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Synaptic plasticity and memory: new insights from hippocampal left-right asymmetries

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Abstract

All synapses are not the same. They differ in their morphology, molecular constituents and malleability. A striking left-right asymmetry in the distribution of different types of synapse was recently uncovered at the CA3-CA1 projection in the mouse hippocampus, whereby afferents from the CA3 in the left hemisphere innervate small, highly plastic synapses on the apical dendrites of CA1 pyramidal neurons while those originating from the right CA3 target larger, more stable synapses. Activity-dependent modification of these synapses is thought to participate in circuit formation and remodelling during development; in adulthood, further plastic changes may support memory encoding. Therefore, exploiting the CA3-CA1 asymmetry provides a promising opportunity to investigate the roles that different types of synapse play in these fundamental properties of the CNS. Here we describe the discovery of these segregated synaptic populations in the mouse hippocampus, and discuss what we have already learnt about synaptic plasticity from this asymmetric arrangement. We then propose models for how the asymmetry could be generated during development, and how the adult hippocampus might utilise these distinct populations of synapses differentially during learning and memory. Finally, we outline the potential implications of this left-right asymmetry for human hippocampal function, as well as dysfunction in memory disorders such as Alzheimer's disease.

1 Introduction

Synaptic plasticity dominates contemporary models of the cellular and molecular mechanisms of memory, and their alteration during disease. The synaptic plasticity and memory hypothesis states that "activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation and is both necessary and sufficient for the encoding and trace storage of the type of memory mediated by the brain area in which it is observed" (Martin and others 2000). Of particular interest is long-term potentiation (LTP), an activity-dependent, input specific enhancement in synapse strength that can last several months. LTP was first discovered at glutamatergic inputs into the hippocampus (Bliss and Lomo 1973), a structure involved in the processing and initial storage of spatial and episodic memories (Andersen and others 2007). Substantial correlative evidence points to a critical role for LTP in mediating the changes that support hippocampus-dependent learning and memory (Neves and others 2008; Takeuchi and others 2014). The mechanisms regulating the induction, expression and long-term maintenance of LTP have therefore attracted much attention.

One of the best-studied examples of synaptic plasticity is LTP of the fast, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)-mediated component of the excitatory response at synapses between CA3 and CA1 pyramidal neurons (CA3-CA1 synapses; Figure 1), which is the final part of the classical hippocampal trisynaptic circuit (Box 1). Here, strong activation of *N*-methyl-D-aspartate receptors (NMDARs) by stimulation patterns that cause simultaneous glutamate release and postsynaptic depolarization results in a persistent increase in the number of AMPARs at the postsynaptic elements, organised as tiny dendritic protrusions known as spines (Huganir and Nicoll 2013; Granger and Nicoll 2014). Parallel increases in spine volume and the area of the post-synaptic density (PSD) also occur (Meyer and others 2014). At the core of these coordinated post-synaptic changes is the calcium-calmodulin dependent protein kinase II (CaMKII) (Lisman and others 2012). Presynaptic increases in release probability have also been reported under some strong induction protocols (MacDougall and Fine 2014; Padamsey and Emptage 2014), although their general importance for LTP at this synapse has been questioned (Granger and Nicoll 2014).

Electrophysiological and imaging approaches in rodents have revealed a great degree of heterogeneity in the spine structure, spine size and AMPA and NMDA receptor composition at glutamatergic synapses, even within the same neuron type and developmental stage (Sobczyk and others 2005; Tønnesen and others 2014). Such heterogeneity correlates tightly with the capacity to induce LTP (e.g. Matsuzaki and others 2004; Lee and others 2010). Intriguingly,

recent studies in mice have revealed that inputs arriving from the left CA3 tend to innervate small spines while those coming from the right CA3 have a preference for large, mushroom-shaped spines (Kawakami and others 2003; Wu and others 2005; Shinohara and others 2008). Furthermore, there are differences in the molecular composition of these spine types, with a higher density of GluN2B subunits in postsynaptic spines receiving left CA3 input (Kawakami and others 2003; Shinohara and others 2008). This asymmetry has a clear functional correlate; left inputs show robust LTP whilst right inputs do not (Kohl and others 2011). Here we review recent advances in our understanding of LTP, and demonstrate how the left-right asymmetry in synaptic function could serve as a window into understanding the mechanisms that regulate the capacity for plasticity at synapses. We then discuss the implications of these insights for hippocampal function and dysfunction.

2 LTP capacity: insights from left-right asymmetry

A major aspect of the heterogeneity at the mouse CA3-CA1 synapse is the subunit composition of the two main classes of glutamatergic receptors: AMPARs and NMDARs. AMPARs are tetrameric complexes composed of GluA1-4 subunits (Figure 1; Dingledine and others 1999). NMDARs are also tetramers, composed of two compulsory GluN1 subunits and two subunits from the GluN2(A-D) and/or GluN3(A/B) subfamilies (Dingledine and others 1999). At adult CA3-CA1 synapses, GluN2A- and GluN2B-containing NMDARs predominate (Figure 1; Tovar and others 2013). Subunit composition is functionally significant as it influences the kinetics, desensitization and molecular interactions of receptors. For example, the presence of the GluN2B subunit confers higher calcium permeability, slower kinetics and lower open channel probability on the NMDAR, and allows selective binding with intracellular partners (Yashiro and Philpot 2008; Hansen and others 2014). In addition, the synaptic context in which receptors find themselves is critical. Spine structure (including head size, neck length and width, PSD area and level of actin cytoskeleton branching) and composition are gaining renewed attention as key regulators of spine function and plasticity.

Recent studies have revealed an unexpected relationship between the molecular composition and morphology of spines at apical CA3-CA1 synapses and the hemispheric origin of their presynaptic input (Figure 2). In mice with a transected ventral hippocampal commissure (Box 1), immunogold electron microscopy (EM) revealed that isolated ipsilateral (Schaffer collateral; SC) inputs from the left CA3 onto apical CA1 synapses exhibited a 50% higher GluN2B, and a 35% lower GluA1, density at the PSD relative to their right counterparts (Shinohara and others 2008). Injection of lentivirus expressing GFP into left or right CA3, combined with EM to colocalize GFP-expressing axons with CA1

spines, further revealed that right SC and commissural (contralateral) CA3-CA1 inputs exhibited on average 67% larger spine volumes, 36% larger PSD areas and a 94% increase in the proportion of mushroom shaped spines compared to their left counterparts (Shinohara and others 2008; Figure 2). These synaptic asymmetries did not extend to CA3 inputs to GABAergic interneurons (Wu and others 2005), although as yet undetected, other hemispheric differences may still be present in the interneuron population.

To investigate the functional consequences of the left-right asymmetry at the CA3-CA1 excitatory synapse, Kohl and others used an adeno-associated viral vector to express the blue light-activated cation channel channelrhodopsin2 (ChR2; Box 2) in either left or right mouse hippocampal CA3 pyramidal neurons. Optogenetically-evoked NMDAR-dependent excitatory postsynaptic currents (EPSCs) in CA1 pyramidal neurons were 60% more sensitive to GluN2B-blockade by 0.5 mM Ro 25-6981, a highly GluN2B-selective allosteric antagonist, at left compared to right apical CA3 inputs (Kohl and others 2011), confirming earlier findings at isolated SC synapses (Kawakami and others 2003). The authors used optogenetic stimulation to assess the plastic capacity of left versus right apical CA3-CA1 synapses following LTP induction; surprisingly, left SC and commissural inputs expressed robust LTP while the right inputs did not (Kohl and others 2011). A key question is, therefore, what, if any, is the relationship between the molecular and ultrastructural differences at the two inputs and the dramatic difference in their capacity for LTP? The answers to this question may shed light on recent important mechanistic advances in our understanding of LTP.

