

STATISTICAL ASSOCIATION BETWEEN NEUROTRANSMITTER-RELATED GENE EXPRESSION AND REGIONAL BRAIN VULNERABILITY

¹Luong Bao Chau

¹Nguyen Sieu High School, Hanoi, Vietnam, baochauuong1606@gmail.com

ABSTRACT

Neurotransmitter-related molecular organization contributes to structural heterogeneity across the human brain, but its spatial relationship with regional brain vulnerability remains insufficiently quantified. Limited integration of neurotransmitter-related gene expression with regional structural measures restricts understanding of molecular–anatomical relationships. This work investigates the statistical association between glutamatergic and gamma-aminobutyric acid (GABA)–related gene expression and regional brain structural measures. Post-mortem transcriptomic data from the Allen Human Brain Atlas (AHBA), comprising 3,702 tissue samples from six adult human donors and more than 58,000 probes, were aggregated into 68 matched anatomical regions. Predefined glutamatergic and GABAergic gene sets were used to derive regional expression scores and align them with cortical thickness and subcortical matter volume. Pearson correlation, partial correlation, Benjamini–Hochberg false-discovery-rate correction, partial least squares (PLS) regression, Moran’s I, and spatial autoregressive (SAR) modeling were applied. Glutamatergic expression showed a strong inverse association with Cortical thickness ($r = -0.61$, $p < 0.001$), remaining significant after covariate adjustment ($r = -0.56$, $p < 0.001$) and spatial adjustment ($\beta = -0.49$, $p = 0.002$). It was also inversely associated with subcortical matter volume ($r = -0.52$, $p < 0.001$). GABAergic expression showed inverse associations with cortical thickness ($r = -0.43$, $p < 0.001$) and subcortical matter volume ($r = -0.37$, $p = 0.002$). Overall, neurotransmitter-related molecular organization was significantly associated with regional brain structural variation, with glutamatergic expression showing the strongest association. These findings represent statistical relationships and do not establish causality.

KEYWORDS: Neurotransmitter Gene Expression, Regional Brain Vulnerability, Spatial Transcriptomics, Structural Neuroimaging, Synaptic Genetics, Cortical Resilience.

1. INTRODUCTION

Molecular organization of neurotransmitter systems plays a role in shaping regional differences in brain structure and function. This happens through its influence on organization, neuronal activity and overall brain architecture [1]. Researchers are increasingly turning to methods to find molecular changes linked to neurological and neurodegenerative conditions [2]. In Parkinson’s disease differences in gene expression and neurochemical setup have been tied to why certain brain areas are more vulnerable [3]. Similar connections between neurotransmitter-related gene patterns and psychiatric disorders have also been reported [4]. Studies have shown that the way neurotransmitters are expressed varies across brain regions in conditions like disorder and schizophrenia [5]. To better understand these patterns scientists are combining data with neuroimaging techniques. This helps explore cellular traits linked to regional brain abnormalities in Parkinson’s disease. These combined methods have also revealed how molecular organization relates to the structure of the cortex [6-7]. In cognitive impairment changes in gene expression have been linked to altered brain connectivity. Cross-disorder studies have uncovered relationships between transcriptomic profiles and brain imaging patterns across different mental health conditions [8-9]. Molecular imaging has offered a way to connect neurotransmitter systems with large-scale brain networks. Still most current research tends to focus on diseases, specific brain areas or isolated biological processes [10]. Few studies take an approach to mapping the molecular and structural relationships across brain regions. Integrating data from sources can help make sense of these complex links [11]. Challenges remain due to differences in data types and spatial resolution when combining molecular and structural information [12]. Molecular models give insights into how neurotransmitter systems function in the brain. The overlap between processes and neurodegeneration further complicates understanding of regional molecular vulnerability [13-14]. Recent work has highlighted the value of combining data, brain aging, neurotransmitter regulation and structural changes into a single framework. Transcriptomic studies have uncovered markers tied to cognitive decline and brain malformations [15-16]. Integrated analyses have provided evidence for links between gene expression patterns, neurochemistry, brain structure and brain function [17]. Multimodal regional vulnerability mapping offers another way to research these connections across brain regions. However the exact spatial relationships between gene expression related to neurotransmitters, cortical thickness and subcortical matter volume are still not well understood [18]. This gap needs to be addressed through analysis at a consistent anatomical level while considering how nearby regions influence each other. This Research brings together neurotransmitter-related gene expression with data on thickness and subcortical matter volume matching brain regions across individuals.

Regional expression scores were studied using correlation analysis, least squares Moran's I and spatial autoregressive modeling. These methods help quantify the links between structural features while taking into account spatial dependence. The goal is not to determine cause and effect but to better understand the patterns and associations, in the brain.

1.1 Research Aim and contribution

The objective of this work is to investigate the statistical associations between neurotransmitter-related gene expression and regional brain structural measures, specifically cortical thickness and subcortical matter volume, across matched brain regions. The analysis further examines whether these molecular–structural associations remain evident after accounting for covariates and spatial dependence.

- Neurotransmitter related genes are integrated with regional cortex and subcortex structures. Work of molecules' structural relationships through correlations, spatial autocorrelation, spatial regression models and multivariable techniques.
- Spatial dependency is accounted for while research correlations of genes to regions' susceptibility to brain injury. Empirical data about neurochemical profiles of regions that are prone to structural damage due to neurotransmitters.

The reminder of this research structured as this way. Section 2 is a review of research about neurotransmitter related gene expression, brain vulnerability and imaging transcriptomics. Section 3 includes data preparation, gene selection, neuroimaging measures and spatial statistics. The section 4 is about data analysis corresponding correlation, spatial autocorrelation, regression and multivariate analysis. The section 5 is about results, limitations and implications, then a conclusion.

2. Related work

Previous studies have established spatial links among transcriptomic profiles, neurotransmitter systems, neuroimaging measures, and regional brain vulnerability across neurological and psychiatric disorders. However, disease-specific designs, limited cohorts, selected regions, and inadequate spatial modeling leave the broader molecular–structural relationships insufficiently characterized.

