Habenula alterations in resting state functional connectivity among autistic individuals

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Keywords: autism, autism spectrum disorder, ASD, habenula, functional magnetic resonance imaging, fMRI, resting state, functional connectivity

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Abstract

Background: The reward-based theoretical framework of autism suggests that altered reward circuitry contributes to core symptoms. Recent prior research has revealed autism-related structural alterations in the habenula, a small epithalamic structure associated with motivation and emotion; however, potential alterations in functional connectivity (FC) remain unexplored.

Methods: Anatomical and resting state functional magnetic resonance imaging (rs-fMRI) data were accessed for 1,584 participants (N=705 autism; mean age: 16.26 ± 8.15 years) in the Autism Brain Imaging Data Exchange (ABIDE). To investigate habenula alterations, we conducted a whole-brain resting state FC analysis, followed by regression analyses to explore age and brain-behavior interactions.

Results: Across the entire sample, extensive habenula connectivity was observed within the midbrain dopaminergic reward system. Compared to neurotypical (NT) controls, autistic participants exhibited significantly increased habenular connectivity with the right middle temporal gyrus and bilateral superior temporal gyri. From childhood to early adulthood, habenula FC increased in autistic adolescents, and inversely decreased in NTs, with the left culmen and left parahippocampus. Between groups, habenula hyperconnectivity was inversely associated with behavioral scores for social motivation, executive functioning, and daily living skills, but not social communication.

Conclusions: This study provides novel evidence of habenula connectivity alterations in autism, highlighting atypical FC with the auditory cortex. Further findings suggest that habenula circuitry develops differently among autistic adolescents, with links between habenula hyperconnectivity and motivation and adaptive behaviors. Taken together, these results contribute to emerging evidence that the dopaminergic reward system may play a critical role in the pathophysiology of autism.

Introduction

Autism is a lifelong neurodevelopmental disability characterized by social communication differences, as well as restrictive interests and/or repetitive behaviors (RRB) (1). Extending beyond the core criteria, autistic individuals[1] face everyday challenges in achieving positive life outcomes (5), with previous research highlighting below age-expected levels of executive functioning (EF) (6) and daily living skills (DLS) (7) among autistic adolescents. The social motivation (SM) theory argues that these differences, and challenges, are due to diminished social orienting, social reward, and social maintenance (8), thereby providing a theoretical framework of understanding autism centered on social functioning. This emphasis aligns with many neuroimaging studies that have aimed to elucidate underlying neurobiological mechanisms of autism, yielding a predominance of studies that have largely focused on structural and functional alterations in areas of the "social brain" (9). However, to better capture the autistic behavioral spectrum, the social motivation framework was expanded to a reward-based framework that is centered more broadly around constructs related to motivation and affect, thus linking the social differences and RRB that are observed in autism (10,11).

The reward-based theoretical framework suggests that alterations in the brain's reward circuitry contribute to the core behaviors associated with autism. The reward network, which includes the anterior cingulate cortex, orbital prefrontal cortex, ventral striatum, ventral pallidum, and midbrain dopamine neurons (12), has been found to play a critical role in adaptive motivated behavior (13), as well as guiding both social and nonsocial learning and behavior throughout development (14). Of the regions comprising the reward network, the striatum is repeatedly implicated in autism given its functions that relate to the regulation of behavioral flexibility, motivational state, goal-directed learning, and attention (15). As a key dopaminergic region, the cortico-striatal system shows robust evidence of autism-related alterations in function (16) and structure (17) across development, supporting the reward-based theoretical framework of autism. Dopaminergic pathways within the reward network, including the striatum, are modulated by the habenula, a paired midline structure located on the dorsal surface of the thalamus. Importantly, the functional role of the habenula in autism has yet to be studied.

The habenula is a small epithalamic structure that is divided into two functionally and cytologically distinct medial and lateral nuclei that serve as a connecting link among basal forebrain, striatal, and midbrain regions (18). Task-based animal models have suggested that the habenula plays a substantial role in reward prediction, motivation (19), and aversion processing (20), with replicated involvement in reward prediction in human models (21). To better understand the functional role of the human habenula, neuroimaging studies have mapped resting state habenula connectivity using 3T (22) and 7T functional magnetic resonance imaging (fMRI) (23) among neurotypical (NT) individuals. Torrisi et al. (2017) highlighted habenula coupling with forebrain regions that were strongly implicated in emotion and motivation processing, postulating that the habenula plays a role in establishing and maintaining emotional states in humans. Due to its linkage to numerous functional domains relevant to psychopathology, habenula structural and functional connectivity alterations have been investigated in autism co-occurring behaviors such as those characterized by ADHD (24), major depressive disorder (25), and schizophrenia (26). Although structural alterations in the habenula have been observed in autism

[1] In the current manuscript, we used identity-first language, as recommended by Toboas et. al. (2023), Bury et. al. (2023), and Kenny et al. (2016).

(27), potential functional alterations, which may contribute to autistic behaviors relating to emotion and motivation processing, currently remain unexplored.

Addressing this gap in the autism literature, we accessed resting state fMRI data from the Autism Brain Imaging Data Exchange (ABIDE) (28,29) to explore the habenula functional connectivity alterations underlying autism. Primarily, we sought to map habenula functional connectivity in autistic individuals by conducting a seed-based, whole-brain resting state functional connectivity (rsFC) analysis. Given that differences in striatal volume (30,31) are associated with functional connectivity alterations in autism (32), we hypothesized that the known structural differences in the habenula might similarly correspond to atypical habenula functional connectivity among autistic individuals compared to NT controls. To provide supplementary insight into autism-related habenula connectivity patterns, we performed two separate regression analyses. In the first regression analysis, we probed for age-related changes in habenula connectivity between autistic individuals and NT controls. Due to recent work revealing an increase in striatal connectivity with cerebellar regions from childhood to early adulthood in autism (33), we hypothesized to observe similar age effects in habenula connectivity. In the second exploratory regression analysis, we aimed to examine the relationship between altered habenula connectivity and autistic behaviors by accessing the phenotypic data available in the ABIDE dataset. To capture the broader domains that influence everyday functioning, we selected phenotypic measures that assessed the level of impairment an individual experienced in SM, social communication (SC), EF, and DLS. As the habenula is primarily implicated in modulating motivation and adaptive behavior, we hypothesized that habenula connectivity would be significantly associated with SM and DLS, but not SC or EF.

Methods

Participants

Participants for the current study were selected from the large-scale, multisite ABIDE I and II datasets. The combined ABIDE dataset consisted of neuroimaging data, as well as, demographic and phenotypic information from approximately 2,000 participants across 24 international sites. Written informed consent was obtained through institutional IRB. Further information regarding the ABIDE data collection can be found at http://fcon_1000.projects.nitrc.org/indi/abide/abide_I.html. Demographic information was provided, including age at scan and sex, and autism spectrum disorder[2] (ASD) diagnoses were made according to the Diagnosis and Statistical Manual of Mental Disorders—4th edition (DSM-IV) (34) and 5th edition (DSM-5) (35).

Phenotypic Measures

The phenotypic measures included in this study assessed behavioral differences commonly occurring in autism, encompassing SM, SC, EF, and DLS. SM refers to the extent to which an individual is generally motivated to engage in social-interpersonal behavior, which was measured with the 11-item Social Responsiveness Scale (SRS) Social Motivation subscale (36). SC refers to the reciprocal and expressive communication in social situations, which was measured with the 22-item SRS Social Communication subscale (36). EF refers to working memory, flexible thinking, and self-control, which was measured

[2] When discussing data accessed from ABIDE, we use the term 'ASD' when referring to autism to align with the dataset's terminology.

through the Behavior Rating Inventory of Executive Function (BRIEF) Global Executive Composite Score (GEC) T-score (37). The BRIEF GEC T-score measures EF by compiling scores from three composite indexes that test for behavior regulation, emotional recognition, and cognitive regulation. DLS are a measure of adaptive behavior encompassing everyday tasks necessary for independent living, including personal care, household responsibilities, and community activities such as maintaining hygiene, preparing meals, and managing money and time. DLS were measured with the DLS domain of Vineland-2nd edition (38).

Neuroimaging Data Acquisition and Preprocessing

Resting state, functional, and structural MRI data were acquired across the 24 scanning sites using 3T MRI scanners. For all participants, a T1-weighted structural image was collected and used for registration to Montreal Neurological Institute (MNI) space. Full details for acquisition parameters, informed consent, and site-specific protocols can be found at http://fcon_1000.projects.nitrc.org/indi/abide/abide_I.html. Data were preprocessed using fMRIPrep 23.1.3, which utilizes the Brain Imaging Data Structure (BIDS) to ensure high-quality preprocessing with minimal user intervention (39,40). The anatomical images were intensity-corrected, skull-stripped, segmented, and spatially normalized to a standard brain template in MNI152 space. Furthermore, the preprocessed data underwent both manual and automated quality control. Using the ratings reported by independent raters for ABIDE I, we manually excluded participants that received a "fail" rating from any of the raters. We then used MRIQC 23.1.0 to inspect, flag, and remove participants, sessions, or runs (39) if they had excessive head motion defined by a framewise displacement greater than 0.35mm or had less than 100 usable time points following motion censoring (41). Lastly, denoising was performed on the remaining participants using AFNI's `3dTproject`, which utilizes a linear regression model to nuisance time series from each voxel within a dataset.

