

Sleep Methodologies in CNS Trials

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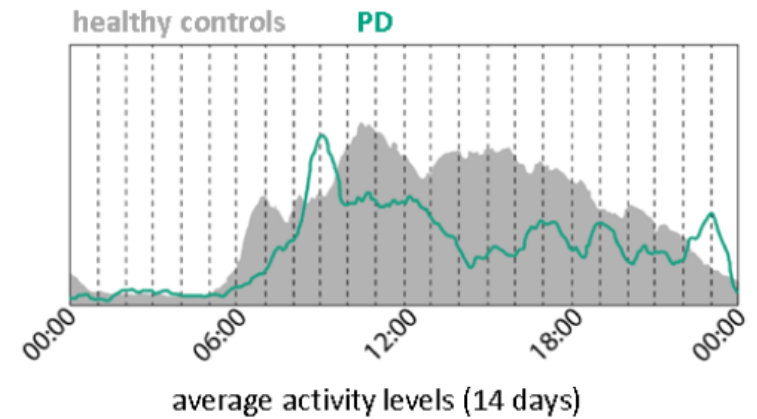
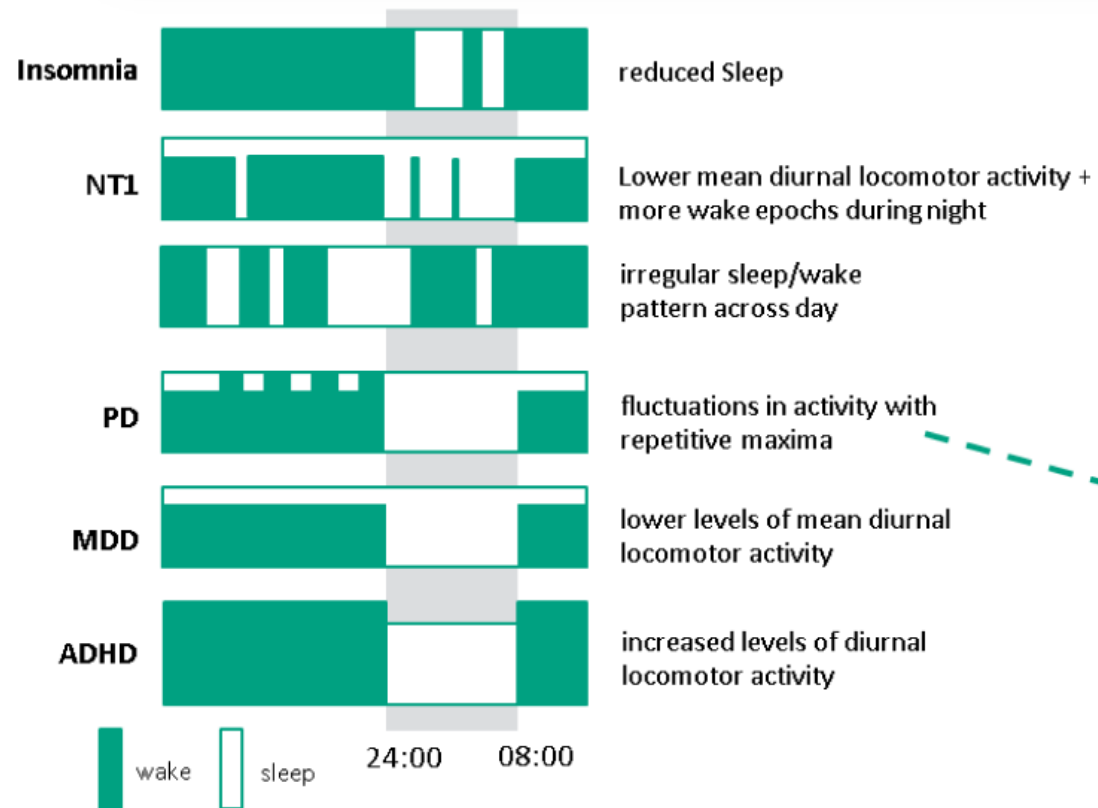
³Eisai

Disclosures

Georg Dorffner: Shareholder and part-time employee of The Siesta Group Schlafanalyse GmbH

Margaret Moline: full-time employee of Eisai, Inc.

Sleep in CNS Disorders



60 % of patients with PD suffer from insomnia, 30 % from excessive daytime sleepiness.

