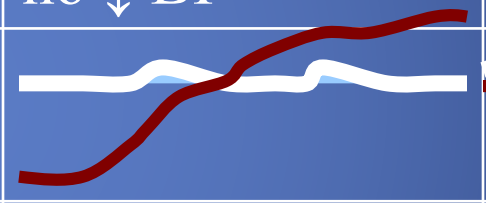
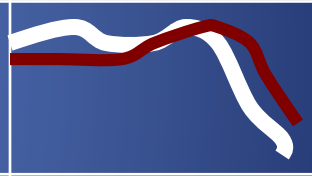
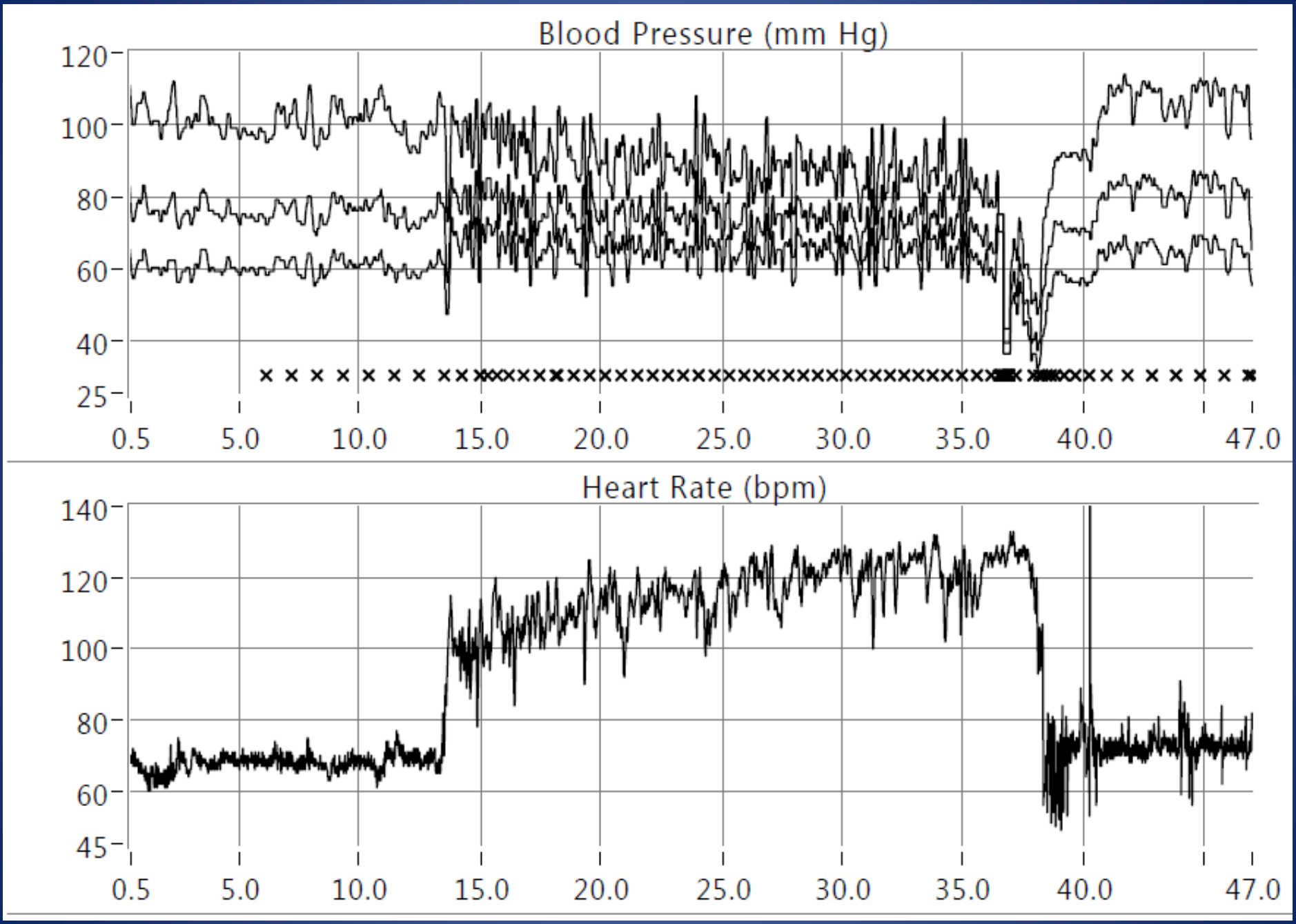
The 3 Orthostatic Syndromes

	Orthostatic Hypotension	Postural Tachycardia	Reflex Syncope
Definition	Gradual sustained ↓ sBP>20 dBP>10 ≤3’	↑HR>30 in 10’ no ↓ BP	Sudden ↓ BP ± HR
BP / HR Pattern			
Physiology	Arterial denervation impacts ***diastole***	Venous return impact ***systole***	Brainstem ***threshold***
CV reflexes	Usually abnormal	Usually normal	Usually nl
Associated Dysauton.	Disease-based Poor prognosis	Syndromic Good Prognosis	Syndromic


Blood Pressure (mm Hg)
120
100
80
60
40
25
0.5
5.0
10.0
15.0
20.0
25.0
30.0
35.0
40.0
47.0
Heart Rate (bpm)
140
120
100
80
60
45
0.5
5.0
10.0
15.0
20.0
25.0
30.0
35.0
40.0
47.0

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Why Should PAIN & POTS Overlap?

Inhibitory Mechanisms

Descending System

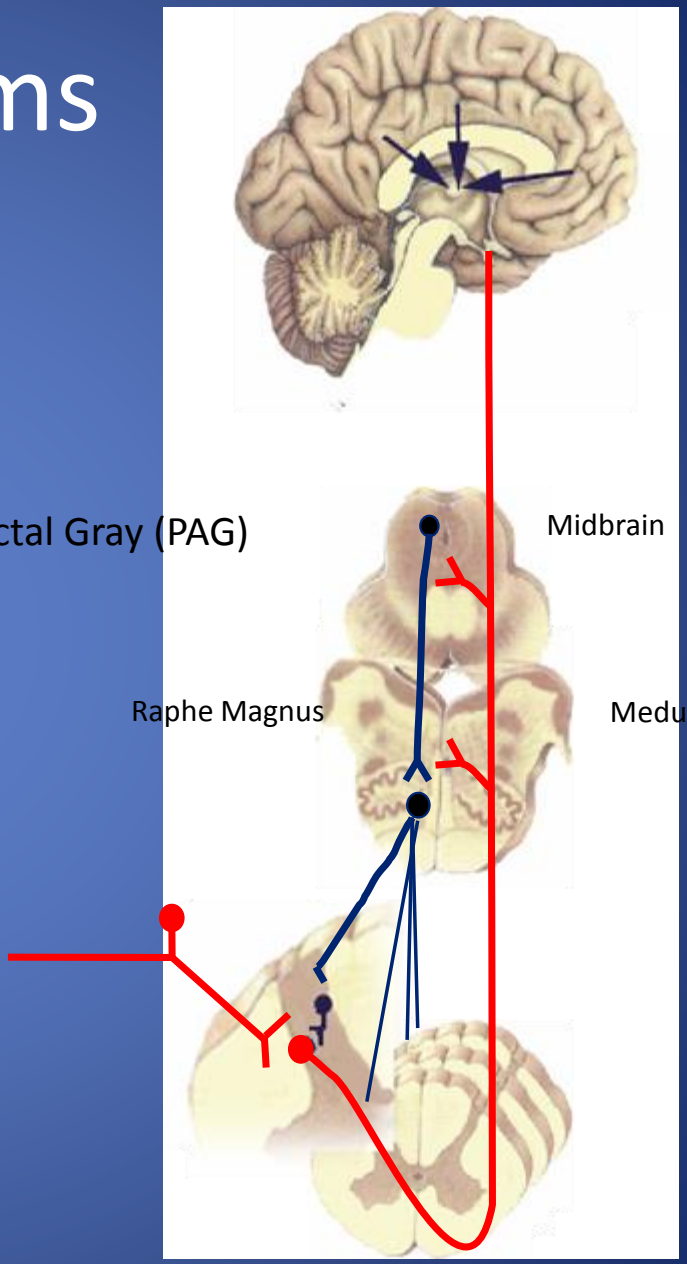
Diffuse

Noxious

Inhibitory

Control

spinal–supraspinal–spinal loop

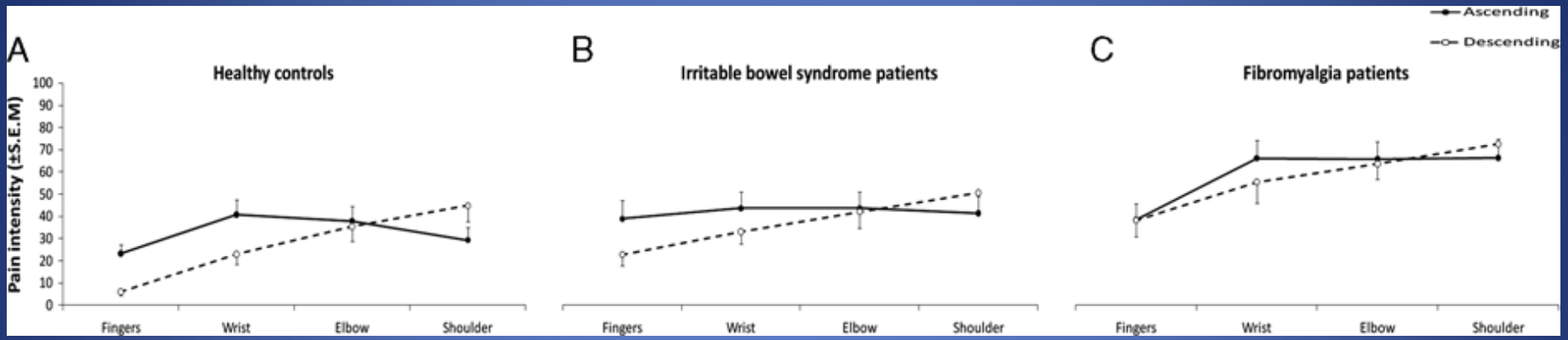


Picture: Courtesy of Dr. Serge Marchand

Comparing Pain Modulation and Autonomic Responses in Fibromyalgia and Irritable Bowel Syndrome Patients

Philippe Chalaye, MSc, Philippe Goffaux, PhD,* Patricia Bourgault, RN, PhD,† Sylvie Lafrenaye, MD, MSc,‡ Ghislain Devroede, MD, MSc,* Alain Watier, MD,§ and Serge Marchand, PhD**

(*Clin J Pain* 2012;28:519–526)



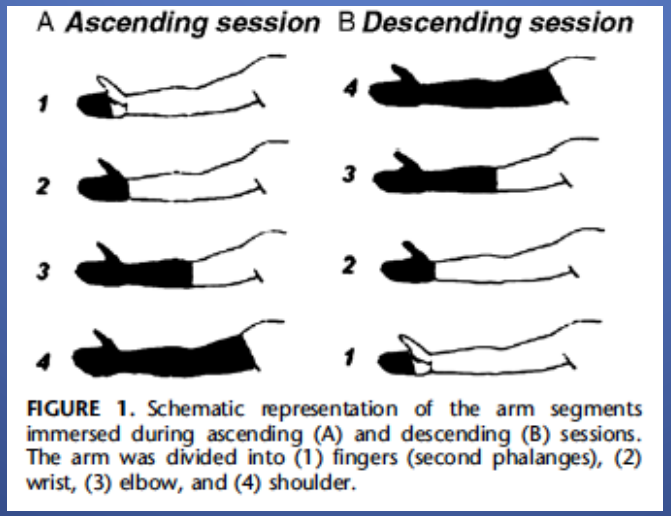


FIGURE 1. Schematic representation of the arm segments immersed during ascending (A) and descending (B) sessions. The arm was divided into (1) fingers (second phalanges), (2) wrist, (3) elbow, and (4) shoulder.

