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Supplementary information

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Mapping histamine pathway networks in the human brain across cognition and psychiatric disorders

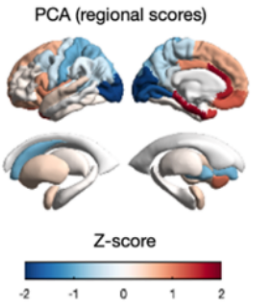
In the format provided by the authors and unedited

Supplementary

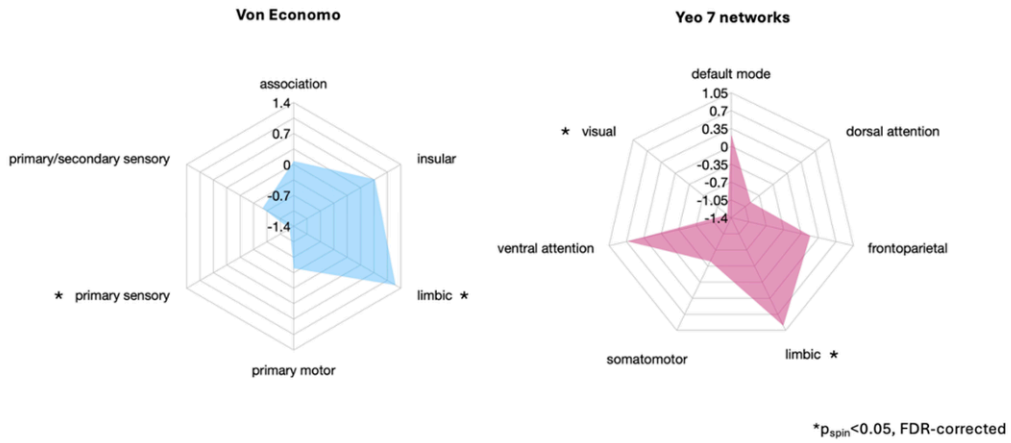
Supplementary Figure S1. Histamine pathway gene expression in the human brain (principal component analysis). Table on the left displays the loadings of each gene in the first principal component analysis. Map on the right displays regional variation of PCA1 score. Only parcels of the left brain are displayed. Warmer colours indicate higher PCA1 loadings (Z-score), while cooler colours represent lower loadings. Abbreviations: histamine receptor 1 (HRH1), histamine receptor 2 (HRH2), histamine receptor 3 (HRH3), histamine receptor 4 (HRH4), Histidine-N-methyltransferase (HNMT), L-histidine-Decarboxylase (HDC), Monoamine Oxidase-B (MAOB), Aldehyde Dehydrogenase enzyme 7 family member A1 (ALDH7A1).

Component Loadings

	Component 1	Uniqueness
HRH1	0.690	0.524
HRH2	-0.663	0.560
HRH3	0.408	0.834
HRH4	0.442	0.804
HNMT	0.701	0.509
HDC	0.688	0.527
MAOB	0.909	0.173
ALDH7A1	0.468	0.781



