

USING CAUSALLY INFORMED FUNCTIONAL CONNECTIVITY METHODS TO IDENTIFY PREFRONTAL-CINGULATE TMS TARGET FOR REWARD POSITIVITY MODULATION

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INTRODUCTION

- **Anterior midcingulate cortex (MCC)** dysfunction has been implicated in various substance use disorders (e.g., nicotine dependence) as well as other psychiatric disorders, (e.g., depression¹).
- 10-Hz repetitive transcranial magnetic stimulation (TMS) to the left dorsal lateral prefrontal cortex (DLPFC) has been shown to stimulate neural response patterns in the cingulate cortex.
- **The problem:** Given the limitations and variability of conventional TMS methods, the optimal TMS targeting protocol for MCC modulation is currently unknown.
- **The Solution:** Resting-state functional connectivity (RSFC) has become a widely used measurement of human brain connectivity, we propose that RSFC-based DLPFC-MCC targets may improve TMS efficacy to modulate MCC via network dynamics.
- **The goal of this study** is to use TMS to counteract the aberrant MCC-related processes observed in nicotine dependence. To accomplish this goal, we will use RSFC maps to select individualized DLPFC targets displaying maximal FC with MCC, and then measure the effectiveness of applying 10-Hz rTMS for the purpose of modulating MCC function, as evaluated by the reward positivity and the N200.

OPTIMIZING RSFC TARGET SELECTION

- Moving forward in the field, we ask whether TMS targets change as a function of analysis technique?
- To test this idea, we utilized novel functional connectivity (FC) methods that are grounded in stronger causal principles than standard correlation approaches and produce FC targets that may accurately represent the functional connections between two regions.

METHODS

- **Combined EEG-fMRI.**
- 18 healthy participants
- Age: 23.78 years
- 13 male, 10 female
- **Functional Connectivity methods:**
 - Pearson correlation
 - Multiple Regression
 - Combined FC
 - A novel method that uses partial correlations to avoid unauthentic edges produced by confounders and causal chains, and then removes those edges arising from conditioning on colliders if the bivariate correlations is marked as zero (Fig. 7)³.

