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RESEARCH ARTICLE OPEN ACCESS

Resting-State Brain Activity Changes and Their Genetic Correlates in Mild Traumatic Brain Injury

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Received: 13 December 2024 | **Revised:** 21 May 2025 | **Accepted:** 26 May 2025

Funding: This work was supported by the National Natural Science Foundation of China (82102318), Tianjin Natural Science Foundation (24JCQNJC00670) Tianjin Health Research Project (TJWJ2024QN003), Tianjin Education Commission Research Project (2023KJ119), and Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDXK-001A).

Keywords: gene expression | mild traumatic brain injury | neuroimaging meta-analysis | resting-state brain activity | transcription-neuroimaging association

ABSTRACT

Mild traumatic brain injury (mTBI) often leads to persistent cognitive and emotional symptoms, but the underlying neurobiological mechanisms remain unclear. Although previous studies have reported alterations in resting-state brain activity in mTBI patients, the findings have been inconsistent, and the genetic basis of these changes has not been fully explored. A coordinate-based voxel-wise meta-analysis was conducted to investigate resting-state brain activity changes in mTBI, using nine datasets from 374 patients and 302 healthy controls (HCs). Transcription-neuroimaging association analyses were performed using gene expression data from the Allen Human Brain Atlas (AHBA) to identify genes associated with brain activity alterations. Enrichment analyses were conducted to explore the biological functions of these genes. Compared to HCs, mTBI patients showed increased resting-state brain activity in the left insula and right fusiform gyrus, and decreased activity in the bilateral middle frontal gyrus. Transcription-neuroimaging association analyses identified 840 genes significantly correlated with these brain activity changes. Enrichment analyses revealed 15 biological processes significantly associated with the identified genes, primarily involving chemical synaptic transmission, multicellular organism development, and cell–cell signaling. These genes were also enriched in Pnoc+, Ntsr+, and Cort+ neurons and were expressed predominantly from the late fetal to early adulthood stages. Our findings suggest that alterations in resting-state brain activity in mTBI are linked to specific gene expression patterns, highlighting potential biological pathways involved in mTBI-related brain changes.

1 | Introduction

Traumatic brain injury (TBI) is a global health concern, with more than 50 million individuals estimated to experience TBI each year worldwide, contributing to significant death and disability (Dams-O'Connor et al. 2023; Dewan et al. 2019). Mild TBI (mTBI) accounts for the majority of cases (75%–90%) (Capizzi et al. 2020; Holm et al. 2005), and is often associated

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with prolonged cognitive and emotional disturbances, which can interfere with work, social activities, and daily functioning. These symptoms often result in chronic impairments, severely impacting long-term prognosis and quality of life (Benedictus et al. 2010; Hawthorne et al. 2009; Ponsford et al. 2008; Proctor and Best 2019; Rosema et al. 2012). Although acute symptoms are thought to result directly from injury, the neurobiological processes underlying symptom persistence remain unclear, posing challenges to the development of targeted and effective therapies (Aungst et al. 2014; Shultz et al. 2017).

Previous studies have demonstrated abnormal neural activity in mTBI patients, suggesting that these changes may underlie the persistent symptoms following injury (Eakin and Miller 2012; Gosselin et al. 2011; Huang et al. 2020). Resting-state functional magnetic resonance imaging (rs-fMRI), which measures blood oxygen level dependent (BOLD) signals, has emerged as a key tool for assessing resting-state neural activity abnormalities in mTBI (Arabshahi et al. 2024; Tan et al. 2022). Analytic methods such as regional homogeneity (ReHo), amplitude of low-frequency fluctuations (ALFF), and fractional ALFF (fALFF) are commonly employed to detect these activity patterns. ReHo quantifies the synchronization of neural activity within neighboring regions, providing insights into local activity coherence (Zang et al. 2004). ALFF assesses the magnitude of low-frequency oscillations, capturing the intensity of spontaneous fluctuations in the BOLD signal (Zang et al. 2007), while fALFF measures the relative contribution of low-frequency oscillations to the overall signal spectrum (Zou et al. 2008). Additionally, arterial spin labeling (ASL), a noninvasive MRI technique, measures cerebral perfusion by using magnetically labeled arterial blood water as an endogenous tracer, offering an alternative measure of resting-state neural activity through its relationship with cerebral blood flow (Petcharunpaisan et al. 2010). Despite previous studies identifying changes in resting-state brain activity across multiple regions in mTBI patients, including the insula (Shi et al. 2021; Zhan et al. 2015), precentral gyrus (Duan et al. 2022; Zhan et al. 2015), postcentral gyrus (Duan et al. 2022; Zhan et al. 2015), superior frontal gyrus (Duan et al. 2022; Li, Lu, Shang, et al. 2020), middle frontal gyrus (Li, Lu, Shang, et al. 2020; Zhan et al. 2016), and middle occipital gyrus (Shi et al. 2021; Vedaei et al. 2021; Zhan et al. 2016), findings have been inconsistent. These discrepancies may result from variations in demographic and clinical characteristics, imaging protocols, and data analysis techniques, as well as small sample sizes. To overcome these inconsistencies, researchers are increasingly turning to neuroimaging meta-analytic techniques, which allow for a more comprehensive understanding of the neural mechanisms involved in mTBI (Aoki and Inokuchi 2016; Eierud et al. 2014; Mavroudis et al. 2022). Nevertheless, no quantitative meta-analysis to date has specifically examined resting-state brain activity in mTBI, leaving a critical gap in systematically identifying consistent abnormalities in spontaneous neural activity associated with mTBI.