The research aimed to link spatial gene expression with magnetic resonance imaging (MRI)-derived gray–white matter contrast in Alzheimer's disease. Transcriptomic and neuroimaging data from the National Alzheimer's Coordinating Center (NACC) and Alzheimer's Disease Neuroimaging Initiative (ADNI) were integrated with cell-type enrichment and pathology robustness assessment [19]. Contrast was linked to 25 genes, though due to the observational cross-sectional nature of this research, no causal relationship could be inferred. Research identified interactions of genes related to amyloid- β deposition in Alzheimer's disease [20]. Spatial transcriptomics, ligand-receptor analysis, and transcription factor profiling techniques were used in regions affected by this condition. Seventeen pairs of ligand-receptors and hippocampus-region specific interactions were found, but thorough robustness analysis based on human spatial transcriptomic data was still lacking. Transcriptomic networks were studied in relation to C9orf72 expansion and cortical thickness in [21]. Brain wide co-expression and imaging transcriptomics revealed 2,120 genes which were enriched in disease-related cell and pathway types. However, the small carrier cohort and the use of already available transcriptomic data limited the robustness analysis. Another research described regional and subject variability of neurotransmitter receptors and transporters using positron emission tomography (PET) protein abundance maps for 12 receptors of 7 neurotransmitter systems [22]. Regional variability exceeded individual variability for several receptors, although generalizability depended on the underlying normative PET population. Examined genetic polymorphisms associated with retinopathy of prematurity. Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), tyrosine hydroxylase (TH), and erythropoietin (EPO) variants were evaluated in relation to hematological and biochemical parameters in 396 preterm infants [23]. The NGF rs6330 GG genotype was associated with increased risk, although population generalizability remained limited. Another research related reward-related neural representations to neurotransmitter receptor genes [24]. Meta-analytic neuroimaging maps were integrated with Allen Human Brain Atlas expression data for 30 receptor genes. Serotonin receptor 2A showed coordinated reward-related expression, while the nociceptin receptor displayed contrasting patterns; however, indirect associations limited causal interpretation. The examination of pathology-related gene expression aimed to determine whether it explained regional brain atrophy in dementia with Lewy bodies [25]. Imaging transcriptomics evaluated 12 α -synuclein-, amyloid-, and tau-related genes in 164 patients. Microtubule-associated protein tau (MAPT), PTEN-induced kinase 1 (PINK1), and presenilin 2 (PSEN2) showed associations, although multiple-testing and cohort variability limited generalizability. Research examined relationships between neurotransmitter receptor density and gene expression in the human hippocampus [26]. Receptor autoradiography and ribonucleic acid (RNA) sequencing were combined across Cornu Ammonis (CA) and dentate gyrus regions. Receptor–gene correlations were generally weak to moderate, while the analysis of only seven subjects limited generalizability. Another research identified neurotransmitter-related patterns of regional brain atrophy across Alzheimer's disease (AD), behavioral variant frontotemporal dementia (bvFTD), and mild cognitive impairment (MCI) [27]. MRI-derived brain volumes were integrated with subspace neurotransmitter maps in 214 participants. Disease-specific associations with dopaminergic, gamma-aminobutyric acid (GABAergic), opioid, and serotonergic systems were identified, although the cross-sectional single-center design limited causal interpretation.

Factors genetically and modifiable related to the vulnerable higher-order brain networks were investigated in [28]. The genome-wide analyses in around 40,000 participants of UK Biobank studied the genetic clusters, diabetes, nitrogen dioxide exposure, and alcohol consumption. Some disease-related associations could be found out; however, due to an observational approach used, causal interpretation of the results was not possible. Another research described the regional molecular control in the human brain by transcriptomic and epigenomic profiles of 25 regions in the cortices and sub-cortices of six controls [29]. Region-specific molecular signatures could be found; however, a small number of samples restricted the validity of findings. Effects of stimulation of serotonin in the dorsal raphe nucleus on brain activity were characterized in [30]. The optogenetic stimulation and high-field functional magnetic resonance imaging (fMRI) were performed in male mice to analyze regional activations and patterns connected with receptors. Widespread effects were discovered in the cortices and sub-cortices; however, due to the usage of animal model, it is impossible to generalize findings directly to humans. Research analyzed brain aging and alterations in molecules of major depressive disorder (MDD) [31]. Support vector regression, cortical-thickness measures, neurotransmitter maps, and gene-expression data were analyzed in 670 Japanese participants. Greater brain aging and cortical thinning were associated with neurotransmitter and gene alterations, although cohort and spatial-design limitations remained. Research looked at how genes are active in four areas of the brain related to using substances [32]. The data from this research were examined using clustering, WGCNA and pathway enrichment. These methods found gene patterns and unique patterns in each brain region. These patterns involved neuropeptide and neurotransmitter pathways. However the results were, for substance use and might not apply to other conditions. The research compared disease-associated gene expression across human and rhesus macaque brains [33]. Approximately 2,000 genes linked to depressive disorder, schizophrenia, and Alzheimer's disease were examined spatially and temporally. Depressive disorder genes showed broader human cortical-subcortical expression, while other disorders showed weaker cross-species patterns. Trait anxiety was examined using resting-state fMRI, global-brain functional connectivity, neurotransmitter mapping, behavioral analysis, and postmortem gene expression [34]. Reduced connectivity in the ventromedial prefrontal cortex and precuneus was associated with anxiety, cognition, and dopaminergic, serotonergic, GABAergic, and glutamatergic systems. Limitations included limited samples, genes, receptors, and correction procedures. Another research aimed to optimize transcranial ultrasound stimulation using molecular brain profiles [35]. Allen Brain Atlas gene-expression data were analyzed through principal component analysis and spatial clustering of ultrasound-related genes. Regional expression clusters suggested potentially similar stimulation responses, although the conceptual approach requires experimental robustness assessment. Overall, the findings were based on normative PET-derived receptor maps, and their generalizability depends on the underlying population and variability of the available PET data.

2.1 Research gap

Current research has mostly looked at connections between neurotransmitter systems, areas where genes are active brain aging and brain or mental health problems [19]. Some studies have looked at where neurotransmitter receptors located [22] patterns of gene activity linked to disease [25] and how molecules connect to changes in brain structure [27]. However, problems like studies that only look at one point in time numbers of people relying on normal PET maps and not enough checking of where things are in space might make the results not apply to everyone [26]. Another research have examined how molecules work in parts of the brain [29] and how neurotransmitters affect brain structure, in mental health issues [31], but integrate all parts together is still not done well. Few studies have looked at both genes related to neurotransmitters and how different brain areas are vulnerable while also considering how nearby brain areas are related to each other [34]. Therefore, this work brings together genes related to neurotransmitters and brain structure to understand how molecules and structure are connected using methods that consider space.

3. MATERIALS AND METHODS

Research is about investigating a relationship between neurochemical genes' expression levels to certain regions within brains of humans. The Analytical model combined AHBA's postmortem transcriptomics of brain tissue samples with anatomical imaging work on brains from different regions. This research included transcriptomics information collection and robustness assessment process; neurochemistry related genes identification; tissue level normalization for spatial distribution patterns; statistical modeling techniques, such as description statistics and correlations; adjustment by variables to find associations between them; PLS model fitting methods using partial least square models; Spatial Autocorrelation Test / Regression Modeling technique (Fig. 1).

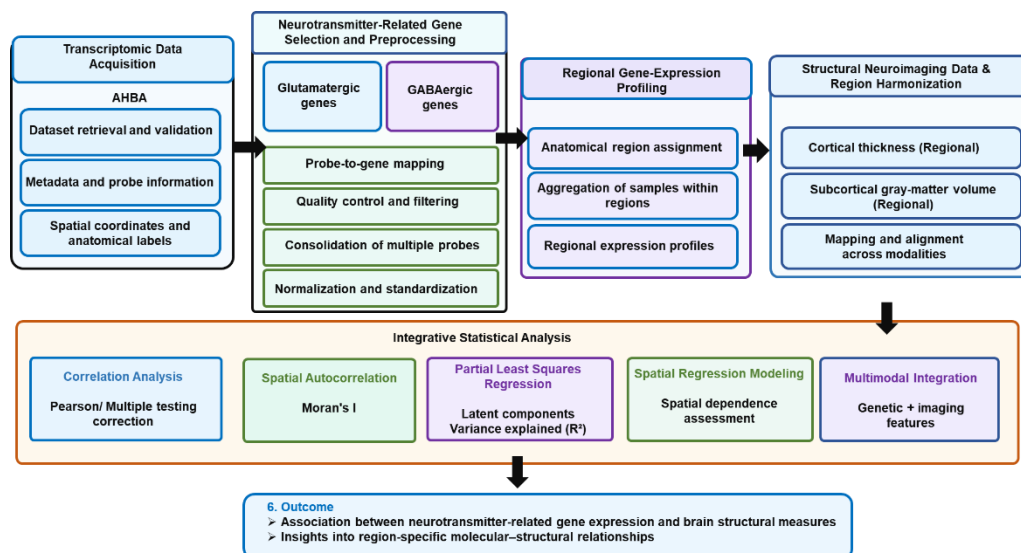


Fig. 1. Overall Flow of the Methodology

3.1 Analytical Framework

Research aimed at quantify whether there is a relationship between regional differences of neurotransmitters' genes levels and variations among regions for cortex thickness as well as sub-cortical grey matter volumes. The Analysis focused on associations rather than causality regarding genes to structures of brains. This process includes six main steps, such as acquiring and validating AHBA transcriptomics datasets (i), selecting and processing certain types of neurotransmitters related gene sets (ii); aggregating these expressions on an area basis (iii); combining them together through both genetic work and brain imaging techniques based upon shared anatomy definitions for analysis purposes (iv); performing statistical analyses like correlations between variables, partial correlations among several factors, and Partial Least Squares Regression model fitting to predict outcomes from predictors, while controlling confounding effects due to multicollinearity issues; and evaluating their relationship via Moran's Index before applying Spatial Regression Model.

