

# Multiple forms of metaplasticity at a single hippocampal synapse during late postnatal development



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## ABSTRACT

Metaplasticity refers to adjustment in the requirements for induction of synaptic plasticity based on the prior history of activity. Numerous forms of developmental metaplasticity are observed at Schaffer collateral synapses in the rat hippocampus at the end of the third postnatal week. Emergence of spatial learning and memory at this developmental stage suggests possible involvement of metaplasticity in the final maturation of the hippocampus. Three distinct metaplastic phenomena are apparent. (1) As transmitter release probability increases with increasing age, presynaptic potentiation is reduced. (2) Alterations in the composition and channel conductance properties of AMPARs facilitate the induction of postsynaptic potentiation with increasing age. (3) Low frequency stimulation inhibits subsequent induction of potentiation in animals older but not younger than 3 weeks of age. Thus, many forms of plasticity expressed at SC-CA1 synapses are different in rats younger and older than 3 weeks of age, illustrating the complex orchestration of physiological modifications that underlie the maturation of hippocampal excitatory synaptic transmission. This review paper describes three late postnatal modifications to synaptic plasticity induction in the hippocampus and attempts to relate these metaplastic changes to developmental alterations in hippocampal network activity and the maturation of contextual learning.

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## 1. Introduction

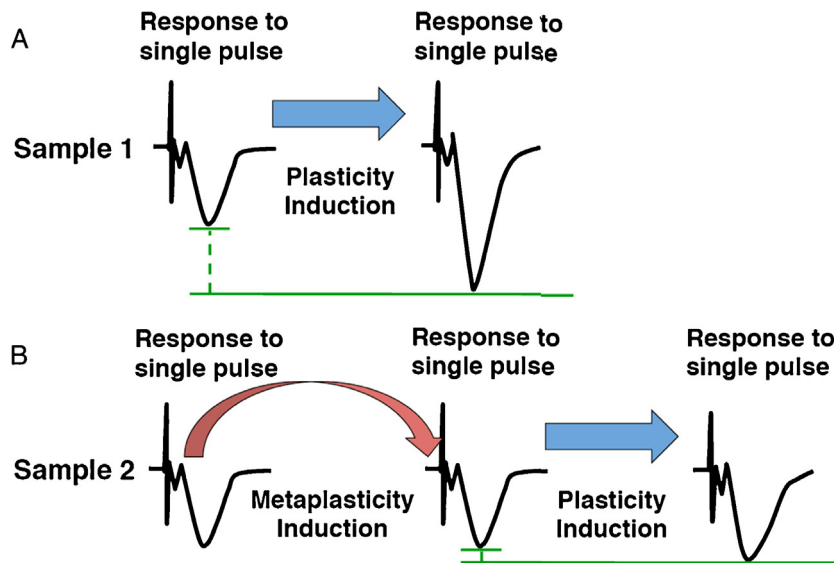
What is the difference between synaptic plasticity and metaplasticity? Synaptic plasticity refers to a change in synaptic function following patterned input activity (Fig. 1). Forms of synaptic plasticity vary in how long they persist after induction, ranging from milliseconds to weeks, and different forms of synaptic plasticity are supported by different underlying molecular and biophysical mechanisms. This review focuses on homosynaptic

long-term potentiation (LTP) and long-term depression (LTD) of synaptic efficacy, where the plasticity-inducing stimulus impacts the synaptic population that is stimulated (in contrast to heterosynaptic plasticity where stimulation of one synaptic population alters the strength of another synaptic population). LTP and LTD are individually defined by the direction of change in synaptic efficacy after patterned stimulation but both persist for many tens of minutes to hours in acutely prepared slice preparations (Malenka and Bear, 2004; Collingridge et al., 2010). LTP is a lasting increase in synaptic efficacy following moderate to high input activation frequencies. LTD is a lasting decrease in synaptic efficacy following low to moderate input activation frequencies.

