

Lateralized, sex specific habenular modulation of substantia nigra and ventral tegmental area resting connectivity in healthy adults

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Background

The **habenula (Hb)** is a key regulator of midbrain dopamine function, exerting inhibitory control over the **substantia nigra (SN)** and **ventral tegmental area (VTA)**^{1, 2}. It has gained prominence because its depression-related hyperactivity can be reversed by neuromodulatory interventions (e.g., ketamine)³.

While neuroimaging studies suggest left-right asymmetry and sex differences in Hb function⁴, it remains unclear how spontaneous Hb activity shapes dopaminergic connectivity in the healthy brain.

Aim

To test whether resting left/right habenular activity moderates functional connectivity of ipsilateral and contralateral SN and VTA with projection areas in healthy adults.

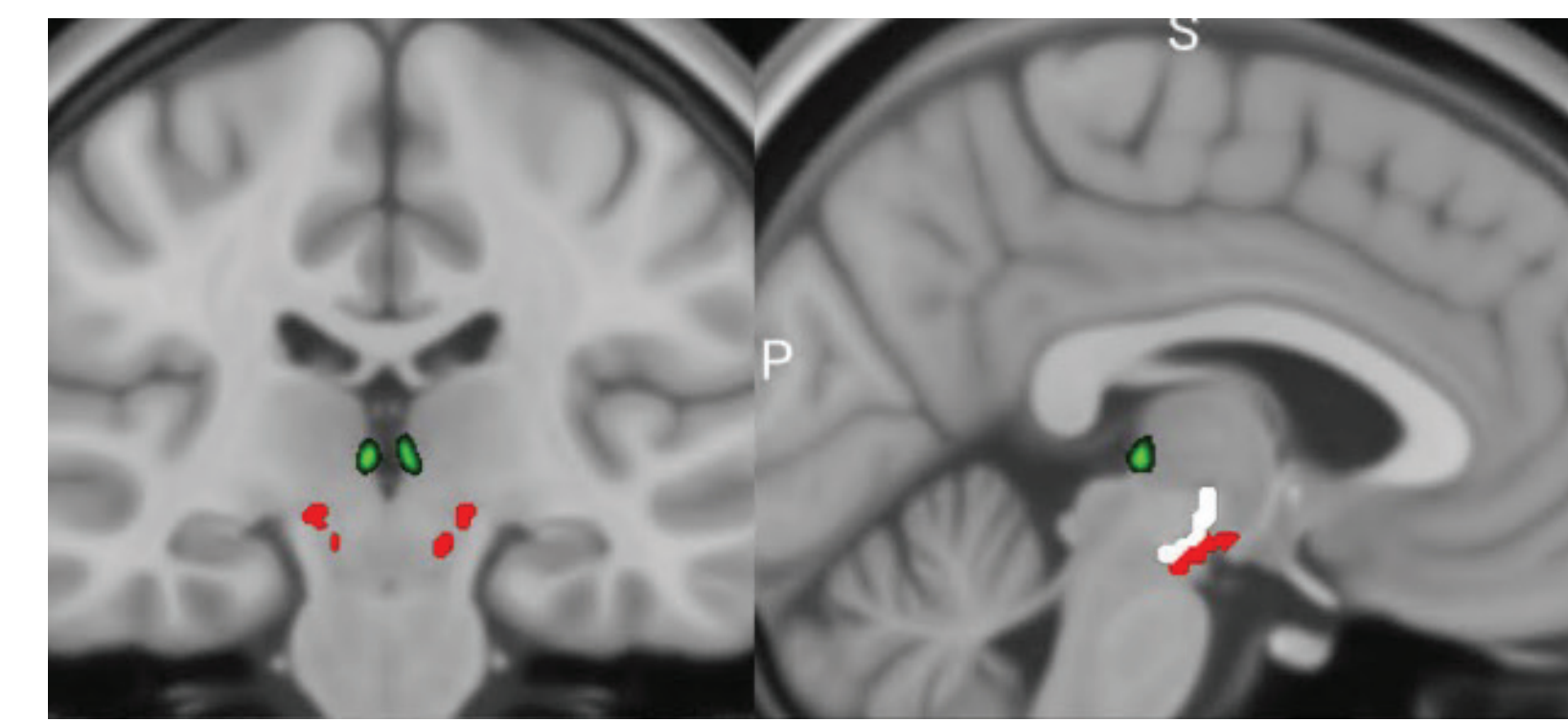


FIGURE 1: Regions of interest (ROIs) on MNI template. Left and right Hb (green; Automated Human Habenula Segmentation toolbox), SN and VTA (red and white, respectively; BrainstemNavigator).

