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► To cite this version:

Giulia Faini, Filippo del Bene, Shahad Albadri. Reelin functions beyond neuronal migration: from synaptogenesis to network activity modulation. *Current Opinion in Neurobiology*, 2021, 66, pp.135-143. 10.1016/j.conb.2020.10.009 . hal-03280328

HAL Id: hal-03280328

<https://hal.sorbonne-universite.fr/hal-03280328v1>

Submitted on 7 Jul 2021

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Reelin functions beyond neuronal migration: from synaptogenesis to network activity modulation

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Abstract

Reelin, a glycoprotein of the extracellular matrix, has been the focus of several studies over the years, mostly for its role in cell migration. Here we report the role of this molecule and of its downstream pathways in post-mitotic neurons and how they contribute to neural circuit assembly, refinement and function. Accumulating evidence has pointed at a major role for Reelin in axonal guidance, synaptogenesis and dendritic spine formation. In particular new evidence points at a direct role in axonal targeting and refinement at the target site. In addition, recent advances highlight new functions of Reelin in the modulation of synaptic activity, plasticity and behavior and it directly regulates GABA receptors expression and stability. We discuss these findings in the context of neurodevelopmental disorders.

Highlights

- Reelin signaling is required for axonal targeting and refinement at the target site.
- Reelin signaling regulates dendritogenesis and spine formation in mature neurons.
- Reelin modulates GABA receptors expression and stability, pre-and-post-synaptically.
- Reelin is important for hippocampal integrity, synaptic plasticity and behavior.

Introduction

Functional neural circuits arise through a series of sequential steps including neurogenesis, cell migration, axonal navigation and synaptogenesis. Perturbations of these events, which start during early embryogenesis, have been linked with the etiology of neurodevelopmental disorders. Reelin is an extracellular matrix (ECM) glycoprotein that acts as a key regulator of different steps of brain wiring. In the mammalian neo-cortex, Reelin regulates neuronal migration and layer formation, dendritic arborization and synaptogenesis¹. It regulates these distinct processes by acting through two receptors, ApoER2 and VLDLR, which are differentially expressed throughout the nervous system and display specific functions^{2,3}. Although it is well established that Reelin and its pathway play an essential role in neuronal migration, accumulating evidence support additional functions in multiple other distinct biological processes such as axon guidance, dendritogenesis and synaptogenesis. In addition, recent work shows that Reelin signaling and its interactors are essential for the modulation of synaptic function and network activity as well as synaptic plasticity. This short review will focus on these recent findings and highlight the importance of Reelin signaling in the regulation of learning, memory and behavior abilities in adulthood, all implicated in Reelin-associated neurological disorders.

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Reelin role in axon guidance

Until recently, the role of Reelin in axon guidance was dismissed as early reports failed to detect any involvement in this process⁴. However, accumulating evidence point at a role for Reelin in axon growth and synaptic targeting, essentially analyzing the role of this ECM protein in the entorhinal cortex and the visual system.

In the entorhino-hippocampal and commissural projections of *reeler* mice, several alterations including reduced axonal branching, decreased number of synapses, and abnormal topography of synapses were observed^{5,6}. Other defects such as the presence of misrouted fibers and the formation of ectopic termination patches were also reported. These early studies therefore hinted at new role for Reelin in axon guidance. However a parallel study rather suggested that the observed abnormalities of hippocampal cells projections onto the entorhinal cortex were instead primarily independent of the Reelin pathway⁴. Nevertheless, later work performed in *dab1*-deficient mice revealed a similar phenotype characterized by entorhinal afferents targeting inappropriate layers in the hippocampus, thus indicating that Reelin can in fact act as guidance factor via Dab1⁷. Moreover, by using combinations of entorhinal and hippocampal organotypic co-cultures from wild type and mutants, this same study showed that Dab1 is required for both ingrowing axons and for the target tissue to ensure a normal projection pattern⁷. In addition, exposure to Reelin of entorhinal and dorsal root ganglia axons lead to the reduced axonal growth in explant cultures⁷.

