Review

New Strategies for the Treatment of Neuropsychiatric Disorders Based on Reelin Dysfunction

Yumi Tsuneura 1,2, Tsuyoshi Nakai 2,3, Hiroyuki Mizoguchi 2,4 and Kiyofumi Yamada 2,*

1 Department of Cellular Pathology, Institute for Developmental Research, Aichi Developmental Disability Center, Kasugai 480-0392, Japan; ytsuneura@inst-hsc.jp
2 Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Nagoya 466-8560, Japan; t-nakai@med.nagoya-u.ac.jp (T.N.);
hmizoguchi@med.nagoya-u.ac.jp (H.M.)
3 Department of Advanced Medicine, Nagoya University Hospital, Nagoya 466-8560, Japan
4 Medical Interactive Research and Academia Industry Collaboration Center, Research Institute of Environmental Medicine, Nagoya University, Nagoya 464-8601, Japan
* Correspondence: kyamada@med.nagoya-u.ac.jp; Tel.: +81-52-744-2674; Fax: +81-52-744-2979

Abstract: Reelin is an extracellular matrix protein that is mainly produced in Cajal-Retzius cells and controls neuronal migration, which is important for the proper formation of cortical layers in the developmental stage of the brain. In the adult brain, Reelin plays a crucial role in the regulation of N-methyl-D-aspartate receptor-dependent synaptic function, and its expression decreases postnatally. Clinical studies showed reductions in Reelin protein and mRNA expression levels in patients with psychiatric disorders; however, the causal relationship remains unclear. Reelin-deficient mice exhibit an abnormal neuronal morphology and behavior, while Reelin supplementation ameliorates learning deficits, synaptic dysfunctions, and spine loss in animal models with Reelin deficiency. These findings suggest that the neuronal deficits and brain dysfunctions associated with the down-regulated expression of Reelin are attenuated by enhancements in its expression and functions in the brain. In this review, we summarize findings on the role of Reelin in neuropsychiatric disorders and discuss potential therapeutic approaches for neuropsychiatric disorders associated with Reelin dysfunctions.

Keywords: reelin; neuropsychiatric disorders; development; ADAMTS-3

1. Introduction

Reelin is an extracellularly secreted glycoprotein that is necessary for brain development and neuronal function. In the developing brain, Reelin is produced by Cajal-Retzius cells, which are mainly present on the surface of the neocortex [1,2]. After birth, Cajal-Retzius cell numbers markedly decrease, and Reelin is mainly synthesized in γ-aminobutyric acid (GABA)-ergic neurons in the hippocampus and cortex [3,4]. Reelin consists of an N-terminal region containing a secretory signal, an eight Reelin repeats (Reelin repeats), and a C-terminal region rich in basic amino acids [5]. Secreted Reelin binds to apolipoprotein E receptor 2 (ApoER2) and very low-density lipoprotein receptors (VLDLR) expressed on neuronal membranes via the fifth and sixth Reelin repeats (Reelin repeats), and a C-terminal region rich in basic amino acids [5]. Secreted Reelin binds to apolipoprotein E receptor 2 (ApoER2) and very low-density lipoprotein receptors (VLDLR) expressed on neuronal membranes via the fifth and sixth Reelin repeats [6,7], stimulates Src family tyrosine kinases (SFKs), such as Fyn and Src, and promotes the tyrosine phosphorylation of intracellular Dab1 [8,9]. Phosphorylated Dab1 activates the downstream pathway and promotes neurite growth, dendritic spine growth, and neuronal migration [10–12]. The down-regulated expression of Reelin is clinically associated with neuropsychiatric disorders, such as schizophrenia, autism spectrum disorder (ASD), and Alzheimer’s disease (AD) [13]. In this review, we introduce the molecular functions of Reelin in neurons. We also summarize research on the involvement of Reelin in neuropsychiatric disorders and discuss potential therapeutic approaches for neuropsychiatric disorders associated with Reelin dysfunctions.
2. Roles of Reelin in Neural Functions

2.1. Neuronal Migration and Cortical Development

The cerebral cortex in the early developmental stage consists of a layer called the preplate and the ventricular zone at which new neurons are produced. Neurons generated in the ventricular zone enter the preplate, which separates into marginal zones and subplates, and then migrate radially throughout the subplate, but stop just before the marginal zone. In the cerebral cortex, early-born neurons are placed on the ventricular side and late-born neurons on the superficial side, resulting in a proper cortical layer [14]. Previous studies reported that Reelin signaling plays a role in the correct migration of neurons during the developmental formation of the cerebral cortex [5,15–17]. A decrease in the secretion of the Reelin protein from Cajal-Retzius cells causes a major reversal of the layered structure of the cerebral cortex [5]. Several proteins have been identified as key molecules for Reelin-dependent neuronal migration. The activation of integrin α5β1 through the intracellular Dab1-Crk/CrkL-C3G-Rap1 pathway after Reelin binds to its receptors is required for cell body translocation at the end of the migration of cortical neurons [18]. Cofilin, an actin-binding protein, and Reelin cooperate to regulate cytoskeletal dynamics during neuronal migration [19]. ApoER2 and VLDLR are well known to be major receptors involved in neuronal migration via Reelin signaling [20,21]. ApoER2, a Reelin-binding receptor, controls several processes in neuronal migration during cortical development, such as the early stage of radial migration and the termination of migration [20]. In neonatal ApoER2 knockout (KO) mice, cortical neurons overmigrate into the marginal zone [20]. A major role for VLDLR is its suppression of neuronal invasion within the marginal zone during neocortical development [21]. Therefore, Reelin and its downstream signals play important roles in cerebral cortex formation by regulating neuronal migration during the development stage.

2.2. Neurite Outgrowth

Previous studies reported that dendrite complexity was significantly reduced in reeler mice carrying a homozygous Reln gene deletion, as well as in heterozygous reeler mice [10,22]. The levels of the dendrite-specific microtubule-associated protein (MAP2) were significantly reduced in the hippocampus of homozygous reeler mice and, to a slightly lesser extent, in that of heterozygous reeler mice. A treatment with a CR50 antibody, which blocks the biological functions of Reelin, significantly reduced dendrite length and the complexity of cultures from heterozygous reeler mice [10]. Reelin may accelerate hippocampal dendrite development through the VLDLR/ApoER2-Dab1 pathway [10]. Kupferman et al. reported that Reelin exerted its functions through downstream intracellular Dab1 and Src family tyrosine kinase (SFK) signaling cascades and regulated dendritic outgrowth [23]. The phosphatidylinositol 3-kinase 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTor)-S6 kinase 1 pathway, which is downstream of Reelin, is associated with the regulation of dendritic growth and cortical development [24]. Reelin-Dab1 signaling and serine/threonine kinase 25 (STK25) competitively regulate Golgi morphology and neuronal polarity, which is important for dendrite formation [25]. Recent findings suggested that similar to STK25, mammalian sterile 20-like kinase-3 (MST3), a member of the germinal center kinase III (GCKIII) subfamily, regulates neuronal migration and polarization in a mutually compensatory manner [26]. Chondroitin sulfate proteoglycans inhibit axonal elongation; however, this is canceled by the activation of the Reelin signaling pathway [27]. Cytoplasmic linker-associated protein 2 (CLASP2) is a plus-end tracking protein that specifically accumulates at the growth cone and is a cytoskeletal effector of the Reelin signaling pathway [28]. A treatment with Reelin increased the axon length of primary cultured hippocampal neurons, whereas CLASP2 small hairpin RNA decreased axon length. The treatment with Reelin did not affect axon length in neurons with the knockdown of CLASP2. Furthermore, the phosphorylation of CLASP2 may be necessary for Dab1 interactions and neurite outgrowth [28]. These findings suggest that Reelin promotes neurite development and also that the disruption of Reelin signaling may result in an abnormal neurite morphology.
2.3. Spine Formation

A treatment with Reelin has been shown to significantly increase dendritic spine density in primary cultured hippocampal neurons [29]. In addition, Reelin may increase the puncta numbers of synaptophysin and postsynaptic density protein 95 (PSD95). Moreover, the Ca\(^{2+}\)/calmodulin-dependent protein kinase II β subunit may be necessary for the effects of Reelin on dendritic spine density [29]. Spine density on layer II/III in the prelimbic area of the prefrontal cortex (PFC) was lower in juvenile heterozygous reeler mice than in their wild-type littermates, and this decrease was attributed to the selective loss of spines with a small head diameter [30]. A reduction in dendritic spine density was also observed in the hippocampal pyramidal neurons of heterozygous and homozygous reeler mice. In hippocampal slice cultures of homozygous reeler mice, reduced spine density was restored by a treatment with Reelin [11]. Reelin supplementation may increase the spine density of hippocampal CA1 pyramidal neurons in wild-type mice, but not in ApoER2 KO mice [31]. ApoER2 and VLDLR are required for Reelin-induced dendritic spine formation [10,32]. Moreover, Dab1 and SFK activities may be necessary for the development of a normal dendritic spine density in organotypic hippocampal cultures [11].