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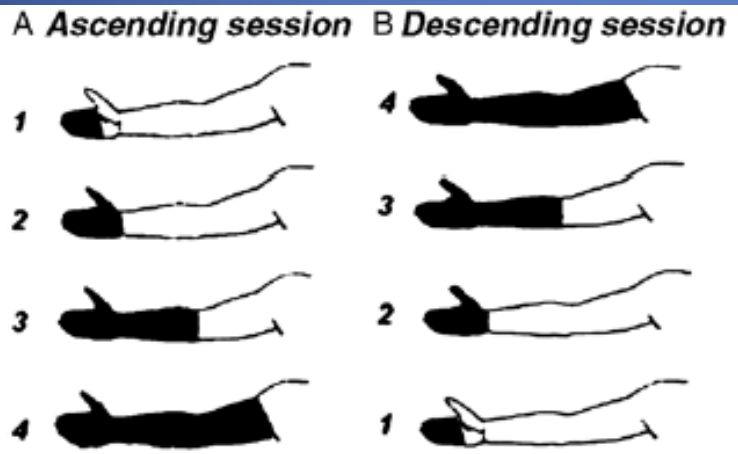
	HCs	IBS	FM
LF baseline	62.66 (5.99)	65.18 (5.00)	51.14 (7.21)
LF small pain	48.51 (5.05)	61.22 (4.56)	59.48 (5.73)
HF baseline	30.73 (4.56)	28.40 (4.02)	40.50 (6.66)
HF small pain	42.15 (4.26)	28.85 (3.53)	31.19 (4.40)



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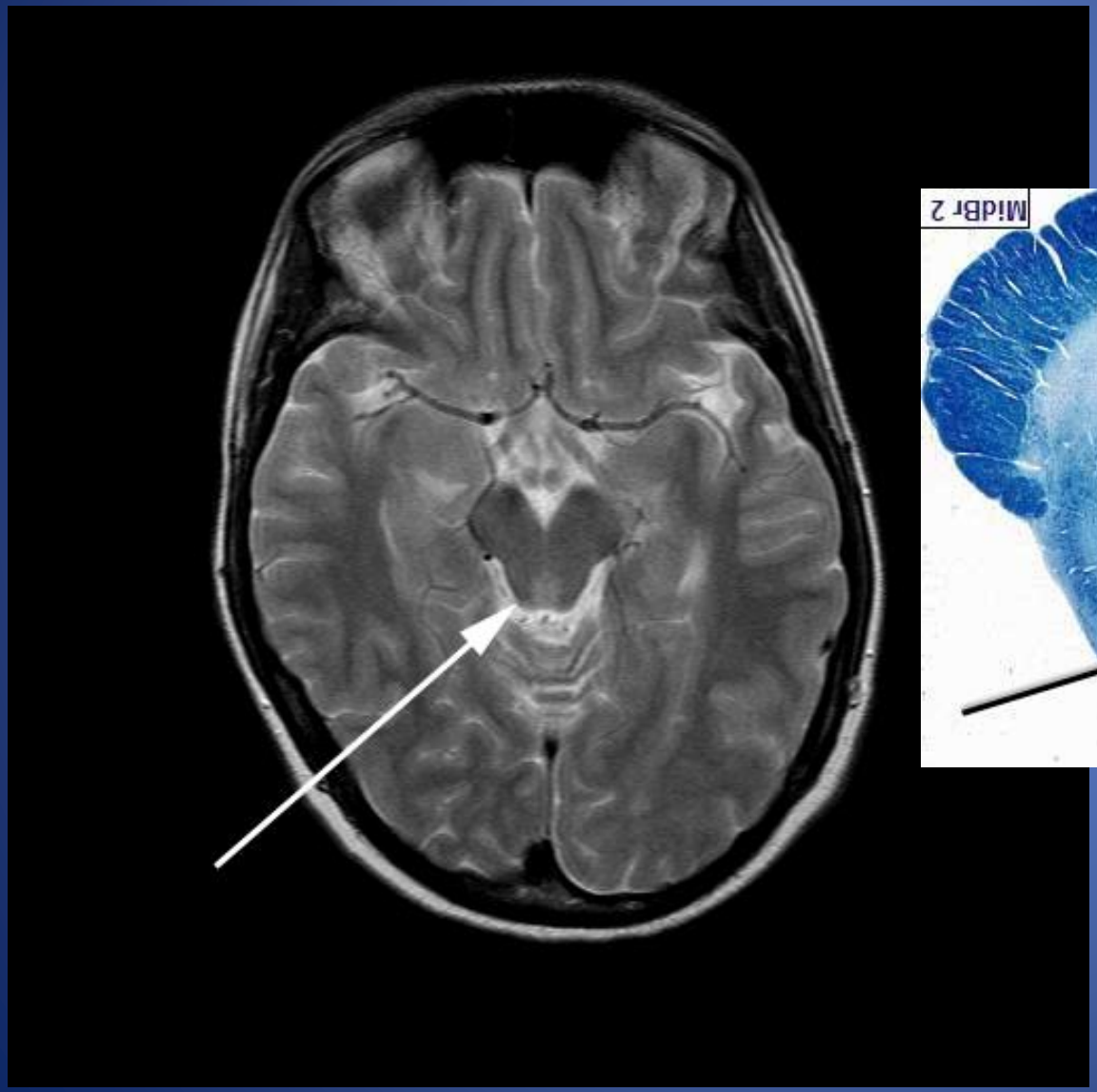
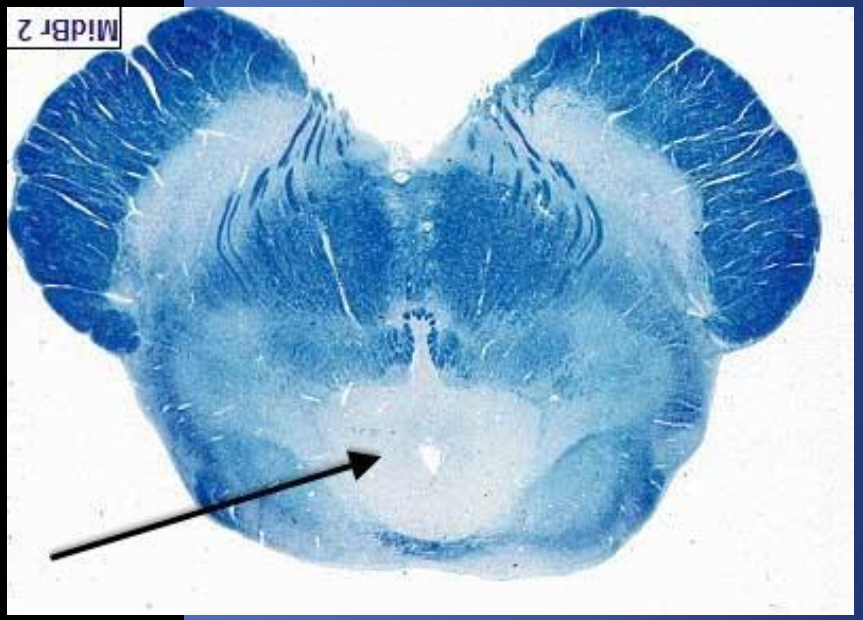
Periaqueductal Gray

