Alpha Psychiatry

Alpha Psychiatry **2026**; 27(3): 46200
https://doi.org/10.31083/AP46200

Original Article

GRIA Gene Expression in Schizophrenia: A Participant-Level Meta-Analysis

Adan Baumel[1], Assif Yitzhaky[2], Libi Hertzberg[1,2,3,*]

[1]School of Medicine, Faculty of Medical and Health Sciences, Tel Aviv University, 6997801 Tel Aviv, Israel
[2]Department of Physics of Complex Systems, Weizmann Institute of Science, 7610001 Rehovot, Israel
[3]Adult Inpatient Ward, Shalvata Mental Health Center, 45100 Hod Hasharon, Israel
*Correspondence: libi.hertzberg@gmail.com (Libi Hertzberg)

Academic Editor: Francesco Bartoli
Submitted: 31 August 2025 Revised: 24 December 2025 Accepted: 14 January 2026 Published: 21 May 2026

Abstract

Background: Schizophrenia is a complex mental disorder with an estimated heritability of 80%, yet its underlying pathophysiology remains poorly understood. Emerging evidence implicates the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor—a key player in fast excitatory synaptic transmission, encoded by Glutamate Ionotropic Receptor AMPA Type Subunits 1-4 (*GRIA1-4*)—in the disorder's pathophysiology. However, findings from postmortem brain samples regarding *GRIA1-4* expression have been inconsistent. This study aimed to systematically evaluate the differential expression of *GRIA1-4* genes in schizophrenia by integrating transcriptomic data from postmortem brain tissue and patient-derived cerebral organoids. **Methods**: We conducted a participant-level meta-analysis of seven postmortem brain sample datasets (n = 295; 151 schizophrenia, 144 controls) and analyzed an independent organoid dataset (n = 16). Expression differences between schizophrenia and control samples were quantified using Hedges' g under a random-effects model, with heterogeneity assessed using the I^2 statistic. **Results**: Our analysis revealed significant downregulation of all four *GRIA* genes (*GRIA1-4*) in postmortem brain tissue from individuals with schizophrenia, with the effect concentrated in a subgroup of patients. No substantial heterogeneity was attributable to differences in brain regions or measurement platforms. Consistent downregulation of *GRIA1-3* was observed in patient-derived cerebral organoids, which model early neurodevelopmental stages. **Conclusions**: Our findings highlight AMPA receptor dysfunction as a potential contributor to schizophrenia pathophysiology in a subgroup of patients, consistent with the broader role of glutamatergic signaling disruption in this disorder. The convergent evidence from postmortem brain tissue and developmental models underscores the need for further investigation of *GRIA* genes as potential biomarkers for patient stratification and as therapeutic targets. While further study is needed to understand the functional consequences of our findings, such insights may inform the development of personalized treatment strategies targeting glutamatergic dysfunction in schizophrenia.

Keywords: gene expression profiling; organoids; receptors; AMPA; glutamate; schizophrenia

Main Points

(1) Glutamate Ionotropic Receptor AMPA Type Subunits 1-4 (*GRIA1-4*) expression is significantly reduced in schizophrenia across seven postmortem brain datasets.

(2) A coordinated downregulation of *GRIA1-4* characterizes a distinct molecular subgroup of individuals with schizophrenia.

(3) Similar downregulation of *GRIA1-3* is present in schizophrenia-derived cerebral organoids, supporting developmental involvement.

(4) These findings highlight α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor signaling as a potential biomarker and therapeutic target.

1. Introduction

Schizophrenia is a chronic psychiatric disorder with a lifetime prevalence of about 0.7% [1], characterized by a complex constellation of symptoms that span three primary domains: positive symptoms, such as hallucinations and delusions; negative symptoms, including social withdrawal and flattened affect; and cognitive impairments, including deficits in working memory and verbal learning. Unlike the transient nature of psychosis, these persistent symptomatic clusters, especially cognitive and negative symptoms, drive significant social and occupational disability. Consequently, the disorder imposes a profound socioeconomic and emotional burden on affected individuals, their families, and global healthcare systems [2–4].

Schizophrenia has a strong genetic component, with heritability estimated at about 80% [5]. Genome-wide association studies (GWAS) have identified more than 290 risk loci, each contributing only a modest increase in risk [6], and together explaining 25–50% of genetic liability [7,8]. Many of the associated variants are located in noncoding regions, which are enriched with regulatory sequences that influence gene expression rather than protein structure [9]. Therefore, it is essential to examine gene expression patterns and identify genes with differential expression in schizophrenia to better understand the genetic and molecular basis of the disease.

For decades, the dopamine hypothesis has dominated the neurochemical understanding of schizophrenia, proposing that symptoms result from increased dopaminergic activity in the striatum and decreased activity in prefrontal regions [10–13]. Another hypothesis that has gained significant support in recent decades is the involvement of glutamatergic signaling in schizophrenia. Glutamatergic dysfunction has been associated with both psychotic symptoms and cognitive deficits [14–16]. This hypothesis is mainly supported by the psychotomimetic effects of non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine and phencyclidine [17–20], suggesting that NMDA receptor hypofunction may play a role in symptom development. However, focusing only on NMDA receptor dysfunction might oversimplify the underlying pathophysiology. Clinical trials targeting glutamatergic transmission have shown limited therapeutic benefit [21], indicating that glutamate-related changes probably go beyond receptor binding and involve more extensive synaptic and circuit-level processes.

Glutamate receptors are divided into two main groups: (1) Ionotropic receptors, which respond to synthetic glutamate derivatives like NMDA, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), and kainate; and (2) G-protein coupled metabotropic receptors that produce longer-lasting neuromodulatory effects of glutamate [22].

NMDA receptors co-localize with AMPA receptors (AMPARs) at excitatory synapses throughout the brain, where AMPAR activation modulates N-methyl-D-aspartate receptors (NMDARs) function [23,24]. AMPARs are multimeric structures composed of four subunits, encoded by the Glutamate Ionotropic Receptor AMPA Type Subunits 1-4 (*GRIA1-4*) genes (referred to as *GluR1–4* in earlier literature) [23,25], which can assemble in multiple homo- or heteromeric combinations, contributing to substantial receptor diversity. AMPARs mediate fast excitatory neurotransmission through Na^+ influx and subsequent postsynaptic depolarization, which relieves the Mg^{2+} block of the NMDA receptor channel and allows Ca^{2+} entry [23,26]. NMDARs-dependent long-term potentiation and depression (LTP/LTD), both critical mechanisms underlying learning and memory, rely on the dynamic regulation of AMPAR trafficking [27,28]. Individuals with schizophrenia experience cognitive impairments, including various learning and memory deficits [29]. It has also been suggested that enhancing AMPA receptor activity could be a practical way to address NMDA receptor hypofunction and the associated cognitive impairments in schizophrenia [26]. Animal studies further highlight the role of AMPARs in behaviors associated with schizophrenia. *GRIA1* knockout mice exhibited behavioral abnormalities linked to schizophrenia, including increased locomotor activity in response to novelty, impaired prepulse inhibition, disorganized social behaviors, and a lack of pleasure responses [30–32].

At the genetic level, *GRIA* genes are highly conserved among mammals [33]. *GRIA1* was found to be associated with schizophrenia in a GWAS that identified 108 associated loci [34], as well as in a study of a Korean population [35]. Importantly, *GRIA3* was identified as one of 10 genes with ultra-rare variants that were associated with schizophrenia, in a study of the Schizophrenia Exome Sequencing Meta-Analysis (SCHEMA) consortium [36]. Findings regarding the associations of *GRIA2* and *GRIA4* with schizophrenia have been inconsistent across studies [37–40].

A systematic review of postmortem studies examining AMPA receptor subunits' expression and binding in patients with schizophrenia reported inconsistent results. This inconsistency was observed across studies investigating AMPA receptor binding, subunit protein expression, and subunit messenger RNA (mRNA) expression [41]. Few studies have observed a reduction in AMPA subunits' mRNA expression in brain samples from patients with schizophrenia compared to healthy control subjects [42–44], while others found no significant difference [45,46], and a few studies reported increased mRNA expression [47,48]. Few studies have reported a decrease in AMPA expression at the protein level [49,50], while others did not find any significant difference [51–53], and some observed increased protein levels [54,55]. Similarly, findings on AMPA receptor binding were inconsistent. Some studies found reduced receptor binding in brain samples from individuals with schizophrenia [56,57], whereas others reported no significant differences [44,58–60], or increased receptor binding [61,62].

Preclinical studies demonstrate that positive allosteric modulators, such as AMPAkines, enhance synaptic plasticity and cognitive performance and may potentiate antipsychotic efficacy in the context of glutamatergic dysfunction [63,64]. Therapeutic modulation of AMPARs has therefore emerged as a promising avenue for treating schizophrenia. However, translation to clinical efficacy has been limited by challenges related to drug potency, subunit selectivity, and tolerability [64,65].

Brain samples from individuals with schizophrenia are only accessible postmortem, which may not reflect changes that occur during the early stages of the disease. Furthermore, the differential expression observed in postmortem samples might be influenced by confounding factors such as medication and duration of illness. Brain organoid models, created from induced pluripotent stem cells (iPSCs), serve as valuable tools for studying early human brain development in the context of neurodevelopmental disorders. A study using organoids derived from individuals with schizophrenia reported altered expression of genes involved in synaptic and neurodevelopmental processes compared to healthy controls, including downregulation of *GRIA1-3* [65].