Genetic factors are known to influence not only the risk of mTBI but also the acute responses and recovery processes following the injury (Feigen et al. 2024; Zeiler et al. 2021). However, the molecular mechanisms driving changes in resting-state neural activity remain poorly understood. While genome-wide association studies (GWAS) have identified genetic variants associated with mTBI prognosis (Kals et al. 2022; Merritt et al. 2024), this approach is limited in its ability to capture the genetic mechanisms underlying group-level phenomena, such as alterations in resting-state neural activity, due to its reliance on individual-level data. Additionally, many of the genetic variants identified by GWAS are located in intergenic regions, complicating efforts to interpret their functional significance. In recent years, transcription-neuroimaging association analysis has gained recognition as a promising method for investigating the molecular basis of neuroimaging phenotypes (Arnatkeviciute et al. 2023; Wang et al. 2025; Xue et al. 2022). By leveraging gene expression data from resources such as the Allen Human Brain Atlas (AHBA), several studies have successfully identified gene expression profiles associated with structural and functional brain changes in neuropsychiatric disorders (Cai et al. 2024; Ma et al. 2023; Xia et al. 2022). Nevertheless, no transcription-neuroimaging association analyses have been conducted to establish the link between gene expression and resting-state neural activity alterations in mTBI. These gaps motivate a comprehensive investigation that integrates neuroimaging and transcriptomic data to advance understanding of neural activity abnormalities in mTBI.

Building on these findings, in this study, we aimed to identify consistent resting-state brain activity alterations in mTBI and investigate their molecular mechanisms through integrated imaging-transcriptomic analyses. To this end, we first employed a coordinate-based meta-analysis to identify consistent patterns of resting-state brain activity alterations in mTBI patients. Next, transcription-neuroimaging association analyses were conducted to determine which gene expression levels were significantly correlated with these brain activity changes. Finally, comprehensive enrichment analyses were performed on the identified genes to explore their potential biological functions and roles in mTBI. A schematic workflow of this study is presented in Figure 1.

2 | Methods

2.1 | Literature Search and Selection

A comprehensive search of relevant studies was conducted using the Web of Science, PubMed, and Embase databases to retrieve studies published before July 2024. The following keywords were used: ("mild traumatic brain injury" or "mTBI" or "mild TBI" or "concussion" or "rmTBI" or "repetitive mild traumatic brain injury") and ("fMRI" or "functional magnetic resonance imaging" or "ReHo" or "regional homogeneity" or "local consistency" or "ASL" or "arterial spin labeling" or "ALFF" or "amplitude of low-frequency fluctuations" or "fALFF" or "fractional amplitude of low-frequency fluctuations") and ("resting-state" or "resting state" or "resting"). The reference lists of the included studies, as well as those of relevant reviews and meta-analyses, were also screened for additional eligible studies.

Studies were eligible for inclusion if they met the following criteria: (1) they were original research articles published in English in peer-reviewed journals; (2) they involved adults aged 18–65 years who had experienced mTBI, compared with healthy controls (HCs); (3) they conducted whole-brain voxel-wise