Metaplasticity is the dynamic regulation of the ability to induce activity-dependent synaptic plasticity and is

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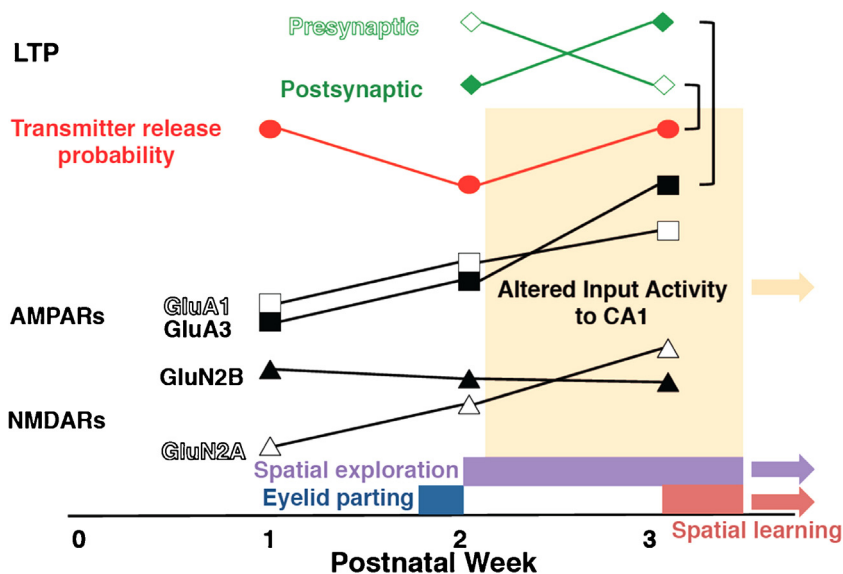
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**Fig. 1.** Illustration of the basic difference between synaptic plasticity and metaplasticity. (A) In a naïve sample (Sample 1), a plasticity-inducing stimulus results in potentiation of the synaptic response. (B) During Sample 2, following a metaplastic event, the same plasticity-inducing stimulus no longer alters synaptic efficacy. Green bars depict the difference in the amplitude of the evoked synaptic event before and after the plasticity-inducing stimulus. This example does not reflect all types of metaplasticity.

governed by the prior history of activity (i.e. the plasticity of synaptic plasticity, Abraham and Bear, 1996). In empirical tests, synaptic metaplasticity is commonly defined as a shift in the threshold activity level to induce lasting alterations in LTP or LTD due to alterations in baseline activity levels (Bienenstock et al., 1982; Mockett and Hulme, 2008). During the maturation of Schaffer collateral to CA1 pyramidal cell (SC-CA1) synapses, alterations to both presynaptic and postsynaptic elements of synaptic transmission produce separate forms of metaplasticity. Presynaptic metaplasticity can be observed as a function

of increased baseline transmitter release probability that impacts the constraints for induction of presynaptic LTP. On the postsynaptic side, a change in the types of ionotropic glutamate receptors that are present enhances postsynaptic excitation and shifts the threshold for induction of postsynaptic LTP (Fig. 2). Unlike sensory systems, where the causes for increased input activity are easily defined (i.e. birth enriches olfactory/gustatory/somatosensory input, parting of the eyelids enhances visual input, opening of the auditory meatus augments auditory input), the trigger for increased input activity in the hippocampus is



**Fig. 2.** Summary of pertinent developmental events in the hippocampus. Age related changes in LTP, transmitter release probability, and postsynaptic glutamate receptors are shown in relation to eyelid parting, spatial exploration, and spatial learning. Brackets denote relationships between alterations in synaptic plasticity and baseline transmission.

not clear. One thought is that exploration away from the nest, coordinating vestibular and visual input, provides the increase in synaptic drive that produces metaplasticity. It should be noted that the progression of synaptic maturation in the hippocampus can be altered by experimental manipulation of sensory experience (Dumas, 2004) and is sensitive to steroid hormones (Yildirim et al., 2008; Filová et al., 2013) and early life stress (Brunson et al., 2003), supporting activity-dependency. Alterations in the induction thresholds for pre- and postsynaptic LTP clearly have the potential to influence information processing and may play separate roles in the final maturation of the hippocampus during late postnatal development.