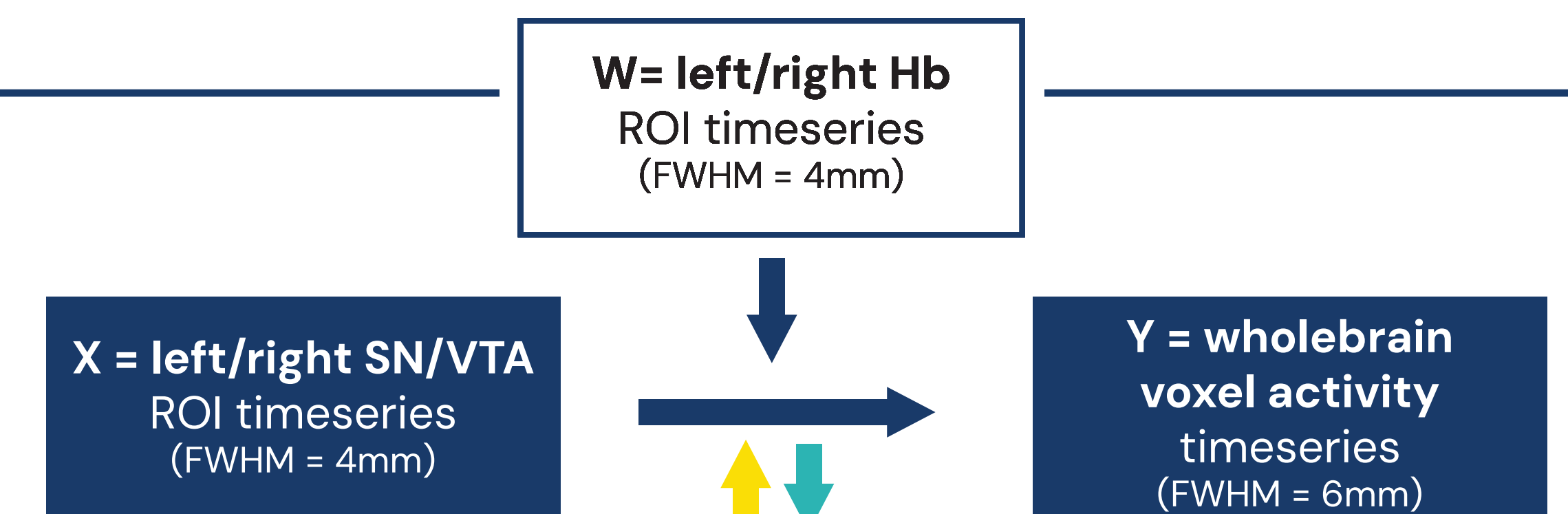
Methods

- Sample:** N=190 healthy adults (100 women, biological sex), 25.7 ± 5.0 years.
- MRI acquisition:** 8 min resting-state fMRI (eyes open), 2 mm isotropic.
- Preprocessing:** fMRIPrep (bias correction, skull stripping, CompCor denoising, motion correction, MNI152NLin2009cAsym).
- Denoising and ROI timeseries extraction:** CONN toolbox (5 WM/CSF components, motion regressors, ART outliers, band-pass 0.008–0.09 Hz).

Does the activity of the Hb moderate the functional connectivity between SN/VTA and their projection areas?

$$Y = \beta_o + \beta_x X_c + \beta_w W_c + \beta_{xw} (X_c \cdot W_c) + \epsilon$$

Multilevel moderation analysis (SPM25)



Results

Results summary: In men, left Hb activity decreased connectivity of both left SN (with frontal and postcentral gyri) and bilateral VTA (with anterior insula). Right Hb activity increased right VTA coupling with occipital/parietal regions in men, but reduced left VTA coupling with the postcentral gyrus in women. A sex difference emerged in left VTA-bilateral anterior insula connectivity: men showed significant negative moderation by left Hb, an effect stronger than in women (see FIGURES 2–5).

