

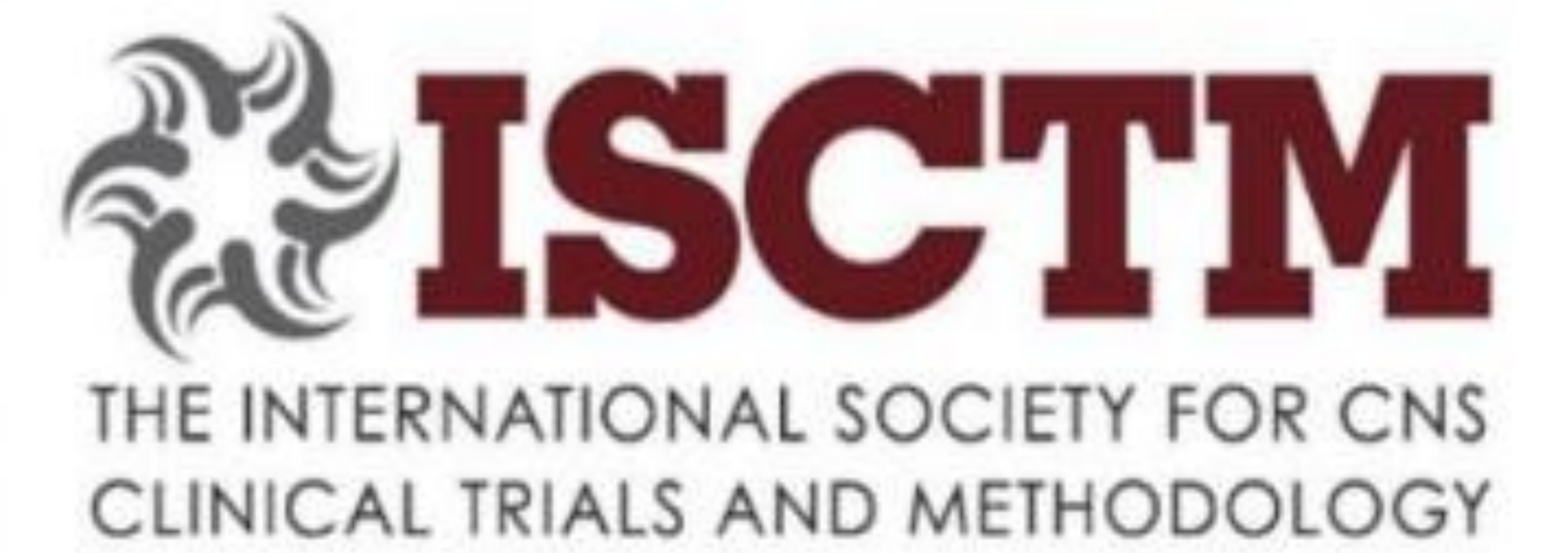
# CREATE: A Multimodal Digital Platform for Emotion Regulation, Working Memory and Dopaminergic Target Engagement in CNS Clinical Trials

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## 1. Methodological Issue Being Addressed

- There is a growing methodological need in central nervous system (CNS) clinical trials for scalable, mechanism-sensitive digital phenotyping tools that enable early participant stratification, enrichment, and endpoint innovation beyond symptom-level outcomes. Current solutions rarely quantify cognitive control, affective processing, and dopaminergic responsivity in an integrated manner, while also accounting for sleep-related modulation.
- To address this gap, we present the first pilot data which validate in a healthy cohort the CREATE, a multimodal digital platform that unifies working memory (WM) performance, affective-aesthetic response profiling, expressive writing sentiment analysis, and spontaneous eye-blink rate (sEBR) as a dopaminergic proxy, designed for CNS clinical trial readiness.

## 2. Introduction

- CREATE was conceptualized as a neurocognitive-affective digital phenotyping framework aligned with modern precision trial paradigms. It enables simultaneous assessment of emotion regulation (ER), WM capacity, dopaminergic plasticity signals, and sleep-related variability, supporting objective, mechanism-informed participant profiling suitable for stratification and enrichment strategies.

## 2. Methods

- A pilot sample of 27 healthy adults (aged 21–44 years) completed:
  - (i) an adaptive Corsi-based WM training task
  - (ii) an art-driven affective evaluation task with valence-arousal ratings
  - (iii) expressive writing per stimulus, analyzed for polarity, subjectivity, and average word length
  - (iv) tasks 1-3 were performed only once. The sEBR measurement was performed before and after the one-shot training. It involved a computer vision task for identifying spontaneous eye blink rates through custom-based Python code employing the Google MediaPipe library. Its duration was 5 minutes during which the participants looked at the laptop's camera. Tasks 1-3 and Task 5 lasted for 60 minutes and
  - (v) sleep quality assessment via the Pittsburgh Sleep Quality Index (PSQI).Analyses included non-parametric and partial rank correlations (controlling for baseline sEBR), and regression modeling assessing how high-valence, high-arousal (HVHA) affective response deviation predicted WM performance.

## 3. Results

- WM performance correlated positively with ER capacity. Post-training sEBR correlated with ER, suggesting dopaminergic target sensitivity. Lower sleep efficiency attenuated sEBR gain, indicating a sleep-related moderating effect. Linguistic expressiveness in narrative responses tracked sleep-related affective variability. HVHA arousal predicted reduced WM performance, reflecting a cognitive-affective trade-off detectable via CREATE's integrated metrics.

## 4. Conclusions

- We provided the first evidence of employing CREATE in a healthy population cohort. Its second pilot phase would investigate normative rating across the healthy lifespan and comparison with patient (neurodegeneration and depression) populations. It enables early-layer participant profiling, cognitive-affective stratification and dopaminergically aware endpoint development beyond traditional scales. By integrating behavioral, linguistic, and physiological measures within a theoretically grounded cognitive-affective control framework, CREATE provides a scalable infrastructure that can support participant stratification, exploratory enrichment strategies, and mechanism-proximal digital endpoints in early-phase neurocognitive intervention and drug trials. The present data demonstrate feasibility, interpretability, and state-dependent signal variability, illustrating how CREATE outputs could be operationalized for enrichment and early signal detection rather than serving as validated trial decision tools.