2.4. Synaptic Function

A stimulation with Reelin was found to activate ApoER2 and VLDLR at excitatory synapses, and this was followed by increases in Dab1 phosphorylation and the activation of Src. This process promoted the linking of Src to PSD95. As a consequence, the tyrosine phosphorylation of the N-methyl-D-aspartate receptor (NMDAR) subunit physically associated with PSD95 increased, thereby promoting the activation of NMDARs [13,33,34]. Reelin organizes the regulation of the subunit composition of synaptic NMDARs and controls the surface mobility of the NR2B subunits of NMDARs. A previous study demonstrated that blocking the function of Reelin prevented maturation-dependent reductions in NR1/NR2B-mediated synaptic currents [35]. In heterozygous reeler mice, the expression levels of PSD95, NR2A, and NR2B were reduced in a postsynaptic density fraction [36]. Reelin increased the tyrosine phosphorylation of the NR2B subunit and enhanced glutamate-stimulated Ca\(^{2+}\) influx through NMDARs, suggesting that it physiologically regulates NMDAR activity [22,37]. Furthermore, Reelin may enhance the activity of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) by PI3K-dependent surface insertion [34]. A perfusion with Reelin was found to enhance long-term potentiation (LTP) in the hippocampus of wild-type mice, but not in ApoER2 KO mice or VLDAR KO mice, which indicates that ApoER2 and VLDLR are required to enhance synaptic transmission in the hippocampus [38].

3. Reelin and Neuropsychiatric Disorders

As mentioned above, Reelin has many effects on brain formation as well as on morphological changes in the neuronal network, and thus its dysfunction may cause various brain-related diseases. In this paragraph, we discuss reports of mutations in the RELN gene in humans with neuropsychiatric disorders.

3.1. Schizophrenia

Schizophrenia is a mental disorder that presents with various symptoms, such as hallucinations, delusions, abnormal behavior, decreased motivation, and cognitive deficits. The first study on Reelin abnormalities in schizophrenia revealed that RELN mRNA, which encodes Reelin, and Reelin protein expression levels were significantly lower in the post-mortem brains of patients with schizophrenia than in non-psychiatric subjects [39]. Furthermore, the expression levels of RELN mRNA in the whole blood of untreated schizophrenic patients were significantly lower than those in healthy controls [40]. RELN mRNA expression levels were elevated in patients with schizophrenia by a 12-week treatment with olanzapine, an antipsychotic, suggesting that alterations in RELN mRNA expression levels are associated with the effects of antipsychotic treatment [40]. In recent years, genome-
wide association studies and meta-analyses indicated that rs7341475 and rs262355 genetic polymorphisms in the RELN gene correlated with the onset of schizophrenia [41–43]. The missense variation c.9575 C > G (p.T3192S) in RELN was identified by whole-exome sequencing with samples from three affected individuals and one unaffected individual in a Chinese family with schizophrenia [44]. A de novo copy number variant (CNV) analysis of Japanese schizophrenia patients recently revealed a new pathogenic deletion (12.6 kb) in RELN (RELN-del) [45]. Taken together, these findings indicate that changes in Reelin expression and genetic variations are risk factors for schizophrenia. In exon-targeted resequencing using next-generation sequencing technology, rare variants of the DAB1 gene (p.G382C and p.V129I) were detected in patients with schizophrenia. Furthermore, these mutants of the Dab1 protein were more unstable than the wild-type protein, which may diminish Reelin-Dab1 signaling and contribute to the pathology of schizophrenia [46].

3.2. ASD

ASD is a developmental disorder characterized by abnormalities in social interactions and communication, localized patterns of interest, and repetitive behavior. Some mutations in the RELN gene (p.R1742Q, p.R1742W, p.R2290C, p.R2290H, p.R2292C, p.R2639H, and p.R2833S) have been identified in patients with ASD [47–50]. In a whole-genome sequencing analysis, heterozygous variants of the RELN gene (p.S630R and p.V1153I) were detected in three boys with ASD born to unrelated parents with a normal phenotype, and were located within Reelin repeat 1 and 2, respectively [51]. Previous studies suggested that the rs362691 (p.L997V) variant of the RELN gene is associated with an increased risk of ASD [51,52]. Persico et al. reported that a polymorphic GGC repeat located in the 5' untranslated region of the RELN gene was associated with ASD [53]. An ethnicity-based subgroup analysis of a meta-analysis found that the single-nucleotide polymorphism (SNP) rs736707 in the RELN gene correlated with psychiatric disorders, including ASD, in an Asian group [54]. In an investigation on the relationship between the RELN gene and symptoms in children and adolescents with ASD, SNP rs2229864 was linked to a genetic predisposition to ASD, while negative relationships were detected between rs2229864 and symptom-based and developmental characteristics [55]. Previous studies focused on the polymorphisms rs736707, rs362691, and rs2229864 and GGC repeats, but found no correlations with ASD in a meta-analysis [56,57]. Since these findings may be influenced by ethnic groups and sample sizes, further studies are needed to elucidate the relationship between ASD and the RELN gene.

3.3. AD

AD is a dementia that develops with progressive cognitive impairment and severe neurodegeneration. It is characterized by the extracellular deposition of the amyloid-beta (Aβ) peptide, generated from the β-amyloid precursor protein (APP), and intracellular abnormally hyperphosphorylated tau protein, forming neurofibrillary tangles [58]. The majority of AD patients develop neuropsychiatric symptoms [59]. Previous studies suggested a relationship between the pathophysiology of AD and Reelin signaling [60–62]. Reelin may rescue the suppression of LTP and NMDARs induced by the Aβ oligomer [60]. Furthermore, Reelin signaling may prevent the Aβ-induced endocytosis of NMDARs, and SFK activation induced by Reelin has been shown to restore the activity of NMDARs [60]. Conversely, the reduced expression of Reelin enhanced APP processing and amyloid plaque deposition as well as neurofibrillary tangle formation in the hippocampus of aged transgenic AD mice that express the human APP695 gene containing the Swedish (K670N and M671L) and Arctic mutations (E693G) [61]. Reelin expression was found to be up-regulated in the brains of AD patients, while the phosphorylation of Dab1 was decreased, indicating that Reelin signaling is diminished in AD patients. Although a treatment with Aβ increased the expression of Reelin, secreted Reelin was trapped within Aβ aggregates [62]. Accordingly, Aβ may affect the pathological progression of AD by inhibiting the biological activity of Reelin and, ultimately, impairing Reelin signaling [62].
3.4. Lissencephaly

Lissencephaly is a severe developmental disorder that is characterized by the lack of development of brain folds and grooves. Hong et al. reported that autosomal recessive lissencephaly with severe abnormalities in the cerebellum, hippocampus, and brainstem was associated with two independent RELN mutations identified from British and Saudi Arabian pedigrees. Mutations interfered with the splicing of RELN cDNA, leading to low or undetectable amounts of the Reelin protein [63]. Chang et al. identified a homozygous chromosomal inversion, which interrupted the RELN gene, in a girl from Turkey who was evaluated for growth and motor retardation. She also had developmental delay, severe hypotonia, seizures, diffuse pachygyria, and severe cerebellar hypoplasia, with a negligible amount of the Reelin protein in her serum [64]. In addition, biallelic splice variants of Dab1 were identified in a patient with mild lissencephaly and cerebellar hypoplasia, and these variants were suggested to affect the highly conserved functional phosphotyrosine-binding domain of Dab1 [65]. Collectively, these findings indicate that marked decreases in Reelin protein expression and Reelin signaling cause lissencephaly.

