Eph receptors in the adult brain
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The Eph receptors are a large family of receptor tyrosine kinases with important roles in the establishment of neuronal and vascular networks during embryonic development. The functions of Eph receptors in the adult brain have only recently been investigated, and the results are forcing us to amend the conventional view that these molecules function predominantly in a developmental context. This review summarizes this rapidly expanding new area of research, which has shown that the Eph receptors regulate the structure and physiological function of excitatory synapses through multiple mechanisms, and might thus play a significant role in higher brain functions.

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Abbreviations
Arp2/3 actin-related protein 2/3
LTP long-term potentiation
NMMA N-methyl-D-aspartate
N-WASP neuronal Wiskott-Aldrich syndrome protein
Pak p21 activated kinase
PDZ postsynaptic density, discs-large, zona occludens-1
SH2 Src homology 2

Introduction
Mammals have fourteen Eph receptor genes (nine EphA and five EphB genes) [1]. These Eph receptors function in concert with their membrane-anchored ligands, the ephrins. The five mammalian A-ephrins are attached to the cell surface through a glycosylphosphatidylinositol (GPI) linkage and preferentially bind EphA receptors (Figure 1a). The three B-ephrins are transmembrane proteins and preferentially bind EphB receptors. Eph receptor–ephrin binding results in the assembly of multimeric clusters that bridge juxtaposed cell surfaces and mediate cell–cell adhesion (Figure 1b). The activation of Eph signaling pathways, however, can lead to the separation of the contacting cell surfaces, thus converting the adhesion into repulsion and eventually terminating the signal. Two mechanisms that allow Eph signaling to overcome adhesive effects are cleavage of ephrins by metalloproteases and removal of Eph–ephrin complexes from the cell surface through a bidirectional endocytolytic process [2,3,4,5].

Another notable feature of Eph–ephrin signaling is that it is bidirectional, therefore allowing reciprocal communication between cells (Figure 1b). Clustered Eph receptors autophosphorylate on numerous cytoplasmic tyrosines [6,7]. Phosphorylation stabilizes the active conformation of the kinase domain and recruits Src homology 2 (SH2) domain-containing proteins. Other Eph receptor-binding proteins include nucleotide exchange factors and postsynaptic density, discs-large, zona occludens-1 (PDZ) domain-containing proteins. The transmembrane B-ephrins also bind PDZ domain proteins and are phosphorylated by Src family kinases [7,8]. Tyrosine phosphorylation of ephrin-B ligands enables binding of at least one SH2 domain protein, the adaptor growth factor receptor-bound protein 4 (Grb4) [9]. Src kinases also participate in ephrin-A signaling, presumably through interactions occurring within lipid rafts [10]. Comprehensive reviews on Eph–ephrin signaling by Murai and Pasquale, and Kullander and Klein present a more complete picture [1,11].

Recent progress in the field has shown that Eph receptors and ephrins (collectively designated here as ‘Eph proteins’) affect multiple aspects of adult brain function. Although the exact signaling mechanisms that underlie most Eph activities in the adult brain remain to be elucidated, the basic features of Eph signaling outlined above, which were established through biochemical and cell culture experiments, are probably preserved in the adult brain. Here, we review the newly discovered roles of Eph proteins in the adult brain. In contrast to the large number of Eph receptor and ephrin genes in mammals, lower animals such as Caenorhabditis elegans and Drosophila have only one Eph receptor and few ephrins. It is tempting to speculate that the remarkable expansion of Eph genes during evolution might have occurred to keep pace with the increasing complexity of the brain [12].

Eph receptors and ephrins in the adult brain
Eph proteins are expressed at highest levels in the embryonic nervous system, where their striking spatial gradients of expression underlie a role as topographic labels in neural development [13,14]. However, many Eph proteins maintain a respectable presence in the adult
A recent survey of Eph expression in the adult human brain using real time reverse transcriptase-polymerase chain reaction (RT-PCR) found greatest expression of the EphA4, EphA6, EphA7, EphB4, and EphB6 receptors (EphA5 and EphA10 were not examined) and the ephrin-A5 and ephrin-B2 ligands [15]. Most other Eph receptors and ephrins were also detected at substantial levels, in agreement with previous studies focusing on specific Eph genes [16,17,18**,**19,20]. Eph expression occurs predominantly in regions where neuronal connections continue to form and undergo remodeling in the adult, such as the olfactory system, hippocampus, cortex, and cerebellum. Interestingly, both Eph receptors and ephrins are typically expressed in neurons, although some ephrins are also expressed in glial cells [18**,19]. The expression patterns are complex, and multiple Eph receptors and ephrins can be expressed in the same neuronal population, such as hippocampal CA1 pyramidal neurons [17,19].