In the visual system, several studies have implicated Reelin and its pathway in the proper patterning of synaptic connectivity of the visual circuits. In 2001, Rice and colleagues showed the first evidence of an involvement of Reelin pathway in the regulation of the visual circuits anatomy and function by analyzing the effect of Reelin and Dab1a loss of functions^{8,9}. In this work, the authors observed alterations in the projection patterns of rod bipolar cells and All amacrine cells in the retinal inner plexiform layer of *reelin* and *dab1* mutant mice. Later studies performed in the *reeler* mouse and *reelin* mutant rat reported defects in the trajectories of retinal afferents to the *superior colliculus* but could not link these effects directly to the loss of Reelin function as the architecture of this tissue is itself affected in these animals^{10,11}. However a subsequent study reported misrouted axonal projections of intrinsically photosensitive retinal ganglion cells to their appropriate partners in the lateral geniculate nucleus, which rather project to other non-retino-recipient thalamic regions of the *reeler* and *dab1* mice brains¹². Unlike the previous observations made in the superior colliculus, these defects and the mis-targeting phenotype observed in these mutants are unlikely to arise from lamination defects or neural mis-positioning. More recently, a study in zebrafish showed that *reelin* is expressed as a gradient in the fish brain retino-recipient, the optic tectum, to differentiate the laminae where RGC axons project¹³. This work elucidated the role of Reelin in the proper establishment of synaptic stratification in the tectal neuropil, where RGCs axons and dendrites from periventricular neurons form both synaptic contacts. Through loss-of-function analysis of components of the Reelin pathway, the authors demonstrated that alterations of Reelin, Dab1a and Vldlr in zebrafish lead to the disruption of RGCs targeting in the optic tectum as well as the stratification of periventricular neurons in the tectal neuropil, both in an independent manner¹³ (Fig 1). Reelin signaling is required in this context in a cell autonomous manner to guide precise axonal lamination. The general similarity in the global organization of the teleost optic tectum and the mammalian cortex, where incoming axonal inputs contact apical dendrites or neuropils of recipient neurons, raises the intriguing possibility that Reelin acts, after migration, in the orchestrated wiring of layer 1 of the mammalian neocortex (Fig 2). In this structure, Reelin is produced by two neuronal types: the superficially located Cajal-Retzius cells that secrete Reelin throughout embryogenesis and early postnatal life in mouse and a subset of interneurons that start expressing Reelin from birth. In this brain region Reelin could act similarly to what observed in the zebrafish optic tectum to regulate the precise stratification of incoming thalamocortical axons that project into layer 1.

111
112 At the cell intrinsic level, other recent studies have also implicated Reelin in axonal wiring via
113 the identification of its crucial regulatory interaction with Cofilin^{14,15}, a central hub for axon
114 elongation and axonal growth cone steering¹⁶⁻¹⁸. In this context, Reelin's role in the stabilization
115 of the Actin cytoskeleton through Cofilin phosphorylation was shown to be an important
116 prerequisite for the stability of pyramidal cells leading process. Another recent study further
117 implicated Reelin-Cofilin interaction in cortical neuron dendritic growth dynamic and branching
118 by evaluating the effect of alcohol exposure on Reelin-Dab1 signaling¹⁹. Time-lapse imaging
119 revealed that cortical neurons exposed to ethanol displayed similar phenotypic defects as
120 observed in the case of Reelin-deficiency (through the blockade of the Reelin-Dab1 tyrosine
121 kinase signaling pathway). This phenotype is mediated by the sustained dephosphorylation
122 and activation of Cofilin.

123
124 Altogether these results indicate that Reelin signaling plays an important role both in the
125 targeting and refining of axonal connections at the target site.

126 127 128 **Reelin physiological function in synaptogenesis and dendritic spine formation**

129
130 During development, Reelin mediates its neuronal guidance action through the binding to the
131 lipoprotein receptors VLDLR and ApoER2 that results in cytoplasmic phosphorylation of Dab1
132 via the Src family of tyrosine kinases (reviewed in²⁰). Once neurons have reached their
133 destination, Reelin continues to modulate synaptic signaling pathways, regulates synaptic
134 plasticity as well as axonal and dendritic outgrowth. However, since these anatomical studies
135 were performed on mice in which Reelin signaling components were disrupted from the early
136 embryonic stages, it could not be determined if Reelin signaling regulates the formation, the
137 maturation and/or the maintenance of dendrites or spines in mature neurons.

138 To test these hypotheses, *in vitro* and *in vivo* analyses of juvenile and adult *reeler* mutant mice
139 revealed a reduction in dendritic tree complexity and dendritic spine density in neurons²¹⁻²³.
140 These studies together indicate that Reelin is important for circuit establishment, thus
141 impacting dendrite and spine development (reviewed in²⁴). Indeed, interference with Reelin
142 signaling was shown to strongly perturb dendritogenesis and reduce spine density in mature
143 hippocampal neurons. In particular, the expression of a mutant *ApoER2* form, which blocks its
144 interaction with postsynaptic density protein 95 (PSD-95) and hence cannot transduce Reelin
145 signaling, resulted in the reactivation of dendritogenesis in mature hippocampal neurons²⁵. By
146 immunofluorescence, the authors observed that Reelin-signaling impairment reduced synaptic
147 PSD-95 levels. Together these results indicate that Reelin/ApoER2/PSD-95 signaling is
148 important for neuronal structure maintenance in mature neurons.

149 A concurrent study demonstrated the impact of the Reelin/Dab1 pathway on the
150 synaptogenesis of newborn granule cells (GCs) in the young-adult mouse hippocampus²⁶. The
151 authors showed that neither *reelin* overexpression nor the inactivation of its intracellular
152 adapter Dab1 substantially altered dendritic spine numbers in these neurons. In contrast, by
153 3D-electron microscopy, they revealed that the mis-regulation of the Reelin/Dab1 pathway
154 leads to both transient and permanent changes in the types and morphology of dendritic
155 spines, mainly altering mushroom, filopodial, and branched GC spines. Furthermore, they
156 found that the Reelin/Dab1 pathway controls synaptic configuration of presynaptic boutons in
157 the dentate gyrus and that its deregulation leads to a substantial decrease in multi-synaptic
158 boutons innervation. In addition, in astroglia cells, Reelin/Dab1 pathway was shown to control
159 ensheathment of synapses²⁶. Other work also pointed at a possible role for Reelin in dendrites
160 and spine formation in the neocortex by comparing the subcellular localization of Reelin in the
161 cortex and hippocampus in wild-type mice and in heterozygous *Reeler* mice²⁷. Thus, the Reelin
162 pathway is a key regulator of adult-generated GC integration, by controlling dendritic spine
163 types and shapes, their synaptic innervation patterns, and glial ensheathment. These findings
164 reveal a new mode for reactivating dendritogenesis in neurological disorders where dendritic
165 arbor complexity is limited, such as in depression, Alzheimer's disease (AD), and stroke.

