

Regional Gray Matter Volume Differences and Clinical Correlates in Anorexia Nervosa

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Abstract

Objective

Structural MRI findings in anorexia nervosa are widespread, but the regional pattern and its clinical and neurochemical meaning remain incompletely defined.

Methods

We analyzed T1 weighted MRI and clinical data from the BEACON and SCAN datasets, including 122 participants with anorexia nervosa and 128 healthy controls. Gray matter volume was extracted for 163 AAL3 regions and compared between groups with models adjusted for age, total intracranial volume and cohort. Within the anorexia nervosa group, partial Spearman correlations and restricted cubic splines assessed relationships of diagnosis selected regions with body mass index, eating disorder symptoms and affective symptoms. The pooled diagnostic contrast was also compared with 39 normative PET and SPECT maps across 148 AAL3 regions using spatial null permutations.

Results

Anorexia nervosa was associated with lower gray matter volume in the right olfactory cortex, left olfactory cortex and left inferior parietal gyrus. The adjusted differences were 0.0421, 0.0417 and 0.3209 mL in magnitude, with q values from 0.0210 to 0.0268. Effects had the same direction in both cohorts, although no region survived correction within either cohort alone. Partial rank correlations were not significant. Restricted cubic splines identified nonlinear associations of left inferior parietal volume with body mass index and dietary restraint. The diagnostic t map showed negative spatial correlations with normative mGluR5, SV2A, GABA_A and 5 HT2A maps.

Conclusion

These results localize a reproducible structural pattern while separating diagnostic anatomy from clinical variation and normative neurochemical organization, providing specific targets for longitudinal and multimodal studies of anorexia nervosa.

Introduction

Anorexia nervosa (AN) is a severe eating disorder in which restricted energy intake, fear of weight gain and disturbed evaluation of body weight or shape coexist with profound physical and psychological impairment ^[1]. Elevated mortality and often prolonged recovery make understanding its neurobiology a clinical priority ^[2, 3]. AN also involves substantial endocrine adaptation to energy deprivation, including

changes in hypothalamic pituitary function and appetite-regulating hormones^[4]. Genome-wide evidence has strengthened this biological perspective by identifying genetic correlations with psychiatric, metabolic and anthropometric traits, supporting a metabo-psychiatric account of the disorder^[5]. These converging observations make it important to determine how nutritional depletion and eating disorder psychopathology are reflected in the brain. Structural MRI provides a noninvasive way to examine this relationship, but its clinical value depends on resolving the anatomical pattern and its links to distinct illness dimensions. A regional account that connects morphology with nutritional status and restrictive attitudes can move beyond a general association between AN and lower brain volume and provide specific targets for studies of illness persistence and recovery.

Structural MRI studies have established substantial brain changes in AN, while leaving the distribution and interpretation of regional abnormalities incompletely resolved. The coordinated ENIGMA study found widespread reductions in cortical thickness and subcortical volume that were associated with lower body mass index (BMI) and were less pronounced after partial weight restoration^[6]. Longitudinal imaging demonstrated rapid reversal of cortical thinning during weight restoration, underscoring the responsiveness of brain morphology to nutritional change^[7]. Nevertheless, regional findings vary across studies, with both lower and relatively greater gray-matter volume (GMV) reported in AN^[8, 9]. Meta-analytic evidence has also identified reductions in reward and somatosensory territories, including the left inferior parietal region^[10]. This variation is clinically relevant because a similar overall volume reduction can arise from different regional patterns, with different implications for sensory processing, cognitive control and illness expression. These patterns need to be examined across the whole brain with a consistent regional definition rather than through selected structures or global averages. Combining clinically different cohorts with a common analysis can identify regional effects that warrant further investigation and assess their directional consistency across samples. This approach complements large consortium studies by linking regional case control differences to clinical and molecular analyses. It also provides a clear basis for comparing evidence across anatomical and functional network scales without treating every detected difference as equally informative.

Clinical associations are essential to this regional interpretation because low BMI and restrictive psychopathology measure different aspects of AN. In an early voxel-based study, dietary restraint and BMI jointly accounted for variation in right dorsolateral prefrontal volume^[11]. A multicentre investigation subsequently related restraint to greater ventromedial prefrontal GMV^[9], whereas research encompassing AN and atypical AN found positive BMI associations with parietal, frontal and temporal GMV without corresponding associations with overall eating-disorder severity^[12]. Together, these results suggest that nutritional and psychological dimensions need not share the same anatomical correlates. Functional evidence linking inferior parietal responses to viewing one's own body further illustrates the potential relevance of regional brain variation to core eating-disorder experiences^[13]. However, different associations across brain regions and clinical measures cannot be adequately characterized by assuming a single monotonic relationship. Flexible modelling is needed to determine whether morphology varies differently across the ranges of BMI and restrictive attitudes. Examining linear and

nonlinear relationships within regions identified by the diagnostic comparison can thus connect group differences with clinically meaningful heterogeneity, while distinguishing findings that reflect nutritional state from those associated with specific symptom dimensions.

The molecular context of structural abnormalities represents a further opportunity to refine their biological interpretation. Direct SPECT imaging reported lower cortical serotonin 5-HT_{2A} receptor binding in low-weight AN, including frontal, parietal and occipital regions^[14]. PET imaging also identified reduced binding after recovery in mesial temporal and cingulate regions, with additional parietal and occipital differences in a subset^[15]. These observations support serotonergic involvement, but a single receptor system cannot fully contextualize the distributed structural phenotype. Normative molecular atlases show that neurotransmitter receptor and transporter distributions are systematically related to cortical structure, functional organization and connectivity^[16]. JuSpace and neuromaps provide tools for relating MRI-derived patterns to independently acquired molecular and other brain maps^[17, 18]. Applying this approach to the complete regional diagnostic contrast, rather than only thresholded abnormalities, permits a broader assessment of whether AN-related morphology follows particular neurochemical topographies. This strategy connects macroscopic anatomy with the spatial organization of several receptor, transporter and synaptic markers within one analysis. This approach provides biologically grounded hypotheses for targeted investigation. The spatial associations reflect correspondence with normative architecture and do not measure receptor availability in the patients.

