Ecological momentary analysis of high-frequency cognitive testing and its relationship to fatigue and sleep across neurodegenerative and inflammatory disorders

The methodological question: Do high-frequency cognitive tasks, done within a naturalistic environment, track fluctuations in transdiagnostic symptoms like fatigue and sleepiness?

Background

Cognitive performance, fatigue and sleep-quality vary within and between individuals over time. Given the prevalence of fatigue and sleep disturbances across diseases, the IDEA-FAST consortium is investigating objective digital biomarkers that can be assessed through high-frequency tests in a home environment. Here, we compare methods for best estimating whether fluctuations in cognitive performance can provide objective digital biomarkers for self-reported sleep and fatigue. Ecological momentary analysis is used to track fluctuations within individuals over time, both within and across days, and may be more sensitive to changes in other variables such as mood, fatigue or sleep.

Methods

The IDEA-FAST feasibility study includes data from patients with Huntington's and Parkinson's disease (neurodegenerative disease, NDD) and patients with primary Sjogren's syndrome, rheumatoid arthritis and systemic lupus erythematosus (immune-mediated inflammatory diseases, IMID).

A psychomotor vigilance test (PVT) for alertness and attention and a digit substitution test (DST) of global cognition were administered twice a day, via smartphone, for five days, over four weeks. Self-reported fatigue, mood and sleep (PROs) were also collected via smartphone using validated scales. We used daily aggregated means for performance in the cognitive tests and related this to PROs for sleep and fatigue using correlation, mediation and mixed effect linear models. Autocorrelation was used to capture temporal dependency in time series data and mean square successive difference (MSSD) estimated variability and temporal dependency in cognition, sleep and fatigue.

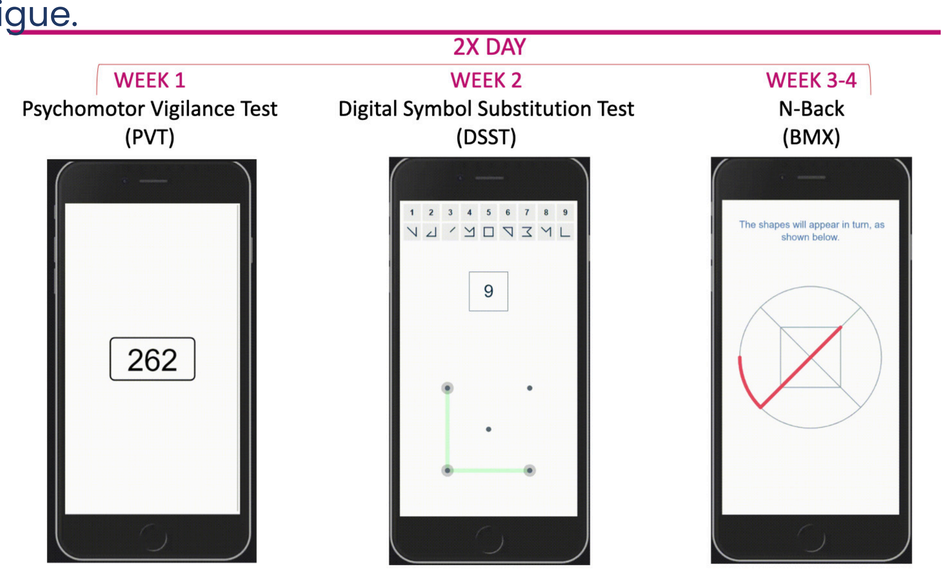


Figure 1: Cognitive tasks delivered via smartphone app. Cognitive tasks were delivered twice a day for five days across a total of 4 weeks. The PVT measures attention and alertness, the DSST measures global cognition and the N-Back measures working memory.

Demographics

		NDD			IMI		
	Healthy Controls	PD	HD	IBD	SLE	PSS	RA
N (M)	31	21	4	14	14	17	19
Mean Age (SD)	44 (11)	63 (10)	52(6)	36 (12)	49 (15)	59 (14)	64 (13)
MOCA	28(1)	27(3)	NA	28(2)	29(2)	28(2)	28(2)
Mean MFI total score (SD)	64(1)	58(5.5)	NA	59(5.5)	63(5.3)	60(4)	60(5)
Mean ESS (IQR)	3.8(3)	10.6(4.8)	NA	6.8(5.5)	9.4(4)	7.8(6.8)	7.2(7)
Mean PSQI (IQR)	3.9(2)	7.3(4)	NA		10.2(4)	7.6(3.5)	7.3(6.3)
Mean Godin Score (IQR)	50(4.5)	48(13)	32(1.5)	36(20.3)	25(26.3)	32(27)	35(27.3)

Table 1: Demographics across cohorts. MOCA – Montreal Cognitive Assessment; ESS – Epworth Sleepiness Scale; PSQI- Pittsburgh Sleep Quality Index; Godin-Shephard Leisure-Time Physical Activity Questionnaire. NA indicated missing data