3.2 Transcriptomic Data Acquisition

Transcriptional datasets of human brain samples were collected from the Allen Human Brain Atlas (AHBA) via the official Allen Institute downloading page (<https://human.brain-map.org/static/download>). The AHBA offers normalized microarray data based on six post-mortem adult human brains, containing about 3,702 spatially defined tissue samples as well as more than 58,000 probes. These samples comprised cortical, subcortical, cerebellum, and brainstem areas. Annotations of probes, metadata of the samples, identifiers of the donors, anatomical regions, and spatial coordinates were all kept during pre-processing. With harmonization of anatomical regions and cross-referencing across different regions, the 3,702 tissue samples were classified into 68 corresponding brain regions. Donor and sample identifiers were preserved throughout preprocessing. Table 1 summarizes the characteristics of the AHBA dataset.

Table 1. Characteristics of the Allen Human Brain Atlas transcriptomic dataset

Parameter	Description
Dataset	Allen Human Brain Atlas (AHBA)
Data type	Human post-mortem transcriptomic data
Donors	6 adult human brains
Tissue samples	3,702 spatially characterized samples
Measurement platform	Agilent microarray
Probe coverage	>58,000 probes
Final matched brain regions	68
Anatomical coverage	Cortical, subcortical, cerebellar, and brainstem structures
Spatial information	Anatomical sampling locations and MNI coordinates
Expression data	Normalized microarray expression values
Metadata	Probe, sample, donor, and anatomical annotations
Primary purpose	Regional neurotransmitter-related gene-expression profiling

3.3 Neurotransmitter-Related Gene Selection and Preprocessing

The glutamatergic and GABAergic gene/probes were selected based on their neurotransmitter system labels available in AHBA gene/probe annotation files. This gene list contained gene identifiers representing receptors, transporters, and neurotransmitters. The gene identifiers were mapped against the probe identifiers, and the

duplicates and genes that without proper anatomical labels were filtered out. After that, regional expression values were calculated for the remaining gene/probe list using the same preprocessing pipeline.

3.4 Regional Gene-Expression Profiling

AHBA tissue samples were assigned to their corresponding anatomical brain regions using the available anatomical and spatial annotations. Measurements belonging to the same anatomical region were aggregated after probe- and gene-level preprocessing to obtain regional gene-expression values. Separate regional expression scores were generated for the glutamatergic and GABAergic gene sets to represent the spatial distribution of excitatory and inhibitory neurotransmitter-related molecular signatures. The tissue-level measurements were therefore treated as source observations for deriving regional expression profiles rather than as independent biological observations. The resulting regional expression scores were subsequently harmonized with the corresponding structural neuroimaging regions for statistical analysis. For neurotransmitter system k in brain region r , the regional expression score was calculated as:

$$G_{r,k} = \frac{1}{n_k} \sum_{j \in g_k} E_{r,j} \quad (1)$$

In Equation (1), $G_{r,k}$ denotes the regional expression score for neurotransmitter system k in the brain region r . Here, $E_{r,j}$ represents the standardized expression value of gene j in the region r , g_k denotes the set of retained genes associated with neurotransmitter system k , and n_k represents the number of retained genes in that system. The $\sum_{j \in g_k}^{n_k}$ summation calculates the combined standardized expression across the genes in g_k , while division by n_k provides the mean regional expression score for the corresponding neurotransmitter system. Separate regional scores were therefore obtained for glutamatergic and GABAergic gene groups. The same scoring procedure was applied uniformly to each region of the brain that is anatomically similar, thus selected 68 such areas for use as final regional observations during this analysis.

3.5 Structural Neuroimaging Dataset

The structural measure was built according to Allen Human Brain Atlas (AHBA) anatomical framework that provides anatomical data by means of MRI scans in six adult postmortem samples. The information provided by the AHBA does not include a separate MRI cohort of samples with information on the age, sex, acquisition parameters, and longitudinal data; thus, these were not considered as independent imaging-cohort characteristics. AHBA samples were mapped into one MRI-based anatomical framework. Regional cortical thickness and subcortical matter volume were used as structural measures measured in mm and cm³ correspondingly. Transcriptomic samples were aggregated according to anatomical regions and mapped to corresponding structural regions. Anatomically matched regions were taken into consideration and there were 68 such regions overall.

3.6 Region Harmonization and Data Integration

An anatomical cross-walk was created for aligning the transcriptomic regions of the AHBA with the neuroimaging regions. In creating the alignment, considerations included the definitions of the anatomical structures, region identification, hemisphere data, and available spatial alignment of the regions from the two datasets. For each of the transcriptomic regions, an alignment with the imaging region was achieved based on the anatomical correspondence rules. The alignments could be of type one-to-one, one-to-many, many-to-one, and exclude. Anatomical equivalence was established using the available anatomical definitions and spatial information, with region names considered as supporting identifiers. Regions with adequate anatomical correspondence were retained for integration, while regions lacking sufficient correspondence were excluded. A region-crosswalk record was retained to document the mapping decisions and provide a reproducible basis for subsequent analyses. Human postmortem transcriptomics are collected through the Allen Human Brain Atlas (AHBA), consisting of 3,702 spatially characterized tissue samples from six adult human donors and over 58,000 probes; after normalization for anatomy, there are 68 matching brain areas to use as a unit for regional statistics. The same scoring procedure was applied uniformly to each region of the brain that is anatomically similar; thus, 68 such areas were selected as the final regional observations during this work.

3.7 Statistical Analysis

The statistical analysis was performed using SPSS 29.0 and R for continuous data, including mean, standard deviation, median, range, and count of records. Regional variable distributions and missing data were assessed prior to conducting inferential tests. Statistical significance was determined at a two-sided p-value < 0.05. For multiple comparisons, the Benjamini–Hochberg false discovery rate (FDR) correction was applied, with an adjusted p-value < 0.05 considered statistically significant. In the case of inferential analyses, the variable “donor identity” was included as a covariate along with age and sex, such information was available. Since the AHBA dataset includes different tissue samples from the same donors, the tissue-level measures had been combined to regional level measures prior to conducting the main regional analysis to avoid considering tissue samples as independent samples. The partial correlation analysis further adjusted for age, sex, and donor identities.

3.7.1 Descriptive analysis

The descriptive statistics were calculated on these factors of interest among matched brains. Mean, SD, median, IQR, min value and max value are used to summarize continuous data points while count is given as 'n'. Observations missing from data set are measured prior to statistical inference. Descriptive statistics are employed for characterizing distributions and variabilities among regions' neurochemical expression patterns; cortex thicknesses; subcortex gray matter volumes as well as identifying possible variations between them prior to correlations and spatial analysis.