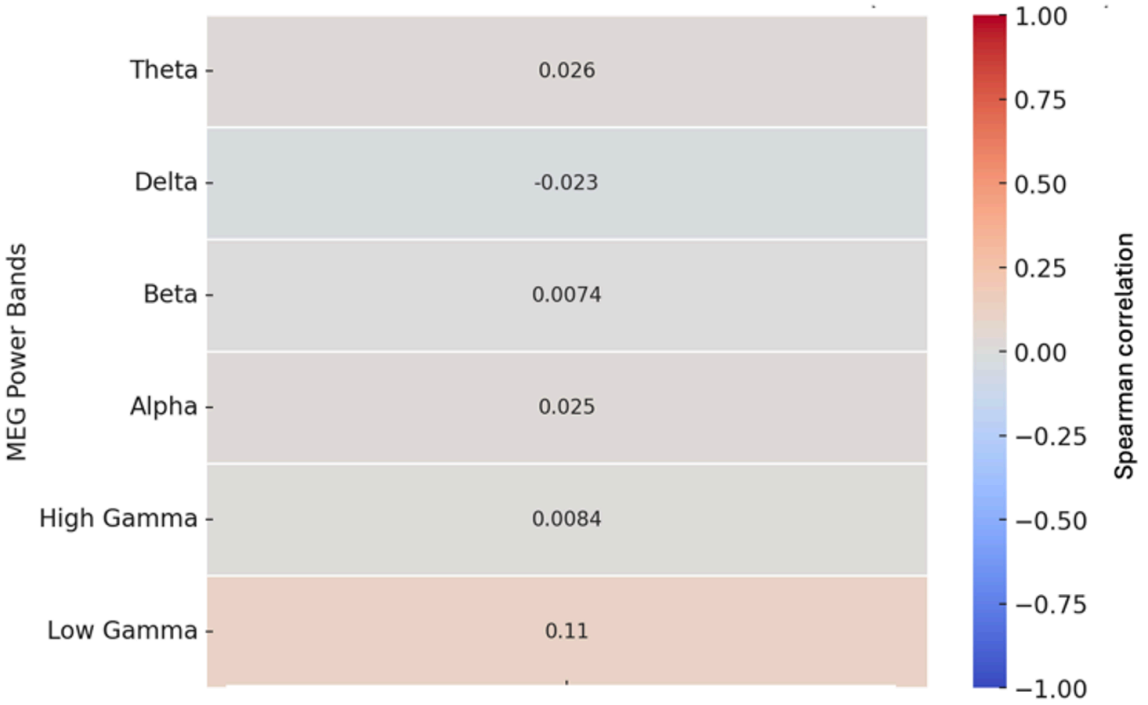
Supplementary Figure S2. Distribution of histamine pathway gene expression (first principal component) across large scale networks. Radar plots show the mean PCA1 loadings in large scale networks as defined by the *von Economo* classification of the cortex (left panel) and the 7 Yeo resting-state networks (right panel). Significance was assessed using permutation testing on spin rotations of the cortical map of PCA1 (two-sides).



Supplementary Table S1. Correlations between regional PCA1 scores and oscillatory neural dynamics in the living human brain. Spearman correlations with cortical maps of magnetoencephalography oscillatory power distribution provided by Hansen et al., 2022[99]. Significance was calculated using 1000 spin rotations of the PCA1 map.

Band frequency	Spearman Correlation	P_{spin}
Theta	0.026	0.871
Delta	-0.023	0.928
Beta	0.007	0.970
Alpha	0.025	0.895
High Gamma	0.008	0.955
Low Gamma	0.110	0.417

Supplementary Figure S3 - Correlations between regional PCA1 scores and the constitutive the oscillatory dynamics of the living human brain. The heatmap displays spearman correlations with cortical maps of magnetoencephalography oscillatory power distribution provided by Hansen et al., 2022[48]. Significance was assessed using permutation testing on spin rotations of the cortical map of PCA1 scores (two-sides). Colour bars depict spearman correlation coefficients



Supplementary Table S2 – Summary of the molecular imaging normative templates. Brief description of the tracer used, molecular target, gender and age characteristics of the healthy samples. Abbreviations: serotonin receptor 1a (5HT1a), serotonin receptor 1b (5HT1b), serotonin receptor 2a (5HT2a), serotonin receptor 4 (5HT4), serotonin receptor 6 (5HT6), serotonin transporter (5HTT), nicotinic receptor (A4B2), cannabinoid receptor 1 (CB1), dopamine receptor 1 (D1), dopamine receptor 2 (D2), dopamine transporter (DAT), histamine receptor (H3), Muscarinic receptor 1 (M1), Mu-opioid receptor (MOR), Kappa opioid receptor (KOR), Dynorphin opioid receptor (DOR), Noradrenaline transporter (NAT), Vesicular acetylcholine transporter (VAcht), GABA receptor A (GABAAR), metabotropic glutamate receptor 5 (mGluR5).

