

Sustained effects of S-ketamine on cortical excitability and resting-state brain activity

See all
CHDR posters:



Catherine M.K.E. (Kaye) de Cuba^{1,2}, Annika A. de Goede¹, Joost C. van Mechelen¹, Laura G.J.M. Borghans¹, Liam van der Aa^{1,2}, Erik Olofsen^{1,5}, Maria J. Juachon¹, Robert J. Doll^{1,2}, Amy Gillespie⁴, Catherine J. Harmer⁴, Gabriël E. Jacobs^{1,3}, Jules A.A.C. Heuberger¹

1) Centre for Human Drug Research, Leiden, The Netherlands, 2) Leiden University Medical Centre, Leiden, The Netherlands, 3) Department of Psychiatry, Leiden University Medical Centre, Leiden, The Netherlands, 4) Department of Psychiatry University of Oxford, Oxford, The United Kingdom, 5) Department of Anesthesiology, Leiden University Medical Centre, Leiden, The Netherlands.

Introduction

- Sustained efficacy of single-dose of rapid-acting antidepressant drugs (RAADs) such as S-ketamine may be related to delayed pharmacodynamic (PD) effects following their systemic clearance.
- Reliable biomarkers capturing such potential delayed PD effects remain limited.

Hypothesis

- Delayed PD effects emerging following clearance of S-ketamine are mechanistically distinct from acute, peak-concentration-driven psychomimetic and CNS-depressant effects.

Methods

- Randomized, double-blind, double-dummy, placebo-controlled, 4-way crossover study evaluating effects of oral and intravenously administered S-ketamine on cortical excitability and resting-state EEG in healthy participants (Figure 1).
- TMS-EMG and TMS-EEG were recorded simultaneously including both single- and paired-pulse paradigms (interstimulus intervals 2, 50, 100 and 300 ms).
- Stimulation targeted the motor hotspot of the dominant abductor digiti minimi muscle.
- Resting-state EEG was recorded with 5-min alternating periods of eyes closed and open every 64 seconds (s).
- Plasma concentrations were measured over time for S-ketamine, S-norketamine and S-hydroxynorketamine, non-compartmental analysis was performed, and concentration-effect relationships were explored.
- Outcomes were analyzed using mixed-effects ANCOVA and cluster-based permutation testing.