Measurement Instruments for Sleep



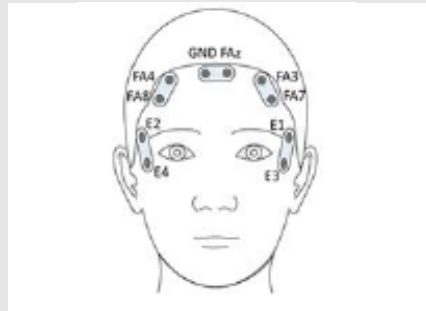
Portable PSG



Supervised In-Lab Polysomnography (PSG)



Actigraphy (Accelerometer)



Reduced Montage PSG



Single Channel EEG



Heart Rate (Photoplethysmography)



Heart Rate + Actigraphy

Measurement Instruments for Vigilance

Subjective scales: ESS, KSS

Epworth Sleepiness Scale (ESS)

Situation	0	1	2	3
Sitting and reading	0	1	2	3
Watching television	0	1	2	3
Sitting inactive in a public place—for example, a theater or meeting	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after lunch (when you've had no alcohol)	0	1	2	3
In a car, while stopped in traffic	0	1	2	3
Total Score				

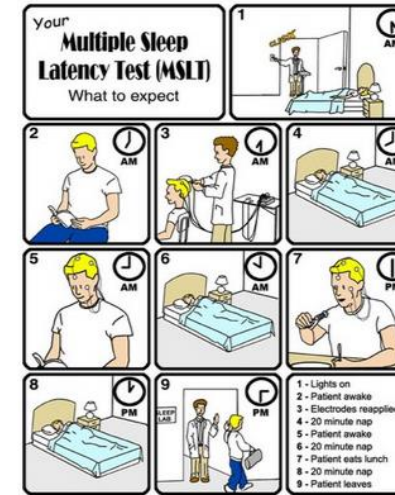
0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing
Johns MW. Sleep. 1991;14:540.

Karolinska Sleepiness Scale

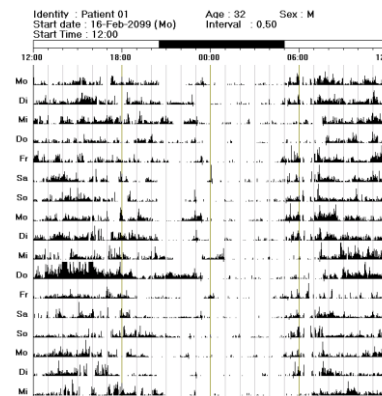
Here are some descriptors about how alert or sleepy you might be feeling right now. Please read them carefully and then circle the number that best corresponds to the statement describing how you feel at the moment.

1	Extremely alert
2	
3	Alert
4	
5	Neither alert nor sleepy
6	
7	Sleepy but no difficulty remaining awake
8	
9	Extremely sleepy, fighting sleep

MSLT, MWT

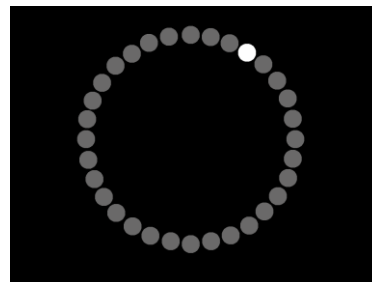
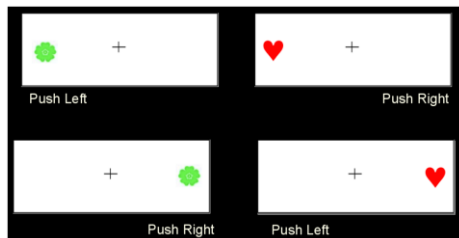


