



*Dr. Jeroen Van Cutsem*

**Trait Interindividual  
Differences in The  
Effectiveness of Modafinil**

*VIPER Research Unit*



**U.S. Air Force report:**

- 3.9% of mishaps were fatigue-related
- ¼ classified as severe mishap
- \$2.1 billion of medical expenses and property damage

Around the clock operations

Long flights

Variable scheduling

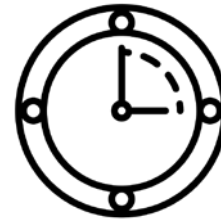
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In-flight countermeasures

Pre-/postflight countermeasures





Strategic use



### Never the first choice

Unwanted side effects

Stimulant dependency



### Sustained operations

- Sleeping rooms next to runway

### Change of flight schedule

- Night → day-flights

### Flights that entail crossing time zones

- Transatlantic flights



1987

International NATO defense meeting in Lyon:

- Modafinil and its potential military application are introduced



1995

**Interest of modafinil, a new psychostimulant, during a sixty-hour sleep deprivation experiment**

D Lagarde, D Batejat, P Van Beers, D Sarafian, S Pradella

*Institut de Médecine Aéronautique (Imassa-Cerma), Département Sciences Cognitives et Ergonomie, BP 73, 91223 Brétigny-sur-Orge, France*



- Positive effects on cognitive performance
- No consistent adverse effects

2009

U.S. Air Force:



- Authorization to use modafinil → Long-range U.S. Air Force combat aviation missions

- January 1991 → Daguet operation
- January/February 1991 → Operation Desert Storm

2011

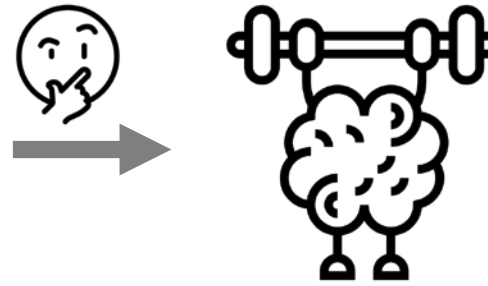
Republic of Singapore Air Force:



- Approval of modafinil as a fatigue countermeasure:
  - ✓ Circadian misalignment (i.e., flying during your normal sleep time)
  - ✓ Anticipating on highly fatiguing situations (e.g., extended flying)

# A State-of-the-Art Review on the Use of Modafinil as A Performance-enhancing Drug in the Context of Military Operationality

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**1. Dose-response relationship? → unclear**

**2. Modafinil appears to improve cognitive performance:**

- In individuals with a non-optimal cognitive ability
- If the task-complexity is higher

**3. Acute effects that should be further investigated:**

- Risk for overconfidence?

**4. No research available into long-term effects**



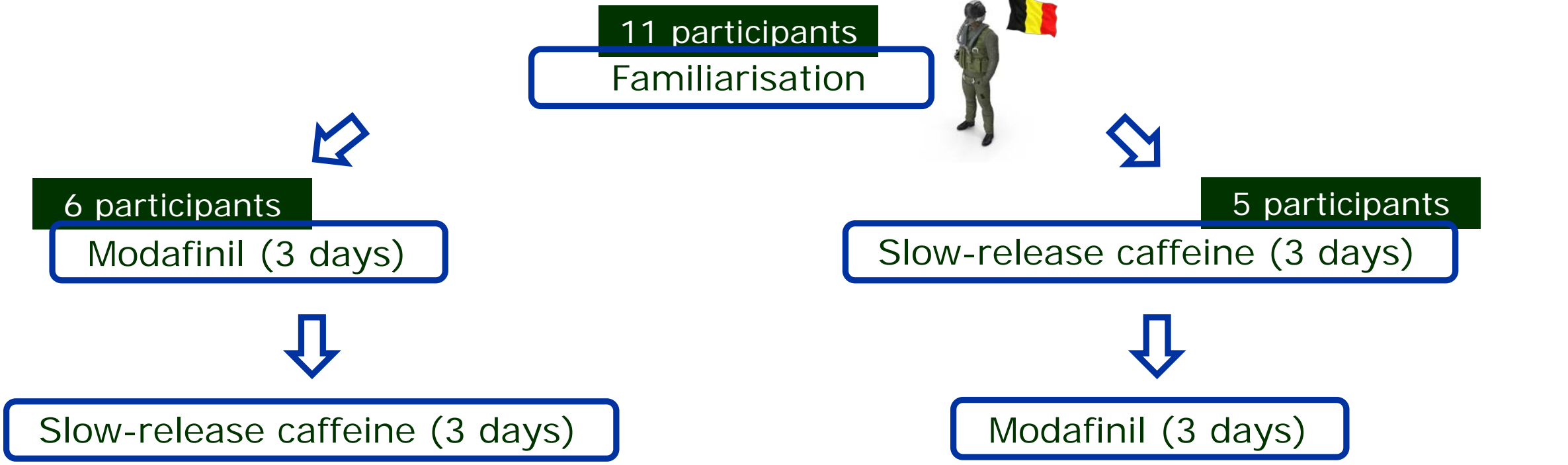
Interindividual differences





To investigate the effectiveness of **modafinil** as a cognitive enhancer and fatigue and/or sleepiness countermeasure on an **individual level**





Modafinil



Slow-release caffeine

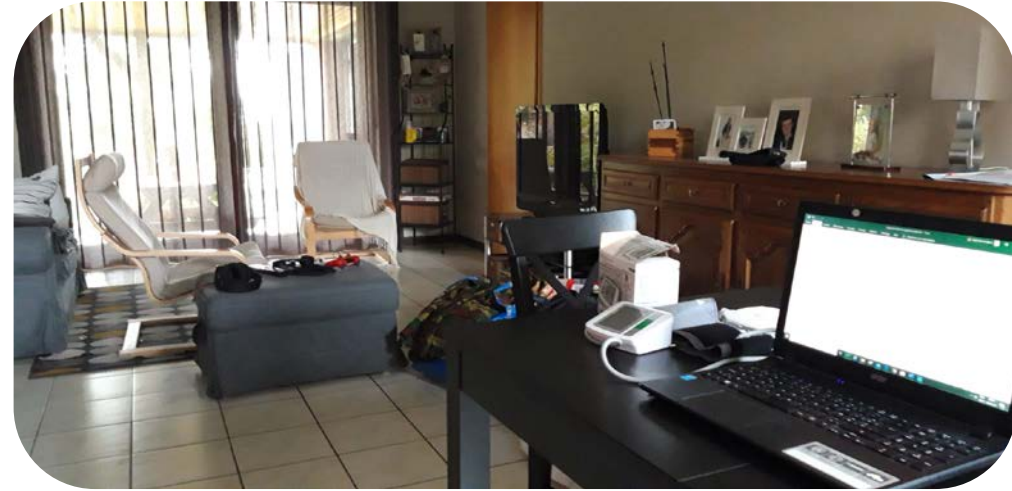


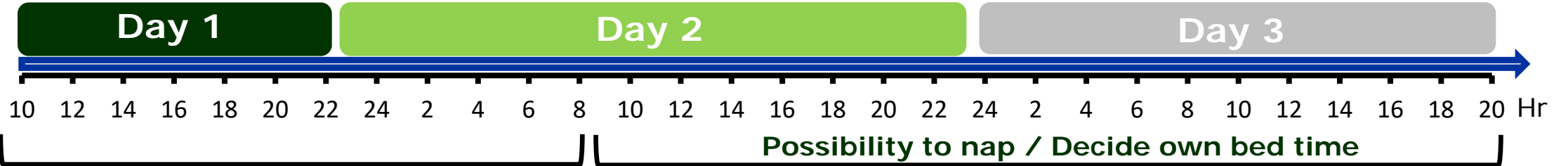
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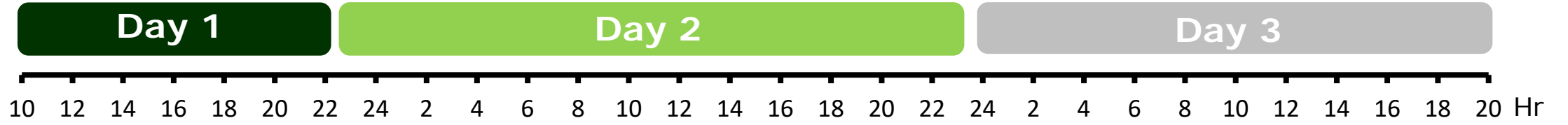
2 x 200 mg



COVID-19







**Flying experience**

**Chronotype**

**Sleep quality**

**Daytime sleepiness**



- Oginska
- SIC

- PSQI

- ESS



**Introduction**

**Methods**

**Results**

**Discussion**

**Conclusion**



Day 1

Day 2

Day 3

10 12 14 16 18 20 22 24 2 4 6 8 10 12 14 16 18 20 22 24 2 4 6 8 10 12 14 16 18 20 Hr