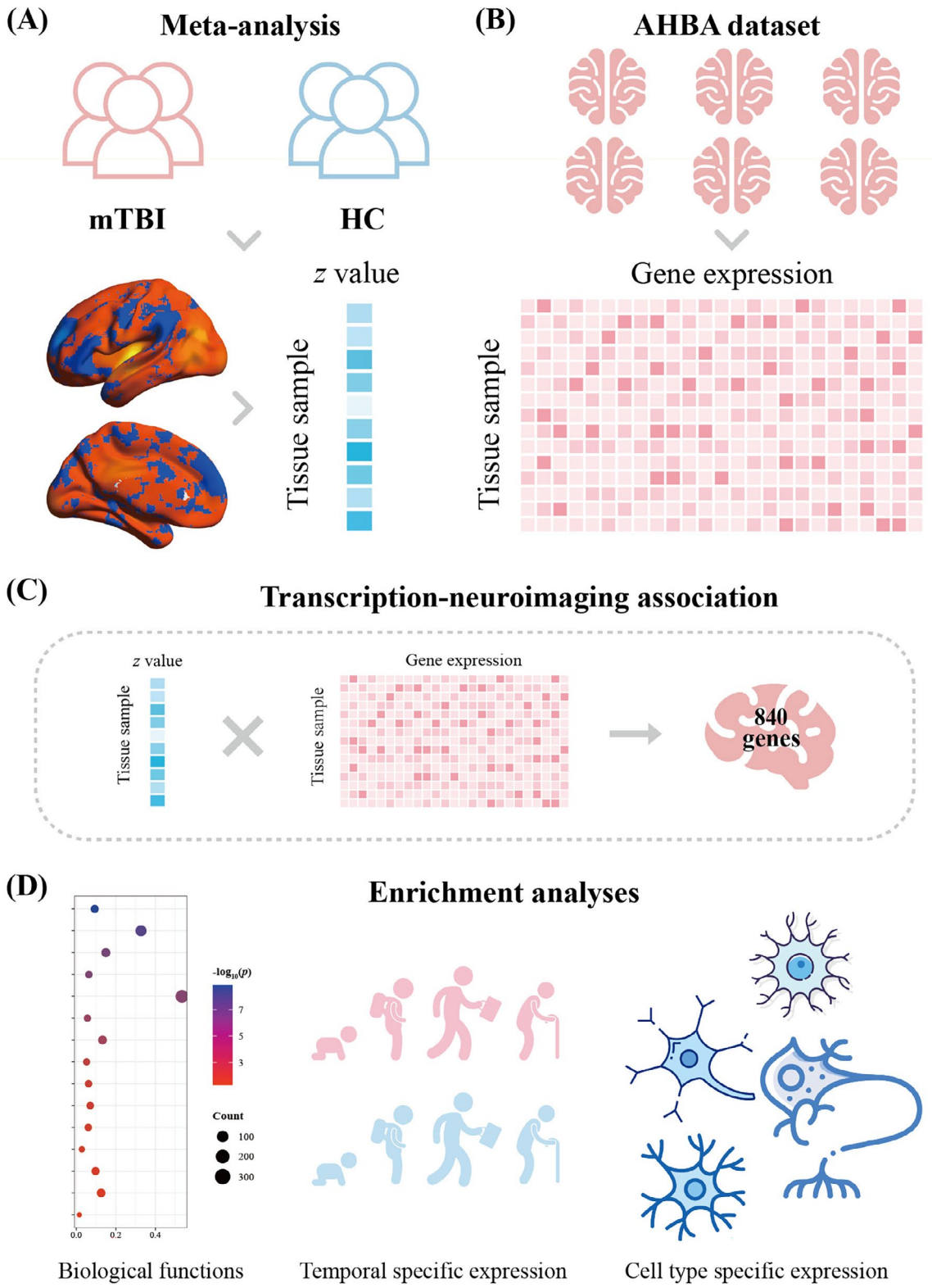

FIGURE 1 | A schematic workflow of the study protocol. (A) A meta-analysis of neuroimaging studies was conducted to identify consistent resting-state brain activity changes in mTBI. (B) Gene expression data from the AHBA dataset were processed to obtain the normalized gene expression matrix. (C) Transcription-neuroimaging association analysis was performed to identify genes associated with alterations in resting-state brain activity in mTBI by integrating the results of the meta-analysis with the normalized gene expression matrix. (D) Enrichment analyses were performed to reveal the biological functions and specific expression patterns of the genes related to resting-state brain activity changes in mTBI. AHBA, Allen Human Brain Atlas; HC, healthy control; mTBI, mild traumatic brain injury.

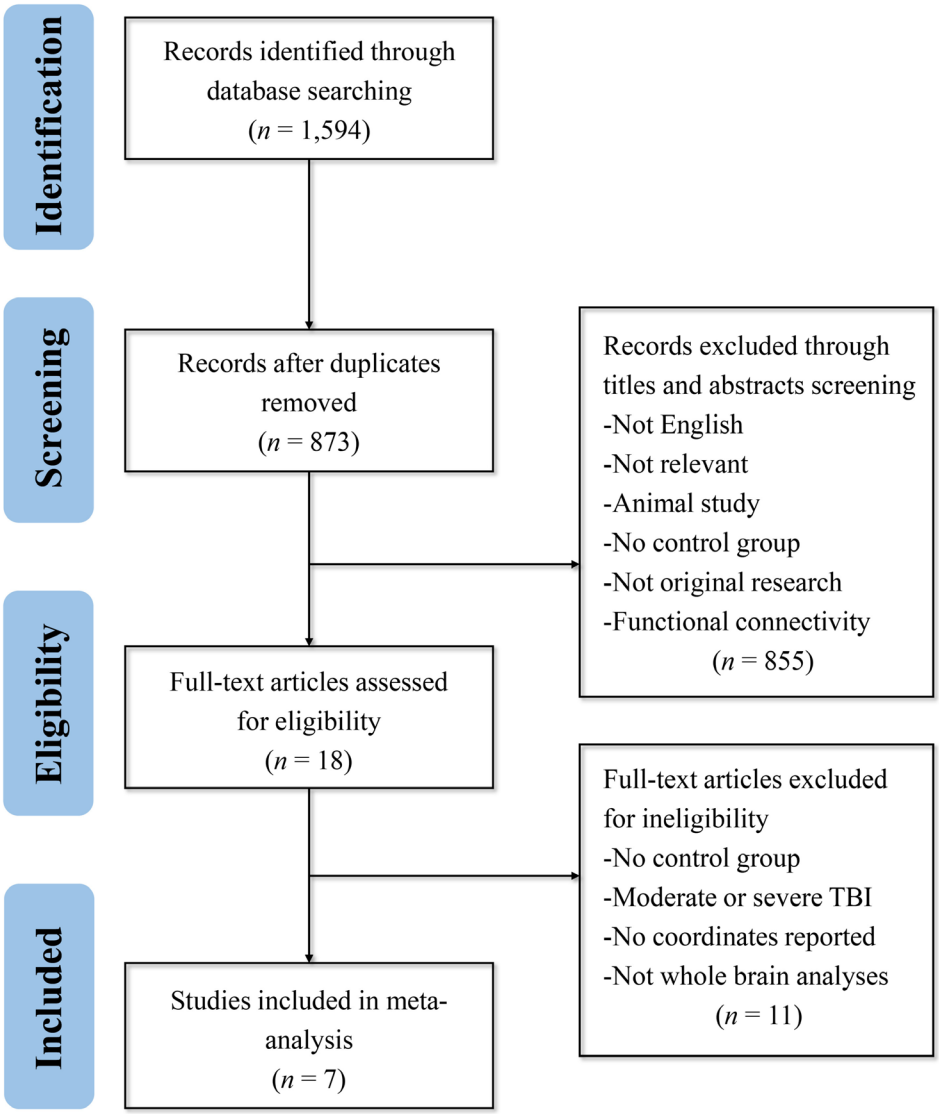

FIGURE 2 | The flowchart of the literature search and selection for the meta-analysis. Abbreviations: mTBI, mild traumatic brain injury; *n*, number.

analyses to assess regional resting-state brain activity differences between mTBI individuals and HCs; (4) they reported three-dimensional peak coordinates in Montreal Neurological Institute (MNI) or Talairach space for significant findings, or provided null results; (5) they applied a consistent statistical threshold across the whole brain. The exclusion criteria were as follows: (1) the studies focused on moderate or severe TBI; (2) they exclusively reported findings from region-of-interest analyses; (3) the necessary data (e.g., peak coordinates, *T* or *Z* statistics) required for meta-analysis could not be obtained from the original articles or through author correspondence; (4) fewer than 10 participants were included in either the mTBI or control groups. If the subjects in two studies overlapped, only the study with the larger sample size was included. If a study presented multiple independent patient samples or neuroimaging metrics, each was treated as a separate dataset. The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009), and a detailed summary of the study selection process is provided in Figure 2.

Two authors independently searched and assessed the literature. The following data were extracted from each study: demographic characteristics of individuals with mTBI and HCs (including mean age, gender, sample size, and education), clinical characteristics (including time since injury), technique details (such as MRI scanner, echo time, repetition time, and smoothing kernel size), as well as peak coordinates and statistics (e.g., *T* or *Z* statistics). The quality of the selected studies was assessed using a 10-point checklist (Baiano et al. 2007; Cai et al. 2024), with the detailed checklist and scores for the included studies provided in the Supporting Information and Tables S1 and S2.

