Connectivity of the human habenula using 7T resting state and meta-analytic coactivation modeling

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Introduction

The habenula, a small, bilateral region posterior to the medial thalamus and dorsal to the posterior commissure, has been of interest in research on reward processing and goal-directed behavior. It receives input from the prefrontal cortex and several subcortical regions and projects to the serotonergic dorsal raphe nucleus, as well as the dopaminergic substantia nigra (SN)[1].

Despite the habenula's critical involvement in reward processing and dopamine modulation, few neuroimaging studies have focused on this region. As such, we used complementary approaches to assess the whole brain functional connectivity of the habenula both at rest and during task to characterize how this region may be differentially engaged across cognitive states.

Furthermore, the habenula's participation in large-scale brain networks has yet to be assessed, prompting a whole-brain, graph theoretic analysis focused on the habenula.

Methods

7T resting state fMRI from 28 healthy participants

- T1-weighted structural scans: 0.63mm x 0.63mm x 0.60mm
- EPI resting state data: 5:00 minutes at 0.85mm x 0.85mm x 1.5mm

fMRI data preprocessing & seed-to-voxel analysis

- Habenula were manually traced on each subject following guidelines from Lawson et al. [2]
- Preprocessing included motion correction, anatomical CompCor denoising, high-motion volume censoring, high-pass filtering at 0.01Hz, and 3mm FWHM spatial smoothing
- FSL's FLIRT was used for coregistration; FNIRT, for normalization to the MNI152 template space
- FSL's FEAT for subject-level analysis; randomise, for nonparametric group-level analysis
- Graph theoretic analysis was performed using nilearn (version 0.3.0) & Brain Connectivity Toolbox for Python (version 0.5.0) [3] in Python 2.7.13
- 264 cortical nodes defined from functional analysis by Power et al. [4], and 14 subcortical nodes from the Harvard-Oxford Maximum Probability Atlas

Meta-analytic connectivity modeling

- Seed-based BrainMap query using hand-drawn habenula ROI on MNI152 template brain
- Coactivation assessed with ALE, voxel-level $p < 0.001$ & cluster-level corrected $p < 0.05$

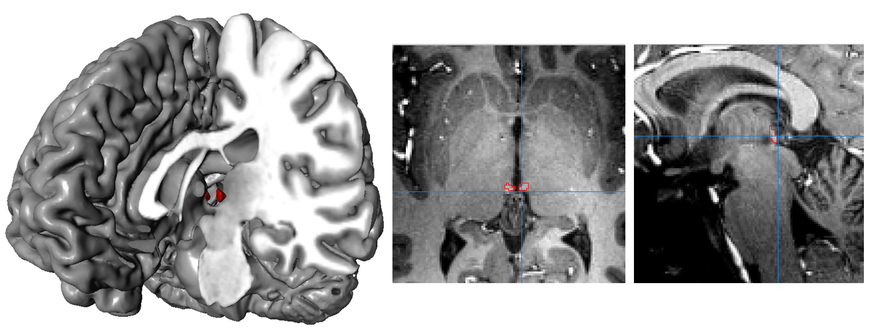

Figure 1. Manual definition of the human habenula
The habenula was traced on each individual's T1 structural image [2]

