"I Can't Think Properly" – Brian Fog & POTS

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Case Presentation - AP

- **ONSET**
  - Age 26 years; SWF; works in music industry
  - Dx “Pneumonia” -> inhalers
  - Developed “spells of tachycardia”
  - Cardiologist#1 proposed EP Study/Ablation
  - Cardiologist#2 -> Tilt Test
  - Associated Symptoms
    - Lightheaded/presyncope (standing)
    - Intermittent stabbing chest pains (standing)
    - Mental clouding (“brain fog”)
    - Severe fatigue

Case Presentation – AP (2)

- **ORTHOSTATIC CHALLENGE**
  - **Standing Time (min):10**
  - **15 min Supine: HR - 73 bpm; BP - 103/72 mmHg**
  - **1 min Upright: HR - 106 bpm; BP - 109/80 mmHg**
  - **3 min Upright: HR - 105 bpm; BP - 106/83 mmHg**
  - **5 min Upright: HR - 122 bpm; BP - 118/75 mmHg**
  - **10 min Upright: HR - 121 bpm; BP - 118/78 mmHg**

Case Presentation – AP (3)

- **Treatments**
  - **Midodrine -> "bugs in hair"**
  - **Fludrocortisone > bloated**
  - **Propranolol 20mg TID**
  - **NaCl 1 gm TID**
  - **Vit B12**
  - **OCP: Yaz -> Desogen**
  - **DDAVP 0.2mg PRN (infrequent)**
  - **Waist high compression stockings**

- Unable to continue working due to "**brain fog**"


Brain Fog
@mrsuelchez
I can't express to you how bad I hate having brain fog. it's embarrassing and upsetting. It's like one minute I'm in a serious conversation about something and the next minute I forget where I'm at.
Wait... What was I talking about again?

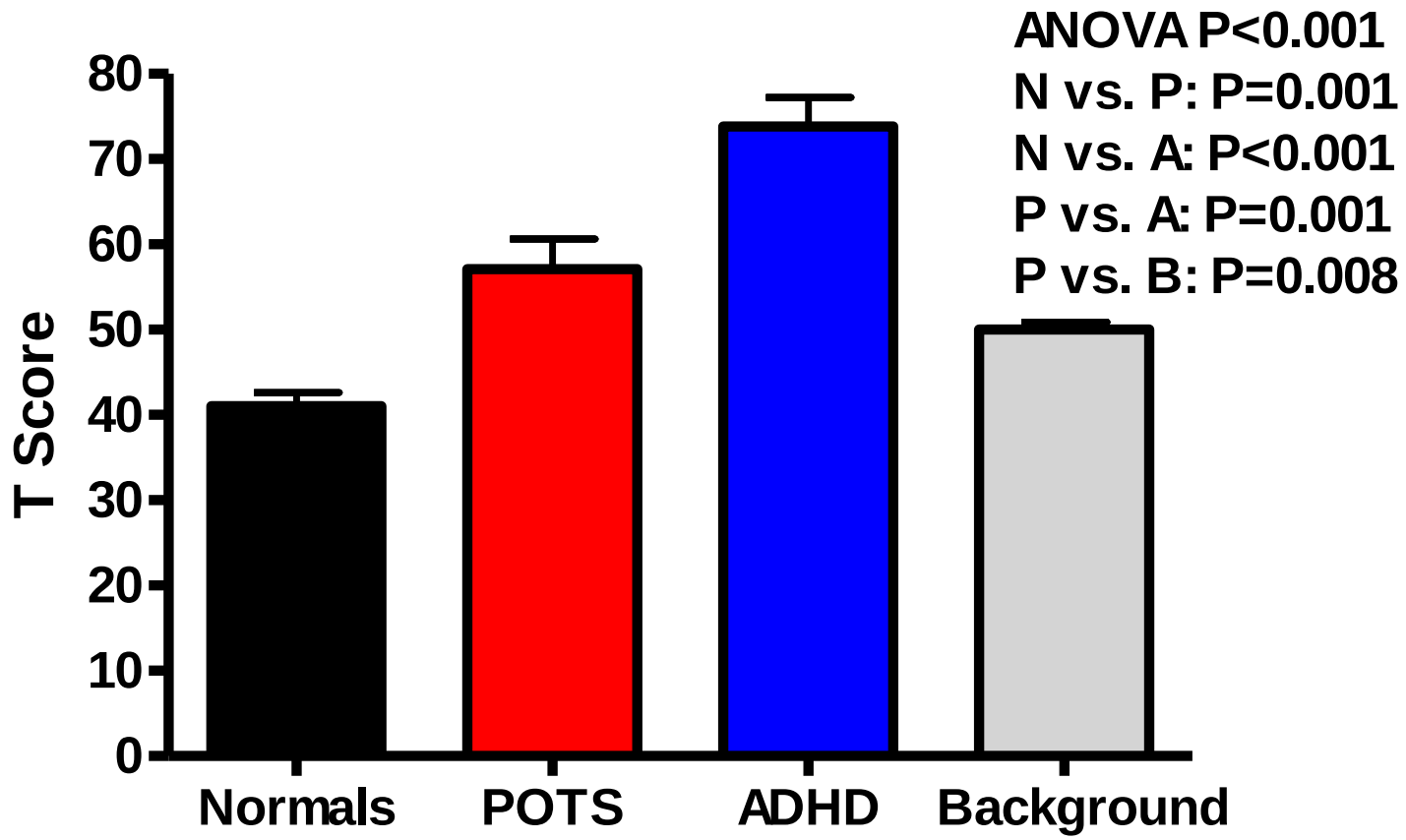
Brain Fog in POTS

- **Mental clouding or brain fog is an *almost universal* complaint among POTS patients (80-90% of patients in our center) even while lying down or seated.**

- **Described as:**
  - **difficulty thinking,**
  - **concentrating,**
  - **paying attention;**
  - **trouble remembering things;**
  - **cloudy or fuzzy feeling in head;**
  - **having problems finding right words."**