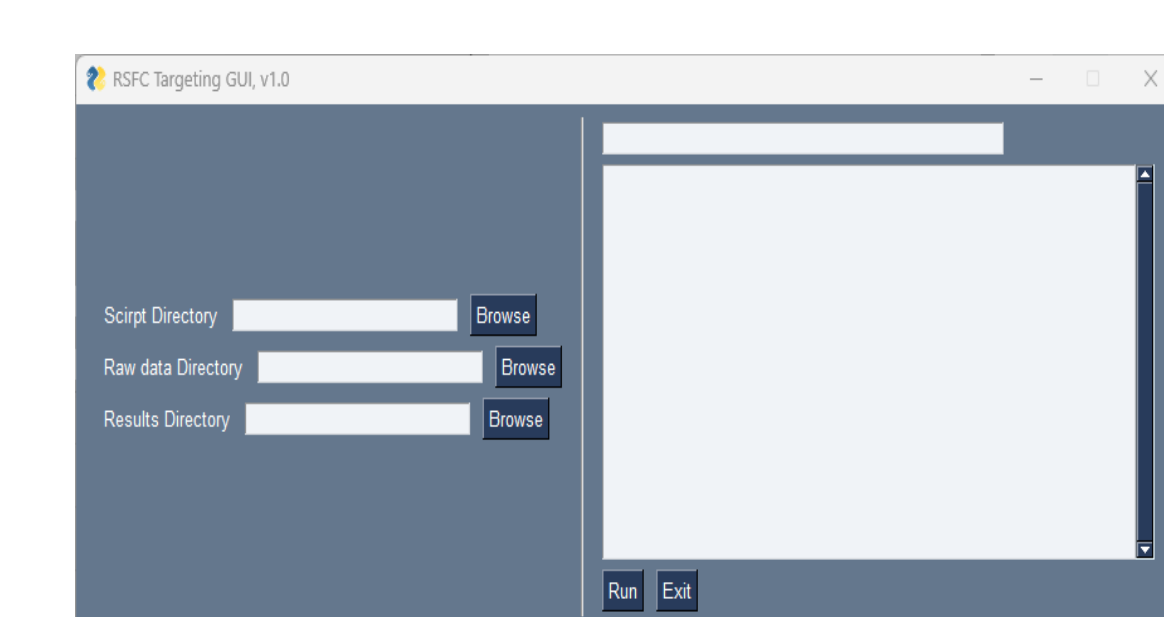
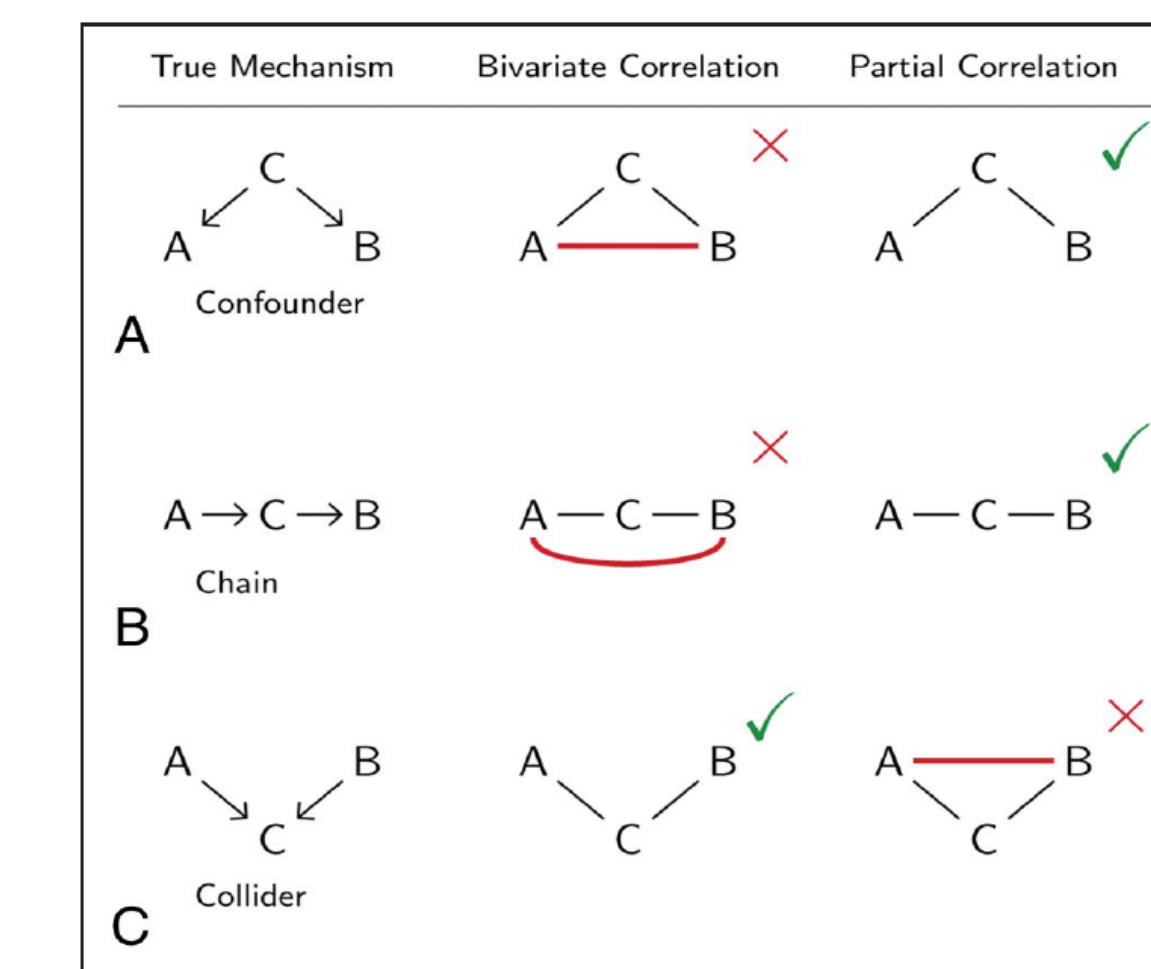


Figure 7. An image of the custom-made Python graphical user interface used for running the resting-state functional connectivity pipeline. Once the appropriate directories have been selected, simply click on 'Run' and the pipeline will run via the command line with the outputs shown on the right.

Figure 6. Pattern of spurious causal inferences for bivariate and partial correlations. Adapted from Sanchez-Romero & Cole, 2021.