Neurotransmitter	Tracer	Description	N (males)	Age (years)	Primary reference(s)
Acetylcholine	[^{18}F]-FEOBV	PET tracer binding (SUVR) to VAChT (acetylcholine transporter)	18 (5)	66.8 +/- 6.8	Aghourian et al., 2017[101]

	[^{18}F]-FEOBV	PET tracer binding (SUVR) to VAChT (acetylcholine transporter)	5 (4)	68.3 +/- 3.1	Bedard et al., 2019[102]
	[^{18}F]-FEOBV	PET tracer binding (SUVR) to VAChT (acetylcholine transporter)	4 (3)	37 +/- 10.2	Hansen et al., 2022[99]
	[^{18}F]-Flubatine	PET tracer binding (Vt) to a4b2 (acetylcholine receptor)	30 (20)	33.50 +/- 10.71	Hillmer et al., 2016[103]
	[^{11}C]-LSN3172176	PET tracer binding (BPnd) to M1 (acetylcholine receptor)	24 (13)	40.45 +/- 11.71	Naganawa et al., 2020[104]
Dopamine	[^{11}C]-Raclopride	PET tracer binding (BPnd) to D2 (dopamine receptor)	7 (7)	24 +/- 2	Alakurtti et al., 2015[105]
	[^{11}C]-Raclopride	PET tracer binding (BPnd) to D2 (dopamine receptor)	156 (120)	27.76 +/- 9.44	Malen et al., 2022[106]
	[^{11}C]-FLB457	PET tracer binding (BPnd) to D2 (dopamine receptor)	37 (17)	48.36 +/- 16.93	Smith et al., 2017[107]
	[^{11}C]-FLB457	PET tracer binding (BPnd) to D2 (dopamine receptor)	55 (26)	32.45 +/- 9.69	Sandiego et al., 2015[108]
	[^{18}F]-Fallypride	PET tracer binding (BPnd) to D2 (dopamine receptor)	49 (16)	18.41 +/- 0.57	Jaworska et al., 2020[109]

	^{3}[H]-SCH23390	PET tracer binding (BPnd) to D1 (dopamine receptor)	13 (6)	33 +/- 13	Kaller et al., 2017[110]
	[^{18}F]-FEPE2i	PET tracer binding (BPnd) to DAT (dopamine transporter)	6 (6)	31.06 +/- 7.7	Sasaki et al., 2012[111]
	[^{18}F]-FPCIT	SPECT tracer binding (SUVR) to DAT (dopamine transporter)	174 (109)	61 +/- 11	Dukart et al., 2018[112]
Serotonin	[^{11}C]-Cumi101	PET tracer binding (Bmax) to 5-HT1a (serotonin receptor)	8 (3)	28.4 +/- 8.8	Beliveau et al., 2017[113]
	^{3}[H]-WAY100635	PET tracer binding (BPnd) to 5-HT1a (serotonin receptor)	35 (18)	26.3 +/- 5.2	Savli et al., 2012[114]
	[^{11}C]-AZ10419369	PET tracer binding (Bmax) to 5-HT1b (serotonin receptor)	36 (24)	27.8 +/- 6.9	Beliveau et al., 2017[113]
	[^{11}C]-P943	PET tracer binding (BPnd) to 5-HT1b (serotonin receptor)	65 (49)	28.7 +/- 7	Gallezot et al., 2010[49]
	[^{11}C]-P943	PET tracer binding (BPnd) to 5-HT1b (serotonin receptor)	23 (15)	28.7 +/- 7	Savli et al., 2012[114]
	[^{11}C]-Cimbi36	PET tracer binding (Bmax) to 5-HT2a (serotonin receptor)	29 (15)	22.6 +/- 2.7	Beliveau et al., 2017[113]

	[^{18}F]-Altanserin	PET tracer binding (BPnd) to 5-HT2a (serotonin receptor)	19 (11)	28.2 +/- 5.7	Savli et al., 2012[114]
	[^{11}C]-SB207145	PET tracer binding (Bmax) to 5-HT4 (serotonin receptor)	59 (41)	25.9 +/- 5.3	Beliveau et al., 2017[113]
	[^{11}C]-GSK215083	PET tracer binding (BPnd) to 5-HT6 (serotonin receptor)	30 (30)	36.6 +/- 9.04	Radhakrishnan et al., 2018[62]
	[^{11}C]-DASB	PET tracer binding (Bmax) to 5-HTT (serotonin transporter)	100 (29)	25.1 +/- 5.8	Beliveau et al., 2017[113]
	[^{11}C]-DASB	PET tracer binding (BPnd) to 5-HTT (serotonin transporter)	18 (12)	30.5 +/- 9.5	Savli et al., 2012[114]
	[^{11}C]-MADAM	PET tracer binding (BPnd) to 5-HTT (serotonin transporter)	10 (8)	51-67	Fazio et al., 2016[115]
Noradrenaline	[^{11}C]-Methyl-Reboxetine	PET tracer binding (BPnd) to NET (norepinephrine transporter)	77 (50)	33.4 +/- 9.17	Ding et al., 2010
	[^{11}C]-Methyl-reboxetine	PET tracer binding (BPnd) to NET (norepinephrine transporter)	10 (n/a)	33.3 (mean)	Hesse et al., 2017[116]
GABA	[^{11}C]-Flumazenil	PET tracer binding (BPnd) to GABAa (gaba receptor)	6 (6)	43 +/- 4	Dukart et al., 2018[112]

