TMS-EMG and TMS-EEG as a biomarker for pharmacological effects on cortical excitability

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Introduction

Transcranial magnetic stimulation (TMS) combined with electromyography (EMG) or electroencephalography (EEG) offers a non-invasive opportunity to study cortical excitability. This potentially makes TMS a valuable biomarker to study effects of drugs that are expected to affect nerve or cortical excitability in clinical trials.

Aim

To evaluate effects of oral levetiracetam, valproic acid, and lorazepam on cortical excitability measurements in healthy volunteers as measured by single pulse (SP) TMS-EMG and TMS-EEG and validate the method as a biomarker.

Methods

In this double-blind, placebo-controlled four-way single dose cross-over study subjects received in a randomized order: levetiracetam (LEV) 2000 mg, valproic acid (VPA) 1000 mg, lorazepam (LOR) 2 mg, or placebo. TMS-EMG and TMS-EEG was performed pre-dose and 1.5h, 7h, and 24h post-dose. Analysis was performed using a mixed model with baseline as covariate estimating differences up to the 7h time point. TMS-EEG analysis was performed using two approaches: analysis at the single lead Cz and cluster-based permutation analysis (CBPA) incorporating all leads.

Results

A total of 16 healthy male subjects completed the study. All three treatments significantly decreased the MEP amplitude in the TMS-EMG response (LEV, p=.001; VPA, p=.047; LOR, p=.017), see Fig. 1. For SP-TMS-EEG, the following effects were observed:

Levetiracetam:
- Cz: N100 decreased (p=.039) (Fig. 2a)
- CBPA: N45 increased (p=.004) (Fig. 3a)
  N100 decreased (p=.001) (Fig. 3b)

Valproic acid:
- Cz: N15 increased (p=.045) (Fig. 2b)
- CBPA: No significant effects

Lorazepam:
- Cz: N100 decreased (p=.039) (Fig. 2c)
- CBPA: No significant effects

Conclusions

LEV, VPA, and LOR show significant effects on cortical excitability, as measured by TMS-EMG and TMS-EEG, encouraging further development of TMS as a useful biomarker for pharmacodynamic effects of drugs targeting cortical excitability.

