Autonomic Dysfunction in Parkinson Disease and Other Neurological Disorders

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Disclosures

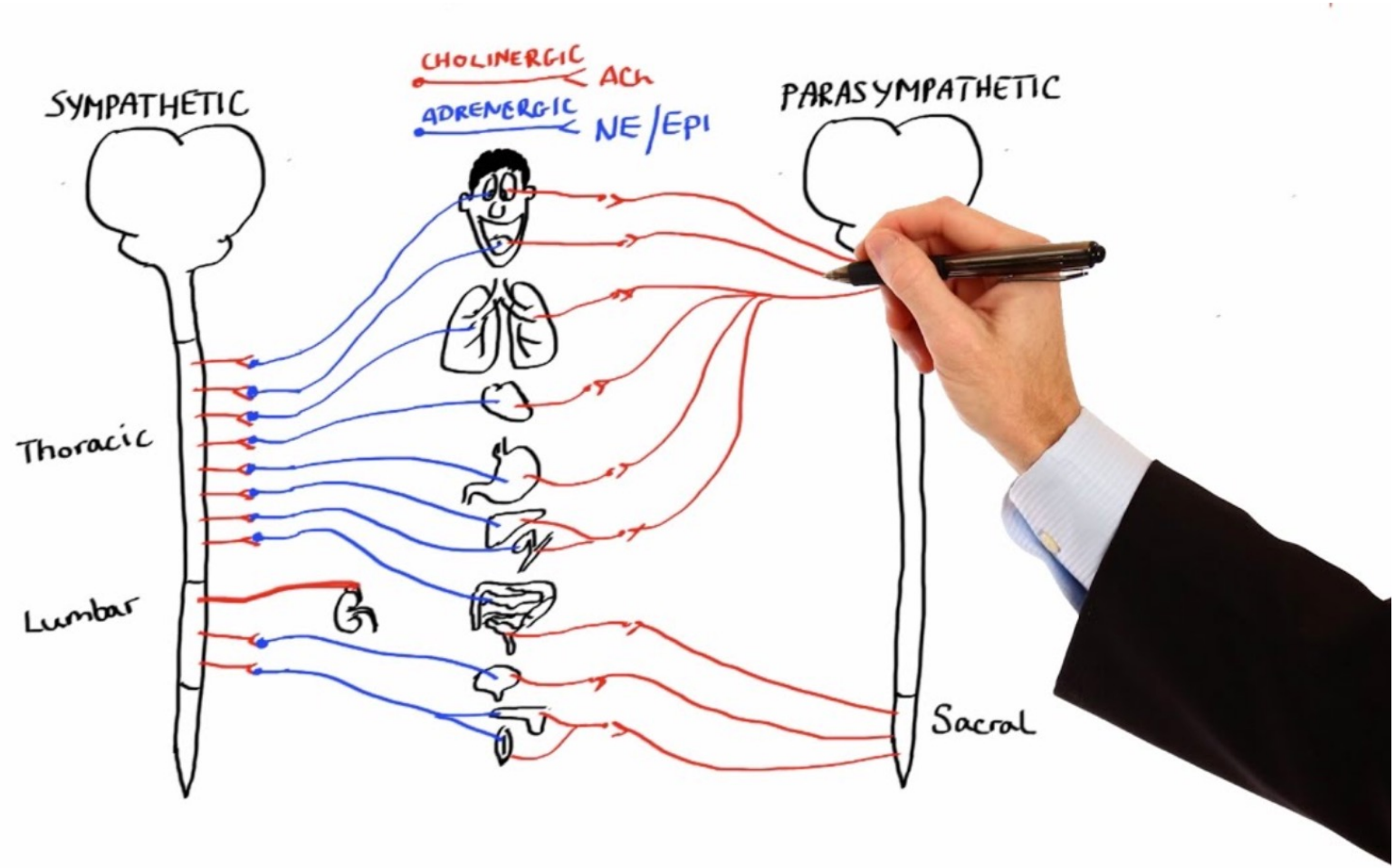
Speaker Honoraria and Consultancies

- Abbott Laboratories
- Abbvie
- Medtronic
- Theravance BioPharma

Grant Support

- NIH
- Lundbeck
- Abbvie

The Autonomic Nervous System



The Nondeclaration of Nonmotor Symptoms of Parkinson's Disease to Health Care Professionals: An International Study Using the Nonmotor Symptoms Questionnaire

Multicenter International Study (13 Centers)

242 PD patients were asked to fill in the NMSQ

After completion they were asked if they had discussed the positive symptoms with any Health Care Professional before

Movement Disorders
Vol. 25, No. 6, 2010, pp. 704–709

The Nondeclaration of Nonmotor Symptoms of Parkinson's Disease to Health Care Professionals: An International Study Using the Nonmotor Symptoms Questionnaire

Symptom	Positive	Non-declared
Dribbling	41.7%	45.5%
Constipation	47.5%	46.1%
Urinary Urgency	59.9%	42.1%
Dizziness	38.8%	50.0%
Sweating	30.6%	33.8%

Movement Disorders
Vol. 25, No. 6, 2010, pp. 704–709

Orthostatic hypotension in Parkinson's disease: Does it matter if asymptomatic?

121 consecutive PD patients:

	OH- (n= 84)	**OH+** (n= 37)	
		Asymptomatic (n= 14)	***Symptomatic*** (n= 23)
UPDRS-II	10.2	15	17.2
PDQ-8	6.6	9.9	10.5
Falls	16.7%	50%	47.8%

Parkinsonism and Related Disorders 33 (2016) 65–71

Autonomic dysfunction in subjects at high risk for Parkinson's disease

Pre-Motor PD (n= 40):
SN hyperecogenicity + hyposmia + depression + mild motor alterations suggestive of extrapyramidal involvement

Compared to:

a) **Healthy Controls** (n= 50)
b) **PD patients** (n= 113)

J Neurol (2015) 262:2643–2652

Autonomic dysfunction in subjects at high risk for Parkinson's disease

	Healthy Controls	Pre-Motor PD	PD
Urinary Dysfunction	6%	18%	44%
Bowel Dysfunction	4%	11%	34%
Sexual Dysfunction	12%	15%	35%
OH	0%	7.5%	28.1%