METHODS

- Participants**
- 25 nicotine users:
 - 11 active TMS
 - 13 SHAM
 - Age: 39 years
 - 19 male, 6 female
- ERPs**
- **N200:** base-to-peak amplitude
 - **Reward Positivity:** difference wave between positive and negative feedback

Figure 1 – Experimental Sessions

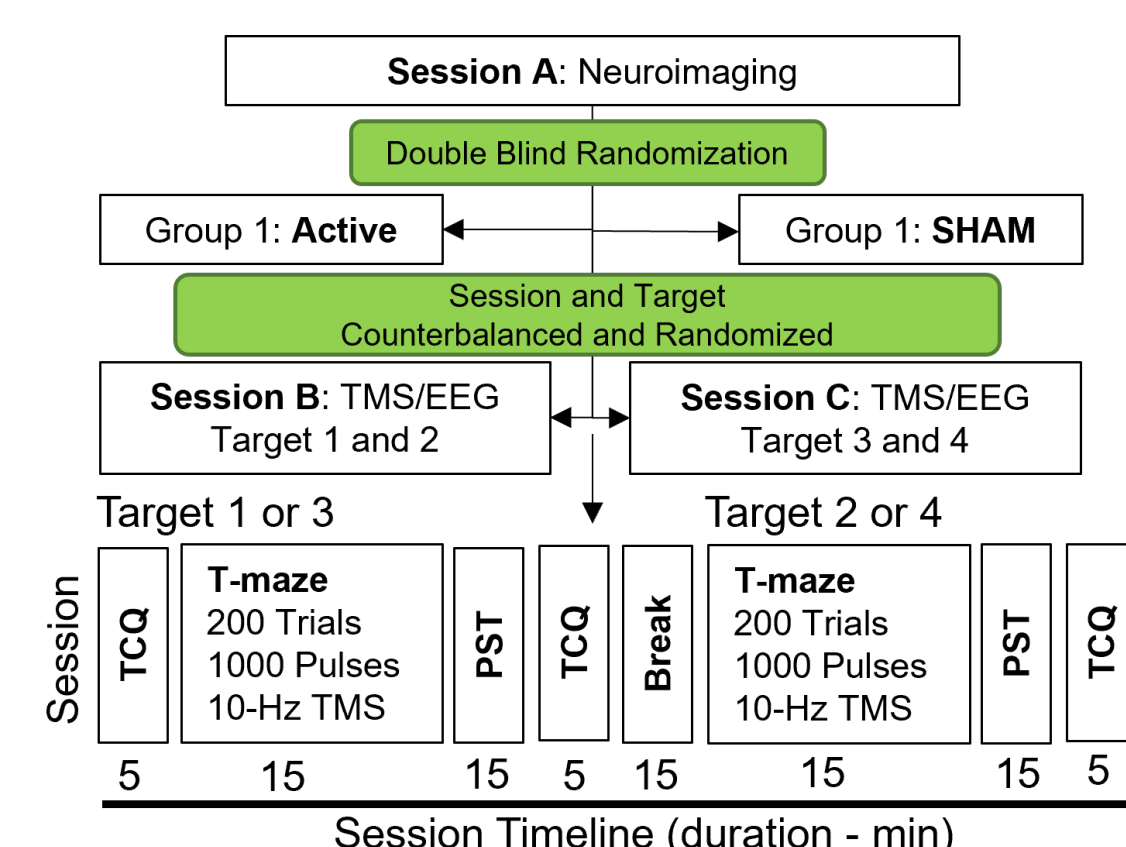


Figure 2 – Probabilistic Selection task

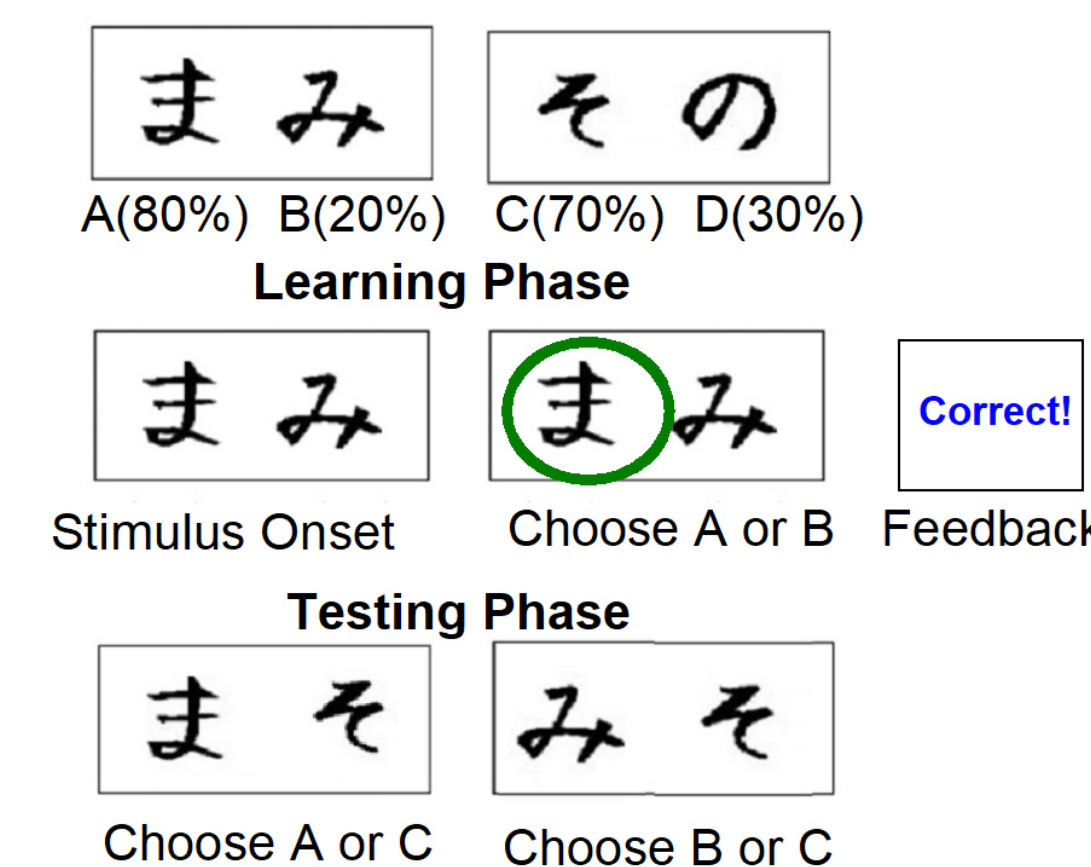
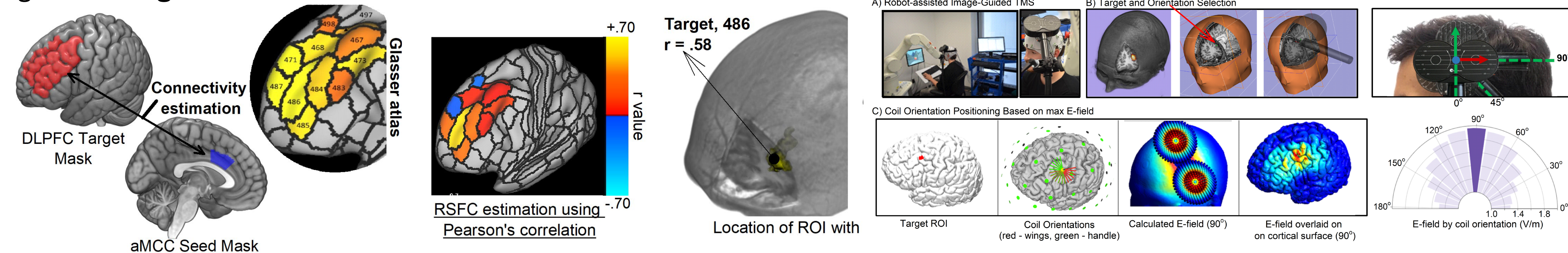