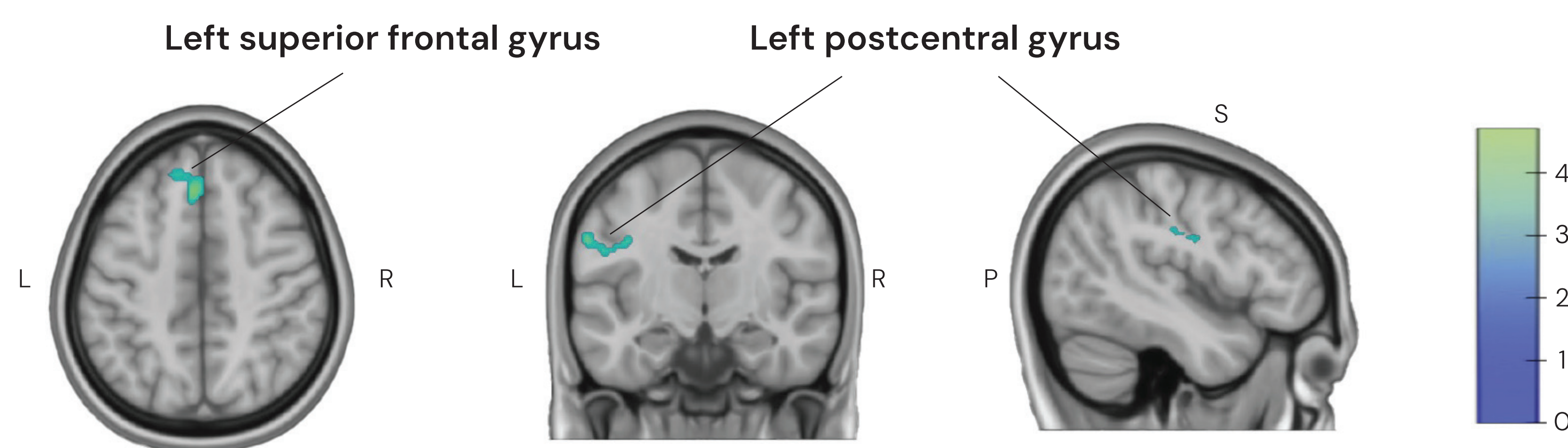


FIGURE 2: Moderation effect of the left Hb upon left SN functional connectivity. In **men**, left Hb **decreases** left SN coupling with left superior frontal gyrus (–4, 30, 44; p=0.003; k=234) and post central gyrus (–60, –12, 32; p=0.028; k=143).

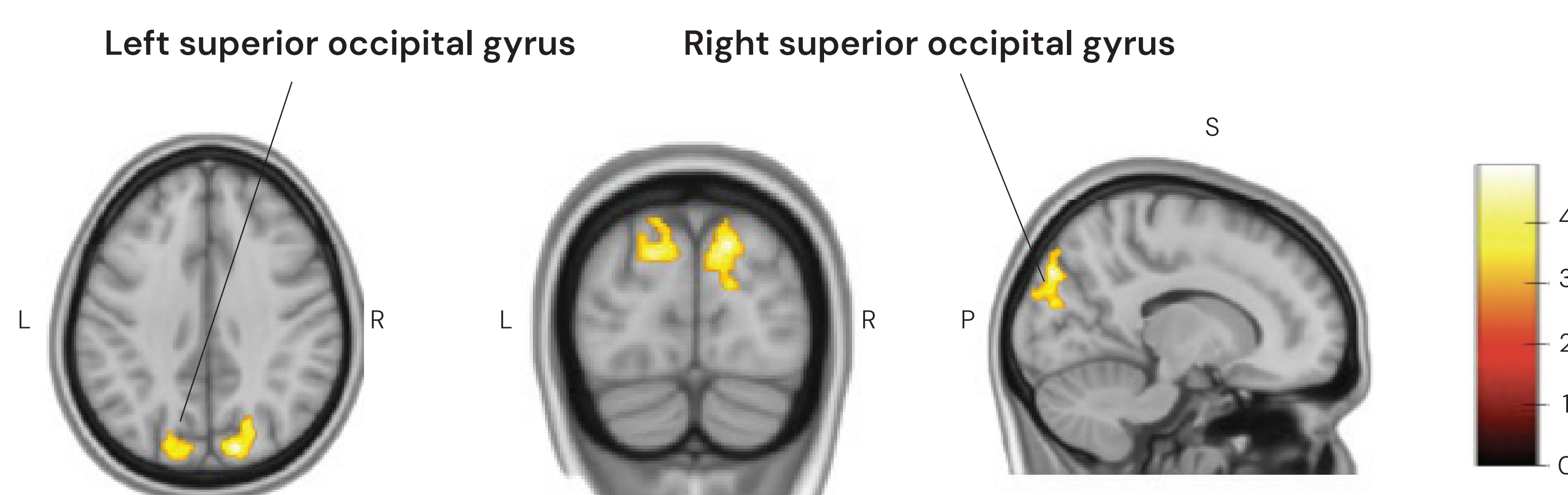


FIGURE 3: Moderation effect of the right Hb upon right VTA functional connectivity. In the **whole sample**, right Hb **increases** right VTA coupling with left (–16, –84, 32; p=0.006; k=213) and right (14, –84, 36; p<0.001; k=446) superior occipital gyri (–16, –84, 32; p<0.006). In **men**, effects expanded to right superior parietal lobule (p=0.008), right cuneus (p=0.017), and inferior occipital gyrus (p=0.045) – *not shown in figure*.