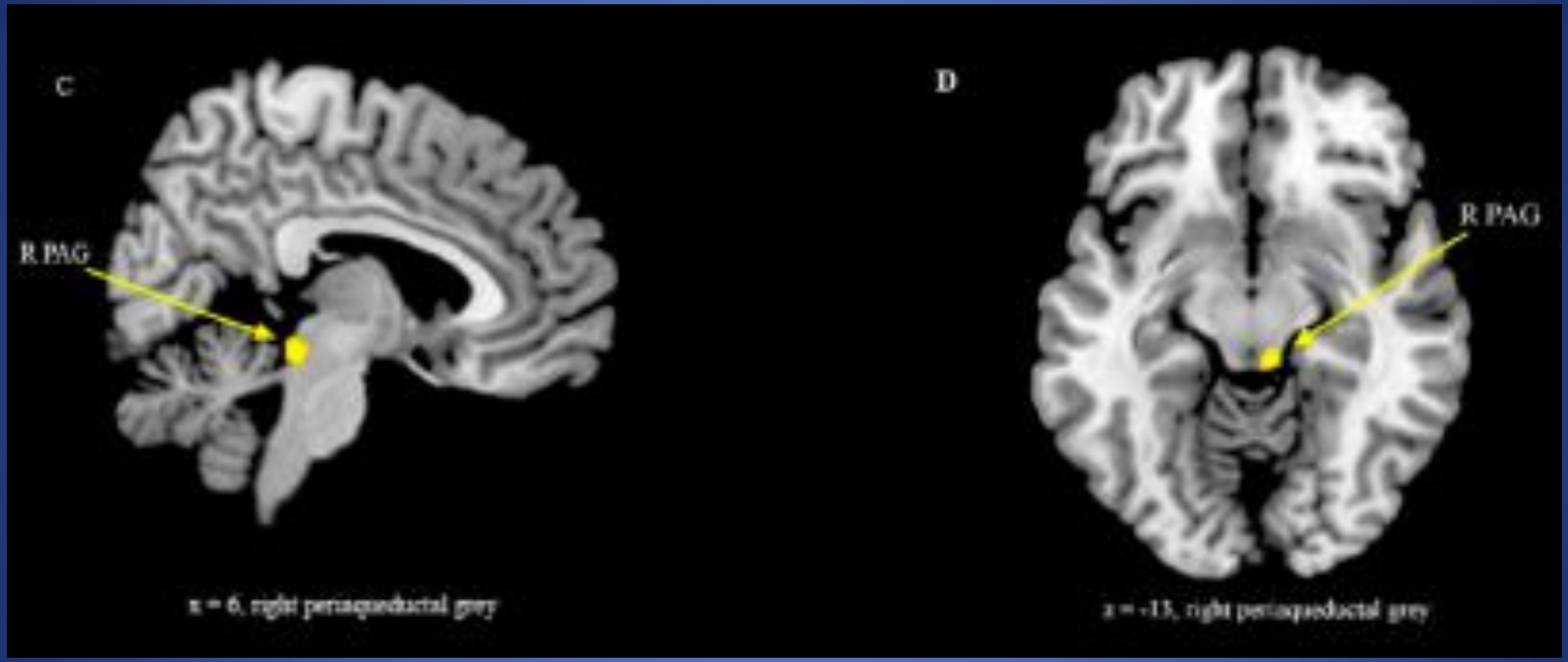




Role of Periaqueductal Gray

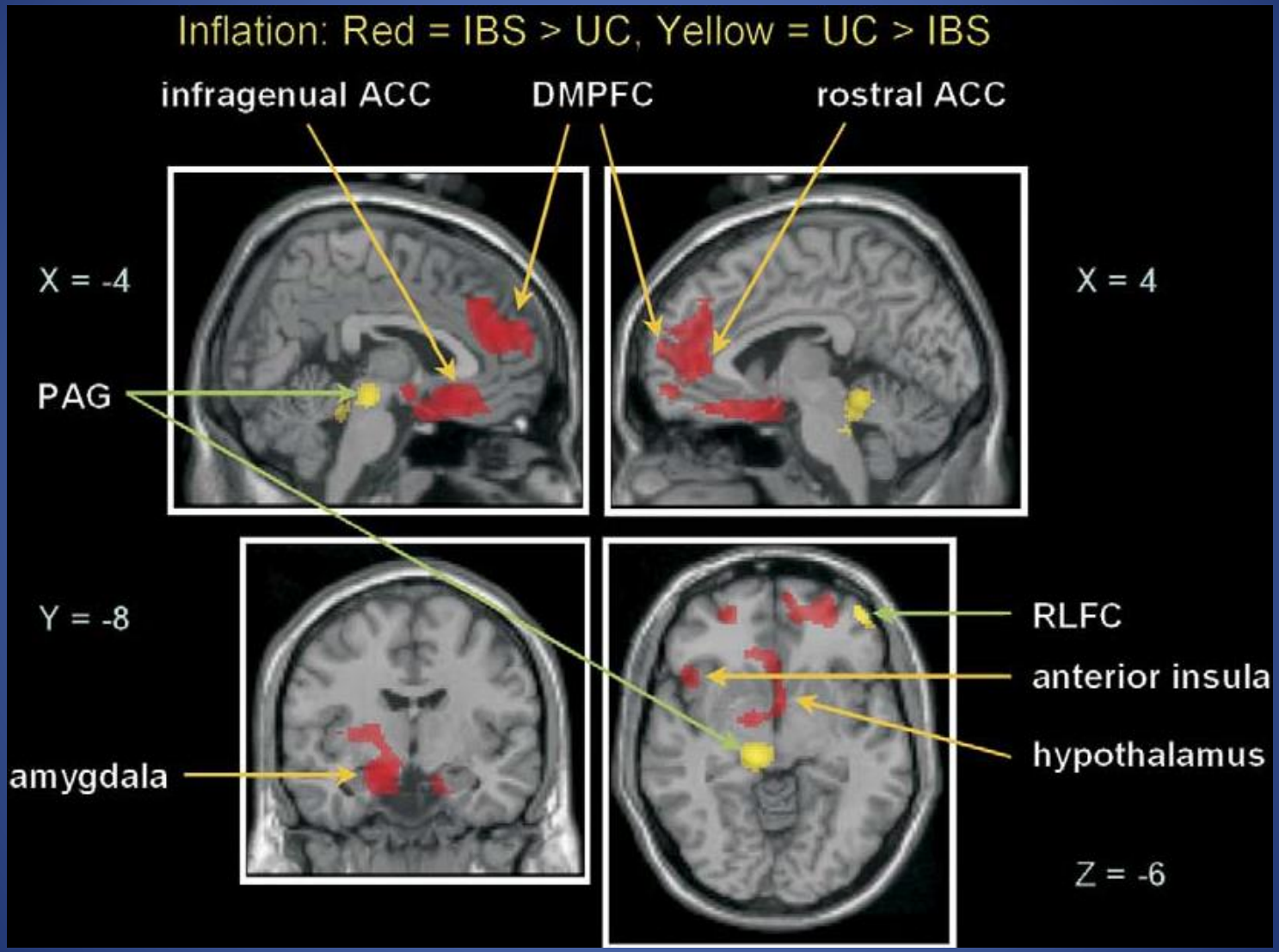
- Ventral PAG is the classic site of deep brain stimulation to reduce pain.
- Highly connected to blood pressure and heart rate modulation
- Controls bladder
- ? Bowel

Periaqueductal Gray in Pelvic Pain



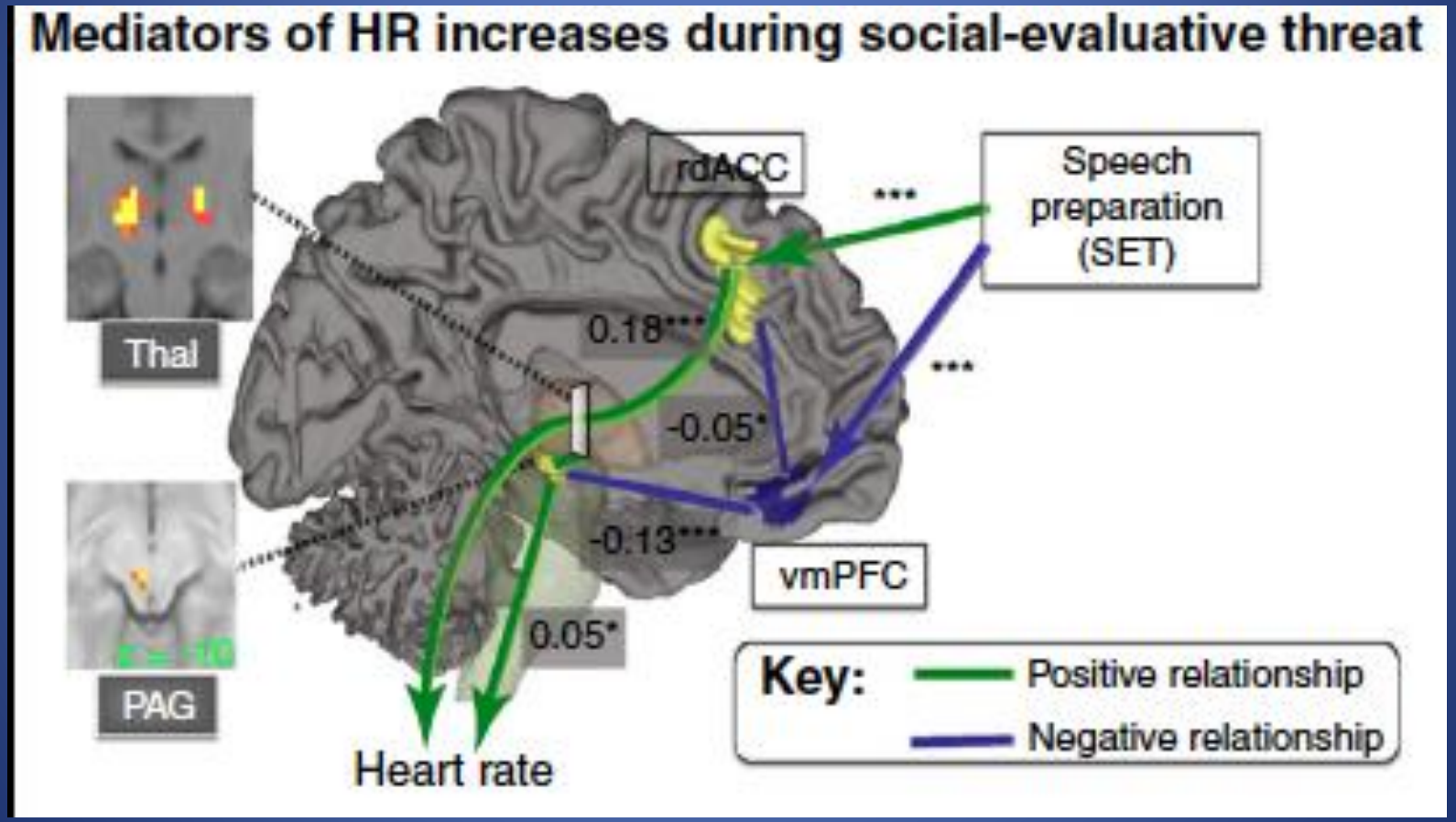
As-Sanie et al, voxel-based morphometry in women with endometriosis, Pain 2012

What Controls PAG?



Mayer et al, Pain 2005

Medial Prefrontal Cortex



Unifying Model

- Prefrontal cortex normally sets a switch that
  - *biases* the PAG to stop pain signals
  - increases vagal power and reduces sympathetic (threat) tone
- Absence of this switch
  - Allows pain signals through
  - Exaggerates responses to standing

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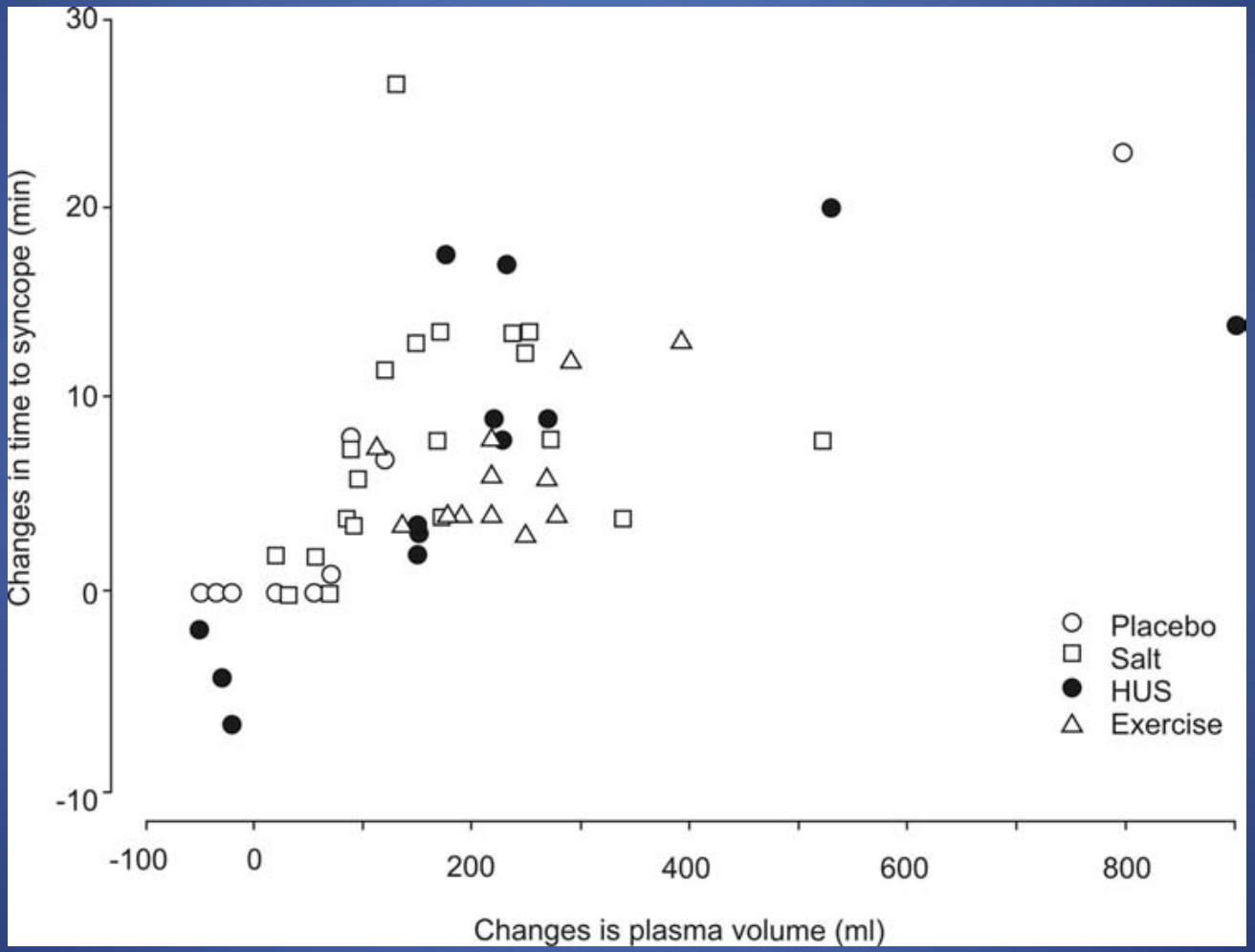
Management of all functional autonomic disorders

- Taper Opiates
- Taper Benzodiazepines
- Start Exercise Program with PT for conditioning
- Achieve Excellent Sleep
  - Tricyclic agents such as doxepin or amitriptyline
- Consider anticonvulsant
- Cognitive Behavior Therapy with Psychologist

Management of Orthostasis: Increasing Central Volume

- Salt loading (U_{Na} > 150 meq)
  - May require 3 to 15 g per day
- Elevate head of bed
  - Reduces nocturnal microgravity
- High-pressure hose with abdominal binder
- Exercise training
- Water jogging