LTP at CA3-CA1 synapses involves coordinated changes in the size of the of the fast AMPAR component and the structure, size and composition of the spine and PSD (Huganir and Nicoll 2013; Meyer and others 2014). The dodecameric serine/threonine protein kinase CaMKII lies at the core of the mechanisms that mediate these changes (Hell 2014). Calcium influx through NMDARs causes binding of the calcium-calmodulin complex to the regulatory segment of the CaMKII enzyme, inducing a conformational change that opens up the CaMKII dodecamer and allows autophosphorylation of neighbouring CaMKII monomers on threonine 286. Autophosphorylation at T286 results in an autonomously active enzyme, that is independent of further calcium-calmodulin binding and hence can persist in activity beyond the initial activation of NMDARs (Hell 2014). Activated CaMKII enhances AMPAR conductance via phosphorylating serine 831 on the GluA1 subunit (Kristensen and others 2011). Furthermore, CaMKII phosphorylates the transmembrane AMPA regulatory proteins (TARPs) γ2 (stargazin) and possibly γ8, which enhances their interaction with PSD-95 and thereby traps more AMPAR-TARP complexes at the PSD (Opazo and others 2010). In addition, CaMKII participates in activity-dependent increases in spine size (Matsuzaki and others 2004; Pi and others

2010a), possibly through regulating the dynamics of the actin cytoskeleton (Okamoto and others 2009). CaMKII is, therefore, a central organizer of activity-dependent increases in synaptic strength, involved in mediating most, if not all, of the coordinated changes underlying LTP at CA3-CA1 synapses.

A plethora of theoretical considerations and experimental findings suggest that GluN2B-rich spines have a greater capacity for LTP than those with lower GluN2B density (Yashiro and Philpot 2008; Shipton and Paulsen 2013). Crucially, the C-terminal tail of the GluN2B subunit has high affinity binding sites that are critical to anchor autonomously active CaMKII at the PSD (Strack and Colbran 1998; Figure 1). Activity-dependent recruitment of CaMKII to spines and the PSD is lost in GluN2B(L1298A/R1300Q) knock-in mice in which CaMKII binding to GluN2B is eliminated, with a concomitant 50% reduction in LTP (Halt and others 2012). This recruitment involves two processes: an initial rapid (milliseconds to seconds) movement of CaMKII from its F-actin-anchoring sites in the spine to the PSD, followed by a slower (1-2 minutes) redistribution of CaMKII from the dendritic shaft to the spine head (Shen and Meyer 1999; Shen and others 2000; Otmakhov and others 2004). Anchoring at the PSD serves to bring CaMKII close to the source of calcium that is needed for its activation, and also increases its proximity to its substrates at the PSD. For example, NMDA-induced serine 831 phosphorylation of GluA1 subunits is lost in GluN2B(L1298A/R1300Q) knock-in mice (Halt and others 2012). Furthermore, interaction with the GluN2B C-terminal tail enhances the affinity of CaMKII for Ca^{2+}/CaM (so called calcium/calmodulin trapping), prolongs the autonomously active T286 autophosphorylated state (by protecting CaMKII from the inhibitory T305/T306 phosphorylation and T286 dephosphorylation) and, additionally, supports T286-phosphorylation-independent autonomous CaMKII activity (Bayer and others 2001). Thus, CaMKII binding to the GluN2B C-terminal tail has the dual effect of recruiting CaMKII to the PSD following activity-induced calcium influx, giving it better access to its substrates and interacting partners, and altering its enzymatic activity, both enhancing and prolonging it.

Given its role in CaMKII localization and activity, the increased GluN2B density at left compared to right synapses might explain the dramatic left-right difference in LTP (Kohl and others 2011). However, the differences are likely to extend beyond the induction of LTP. The increased spine volume, PSD area, and GluA1 density at the PSD in right compared to left CA3 inputs to the CA1 are all indicative of a close-to-saturation state of synapses that are innervated by the right CA3 (Shinohara and others 2008; 2009). This would, in turn, predict a reduced capacity for LTP expression at right inputs. Indeed, large mushroom-shaped spines of rat CA1 pyramidal neurons show only a transient enlargement following repetitive glutamate uncaging; in contrast, this uncaging protocol causes a stable increase in

spine size at small thin spines in the same neurons, indicative of stable LTP expression (Matsuzaki and others 2004). Such a reduced capacity for LTP expression at large spines would be necessary to prevent run-away potentiation at individual synapses (Abraham 2008).

The co-existence of reduced LTP induction capacity, in the form of lower GluN2B density, with a reduced capacity for LTP expression, due to spines being large and potentially saturated, suggests that coordinated changes occur at individual synapses that converge to limit the capacity for further increases in synaptic strength. Indeed, EM studies have revealed a significant negative correlation between GluN2B density and spine size at mouse CA1 spines (Shinohara and others 2008; 2009). A similar negative correlation was seen in rat CA1 pyramidal neurons between the spine size, as measured using 2-photon imaging, and the sensitivity of glutamate uncaging-evoked NMDA EPSCs to Ro 25-6981 (Sobczyk and others 2005). Furthermore, whilst spine volume, PSD area and AMPAR density are generally correlated, recent evidence suggests that their regulation is dissociable. Super-resolution 2-photon and EM imaging of potentiated synapses demonstrated that the increase in PSD area was temporally and mechanistically uncoupled from spine enlargement, with the former occurring 30 minutes later and uniquely requiring protein synthesis (Bosch and others 2014). Moreover, the phosphomimetic CaMKII mutant T286D, which has additionally been made catalytically dead, increases spine size without affecting synapse strength, and the T286D/T305D/T306D triple mutation causes increased spine size but actually decreases synaptic strength (Pi and others 2010a; Pi and others 2010b). These findings indicate that the mechanisms regulating spine volume, PSD area and AMPAR density are, in principle, dissociable. Thus, the coordination of these distinct mechanisms, in addition to those mediating the difference in GluN2B density, must have occurred during development in order to produce the correlated pattern of changes in right compared to left spines. These coordinated changes converge on optimizing the capacity for both LTP induction and expression at left compared to right CA3 inputs to CA1.

3 Development of asymmetry in LTP capacity

The differences between CA1 spines innervated by the left or right CA3 suggest that a tightly controlled developmental programme is responsible for the generation and maintenance of the asymmetry. A key element in the symmetry-breaking process early in development involves the motor protein left-right dynein (Lrd; Nonaka and others 1998). *Inversus viscerum* (*IV*) mice, which are homozygous for a spontaneous mutation in *Lrd* gene, exhibit a loss of hippocampal asymmetry (Kawakami 2008). Instead, isolated SC synapses from both left and right CA3 at CA1 apical

dendrites exhibit a similarly low sensitivity of NMDAR EPSCs to Ro 25-6981 indicative of a 'right' phenotype (Kawakami and others 2008). This effect suggests that the 'right' phenotype of apical CA3-CA1 spines with a lower density of GluN2B is the default phenotype and that symmetry breaking is necessary to generate the GluN2B-rich 'left' phenotype.