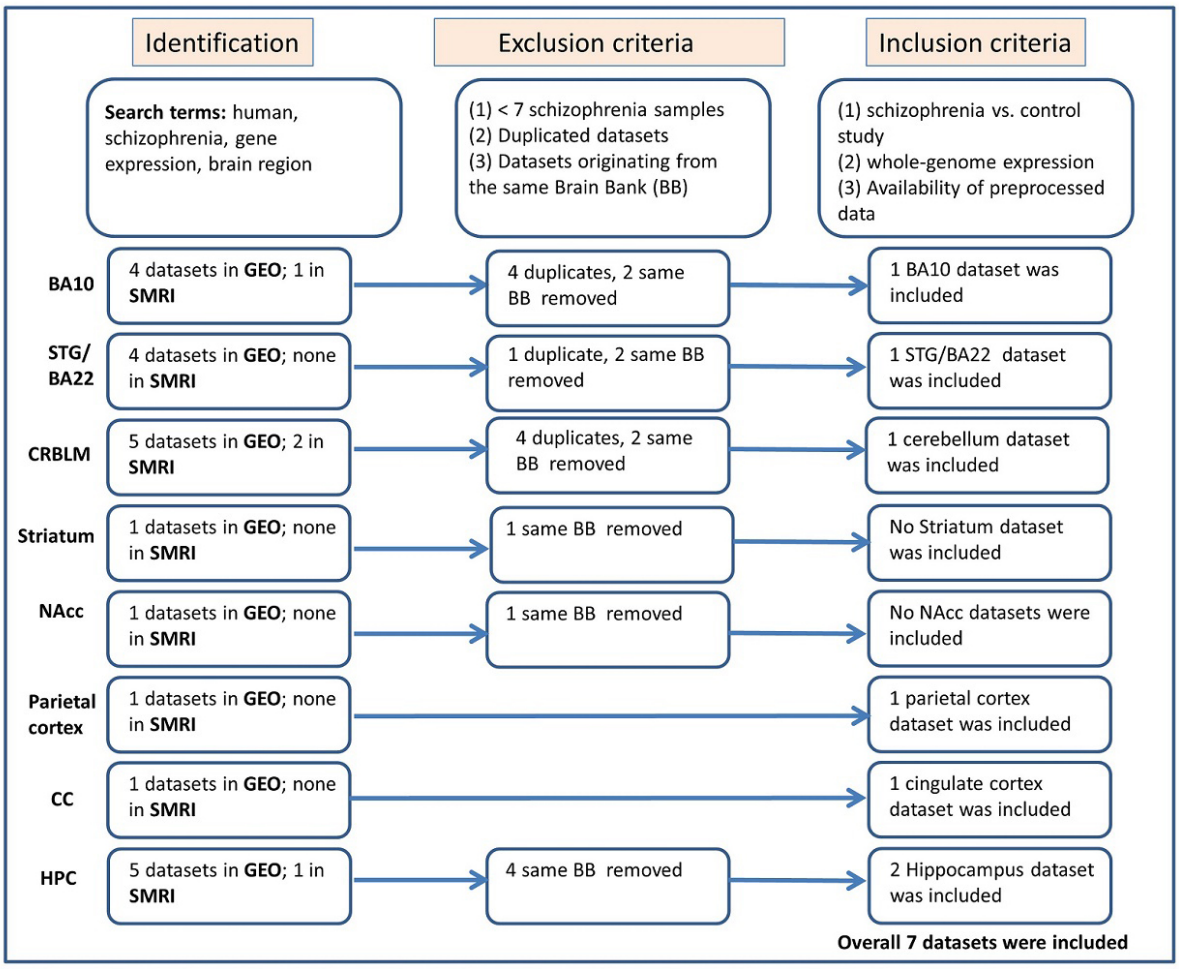

Fig. 1. Diagram illustrating the study identification and selection process conducted in accordance with PRISMA 2020 guidelines. The flowchart summarizes dataset retrieval, screening stages, and final inclusion criteria. Abbreviations: SMRI, Stanley Medical Research Institute; GEO, Gene Expression Omnibus; CMC, Common Mind Consortium; CC, cingulate cortex; BA, brodmann area; STG, Superior Temporal Gyrus; CRBLM, cerebellum; NAcc, Nucleus Accumbens; HPC, hippocampus; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Given the important role of glutamate signaling in schizophrenia, the evidence for an association at the genetic level, and the inconsistent findings on *GRIA* gene expression, we systematically compared *GRIA* expression levels in brain samples from patients with schizophrenia and healthy individuals. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [66], we conducted a participant-level meta-analysis of seven publicly available datasets (overall 295 samples). Additionally, we analyzed an organoid dataset, produced from patients with schizophrenia and controls, to explore *GRIA* during early neurodevelopment.

2. Methods and Materials

2.1 Dataset Identification and Selection

Gene expression datasets were identified through a structured search of the National Center for Biotechnology Information Gene Expression Omnibus (NCBI GEO; https://www.ncbi.nlm.nih.gov/geo/) and the Stanley Medical Research Institute (SMRI) Array Collection (https://www.stanleyresearch.org/brain-research/array-collection/). Searches included the terms schizophrenia, gene expression, human, and brain. Dataset screening and selection procedures followed the PRISMA 2020 guidelines [66], and the full workflow is illustrated in Fig. 1. Studies were eligible if they: (1) included postmortem human brain samples from individuals with schizophrenia and healthy controls, (2) provided normalized expression matrices, and (3) sampled one of the following brain regions: Brodmann area (BA) 10, superior temporal gyrus (BA22), cerebellum, parietal cortex, anterior cingulate cortex, nucleus accumbens, striatum, or hippocampus. Datasets were excluded when they contained overlapping samples obtained from the same brain bank. Study metadata included sample sizes, demographic information,

Table 1. Summary of clinical profiles and technical specifications for all datasets used in the meta-analysis.

Postmortem Brain sample datasets (295 samples)								
Accession	Publication	Brain region; Brain bank	# SZ (151 samples)	# CNT (144 samples)	Platform	Mean Age (standard dev.)	Mean PMI (standard dev.)	Mean pH (standard dev.)
GDS4523	(Maycox *et al*., 2009) [67]	BA10; CCHPC	27 19M:8F	23 12M:11F	HG U133 Plus 2.0	SZ: 73 (15) CNT: 69 (22) $p = 0.45$	SZ: 8.2 (7) CNT: 10 (4) $p = 0.30$	SZ: 6.1 (0.2) CNT: 6.5 (0.3) $\mathbf{p = 8 \times 10^{-6}}$
GSE37981	(Pietersen *et al*., 2014) [68]	STG Pyramid.; HBTRC	9 4M:5F	8 4M:4F	U133 X3P Array	SZ: 67 (20) CNT: 67 (21) $p = 0.99$	SZ: 17 (5) CNT: 18 (3) $p = 0.71$	Not provided
GDS1917	(Paz *et al*., 2006) [69]	CRBLM; Maryland	13 13M:0F	14 14M:0F	U133 Plus 2.0 Array	SZ: 46 (12) CNT: 43 (10) $p = 0.50$	SZ: 12.8 (5) CNT: 15.6 (6) $p = 0.18$	Not provided
GSE35978	(Chen *et al*., 2013) [70]	Parietal cortex; SMRI	51 37M:14F	45 31M:14F	Gene 1.0 ST Array	SZ: 43 (10); CNT: 46 (9) $p = 0.14$	SZ: 31 (16) CNT: 27 (12) $p = 0.17$	SZ: 6.4 (0.3) CNT: 6.5 (0.3) $\mathbf{p = 0.015}$
GSE80655	(Ramaker *et al*., 2017) [71]	ACC; Pritzker	23 20M:3F	24 21M:3F	Illumina HiSeq 2000	SZ: 43 (9); CNT: 50 (13) $p = 0.043$	SZ: 21 (9) CNT: 22 (7) $p = 0.62$	SZ: 6.8 (0.2) CNT: 6.9 (0.1) $\mathbf{p = 0.044}$
GSE53987	(Lanz *et al*., 2019) [72]	HPC; Pittsburgh	15 9M:6F	18 9M:9F	HG U133 Plus 2.0	SZ: 46 (9); CNT: 48 (11) $p = 0.49$	SZ: 19 (7) CNT: 19 (5) $p = 0.99$	SZ: 6.4 (0.3) CNT: 6.6 (0.2) $p = 0.055$
GSE138082	(Perez *et al*., 2021) [73]	HPC CA3; Dallas	13 9M:4F	12 9M:3F	Illumina HiSeq 2500	SZ: 54 (11); CNT: 56 (9) $p = 0.59$	SZ: 23 (7) CNT: 20 (4) $p = 0.20$	Not provided

Organoid samples dataset (16 samples)					
Accession	Publication	Samples type	# SZ (8 samples)	# CNT (8 samples)	Platform
GSE133534	(Kathuria *et al*., 2020) [74]	iPSC derived cerebral organoids	8 5M:3F	8 6M:2F	Illumina NovaSeq 6000

#, number of; SZ, schizophrenia; CNT, controls; PMI, postmortem interval; ACC, anterior cingulate cortex; CA3, Cornu Ammonis 3; pyramid., pyramidal; parvalb., parvalbumin; M, males; F, females; Pritzker, Pritzker Neuropsychiatric Disorders Research Consortium; Pittsburgh, Brain Tissue Donation Program at the University of Pittsburgh; Dallas, Dallas Brain Collection; Maryland, Maryland Brain Collection; HBTRC, The Harvard Brain Tissue Resource Center; CCHPC, Charing Cross Hospital Prospective Collection; iPSC, induced pluripotent stem cells; Two-sided *t*-test associated *p*-values are listed for each dataset, for having different (SZ vs. CNT) mean age, PMI, and pH; Statistically significant differences (p-value < 0.05) appear in bold.