## 2. Three forms of metaplasticity exist at SC-CA1 synapses in the hippocampus during late postnatal development

### 2.1. The threshold for induction of presynaptic LTP increases with increasing age during the third postnatal week

Synaptic recordings have been made in acute hippocampal slices prepared from animals ranging in age from under 1 week to adulthood. Extracellular and intracellular recordings of excitatory postsynaptic potentials (EPSPs) and currents (EPSCs) indicate multiple phases to the development of transmitter release probability (Fig. 2). In the first postnatal week, release probability is high and declines with increasing age to the end of the second postnatal week (Bolshakov and Siegelbaum, 1995). Transmitter release probability then increases again during the third postnatal week to reach adult levels by the end of the first month of life (Muller et al., 1989; Dumas and Foster, 1995) (Fig. 2). Conversely, LTP is difficult to induce in slices from neonates, is largest in magnitude at 2 weeks of age, and declines thereafter (Harris and Teyler, 1984; Dudek and Bear, 1993; Durand et al., 1996; Dumas, 2012). Intracellular recording of unitary EPSPs and EPSCs and quantal analyses have shown that LTP in the 2-week-old hippocampus is more strongly supported by presynaptic mechanisms (Kuhnt et al., 1992) and the ability to induce presynaptic LTP is inversely related to baseline transmitter release probability (Foster and McNaughton, 1991; Kullmann and Nicoll, 1992; Larkman et al., 1992). Thus, as baseline presynaptic strength increases from 2 weeks of age forward, LTP magnitude dissipates due, in part, to a loss of at least one type of presynaptic potentiation (Dumas, 2012).

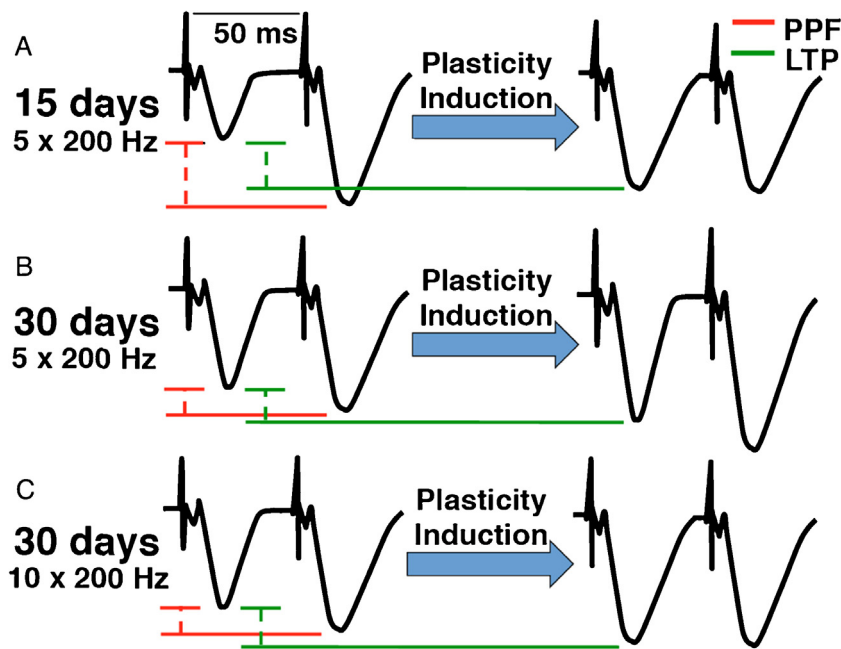
Analogous to the initial argument put forth by Bienenstock et al. (1982), the developmental increase in baseline presynaptic function concomitant with a decrease in presynaptic LTP supports a metaplastic relationship. That is, the developmental increase in transmitter release probability directly alters induction of presynaptic LTP (Lauri et al., 2007). Although the developmental increase in baseline release probability occurring beyond 2 weeks of age is likely activity-dependent (Chavez-Noriega and Stevens, 1992, 1994; Lauri et al., 2005), network activity patterns that occur in the hippocampus *in vivo* are not maintained in the acute slice preparation. Thus, persistence of age-related effects on presynaptic LTP in the slice

preparation provides additional support for metaplasticity, that the modification to plasticity induction outlasts the modifying stimulus (Abraham and Bear, 1996).