We integrated regional anatomy, clinical phenotypes and normative neurochemical topography using structural MRI from the openly available BEACON and SCAN datasets^[19, 20]. Our primary objective was to identify AN and control GMV differences across a common whole-brain parcellation after accounting for age, intracranial volume and cohort. We then examined the consistency of those effects across cohorts and cortical networks, and tested associations between diagnosis-selected regions and BMI, eating-disorder symptoms and affective symptoms within AN. Restricted cubic splines complemented partial rank correlations to characterize potentially nonlinear clinical relationships. Finally, we compared the full regional AN and control contrast with multiple normative PET/SPECT maps. Guided by existing evidence, we tested whether AN was associated with lower regional GMV, whether nutritional status and restrictive psychopathology showed distinguishable anatomical relationships, and whether the distributed structural pattern corresponded to neurochemical organization. By bringing these complementary questions into a common framework, the study extends conventional case control morphometry toward a clinically and molecularly informed account of AN, with defined regional targets for subsequent longitudinal and multimodal investigation.

Methods

Data and participants

This analysis used anonymized structural MRI and clinical data from the openly available BEACON and SCAN datasets (OpenNeuro ds007606 and ds007741, version 1.0.0).^[19, 20, 21] BEACON session 01 was used. Participants labeled acute anorexia nervosa were harmonized to AN, whereas the separately labeled weight restored group was excluded. SCAN diagnostic labels were retained. The pooled sample included 250 participants, including 122 with AN and 128 healthy controls (HCs). BEACON contributed 53 participants with AN and 58 HCs. SCAN contributed 69 participants with AN and 70 HCs. The SCAN source cohort included participants with a history of low-weight AN who did not consider themselves recovered, irrespective of BMI at assessment.^[22, 23]

Participants were eligible when a suitable three-dimensional T1-weighted image, diagnostic label, age, positive BMI, native CAT12 segmentation and modulated gray-matter image were available. Three BEACON baseline scans acquired with a two-dimensional thick-slice T1 protocol were excluded (two AN and one HC participants). Clinical analyses used analysis-specific complete cases without imputation. The original BEACON and SCAN studies received research ethics approval and obtained informed consent.^[22, 23] Because the present study used only anonymized, publicly available data, no new recruitment or data collection was performed.

Clinical measures

Body mass index was expressed in kg/m². For four participants in the BEACON sample (two AN and two HC) with missing BMI at scanning, deposited baseline BMI was used. Eating-disorder psychopathology was assessed with the Eating Disorder Examination Questionnaire (EDE-Q), including restraint, eating concern, shape concern, weight concern and total scores.^[24] Anxiety and depression symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS). SCAN HADS total scores were calculated as the sum of its anxiety and depression subscales.^[25] BMI was available for all 122 AN participants and the harmonized clinical measures for 115 AN participants.

MRI acquisition and preprocessing

BEACON T1-weighted images were acquired on a 3-T GE Discovery MR750 scanner using a 32-channel coil. The deposited acquisition parameters were repetition time 7.312 ms, echo time 3.016 ms, inversion time 400 ms, flip angle 11° and slice thickness 1.2 mm. The SCAN source study used a 3-T GE MR750 scanner with a 12-channel coil, 256 × 256 matrix, 270-mm field of view, 11° flip angle and 1.2-mm slice thickness.^[23]

T1-weighted images were processed with CAT12 in SPM12 running MATLAB R2018b.^[26, 27, 28] The pipeline included bias-field correction, tissue segmentation and nonlinear registration to the MNI152NLin2009cAsym template using fast optimized shooting. Modulated normalized gray-matter images were generated at 1.5-mm isotropic resolution without additional smoothing. Total intracranial

volume (TIV) was reconstructed from the native CAT12 partial-volume tissue maps as the summed volumes of cerebrospinal fluid, gray matter, white matter and white-matter hyperintensity tissue classes.

Regional gray-matter volume was extracted with the CAT-supplied Automated Anatomical Labeling 3 (AAL3) atlas. ^[29] Atlas labels were resampled to the normalized gray-matter grid using nearest-neighbor interpolation. For each participant, regional GMV was calculated as the sum of modulated gray-matter values multiplied by voxel volume and expressed in milliliters. The analysis included 163 AAL3 regions with nonempty support.

Statistical analysis

Continuous variables were summarized as mean $\pm$ standard deviation. Age and TIV were compared using two sided Student t tests, whereas BMI was compared using a two sided Welch t test because group variances differed. Questionnaire scores were summarized as median and interquartile range and compared using two sided Mann Whitney U tests. For each AAL3 region, ordinary least squares regression modeled GMV as a function of diagnostic group, age, TIV and cohort. Age and TIV were standardized within each analysis sample. BMI was not included in the diagnostic model. AN and BEACON were coded as 1, while HC and SCAN were coded as 0. The diagnostic coefficient represented the adjusted difference between AN and HC in milliliters. Benjamini Hochberg false discovery rate correction was applied across the 163 regional tests. A q value below 0.05 was considered significant. ^[30] Cohort-stratified models included age and TIV and were corrected across the 163 regions within each cohort.

Network analyses used the seven-network Yeo cortical parcellation, with standard and liberal cortical masks analyzed separately. ^[31] Network GMV was tested using the same covariates, with FDR correction across seven networks for each mask. HC3 heteroscedasticity-consistent covariance estimates were used as a sensitivity analysis. ^[32]

Within the AN group, partial Spearman correlations examined associations between the three regions identified by the diagnostic contrast, namely the bilateral olfactory cortex and left inferior parietal gyrus, and BMI, the five EDE Q scores and HADS total. ROI volume, phenotype, age and TIV were rank transformed. The binary cohort indicator was retained. Ranked ROI and phenotype values were residualized for age, TIV and cohort before correlation. These analyses were exploratory because the ROIs were selected from the same diagnostic contrast. ^[33]

Nonlinear associations were assessed with restricted cubic splines for BMI and each clinical measure. ^[34] Four knots were placed at the 5th, 35th, 65th and 95th percentiles of each exposure. Models included age, TIV and cohort, and nonlinearity was tested with HC3-robust joint Wald tests of the two nonlinear terms. Sensitivity analyses used a quadratic term, three knots at the 10th, 50th and 90th percentiles, the common exposure range of the two cohorts, and exclusion of observations with Cook's distance $> 4/n$. ^[35] FDR correction was performed across the three ROIs within each phenotype and model family.