Seed-to-voxel connectivity

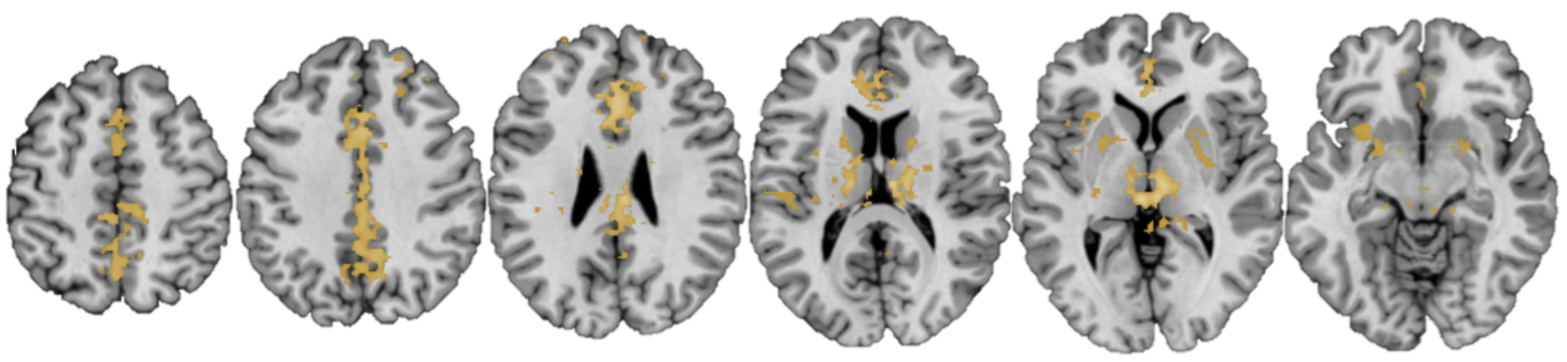

Figure 2. Seed-to-voxel functional connectivity of the human habenula at rest.
In the task-independent state, the habenula was connected with anterior, mid-, and posterior cingulate cortices, left insula, as well as caudate, putamen, & precuneus.

Results & Discussion

At rest, the habenula was connected with regions including the anterior cinculate cortex, caudate, putamen, and supplementary motor area. Graph theoretic modularity analysis revealed a community structure in which the habenula was grouped with the aforementioned regions, in addition to angular gyrus, middle and inferior frontal gyri, as well as inferior parietal lobule. Agreement between these results indicates a habenular network that includes a number of regions involved with associative learning, in which the habenula has displayed high betweenness centrality. Previous research has shown that the habenula and anterior cingulate cortex play related roles in reward prediction [5] and that the basal ganglia are associated with motor learning. In contrast, task-based meta-analytic coactivation modeling suggested that the habenula is connected with key nodes of the salience network, including bilateral insulae and both anterior and mid cingulate cortices, exhibiting minimal overlap with the resting state seed-to-voxel connectivity results.

Together, these results suggest that the habenula may form a number of context-dependent relationships with other areas of the brain. Further work should extend this investigation to the task-dependent role(s) of the habenula.