Table 2. Glutamate Ionotropic Receptor AMPA (*GRIA)* genes meta-analysis results.

	Gene symbol	Random effects Hedges	Lower	Upper	*p*-value	τ^2	I^2	Q	Q *p*-value
1	*GRIA1*	–0.44	–0.67	–0.21	0.00021	0	0	2.4	0.88
2	*GRIA2*	–0.31	–0.54	–0.08	0.0083	0	0	2.9	0.82
3	*GRIA3*	–0.24	–0.47	–0.01	0.043	0	0	3.5	0.75
4	*GRIA4*	–0.49	–0.72	–0.26	4.10×10^{-5}	0	0	5.9	0.43

The standardized mean difference (Hedges' g, random effects model) is negative (bluish) when expression is lower in schizophrenia compared to controls. The color intensity is proportional to the Hedges' g value. The lower and upper 95% confidence interval limits are given in the 4th and 5th columns. The associated *p*-values are given in the 6th column. Heterogeneity measures - I^2, τ^2, and Cochran's Q test and its associated *p*-value are given in columns 7th–10th. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.

assay platform, postmortem interval (PMI), and tissue pH (Table 1, Ref. [67–74]). Additional preprocessing steps, normalization, quality control, and outlier removal are reported in the **Supplementary Materials**.

2.2 Postmortem Brain Samples Differential Gene Expression Meta-Analysis

Differential expressions of *GRIA* genes were assessed using an individual participant-level meta-analytic framework. Standardized mean differences between schizophrenia and control groups were quantified using Hedges' g [75], with positive values representing higher expression among schizophrenia samples and negative values indicating reduced expression. Effect sizes and 95% confidence intervals were estimated using the "metacont" function from the R *meta* package (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria) [76]. Because the included datasets differed in brain regions, platforms, and preprocessing strategies, pooled effect sizes were calculated using a random-effects model [77], which accounts for both study and between-study variability and improves generalizability [78].

To assess heterogeneity across the datasets included in the meta-analysis, we quantified between-study variability using three complementary measures: Cochran's Q, I^2, and τ^2. Cochran's Q provides a formal statistical test for heterogeneity by evaluating whether the observed variability in effect sizes exceeds what would be expected by chance alone, based on the weighted sum of squared deviations from the pooled effect size [79]. To quantify the degree of inconsistency that could be attributed to genuine between-study variation rather than chance, the I^2 (Inconsistency) statistic was calculated, expressing the proportion of total variation due to heterogeneity [80]. Furthermore, the magnitude of the between-study variance was estimated using τ^2, which provided the essential variance component for the subsequent random-effects model employed in the meta-analysis [81]. Together, these metrics allowed us to evaluate the extent and nature of heterogeneity among the included datasets and to interpret the robustness of the meta-analytic findings.

2.3 Analysis of Human iPSCs-Derived Cerebral Organoids of Patients With Schizophrenia

Differential expression of *GRIA* genes was measured in a patient-derived organoid dataset, which was downloaded from the GEO database (GSE133534) and comprised 16 samples (8 from patients with schizophrenia and 8 from controls). Study metadata included sample sizes, sex, and assay platform (Table 1). Additional preprocessing steps, normalization, quality control, and outlier removal are reported in the **Supplementary Materials**. Differential $\log_2$ expression was calculated using a two-sided *t*-test.

2.4 Analysis of Potential Confounding Variables

To assess whether group differences in gene expression could be influenced by clinical or biological covariates, multiple linear regression models were fitted for each dataset using the MATLAB "fitlm" function [82]. Available covariates included age, sex, PMI, tissue pH, and antipsychotic medication history. Schizophrenia diagnosis served as the primary predictor variable. Regression results are reported as *t*-statistics and *p*-values, indicating whether differential expression remained significant after adjustment.

3. Results

3.1 Meta-Analysis Reveals Reduced GRIA1-4 Expression in Schizophrenia

A meta-analysis of GRIA1-4 differential expression was conducted, revealing significant downregulation of all four genes in individuals diagnosed with schizophrenia relative to control subjects (Fig. 2; Table 2).

3.2 GRIA1-3 are Downregulated in Human iPSCs-Derived Cerebral Organoids of Patients With Schizophrenia

GRIA1-3 were previously shown to be significantly downregulated in schizophrenia in a study of organoids derived from patients, modeling early developmental stages. However, the differential expression of *GRIA4* was not referred to [65]. We analyzed the same organoids gene expression dataset, from the GEO database (GSE133534) and comprised of 16 samples (8 schizophrenia and 8 controls). *GRIA1-3* were indeed downregulated in schizophrenia (Fig. 3; p = 0.071, 0.005, 0.023, respectively), while

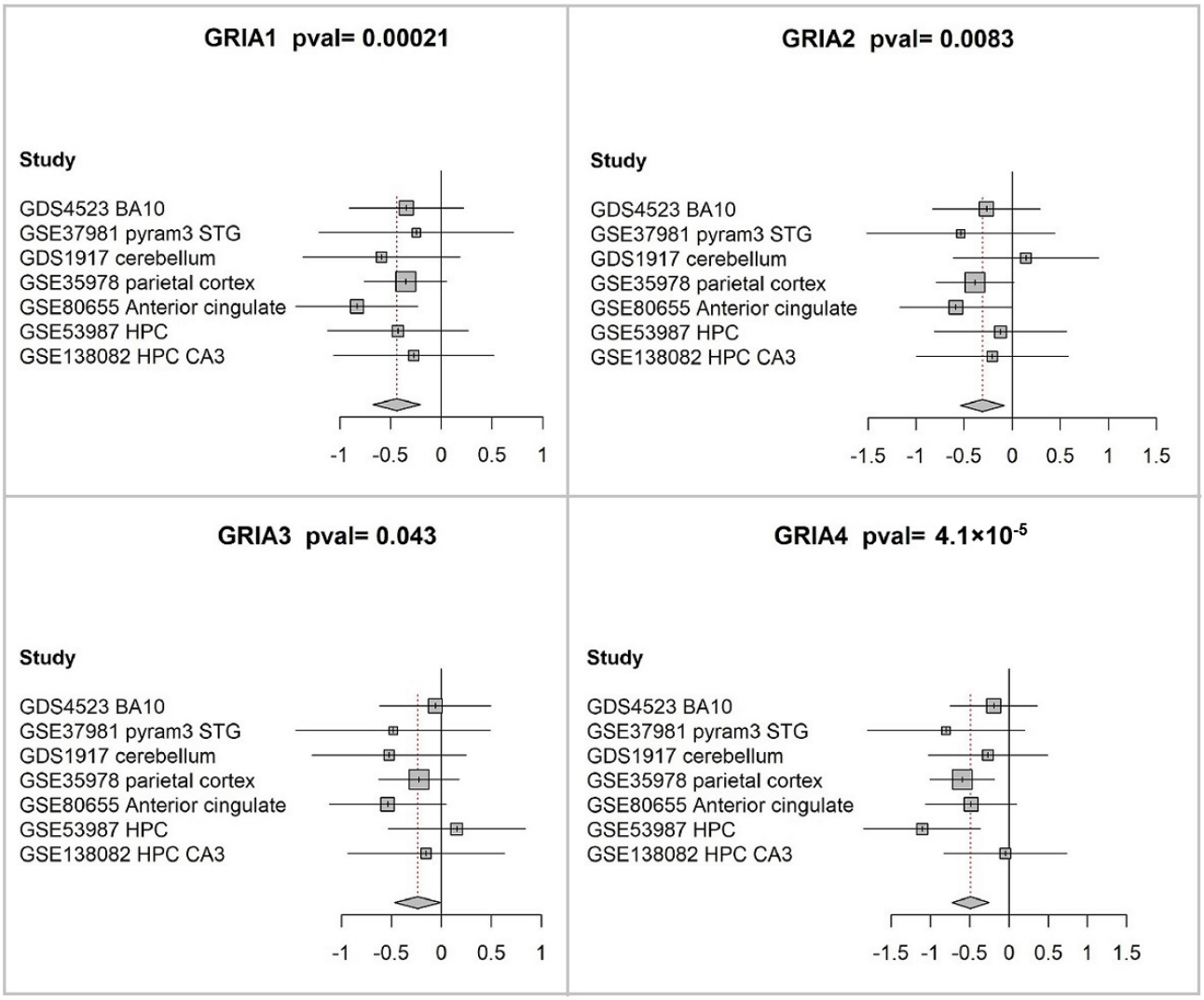

Fig. 2. Reduced expression of *GRIA1-4* in postmortem brain tissue from patients with schizophrenia. Forest plots show the differences in expression levels of *GRIA1* (A), *GRIA2* (B), *GRIA3* (C), and *GRIA4* (D) between individuals with schizophrenia and healthy controls across all datasets included in the meta-analysis. Forest plots were generated using the meta package in R *meta* package (version 3.6.1) with its built-in plotting function. In each panel, the square symbols represent the standardized mean difference (Hedges' g) for individual datasets, and their size reflects the relative analytical weight determined largely by sample size. The corresponding 95% confidence intervals are represented by horizontal bars extending from each square. A vertical line indicates the point of zero difference. The standardized mean difference is positive (negative) if the expression is higher (lower) in schizophrenia compared to the control group. The center of the diamond represents the overall difference across all studies, and its width represents the corresponding 95% confidence interval. The associated *p*-values are reported in the figure titles.