Normative PET and SPECT maps were obtained from the JuSpace v2.1 collection. ^[16, 17, 18] Associations were calculated as Spearman correlations across the 148 AAL3 regions with finite values in the disease map and every reference map. A spatial null procedure generated 1,000 accepted randomizations per map. Two sided Monte Carlo P values used the plus one correction and were adjusted with Benjamini Hochberg false discovery rate across all 39 maps. These analyses quantify regional correspondence with normative reference maps and do not measure neurotransmitter availability in the study participants.

Analyses were performed in Python using NumPy, SciPy, pandas, NiBabel, Nilearn and statsmodels. CAT12 preprocessing and the original JuSpace extraction used MATLAB. A two-sided test was used, with a significance level of $\alpha = 0.05$.

Results

Participant characteristics

The study included 122 participants with AN and 128 HCs. The groups were similar in age and TIV, whereas BMI was lower in AN, at 17.05 ± 2.21 versus 22.19 ± 3.48 kg/m² in HC, $P < 0.001$. EDE Q total and subscale scores and HADS total scores were higher in AN, all $P < 0.001$, as shown in Table 1.

Table 1
Demographic and clinical characteristics of the pooled sample

Characteristic	HC n	HC	AN n	AN	Statistic	P
Age (years)	128	20.55 (2.98)	122	20.45 (2.82)	-0.262	0.794
BMI (kg/m ²)	128	22.19 (3.48)	122	17.05 (2.21)	-14.001	< 0.001
TIV (mL)	128	1402.12 (123.23)	122	1401.96 (121.26)	-0.010	0.992
EDE-Q restraint	122	0.00 [0.00, 0.55]	115	3.40 [2.20, 4.70]	13034	< 0.001
EDE-Q eating concern	122	0.00 [0.00, 0.20]	115	3.20 [2.00, 4.00]	13574	< 0.001
EDE-Q shape concern	122	0.62 [0.25, 1.25]	115	4.50 [2.88, 5.50]	13095.5	< 0.001
EDE-Q weight concern	122	0.40 [0.05, 1.15]	115	3.80 [2.30, 5.20]	12903.5	< 0.001
EDE-Q total	122	0.33 [0.14, 0.73]	115	3.86 [2.38, 4.70]	13354	< 0.001
HADS total	124	7.00 [4.00, 11.00]	115	20.00 [15.00, 25.00]	13083	< 0.001
Note: Values are mean (SD) for age, BMI and TIV, and median [IQR] for questionnaire scores. <i>P</i> values are from two sided Student <i>t</i> tests for age and TIV, a Welch <i>t</i> test for BMI, and Mann Whitney <i>U</i> tests for questionnaire scores. The statistic is <i>t</i> or <i>U</i> , respectively.						

Regional gray matter volume differences

After adjustment for age, TIV and cohort, GMV was lower in AN in three of 163 AAL3 regions after FDR correction, as shown in Table 2 and Fig. 1. The adjusted differences between AN and HC were - 0.0421 mL in the right olfactory cortex (95% CI, - 0.0635 to - 0.0206, *q* = 0.0210), - 0.0417 mL in the left olfactory cortex (- 0.0639 to - 0.0196, *q* = 0.0210) and - 0.3209 mL in the left inferior parietal gyrus (- 0.4998 to - 0.1419, *q* = 0.0268).

Table 2
AAL3 regions with lower gray matter volume in anorexia nervosa

Region	HC GMV, mL	AN GMV, mL	Adjusted difference (95% CI), mL	<i>t</i>	<i>P</i>	<i>q</i>
Right olfactory cortex	1.241 (0.117)	1.200 (0.114)	-0.042 (-0.064 to -0.021)	-3.856	0.0001	0.0210
Left olfactory cortex	1.220 (0.118)	1.179 (0.118)	-0.042 (-0.064 to -0.020)	-3.709	0.0003	0.0210
Left inferior parietal gyrus	9.049 (0.892)	8.738 (0.929)	-0.321 (-0.500 to -0.142)	-3.532	0.0005	0.0268
Note: Values are unadjusted mean (SD). Adjusted differences and <i>t</i> statistics between AN and HC were estimated with age, TIV and cohort covariates. <i>q</i> values use FDR correction across all 163 analyzed regions.						

The three adjusted differences were negative in both cohorts, but no region survived FDR correction when either cohort was analyzed separately. No difference survived FDR correction across the seven networks of the standard Yeo atlas (minimum $q = 0.0507$). With the liberal cortical mask, GMV in the ventral attention/salience network was lower in AN ($q = 0.0490$). This result did not survive HC3-robust inference ($q = 0.0553$).

Clinical associations within anorexia nervosa

None of the 21 partial Spearman correlations between the three diagnosis-selected ROIs and BMI, EDE-Q measures or HADS total survived FDR correction. In exploratory spline analyses, left inferior parietal GMV showed a nonlinear association with BMI ($F = 4.63$, $q = 0.0350$, partial $R^2 = 0.0614$), as shown in Fig. 2. The association persisted within the BMI range shared by both cohorts (from 11.675 to 18.427 kg/m², $n = 99$, $q = 0.0325$) and after exclusion of influential observations, but not in the quadratic or three-knot spline sensitivity models. Neither olfactory ROI showed significant BMI nonlinearity.

EDE-Q restraint was also nonlinearly associated with left inferior parietal GMV ($F = 5.80$, $q = 0.0121$, partial $R^2 = 0.0877$), as shown in Fig. 2. Predicted GMV was highest at intermediate restraint scores. The nonlinearity remained after restriction to the shared score range (from 0 to 5.8, $n = 113$, $q = 0.0496$), in the quadratic and three-knot models, and after exclusion of influential observations. No other clinical phenotype showed significant nonlinearity in the primary four-knot model, and no curve-by-cohort interaction survived the corresponding within-phenotype correction.

Spatial associations with normative neurochemical maps

Four of 39 normative reference maps showed FDR significant spatial correlations with the regional *t* map comparing AN with HC across 148 jointly finite AAL3 regions, as shown in Table 3 and Fig. 3.