### Physiological parameters

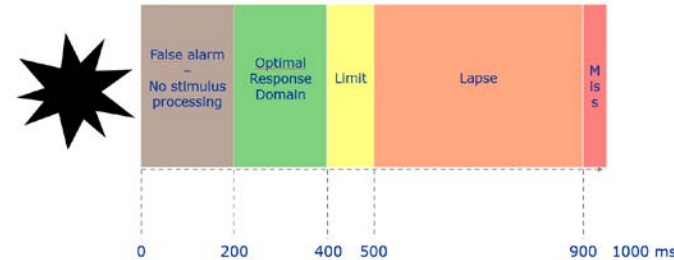
### Cognitive performance

### Questionnaires

- HR
- Tcore
- BP
- RR

- PVT

- Motivation
- Fatigue
- Sleepiness
- Mood
- Workload
- Side effects





Day 1

Day 2

Day 3

10 12 14 16 18 20 22 24 2 4 6 8 10 12 14 16 18 20 22 24 2 4 6 8 10 12 14 16 18 20 Hr





Day 1

Day 2

Day 3

10 12 14 16 18 20 22 24 2 4 6 8 10 12 14 16 18 20 22 24 2 4 6 8 10 12 14 16 18 20 Hr

Naps / Go to bed when you want



Introduction

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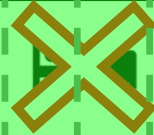
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Day 2

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10 12 14 16 18 20 22 24 2 4 6 8 10 12 14 16 18 20 22 24 2 4 6 8 10 12 14 16 18 20 Hr

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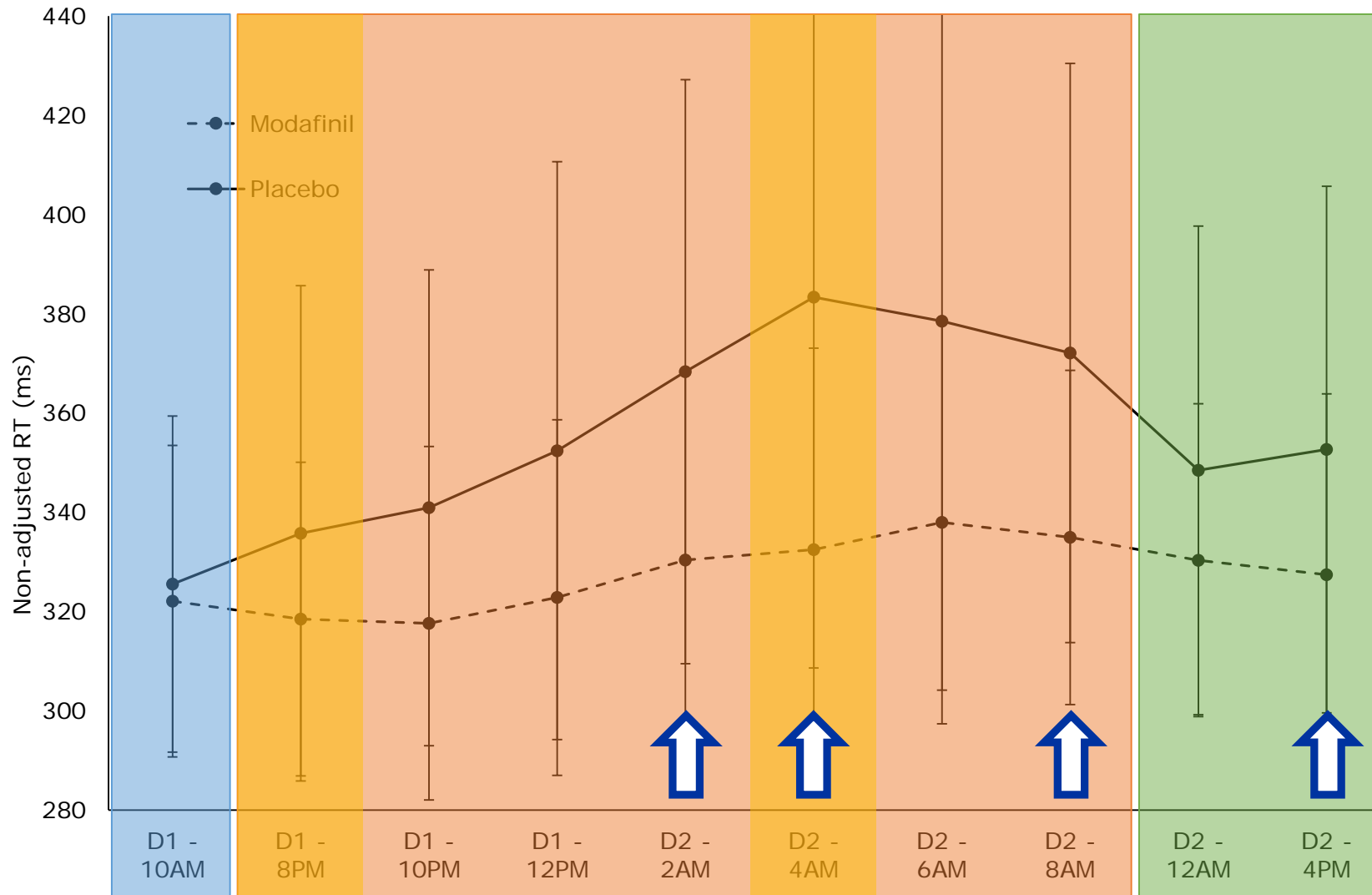
Introduction