- **Precise nature of brain fog and optimal therapeutic strategies have not been described in POTS.**

CAARS DSM-IV Inattention Scores



V Raj et al. , J Neurol Neurosurg Psychiatry 2009; 80: 339-344

Study: Origins of Brain Fog

Amy Arnold

Psychometric Test Battery

Neuropsychological Test	Tests What?
Weschler Test of Adult Reading (WTAR)	Intelligence (IQ)
Ruff 2&7 Speed	Selective Attention
Ruff 2&7 Accuracy	Sustained Attention
Trails A	Psychomotor Speed
Trails B	Executive Function
Symbol Digit Modality Test (SMDT)	Cognitive Processing Speed
Stroop Word Color	Executive Function
Randt – Short Story	Memory - Semantic
Randt – Paired Words	Memory - Associative
Randt – Repeating Numbers	Memory - Working
Controlled Oral Word Association (COWA)	Verbal Fluency

AC Arnold et al. *Clin Sci (Lond)* 2015; 128:39-45.

Origins of Brain Fog: Subjects

	Healthy (n=24)	POTS (n=28)	P value
Disease duration (y)		2.2 ± 1.9	
Age (y)	30 ± 6	31 ± 9	0.85
BMI (kg/m^2)	22 ± 3	22 ± 3	0.60
Race, Caucasian	92% (22)	96% (27)	0.20
Education (y)	18 ± 2	16 ± 3	0.007
IQ Scores	112 ± 5	110 ± 7	0.24
Seated Vitals			
SBP (mmHg)	101 ± 7	100 ± 11	0.54
DBP (mmHg)	64 ± 8	64 ± 8	0.80
HR (bpm)	69 ± 9	78 ± 11	0.01

Mean ± SD

AC Arnold et al. *Clin Sci (Lond)* 2015; 128:39-45.

Psychometric Tests - Differences

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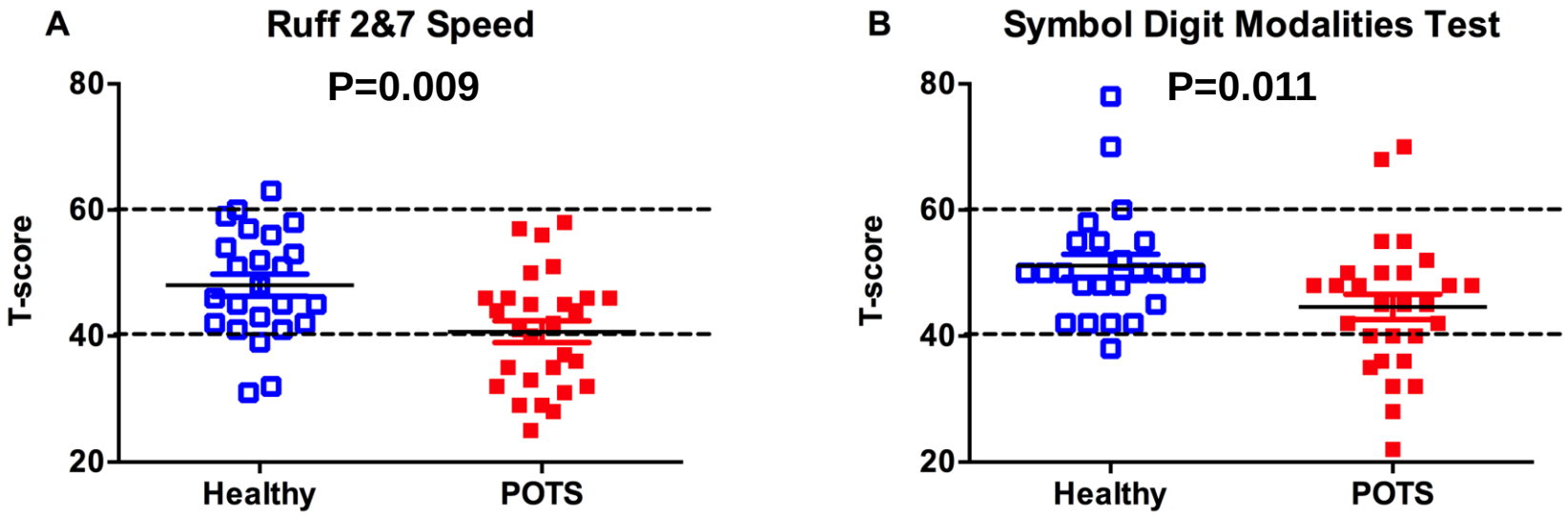
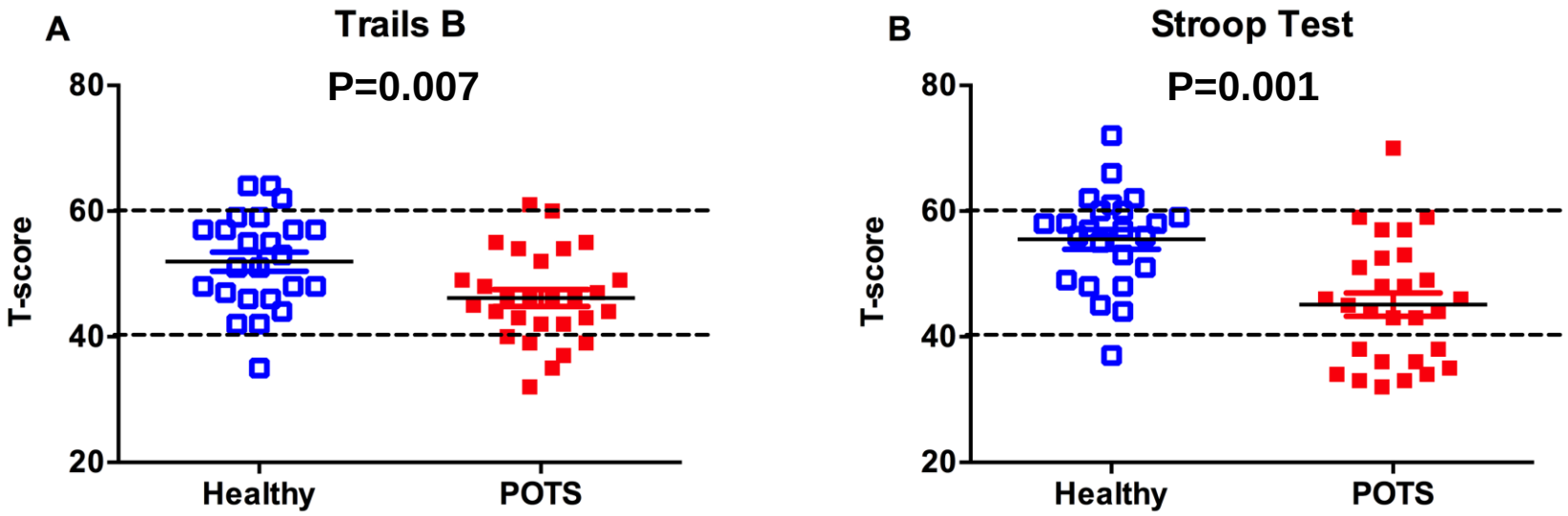
Abnormal Selective Attention & Abnormal Cognitive Processing Speed