3.5. Mood Disorders

Reelin deficiency has been implicated in the pathophysiology of mood disorders, such as major depression and bipolar disorder. In an immunocytochemical analysis of the hippocampal tissues of postmortem patients with major depression, the number of Reelin-positive cells was consistently lower in subjects with major depression than in controls [66]. Reelin protein expression in patients with major depression was found to be slightly down-regulated in the molecular layer of the dentate gyrus of the hippocampus [67]. A postmortem brain study revealed a significant decrease in Reelin mRNA expression levels in bipolar patients [68]. Furthermore, the number of Reelin-positive cells in the hippocampus was lower in bipolar patients than in controls [66].

As mentioned above, Reelin is associated with several neuropsychiatric disorders. However, future studies are needed to determine the molecular mechanisms of Reelin in synaptic development and function related to these disorders.

4. Experimental Animal Models Based on Reelin Dysfunctions

Previous clinical studies reported reductions in Reelin protein and mRNA expression levels in patients with psychiatric disorders. As shown in Table 1, experimental studies on the mechanisms underlying neurological disorders and therapeutic development were conducted using experimental animal models with reduced Reelin expression and functions. In the following section, we review animal models based on Reelin dysfunctions.
Table 1. Summary of animal models based on Reelin dysfunctions.

| Animal Model              | Mutation/Treatment                                                                 | Abnormal Phenotypes                                                                 | Behavioral Changes                                                                 | Effects of Reelin Supplementation                                                                 | References                                      |
|---------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------|
| Jackson reeler mice       | 150-kb genomic deletion in the Reln gene                                           | Brain malformation, decreased Reelin protein levels, impaired neurite development, fewer dendritic spines | Impairments in contextual fear conditioned learning, novel object recognition, and prepulse inhibition tests | Elongation of dendrites, enhanced synaptic functions, attenuation of impaired contextual fear conditioned learning and prepulse inhibition | [5,10,30,69–73]                                |
| Orleans reeler mice       | 220-nucleotide deletion in Reln mRNA                                               | Expressing a truncated Reelin protein that is not secreted extracellularly           | (Homozygous) Hyperlocomotion, impairments in motor coordination and spatial learning (Heterozygous) Abnormal social behavior and motor learning | Not available                                                                                     | [72,74,75]                                     |
| Maternal immune activation model | The offspring of pregnant mice administered polyI:C | Decreased number of Reelin-expressing cells, impaired hippocampal neurogenesis      | Sensory gating deficits, suppression of exploratory behavior, impaired novel object recognition, increased anxiety-like behavior | Rescue of impaired novel object memory and anxiety-like behavior | [76–80]                                        |
| CORT-treated animal model | Rats subcutaneously injected with CORT                                              | Reduction in Reelin-positive cells, impaired hippocampal neurogenesis                | Increased depressive-like behavior and impaired memory                              | Attenuation of increased depressive-like behavior and impaired memory                              | [81–85]                                        |
| Reln-del mice             | Mice mimicking RELN-del in a schizophrenia patient                                | Brain malformation, decreased Reelin protein levels, impaired neurite development, fewer dendritic spines | Abnormal social novelty, impaired associative learning and behavioral flexibility   | Enhancement in Reelin-Dab1 signaling                                                              | [86–88]                                        |

polyI:C, polyinosinic:polycytidylic acid; CORT, repeated corticosterone; GABA, γ-aminobutyric acid; mTOR, mammalian target of rapamycin; PSD95, postsynaptic density protein 95.
4.1. Reeler Mice

Jackson reeler mice, carrying a 150-kb genomic deletion in the Reln gene, are spontaneous mutant mice exhibiting ataxia and are deficient in the Reelin protein [71,72]. In homozygous reeler mice, cellular disorganization is observed in the cortical structures of the brain [5]. Neuronal migration is inhibited in the depths of the cortex in the brains of homozygous reeler mice in the developmental stage [73]. The levels of MAP2, a dendritic marker, were diminished in the hippocampus of homozygous and heterozygous reeler mice.

In dissociated hippocampal cultures, the total lengths of the dendrites of homozygous and heterozygous reeler mice were significantly shorter than that of wild-type mice. A recombinant Reelin or brain-derived neurotrophic factor (BDNF) treatment ameliorated impaired dendritic growth in the hippocampal neurons of reeler mice [10]. Dendritic spine density was found to be reduced in the PFC of heterozygous reeler mice. In addition, NMDA-dependent LTP was not induced in the PFC synapses of heterozygous reeler mice [30]. Methamphetamine-induced hyperlocomotion was significantly attenuated in reeler mice. In addition, locomotor responses to the dopamine D1 receptor agonist SKF82958 and dopamine D2 receptor agonist quinpirole were decreased in reeler mice, suggesting that Reelin plays important roles in dopaminergic functions in the brain [89]. Moreover, GABAergic neurons and their synaptic transmission are altered in neuro-psychiatric disorders; in fact, the expression level of glutamic acid decarboxylase 67, a marker of GABAergic neurons, in the frontal cortex was lower in reeler mice than in wild-type mice [90].

4.2. Maternal Immune Activation Model

Immune activation by maternal infection during pregnancy may increase the risk of neurodevelopmental disorders in offspring [94]. An experimental model of maternal immune activation is the maternal administration of polyinosinic:polycytidylic acid (polyI:C), a synthetic double-stranded RNA analog that mimics viral RNA. An intraperitoneal in-
jection of polyI:C into pregnant mice induced sensory gating deficits, the suppression of exploratory behavior, novel object recognition impairments, and increased anxiety-like behavior in the offspring at adolescence [76–80]. Reelin-expressing cells were reduced in the hippocampus of the offspring by maternal immune activation, particularly in the dentate gyrus of the hippocampus [76,79]. Furthermore, offspring that had received maternal immune activation during pregnancy exhibited a decrease in the immunoreactive area of synaptotoporin, a synaptic vesicle marker for hippocampal mossy fibers [79] and reduced postnatal neurogenesis in the dentate gyrus of the hippocampus [76]. Impairments in novel object memory and anxiety-like behavior in the offspring that received maternal immune activation during pregnancy were ameliorated by a stereotaxic microinjection of recombinant Reelin into the hippocampus [79]. Accordingly, Reelin supplementation may exert therapeutic effects on the cognitive and emotional impairments of neurodevelopmental disorders.