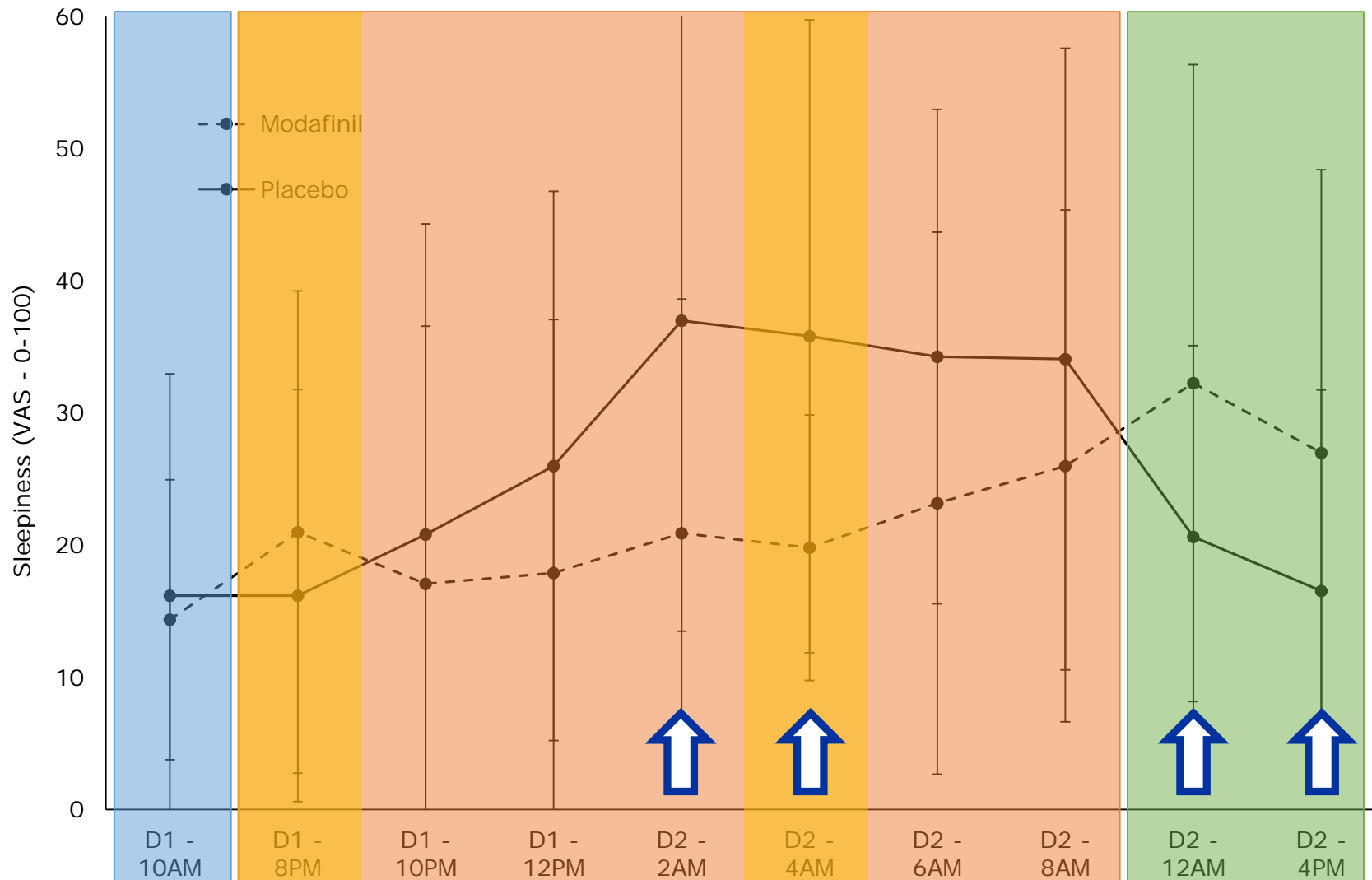
Methods

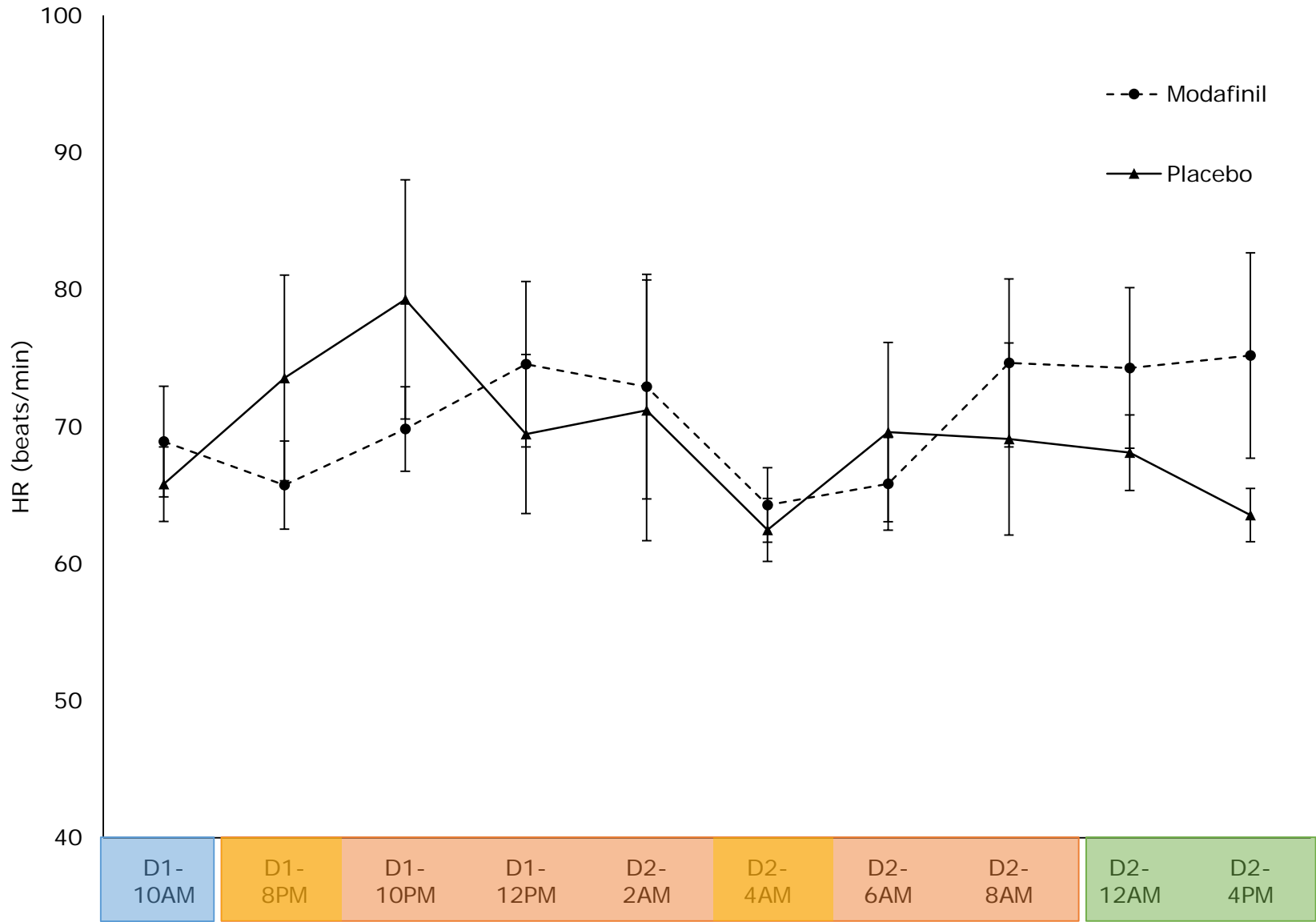
Results

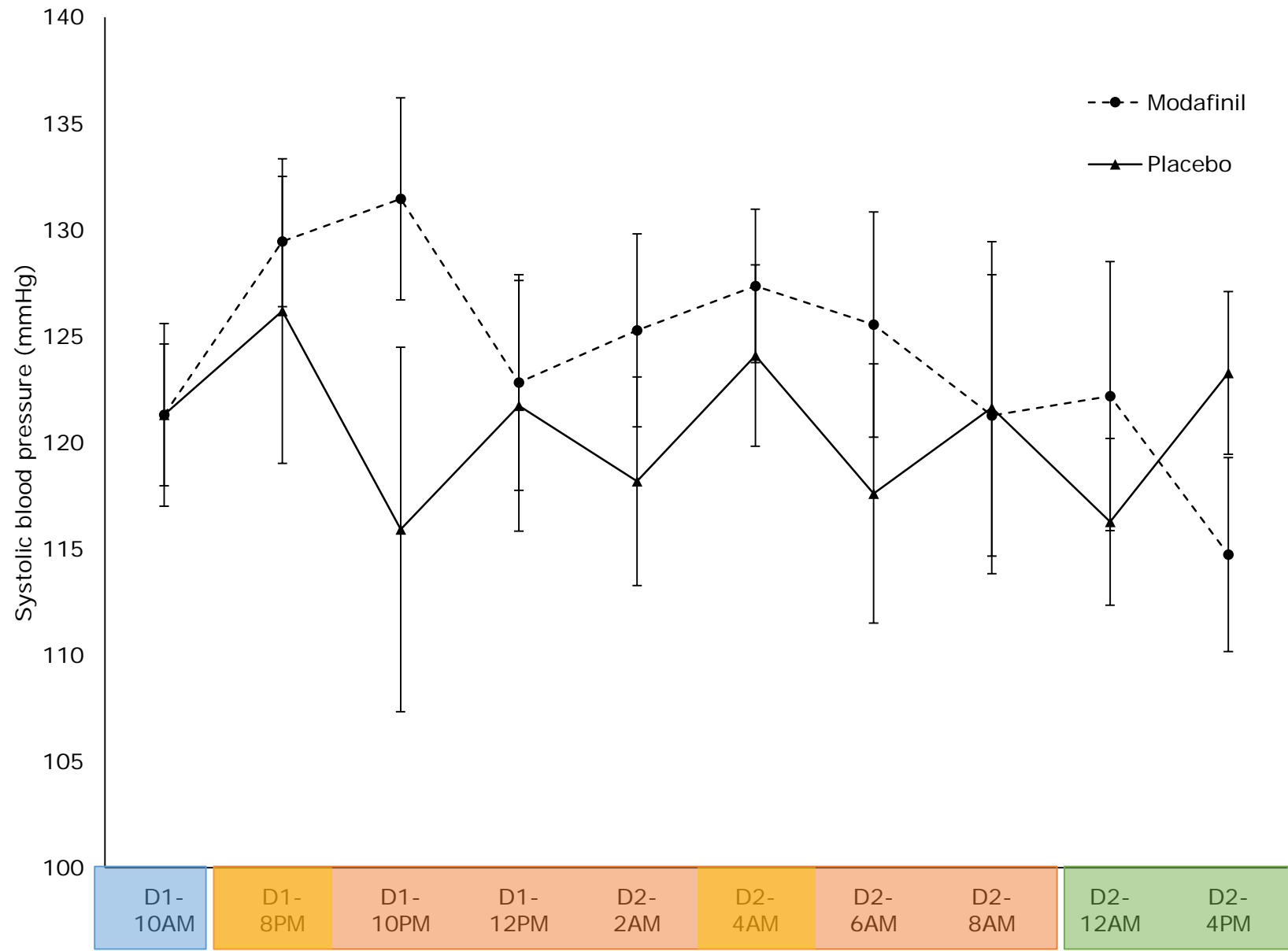
Discussion