AC Arnold et al. *Clin Sci (Lond)* 2015; 128:39-45.

Abnormal Executive Function



AC Arnold et al. *Clin Sci (Lond)* 2015; 128:39-45.

Origins of Brain Fog: What We Found 1

- Deficits in selective attention and cognitive processing in POTS patients.
- No differences in psychomotor speed, sustained attention, memory or verbal fluency suggesting selectivity in cognitive deficits.
- No association with psychiatric symptoms (depression, anxiety).

AC Arnold et al. *Clin Sci (Lond)* 2015; 128:39-45.

Origins of Brain Fog: What We Found 2

- These problems were observed in the **seated position** when orthostatic symptoms and tachycardia are minimized. *This may indicate it is part of the disorder itself and not due to increased heart rate and symptoms with standing.*

- Further studies are needed to determine impact of standing, the underlying causes and optimal treatment strategies.

AC Arnold et al. *Clin Sci (Lond)* 2015; 128:39-45.

Brain Fog & Standing

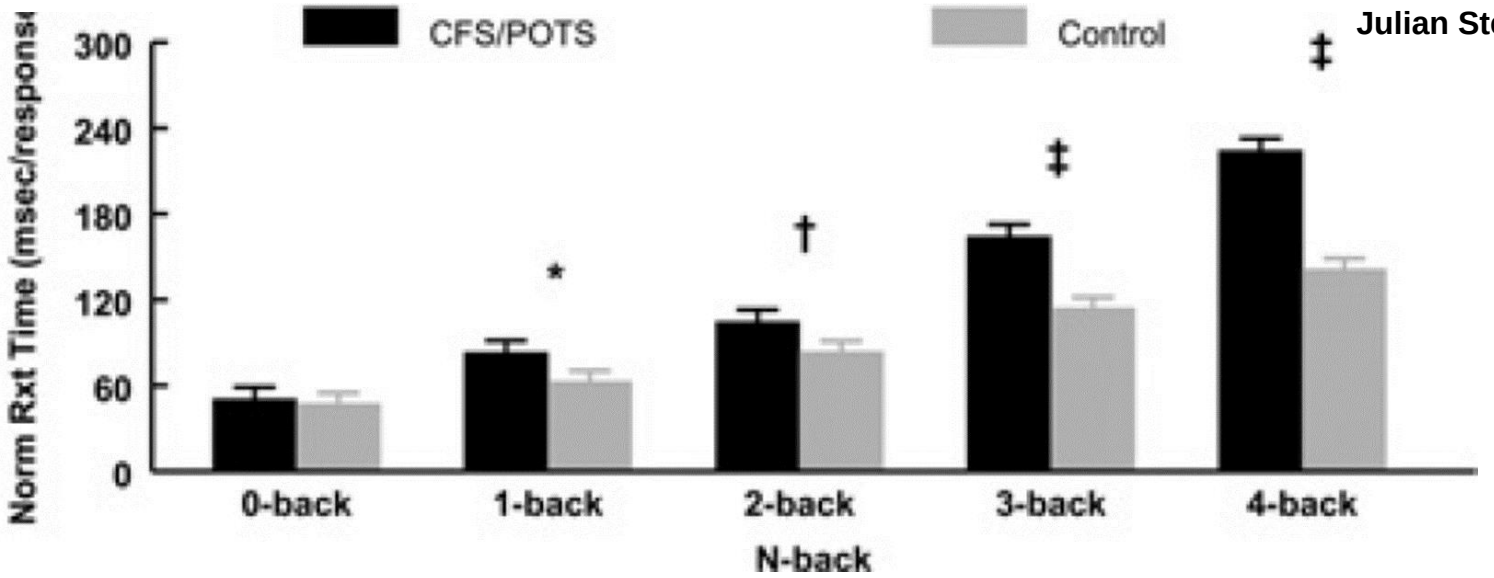
N-Back Test (Executive Function)

- Mark the letter that is a repeat of the same letter N-x characters back

N-1	A k w l c k c j e d s s d r
N-2	A k w l c k c j e d s s d r
N-3	A k w l c k c j e d s s d r
N-4	A k w l c k c j e d s s d r