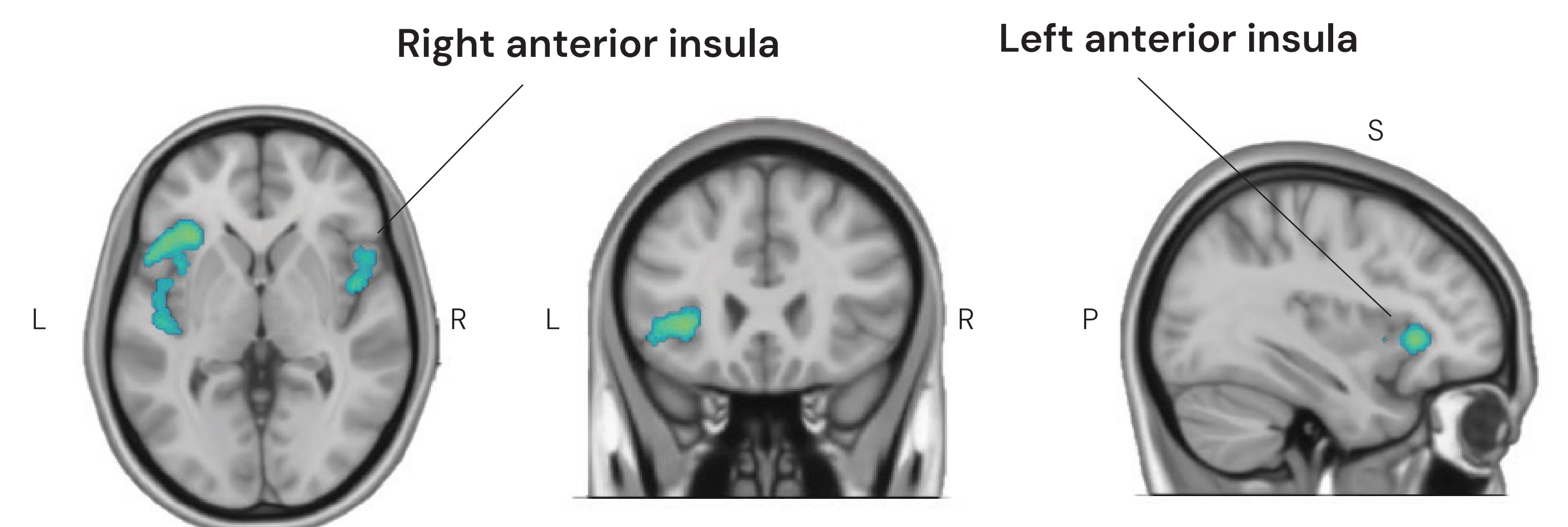


FIGURE 4: Sex difference in Hb moderation of VTA–anterior insula connectivity. In **women**, right Hb **decreased** left VTA connectivity with right postcentral gyrus (p=0.004); whereas in **men**, left Hb activity **decreased** right and left VTA coupling with the left anterior insula (p=0.001 and p=0.47, respectively) – *not shown in figure*. This negative effect was significantly **stronger** in **men** than in women, within clusters in left (–34, 24, 0; p<0.001; k=844) and right (44, 0, 0; p=0.01; k=200) anterior insula.



FIGURE 5: Sex differences in Hb moderation of VTA–insula connectivity. Violin plots show subject-level mean moderation effects extracted from significant clusters identified in sex difference contrast (see FIGURE 4). **Men exhibit more negative moderation effects than women.** Statistical significance is based on the FWE-corrected voxel-wise analysis; plots are provided for visualization only.

p significance: FWE-corrected at cluster level.

Conclusions

The habenula shapes dopaminergic resting state connectivity in a lateralized and sex-dependent way.

In **men**, the left Hb dampens SN/VTA connectivity with frontal and insular cortices, whereas the right Hb enhances coupling with occipital/parietal regions; negative Hb–VTA–anterior insula moderation is men-specific.

In **women**, the right Hb reduces left VTA coupling with right postcentral gyrus

These normative patterns provide a baseline reference for interpreting Hb-centered disinhibition in depression, and its reversal by neuromodulatory interventions (e.g., ketamine)^{3, 5}. This is the first large-sample demonstration of sex-specific Hb moderation of SN/VTA connectivity in the healthy brain.

References

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