Figure 3 – Target orientation and TMS



RESULTS

Figure 4 – Behavioral Results

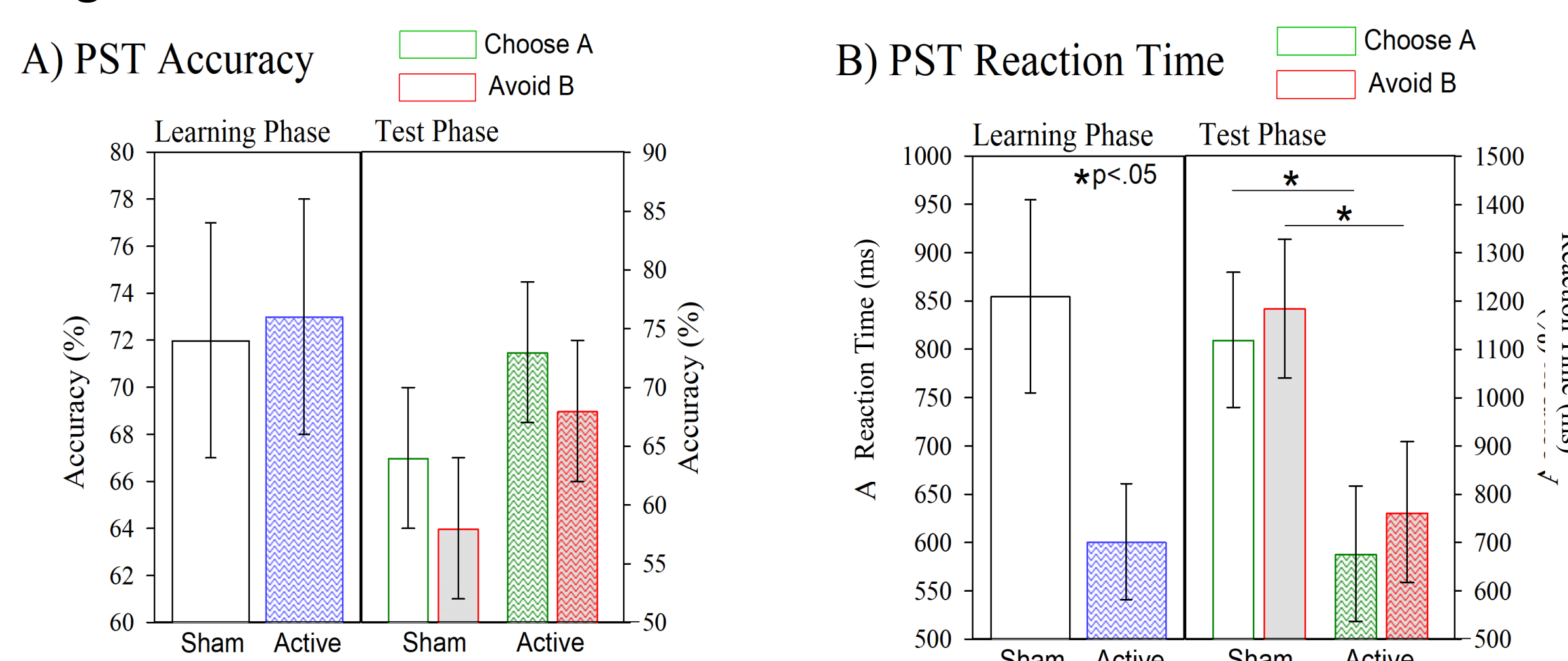


Figure 4. (A) Accuracy in the learning (left) and test (right) phases are shown. No difference in accuracy was observed. (B) Reaction time (msec) for both learning (left) and test (right) phases. There was a significant difference between the active and sham groups in the learning phase and test phase reaction time ($p < 0.05$).