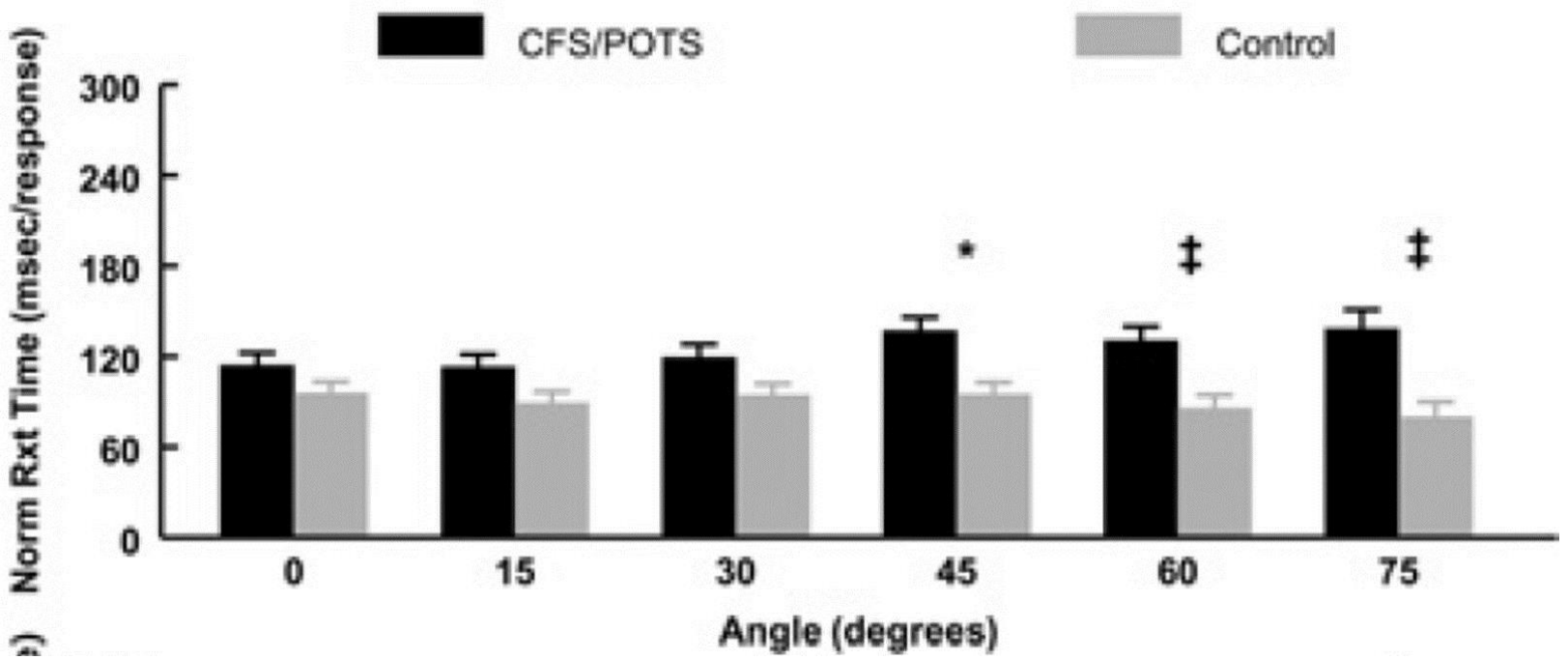
POTS Patients Do Worse on N-back with Higher N-back

Julian Stewart



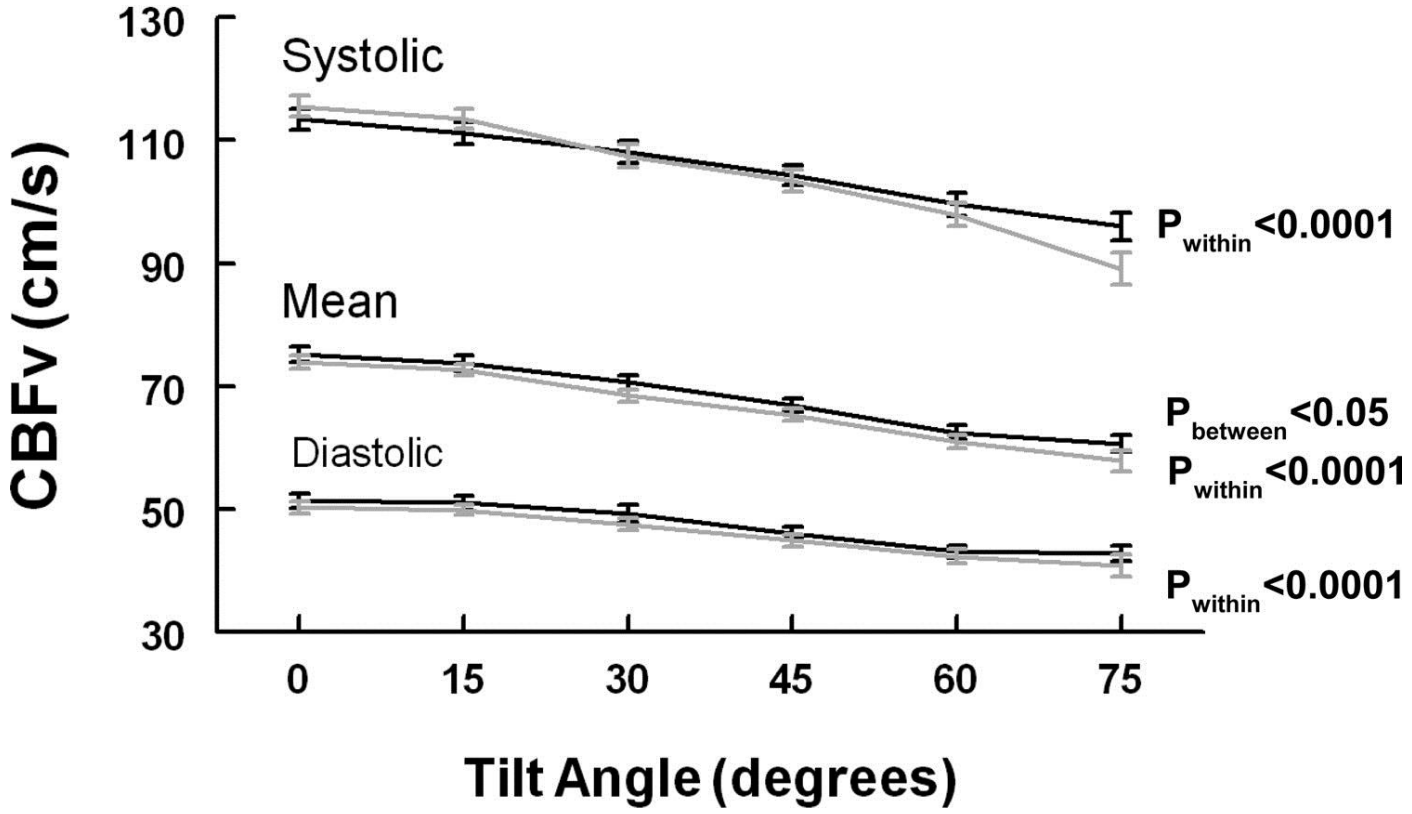
Anthony J. Ocon et al. Clin. Sci. 2012;122:227-238