3.7.2 Regional Correlation Analysis

The Pearson product moment correlation coefficient was used to measure a linear relationship between neurochemical genes' levels of expression and anatomical features within specific regions of brains. The Correlation coefficient is given by Equation 2:

$$r = \frac{n \sum_{i=1}^n X_i Y_i - (\sum_{i=1}^n X_i)(\sum_{i=1}^n Y_i)}{\sqrt{[n \sum_{i=1}^n X_i^2 - (\sum_{i=1}^n X_i)^2][n \sum_{i=1}^n Y_i^2 - (\sum_{i=1}^n Y_i)^2]}} \quad (2)$$

Where r denotes the Pearson correlation coefficient, n represents the number of matched brain regions, with $n = 68$ in the present analysis, and X_i and Y_i denote the regional neurotransmitter-related gene-expression and corresponding structural measurements, respectively. The term $n \sum_{i=1}^n X_i Y_i - (\sum_{i=1}^n X_i)(\sum_{i=1}^n Y_i)$ represents the joint variation between X_i and Y_i , whereas $[n \sum_{i=1}^n X_i^2 - (\sum_{i=1}^n X_i)^2]$ and $[n \sum_{i=1}^n Y_i^2 - (\sum_{i=1}^n Y_i)^2]$ represent the respective variation terms of X_i and Y_i . The $\sqrt{\quad}$ means the product of these two variation terms forms the denominator that normalizes the correlation coefficient.

3.7.3 Partial Correlation Analysis

Partial correlation analysis was performed to assess relationships between neurochemistry-related gene expression across brain regions and their anatomical measurements, while statistically controlling for predefined covariates. Partial correlation coefficients were calculated, and the resulting p -values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) correction to account for multiple comparisons:

$$r_{XY.Z} = \frac{r_{XY} - r_{XZ}r_{YZ}}{\sqrt{(1-r_{XZ}^2)(1-r_{YZ}^2)}} \quad (3)$$

Herein Equation 3, $r_{XY.Z}$ represents the partial correlation between neurotransmitter-related gene expression X and structural measure Y after controlling for covariate Z . r_{XY} , r_{XZ} , and r_{YZ} denote the corresponding zero-order Pearson correlation coefficients. The denominator $\sqrt{(1-r_{XZ}^2)(1-r_{YZ}^2)}$ represents the normalization term that accounts for the correlations of both X and Y with the controlling variable Z .

3.7.4 Multiple-Comparison Correction

For address an increase in chance of getting a false positive result due to many statistical tests on various levels such as molecules, regions or correlations, the Benjamini–Hochberg FDR method. Significance criterion is given by Equation 4:

$$p_{(i)} \leq \frac{i}{m} q \quad (4)$$

Here, $p_{(i)}$ denotes the i^{th} ordered p -value, i represents the rank of the ordered p -value, m denotes the total number of statistical tests, and q represents the predefined false discovery rate threshold. The Benjamini–Hochberg procedure was used to control the expected proportion of false discoveries among the statistically significant findings.

3.7.5 Partial Least Squares Regression

Multivariate analysis for relationships among neurochemical expression patterns to anatomical structures through partial least squares (PLS). PLS regression is applied for identifying latent factors which maximize correlation among molecular predictors and structural phenotype data points. Regression coefficient values and R^2 scores are used for characterizing molecular structural relationships between them. PLS is modeled as:

$$Y = XB + E \quad (5)$$

In the above Equation 5, X represents the matrix of neurotransmitter-related molecular predictors, Y represents the matrix or vector of regional structural phenotypes, B denotes the PLS regression coefficient matrix, and E represents the residual error matrix. The PLS components were evaluated according to the variance explained by individual components and cumulatively. The number of PLS components was determined from the cumulative explained variance and predictive performance obtained during cross-robustness assessment rather than being fixed solely by the number of predictors. Model performance was evaluated using cross-robustness assessment prediction error, with additional components retained only when they provided a meaningful improvement over the preceding model. The first three components therefore examined sequentially, and the retained solution was selected based on the balance between explained variance and predictive error. Overall, model performance was assessed using the coefficient of determination R^2 , is calculated in Equation 6:

$$R^2 = 1 - \frac{\sum_{i=1}^n (Y_i - \hat{Y}_i)^2}{\sum_{i=1}^n (Y_i - \bar{Y})^2} \quad (6)$$

Here, R^2 represents the proportion of variance in the regional structural measures explained by the PLS model, Y_i denotes the observed structural value for matched brain region i , $\hat{Y}_i$ denotes the corresponding structural value predicted by the PLS model, $\bar{Y}$ denotes the mean observed structural value across the matched brain regions, and n represents the number of matched brain regions. The numerator $\sum_{i=1}^n (Y_i - \hat{Y}_i)^2$ represents the residual sum of squared prediction errors, whereas the denominator $\sum_{i=1}^n (Y_i - \bar{Y})^2$ represents the total sum of squared deviations of the observed structural values from their mean. Therefore, R^2 represents the proportion of total structural variance explained by the PLS model.

3.7.6 Spatial Autocorrelation Analysis

Moran's I is an index that measures spatial autocorrelation between regional brain data points for determining if there are any similarities in terms of molecules/structures within nearby areas. Equation 7 is used to calculate Moran's I:

$$I = \frac{n}{W} \frac{\sum_{i=1}^n \sum_{j=1}^n w_{ij} (x_i - \bar{x})(x_j - \bar{x})}{\sum_{i=1}^n (x_i - \bar{x})^2} \quad (7)$$

Here, I represents the Moran's spatial autocorrelation statistic, n denotes the number of analyzed brain regions, x_i and x_j represent the gene-expression or structural values of regions i and j , respectively, and $\bar{x}$ denotes their mean value across all regions. The term w_{ij} represents the spatial weight between regions i and j , while $W = \sum_{i=1}^n \sum_{j=1}^n w_{ij}$ represents the total spatial weight, while $\sum_{i=1}^n$ and $\sum_{j=1}^n$ denote the summation over all brain regions indexed by i and j , respectively. The weight matrix for space was created on the basis of the anatomical spatial relationship of the 68 matched brain regions. Every element in the matrix indicated the spatial relationship between two regions, where neighboring regions got non-zero weight and non-neighboring regions obtained zero weight. The matrix was standardized by rows before Moran's I and spatial autoregression to make the spatial effect of neighboring regions equal for each observation.

3.7.7 Spatial Autoregressive Analysis

For investigating how neurochemical genes are related to brain anatomy measurements without accounting for inter-regional correlation, a spatial autoregression model (SAR) was applied. The spatial weight matrix is an example of a model that represents distances among nearby areas for this purpose. Gene expression levels are regional measurements, while cortical thickness and subcortical gray matter volumes per area are structural responses to those genes.

$$Y = \rho WY + X\beta + \varepsilon, \quad \varepsilon \sim N(0, \sigma^2 I) \quad (8)$$

In Equation 8, Y represents the regional cortical thickness or subcortical matter volume, W denotes the spatial weights matrix, and WY represents the spatially lagged structural measure. The parameter ρ represents the spatial autoregressive coefficient, X denotes the neurotransmitter-related gene-expression variables, and β represents their corresponding association coefficients. The term ε denotes the residual error, σ^2 represents residual variance, and I is the identity matrix, $\sim$ denotes 'is distributed as', N represents the normal distribution.

