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Neuroimaging Procedures from High Risk Cohort

The HRC project aimed to evaluate 750 children using Magnetic Resonance Imaging (MRI). This number was set in accordance to the project budget. Therefore, the procedure involved inviting the first set of subjects who had successfully completed the household interview, based on the dates in which they were enrolled in the project. We screened the first 1159 subjects who completed the parent- and self-report at baseline; 136 (11.5%) refused to participate in a phone interview for MRI eligibility, and 59 (5.0%) had reported using braces (n=19) or screened positive for medical restriction (n=40). Application of these rules led us to evaluate 964 eligible subjects. From these 964, 876 (90.9%) met criteria for scanning and were scheduled, 38 (3.9%) could not be contacted to schedule the scans in the allotted time, and 50 (5.2%) refused to attend to the MRI session. Finally, we acquired T1 and Resting-state fMRI data on 741 (76.9%) participants. No statistically-significant differences emerged for age (p=.634), sex (p=.391), site (p=.365), and socioeconomic status (p=.686) among eligible subjects who did and did not provide MRI data. Mother´s level of education was higher in subjects who provided MRI data (p=.047).

Before scanning, we trained participants to minimize head movement by desensitizing them to enclosed spaces and scanner noise in a simulated scanning environment. From 741 subjects attending the MRI sessions, data were excluded for 86 subjects. These subjects included 9 (1.2%) with missing clinical data, 38 (5.1) who aborted the scan session, and 39 (5.3%) whose

data contained artifacts or failed to pass quality-control procedures for other reasons (5.3%). Table S1a compares characteristics between the 86 (11.6%) excluded subjects and the remaining 655 (88.4%). Included subjects tended to be older (p=.063) and scanned at the Porto Alegre site. Table S1b compares baseline characteristics in subjects who did (n=585) or did not (n=52) complete the follow-up assessment. A higher proportion of subjects from the Porto Alegre site completed the follow-up (chi-square= 5.07; p=.024), but there were no other differences between these two groups.

TABLE S1. Demographic and Clinical Characteristics of the HRC Study Participants: Exclusions and Losses at Follow-Up

Table S1a. Demographic and clinical characteristics of the HRC study participants: exclusions at MRI

	Excluded: Failed to complete T1 and/or resting-state MRI (n=86) [a]	Successfully Completed T1 and resting-state MRI (n=655)	p
	n (%)	n (%)	
Sociodemographic at baseline			
Sex, F/M	31/49 (38.8/61.3)	311/344 (47.5/52.5)	.139
Site, Porto Alegre City/São Paulo City	25/55 (31.3/68.8)	342/313 (52.2/47.8)	<.001
Age at MRI Scan, mean (SD), y	10.2 (1.8)	10.7 (1.9)	.063
Maternal education – completed high school, Y/N [b]	29/49 (62.8/37.2)	283/363 (43.8/56.2)	.264
Socioeconomic score, mean (SD)	19.6 (5.6)	20.1 (4.5)	.173
Clinical features at baseline			
Any anxiety disorder, Y/N	9/71 (11.3/88.8)	99/556 (15.1/84.9)	.357
ADHD, Y/N	9/71 (11.3/88.8)	80/575 (12.2/87.8)	.803
Depressive Disorder, Y/N	2/78 (2.5/97.5)	28/627 (4.3/95.7)	.449

Table S1b. Demographic and clinical characteristics of the HRC study participants: exclusions due to loss at follow-up

	Excluded: Loss at Follow-up (n=52)	Successfully Completed Household Follow-up (n=585)	p
	n (%)	n (%)	
Sociodemographic at baseline			
Sex, F/M	24/28 (46.2/53.8)	278/307 (47.5/52.5)	.850
Site, Porto Alegre City/São Paulo City	19/33 (36.5/63.5)	309/276 (52.8/47.2)	.024
Age at MRI Scan, mean (SD), y	10.5 (2.1)	10.7 (1.9)	.425
Maternal education – completed high school, Y/N [c]	23/27 (46.0/54.0)	252/328 (46.4/56.6)	.727
Socioeconomic score, mean (SD)	19.8 (4.3)	20.2 (4. 6)	.710
Clinical features at baseline			
Any anxiety disorder, Y/N	3/49 (5.8/94.2)	88/497 (15.0/85.0)	.067
ADHD, Y/N	6/46 (11.5/88.5)	66/519 (11.3/88.7)	.955
Depressive Disorder, Y/N	3/49 (5.8/94.2)	66/561 (4.1/95.9)	.568
Movement parameters			
FD, mean (SD), mm (Pre-Scrubbing)	0.11 (0.10)	0.16 (0.24)	.075
Number of scrubbed volumes, mean (SD)	10.17 (17.3)	17.5 (27.7)	.111
FD, mean (SD), mm (Pos-Scrubbing)	0.08 (0.04)	0.08 (0.04)	.893

[a] Numbers vary due to missing data; [b] missing for 17 subjects; [c] missing for 7 subjects; chi-square for categorical variables; Mann-Whitney Test for scale variables not normally distributed. Abbreviations: F/M, female/male; SD, standard deviation; FD, frame displacement; ADHD, attention-deficit/hyperactivity disorder; FUP, follow-up; Y/N, yes/no.

