Schizophrenia and reelin: a model based on prenatal stress to study epigenetics, brain development and behavior

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Abstract
Schizophrenia is a severe psychiatric disorder that results in a significant disability for the patient. The disorder is characterized by impairment of the adaptive orchestration of actions, a cognitive function that is mainly dependent on the prefrontal cortex. This behavioral deficit, together with cellular and neurophysiological alterations in the prefrontal cortex, as well as reduced density of GABAergic cells and aberrant oscillatory activity, all indicate structural and functional deficits of the prefrontal cortex in schizophrenia. Among the several risk factors for the development of schizophrenia, stress during the prenatal period has been identified as crucial. Thus, it is proposed that prenatal stress induces neurodevelopmental alterations in the prefrontal cortex that are expressed as cognitive impairment observed in schizophrenia. However, the precise mechanisms that link prenatal stress with the impairment of prefrontal cortex function is largely unknown. Reelin is an extracellular matrix protein involved in the development of cortical neural connectivity at embryonic stages, and in synaptic plasticity at postnatal stages. Interestingly, down-regulation of reelin expression has been associated with epigenetic changes in the reelin gene of the prefrontal cortex of schizophrenic patients. We recently showed that, similar to schizophrenic patients, prenatal stress induces down-expression of reelin associated with the methylation of its promoter in the rodent prefrontal cortex. These alterations were paralleled with altered prefrontal cortex functional connectivity and impairment in prefrontal cortex-dependent behavioral tasks. Therefore, considering molecular, cellular, physiological and behavioral evidence, we propose a unifying framework that links prenatal stress and prefrontal malfunction through epigenetic alterations of the reelin gene.

Keywords: Schizophrenia, Prefrontal cortex, Prenatal stress, Functional connectivity, DNA methylation, Reelin

Background
Schizophrenia is a chronic psychiatric disorder that affects 0.5–1 % of the world’s population. It is characterized by a complex set of disturbances of thought, perception, and affective and social behavior that result in high social disability [1]. Although the causes of this disorder are not completely understood, clinical research has identified some factors that provide insight into the pathophysiology of this disease [2]. For example, schizophrenia is characterized by impairment of cognitive functions dependent on the prefrontal cortex (PFC; [3]), which coincides with cellular and neurophysiological alterations observed in the PFC of schizophrenic patients [4, 5]. It is also known that prenatal stress (PNS) is an important etiologic factor for the development of this disorder [6], which implies that PNS induces neurodevelopmental alterations in the PFC that are manifested as cognitive alterations observed in schizophrenic patients. In this review, we propose that PNS-induced epigenetic changes in the reelin gene, which codes for an extracellular protein involved in cortical development, could be a molecular link between prenatal stress and PFC dysfunction.

The deficit in cognitive control in schizophrenia suggests functional impairment of PFC function
The symptomatology of schizophrenia has provided some clues about the neurophysiology of the disorder.
Symptoms are classified as cognitive, positive, and negative [1]. Among these symptoms, cognitive impairments are especially relevant because they impact on the normal life performance of patients. These cognitive impairments, like reduced working memory [3, 7–9], selective attention [10], and set-shifting [11], can be globally grouped as a detriment to executive control; i.e. the proper orchestration of thoughts and actions in accordance with internal goals [12]. It has been suggested that the degree of cognitive impairments, and not the severity of psychosis, is the best predictor of long-term functional outcome for affected individuals, leading to the view that cognitive deficits are the core abnormalities of the illness [13, 14]. Thus, the deficit of executive control appears to be a hallmark of schizophrenia [3, 9, 15].

The PFC is considered the main brain area involved in executive control [12, 16]. The cognitive symptoms of schizophrenia suggest a functional impairment in the PFC as a core neurological dimension, a feature known as “hypofrontality” [3]. This functional deficit seems to be strongly related to altered neural oscillatory synchrony in the PFC [17–19], functional alterations that correlate with cognitive deficits in schizophrenic patients [4, 20]. The gamma-frequency band (30–80 Hz), the most evident neurophysiological parameter affected in schizophrenia, is required for the implementation of executive control by the PFC [21, 22], suggesting that altered gamma oscillations are implicated in cognitive dysfunction [23]. It has been shown that transmagnetic stimulation applied to the gamma-frequency band in the PFC alleviates cognitive symptoms in some schizophrenic patients [24].

