Insular networks in transdiagnostic emotion dysregulation and brain stimulation

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1. Introduction

The neural processes underlying emotional reactivity and emotional regulation in transdiagnostic clinical populations are not well-characterized. However, the insula is commonly implicated in aberrant affective and salience processing.

2. Objective

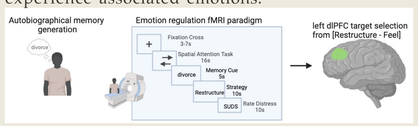
To identify functional connectivity associated with the insula that may underlie transdiagnostic emotion dysregulation and may be modulated by neurostimulation in dysregulated individuals.

3. Participants

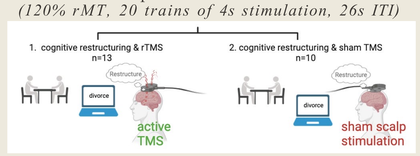
- Double-blinded clinical trial
- n = 33; mean age = 33.8Y; 82% F
- Eligibility criteria included:
  - *Difficulties in Emotion Regulation Scale* total ≥ 89
  - ≥ 1 psychiatric disorder Naïve
  - to transcranial magnetic stimulation (TMS) No medical
  - exclusions for MRI or TMS
- 10 participants dropped out before follow-up MRI
- Pre-post analyses include 10 active TMS and 13 sham TMS participants

4. Study Design

Baseline 3T MRI: Participants were cued to recall negative or neutral autobiographical memories and then asked to regulate or experience associated emotions.



Intervention: Participants were taught cognitive restructuring and randomized to either active or sham repetitive TMS over the left dorsolateral prefrontal cortex
(120% rMT, 20 trains of 4s stimulation, 26s ITI)



Follow-up 3T MRI: Participants completed the emotion regulation paradigm using the same memories and completed emotion dysregulation ratings.

5. Analysis

- FC analyses used a generalized whole-brain psychophysiological interaction (PPI) approach implemented in FSL.
- Functional insula region-of-interest masks **(Figure 5)** were created as unilateral seeds using the Brainnetome atlas (Fan et al., 2016).
- In the pre-post intervention analyses, within-person FC changes across sessions were aggregated in a mixed effects model examining stimulation condition (active vs. sham) effects.
- The change in total DERS score from pre- to post-intervention was included as a model covariate to test the clinical improvement x group x session interaction.

All final models were statistically thresholded at a voxelwise threshold of z ≥ 2.3 using FSL's FLAME1 mixed effects model and a clusterwise threshold of p < 0.05.

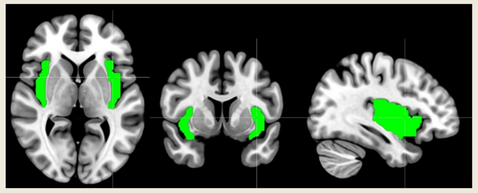


Figure 5: Functional insula seeds for PPI analyses.

7. Conclusion

Hyperconnectivity between the insula and the dlPFC may be a neural signature of transdiagnostic emotion dysregulation. Initial reactivity to negative emotional memories is associated with higher FC between the insula and the medial PFC; this circuit is differentially modulated by active TMS compared to sham stimulation. Additional research is needed to parse the relationship between parietal and insular cortices in transdiagnostic emotional reactivity as well as in post-intervention clinical improvement.

08. References

Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., ... & Jiang, T. (2016). The human brainnetome atlas: a new brain atlas based on connectional architecture. Cerebral cortex, 26(8), 3508-3526.

6a. Baseline results

- Both the left and right insula showed increased functional coupling (FC) with the right dlPFC **(Figure 1)** when they reframed negative emotions compared to when they were instructed to feel negative emotions.
- During reframing versus feeling negative emotions, the strength of connectivity between the left insula and the right dlPFC was significantly associated with higher emotion dysregulation (**Figure 2).**

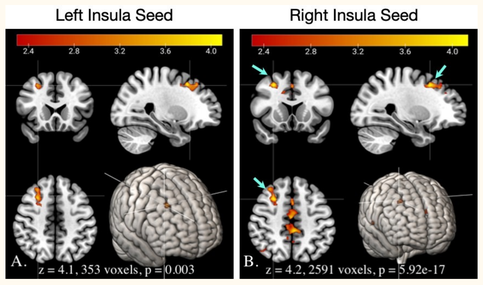


Figure 1. Baseline [Reframe _Negative > Feel_Negative].

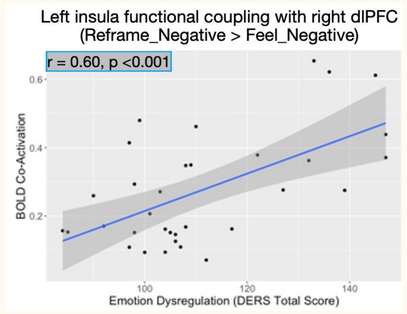


Figure 2. Insula-dlPFC FC is associated with higher emotion dysregulation severity.

- Compared to cued recall of negative autobiographical memories, reframing negative emotions was associated with: 1) decreased FC between the left insula and the left superior parietal lobule **(Figure 3a)**; 2) decreased FC between the right insula and the left postcentral gyrus **(Figure 3b)**; and 3) increased FC between the right insula and the right dmPFC **(Figure 3c).**

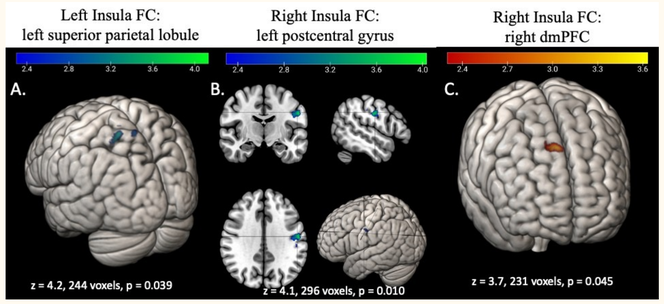


Figure 3. Baseline [Reframe_Negative > Cue_Negative.

6b. Post-TMS results

- When comparing reframing negative emotions to the cued recall of negative memories, the left insula showed greater decreases in between-session FC with both the right dmPFC and the right middle temporal gyrus **(Figure 4a)** in participants who received active TMS compared to sham.
- Greater improvement in emotion dysregulation symptoms from pre- to post-intervention was associated with increased left insula FC with the right inferior parietal cortex **(Figure 4b)** in the active TMS group vs. sham during reframing negative emotions vs. cued recall of negative memories.
- We did not find Group x Session differences in insula FC when comparing reframing to feeling negative emotions.

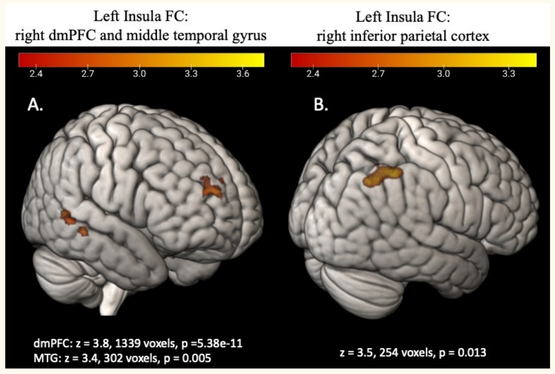


Figure 4. Post-intervention insula FC changes significantly different between groups (A) and associated with improvement in emotion dysregulation symptoms.