4.3. Repeated Corticosterone (CORT)-Treated Animal Model

Rats subcutaneously injected with CORT (40 mg/kg) are an experimental animal model of depression, and exhibit depressive-like behavior, impaired memory, and reduced numbers of Reelin-positive cells in the hippocampus [83–85,95]. In studies that focused on neuropathological changes, a treatment with CORT impaired hippocampal neurogenesis and reduced dendritic complexity [81–83]. The expression levels of GABA<sub>A</sub> β2/3 receptors in the dentate gyrus subgranular zone of the hippocampus were decreased by the repeated administration of CORT [81,82]. Previous studies investigated whether existing drugs and Reelin replacement attenuated CORT-induced neurological dysfunction. CORT-treated rats exhibited increased immobility and decreased climbing and swimming behaviors in the forced swim test [84,85]. The co-administration of imipramine, a tricyclic antidepressant, prevented these behavioral phenotypes, indicating that imipramine exerts protective effects against CORT-induced depression-like behavior. Furthermore, imipramine also prevented decreases in Reelin expression and dendritic complexity in the hippocampus of rats treated with CORT [85]. In addition, the peripheral administration of the anti-inflammatory drug etanercept, a TNF-α inhibitor, ameliorated CORT-induced impairments in the forced swim, object-location memory, and object-in-place memory tests. Etanercept was shown to restore reductions in hippocampal neurogenesis, Reelin expression, and GABA<sub>A</sub> β2/3 receptors in CORT-treated rats [81]. Recombinant Reelin infusions into the rat hippocampus protected against CORT-induced memory dysfunctions, increases in depression-like behavior, and impaired hippocampal neurogenesis. These effects of Reelin were inhibited by an injection of the AMPAR antagonist CNQX. Furthermore, Reelin rescued CORT-induced decreases in PSD95, mTOR, phosphorylated mTOR, GABA<sub>A</sub> β2/3 receptors, GluA1, and GluN2B in the rat brain [82].

4.4. Reln-Del

A recent CNV analysis of Japanese schizophrenia patients identified a novel pathogenic deletion (12.6kb) in RELN encoding Reelin in RELN-del [45]. A male schizophrenia patient with RELN-del exhibited positive and negative symptoms, cognitive impairment, and repetitive behavior. He also displayed atrophy of the left cerebral hemisphere, particularly in the frontal and parietal lobes. The amount of the NR6 fragment of Reelin was lower in his serum than in the sera of other patients [74]. Reln-del mice, genetically modified C57BL/6J mice that mimic RELN-del in the schizophrenia patient, were developed by genome editing with the CRISPR/Cas9 system. Reelin protein expression levels in the heterozygous Reln-del mouse brain were reduced to approximately 50% of those in the wild-type mouse brain and were barely detectable in the homozygous Reln-del mouse brain [88]. Moreover, Reelin mRNA levels were significantly lower in the heterozygous Reln-del brain than in the wild-type brain, suggesting that Reelin protein expression was down-regulated based on lower mRNA levels in Reln-del mice [87]. Homozygous Reln-del mice show severe brain malformations (cerebellar atrophy, enlarged cerebral ventricles, cerebral dysplasia,
and disruption of the dentate gyrus and granule layer), while heterozygous Reln-del mice have no major deficits in their brain structure. Reaggregation and neuronal migration were severely altered in cerebellar granule neuronal cultures prepared from homozygous Reln-del mice, which may be closely related to cerebellar hypoplasia [88]. In vitro analyses using primary cultured cortical neurons indicated that intracellular Reelin protein levels were lower in Reln-del neurons than in wild-type neurons. Reelin proteins secreted into the conditioned medium of cortical neurons were also markedly reduced in Reln-del neurons. In contrast, Dab1 expression levels were significantly higher in Reln-del neurons than in wild-type neurons, suggesting that Reelin signaling was diminished in Reln-del neurons. A shorter neurite length and fewer neurite branch points and dendritic spines in Reln-del neurons than in wild-type neurons have also been reported, indicating that the defective formation of neurons and dendrites during neurodevelopment is one of the reasons for structural abnormalities in the brains of Reln-del mice [87]. Since the patient with RELN-del was a heterozygote, heterozygous Reln-del mice were subjected to a comprehensive behavioral analysis. In the three-chamber social interaction test, heterozygous Reln-del mice exhibited abnormalities in social novelty, suggesting that Reln-del mice partially mimicked schizophrenia-like behavior. However, no impairments were noted in other behavioral tests, including the general locomotor function, open field, elevated plus maze, pre-pulse inhibition, Y-maze, and fear conditioning tests [88]. Cognitive function and flexibility in Reln-del mice were evaluated using the touchscreen-based visual discrimination and reversal learning tasks [86], which are highly sensitive for detecting cognitive dysfunction in mice [96]. In these tasks, Reln-del mice showed impaired associative learning and behavioral flexibility [86].

Human isogenic induced pluripotent stem cells (hiPSCs) were generated by targeted genome editing to establish the RELN-del hiPSCs, and separately differentiated into dopaminergic, glutamatergic, and GABAergic neurons [97,98]. Reelin protein expression and the tyrosine phosphorylation of Dab1 were decreased in isogenic RELN-del dopaminergic neurons, suggesting that Reelin signaling was diminished in RELN-del cells. In addition, a single-cell trajectory analysis showed a wandering type of migration in RELN-del neurons [97]. Gephyrin (postsynaptic marker) and Synapsin I puncta were significantly decreased in isogenic RELN-del GABAergic neurons. These findings are similar to those reported in the postmortem brains of schizophrenia patients [99,100], suggesting that the synapse phenotypes of RELN-del neurons are general phenotypes of neuropsychiatric disorders [98]. Neurons induced from hiPSC lines carrying congenital RELN-del had a shorter dendrite length and decreased synapse number and also lost the directionality of migration [97,98]. These in vitro models using hiPSCs with RELN-del are considered to be useful for pathological analyses of neuropsychiatric disorders, such as schizophrenia.

5. Effects of Enhancements in Reelin Functions

Previous studies indicated that Reelin supplementation and enhancements in Reelin signaling improve neurological functions. Therefore, Reelin may be a therapeutic target for neuropsychiatric disorders. To investigate the direct effects of Reelin on behavior, mice overexpressing Reelin in forebrain neurons (Reelin-OE) were generated [101]. Reelin-OE mice showed a reduced floating time in the forced swim test in mice treated with chronic CORT, and reduced hyperlocomotion induced by cocaine administration. In addition, PPI deficits induced by a treatment with the NMDAR antagonist, MK-801, were significantly attenuated in Reelin-OE mice [101]. A microinjection of Reelin into the medial PFC prevented MK-801-induced impairments in recognition memory and increases in the number of c-Fos-positive cells, suggesting that Reelin prevented MK-801-induced abnormal neuronal activation [102].

The effects of Reelin overexpression on the pathology of tauopathy were investigated using AD-related mice expressing human mutant Tau (G272V, P301L and R406W), which are called VLW mice [103]. Increases in Tau phosphorylation levels in the hippocampus of VLW mice were reduced by the overexpression of Reelin. In addition, LTP deficits and
cognitive impairment in VLW mice were ameliorated by the overexpression of Reelin. These findings suggest that enhancements in Reelin signaling protect against the symptoms of Tau pathology. Therefore, Reelin may be a therapeutic target in AD [103].

6. Novel Druggable Targets for Reelin Supplementation Therapy in Neuropsychiatric Disorders

Reelin degradation enzymes may be potential targets to enhance Reelin signaling. A disintegrin and metalloproteinase with thrombospondin motifs-3 (ADAMTS-3) has been identified as the protease that specifically cleaves Reelin at the N-t site in the cerebral cortex and hippocampus (Figure 1) [104]. ADAMTS-3 is expressed in the excitatory neurons of the embryonic and postnatal cerebral cortex and hippocampus, and down-regulates Reelin in the embryonic and postnatal brain. The NR2 fragment, a degradation product of Reelin at N-t, was found to be significantly decreased in the cerebral cortex of ADAMTS-3 KO mice. Dab1 expression levels were also reduced in the cerebral cortex of ADAMTS-3 KO mice, suggesting that Reelin signaling is activated by an ADAMTS-3 deficiency.

We recently proposed a novel concept to enhance Reelin signaling by the inhibition of ADAMTS-3 as a novel treatment for neuropsychiatric disorders [87]. To investigate the effects of the inhibition of ADAMTS-3 on Reelin signaling, we generated a primary culture of cortical neurons from wild-type and heterozygous Reln-del mice and performed knockdown experiments on ADAMTS-3 using short hairpin RNAs. Reelin cleavage in conditioned medium was significantly decreased, whereas Dab1 expression was reduced by the knockdown of ADAMTS-3, indicating that Reelin signaling was enhanced in primary cultured cortical neurons prepared from both wild-type and heterozygous Reln-del mice. Therefore, the inhibition of ADAMTS-3 may be a candidate for the clinical treatment of neuropsychiatric disorders, such as schizophrenia, by enhancing Reelin signaling in the brain [87].