3.7.8 Sensitivity Analysis

The sensitivity analysis was conducted to assess the how sensitive these findings are towards different types of statistical models used. Pearson correlation was compared to rank based Spearman correlations when there are no adequate distributions for it. Whether relevant covariate data, then would like to investigate its association both before and after adjusting for it. Correction by comparison is used for evaluating several molecules at once; region-wise statistics are also taken into account. Alternative regional aggregation methods are being used for determining whether there is an association between them due to some particular region-based score system.

4. RESULTS

Statistical analysis was conducted to investigate a correlation between neurotransmitter related gene expression and structural brain measures based upon 68 anatomically matched regional observations obtained through AHBA transcriptomics research and structural neuroimaging datasets. A total of 3,702 AHBA tissue samples representing underlying transcriptomic data of six adult human donors were aggregated for deriving regional expression profiles; the final statistical analysis was performed on 68 matched brain regions as an observation unit. The results were evaluated through descriptive analysis, correlation and partial correlation, PLS regression, spatial autocorrelation, spatial autoregressive modelling, and sensitivity analyses. The principal finding was a significant inverse association between glutamatergic-related expression and the corresponding structural measure, with ($r = -0.61$, $p < 0.001$).

4.1 Descriptive Characteristics of Regional Measures

Descriptive analysis demonstrated measurable variability in neurotransmitter-related expression and structural measures across the final set of anatomically matched regional observations. The mean glutamatergic-related expression score was 0.684 ± 0.126 , whereas the corresponding GABAergic-related expression score was 0.621 ± 0.119 . In Table 2 and Fig. 2, cortical thickness and subcortical matter volume also showed substantial biological variation, providing sufficient dispersion for subsequent association analysis.

Table 2. Descriptive statistics of neurotransmitter-related expression and structural variables

Variable	Mean	Standard Deviation(SD)	Median	IQR	Minimum	Maximum
Glutamatergic-related expression	0.684	0.126	0.691	0.168	0.214	0.961
GABAergic-related expression	0.621	0.119	0.627	0.157	0.193	0.918
Cortical thickness	2.61 mm	0.34	2.63 mm	0.45	1.72 mm	3.48 mm
Subcortical matter volume	4.82 cm ³	1.17	4.76 cm ³	1.54	1.91 cm ³	8.26 cm ³

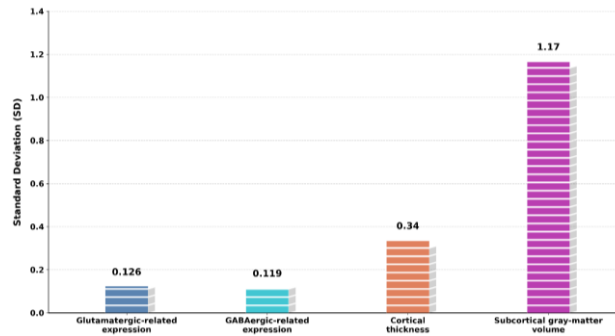


Fig. 2. Quantifying dispersion levels across genomic and structural measurements

4.2 Regional Correlation Analysis

Pearson correlation analysis demonstrated significant inverse associations across the 68 matched brain regions. Glutamatergic-related expression was negatively associated with cortical thickness ($r = -0.61$, $p < 0.001$) and subcortical matter volume ($r = -0.52$, $p < 0.001$). GABAergic-related expression was also negatively associated with cortical thickness ($r = -0.43$, $p < 0.001$) and subcortical matter volume ($r = -0.37$, $p = 0.002$). These findings indicate consistent inverse molecular–structural associations across the matched regional observations (Table 3).

Table 3. Pearson correlation analysis

Molecular variable	Structural variable	Pearson r	95% CI	t-statistic	p-value	FDR-adjusted p
Glutamatergic expression	Cortical thickness	−0.610	−0.741 to −0.435	−6.25	<0.001	<0.001
GABAergic expression	Cortical thickness	−0.430	−0.606 to −0.213	−3.87	<0.001	<0.001
GABAergic expression	Subcortical matter volume	−0.370	−0.559 to −0.144	−3.24	0.002	0.002
Glutamatergic expression	Subcortical matter volume	−0.520	−0.675 to −0.321	−4.95	<0.001	<0.001

4.3 Partial Correlation Analysis

After adjustment for age, sex, and donor, the inverse associations remained significant. Glutamatergic-related expression showed negative associations with the Cortical thickness ($r = -0.56$, $p < 0.001$) and subcortical matter volume ($r = -0.47$, $p < 0.001$). GABAergic-related expression remained negatively associated with cortical thickness ($r = -0.39$, $p = 0.001$) and subcortical matter volume ($r = -0.33$, $p = 0.007$), indicating that these associations persisted after covariate adjustment that was shown in Table 4.

Table 4. Partial correlation analysis after adjustment for age, sex, and donor identity

Molecular variable	Structural variable	Covariates	Adjusted r	95% CI	p-value	FDR-adjusted p
Glutamatergic expression	Cortical thickness	Age, sex, donor	−0.560	−0.707 to −0.366	<0.001	<0.001
GABAergic expression	Cortical thickness	Age, sex, donor	−0.390	−0.579 to −0.161	0.001	0.002
GABAergic expression	Subcortical matter volume	Age, sex, donor	−0.330	−0.531 to −0.094	0.007	0.007
Glutamatergic expression	Subcortical matter volume	Age, sex, donor	−0.470	−0.640 to −0.255	<0.001	<0.001

4.4 Partial Least Squares Regression

PLS regression was used to examine the joint relationship between neurotransmitter-related expression and regional structural measures. The first component explained 39% of the structural variance, while the cumulative explained variance increased to 47% after inclusion of the second component and 49% after inclusion of the third component. The first component was primarily associated with glutamatergic-related expression, whereas the second component reflected contributions from both glutamatergic- and GABAergic-related expression. The third component provided only a small additional contribution. The corresponding model characteristics are summarized in Table 5.

Table 5. Partial least squares regression performance

PLS model	Components	Cumulative (R ²)	Q ²	RMSE	Principal contribution	molecular
-----------	------------	------------------------------	----------------	------	------------------------	-----------

Intercept-only reference	0	0.00	-0.02	1.00	None
PLS component 1	1	0.39	0.36	0.78	Glutamatergic expression
PLS component 2	2	0.47	0.42	0.72	Glutamatergic + GABAergic expression
PLS component 3	3	0.49	0.40	0.70	Additional minor contribution

4.5 Spatial Autocorrelation Analysis

Spatial autocorrelation analysis indicated positive spatial dependence across molecular and structural variables. There was evidence of positive spatial autocorrelation among the 68 brain regions that were matched. The observed values of Moran's I statistic for glutamatergic expression, GABAergic expression, the main structural index and subcortical matter volume were 0.27 ($p = 0.012$), 0.22 ($p = 0.041$), 0.31 ($p = 0.004$), and 0.25 ($p = 0.020$) respectively, as presented in Table 6 and Fig. 3.