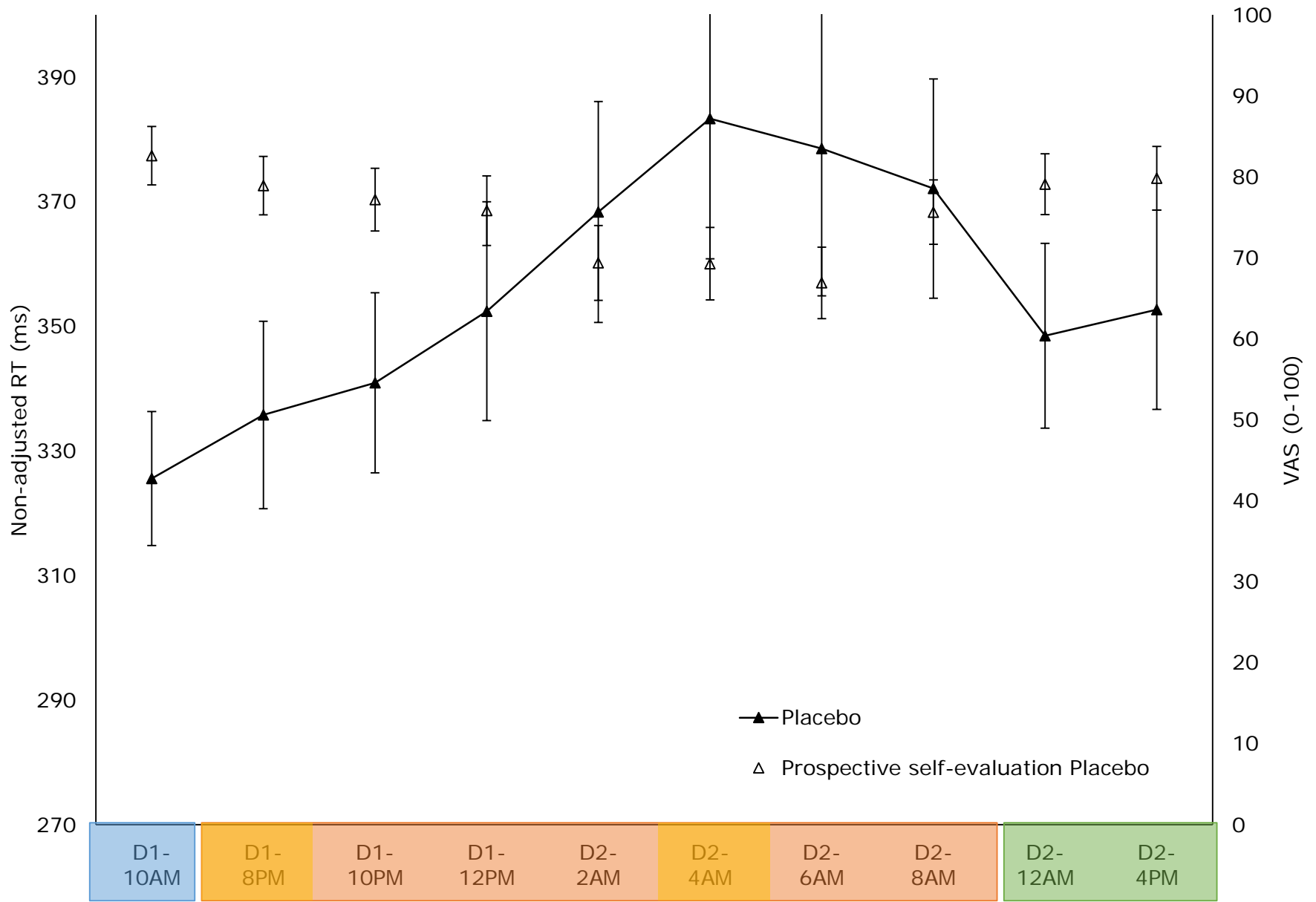
Conclusion

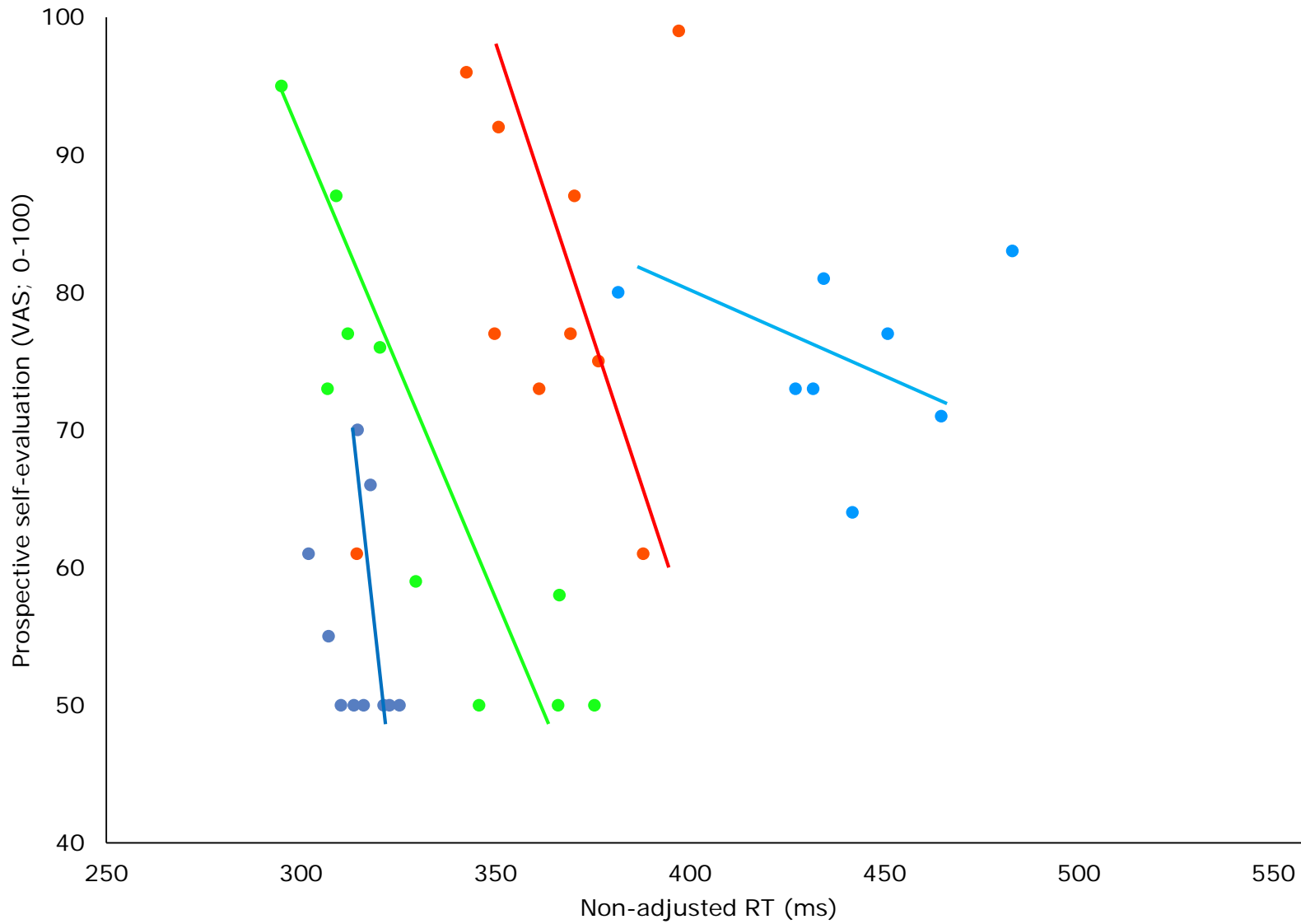






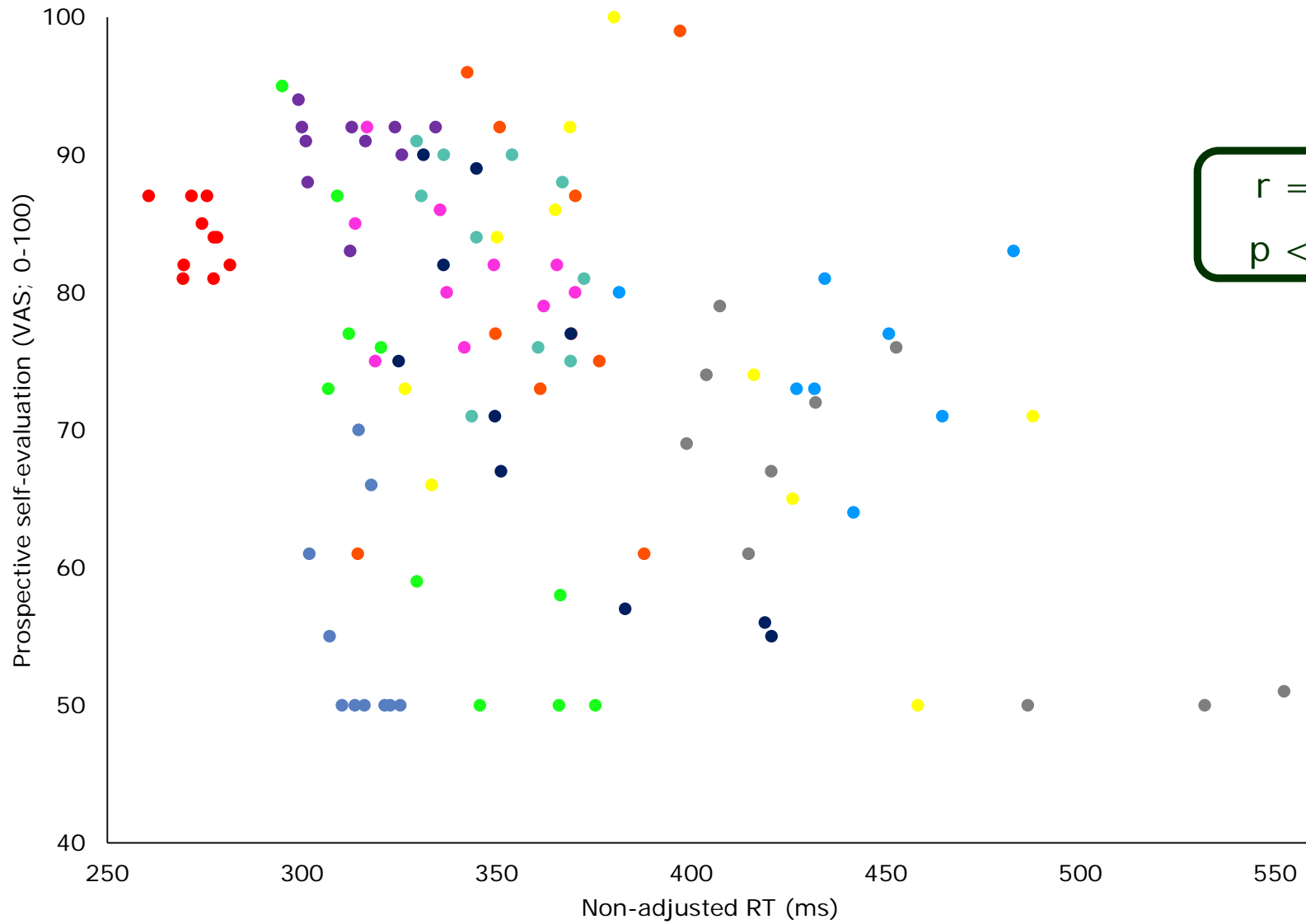








