Chapter

Temporal and Spatial Differential Expression of Glutamate Receptor Genes in the Brain of Down Syndrome

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Abstract

Studying the dysregulation of expression of glutamate receptors is crucial to better understand the mechanisms associated with cognitive disabilities in Down syndrome (DS) patients. By using data of microarray experiments previously deposited in GEO Dataset, we studied the expression of 26 glutamate receptor genes in DS brain samples since prenatal to adult age in several brain structures. Overall, our results showed a complexity in the expression of the genes which were dependent mainly on the brain structure analyzed; especially, the hippocampus showed a different expression pattern. While in the general brain analysis the overexpressed genes were GRIN3A and GRIN2C, higher expression levels of GRM1, GRID2, and GRIK1 gene receptors were recorded in hippocampus. Our results suggest that the glutamatergic system in association with other neurotransmitter systems in the human brain would associate with glutamatergic receptor alterations to bring upon synaptic changes and cognitive deficits in DS models.

Keywords: glutamatergic system, gene expression, Down syndrome, brain, bioinformatics

1. Introduction

Down syndrome (DS) or trisomy 21 is the leading cause of genetically defined intellectual disability, developmental brain abnormalities, and congenital birth defects. The phenotypical features of this syndrome affect almost all body systems, including neurodevelopment and cognitive aspects [1, 2]. Brains of individuals with DS show decreased volume and reduced neuronal density in diverse areas including the cortex, hippocampus, and cerebellum [3–7], leading to delayed cognitive progress in infancy and childhood and mild-to-moderate intellectual disability [8–11]. Also, during adulthood, there is a loss of cognitive abilities and the development of Alzheimer's disease (AD) by the fourth decade of life [12, 13]. Glutamate is the principal and main excitatory neurotransmitter in the body [14–16]. Glutamate receptors are classified into metabotropic—G-coupled protein receptors—and

ionotropic—ligand-gated ion channels [17–26]. Many studies have agreed that a major function of glutamate receptors is the modulation of synaptic plasticity, which is the ability of neurons to change its connections in response to a stimuli; this mechanism is thought to be vital for memory and learning processes. An increase or decrease in the number of ionotropic glutamate receptors on a postsynaptic cell may lead to long-term potentiation or long-term depression of that cell, respectively [27–30].

According to Tan et al. [31], there is evidence that reduction in hippocampal glutamate concentrations is associated with improved cognitive function by modulating glutamatergic neurotransmission in non-DS people with AD. Also, murine models of DS suggest that there is an imbalance between hippocampal inhibitory and excitatory inputs [9, 24], changes in the levels of the glutamate transporter and vesicular glutamate transporter 1 (VGLUT1) [25], and impairments in signaling mechanisms downstream of the N-methyl-D-aspartate (NMDA) receptor [26]. In this context, it can be put into consideration that malfunctions in the glutamate metabolism and the glutamatergic system are major contributors to cognitive abnormalities.

In recent studies, it has been shown that patients with DS present a diminution of glutamate and glutamatergic synapses. In the research made with mice by Kaur et al. [32], the results indicated a downregulation of hippocampal glutamate associated with behavioral impairments and intellectual disabilities. In this context, our study aimed to analyze the differential expression of 26 glutamate receptor genes in DS brain samples from prenatal patients to adult age in several brain structures. Overall, our result showed the complexity in the expression of the 26 glutamate receptors encoding genes. Also, a general overexpression in brain samples of GRIN3A and GRIN2C, and higher expression levels of GRM1, GRID2, and GRIK1 in hippocampus, in comparison with some structures of brain cortex. We hypothesize that disruption of glutamatergic brain gene expression would be a crucial early step in the pathogenesis of cognitive disability in DS.

2. Glutamate receptors and DS

Glutamate is known to be the main excitatory neurotransmitter in the brain and under normal physiological conditions, mediates learning and memory, as well as other integrating brain functions of higher order; however, it is also known that the pathological signaling of glutamate contributes to neuronal cell death. This neurotransmitter is released in the synapse after the depolarization of the presynaptic neurons, and it is eliminated by means of the GLT transporter in astrocytes, in normal physiological conditions, glutamate elimination being rapid and neuroprotective [33]. Glutamate has action on ionotropic (iGluR) and metabotropic (mGluRs) receptors. The ionotropic GluRs are ion channels (voltage sensitive), integral membrane proteins composed by four large subunits that form a central ion channel pore [34]. Glutamate receptor subunits are modular structures that contain the following domains: the extracellular amino-terminal domain (ATD), the extracellular ligand-binding domain (LBD), the transmembrane domain (TMD), and an intracellular carboxyl-terminal domain (CTD) [34].