166 Interestingly it should be known that in recent years, mounting evidence has linked the Reelin
167 pathway to AD. For instance, Reelin levels are elevated in the brain of AD patients, but a lower
168 amount of intracellular ApoER2 fragments is detected, suggesting that Reelin signaling is
169 altered in AD^{28,29}. Furthermore, the amyloid- β peptide 1–42 alters Reelin glycosylation and
170 compromises its capacity to bind to ApoER2 and the γ -secretase component Presenilin-1 can
171 modulate Reelin signaling by directly processing ApoER2 intracellular domain³⁰⁻³².

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174 **Reelin modulates synaptic function and network activity**

175

176 Increasing evidence suggest that Reelin signaling is involved in the regulation of neuronal
177 activity and synaptic function, both at the level of single synapses and network activity.

178

179 At the glutamatergic synapses, it is well established that Reelin signaling mediates the
180 composition, the number and the trafficking of both AMPA and NMDA receptors (AMPA and
181 NMDAR respectively), both pre- and -post synaptically, thus playing an important role in the
182 maturation, organization, stabilization, functionality and plasticity of excitatory synapses³³⁻³⁵.
183 Although these roles for Reelin at the excitatory glutamatergic synapse have been extensively
184 identified, less attention has been devoted to shed light on the implication of the glycoprotein
185 in modulating GABAergic inhibitory synaptic activity. Recently, several studies have unraveled
186 a novel synaptic function of Reelin on GABA synapses and circuits. It was suggested for the
187 first time a potential interaction between Reelin and GABA receptors (GABA_AR and
188 GABA_BR)³⁶. In the prefrontal cortex of *reeler* haplo-insufficient mice, postsynaptic GABA-
189 currents into pyramidal neurons were measured and it was shown that GABAergic
190 transmission mediated by ionotropic GABA_AR is altered in absence of *reelin* and is associated
191 with a disruption of the Excitation/Inhibition (E/I) balance, which in turn affects information
192 processing. Another study demonstrated the link between Reelin and postsynaptic GABA_AR
193 by performing an accurate and high-resolution analysis of GABA_AR subunits expressed
194 specifically in different cell types including *reelin*-expressing neurons³⁷. This study indicated
195 that Reelin-positive cells, that are also grid cell candidates, express selectively the $\alpha 3$ subunit
196 of the GABA_AR and that this selective pattern is responsible for both tonic and phasic inhibition.
197 In addition to its involvement in inhibitory postsynaptic activity, a new role of Reelin in
198 modulating presynaptic GABA function has been identified³⁸. In this study, the conditional
199 absence of *reelin* (RelnKO) induced an alteration of spontaneous release in glutamatergic
200 neurons via pre-synaptic GABA_BRs, leading to hyper-excitability network. The main function of
201 metabotropic GABA_BR at presynaptic sites is to inhibit Ca²⁺ channels, which in turn blocks
202 neurotransmitter release. Accordingly, Ca²⁺ spiking activity in RelnKO were increased.
203 Interestingly, these results indicate that an absence of Reelin is responsible for a down-
204 regulation of GABA_BRs at the presynaptic cell surface, due to alteration of their
205 phosphorylation status as well as proteolytic receptor processing. This in turn leads to a
206 possible disruption of an interaction between the non-receptor tyrosine kinase
207 Src and the G-protein of the GABA_BR, G α_0 (Fig 3A). This is in agreement with a previous study
208 reporting that Reelin signaling induces a crosstalk between Src and G protein-coupled
209 receptors³⁹. Taken together, these findings argue for a novel function for Reelin signaling in
210 controlling presynaptic activity and excitability through the modulation of GABA_BRs expression
211 and their stability at the neuronal surface.

212

213 In addition to the modulation of presynaptic GABA transmission mentioned above, another
214 Reelin-mediated presynaptic mechanism has been reported in hippocampal slices *in vitro*,
215 where Reelin regulates presynaptic spontaneous neurotransmission. Here, Reelin signaling
216 through both ApoER2 and VLDLR receptors, present at the presynaptic membrane, induces
217 an elevation of intracellular Ca²⁺ which specifically increases the fusion of vesicles containing
218 vesicle-associated membrane protein 7 (VAMP7), and is associated with activity of the PI3
219 kinase^{33,34,40} (Fig 3B). Importantly, presynaptic neurotransmission regulation mediated by
220 VAMP7 has been shown to modulate synaptic strength and plasticity⁴¹.