Habenular Region of Interest

Bilateral habenula ROIs were manually defined on the MNI's 152-subject averaged T1 template brain (i.e., ICBM152) (42,43). Using Mango Image Viewer (http://mangoviewer.com), we followed the procedure for manual habenula delineation outlined by Lawson et al. (44). To account for habenula structural enlargement in ASD (27), as well as individual differences and deviations in registration on this probabilistic group template, the resultant ROI was dilated by 2mm in each direction. This process yielded an ROI representing an approximation of the habenula, which measured 523mm^3 in volume and was centered at MNI coordinate [0, -24, 2].

Whole-Brain Habenula Functional Connectivity Analysis

Group Averaged Habenula Connectivity

Participant-level functional connectivity analyses were conducted using AFNI (v22.3.05) (45). Voxelwise time series were extracted from each ROI (i.e., left and right habenula) using the unsmoothed, preprocessed, and denoised data via AFNI's `3dmaskave`. For each participant, averaged ROI time series were generated by calculating the mean voxel value for each time point across non-zero voxels respective to each region. The averaged ROI time series were entered into a general linear model to generate whole-brain correlation maps for each participant. The resulting z-transformed (Fisher r-to-z transformation) correlation maps were entered into group-level regression models with diagnosis (ASD, NT) as a

categorical factor and age as a continuous factor, controlling for sex and scanning site using AFNI's `3dLMEr` (46,47). A group-averaged map (ASD+NT) was generated to visualize regions exhibiting positive and negative habenula connectivity for the combined ASD and NT groups. Thresholded z-maps were generated using `3dClustSim` to compute a cluster size at a voxel threshold of $p = 0.0001$, and a cluster threshold of $p = 0.01$.

Group Differences in Habenula Connectivity

The group-averaged map was used to mask regions functionally connected with the habenula in both the ASD and NT groups. A group-difference map was generated to identify regions that exhibited atypical habenula rsFC among ASD participants (ASD vs. NT). Thresholded z-maps were generated at a voxel threshold of $p = 0.0001$ and a cluster threshold of $p = 0.01$.

Age-Related Variability in Habenula Connectivity

Next, a whole-brain regression analysis was performed to probe for age-related changes in habenula connectivity. Previous studies have identified substantial rsFC variability from childhood to early adulthood, characterized by a refinement of functional networks in the brain (48). Thus, we chose to focus on participants aged 5-21 years, which included the majority of ABIDE participants. Prior to testing for age-related differences, the above-described whole-brain group analysis was rerun for the age-restricted subset of participants to confirm habenula connectivity patterns remained consistent within the subsample. Next, z-transformed participant-level correlation maps were analyzed using a linear effects model to probe for age-by-group interactions, controlling for sex and scanning site. Thresholded z-maps were generated with a voxel threshold of $p = 0.005$ and a cluster threshold of $p = 0.05$. Clusters exhibiting significant age interactions in habenula connectivity between groups were identified; 5mm spherical masks were placed on the centers of peak coordinates for these clusters to extract z-scored beta coefficients. For each of the clusters, beta coefficients were averaged and entered into a linear regression model to determine the direction of developmental changes in connectivity for each group, following the approach outlined by Padmanabhan et al. (2013).

Functional Decoding of Habenula Connectivity

We performed functional decoding (49) on each of the thresholded z-maps to provide additional information regarding the functional role of the habenula among ASD participants. Specifically, decoding was conducted to characterize the functional role of the regions identified in each step of our analysis. To perform functional decoding, we utilized `Gradec` (v0.0.1rc5), a Python package designed for meta-analytic functional decoding (50). Within this package, the decoder algorithms utilize the Neurosynth database to conduct large-scale, automated synthesis of fMRI data (51). Currently, the Neurosynth has over 500,000 activation coordinates from 14,371 task-based neuroimaging studies (51). Using `Gradec`, we extracted Neurosynth terms that were correlated with the habenula connectivity maps and generated word clouds and radar plots to visualize the correlations between the terms and the spatial distribution of connectivity (50).

Associations Between Habenula Connectivity and Autism Symptomatology

Lastly, a separate regression analysis was performed to examine associations between atypical habenula connectivity and phenotypic measures, including SM, SC, EF, and DLS. Matching the approach used in the age-related regression analysis, z-scored beta coefficients were extracted from clusters showing atypical habenula connectivity using a 3mm spherical mask. Given that fewer participants had scores for each phenotypic measure, we tested clusters for significant phenotypic main effects among ASD participants, as well as phenotypic interactions between ASD and NT groups ($p < 0.05$) using group as a categorical factor and age as a continuous factor, while controlling for sex and scanning site. For clusters that were identified to exhibit a significant effect, correlation coefficients were entered into a linear regression model as a function of subscore for each of the phenotypic measures. To correct for multiple comparisons, the Benjamini-Hochberg procedure was applied to control the false discovery rate ($p < 0.05$) (52).

Results

Sample Selection

From ABIDE participants who reported complete baseline demographic information, we excluded participants from the current study if their MRI data did not meet the previously defined inclusion criteria. The final sample included 1,584 participants (mean age: 16.26 ± 8.15 years) from the ABIDE I and II datasets, with 705 ASD participants (**Table 1**). Among the included participants, only a fraction completed the phenotypic measures; therefore, we accessed SM and SC scores for 300 ASD and 361 NT, EF scores for 134 ASD and 201 NT, and DLS scores for 104 ASD and 68 NT. Of the included demographic variables (i.e., age, sex, handedness, diagnostic category, comorbidity, and medication status), significant differences ($p < 0.001$) between the ASD and NT groups were found for sex, diagnostic category, and medication status.

Table 1. **Participant Information.**

	ASD (*N* = 705)		NT (*N* = 879)			
	M	*SD*	*M*	*SD*	*t-value*	*p-value*
Age (in years)	16.53	8.33	16.04	8.01	1.18	0.24
	N		*N*		*χ2 -value*	*p-value*
Sex	--		--		34.50	**< 0.001**
Male	607		651		--	--
Female	98		228		--	--
Handedness	--		--		9.33	0.009
Right	487		668		--	--
Left	58		44		--	--
Mixed	24		23		--	--
Diagnostic Category	--		--		693.8	**< 0.001**
Control	0		410		--	**--**
Autism	66		0		--	--
Asperger's	227		0		--	--
PDD-NOS	40		0		--	--
Comorbidity	--		--		0.87	0.83
ADHD	7		0		--	--
Anxiety	18		1		--	--
Disruptive Disorder	2		0		--	--
Mood Disorder	7		0		--	--
Medication Status	--		--		199.91	**< 0.001**
Medicated	176		15		--	--
Not Medicated	411		713		--	--

Note: Values are provided as mean (M) ± standard deviation (SD). t-value was obtained using a two-sample t-test. χ2 values were obtained using chi-squared tests. < 0.001 indicates significant differences between the ASD and NT groups for demographic variables. Abbreviations: ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; M, mean; NT, neurotypical; PPD-NOS, pervasive developmental disorder-not otherwise specified; SD, standard deviation.

Whole-Brain Habenula Functional Connectivity Analysis

Group-Averaged Habenula Connectivity

The whole-brain, group-averaged (ASD+NT) habenula connectivity map (**Fig. 1A-B**) depicts positive and negative habenula connectivity through an extensive network of bilateral cortical and subcortical regions (**Table 2**). Neurosynth-based functional decoding revealed that this connectivity pattern is commonly associated with terms for fear, reward, and emotion processing (**Fig. 1C**).