Correlations were negative for mGluR5 ($\rho = -0.419$, $q = 0.039$), SV2A ($\rho = -0.399$, $q = 0.019$), GABAa ($\rho =$

-0.339, $q = 0.019$) and 5-HT2A ($\rho = -0.317$, $q = 0.039$). These associations indicate that more negative regional AN and HC t-statistics occurred where normative reference map values were higher. SV2A is a synaptic vesicle marker. The findings are conditional on the spatial null model and do not represent receptor measurements in the study participants.

Table 3
Normative neurochemical maps associated with the regional AN and HC t-map

Reference map	Spearman ρ	Spatial P	q
5-HT2A (ALT, HC19)	-0.317	0.0040	0.0390
GABAa (flumazenil, HC16)	-0.339	0.0010	0.0195
mGluR5 (ABP688, HC73)	-0.419	0.0030	0.0390
SV2A (UCB-J, HC10)	-0.399	0.0010	0.0195
Note: Correlations used the same 148 AAL3 regions for all 39 reference maps. Spatial P values came from 1,000 null maps. q values use FDR correction across all 39 tests.			

Discussion

In this pooled MRI study, the corrected gray-matter volume differences associated with anorexia nervosa were concentrated in the bilateral olfactory cortex and left inferior parietal gyrus. The parietal region also showed nonlinear relationships with body mass index and dietary restraint, while the full regional contrast between AN and control aligned with four normative neurochemical maps. Together, these findings add anatomical, clinical and molecular specificity to the established structural MRI phenotype of AN.

The regional pattern is informative in the context of the widespread brain changes reported in AN. Large multicentre studies have identified extensive cortical or GMV reductions, particularly in acutely underweight patients [6, 9]. Longitudinal imaging has shown that much of the cortical change can lessen during weight restoration [7]. Our analysis focused on which atlas defined regional differences remain detectable when two cohorts with different clinical compositions are analyzed together. After adjustment for age, intracranial volume and cohort, three of 163 regions survived FDR correction, and each effect had the same direction in BEACON and SCAN. This cross-cohort directional agreement strengthens the anatomical coherence of the pooled result. The limited number of corrected parcels should not be taken to mean that the rest of the brain is unaffected. It identifies the regions with the clearest evidence under the present regional analysis.

The bilateral olfactory cortex was the most consistent anatomical finding. Its adjusted volume differences were almost identical on the two sides, and both survived correction across the regional tests. Olfactory processing is closely linked to the sensory evaluation of food, making this paired finding a biologically relevant direction for AN research. At the same time, a meta-analysis of behavioral studies

found no uniform diagnostic impairment of overall olfactory performance, although some olfactory measures varied with illness severity^[36]. The present anatomical result therefore adds a distinct level of evidence. It identifies a bilateral cortical locus to investigate with odor identification, food odor valuation and nutritional state measures in the same individuals. It does not require that every patient with AN have a measurable smell deficit.

The left inferior parietal result provides a second, clinically connected anatomical focus. A voxel-based meta-analysis previously identified lower GMV in a left inferior parietal territory in AN^[10], and a more recent study found prominent parietal GMV differences in both AN and atypical AN^[12]. Although the anatomical definitions differ from our AAL3 parcel, these observations place the present finding within a recurring parietal signal. Functional work has also linked nearby inferior parietal territories to viewing one's own body in eating disorders^[13]. The current data do not directly measure body representation. The convergence of a corrected structural difference with within AN clinical variation makes this region more than an isolated atlas result. It becomes a specific target for testing how parietal anatomy relates to eating disorder behavior.

The clinical analyses sharpen the distinction between diagnostic differences and variation within AN. None of the partial rank correlations survived correction, yet spline models detected nonlinear associations of left inferior parietal GMV with BMI and EDE-Q restraint. The restraint association was the more consistent of the two. Its shape persisted across the quadratic and three-knot models, the shared score range and the influence analysis, whereas the BMI finding was sensitive to model specification. Earlier work linked restraint and BMI to right dorsolateral prefrontal volume in a small AN cohort^[11], and a multicentre study related restraint to ventromedial prefrontal GMV^[9]. In a study including AN and atypical AN, BMI, but not overall eating-disorder severity, was associated with parietal GMV^[12]. These regionally different findings reinforce the value of separating nutritional status from restrictive psychopathology. Our analysis further shows that a linear model can miss their relationship with parietal anatomy. The observed peak at intermediate restraint scores is a feature of the fitted association, not evidence of a beneficial level of restraint.

The neurochemical analysis adds a complementary perspective on the distributed case-control pattern. Across 148 comparable regions and 39 reference maps, more negative AN and control t-statistics preferentially occurred where normative mGluR5, SV2A, GABA_A and 5-HT_{2A} map values were higher. Direct molecular imaging provides a disease-specific comparison for one of these systems. A SPECT study found lower cortical 5-HT_{2A} binding in low-weight AN, including parietal regions^[14], while a PET study found reduced binding after recovery in mesial temporal and cingulate regions, with parietal and occipital differences in a subset^[15]. Our result addresses a different question. It places the full structural contrast within independently derived molecular topographies^[16, 17], rather than measuring receptor availability in these participants. The four associations point to plausible systems for focused multimodal investigation, especially glutamatergic and synaptic markers, while the shared cortical organization of these maps makes a single-transmitter explanation unlikely.

Taken together, the findings show that the regional MRI signal in AN is not clinically uniform. Bilateral olfactory differences define the clearest case control anatomy, whereas the left inferior parietal difference is the region in which nutritional and restraint-related variation was detectable. The neurochemical correspondences then place the broader anatomical pattern in a molecularly informed spatial context. This separation of diagnostic topography, within AN heterogeneity and normative molecular architecture is the main value of combining the three analyses. It yields more precise questions than a global GMV comparison alone can provide.