The PFC of schizophrenic patients also displays profound alterations at the cellular level, like a reduction of the mean clustering distance between cells by alterations in neuropile volume [25]. It has also been observed that schizophrenics have fewer dendritic spines in pyramidal neurons than non-schizophrenic post-mortem subjects [26]. However, the inhibitory GABAergic neurons seem to be the most affected neuronal population in the PFC of schizophrenic patients. One of the most consistent findings in postmortem studies in the PFC of individuals with schizophrenia is the reduced mRNA expression of GAD67, the enzyme that synthesizes GABA [27]. In addition, reduced density of GABAergic cells, and decreased amounts of inhibitory axon terminals have been found post-mortem in the PFC of schizophrenic patients [5, 28, 29]. This evidence has led to consider schizophrenia as a disease of impaired inhibitory transmission in the PFC [30–32]. Given that GABAergic interneurons are strongly implicated in the emergence of gamma-frequency oscillations in cortical networks [33–35], this evidence suggests that cellular impairments may underlie neurophysiological PFC alterations related to cognitive impairment in schizophrenia [32].

**The effects of prenatal stress on the PFC as a neurodevelopmental factor for schizophrenia**

Some cognitive and neurophysiological alterations observed in schizophrenic patients are evident during early childhood, before patients manifest diagnosed symptoms [36–39]. This, together with the prenatal development of cellular components altered in schizophrenia, like cortical microcircuit connectivity and GABAergic transmission [26, 40, 41], all suggest that schizophrenia can also be considered a neurodevelopmental disorder, especially focused on the development of the PFC [38, 42, 43]. Thus, current evidence indicates that neurodevelopmental cellular alterations in the PFC, particularly those related to inhibitory transmission, is associated to abnormal functional connectivity in the PFC, resulting in an impairment of executive functions in schizophrenic patients [43]. But, how are these neurodevelopmental alterations in the PFC acquired?

Among the several acquired and environmental factors involved in the development of schizophrenia [44], the suffering of threatening situations by the pregnant mother during gestation, i.e. PNS, has been considered a strong environmental risk factor [6]. In support of this idea, it has been shown that the number of individuals with diagnoses of schizophrenia is significantly higher among individuals with prenatal loss of their fathers than among individuals whose fathers died during their first year of childhood [45]. Accordingly, van Os and Selten [46] found a higher cumulative incidence of schizophrenia among individuals prenatally exposed to the 1940 invasion of the Netherlands by the German army, suggesting that maternal stress during pregnancy may contribute to the development of vulnerability to schizophrenia. Similarly, Betts et al. [47] showed that stressful prenatal life events predicted psychotic experiences in adulthood. Finally, Levine et al. [48] found that PNS associated to exposure to the holocaust constitutes a consistent risk factor for schizophrenia. Thus, taking in consideration the essential role of PNS as a development risk factor for schizophrenia, and that this disorder is characterized by functional impairment of the PFC, two critical questions arise: (1) Does PNS produce functional impairment of the PFC associated with schizophrenia? And if so, (2) How does this process occur?

It has been shown in humans that stressing situations experienced by the mother during pregnancy affect PFC-dependent cognitive functions of the offspring, like working memory, control of anxiety, and learning strategies [49–52]. Similarly, research in rodents have shown that PNS affects cognitive functions dependent on the limbic
and prelimbic cortex, (the rodent homologue and analogue to the human PFC [53]), manifested as impairment of working memory [54], increase of aversive remote memory [55] (Fig. 1) or decreased recall of the extinction of conditioned fear [56]. These data indicate that PNS affects cognitive functions dependent on the PFC at adulthood [57, 58], which could be related to the pathogenesis of schizophrenia [48, 59]. At a neurophysiological level, PNS alters neuronal synchronization between the PFC and the hippocampus, connectivity relevant to the consolidation of memories [58, 60] together with a decreased firing rate in the PFC in vivo [55] (Fig. 2). Coincidently, these neurophysiological alterations are paralleled with the persistence of aversive remote memory [53, 55] (Fig. 1), a PFC-dependent cognitive function [61].

At the cellular level, there is abundant evidence suggesting that PNS affects the correct development of the PFC in rodents. For example, dendritic ramification of pyramidal neurons is disrupted in prenatally stressed adults rats [62], morphological alterations that are also evident during earlier developing stages like early childhood [63] and adolescence [64]. PNS not only affects pyramidal neurons in the PFC, but also the development of inhibitory neurons. For example, PNS decreases the number of PV+ interneurons in the PFC [65], and delays tangential migration of inhibitory neurons in the developing neocortex [64]. This is especially important since, as mentioned above, a reduction in inhibitory neuronal activity in the PFC has been proposed as an important physiopathological feature of schizophrenic patients [31, 32]. Altogether, these data suggest that PNS induces cellular neurodevelopmental alterations expressed as neurophysiological alterations in the PFC, as observed in schizophrenia [66]. However, the precise molecular mechanism by which PNS contributes to the development of schizophrenia remains elusive.