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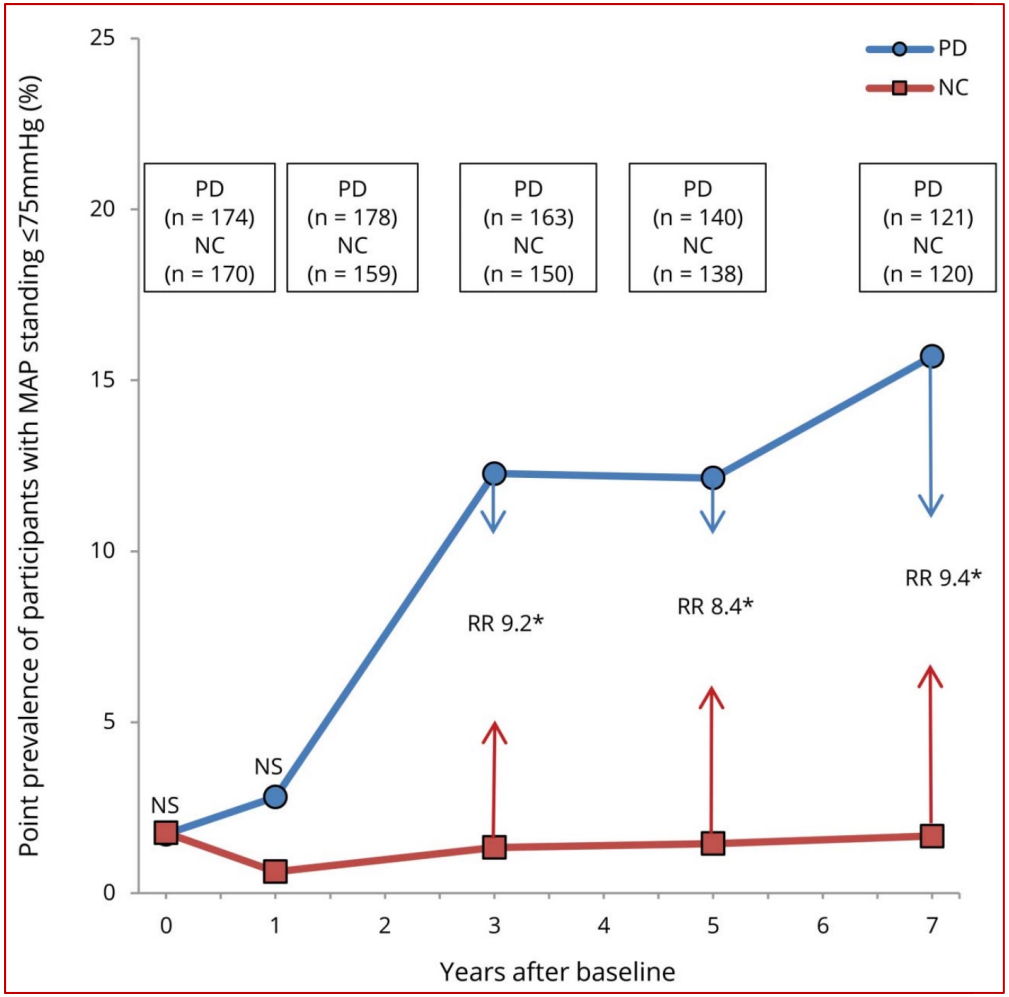
OH Prevalence in Parkinson Disease



Neurology, Volume 93, Number 16, 2019

Tilt Table Testing

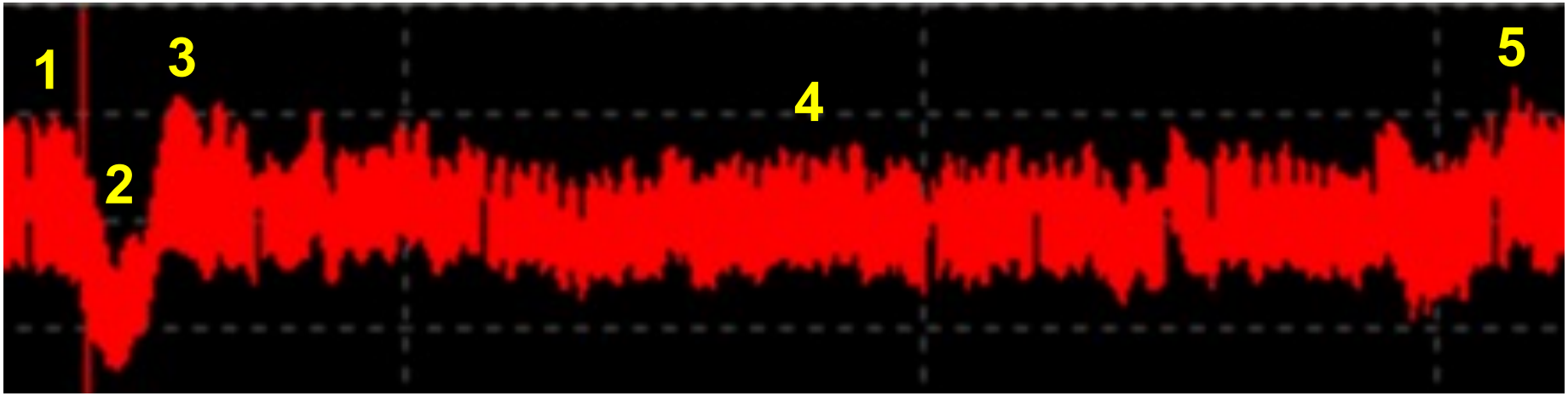
Lay down for 5 minutes to reach a stable baseline of BP and HR

The table is tilted up laying → > 60° for 5 minutes while recording BP and HR

Lay down for 5 minutes while recording BP and HR

Head-up Tilt: Normal BP Response

1) Initial Blood Pressure rise (3 sec)→ sympathetic transient activation
2) Stand up (7 sec)→ Blood Pressure fall
3) Overshoot → sympathetic activation / Inibithion of parasimpathetic output
4) Blood Pressure stabilitation
5) Gradual blood pressure and heart rate increase