POTS Patients Do Worse on N-back with Head-Up Tilt



Anthony J. Ocon et al. Clin. Sci. 2012;122:227-238

…but Upright Cerebral Blood Flow was not reduced in POTS patients



JM Stewart et al. Am J Physiol Heart Circ Physiol 2012;302:H1185-H1194

Brain Fog in POTS: What We Know

- There is a problem with executive function and selective memory while seated
- Executive Function gets worse while upright
- This is NOT due to decreased cerebral blood flow velocity

Brain Fog & POTS: What to do?

How do we treat cognitive deficits in POTS?

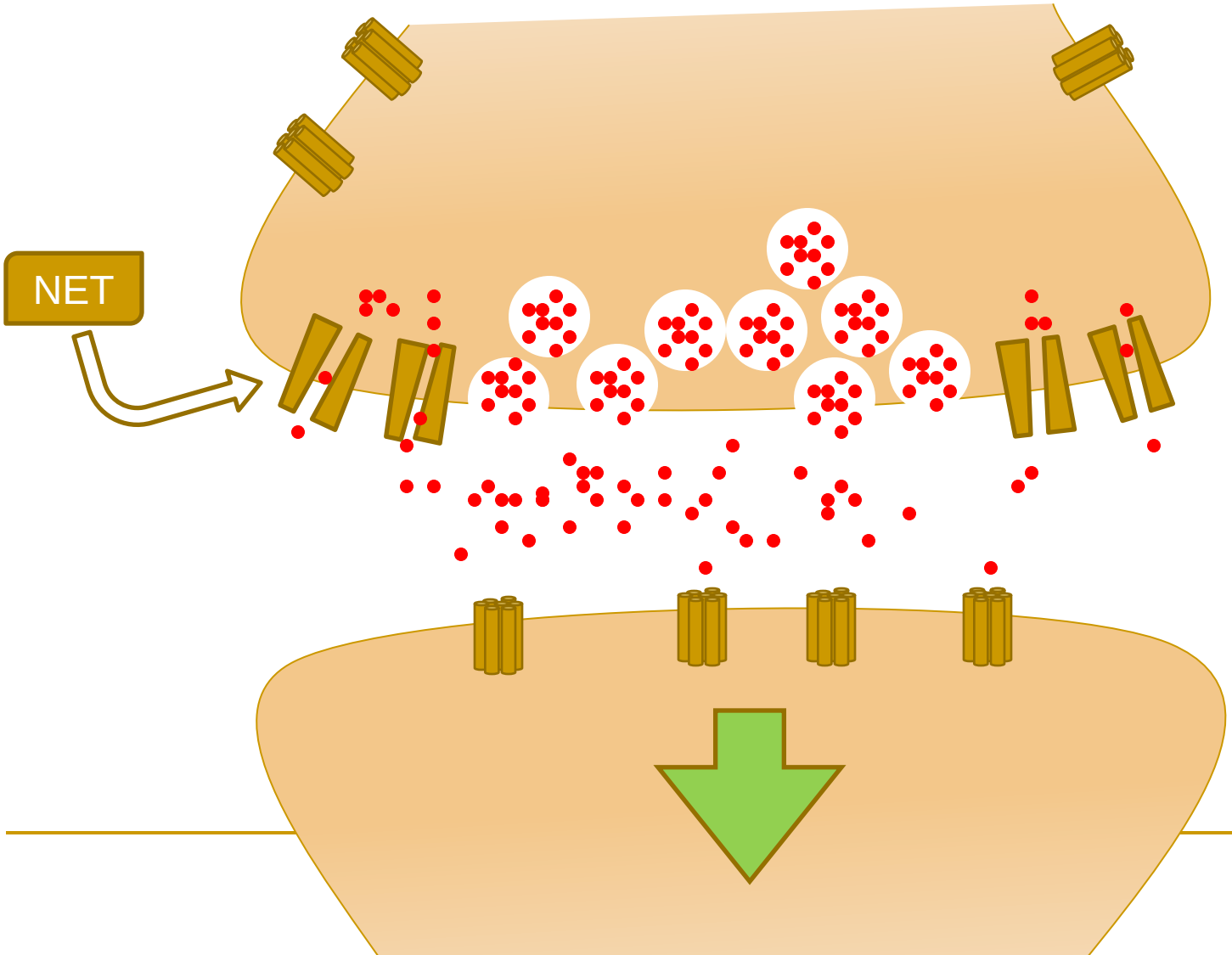
- There have been no studies looking at treatment strategies for brain fog in POTS.