Several limitations define the scope of these inferences. The cross-sectional design cannot distinguish pre-existing differences from effects of illness or malnutrition, and BEACON and SCAN differed in clinical composition and image acquisition. Although the regional effects had concordant directions, neither cohort yielded separately FDR-significant findings. The diagnostic model adjusted for intracranial volume but not BMI or total GMV, so the regional differences cannot be interpreted as independent of nutritional status or global tissue loss. Phenotype analyses were confined to regions selected by the case control contrast, the BMI spline changed with model specification, and scan-time BMI was unavailable for two BEACON participants with AN. Finally, T1-derived GMV does not resolve cellular mechanisms, and spatial correlations with interrelated normative PET/SPECT maps cannot establish receptor or synaptic changes in individual patients. An independent longitudinal sample with harmonized clinical measures and patient-level molecular imaging would test which of these anatomical and clinical patterns persist through weight restoration.

This study moves beyond a description of generalized brain-volume reduction in AN by identifying where corrected regional differences concentrate, which of those regions carries measurable clinical variation, and how the wider structural pattern relates to normative neurochemical organization. The resulting map connects anatomy to testable dimensions of illness without reducing AN to a single region or transmitter system. Determining which features recover with nutrition and which persist with psychopathology could turn these regional findings into a more informative account of disease state and recovery.

Declarations

Competing interests

The authors declare no competing interests.

Ethics declaration

Ethics approval for the BEACON study was granted by the National Research Ethics Committee (17/LO/2071) and for the SCAN study by the London–South East Research Ethics Committee (21/LO/0368). Participants in both studies provided written informed consent. The present work analyzed de-identified, individual-level MRI and clinical data released through OpenNeuro (ds007606 and ds007741). No new participants were recruited or contacted for this secondary analysis.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During preparation of this manuscript, the authors used AI solely to improve English language and readability. The authors subsequently reviewed and edited the text and take full responsibility for the content of the article.

Consent for publication

Not applicable. This study used de-identified, publicly available data and involved no new contact with participants.

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Author Contribution

Lei Zhang and Yong Han: Conceptualization; Writing – original draft. Jia Lv and Haosheng Yang: Investigation. Chun Yang and Junqing Li: Supervision; Writing – review & editing. Yong Han: Supervision; Validation; Writing – review & editing. All authors reviewed and approved the final manuscript.

Data Availability

The de-identified MRI and clinical datasets analyzed in this study are publicly available from OpenNeuro under accession numbers ds007606 and ds007741. The derived summary results supporting the conclusions are provided in Additional file 1. Analysis scripts are available from the corresponding author on reasonable request.

References

1. Treasure J, Duarte TA, Schmidt U. Eating disorders. *Lancet*. 2020;395(10227):899–911. 10.1016/S0140-6736(20)30059-3.
2. Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders: a meta-analysis of 36 studies. *Arch Gen Psychiatry*. 2011;68(7):724–31. 10.1001/archgenpsychiatry.2011.74.
3. Eddy KT, Tabri N, Thomas JJ, Murray HB, Keshaviah A, Hastings E, et al. Recovery from anorexia nervosa and bulimia nervosa at 22-year follow-up. *J Clin Psychiatry*. 2017;78(2):184–9. 10.4088/JCP.15m10393.

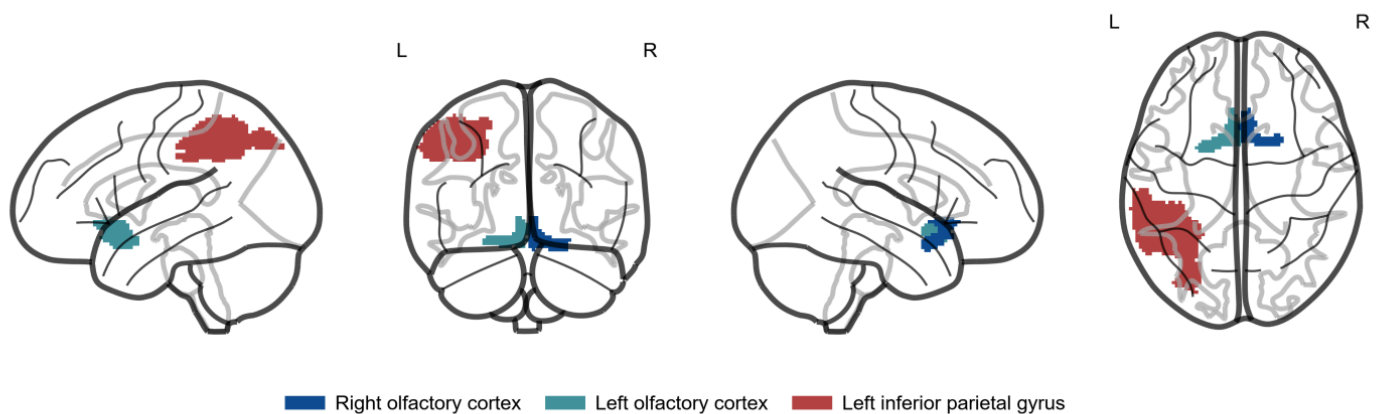
4. Schorr M, Miller KK. The endocrine manifestations of anorexia nervosa: mechanisms and management. *Nat Reviews Endocrinol.* 2017;13(3):174–86. 10.1038/nrendo.2016.175.
5. Watson HJ, Yilmaz Z, Thornton LM, et al. Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nat Genet.* 2019;51(8):1207–14. 10.1038/s41588-019-0439-2.
6. Walton E, Bernardoni F, Batury VL, Bahnsen K, Larivière S, Abbate-Daga G, et al. Brain structure in acutely underweight and partially weight-restored individuals with anorexia nervosa: a coordinated analysis by the ENIGMA Eating Disorders Working Group. *Biol Psychiatry.* 2022;92(9):730–8. 10.1016/j.biopsych.2022.04.022.
7. Bernardoni F, King JA, Geisler D, Stein E, Jaite C, Nätsch D, et al. Weight restoration therapy rapidly reverses cortical thinning in anorexia nervosa: a longitudinal study. *NeuroImage.* 2016;130:214–22. 10.1016/j.neuroimage.2016.02.003.
8. King JA, Frank GK, Thompson PM, Ehrlich S. Structural neuroimaging of anorexia nervosa: future directions in the quest for mechanisms underlying dynamic alterations. *Biol Psychiatry.* 2018;83(3):224–34. 10.1016/j.biopsych.2017.08.011.
9. Tose K, Takamura T, Isobe M, Hirano Y, Sato Y, Kodama N, et al. Systematic reduction of gray matter volume in anorexia nervosa, but relative enlargement with clinical symptoms in the prefrontal and posterior insular cortices: a multicenter neuroimaging study. *Mol Psychiatry.* 2024;29(4):891–901. 10.1038/s41380-023-02378-4.
10. Titova OE, Hjorth OC, Schiöth HB, Brooks SJ. Anorexia nervosa is linked to reduced brain structure in reward and somatosensory regions: a meta-analysis of VBM studies. *BMC Psychiatry.* 2013;13:110. 10.1186/1471-244X-13-110.
11. Brooks SJ, Barker GJ, O'Daly OG, Brammer M, Williams SCR, Benedict C, et al. Restraint of appetite and reduced regional brain volumes in anorexia nervosa: a voxel-based morphometric study. *BMC Psychiatry.* 2011;11:179. 10.1186/1471-244X-11-179.
12. Lyall AE, Breithaupt L, Ji C, Haidar A, Kotler E, Becker KR, et al. Lower region-specific gray matter volume in females with atypical anorexia nervosa and anorexia nervosa. *Int J Eat Disord.* 2024;57(4):951–66. 10.1002/eat.24168.
13. Vocks S, Busch M, Grönemeyer D, Schulte D, Herpertz S, Suchan B. Neural correlates of viewing photographs of one's own body and another woman's body in anorexia and bulimia nervosa: an fMRI study. *J Psychiatry Neurosci.* 2010;35(3):163–76. 10.1503/jpn.090048.
14. Audenaert K, Van Laere K, Dumont F, Vervaet M, Goethals I, Slegers G, et al. Decreased 5-HT_{2a} receptor binding in patients with anorexia nervosa. *J Nucl Med.* 2003;44(2):163–9. PMID:12571204.
15. Frank GK, Kaye WH, Meltzer CC, Price JC, Greer P, McConaha C, et al. Reduced 5-HT_{2A} receptor binding after recovery from anorexia nervosa. *Biol Psychiatry.* 2002;52(9):896–906. 10.1016/S0006-3223(02)01378-1.
16. Hansen JY, Shafiei G, Markello RD, Smart K, Cox SML, Nørgaard M, et al. Mapping neurotransmitter systems to the structural and functional organization of the human neocortex. *Nat Neurosci.*