Forebrain synapses begin their lives as small, GluN2B-rich 'silent' synapses, which have little or no GluA1 (Yashiro and Philpot 2008; Hanse and others 2013). As synapses mature, spine volumes and PSD areas increase, AMPARs are inserted, and the GluN2A/GluN2B ratio increases by an activity dependent process (Yashiro and Philpot 2008; Hanse and others 2013). CA1 spines transform from being predominantly populated by GluN1/GluN2B diheteromers in juvenile animals to containing a mixture of GluN1/GluN2A and GluN1/GluN2B diheteromers and GluN1/GluN2A/GluN2B triheteromers in adults (Yashiro and Philpot 2008; Tovar and others 2013). Various mechanisms contribute to this developmental change, which include an increased transcription/translation and forward trafficking of GluN2A subunits, decreased retention of GluN2B-containing NMDARs at the PSD, and increased GluN2B endocytosis (Yashiro and Philpot 2008). Left apical CA3-CA1 inputs must therefore be at least partially protected from this developmental 'default' increase in GluN2A/GluN2B ratio, and concomitant changes in spine size, PSD area and GluA1-content, and ultimately in LTP capacity. Consequently, they are effectively trapped in an immature plastic state. A key prediction is, therefore, that in early postnatal development, both left and right CA3-CA1 synapses will have a similar synaptic composition and capacity for LTP, with subsequent gradual loss of LTP capacity preferentially at right inputs as the synaptic composition matures into its adult state.

Based on these considerations, at least two potential models for left-right asymmetry at apical CA3-CA1 synapses can be proposed (Figure 3). In one model, a global increase in the GluN2A/GluN2B ratio occurs due to increased transcription, translation and/or net forward trafficking of GluN2A relative to GluN2B. However, left-innervated spines are partially protected from this via as yet unidentified presynaptic factors, perhaps trans-synaptic proteins that influence post-synaptic signalling. Potential candidates include the type I family of major histocompatibility complex (MHC) proteins, since left-right asymmetry at CA3-CA1 synapses was abolished by knockout of the gene encoding the critical β2-microglobulin (β2m) light chain, a protein which binds to MHC and alters its function (Kawahara and others 2013). These MHC type 1 proteins are expressed in hippocampal pyramidal cells (Kawahara and others 2013) and may exhibit differential targeting/function in left versus right axons and, hence, form part of the mechanism that regulates CA3-CA1 asymmetry (Figure 3). An alternative model involves input-specific, activity-dependent changes that occur in

postnatal development, perhaps due to differences in the intensity, patterns and/or timing of activity at right relative to left CA3 afferents (Figure 3). Such activity differences could arise within the hippocampus very early in development due to left-right differences in the developmental time-windows for neurogenesis and/or synaptogenesis. Slightly later in development, left-right differences in the expression of ion channels that determine cell excitability, or asymmetric regulation by interneuron populations, could generate hemispheric differences in CA3 activity levels. Asymmetric activity could also be inherited from asymmetries in upstream brain regions; for example, hemispheric differences in sensory processing have been reported (e.g. Kishimoto and others 2013; Rybalko and others 2006; 2010), as well as left-right differences in metabolism in the lateral entorhinal cortex (Khan and others 2014). It is well established that neuronal activity can regulate the capacity for synaptic plasticity, a phenomenon termed metaplasticity (Abraham 2008), such as the induction of NMDAR-dependent LTP reducing the capacity for subsequent LTP (Huang and others 1992; Roth-Alpermann and others 2006). Indeed, LTP increases the GluN2A/GluN2B ratio at single synapses, while silencing synapses decreases GluN2A/GluN2B ratio and concomitantly enhances the subsequent induction of LTP (Lee and others 2010). In addition, LTP could occlude subsequent potentiation as increases in spine size, PSD area and AMPAR numbers bring synapses closer to saturation (Roth-Alpermann and others 2006). It is important to note that the two models discussed above are not mutually exclusive. Indeed, MHC type I proteins have been implicated in activity-dependent synapse maturation and circuit remodelling during development, as well as in adult plasticity (Huh 2000), so their involvement does not provide evidence that a solely genetically predetermined mechanism generates asymmetry. The use of pharmacological manipulations and/or optogenetic silencing (Box 2) to inhibit LTP induction during postnatal development would allow insights into the possible role of differential plasticity-inducing activity at left and right CA3-CA1 afferents in generating or maintaining the asymmetry.

4 Implications for hippocampus-dependent learning and memory

The hippocampus has a critical involvement in episodic memories in humans (Burgess and others 2002) and spatial memories in both humans and rodents (O'Keefe and Nadel 1978; Morris and others 1982; Burgess and others 2002). Some pyramidal cells in the rodent dorsal hippocampus fire at higher rates at distinct locations within an environment (O'Keefe and Dostrovsky 1971). These are known as ‘place cells’ and receive spatial information from the medial entorhinal cortex and integrate it with item information from the lateral entorhinal cortex (Hargreaves and others 2005). Small changes in an environment, or in the task an animal has to perform, can induce rate remapping of place cells, where their firing rate changes but their spatial selectivity remains unaltered (Leutgeb and others 2005; Leutgeb

and others 2007). This remapping is thought to encode the association between a particular location and salient non-spatial information, such as aversive or rewarding items or events. Indeed, in rats that learnt a place-object association task, it was found that place cells were converted into conjunctive place-item cells, which encoded both the location and identity of an item (Komorowski and others 2009). Furthermore, the proportion of these newly emerging place-item cells correlated with each rat's performance on the task and the item-specificity of these cells was completely lost in error trials (Komorowski and others 2009). Thus conjunctive place-item cells could represent a neural correlate for associative learning.

The sites and cellular mechanisms of associative learning are currently debated, but one attractive candidate is LTP at the CA3-CA1 synapse (Martin and others 2000; Neves and others 2008; Takeuchi and others 2014, but see Bannerman and others 2014). Pharmacological blockade of NMDARs and genetic knockout of the *Grin1* gene encoding the essential GluN1 subunit in the CA1 subregion impair learning of the hippocampus-dependent Morris water maze (MWM) task, in which an animal uses extra-maze cues to navigate to a hidden escape platform (Morris and others 1986; Tsien and others 1996, however see Bannerman and others 2012 and Taylor and others 2013). A key prediction is, therefore, that the plastic left CA3-CA1 synapses are capable of storing learnt associations through LTP whilst the less plastic right CA3-CA1 synapses are not. In support of this hypothesis, *IV* mice, in which all CA3-CA1 synapses exhibit a 'right' phenotype regardless of their hemispheric origin, are impaired in hippocampus-dependent learning tasks (Kawakami and others 2008; Goto and others 2010). However, mice with long-term genetic mutations may have additional changes that could account for such behavioural impairments, especially if such manipulations are not regionally-specific.