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TMS-EMG

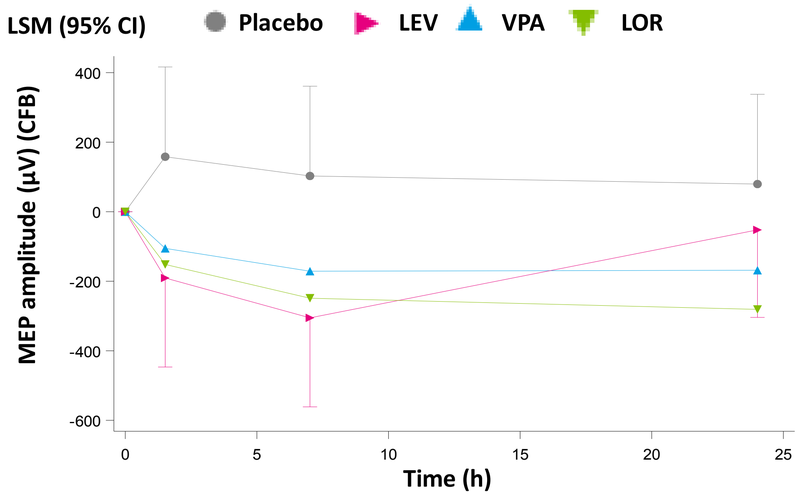

Fig. 1: Change from baseline of MEP amplitude (µV) using SP-TMS

TMS-EEG

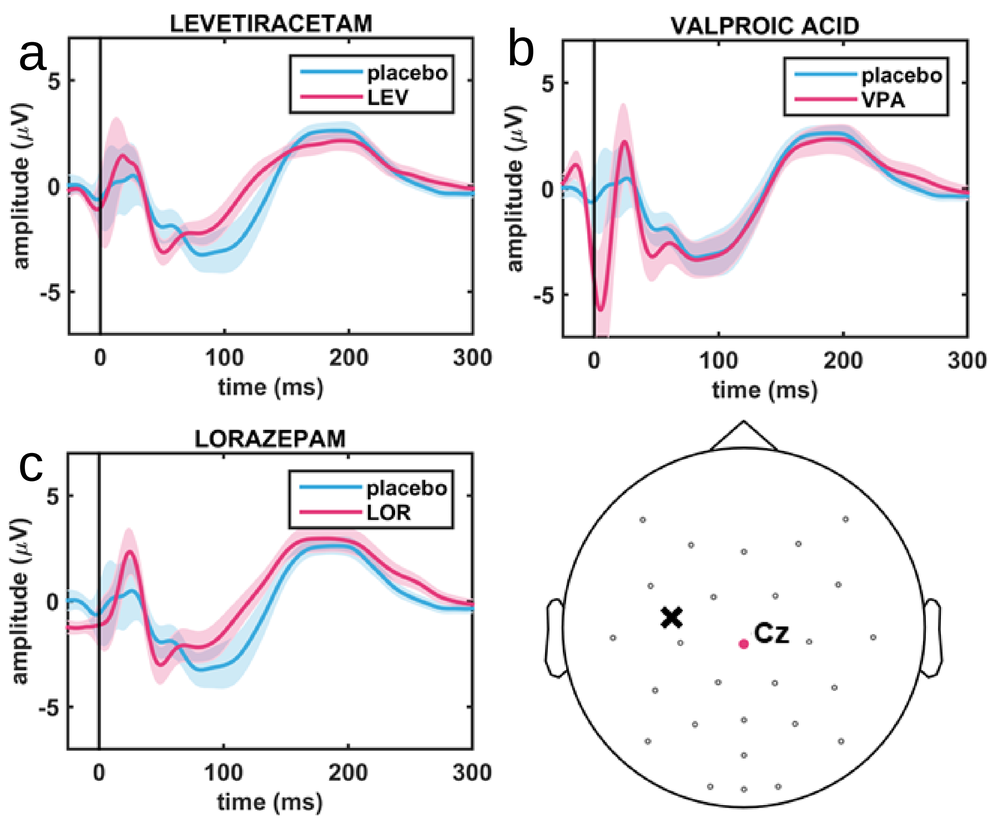

Fig. 2: SP-TEP response at single lead (Cz) for a. LEV; b. VPA; c. LOR.

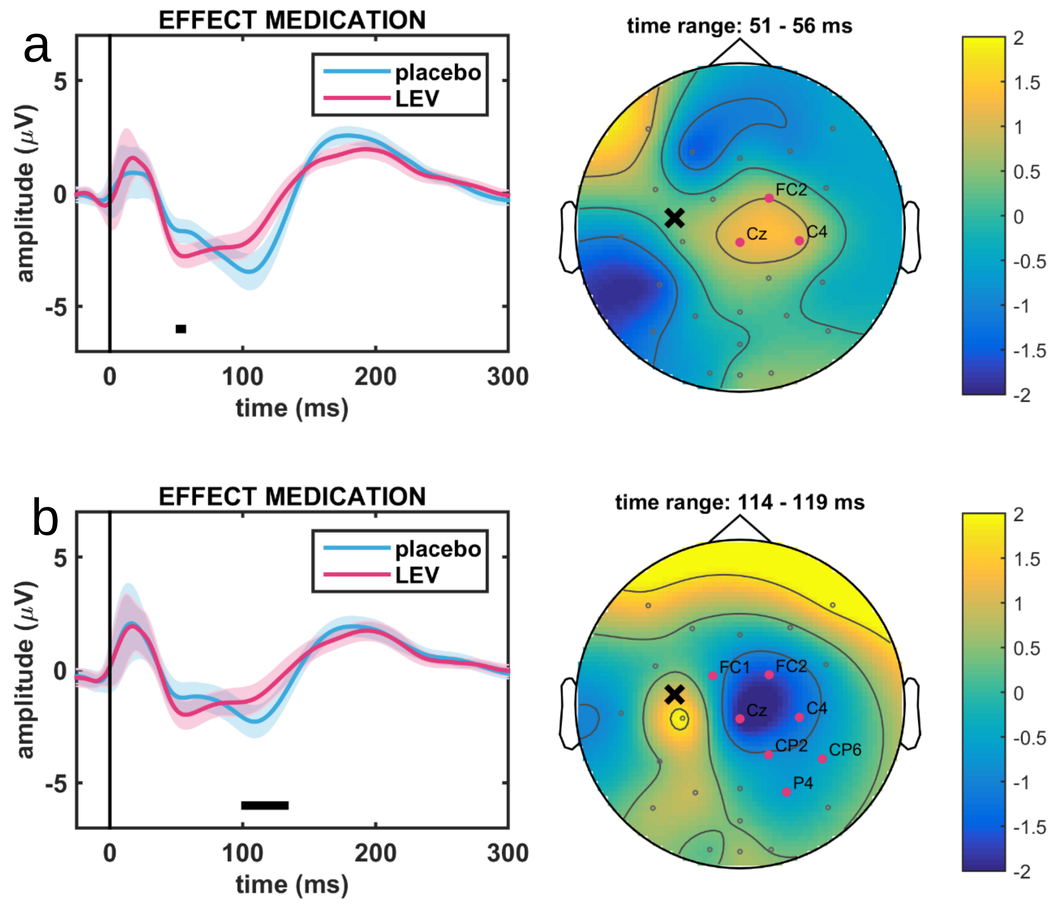

Fig. 3: CBPA of SP-TEP response, LEV vs. placebo