Attention Deficit Disorder Drugs

- **Stimulants**
  - **Amphetamines (e.g. Vyvanase, Adderall)**
  - **Methylphenidate (e.g. Ritalin)**
  - **Atomoxetine**
- **Drugs block Reuptake Transporters**
  - **Dopamine**
  - **Norepinephrine**

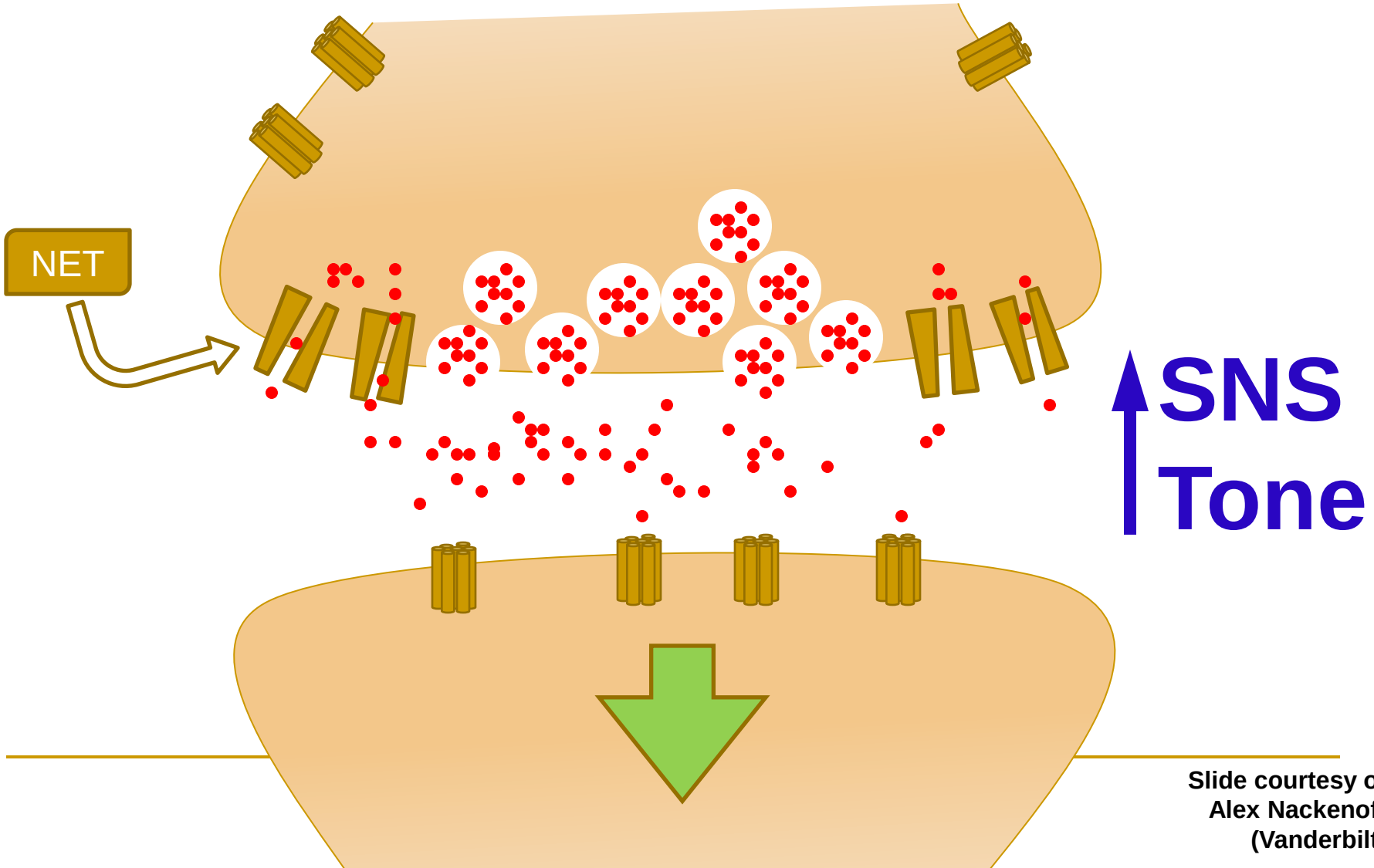
- **Can INCREASE/WORSEN heart rate**

A Norepinephrine Synapse



Slide courtesy of
Alex Nackenoff
(Vanderbilt)