Figure 1. Study design

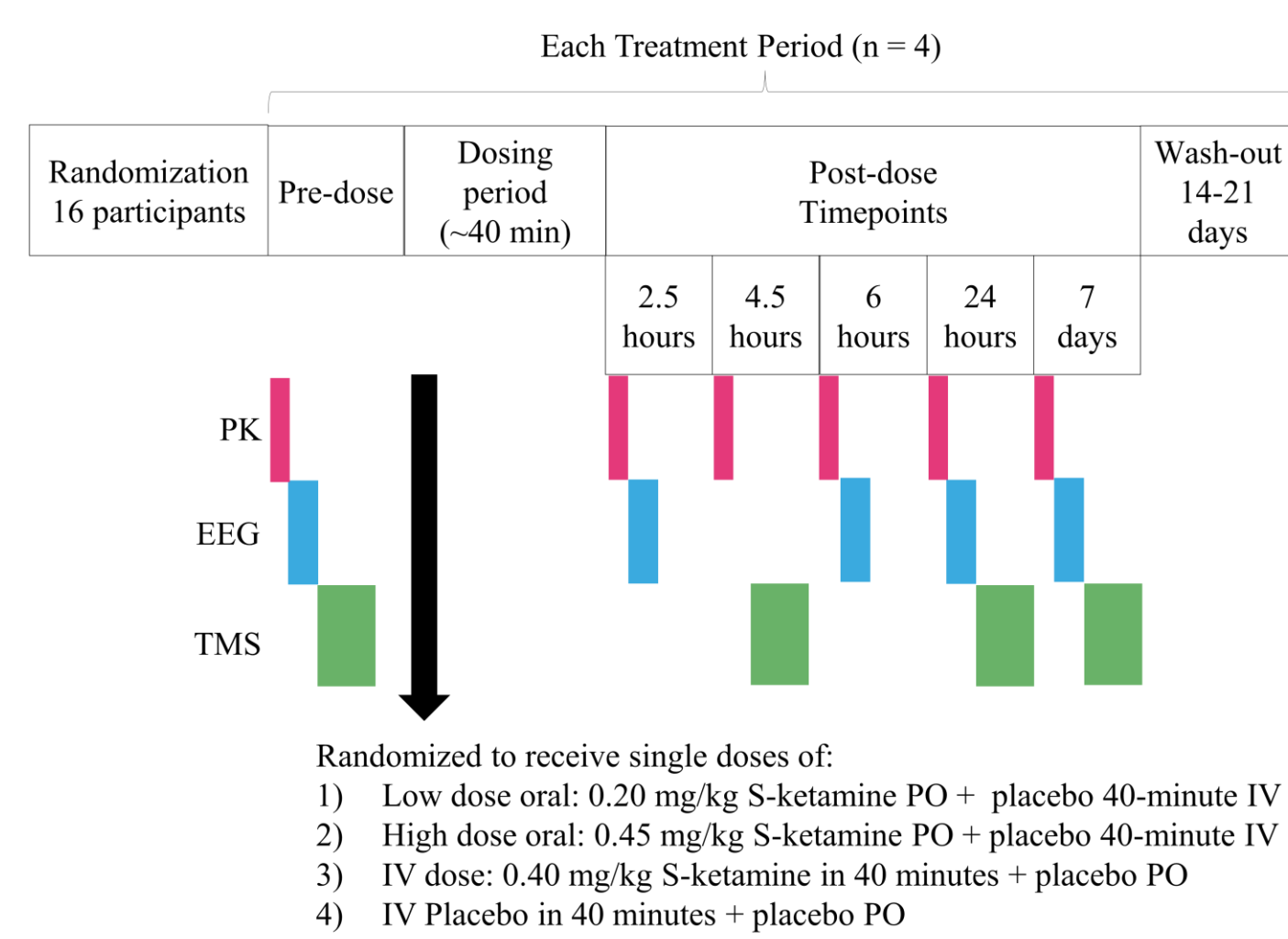


Figure 2. Plasma concentrations profiles over time