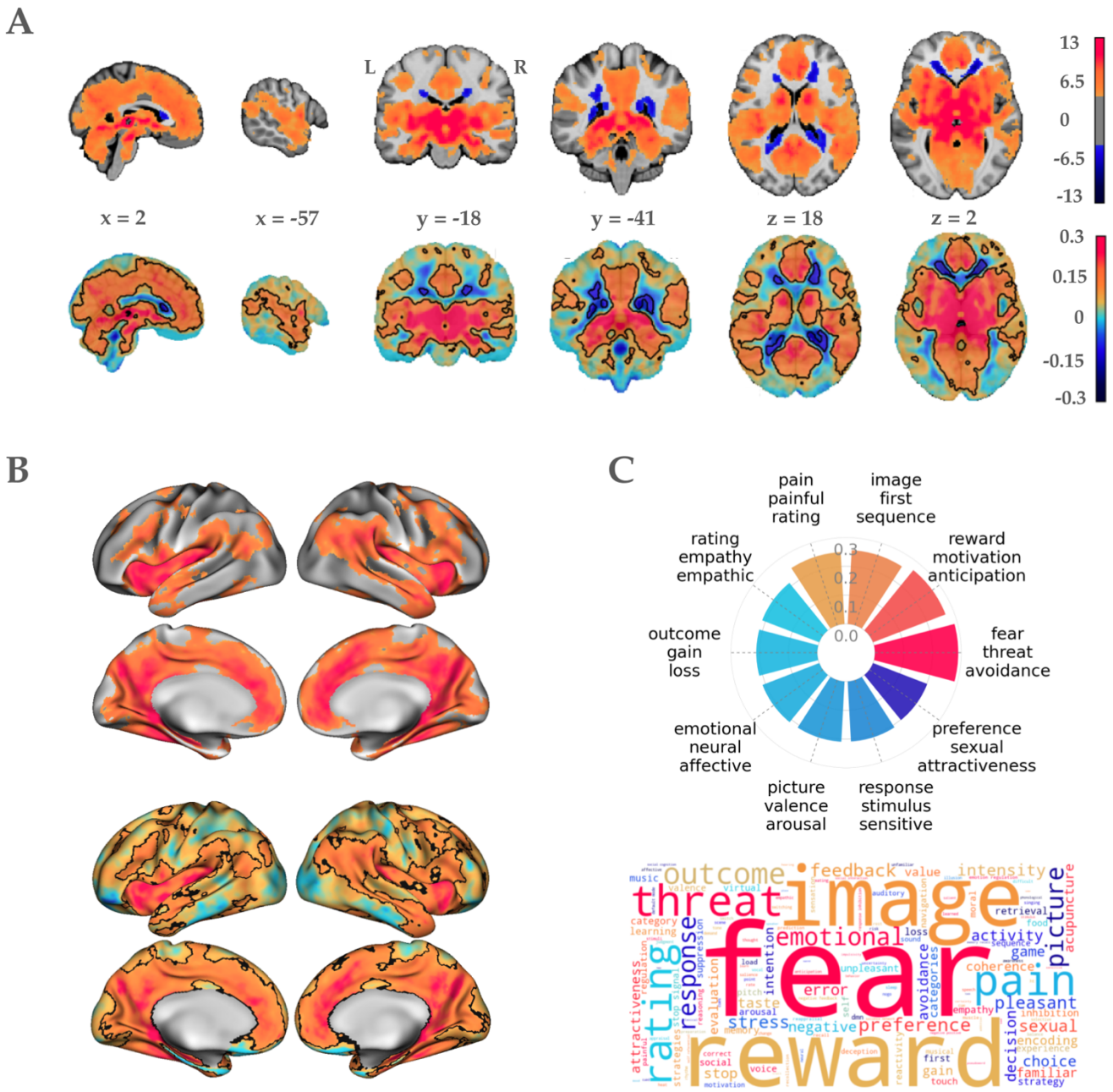


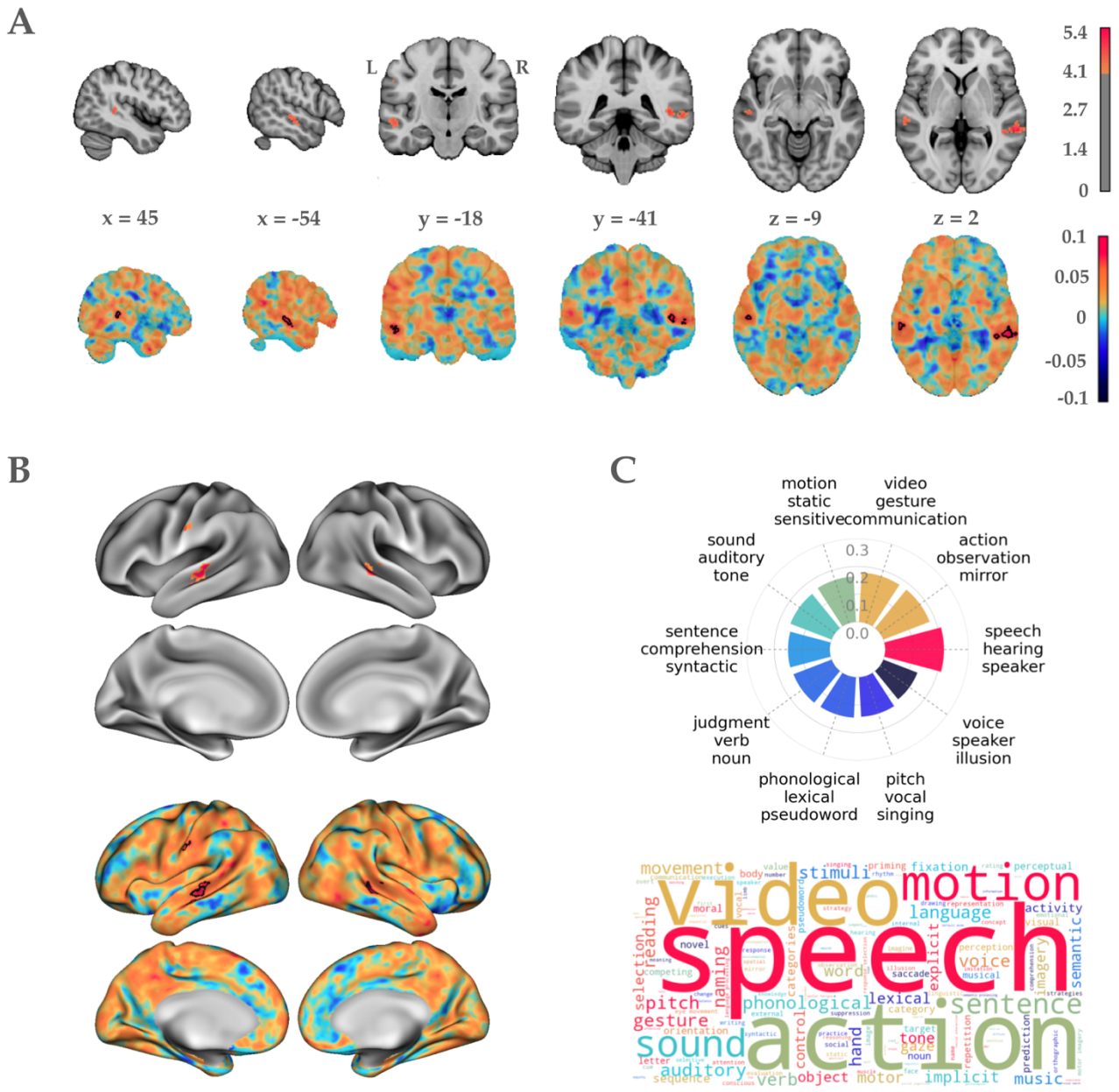
Figure 1. Group-Averaged (ASD+NT) Habenula Connectivity. Thresholded z-maps and Cohen's *d* effect maps were generated using 3dClustSim to compute a cluster size at a voxel threshold of $p = 0.0001$ and a cluster threshold of $p = 0.01$. Warm colors denote areas of positive connectivity with the habenula and cool colors denote areas of negative connectivity. **A)** Volumetric brain slices and **B)** surface plots for the *z*-values (top) and Cohen's *d* effect sizes (bottom) depict regions showing significant habenula connectivity across all subjects. **C)** Functional decoding results for the group-averaged habenula connectivity z-map shown as a radar plot (top) and word cloud (bottom).

Table 2. **Peak coordinates for clusters of positive and negative group-averaged (ASD+NT) habenula connectivity, controlling for age, sex, and scanning site.**

X	Y	Z	Peak Stat	Cluster Size	Region
			Positive Habenula Connectivity		
0	-28	2	38.28	645,336	Thalamus
-28	34	26	6.61	3,728	Left Middle Frontal Gyrus (BA 9)
26	32	40	6.09	3,536	Right Middle Frontal Gyrus (BA 8)
-32	-56	44	6.04	936	Left Angular Gyrus (BA 39)
-20	-44	72	5.87	488	Left Postcentral Gyrus (BA 7)
-22	-30	70	4.97	904	Left Postcentral Gyrus (BA 3)
28	54	6	4.84	480	Right Superior Frontal Gyrus (BA 10)
			Negative Habenula Connectivity		
-18	-6	32	9.12	16,136	Left Cingulate Gyrus (BA 24)
-30	-42	10	6.97	528	Left Caudate
30	-40	22	6.23	2,792	Right Insula (BA 13)

Group Differences in Habenula Connectivity

The whole-brain group-difference (ASD>NT) habenula connectivity map (**Fig. 2A-B**) depicts regions of *increased* habenula connectivity for the ASD group (**Table 3**). Connectivity was observed with peaks in the auditory association and lateral temporal cortices, with comparatively weaker, yet still significant, connectivity within the primary auditory cortex and Wernicke's area. Neurosynth-based functional decoding revealed that these regions of increased habenula connectivity among ASD participants are commonly associated with terms for speech, language, and action processing (**Fig. 2C**). No statistically significant regions of *decreased* ASD connectivity were observed.