**Reelin as a molecular candidate for cellular alterations in schizophrenia**

Among molecular candidates involved in the development of schizophrenia [66–69], reelin seems to be an important link between prenatal stress and cellular and physiological alterations observed in schizophrenia. Reelin is a 400– kD extracellular matrix glycoprotein coded by a 450-bp gene located in the human chromosome 7q22 and in the murine chromosome 5 [70]. The reelin gene has multiple cis elements, including for transcription factors involved in neurodevelopment like Sp1, Tbr-1 and Pax6, and for signal transduction like CREB [71, 72]. The protein exerts its function through the union with the VLDLR and ApoER2 receptors. This coupling elicits the intracellular phosphorylation and activation of the adaptor protein disabled 1 (mDab1), which initiates a signaling pathway that ends with the modulation of the cytoskeleton of actin and microtubules [73]. Among the several molecular candidates for the physiopathology of schizophrenia (for review see [74]), clinical and preclinical evidence indicates reelin is a relevant component [75–78]. Below we review the evidence that supports reelin as a molecular candidate for the cellular disruptions produced in schizophrenia.
Reelin participates in prenatal development and shapes post-natal neural connectivity in the neocortex

Reelin protein is expressed in mammals during brain development, principally by Cajal-Retzius neurons in superficial layers of the neocortex and the hippocampus [79–81]. In rodents, cortical and hippocampal Cajal-Retzius neurons degenerate progressively to postnatal day 14 [82, 83], limiting the production and secretion of reelin to GABAergic interneurons from postnatal day 8 to adulthood [83–85]. The role of reelin in neurodevelopment has been well demonstrated, especially by regulating the radial migration of excitatory neurons and the establishment of the “inside-out” neurogenetic gradient [73, 86–88]. The reeler mouse (homocygote knock-out for reelin, and thereby deficient for reelin; [89]), has a clear disruption of cortical layers. In addition it has been demonstrated that reeler mice display an aberrant disposition of interneurons in the neocortex [90, 91], and that positioned neurons fail to connect to each other and to form a correct cortical architecture [73, 80, 92]. On the other hand, the heterozygous reeler mouse (HRM), which has 50 % expression of reelin and is used as a model for schizophrenia [93], does not have the inversion of the cortical layers observed in homozygous reeler mice [94]. However, it has reduced dendritic length and complexity and spine density compared with wild type animals [95, 96]. Importantly, the HRM mouse also displays decreased cortical GABA biosynthesis [97] and decreased cortical GAD67 [96, 98].

Reelin also participates in the remodeling of neuronal connectivity in the adult brain modulating synaptogenesis [99], synaptic plasticity [100–104] and neurotransmitter release [105]. The HRM display a decrease in spine density in parallel to lack of NMDA receptor dependent long-term potentiation in the PFC [106]. Furthermore, in vivo enhancement of reelin signaling increases cognitive ability, synaptic plasticity, and dendritic spine density [103]. Altogether, this evidence indicates that reelin
modulates cortical neuronal connectivity in both pre- and postnatal stages.

**Reduced expression of reelin and hypermethylation of the reelin promoter is found in the PFC of schizophrenic patients**

Impagniello et al. [107] were the first to report that reelin mRNA and protein expression were significantly lower in the PFC of post-mortem schizophrenic patients. This reduction in reelin expression reached 50%, and was especially evident in superficial cortical layers [107]. This finding was later replicated by others [76, 108–110].

In recent years it has been proposed that epigenetic mechanisms like DNA methylation play an important role in the gene-environment interaction in the development of psychiatric disorders, including schizophrenia [111–113]. It has been shown that the promoter of the reelin gene, together with sequences flanking exon 1, contains near 120 CpG islands [114]. The reelin promoter in in vitro assays is methylated in non-reelin expressing cells, and demethylated in reelin expressing cells [114], indicates that reelin expression is controlled by the methylation of its promoter. The reelin promoter is hypermethylated in the brain of schizophrenic post-mortem patients [39, 72, 115–117]. This reduction of reelin promoter hypermethylation [114], especially in GABAergic neurons.