These receptor subunits are proteins assembled into heterotetrameric or homotetrameric receptors, including the N-methyl-D-aspartate receptor (NMDA) consisting of the subunits GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A, and GluN3B, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) with the subunits GluA1, GluA2, GluA3, and GluA4, and the Kainate receptors with the subunits GluK1, GluK2, GluK3, GluK4, and GluK5 that function as mediators of

the rapid synaptic responses to glutamate, contrary to what happens with mGluRs where their activation by glutamate is sensitive to ligand binding and produces slower and longer modulating alterations in synaptic activity [33, 35–37]. NMDA receptors are present in high density within the hippocampus and the cerebral cortex performing fundamental physiological and pathophysiological functions in the central nervous system [38], among which learning, memory, brain plasticity, and recovery of injuries stand out. In these brain structures, differential expression of these receptors is evidenced, where a change in their dynamics could contribute to changes in cognitive and synaptic function [39]. When treated in conjunction with AMPA, they are attributed an important role in plasticity and synaptic transmission in many postsynaptic membranes [35, 40], with the latter receptors participating in protein-protein interactions with scaffolding proteins, such as PICK1 and GRIP1, and the TARP accessory proteins that help in AMPA receptor traffic and present additional targets for regulation [37].

Metabotropic glutamate receptors are members of the superfamily of G protein-coupled receptors. There are eight mGluR subtypes divided into three groups based on sequence homology, G-protein coupling specificity, and pharmacological profile. In general, mGluRs of group I and their interacting proteins have the ability to function as both neuroprotective and neurotoxic and have also been implicated in neurodegenerative diseases, especially mGluR5 [33]. On the other hand, members of group II act by inhibiting neuronal responses in rats according to the studies of Copeland et al. [41], which has been associated with the onset of cognitive deficit, a characteristic that can be observed in people with DS. About this syndrome, it should be noted that it has been associated with an imbalance of excitatory/inhibitory neurotransmitter systems, as highlighted in studies of murine with DS where the presence of alterations in the activity of glutamatergic neurotransmission, mainly affecting ionotropic receptors, an event that has also been evidenced when studying the overexpression of HSA21 genes in DS [42].

3. Glutamatergic system, cognition, and DS: our main approach

The glutamatergic system of the brain is one of the two major amino acid systems, being the GABAergic system the major one. This system is very important for information processing in neuronal networks of the neocortex and hippocampus in particular [43, 44], which is why we decided to analyze not only the brain as a whole, but the hippocampus apart. Also, this brain structure has been studied in several articles related to DS [3, 45–47] because of the significant functional repercussion in memory processes and intellectual potential that follows the poor hippocampal development presented by individuals with DS. Because the glutamatergic system is key in cognition processes such as memory and learning [48, 49], we consider that the deregulation of the glutamate receptors could be critical in the pathophysiology of DS, specifically in the neurodevelopmental and neurocognitive defects. This can be a starting point for developing therapeutic strategies aimed to reduce the effects of altered brain structures in individuals with DS.

3.1 Our methodological approach

Our initial approach was to analyze the expression of glutamate receptors—ionotropic and metabotropic—(**Table A1**) in DS brain samples and compare it to euploid controls. In order to accomplish this goal, we calculated the values of expression for selected genes by using the log10 transformed expression values of a DNA microarray experiment whose registration code and free access in the

GEO database was GSE59630 (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE59630), previously deposited by Olmos-Serrano et al. [50], which fitted the statistical significance sample size to obtain trustable information about the functional neurogenomics in DS. The microarray experiment selected included gene expression data of 47,000 probes from 58 postmortem brain samples of DS patients and 58 postmortem brain samples of healthy controls classified by gender (25 from females and 33 from males of each condition), age (from 16 prenatal weeks to 42 years old), and in 11 structures: dorsolateral prefrontal cortex (DFC), visual cortex (V1C), cerebellar cortex (CBC), orbitofrontal cortex (OFC), ventral frontal cortex (VFC), inferior temporal cortex (ITC), hippocampus (HIP), medial frontal cortex (MFC), somatosensory cortex (S1C), inferior parietal cortex (IPC), and superior temporal cortex (STC).

3.2 Functional analysis

The software Cytoscape 3.6 [51] was used for visualizing and analyzing the protein-protein interaction network among the selected human glutamate receptors encoding genes. We use the BIOGrid database to obtain protein interaction data of each one of the genes evaluated. Biological Networks Gene Ontology plugin—BiNGO tool—[52] was used to search in which gene ontology (GO) categories are significantly overrepresented in a set of genes. A hypergeometric test was applied to determine which were the significantly represented categories (p-value <0.05); significant values were adjusted using the Bonferroni family wise error rate correction [53]. From network analyzer plugin of the Max Planck Institute Informatik, network topology parameters were calculated. Moreover, a genetic interaction network was made in GENEMANIA (https://genemania.org/).