Non-pharmacologic Effect on BP



Management of Orthostasis: Conditioning Exercises/Reflexes

- Frequent small meals
  - Insulin is mild vasodilator
- Self-tilt exercises (Ector, 1998, 2002)
- Physical counter maneuvers (Bouvette, 1996, Wieling 2003)
- Water drinking (16 oz in am; Shannon, 2002)

JOURNAL OF PACING AND CLINICAL ELECTROPHYSIOLOGY, Volume 25, No. 10, October 2002

Long-Term Follow-Up Results of Tilt Training Therapy in Patients with Recurrent Neurocardiogenic Syncope

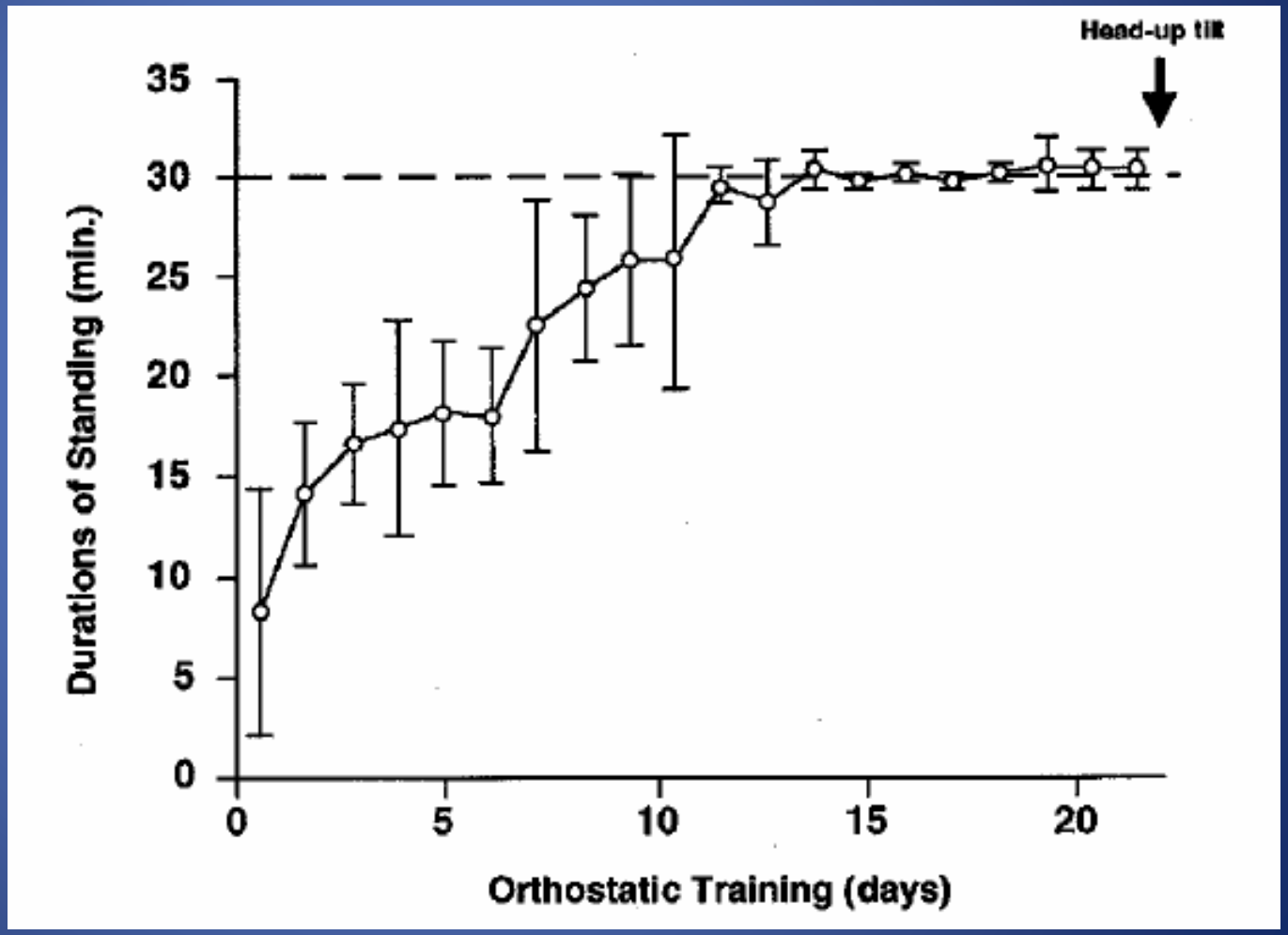
TONY REYBROUCK, HEIN HEIDBÜCHEL, FRANS VAN DE WERF, and HUGO ECTOR

From the Departments of Cardiology and Cardiovascular Rehabilitation, University Hospital Gasthuisberg and Department of Rehabilitation Sciences, University of Leuven, Leuven, Belgium

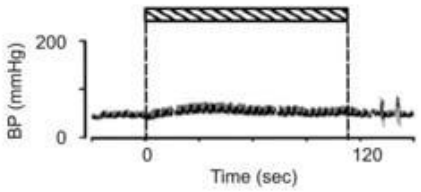
- 38 patients with syncope
- Follow-up at 43 months (mean)
  - 9 were continuing the training
  - 25 completely asymptomatic
  - 6 still had syncope/pre-syncope
    - All of these had stopped the training
    - When they resumed, spells left

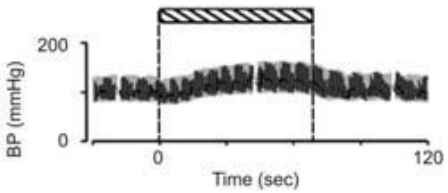
Tilt training – Japanese study

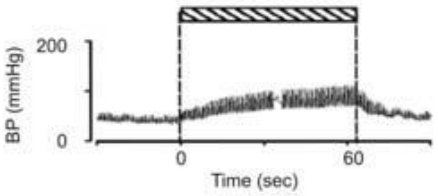
- Japanese study 24 patients

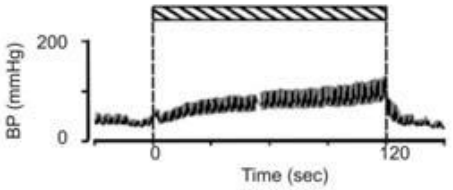


Abe, 2002

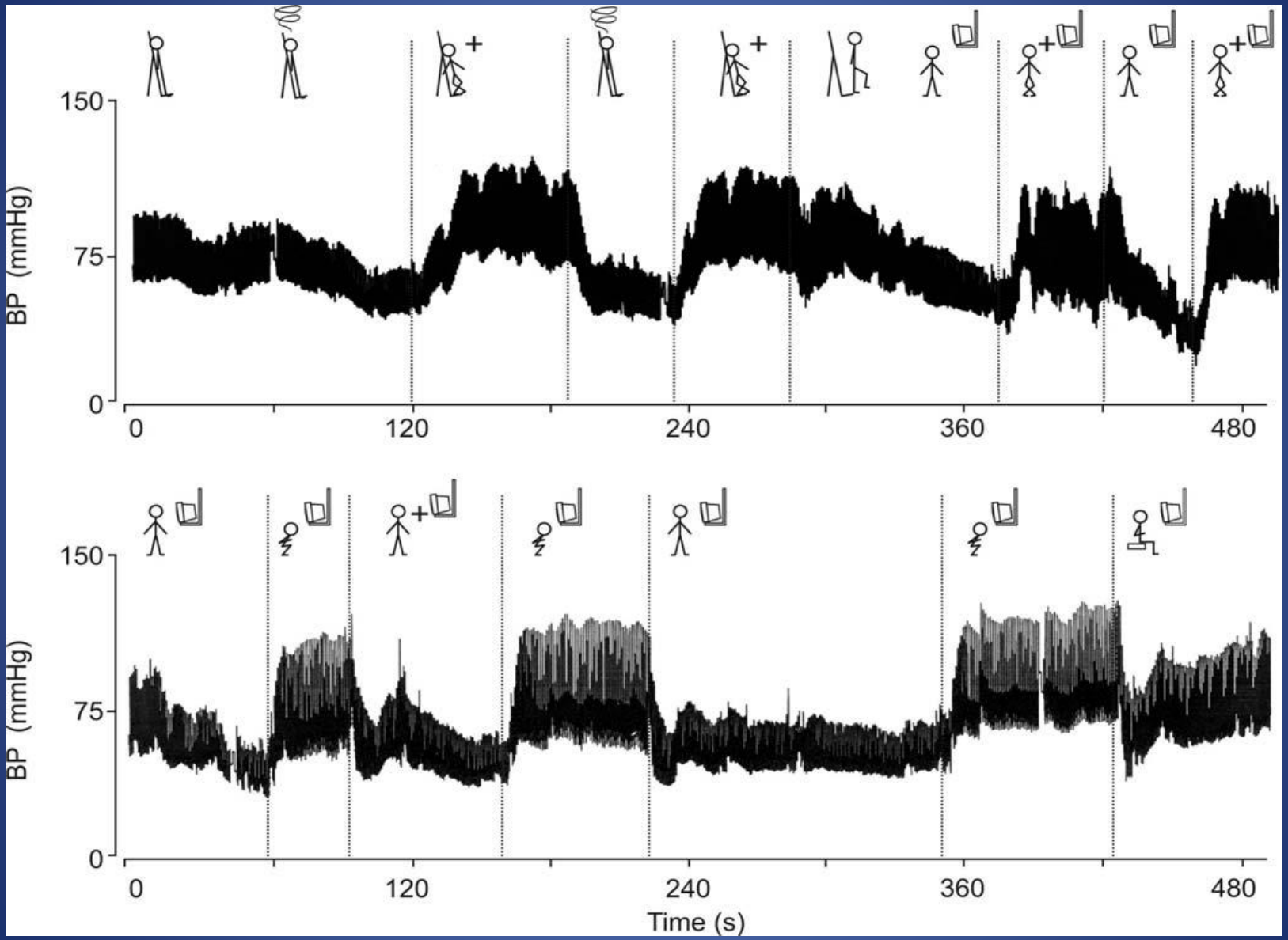

BP (mmHg)
200
0
0
120
Time (sec)


BP (mmHg)
200
0
0
120
Time (sec)


BP (mmHg)
200
0
0
60
Time (sec)