A
L
R
5.4
4.1
2.7
1.4
0
x = 45
x = -54
y = -18
y = -41
z = -9
z = 2
0.1
0.05
0
-0.05
-0.1
B
C
motion
static
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gesture
communication
sound
auditory
tone
action
observation
mirror
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sentence
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syntactic
speech
hearing
speaker
judgment
verb
noun
voice
speaker
illusion
phonological
lexical
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naming
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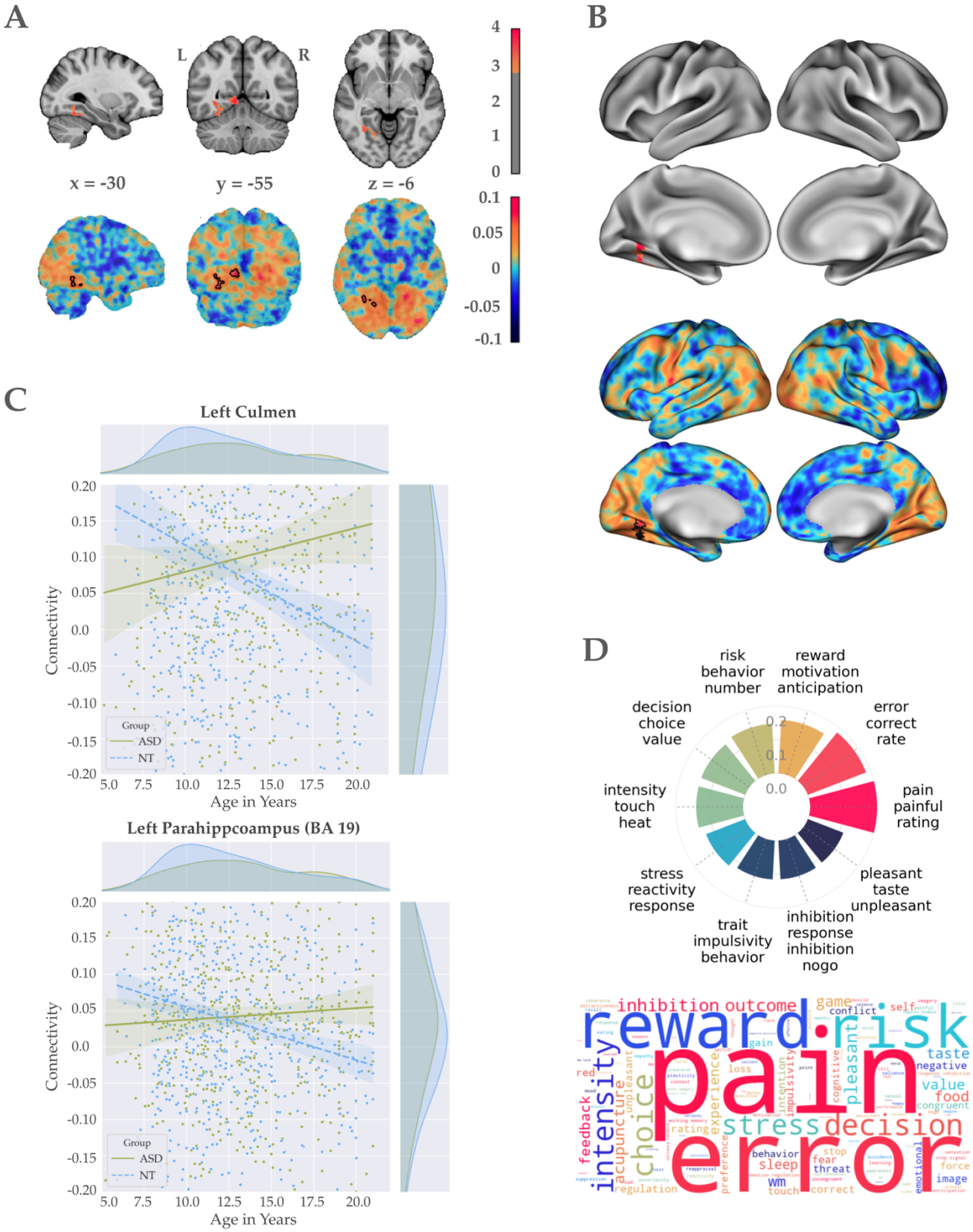
explicit
control
hand
tone
gaze
noun
prediction
repetition
moral
novel
word
saccade
musical
perception
visual
orientation
letter
sequence
target
social
practice
syntactic
external
category
suppression
writing
attention
conscious
face
static
image
graphic
orthographic
rhythm
priming
drawing/representation
strategy
concept
internal
imagine
hearing
response
spatial
error
meaning
competing
change
strategies
comprehension
value
number
speaker
body
pseudoword
novel
rating
singing
overt
communicate
measure
action
strategy
concept
imagine
hearing
response
spatial
error
meaning
change
syntactic
external
category
suppression
practice
social
static
image
face
conscious
attention
writing
orientation
letter
sequence
target
repetition
name
graphic
orthographic
rhythm
priming
drawing/representation
strategy
concept
internal

Table 3. **Peak coordinates for clusters of increased habenula connectivity among ASD participants compared to neurotypical controls (ASD>NT), controlling for age, sex, and scanning site.**

X	Y	Z	Peak Stat	Cluster Size	Region
60	-38	0	5.40	1,256	Middle Temporal Gyrus (BA 22)
48	-40	4	4.88	--	Superior Temporal Gyrus (BA 41)
-52	-24	-2	4.93	1,160	Superior Temporal Gyrus (BA 21)
-60	-28	4	4.64	--	Superior Temporal Gyrus (BA 22)

Age-Related Variability in Habenula Connectivity

Next, we probed for age-related variability from childhood to early adulthood in habenula connectivity among participants between the ages of 5 and 21 years. Prior to conducting this analysis, we repeated computations for whole-brain group-averaged habenula connectivity in this participant subsample (i.e., without the older participants over the age of 21 years). Results yielded a similar group-averaged habenula connectivity pattern as described above, thus validating the exclusion of older participants when testing for age-related differences. The age-related variability connectivity map (**Fig. 3A-B**) depicts regions that exhibit altered developmental trajectories in habenula connectivity between the ASD and NT groups (**Table 4**). Situated in the left anterior cerebellum, peak connectivity differences were observed in the culmen, specifically cerebral lobules IV and V, as well as in the left parahippocampus (BA 19) within the associative visual cortex and extending anteriorly through the fusiform gyrus. Extracting and entering the z-scored beta coefficients from these regions into a linear regression model revealed habenula connectivity increases across development for ASD participants, whereas NTs inversely decrease (**Fig. 3C**). Among both groups, these regional changes across development were more prominent in the culmen than the parahippocampus (BA 19). Neurosynth-based functional decoding revealed that the regions exhibiting age-related variability in habenula connectivity are commonly associated with terms related to reward, risk, and negative outcomes (**Fig. 3D**).


A
L
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x = -30
y = -55
z = -6
4
3
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0.1
0.05
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Left Culmen
Connectivity
Age in Years
Group
ASD
NT
Left Parahippcoampus (BA 19)
D
risk behavior number
reward motivation anticipation
error correct rate
pain painful rating
pleasant taste unpleasant
inhibition response inhibition nogo
trait impulsivity behavior
stress reactivity response
intensity touch heat
decision choice value
0.2
0.1
0.0
reward
risk
pain
error
stress
decision
intensity
choice
inhibition
outcome
pleasant
taste
negative
value
food
congruent
feedback
acupuncture
unpleasant
experience
impulsivity
cognitive
behavior
sleep
fear
threat
wm
touch
correct
regulation
emotional
force
image
conflict
game
self
gain
loss
red
rating
preference
stop

Figure 3. Age-Related Variability in Habenula Connectivity. Thresholded z-maps and Cohen's *d* effect maps were generated with a voxel threshold of $p = 0.005$ and a cluster threshold of $p = 0.05$. Warm colors denote areas of increased connectivity with the habenula and cool colors denote areas of decreased connectivity. **A)** Volumetric brain slices and **B)** surface plots of the *z* values (top) and Cohen's *d* effect sizes (bottom) depict regions with age-related variability in habenula connectivity. **C)** Z-scored beta coefficients from the left culmen (top) and left hippocampus (bottom) were entered into a linear regression model as a function of age to determine differences in developmental slope between the ASD (green) and NT (blue) groups. **D)** Functional decoding results for the group-averaged habenula connectivity z-maps, shown as a radar plot (top) and word cloud (bottom).