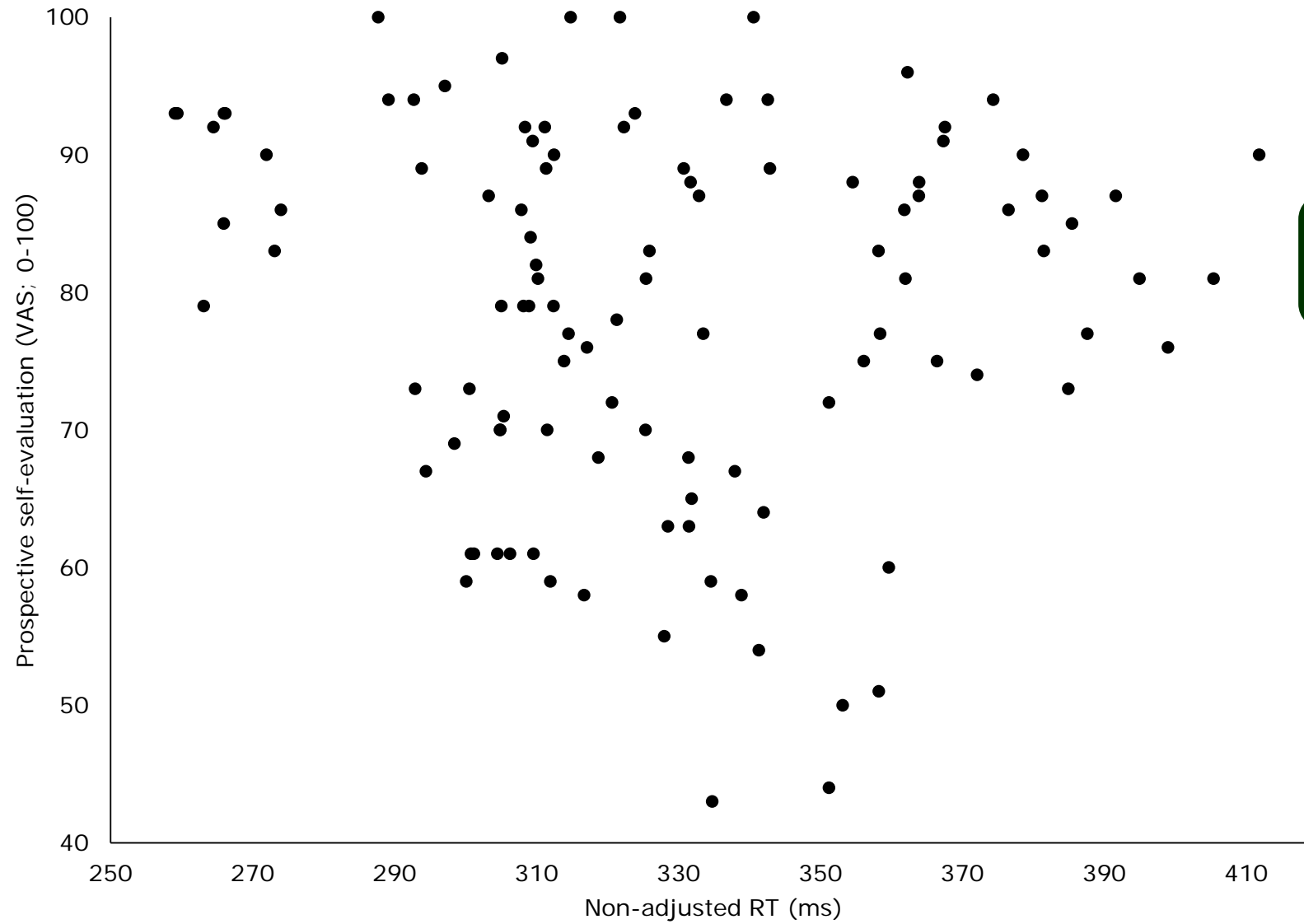
# Placebo







## Modafinil





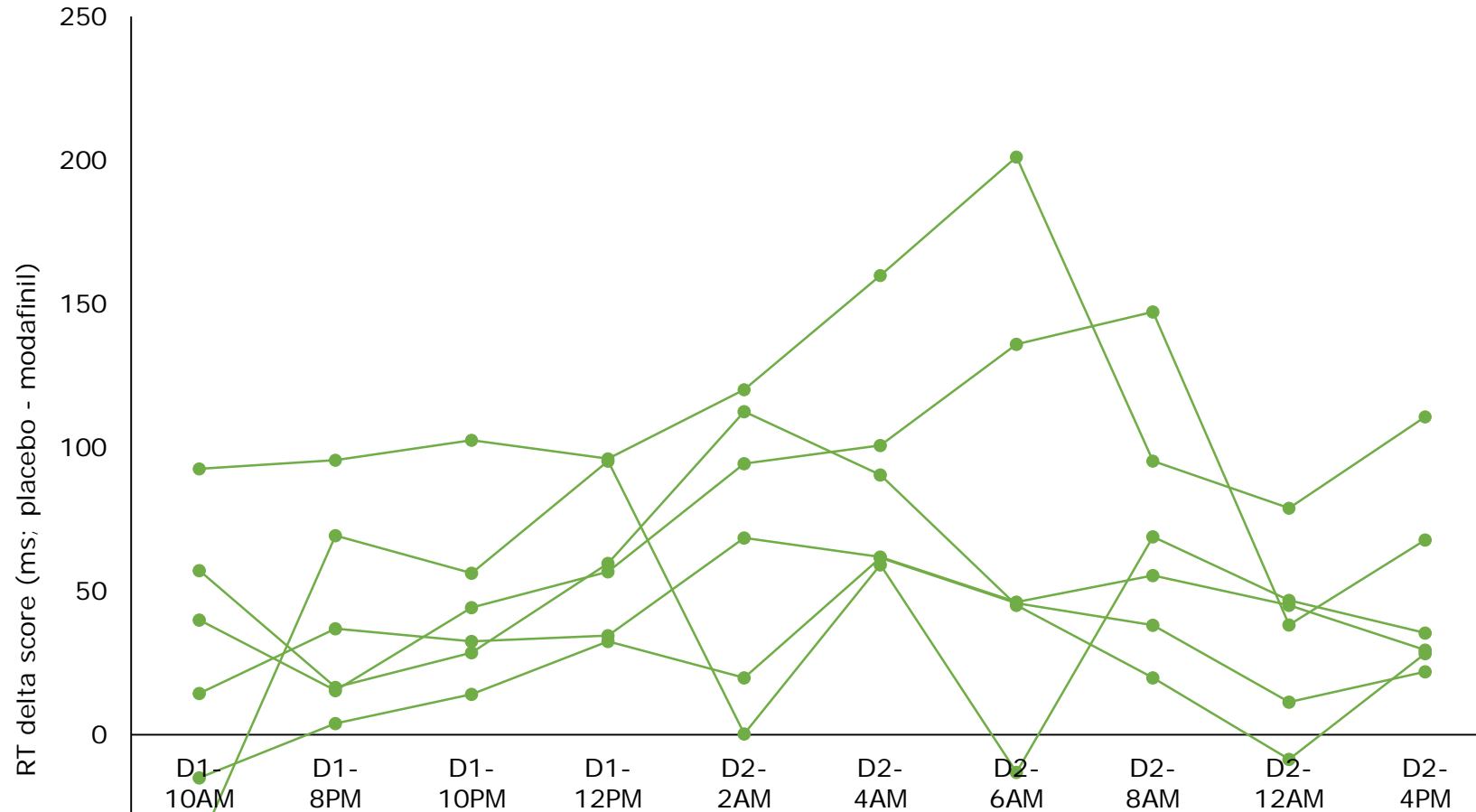
- Headache (x3)
- Diarrhea (x2)

