HABENULAR ALTERATIONS IN RESTING STATE FUNCTIONAL CONNECTIVITY AMONG AUTISTIC INDIVIDUALS

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AIM To address a critical gap in autism reward-based literature, this study examined habenula resting state functional connectivity (rsFC) using functional magnetic resonance imaging (fMRI) data.

BACKGROUND

- **Autism** is a neurodevelopmental disability characterized by social communication differences + restrictive interests and/or repetitive behaviors [1].
- The **reward-based theoretical framework** suggests that altered reward circuitry contributes to core autism symptoms [2,3], which has been supported by robust evidence of altered reward-based cortico-striatal circuitry [4] across development [5].
- Recent research has revealed autism-related structural alterations in the **habenula** [6], a small epithalamic structure that modulates the dopaminergic pathways of the reward network and is associated with **motivation and emotion** [7].
- Despite these findings, the potential alterations in habenular functional connectivity (FC) remain unexplored.

METHODS

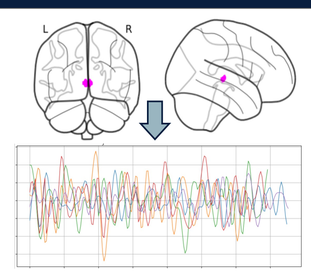
Neuroimaging Data

- Resting state functional MRI (rs-fMRI) data were accessed for 1,584 ABIDE participants (N=705 autism; M=16.26±8.15 years) [8, 9].
- rs-fMRI data for autistic (ASD) and neurotypical (NT) individuals were preprocessed and quality controlled using fMRIPrep [10] and MRIQC [11].

ABIDE Autism Brain Imaging Data Exchange

Habenula Region of Interest

- Voxelwise time series were extracted from a hand-drawn bilateral habenula ROI defined using the MNI 152-subject averaged T1 template brain [12, 13].



Analyses

1. Mapped habenula FC in autistic individuals by conducting a whole-brain rsFC analysis (ASD+NT, ASD>NT).

2. Probed for age-related changes in habenula FC from childhood to early adulthood (5–21 years) between ASD and NTs.

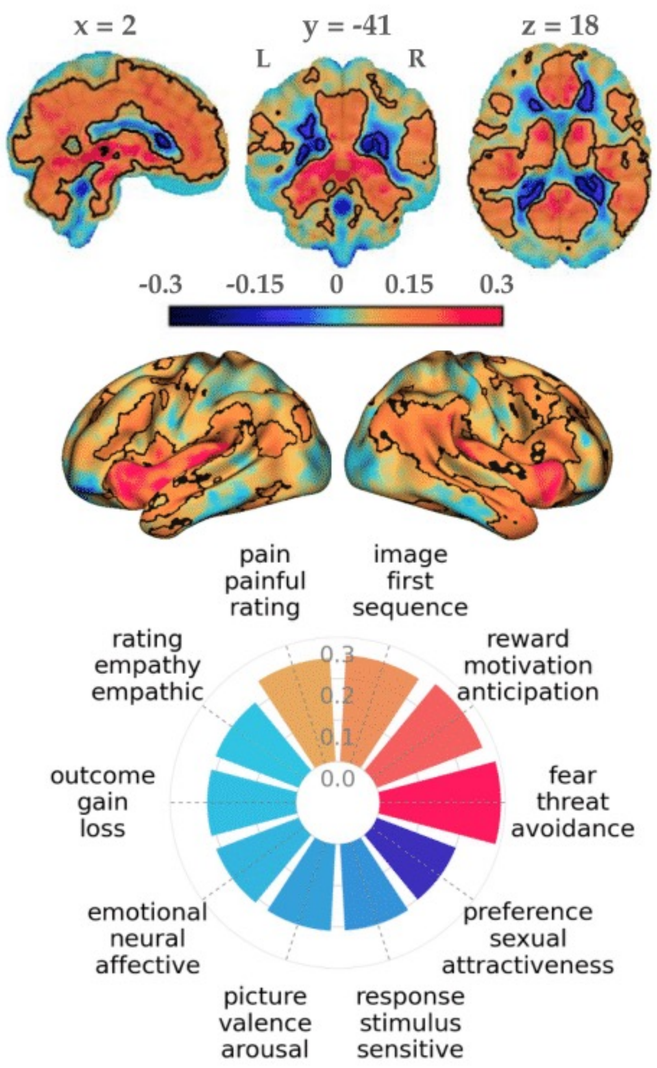
3. Examined relationships between altered habenula FC and behavior with measures of social motivation (SM), social communication (SC), executive functioning (EF), and daily living skills (DLS).

- All thresholded rsFC maps were generated using Nilearn [14] Python package and functionally decoded with Neurosynth [15].