2.2 | Neuroimaging Meta-Analysis

To investigate resting-state brain activity alterations in individuals with mTBI, a coordinate-based voxel-wise meta-analysis was conducted using the Seed-based *d* Mapping with Permutation of Subject Images (SDM-PSI) software package (version 6.22 for Windows, http://www.sdmproject.

com) (Albajes-Eizagirre et al. 2019). The following procedures were performed: (1) the reported peak coordinates and their corresponding statistics (e.g., *t*- or *z*-values) were extracted and formatted according to SDM criteria; (2) possible effect size images were generated using default parameters (full anisotropy = 1, full width half maximum = 20 mm, and voxel size = 2 mm); (3) effect size estimation was carried out using MetaNSUE based on multiple imputations; (4) a random-effects model was applied to produce the mean map, with Rubin's rules used to combine results from multiple meta-analyses of different imputed datasets, and (5) a map of mTBI-control resting-state brain activity differences (*z*-map) was generated. Additionally, meta-regression analyses were conducted to investigate the influence of mean age and time since injury on resting-state brain activity changes in mTBI. To optimize the balance between false positives and negatives, statistical significance was set at $p < 0.005$, with a peak height of $Z > 1$ and a cluster extent of more than 10 voxels (Radua et al. 2014; Zhao et al. 2022).

Several additional analyses were conducted to assess the robustness and reliability of our meta-analysis findings (Cai et al. 2022; Zhang et al. 2025). First, a heterogeneity test using Cochran's *Q* test and I^2 statistics, was performed to investigate potential variations, with I^2 values of 25%, 50%, and 75% indicating low, medium, and high heterogeneity, respectively (Higgins and Thompson 2002; Huedo-Medina et al. 2006). Second, a funnel plot and Egger's test were employed to visually and quantitatively examine the potential publication bias for the significant findings (Stanley et al. 2021; Sutton et al. 2000). Finally, a whole-brain voxel-wise jackknife sensitivity analysis was performed by iteratively repeating the main analysis and excluding one study at a time. If a previously significant finding remained consistent across most or all combinations of studies, it was considered replicable.

2.3 | Transcription-Neuroimaging Association Analysis

To identify genes correlated with alterations in resting-state brain activity in mTBI, brain gene expression profiles were obtained from the AHBA database (http://human.brain-map.org), which contains standardized microarray expression data from six human brains, covering over 20,000 genes across 3702 brain tissue samples (Hawrylycz et al. 2012). Tissue samples were obtained from six human donor brains, aged 24–57 years, with no known history of neuropsychiatric or neuropathological conditions. Detailed demographic information for each donor is provided in Table S3. The *abagen* toolbox in Python was used for processing the gene expression data, and a detailed description of the procedure is provided in the Supporting Infromation. As a result, a gene expression matrix at the sample level, consisting of 1581 samples and 15,633 genes, was generated for subsequent analyses.

Spatial correlations between gene expression and resting-state brain activity changes associated with mTBI were examined. Specifically, we first extracted the mean *z*-value from a 6-mm radius sphere centered on each tissue sample's coordinate within the voxel-wise meta-analysis *z*-map (Liu et al. 2019), designating this value as the case–control resting-state brain activity difference for that sample. Pearson's correlation method was then employed to examine cross-sample spatial correlations between gene expression and resting-state brain activity changes associated with mTBI. Multiple comparisons were corrected using the false discovery rate (FDR) method ($p < 0.05$).

To test the significance of the spatial relationship between gene expression and resting-state brain activity changes, we conducted a permutation test (1000 permutations) to evaluate whether the number of identified genes exceeded the random level. Considering the spatial autocorrelation characteristics of brain maps, 1000 surrogate maps of the case–control resting-state brain activity difference were generated using the Brain Surrogate Maps with Autocorrelated Spatial Heterogeneity toolbox (BrainSMASH, https://github.com/murraylab/brainsmash) (Burt et al. 2020; Markello and Misic 2021). These surrogate maps preserved spatial autocorrelation and were based on the empirical case–control resting-state brain activity difference and the corresponding distance matrix. In each permutation, we repeated the spatial correlation analyses and recorded the number of identified genes to generate a null distribution. Based on the position of the number of genes significantly correlated with real resting-state brain activity difference maps within the null distribution, we assessed the significance of our results ($p_{perm} < 0.05$).

2.4 | Gene Enrichment Analysis

After identifying genes correlated with changes in resting-state brain activity in mTBI, we performed a comprehensive set of enrichment analyses to elucidate their underlying biological functions. First, to explore the functional roles of the identified genes, we utilized the online g:Profiler tool (https://biit.cs.ut.ee/gprofiler/gost) (Raudvere et al. 2019) based on the Gene Ontology (GO) biological process and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases, retaining the GO and KEGG terms that met the FDR correction threshold of $p < 0.05$. To further validate these findings, we conducted gene-category enrichment analysis (GCEA) using a spatial brain phenotype–spatial ensemble-based null model (https://github.com/benfulcher/GeneCategoryEnrichmentAnalysis) (Fulcher et al. 2021), performing a permutation test (1000 times) for each GO category (detailed in the Supporting Information). Additionally, we analyzed gene expression specificity across cell types, brain regions, and developmental stages using the specific expression analysis (SEA) enrichment toolbox (http://doughertytools.wustl.edu/) (Dougherty et al. 2010), evaluating gene set enrichment in specific terms with the specificity index probability (PSI) at a threshold of FDR-corrected $p < 0.05$ (PSI = 0.05) (Dougherty et al. 2010; Xu et al. 2014).