Table 4. **Peak coordinates for clusters of regions that showed an age by group interaction, controlling for sex and scanning site.**

X	Y	Z	Peak Stat	Cluster Size	Region
-8	-54	-2	3.99	1,904	Culmen
-32	-56	-6	3.56		Parahippocampus (BA 19)

Associations Between Habenula Connectivity and Autism Symptomatology

Given the small sample sizes with completed phenotypic information, we note the following analyses were considered exploratory. Four clusters exhibited altered habenula connectivity between the ASD and NT groups (**Table 3**); z-scored beta coefficients were extracted from these clusters and entered into a linear regression model to test for significant ($p < 0.05$) main and between-group interaction effects (**Table 5**) for each of the phenotypic measures. For SM, a significant interaction was identified in the right middle temporal gyrus (rMTG) and the left superior temporal gyrus (lSTG). Higher SM scores were associated with constant or slightly decreasing habenula connectivity in the ASD group, whereas the NT group showed increasing connectivity (**Fig. 4A**). For SC, no significant main or interaction effects were found. For EF, a significant between-group interaction effect was identified in the rSTG. Higher EF scores were associated with increasing habenula connectivity in the ASD group, whereas the NT group showed decreasing connectivity (**Fig. 4B**). For DLS, we observed a significant main effect for the ASD group, as well as a significant interaction effect in the lSTG. Higher DSL scores were associated with increasing habenula connectivity in the ASD group, whereas the NT group showed decreasing connectivity (**Fig. 4C**). However, none of these findings survived the correction for multiple comparisons.

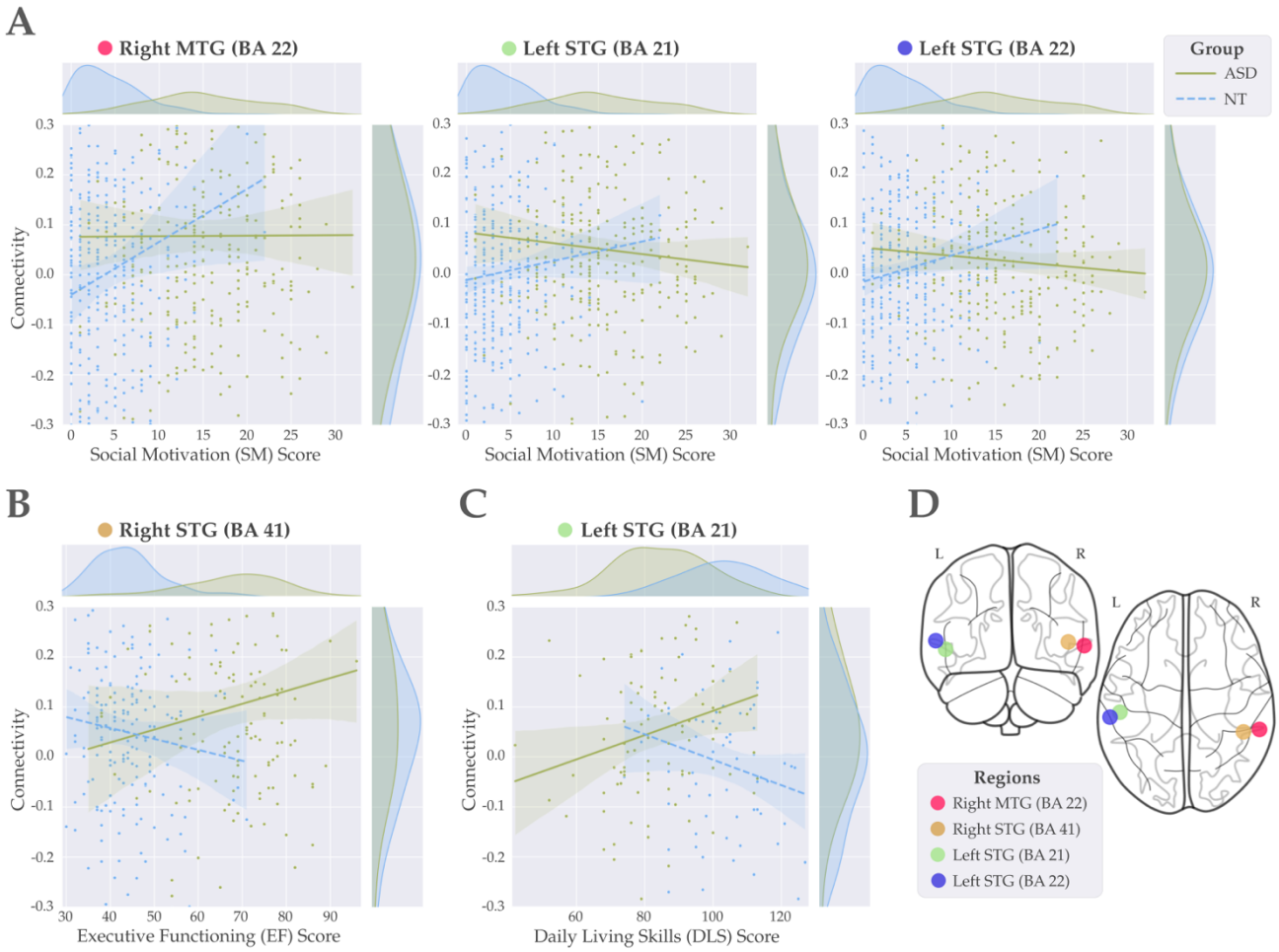

Figure 4. Associations Between Habenula Connectivity and ASD Symptomatology. Z-scored beta coefficients were extracted from regions that displayed increased habenula connectivity for the ASD group and entered into a linear regression model to test for significant phenotypic main and interaction effects ($p < 0.05$). The regression lines for the ASD (solid green) and NT (dashed blue) groups denote the relationship between the phenotypic score and connectivity for each region. **A)** Significant interactions effects were identified for SM Score in the rMTG (BA 22) and lSTG (BA 21,22) and **B)** EF Score in the rSTG (BA 41). **C)** A significant main effect and interaction was identified for DLS Score in the lSTG (BA 21). **D)** Glass brains were plotted to show the centers of peak coordinates for the clusters from which z-scored beta coefficients were extracted using a spherical mask.

Table 5. **Group-difference (ASD>NT) main effect and interaction of phenotypic measures on habenula connectivity.**

		Group Interaction				ASD Main Effect			
Region	BA	*Estimate*	*SE*	*p-value*	p_{FDR}*-value*	*Estimate*	*SE*	*p-value*	p_{FDR}*-value*
				Social Motivation					
rMTG	22	-0.083	0.037	0.026	0.133	-0.002	0.018	0.888	0.947
rSTG	41	-0.024	0.024	0.330	0.480	-0.004	0.013	0.770	0.897
lSTG	21	-0.044	0.021	**0.045**	0.132	-0.025	0.013	0.059	0.471
lSTG	22	-0.051	0.021	0.013	0.111	-0.011	0.011	0.353	0.817
				Social Communication					
rMTG	22	-0.089	0.047	0.058	0.133	-0.010	0.021	0.641	0.879
rSTG	41	-0.021	0.030	0.481	0.641	0.007	0.016	0.660	0.879
lSTG	21	-0.017	0.028	0.545	0.653	-0.013	0.015	0.409	0.817
lSTG	22	-0.044	0.026	0.085	0.170	-0.005	0.013	0.691	0.879
				Executive Functioning					
rMTG	22	0.013	0.052	0.805	0.860	-0.014	0.036	0.685	0.879
rSTG	41	0.074	0.037	**0.047**	0.133	0.030	0.026	0.254	0.817
lSTG	21	-0.019	0.033	0.571	0.653	-0.024	0.025	0.349	0.817
lSTG	22	-0.001	0.035	0.985	0.986	0.001	0.025	0.963	0.963
				Daily Living Skills					
rMTG	22	0.042	0.040	0.287	0.459	0.022	0.025	0.380	0.817
rSTG	41	0.050	0.035	0.150	0.266	0.027	0.021	0.196	0.817
lSTG	21	0.083	0.031	**0.009**	0.111	0.047	0.020	0.020	0.313
lSTG	22	0.057	0.029	0.054	0.133	-0.007	0.018	0.718	0.879

Note: Main effects and interactions were significant at $p < 0.05$ when controlling for age, sex, and scanning site. Abbreviations: BA, Brodmann area; FDR, false discovery rate; MTG, Middle Temporal Gyrus; SE, standard error; STG, Superior Temporal Gyrus.

Discussion

We investigated resting state functional connectivity of the habenula among autistic individuals. Across the entire sample, group-averaged (ASD+NT) results confirmed existing evidence that the human habenula functionally interacts with the midbrain dopaminergic reward system (53). Group-difference (ASD>NT) analyses identified atypical habenula hyperconnectivity in autism within the primary and associative auditory cortices, as well as the temporal cortex and Wernicke's area. Further investigation of variability through age-related regression analyses revealed alterations in connectivity from childhood to early adulthood (ages 5–21) between autistic individuals and NTs, particularly with the anterior cerebellum (lobules IV-V) and associative visual cortex. Finally, a second exploratory regression analysis demonstrated that atypical hyperconnectivity in autism had a significant interaction effect with social motivation (SM), executive function (EF), and daily living skills (DLS), but not social communication (SC). However, due to the small sample of individuals with completed phenotypic information, these results did not survive multiple comparison corrections.