221
222
223 Different studies investigated how Reelin controls and modulates brain network activity,
224 integrity and function. In particular, a recent study showed a link between hippocampal
225 oscillations, dopamine and Reelin⁴². This work revealed that dopamine influences oscillations
226 in the γ -band, and that their modulation, mediated by NMDAR–PI3K signaling, is altered in
227 *reelin* haplo-insufficient mice. These results as such highlight an important implication of Reelin
228 in Schizophrenia where γ oscillations and NMDA transmission are affected¹. Finally, a role for
229 Reelin signaling in promoting network integrity and activity, especially in the hippocampus was
230 described^{43,44}. *NDEL1* mutant mice, a gene encoding for a cytoskeleton protein, showed Reelin
231 depletion together with a loss of both excitatory and inhibitory synapses, leading to marked
232 alteration in integrity and connectivity within the CA1 area of the hippocampus. Importantly, a
233 single application of Reelin in CA1 improved ultra-structural, cellular, morphological, and
234 anatomical defects as well as spatial learning and memory.

235
236 Altogether these recent findings illustrate that Reelin signaling is crucial for the proper E/I
237 balance of brain networks, acting both on glutamatergic and GABAergic neurotransmission,
238 and at both pre-and-post synaptic sites. Importantly, an imbalance between the E/I ratio leads
239 to neurological disorders such as epilepsy, autism, schizophrenia and AD, pathologies where
240 Reelin has been shown to be affected¹. In addition, these results highlight the role of Reelin in
241 controlling and regulating the integrity of neuronal networks, especially in a highly plastic region
242 like the hippocampus.

243 244 245 **Reelin modulates synaptic plasticity, learning and behavior**

246
247 A variety of studies demonstrated the importance of Reelin signaling in synaptic plasticity,
248 memory formation and cognitive function. Indeed, it is well documented that Reelin regulates
249 the insertion of AMPAR and the phosphorylation of NMDAR, resulting in enhancement of long-
250 term potentiation in the cortex and hippocampus (reviewed in^{33,45}). Nevertheless, synaptic
251 plasticity also involves the interaction between Reelin and other partners as described below.

252
253 Recently, an interesting component of Reelin signaling involved in the modulation of
254 hippocampal synaptic plasticity was identified⁴⁶. The multi-scaffold protein Intersectin-1
255 (ITSN1) was indeed shown to be directly associated with elements of the Reelin canonical
256 pathway, and mice lacking ITSN1 revealed alterations of NMDA-long-term potentiation in
257 response to Reelin stimulation. Molecularly, it has been suggested that ITSN1 acts as a
258 molecular bridge that facilitates the interaction between VLDLR and its intracellular adaptor
259 Dab1, favoring its phosphorylation and downstream signaling, with the potential help of other
260 factors such as Ephrin B, known to be associated with both ITSN1 and Reelin signaling (Fig
261 3C). In accordance with these results, ITSN1 was shown to be involved in hippocampal-
262 dependent functions such as learning and memory⁴⁷.

263
264 It was recently shown that Notch1, a transmembrane receptor and substrate of the γ -
265 secretase, contributes to Reelin-mediated synaptic potentiation via a non-canonical pathway
266 which stimulates Erk1/2 activity and CREB-dependent transcription⁴⁸. In the CA region of the
267 hippocampus, Notch1 functionally interacts with ApoER2 and NMDAR at the postsynaptic
268 sites, and the targeted loss of *Notch1* resulted in an impairment of Reelin signaling. To date, it
269 is not clear how the two functional complexes (Notch1/ApoER2/Dab1 and Notch1/NMDAR)
270 are connected or if they are part of the same synaptic super-complex. Furthermore, Reelin
271 bath application in these mutants failed to promote long-term potentiation, in contrast to wild-
272 type animals. These results highlight a crosstalk of Notch1 and Reelin pathways in regulating
273 mechanisms involved in synaptic plasticity and memory formation (Fig 3D).

274

275 Components of the extracellular matrix, and in particular Chondroitine-and-Heparan-sulfate
276 proteoglycans (CSPG and HSPG respectively), are also known to be involved in brain stability
277 and plasticity^{49,50}. Specialized extracellular matrix structures called Perineuronal Nets (PNNs),
278 which enwrap *parvalbumin*-expressing interneurons, play a crucial role in visual plasticity. As
279 such, a disruption of PNNs reactivates visual plasticity^{51,52}. Importantly, Reelin interacts and
280 co-localizes with both CSPGs and HSPGs, as shown in two recent papers^{13,53}. Along this line,
281 an interesting recent study demonstrated a new role for Reelin in modulating cortical
282 plasticity⁵⁴. The lack of *reelin* prolonged experience-dependent plasticity in the visual cortex
283 into adulthood, similarly to the effect of PNN enzymatic degradation on visual plasticity. This
284 work, once again, puts Reelin at the center of brain plasticity modulation in the postnatal brain.
285

286 Finally, accordingly with previous and more recent studies^{55,56-58}, the contribution of Reelin
287 signaling to the genetic and behavioral expression of learning and memory has been
288 confirmed^{59,60}. Indeed, an interesting work using epigenomic analysis revealed that the binding
289 of Reelin to its receptor results in the expressions of immediate early genes involved in
290 synaptic plasticity, and that these epigenomic changes possibly involve nuclear translocation
291 of the intracellular domain of ApoER2⁶¹.
292