3 | Results

3.1 | Included Studies

The search strategy identified 1594 studies, 7 of which met our inclusion criteria, resulting in nine datasets encompassing a total of 374 patients with mTBI and 302 HCs (Arabshahi

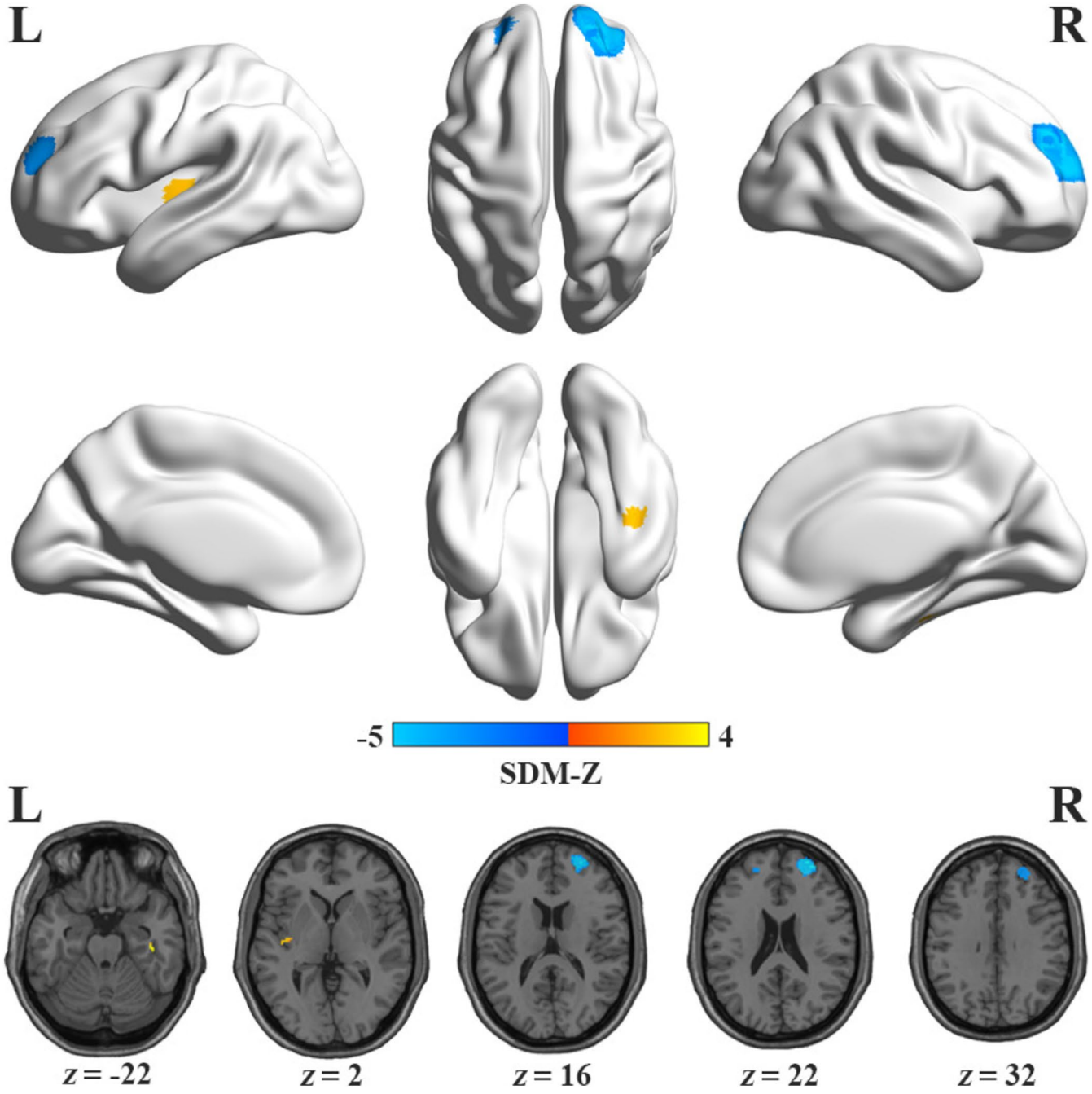

FIGURE 3 | Resting-state brain activity alterations in patients with mTBI. Regions of significantly increased (warm color) and decreased (cold color) resting-state brain activity in patients with mTBI were identified through voxel-wise meta-analysis. Abbreviations: L, left; mTBI, mild traumatic brain injury; R, right; SDM, seed-based *d* mapping.

et al. 2024; Duan et al. 2022; Li, Lu, Shang, et al. 2020; Shi et al. 2021; Vedaei et al. 2021; Zhan et al. 2016, 2015). One of these studies divided the mTBI group into two subgroups (Duan et al. 2022), and another study used different neuroimaging metrics (Vedaei et al. 2021), resulting in two separate datasets from each study. Statistical analysis using sample size-weighted *t* tests revealed no statistically significant differences in the mean age ($p = 0.569$) or gender ratio ($p = 0.664$) between the patient and control groups. The demographic and clinical characteristics of the included studies are summarized in Table S4, and the technical details are provided in Table S5.

3.2 | Resting-State Brain Activity Changes in mTBI

Compared to HCs, individuals with mTBI showed increased resting-state brain activity in the left insula and right fusiform gyrus, and decreased activity in the bilateral middle frontal gyrus, as depicted in Figure 3 and Table 1. Cochran's Q test and I^2 statistics indicated no substantial between-study heterogeneity within any significant cluster ($p > 0.05$, $I^2 < 25\%$; Table 1). Egger's test and the funnel plot did not reveal any significant publication bias in any of the peaks or clusters ($p > 0.05$; Table 1 and Figure S1). Additionally, the

TABLE 1 | Resting-state brain activity alterations in mTBI patients in the meta-analysis.