- Light nausea (x1)
- Palpitations, nervousness (x1)

Participant	Baseline	*FD 08PM *	FD 10PM	FD 12PM	FD+1 02AM	*FD+1 04AM *	FD+1 06AM	FD+1 08AM	FD+1 12AM	FD+1 04PM	FD+1 08PM	FD+2 08AM	FD+2 12AM	FD+2 4PM	FD+2 8PM
Pil19-1	V	V	V	V	V	V	X	X	X	X	X	V	V	V	V
Pil19-2	V	V	V	V	V	V	V	V	V	X	V	V	V	V	V
Pil19-3	V	V	X	X	X	V	X	X	V	V	X	V	V	V	V
Pil19-4	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Pil19-5	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Pil19-6	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Pil19-7	V	V	V	V	V	V	V	V	X	V	V	V	V	V	V
Pil19-8	V	X	X	X	V	V	V	V	V	V	V	V	V	V	V
Pil19-9	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Pil19-10	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Pil19-11	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V

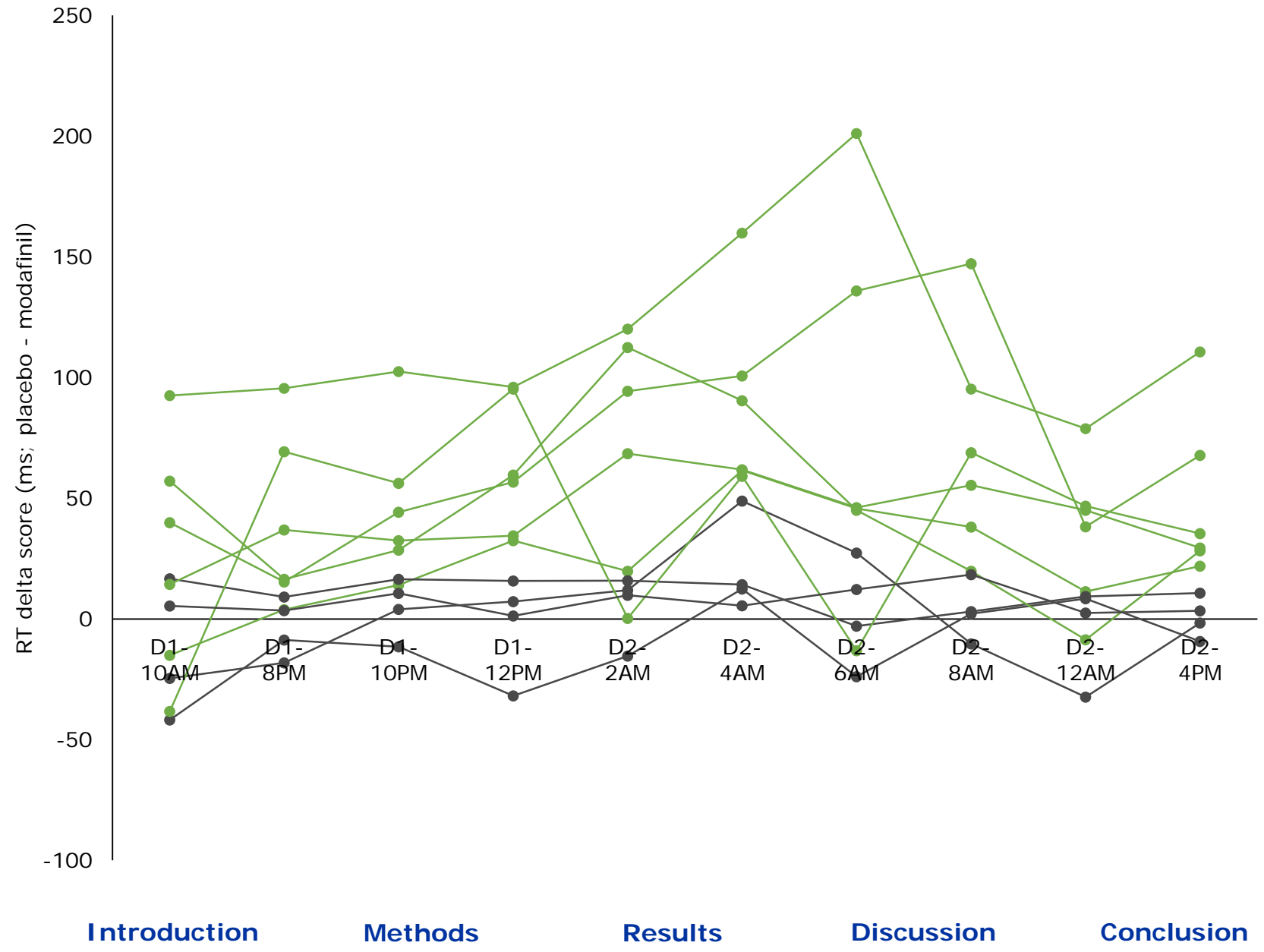
Interindividual differences

### Individual modafinil-effectiveness



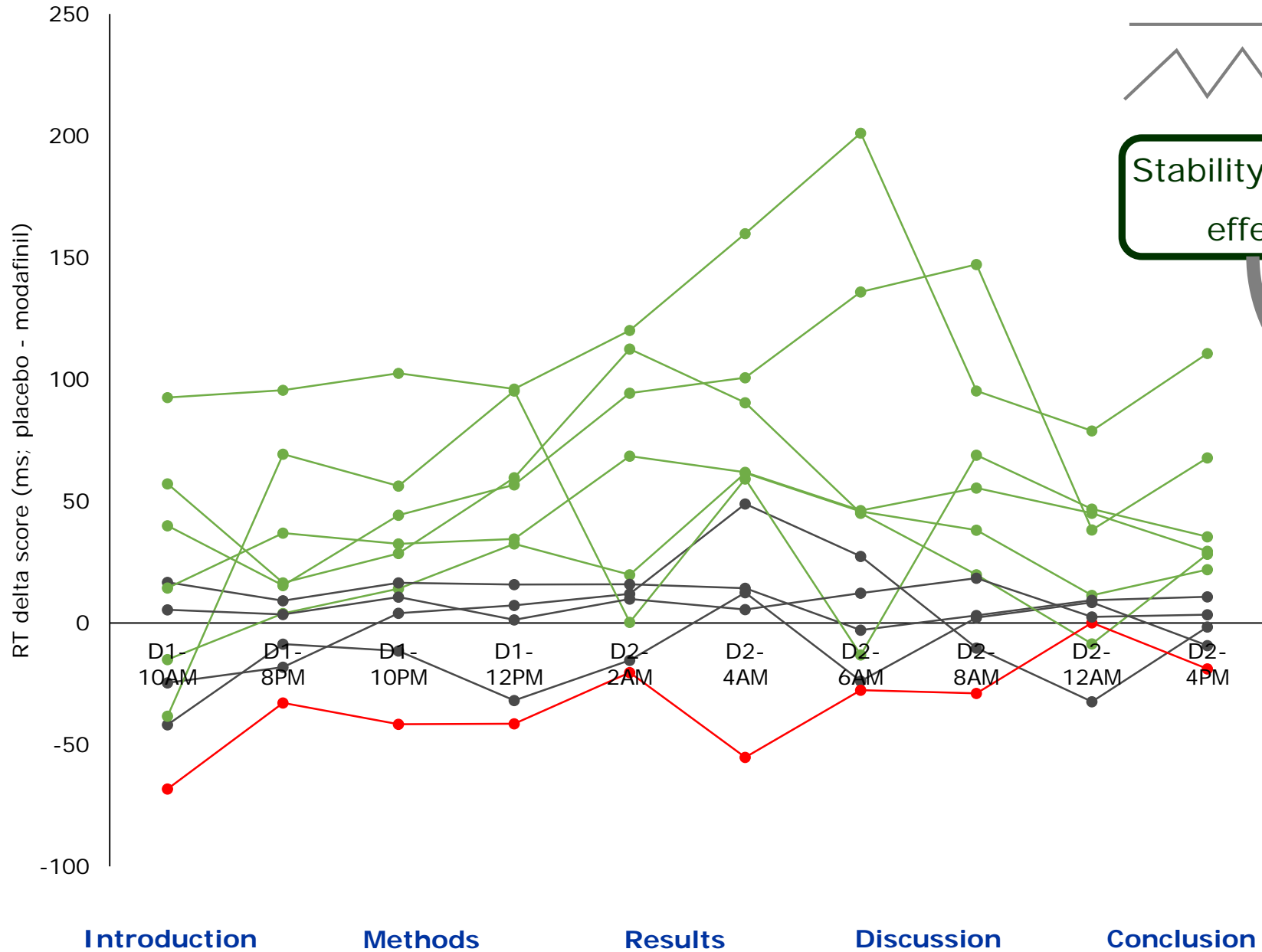
Interindividual differences

Individual modafinil-effectiveness



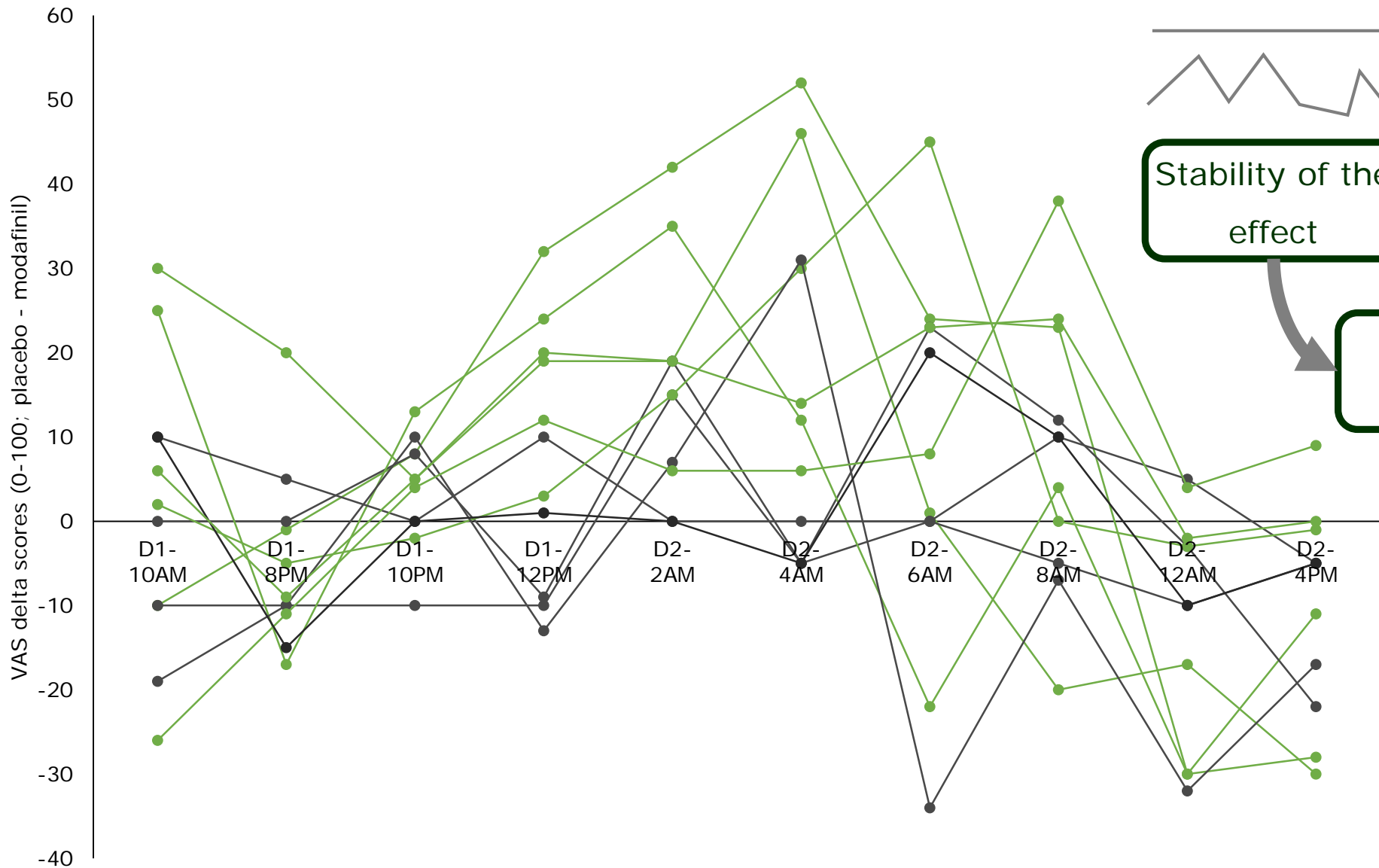
Interindividual differences

### Individual modafinil-effectiveness



Interindividual differences