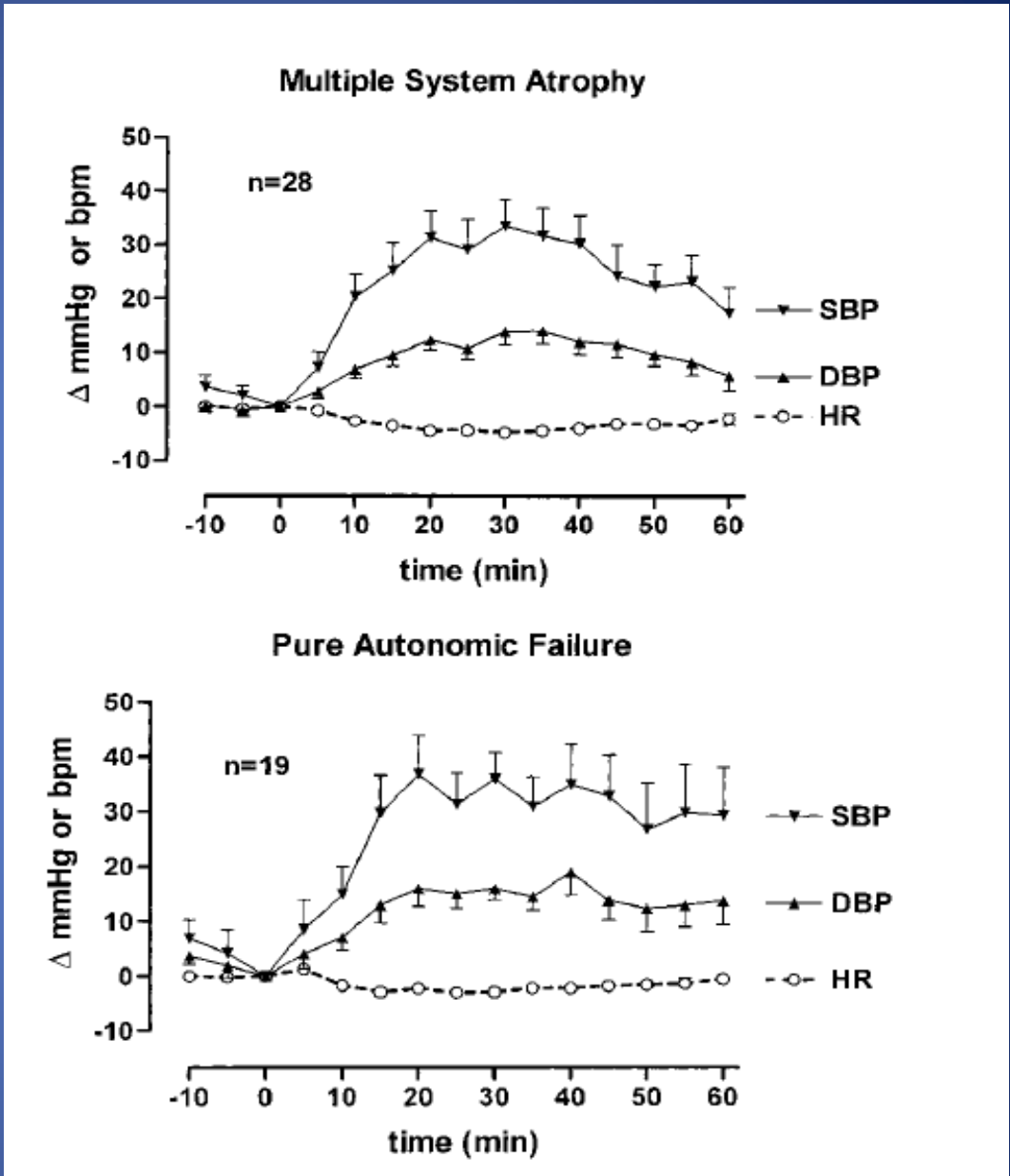

BP (mmHg)
200
0
0
120
Time (sec)

Biofeedback Effect on BP



Water Drinking

- 240 cc water
- Temperature does not matter
- Must be hypo-osmolar
- 480 cc a little better



Jordan, 2000

Salt Supplementation

- Reduces endothelial nitric oxide synthase activity
  - 5 mmol/L increase (eg 137 to 142) produces 25% reduction in NO production
  - 10 mmol/L -> 45% reduction
  - Li et al, J Nutr, 2009; 139: 447-451.
- Start with 2 g bid, and titrate based on response.

EXERCISE

- Levine 3 month Protocol
  - Target HR 75% max
  - 2-4 x/wk 30-45’ recumbent or water
  - Month 2: 100% HR max, longer sessions
  - Month 3: upright 5-6h/wk
  - Resistance training 1/wk to 2/wk

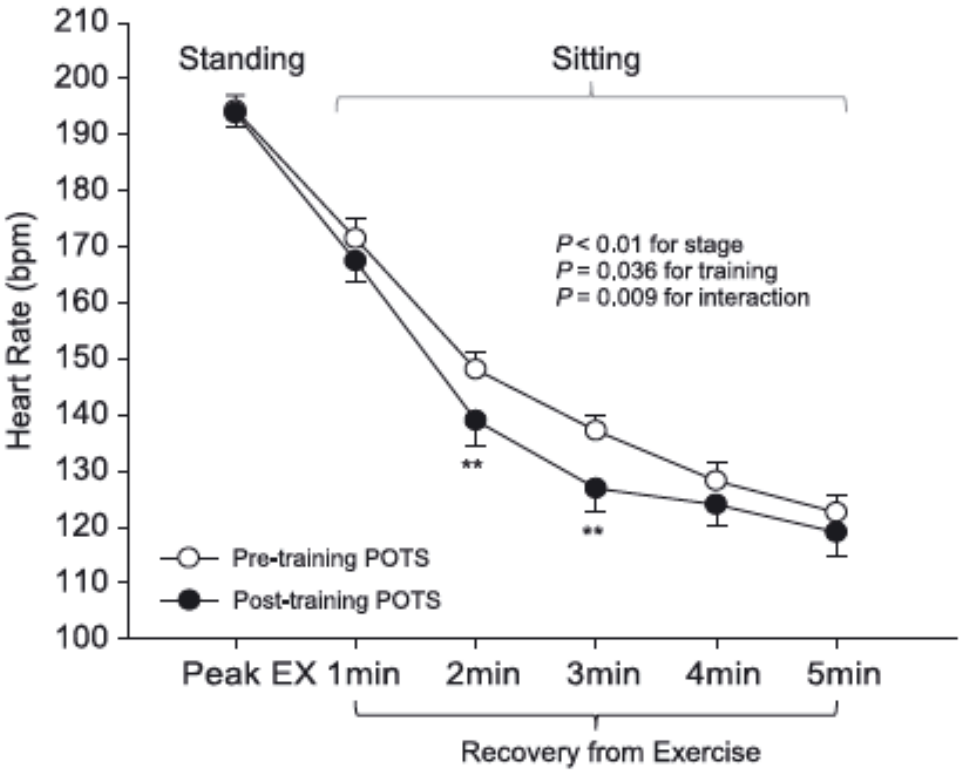


Figure 3. Heart rate (HR) recovery from exercise in POTS patients before and after exercise training. Peak EX, maximal exercise

Values are means ± SEM. $^{**}P < 0.01$ compared with pre-training in POTS.

SUPPLEMENTS

- CoQ10
- L-Carnitine
- Alpha-lipoic acid
- Riboflavin
- Creatine monophosphate or monohydrate

FIX ME SECTION

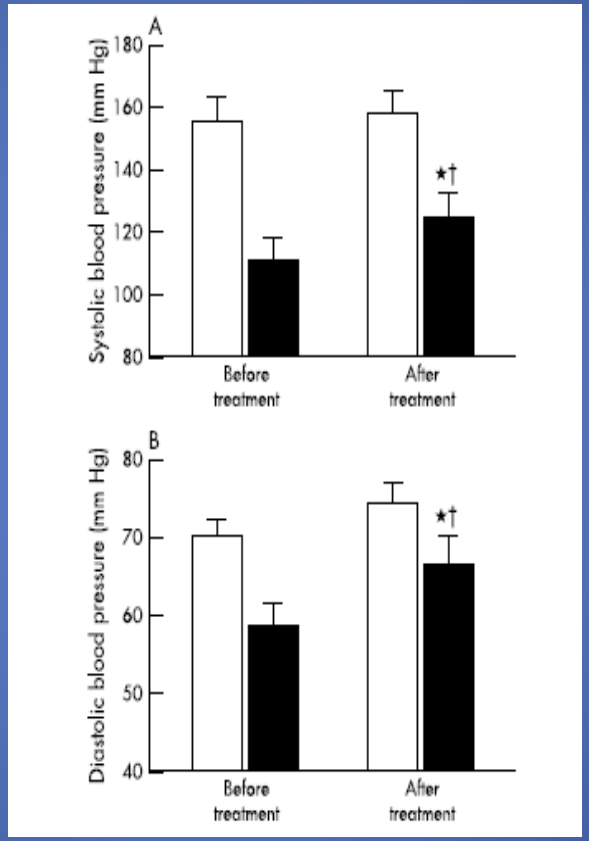
Fludrocortisone

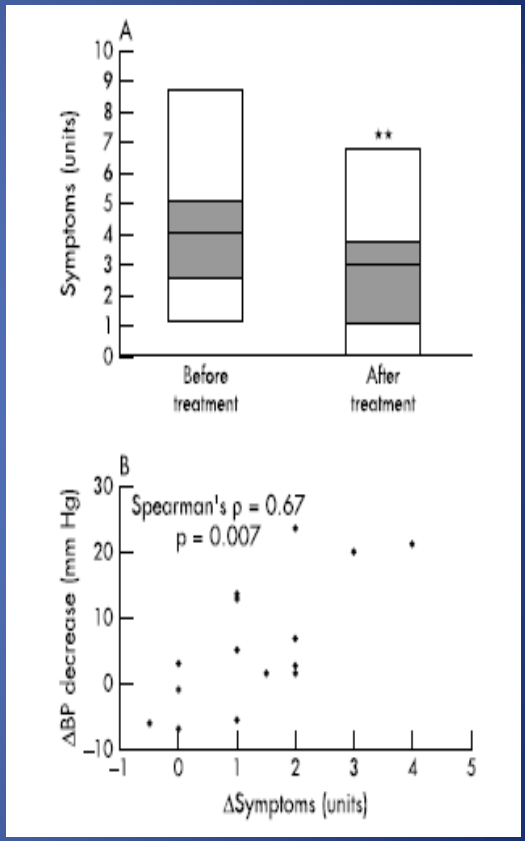
- Fludrocortisone
  - Mineralocorticoid
  - High-dose: aldosterone-like action, increases volume
  - Low-dose (<0.2mg/day): sensitizes alpha receptors (Davies, 1978)

Pyridostigmine

Singer et al, 2003

- 15 patients, 10 central and 5 peripheral
- Prospective open label single dose trial, based on 5’ tilt table test
- Increased ganglionic sympathetic traffic
- Traffic increases mainly in the upright position
- Little supine hypertension





Droxidopa

- Droxidopa [also, known as L-threo-3,4-dihydroxyphenylserine, L-threo-DOPS, or L-DOPS]
- Synthetic amino acid precursor of norepinephrine (NE)
- Originally developed by Sumitomo in Japan, approved since 1989
- Droxidopa improves symptoms of orthostatic hypotension in many conditions, including:
  - Shy-Drager syndrome (Multiple System Atrophy)
  - Pure Autonomic Failure
  - Parkinson's disease
- Very low incidence of AEs
  - well tolerated with an adverse event (AE) profile similar to placebo group in clinical studies
- FDA just approved in March 2014.