	[^{11}C]-Flumazenil	PET and autoradiography informed GABAa benzodiazepine binding-site density (Bmax; gaba receptor)	16 (7)	26.6 +/- 8	Norgaard et al., 2021[117]
Histamine	[^{11}C]-GSK189254	PET tracer binding (Vt) to H3 (histamine receptor)	8 (7)	31.69 +- 8.95	Gallezot et al., 2017[97]
	[11C]MK-8278	PET tracer binding (Vt) to H3 (histamine receptor)	12 (9)	30.3 (11.5)	Arumuham et al.,2023[118]
Glutamate	[^{18}F]-GE179	PET tracer binding (Vt) to NMDA (glutamate receptor)	29 (21)	40.9 +/- 12.7	Hansen et al., 2022[99]
Cannabinoids	[^{18}F]-FMPEPD2	PET tracer binding (Vt) to CB1 (cannabinoid receptor)	22 (11)	27.5 +/- 8.05	Laurikainen et al., 2019[119]
	[^{11}C]-OMAR	PET tracer binding (Vt) to CB1 (cannabinoid receptor)	77 (49)	30.01 +/- 8.87	Normandin et al., 2015[120]
Glutamate	[^{11}C]-ABP688	PET tracer binding (BPnd) to mGluR5 (glutamate receptor)	22 (12)	67.9 +/- 9.6	Hansen et al., 2022[99]
	[^{11}C]-ABP688	PET tracer binding (BPnd) to mGluR5 (glutamate receptor)	28 (15)	33.1 +/- 11.2	Dubois et al., 2016[121]
	[^{11}C]-ABP688	PET tracer binding (BPnd) to mGluR5 (glutamate receptor)	73 (25)	19.9 +/- 3.04	Smart et al., 2019[122]

	[^{11}C]K-2	PET tracer (BPnD) to AMPA	70	20-40	Hatano et al. 2024[123]
Opioid	[^{11}C]-Carfentanil	PET tracer binding (BPnd) to MOR (mu-opioid receptor)	39 (19)	39.38 +/- 5.05	Turtonen et al., 2021 [124]
	[^{11}C]-Carfentanil	PET tracer binding (BPnd) to MOR (mu-opioid receptor)	204 (132)	32.3 +/- 10.8	Kantonen et al., 2020 [125]
	[^{11}C]-LY2795050	PET tracer binding (BPnd) to KOR (kappa-opioid receptor)	10 (9)	28.7+/- 7.4	Shokri-Kojori et al., 2021 [126]
	[^{11}C]-Methylnaltrindole	PET tracer binding (BPnd) to DOR (kappa-opioid receptor)	10 (10)	31.8+/- 7.8	Shokri-Kojori et al., 2021 [126]

Supplementary Table S3. Macroscale functional decoding of regional variation of the expression of genes of the histamine pathway in the postmortem human brain. Significance was assessed using spin rotation two-sided permutation tests.