Subcellular localization studies have revealed that EphA4, EphA7, EphB2, EphB3, and ephrin-B2 are in the postsynaptic region of central synapses (Figure 2; [21,22,23**]), a localization consistent with their binding to synaptic PDZ domain proteins [22,24–26]. The limited data available suggest that Eph receptors and ephrins can be sorted to different membrane compartments of the same neuron. For example, in cultured mouse hippocampal neurons B-ephrins are detected in different dendritic clusters than EphB receptors, in addition to being on some axons [27], and the Drosophila Eph receptor is on the axons of developing interneurons, whereas the ephrin is on the cell bodies [28]. Another intriguing issue is whether or not Eph localization depends on the type of synapse, because recent evidence suggests that B-ephrins are presynaptic in area CA3 of the hippocampus but postsynaptic in area CA1 (Figure 2; [23**,**29,30]). Further studies are needed to establish whether or not local mRNA translation contributes to the subcellular localization of Eph proteins in mature neurons [31], whether or not splice forms of Eph proteins have differential localization that correlates with their different structure and function [32,33], and whether or not synaptic transmission might regulate Eph expression [30].
These studies will elucidate how Eph proteins regulate synaptic architecture and plasticity by mediating neuron–neuron and neuron–glia cell communication.

**EphB receptors regulate dendritic spine development**

The synapse is one of the most interesting sites of cell–cell communication. It consists of the presynaptic and postsynaptic terminals, which in many synapses are surrounded by glial processes [34]. Cell contact-dependent Eph signaling plays an important part in the formation, maintenance, and physiological function of synapses. Both Eph receptors and ephrins have been localized to lipid rafts (Figure 1; [10,25,35]), which are compartments of the plasma membrane that function as signaling platforms and are crucially important for the organization of synaptic junctions [36]. Ephrin-B binding to EphB receptors induces the formation of large raft-like patches on the neuronal cell surface that contain N-methyl-D-aspartate (NMDA) neurotransmitter receptors and other synaptic components, which suggests a role for EphB–ephrin-B complexes in the assembly of postsynaptic specializations [37].

The synaptic roles of EphB receptors and their signaling pathways have been most extensively studied in the context of dendritic spine morphogenesis. Dendritic spines are numerous tiny protrusions present on the surface of dendrites, and are the sites that receive most excitatory inputs [38,39]. Mature spines typically have a narrow stalk and a spherical head that contains the postsynaptic density, where ion channels and postsynaptic signaling proteins are assembled in multimolecular complexes [26,40]. During early postnatal development, spines replace the elongated filopodial-like protrusions that are present in immature neurons, which might help to establish synaptic contacts [41]. In the adult brain synaptic connections are plastic and spines continue to form and dynamically change shape, for example in response to synaptic activity [39,42]. Spine geometry in turn affects calcium compartmentalization and synaptic transmission [39].

The functional role of Eph receptors in spine morphogenesis was first demonstrated by transfecting kinase inactive EphB2 into cultured hippocampal neurons [43]. Dendritic protrusions remain filopodial in the presence of this dominant negative form of EphB2, demonstrating that EphB receptor signaling pathways are required for spine morphogenesis. A similar phenotype was subsequently observed in triple EphB1, EphB2, and EphB3 knockout mice, indicating that multiple EphB receptors cooperate to promote spine morphogenesis [27*]. In addition, activation of EphB receptors by exogenous ligand (immunoglobulin Fc fusion proteins of ephrin-B1 or ephrin-B2, designated here ephrin-B1 Fc and ephrin-B2 Fc) induces the rapid formation of dendritic protrusions with enlarged heads in immature hippocampal and cortical neurons [27*,44**]. Thus, EphB kinase activity is both necessary and sufficient for spine morphogenesis. The reduced spine sizes and densities recently observed in vivo in double and triple EphB knockout mice confirm the physiological role of EphB receptors in regulating spine development and structure, particularly in area CA3 of the hippocampus [27*,29]. Unfortunately, there is essentially no information with
regard to which ephrins regulate spine morphogenesis through the EphB receptors. This is an important issue that urgently needs to be addressed. Ephrin-B3 is a good candidate ligand, at least for the EphB receptors expressed in the spines of CA3 pyramidal neurons, because it is expressed in the granule neurons of the dentate gyrus, which project to CA3 neurons.

