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Testosterone application modulates resting state connectivity in emotion regulation network

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Introduction

Emotion regulation engages a complex brain network of subcortical and cortical brain regions. Recently, Etkin and colleagues (2015) proposed a neural model for emotion regulation, which consists of three clusters of brain regions: a) ventromedial prefrontal cortex (VMPFC), b) amygdala, insula and dorsal anterior cingulate (dACC), c) ventral-lateral prefrontal cortex (VLPFC), dorsa-lateral prefrontal cortex (DLPFC), parietal cortex and supplementary motor area (SMA) [1].

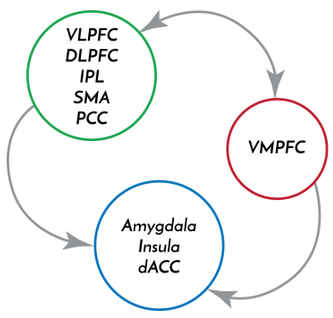


Figure 1. Neural model for emotion regulation, adapted from Etkin et al 2015

Evidence from functional MRI and behavioral studies indicates that hormones, such as testosterone, affect the regulation of emotional responses [2]. However, how testosterone modulates the connectivity between regions involved in emotion regulation is unclear.

Thus, this study aims to reveal how exogenous testosterone affects resting state connectivity within the emotion regulation network. Moreover, modulatory effects of trait impulsivity and aggression on the relationship between testosterone and connectivity within this network will be investigated.

Methods

We recruited 103 healthy male participants. For half of the subjects, we applied 5g Testim™ gel (containing 50mg testosterone), for the other half a placebo gel [for details see 3].

In total, 98 subjects (46 placebo and 52 testosterone) underwent resting state scanning. After taking a blood sample as baseline (T1), the respective gel was applied. Before the fMRI session, a second blood sample was taken (T2), and two further samples were assessed after each fMRI task (T3 and T4). The last sample (T4) was obtained just before resting-state scanning. Before the scanning session, participants filled out questionnaires assessing trait impulsivity (BIS-11) and aggression (AQ).

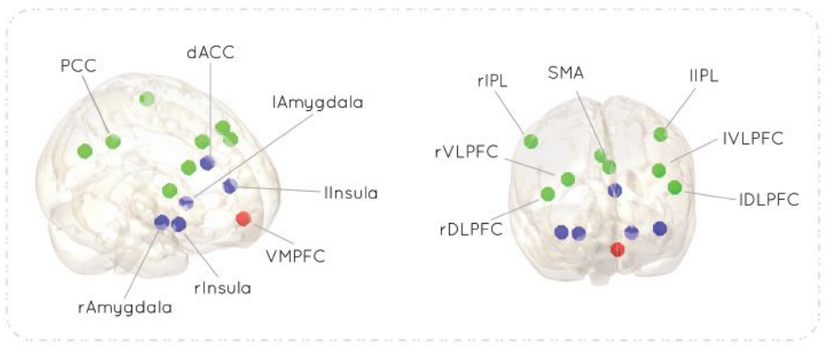


Figure 2. 14 ROIs (5mm spheres) based on mask from Neurosynth

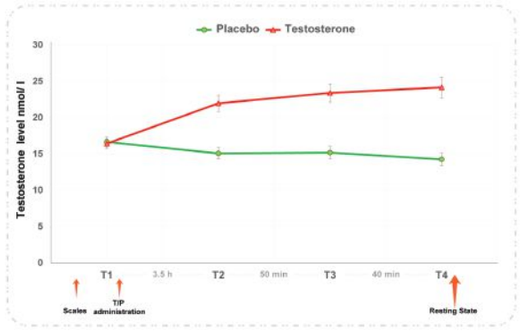
We used Neurosynth online software for the term "emotion regulation", which contained 161 fMRI studies, to create an automated meta-analysis. Based on acquired mask, we created 14 ROIs: left and right amygdala, insula, DLPFC, inferior parietal lobule (IPL), VLPFC and PCC, VMPFC, dACC. Next, we tested the connectivity difference between the testosterone and the placebo group for the three clusters of ROIs as proposed by Etkin's model (Figure 2).

For each participant, the time course of each region's BOLD signal was extracted as the first eigenvariate of activity in this region's gray-matter voxels. Within each network, Fisher's Z–transformed functional connectivity values were submitted to two-sample t-tests for each pairwise connection (Bonferroni corrected).

Resting state fMRI data were acquired with a 3-T MR scanner using gradient-echo echo-planar imaging (TR = 2000 ms; TE = 30 ms). Data of each participant was cleaned for physiological and movement artifacts by applying FIX (FMRIB's ICA-based Xnoiseifier [4]) with the standard training dataset and recommended settings [5]. Resting-state data were preprocessed by SPM8 and in-house Matlab tools. Dynamic casual modeling (DCM) was performed using DCM10 as implemented in SPM12.