Graph theoretic modularity & centrality

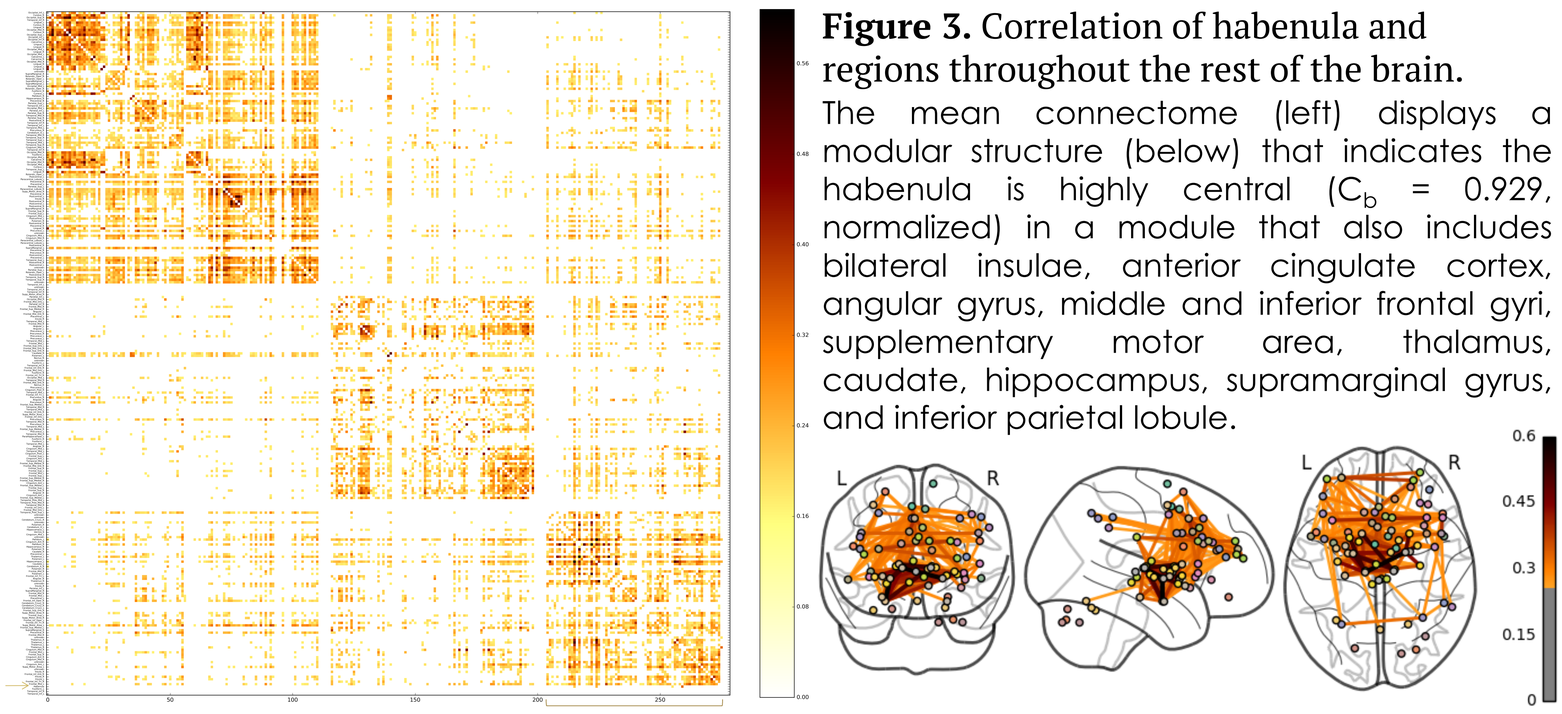

Figure 3. Correlation of habenula and regions throughout the rest of the brain.
The mean connectome (left) displays a modular structure (below) that indicates the habenula is highly central (C_b = 0.929, normalized) in a module that also includes bilateral insulae, anterior cingulate cortex, angular gyrus, middle and inferior frontal gyri, supplementary motor area, thalamus, caudate, hippocampus, supramarginal gyrus, and inferior parietal lobule.

Meta-analytic coactivation modeling

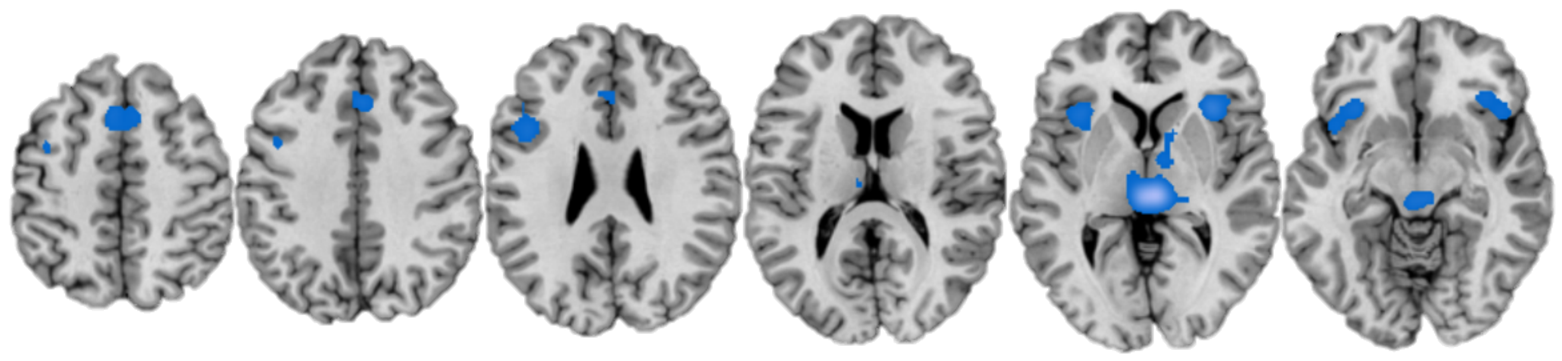

Figure 4. Meta-analytic convergence of regions frequently coactivated with the habenula.
Across a wide variety of fMRI tasks and paradigms, the habenula is consistently coactivated with bilateral anterior insula, middle frontal gyrus, basal ganglia, and cingulate cortex.

References

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