If retaining synaptic plasticity into adulthood is necessary for associative modifications, what possible advantage could the presence of the less plastic right CA3-CA1 synapses have? One possibility is highlighted by the recent finding of preconfigured, sequentially active CA1 cell assemblies in the hippocampus of experimentally naïve animals that fire during sleep and rest, and which subsequently become selected to represent a particular trajectory after a spatial learning event (Dragoi and Tonegawa 2013; 2014). The apparent lack of recurrent connectivity in the adult CA1 (Amaral and Lavenex 2007; Box1) suggests that pre-configured CA1 cell assemblies may be the result of biased inputs from the strongly recurrently connected CA3 pyramidal neurons. Biases in hippocampal connectivity exist as early as the onset of synaptogenesis, since CA3 and CA1 cells that underwent neurogenesis and synaptogenesis within a similar time-window form significantly more synapses with each other than those selected at random (Deguchi and

others 2011). Such biased connectivity could be at least partially responsible for forming the pre-configured cell assemblies, with further synaptic plasticity during postnatal development likely strengthening intra-assembly connectivity. An important advantage of such a mechanism is that it could support the one-trial formation of spatial representations in the hippocampus, since external information from a single run through an environment would only need to select a pre-configured cell assembly rather than instruct the formation of *de novo* cell assemblies on an unbiased background of connectivity. Indeed, CA3 output is important for rapid, one-trial learning and CA1 place cell specificity in novel environments (Nakashiba and others 2008). The stable right CA3-CA1 synapses could therefore reflect connectivity of pre-configured cell assemblies, which may have emerged during postnatal development and then became selected to generate spatial representations of different environments. This would provide a neural substrate for spatial representations on which to incorporate specific associations more rapidly. Such associative learning could be achieved by LTP at a relatively small number of synapses formed by left CA3 inputs onto CA1 cells that are part of these pre-configured cell assemblies (Figure 3). Learning may alternatively, though not mutually exclusively, involve the recruitment of new place cells to more accurately represent a particularly salient location within an environment (Figure 3). Indeed, after rats learnt a variant of the MWM, it was found that there was almost double the number of place cells representing the location of the escape platform compared to other, equivalently sized, regions of the maze (Hollup and others 2001). Therefore, another role of plasticity at left CA3-CA1 synapses could be to mediate the recruitment of these new place cells. For example, it is known that artificial depolarisation can cause place field activity to rapidly emerge in otherwise silent, apparently spatially untuned CA1 cells for the duration of the manipulation (Lee and others 2012); synaptic plasticity could cause a more permanent emergence of place field activity. Overall, such an anatomical dissociation between spatial and associative learning processes would provide an efficient division of labor between the two hemispheres, while retaining the ability to integrate both functions at the level of convergent left and right CA3 inputs onto the CA1.

The established left-right asymmetry of plasticity in the mouse hippocampus, combined with the models that we propose for how such asymmetry may translate to function, would predict distinct behavioural consequences of left and right-sided unilateral manipulations. A study in which transection of commissural fibres and unilateral visual deprivation forced animals to use only one hemisphere, suggested that mice using their right hippocampus showed better accuracy of spatial memory, especially when the task demands were increased (Shinohara and others 2012a). However, in a unilateral hippocampal lesion study, where possible sensory asymmetries could not influence results, no clear difference between left and right was observed (Gerlai and others 2002). More work has been done using

unilateral manipulations in rats, although we do not yet know whether an equivalent synaptic asymmetry is present in this species. In any case, these data are inconclusive regarding a possible functional lateralization; whilst some studies observed no effects of unilateral hippocampal lesions on the acquisition and retention of spatial memory tasks (e.g. Li and others 1999), other studies suggested that pharmacological inactivation of the left, but not the right, rat hippocampus during learning of the MWM task impaired memory retention (Klur and others 2009). Such discrepancies could arise from the nature of the unilateral manipulations used, the tasks performed and/or the strategies employed by the rodents to solve these tasks. Crucially, chronic manipulations may allow adaptive compensatory changes to occur in the other hemisphere such that performance of a given task is minimally affected (e.g. see Goshen and others 2011). Furthermore, some of the reported manipulations span multiple hippocampal and extra-hippocampal regions, which may exhibit distinct asymmetries to that observed at CA3-CA1 inputs, complicating the interpretation of any behavioural effects. Future studies will need to achieve more acute and subregion-specific interference, which is now possible using newly developed optogenetic and chemogenetic tools (e.g. halorhodopsin and archaerhodopsin; Yizhar and others 2010 and/or designer receptors exclusively activated by designer drugs (DREADDs); Rogan and Roth 2011; Stachniak and others 2014; Box 2). These tools in conjunction with place-cell recordings will hopefully provide further information about when different hippocampal subregions are recruited and required for task performance. Specifically, according to the models outlined above, silencing the left CA3-CA1 synapse would be predicted to reduce learning-induced increases in conjunctive place-item cells and/or reduce recruitment of new place-cells at salient locations (Figure 3).

5 Possible relationships to human memory

Our understanding of hippocampus-dependent memory in humans begins at the other end of the spectrum to that in rodents. Whilst we now have knowledge of the minutiae of the mouse CA3-CA1 network at the synaptic level, further work is required to establish whether or not the hemispheric asymmetry in this circuit is behaviourally relevant. In contrast, left-right differences in human hippocampal function are well established but the possible circuit basis is unknown. A long-standing explanation for such hippocampal lateralization in humans is that it emerges from external hemispheric functional asymmetries (Squire 1992), namely the left hemispheric dominance in language encoding and a greater involvement of the right hemisphere in visuospatial processing (Levy 1977). Indeed, there is evidence that such extra-hippocampal interactions can play an important role; for example, there is a greater engagement of the left hippocampus when semantic information is more pertinent to a pattern separation task, compared to higher activity

in the right hippocampus when spatial information is more relevant (Motley and Kirwan 2012).

It is particularly important that we begin to examine the types of computation employed by the human hippocampus if we want to establish whether there are overriding principles that are shared across mammals. Functional magnetic resonance imaging (fMRI) in human subjects during memory tasks has revealed differential recruitment of the left and right hippocampus according to the processes engaged, which provides some insight into what such computations may be. For example, an fMRI study demonstrated a preferential activation of the right hippocampus when an allocentric (world-centred) strategy was used to solve spatial tasks, whilst the left hippocampus showed more activity when a sequential egocentric (self-centred) strategy was employed (Iglói and others 2010). Recordings from human place cells and spatial view cells (which fire at higher rates when the subject is viewing, rather than being at, a particular location) during spatial and episodic memory tasks (Ekstrom and others 2003) should reveal whether this dissociation arises from functional differences in the roles of hippocampal subfields between hemispheres. Furthermore, the fMRI-deduced activation patterns of the left, but not right, human hippocampus appear to reflect associative match-mismatch detection. Specifically, the left hippocampus is active when one of either the spatial or temporal arrangements of novel sensory stimuli is similar (match) but the other is different (mismatch) to the arrangements of previously encountered inputs (Kumaran and Maguire 2007). Right hippocampal activation was seen only in cases when there was a complete match between novel and previously encountered inputs (Kumaran and Maguire 2007). The left hippocampus might therefore be preferentially involved in updating internal representations in response to changes in sensory experience.

In order to determine how closely the principles gleaned from studying the synaptic basis of learning in the mouse hippocampus apply to humans, it now becomes important to analyse post-mortem human brain tissue to determine if humans share a hemispheric asymmetry of synapse distribution. The basic hippocampal trisynaptic circuit is similar across all mammals but, whilst rodents exhibit strong commissural CA3-CA3 and CA3-CA1 projections, primates including humans have few such connections (Amaral and Lavenex 2007; Box 1). Thus, it is possible that the types of CA1 synapses in humans and primates are determined not only by the source of CA3 afferents, but simply by which hemisphere they are in. If such an additional segregation of synapses is present, however, it would preclude a learning mechanism that is primarily dependent on the direct convergence of differentially plastic inputs from left and right CA3 onto the same CA1 cell assemblies. Nevertheless, there are possible sources of indirect communication, such as the projections of the dorsal hippocampal commissure (Amaral and Lavenex 2007). Testing the models discussed in Figure 4 would elucidate whether such convergence is required for associative learning, and hence would be

informative about the computations performed by human hippocampal circuitry.