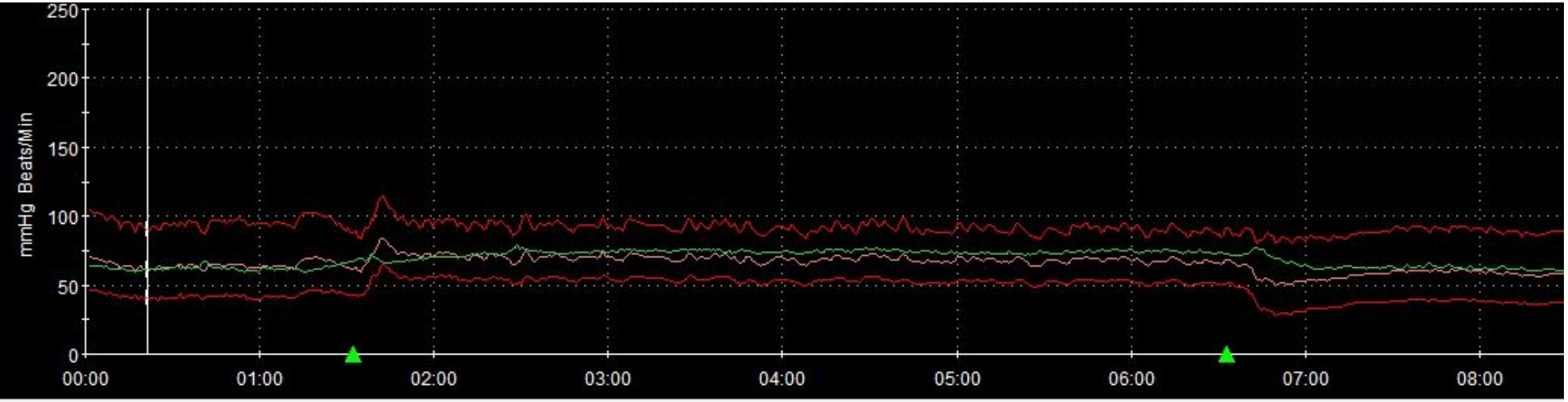


Tilt Table Testing

Systolic blood pressure

Heart Rate

Diastolic blood pressure



The table is tilted up laying → 70°

The table is tilted down 70° → laying

Orthostatic Hypotension (OH)

Head-up tilt (HUT): BP fall ≥ 20 mmHg (systolic) and/or 10 mmHg (diastolic) within 3 minutes of standing or HUT to at least 60°. Some Authors advocate for a BP fall threshold of 30/15 mmHg if supine hypertension is present or to fulfill MSA diagnostic criteria.

Sit-to stand test: technically simpler test than standard HUT, with screening purposes; the diagnostic threshold of BP drop is ≥ 15 mmHg (systolic) and/or 7 mmHg (diastolic).

Initial OH: BP fall ≥ 40/20 mmHg within 15 seconds of active standing. No clear pathologic meaning, but it can lead to orthostatic symptoms or syncope. Detectable with beat-to-beat technology only.

Delayed OH: OH ensuing after 3 minutes of upright standing, up to 10-30 minutes after standing. Represents a milder degree of autonomic failure and can mimic vaso-vagal syncope.

Tilt Table Testing

Systolic blood pressure

Heart Rate

Diastolic blood pressure

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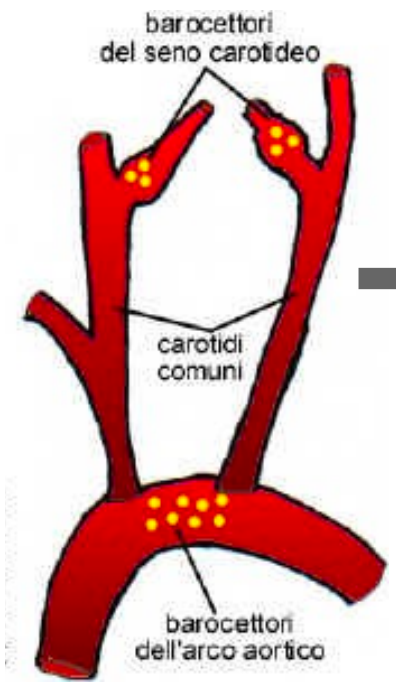
Pathological Alterations in the Baroreflex



Nucleus Tractus Solitarious

MVLC – MVLR (Sympathetic)

Nucleus Ambiguos

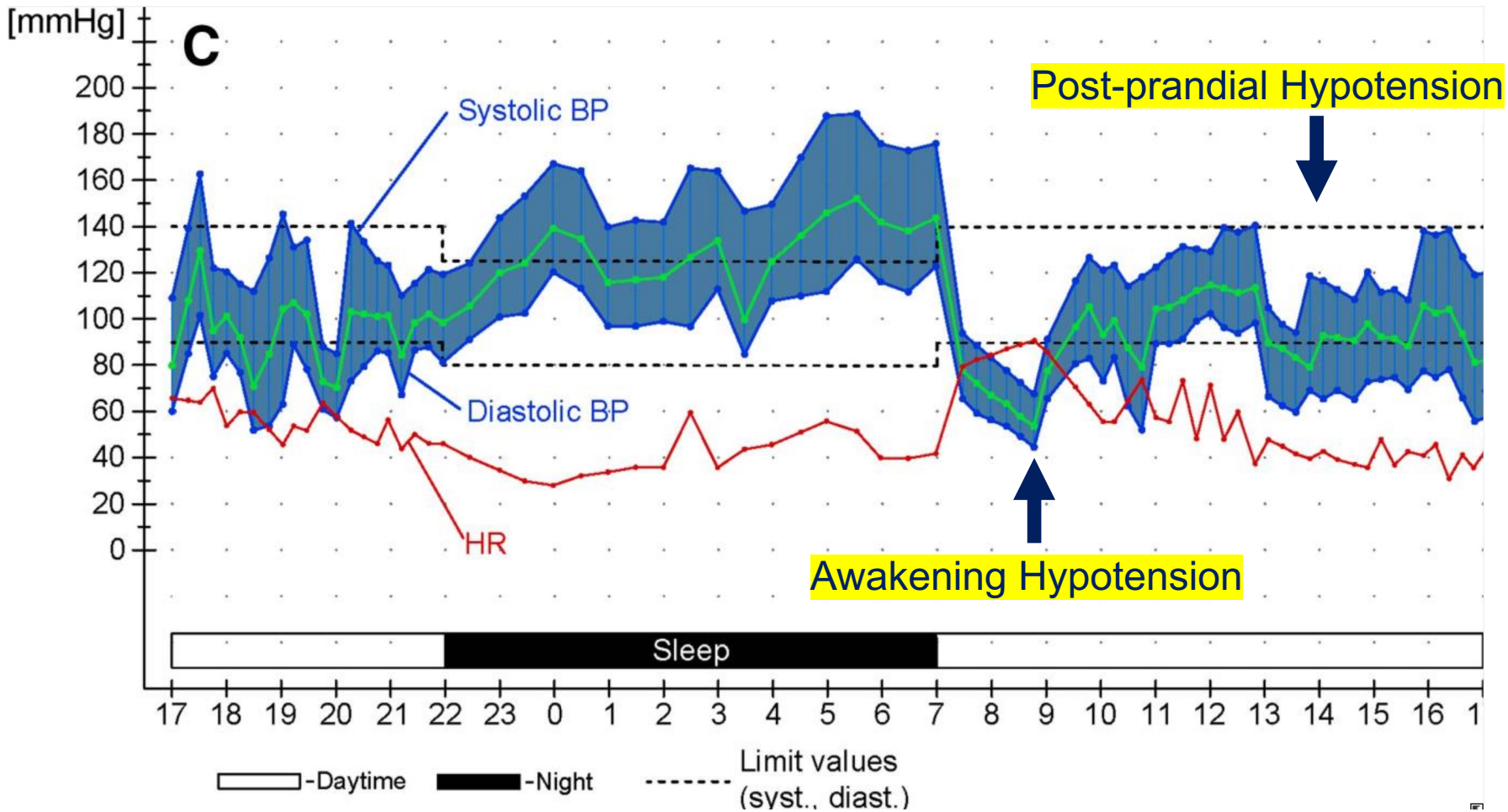
Blood Vessels

Vagal Nerve Parasympathetic

AV

SA

Abnormalities in the Circadian Rythm



Clin Auton Res. 2018 Aug;28(4):355-362. doi: 10.1007/s10286-018-0529-8.