### 2.2. The induction threshold for postsynaptic LTP decreases with increasing age during the third postnatal week

AMPA receptors are the ionotropic receptors responsible for fast excitatory synaptic transmission, the rapid postsynaptic depolarization that occurs upon binding of glutamate. AMPAR levels at neonatal hippocampal SC-CA1 synapses are low and a large number of synapses contain only NMDARs, referred to as “silent synapses” (Durand et al., 1996; Liao and Malinow, 1996; Wu et al., 1996; Rumpel et al., 1998). During the first three postnatal weeks, AMPARs are inserted into hippocampal synapses in an activity-dependent manner (Liao et al., 1999), the number of silent synapses is reduced (Durand et al., 1996; Ben-Ari et al., 1997), and population synaptic efficacy increases (Bekstein and Lothman, 1991; Hussain and Carpenter, 2001) (Fig. 3). AMPARs can also be driven into immature synapses with LTP inducing stimulation (Isaac et al., 1995; Liao et al., 1995; Mack et al., 2001). This process of synapse induction involves the insertion of AMPARs containing GluA1 that are then replaced by AMPARs containing GluA3 subunits through constitutive recycling (Shi et al., 1999; Hayashi et al., 2000). Moreover, at the end of the third postnatal week, GluA3 expression overtakes GluA1 expression (Martin et al., 1998; Durand and Zukin, 1993; Blair et al., 2013). Replacement of GluA1 by GluA3, combined with other modifications to the AMPAR protein complex, such as increased incorporation of the transmembrane AMPAR regulatory protein (TARP), causes AMPAR responses to become more prolonged (Blair et al., 2013). Cornichon proteins may also regulate the increase in AMPAR response duration that occurs at 3 weeks of age (Herring et al., 2013). Longer duration AMPAR responses equate to increased synaptic drive and a larger temporal window for EPSP summation, which translates to a reduction in the stimulation frequency required for summation. Since EPSPs can summate at lower frequencies, LTP can be induced at lower frequencies (Dumas, 2012; Blair et al., 2013).

The developmental switch to GluA3-containing AMPARs and resultant increased excitatory drive concomitant with an increase in postsynaptic LTP supports a metaplastic relationship. More specifically, prolonging of AMPAR responses due to modification in the composition of AMPARs directly increases the likelihood of subsequent LTP-dependent insertion of additional AMPARs. This reduction in the threshold for postsynaptic LTP induction is an example of metaplasticity because the activity that drives the developmental insertion of AMPARs into excitatory synapses (Isaac et al., 1995; Liao et al., 1995) is not present in the slice preparation in which the alteration in LTP induction is observed. A residual marker of the endogenous network activity is maintained in the slice preparation, that being the increased presence of AMPARs with GluA3 subunits. Combined with the metaplastic change in presynaptic plasticity, these data represent a



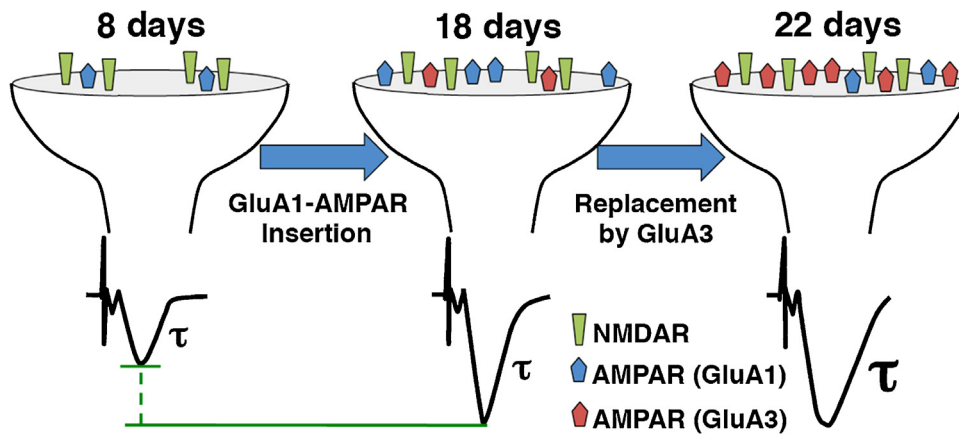
**Fig. 3.** Presynaptic LTP is reduced in concert with the developmental increase in baseline transmitter release probability. (A) At 15 days of age, transmitter release probability is low, as reflected by large magnitude paired-pulse facilitation (PPF). Subsequently, LTP magnitude is large and there is a reduction in PPF during LTP expression. (B) At 30 days of age, transmitter release probability is increased, as reflected by an increase in the baseline EPSP amplitude and reduced PPF compared to 15 days of age. At this developmental stage, the same plasticity-inducing stimulus ( $5 \times 200$  Hz) does not elicit presynaptic LTP. (C) The increased induction threshold for presynaptic LTP at 30 days of age can be overcome with a stronger plasticity-inducing stimulus ( $10 \times 200$  Hz). Red bars depict the difference in amplitude of the evoked response across paired stimulus pulses (50 ms inter-pulse interval). Green bars depict the difference in the amplitude of the evoked synaptic event before and after the plasticity-inducing stimulus.