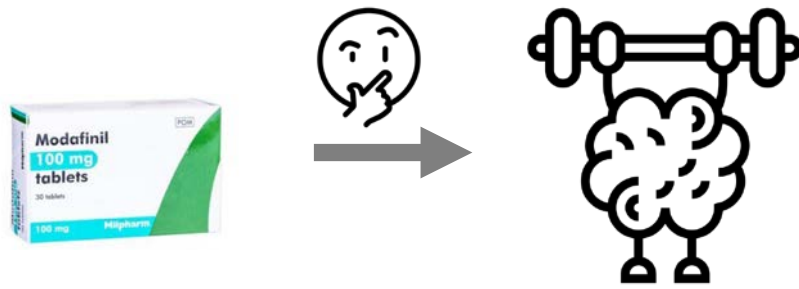
### Individual Sleepiness Profiles



Stability of the effect



ICC = 0.19



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- Risk for overconfidence?

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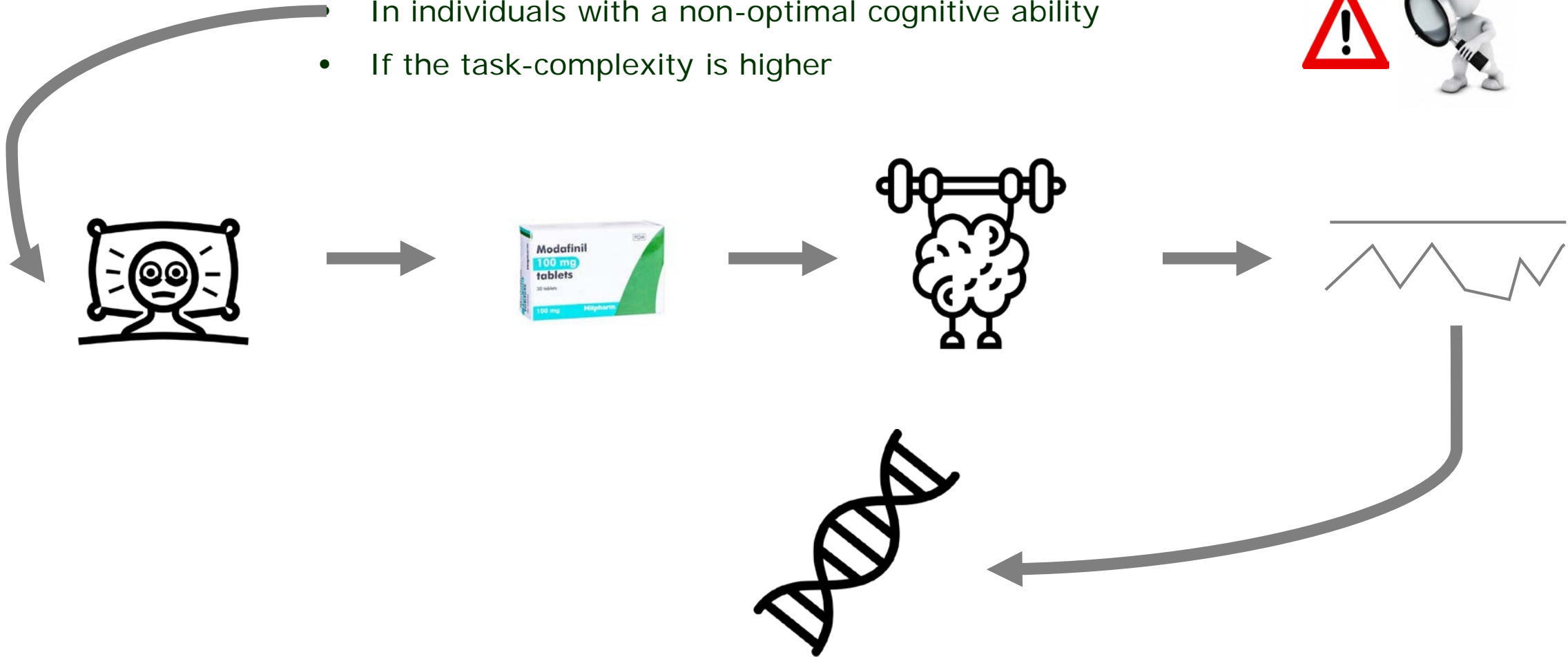
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Interindividual differences





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Interindividual differences



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Pil19-1	V	V	V	V	V	V	X	X	X	X	X	V	V	V	V
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Pil19-3	V	V	X	X	X	V	X	X	V	V	X	V	V	V	V
Pil19-4	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Pil19-5	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Pil19-6	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
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Pil19-8	V	X	X	X	V	V	V	V	V	V	V	V	V	V	V
Pil19-9	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Pil19-10	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Pil19-11	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V

Importance of a modafinil ground test!