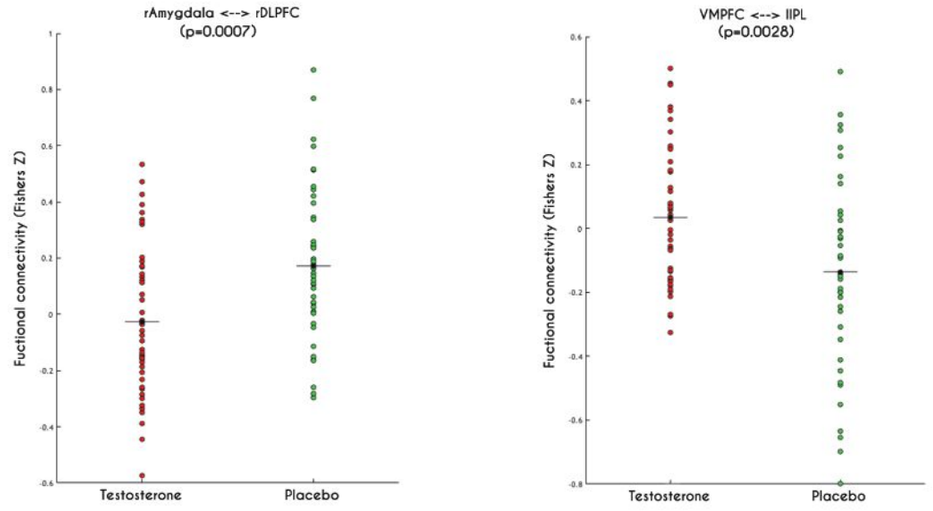
Results

Hormone level



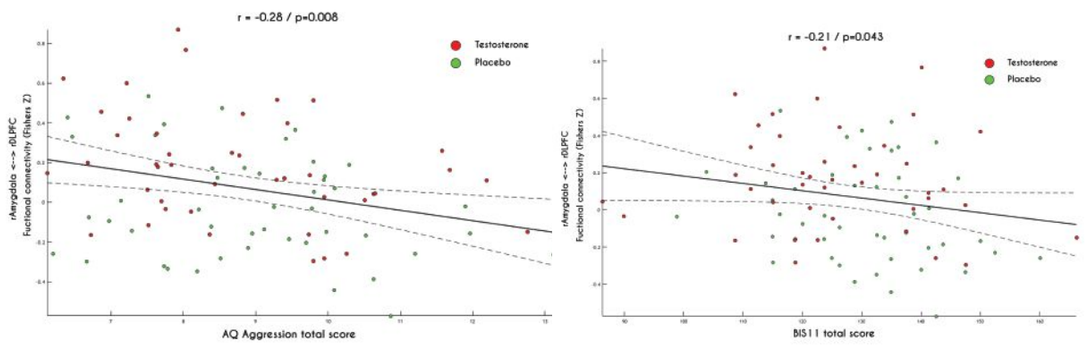
At baseline, testosterone levels did not differ between the placebo and testosterone group. Comparing testosterone levels at T1, T2, T3 and T4 between groups revealed a main effect of time and group and a significant time by group interaction (all $p < 0.05$), confirming significantly higher testosterone levels in the testosterone group but not the placebo group after gel application.

Resting state network connectivity



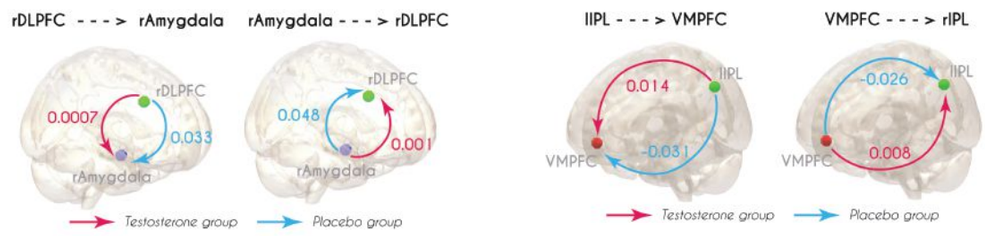
The resting state connectivity analysis revealed decreased connectivity between the right DLPFC and the right amygdala in the testosterone group as well as, increased connectivity between the VMPFC and the left IPL (both $p<0.005$) relative to the placebo group.

Correlation with traits



Self-reported aggression and impulsivity total score were negatively correlated with functional connectivity between the right amygdala and right DLPFC.

Dynamic casual modeling



DCM analysis confirmed and revealed significant difference in connectivity pattern between testosterone and placebo groups, for both ROI pairs for both directions.

Conclusion

Our findings indicate that the exogenous application of testosterone modulates resting state connectivity within the emotion regulation network. These results provide a new insight on the role of testosterone in reducing regulatory control of the DLPFC over the amygdala and in increasing frontal-parietal connection. Testosterone-dependent connectivity differences in within the emotion regulation network might constitute an underlying neural substrate of impaired regulation of negative emotions, supporting previous findings relating testosterone to aggressive and dominant behavior.

References

[1] Etkin, A., Büchel, C., & Gross, J. J. (2015). The neural bases of emotion regulation. Nature Reviews Neuroscience, 16(11), 693-700.
[2] Peper, J. S., van den Heuvel, M. P., Mandl, R. C., Pol, H. E. H., & van Honk, J. (2011). Sex steroids and connectivity in the human brain: a review of neuroimaging studies. Psychoneuroendocrinology, 36(8), 1101-1113.
[3] Wagels, L., Radke, S., Goerlich, K. S., Habel, U., & Votinov, M. (2017). Exogenous testosterone decreases men's personal distance in a social threat context. Hormones and Behavior, 90, 75-83.
[4] Salimi-Khorshidi, G., Douaud, G., Beckmann, C. F., Glasser, M. F., Griffanti, L., & Smith, S. M. (2014). Automatic denoising of functional MRI data: combining independent component analysis and hierarchical fusion of classifiers. Neuroimage, 90, 449-468.

Disclosure

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