Resting-State Connectivity of the Human Habenula: Associations with Subclinical Depression

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Introduction: The habenula (Hb) plays an important role in reward and punishment processing in many species by inhibiting midbrain monoamine signaling; in particular, Hb-mediated decreases in ventral tegmental area (VTA) dopamine release are associated with depressive phenotypes. However, the small size of the Hb has limited its *in vivo* characterization. Using a unique, high-resolution neuroimaging dataset, we examined Hb resting-state whole-brain functional connectivity and its relationship to depressive symptomatology.

Methods: Data were acquired from 50 healthy young adults (25 high, 25 low subclinical depression scores) in the Human Connectome Project 500 Subjects Release. Using a novel semi-automated segmentation and anatomical-to-functional resolution interpolation approach to create individual-specific Hb seeds (**Fig 1**), connectivity maps were generated for the entire cohort and high vs. low subclinical depression groups.

Results: In the entire cohort (**Fig 2**), the Hb exhibited functional connectivity with the VTA, brainstem, insula, dorsolateral prefrontal cortex, medial prefrontal cortex (mPFC), anterior cingulate (ACC), and posterior cingulate (PCC), as well as several thalamic and sensorimotor areas. High and low subclinical depression groups (**Fig 3**) differed in Hb connectivity with regions including the amygdala, mPFC, ACC, and PCC.

Conclusions: Consistent with preclinical research, we found Hb functional connectivity with the VTA and brainstem, supporting the notion of a similar role regulating monoamine circuitry in humans. The Hb also demonstrated connectivity with numerous executive control and sensorimotor areas. Interestingly, subjects with high subclinical depression scores exhibited altered Hb connectivity with several regions previously linked to depression, highlighting the importance of the Hb as a potential target for future research and treatment.

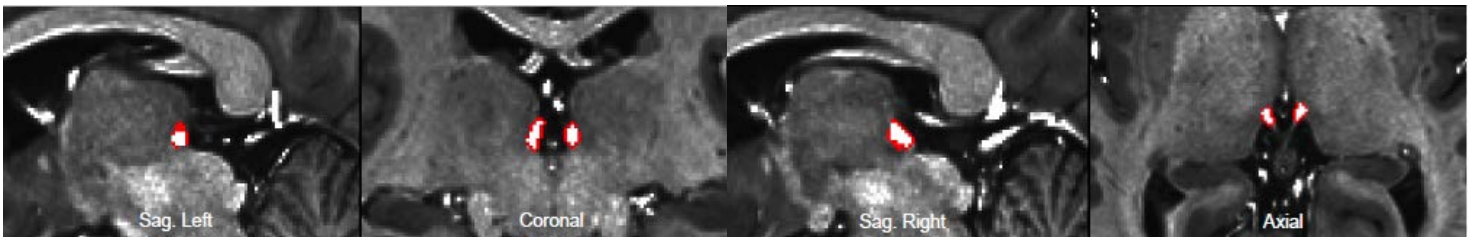

Fig 1: Representative semi-automatic Hb segmentation overlaid on a 0.7mm isotropic myelin map. Border voxels (red) contain partial volumes of Hb and surrounding tissue; central voxels (white) are entirely within Hb.

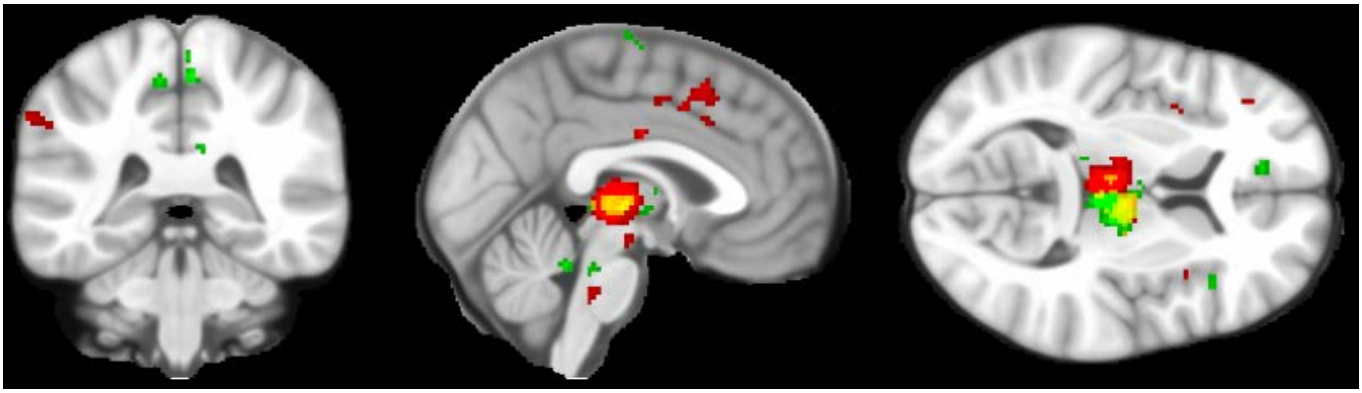

Fig 2: Regions with significantly (p<0.001, k≥10) positive resting-state functional connectivity with the left habenula (red) and right habenula (green) in 50 healthy subjects.

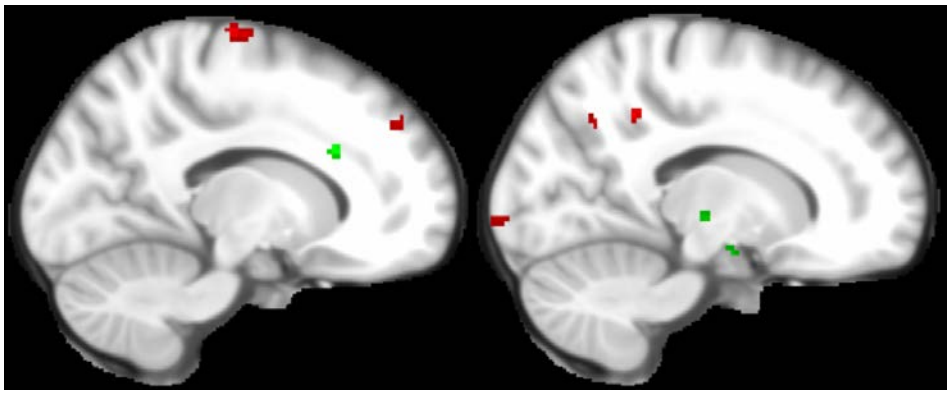

Fig 3: Regions where Hb functional connectivity was significantly (left) higher and (right) lower in healthy subjects with low (n=25) vs. high (n=25) subclinical depression scores. Red=left Hb, green=right Hb, p<0.001, k≥10.