late postnatal shift from presynaptic to postsynaptic LTP induction at SC-CA1 synapses.

### 2.3. Low frequency stimulation increases the threshold for induction of LTP in animals over, but not under, 3 weeks of age

Numerous reports indicate that it becomes more difficult to induce LTD with increasing age during the postnatal period (Dudek and Bear, 1993). In fact, the same stimulation protocols that robustly induce LTD in slices prepared from animals under 3 weeks of age are completely ineffective after the end of the third postnatal week (Dumas, 2012). If high frequency stimulation is delivered after induction of LTD in immature slices, synaptic efficacy returns to a level observed before induction of LTD (i.e. it is re-potentiated back to baseline). Interestingly, while the LTD inducing stimulation does not alter synaptic strength in slices from more mature animals, it blocks subsequent attempts to induce LTP (Dumas, 2012). A similar effect has been shown following a weak tetanus that produced only transient potentiation (Huang et al., 1992; Moody et al., 1999; Gisabella et al., 2003; Le Ray et al., 2004) or baseline stimulation in nominal  $Mg^{2+}$ , which permitted activation of NMDARs (Coan et al., 1989). These phenomena represent metaplastic alterations in perhaps the most pure form, where the alteration in plasticity induction (subsequent inhibition of LTP) occurs in the absence of a change in baseline transmission (no observable lasting effect of initial metaplasticity inducing stimulation).

The ability of low frequency stimulation to inhibit subsequent induction of LTP has been attributed to activation of NMDARs (Coan et al., 1989; Huang et al., 1992). Similar numbers of NMDARs are present at hippocampal synapses in animals just under and over 3 weeks of age (Al-Hallaq et al., 2007). Therefore, age related differences in 1 Hz dependent metaplasticity cannot be explained by differences in numbers of NMDARs. Instead, the composition of NMDARs changes across testing ages. In animals under 3 weeks of age, hippocampal NMDARs predominantly contain GluN2B subunits. With increasing age, diheteromeric NMDARs containing GluN2B subunits are replaced by NMDARs with GluN2A subunits and/or triheteromeric NMDARs with one GluN2B and one GluN2A subunit (Paoletti, 2011), both leading to increase in total GluN2A content. Therefore it is possible that NMDARs with GluN2B subunits can support LTD in response to 1 Hz stimulation (Shipton and Paulsen, 2013) and re-potentiation by 100 Hz stimulation, while NMDARs with GluN2A subunits cannot support LTD as readily (Köhr et al., 2003; Ge et al., 2010; Moulton and Harvey, 2011) and, when activated at suboptimal frequencies, they inhibit subsequent attempts to induce LTP. An alternative explanation might be that the 1 Hz stimulation alters the types of NMDARs that are present at synapses. However, prior research suggests that NMDAR composition is not altered by 1 Hz stimulation at SC-CA1 synapses in hippocampal slices (Bellone and Nicoll, 2007). More likely, the 1 Hz stimulation alters the phosphorylation state of LTP-regulating signaling proteins in the postsynaptic density. Low frequency stimulation results in