The EphB receptors probably regulate the cytoskeleton of dendritic spines, which is composed predominantly of actin filaments [38,39]. Indeed, filamentous actin is absent from dendritic protrusions lacking EphB receptors [27]. An emerging view is that EphB receptors physically associate with guanine nucleotide exchange factors, thereby regulating the activity of Rho GTPases. Several of these GTPases are indeed known to affect different aspects of spine development and structure (Van Aelst and Cline, this issue). At least two pathways link EphB receptors to the Rho family in spine morphogenesis, one involving Cdc42 [45] and the other involving Rac1 (Figure 3a; [44]). In the first pathway, EphB2 associates with intersectin, an exchange factor for Cdc42 predominantly expressed in neurons, and promotes its exchange activity in concert with the adaptor protein neuronal Wiskott-Aldrich syndrome protein (N-WASP). Activated Cdc42 and N-WASP together activate the actin-related protein 2/3 (Arp2/3) complex, and Arp2/3-mediated polymerization of branched actin filaments is likely to contribute to the expansion of the dendritic spine head. Consistent with a functional role of this pathway, ephrin-B treatment of hippocampal neurons induces Cdc42 activation with a time course similar to that of EphB2 activation, and dominant negative forms of Cdc42, intersectin, and N-WASP inhibit spine morphogenesis. The second pathway involves Kalirin, an exchange factor for Rac whose two isoforms, Kalirin-5 and Kalirin-7, contain a PDZ-binding motif and are found in dendritic spines. Activation of EphB receptors by ephrin-B1 Fc induces clustering, tyrosine phosphorylation, and synaptic translocation of Kalirin. These events trigger the localization to spines of the activated p21 activated kinase (Pak) serine-threonine kinase, a Rac1 effector that promotes actin cytoskeleton rearrangement. In support of a functional role of this pathway, transfection of dominant negative forms of Kalirin, Rac1, and the Pak inhibitory domain all prevent spine morphogenesis induced by ephrin-B1.

The requirement for EphB kinase activity in spine morphogenesis suggests an involvement of EphB-dependent phosphorylation of target proteins. Although the role of Kalirin phosphorylation has not been determined, tyrosine phosphorylation of syndecan-2 downstream of EphB receptors has been implicated in the clustering of this transmembrane proteoglycan, which is a crucial step for syndecan-2 to induce dendritic spine morphogenesis [43]. Other downstream targets of Eph receptors, such as Src and Abl family kinases [46,47,48,49], might also contribute to Eph-mediated actin reorganization and changes in dendritic spine morphology given the synaptic localization of these kinases and their ability to regulate actin cytoskeleton dynamics [50,51]. Therefore, a balance of

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**Figure 3**

Eph receptor signaling pathways at synapses. (a) EphB2 affects dendritic spine structure by signaling to Rho GTPases and the actin cytoskeleton. (b) EphB2 enhances NMDA-dependent calcium fluxes through the cytoplasmic tyrosine kinase Src, which phosphorylates the NMDA receptor. Tyrosine phosphorylation sites are represented by yellow circles.
multiple EphB signaling pathways is likely to regulate spine development.

**EphA neuronal–glial communication**

The EphA receptors participate in cell–cell communication in the extrasynaptic regions of the dendritic spine, where spines are in close proximity with astrocytes \[18\]. At least one ephrin, ephrin-A3, is expressed by astrocytes in the adult mouse hippocampus, whereas the EphA4 receptor, which is activated by ephrin-A3, is highly expressed on the dendritic spines of hippocampal pyramidal neurons. What could be the function of extrasynaptic activation of EphA4? Dendritic spines in hippocampal slices stimulated with ephrin-A3 Fc become shorter and some even collapse. This effect is reminiscent of the retraction and collapse induced by ephrins in EphA receptor-positive growth cones \[52\]. Such repulsive signals might also regulate dendritic spine morphology in the adult nervous system and, therefore, synaptic plasticity. Indeed, new imaging technologies have revealed that dendritic spines undergo remodeling both in vivo in the mouse brain and in organotypic cultures \[53,54\]. A putative hypothesis for this remodeling is that transient contacts with the surrounding astrocytic processes limit spine extension, thus allowing dynamic changes in morphology while maintaining overall spine organization.