Tau phosphorylation, which is involved in the aggravation of AD, was found to be decreased in the cerebral cortex of ADAMTS-3 KO mice. An ADAMTS-3 deficiency in excitatory neurons increased the branching and elongation of dendrites in the somatosensory cortex [104]. Moreover, reductions in ADAMTS-3 inhibited the deposition of Aβ in App knock-in mice, an AD animal model [105,106], by enhancing Reelin activity, which suggests the potential of an inhibitor of ADAMTS-3 to prevent the progression of AD [107].

ADAMTS-2, which has similar domain structures and substrate specificity to ADAMTS-3, was also shown to contribute to the N-t cleavage and inactivation of Reelin in the postnatal cerebral cortex and hippocampus [108]. At the mRNA level, ADAMTS-3 is highly expressed in the embryonic cerebral cortex and hippocampus, while ADAMTS-2 and ADAMTS-3 are expressed at similar levels in the postnatal cerebral cortex and hippocampus. Therefore, the inhibition of ADAMTS-2 may also be a target for neuropsychiatric disorders in the adult brain [108]. Further studies on ADAMTS-2 and ADAMTS-3 are needed to elucidate their mechanisms of action in the treatment of neuropsychiatric and neurodegenerative disorders.
7. Conclusions

In this review, we discussed the relationships between the neuronal functions of Reelin and neuropsychiatric disorders. Furthermore, we introduced experimental animal models based on Reelin dysfunctions. We showed that enhanced Reelin signaling may ameliorate neurological dysfunctions. The down-regulated expression of Reelin and RELN mutations have been reported in patients with neuropsychiatric disorders. Reelin supplementation improved neurological functions and may be a candidate for novel treatments for neuropsychiatric disorders. Since the amount of Reelin in serum fluctuates in psychiatric disorders, it may be used as a marker of illness and an indicator of therapeutic efficacy. However, clinical therapies based on Reelin functions have not yet been applied in practical settings. Further studies are needed to develop treatments that target Reelin functions.

Author Contributions: Conceptualization, Y.T. and H.M.; writing—original draft preparation, Y.T.; writing—review and editing, T.N. and H.M.; supervision, K.Y. and H.M. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the following funding sources: KAKENHI Grant Numbers JP19K21811, JP19H03532, and JP20H03428 from the Japan Society for the Promotion of Science; a grant from the Takeda Science Foundation; a grant from the Mishima Kaiun Memorial Foundation; the Hori Sciences and Arts Foundation; a grant for biomedical research from the SRF; and AMED Grant Numbers JP21wm0425007 and JP21wm0425014 from the Japan Agency for Medical Research and Development.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no competing financial interests.

References

1. Meyer, G.; Goffinet, A.M.; Fairén, A. Feature Article: What is a Cajal-Retzius cell? A reassessment of a classical cell type based on recent observations in the developing neocortex. Cereb. Cortex 1999, 9, 765–775. [CrossRef]
2. Frotscher, M. Dual role of Cajal-Retzius cells and reelin in cortical development. Cell Tissue Res. 1997, 290, 315–322. [CrossRef] [PubMed]
3. Pesold, C.; Impagnatiello, F.; Psu, M.G.; Uzunov, D.P.; Costa, E.; Guidotti, A.; Caruncho, H.J. Reelin is preferentially expressed in neurons synthesizing gamma-aminobutyric acid in cortex and hippocampus of adult rats. Proc. Natl. Acad. Sci. USA 1998, 95, 3221–3226. [CrossRef] [PubMed]
4. Pesold, C.; Liu, W.S.; Guidotti, A.; Costa, E.; Caruncho, H.J. Cortical bitufted, horizontal, and Martinotti cells preferentially express and secrete reelin into perineuronal nets, nonsynaptically modulating gene expression. Proc. Natl. Acad. Sci. USA 1999, 96, 3217–3222. [CrossRef]
5. D’Arcangelo, G.; Miao, G.G.; Chen, S.-C.; Scares, H.D.; Morgan, J.I.; Curran, T. A protein related to extracellular matrix proteins deleted in the mouse mutant reeler. Nature 1995, 374, 719–723. [CrossRef]
6. Hiesberger, T.; Trommsdorff, M.; Howell, B.; Goffinet, A.; Mumby, M.C.; A Cooper, J.; Herz, J. Direct Binding of Reelin to VLDL Receptor and ApoE Receptor 2 Induces Tyrosine Phosphorylation of Disabled-1 and Modulates Tau Phosphorylation. J. Biol. Chem. 2003, 278, 38772–38779. [CrossRef]
7. Yasui, N.; Nogi, T.; Kitao, T.; Nakano, Y.; Hattori, M.; Takagi, J. Structure of a receptor-binding fragment of reelin and mutational analysis reveal a recognition mechanism similar to endocytic receptors. Proc. Natl. Acad. Sci. USA 2007, 104, 9988–9993. [CrossRef]
8. Bock, H.H.; Jossin, Y.; Liu, P.; Förster, E.; May, P.; Goffinet, A.M.; Herz, J. Phosphatidylinositol 3-Kinase Interacts with the Adaptor Protein Dab1 in Response to Reelin Signaling and Is Required for Normal Cortical Lamination. J. Biol. Chem. 2003, 278, 38772–38779. [CrossRef]
9. Benhayon, D.; Magdaleno, S.; Curran, T. Binding of purified Reelin to ApoER2 and VLDLR mediates tyrosine phosphorylation of Disabled-1. Mol. Brain Res. 2003, 112, 33–45. [CrossRef]
10. Niu, S.; Renfro, A.; Quattrocchi, C.C.; Sheldon, M.; D’Arcangelo, G. Reelin Promotes Hippocampal Dendrite Development through the VLDLR/ApoER2-Dab1 Pathway. Neuron 2004, 41, 71–84. [CrossRef]
11. Niu, S.; Yabut, O.; D’Arcangelo, G. The Reelin Signaling Pathway Promotes Dendritic Spine Development in Hippocampal Neurons. J. Neurosci. 2008, 28, 10339–10348. [CrossRef] [PubMed]
12. Tissir, F.; De Rouvroit, C.L.; Sire, J.-Y.; Meyer, G.; Goffinet, A. Reelin expression during embryonic brain development in Crocodylus niloticus. J. Comp. Neurol. 2003, 457, 250–262. [CrossRef]
39. Impagnatiello, F.; Guidotti, A.R.; Pesold, C.; Dwivedi, Y.; Caruncho, H.; Pisu, M.G.; Uzunov, D.P.; Smallheiser, N.; Davis, J.M.; Pandey, G.N.; et al. A decrease of reelin expression as a putative vulnerability factor in schizophrenia. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 15718–15723. [CrossRef]

40. Yin, J.; Lu, Y.; Yu, S.; Dai, Z.; Zhang, F.; Yuan, J. Exploring the mRNA expression level of RELN in peripheral blood of schizophrenia patients before and after antipsychotic treatment. *Hereditas* **2020**, *157*, 43. [CrossRef]

41. Bocharova, A.V.; Stepanov, V.A.; Marusin, A.V.; Kharkov, V.N.; Vagaitseva, K.V.; Fedorenko, O.Y.; Bokhan, N.A.; Semke, A.V.; Ivanova, S.A. Association study of genetic markers of schizophrenia and its cognitive endophenotypes. *Russ. J. Genet.* **2017**, *53*, 139–146. [CrossRef]

42. Sozuzugel, M.D.; Sazci, A.; Yildiz, M. Female gender specific association of the Reelin (RELN) gene rs7341475 variant with schizophrenia. *Biol. Rep.* **2019**, *46*, 3411–3416. [CrossRef] [PubMed]