GRIA4 did not show significant differential expression ($p = 0.35$). While the downregulation of *GRIA1* is only marginally significant ($p = 0.071$), this is likely due to the small cohort size (8 schizophrenia samples and 8 controls). This explanation is further supported by the positive correlation observed with *GRIA3* expression (Fig. 4).

3.3 Coordinated Expression of GRIA1-3 Across Brain Tissue and Schizophrenia-Derived Organoids

To examine the consistency of transcriptional relationships among the *GRIA* genes, we computed Pearson correlation coefficients for all pairwise gene combinations within each dataset, restricted to schizophrenia samples.

In postmortem brain datasets, all *GRIA* gene pairs demonstrated strong positive correlation (**Supplementary Fig. 1**). For example, the correlation between *GRIA1* and *GRIA2* expression = 0.74, *p*-value = 3.7×10^{-25} (Fig. 4). A similar analysis was performed on the organoids dataset GSE133534 [65] and revealed coordinated expression patterns among *GRIA1-3*, whereas *GRIA4* did not exhibit comparable correlation with the other members of the gene family (**Supplementary Fig. 2**). Because genes involved in

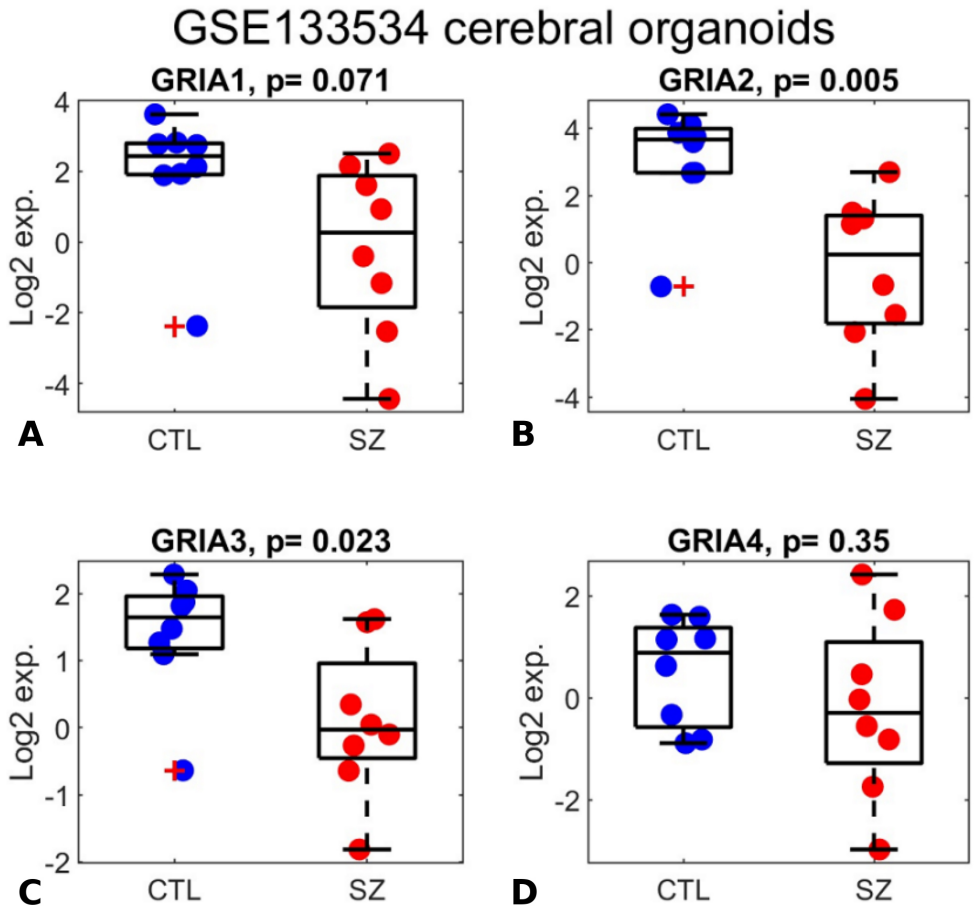

Fig. 3. *GRIA1-3* expression is downregulated in human iPSC-derived cerebral organoids from individuals with schizophrenia. (A–D) Box plots display expression levels for *GRIA1* (A), *GRIA2* (B), *GRIA3* (C), and *GRIA4* (D). The *y*-axis represents $\log_2$-transformed expression values. Each dot corresponds to the $\log_2$ expression level of an individual in the GSE133534 cerebral organoid dataset, including healthy controls (blue dots; labeled "CTL") and individuals with schizophrenia (red dots; labeled "SZ"). The central mark indicates the median, while the bottom and top edges of each box represent the 25th and 75th percentiles, respectively. Two-sided *t*-test *p*-values are reported in the subplot titles.

the same molecular pathway, such as the AMPA receptor subunits, are typically co-regulated to maintain functional integrity [83], the observation of reproducible positive correlations for *GRIA1-3* across both adult brain and early neurodevelopmental models reinforces the robustness of our findings and suggests that the observed patterns are unlikely to reflect technical artifacts or random variation.

3.4 Expression of GRIA Genes Shows a Significant Positive Correlation With NMDA Receptor–Encoding Genes in Postmortem Schizophrenia Brain Samples

We further examined whether *GRIA1-4* have positively correlated expression with NMDA receptor genes. As can be seen in **Supplementary Fig. 1**, several NMDA receptor genes are positively correlated with *GRIA1-GRIA4*. For example, Glutamate Ionotropic Receptor NMDA Type Subunit 2A (*GRIN2A*), encoding NMDA receptor subunit 2A, is positively correlated with *GRIA1* (Fig. 5; combined data corr. = 0.7, *p*-value = 3×10^{-21}).

3.5 Evaluation of Confounding Variables

To assess whether clinical or technical variables might influence the expression results, we constructed a linear regression model that included age, sex, pH, PMI, and antipsychotic exposure as covariates for each of the seven datasets (see Methods). Summary outcomes of this analysis are reported in **Supplementary Table 1**. However, data on these factors were not available for all datasets, and information on lifetime antipsychotic treatment was specifically available only for the parietal cortex dataset [70] (GSE35978). To summarize the linear regression analysis, the mean t-statistic values were calculated for each of the four *GRIA* genes. A consistent downward trend in expression remained even after adjusting for these confounding variables (**Supplementary Table 1**; mean *t*-statistic = –1.4, –0.71, –0.35, –1.04, respectively).

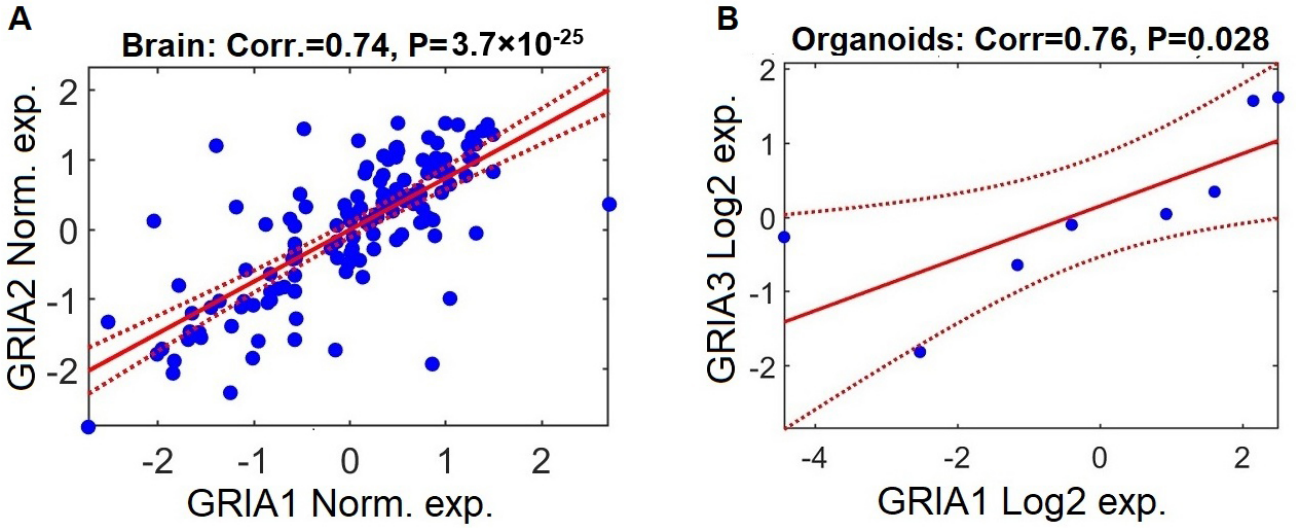

Fig. 4. *GRIA* gene expression patterns are positively correlated in brain samples and cerebral organoids from individuals with schizophrenia. (A) Scatter plot demonstrating the relationship between log_2-normalized expression levels of *GRIA2* and *GRIA1* in postmortem brain samples from individuals with schizophrenia, based on aggregated data from the seven datasets included in the meta-analysis. Each data point reflects expression values for a single participant. Normalization was performed independently within each dataset (z-scoring: mean = 0, standard deviation = 1). The solid red line shows the fitted linear regression trajectory, and the dashed red curves represent the 95% confidence interval. (B) Parallel analysis depicting the association between log_2-normalized expression levels of *GRIA3* and *GRIA1* in schizophrenia-derived cerebral organoids.