**Fig. 4.** Alterations in AMPAR number and composition at SC-CA1 synapses across postnatal development. The number of AMPARs increases across the first three postnatal weeks through insertion of AMPARs containing GluA1 (left to middle transition). The increase in AMPAR number results in an increase in synaptic efficacy (bottom waveforms). AMPARs containing GluA1 are replaced by AMPARs with GluA3 such that, by the end of the third postnatal week, more AMPARs contain GluA3 than GluA1 (middle to right transition). This change in AMPAR composition prolongs AMPAR-mediated synaptic responses (bottom waveforms). The increased duration of AMPAR-mediated synaptic responses at 3 weeks of age reduces the threshold for LTP induction. Green bars depict the difference in the amplitude of the evoked synaptic event as more AMPARs are inserted into maturing synapses.

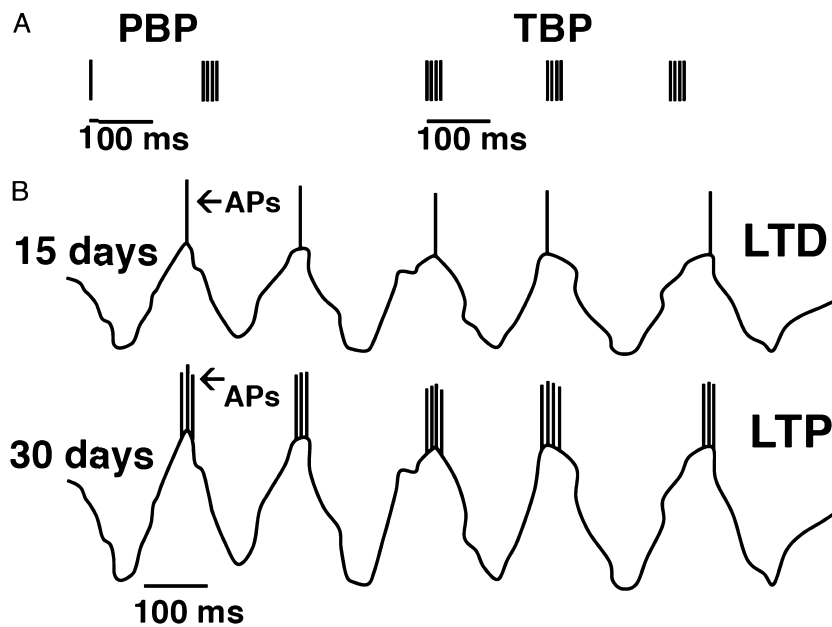
dephosphorylation of calcium calmodulin-dependent protein kinase II (CaMKII) (Huang et al., 2001), the synaptic kinase considered to be absolutely necessary for NMDAR-dependent LTP at mature synapses (Malenka and Bear, 2004). Dephosphorylation of CaMKII results in its movement away from the synapse (Yoshimura et al., 1999; Dong and Rosenberg, 2004; Mullasseril et al., 2007), which would increase the threshold for LTP induction because synapses would be less primed to engage mechanisms responsible for LTP expression. This low frequency dependent CaMKII translocation process may also occur at less mature synapses in animals under 3 weeks of age, but LTP (re-potential) is not inhibited because LTP is more reliant on protein kinase A than on CaMKII at this developmental stage (Wikström et al., 2003; Yasuda et al., 2003).

### 3. Late postnatal changes in network oscillations and excitability levels influence what types of plasticity will be expressed

At this point, it may be safe to assume that alteration to the threshold for plasticity induction influences the forms of plasticity that can be expressed. However, investigators should be careful to note that plasticity thresholds determined through artificial stimulation patterns and in ex vivo preparations likely better represent absolute limits to plasticity induction rather than reflect what occurs in vivo. For instance, even if the induction threshold for LTP is moderate, if the natural input frequencies are low, no LTP will be induced. As well, the state of the postsynaptic neuron is as important as the frequency of afferent stimulation in determining both the direction and magnitude of synaptic plasticity.