The simple anatomical arrangement of spines with different morphology, molecular complements and capacity for plasticity in the mouse hippocampus offers a model to investigate human disorders of memory that are characterised by synaptic failure. This experimental system is promising irrespective of whether an equivalent distribution of synapses is found in the human hippocampus, because it allows the isolation of two synaptic populations with distinct properties to determine whether they are differentially vulnerable to pathological processes in mouse models of disease. Alzheimer's disease (AD) is a neurodegenerative disorder, distinguished by neurofibrillary tangles and amyloid plaques (Braak and Braak, 1995), which manifests initially as dementia and concomitant loss of hippocampal synapses. Oligomers of the peptide amyloid beta (Aβ) are thought to play a key role in this pathogenic process, and one of the most robust effects of these Aβ oligomers is the impairment of LTP at CA3-CA1 synapses (e.g. Cullen and others 1997). Nevertheless, many contradictory effects of Aβ oligomers have been reported (Goto and others 2006; Hsieh and others 2006; Shemer and others 2006) that could form the synaptic basis of this effect; it is possible that some of these opposing findings may arise because a heterogeneous population of synapses is being studied, and Aβ oligomers have distinct effects on these different populations of synapses. Consequently, the ability to simplify such complexity by optogenetically distinguishing between these synaptic types in the mouse may help elucidate individual pathological processes. In particular, if synapses typical of either left or right CA3-CA1 proved more vulnerable to pathology, this would provide a unique set of molecular identifiers that might be promising therapeutic targets. It will, however, be important to distinguish between processes that are inextricably linked to the molecular and anatomical characteristics of spines and those that occur because synapses are engaged in distinct functions and hence have different activity levels, since it is known that brain regions with higher activity are more at risk of developing pathology (Khan and others 2014). Thus, whilst more work is required to elucidate the underlying causes, it remains an intriguing observation that pathology develops asymmetrically in humans, with atrophy in the left hemisphere being a better predictor of the progression from mild cognitive impairment to AD (Douaud and others 2013). The utility of the mouse asymmetry model may also extend to other CNS disorders, such as schizophrenia (Stephan and others 2009), in which aberrant regulation of synaptic plasticity is implicated.

Conclusions

Left-right asymmetry in mice serves as a window into understanding the regulation of LTP capacity. It remains to be

seen how widely applicable are the hippocampal circuit properties that are now being unravelled in the mouse, and a number of questions remain (Box 3). Nevertheless, the left-right asymmetry in the distribution of mouse hippocampal synapses provides a powerful system in which to explore the contributions of the different types of synapse to learning and memory, and the ways in which they may be affected in disease.

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Figure Legends

Figure 1. Schematic representation of a typical glutamatergic synapse

The presynaptic bouton (top) contains glutamate-filled synaptic vesicles, some of which are docked at the active site of the presynaptic membrane ready for release. Glutamate receptors are anchored in the plasma membrane of postsynaptic dendritic spines (bottom). These receptors are of two major classes: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors, each of which is composed of different assemblies of receptor subunits. Several signalling molecules are docked at the postsynaptic density, and some of these interact directly with the C-terminal domains of glutamate receptors; for example, the calcium/calmodulin-dependent protein kinase II (CaMKII) binds with high affinity to the GluN2B C-terminal tail.

Figure 2. Left-right asymmetry in morphology and receptor composition of CA3-CA1 synapses

Left CA3 inputs innervate dendritic spines that are smaller, but with higher density of GluN2B-containing NMDARs, than those receiving right CA3 inputs (top left and right). Only spines receiving input from the left CA3 show LTP (bottom left and right).

Figure 3. Development of left-right asymmetry at CA3-CA1 inputs

Two possible models could explain how CA1 synapses mature differentially depending on their input from the left or right CA3. Both begin as small, GluN2B-rich spines. According to the first model (left), gene transcription-dependent factors are transported from the soma to the entire dendritic tree of CA1 pyramidal cells where they enable synapse maturation (increase in spine size, PSD area, GluN2A/GluN2B ratio and GluA1 content), but the left-innervated spines are partially protected from this global factor via a negative, transsynaptic factor. In the second model (right), differential rate, timing, and/or pattern of activity between right and left inputs to CA1 during postnatal development causes preferential induction of LTP at right innervated spines, with associated input-specific increases in spine size, PSD area, GluA1 content and GluN2A/GluN2B ratio. This would prevent the induction of, and/or occlude, further LTP in adulthood.

Figure 4. Models for differential involvement of left and right CA3-CA1 inputs in associative learning.

Strongly interconnected, pre-configured cell assemblies exist bilaterally within the recurrently-connected CA3 network; there are additional strong connections from the right CA3 to both left and right CA1 pyramidal neurons (top panel). During exploration of a novel environment, some of these pre-configured cell assemblies involving the right CA3 and their inputs to the CA1 are selected to represent allocentric positions and trajectories within the environment. In **Model 1** (left), associative learning, mediated by potentiation of inputs from item representations in the left CA3 onto CA1 place cells, converts these cells from pure place cells into conjunctive place-item cells that encode both the animal's allocentric position and the item/reward/punishment encountered at this position. In **Model 2** (right), potentiation at left inputs could instead (or additionally) mediate the recruitment of new place cells at salient locations within a learnt environment, which would allow a stronger or higher-resolution representation of this location.

Boxes

Box 1. The hippocampal trisynaptic circuit

At the core of the hippocampus lies a highly conserved trisynaptic circuit: granule cells in the dentate gyrus (DG) send glutamatergic mossy fibers to synapse with CA3 pyramidal neurons, which, in turn, synapse onto CA1 pyramidal neurons via glutamatergic Schaffer collaterals. In addition, adult CA3, but not CA1, pyramidal neurons are interconnected via recurrent connections. Excitatory glutamatergic fibres from the entorhinal cortex form the major input into the hippocampal trisynaptic circuit, and CA1 pyramidal cells form its major output, sending excitatory glutamatergic fibers to the subiculum and entorhinal cortex as well as subcortical targets (e.g. lateral hypothalamus, nucleus accumbens, amygdala, mammilary nuclei and septal nuclei). Additional complexity exists within the hippocampus; for example, there is thought to be mutual inhibition between a recently described DG-CA2-CA1 trisynaptic circuit and the classical DG-CA3-CA1 trisynaptic circuit (Kohara et al., 2014).

In addition to ipsilateral connections, the rodent hippocampus exhibits extensive inter-hemispheric connectivity via the fibers of the ventral hippocampal commissure. In rodents, commissural connections from CA3 pyramidal neurons onto the contralateral CA3 and CA1 are prominent, in addition to CA3-CA3 and DG-DG projections. In contrast, such commissural connections are extremely sparse in the primate (including human) hippocampus, suggesting a lack of direct communication between the left and right hippocampi of higher mammals. For details, see (Amaral and Lavenex 2007).