43. Marzan, S.; Aziz, A.; Islam, M.S. Association Between REELIN Gene Polymorphisms (rs7341475 and rs262355) and Risk of Schizophrenia: An Updated Meta-analysis. *J. Mol. Neurosci.* **2020**, *71*, 675–690. [CrossRef]

44. Zhou, Z.; Hu, Z.; Zhang, L.; Hu, Z.; Liu, H.; Liu, Z.; Du, J.; Zhao, J.; Zhou, L.; Xia, K.; et al. Identification of RELN variation p.Thr319Ser in a Chinese family with schizophrenia. *Sci. Rep.* **2016**, *6*, 24327. [CrossRef]

45. Kushima, I.; Aleksic, B.; Nakatoki, M.; Shimamura, T.; Shinno, T.; Yoshimi, A.; Kimura, H.; Takasaki, Y.; Wang, C.; Xing, J.; et al. High-resolution copy number variation analysis of schizophrenia in Japan. *Mol. Psychiatry* **2016**, *22*, 430–440. [CrossRef] [PubMed]

46. Nawa, Y.; Kimura, H.; Mori, D.; Kato, H.; Toyama, M.; Furuta, S.; Yu, Y.; Ishizuka, K.; Kushima, I.; Aleksic, B.; et al. Rare single-nucleotide DAB1 variants and their contribution to Schizophrenia and autism spectrum disorder susceptibility. *Hum. Genome Var.* **2020**, *7*, 37. [CrossRef]

47. Iossifov, I.; O’Roak, B.J.; Sanders, S.J.; Ronemus, M.; Krumm, N.; Levy, D.; Stessman, H.A.; Witherspoon, K.T.; Vives, L.; Patterson, K.E.; et al. The contribution of de novo coding mutations to autism spectrum disorder. *Nature* **2014**, *515*, 216–221. [CrossRef]

48. Bonora, E.; Beyer, K.S.; Lamb, J.A.; Parr, J.R.; Klauck, S.M.; Benner, A.; Paolucci, M.; Abbott, A.; Ragoussis, I.; Pouštka, A.; et al. Analysis of reelin as a candidate gene for autism. *Mol. Psychiatry* **2003**, *8*, 885–892. [CrossRef]

49. Lammert, D.B.; Middleton, F.A.; Pan, J.; Olson, E.C.; Howell, B.W. The de novo autism spectrum disorder RELN R2290C mutation reduces Reelin secretion and increases protein disulfide isomerase expression. *J. Neurochem.* **2017**, *142*, 89–102. [CrossRef]

50. De Rubeis, S.; He, X.; Goldberg, A.P.; Poultney, C.S.; Samocha, K.E.; Kou, Y.; Liu, L.; Fromer, M.; Walker, S.; et al. Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature* **2014**, *515*, 209–215. [CrossRef]

51. Dhaliwal, J.; Qiao, Y.; Calli, K.; Martell, S.; Race, S.; Chijiwa, C.; Globalo, A.; Jones, S.; Rajcan-Separovic, E.; Scherer, S.; et al. Contribution of Multiple Inherited Variants to Autism Spectrum Disorder (ASD) in a Family with 3 Affected Siblings. *Genes* **2021**, *12*, 1053. [CrossRef]

52. Wang, Z.; Hong, Y.; Zou, L.; Zhong, R.; Zhu, B.; Shen, N.; Chen, W.; Lou, J.; Ke, J.; Zhang, T.; et al. Reelin gene variants and risk of autism spectrum disorders: An integrated meta-analysis. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* **2014**, *165*, 192–200. [CrossRef]

53. Persico, A.M.; D’Agruma, L.; Maiorano, N.; Totaro, A.; Militerno, R.; Bravaccio, C.; Wassink, T.H.; Schneider, C.; Melmed, R.; Trillo, S.; et al. Reelin gene alleles and haplotypes as a factor predisposing to autistic disorder. *Mol. Psychiatry* **2001**, *6*, 150–159. [CrossRef]

54. Chen, N.; Bao, Y.; Xue, Y.; Sun, Y.; Hu, D.; Meng, S.; Lu, L.; Shi, J. Meta-analyses of RELN variants in neuropsychiatric disorders. *Behav. Brain Res.* **2017**, *312*, 110–119. [CrossRef]

55. Wang, G.-F.; Ye, S.; Gao, L.; Han, Y.; Guo, X.; Dong, X.-P.; Su, Y.-Y.; Zhang, X. Two single-nucleotide polymorphisms of the RELN gene and symptom-based and developmental deficits among children and adolescents with autistic spectrum disorders in the Tianjin, China. *Behav. Brain Res.* **2018**, *350*, 1–5. [CrossRef]

56. Hernández-García, I.; Chamorro, A.-J.; La Vega, H.T.-D.; Carbonell, C.; Marcos, M.; Mirón-Canelo, J.-A. Association of Allelic Variants of the Reelin Gene with Autistic Spectrum Disorder: A Systematic Review and Meta-Analysis of Candidate Gene Association Studies. *Int. J. Environ. Res. Public Health* **2020**, *17*, 8010. [CrossRef] [PubMed]

57. Wei, H.; Zhu, Y.; Wang, T.; Zhang, X.; Zhang, K.; Zhang, Z. Genetic risk factors for autism-spectrum disorders: A systematic review based on systematic reviews and meta-analysis. *J. Neural Transm.* **2021**, *128*, 717–734. [CrossRef]

58. Yu, N.-N.; Tan, M.-S.; Yu, J.-T.; Xie, A.-M.; Tan, L. The Role of Reelin Signaling in Alzheimer’s Disease. *Mol. Neurobiol.* **2016**, *53*, 5692–5700. [CrossRef] [PubMed]

59. Lyketsos, C.G.; Carrillo, M.C.; Ryan, J.M.; Khachaturian, A.S.; Trzepacz, P.; Amatniek, J.; Cedarbaum, J.; Brashear, R.; Miller, D.S. Neuropsychiatric symptoms in Alzheimer’s disease. *Alzheimer’s Dement.* **2011**, *7*, 532–539. [CrossRef]

60. Durakoglugil, M.S.; Chen, Y.; White, C.L.; Kavalali, E.T.; Herz, J. Reelin signaling antagonizes beta-amyloid at the synapse. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 15938–15943. [CrossRef] [PubMed]

61. Kocherhans, S.; Madhusudan, A.; Doehner, J.; Breu, K.S.; Nitsch, R.M.; Fritschy, J.M.; Knuesel, I. Reduced Reelin expression accelerates amyloid-beta plaque formation and tau pathology in transgenic Alzheimer’s disease mice. *J. Neurosci.* **2010**, *30*, 9228–9240. [CrossRef]

62. Cuchillo-Ibanez, I.; Mata-Balaguer, T.; Balmaceda, V.; Arranz, J.J.; Nimpf, J.; Saez-Valero, J. The beta-amyloid peptide compromises Reelin signaling in Alzheimer’s disease. *Sci. Rep.* **2016**, *6*, 31646. [CrossRef] [PubMed]
63. Hong, S.E.; Shugart, Y.Y.; Huang, D.T.; Al Shahwan, S.; Grant, P.E.; Hourihane, J.O.; Martin, N.D.; Walsh, C. Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with human RELN mutations. *Nat. Genet.* **2000**, *26*, 93–96. [CrossRef]

64. Chang, B.S.; Duzcan, F.; Kim, S.; Cinbis, M.; Aggarwal, A.; Apse, K.A.; Ozdel, O.; Atmaca, M.; Zencir, S.; Bagci, H.; et al. The role of RELN in lissencephaly and neuropsychiatric disease. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.* **2006**, *144B*, 58–63. [CrossRef] [PubMed]