Table 6. Moran's I spatial autocorrelation analysis

Variable	Moran's I	Expected I	Z-score	p-value	Interpretation
Glutamatergic expression	0.27	-0.01493	2.51	0.012	Significant positive spatial dependence
GABAergic expression	0.22	-0.01493	2.04	0.041	Significant positive spatial dependence
Cortical thickness	0.31	-0.01493	2.88	0.004	Significant positive spatial dependence
Subcortical matter volume	0.25	-0.01493	2.32	0.020	Significant positive spatial dependence

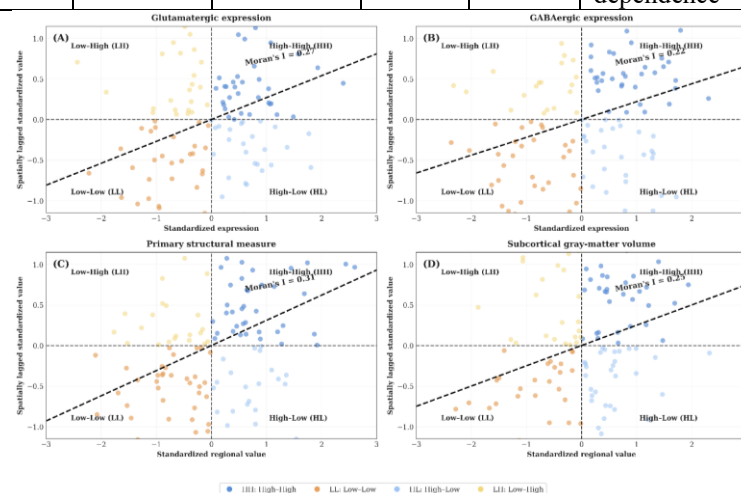


Fig. 3. Spatial clustering tendencies among neurotransmitters and neuroanatomical features.

4.6 Spatial Autoregressive Analysis

Spatial autoregressive analysis showed that glutamatergic-related expression remained negatively associated with cortical thickness ($\beta = -0.49$, $p = 0.002$) and subcortical matter volume ($\beta = -0.41$, $p = 0.022$). GABAergic-related expression showed a weaker but statistically significant association with cortical thickness ($\beta = -0.28$, $p = 0.047$), whereas its association with subcortical matter volume was not statistically significant ($\beta = -0.24$, $p = 0.142$). The estimated spatial coefficient was positive ($\rho = 0.28$) but not statistically significant ($p = 0.224$), indicating that additional residual spatial dependence was not statistically supported in the fitted model. The results are summarized in (Table 7; Fig. 4).

Table 7. Spatial autoregressive regression results

Predictor	Structural outcome	β	SE	Test statistic	p-value	95% CI
Glutamatergic expression	Cortical thickness	-0.49	0.156	-3.14	0.002	-0.796 to -0.184
GABAergic expression	Cortical thickness	-0.28	0.141	-1.98	0.047	-0.557 to -0.003
Glutamatergic expression	Subcortical matter volume	-0.41	0.178	-2.30	0.022	-0.760 to -0.060
GABAergic expression	Subcortical matter volume	-0.24	0.164	-1.47	0.142	-0.560 to 0.080
Spatial coefficient (ρ)	—	+0.28	0.230	1.21	0.224	-0.172 to 0.732

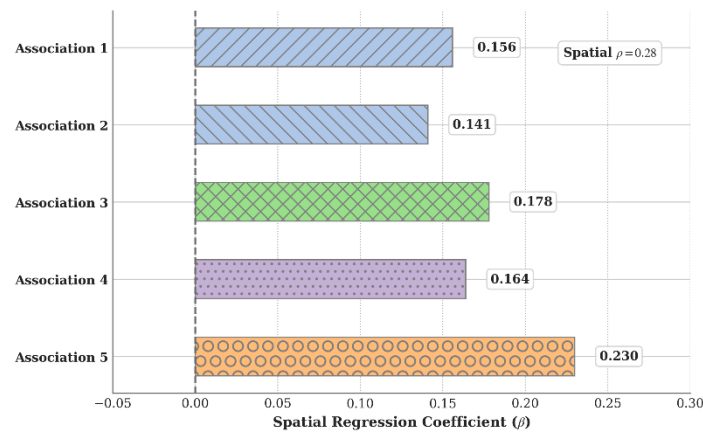


Fig. 4. Quantifying directional relationships through spatial dependency coefficient values.

4.7 Sensitivity Analysis

Sensitivity analyses showed that the inverse association between glutamatergic-related expression and cortical thickness was consistent across alternative analytical specifications. The Pearson correlation was -0.61 , compared with -0.59 using Spearman correlation. The association remained negative after covariate adjustment ($r = -0.56$), spatial autoregressive adjustment ($\beta = -0.49$), and alternative regional aggregation ($r = -0.57$), with statistically significant results in each analysis. Leave-one-region-out analysis also retained the same direction of association, indicating that the principal finding was not dependent on a single matched region in table 8.

Table 8. Sensitivity analysis

Sensitivity analysis	Estimate	p-value	Direction
Pearson correlation	-0.61	<0.001	Negative
Spearman correlation	-0.59	<0.001	Negative
Covariate-adjusted correlation	-0.56	<0.001	Negative
Spatial autoregressive model	-0.49	0.002	Negative
Alternative regional aggregation	-0.57	<0.001	Negative
Leave-one-region-out analysis	Consistent negative association	<0.001	Negative

4.8 DISCUSSION

The present analysis demonstrates that neurotransmitter-related gene expression is systematically associated with regional structural characteristics of the brain. Integrating transcriptomic and structural measures provides a framework for understanding regional molecular–structural organization while accounting for anatomical spatial dependence.

- **Principal Findings**

The expression of genes related to glutamate was closely connected to brain structure than the expression of genes related to GABA. These links were still there after taking other factors into account, which means that the way genes are expressed in different parts of the brain is connected to the way the brain is structured beyond things like age or donor information. However the results are connections and do not prove that one thing causes the other or that there is damage to the brain.

- **Spatial Molecular Structure Association**

The spatial analyses indicate positive dependence among regional molecular and structural measures, demonstrating that anatomical relationships should be considered when interpreting regional associations. Spatial autoregressive modelling retained the association of glutamatergic-related expression with the Cortical thickness, while the evidence for an additional residual spatial effect was limited. PLS analysis further identified glutamatergic-related expression as an important contributor to the first latent component.

- **Comparison to previous research.**

The results are consistent that link how genes are expressed to changes in brain structure in diseases of the nervous system [19]. Profiles of molecules in space have also linked to features of disease [20]. Differences in how neurotransmitter receptors are arranged in different areas have been shown using imaging techniques [22] and the link between the number of these receptors and gene expression has found in the human hippocampus [26]. Another research have linked features related to neurotransmitters to changes in brain structure and aging [27]. Differences in how genes expressed in different parts of the brain have also been reported [29]. This research adds to these results by looking at both glutamate-related and GABA-related gene expression with brain structure using the same brain structure map and taking into account how parts of the brain are connected.

- **Theoretical Implications**

The findings support a theoretical view of regional brain organization in which molecular characteristics and anatomical structure are spatially interconnected rather than independently distributed. Neurotransmitter-related gene expression may therefore represent one molecular component associated with regional structural

heterogeneity. However, the observed associations cannot establish direct biological mechanisms or causal effects.

- **Practical Implications:**

Specifically, higher regional glutamatergic-related gene expression was associated with differences in the measured structural characteristics, indicating a relationship between excitatory neurotransmitter-related molecular signatures and regional structural variation. Correlation, PLS, Moran's I, and spatial autoregressive analyses offer complementary information about these relationships. These results indicate that integrating transcriptomic and structural neuroimaging measures can characterize regional molecular–structural associations across the matched brain regions. The findings describe spatial patterns of association and should not be interpreted as direct evidence of neurological damage, disease vulnerability, or causal structural deterioration.