TABLE S2. Regions of Interest of the Reward Network – Montreal Neurological Institute (MNI) Coordinates

ROI	X	Y	Z
Left Ventral Striatum (L VS)	–12	12	–6
Right Ventral Striatum (R VS)	12	10	–6
Ventromedial Prefrontal Cortex (VmPFC)	2	46	–8
Left Anterior Insula (L Ins)	–30	22	–6
Right Anterior Insula (R Ins)	32	20	–6
Posterior Cingulate (PCC)	–4	–30	36
Brainstem - Ventral Tegmental Area (VTA)	–2	–22	–12
Anterior Cingulate (ACC)	–2	28	28
Pre-Supplementary motor area (Pre-SMA)	–2	16	46
Left Thalamus (L Th)	–6	–8	6
Right Thalamus (R Th)	6	–8	6

TABLE S3. Discovery and Replication of Correlations Between Regions of Interest of the Reward Network

Edge (node-node)	Site 1 Discovery Bonferroni Corrected (p<.00091)		Site 2 Replication Uncorrected p (p<.05)	
	n = 328		n = 309	
	t	*p*	t	*p*
ACC-VTA	11.22	<.00001	13.52	<.00001
ACC-L Ins	28.92	<.00001	31.13	<.00001
ACC-L VS	15.75	<.00001	17.50	<.00001
ACCL Th	11.67	<.00001	13.00	<.00001
ACC-PCC	14.23	<.00001	13.79	<.00001
ACC-PreSMA	33.25	<.00001	30.63	<.00001
ACC-R Ins	28.11	<.00001	27.45	<.00001
ACC-R VS	11.31	<.00001	16.45	<.00001
ACC-R Th	8.98	<.00001	12.52	<.00001
ACC-VMPFC	3.91	.00011	–0.57	.57176
VTA-L Ins	16.99	<.00001	19.81	<.00001
VTA-L VS	14.90	<.00001	19.64	<.00001
VTA-L Th	1.60	.11086	12.31	<.00001
VTA-PCC	7.63	<.00001	6.66	<.00001
VTA-PreSMA	14.46	<.00001	14.64	<.00001
VTA-R Ins	17.50	<.00001	19.83	<.00001
VTA-R VS	12.85	<.00001	20.06	<.00001
VTA-R Th	–.01	.99193	13.03	<.00001
VTA-VMPFC	5.69	<.00001	–0.84	.40176
L Ins-L VS	22.56	<.00001	28.61	<.00001
L Ins-L Th	4.53	<.00001	13.85	<.00001
L Ins-PCC	4.03	.00007	–0.34	.73152
L Ins-PreSMA	34.04	<.00001	33.10	<.00001
L Ins-R Ins	43.98	<.00001	55.56	<.00001
L Ins-R VS	17.41	<.00001	27.16	<.00001
L Ins-R Th	1.21	.22668	10.72	<.00001
L Ins-VMPFC	9.08	<.00001	6.26	<.00001
L VS-L Th	6.41	<.00001	18.98	<.00001
L VS-PCC	8.13	<.00001	4.22	.00003
L VS-PreSMA	13.93	<.00001	18.21	<.00001
L VS-R Ins	19.28	<.00001	25.50	<.00001
L VS-R VS	30.66	<.00001	47.85	<.00001
L VS-R Th	4.63	<.00001	18.37	<.00001
L VS-VMPFC	15.49	<.00001	12.16	<.00001
L Th-R Th	43.58	<.00001	50.74	<.00001
PCC-L Th	–.94	.34719	6.07	<.00001
PCC-PreSMA	1.30	.19347	–2.45	.01474
PCC-R Ins	1.16	.24575	–0.39	.69931
PCC-R VS	3.08	.00224	3.67	.00028
PCC-R Th	–3.38	.00081	2.96	.00329
PCC-VMPFC	15.61	<.00001	12.16	<.00001
PreSMA-L Th	11.77	<.00001	14.38	<.00001
PreSMA-R Ins	26.64	<.00001	28.48	<.00001
PreSMA-R VS	9.93	<.00001	15.18	<.00001
PreSMA-R Th	8.11	<.00001	11.66	<.00001
PreSMA-VMPFC	–8.55	<.00001	–12.23	<.00001
R Ins-L Th	6.06	<.00001	8.33	<.00001
R Ins-R VS	20.44	<.00001	29.40	<.00001
R Ins-R Th	7.36	<.00001	12.40	<.00001
R Ins-VMPFC	6.62	<.00001	6.29	<.00001

R VS-L Th	6.63	<.00001	17.46	<.00001
R VS-R Th	7.39	<.00001	19.45	<.00001
R VS-VMPFC	12.22	<.00001	13.10	<.00001
VMPFC-L Th	–4.93	<.00001	0.87	.38514
VMPFC-R Th	–6.05	<.00001	–0.18	.85705

Note: For abbreviations, see Table S2.