RESULTS

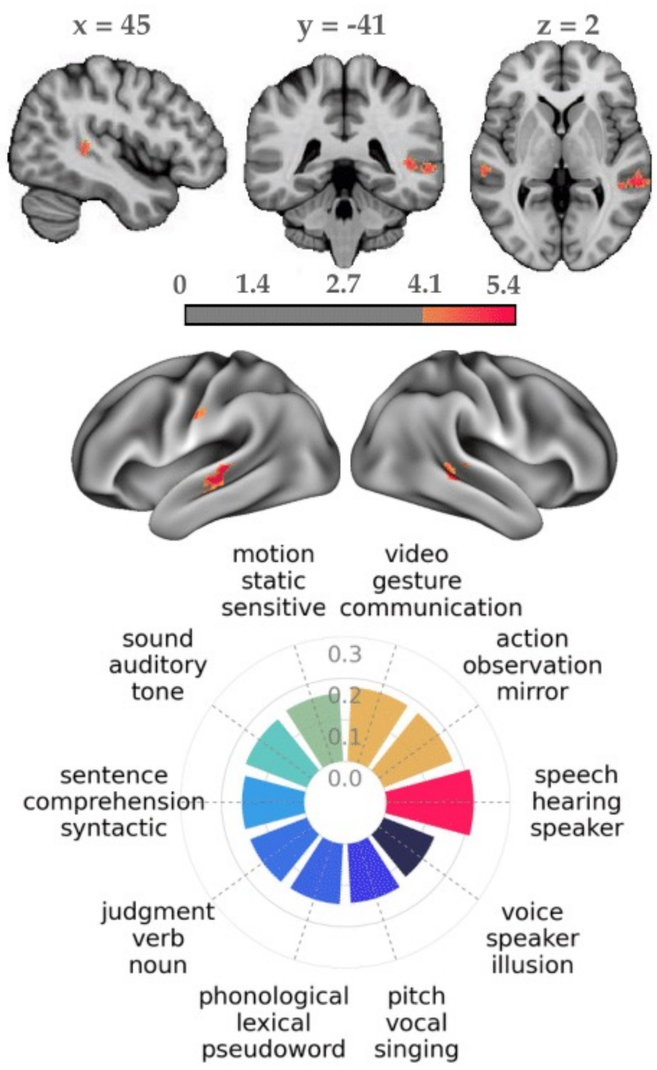
1. Group Averaged (ASD+NT) Habenula FC

(p_{voxel}=0.0001, $p_{cluster}$=0.01)



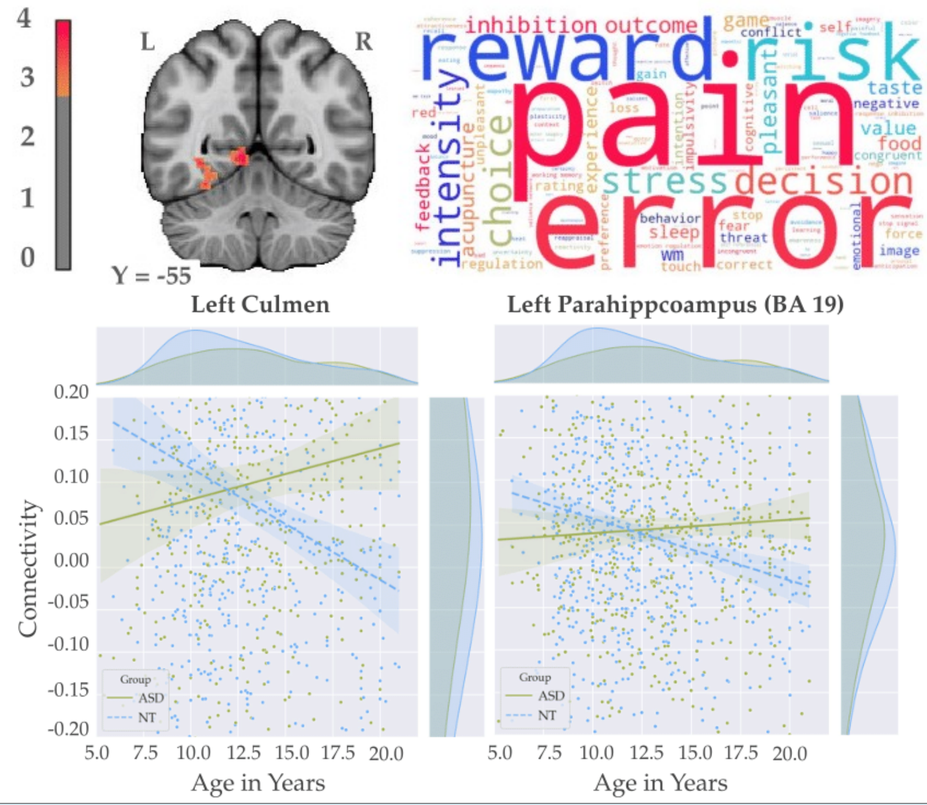
Group Difference (ASD>NT) Habenula FC

(p_{voxel}=0.0001, $p_{cluster}$=0.02)