Neurogenic vs. Non-Neurogenic OH

OH can be distinguished in:

a) Neurogenic (nOH) → Cardiovascular autonomic neuropathy
b) Non-neurogenic OH → Dehydration, hypovolemia, cardiac pump failure, and venous pooling

In nOH the expected compensatory heart rate (HR) increase is reduced.

Suggested cut-off to support the diagnosis of nOH:

-Standing HR increase < 15 bpm in the presence of OH.

-ΔHR/ Δ SBP ratio < 0.5 bpm/mmHg

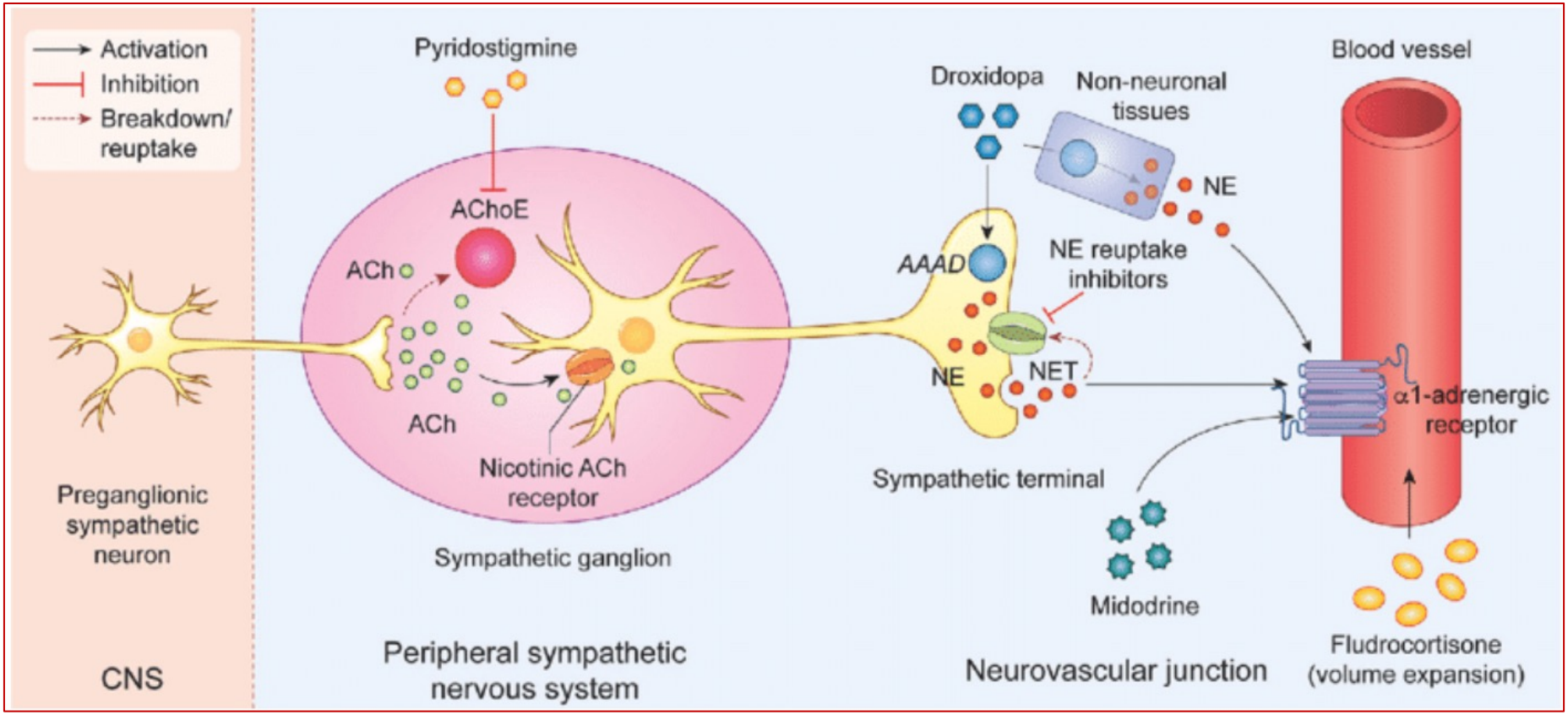
Orthostatic hypotension in Parkinson Disease: Impact on Health Care Utilization

Healthcare utilization cost in United States Dollars per patient per year.

	PD-OH+ (n = 93)	PD-OH− (n = 224)	P-value
Hospitalizations	$22,813 ± $6280	$7995 ± $4001	**0.038**
ER visits	$1425 ± $426	$911 ± $302	**0.044**
Outpatients visits	$863 ± $61	$852 ± $47	0.854
Telephone calls/e-mails	$62 ± $7	$39 ± $5	**0.006**
TOTAL	$25,205 ± $6546	$9831 ± $4167	**0.037**

Parkinsonism and Related Disorders 47 (2018) 45–49

Orthostatic Hypotension: Therapies



Mov Disord. 2018 Mar;33(3):372-390

Supine Hypertension: Definitions

Mild SH= Systolic ≥140 mmHg e/o Diastolic ≥90 mmHg after 5 or more minutes of supine resting

Moderate SH= Systolic ≥160 mmHg e/o Diastolic ≥100 mmHg after 5 or more minutes of supine resting

Severe SH= Systolic ≥180 mmHg e/o Diastolic ≥110 mmHg after 5 or more minutes of supine resting