Figure 5 – ERP Results

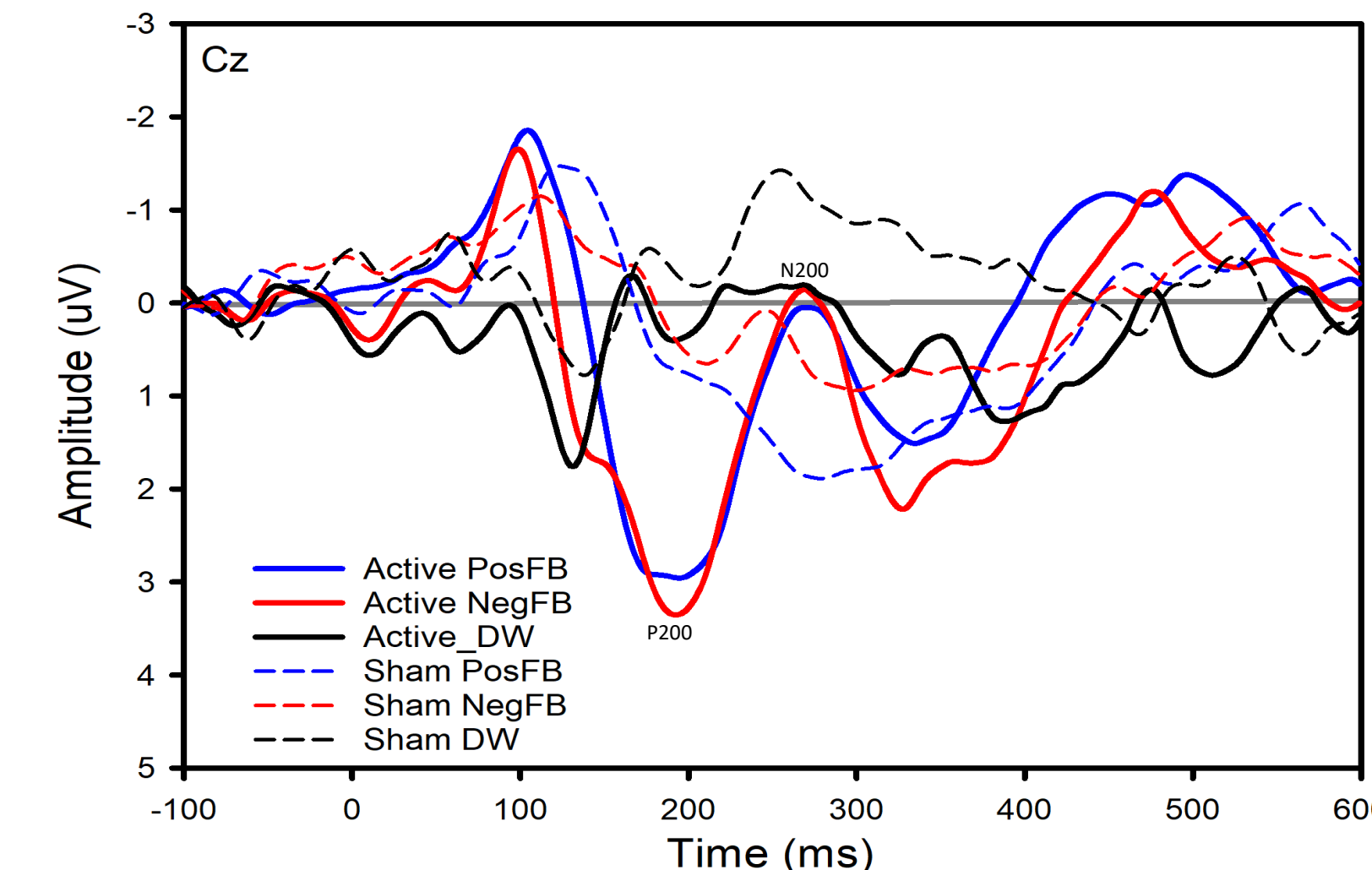


Figure 5. Feedback-locked ERPs during the PST separated by feedback type and group. DW = difference wave. The active group had a larger N200 compared to the sham group for both the positive ($M_{active} = -4.69 \mu V$; $M_{sham} = -1.46 \mu V$) and negative ($M_{active} = -5.01 \mu V$; $M_{sham} = -2.06 \mu V$) feedback. No groups difference were observed for the Reward Positivity.

CONCLUSIONS

- We show that applying TMS to a DLPFC-MCC target increased the amplitude of the N200, confirming stimulation of the MCC using RSFC target selection.
- However, no difference in reward positivity amplitude was observed between groups. This may suggest that the probability of the feedback in the PST may not be ideal for eliciting the reward positivity, or RSFC TMS targets based on Pearson's correlation was not effective in modulating reward-related MCC activity.