**Reduced expression of reelin in animal models produces schizophrenic-like features**

Genetic animal models in which the expression of reelin is decreased display cognitive, physiological and cellular features similar to those found in schizophrenic patients. For example, reeler mice show increased cognitive impairment and stereotypic behavior [98]. Importantly, the HRM displays a deficit in PFC-dependent cognitive abilities, such as reversal learning and recall of fear extinction [106, 119], together with impairment in the acquisition of operant tasks [120] and increased anxiety [121]. Moreover, overexpression of reelin prevents the manifestation of behavioral phenotypes related to schizophrenia [122]. Although it has not been as heavily described as the reeler mice, the HRM also displays cellular features in the PFC similar to those of schizophrenic patients, such as decreased GAD67 mRNA, GAD67 protein, and fewer GAD67 positive cells in the PFC [96, 119]. Finally, reelin knockdown animals specifically in the PFC show decreased working memory [123]. Together, this evidence suggests a critical role for reelin in the deficits observed in schizophrenia.

**Interaction between PNS, reelin expression and PFC-cognitive impairment observed in schizophrenia**

Prenatal stress may induce DNA methylation of several gene promoters, including reelin [124]. Our research and that of others have shown that PNS in rodents reduces the expression of reelin in the PFC in adulthood [125, 126] (Fig. 3), which is accompanied by increased methylation of the reelin promoter [125, 126] (Fig. 3). PNS-induced own-regulation of reelin by DNA methylation is similar to that found in schizophrenic patients [115]. Together, this evidence places reelin and the epigenetic regulation of its expression as likely targets for the development of PNS-induced neuropsychiatric pathology. We have shown that PNS impairs cognitive functions dependent on the PFC, such as the consolidation of memory and passive avoidance (Fig. 1; [55, 125]). In the first case, this behavioral impairment is paralleled with decreased neural activity in the PFC and altered neuronal synchrony between the PFC and hippocampus [55] (Fig. 2). Altogether, the evidence suggests a relationship between epigenetic alterations induced by PNS on the reelin gene, with PFC impairment observed in schizophrenia.

**Conclusion**

Considering molecular, histological, and physiological evidence based on the PNS paradigm, we propose a model that links molecular, neurophysiological and cognitive alterations observed in schizophrenia (Fig. 4). In this model, PNS-induced epigenetic modifications in the reelin promoter produce down-expression of reelin during prenatal development [125, 126]. As several other researchers have shown, this results in the prenatal reduction of the number of interneurons synthesizing GABA, together with an aberrant layer positioning of cortical interneurons [31, 91, 127] and the reduction of dendritic length and complexity of pyramidal neurons in the PFC [63, 95, 96]. Thus, PNS may impair the development of correct neuronal connectivity in the PFC before birth, which in subsequent developmental stages is expressed as an aberrant functional connectivity of the
neural network in the PFC, or between PFC and other structures [19, 55]. Finally, the alteration of the functional connectivity required to implement executive control by the PFC [21, 22] is evidenced as abnormal PFC-dependent cognitive functions [4, 20, 23], which are a hallmark of schizophrenia [3, 9, 19].

Note however that this model does not imply that reelin is the only link between PNS and schizophrenia, as other PNS-regulated genes like GAD67 and BDNF [126, 128] may also impact on the symptomatology of schizophrenia. Finally, due to lack of experimental evidence, this model has some gaps in important aspects. For example, it is unknown whether PNS affects the neurophysiological properties of GABAergic interneurons and therefore, the proper functioning of the prefrontal neural network. It is also unknown how these cellular alterations induced by PNS affect the functional connectivity within the PFC and between the PFC and other structures, specifically during the implementation of executive behavioral functions. Future
research will assess these undetermined issues, which can contribute to understanding the neurobiology of schizophrenia.

**Abbreviations**

PNS: prenatal stress; PFC: prefrontal cortex; HRM: heterozygous reeler mice.

**Authors’ contributions**

All authors wrote the draft, and read and approved the final manuscript. All authors read and approved the final manuscript.