Input frequencies in hippocampal networks are determined in large part by population oscillatory events. Theta (4–12 Hz) oscillations are present in local field potential recordings collected from the hippocampus

of adult animals while they explore and solve mazes and have been shown to have a role in synaptic plasticity (Kleshchevnikov, 1999) and learning and memory (Buzsáki, 2005; Hasselmo and Stern, 2014). Stimulation patterns set to mimic APs riding on an endogenous theta wave, i.e. primed-burst (Diamond et al., 1988) or theta burst stimulation (Larson et al., 1986), induce LTP in adult hippocampal slices (Fig. 4A). Primed-burst stimulation is much more effective in eliciting LTP in slices collected from animals over 3 weeks of age compared to animals just under 3 weeks of age (Dumas, 2012). Additionally, pairing of postsynaptic discharge with presynaptic activation becomes a more potent regulator of LTP as rats mature beyond 3 weeks of age (Buchanan and Mellor, 2007). These findings suggest that hippocampal synapses are more sensitive to associative input at theta frequencies in adult versus juvenile animals. Also, theta power increases with increasing age during late postnatal development (Langston et al., 2010; Wills et al., 2010), which produces a greater match between population oscillation frequencies and the synaptic activation frequencies that drive LTP induction. Thus, it appears that the patterns of activity that induce endogenous plasticity in individual neurons might change in synchrony with the development of the population theta rhythm. However, postsynaptic depolarization is less likely to produce bursts of action potentials in animals less than 3 weeks of age (Sanchez-Andres et al., 1993) (Fig. 4B). As such, it might be the case that increased theta power and pyramidal cell bursting with increasing age, more than alterations to plasticity induction thresholds, regulates experience dependent modification to synaptic strength in developing rats. In general, the combination of discharge properties and NMDAR composition in immature networks would facilitate induction of LTD, while increased bursting and more NMDARs with GluN2A subunits would promote LTP induction in more mature networks.



**Fig. 5.** Experimental theta stimulation protocols and illustrations of endogenous theta oscillations in an immature and mature hippocampal network. (A) Artificial stimulus protocols have been shown to robustly induce LTP in adult hippocampal slices. At left is the stimulus pattern for primed-burst potentiation (PBP). At right is the stimulus pattern for theta-burst potentiation (TBP). (B) An illustration of a filtered EEG trace recorded in area CA1 of the hippocampus at 15 days of age. Action potentials (APs) from a single neuron are superimposed. Theta power is reduced relative to more mature animals and CA1 pyramidal neurons do not burst. The result is an increased proclivity to induce LTD during bouts of theta (Kleshchevnikov, 1999). (C) An illustration of a filtered EEG trace recorded in area CA1 of the hippocampus at 30 days of age. Theta power is increased relative to less mature animals and CA1 pyramidal neurons burst in relation to the theta rhythm. The result is an increased proclivity to induce LTP during bouts of theta activity.