- 2022;25(11):1569–81. 10.1038/s41593-022-01186-3.
17. Dukart J, Holiga S, Rullmann M, Lanzenberger R, Hawkins PCT, Mehta MA, et al. JuSpace: A tool for spatial correlation analyses of magnetic resonance imaging data with nuclear imaging derived neurotransmitter maps. *Hum Brain Mapp.* 2021;42(3):555–66. 10.1002/hbm.25244.
 18. Markello RD, Hansen JY, Liu ZQ, Bazinet V, Shafiei G, Suárez LE, et al. neuromaps: structural and functional interpretation of brain maps. *Nat Methods.* 2022;19(11):1472–9. 10.1038/s41592-022-01625-w.
 19. Tchanturia K, Williams S, Leppanen J, Halls D, Sader M. BEACON [dataset]. *OpenNeuro.* 2026. 10.18112/openneuro.ds007606.v1.0.0
 20. Leppanen J, Bailey O, Halls D, Allen K, Tchanturia K, Williams S. SCAN [dataset]. *OpenNeuro.* 2026. 10.18112/openneuro.ds007741.v1.0.0
 21. Markiewicz CJ, Gorgolewski KJ, Feingold F, Blair R, Halchenko YO, Miller E, et al. The OpenNeuro resource for sharing of neuroscience data. *eLife.* 2021;10:e71774. 10.7554/eLife.71774.
 22. Sader M, Halls D, Kerr-Gaffney J, Waiter GD, Gillespie-Smith K, Duffy F, et al. Neuroanatomical associations with autistic characteristics in those with acute anorexia nervosa and weight-restored individuals. *Psychol Med.* 2025;55:e120. 10.1017/S0033291725001047.
 23. Leppanen J, Bailey O, Halls D, Allen K, Tchanturia K, Williams S. Evoked emotions in anorexia nervosa: neural and behavioural correlates of social-emotional processing. *Translational Psychiatry.* 2026;16(1):128. 10.1038/s41398-026-03819-8.
 24. Fairburn CG, Beglin SJ. Assessment of eating disorders: Interview or self-report questionnaire? *Int J Eat Disord.* 1994;16(4):363–70. 10.1002/1098-108X(199412)16:4%3C363.::AID-EAT2260160405>3.0.CO;2-#.
 25. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta psychiatrica Scandinavica.* 1983;67(6):361–70. 10.1111/j.1600-0447.1983.tb09716.x.
 26. Gaser C, Dahnke R, Thompson PM, Kurth F, Luders E. the Alzheimer's Disease Neuroimaging Initiative. CAT: a computational anatomy toolbox for the analysis of structural MRI data. *GigaScience.* 2024;13:giae049. 10.1093/gigascience/giae049.
 27. Ashburner J, Friston KJ. Unified segmentation. *NeuroImage.* 2005;26(3):839–51. 10.1016/j.neuroimage.2005.02.018.
 28. Ashburner J, Friston KJ. Diffeomorphic registration using geodesic shooting and Gauss–Newton optimisation. *NeuroImage.* 2011;55(3):954–67. 10.1016/j.neuroimage.2010.12.049.
 29. Rolls ET, Huang CC, Lin CP, Feng J, Joliot M. Automated anatomical labelling atlas 3. *NeuroImage.* 2020;206:116189. 10.1016/j.neuroimage.2019.116189.
 30. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J Royal Stat Soc Ser B: Stat Methodol.* 1995;57(1):289–300. 10.1111/j.2517-6161.1995.tb02031.x.