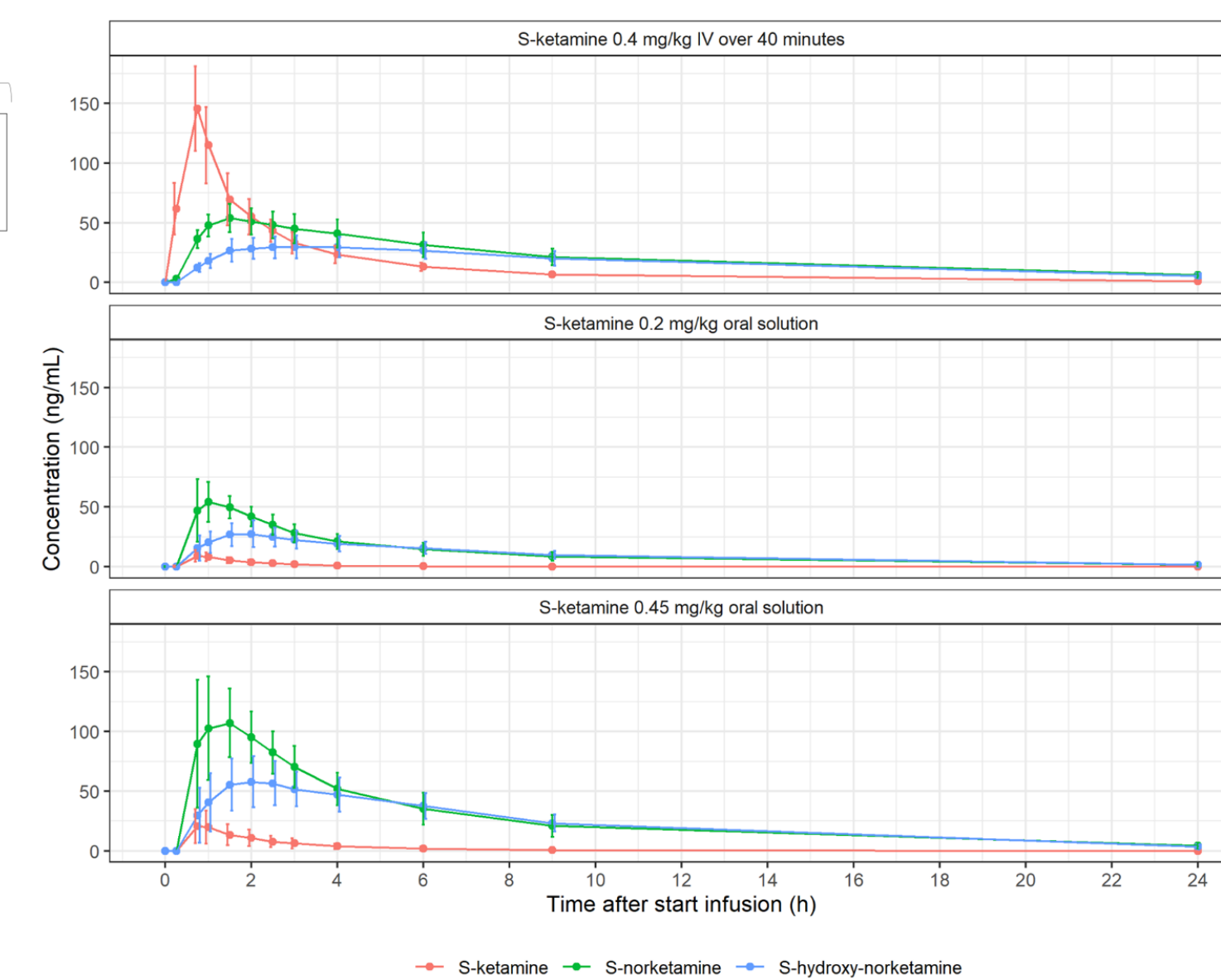
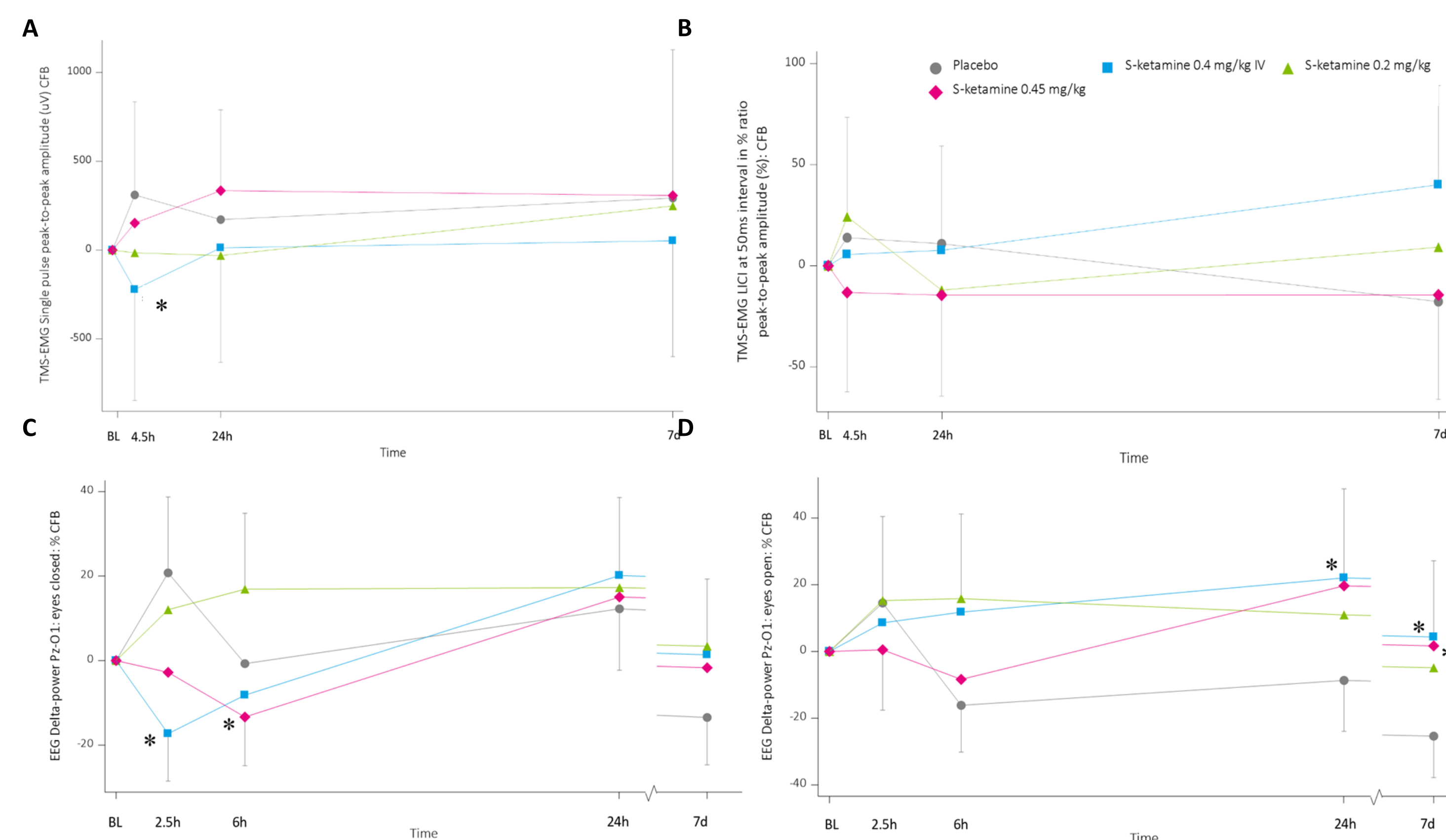
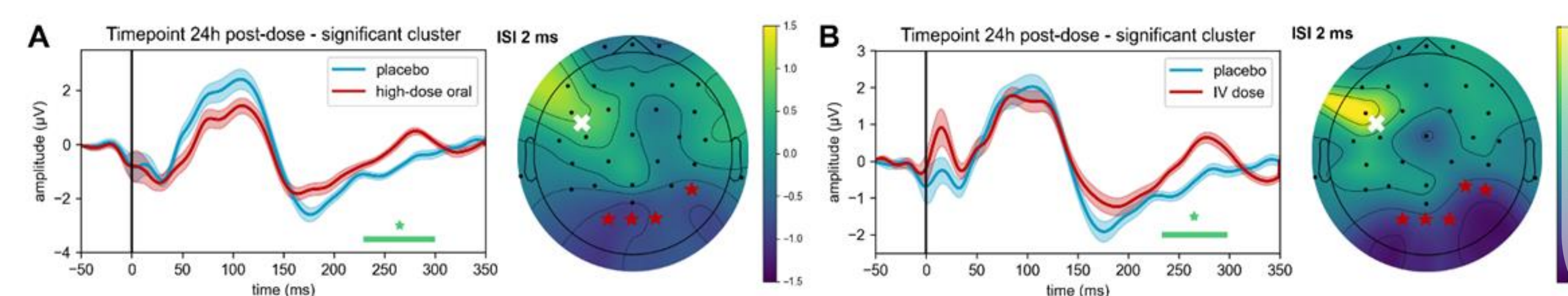