3.3 Z-score transformation

Log2 data for each gene in the DNA microarray experiment was log10 transformed and then used for the calculation of Z score [54]. Z scores were calculated by subtracting the mean log gene intensities (within a single experiment) from the log intensity data for each gene, and dividing that result by the SD of all measured log intensities, according to Eq. (1):

Z-score transformation:

$$Z - score = \frac{\left(Log\ intensity\ of\ G - mean\ \log intensity\ G...Gn\right)}{Standard\ Deviation\ \log G...Gn} \quad (1)$$

All Z-score values were normalized on a linear scale −3.0 < 0 > +3.0. In it, the corresponding gene is overexpressed if the value of Z-score is greater than zero and on contrary is under-expressed if its value is negative.

3.4 Multivariate statistical analysis

Nonparametric analyses for comparing median values of Z-score were performed among gender and age variables between DS patients and healthy control. Wilcoxon signed-rank test was used to calculate the differences between medians of two samples. Hierarchical clustering analysis (HCA) was selected as a method of cluster analysis that seeks to build a hierarchy of clusters [55]. To perform the HCA, Euclidean distance was used as a measure of distance between DS and control samples of Z-score values in several structures of brain cortex; $p < 0.05$ was defined as a threshold. Moreover, principal component analysis (PCA) was employed as

a computational procedure for the classification of multiclass gene expression in brain cortex structures between DS and control samples per sex and age. All analyses were run in SPSS program version 22 [56].

4. Our results

4.1 Protein-protein interaction (PPI) network and gene interactions

The PPI network made in Cytoscape 3.6 with all ionotropic and metabotropic receptors had 142 nodes and 3 connected components (**Figure 1**). The proteins encoded by GRIA2 and GRIN2B had the highest amount of interactions (33 and 30, respectively). GRIA2 gene encodes a subunit of the family of glutamate AMPA receptors; these types of receptors mediate fast excitatory synaptic transmission. GRIN2B is also a subunit but, in this case, of a NMDA receptor which are involved in brain development, synaptic plasticity, learning, and memory. The malfunction of these two genes has been previously associated to neurodevelopmental disorders characterized by intellectual disability and delayed development of speech and motor skills [57–59]. Here, it is important to highlight that the many connections they have among the glutamatergic system make them key proteins in the brain protein homeostasis. Among the biological processes ontology categories associated to the network, there was synaptic transmission (P-value Bonferroni 6.44E-17) and transmission of nerve impulse (P-value Bonferroni 1.20E-15).

On the other hand, the gene interaction network made in GENEMANIA showed that the physical interactions with the highest weight are GRIN2A-GRIN1 (9.40E-01), CACNG2-GRIA1 (8.66E-01), and GRIK1-GRIK2 (8.35E-01). The gene GRIN2A encodes a subunit of a subset of NMDA receptors called GluN2A, mainly expressed in regions in the brain involved in speech and language; this gene is consistently referred to in the literature as associated with speech disorders such as impaired intelligibility of