Brain regions	SDM-*Z*	*p*	Peak MNI coordinates			Cluster size (voxels)	Heterogeneity test		Egger's test
			x	*y*	*z*		*Q* (*p* value)	I^2 (%)	*p* value
mTBI > HC									
Left insula	3.216	0.00065	−40	−14	4	19	4.286 (0.830)	1.379	0.922
Right fusiform gyrus	3.088	0.00101	40	−20	−22	13	1.021 (0.998)	3.633	0.713
mTBI < HC									
Right middle frontal gyrus	−4.962	~0	22	50	28	470	3.335 (0.912)	10.566	0.411
Left middle frontal gyrus	−3.164	0.00078	−22	50	24	22	1.887 (0.984)	8.016	0.631

Abbreviations: HC, healthy control; MNI, Montreal Neurological Institute; mTBI, mild traumatic brain injury; *Q*, Cochran's *Q* statistic; SDM, seed-based *d* mapping.

meta-regression analyses revealed no significant associations between either mean age or time since injury and resting-state brain activity alterations in mTBI patients. Jackknife analysis showed that all regions were robust in more than 75% of iterations, with the right middle frontal gyrus preserved in all iterations (Table S6 and Figure S2).

3.3 | Genes Associated With Alterations in Resting-State Brain Activity in mTBI

Gene-wise cross-sample spatial correlation analyses were conducted to examine the relationship between gene expression data and case–control differences in resting-state brain activity. At a statistical threshold of FDR-corrected $p < 0.05$, 840 genes were found to have significant correlations with resting-state brain activity changes in mTBI patients, as shown in Table S7. The spatial autocorrelation-preserved permutation test further validated the robustness of these findings, revealing that the number of significant genes exceeded a random level ($p_{perm} = 0.004$). To assess the influence of probe selection strategy on these results, we repeated the analyses using two alternative approaches. Notably, both alternatives yielded substantially fewer significant gene associations compared to the differential stability method. Detailed findings are presented in the Supporting Information and Tables S8 and S9.

3.4 | Enrichment Analyses

Enrichment analysis of the 840 identified genes revealed 15 significant GO biological processes and 3 KEGG pathways associated with alterations in resting-state brain activity in mTBI. These were primarily related to chemical synaptic transmission, multicellular organism development, and cell–cell signaling (Table S10 and Figure 4A). All the reported GO biological processes remained significant after GCEA with 1000 permutation tests ($p < 0.001$). Cell-type SEA indicated that these genes were specifically enriched in Pnoc+ neurons, Ntsr+ neurons, and Cort+ neurons in the cortex ($p < 0.05$, FDR corrected; Figure 4B). Brain regional and developmental SEA further revealed that these genes were predominantly expressed from the late fetal to neonatal/early infancy stages, and from early childhood to young adulthood, in several brain regions such as the cortex, cerebellum, and thalamus ($p < 0.05$, FDR corrected; Table S11 and Figure 4C).

4 | Discussion

This study represents the first comprehensive investigation into resting-state brain activity alterations in mTBI patients and their underlying molecular mechanisms. Our meta-analysis revealed increased activity in the left insula and right fusiform gyrus, alongside decreased activity in the bilateral middle frontal gyrus, highlighting the complexity of brain activity changes associated with mTBI. By conducting transcriptome–neuroimaging association analyses, we identified 840 genes linked to these alterations. Enrichment analyses highlighted that these genes are primarily involved in key biological processes, including synaptic transmission, signal transduction, development, intracellular transport, and cell death and survival, with enrichment observed in specific neuron types, such as Pnoc+, Ntsr+, and Cort+ neurons. Additionally, these genes showed significant expression patterns from the late fetal stages through young adulthood. Together, these findings provide deeper insights into the molecular and functional alterations in mTBI, offering potential avenues for therapeutic intervention.

In our meta-analysis, patients with mTBI showed increased resting-state brain activity in the left insula and right fusiform gyrus compared to HCs. The insula, which integrates sensory, emotional, and cognitive processes (Jones et al. 2010; Namkung et al. 2017), plays a crucial role in emotion recognition and regulation. Previous studies have shown that damage to the left insula, as part of a bilateral fronto-temporo-limbic network, is associated with impaired recognition of unpleasant emotions in TBI patients (Cristofori et al. 2024; Dal Monte et al. 2013). The increased activity observed in mTBI patients may reflect compensatory mechanisms due to the insula's involvement in emotion processing. This is consistent with findings linking the insula to pain perception and emotional regulation, both

