Effective brain connectivity at rest and its association with emotion regulation ability after estradiol administration

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INTRODUCTION

Emotion regulation (ER) plays a crucial role in physical and mental well-being. ER ability has been linked to physical factors like sex and hormones.

Estradiol (E2) is an ovarian hormone that fluctuates depending on the menstrual cycle phase.

- Has been shown to have an influence on ER on a behavioural and neural level (Rehbein, 2021)

RESEARCH AIM

The aim of this study was to examine the neural networks underlying ER depending on E2 in a resting-state functional magnetic resonance (fMRI) analysis.

- Intrinstic effective connectivity (EC = causal interactions between regions) within ER-related neural networks at rest after E2 administration
- Associations between group differences in EC and prospective behavioural ER ability

METHODS

Participants were 29 naturally cycling women (mean age = 24.1 ± 3.1 yrs) in their follicular menstrual cycle phase, that is characterized by low E2 levels to prevent results due to intertwined homone effects. Pills were administered in a double-blind and counterbalanced order (**Fig. 1**).

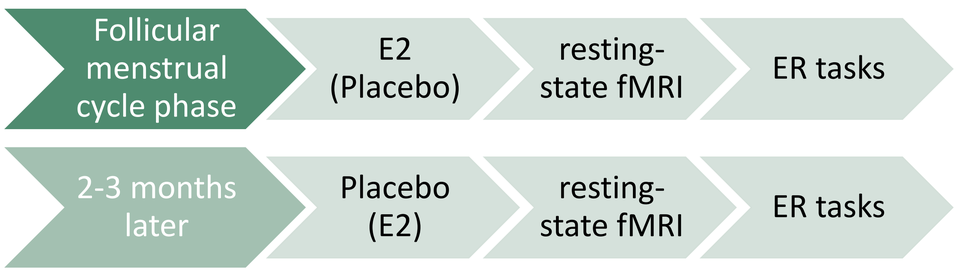

Figure 1 | Study design.

ER tasks were a negative emotion regulation task inside the scanner and a positive emotion regulation task outside of the scanner.

- Emotional state ratings were used to compute regulation success

Regions of interest (ROIs) for the EC analysis were taken from a recent meta-analysis, which investigated neural networks of reappraisal (Morawetz, 2022). Three networks, relating to three reappraisal goals (decrease, increase, maintain) were computed, independent of regulation strategy, valence and arousal of the stimuli (**Fig. 2**).

- Decrease network: *n* = 7 ROIs (frontal, temporal, parietal)
- Increase network: *n* = 5 ROIs (frontal, temporal, insula)
- Maintain network: *n* = 8 ROIs (temporal, parietal, limbic)

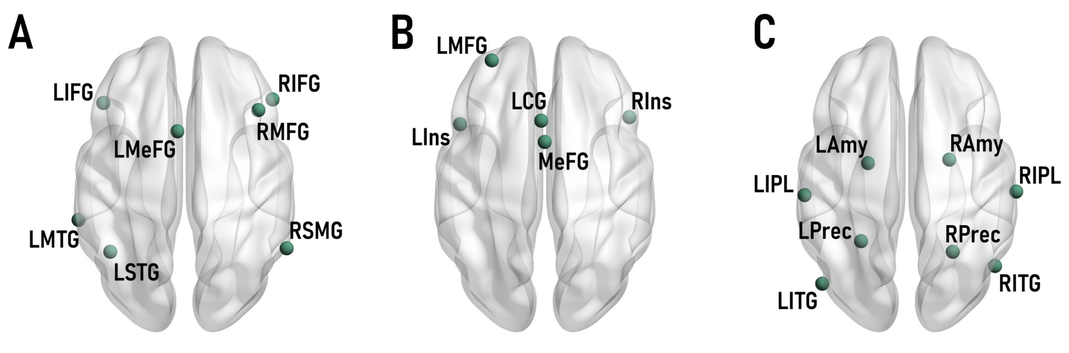

Figure 2 | Regions of interest within the three emotion regulation related brain networks: decrease (A), increase (B), and maintain (C).

Using spectral dynamic causal modeling (spDCM), we examined group differences in EC at rest within the three networks (Friston, 2014).

- At the first level, fully connected models of each network were created for each participant
- On the second level, models were reduced, averaged and weighted by their model evidence. Drug condition was modelled as the main regressor of interest

To identify effective connections that predict task-based regulation success, stepwise linear regressions were used.

- Emotional state ratings were set as independent variables and effective connections that were differing between groups as dependent variables

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RESULTS

On the first level, results revealed the following model convergences in the networks, indicating average variances explained by each participants' reduced model of:

- Decrease network: M = 89.71 (*SD* = 2.27, range = 83.01 – 95.13)
- Increase network: M = 90.28 (*SD* = 2.83, range = 84.38 – 96.54)
- Maintain network: M = 89.33 (*SD* = 3.22, range = 78.83 – 95.96)

On the second level, differential connectivity patterns for all three ER-networks between the groups (E2 > placebo) were revealed (**Fig. 3**).