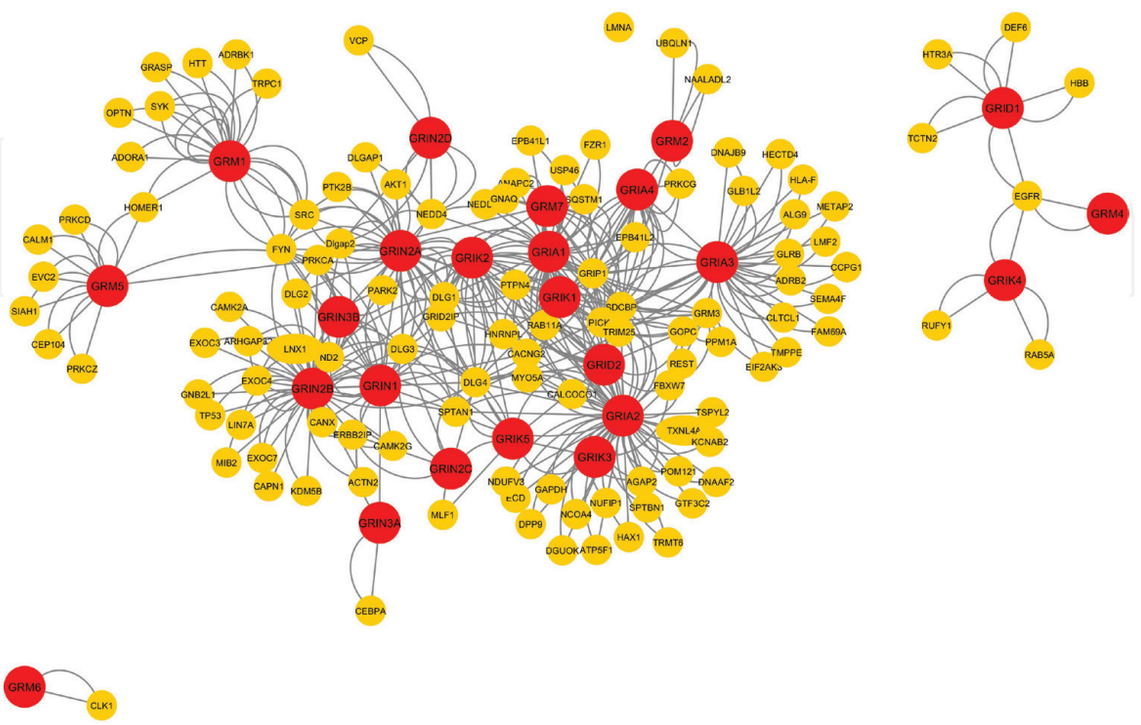

Figure 1.
PPI network made with glutamate receptors in Cytoscape 3.6. The receptors analyzed in this study are shown in red; the interactors are shown in yellow.

conversational speech [60]. GRIN1, on the other hand, also encodes a subunit of NMDA receptors called GluN1, which, along with other members of this superfamily, plays a key role in memory and learning. According to Chen et al. [61], several mutations on this gene have been associated with neurodevelopmental disorders such as epilepsy, causing in some patients hypotonia and facial dysmorphisms. GRIK1 and GRIK2 encode subunits of the kainite family of glutamate receptors, associated with behavior according to the GWAS Catalog (https://www.ebi.ac.uk/gwas/) and with intellectual disability [62].

4.2 Temporal and spatial gene expression in postmortem brains of DS patients

According to the temporal gene expression analysis made, there were no significant differences among the DS brain samples and the control group (**Figure 2**). This is contrasting to the results obtained in other studies focused on mice like the article published by Zhao et al. [63] where they found a difference between older and younger organisms when measuring the expression of glutamate receptors; in their experiment, they found that NMDA receptor functions, receptor subunit composition, and/or the environment in which the receptor interacted were not the same in the old mice as in younger mice which may contribute to the memory decline seen during aging. Also, there is a study made on embryo chicks and 1-year-old chicks by Batista et al. [64] where they found that AMPA receptors exhibit temporal expression changes during tectal development of chicks that are compatible with such a role for glutamate. All the glutamate receptor subunits tested in that experiment—GluR1, GluR2/3, and GluR4—showed an early expression suggesting some function in neurogenesis and migration.

The analysis of gene expression along the different brain structures (**Table 1**) showed an overexpression of the genes Glutamate Ionotropic Receptor NMDA Type Subunit 2C (GRIN2C) (Z-ratio 2.61) and the Glutamate Ionotropic Receptor NMDA Type Subunit 3A (GRIN3A) (2.94). GRIN2C encodes a subunit of an NMDA receptor, which is a subtype of ionotropic glutamate receptor involved in excitatory neurotransmission and in neuronal cell death. On the other hand, GRIN3A also encodes a subunit of a NMDA receptor and its deficit increases spine density and initiates synapse maturation and memory consolidation in early postnatal neurodevelopment; both of these genes have been previously associated with schizophrenia.

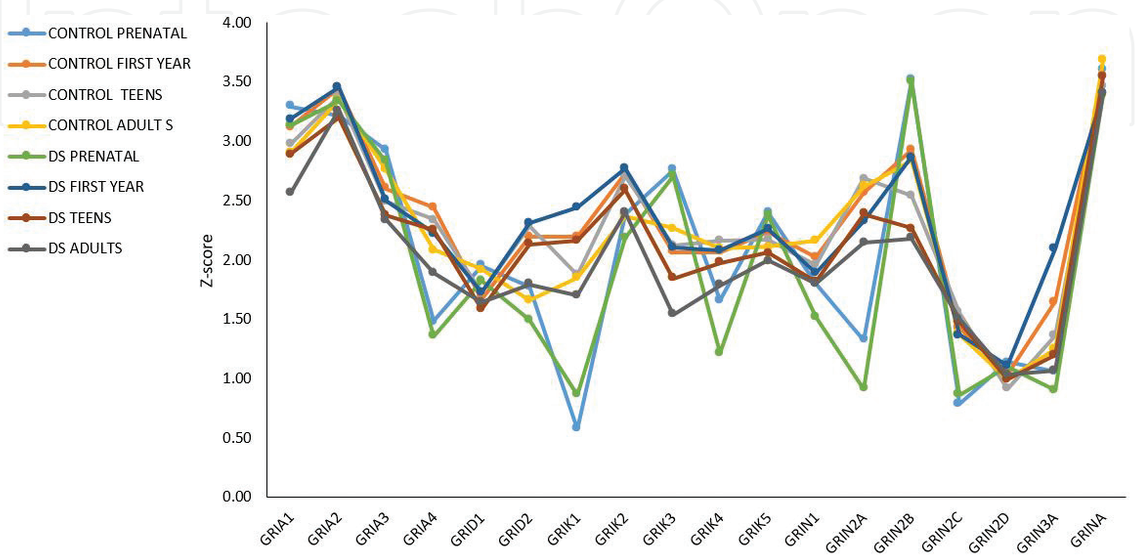

Figure 2.
Z-score of glutamate ionotropic receptors per age-range of control and DS brain samples. Prenatal: 16–22 pregestational weeks, 8 months to 1 year; teens: 12–18 years; and adults: 19–42 years.