Actigraphy

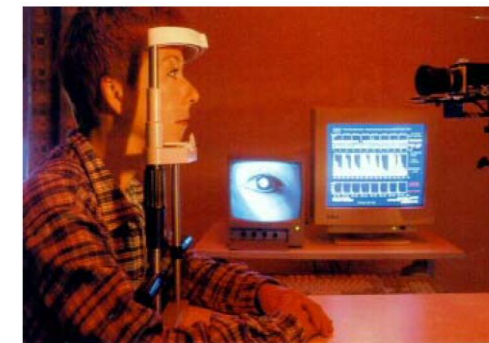


<https://quizlet.com/145582584/msltmwt-flash-cards/>

PVT, other vigilance tests



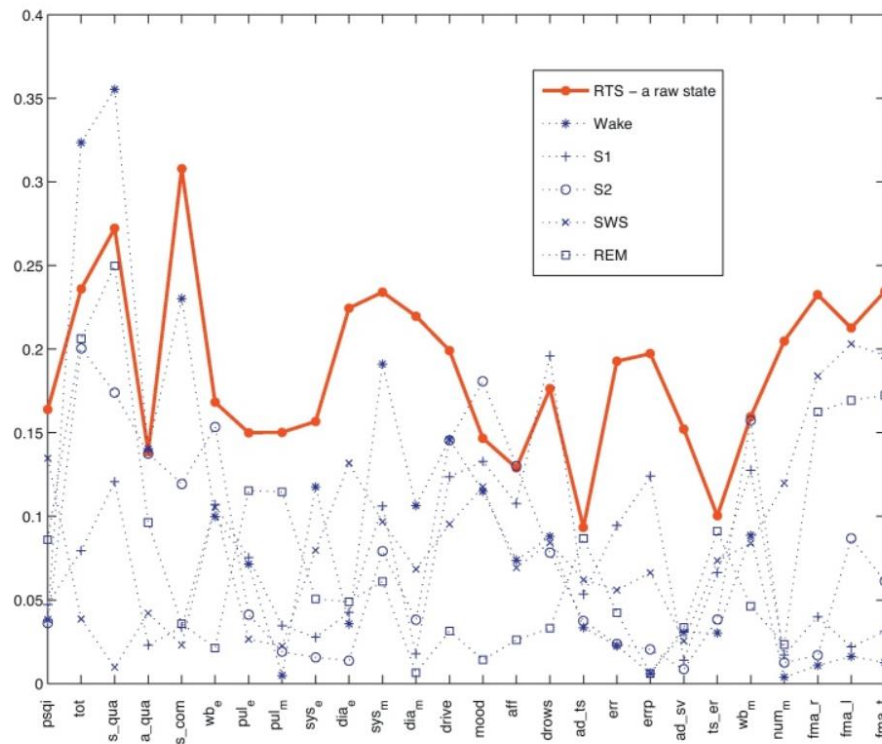
Pupillography



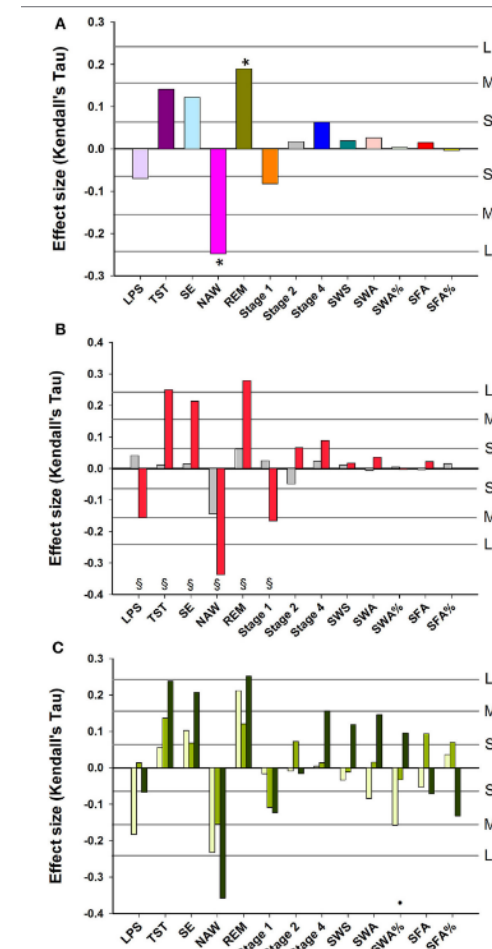
Possible Foci of the Working Group

- A critical assessment of various modalities for characterizing sleep, wakefulness and related states and for assessing the impact of clinical trial interventions for different sleep disorders. The analysis of alternative methods of measuring sleep and wakefulness and their potential applicability in CNS trials.
- Criteria for proper validation of such methods against the gold standard
- The relationship of objective methods of measurement with subjective assessments of sleep and wakefulness and the exploitation thereof
- Necessary activities to achieve acceptance for alternative instruments by regulatory bodies