RESULTS

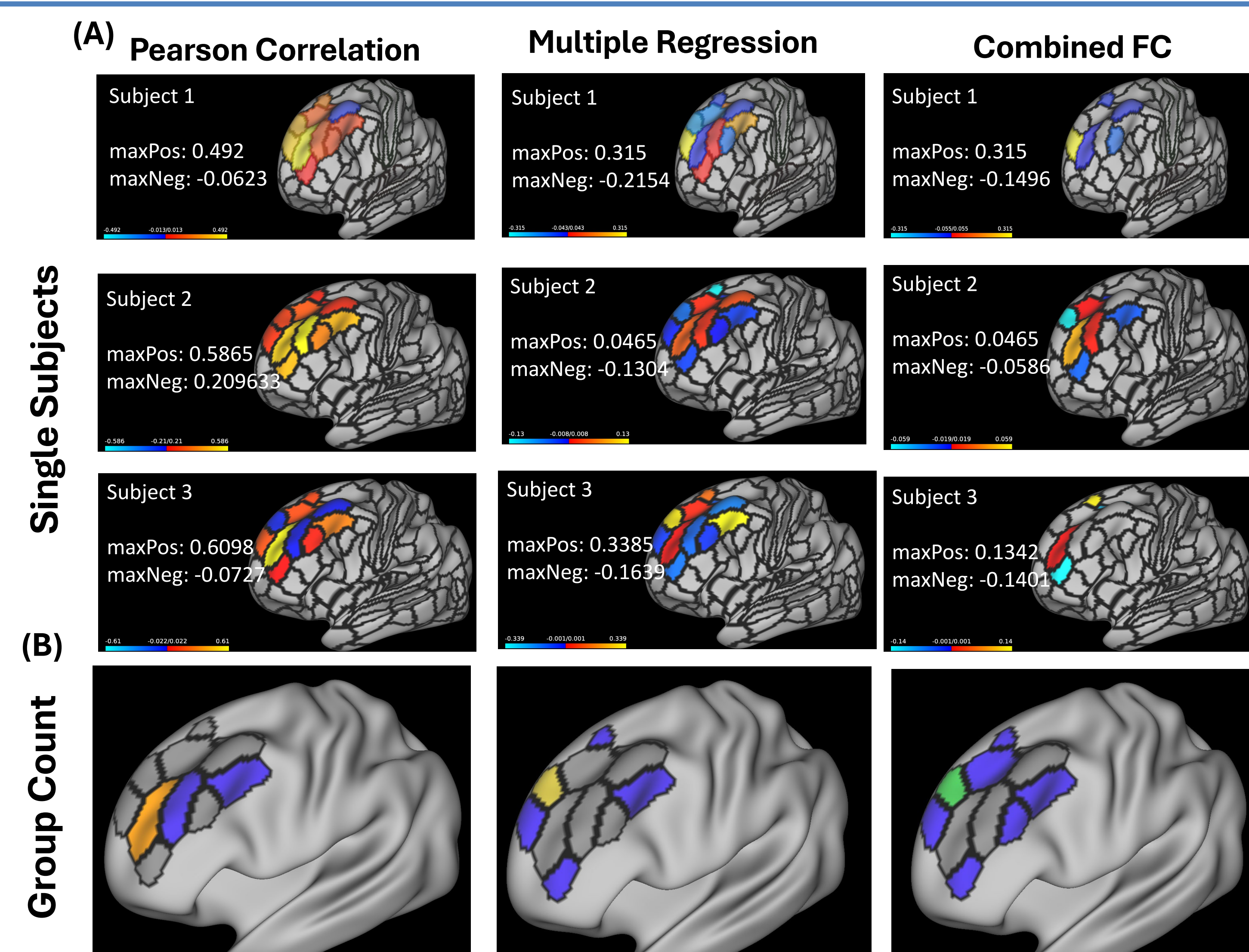


Figure 8. (A) Functional connectivity maps for the maximum positive and negative regions in the DLPFC for 3 out of the 18 participants analyzed. The ROIs are based on the Cole-Anticevic Brain-wide Network Partition (CAB-NP)⁴. (B) Functional connectivity maps for the number of participants that had their maximum positive peak for each of the 11 DLPFC regions of interest.

CONCLUSIONS

- Pearson's correlation shows different DLPFC-MCC FC patterns compared to multiple regression and CombinedFC.
 - These connections are likely false positives and could have ineffective or even detrimental outcomes if used as TMS targets for therapy.
- Combined FC is a novel method that has stringent requirements to improve FC-based causal inferences, especially for individualized targeting.
- Future studies will test the effectiveness of these targeting method in modulating the reward positivity and N200.

REFERENCES

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3. Sanchez-Romero R, Cole MW (2021). "Combining multiple functional connectivity methods to improve causal inferences". *Journal of Cognitive Neuroscience*. 33(2):180-194.
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ACKNOWLEDGEMENTS

Research reported was supported by the National Institute On Drug Abuse under Award Number UG3DA054787 NIGMS of the National Institutes of Health under award number 5T32GM140951. Thank you to Daniel Robles and Emily Zhang for their contributions to this project.