293 Altogether, these results indicate that Reelin signaling regulates synaptic plasticity, learning
294 and memory - mainly in the adult hippocampus - and that alterations of Reelin pathways can
295 drastically affect these neural processes and behavior, leading to irreversible neurological
296 diseases.
297

298 **Funding**

300 This work has received funding from French National Research Agency (ANR-18-CE16-0017-
301 01), the Fondation Simone and Cino del Duca and UNADEV/AVIESAN (UNADEV-19UU51-
302 DEL BENE). The Del Bene laboratory is supported by the Programme Investissements
303 d'Avenir IHU FOReSIGHT (ANR-18-IAHU-01).
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306 **Conflict of interest statement**

307 Declarations of interest: none
308

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349 important chemico-attractant molecule for the proper laminar targeting of RGC axons in
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388 vitro in hippocampal neurons. The overexpression of a dominant-negative form of
389 ApoER2, unable to interact with PSD95, led to increased dendritogenesis and reduced
390 spine density in mature hippocampal neurons. This study therefore shows an important
391 role for Reelin/ApoER2/PSD95 signaling in dendritogenesis and network maintenance.
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450 of both excitatory and inhibitory neurons, as shown by electrophysiological recordings,
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461 paper identified Intersectin 1, a multi-scaffold protein involved in Down Syndrome, to be
462 associated with reelin signaling via its interaction with ApoER2 receptor. Importantly, the
463 protein regulates neuronal migration and synaptic plasticity in the hippocampus, as shown
464 by deficits of these aspects in mice knocked-out for Intersectin 1. Molecularly, the protein
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466 results indicate that a manipulation of reelin signaling, may be helpful for the treatment of
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 508 dependent LRP8 signaling. These LRN enhancers were found present in the promoter
 509 region of genes implicated in synaptic plasticity and were shown to be activated by
 510 Reelin that mediates the delivery of the LRP8 intracellular domain which take parts in
 511 the activation of these enhancers.
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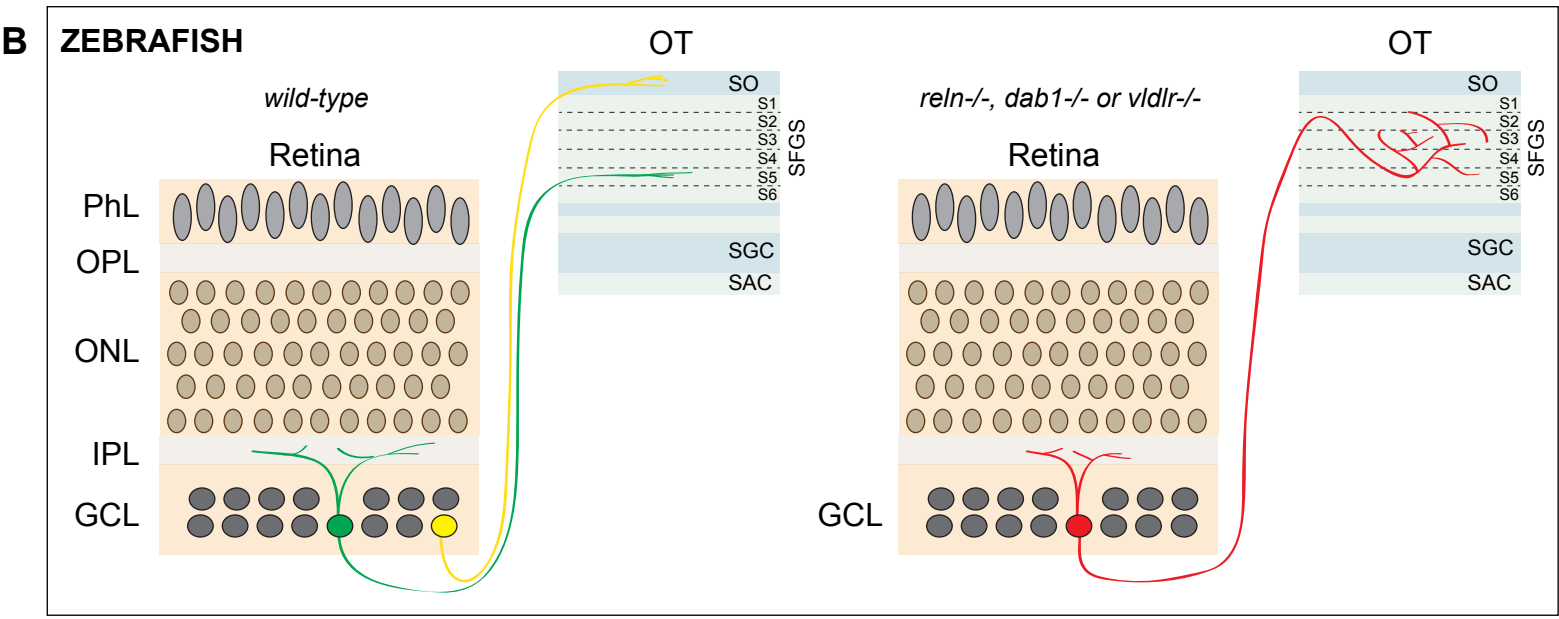
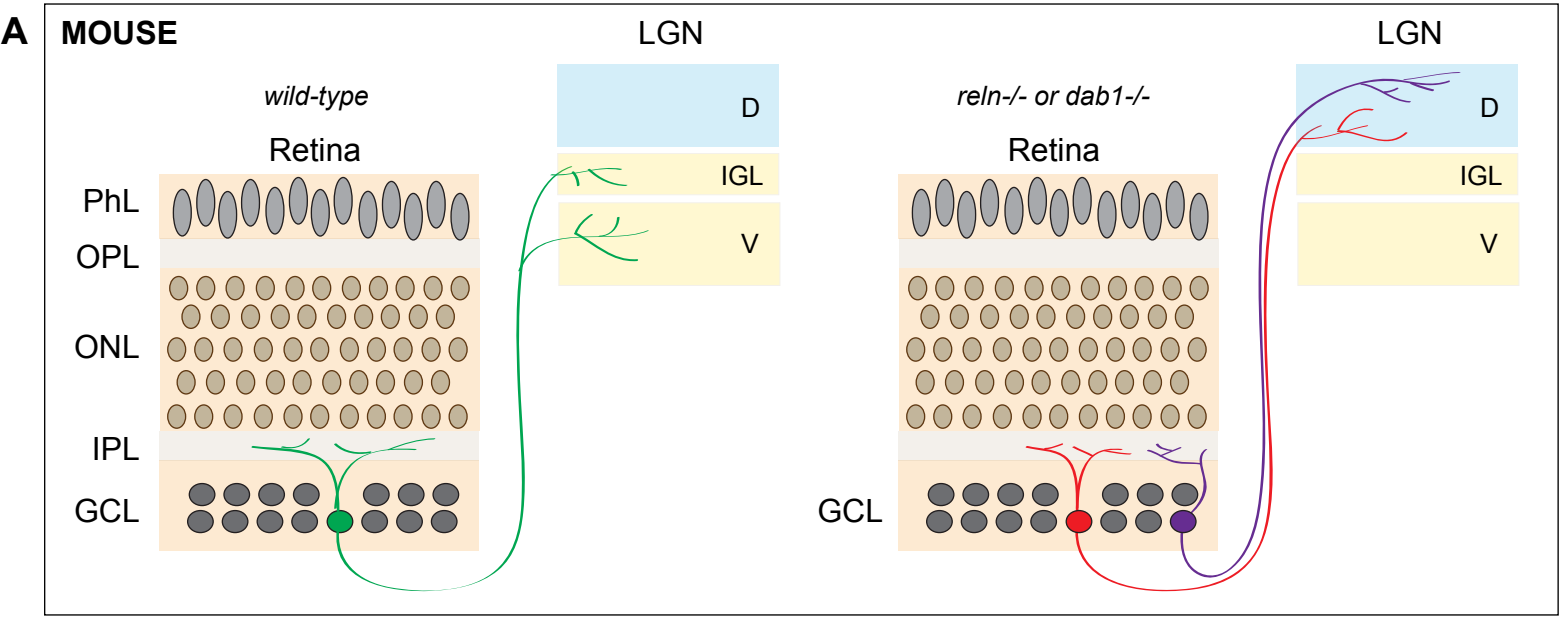
514 **FIGURE CAPTIONS**