Pharmacological Therapies for Supine Hypertension

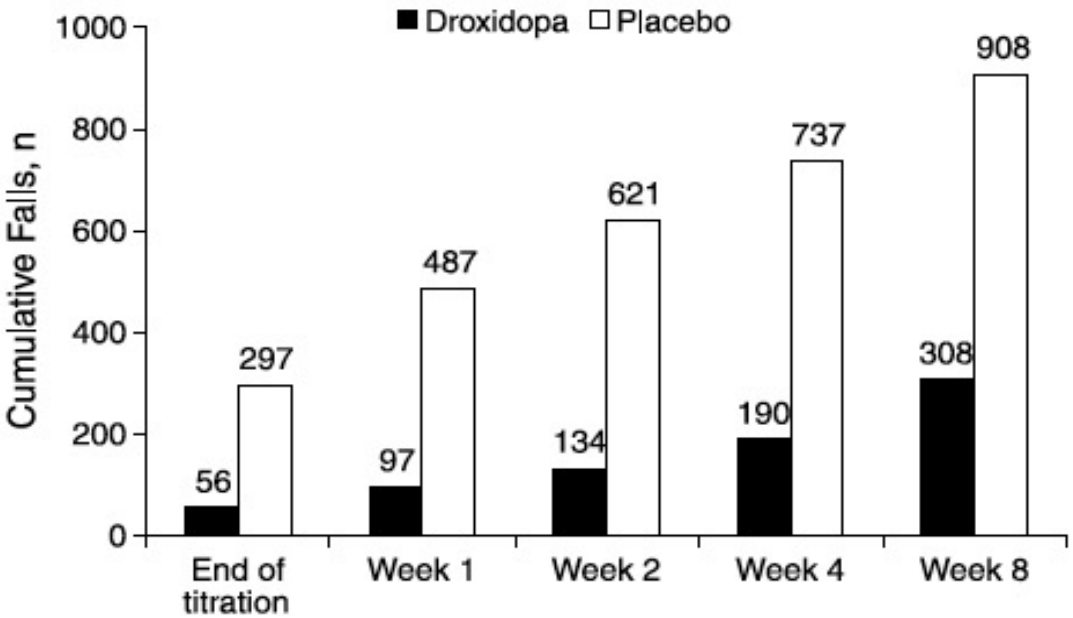
- Captopril 25 mg
- Clonidine 0.1 mg (risk of ”awakening hypotension”)
- Hydralazine 10-25 mg
- Losartan 50 mg
- Nitroglycerine patch 0.1 mg/h

Clin Auton Res. 2018 Aug;28(4):355-362.

Impact of Pharmacological Therapy

Droxidopa and Reduced Falls in a Trial of Parkinson Disease Patients With Neurogenic Orthostatic Hypotension

Phase 3, randomized, placebo controlled, double-blind study
225 PD, non-demented patients with OH



Clinical Neuropharmacology, 39, 2016

POTS – Postural Orthostatic Tachycardia Syndrome

Heart rate increment of ≥30 bpm within 10 min of standing or head-up tilt associated with lightheadedness, palpitations, sweating, or tremulousness, relieved by recumbency. Standing heart rate is often ≥120 bpm.

1. Neuropathic POTS (small orthostatic decrease of BP, not fulfilling OH criteria, reduced leg sweating) → *vasoconstrictor (α1 agonists, droxidopa)*

2. Hyperadrenergic POTS (orthostatic BP increase with elevated plasma norepinephrine) → *β-blockers, clonidine, ivabradine*

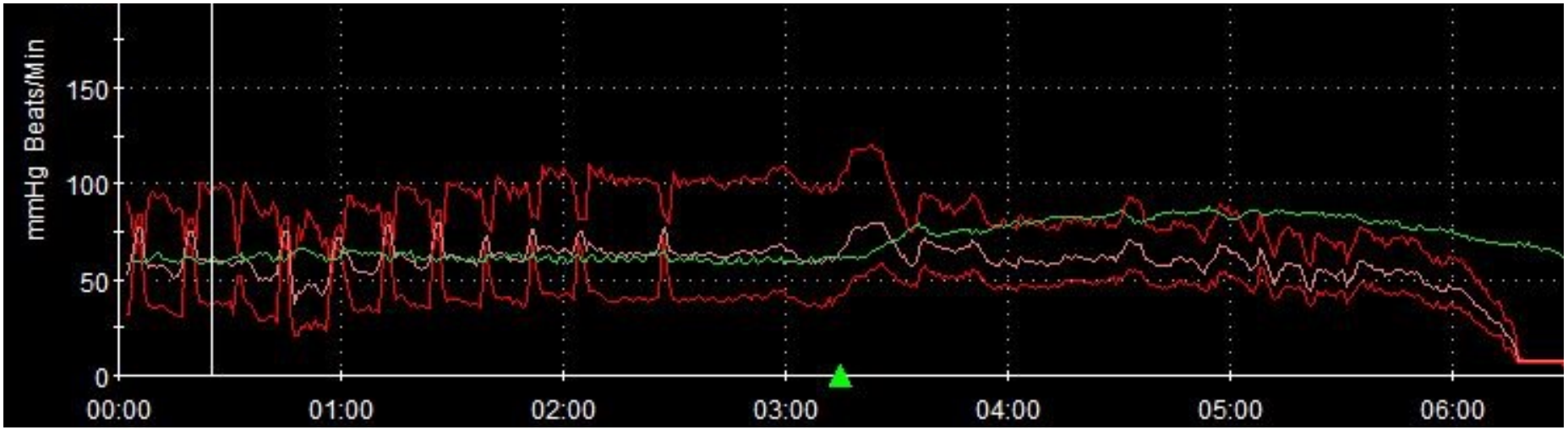
3. Deconditioned/Hypovolemic POTS (orthostatic reduction in pulse pressure, consequent to physical deconditioning or inadequate sodium and fluid intake) → *fludrocortisone, water, and salt*

Tilt Table Testing

Systolic blood pressure

Heart Rate

Diastolic blood pressure



The table is tilted up laying → 70°

Neurally mediated (reflex) syncope

Sudden change in autonomic nervous system activity that leads to a fall in cerebral perfusion with **cardiodepressive**, **vasodepressive**, or **mixed** components.

Reflex syncope encompasses:

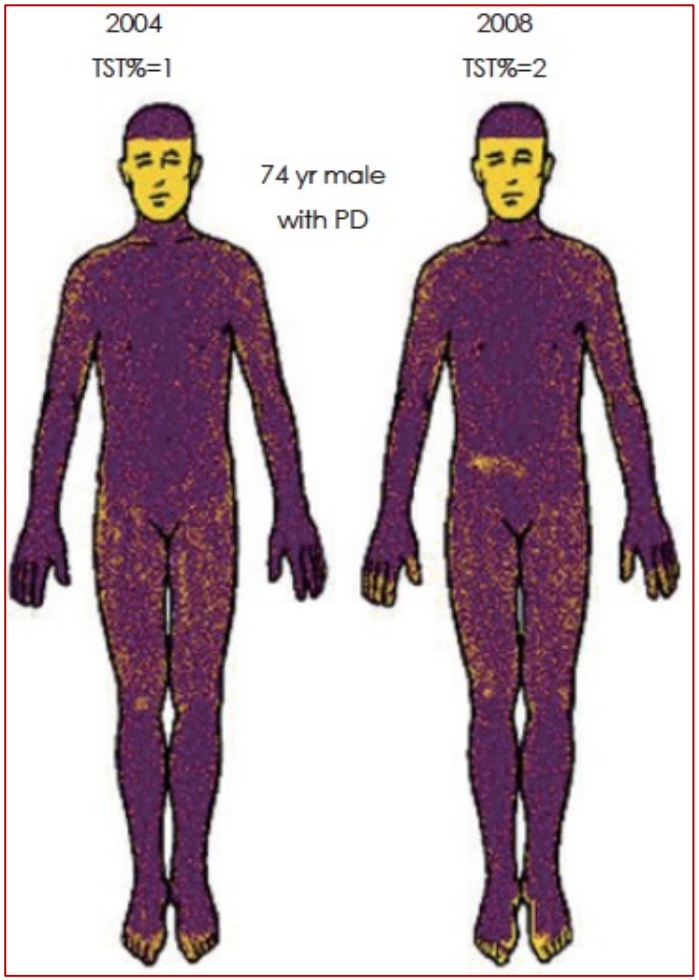
a) **Vasovagal syncope**: triggered by orthostasis, emotions, or pain
b) **Situational syncope**: triggered by micturition, cough, or other visceral stimuli
c) **Carotid Sinus Hypersensitivity**: triggered by hypersensitivity of the carotid sinus baroreceptors

