TITLE: The analysis of TMS-EEG data in a Bayesian multivariate Copula model for prediction of clinical efficacy

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ABSTRACT:

Background:
The analysis of Transcranial Magnetic Stimulation-Electroencephalography (TMS-EEG) data is used to evaluate the effects of drugs in the brain. The number of TMS-EEG variables to analyse can be substantial. Analysis of such data using frequentist methods to identify the brain regions of interest lead to a high false positive rate due to the number of tests carried out leading to challenges to replicate the published results. In this study, we deployed Bayesian multivariate models to avoid an increase in false positive rate and at the same time account for the correlation between the different variables. We also used a Copula model to correlate the TMS-EEG parameter with a clinical variable of interest in a motivating dataset consisting of healthy volunteers.

Methods:
Multivariate Bayesian fixed and random effects models have been employed to analyse 18 TMS-EEG parameters collected in a 2x2 crossover trial where subjects received an experimental treatment or placebo. The variables were ranked according to the estimated Cohen's D value. Simulations were performed to evaluate the consistency of the ranking. Next, a Copula model and Bayesian Gamma regression model were used to correlate and construct the relationship between a specific TMS-EEG variable and a clinical outcome, based on clinical data published in healthy volunteers and patients with autism spectrum disorder (ASD). We extrapolated the results on our motivating dataset to predict potential clinical response in an experimental treatment.

Results:
The Bayesian multivariate model allowed for an ordering of the variables that are likely to show drug activity in the brain taking into account the correlations between these variables. These results were consistent across different modelling scenarios. Simulations confirmed the ranking order of the TMS variables where a drug response was likely to be observed. The copula model also enabled the establishment of a relationship between a TMS-EEG outcome and the clinical variable. It was shown that with a high enough dose that clinical effect may be achieved.

Conclusions:
The Bayesian multivariate model allowed to evaluate multiple TMS-EEG variables simultaneously therefore reduce the false positive rate issue associated with multiple testing. The copula model allowed for correlating the TMS-EEG variable published in literature with a clinical outcome