Consistent with a restrictive effect of astrocytic processes on spine movement, dendritic spines with limited cell contacts are more motile \[53\]. Other observations support a physiological role for EphA4 signaling in regulating dendritic spine structure. First, inhibiting binding of EphA4 to endogenous ephrin-A3 with a soluble form of the EphA4 extracellular domain (EphA4 Fc) in hippocampal slices induces the formation of irregular protrusions that distort spine shape. Second, EphA4 knockout mice or mice expressing kinase inactive EphA4 following transfection have dendritic spines that are irregularly shaped and longer than normal. This evidence suggests that EphA4 and ephrin-A3 mediate a form of communication between glial cells and neurons that enables spine remodeling and synaptic plasticity (such as that occurring during learning) while maintaining the overall organization of neuronal circuits necessary to retain memories.

An interesting hypothesis is that neuroglial crosstalk through EphA4 and ephrin-A3 might also mediate the complementary changes in the volume of astrocytes and dendritic spines that have been observed during the estrous cycle and in brain pathologies characterized by gliosis \[55\]. Further studies are needed, however, to investigate whether or not ephrin-A3 knockout mice show defects in dendritic spine morphology similar to those of the EphA4 knockout mice. Furthermore, it will be interesting to determine whether or not a signaling pathway involving activation of Rho and its effectors, possibly through an exchange factor such as Ephexin, mediates repulsion in dendritic spines as it does in growth cones \[56,57\]. It is also unknown whether or not the communication is bi-directional and ephrin-A3 initiates signals that affect the properties of astrocytes that come in contact with EphA4-positive dendrites.

**Eph receptors and ephrins regulate synaptic plasticity through both forward and reverse signaling**

Eph receptors and ephrins appear to have different localization and take diverse roles in different synaptic contexts (Figure 2). Furthermore, both forward and reverse mechanisms have been proposed to affect distinct types of synaptic plasticity. An influence of Eph receptors on synaptic plasticity and higher brain function was first discovered for EphA receptors. It was shown that application of EphA5 Fc in mouse hippocampal slices impairs activity-induced changes in synaptic responsiveness, such as long-term potentiation (LTP) in Schaffer collateral-CA1 neuron synapses \[58\]. This form of LTP is believed to depend mainly on postsynaptic mechanisms. By contrast, ephrin-A5 Fc induces an LTP-like enhancement of basal synaptic transmission. Furthermore, in the mouse hippocampus, infusion of EphA5 Fc impairs performance in behavioral paradigms, whereas infusion of ephrin-A5 Fc enhances performance and improves anesthesia-induced memory loss \[59,60\]. These effects on synaptic plasticity and memory could depend on EphA-mediated spine morphological changes or other as yet undiscovered pathways that are influenced in opposite ways by EphA5 Fc (which is both an EphA inhibitor and an ephrin-A activator) and ephrin-A5 Fc (which is both an EphA activator and an ephrin-A inhibitor).

As for EphB receptors, EphB2 knockout mice show deficits in NMDA-dependent synaptic plasticity in the hippocampus, such as LTP and long-term depression (LTD), and might also have minor defects in spatial memory \[17,30\]. Interestingly, these abnormalities in synaptic plasticity and behavior were not detected when EphB2 was replaced by a truncated form that lacked most of the cytoplasmic domain \[17\]. Thus, the kinase domain of EphB2 is dispensable for its function in NMDA-dependent synaptic plasticity as it is for its association with the NR1 subunit of the NMDA receptor \[17,37\]. The absence of EphB2 could lead to NMDA receptor destabilization at synapses and explain the observed reduction in synaptic NMDA receptors \[30\] that perhaps contributes to the defects in synaptic function of EphB2 knockout mice.