Cognitive Function	Spearman Correlation	P_{spin}	FDR-Corrected
action	-0.518	<0.001	<0.001
adaptation	-0.304	0.015	0.029
addiction	0.54	<0.001	<0.001
anticipation	0.238	0.029	0.054
anxiety	0.663	<0.001	<0.001
arousal	0.563	<0.001	<0.001
association	0.295	<0.001	<0.001
attention	-0.628	<0.001	<0.001
autobiographical_memory	0.333	<0.001	<0.001

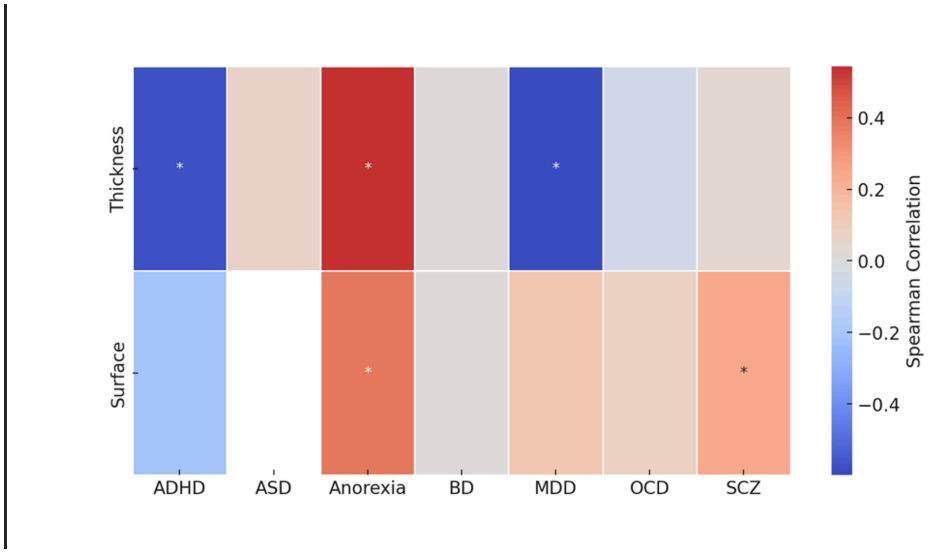
balance	0.195	0.191	0.264
belief	-0.025	0.809	0.836
categorization	-0.491	<0.001	<0.001
cognitive_control	0.255	0.015	0.029
communication	0.043	0.632	0.694
competition	-0.354	<0.001	<0.001
concept	0.277	0.059	0.094
consciousness	-0.177	0.191	0.264
consolidation	0.14	0.162	0.237
context	0.42	<0.001	<0.001
coordination	-0.441	<0.001	<0.001
decision	0.242	0.059	0.094
decision_making	0.236	0.059	0.094
detection	-0.378	<0.001	<0.001
discrimination	-0.363	<0.001	<0.001
distraction	0.336	0.015	0.029
eating	0.484	<0.001	<0.001
efficiency	-0.105	0.279	0.358
effort	-0.295	0.074	0.112
emotion	0.698	<0.001	<0.001
emotion_regulation	0.664	<0.001	<0.001
empathy	0.393	<0.001	<0.001
encoding	-0.091	0.485	0.574
episodic_memory	0.17	0.103	0.153
expectancy	0.06	0.544	0.631
expertise	-0.356	<0.001	<0.001
extinction	0.443	<0.001	<0.001
face_recognition	0.128	0.279	0.358
facial_expression	0.058	0.779	0.812
familiarity	0.143	0.191	0.264
fear	0.656	<0.001	<0.001
fixation	-0.511	<0.001	<0.001
focus	-0.375	<0.001	<0.001
gaze	-0.589	<0.001	<0.001
goal	-0.147	0.338	0.416
hyperactivity	0.532	<0.001	<0.001
imagery	-0.616	<0.001	<0.001

impulsivity	0.55	<0.001	<0.001
induction	0.185	0.206	0.281
inference	-0.019	0.882	0.904
inhibition	0.132	0.235	0.318
insight	0.299	0.059	0.094
integration	-0.439	<0.001	<0.001
intelligence	-0.158	0.279	0.358
intention	-0.058	0.647	0.698
interference	-0.041	0.647	0.698
judgment	-0.12	0.279	0.358
knowledge	0.175	0.074	0.112
language	-0.296	0.044	0.076
language_comprehension	-0.06	0.588	0.658
learning	0.132	0.324	0.406
listening	0.109	0.588	0.658
localization	-0.206	0.176	0.255
loss	0.578	<0.001	<0.001
maintenance	-0.056	0.559	0.636
manipulation	-0.492	<0.001	<0.001
meaning	-0.377	<0.001	<0.001
memory	0.081	0.529	0.62
memory_retrieval	0.417	<0.001	<0.001
mental_imagery	-0.482	<0.001	<0.001
monitoring	-0.05	0.618	0.684
mood	0.543	<0.001	<0.001
morphology	0.586	<0.001	<0.001
motor_control	-0.355	<0.001	<0.001
movement	-0.589	<0.001	<0.001
multisensory	-0.641	<0.001	<0.001
naming	-0.276	0.029	0.054
navigation	-0.303	0.044	0.076
object_recognition	-0.437	<0.001	<0.001
pain	0.444	<0.001	<0.001
perception	-0.426	<0.001	<0.001
planning	-0.432	<0.001	<0.001
priming	-0.228	0.074	0.112
psychosis	0.032	0.765	0.804