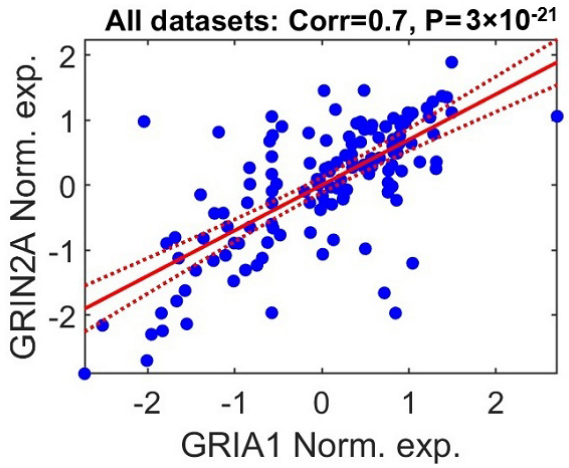

Fig. 5. *GRIA1* and *GRIN2A* expression patterns are positively correlated. The scatter plot illustrates the relationship between log_2-normalized expression values of *GRIN2A* and *GRIA1* in postmortem brain samples from individuals with schizophrenia. Each point represents a single participant aggregated across the seven datasets included in the meta-analysis. Gene expression values were independently standardized within each dataset (z-scored: mean = 0, standard deviation = 1). The solid red line indicates the fitted linear regression model, and the dashed lines depict the 95% confidence interval for the regression estimate.

3.6 Per-Sample Fold Change Analysis

To determine whether the observed reduction in expression is consistent across individuals or confined to a subset of individuals, we conducted a per-sample log_2 fold-change analysis. As illustrated in Fig. 6, across four of the seven datasets, the decrease in expression of *GRIA1-4* appears to be restricted to a distinct subgroup of patients. Individuals exhibiting coordinated reduction (represented by bluish values) with mean log_2 fold change values <-0.25 are highlighted with a red bar along the x-axis. In contrast, the remaining patients show no uniform pattern of reduction, and some display evidence of increased expression (yellow shades). This subgroup-specific pattern was replicated in the majority of datasets examined (**Supplementary Fig. 3**), supporting the notion that the downregulation is not uniformly present across the schizophrenia cohort.

To examine whether the down-regulation signal was linked to specific clinical characteristics of the patients, we calculated Pearson correlations between *GRIA* genes' expression and the available patient variables: age, sex, and antipsychotic treatment and suicide status (treatment and suicide status were available only in one dataset). No significant associations were observed (*GRIA1* combined *p*-values = 0.3, 0.27, 0.71, 0.66, respectively; **Supplementary Figs. 4–7**; similar results were observed for *GRIA2-4*).

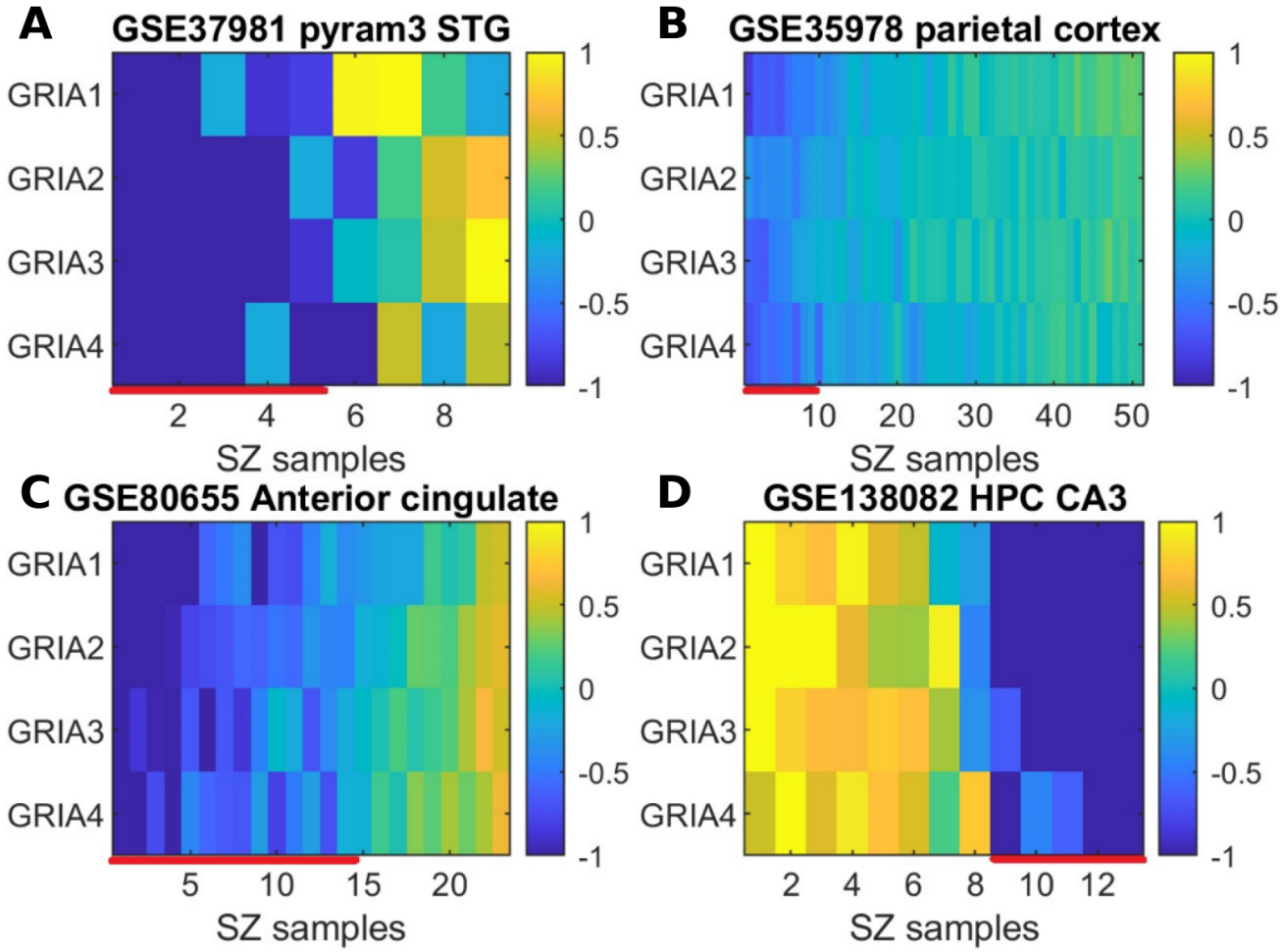

Fig. 6. Log_2 fold change per-sample analysis: subgroup-specific reduction in *GRIA1-4* expression. (A–D) display per-sample expression patterns for each dataset, with the corresponding brain region and dataset identifier indicated in the title. Within each heatmap, rows represent individual *GRIA* genes and columns correspond to schizophrenia samples. The color intensity at position (i, j) reflects the log_2 fold change of gene *i* in patient *j*, calculated relative to the average expression in the control group. Samples exhibiting downregulation across *GRIA* genes, with mean log_2 fold change values <-0.25, are highlighted by red bars along the x-axis to denote this subgroup.

4. Discussion

In this study, we conducted a participant- level meta-analysis of the expression of *GRIA1-4* genes in brain samples from individuals with schizophrenia compared to healthy controls, by integrating seven independent gene expression datasets (a total of 295 samples, 151 with schizophrenia and 144 controls). Our analysis detects significant downregulation of the four genes encoding AMPA receptors, *GRIA1-4*, in schizophrenia. Additionally, our re-analysis of the organoid dataset from [65] confirmed downregulation of *GRIA1-3* in schizophrenia-derived organoids (p = 0.071, 0.005, 0.023, respectively), while *GRIA4* showed no significant differential expression (p = 0.35) (Fig. 3). The positive correlation between their expression patterns in both brain and organoids (Fig. 4) further supports the validity of these results and reduces the likelihood that this signal results from technical or arbitrary noise.

Genes of the *GRIA* family, which encode subunits of the AMPA glutamate receptor, play essential roles in synaptic plasticity, learning, and memory, functions strongly implicated in the cognitive and negative symptoms of schizophrenia [27,28]. Disruption of these systems may aggravate cognitive symptoms in schizophrenia. Downregulation of these genes may impair glutamate transmission, potentially affecting a wide range of cognitive and neurological functions.

Furthermore, we found that *GRIA* genes have a positive correlation in expression with several NMDA receptor genes, including *GRIN2A*. *GRIN2A*, along with *GRIA3*, was included in the list of ten genes with ultra-rare variants associated with schizophrenia in the SCHEMA consortium study [36]. NMDA receptors are glutamate receptors involved in the development and course of both psychotic and negative symptoms in schizophrenia [14–16]. A linked

regulation of genes encoding glutamate receptors, such as *GRIA* and *GRIN*, may suggest a higher-level dysregulation of glutamatergic signaling in schizophrenia. This mutual regulation could be important in understanding the complex interactions of molecular components that lead to the disease's pathophysiology.