EphB proteins also regulate NMDA-independent forms of synaptic plasticity through a distinct molecular mechanism \[29\]. Mossy fiber-CA3 LTP, which is believed to be dependent on presynaptic changes in glutamate release probability, is reduced by inhibiting the cytoplasmic interaction between the postsynaptic EphB2 and the synaptic PDZ glutamate receptor-interacting protein.
(GRIP), which also binds z-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors. Furthermore, mossy fiber LTP is also impaired by extracellular application of ephrin-B1 Fc to inhibit EphB interactions with B-ephrins that are presumably localized presynaptically (Figure 2a). Conversely, extracellular application of EphB2 Fc, which activates B-ephrins, increases basal excitatory transmission and occludes subsequent LTP. These data suggest a retrograde trans-synaptic effect of EphB receptors that requires EphB cytoplasmic interactions in the postsynaptic terminal and affects ephrin-B presynaptic function.

There is now evidence that the Eph–ephrin system also operates in an inverted manner [23**]. In CA1 synapses, B-ephrins are localized postsynaptically (Figure 2b) and the absence of ephrin-B2 or ephrin-B3 causes strong defects in LTP and LTD, another form of NMDA-dependent synaptic plasticity. In contrast to the defects in EphB2 knockout mice, which are mild and affect predominantly the late phases of LTP [17], ephrin-B knockout mice have strong defects in both the early and the late phases of LTP. In addition, the phenotype is present even when the B-ephrin gene is conditionally inactivated two weeks postnatally, which indicates that the synaptic defect is unlikely to be developmental. A candidate receptor that might activate reverse signaling through postsynaptic B-ephrins is EphA4 (Figure 2; [23**]), because this receptor can bind ephrin-B2 and ephrin-B3 and mice lacking EphA4 have defects in synaptic plasticity that closely resemble those of the ephrin-B knockout mice. Furthermore, the defects are independent of the EphA4 cytoplasmic domain.

Eph proteins have also been implicated in other forms of long-term plasticity in the adult brain, such as sprouting and reorganization of hippocampal projections following high levels of neuronal activation [61]. Intraventricular infusion of EphA5 Fc and ephrin-A5 Fc proteins modulates the development of behavioral seizures induced by kindling, an experimental model of epilepsy, as well as the extent of kindling-induced mossy fiber sprouting. Additionally, upregulated Eph proteins might be involved in modulating sprouting following deafferentiation or injury in the hippocampus [20,62].

EphB–ephrin-B signaling also regulates synaptic efficacy in dorsal horn neurons that receive nociceptor afferents in the spinal cord [49*]. Similarities between LTP and central sensitization of nociceptive neurons in the dorsal horn [63] suggest that the Eph–ephrin system might operate in various types of synaptic plasticity, not limited to those in the hippocampus.

Signaling pathways initiated by both synaptic and extrasynaptic Eph receptors might modulate synaptic transmission and plasticity. For example, Src activated downstream of EphB2 phosphorylates the NMDA receptor, thus potentiating NMDA receptor-dependent calcium currents and transcription factor activation (Figure 3b; [48*] and Nong, Huang and Salter this issue). It will be interesting to determine if Eph receptors also inhibit extrasynaptic NMDA receptors because, remarkably, extrasynaptic NMDA currents have opposite consequences to synaptic currents [64]. In addition, it is not known if the Eph receptors — similar to other receptor tyrosine kinases [65] — might trigger calcium release from intracellular stores, thus enhancing NMDA receptor effects on cytoplasmic calcium levels. Eph receptors might also influence protein trafficking and synaptic ion currents [66,67] through bidirectional internalization of Eph–ephrin complexes, which occurs together with patches of their surrounding plasma membrane and might therefore trigger internalization of other co-localized proteins, such as ion channels [3*,4*]. Future studies will reveal whether Eph receptors could influence synaptic transmission by regulating additional signaling molecules in spines, such as integrins [68,69], the Ras-MAP (mitogen activated protein) kinase pathway ([17,70,71] and Sweatt, this issue), the Jak-Stat (Janus kinase-signal transducer and activator of transcription) pathway [72,73], and other pathways leading to transcriptional regulation [48*]. Regardless of their synaptic or extrasynaptic activity and whether or not they affect spine morphology and ion currents, the Eph receptors ultimately modulate synaptic transmission and plasticity.