Whole-Brain Habenula Functional Connectivity: ASD+NT and ASD>NT

Our study identified widespread habenula connectivity among the entire sample in task-positive brain regions (54). Specifically, we report prominent positive habenula connectivity with key subcortical regions of the reward network, such as the thalamus, striatum, and several midline structures, aligning with previous studies (22,23,55). Moreover, we replicated strong positive cortical habenula connectivity with the dorsolateral prefrontal cortex (dlPFC; BA 9), as well as across primary and associative somatosensory cortices. Positive connectivity was also observed with the amygdala, in agreement with Ely et al. (2017) and supported by the amygdala's role in regulating innate and learned behaviors (56). While other previous studies conducted at 3T (55) and 7T (23) reported no significant connectivity between the human habenula and amygdala, we note that the work of Ely et al. (2017) and the present study included a more robust sample size. Finally, negative connectivity was observed in a few regions of the default mode network, most prominently with the anterior cingulate cortex. Overall, the patterns of resting state connectivity identified in the current study are consistent with the most recent habenular literature. Extending this, functional decoding highlighted the habenula's involvement in reward and aversion processes and indicated associations with multiple stimulus types, suggesting that the habenula may serve as a hub for the integration of aversive and appetitive sensory signals. In line with this, animal-based studies have shown that the lateral habenula supports a bottom-up multimodal sensory pathway and produces concurrent emotional effects and motor responses that allow animals to efficiently avoid unfavorable environments (57). In humans, the habenula is speculated to play a role in low-level processing of sensory stimuli by receiving early, low-latency information from multiple sources that rapidly drops off as information propagates through higher sensory processing areas (22). While our decoding results align with findings from Torrisi and Ely, they also provide important additional insights into the sensory processing functions of the habenula.

Among autistic individuals, there is an understanding that atypical sensory perception is a fundamental characteristic and core diagnostic symptom of the disorder (35). Autism-related neuroimaging research has extended this with evidence indicating that atypical sensory traits are rooted in low-level processing across sensory modalities and during multimodal perception in primary sensory cortices (58). Our results revealed atypical habenula hyperconnectivity in autism with the rMTG and bilateral STG. Structural differences in these regions, such as increased gray matter volume, have been documented in autism (59). These regions within the primary and associative auditory cortices are essential for sound processing and speech perception (60). Within the language network, the lateral temporal cortex and Wernicke's area are critical for language comprehension and semantic processing (61). While these areas have largely been linked to auditory related processing, previous studies have shown these bilateral STG regions participate low-level, multi-sensory processing, such as the integration of auditory and visual signals (62,63), as well as temporal discrimination of tactile stimuli (64) and processing of olfactory information (65). Our functional decoding results provide further evidence that habenula hyperconnectivity in autism is implicated in multimodal sensory processing, with an emphasis on auditory and visual processes. Given these findings, we posit that habenula connectivity alterations with low-level sensory processing regions may contribute to atypical sensory processing experienced among autistic individuals.

Age-Related Variability in Habenula Connectivity

Throughout childhood and adolescence, the brain undergoes a multifaceted and dynamic maturation process, wherein alterations of the brain's development are hypothesized to contribute to autistic

behaviors. Although the reorganization of reward circuitry during adolescence is integral to human development (66), developmental alterations of the reward network in autism have only been studied in the striatum. Our results contribute to characterizing age-related variability of the reward network in autism by revealing significant age-related effects on habenula connectivity with the anterior cerebellum and associative visual cortex. Within these regions, habenula connectivity exhibited an altered age-related trajectory that increased from childhood to early adulthood (age 5-21 years) in autistic individuals but decreased for NTs, replicating the corticostriatal connectivity trajectory observed by Padmanabhan et al. (2017) Furthermore, the observed age-related alterations in habenula connectivity align with prior findings of atypical gray matter volume (GMV) developmental trajectories in autism (67). However, while Guo et al. (2021) reported a slightly stronger age-related effect on GMV within the associative visual cortex, our results identified the most pronounced habenula connectivity age effect with the cerebellum. Aligning with this, alterations in cerebellar connectivity have been hypothesized to be a key component of autism (68), with the suggestion that alterations in cerebellar activity during sensitive developmental periods may lead to decreased cognitive flexibility and social dysfunction (69–71). Functional decoding of habenular age-related effects observed in the anterior cerebellum and associative visual cortex revealed terms related to processing pain and decision-making, suggesting that these alterations may reflect differences in the evaluation of potential risks when engaging in reward-seeking behavior. This is consistent with the role of the lateral habenula, which is activated by primary aversive stimuli, cues predicting imminent aversive events, unexpected reward omissions, and cues associated with the omission of an anticipated reward (72). Consistent with this, behavioral studies have demonstrated that while autistic youth may not perform differently in decision-making tasks, their choices are often driven by a motivation to avoid potential losses rather than to seek possible rewards (73) Therefore, considering the habenula's inhibitory role, it is possible age-related variability in habenula connectivity in autism could underlie these behaviors.

Associations Between Habenula Connectivity and Autism Symptomatology

A central challenge in autism research has been to link the pathophysiology of autism with its complex and heterogeneous behaviors. Here, we provide evidence of the habenula's involvement in seemingly disparate autistic behaviors. As hypothesized, we observed an association with SM in autistic individuals compared to NTs, but no association with SC. In agreement with previous evidence of the habenula guiding animal social behaviors (74,75), our findings suggest the human habenula is more closely associated with the motivation to engage in social interactions, rather than the reciprocal and expressive aspects of SC. In indicating that SM and SC may be distinct constructs with separate relationships to reward-related processing in autism, our results also challenge SM theory (8), which states that all social behaviors are derived from SM. In addition, we found an association between habenula connectivity and DLS among autistic individuals compared to NTs, in agreement with our hypotheses. Given the habenula's well-known role in adaptive behaviors, such as modulating responses to changing environments (76) and to aversive and rewarding stimuli (76), it follows that habenula connectivity would be associated with DLS, a key measure of adaptive behavior that encompasses everyday tasks essential for independent living. Our study represents the first to link the habenula with DLS; notably, this was observed as a main effect for both autistic individuals and NTs. Finally, we also identified an association between habenula connectivity and EF among autistic individuals. Although an unexpected finding, we note that EF, which spans working memory, flexible thinking, and self-control, has emerged as a critical predictor of adaptive behavior in autism (77). It should be underscored that the measure of EF used in the current study included emotion regulation, a key trait of adaptive functioning, which may have

contributed to this finding. Taken together, these results emphasize 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 (78).

Limitations and Future Directions

Several key limitations of the present study should be noted. First, due to the small size of the habenula, we did not attempt to parcellate the habenula ROI into medial and lateral portions. Although the lateral and medial habenular systems are largely separate from each other (79), a smaller ROI would likely have led to overlap between the two regions, thus skewing any meaningful results that could have been made about their distinct functions. Second, our analysis of age-related variability relied on cross-sectional data from individuals at different developmental stages. While these findings provide valuable insights into connectivity across adolescence, a longitudinal design would offer a more robust understanding of how these neural trajectories evolve over time in autism. Third, as the ABIDE dataset is a multisite consortia, there was variability in scanning protocols, which contributed to discrepancies in collected demographic information and limited availability of phenotypic data. Particularly of interest, data collection of the groups were imbalanced with some sites scanning more NT than autistic individuals. While we accounted for site-related variance in our analysis, future studies should aim for more controlled data collection to minimize these confounds. Lastly, although our results linking habenula connectivity with autism symptomatology are noteworthy, they did not survive multiple comparison correction. While this does not invalidate our findings, it does highlight the need for replication in datasets with larger phenotypic data sample sizes are needed to ensure the robustness of these associations. Despite these limitations, our results remain interesting and highlight the potential importance in targeting the dopaminergic pathways in autism as they may provide a more unified approach to addressing disruptions in motivated and adaptive functioning. Future studies should incorporate repeated measures within individuals to track habenula connectivity changes across development and further investigate FC alterations of other dopaminergic reward regions.

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/. Additional thanks to the FIU Instructional and Research Computing Center (IRCC, http://ircc.fiu.edu) for providing the HPC and computing resources that contributed to the research results reported within this paper. Results were presented at the Florida Consortium on the Neurobiology of Cognition Annual Meeting, Miami, FL, April 2024 and the University of Miami's 34th Annual Neuroscience Research Day, Miami, FL, December 2024.