Gene symbol	Z-score control	Z-score DS	ΔZ-score	Z ratio*
Ionotropics				
GRIA1	1.88	1.75	−0.12	0.93
GRIA2	2.28	2.21	−0.07	0.97
GRIA3	1.46	1.21	−0.25	0.83
GRIA4	0.97	0.79	−0.18	0.82
GRID1	0.45	0.32	−0.13	0.71
GRID2	0.71	0.76	0.05	1.07
GRIK1	0.58	0.74	0.16	1.28
GRIK2	1.36	1.36	0.00	1.00
GRIK3	0.91	0.59	−0.32	0.65
GRIK4	0.77	0.59	−0.18	0.77
GRIK5	0.91	0.85	−0.05	0.94
GRIN1	0.74	0.49	−0.24	0.67
GRIN2A	1.30	0.92	−0.37	0.71
GRIN2B	1.69	1.32	−0.38	0.78
GRIN2C	0.01	0.02	0.01	2.61
GRIN2D	−0.45	−0.38	0.07	0.85
GRIN3A	0.02	0.07	0.05	2.94
GRINA	2.52	2.36	−0.16	0.94
Metabotropics				
GRM1	0.29	0.20	−0.09	0.69
GRM2	0.27	−0.15	−0.43	−0.57
GRM3	1.66	1.54	−0.13	0.92
GRM4	0.28	0.33	0.06	1.20
GRM5	1.35	1.39	0.05	1.03
GRM6	−0.99	−0.96	0.03	0.97
GRM7	0.48	0.34	−0.15	0.69
GRM8	−0.52	−0.70	0.18	1.34

Log2 data for gene expression were obtained from the microarray experiment consigned in the GEO database with ID GSE59630, previously deposited by Olmos et al.

**Z-Ratio ≥ 1.50 is statistically significant; alpha 0.05.*

Table 1.
Differential expression values (Z-score and Z-ratio) of glutamate receptor encoding genes in the brain of patients with Down syndrome.

According to Ohi et al. [65], GRIN3A expression levels in the dorsolateral prefrontal cortex were elevated by approximately 30% in schizophrenia patients relative to controls, which suggest that aberrant enhanced GRIN3A function could be involved in the pathophysiology of schizophrenia and its cognitive impairments. Another study by Marco et al. [66] in patients with Huntington's disease (HD) and in a mouse model of HD found something similar; a knockout of this gene decreased motor and cognitive dysfunction compared with no knockout and prevented striatal atrophy and synaptic disconnection. These findings correlate with our results of human DS brains, leading us to propose that a similar process might take place in the pathophysiology of DS.

Moreover, we decided to analyze the hippocampus apart because of its highly recognized importance not only in Down syndrome, but also in cognition processes, which are mainly regulated by the glutamatergic system [67]. Several studies have agreed that NMDA receptor (NMDAR)-dependent LTP or an LTP-like process in the hippocampus are the neural substrate for associative spatial learning and memory [68]. In this study, we found that this brain structure has some differences in gene expression when compared to the brain as a whole. While the general analysis of the brain showed an overexpression of the gene GRIN3A, at the hippocampus, we encountered an under-expression if this gene in DS samples. On the other hand, a gene that encodes the Glutamate

Gene symbol	Z-score control	Z-score DS	ΔZ-score	Z ratio*
Ionotropics				
GRIA1	2.15	2.25	0.10	1.04
GRIA2	2.48	2.35	−0.13	0.95
GRIA3	1.59	1.62	0.03	1.02
GRIA4	0.14	−0.07	−0.21	−0.49
GRID1	0.59	0.55	−0.04	0.93
GRID2	0.18	0.47	0.29	2.61
GRIK1	0.37	0.60	0.23	1.62
GRIK2	1.35	1.20	0.15	0.88
GRIK3	0.58	−0.19	−0.77	−0.32
GRIK4	0.96	0.95	−0.01	0.99
GRIK5	1.14	1.22	0.08	1.07
GRIN1	0.74	0.49	−0.25	0.67
GRIN2A	1.28	1.15	−0.13	0.90
GRIN2B	1.74	1.73	−0.01	0.99
GRIN2C	0.19	0.34	0.15	1.85
GRIN2D	−0.56	−0.41	0.15	0.73
GRIN3A	0.35	−0.22	−0.57	−0.62
GRINA	2.40	2.28	−0.12	0.95
Metabotropics				
GRM1	0.10	0.22	0.12	2.22
GRM2	0.10	−0.54	−0.64	−5.62
GRM3	1.68	1.30	−0.38	0.77
GRM4	0.12	0.05	−0.07	0.44
GRM5	1.51	1.62	0.11	1.07
GRM6	−0.96	−0.87	0.09	0.91
GRM7	0.71	0.51	−1.22	0.72
GRM8	−0.54	−0.75	−0.21	1.37

Log2 data for gene expression were obtained from the microarray experiment consigned in the GEO database with ID GSE59630, previously deposited by Olmos et al.