We note that our findings for *GRIA1-4* do not align with several previous studies that reported up-regulation in brain samples from individuals with schizophrenia. For example, Kimoto *et al.* [84] found *GRIA1* and *GRIA4* to be up-regulated in samples from 36 individuals with schizophrenia compared to 26 controls. In contrast, Beneyto and Meador-Woodruff [44] observed downregulation of *GRIA4*, consistent with our findings, but did not detect significant differential expression of *GRIA1* between 15 individuals with schizophrenia and 15 controls. One possible explanation for these inconsistencies is that *GRIA1-4* is downregulated in a subgroup of individuals with schizophrenia, and the results depend on the proportion of this subgroup within each study. Supporting this hypothesis, our per-sample fold-change analysis showed that downregulation is concentrated in a specific subgroup of patients across most datasets in our meta-analysis (Fig. 6; **Supplementary Fig. 2**). Identifying heterogeneity in gene expression patterns is essential for advancing precision medicine in schizophrenia. Stratifying patients based on molecular signatures may enable more targeted therapeutic approaches and ultimately improve treatment response and clinical outcomes. Our results indicate no substantial heterogeneity attributable to differences in brain regions or measurement platforms (Table 2; $I^2 = 0\%$).

Limitations

We recognize that our study, like other postmortem studies, is limited by several factors. This postmortem examination provides a snapshot of neurobiology at the end of life and cannot detect abnormalities that may have arisen when the disease first manifested itself. This is especially important in the case of schizophrenia, as research suggests that its pathophysiology develops in its early stages [85]. Additionally, the observed differential expression may be influenced by confounding factors, such as medication and illness duration. While our linear regression analyses suggest that the observed downregulation cannot be explained solely by age or sex, several potential confounders were not fully assessed. Information on PMI and pH was incomplete across studies, antipsychotic medication data were available for only one dataset, and duration of illness was not reported. Therefore, we cannot exclude the possibility that these or other confounding factors contribute to the observed downregulation.

However, the study of schizophrenia iPSCs-derived cerebral organoids, which represent early human brain development [65] and our re-analysis (Figs. 3,4), suggests that the downregulation of *GRIA1-3* is already present in the early stages of the disease. Furthermore, the significant correlation we observe between *GRIA* genes' expression, in both brain and organoid samples (**Supplementary Fig. 1,2**), provides additional validation for its downregulation in schizophrenia. Although *GRIA1-3* showed consistent downregulation across both postmortem brain tissue and organoids, *GRIA4* did not demonstrate differential expression in the developmental model. This discrepancy may indicate temporal heterogeneity in AMPA receptor subunit vulnerability, where *GRIA4* changes either emerge later in neurodevelopment or are restricted to a more specific clinical subgroup. Alternatively, *GRIA4* dysregulation may require environmental or pharmacological exposure not captured in early organoid models. Together, these patterns support the interpretation that *GRIA1-3* represent a core early neurodevelopmental AMPAR signature, while *GRIA4* may participate in a downstream or secondary phase of disease-related synaptic remodeling.

Another limitation is that transcript levels do not necessarily reflect protein abundance or receptor functionality, and caution is required in interpreting downstream physiological implications. Future studies integrating proteomic, electrophysiological, and functional readouts are required for clarifying the biological consequences of altered *GRIA* expression in schizophrenia.

In summary, our analysis identifies a subgroup of individuals with schizophrenia showing coordinated downregulation of *GRIA1-4*, which encodes AMPA receptor subunits. The identification of distinct molecular subgroups is an essential step toward the development of personalized medicine in schizophrenia. The downregulation of *GRIA1-3* in organoid models suggests that these changes arise before disease onset. Combined with the established genetic link between *GRIA* genes and schizophrenia, as well as the critical role of glutamate signaling in its pathophysiology, our findings indicate that this differential expression may contribute to disease development.

This research underscores the need for further investigation into AMPA receptor modulation as a potential biomarker and therapeutic target for a distinct subgroup of patients with schizophrenia. Such insights could pave the way for the development of personalized treatment approaches.

5. Conclusions

GRIA1-4 are significantly downregulated in a subgroup of individuals with schizophrenia, with changes in *GRIA1-3* already evident in cerebral organoids, suggesting an early neurodevelopmental origin. While no clear clinical characteristics were found to distinguish this subgroup, these findings indicate a distinct molecular subgroup of patients and highlight *GRIA* expression as a potential biomarker and therapeutic target for advancing personalized treatment in schizophrenia.

Abbreviations

ACC, anterior cingulate cortex; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; AMPARs, AMPA receptors; BA, brodmann area; CA3, Cornu Ammonis 3; CC, cingulate cortex; CCHPC, Charing Cross Hospital Prospective Collection; CNT, controls; CRBLM, cerebellum; GEO, Gene Expression Omnibus; GRIA, Glutamate Ionotropic Receptor AMPA Type Subunit; HBTRC, The Harvard Brain Tissue Resource Center; HPC, hippocampus; iPSCs, Induced Pluripotent Stem Cells; NAcc, Nucleus Accumbens; NMDA, N-methyl-D-aspartate; NMDARs, NMDA receptors; PMI, postmortem interval; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SMRI, Stanley Medical Research Institute; STG, Superior Temporal Gyrus; SZ, schizophrenia.

Availability of Data and Materials

All datasets analyzed in this study were previously published and are publicly accessible through the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/).

Author Contributions

LH: Supervision, Conceptualization, Methodology, Writing - Reviewing and Editing. AB: Conceptualization, Methodology, Investigation, Writing- Original draft preparation. AY: Methodology, Software, Data Curation, Visualization. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We thank Professor Eytan Domany for his help with the infrastructure that enabled the performance of this project.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/AP46200.

References

[1] McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiologic Reviews. 2008; 30: 67–76.

[2] Carter CS, Barch DM, Buchanan RW, Bullmore E, Krystal JH, Cohen J, *et al*. Identifying cognitive mechanisms targeted for treatment development in schizophrenia: an overview of the first meeting of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia Initiative. Biological Psychiatry. 2008; 64: 4–10. https://doi.org/10.1016/j.biopsych.2008.03.020.

[3] Lewis DA, Lieberman JA. Catching up on schizophrenia: natural history and neurobiology. Neuron. 2000; 28: 325–334. https://doi.org/10.1016/s0896-6273(00)00111-2.

[4] Mueser KT, McGurk SR. Schizophrenia. Lancet (London, England). 2004; 363: 2063–2072. https://doi.org/10.1016/S0140-6736(04)16458-1.

[5] Smoller JW, Andreassen OA, Edenberg HJ, Faraone SV, Glatt SJ, Kendler KS. Psychiatric genetics and the structure of psychopathology. Molecular Psychiatry. 2019; 24: 409–420. https://doi.org/10.1038/s41380-017-0010-4.

[6] Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, *et al*. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature. 2022; 604: 502–508. https://doi.org/10.1038/s41586-022-04434-5.

[7] Lee SH, DeCandia TR, Ripke S, Yang J, Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC-SCZ), International Schizophrenia Consortium (ISC), *et al*. Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. Nature Genetics. 2012; 44: 247–250. https://doi.org/10.1038/ng.1108.

[8] Henriksen MG, Nordgaard J, Jansson LB. Genetics of Schizophrenia: Overview of Methods, Findings and Limitations. Frontiers in Human Neuroscience. 2017; 11: 322. https://doi.org/10.3389/fnhum.2017.00322.

[9] Roussos P, Mitchell AC, Voloudakis G, Fullard JF, Pothula VM, Tsang J, *et al*. A role for noncoding variation in schizophrenia. Cell Reports. 2014; 9: 1417–1429. https://doi.org/10.1016/j.celrep.2014.10.015.

[10] Guillin O, Abi-Dargham A, Laruelle M. Neurobiology of dopamine in schizophrenia. International Review of Neurobiology. 2007; 78: 1–39. https://doi.org/10.1016/S0074-7742(06)78001-1.

[11] McCutcheon RA, Abi-Dargham A, Howes OD. Schizophrenia, Dopamine and the Striatum: From Biology to Symptoms. Trends in Neurosciences. 2019; 42: 205–220. https://doi.org/10.1016/j.tins.2018.12.004.

[12] Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. The American Journal of Psychiatry. 2003; 160: 13–23. https://doi.org/10.1176/appi.ajp.160.1.13.

[13] Seeman MV. History of the dopamine hypothesis of antipsychotic action. World Journal of Psychiatry. 2021; 11: 355–364. https://doi.org/10.5498/wjp.v11.i7.355.

[14] Iasevoli F, Tomasetti C, Buonaguro EF, de Bartolomeis A. The glutamatergic aspects of schizophrenia molecular pathophysiology: role of the postsynaptic density, and implications for treatment. Current Neuropharmacology. 2014; 12: 219–238. https://doi.org/10.2174/1570159X12666140324183406.

[15] Coyle JT, Basu A, Benneyworth M, Balu D, Konopaske G. Glutamatergic synaptic dysregulation in schizophrenia: therapeutic implications. Handbook of Experimental Pharmacology. 2012; 267–295. https://doi.org/10.1007/978-3-642-25758-2_10.