31. Thomas Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol.* 2011;106(3):1125–65. 10.1152/jn.00338.2011.
32. MacKinnon JG, White H. Some heteroskedasticity-consistent covariance matrix estimators with improved finite sample properties. *J Econ.* 1985;29(3):305–25. 10.1016/0304-4076(85)90158-7.
33. Kriegeskorte N, Simmons WK, Bellgowan PSF, Baker CI. Circular analysis in systems neuroscience: the dangers of double dipping. *Nat Neurosci.* 2009;12(5):535–40. 10.1038/nn.2303.
34. Harrell FE. *Regression Modeling Strategies.* Springer Series in Statistics. 2015. 10.1007/978-3-319-19425-7
35. Cook RD. Detection of Influential Observation in Linear Regression. *Technometrics.* 1977;19(1):15–8. 10.1080/00401706.1977.10489493.
36. Mai Y, Zhang X, Li Z, Wu X, Zeng B, Fang Y, et al. Olfaction is a marker of severity but not diagnosis in anorexia nervosa: a systematic review and meta-analysis. *Neuropsychol Rev.* 2020;30(2):251–66. 10.1007/s11065-020-09438-4.

Figures

A



B

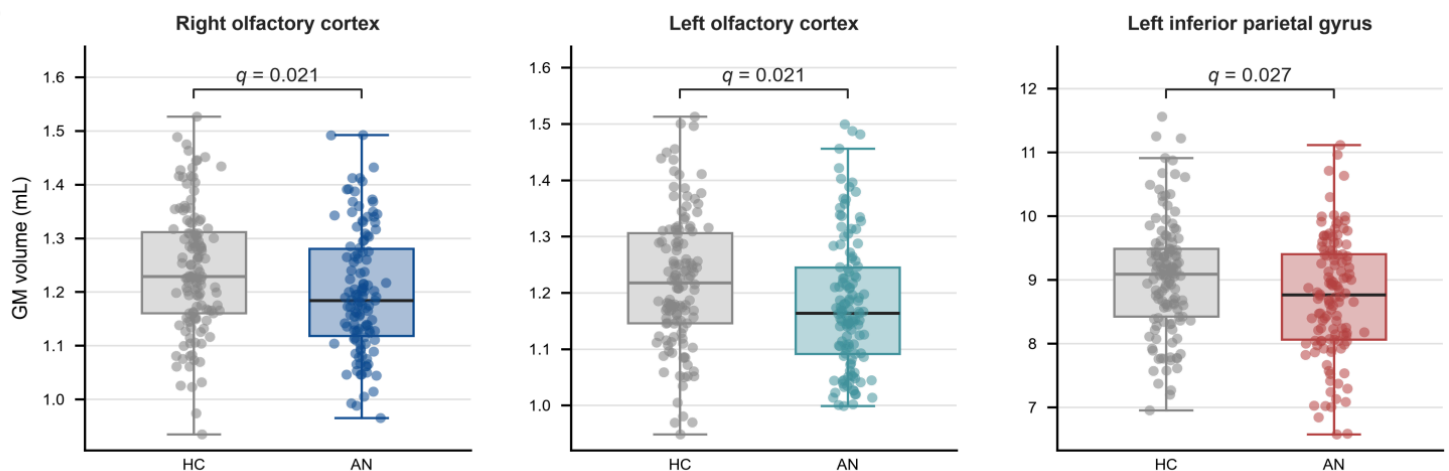


Figure 1

Regional gray matter differences. Panel A shows the anatomical locations of the three AAL3 regions that passed whole atlas BH FDR in the pooled model, with lower GMV in AN than HC. Panel B shows pooled individual volumes for HC on the left and AN on the right. Points show unadjusted individual ROI gray matter volumes. Boxes show medians and interquartile ranges, with whiskers extending to the most extreme observations within 1.5 IQR. Bracket labels are BH FDR q values from the original covariate adjusted models.