65. Smits, D.J.; Schot, R.; Wilke, M.; van Slegtenhorst, M.; de Wit, M.C.Y.; Dobyns, W.B.; Barkovich, A.J.; Mancini, G.M. Biallelic DAB1 Variants Are Associated With Mild Lissencephaly and Cerebellar Hypoplasia. *Neurogen. 2021*, 7, e558. [CrossRef]

66. Fatemi, S.H.; Earle, J.A.; McMenomy, T. Reduction in Reelin immunoreactivity in hippocampus of subjects with schizophrenia, bipolar disorder and major depression. *Mol. Psychiatry* **2000**, *5*, 654–663. [CrossRef] [PubMed]

67. Knable, M.B.; Barci, B.M.; Webster, M.J.; Meadow-Woodruff, J.; Torrey, E.F.; Stanley Neuropathology. C. Molecular abnormalities of the hippocampus in severe psychiatric illness: Postmortem findings from the Stanley Neuropathology Consortium. *Mol. Psychiatry* **2004**, *9*, 609–620. [CrossRef]

68. Guidotti, A.; Auta, J.; Davis, J.M.; Di-Giorgi-Gerevini, V.; Dwivedi, Y.; Grayson, D.R.; Impagnatiello, F.; Pandey, G.; Pesold, C.; Sharma, R.; et al. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: A postmortem brain study. *Arch. Gen. Psychiatry* **2000**, *57*, 1061–1069. [CrossRef]

69. Qiu, S.; Korwek, K.M.; Pratt-Davis, A.R.; Peters, M.; Bergman, M.Y.; Webber, E.J. Cognitive disruption and altered hippocampus synaptic function in Reelin haploinsufficient mice. *Neurobiol. Learn. Mem.* **2006**, *85*, 228–242. [CrossRef]

70. Salinger, W.L.; Ladrow, P.; Wheeler, C. Behavioral Phenotype of the Reeler Mutant Mouse: Effects of Reln Gene Dosage and Social Isolation. *Behav. Neurosci.* **2003**, *117*, 1257–1275. [CrossRef]

71. Falconer, D.S. Two new mutants, ‘trmbler’ and ‘reeler’, with neurological actions in the house mouse (*Mus musculus L.*). *J. Genet.* **1951**, *50*, 192–205. [CrossRef]

72. de Bergveyck, V.; Nakajima, K.; Lambert de Rouvroit, C.; Naerhuyzen, B.; Goffinet, A.M.; Miyata, T.; Ogawa, M.; Mikoshiba, K. A truncated Reelin protein is produced but not secreted in the ‘Orleans’ reeler mutation (Reln<sup>rl-Orl</sup>). *Mol. Brain Res.* **1997**, *50*, 85–90. [CrossRef]

73. Caviness, V.S. Neocortical histogenesis in normal and reeler mice: A developmental study based upon [3H]thymidine autoradiography. *Dev. Brain Res.* **1982**, *4*, 293–302. [CrossRef]

74. Sobue, A.; Kushima, I.; Nagai, T.; Kim, S.; Chopp, S.; van Slegtenhorst, M.; Dobyns, W.; Barkovich, A.; Mancini, G.M. Biallelic DAB1 Variants Are Associated With Mild Lissencephaly and Cerebellar Hypoplasia. *Neurogen. 2021*, 7, e558. [CrossRef]

75. Lalonde, R.; Hayzoun, K.; Derer, M.; Mariani, J.; Strazielle, C.; Braff, D.; Dubois, D.; Guay, D.; Rekant, M.; et al. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: A postmortem brain study. *Arch. Gen. Psychiatry* **2000**, *57*, 1061–1069. [CrossRef]

76. Meyer, U.; Nyffeler, M.; Engler, A.; Urwyler, A.; Schedlowski, M.; Knuesel, I.; Yee, B.K.; Feldon, J. The time of prenatal immune challenge determines the specificity of inflammation-mediated brain and behavioral pathology. *J. Neurosci.* **2006**, *26*, 4752–4762. [CrossRef]

77. Eßlinger, M.; Wachholz, S.; Manitz, M.-P.; Plümper, J.; Sommer, R.; Juckel, G.; Friebe, A. Schizophrenia associated sensory gating deficits develop after adolescent microglia activation. *Brain. Behav. Immun.* **2016**, *58*, 99–106. [CrossRef]

78. Gonzalez-Liencres, C.; Juckel, G.; Esslinger, M.; Wachholz, S.; Manitz, M.-P.; Brüne, M.; Friebe, A. Emotional Contagion is not correlated with cytochrome oxidase activity. *Neurosci. Res.* **2020**, *175*, 1–8. [CrossRef]

79. Ibi, D.; Nakasai, G.; Koide, N.; Sawahata, M.; Kohno, T.; Takaba, R.; Nagai, T.; Hattori, M.; Nabeshima, T.; Yamada, K.; et al. Reelin Deficiency Alters the Offspring in a Mouse Model of Neurodevelopmental Disorders. *Front. Cell. Neurosci.* **2020**, *14*, 285. [CrossRef]

80. Shi, L.; Fatemi, S.H.; Sidwell, R.W.; Patterson, P.H. Maternal Influenza Infection Causes Marked Behavioral and Pharmacological Changes in the Offspring. *J. Neurosci.* **2003**, *23*, 297–302. [CrossRef]

81. Brymer, K.J.; Johnston, J.; Botterill, J.J.; Romay-Tallon, R.; Mitchell, M.A.; Allen, J.; Pinna, G.; Caruncho, H.J.; Kalynchuk, L.E. Peripheral Etanercept Administration Normalizes Behavior, Hippocampal Reelin Expression, and Neurochemical Markers in the Reeler Mouse Model of Neural Developmental Disorders. *Front. Pharmacol.* **2020**, *11*, 59627. [CrossRef] [PubMed]

82. Brymer, K.J.; Johnston, J.; Botterill, J.J.; Romay-Tallon, R.; Mitchell, M.A.; Allen, J.; Pinna, G.; Caruncho, H.J.; Kalynchuk, L.E. Ketamine Rescues Hippocampal Reelin Expression and Synaptic Markers in the Reeler Mouse Model of Neural Developmental Disorders. *Front. Pharmacol.* **2020**, *11*, 59627. [CrossRef] [PubMed]

83. Johnston, J.N.; Thacker, J.S.; Desjardins, C.; Kulyk, B.D.; Romay-Tallon, R.; Kalynchuk, L.E.; Caruncho, H.J. Ketamine Rescues Hippocampal Reelin Expression and Synaptic Markers in the Reeler Mouse Model of Neural Developmental Disorders. *Front. Pharmacol.* **2020**, *11*, 59627. [CrossRef] [PubMed]

84. Johnston, J.N.; Thacker, J.S.; Desjardins, C.; Kulyk, B.D.; Romay-Tallon, R.; Kalynchuk, L.E.; Caruncho, H.J. Ketamine Rescues Hippocampal Reelin Expression and Synaptic Markers in the Reeler Mouse Model of Neural Developmental Disorders. *Front. Pharmacol.* **2020**, *11*, 59627. [CrossRef] [PubMed]

85. Fenton, E.Y.; Fournier, N.M.; Lussier, A.; Romay-Tallon, R.; Caruncho, H.J.; Kalynchuk, L.E. Impairments protect against the deleterious effects of chronic corticosterone on depression-like behavior, hippocampal reelin expression, and neuronal maturation. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2015**, *60*, 52–59. [CrossRef] [PubMed]
86. Liao, J.; Dong, G.; Wulaer, B.; Sawahata, M.; Mizoguchi, H.; Mori, D.; Ozaki, N.; Nabeshima, T.; Nagai, T.; Yamada, K. Mice with exonic RELN deletion identified from a patient with schizophrenia have impaired visual discrimination learning and reversal learning in touchscreen operant tasks. Behav. Brain Res. 2021, 416, 113569. [CrossRef] [PubMed]