515
 516 **Fig 1. Reelin and its pathways are required for the proper patterning of synaptic**
 517 **connectivity of retinal ganglion cell axons. (A)** In mouse, Reelin and Dab1 are required for
 518 the proper retinogeniculate targeting of RGC axons. In wild-type animals, RGC axons target
 519 two retino-recipient nuclei of the mouse cortex: the lateral geniculate nucleus (LGN) subdivided
 520 in the dorso (D) and ventro (V) LGN and the intergeniculate leaflet (IGL). In the *reelin* mutant
 521 (*reln^{-/-}*) and *dab1^{-/-}* mutants, reduced pattern of innervation as well as mistargeting of the vLGN
 522 and IGL to the dLGN were observed. **(B)** In zebrafish, alterations of Reelin, Dab1a and Vldlr
 523 lead to the disruption of RGCs targeting in the optic tectum that cross over several sublaminae
 524 of the neuropil unlike in the wild-type condition where RGC axons only project to a single
 525 lamina. PhL, photoreceptor layer; OPL, outer plexiform layer; ONL, outer nuclear layer; IPL,
 526 inner plexiform layer; GCL, ganglion cell layer.
 527

528 **Fig 2. Schematic representations of the anatomical architectures of the zebrafish optic**
 529 **tectum (A) and the mouse upper cortical layers, highlighting their global organization**
 530 **similarities (B).** In blue (SIN and CR neurons) and orange (PVN and interneurons) are
 531 represented *reelin*-expressing cells in both structures. Note how in both cases RGC and
 532 cortical axons project to the most superficial layers in defined synaptic laminae. These
 533 similarities in architecture and organization raise the possibility that, like in the optic tectum,
 534 Reelin could orchestrated the proper wiring of layer 1 of the mammalian neocortex. SO,
 535 *stratum opticum*; SIN, superficial inhibitory neurons; RGC, retinal ganglion cell; PVN,
 536 periventricular neuron; CR, Cajal-Retzius cells; SPV, *stratum periventriculare*; SFGS, *stratum*
 537 *fibrosum et griseum superficiale*; SAC, *stratum album centrale*; SGC, *stratum griseum*
 538 *centrale*.
 539