Conclusions and open questions
Eph receptors and ephrins have emerged as important regulators of structural and electrophysiological properties of synapses as well as excitatory synapse formation in the adult brain. To date, the impact of Eph gene mutations on mental function is unknown. Eph dysfunction might contribute to a variety of neuropsychiatric and mental disorders, such as mental retardation and autism, which are characterized by abnormal dendritic spines [74], and schizophrenia, which is associated with decreased NMDA receptor function as well as abnormal spines [75,76]. Another area of interest is whether or not Eph receptors regulate neurogenesis in the adult brain. There is some evidence that EphB/ephrin-B function is required to limit the proliferative potential of adult brain stem cells [77]. Thus, decreased Eph activity might contribute to the development of brain tumors, which usually originate from stem cells in the subventricular zone. Alternatively, future studies might reveal how to harness Eph function in order to promote neurogenesis for the treatment of depression [78] and for the replacement of damaged neurons in the adult and aging brain.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
•• of outstanding interest


This study and those of Marston et al. [4] and Mann et al. [5] demonstrate that EphB–ephrin-B complexes undergo bidirectional internalization upon contact between cells expressing EphB receptors and cells expressing ephrin-B ligands. This endocytotic-like process is similar to phagocytosis in that plasma membrane fragments from the adjacent cell are also internalized. The internalization requires the Eph and ephrin cytoplasmic domains, suggesting that intracellular signaling (which might involve cytoskeletal assembly) is involved. Endocytosis might be one of the mechanisms by which cells disengage after contact-dependent signal transduction.

4. Marston DJ, Dickinson S, Nobes CD: Rac-dependent

See the annotation to Zimmer et al. [3].


18. Muri1 KK, Nguyen LN, Irie F, Yamaguchi Y, Pasquale EB: Control

This study identifies a new form of neuroglial crosstalk involving the EphA4 receptor, which is enriched on dendritic spines of hippocampal pyramidal neurons, and its ligand ephrin-A3, which is localized on astrocytic processes that envelop the spines. Perturbation of EphA4-ephrin-A3 signaling in hippocampal slices or in genetically modified mice causes changes in dendritic spine morphology and disrupts spine organization.


The authors find that B-ephrins are localized postsynaptically in Schaffer collateral–CA1 synapses and are required for synaptic plasticity. This study also shows that the EphA4 receptor is involved in synaptic plasticity, but independently of its cytoplasmic domain. This suggests a model where the EphA4 extracellular domain, perhaps in concert with the EphB2 extracellular domain [17.30], modulates NMDA-receptor-dependent synaptic plasticity by stimulating signaling of postsynaptic B-ephrins.


27. Henkemeyer M, Iktis OS, Ngo M, Hickmott PW, Ethell JM: Multiple EphB receptor tyrosine kinases shape dendritic spines in the hippocampus. J Cell Biol 2003, 163:1313-1326. By performing a thorough morphological analysis of dendritic spines in double and triple EphB knockout mice, the authors demonstrate that EphB1, EphB2, and EphB3 are involved in dendritic spine morphogenesis and synapse formation to varying degrees. This study also confirms the physiological significance of the prior in vitro findings on the crucial importance of EphB receptors in spine morphogenesis [43.44].


Eph receptors in the adult brain Yamaguchi and Pasquale


34. Haydon PG: Glia: listening and talking to the synapse. 


This study identifies a signaling pathway downstream of EphB receptors that promotes dendritic spine morphogenesis. EphB receptors and Arp2/3-mediated actin polymerization are functionally linked by the Cdc42 exchange factor intersectin, Cdc42, and the adaptor N-WASP. See Penzes et al. [44] for another downstream pathway that links EphB2 to spine morphogenesis.


This study provides evidence that EphB receptors enhance NMDA receptor-dependent signaling pathways. This occurs at least in part through a mechanism involving Src-mediated tyrosine phosphorylation of the NMDA receptor.


This study supports an in vivo role for EphB-ephrin-B interactions in modulating an NMDA receptor-dependent form of synaptic plasticity in the spinal cord that contributes to chronic pain following nerve or tissue damage. The authors also provide in vivo evidence for a role of Src downstream of EphB receptor activation.


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