Box 2. Optogenetic and chemogenetic tools

Recent advances in microbial biology and genetic engineering have led to a new generation of tools that enable temporally and spatially precise interrogation of mammalian CNS function. Optogenetics involves the expression of genes encoding microbial opsins, namely light-activated ion channels and transporters, under the control of mammalian promoters. Channelrhodopsin is a blue light-activated cation channel that is permeable to both sodium and potassium ions, and hence enables rapid and robust depolarization of neurons allowing the reliable generation of action potentials at rates of up to 40 Hz (Yizhar et al., 2011). Halorhodopsin and archaerhodopsin are yellow/green light-activated chloride and proton pumps respectively, which enable hyperpolarization, and thus silencing, of neurons. Variants of these opsins with modified kinetics, light-sensitivity and conductances have been generated (Yizhar et al., 2011). For example, recent molecular engineering has generated chloride permeable channelrhodopsin variants that enable faster hyperpolarization and higher light sensitivity than the hyperpolarizing pumps (Brendt et al., 2014; Wietek et al., 2014).

Chemogenetic tools include 'Designer Receptors Exclusively Activated by Designer Drugs' (DREADDs). These are G-protein-coupled receptors that have been genetically modified to only respond to exogenous ligands, most commonly clozapine-N-oxide (CNO), but retain coupling to endogenous downstream effectors (Rogan and Roth 2011). Whilst they act on a slower timescale than optogenetic tools, DREADDs may be better able to manipulate large volumes of transfected tissue as they can be controlled by systemic application of drugs.

Box 3. Outstanding questions

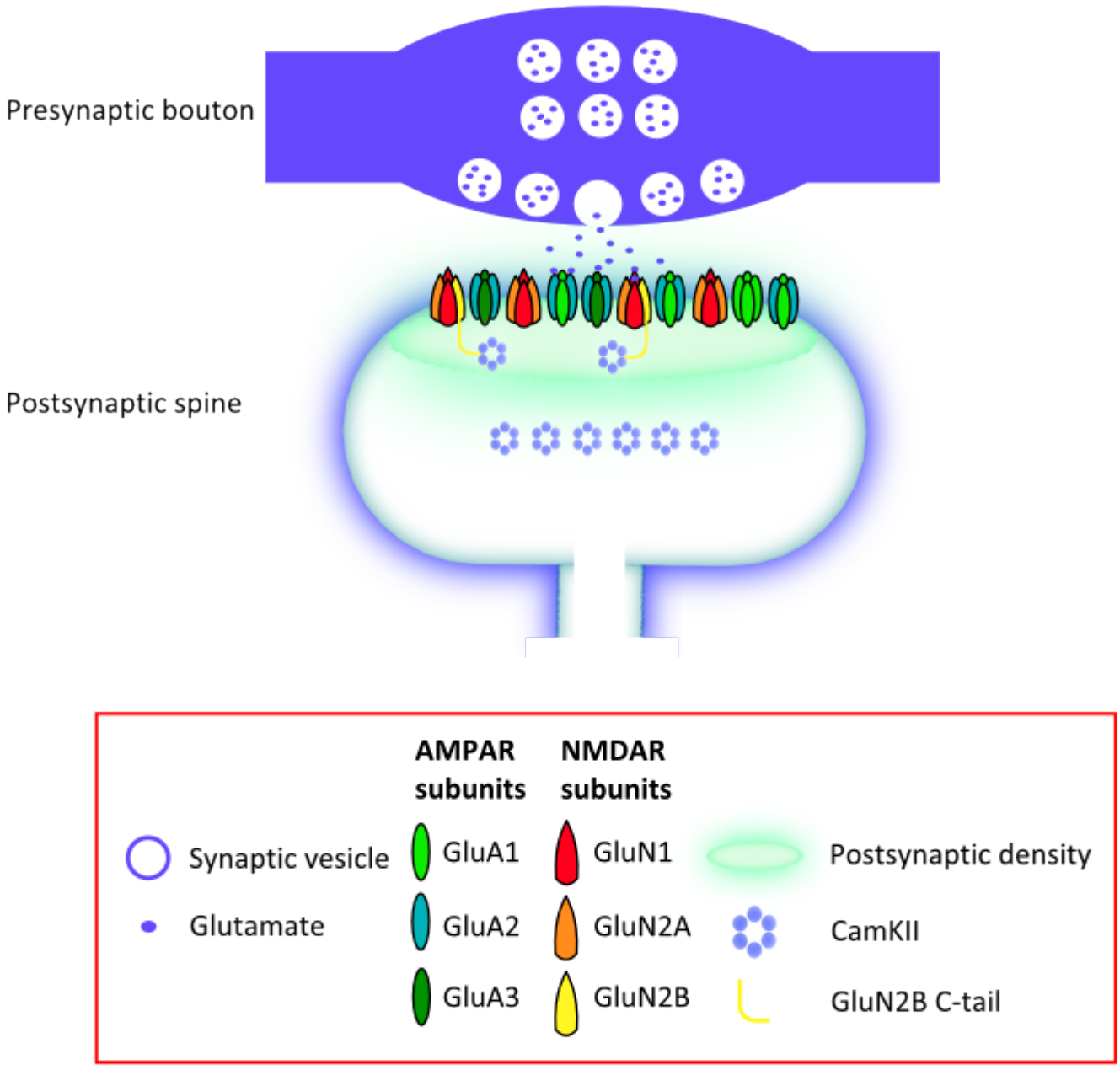
1. What additional left-right asymmetries exist at excitatory hippocampal synapses? Do hemispheric differences extend to GABAergic interneurons?

2. Do other forms of plasticity, such as long-term depression, also show left-right asymmetry at hippocampal synapses?

3. Do left and right CA3 inputs onto CA1 pyramidal neurons carry distinct information arising from upstream extra-hippocampal asymmetries? Or do they carry similar information but process it differently?