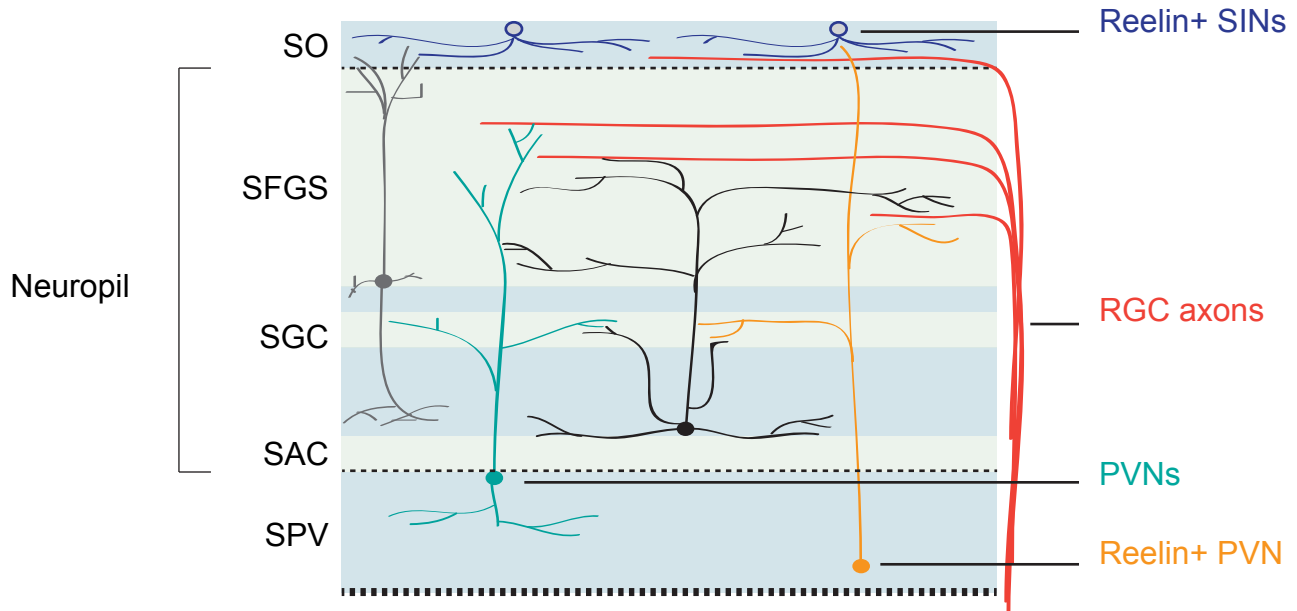
540 **Fig 3. Pre and post -synaptic roles of Reelin in controlling network excitability, synaptic**
 541 **plasticity, learning and memory. (A)** In wild-type animals, Reelin controls network excitability
 542 via the modulation of presynaptic GABA_BR: the binding of Reelin to both receptors (1) and
 543 Dab1 phosphorylation (2) activate members of the Src family tyrosine kinases (SFK, 3) which
 544 interact with the alpha subunit of the G-protein (G α) of GABA_BR (4). This induces the
 545 maintenance of GABA_BR at the cell surface, whose role is to inhibit NMDAR and thus Ca²⁺
 546 influx (5), resulting in a decrease of excitability. In conditional mutants for *reelin* (Reln^{CKO}), non-
 547 activated SFK may disrupt the interaction between SFK and G α (1) and AMPK phosphorylates

548 GABA_BR at the Serine site S783 (2). This induces the degradation of GABA_BR at the cell
549 surface (3) which results in the dis-inhibition of NMDAR and thus in an increase in Ca²⁺ influx
550 (4) and neurotransmitter release. **(B)** Reelin enhances presynaptic spontaneous
551 neurotransmission through the mobilization of VAMP7: Reelin binds to ApoER2 (1) leading to
552 the phosphorylation of Dab1 (2) and activation of PI3K (3) which in turn increases presynaptic
553 Ca²⁺ influx (4). This triggers the fusion of VAMP7-containing synaptic vesicles. **(C)** Reelin
554 signaling regulates synaptic plasticity in the hippocampus: here, the large scaffold protein
555 Intersectin 1 (ITSN1) acts as a molecular bridge that enhances the interaction between Vldlr
556 and Dab1 (1) after Reelin binding (2), favoring Dab1 phosphorylation and downstream
557 signaling (3, 4) which result in an increase in long-term potentiation (LTP, 5). **(D)** Crosstalk
558 between Reelin and Notch1 pathways to regulate synaptic plasticity and memory formation: at
559 the postsynaptic site, Notch1 functionally interacts with both ApoER2/Dab1 (1) and NMDAR
560 (2). These complexes activate downstream effectors (3 and 4), which induce the activation of
561 CREB signaling (5), essential for the establishment of memories.