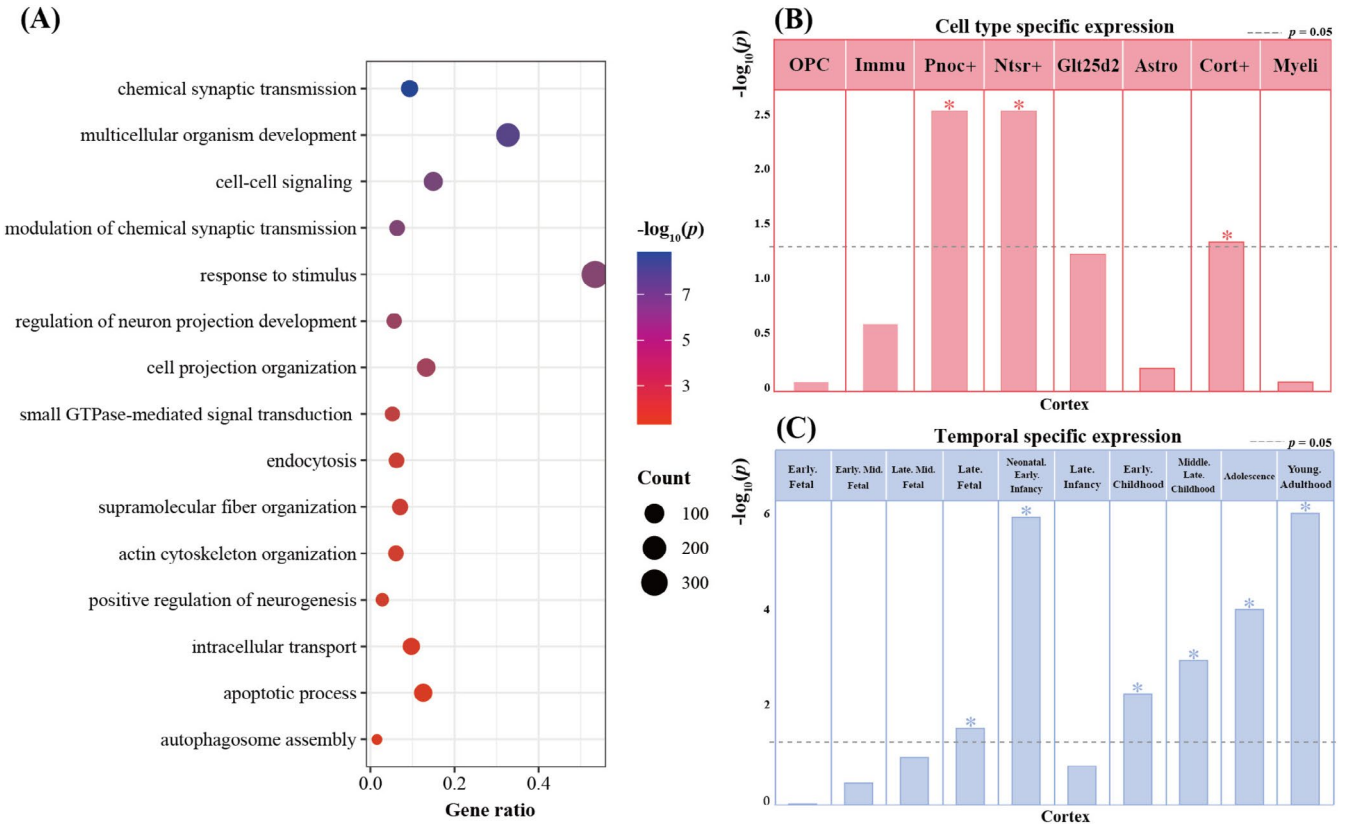

FIGURE 4 | Enrichment analyses of the genes associated with resting-state brain activity changes in mTBI. (A) Enrichment terms associated with the 840 mTBI-related genes, all of which were significant in the gene-category enrichment analysis. The *x*-axis shows the gene ratio (i.e., the ratio of intersection size to query size) for each term, the *y*-axis shows the name of each term, the bubble size indicates the gene count enriched for a term, and the color of the bubbles denotes significance. (B) Specific expression analysis across cell types. The *x* axis shows the cell types, the *y* axis shows the $-\log_{10}(p)$ value, and the gray dashed line indicates the threshold of significance. (C) Specific expression analysis across brain regions and developmental stages. The *x* axis shows the developmental stages, the *y* axis shows the $-\log_{10}(p)$ value, and the gray dashed line indicates the threshold of significance. The results of enrichment analyses were all thresholded with FDR-corrected $p < 0.05$. Astro, astrocytes; Cort+, cortistatin-expressing interneurons; FDR, false discovery rate; Glt25d2, corticopontine neurons; Immu, immune cells; mTBI, mild traumatic brain injury; Myeli, myelinating oligodendrocytes; Ntsr+, corticothalamic neurons; OPC, oligodendrocyte progenitor cells; Pnoc+, prepronociceptin-expressing neurons.

of which are often disrupted in mTBI patients (Li, Lu, Chen, et al. 2020; Li et al. 2024; Orenius et al. 2017). Furthermore, research suggests that the fusiform gyrus plays a key role in protecting cognition from emotional distractions (Ziaei et al. 2014). Therefore, the hyperactivation of this region in individuals with mTBI may represent adaptive changes that help reduce the cognitive impact of emotional distractions or frustration commonly experienced by these patients. Together, these increases in brain activity suggest that mTBI may trigger compensatory neural mechanisms to maintain cognitive function despite the injury. However, whether these compensatory changes are ultimately beneficial or maladaptive remains unclear. Prolonged hyperactivity in the insula and fusiform gyrus has been associated with heightened sensitivity to negative emotions and pain (Alvarez et al. 2015; Frick et al. 2013; Strigo et al. 2014; Zhang et al. 2024), suggesting that such activation may reflect adaptive efforts that could become dysfunctional if sustained over time.

In contrast, decreased resting-state activity was observed in the bilateral middle frontal gyrus, a region essential for executive functions such as working memory and executive control (Wagner et al. 2001; Xu et al. 2024). This hypoactivity may indicate a reduced capacity for these executive functions in patients with mTBI. The middle frontal gyrus is part of the dorsolateral prefrontal cortex, which is, particularly, vulnerable to TBI (Lipton et al. 2009). This hypoactivity could reflect either direct neural damage or a compensatory downregulation of neural activity. These findings highlight the potential long-term impact of mTBI on cognitive control and executive function, stressing the importance of developing targeted therapeutic interventions to address these deficits. The meta-regression analyses revealed no significant effects of mean age or time since injury, which may be attributable to limited statistical power due to sample size constraints, or may indicate that alterations in resting-state brain activity in mTBI represent stable neurobiological traits not strongly influenced by these factors. Additionally, because most of the included studies had already accounted for age by including it as a covariate in their original analyses—except for one study (Zhan et al. 2015)—age-related variability may have been reduced, thereby attenuating any detectable moderating effect in the meta-regression.

Using the transcription-neuroimaging association analyses, we identified genetic correlates of resting-state brain activity alterations in mTBI. The 15 biological processes identified in the enrichment analysis can be categorized into four main groups:

synaptic transmission and signal transduction, developmental and organizational processes, transport and intracellular processes, and cell death and survival processes. The synaptic transmission and signal transduction terms, such as chemical synaptic transmission, modulation of chemical synaptic transmission, were strongly implicated in the mechanisms of mTBI symptoms. These findings are consistent with observed bilateral changes in excitatory synaptic transmission within the hippocampus following mTBI, suggesting that disruptions in synaptic signaling may play a crucial role in the underlying pathology of mTBI (Aungst et al. 2014; Przekwas et al. 2016). Terms related to developmental and organizational processes, such as multicellular organism development and regulation of neuron projection development, have been reported in previous TBI studies (Huang et al. 2018; Song et al. 2022). For instance, a study analyzing the biological significance of miRNA level changes in microglial exosomes using GO and Kyoto Encyclopaedia of Genes and Genomes pathway analyses identified multicellular organism development as one of the top three prominent terms associated with TBI (Huang et al. 2018).