Data and Code Availability

The neuroimaging and phenotypic data included in this project can be found in the publicly available ABIDE dataset (https://fcon_1000.projects.nitrc.org/indi/abide/). The code for the analyses conducted in this project can be found on Github (https://github.com/NBCLab/abide-analysis).

Author Contributions

ARL, CLH conceived and designed the project. CLH, JAP, LMG, FA and FS preprocessed data. CLH, JAP, LMG analyzed data, and CLH, ARL, KEC interpreted data. JAP, KLB, MCR, DDS contributed scripts and pipelines. CLH, ARL wrote the paper and all authors contributed to the revisions and approved the final version.

Disclosures

The authors declare no competing interests.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Fifth Edition. Text revision; 2000.

2. Taboas A, Doepke K, Zimmerman C. Preferences for identity-first versus person-first language in a US sample of autism stakeholders. Autism. 2023 Feb;27(2):565–70.

3. Bury SM, Jellett R, Spoor JR, Hedley D. "It Defines Who I Am" or "It's Something I Have": What Language Do [Autistic] Australian Adults [on the Autism Spectrum] Prefer? J Autism Dev Disord. 2023 Feb;53(2):677–87.

4. Kenny L, Hattersley C, Molins B, Buckley C, Povey C, Pellicano E. Which terms should be used to describe autism? Perspectives from the UK autism community. Autism. 2016 May;20(4):442–62.

5. Steinhausen H -C., Mohr Jensen C, Lauritsen MB. A systematic review and meta-analysis of the long-term overall outcome of autism spectrum disorders in adolescence and adulthood. Acta Psychiatr Scand. 2016 Jun;133(6):445–52.

6. Gentil-Gutiérrez A, Santamaría-Peláez M, Mínguez-Mínguez LA, Fernández-Solana J, González-Bernal JJ, González-Santos J, et al. Executive Functions in Children and Adolescents with Autism Spectrum Disorder in Family and School Environment. IJERPH. 2022 Jun 26;19(13):7834.

7. Baker E, Stavropoulos KKM, Baker BL, Blacher J. Daily living skills in adolescents with autism spectrum disorder: Implications for intervention and independence. Res Autism Spectr Disord. 2021 May;83:101761.

8. Chevallier C, Kohls G, Troiani V, Brodkin ES, Schultz RT. The social motivation theory of autism. Trends Cogn Sci. 2012 Apr;16(4):231–9.

9. Sato W, Uono S. The atypical social brain network in autism: advances in structural and functional MRI studies. Curr Opin Neurol. 2019 Aug;32(4):617–21.

10. Dichter G, Adolphs R. Reward processing in autism: a thematic series. J Neurodevelop Disord. 2012 Dec;4(1):20, 1866-1955-4–20.

11. Tschida JE, Yerys BE. A Systematic Review of the Positive Valence System in Autism Spectrum Disorder. Neuropsychol Rev. 2021 Mar;31(1):58–88.

12. Haber SN, Knutson B. The Reward Circuit: Linking Primate Anatomy and Human Imaging. Neuropsychopharmacol. 2010 Jan;35(1):4–26.

13. McCutcheon JE, Ebner SR, Loriaux AL, Roitman MF. Encoding of Aversion by Dopamine and the Nucleus Accumbens. Front Neurosci [Internet]. 2012 [cited 2024 Sep 19];6. Available from: http://journal.frontiersin.org/article/10.3389/fnins.2012.00137/abstract

14. Fareri DS, Martin LN, Delgado MR. Reward-related processing in the human brain: Developmental considerations. Dev Psychopathol. 2008;20(4):1191–211.

15. Fuccillo MV. Striatal Circuits as a Common Node for Autism Pathophysiology. Front Neurosci [Internet]. 2016 Feb 9 [cited 2024 Sep 19];10. Available from: http://journal.frontiersin.org/Article/10.3389/fnins.2016.00027/abstract

16. Soghomonian JJ. The cortico-striatal circuitry in autism-spectrum disorders: a balancing act. Front Cell Neurosci. 2024 Jan 11;17:1329095.

17. Evans MM, Kim J, Abel T, Nickl-Jockschat T, Stevens HE. Developmental Disruptions of the Dorsal Striatum in Autism Spectrum Disorder. Biol Psychiatry. 2024 Jan 15;95(2):102–11.

18. Hikosaka O. The habenula: from stress evasion to value-based decision-making. Nat Rev Neurosci. 2010 Jul;11(7):503–13.

19. Matsumoto M, Hikosaka O. Lateral habenula as a source of negative reward signals in dopamine neurons. Nature. 2007 Jun 28;447(7148):1111–5.

20. Darcq E, Koebel P, Del Boca C, Pannetier S, Kirstetter AS, Garnier JM, et al. RSK2 signaling in brain habenula contributes to place aversion learning. Learn Mem. 2011 Sep;18(9):574–8.

21. Salas. BOLD responses to negative reward prediction errors in human habenula. Front Hum Neurosci [Internet]. 2010 [cited 2024 Sep 19]; Available from: http://journal.frontiersin.org/article/10.3389/fnhum.2010.00036/abstract

22. Ely BA, Stern ER, Kim JW, Gabbay V, Xu J. Detailed mapping of human habenula resting-state functional connectivity. Neuroimage. 2019 Oct 15;200:621–34.

23. Torrisi S, Nord CL, Balderston NL, Roiser JP, Grillon C, Ernst M. Resting state connectivity of the human habenula at ultra-high field. Neuroimage. 2017 Feb 15;147:872–9.

24. Arfuso M, Salas R, Castellanos FX, Krain Roy A. Evidence of Altered Habenular Intrinsic Functional Connectivity in Pediatric ADHD. J Atten Disord. 2021 Mar;25(5):749–57.

25. Schmidt FM, Schindler S, Adamidis M, Strauß M, Tränkner A, Trampel R, et al. Habenula volume increases with disease severity in unmedicated major depressive disorder as revealed by 7T MRI. Eur Arch Psychiatry Clin Neurosci. 2017 Mar;267(2):107–15.

26. Zhang L, Wang H, Luan S, Yang S, Wang Z, Wang J, et al. Altered Volume and Functional Connectivity of the Habenula in Schizophrenia. Front Hum Neurosci. 2017;11:636.

27. Germann J, Gouveia FV, Brentani H, Bedford SA, Tullo S, Chakravarty MM, et al. Involvement of the habenula in the pathophysiology of autism spectrum disorder. Sci Rep. 2021 Oct 27;11(1):21168.

28. Di Martino A, O'Connor D, Chen B, Alaerts K, Anderson JS, Assaf M, et al. Enhancing studies of the connectome in autism using the autism brain imaging data exchange II. Sci Data. 2017 Mar 14;4:170010.

29. Di Martino A, Yan CG, Li Q, Denio E, Castellanos FX, Alaerts K, et al. The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. Mol Psychiatry. 2014 Jun;19(6):659–67.

30. Estes A, Shaw DWW, Sparks BF, Friedman S, Giedd JN, Dawson G, et al. Basal ganglia morphometry and repetitive behavior in young children with autism spectrum disorder. Autism Research. 2011 Jun;4(3):212–20.

31. Qiu A, Adler M, Crocetti D, Miller MI, Mostofsky SH. Basal Ganglia Shapes Predict Social, Communication, and Motor Dysfunctions in Boys With Autism Spectrum Disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 2010 Jun;49(6):539-551.e4.

32. Di Martino A, Kelly C, Grzadzinski R, Zuo XN, Mennes M, Mairena MA, et al. Aberrant striatal functional connectivity in children with autism. Biol Psychiatry. 2011 May 1;69(9):847–56.

33. Padmanabhan A, Lynn A, Foran W, Luna B, O'Hearn K. Age related changes in striatal resting state functional connectivity in autism. Front Hum Neurosci. 2013;7:814.

34. DSM IV [Internet]. 1000 Wilson Boulevard, Arlington, VA 22209: American Psychiatric Association; 1994 [cited 2024 Aug 20]. Available from: https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890420614.dsm-iv

35. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders [Internet]. Fifth Edition. American Psychiatric Association; 2013 [cited 2024 Aug 20]. Available from: https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596

36. Constantino JN, Gruber CP. Social Responsiveness Scale - Second Edition (SRS-2). Second Edition. Torrance, CA: Western Psychological Services; 2012.

37. Gioia GA, Isquith PK, Guy SC, Kenworthy L. TEST REVIEW Behavior Rating Inventory of Executive Function. Child Neuropsychology. 2000 Sep;6(3):235–8.

38. Sparrow SS, Balla DA, Cicchetti DV, Doll EA. Vineland-II, Vineland adaptive behavior scales : survey forms manual. 2nd edition. Minneapolis, MN, Circle Pines, Minn.: NCS Pearson, Inc. ; AGS Publishing; 2005.

39. Esteban O, Ciric R, Finc K, Blair RW, Markiewicz CJ, Moodie CA, et al. Analysis of task-based functional MRI data preprocessed with fMRIPrep. Nat Protoc. 2020 Jul;15(7):2186–202.