**Z-Ratio ≥ 1.50 is statistically significant; alpha 0.05.*

Table 2.
Differential expression values of glutamate receptor encoding genes in the hippocampus of patients with Down syndrome.

Metabotropic Receptor 1 (GRM1) was overexpressed in the hippocampus (Z-ratio 2.22) as well as the Glutamate Ionotropic Receptor Delta Type Subunit 2 (GRID2) (Z-score 2.61), the Glutamate Ionotropic Receptor Kainate Type Subunit 1 (GRIK1) (Z-score 1.62), and GRIN2C (Z-score 1.85). GRM1 is one of the most abundant mGluRs in the mammalian central nervous system and is present at particularly high levels in Purkinje cells [69]. There is plenty of evidence of its implication in diseases involving glutamatergic dysfunction and abnormal synaptic plasticity [70], which are known to be crucial mechanisms for cognitive processes. GRIK1 has also been reported as overexpressed in studies of DS; the study made on mice by Mazier [71] showed that GRIK mRNA levels are increased by more than 50% in different structures of the trisomic brain, which is coincidental with our findings (**Table 2**).

4.3 Principal component analysis (PCA) and hierarchical cluster analysis (HCA)

According to the PCA performed for the control samples, five principal components explained 80% of the cumulative variance; meanwhile, the PCA performed for the DS samples showed that six principal components explained 83% of the cumulative variance. In **Figure 3**, we present the PCA for the two groups, where we found some differences in the clustering of genes when comparing the group samples, specifically in genes GRID2, GRM1, GRM4, and GRIK2 which were closely grouped in the PCA for controls. Also, even though the gene GRIK1 remained on the same position in both PCA, its association with GRIA1 changed from being separated in the control group, to be near each other in the DS group.

The HCA analysis produced a Heatmap that showed gene expression differences in the hippocampus (**Figure 4**), specifically in the genes Glutamate Ionotropic Receptor Kainate Type Subunit 3 (GRIK3) and GRIN3A which were under-expressed in DS samples as mentioned previously. GRIK3 has not been related to DS in particular, but it has been widely studied for its association with schizophrenia and major depression [72, 73]. Overall, the expression of the glutamate metabotropic receptors was especially high in the OFC in comparison to other brain structures.

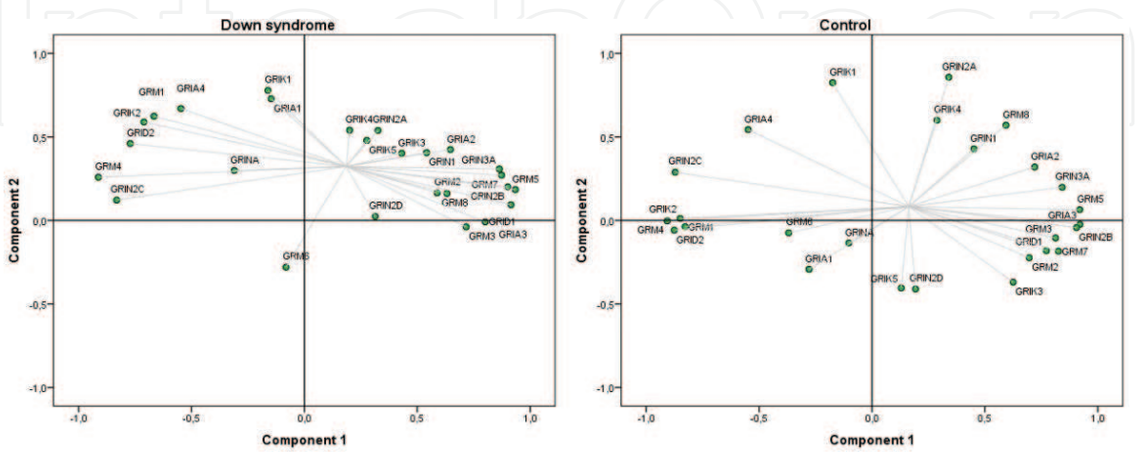

Figure 3.
Principal component analysis in 11 brain structures in DS brain samples and controls: dorsolateral prefrontal cortex (DFC), visual cortex (V1C), cerebellar cortex (CBC), orbitofrontal cortex (OFC), ventral frontal cortex (VFC), inferior temporal cortex (ITC), hippocampus (HIP), medial frontal cortex (MFC), somatosensory cortex (S1C), inferior parietal cortex (IPC), and superior temporal cortex (STC). Analyses were performed in SPSS v 22.0.