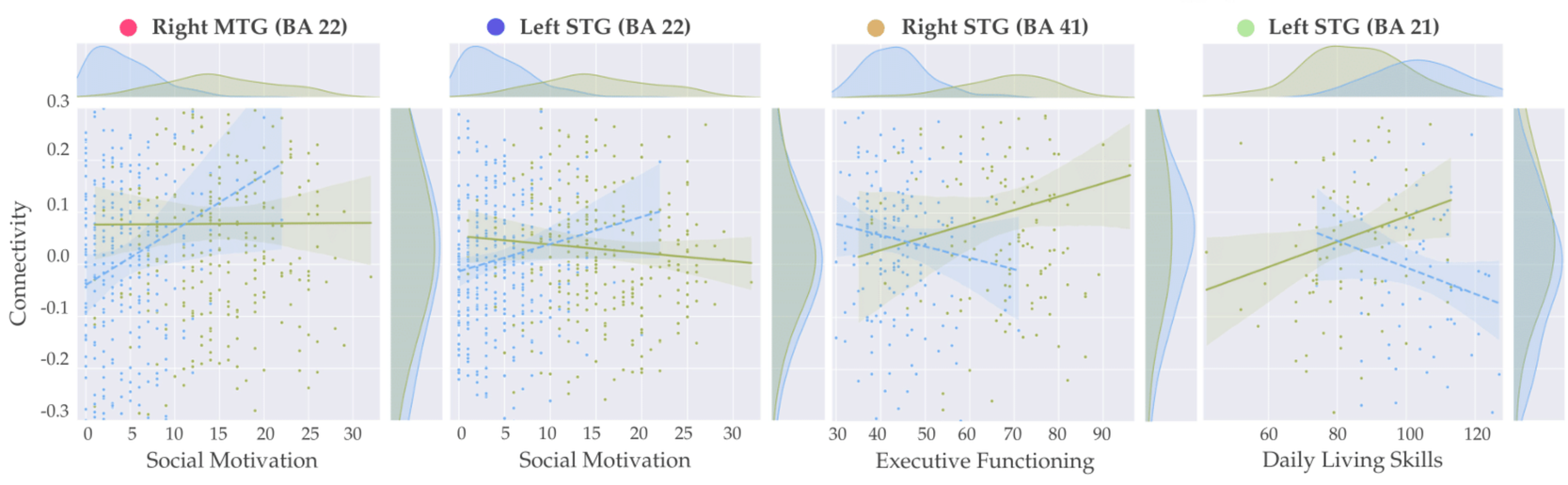
2. Age-Related Variability in Habenula FC

(p_{voxel}=0.005, $p_{cluster}$=0.05)



3. Associations Between Habenula FC and Autism Symptomatology

(p<0.05), controlling for sex and scanning site



CONCLUSIONS

- Extensive habenula connectivity was observed within the midbrain dopaminergic reward system, in agreement with prior work [16, 17].
- Habenula hyperconnectivity was found in autism with the primary and associative auditory cortices, which are speculated to play a role in **multimodal sensory integration** [18].
- From childhood to young adulthood, changes in habenula connectivity with the anterior cerebellum were observed, aligning with hypotheses that cerebellar connectivity alterations are a key component of autism [19].
- Habenula hyperconnectivity was significantly associated with SM, EF, and DLS, emphasizing the critical role of the habenula in **motivated** and **adaptive behaviors**, which are crucial for positive life outcomes and pose challenges for autistic individuals in achieving independence [20].
- **Taken together, these results contribute to the emerging evidence that the dopaminergic reward system plays a critical role in the pathophysiology of autism.**

ACKNOWLEDGMENTS

Primary funding for this project was provided by the FIU Embrace Center for Advancing Inclusive Communities, the FIU Office of Research & Economic Development, and the FIU Undergraduate to Graduate Program. Contributions from co-authors were provided with support from NIH R01-MH09606 (JAP, ARL), U01-DA041156 (ARL), U54-MD012393 (RA), and NIH R35GM153434. This project was also supported by funding provided to each of the contributing ABIDE research institutions, which are listed for each site at https://fcon_1000.projects.nitrc.org/indi/abide.

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