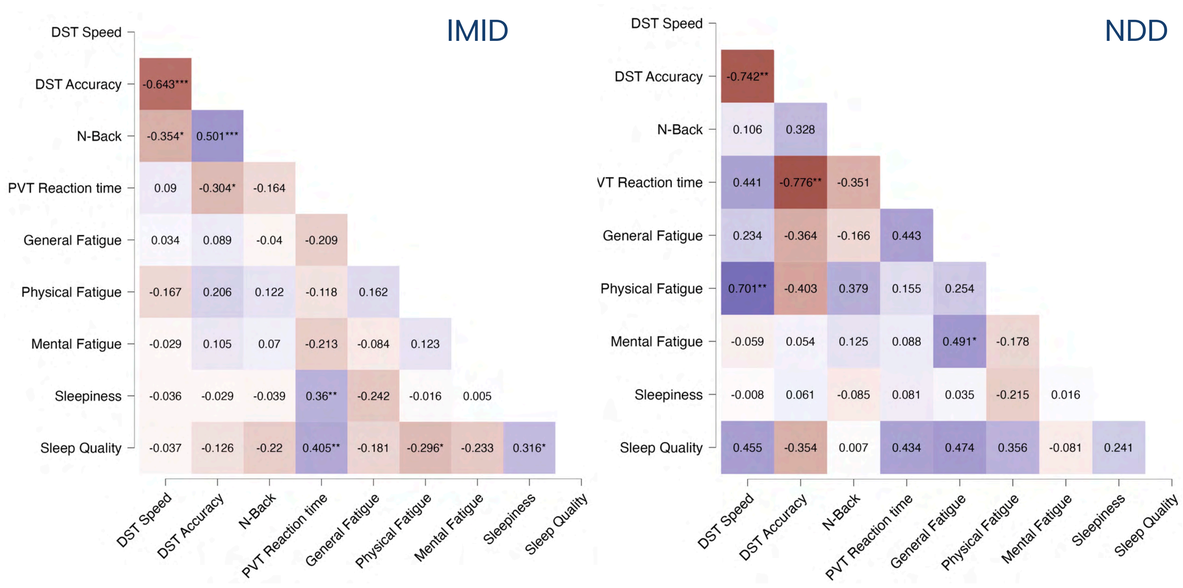


Figure 2: Correlations in measures of cognition, fatigue and sleep in the immune mediated inflammatory disease group - IMID (left panel) and the neurodegenerative disease group- NDD (right panel). *p<0.05; **p<0.01

Univariate analysis

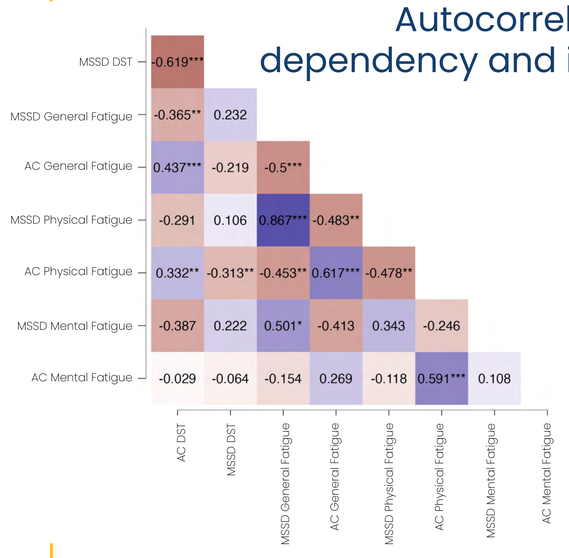
Average daily PVT reaction time showed a significant correlation with baseline sleepiness, r(57)=0.36, p<0.01, and quality of sleep, r(57)=0.41, p<0.01 in the IMID group. DST reaction time and physical fatigue were also significantly correlated, r(16)=0.70, p<0.01, in NDD patients.

Mediation analysis confirmed that the relationship between sleep and PVT performance was not mediated by fatigue, and the relationship between DST and fatigue was not mediated by sleep quality.

Figure 3: Mediation analysis, showing the relationship between sleep, physical fatigue and cognitive test performance. Arrows indicate the direction of the relationship, values represent standardised beta estimates. *p<0.05; **p<0.01

In mixed effect models, daily sleep and fatigue, corrected for age, with group (NDD, IMID, HC) as a random effect, showed daily mean reaction time in the PVT to be a significant predictor of daily sleep quality (F(1,31)=6.30, p<0.05), but not overall daily fatigue (F(1,9.88)=0.1, p=0.76).

Ecological momentary analysis



Autocorrelation and MSSD indexed temporal dependency and instability of cognitive, fatigue and sleep measures.

In age-corrected correlations, autocorrelation in general and physical fatigue was strongly correlated with autocorrelation in reaction time in DST (r=0.51, r=0.49 P<0.001). Temporal stability (MSSD) in DST reaction time was negatively associated with autocorrelation in physical fatigue(r=-0.32, p<0.001).

Conclusions

High-frequency cognitive testing has potential as an objective digital biomarker for fatigue and sleep. We show sensitivity across disease groups (NDD and IMID), and independent effects across self-reported measures of sleep and fatigue at both baseline, and collected daily. Importantly, measures indexing daily fluctuations in self-reported fatigue correlate with fluctuations in cognitive performance. Cognition may be a promising objective marker of subjectively reported fatigue.

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