**Acknowledgements**

We were supported by Millennium Center for the Neuroscience of Memory, NC10-001-F, of the Ministry of Economy, Development and Tourism, Chile (FA); and FONDECYT for postdoctoral grant no. 3140370 to I.N.-O.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. American Psychiatric Association. DSM-V. 2013; 1.
2. Bromet EJ, Bromet EJ, Fennig S, Fennig S. Epidemiology and natural history of schizophrenia. Biol Psychiatry. 1999;46(7):871–81.
3. Senkowski D, Gallinat J. Dysfunctional prefrontal gamma-band oscillations reflect working memory and other cognitive deficits in schizophrenia. Biol Psychiatry. 2015;77(12):1010–9.
4. Basar-Eroglu, Brand A, Hildebrandt H, Karolina Kedzior K, Mathes B, Schmiedt C. Working memory related gamma oscillations in schizophrenia patients. Int J Psychophysiol. 2007;64(1):39–45.
5. Hashimoto T, Volk DW, Eggan SM, Mimics K, Pierré J, Sun Z, Sampson AR, Lewis DA. Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. J Neurosci. 2003;23(15):6315–26.
6. Bixey SN, Gallagher BJ, McFalls JA, Parmelee LF. Gestational and neonatal factors in the etiology of schizophrenia. J Clin Psychol. 1993;49(3):447–56.
7. Park S, Holzman PS. Schizophrenics show spatial working memory deficits. Arch Gen Psychiatry. 1992;49(12):975–82.
8. Goldman-Rakic PS. Cellular basis of working memory. Neuron. 1995;14(3):477–85.
9. Lee J, Park S. Working memory impairments in schizophrenia: a meta-analysis. J Abnorm Psychol. 2005;114(4):599–611.
10. Hepp HH, Maier S, Hermle L, Spitzer M. The Stroop effect in schizophrenic patients. Schizophr Res. 1996;22(3):187–95.
11. Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR. Auditory Working Memory and Wisconsin card sorting test performance in schizophrenia. Arch Gen Psychiatry. 1997;54:159–65.
12. Fuster JM. The prefrontal cortex—an update: time is of the essence. Neurology. 2012;35(12):1871–8.
13. Barch DM. The cognitive neuroscience of schizophrenia. Annu Rev Clin Psychol. 2005;1:321–53.
14. Lewis DA. Cortical circuit dysfunction and cognitive deficits in schizophrenia—implications for preemptive interventions. Eur J Neurosci. 2012;35(12):2071–8.
15. Leish TA, Nienand TA, Minzenberg MJ, Carter CS. Cognitive control deficits in schizophrenia: mechanisms and meaning. Neuropsychopharmacology. 2011;36(1):316–38.
16. Miller ER, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci. 2001;24:167–202.
17. Cho RY, Korecki JO, Carter CS. Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. Proc Natl Acad Sci USA. 2006;103(52):19878–83.
18. Yeragani VK, Cashmere D, Miewald J, Tasi S-Y, Weckert TW, Shannon-Weckert C. Rethinking schizophrenia in the context of normal neurodevelopment. Front Cell Neurosci. 2013;7:60.
19. Tochigi M, Iwamoto K, Bundo M, Komiya A, Sasaki T, Kato N, Kato T. Methyltransferation of the reelin promotor region in the brain of schizophrenic patients. Biol Psychiatry. 2008;63(5):530–3.
20. Zeece S, Hu F, Jakovac I. Interneurons in the developing human neocortex. Dev Neurobiol. 2011;71(11):18–33.
21. Ophir L, Casanova MF. Prefrontal cortical minicolumns: from executive control to disrupted cognitive processing. Brain. 2014;137(Pt 7):1863–75.
22. Arnold SE. Neurodevelopmental abnormalities in schizophrenia: insights from neuropsychopathology. Dev Psychopathol. 1999;11(3):439–56.
23. Beneyto M, Lewis DA. Insights into the neurodevelopmental origin of schizophrenia from postmortem studies of prefrontal cortical cytoarchitecture. Int J Dev Neurosci. 2011;29(3):295–304.
24. King S, Laplante D, Jobner R. Understanding putative risk factors for schizophrenia: retrospective and prospective studies. J Psychiatry Neurosci. 2005;30(5):342–8.
25. Lewis DA, Nitschke P. Prenatal loss of father and psychiatric disorders. Arch Gen Psychiatry. 1978;35(4):429–31.
26. van Os J, Selten JP. Prenatal exposure to maternal stress and subsequent schizophrenia. The May 1940 invasion of The Netherlands. Br J Psychiatry. 1998;172:524–6.
27. Betts KS, Williams GM, Najman JM, Scott J, Alati R. Exposure to stressful life events during pregnancy predicts psychotic experiences via behaviour problems in childhood. J Child Psychol Psychiatry. 2014;55(3):129–9.
28. Levine SZ, Levav I, Yoffe R, Pugachova I. The effects of perinatal-, early-life- and indirectly-initiated exposures to maximum adversities on the course of schizophrenia. Schizophr Res. 2014;158(3):236–40.
29. Mennis M, Steers P, Lagard V, Van den Bergh B. Long-term cognitive sequelae of antenatal maternal anxiety: involvement of the orbitofrontal cortex. Neurosci Bull. 2006;30(8):1078–86.
30. Entringer S, Buss C, Kumsta R, Hehlemann DH, Wadhwa PD, Wust S. Prenatal psychosocial stress exposure is associated with subsequent working memory performance in young women. Behav Neurosci. 2009;123(4):886–93.
31. Buss C, Duro EP, Hobel CJ, Sandman CA. Maternal pregnancy-specific anxiety is associated with child executive function at 6–9 years age. Stress. 2011;14(6):665–76.
32. Schwabe K, Enkel T, Klein S, Schutte M, Koch M. Effects of neonatal lesions of the medial prefrontal cortex on adult rat behaviour. Behav Brain Res. 2004;153(1):21–34.
33. Uylings HBM, Groenewegen HH, Kolb B. Do rats have a prefrontal cortex? Behav Brain Res. 2003;146(1–2):13–17.
34. Gue M, Bravard A, Meunier J, Veyrier R, Gaillat S, Recasens M, Maurice T. Sex differences in learning deficits induced by prenatal stress in juvenile rats. Behav Brain Res. 2004;150(1–2):149–57.
35. Negron-Oyarzo NL, Neira D, Espinosa N, Fuentealba P, Abbotz F. Prenatal stress produces persistence of remote memory and disrupts functional connectivity in the hippocampal-prefrontal cortex axis. Cereb Cortex. 2015;25(9):3132–43.
36. Bingham BC, Sheela Rani CS, Frazer A, Strong R, Morilik DA. Exogenous prenatal corticosterone exposure mimics the effects of prenatal stress.
on adult brain stress response systems and fear extinction behavior. Psychoneuroendocrinology. 2013;38(11):2746–57.