Poor Correlations between Objective Measures and Patient-Reported Sleep Quality

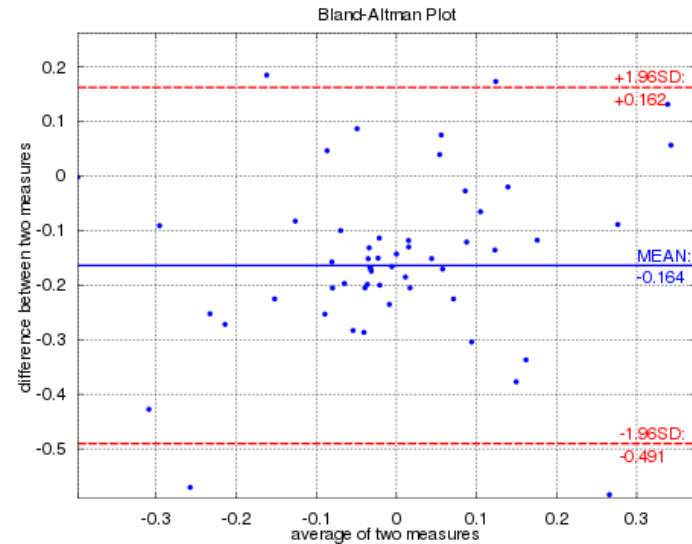
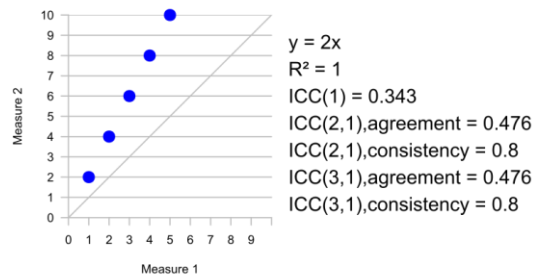
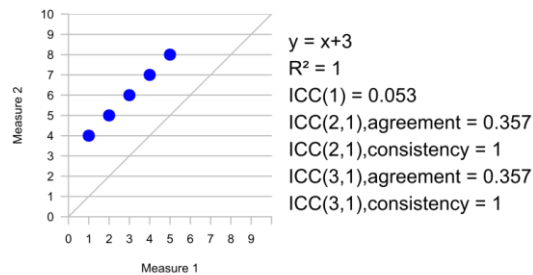
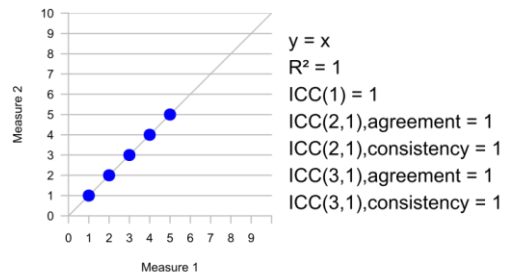
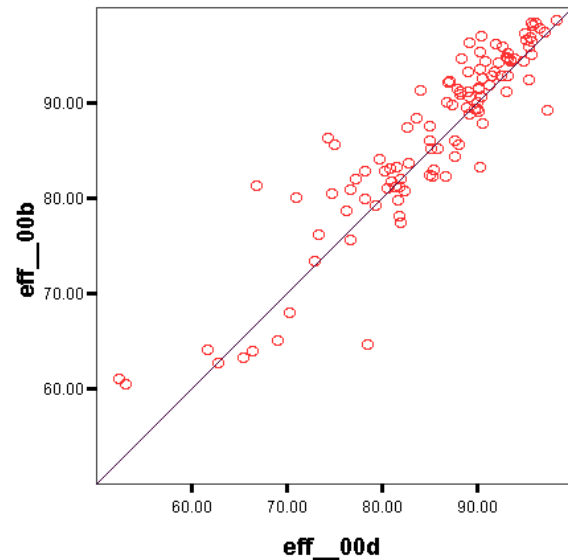


Lewandowski et al., *Comput Methods Programs Biomed.* 2012



Della Rossa et al., *Frontiers in Psychiatry*, 2018

Differences in Validation Methodology: Bias, Correlation, Intra-Class Correlation, etc.



www.wikipedia.org

Validation: How Good Will Be Good Enough?

Cohen's Kappa:

< 0.1:	none
0.1-0.4:	poor
0.4-0.6:	clear
0.6-0.8:	strong
0.8-1.0:	almost perfect

ICC:

< 0.40:	poor
0.40-0.59:	fair
0.60-0.74:	good
0.75-1.0:	excellent

(Cicchetti 1994)

< 0.50:	poor
0.50-0.75:	moderate
0.75-0.90:	good
> 0.90:	excellent

(Koo & Li 2016)

- But “good” or “strong” does not mean “equivalent”
- → Lack of acceptance in the community

Potential Deliverables

1. Systematic reviews on the evidence of the reliability and validity of different instruments for measuring sleep and wakefulness
2. A consensus paper on criteria and validation strategies for measurement instruments
3. Regulatory engagement with FDA
4. The initiation of a pre-competitive study with industry participation aimed at benchmarking certain instruments for their use in CNS trials