Figure 3. Statistically significant acute and delayed TMS-EMG and EEG effects



Description: Change from baseline of the least square means (LSM) with 95% confidence interval (95%-CI) as error bars. Delta power range was set to 1.5 < 6.0 Hz. Significant results compared to placebo (in grey) are marked with an asterisk (*).

Figure 4. Statistically significant delayed TMS-EEG effects



Description: Grand average (mean ± SEM) over all significant electrodes is presented. On the right side, the amplitude difference in topographical distribution (placebo - S-ketamine) at the time of the cluster is presented. The thick green bar represents the time window of significant differences, the white cross the stimulation site, and the black dots the electrode positions with the significant electrodes as red stars.

Results

- 8 male and 8 female healthy participants completed the study
- Plasma-concentration profiles over time are summarized in Figure 2.
- IV S-ketamine reduced motor-evoked potential amplitude at peak plasma concentrations and demonstrated sustained attenuation of long-interval intracortical inhibition at ISI 50 ms at 7 days post-dose (Figure 3); the latter showing a linear concentration-effect relationship with the parent compound.
- IV and high-dose oral S-ketamine showed reductions in alpha, beta, and delta power (eyes closed) at peak plasma concentrations and delayed increases in delta power (eyes open) at 24 hours and 7 days post-dose (Figure 3) with a less analyte-specific linear concentration-effect relationship
- All treatments showed peak concentration driven modulation of early TMS-evoked potential (TEP) components, whereas delayed effects occurred only after IV and high dose oral treatment impacting the late TEP components (Figure 4) at 24 hours post-dose.

Conclusion

- We provide evidence of S-ketamine effects sustained up to 7 days post-dose following its systemic clearance in healthy participants, using TMS and resting-state EEG derived biomarkers.
- Effects were observed for IV and high-dose oral S-ketamine, both treatments leading to high parent compound and metabolite exposures.
- PD effects were showed acute vs. delayed PD effects were markedly distinct, which may be relevant to understand its antidepressant efficacy and for guiding development of new RAADs.