4. What are the implications of the left-right asymmetry of synaptic plasticity for learning and memory?

5. How does asymmetry in the rodent hippocampus relate to functional asymmetries in the human hippocampus?


Presynaptic bouton
Postsynaptic spine
AMPAR subunits
NMDAR subunits
Synaptic vesicle
Glutamate
GluA1
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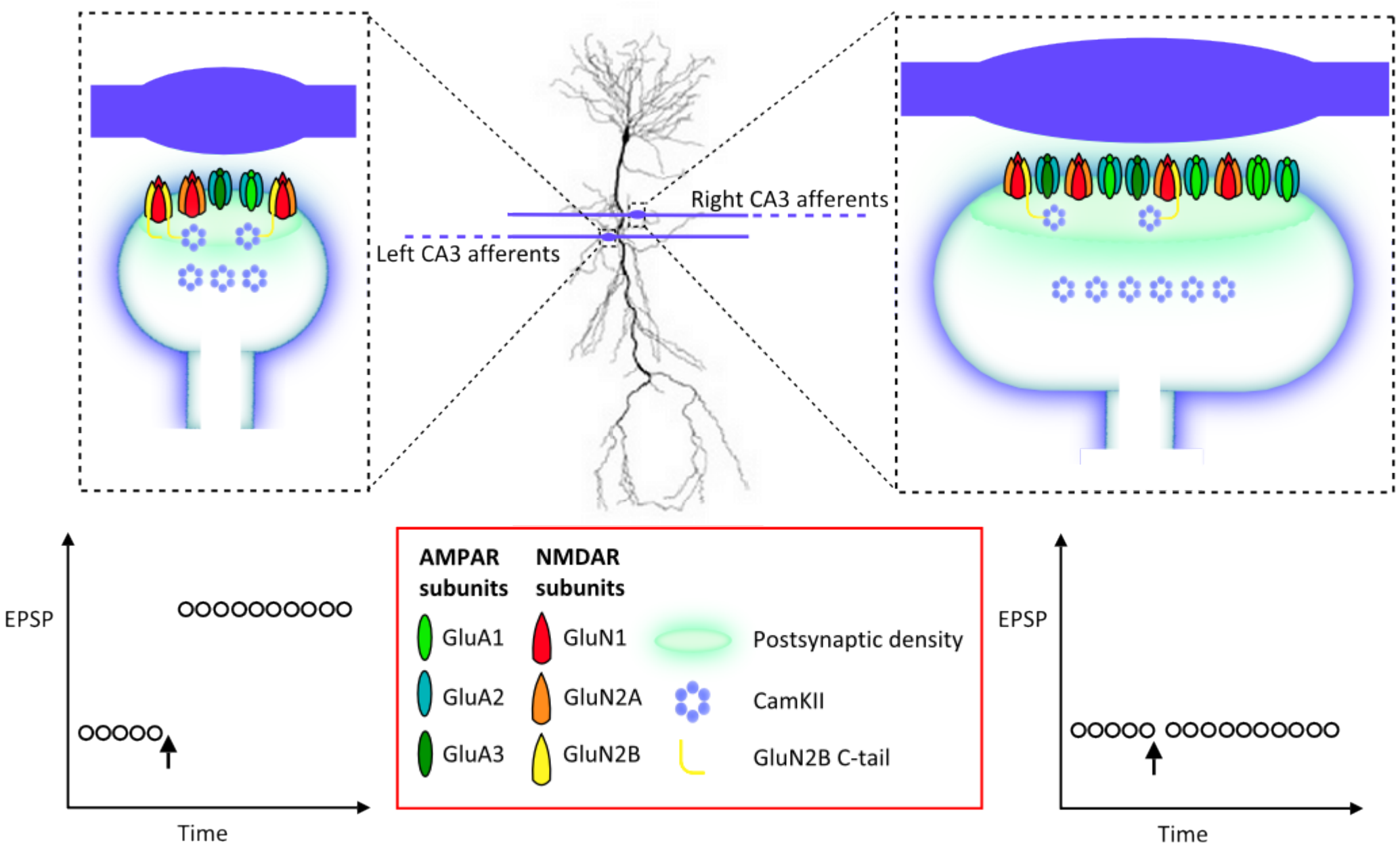
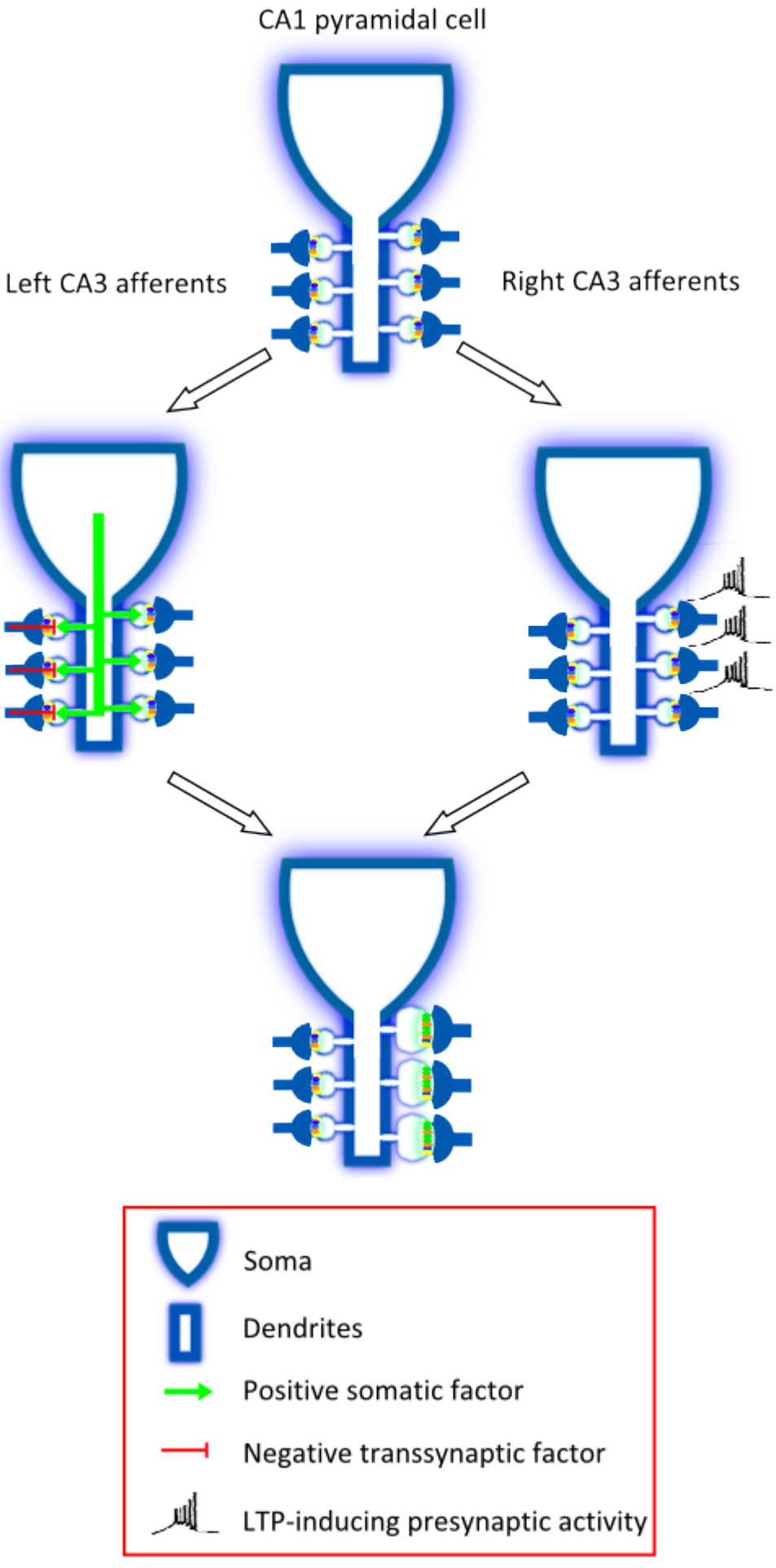
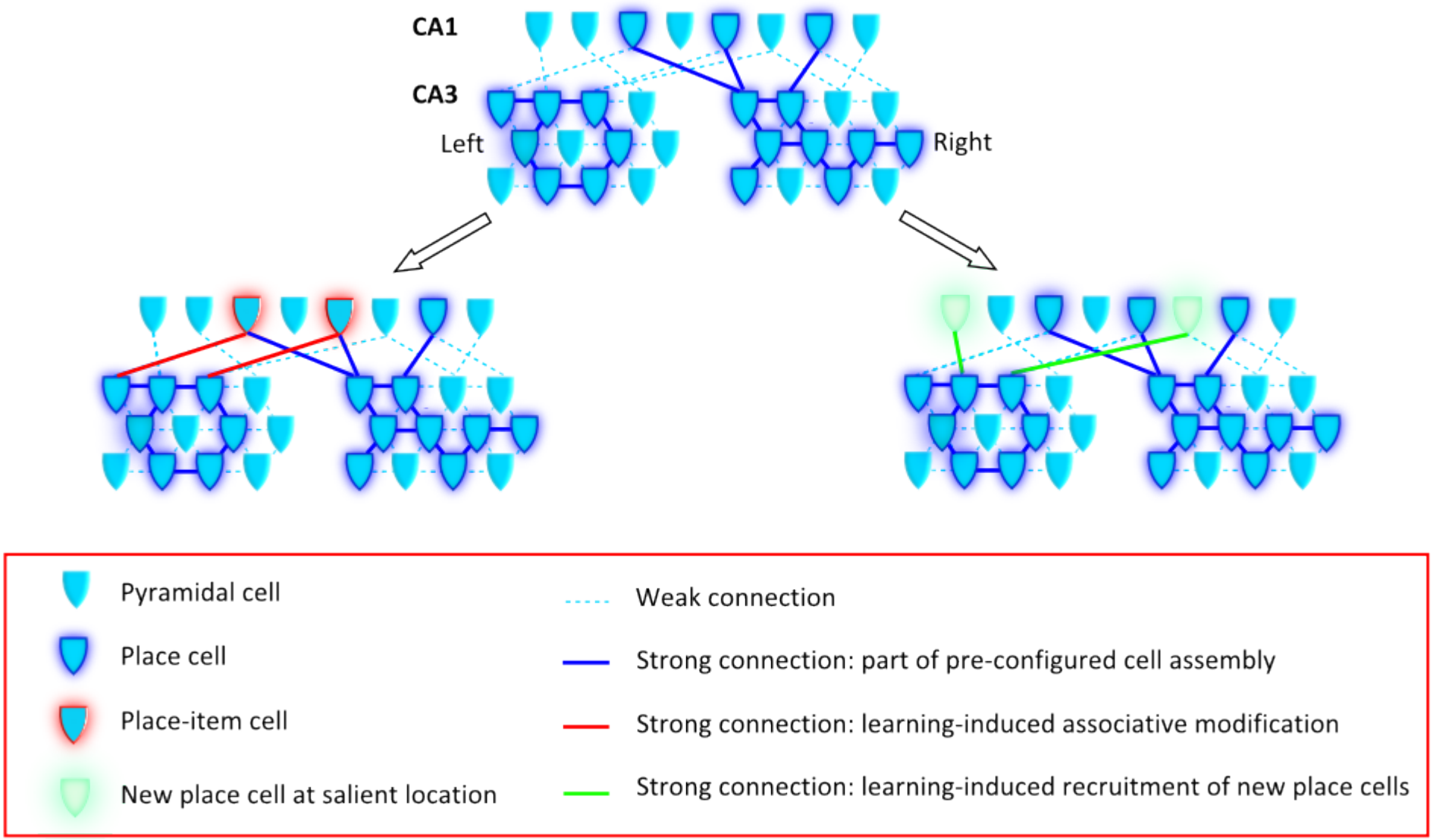
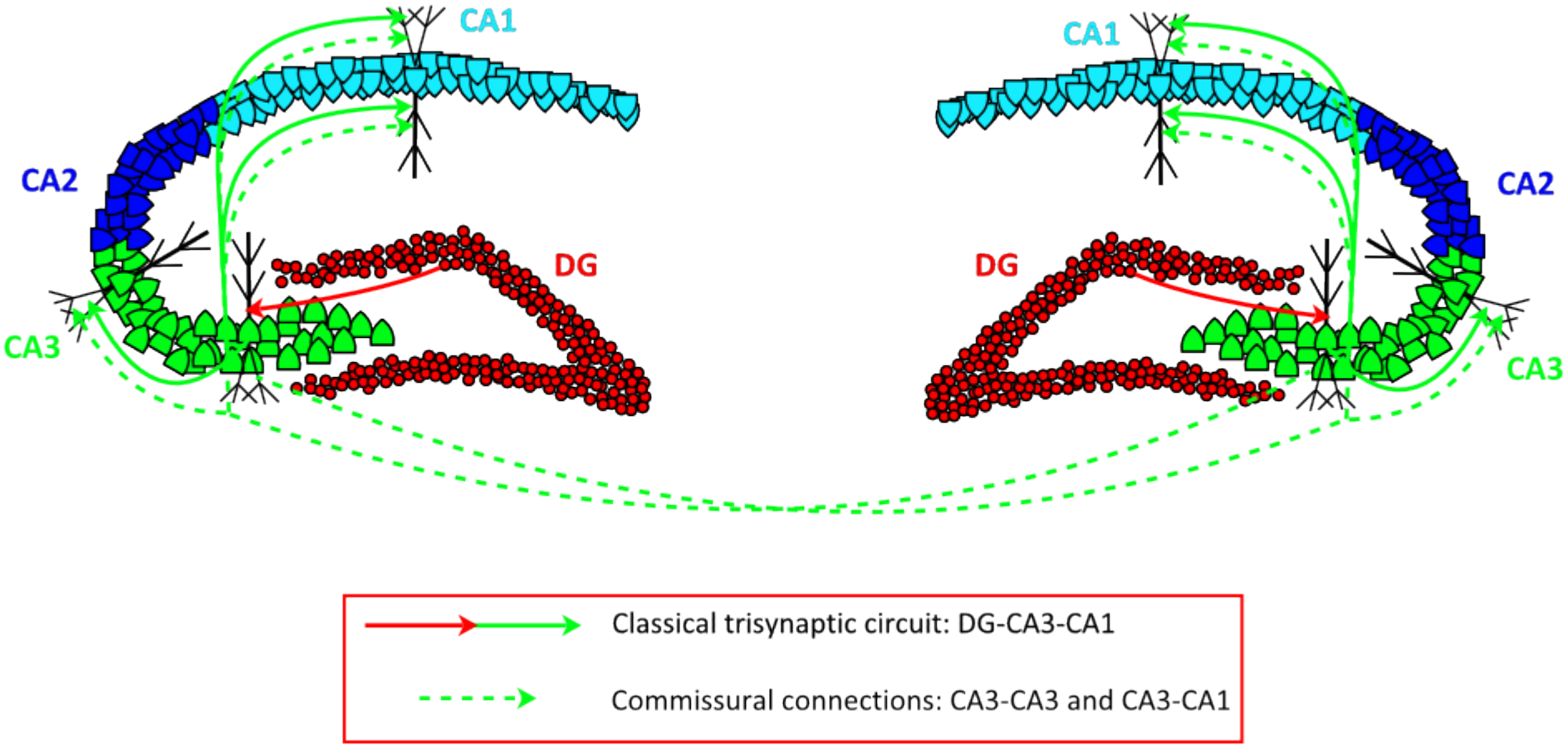
GluA3
GluN1
GluN2A
GluN2B
Postsynaptic density
CamKII
GluN2B C-tail


Right CA3 afferents
Left CA3 afferents
EPSP
Time
AMPAR subunits
NMDAR subunits
GluA1
GluA2
GluA3
GluN1
GluN2A
GluN2B
Postsynaptic density
CamKII
GluN2B C-tail
EPSP
Time


CA1 pyramidal cell
Left CA3 afferents
Right CA3 afferents
Soma
Dendrites
Positive somatic factor
Negative transsynaptic factor
LTP-inducing presynaptic activity


CA1
CA3
Left
Right
Pyramidal cell
Place cell
Place-item cell
New place cell at salient location
Weak connection
Strong connection: part of pre-configured cell assembly
Strong connection: learning-induced associative modification
Strong connection: learning-induced recruitment of new place cells


CA1
CA2
DG
CA3
CA1
CA2
DG
CA3
Classical trisynaptic circuit: DG-CA3-CA1
Commissural connections: CA3-CA3 and CA3-CA1