In addition, we identified several biological processes related to transport and intracellular processes that may contribute to the neural alterations observed in mTBI. Endocytosis plays a critical role in synaptic function and the regulation of neuronal signaling, which can be disrupted following TBI (Bell et al. 2009; Jamjoom et al. 2021). Microvascular disruption, characterized by mechanical damage to cerebral microvessels, has been identified as a key pathological process in TBI. This disruption compromises the integrity of the blood–brain barrier and facilitates the extravasation of cytotoxic molecules into the brain parenchyma (Logsdon et al. 2015). These harmful substances can interfere with cellular processes such as endocytosis and intracellular transport, thereby disrupting synaptic stability and neuronal homeostasis. Disruptions in intracellular transport not only exacerbate oxidative stress and neuroinflammation but also trigger secondary injury cascades such as endoplasmic reticulum stress, apoptosis, and neurodegeneration (Giza and Hovda 2014; Park et al. 2008). Moreover, the enrichment of genes related to cell death and survival processes, such as the apoptotic process, suggests that increased cell death may contribute to disruptions in neural activity, potentially leading to long-term neuronal loss and cognitive decline in mTBI. The autophagy pathway serves as a protective mechanism for maintaining cellular homeostasis after TBI (Liu et al. 2008), and disruptions in cellular homeostasis could further influence the brain's ability to restore normal activity patterns, making it more susceptible to long-term consequences following the injury.

Cell-type SEA revealed that the specific enrichment of genes in Pnoc+ neurons, Ntsr+ neurons, and Cort+ interneurons may contribute to neuronal dysfunction in mTBI. Pnoc+ neurons are involved in pain perception and stress responses (Rodriguez-Romaguera et al. 2020), Ntsr+ neurons participate in corticothalamic communication (Usrey and Sherman 2019), and Cort+ interneurons are associated with inhibitory control within the cortex (Hill et al. 2019). The selective vulnerability of these neuron types suggests that disruptions in pain modulation, sensory integration, and cortical inhibition may underlie cognitive and sensory deficits in mTBI patients. Furthermore, the regional and developmental SEA revealed that the identified genes are predominantly expressed from the late fetal to neonatal/early infancy stages and from early childhood to young adulthood—periods characterized by active synaptogenesis, myelination, and later, peak of synapse elimination (de Graaf-Peters and Hadders-Algra 2006). While most mTBI cases occur in adulthood, this apparent temporal mismatch may reflect the injury-induced reactivation of neurodevelopmental pathways involved in neural plasticity across the lifespan. Supporting evidence includes astrocyte-mediated synaptic remodeling (Sofroniew 2020) and the epigenetic re-engagement of axonal growth programs (Hutson et al. 2019). Additionally, epigenetic priming may permit context-dependent re-expression of genes originally active during development, thereby enabling adaptive responses to brain injury (Gräff and Tsai 2013). The expression of these genes in the cortex, cerebellum, and thalamus suggests their vital role in supporting cognitive development, motor coordination, and sensory processing. Disruptions in these processes may increase the risk of brain activity abnormalities following mTBI.

This study has several limitations that should be considered. First, although we conducted a meta-analysis using multiple datasets, the sample sizes of the individual studies were relatively small, which may reduce the generalizability of our findings. Future studies with larger and more diverse cohorts are necessary to validate these results. Second, sleep-related variables were not examined in our meta-analysis, as the included studies did not report relevant measures. Nevertheless, existing evidence indicates that sleep plays a vital role in neural recovery following TBI by regulating glymphatic clearance, blood–brain barrier integrity, neuroinflammation, and neuroplasticity, thereby influencing long-term brain function (Lucke-Wold et al. 2015). Future studies are needed to incorporate sleep-related measures to more comprehensively elucidate the mechanisms underlying mTBI. Third, the gene expression data used in our transcription-neuroimaging association analysis were derived from the AHBA, which represents adult brain tissue from a limited number of donors and includes only one female brain. Although we selected genes with high differential stability—a commonly used approach to reduce inter-individual variability (Hawrylycz et al. 2015; Xue et al. 2023)—this dataset may still not fully capture the variability in gene expression across different populations or sexes, thereby limiting the generalizability of our genetic findings. Fourth, while we identified several biological processes linked to mTBI-related brain activity changes, the functional interpretation of these findings remains limited. Experimental validation and mechanistic studies are needed to further clarify the biological relevance of the identified genes and pathways. Finally, our validation analysis focused solely on biological process terms in the GO enrichment, as the GCEA toolbox supports only these annotations and does not support KEGG pathways, limiting the exploration of other potential functional categories.

5 | Conclusion

In summary, our meta-analysis identified consistent alterations in resting-state brain activity across several brain regions in mTBI patients, alongside genes whose expression patterns are spatially linked to these changes. These genes are implicated in

critical biological processes, specific neuron types, and various developmental stages, contributing to our understanding of the neural mechanisms involved in mTBI. These findings provide novel insights into the complex neurobiological processes underlying mTBI and highlight potential avenues for future research and therapeutic development.

Author Contributions

Feng Liu, Juanwei Ma, and Linlin Song designed the study concept and reviewed the article. Xinyu Wang, Wei Wang, and Jin Qiao preparedthe data, managed the data, and performed visualization. Zhihui Zhang, Minghuan Lei, Wenjie Cai, and Qi An performed data analysis and interpretation. Yiling Zhang, Lu Wang, and He Wang performed data analysis and wrote the original draft. All the authors have approved the final article.

Acknowledgments

This work was supported by the Natural Science Foundation of China (82102318), Tianjin Natural Science Foundation (24JCQNJC00670), Tianjin Health Research Project (TJWJ2024QN003), Tianjin Education Commission Research Project (2023KJ119), and the Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDXK-001A).

Ethics Statement

All used datasets in this research are publicly available and complied with the ethical statements of original studies.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The AHBA microarray expression data is available at http://human.brain-map.org.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.