[16] Bojesen KB, Ebdrup BH, Jessen K, Sigvard A, Tangmose K, Edden RAE, *et al*. Treatment response after 6 and 26 weeks is related to baseline glutamate and GABA levels in antipsychotic-

naïve patients with psychosis. Psychological Medicine. 2020; 50: 2182–2193. https://doi.org/10.1017/S0033291719002277.
[17] Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. The American Journal of Psychiatry. 1991; 148: 1301–1308. https://doi.org/10.1176/ajp.148.10.1301.
[18] Gilmour G, Dix S, Fellini L, Gastambide F, Plath N, Steckler T, *et al*. NMDA receptors, cognition and schizophrenia–testing the validity of the NMDA receptor hypofunction hypothesis. Neuropharmacology. 2012; 62: 1401–1412. https://doi.org/10.1016/j.neuropharm.2011.03.015.
[19] Hardingham GE, Do KQ. Linking early-life NMDAR hypofunction and oxidative stress in schizophrenia pathogenesis. Nature Reviews. Neuroscience. 2016; 17: 125–134. https://doi.org/10.1038/nrn.2015.19.
[20] Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, *et al*. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Archives of General Psychiatry. 1994; 51: 199–214. https://doi.org/10.1001/archpsyc.1994.03950030035004.
[21] Kruse AO, Bustillo JR. Glutamatergic dysfunction in Schizophrenia. Translational Psychiatry. 2022; 12: 500. https://doi.org/10.1038/s41398-022-02253-w.
[22] Hollmann M, Heinemann S. Cloned glutamate receptors. Annual Review of Neuroscience. 1994; 17: 31–108. https://doi.org/10.1146/annurev.ne.17.030194.000335.
[23] Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, *et al*. Glutamate receptor ion channels: structure, regulation, and function. Pharmacological Reviews. 2010; 62: 405–496. https://doi.org/10.1124/pr.109.002451.
[24] Cull-Candy S, Brickley S, Farrant M. NMDA receptor subunits: diversity, development and disease. Current Opinion in Neurobiology. 2001; 11: 327–335. https://doi.org/10.1016/s0959-4388(00)00215-4.
[25] Keinänen K, Wisden W, Sommer B, Werner P, Herb A, Verdoorn TA, *et al*. A family of AMPA-selective glutamate receptors. Science (New York, N.Y.). 1990; 249: 556–560. https://doi.org/10.1126/science.2166337.
[26] Zarate CA, Jr, Manji HK. The role of AMPA receptor modulation in the treatment of neuropsychiatric diseases. Experimental Neurology. 2008; 211: 7–10. https://doi.org/10.1016/j.expneurol.2008.01.011.
[27] Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. Neuron. 2004; 44: 5–21. https://doi.org/10.1016/j.neuron.2004.09.012.
[28] Shepherd JD, Huganir RL. The cell biology of synaptic plasticity: AMPA receptor trafficking. Annual Review of Cell and Developmental Biology. 2007; 23: 613–643. https://doi.org/10.1146/annurev.cellbio.23.090506.123516.
[29] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th edn. American Psychiatric Association: Arlington, VA. 2013.
[30] Wiedholz LM, Owens WA, Horton RE, Feyder M, Karlsson RM, Hefner K, *et al*. Mice lacking the AMPA GluR1 receptor exhibit striatal hyperdopaminergia and 'schizophrenia-related' behaviors. Molecular Psychiatry. 2008; 13: 631–640. https://doi.org/10.1038/sj.mp.4002056.
[31] Barkus C, Feyder M, Graybeal C, Wright T, Wiedholz L, Izquierdo A, *et al*. Do GluA1 knockout mice exhibit behavioral abnormalities relevant to the negative or cognitive symptoms of schizophrenia and schizoaffective disorder? Neuropharmacology. 2012; 62: 1263–1272. https://doi.org/10.1016/j.neuropharm.2011.06.005.
[32] Austen JM, Sprengel R, Sanderson DJ. GluA1 AMPAR subunit deletion reduces the hedonic response to sucrose but leaves satiety and conditioned responses intact. Scientific Reports. 2017; 7: 7424. https://doi.org/10.1038/s41598-017-07542-9.
[33] Fukata Y, Tzingounis AV, Trinidad JC, Fukata M, Burlingame AL, Nicoll RA, *et al*. Molecular constituents of neuronal AMPA receptors. The Journal of Cell Biology. 2005; 169: 399–404. https://doi.org/10.1083/jcb.200501121.
[34] Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014; 511: 421–427. https://doi.org/10.1038/nature13595.
[35] Kang WS, Park JK, Kim SK, Park HJ, Lee SM, Song JY, *et al*. Genetic variants of GRIA1 are associated with susceptibility to schizophrenia in Korean population. Molecular Biology Reports. 2012; 39: 10697–10703. https://doi.org/10.1007/s11033-012-1960-x.
[36] Singh T, Poterba T, Curtis D, Akil H, Al Eissa M, Barchas JD, *et al*. Rare coding variants in ten genes confer substantial risk for schizophrenia. Nature. 2022; 604: 509–516. https://doi.org/10.1038/s41586-022-04556-w.
[37] Gulsuner S, Stein DJ, Susser ES, Sibeko G, Pretorius A, Walsh T, *et al*. Genetics of schizophrenia in the South African Xhosa. Science (New York, N.Y.). 2020; 367: 569–573. https://doi.org/10.1126/science.aay8833.
[38] Magri C, Gardella R, Valsecchi P, Barlati SD, Guizzetti L, Imperadori L, *et al*. Study on GRIA2, GRIA3 and GRIA4 genes highlights a positive association between schizophrenia and GRIA3 in female patients. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: the Official Publication of the International Society of Psychiatric Genetics. 2008; 147B: 745–753. https://doi.org/10.1002/ajmg.b.30674.
[39] Makino C, Fujii Y, Kikuta R, Hirata N, Tani A, Shibata A, *et al*. Positive association of the AMPA receptor subunit GluR4 gene (GRIA4) haplotype with schizophrenia: linkage disequilibrium mapping using SNPs evenly distributed across the gene region. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: the Official Publication of the International Society of Psychiatric Genetics. 2003; 116B: 17–22. https://doi.org/10.1002/ajmg.b.10041.
[40] Guo S, Shi Y, Zhao X, Duan S, Zhou J, Meng J, *et al*. No genetic association between polymorphisms in the AMPA receptor subunit GluR4 gene (GRIA4) and schizophrenia in the Chinese population. Neuroscience Letters. 2004; 369: 168–172. https://doi.org/10.1016/j.neulet.2004.07.079.
[41] Yonezawa K, Tani H, Nakajima S, Nagai N, Koizumi T, Miyazaki T, *et al*. AMPA receptors in schizophrenia: A systematic review of postmortem studies on receptor subunit expression and binding. Schizophrenia Research. 2022; 243: 98–109. https://doi.org/10.1016/j.schres.2022.02.033.
[42] Eastwood SL, Kerwin RW, Harrison PJ. Immunoautoradiographic evidence for a loss of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate-preferring non-N-methyl-D-aspartate glutamate receptors within the medial temporal lobe in schizophrenia. Biological Psychiatry. 1997; 41: 636–643. https://doi.org/10.1016/S0006-3223(96)00220-X.
[43] Amoah SK, Rodriguez BA, Logothetis CN, Chander P, Sellgren CM, Weick JP, *et al*. Exosomal secretion of a psychosis-altered miRNA that regulates glutamate receptor expression is affected by antipsychotics. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. 2020; 45: 656–665. https://doi.org/10.1038/s41386-019-0579-1.
[44] Beneyto M, Meador-Woodruff JH. Lamina-specific abnormalities of AMPA receptor trafficking and signaling molecule transcripts in the prefrontal cortex in schizophrenia. Synapse (New York, N.Y.). 2006; 60: 585–598. https://doi.org/10.1002/syn.20329.

[45] Popken G, Leggio M, Bunney Jr W, Jones E. Expression of mRNAs related to the GABAergic and glutamatergic neurotransmitter systems in the human thalamus: normal and schizophrenic. Thalamus & Related Systems. 2002; 1: 349–369. https://doi.org/10.1017/S1472928802000080.

[46] Zeppillo T, Schulmann A, Macciardi F, Hjelm BE, Föcking M, Sequeira PA, *et al*. Functional impairment of cortical AMPA receptors in schizophrenia. Schizophrenia Research. 2022; 249: 25–37. https://doi.org/10.1016/j.schres.2020.03.037.

[47] Dracheva S, McGurk SR, Haroutunian V. mRNA expression of AMPA receptors and AMPA receptor binding proteins in the cerebral cortex of elderly schizophrenics. Journal of Neuroscience Research. 2005; 79: 868–878. https://doi.org/10.1002/jnr.20423.

[48] O'Connor JA, Hemby SE. Elevated GRIA1 mRNA expression in Layer II/III and V pyramidal cells of the DLPFC in schizophrenia. Schizophrenia Research. 2007; 97: 277–288. https://doi.org/10.1016/j.schres.2007.09.022.

[49] Corti C, Xuereb JH, Crepaldi L, Corsi M, Michielin F, Ferraguti F. Altered levels of glutamatergic receptors and Na+/K+ ATPase-α1 in the prefrontal cortex of subjects with schizophrenia. Schizophrenia Research. 2011; 128: 7–14. https://doi.org/10.1016/j.schres.2011.01.021.

[50] Toyooka K, Iritani S, Makifuchi T, Shirakawa O, Kitamura N, Maeda K, *et al*. Selective reduction of a PDZ protein, SAP-97, in the prefrontal cortex of patients with chronic schizophrenia. Journal of Neurochemistry. 2002; 83: 797–806. https://doi.org/10.1046/j.1471-4159.2002.01181.x.

[51] Hammond JC, Meador-Woodruff JH, Haroutunian V, McCullumsmith RE. AMPA receptor subunit expression in the endoplasmic reticulum in frontal cortex of elderly patients with schizophrenia. PloS One. 2012; 7: e39190. https://doi.org/10.1371/journal.pone.0039190.