5. CONCLUSION

Research proposes a model that links neurochemical organization of neurons to variations among regions' susceptibility towards neurological disorders due to their anatomy. Combining regional transcriptomics data with structural brain imaging provides an integrated view of these two aspects, which have been researched independently before now. Spatial modeling also enhances it because neighbouring brain areas are not truly independent from each other; hence they must be analyzed according to anatomy rather than statistics alone. Both excitatory and inhibitory neurotransmitter-related molecular organization is relevant for regional structural variations in these findings; however, there are more contributions from glutamate pattern in this research than others. The first PLS component explained 39% of the structural variance, while spatial autoregressive modelling retained a significant glutamatergic association ($\beta = -0.49$, $p=0.002$) after accounting for spatial dependence. It is an empirical model that provides a framework for understanding in summary, these results show statistically significant spatial correlations between signatures of gene expression related to neurotransmitters and regional structural parameters in the studied brain regions. These results confirm the usefulness of combining regional transcriptomic and structural information for the analysis of molecular-structural variation. However, cross-sectional and postmortem research do not allow us to draw conclusions about causality and tissue damage associated with diseases. Furthermore, important is that these are not proof for a causal relationship between them. Post-mortem transcriptomics results need to be interpreted carefully as they are based on an AHBA sample of six adults from which there were 3,702 tissues collected for a total of 68 matched regional observations; however, these cross-sectional structural measurements cannot provide evidence for causality. Future work requires bigger data sets of various types; cells specific molecules' details; better mapping between them spatially; and long-term observations for understanding why some areas are more susceptible than others.

REFERENCES

1. Jiang, L., Genon, S., Ye, J., Zhu, Y., Wang, G., He, R., Valdes-Sosa, P.A., Wan, F., Yao, D., Eickhoff, S.B. and Dong, D., 2025. Gene transcription, neurotransmitter, and neurocognition signatures of brain structural-functional coupling variability. *Nature communications*, 16(1), p.7623. <https://doi.org/10.1038/s41467-025-63000-5>.
2. Martinez-Iglesias, O., Naidoo, V., Carril, J.C., Seoane, S., Cacabelos, N. and Cacabelos, R., 2023. Gene expression profiling as a novel diagnostic tool for neurodegenerative disorders. *International journal of molecular sciences*, 24(6), p.5746. <https://doi.org/10.3390/ijms24065746>.
3. Yan, S., Lu, J., Duan, B., Zhu, H., Tian, T., Qin, Y., Li, Y. and Zhu, W., 2025. Genetic and neurochemical profiles underlying cortical morphometric vulnerability to Parkinson's disease. *Brain Research Bulletin*, 221, p.111222. <https://doi.org/10.1016/j.brainresbull.2025.111222>.
4. Chen, G., Tang, X., Chen, P., Chen, R., Chen, C., Zhang, Y., Wang, Z., Li, F., Fei, J., Lu, D. and Wang, X., 2026. Intrinsic regional brain activity differences and its relationship with neurotransmitter and gene expression in postpartum depression: a voxel-based meta-analysis. *Psychological Medicine*, 56, p.e110. <https://doi.org/10.1017/S0033291726103651>.
5. Medina, A.M., Hagenauer, M.H., Krolewski, D.M., Hughes, E., Forrester, L.C.T., Walsh, D.M., Waselus, M., Richardson, E., Turner, C.A., Sequeira, P.A. and Cartagena, P.M., 2023. Neurotransmission-related gene expression in the frontal pole is altered in subjects with bipolar disorder and schizophrenia. *Translational Psychiatry*, 13(1), p.118. <https://doi.org/10.1038/s41398-023-02418-1>.
6. Bledsoe, X., Betti, M.J. and Gamazon, E.R., 2025. Neuroimaging transcriptomic analyses of Parkinson's disease highlight molecular, cellular, and neurobiological mechanisms. *npj Parkinson's Disease*, 11(1), p.303. <https://doi.org/10.1038/s41531-025-01149-y>.
7. Schmitt, J.E., Alexander-Bloch, A., Seidlitz, J., Raznahan, A. and Neale, M.C., 2024. The genetics of spatiotemporal variation in cortical thickness in youth. *Communications Biology*, 7(1), p.1301. <https://doi.org/10.1038/s42003-024-06956-2>.
8. Ren, P., Ding, W., Li, S., Liu, G., Luo, M., Zhou, W., Cheng, R., Li, Y., Wang, P., Li, Z. and Yao, L., 2023. Regional transcriptional vulnerability to basal forebrain functional dysconnectivity in mild cognitive impairment patients. *Neurobiology of Disease*, 177, p.105983. <https://doi.org/10.1016/j.nbd.2022.105983>.
9. Ardesch, D.J., Libedinsky, I., Scholtens, L.H., Wei, Y. and van den Heuvel, M.P., 2023. Convergence of brain transcriptomic and neuroimaging patterns in schizophrenia, bipolar disorder, autism spectrum disorder, and major