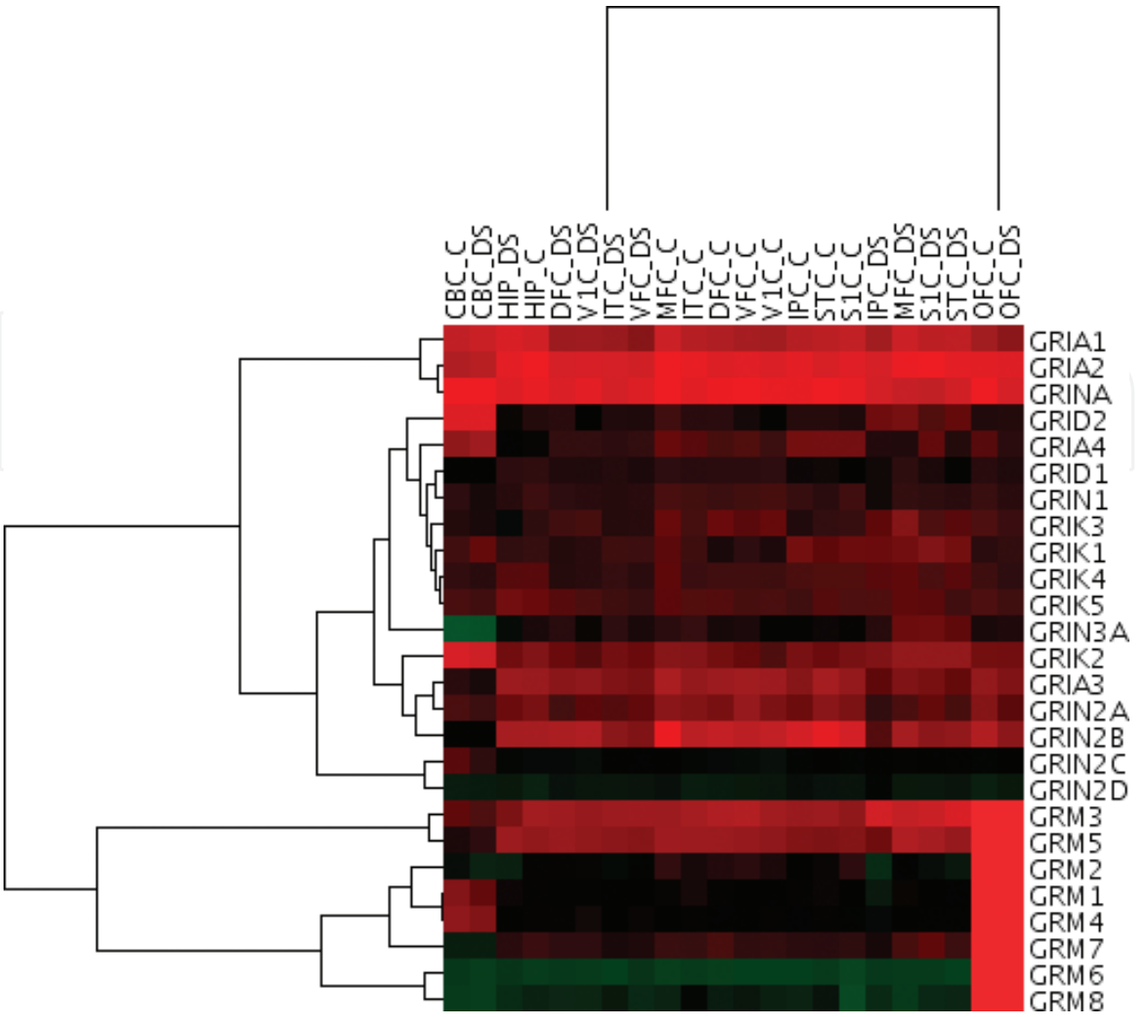

Figure 4.
Heat map of glutamate receptor expression of 11 brain structures in DS brain samples and controls. Green color represents under-expression and red overexpression: dorsolateral prefrontal cortex (DFC), visual cortex (V1C), cerebellar cortex (CBC), orbitofrontal cortex (OFC), ventral frontal cortex (VFC), inferior temporal cortex (ITC), hippocampus (HIP), medial frontal cortex (MFC), somatosensory cortex (S1C), inferior parietal cortex (IPC), and superior temporal cortex (STC); performed in Cytoscape 3.6 software.