reading	-0.547	<0.001	<0.001
reasoning	-0.003	0.956	0.956
recall	0.352	<0.001	<0.001
recognition	-0.147	0.191	0.264
rehearsal	-0.44	<0.001	<0.001
reinforcement_learning	0.016	0.926	0.934
response_inhibition	0.059	0.75	0.795
response_selection	-0.125	0.338	0.416
retention	-0.068	0.676	0.724
retrieval	0.109	0.353	0.43
reward_anticipation	0.229	0.059	0.094
rhythm	-0.183	0.103	0.153
risk	0.561	<0.001	<0.001
rule	-0.021	0.897	0.912
salience	0.378	<0.001	<0.001
search	-0.552	<0.001	<0.001
selective_attention	-0.538	<0.001	<0.001
semantic_memory	0.287	<0.001	<0.001
sentence_comprehension	-0.366	<0.001	<0.001
skill	-0.46	<0.001	<0.001
sleep	0.435	<0.001	<0.001
social_cognition	0.194	0.059	0.094
spatial_attention	-0.631	<0.001	<0.001
speech_perception	-0.234	0.029	0.054
speech_production	-0.324	0.044	0.076
strategy	0.118	0.265	0.354
strength	0.057	0.559	0.636
stress	0.676	<0.001	<0.001
sustained_attention	0.249	<0.001	<0.001
task_difficulty	-0.106	0.309	0.392
thought	0.329	<0.001	<0.001
uncertainty	0.1	0.382	0.461
updating	-0.3	0.029	0.054
utility	0.299	0.029	0.054

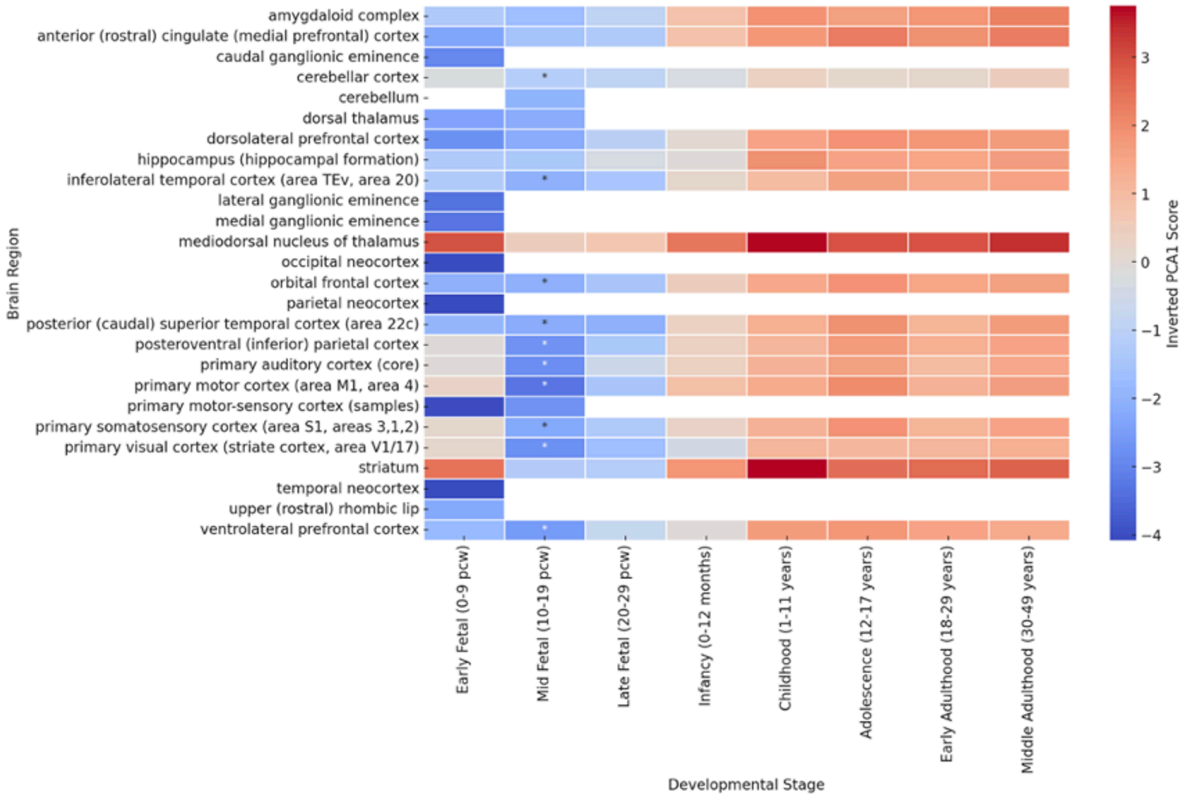
valence	0.585	<0.001	<0.001
verbal_fluency	-0.113	0.471	0.562
visual_attention	-0.676	<0.001	<0.001
visual_perception	-0.651	<0.001	<0.001
word_recognition	-0.258	0.074	0.112
working_memory	-0.23	0.044	0.076