57. Weinstock M. The long-term behavioural consequences of prenatal stress. Neurosci Biobehav Rev. 2008;32(6):1073–86.

58. Richetto J, Riva MA. Prenatal maternal factors in the development of cognitive impairments in the offspring. J Reprod Immunol. 2014;104–105:20–5.

59. Moore H, Susser E. Relating the effects of prenatal stress in rodents to the pathogenesis of schizophrenia. Biol Psychiatry. 2011;70(10):906–7.

60. Nieuwenhuis IL, Takashima A. The role of the ventromedial prefrontal cortex in memory consolidation. Behav Brain Res. 2010;218(2):325–34.

61. Frankland PW, Bontempi S. The organization of recent and remote memories. Nat Rev Neurosci. 2005;6(2):119–30.

62. Muhammad A, Carroll C, Kolb B. Stress during development alters dendritic morphology in the nucleus accumbens and prefrontal cortex. Neuroscience. 2012;216:103–9.

63. Mychasiuk R, Gibb R, Kolb B. Prenatal stress alters dendritic morphology and synaptic connectivity in the prefrontal cortex and hippocampus of developing offspring. Synapse. 2012;66(4):308–14.

64. Markham JA, Mullins SE, Koening JI. Periocular maturation of the prefrontal cortex is sex-specific and is disrupted by prenatal stress. J Comp Neurol. 2013;521(8):1828–43.

65. Uchida T, Furukawa T, Iwata S, Yanagawa Y, Fukuda A. Selective loss of parvalbumin-positive GABAergic interneurons in the cerebral cortex of maternally stressed Gad1-heterozygous mouse offspring. Transl Psychiatry. 2014;4:e371.

66. Farrell MS, Werge T, Sklar P, Owen MJ, O'Donovan MC, Corvin A, Cichon S, Sullivan PF. Evaluating the recent candidate genes for schizophrenia. Mol Psychiatry. 2015; 1–8.

67. Chubb JE, Bradshaw NJ, Soares DC, Porteous DJ, Millar JK. The DISC chromosome 7. Genome Res. 1997;7(2):157–64.

68. Folsom TD, Fatemi SH. The involvement of Reelin in neurodevelopmental disorders. Neuropharmacology. 2009;56(1):240–50.

69. Lewis DA, Mimics K. Transcriptional alterations in schizophrenia: disturbing the functional architecture of the dorsolateral prefrontal cortex. Prog Brain Res. 2006;158:141–52.

70. Costa E, Davis J, Grayson DR, Guidotti A, Beffert U, Herz J. Reelin, lipoprotein receptors and synaptic plasticity. Nat Rev Neurosci. 2005;6(2):131–40.