TABLE S4. Logistic Regression Model. Depressive Disorder by Clinical Rating at 3-Year Follow-Up and Node Strength of the Left Ventral Striatum Within the Reward Network Excluding Subjects With More Than 30 Excluded Volumes After Scrubbing Procedure

Variables in the model	Outcome: MDD at Follow-up (Exposed. n=426; Event. n=40)		
	OR	95% CI	p
Left ventral striatum iFC	1.94	1.20 to 3.14	.007
Depressive disorder at baseline	13.83	4.33 to 44.18	<.001
ADHD at baseline	1.91	.71 to 5.19	.202
Any anxiety at baseline	1.59	.63 to 4.00	.329
Age at MRI	1.53	1.24 to 1.90	<.001
Sex (female)	1.92	.92 to 4.02	.082
Site	.95	.42 to 2.16	.903
Number of Scrubbed Volumes[a]	1.00	.95 to 1.05	.901

[a] Movement parameter. Abbreviations: MDD. major depressive disorder; OR. odds ratio; 95% CI. 95% confidence interval; ADHD. attention-deficit/hyperactivity disorder; MRI. magnetic resonance imaging.

TABLE S5. Left Ventral Striatum Node Strength as a Predictor for Common Adolescent Psychiatric Outcomes

Table S5a. Logistic regression model: any anxiety by clinician rating at 3-year follow-up predicted by left ventral striatum node strength at baseline

	Outcome: any anxiety at follow-up (Exposed. n=500; Event. n=85)		
Variables in the model	OR	95% CI	p
Left ventral striatum node strength	.77	.56 to 1.07	.119
Depressive disorder at baseline	1.86	.70 to 4.91	.212
ADHD at baseline	1.18	.57 to 2.41	.659
Any anxiety at baseline	2.48	1.38 to 4.43	.002
Age at MRI	.98	.86 to 1.11	.718
Sex (female)	1.60	.99 to 2.57	.053
Site	1.32	.78 to 2.22	.296
Number of Scrubbed Volumes[a]	1.00	.99 to 1.01	.814

Table S5b. Logistic regression model: ADHD by clinician rating at 3-year follow-up predicted by left ventral striatum node strength at baseline

	Outcome: ADHD at follow-up (Exposed. n=558; Event. n=27)		
Variables in the model	OR	95% CI	p
Left ventral striatum node strength	1.51	.96 to 2.38	.078
Depressive disorder at baseline	.77	.09 to 6.54	.810
ADHD at baseline	7.51	3.23 to 17.47	.000
Any anxiety at baseline	.60	.18 to 2.01	.408
Age at MRI	.87	.69 to 1.11	.265
Sex (female)	.77	.33 to 1.79	.542
Site	.53	.21 to 1.30	.165
Number of Scrubbed Volumes[a]	.99	.98 to 1.01	.501

Table S5c. Logistic regression model: any substance use by parent-report at 3-year follow-up predicted by left ventral striatum node strength at baseline

	Outcome: Parent-Report Any Substance Use[b] (Exposed. n=469; Event. n=101)		
Variables in the model	OR	95% CI	p
Left ventral striatum node strength	1.06	.78 to 1.43	.721
Depressive disorder at baseline	2.62	.97 to 7.09	.057
ADHD at baseline	1.52	.77 to 2.98	.229
Any anxiety at baseline	.97	.51 to 1.87	.936
Age at MRI	1.65	1.43 to 1.90	<.001
Sex (female)	1.15	.72 to 1.85	.552
Site	.48	.28 to.82	.007
Number of Scrubbed Volumes[a]	1.00	.99 to 1.01	.418

Table S5d. Logistic regression model: any substance use by self-report at 3-year follow-up predicted by left ventral striatum node strength at baseline

	Outcome: Self-Report Any Substance Use[c] (Exposed. n=296; Event. n=224)		
Variables in the model	OR	95% CI	p
Left ventral striatum node strength	.99	.76 to 1.30	.967
Depressive disorder at baseline	1.20	.39 to 3.68	.754
ADHD at baseline	.54	.27 to 1.05	.069
Any anxiety at baseline	1.15	.64 to 2.06	.640
Age at MRI	1.90	1.67 to 2.16	<.001
Sex (female)	1.03	.68 to 1.54	.903
Site	.59	.38 to .92	.020
Number of Scrubbed Volumes[a]	.99	.98 to 1.00	.111

[a] Movement parameter; [b] 15 missing values for this variable; [c] 117 missing values for this variable. Abbreviations: OR. odds ratio; 95% CI. 95% confidence interval; ADHD. attention-deficit/hyperactivity disorder; MRI. magnetic resonance imaging.