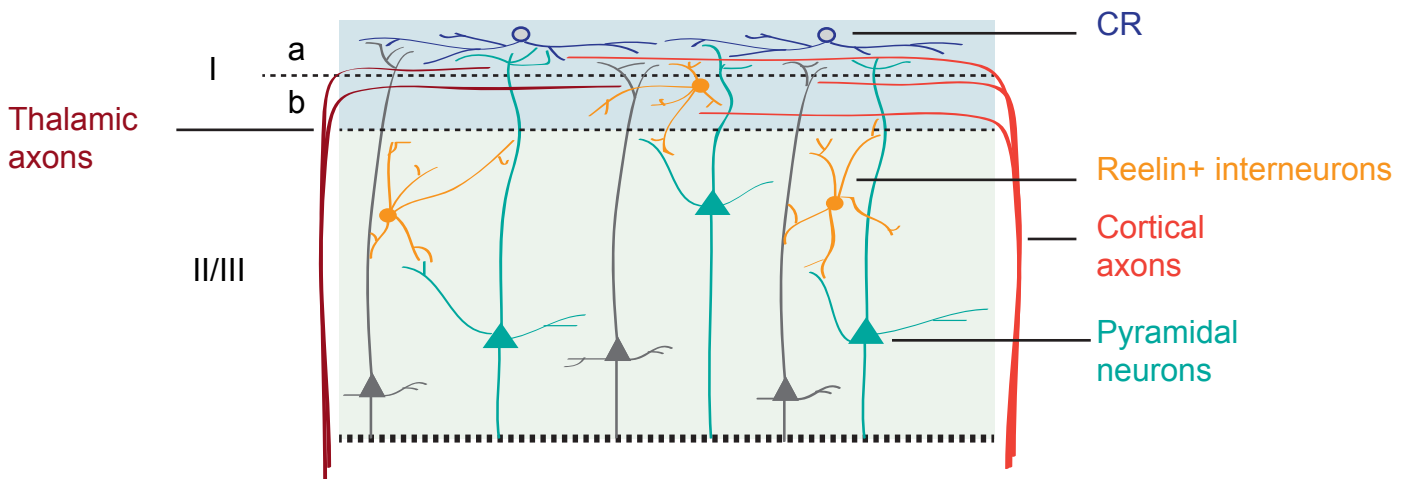
A

ZEBRAFISH OPTIC TECTUM

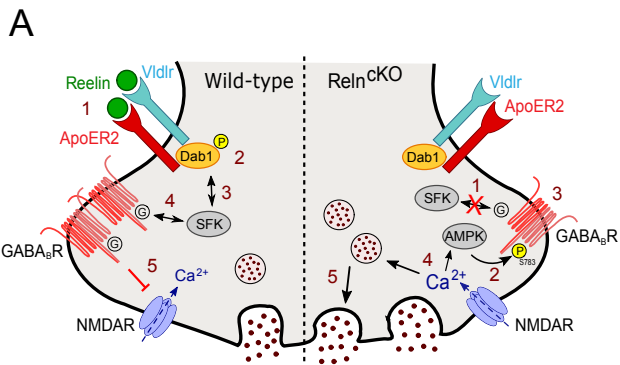


B

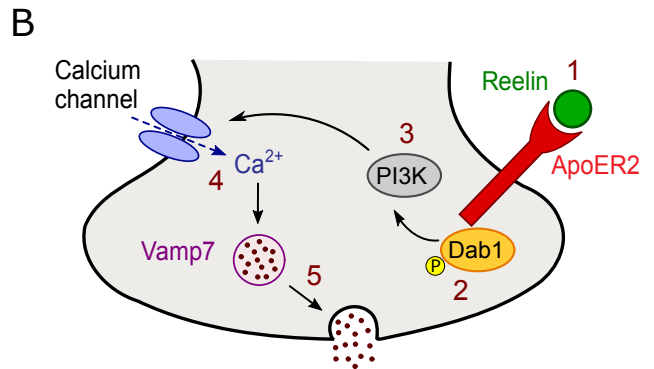
MOUSE UPPER CORTICAL LAYERS



PRESYNAPTIC FUNCTIONS

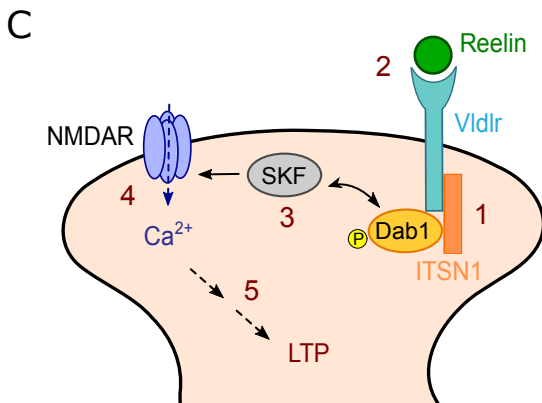


Regulation of excitability via the stabilization of GABA_BR at the membrane



Regulation of neurotransmitter release

POSTSYNAPTIC FUNCTIONS



Regulation of synaptic plasticity, learning and memory