Supplementary Figure S4. Correlations between regional PCA1 scores and the distribution of ENIGMA structural brain changes in the main neuropsychiatric disorders. The heatmap displays spearman correlations between PCA1 scores and structural brain alterations across psychiatric disorders, based on ENIGMA consortium neuroimaging meta-analyses (available as part of the ENIGMA toolbox at https://enigma-toolbox.readthedocs.io/en/latest/index.html)**.** Significance was assessed using permutation testing on spin rotations of the cortical map of PCA1 (two-sides). Abbreviations: Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Bipolar Disorder (BD), Major Depressive Disorder (MDD), Obsessive-Compulsive Disorder (OCD) and Schizophrenia (SCZ).



Supplementary Figure S5. Developmental trajectories of the regional expression of genes from the histamine pathway in the post-mortem human brain. We run PCA on whole brain normalized gene expression across developmental stages to summarize gene expression through principal component analysis. To facilitate interpretation, we display inverted PCA1 scores which were negatively correlated with gene expression so that higher PCA scores indicate higher histaminergic gene expression. The heatmap depicts regional PCA1 scores across developmental stages. Data were extracted from

the BrainSpan Atlas of the Developing Human Brain (https://www.brainspan.org/). Significance was assessed using permutation testing (two-sides) where we shuffled developmental stages across samples. The * denotes p<0.05, after FDR correction.



Supplementary Table S4. A summary of ENIGMA's datasets. Sample sizes of healthy controls and patients, age and sex distribution per disorder (Attention Deficit and Hyperactivity Disorder - ADHD, Autism Spectrum Disorder - ASD, Anorexia Nervosa - AN, Bipolar Disorder - BD, Major Depressive Disorder - MDD, Obsessive-Compulsive Disorder - OCD and Schizophrenia - SCZ).

Disorder	Sample size (HC)	Sample Size (Patients)	Age (yeas)	Percentage of women	Reference
ADHD	1934	2246	19.22 ± 11.31	25.9%	Hoogman et al. 2019[101]
ASD	1651	1571	15.62 ± 8.52	19%	Van Rooij et al. 2019[102]
AN	963	685	21	100%	Walton et al. 2022[103]
BD	4056	2447	-	-	Hibar et al. 2018[104]
MDD	7957	2148	-	-	Schmaal et al. 2017[105]
OCD	1436	1498	-	-	Boedhoe et al. 2018[106]

Disorder	Sample size (HC)	Sample Size (Patients)	Age (yeas)	Percentage of women	Reference
SCZ	5098	4474	HC: 32.8 Patients: 32.3	HC: 47% Patients: 44%	Van Erp et al. 2018[107]