Midodrine

- Midodrine
  - Best for arterial problem (true OH)
  - Pure alpha-1 agonist
  - Does not cross into brain
  - 4 hour duration
  - Give at 8 am, noon and 4 pm
  - Do not lie supine once given

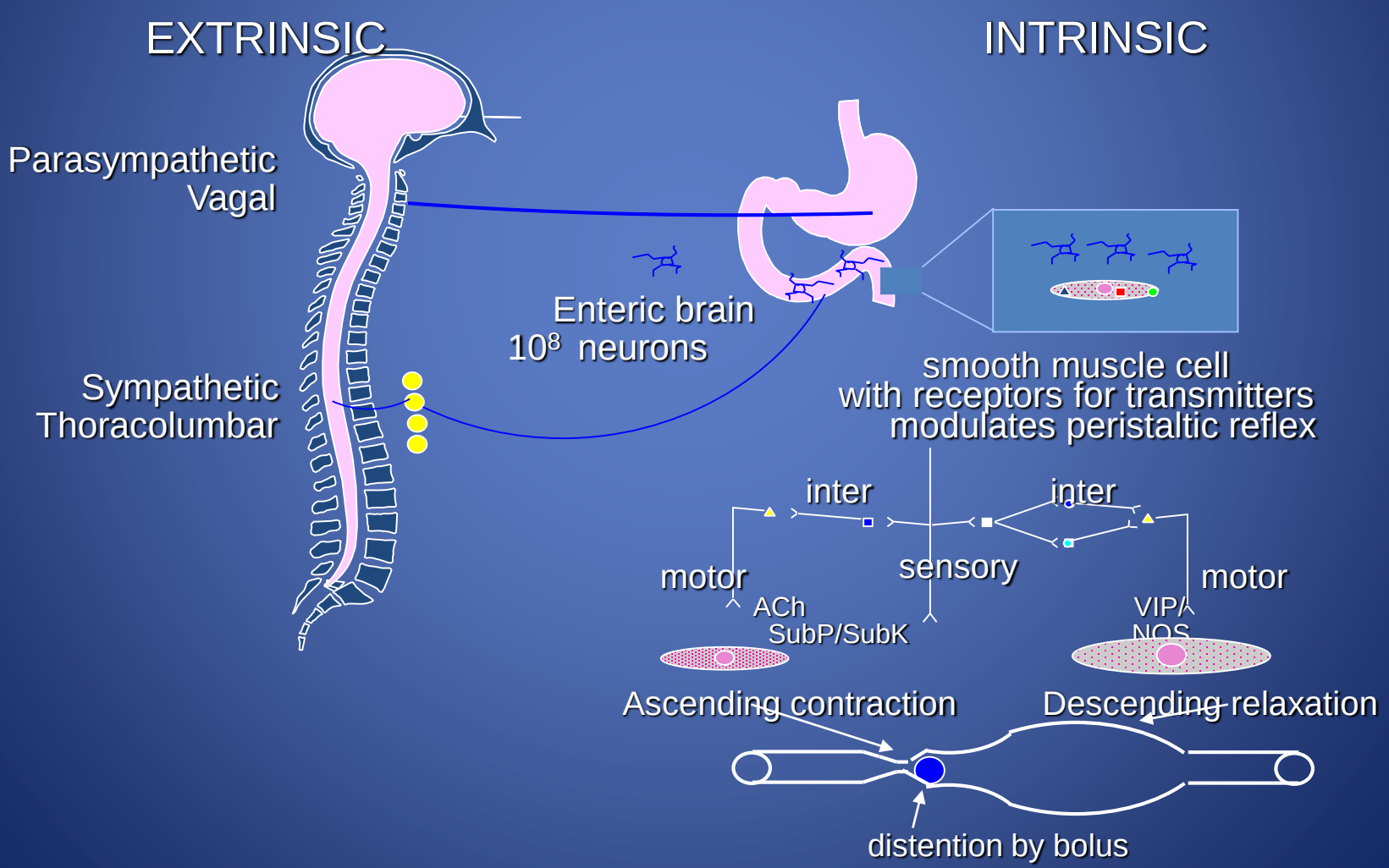
END

Bowel & Bladder

The Bladder

- 3 types of problems:
  - Incontinence - loss of control
  - Inability to void (retention)
  - Urgency
- Loss of control is due to degeneration of autonomic systems that control the bladder
- Urgency is due to changes in the spinal circuits and in the bladder nerves themselves

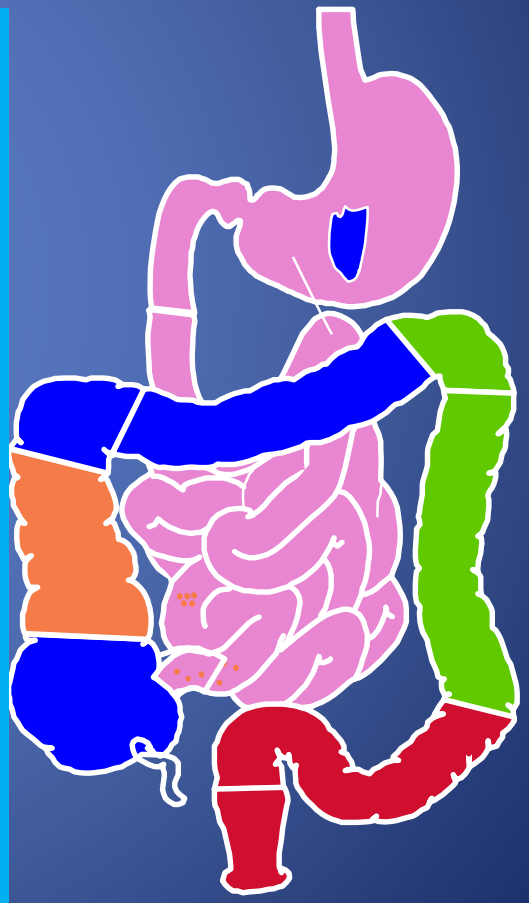
EXTRINSIC AND ENTERIC CONTROL OF GUT MOTIL



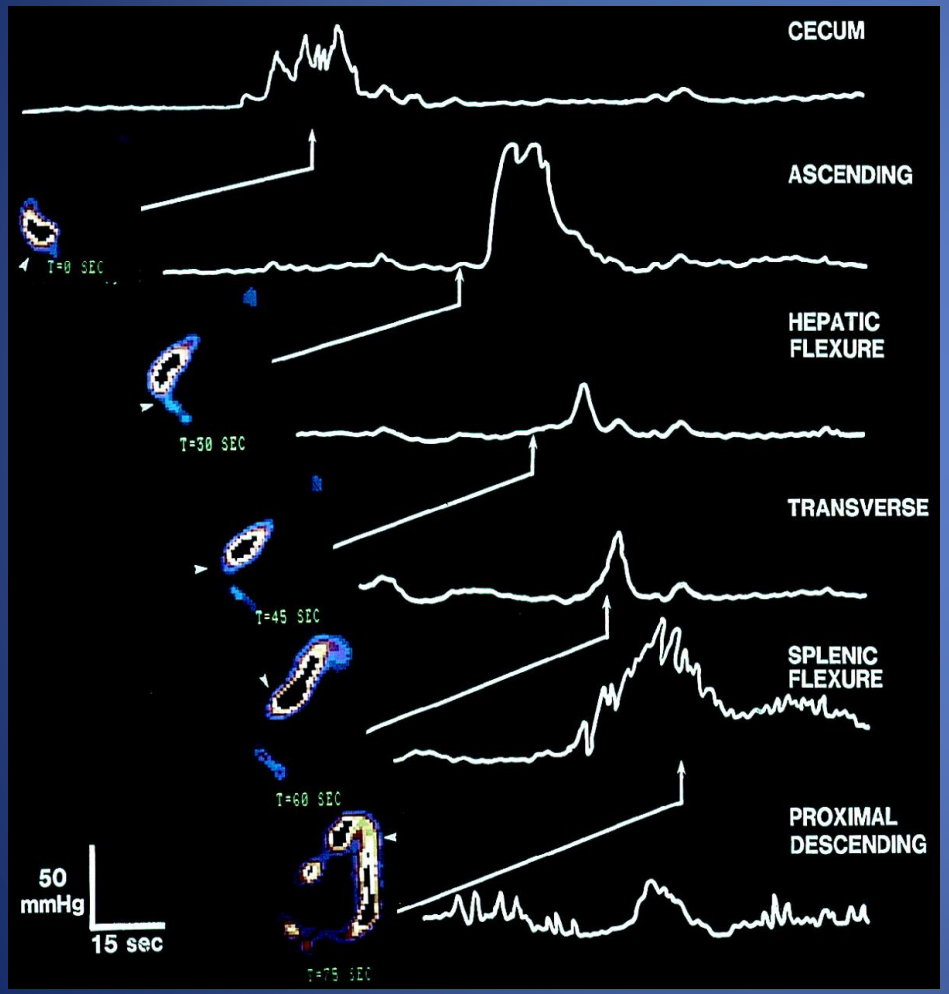
NEUROGASTROENTEROLOGY
Normal GI Motor Functions

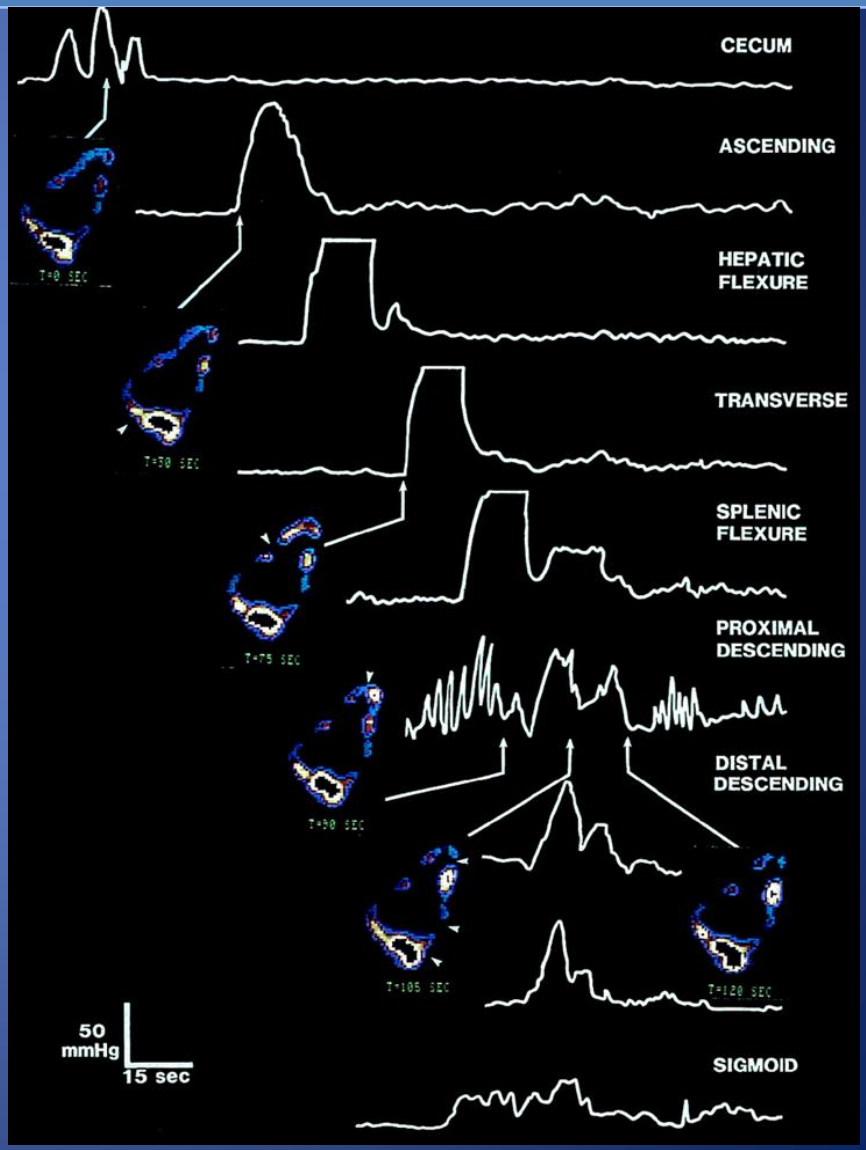
Colon: irregular mixing, absorption, transit:

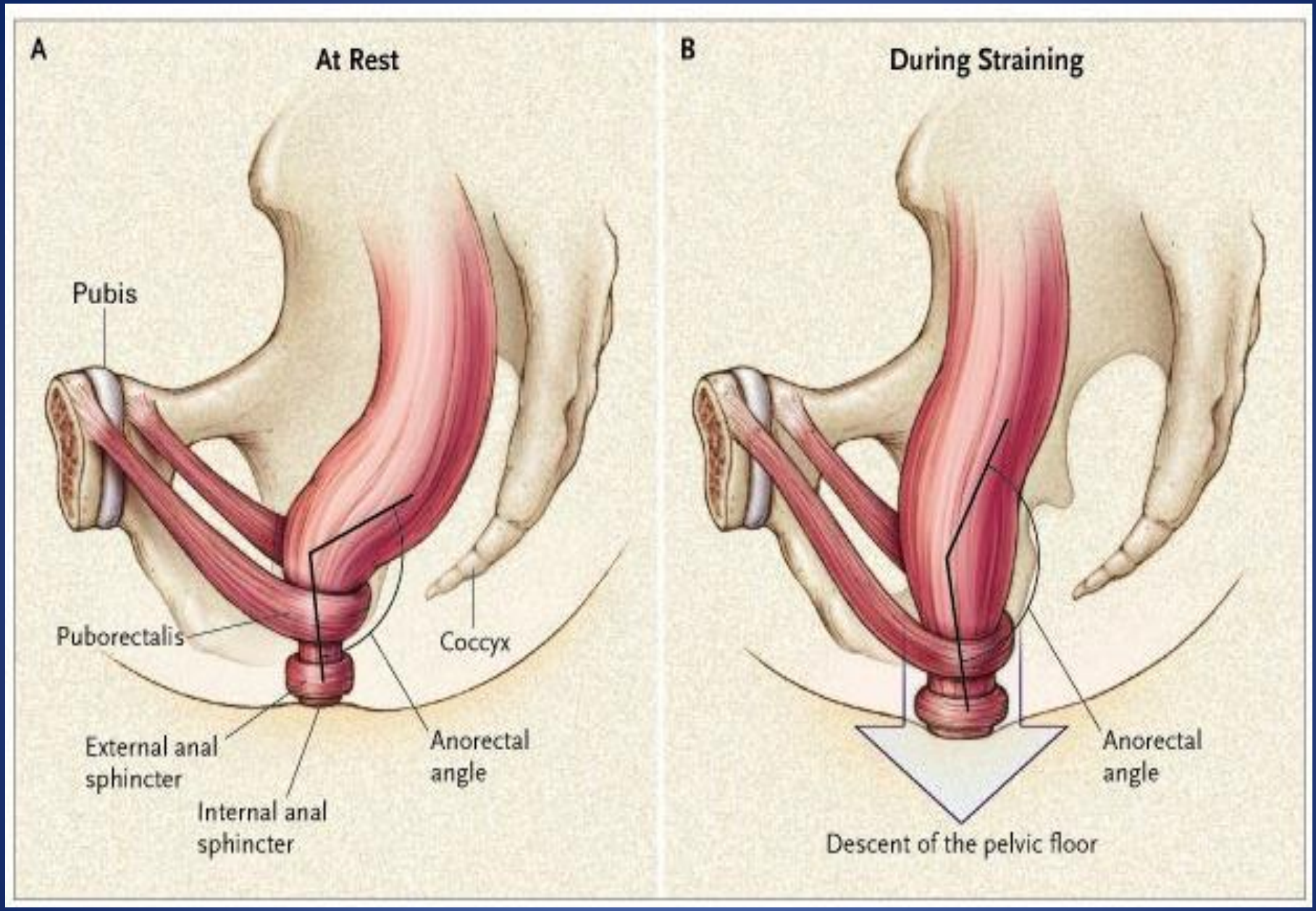
- Ascending, transverse: RESERVOIRS
- Descending: CONDUIT
- Sigmoid/Rectum: VOLITIONAL RESERVOIR



Correlation of Propagating Sequence and Transit in Human Colon





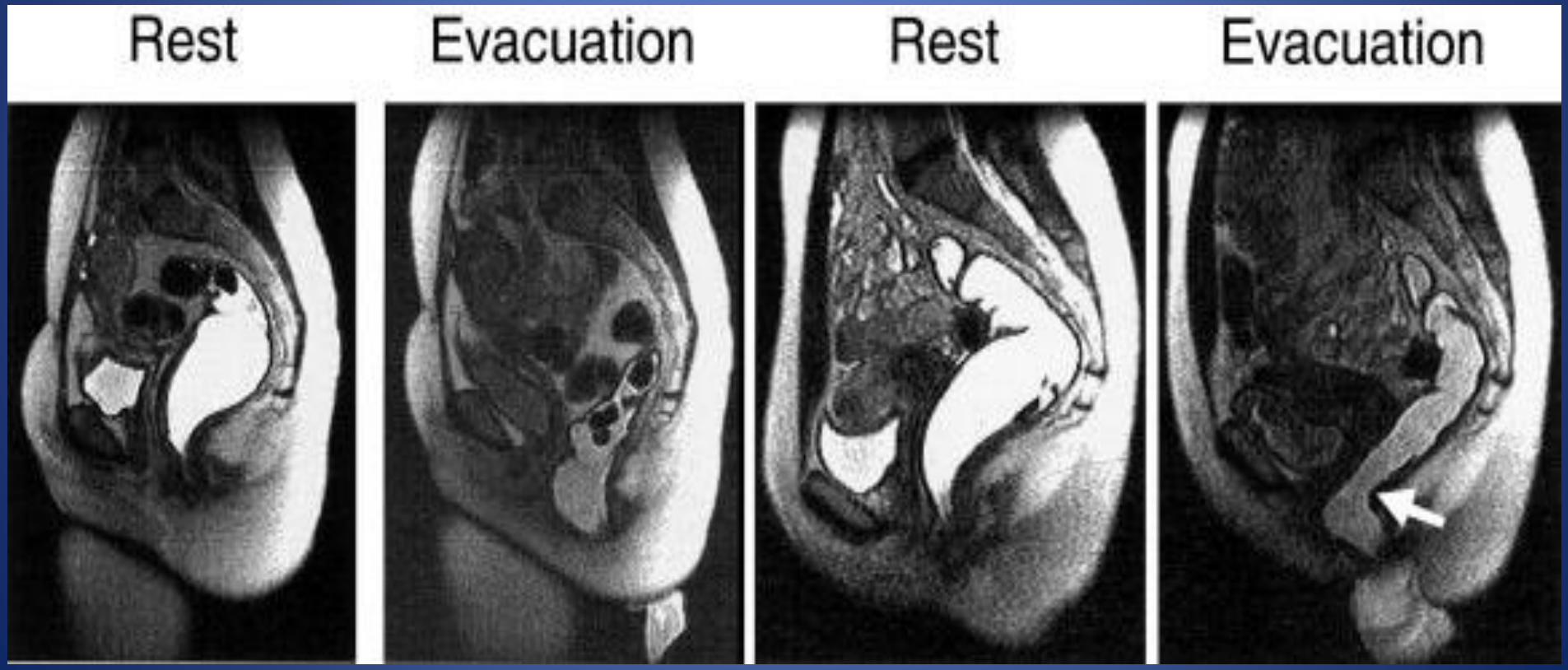


Constipation: importance of evacuation disorders

MRI Dynamic imaging of puborectalis function during rectal evacuation

normal puborectalis relaxation: perineal descent (2.6 cm) and anorectal angle increased by 36°

puborectalis contraction: perineal descent 1.7 cm and anorectal angle decreased by 10°



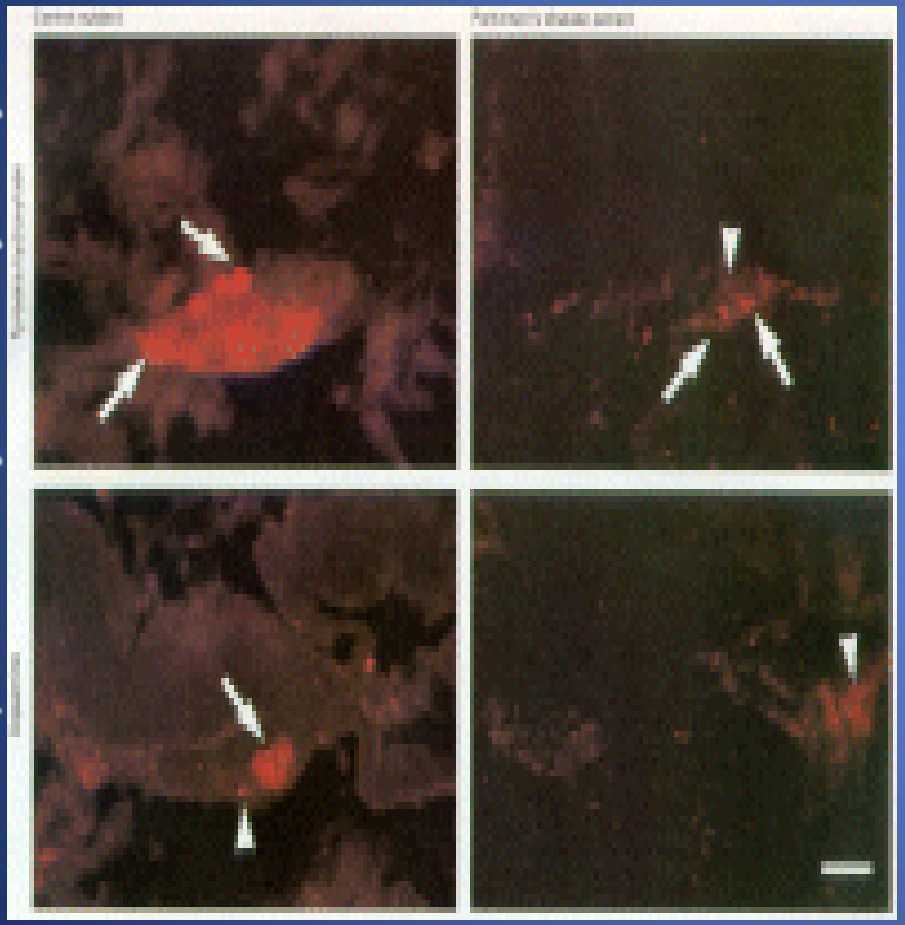
Enteric neuropathology and Constipation

- Selective neurological deficit
- Excitatory or inhibitory neuropathology?
- ICCs

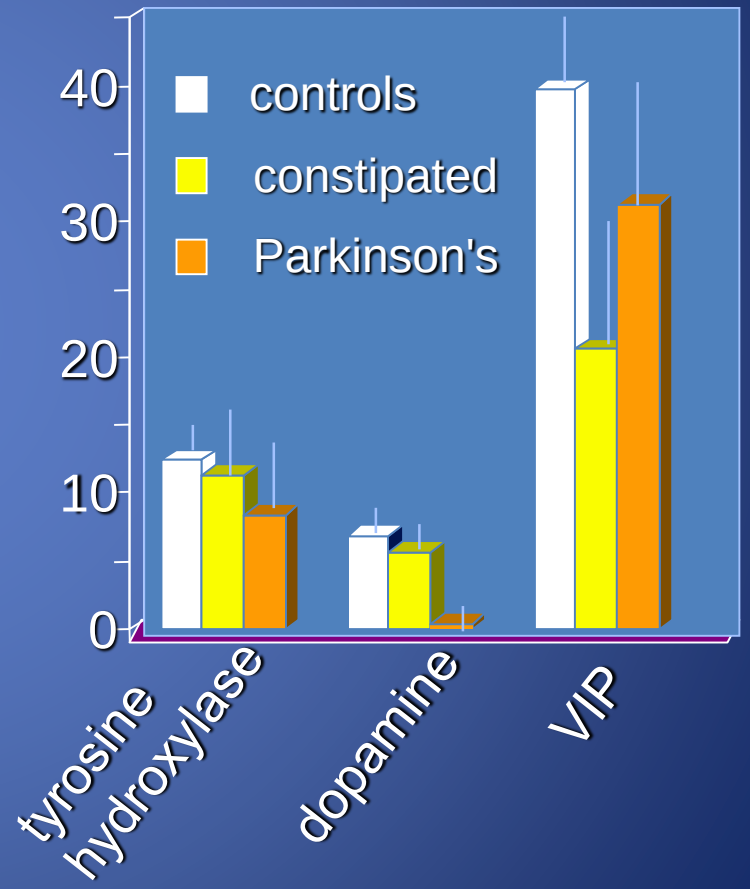
Colonic ENS in Parkinson's: Immunohistochemis