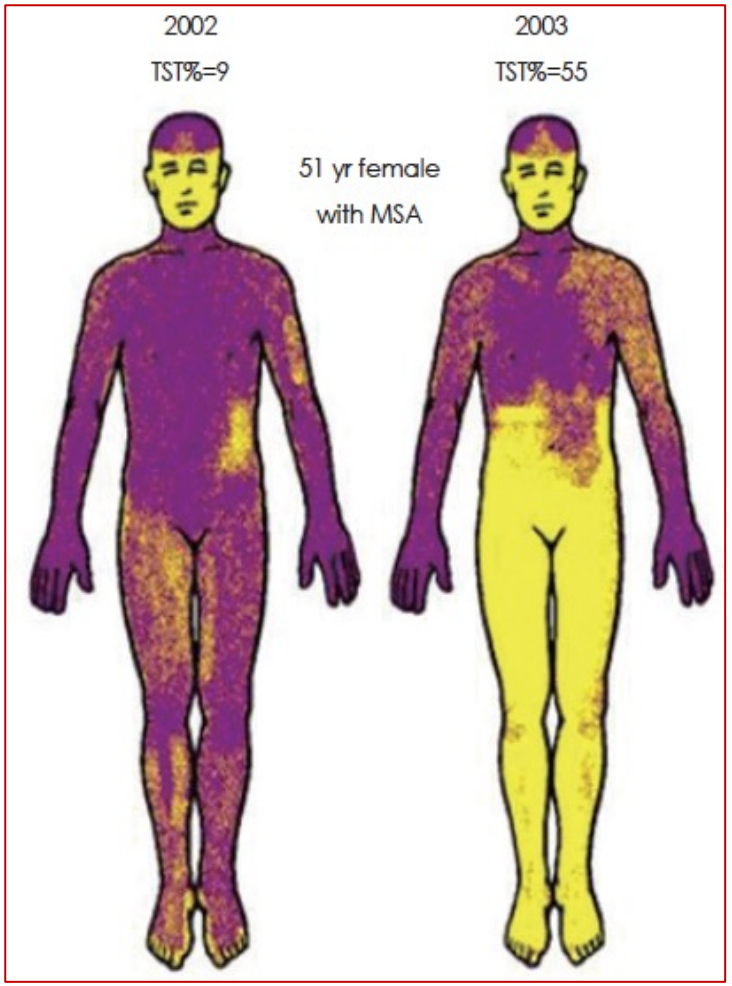
Neurally mediate syncopes **must be distinguished** from nOH-associated syncopes, in which the reduced cerebral perfusion is due to cardiovascular autonomic neuropathy

Pathological Heterogeneity in Autonomic Disorders

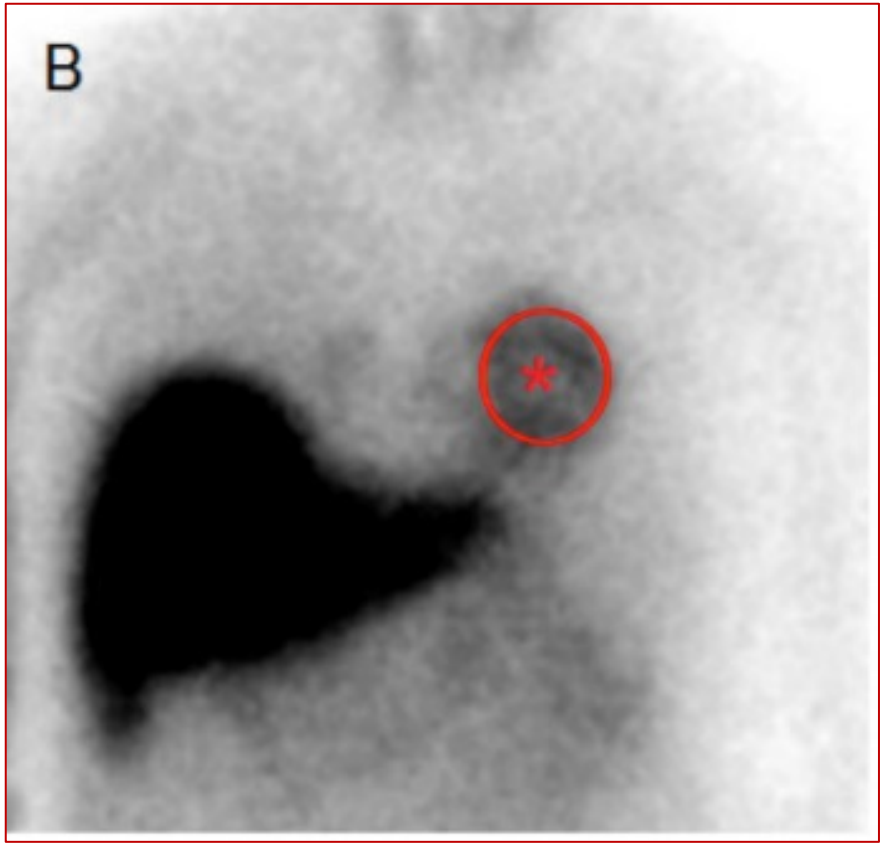
	MSA	PD	PAF
TYPE OF α-SYNUCLEIN DEPOSITS	**Major glial cytoplasmic inclusions**	**Lewy bodies**	**Lewy bodies**
SITE OF α-SYNUCLEIN DEPOSITS	CNS	CNS and PNS	Mostly PNS
ONUF NUCLEUS (segments S2-S4 of the spinal cord)	Degeneration	Normal	Normal
CARDIAC POSTGANGLIONIC SYMPATHETIC FIBERS	Not affected	Affected	Affected
SUDOMOTOR FIBERS	Involvement of preganglionic and postganglionic fibers	Length-dependent involvement of postganglionic fibers	Involvement of postganglionic fibers
AUTONOMIC SKIN NERVE FIBERS	Only one report of p-α-Syn deposition in dermal nerve fibers	P-α-Syn inclusions	P-α-Syn inclusions