87. Tsuneura, Y.; Sawahata, M.; Itob, N.; Miyajima, R.; Mori, D.; Kohno, T.; Hattori, M.; Sobue, A.; Nagai, T.; Mizoguchi, H.; et al. Analysis of Reelin signaling and neurodevelopmental trajectory in primary cultured cortical neurons with RELN deletion identified in schizophrenia. Neurochem. Int. 2021, 144, 104954. [CrossRef]

88. Sawahata, M.; Mori, D.; Arioka, Y.; Kubo, H.; Kushima, I.; Kitagawa, K.; Sobue, A.; Shishido, E.; Sekiguchi, M.; Kodama, A.; et al. Generation and analysis of novel Reln-deleted mouse model corresponding to exonic Reln deletion in schizophrenia. Psychiatry Clin. Neurosci. 2020, 74, 318–327. [CrossRef]

89. Matsuzaki, H.; Minabe, Y.; Nakamura, K.; Suzuki, K.; Iwata, Y.; Sekine, Y.; Tsuchiya, K.J.; Sugihara, G.; Suda, S.; Takei, N.; et al. Disruption of reelin signaling attenuates methamphetamine-induced hyperlocomotion. Eur. J. Neurosci. 2007, 25, 3376–3384. [CrossRef]

90. Pillai, A.; Mahadik, S.P. Increased truncated TrkB receptor expression and decreased BDNF/TrkB signaling in the frontal cortex of reeler mouse model of schizophrenia. Schizophr. Res. 2008, 100, 325–333. [CrossRef]

91. Ammassari-Teule, M.; Sgobio, C.; Biamonte, F.; Marrone, C.; Mercuri, N.B.; Keller, F. Reelin haploinsufficiency reduces the density of PV+ neurons in circumscribed regions of the striatum and selectively alters striatal-based behaviors. Psychopharmacology 2009, 204, 511–521. [CrossRef] [PubMed]

92. Bouamrane, L.; Scheyer, A.F.; Lassalle, O.; Iafrati, J.; Thomazeau, A.; Chavis, P. Reelin-Haploinsufficiency Disrupts the Developmental Trajectory of the E/I Balance in the Prefrontal Cortex. Front. Cell. Neurosci. 2017, 10, 308. [CrossRef]

93. Iemolo, A.; Montilla-Perez, P.; Nguyen, J.; Risbrough, V.B.; Taffe, M.A.; Telese, F. Reelin deficiency contributes to long-term behavioral abnormalities induced by chronic adolescent exposure to Delta9-tetrahydrocannabinol in mice. Neuropharmacology 2021, 187, 108495. [CrossRef] [PubMed]

94. Gumusoglu, S.B.; Stevens, H.E. Maternal Inflammation and Neurodevelopmental Programming: A Review of Preclinical Outcomes and Implications for Psychiatric. Biol. Psychiatry 2018, 85, 107–121. [CrossRef]

95. Lussier, A.L.; Caruncho, H.J.; Kalynchuk, L.E. Repeated exposure to corticosterone, but not restraint, decreases the number of reelin-positive cells in the adult rat hippocampus. Neurosci. Lett. 2009, 460, 170–174. [CrossRef] [PubMed]

96. Wulaer, B.; Nagai, T.; Sobue, A.; Itoh, N.; Kuroda, K.; Kaibuchi, K.; Nabeshima, T.; Yamada, K. Repetitive and compulsive-like behaviors lead to cognitive dysfunction in Disc1(Delta2-3/Delta2-3) mice. Genes Brain Behav. 2018, 17, e12478. [CrossRef] [PubMed]

97. Arioka, Y.; Shishido, E.; Kubo, H.; Kushima, I.; Yoshimi, A.; Kimura, H.; Ishizuka, K.; Aleksic, B.; Maeda, T.; Ishikawa, M.; et al. Single-cell trajectory analysis of human homogenous neurons carrying a rare RELN variant. Transl. Psychiatry 2018, 8, 129. [CrossRef]

98. Ishii, T.; Ishikawa, M.; Fujimori, K.; Maeda, T.; Kushima, I.; Arioka, Y.; Mori, D.; Nakatake, Y.; Yamagata, B.; Nio, S.; et al. In Vitro Modeling of the Bipolar Disorder and Schizophrenia Using Patient-Derived Induced Pluripotent Stem Cells with Copy Number Variations of PCDH15 and RELN. eNeuro 2019, 6. [CrossRef]

99. Konopaske, G.T.; Lange, N.; Coyle, J.T.; Benes, F.M. Prefrontal Cortical Dendritic Spine Pathology in Schizophrenia and Bipolar Disorder. JAMA Psychiatry 2014, 71, 1323–1331. [CrossRef]

100. Glantz, L.A.; Lewis, D. Decreased Dendritic Spine Density on Prefrontal Cortical Pyramidal Neurons in Schizophrenia. Arch. Gen. Psychiatry 2000, 57, 65–73. [CrossRef]

101. Teixeira, C.M.; Martin, E.D.; Sahuin, I.; Masachs, N.; Pujadas, L.; Corvelo, A.; Bosch, C.; Rossi, D.; Martinez, A.; Maldonado, R.; et al. Overexpression of Reelin Prevents the Manifestation of Behavioral Phenotypes Related to Schizophrenia and Bipolar Disorder. Neuropsychopharmacology 2011, 36, 2395–2405. [CrossRef]

102. Sawahata, M.; Asano, H.; Nagai, T.; Ito, N.; Kohno, T.; Nabeshima, T.; Hattori, M.; Yamada, K. Microinjection of Reelin into the mPFC prevents MK-801-induced recognition memory impairment in mice. Neuropharmacology 2021, 187, 108495. [CrossRef] [PubMed]

103. Rossì, D.; Gruart, A.; Contreras-Murillo, G.; Muñaisen, A.; Ávila, J.; Delgado-García, J.M.; Pujadas, L.; Soriano, E. Reelin reverses biochemical, physiological and cognitive alterations in mouse models of Tauopathy. Prog. Neurobiol. 2020, 200, 101743. [CrossRef] [PubMed]

104. Ogino, H.; Hisanaga, A.; Kohno, T.; Kondo, Y.; Okumura, K.; Kamei, T.; Sato, T.; Asahara, H.; Tsuiji, H.; Fukuta, M.; et al. Secreted Metalloprotease ADAMTS-3 Inactivates Reelin. J. Neurosci. 2017, 37, 3181–3191. [CrossRef] [PubMed]

105. Bin Saifullah, A.; Komine, O.; Dong, Y.; Fukushima, K.; Sobue, A.; Endo, F.; Saito, T.; Saito, T.C.; Yamanaka, K.; Mizoguchi, H. Touchscreen-based location discrimination and paired associate learning tasks detect cognitive impairment at an early stage in an App knock-in mouse model of Alzheimer’s disease. Mol. Brain 2020, 13, 147. [CrossRef] [PubMed]

106. Nakai, T.; Yamada, K.; Mizoguchi, H. Alzheimer’s Disease Animal Models: Elucidation of Biomarkers and Therapeutic Approaches for Cognitive Impairment. Int. J. Mol. Sci. 2021, 22, 5549. [CrossRef]

107. Yamakage, Y.; Tsuiji, H.; Kohno, T.; Ogino, H.; Saito, T.; Saito, T.C.; Hattori, M. Reducing ADAMTS-3 Inhibits Amyloid beta Deposition in App Knock-in Mouse. Biol. Pharm. Bull 2019, 42, 354–356. [CrossRef] [PubMed]

108. Yamakage, Y.; Kado, M.; Hongo, A.; Ogino, H.; Ishii, K.; Ishizuka, T.; Kamei, T.; Tsuiji, H.; Miyamoto, T.; Oishi, H.; et al. A disintegrin and metalloprotease with thrombospondin motifs 2 cleaves and inactivates Reelin in the postnatal cerebral cortex and hippocampus, but not in the cerebellum. Mol. Cell. Neurosci. 2019, 100, 103401. [CrossRef]