Norepinephrine Synapse – NET blocked



Slide courtesy of
Alex Nackenoff
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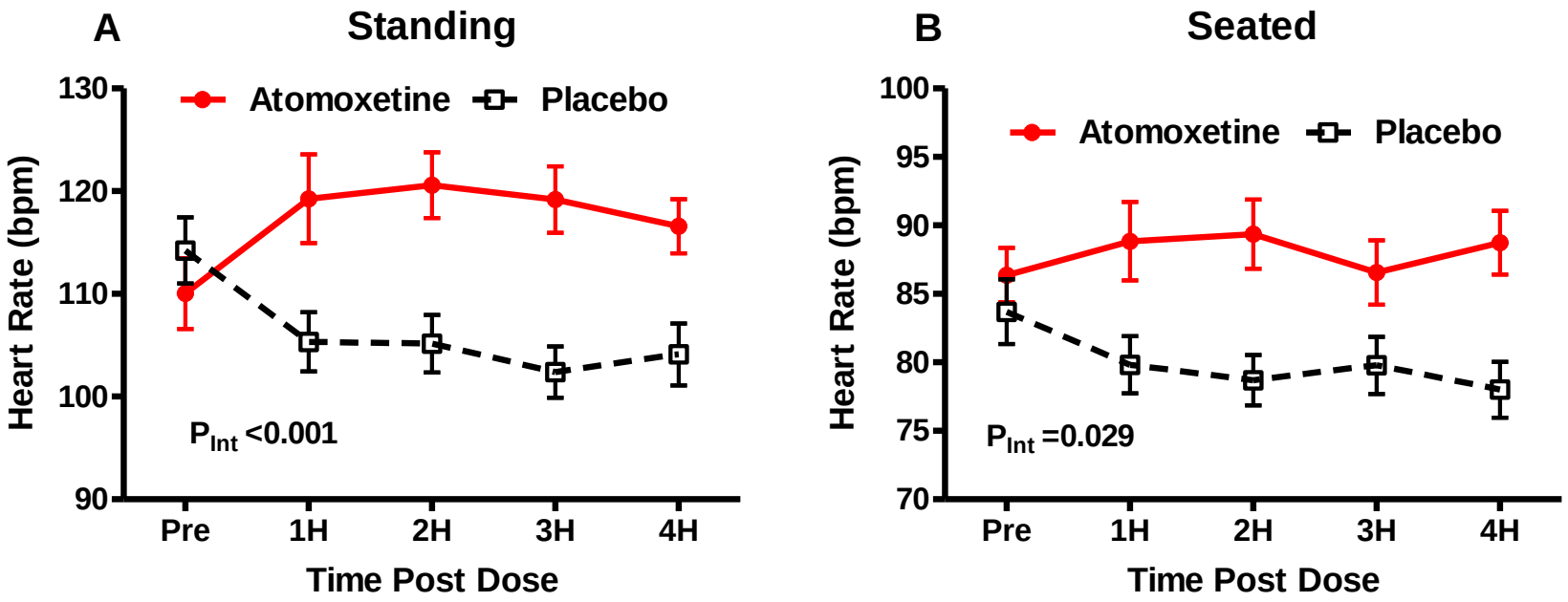
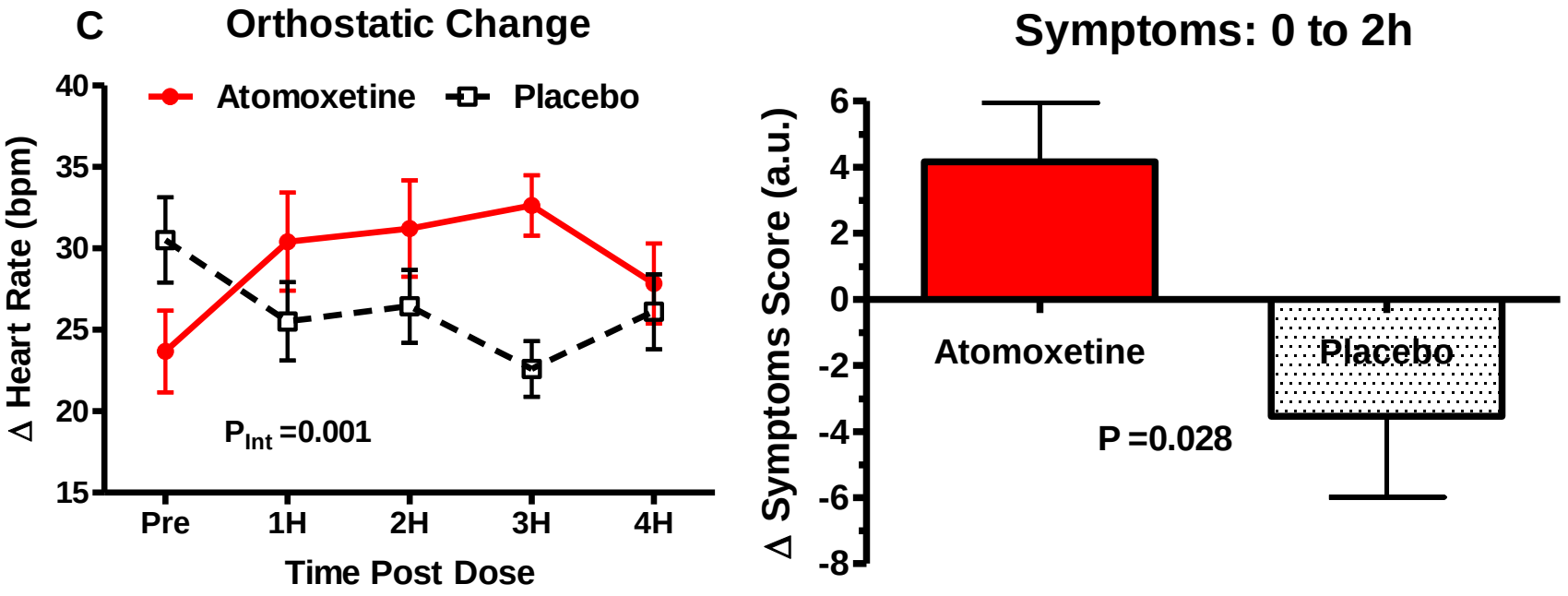
Norepinephrine Transporter Inhibition (e.g. stimulants)



EA Green et al., JAHA 2013;2:e000395

Norepinephrine Transporter Inhibition (e.g. stimulants)