40. Esteban O, Markiewicz CJ, Blair RW, Moodie CA, Isik AI, Erramuzpe A, et al. fMRIPrep: a robust preprocessing pipeline for functional MRI. Nat Methods. 2019;16(1):111–6.

41. Hagler DJ, Hatton S, Cornejo MD, Makowski C, Fair DA, Dick AS, et al. Image processing and analysis methods for the Adolescent Brain Cognitive Development Study. Neuroimage. 2019 15;202:116091.

42. Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J Comput Assist Tomogr. 1994 Apr;18(2):192–205.

43. Evans AC, Kamber M, Collins DL, MacDonald D. An MRI-Based Probabilistic Atlas of Neuroanatomy. In: Shorvon SD, Fish DR, Andermann F, Bydder GM, Stefan H, editors. Magnetic Resonance Scanning and Epilepsy [Internet]. Boston, MA: Springer US; 1994 [cited 2022 Mar 13]. p. 263–74. Available from: http://link.springer.com/10.1007/978-1-4615-2546-2_48

44. Lawson RP, Drevets WC, Roiser JP. Defining the habenula in human neuroimaging studies. Neuroimage. 2013 Jan 1;64:722–7.

45. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res. 1996 Jun;29(3):162–73.

46. Chen G, Pine DS, Brotman MA, Smith AR, Cox RW, Haller SP. Trial and error: A hierarchical modeling approach to test-retest reliability. NeuroImage. 2021 Dec;245:118647.

47. Chen G, Saad ZS, Britton JC, Pine DS, Cox RW. Linear mixed-effects modeling approach to FMRI group analysis. NeuroImage. 2013 Jun;73:176–90.

48. Edde M, Leroux G, Altena E, Chanraud S. Functional brain connectivity changes across the human life span: From fetal development to old age. J of Neuroscience Research. 2021 Jan;99(1):236–62.

49. Rubin TN, Koyejo O, Gorgolewski KJ, Jones MN, Poldrack RA, Yarkoni T. Decoding brain activity using a large-scale probabilistic functional-anatomical atlas of human cognition. PLOS Computational Biology. 2017 Oct 23;13(10):e1005649.

50. Peraza JA, Salo T, Riedel MC, Bottenhorn KL, Poline JB, Dockès J, et al. Methods for decoding cortical gradients of functional connectivity. Imaging Neuroscience [Internet]. 2024 Jan 16 [cited 2024 Aug 23]; Available from: https://direct.mit.edu/imag/article/doi/10.1162/imag_a_00081/119100/Methods-for-decoding-cortical-gradients-of

51. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. Large-scale automated synthesis of human functional neuroimaging data. Nature Methods. 2011 Aug;8(8):665–70.

52. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society: Series B (Methodological). 1995;57(1):289–300.

53. Hennigan K, D'Ardenne K, McClure SM. Distinct midbrain and habenula pathways are involved in processing aversive events in humans. J Neurosci. 2015 Jan 7;35(1):198–208.

54. Hampson M, Driesen N, Roth JK, Gore JC, Constable RT. Functional connectivity between task-positive and task-negative brain areas and its relation to working memory performance. Magn Reson Imaging. 2010 Oct;28(8):1051–7.

55. Ely BA, Xu J, Goodman WK, Lapidus KA, Gabbay V, Stern ER. Resting-state functional connectivity of the human habenula in healthy individuals: Associations with subclinical depression. Hum Brain Mapp. 2016 Jul;37(7):2369–84.

56. Isosaka T, Matsuo T, Yamaguchi T, Funabiki K, Nakanishi S, Kobayakawa R, et al. Htr2a-Expressing Cells in the Central Amygdala Control the Hierarchy between Innate and Learned Fear. Cell. 2015 Nov;163(5):1153–64.

57. Zhang GW, Shen L, Zhong W, Xiong Y, Zhang LI, Tao HW. Transforming Sensory Cues into Aversive Emotion via Septal-Habenular Pathway. Neuron. 2018 Sep;99(5):1016-1028.e5.

58. Robertson CE, Baron-Cohen S. Sensory perception in autism. Nat Rev Neurosci. 2017 Nov;18(11):671–84.

59. Yang X, Si T, Gong Q, Qiu L, Jia Z, Zhou M, et al. Brain gray matter alterations and associated demographic profiles in adults with autism spectrum disorder: A meta-analysis of voxel-based morphometry studies. Aust N Z J Psychiatry. 2016 Aug 1;50(8):741–53.

60. Hullett PW, Leonard MK, Gorno-Tempini ML, Mandelli ML, Chang EF. Parallel Encoding of Speech in Human Frontal and Temporal Lobes [Internet]. 2024 [cited 2024 Nov 5]. Available from: http://biorxiv.org/lookup/doi/10.1101/2024.03.19.585648

61. Price CJ. A review and synthesis of the first 20years of PET and fMRI studies of heard speech, spoken language and reading. NeuroImage. 2012 Aug;62(2):816–47.

62. Coull JT, Vidal F, Nazarian B, Macar F. Functional Anatomy of the Attentional Modulation of Time

Estimation. Science. 2004 Mar 5;303(5663):1506–8.

63. Lewis PA, Miall RC. Brain activation patterns during measurement of sub- and supra-second intervals. Neuropsychologia. 2003 Jan;41(12):1583–92.

64. Bolognini N, Papagno C, Moroni D, Maravita A. Tactile Temporal Processing in the Auditory Cortex. Journal of Cognitive Neuroscience. 2010 Jun 1;22(6):1201–11.

65. Lascano AM, Hummel T, Lacroix JS, Landis BN, Michel CM. Spatio–temporal dynamics of olfactory processing in the human brain: an event-related source imaging study. Neuroscience. 2010 May;167(3):700–8.

66. Walker DM, Bell MR, Flores C, Gulley JM, Willing J, Paul MJ. Adolescence and Reward: Making Sense of Neural and Behavioral Changes Amid the Chaos. J Neurosci. 2017 Nov 8;37(45):10855–66.

67. Guo X, Duan X, Suckling J, Wang J, Kang X, Chen H, et al. Mapping Progressive Gray Matter Alterations in Early Childhood Autistic Brain. Cerebral Cortex. 2021 Feb 5;31(3):1500–10.

68. Wang SSH, Kloth AD, Badura A. The Cerebellum, Sensitive Periods, and Autism. Neuron. 2014 Aug;83(3):518–32.

69. Badura A, Verpeut JL, Metzger JW, Pereira TD, Pisano TJ, Deverett B, et al. Normal cognitive and social development require posterior cerebellar activity. eLife. 2018 Sep 20;7:e36401.

70. Gibson JM, Howland CP, Ren C, Howland C, Vernino A, Tsai PT. A Critical Period for Development of Cerebellar-Mediated Autism-Relevant Social Behavior. J Neurosci. 2022 Mar 30;42(13):2804–23.

71. Verpeut JL, Bergeler S, Kislin M, William Townes F, Klibaite U, Dhanerawala ZM, et al. Cerebellar contributions to a brainwide network for flexible behavior in mice. Commun Biol. 2023 Jun 5;6(1):605.

72. Sosa R, Mata-Luévanos J, Buenrostro-Jáuregui M. The Role of the Lateral Habenula in Inhibitory Learning from Reward Omission. eNeuro. 2021 May;8(3):ENEURO.0016-21.2021.

73. South M, Chamberlain PD, Wigham S, Newton T, Le Couteur A, McConachie H, et al. Enhanced decision making and risk avoidance in high-functioning autism spectrum disorder. Neuropsychology. 2014;28(2):222–8.

74. Ogawa S, Parhar IS. Role of Habenula in Social and Reproductive Behaviors in Fish: Comparison With Mammals. Front Behav Neurosci. 2022 Feb 10;15:818782.

75. van Kerkhof LWM, Damsteegt R, Trezza V, Voorn P, Vanderschuren LJMJ. Functional integrity of the habenula is necessary for social play behaviour in rats. Eur J Neurosci. 2013 Nov;38(10):3465–75.

76. Mizumori SJY, Baker PM. The Lateral Habenula and Adaptive Behaviors. Trends in Neurosciences. 2017 Aug;40(8):481–93.

77. Pugliese CE, Anthony LG, Strang JF, Dudley K, Wallace GL, Naiman DQ, et al. Longitudinal Examination of Adaptive Behavior in Autism Spectrum Disorders: Influence of Executive Function. J Autism Dev Disord. 2016 Feb;46(2):467–77.

78. Saulnier CA, Klaiman C, McQueen E. Adaptive Behavior Profiles in Autism Spectrum Disorder. Curr Psychiatry Rep. 2022 Dec;24(12):749–56.

79. Ables JL, Park K, Ibañez–Tallon I. Understanding the habenula: A major node in circuits regulating emotion and motivation. Pharmacological Research. 2023 Apr;190:106734.