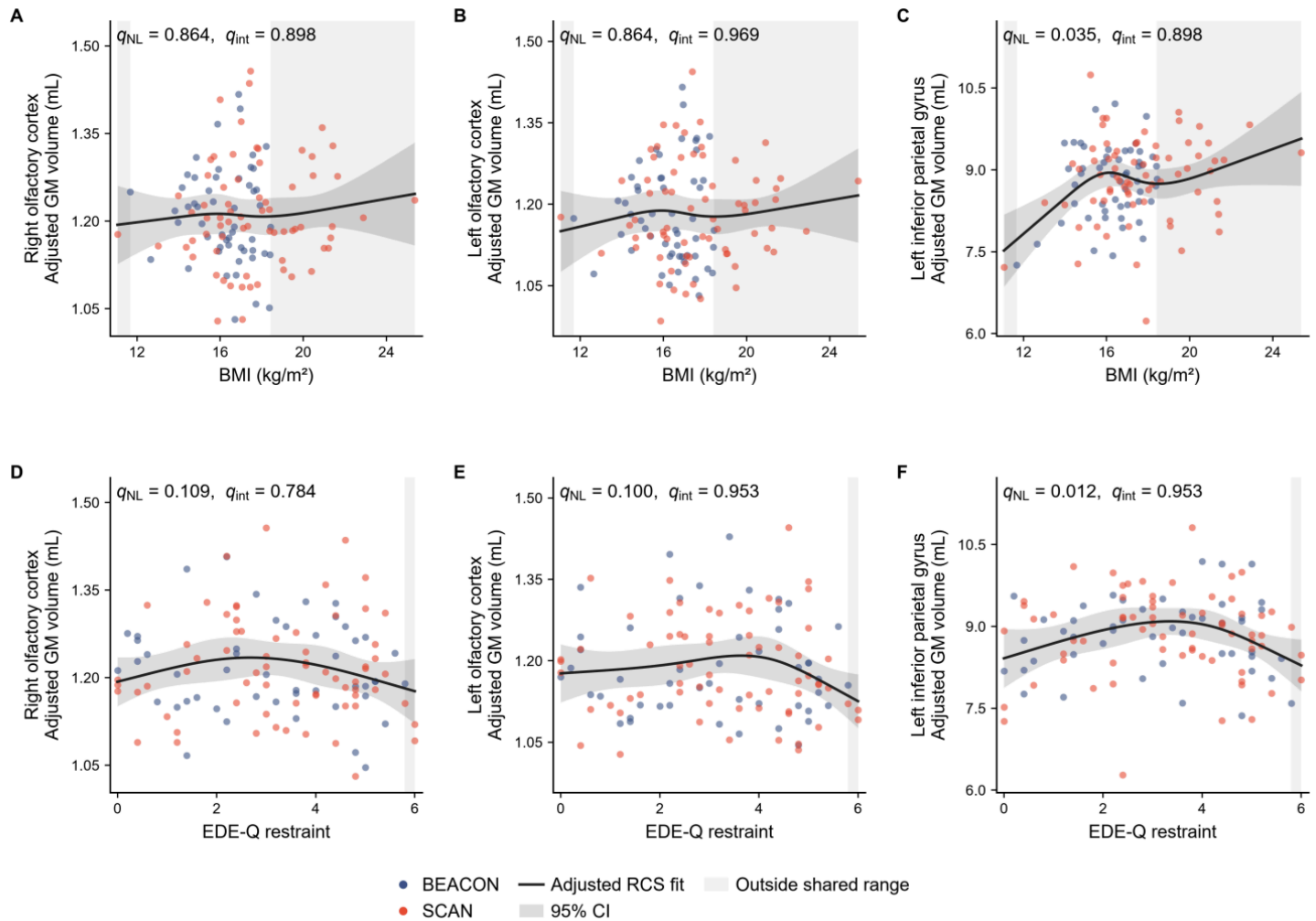


Figure 2

Exploratory associations of BMI in panels A to C and EDE Q restraint in panels D to F with regional GMV in AN. BMI analyses included 122 participants and restraint analyses included 115. Points are adjusted for age, TIV and cohort. Lines are four knot restricted cubic spline fits with pointwise 95% confidence bands. Colors denote cohort. Pale regions lie outside the exposure range shared by both cohorts. q_{NL} is the FDR adjusted nonlinearity test and q_{int} is the FDR adjusted curve by cohort interaction test.

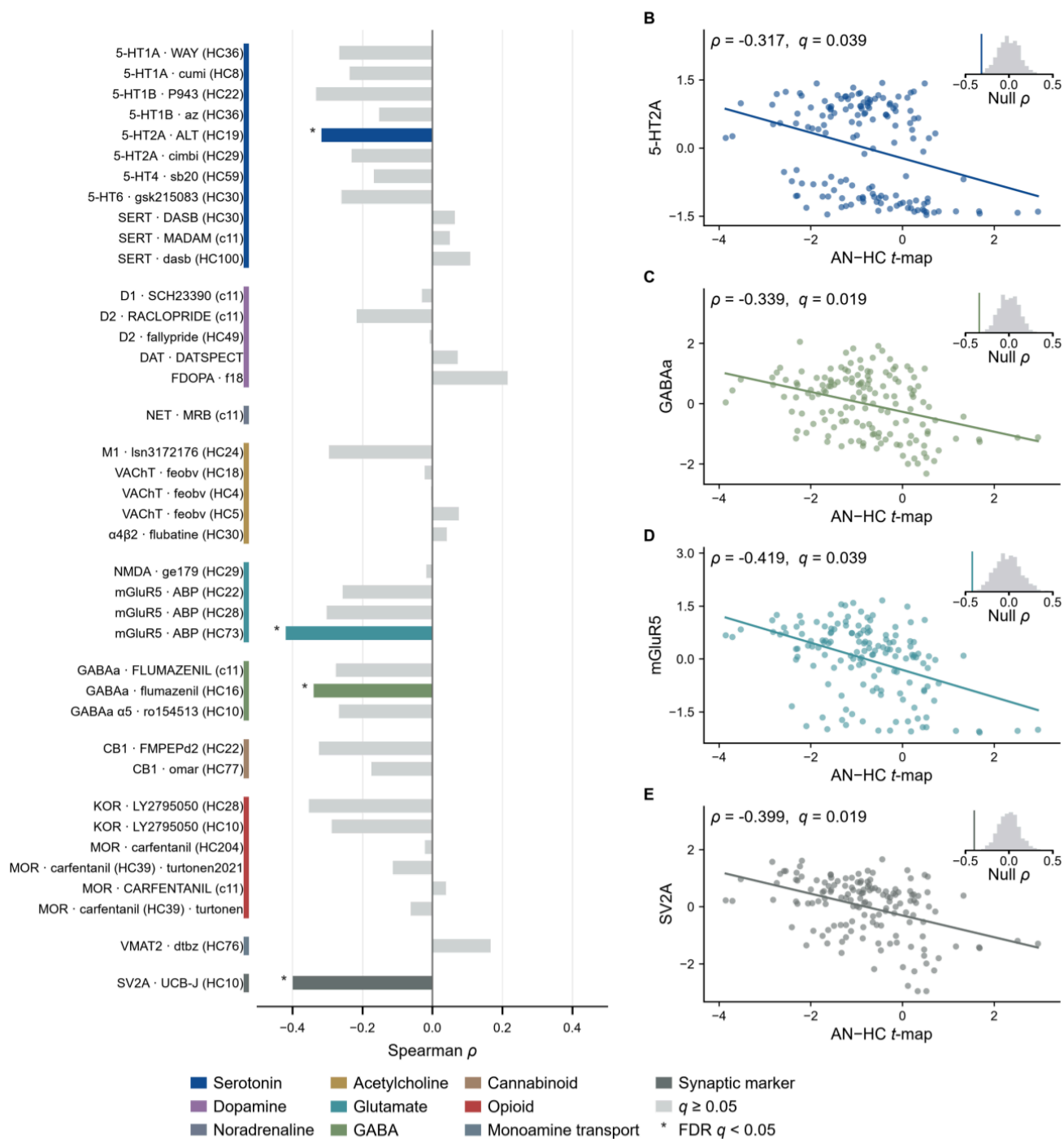


Figure 3

Spatial correspondence between the pooled t map comparing AN with HC and 39 normative PET and SPECT reference maps. Panel A shows Spearman correlations for all maps, with the four FDR significant associations highlighted. Panels B to E show regional associations for 5-HT_{2A}, GABA_A, mGluR5 and SV2A. Each point represents one of 148 AAL3 regions. Insets show 1,000 spatial null correlations and the observed value. A negative ρ indicates more negative t statistics comparing AN with HC in regions with higher normative reference map signal.

Supplementary Files

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