71. Borrell V, Del Rio JA, Alcantara S, Derer M, Martinez A, D'Arcangelo G, Schwegler H, Wolf R. Region-specific alteration of GABAergic markers in the brain of heterozygotic reeler mice. Eur J Neurosci. 2011;33(4):689–98.

72. Caruncho HJ. Reelin is preferentially expressed in neurons synthesizing gamma-aminobutyric acid in cortex and hippocampus of adult rats. Prog Natl Acad Sci USA. 1998;95(6):3221–6.

73. Fuentesa P, Klauserberger T, Karayannis T, Suen WY, Huck J, Tomioka R, Rockland K, Capogna M, Studer M, Morales M, Somogyi P. Expression of COUP-TFI nuclear receptor in restricted GABAergic neuronal populations in the adult rat hippocampus. J Neurosci. 2010;30(5):1595–609.

74. Lambert de Rouvroit C, D'Arcangelo G. A new view of early cortical development: Biochem Pharmacol. 1998;56(11):1403–9.

75. Gilmore GC, Herpin K. Cortical development: receiving reelin. Curr Biol. 2004;10(14):R62–6.

76. Gupta A, Tsai LH, Wynshaw-Boris A. Life is a journey: a genetic look at neocortical development. Nat Rev Genet. 2002;3(5):342–55.

77. D'Arcangelo G, Miao GG, Curran T. Detection of the reelin breakpoint in reeler mice. Brain Res Mol Brain Res. 1996;39(1–2):234–6.

78. Heverhach D, Daza RAM, Englund C, Kohtz J, Fink A. Postnatal shifts of interneuron position in the neocortex of normal and reeler mice: evidence for a role of Reelin. Neuroscience. 2004;124(3):655–68.

79. Hammond V, So E, Gunnersen J, Valcancin H, Kalloniatis M, Tan SS. Layer positioning of late-born cortical interneurons is dependent on Reelin but not on p35 signaling. J Neurosci. 2006;26(15):1646–55.

80. Curran T, D'Arcangelo G. Role of reelin in the control of brain development. Brain Res Rev. 1998;26(1–2):285–94.

81. Costa E, Davis J, Pesold C, Tueting P, Guidotti A. The heterozygote reeler mouse as a model for the development of a new generation of antipsychotics. Curr Opin Pharmacol. 2002;2(1):56–62.

82. Liu WS, Pesold C, Rodriguez MA, Carboni G, Auta J, Laceron P, J. Condie BG, Guidotti A, Costa E. Down-regulation of dendritic spine and glutamate decarboxylase 67 expressions in the reelin haploinsufficient heterozygote reeler mouse. Proc Natl Acad Sci USA. 2001;98(6):3477–82.

83. Nullmeier S, Nicholls PJ, Johnson GA, Wetsel WC. Neuroanatomical phenotypes in the reeler mouse. Neuroimage. 2007;34(4):1363–74.

84. Niu S, Yabut O, D'Arcangelo G. The Reelin signaling pathway promotes dendritic spine development in hippocampal neurons. J Neurosci. 2008;28(41):10339–48.

85. Badea A, Nicholls PJ, Johnson GA, Wetsel WC. Neuroanatomical phenotypes in the reeler mouse. Neuroimage. 2007;34(4):1363–74.

86. Borrell V, Del Rio JA, Alcantara S, Derer M, Martinez A, D'Arcangelo G, Nakajima K, Mikishoba K, Derer P, Curran T, Soriano E. Reelin regulates the development and synaptogenesis of the layer-specific entorhino-hippocampal connections. J Neurosci. 1999;19(4):1345–58.

87. Chen Y, Beffert U, Ertunc M, Tang T-S, Kavalali ET, Bezprozvanny I, Herz J. Reelin modulates NMDA receptor activity in cortical neurons. J Neurosci. 2005;25(36):8209–16.

88. Herz J, Chen Y. Reelin, lipoprotein receptors and synaptic plasticity. Nat Rev Neurosci. 2005;6(11):8209–16.

89. Herz J, Chen Y. Reelin, lipoprotein receptors and synaptic plasticity. Nat Rev Neurosci. 2006;7(11):850–9.

90. Qi S, Weeber EJ. Reelin signaling facilitates maturation of CA1 glutamatergic synapses. J Neurophysiol. 2007;97(3):2312–21.