## Acute effects that should be further investigated:

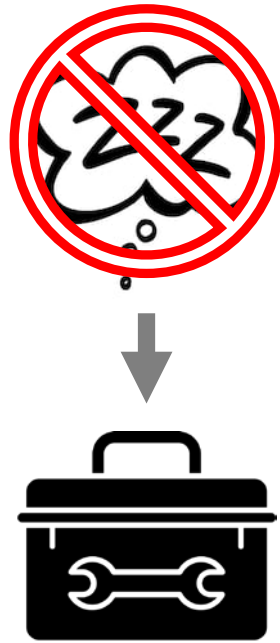


- Risk for overconfidence?

Unclear


- Prospective self-evaluation correlated with performance in PLAC
- Prospective self-evaluation did not correlate with performance in MOD
  - ✓ Inability to predict performance

**Subjective self-evaluation is a bad predictor of performance!**





## Key messages

- Modafinil **improves** human functioning when **sleep deprived**
  - ✓ Watch out for 
- **Stable** interindividual differences in modafinil-effectiveness exist
  - ✓ In cognitive performance
  - ✓ Not in perceived sleepiness
- Importance of a **modafinil ground test**
  - ✓ Exclude negative side effects
  - ✓ Test effectiveness

## References

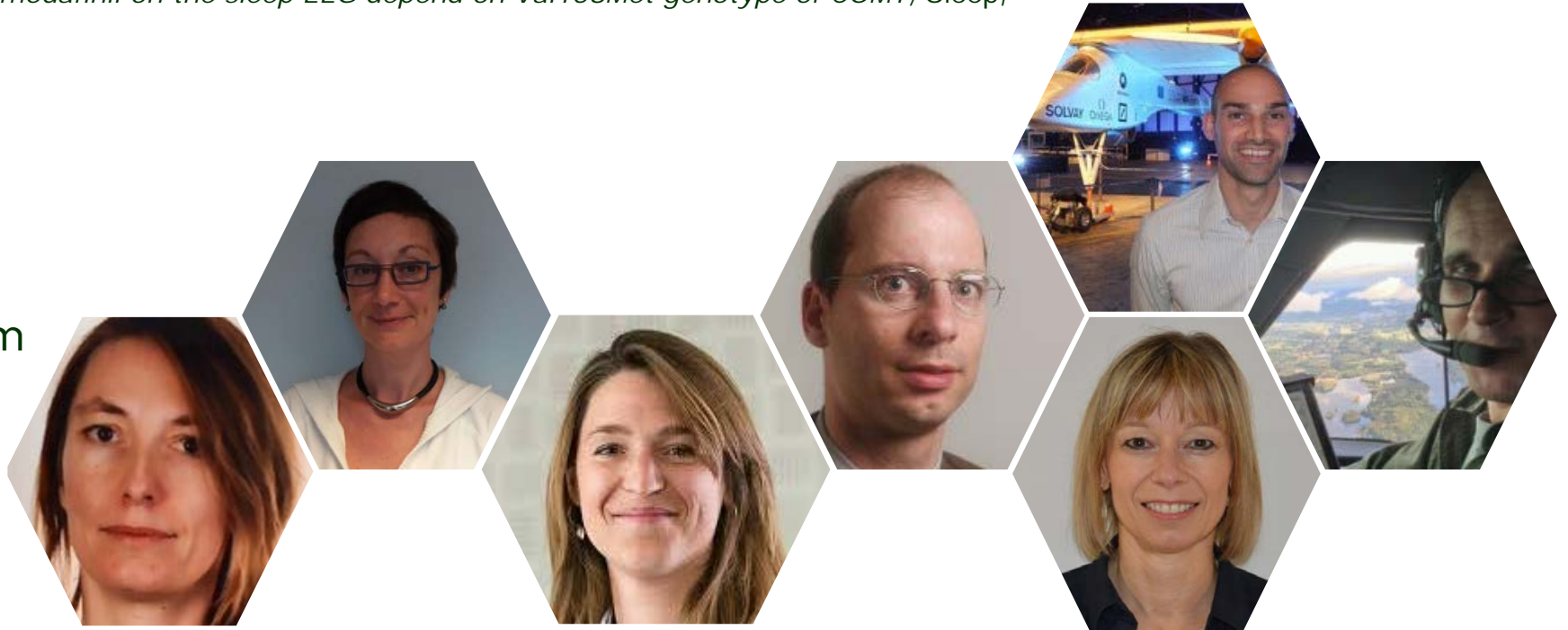
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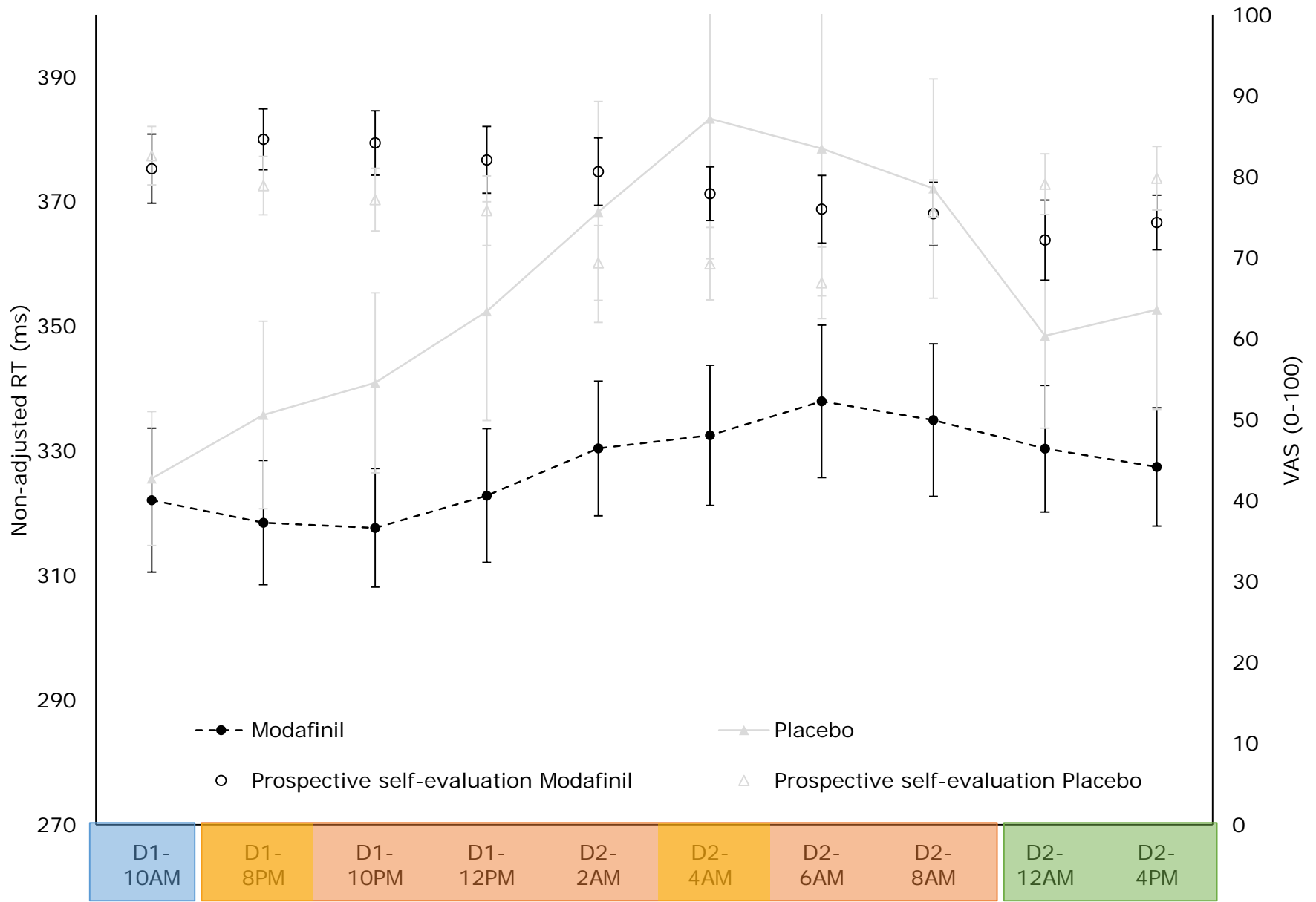


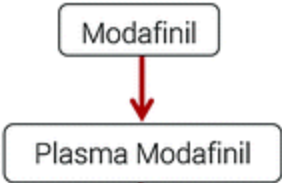
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200-400 mg/day



Peak -> 2.5 h post



Half-life of 9-14 h