[52] Hammond JC, McCullumsmith RE, Haroutunian V, Meador-Woodruff JH. Endosomal trafficking of AMPA receptors in frontal cortex of elderly patients with schizophrenia. Schizophrenia Research. 2011; 130: 260–265. https://doi.org/10.1016/j.schres.2011.04.029.

[53] Breese CR, Freedman R, Leonard SS. Glutamate receptor subtype expression in human postmortem brain tissue from schizophrenics and alcohol abusers. Brain Research. 1995; 674: 82–90. https://doi.org/10.1016/0006-8993(94)01384-t.

[54] Tucholski J, Simmons MS, Pinner AL, Haroutunian V, McCullumsmith RE, Meador-Woodruff JH. Abnormal N-linked glycosylation of cortical AMPA receptor subunits in schizophrenia. Schizophrenia Research. 2013; 146: 177–183. https://doi.org/10.1016/j.schres.2013.01.031.

[55] Hammond JC, McCullumsmith RE, Funk AJ, Haroutunian V, Meador-Woodruff JH. Evidence for abnormal forward trafficking of AMPA receptors in frontal cortex of elderly patients with schizophrenia. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. 2010; 35: 2110–2119. https://doi.org/10.1038/npp.2010.87.

[56] Gao XM, Sakai K, Roberts RC, Conley RR, Dean B, Tamminga CA. Ionotropic glutamate receptors and expression of N-methyl-D-aspartate receptor subunits in subregions of human hippocampus: effects of schizophrenia. The American Journal of Psychiatry. 2000; 157: 1141–1149. https://doi.org/10.1176/appi.ajp.157.7.1141.

[57] Kerwin R, Patel S, Meldrum B. Quantitative autoradiographic analysis of glutamate binding sites in the hippocampal formation in normal and schizophrenic brain post mortem. Neuroscience. 1990; 39: 25–32. https://doi.org/10.1016/0306-4522(90)90219-t.

[58] Scarr E, Beneyto M, Meador-Woodruff JH, Dean B. Cortical glutamatergic markers in schizophrenia. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. 2005; 30: 1521–1531. https://doi.org/10.1038/sj.npp.1300758.

[59] Meador-Woodruff JH, Hogg AJ, Jr, Smith RE. Striatal ionotropic glutamate receptor expression in schizophrenia, bipolar disorder, and major depressive disorder. Brain Research Bulletin. 2001; 55: 631–640. https://doi.org/10.1016/s0361-9230(01)00523-8.

[60] Freed WJ, Dillon-Carter O, Kleinman JE. Properties of [3H] AMPA Binding in Postmortem Human Brain from Psychotic Subjects and Controls: Increases in Caudate Nucleus Associated with Suicide. Experimental Neurology. 1993; 121: 48–56. https://doi.org/10.1006/exnr.1993.1070.

[61] Noga JT, Hyde TM, Herman MM, Spurney CF, Bigelow LB, Weinberger DR, *et al*. Glutamate receptors in the postmortem striatum of schizophrenic, suicide, and control brains. Synapse (New York, N.Y.). 1997; 27: 168–176. https://doi.org/10.1002/(SICI)1098-2396(199711)27:3<168::AID-SYN2>3.0.CO;2-B.

[62] Zavitsanou K, Ward PB, Huang XF. Selective alterations in ionotropic glutamate receptors in the anterior cingulate cortex in schizophrenia. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. 2002; 27: 826–833. https://doi.org/10.1016/S0893-133X(02)00347-0.

[63] de Bartolomeis A, Sarappa C, Magara S, Iasevoli F. Targeting glutamate system for novel antipsychotic approaches: relevance for residual psychotic symptoms and treatment resistant schizophrenia. European Journal of Pharmacology. 2012; 682: 1–11. https://doi.org/10.1016/j.ejphar.2012.02.033.

[64] Kadriu B, Musazzi L, Johnston JN, Kalynchuk LE, Caruncho HJ, Popoli M, *et al*. Positive AMPA receptor modulation in the treatment of neuropsychiatric disorders: A long and winding road. Drug Discovery Today. 2021; 26: 2816–2838. https://doi.org/10.1016/j.drudis.2021.07.027.

[65] Kathuria A, Lopez-Lengowski K, Jagtap SS, McPhie D, Perlis RH, Cohen BM, *et al*. Transcriptomic Landscape and Functional Characterization of Induced Pluripotent Stem Cell-Derived Cerebral Organoids in Schizophrenia. JAMA Psychiatry. 2020; 77: 745–754. https://doi.org/10.1001/jamapsychiatry.2020.0196.

[66] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical Research Ed.). 2021; 372: n71. https://doi.org/10.1136/bmj.n71.

[67] Maycox PR, Kelly F, Taylor A, Bates S, Reid J, Logendra R, *et al*. Analysis of gene expression in two large schizophrenia cohorts identifies multiple changes associated with nerve terminal function. Molecular Psychiatry. 2009; 14: 1083–1094. https://doi.org/10.1038/mp.2009.18.

[68] Pietersen CY, Mauney SA, Kim SS, Lim MP, Rooney RJ, Goldstein JM, *et al*. Molecular profiles of pyramidal neurons in the superior temporal cortex in schizophrenia. Journal of Neurogenetics. 2014; 28: 53–69. https://doi.org/10.3109/01677063.2014.882918.

[69] Paz RD, Andreasen NC, Daoud SZ, Conley R, Roberts R, Bustillo J, *et al*. Increased expression of activity-dependent genes in cerebellar glutamatergic neurons of patients with schizophrenia. The American Journal of Psychiatry. 2006; 163: 1829–1831. https://doi.org/10.1176/ajp.2006.163.10.1829.

[70] Chen C, Cheng L, Grennan K, Pibiri F, Zhang C, Badner JA, *et al*. Two gene co-expression modules differentiate psychotics and controls. Molecular Psychiatry. 2013; 18: 1308–1314. https://doi.org/10.1038/mp.2012.146.

[71] Ramaker RC, Bowling KM, Lasseigne BN, Hagenauer MH, Hardigan AA, Davis NS, *et al*. Post-mortem molecular profiling of three psychiatric disorders. Genome Medicine. 2017; 9:

72. https://doi.org/10.1186/s13073-017-0458-5.
[72] Lanz TA, Reinhart V, Sheehan MJ, Rizzo SJS, Bove SE, James LC, *et al*. Postmortem transcriptional profiling reveals widespread increase in inflammation in schizophrenia: a comparison of prefrontal cortex, striatum, and hippocampus among matched tetrads of controls with subjects diagnosed with schizophrenia, bipolar or major depressive disorder. Translational Psychiatry. 2019; 9: 151. https://doi.org/10.1038/s41398-019-0492-8.
[73] Perez JM, Berto S, Gleason K, Ghose S, Tan C, Kim TK, *et al*. Hippocampal subfield transcriptome analysis in schizophrenia psychosis. Molecular Psychiatry. 2021; 26: 2577–2589. https://doi.org/10.1038/s41380-020-0696-6.
[74] Kathuria A, Lopez-Lengowski K, Watmuff B, Karmacharya R. Comparative Transcriptomic Analysis of Cerebral Organoids and Cortical Neuron Cultures Derived from Human Induced Pluripotent Stem Cells. Stem Cells and Development. 2020; 29: 1370–1381. https://doi.org/10.1089/scd.2020.0069.
[75] Hedges LV. Distribution Theory for Glass's Estimator of Effect Size and Related Estimators. Journal of Educational Statistics. 1981; 6: 107–128. https://doi.org/10.3102/10769986006002107.
[76] Schwarzer G. Meta: An R package for meta-analysis. R news. 2007; 7: 40–45.
[77] Fleiss JL. The statistical basis of meta-analysis. Statistical Methods in Medical Research. 1993; 2: 121–145. https://doi.org/10.1177/096228029300200202.
[78] Xia J, Fjell CD, Mayer ML, Pena OM, Wishart DS, Hancock REW. INMEX–a web-based tool for integrative meta-analysis of expression data. Nucleic Acids Research. 2013; 41: W63–W70. https://doi.org/10.1093/nar/gkt338.
[79] Cochran WG. The Combination of Estimates from Different Experiments. Biometrics. 1954; 10: 101–129. https://doi.org/10.2307/3001666.
[80] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical Research Ed.). 2003; 327: 557–560. https://doi.org/10.1136/bmj.327.7414.557.
[81] DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986; 7: 177–188. https://doi.org/10.1016/0197-2456(86)90046-2.
[82] Andrews DF. A robust method for multiple linear regression. Technometrics. 1974; 16: 523–531. https://doi.org/10.1080/00401706.1974.10489233.
[83] Hartl CL, Ramaswami G, Pembroke WG, Muller S, Pintacuda G, Saha A, *et al*. Coexpression network architecture reveals the brain-wide and multiregional basis of disease susceptibility. Nature Neuroscience. 2021; 24: 1313–1323. https://doi.org/10.1038/s41593-021-00887-5.
[84] Kimoto S, Glausier JR, Fish KN, Volk DW, Bazmi HH, Arion D, *et al*. Reciprocal Alterations in Regulator of G Protein Signaling 4 and microRNA16 in Schizophrenia. Schizophrenia Bulletin. 2016; 42: 396–405. https://doi.org/10.1093/schbul/sbv139.
[85] Gogtay N, Vyas NS, Testa R, Wood SJ, Pantelis C. Age of onset of schizophrenia: perspectives from structural neuroimaging studies. Schizophrenia Bulletin. 2011; 37: 504–513. https://doi.org/10.1093/schbul/sbr030.