Pathological Heterogeneity in Autonomic Disorders

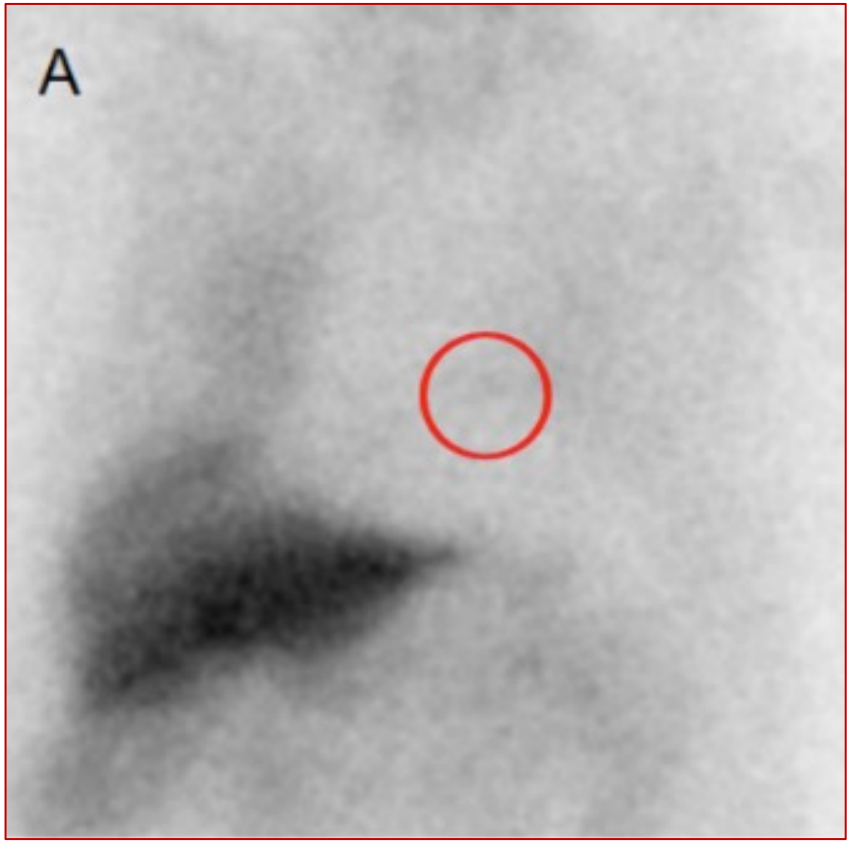




Pathological Heterogeneity in Autonomic Disorders



MSA – Taupaties – Normal



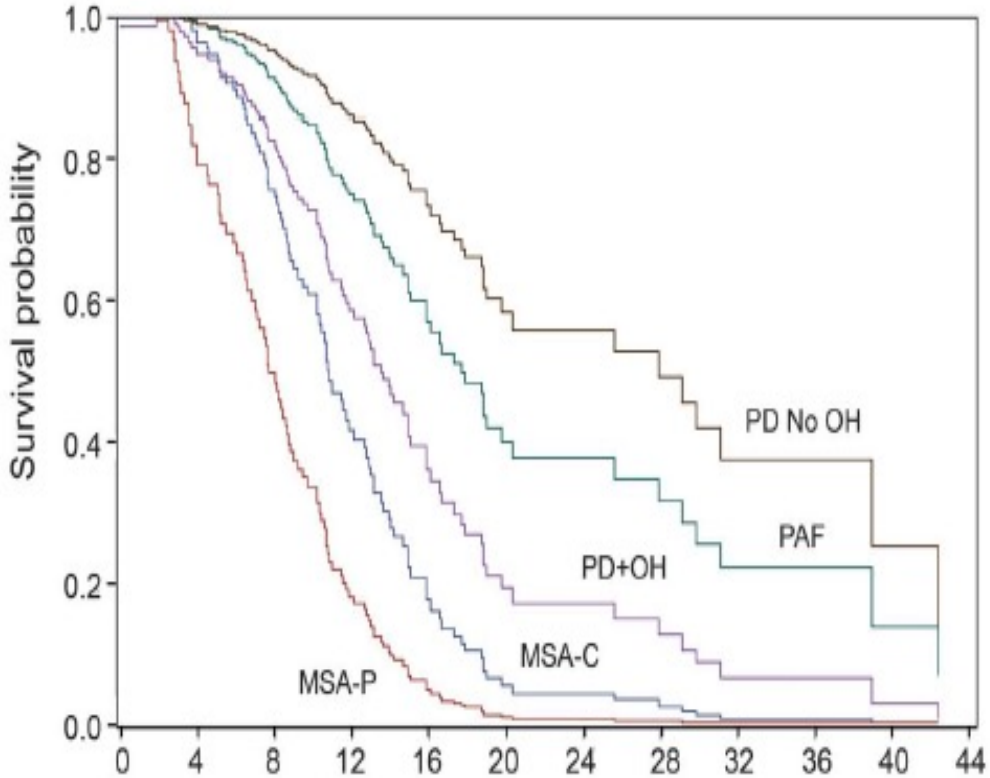
Parkinson – DLB – PAF

Swiss Med Wkly. 2018;148:w14621

Pathological Heterogeneity in Autonomic Disorders

Survival in synucleinopathies

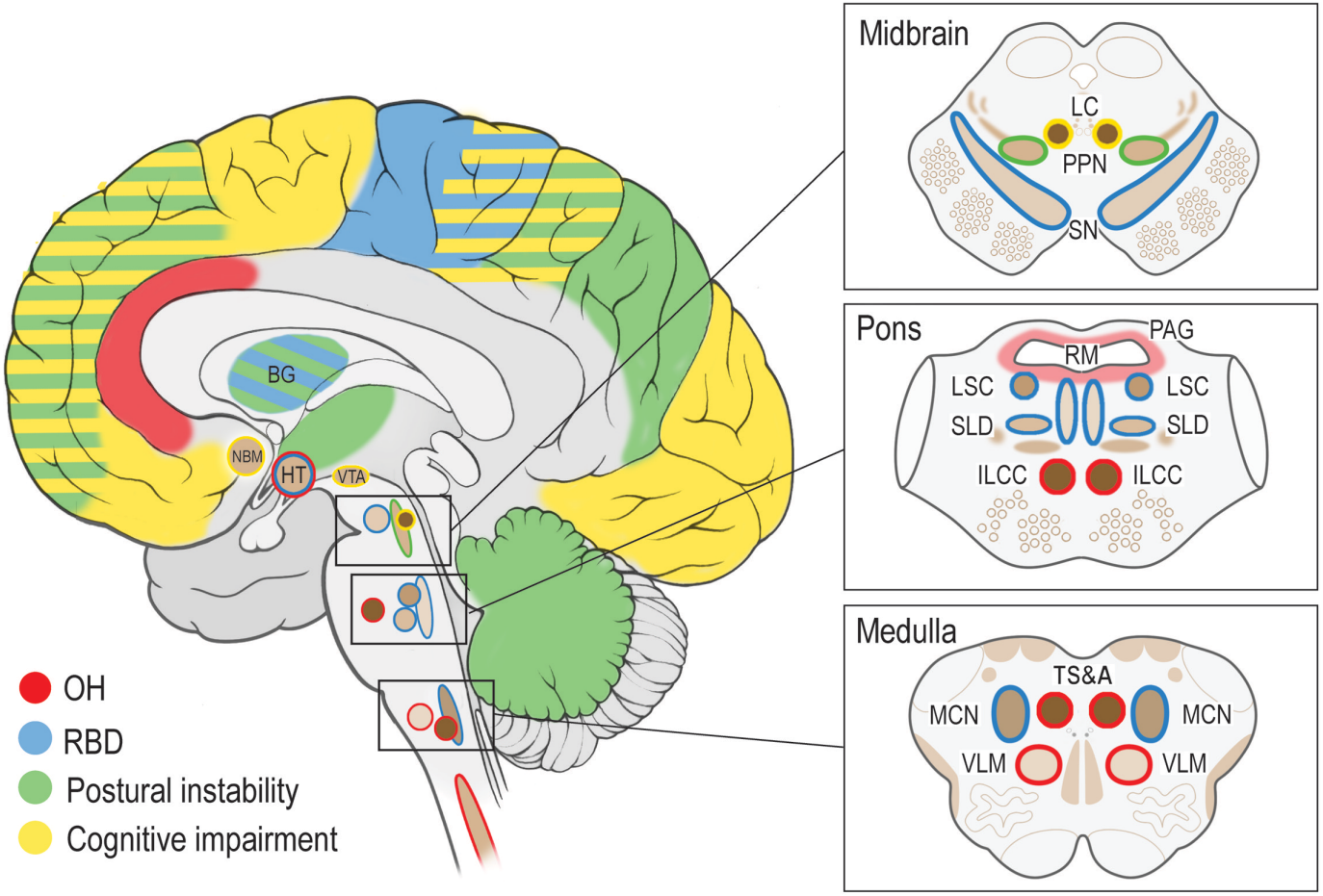
A prospective cohort study