Control Parkinson's

Dopamine tyrosine hydroxylase



myenteric neurons per 100

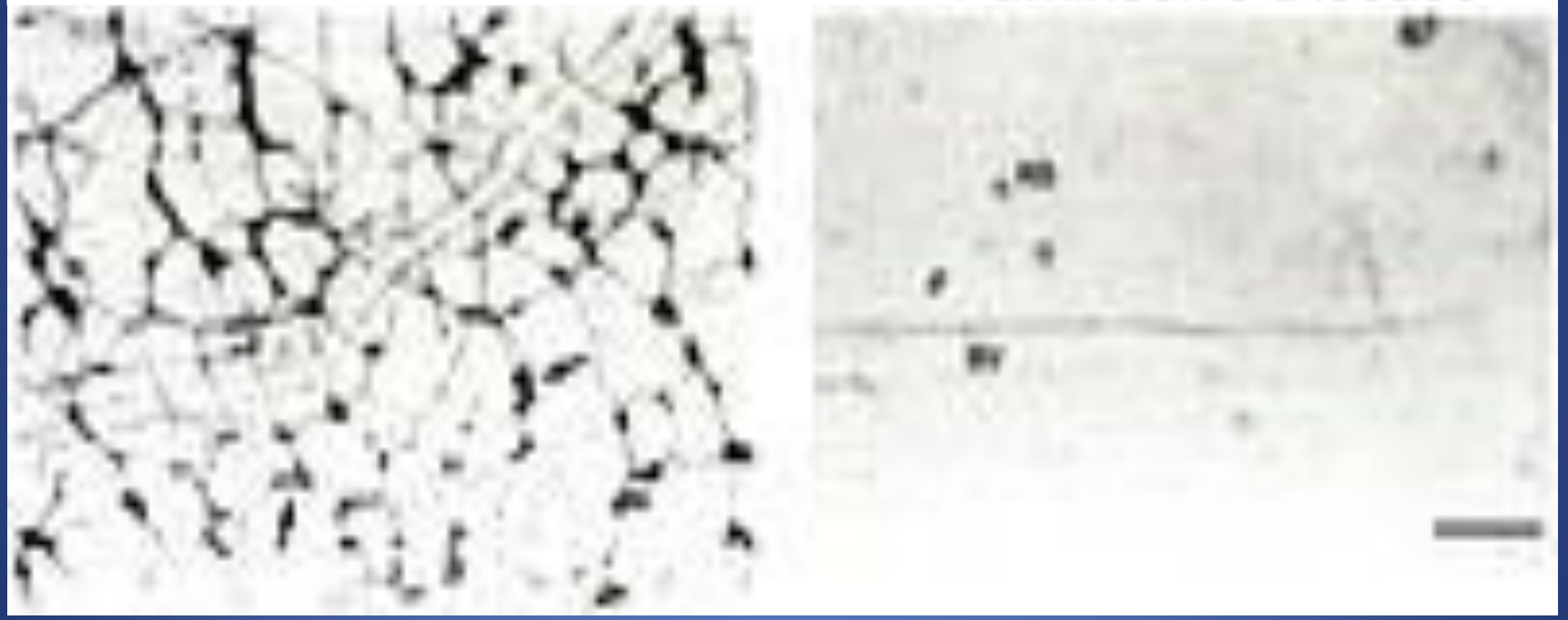


Colonic Myenteric Plexus in Parkinson's Disease

Singaram et al The Lancet; 346: 861-8, 1995

control

Parkinson's Disease



Dopamine in whole mounts of colon INS=internodal strands; NS=non-specific staining of single neurons; BV=blood vessel. Bar=180 micromole.

Constipation in Clinical Practice
Contributing factors especially in Elderly

- Inactivity
- Inappropriate diet
- Depression
- Medications
- Neuromuscular disorders
- Poor rectal sensation and evacuation dynamics
  - impaction

Wald. Drugs & Aging 1993;3:220-31

Read et al. GE 1985;89:959-62

Management of Fecal Incontinence

- Education
- Regulating bowel habits
- Sanitary devices
- Pelvic floor retraining
- Surgery

Managing Diarrhea

- Evaluate for organic cause
  - Endoscopy, biopsies, ? bacterial overgrowth
- Management
  - Consider eliminating fructose, sorbitol, caffeine
  - Loperamide - 2 - 6 mg upto tid, 30 min *before meals*
  - Amitriptyline
  - Clonidine
  - Bile salt binding agents – especially for patients who have had a cholecystectomy
  - Alosetron for refractory diarrhea
  - Pharmacological modulation of anal pressures

Neural Control of Voiding

- Higher brain functions: social continence
- Pontine micturition center
- Onuf's nucleus in cord (promotes storage)
- S2-S4 parasympathetic nerves (promotes voiding)
- Bladder: only two functions, that of storage and emptying…..

Bladder Physiology: Normal

1. Low storage pressures (<10 cm water)
- compliance
- no detrusor activity
- competent sphincter
- guarding reflex
- adequate capacity

2. Low emptying pressures (<10-50 cm water)
- adequate warning
- relaxation of skeletal and smooth muscle sphincters
- sustained detrusor pressure and power

Normal Voiding Parameters

- Voiding occurs 6-7 times a day
- Volumes voided 250-600 cc, peak flows variable [1]
- First sensation at 100-150 cc. The presence of sensation is more important that the volume at which it is felt.
- Adequate warning
- PVR < 50 cc, voided volume dependent
- Large variations are the normal! [2]

1 Gloumb J, Lindner A, Siegal Y,Korczak D. Variability and circadian changes in home uroflowmetry in patients with BPH compared to normal controls. J. Urol 147: 1044-1047, 1992

2 Wyndaele J. Normality in Urodynamics Studied in Healthy Adults. J Urol 161, 899-902, 1999

Pelvic organ symptoms differ with sites of neurological disease

Neurological Lesion	Symptoms of Pelvic Organ Dysfunction
Innervation within the pelvis	Bladder emptying difficulty ED, sometimes FSD
Peripheral neuropathy	ED (early) Bladder emptying difficulties (late) Diarrhea Postural hypotension
Cauda equina	Saddle sensory impairment Stress urinary incontinence Difficulty in initiation of micturition Urgency (occasionally) Sexual sensory loss ED, FSD Constipation Fecal incontinence, difficulty in evacuation
Spinal	Somatic sensory level Urinary urgency Incomplete bladder emptying ED, FSD Difficulty in bowel evacuation (in advanced disease)
Pontine (very rare)	Internuclear ophthalmoplegia Urinary retention
Extrapyramidal	Parkinsonism (advanced in IPD, minor in MSA) ED (early in MSA) Urinary incontinence (early in MSA) Constipation
Frontal	Personality change Urinary urge incontinence Fecal Incontinence (exceptional)

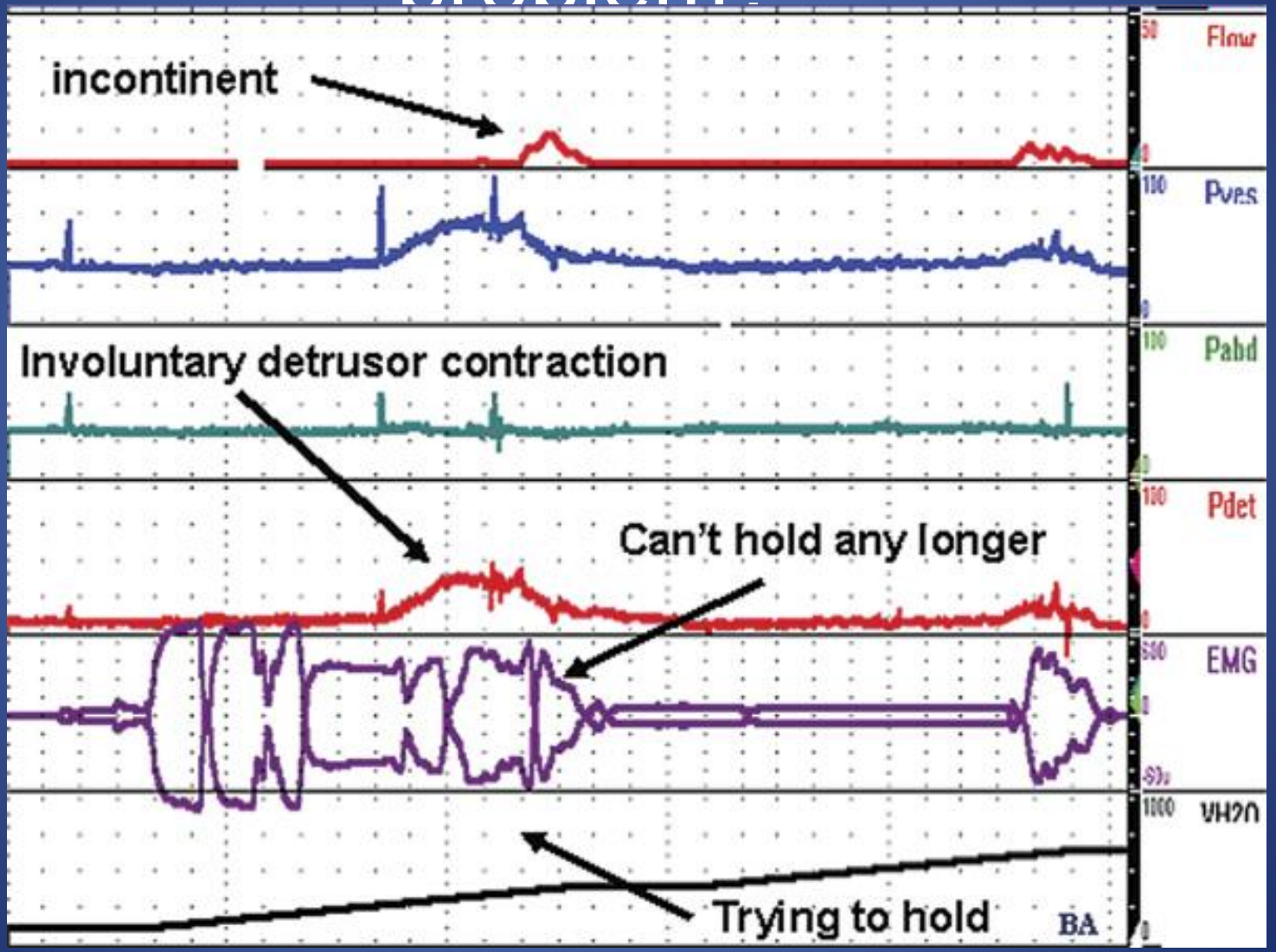
ED, erectile dysfunction; FSD, female sexual dysfunction; IPD, idiopathic Parkinson's disease, MSA, multiple system atrophy

Bladder does just two things: storage and emptying

How do your treat an overactive bladder?

- Behavioral
  - Fluid schedules
  - Treat pelvic floor , constipation
  - Timed/Prompted voiding
  - Absorbent garments
- Anti-muscarinic Medications: Ditropan™, Detrol ™, Vesicare ™, Enablex ™, Oxytrol ™, Gelnique ™, Toviaz ™, oxybutynin

What's the nature of the problem?



Bladder tips

- Evaluate for large prostate in men
- Urgency can be treated by medications such as ditropan, detrol, vesicare etc.
- Retention: can try meds like hytrin, alpha-blockers, but usually difficult to tolerate due to orthostatic hypotension

Self-catheterization

- Can be combined with medications
- Can be done just before bed and first thing in the morning
- Tailor it to needs and to requirements of safety
  - More often -> Less risk to kidneys
  - Less often -> less risk of UTI

Bowel

- Constipation
  - Use regular miralax (polyethylene glycol) as first line treatment, number of tablespoons needed to keep bowel moving.
  - Can add glycerol suppository or clonidine
  - Home”clean-out” quarterly if recurrent obstipation using 1 dose of dulcolax, 6 doses miralax, repeat dulcolax over 8 hours, close to toilet!
- Diarrhea
  - Make sure not due to overflow from obstruction (most often this is the case)
  - Can add a beta-blocker, verapamil, anti-cholinergic agent