5. Conclusions

The glutamatergic system is closely related to cognition as it plays a key role in memory, working memory, and executive functions. It has been proven in mice with DS that a deregulation of this system can be crucial in both the neurodevelopmental and neurodegenerative components of DS. DS patients have intellectual disabilities with individual variability in the severity of both physiological and behavioral phenotypes. At the core of the intellectual disabilities is the phenomenon of synaptic plasticity, which is a functional change in the strength at the points of communication between neurons. Our results indicate hippocampal downregulation of the ionotropic receptor subunit GRIN3A (NMDA family), while in the general analysis of the brain, this gene was overexpressed. Other genes overexpressed in the hippocampus were the metabotropic receptor GRM1, the ionotropic receptor subunit GRID2, and the kainate receptor subunit GRIK1. This deregulation might produce an alteration of both presynaptic and postsynaptic dysfunction at glutamatergic synapses, possibly contributing to behavioral impairments in patients with DS.

In general, our results suggest the existence of a fine regulation mechanism of gene expression networks, which is involved in the glutamatergic synaptic

system in several structures of brain from patients with DS. We hypothesize that disruption of glutamatergic brain gene expression would be a crucial early step in the pathogenesis of cognitive disability in DS. Moreover, our results suggest that glutamatergic system in association with other neurotransmitter systems in human brain, as GABA-mediated synaptic inhibition reported in other DS studies, might associate with glutamatergic receptor alterations to bring upon synaptic changes and cognitive deficits in DS models. Thus, glutamatergic receptor gene expression dysfunction may play a key role in the hippocampal pathogenesis of DS.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Supplementary information

ID	Gene symbol	Subunit	Official full name	Locus
Ionotropic family				
2890	GRIA1	GluA1 ($GluR_1$)	Glutamate ionotropic receptor AMPA type subunit 1	5q33.2
2891	GRIA2	GluA2 ($GluR_2$)	Glutamate ionotropic receptor AMPA type subunit 2	4q32.1
2892	GRIA3	GluA3 ($GluR_3$)	Glutamate ionotropic receptor AMPA type subunit 3	Xq25
2893	GRIA4	GluA4 ($GluR_4$)	Glutamate ionotropic receptor AMPA type subunit 4	11q22.3
2894	GRID1	GluD1 (GluRD1)	Glutamate ionotropic receptor delta type subunit 1	10q23.1-q23.2
2895	GRID2	GluD2 (GlurD2)	Glutamate ionotropic receptor delta type subunit 2	4q22.1-q22.2
Kainate family				
2897	GRIK1	GluK1 ($GluR_5$)	Glutamate ionotropic receptor kainate type subunit 1	21q21.3
2898	GRIK2	GluK2 ($GluR_6$)	Glutamate ionotropic receptor kainate type subunit 2	6q16.3
2899	GRIK3	GluK3 ($GluR_7$)	Glutamate ionotropic receptor kainate type subunit 3	1p34.3

ID	Gene symbol	Subunit	Official full name	Locus
2900	GRIK4	GluK4 (KA-1)	Glutamate ionotropic receptor kainate type subunit 4	11q23.3
2901	GRIK5	GluK5 (KA-2)	Glutamate ionotropic receptor kainate type subunit 5	19q13.2
NMDA family				
2902	GRIN1	GluN1(NR1)	Glutamate ionotropic receptor NMDA type subunit 1	9q34.3
2903	GRIN2A	GluN2A (NR2A)	Glutamate ionotropic receptor NMDA type subunit 2A	16p13.2
2904	GRIN2B	GluN2B (NR2B)	Glutamate ionotropic receptor NMDA type subunit 2B	12p13.1
2905	GRIN2C	GluN2C (NR2C)	Glutamate ionotropic receptor NMDA type subunit 2C	17q25.1
2906	GRIN2D	GluN2D (NR2D)	Glutamate ionotropic receptor NMDA type subunit 2D	19q13.33
116,443	GRIN3A	GluN3A (NR3A)	Glutamate ionotropic receptor NMDA type subunit 3A	9q31.1
2907	GRINA	GluN3B (NR3B)	Glutamate ionotropic receptor NMDA type subunit associated protein 1	8q24.3
Metabotropic family group 1				
2911	GRM1	$mGluR_1$	Glutamate metabotropic receptor 1	6q24.3
2915	GRM5	$mGluR_4$	Glutamate metabotropic receptor 5	11q14.2-q14.3
Metabotropic family group 2				
2912	GRM2	$mGluR_5$	Glutamate metabotropic receptor 2	3p21.2
2913	GRM3	$mGluR_2$	Glutamate metabotropic receptor 3	7q21.11-q21.12
Metabotropic family group 3				
2914	GRM4	$mGluR_3$	Glutamate metabotropic receptor 4	6p21.31
2916	GRM6	$mGluR_6$	Glutamate metabotropic receptor 6	5q35.3
2917	GRM7	$mGluR_7$	Glutamate metabotropic receptor 7	3p26.1
2918	GRM8	$mGluR_8$	Glutamate metabotropic receptor 8	7q31.33

Information taken from the NCBI—Genbank platform.

Table A1.
Description of glutamate receptors encoding genes.

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