- depressive disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 8(6), pp.630-639. <https://doi.org/10.1016/j.bpsc.2022.12.013>.
10. Wu, P., Wang, Z., Deng, C., Zhou, Y., Jiang, X., Kong, L., Zhou, Y., Sun, Q., Sun, T., Tuo, Z. and Wang, L., 2025. Structure-function coupling alterations in adolescent depression correlate with neurotransmitter systems and cell-type-specific transcriptomics. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, Volume 143, p.111573. <https://doi.org/10.1016/j.pnpbp.2025.111573>.
 11. Hu, Z.X., He, Y.Z., Huang, X. and Wen, Z., 2026. Integrative analysis of spontaneous brain activity in Parkinson's disease: associations with gene expression, cell types, and receptor density. *Neuroscience*, 601, pp. 69–82. <https://doi.org/10.1016/j.neuroscience.2026.02.043>.
 12. Lee, H.M., Hong, S.J., Gill, R., Caldarrou, B., Wang, I., Zhang, J.G., Deleo, F., Schrader, D., Bartolomei, F., Guye, M. and Cho, K.H., 2023. Multimodal mapping of regional brain vulnerability to focal cortical dysplasia. *Brain*, 146(8), pp.3404-3415. <https://doi.org/10.1093/brain/awad060>.
 13. Khan, A.F., Adewale, Q., Lin, S.J., Baumeister, T.R., Zeighami, Y., Carbonell, F., Palomero-Gallagher, N. and Iturria-Medina, Y., 2023. Patient-specific models link neurotransmitter receptor mechanisms with motor and visuospatial axes of Parkinson's disease. *Nature Communications*, 14(1), p.6009. <https://doi.org/10.1038/s41467-023-41677-w>.
 14. Zheng, S., Zhan, Y., Ren, Q., Chen, Y., Zheng, M., Wang, T., Li, Q., Zu, M. and Wang, A., 2026. The cortical Morphometric Inverse Divergence in major depressive disorder is associated with neurotransmitter and genetic profiles. *Brain Research Bulletin*, Volume 237, p.111792. <https://doi.org/10.1016/j.brainresbull.2026.111792>.
 15. Liharska, L.E., Park, Y.J., Ziafat, K., Wilkins, L., Silk, H., Linares, L.M., Thompson, R.C., Vornholt, E., Sullivan, B., Cohen, V. and Kota, P., 2026. A study of gene expression in the living human brain. *Molecular Psychiatry*, 31(1), pp.137-157. <https://doi.org/10.1038/s41380-025-03163-1>.
 16. Mao, H., Xu, M., Wang, H., Liu, Y., Wang, F., Gao, Q., Zhao, S., Ma, L., Hu, X., Zhang, X. and Xi, G., 2024. Transcriptional patterns of brain structural abnormalities in CSVD-related cognitive impairment. *Frontiers in Aging Neuroscience*, 16, p.1503806. <https://doi.org/10.3389/fnagi.2024.1503806>.
 17. Xu, M., Li, Y., Luan, J., Yang, A., Zhu, L., Shu, N., Ouyang, G., Xue, Y., Zhang, L. and Ma, G., 2025. Transcriptomic and neurotransmitter correlates of structure and function spatial variations patterns in spinocerebellar Ataxia. *Neurobiology of Disease*, Volume 218, p.107228. <https://doi.org/10.1016/j.nbd.2025.107228>.
 18. Zhu, J., Chen, X., Lu, B., Li, X.Y., Wang, Z.H., Cao, L.P., Chen, G.M., Chen, J.S., Chen, T., Chen, T.L. and Cheng, Y.Q., 2024. Transcriptomic decoding of regional cortical vulnerability to major depressive disorder. *Communications biology*, 7(1), p.960. <https://doi.org/10.1038/s42003-024-06665-w>.
 19. Jafar, T., Chowdhury, N.F. and Irimia, A., 2026. Spatial Transcriptomic Decoupling and Magnetic Resonance Imaging Identify the Genetic and Cytoarchitectonic Correlates of Regional Vulnerability in Alzheimer's Disease. *NeuroImage*, Volume 339, p.122144. <https://doi.org/10.1016/j.neuroimage.2026.122144>.
 20. Wang, S., Greenbaum, J., Qiu, C., Swerdlow, R.H., Haeri, M., Gong, Y., Shen, H., Xiao, H. and Deng, H., 2024. Gene interactions analysis of brain spatial transcriptome for Alzheimer's disease. *Genes & Diseases*, 11(6), p.101337. <https://doi.org/10.1016/j.gendis.2024.101337>.
 21. Broce, I.J., Sirkis, D.W., Nillo, R.M., Bonham, L.W., Lee, S.E., Miller, B.L., Castruita, P.A., Sturm, V.E., Sugrue, L.S., Desikan, R.S. and Yokoyama, J.S., 2024. C9orf72 gene networks in the human brain correlate with cortical thickness in C9-FTD and implicate vulnerable cell types. *Frontiers in neuroscience*, 18, p.1258996. <https://doi.org/10.3389/fnins.2024.1258996>.
 22. Hansen, J.Y., Tuisku, J., Johansson, J., Chang, Z., McGinnity, C.J., Beliveau, V., Guimond, S., Ganz, M., Nørgaard, M., Galovic, M. and Bezgin, G., 2026. Inter-individual variability of neurotransmitter receptor and transporter density in the human brain. *Brain Structure and Function*, 231(1), p.13. <https://doi.org/10.1007/s00429-025-03069-2>.
 23. Fevereiro-Martins, M., Santos, A.C., Marques-Neves, C., Guimarães, H., Bicho, M. and GenE-ROP Study Group, 2025. Influence of Functional Variations in Genes of Neurotrophins and Neurotransmitter Systems on the Development of Retinopathy of Prematurity. *International Journal of Molecular Sciences*, 26(3), p.898. <https://doi.org/10.3390/ijms26030898>.
 24. Matsumori, K., Matsuyanagi, K. and Matsumoto, K., 2025. Neurotransmitter receptor gene expression patterns associated with reward-related neural representations. *Neuroscience Research*, Volume 220, p.104957. <https://doi.org/10.1016/j.neures.2025.104957>.
 25. Habich, A., Baumann, J.M., Schwarz, C.G., Przybelski, S.A., Inganzo, A., Oppedal, K., Blanc, F., Lemstra, A.W., Hort, J., Boeve, B.F. and Aarsland, D., 2026. Regional gene expression and brain atrophy in dementia with Lewy bodies: an imaging transcriptomics study. *npj Parkinson's Disease*, 12(1), p.96. <https://doi.org/10.1038/s41531-026-01355-2>.
 26. Zhao, L., Mühleisen, T.W., Pelzer, D.I., Burger, B., Beins, E.C., Forstner, A.J., Herms, S., Hoffmann, P., Amunts, K., Palomero-Gallagher, N. and Cichon, S., 2023. Relationships between neurotransmitter receptor densities and expression levels of their corresponding genes in the human hippocampus. *Neuroimage*, 273, p.120095. <https://doi.org/10.1016/j.neuroimage.2023.120095>.
 27. Morais, R.F., Sousa, J.M., Koba, C., Andres, L., Jesus, T., Baldeiras, I., Oliveira, T.G. and Santana, I., 2025. Differential involvement of neurotransmitter pathways in AD, bvFTD and MCI: Whole-brain MRI analysis. *Neurobiology of Disease*, 209, p.106897. <https://doi.org/10.1016/j.nbd.2025.106897>.

28. Manuello, J., Min, J., McCarthy, P., Alfaro-Almagro, F., Lee, S., Smith, S., Elliott, L.T., Winkler, A.M. and Douaud, G., 2024. The effects of genetic and modifiable risk factors on brain regions vulnerable to ageing and disease. *Nature Communications*, 15(1), p.2576. <https://doi.org/10.1038/s41467-024-46344-2>
29. Dong, P., Song, L., Bendl, J., Misir, R., Shao, Z., Edelstien, J., Davis, D.A., Haroutunian, V., Scott, W.K., Acker, S. and Lawless, N., 2024. A multi-regional human brain atlas of chromatin accessibility and gene expression facilitates promoter-isoform resolution genetic fine-mapping. *Nature communications*, 15(1), p.10113. <https://doi.org/10.1038/s41467-024-54448-y>.
30. Hamada, H.T., Abe, Y., Takata, N., Taira, M., Tanaka, K.F. and Doya, K., 2024. Optogenetic activation of dorsal raphe serotonin neurons induces brain-wide activation. *Nature communications*, 15(1), p.4152. <https://doi.org/10.1038/s41467-024-48489-6>
31. Dai, H., Niu, L., Peng, L., Li, Q., Zhang, J., Chen, K., Wang, X., Huang, R., Lee, T.M. and Zhang, R., 2025. Accelerated brain aging in patients with major depressive disorder and its neurogenetic basis: evidence from neurotransmitters and gene expression profiles. *Psychological medicine*, 55, p.e71. <https://doi.org/10.1017/S0033291725000418>
32. Veerappa, A. and Guda, C., 2026. Transcriptomic signatures in tetrapartite brain region identifies shared and unique gene signatures for substance-use. *Frontiers in Cellular Neuroscience*, 20, p.1770214. <https://doi.org/10.3389/fncel.2026.1770214>
33. Karunakaran, K.B., Purushottam, M., Balakrishnan, N., Viswanath, B., Amemori, K.I. and Jain, S., 2026. Expression patterns of risk genes associated with three evolutionarily relevant syndromes in rhesus macaque and human brains. *Translational Psychiatry*, 16(1), Article 459. <https://doi.org/10.1038/s41398-026-04198-w>
34. Long, J., Song, X., Wang, C., Peng, L., Niu, L., Li, Q., Huang, R. and Zhang, R., 2024. Global-brain functional connectivity related with trait anxiety and its association with neurotransmitters and gene expression profiles. *Journal of affective disorders*, 348, pp.248-258. <https://doi.org/10.1016/j.jad.2023.12.052>
35. Fan, J.M., Tadayon, E., Krystal, A.D. and Murphy, K.R., 2026. Toward a transcriptomic framework for ultrasound neuromodulation: A perspective on gene expression and regional brain sensitivity. *Imaging Neuroscience*, 4, pp.IMAG-a. <https://doi.org/10.1162/IMAG.a.1294>.