91. Rogers JT, Rusiana I, Trotter J, Zhao L, Donaldson E, Pak DTS, Babus BW, Peters M, Banko JL, Chavis P. Rebeam GW, Hoe HS, Weeber EJ. Reelin supplementation enhances cognitive ability, synaptic plasticity, and dendritic spine density. Learn Mem. 2011;18(9):558–64.

92. Venturini A, Kazdoba TM, Niu S, D'Arcangelo G. Reelin deficiency causes impaired dizocilpine efficacy in heterozygous reeler mice related to GABA turnover downregulation. Neuropharmacology. 2004;46(8):1070–81.

93. Badea A, Nicholls PJ, Johnson GA, Wetsel WC. Neuroanatomical phenotypes in the reeler mouse. Neuroimage. 2007;34(4):1363–74.

94. Chen Y, Beffert U, Ertunc M, Tang T-S, Kavalali ET, Bezprozvanny I, Herz J. Reelin modulates NMDA receptor activity in cortical neurons. J Neurosci. 2005;25(36):8209–16.

95. Chen Y, Beffert U, Ertunc M, Tang T-S, Kavalali ET, Bezprozvanny I, Herz J. Reelin modulates NMDA receptor activity in cortical neurons. J Neurosci. 2005;25(36):8209–16.

96. Herz J, Chen Y. Reelin, lipoprotein receptors and synaptic plasticity. Nat Rev Neurosci. 2006;7(11):850–9.
psychiatric diseases, drives postnatal development of the prefrontal cortex via GluN2B-NMDARs and the mTOR pathway. Mol Psychiatry. 2014;19(4):417–26.

107. Impagnatiello F, Guidotti AR, Pesold C, Dwivedi Y, Caruncho H, Pisu MG, Uzunov DP, Smalheiser NR, Davis JM, Pandey GN, Pappas GD, Tueting P, Sharma RP, Costa E. A decrease of reelin expression as a putative vulnerability factor in schizophrenia. Proc Natl Acad Sci USA. 1998;95(26):15718–23.

108. Guidotti A, Auta J, Davis JM, Di-Giorgi-Gerevini V, Dwivedi Y, Grayson DR, Impagnatiello F, Pandey G, Pesold C, Sharma R, Uzunov D, Costa E. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. Arch Gen Psychiatry. 2000;57(11):1061–9.

109. Eastwood SL, Harrison PJ. Intestinal white matter neurons express less reelin and are abnormally distributed in schizophrenia towards an integration of molecular and morphologic aspects of the neurodevelopmental hypothesis. Mol Psychiatry. 2003;8(9):769, 821–31.

110. Habel G, Schmitt A, Zink M, von Wilmsdorff M, Yeganeh-Doost P, Jatzko Klengel T, S, Schmitt A, Malchow B, Hasan A, Falkai P. The impact of environmental factors in severe psychiatric disorders. Neuropharmacology. 2014;80:115–32.

111. Provencal N, Binder EB. The effects of early life stress on the epigenome: from the womb to adulthood and even before. Exp Neurol. 2015;268:10–20.

112. Chen Y, Sharma RP, Costa RH, Costa E, Grayson DR. On the epigenetic regulation of the human reelin promoter. Nucleic Acids Res. 2002;30(13):2930–9.

113. Abdolmaleky HM, Cheng K, Russo A, Smith CL, Faraone SV, Wilcox M, Tamura Y, Kunugi H, Ohashi J, Hohjoh H. Epigenetic aberration of reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. Mol Psychiatry. 2007;12(4):385–97.

114. Billack B, Serio R, Silva I, Kinsley CH. Epigenetic changes brought about by perinatal stressors: a brief review of the literature. J Pharmacol Toxicol Methods. 2012;66(3):221–31.

115. Stevens HE, Su T, Yamaguchi Y, Vaccarino FM. Prenatal stress down-regulates Reelin expression by methylation of its promoter and induces adult behavioral impairments in rats. PLoS One. 2015;10(2):e0117680.

116. Moehringo F, Tueting P, Dalai I, Kaddou B, Grayson DR, Davis JM, Nicoletti F, Guidotti A. Epigenetic modifications of GABAergic interneurons are associated with the schizophrenia-like phenotype induced by prenatal stress in mice. Neuropharmacology. 2013;68:184–94.

117. Rodriguez JR, Lee RS, Cordner ZA, Ewald ER, Purcell RH, Moghadam AA, Tamashiro KL. Prenatal stress decreases Bdnf expression and increases methylation of Bdnf exon IV in rats. Epigenetics. 2014;9(3):437–47.