- **Decrease network:**
  - more inhibitory along with excitatory interconnectivity within prefrontal regions after E2 administration compared to placebo
  - more inhibitory connectivity was found from prefrontal to temporal regions and less inhibitory connectivity from the parietal to the prefrontal regions
- **Increase network:** less inhibitory connectivity from the dlPFC and more inhibitory connectivity from the cingulate gyrus to the insula, respectively
- **Maintain network:** a mixed pattern of results evolved with a number of inhibitory and excitatory connections that are modulated by E2 administration

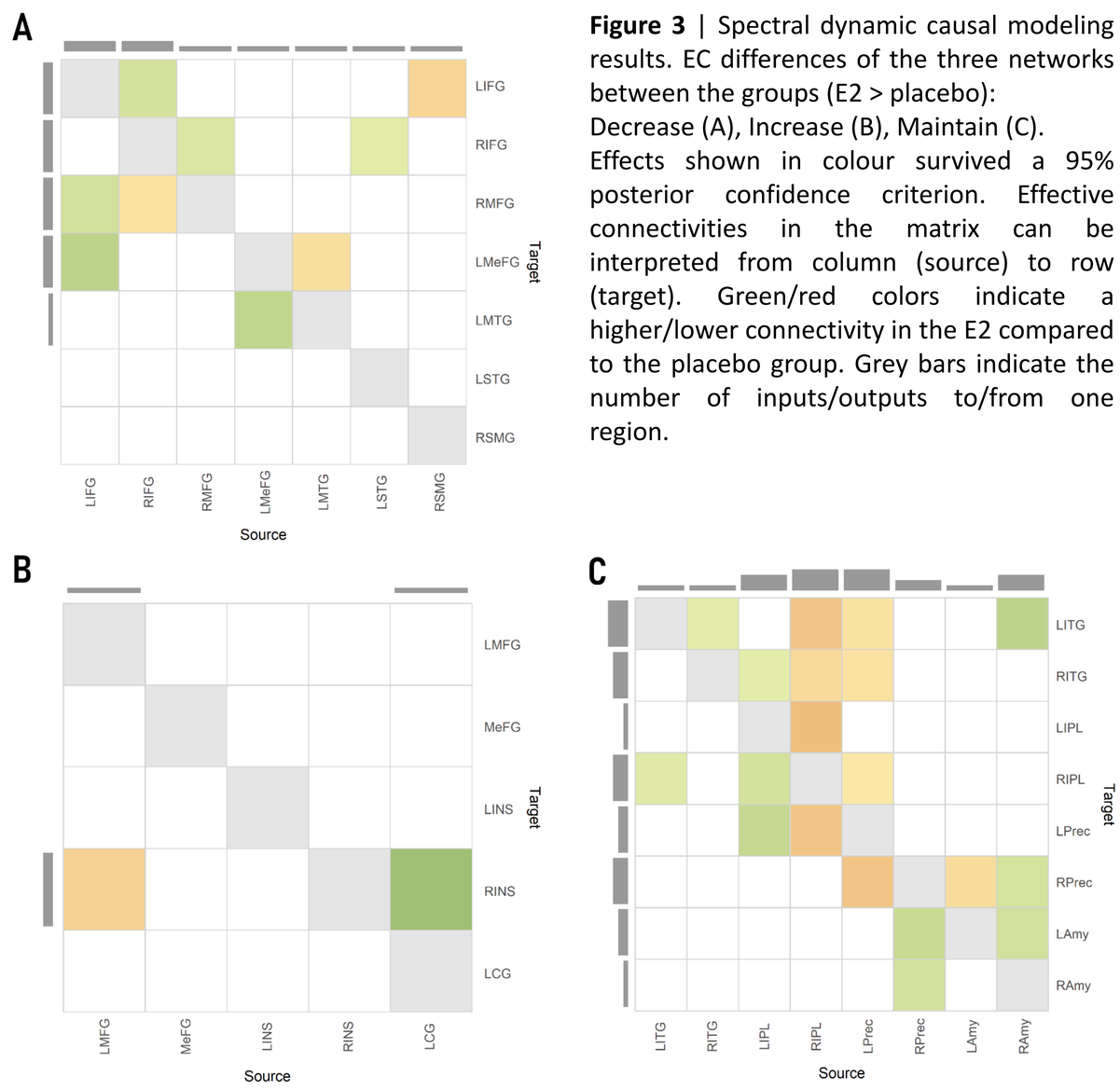

Figure 3 | Spectral dynamic causal modeling results. EC differences of the three networks between the groups (E2 > placebo): Decrease (A), Increase (B), Maintain (C). Effects shown in colour survived a 95% posterior confidence criterion. Effective connectivities in the matrix can be interpreted from column (source) to row (target). Green/red colors indicate a higher/lower connectivity in the E2 compared to the placebo group. Grey bars indicate the number of inputs/outputs to/from one region.

Stepwise regression analyses revealed that decrease success after E2 administration was predicted by inhibitory connectivity from the parietal cortex to vlPFC. There were no significant results for increase success.

CONCLUSIONS

- E2 has a modulatory role on effective connectivity within ER-related brain networks at rest.
- The initial intrinsic causal network dynamics in neural networks related to ER might explain parts of the variance of ER success to down-regulate emotions in women following E2 administration.

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