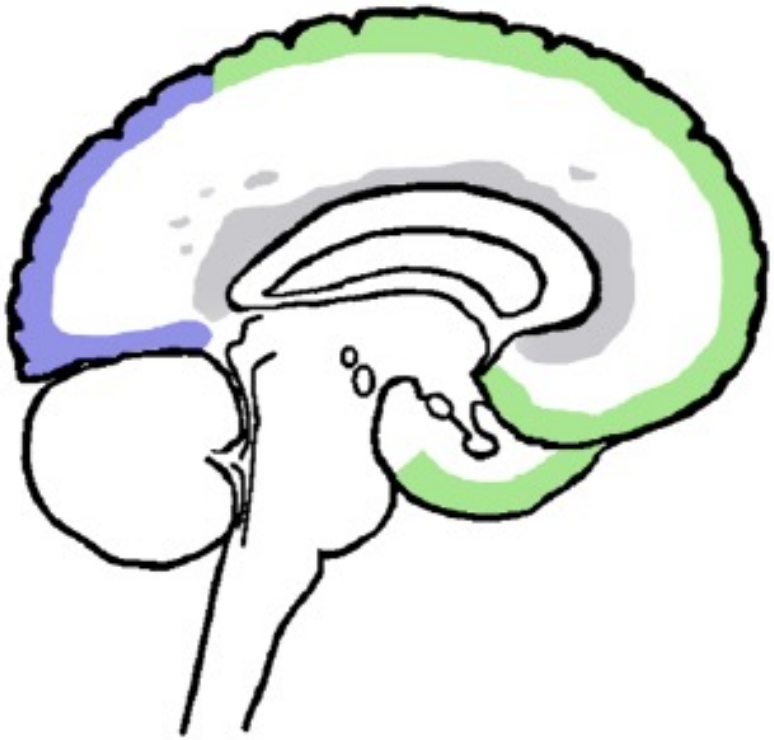
MSA-P	→ 33%
MSA-C	→ 39%
PD/OH+	→ 74%
PAF	→ 87%
PD/OH-	→ 93%

Neurology, 85, Nov 2015

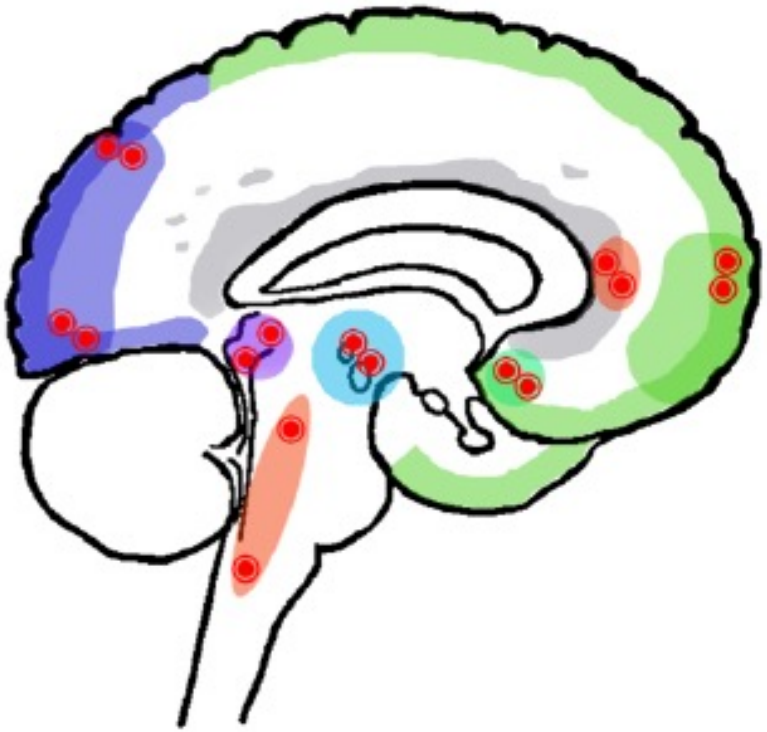
Pathological Heterogeneity in Autonomic Disorders



Pathological Heterogeneity in Autonomic Disorders



"CEREBRAL HYPOPERFUSION"



"SYNERGISTIC IMPACT"

J Neurol Neurosurg Psychiatry 2016;**87**:1311–1321.

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