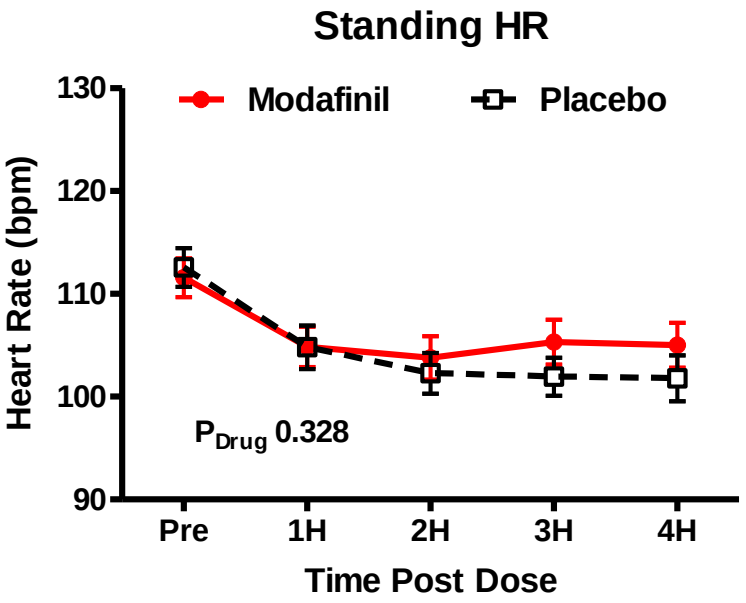
EA Green et al., JAHA 2013;2:e000395

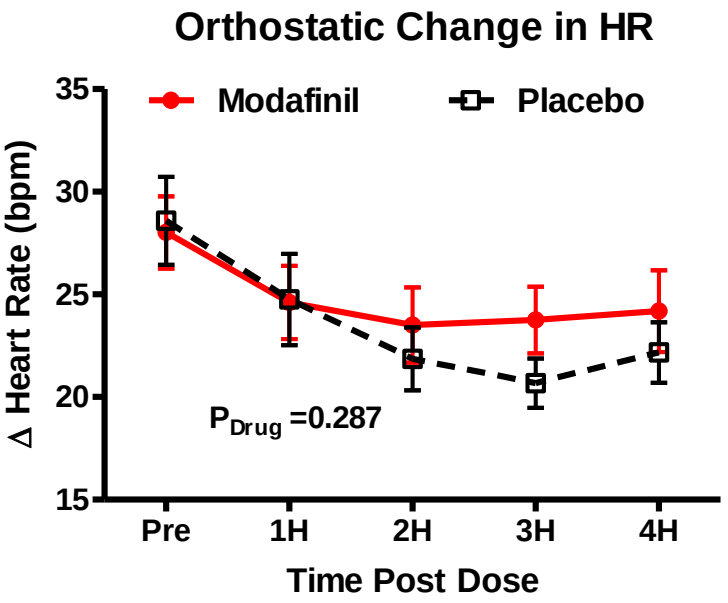
Modafinil

The psychostimulant modafinil has gained increasing interest:

- **wakefulness-promoting agent used in the treatment of narcolepsy, fatigue, depression and sleep deprivation disorders**
- **known ability to improve attention and executive function in other clinical populations with cognitive impairment.**

Modafinil has modest effects on HR





AJ Kpaeyeh Jr. et al., J Clin Psychopharmacol. 2014 Dec;34(6):738-41

POTS & Brain Fog…No Data?

Enroll in Clinical Trial

Modafinil and Cognitive Function in POTS

Hypothesis:

We will test the hypothesis that acute administration of the psychostimulant modafinil improves seated measures of cognitive function in patients with POTS.

Specific Aims:

- **Aim 1:** Does acute **modafinil** improves cognitive function in POTS patients compared with placebo.
- **Aim 2:** To assess whether the beta-blocker **propranolol**, either **alone or in combination with modafinil** to control tachycardia, improves cognitive function in POTS.

Study Design

Study Day 1

- baseline characterization
- autonomic testing
- CogState Training

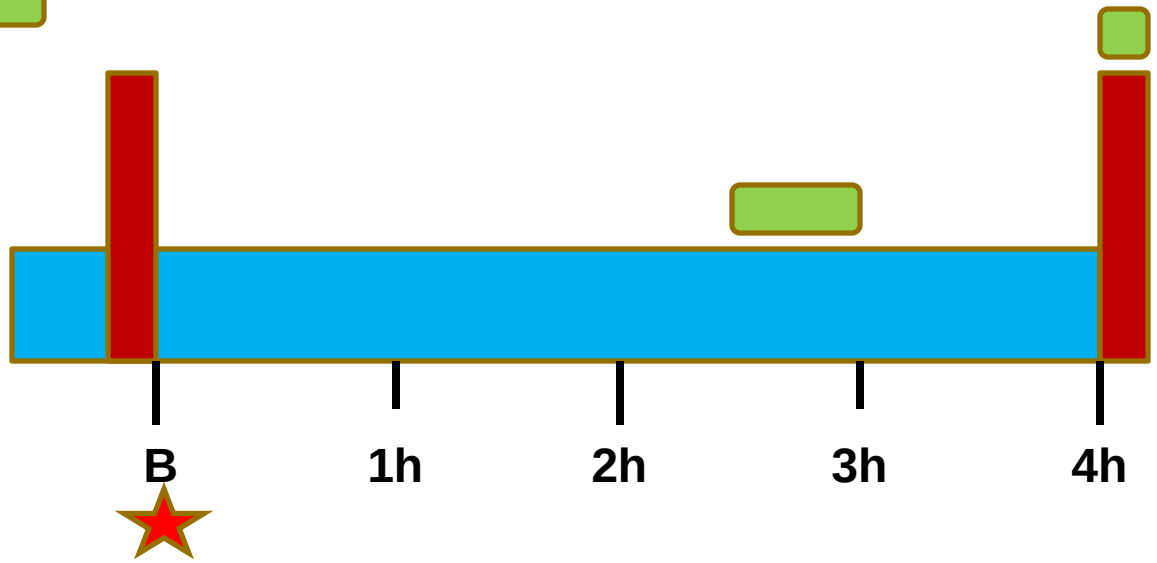
Psychometric Testing

-CogState seated
-CogState standing
-PANAS
-VAS
  -Mood
  -Anxiety
  -Fatigue

Study Days (2-5)

Randomized Order:

1. Modafinil 200mg + placebo
2. propranolol 20mg + placebo
3. Modafinil 200mg + propranolol 20mg
4. double placebo



Current Research Study: Modafinil and Cognitive Function in POTS

Investigators: Amy C. Arnold, PhD MSCI & Satish R Raj MS MSCI

For More Information Contact:
Amy Arnold, PhD or Bonnie Black, RN
Vanderbilt Autonomic Dysfunction Center
Email: adcresearch@vanderbilt.edu

Conclusions

- POTS Patients have problems with:
  - Sleep quality
  - Insomnia
  - Subjective Sleep Latency
  - Executive Function (some)
  - Selective Attention
- No known effective treatments

- ONGOING STUDY -> Please enroll

Questions?

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