#### 4. Developmental changes in metaplasticity align with hippocampal maturation

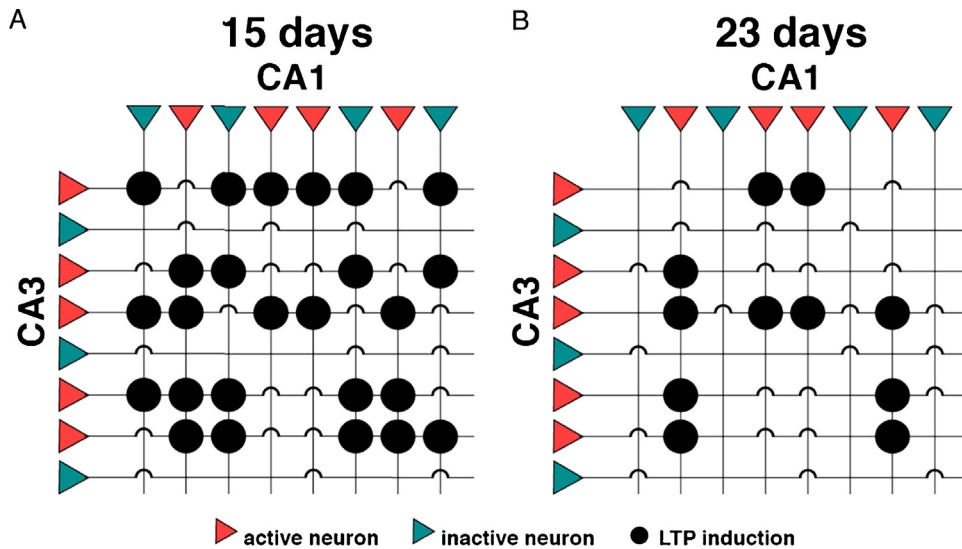
The hippocampus is required for contextual learning in rats and mice. This statement is derived predominantly from hippocampal lesion studies involving contextual learning and memory tasks such as spatial navigation to a goal (Morris, 1984; Sutherland et al., 1983) spontaneous alternation (Douglas and Isaacson, 1965; Douglas, 1972), contextual fear conditioning (Phillips and LeDoux, 1992; Kim and Fanselow, 1992), and object-place-context recognition (Langston and Wood, 2010). Many of these same behavior tasks have been applied to investigate the maturational time course of hippocampal integrity (Albani et al., 2014). While spontaneous alternation, contextual fear conditioning, and spatial learning and memory appear to mature at the end of the third postnatal week (Douglas et al., 1973; Rudy et al., 1987; Paylor et al., 1992; Rudy and Morledge, 1994; Pugh and Rudy, 1996; Dumas, 2005), performance in object-place-context conditioning does not reach adult levels until after 1 month of age (Langston and Lyon, 2013). Thus, the metaplastic alterations at SC-CA1 synapses described above occur at the same developmental stage when most forms of hippocampal-dependent learning and memory first come “on line.”

Neural discharge events in the hippocampus also suggest involvement in sequence learning. While the animal remains motionless on a testing surface, pyramidal neurons in area CA1 display transient extra-field discharge events that replay the animal’s prior path (Foster and Wilson, 2006; Diba and Buzsáki, 2007; Wu and Foster,

2014) and pre-play the animal’s future trajectory (“look ahead”) (Johnson and Redish, 2007; Diba and Buzsáki, 2007; Pfeiffer and Foster, 2013). There are no developmental studies on these phenomena. However, it is reasonable to suspect that maturation of neural encoding and decoding of trajectories at least partially limits the behavioral emergence of spatial navigation at 3 weeks of age. How might the metaplastic changes at hippocampal synapses regulate the emergence of trajectory encoding/decoding and spatial navigation? Each alteration in synaptic function described above may contribute independently to the behavioral change. Brief examples are provided below.

##### 4.1. The increased threshold for induction of presynaptic LTP lessens the impact of non-associative plasticity on neural network representations of space

Presynaptic LTP at immature synapses is large in magnitude and non-associative. When induced in an in vivo network as a result of animal behavior, inclusion of non-associative presynaptic LTP likely produces a different pattern of alterations in synaptic weights than induction of postsynaptic associative plasticity alone (Dumas, 2005). In other words, the added contribution of presynaptic LTP at immature synapses may mask postsynaptic associative plasticity that is smaller in magnitude and interfere in proper context encoding (Fig. 5). Also, the more widespread distribution of non-associative alterations in synaptic weights may add substantial noise in the encoding and decoding of spatial sequences, impairing the ability of the animal to navigate from point A to point B.



**Fig. 6.** Relationships between the type of LTP expressed (non-associative versus associative) and patterns of synaptic strengthening in sparsely connected immature and mature CA3–CA1 neuronal networks. (A) Non-associative LTP induction is dependent solely on the activity state of the presynaptic neuron. Reduction in the constraints for LTP induction results in more synapses undergoing LTP. (B) Associative LTP induction is restricted to synapses with coincident pre- and post-synaptic activity. Adapted from Dumas (2005) (*Hippocampus*, 15:562–578).

This hypothesis can be tested through genetic manipulation at immature synapses to increase transmitter release probability, perhaps by overexpressing SNAP-25b, a presynaptic protein involved in vesicle exocytosis and a primary regulator of the increase in glutamate release at excitatory synapses in the developing hippocampus (Biranowska et al., 2002; Bark et al., 1995). If the original hypothesis of a direct negative link between baseline release probability and presynaptic LTP magnitude is true, presynaptic LTP should be reduced and spatial navigation might be improved by expressing SNAP-25b at just under 3 weeks of age.

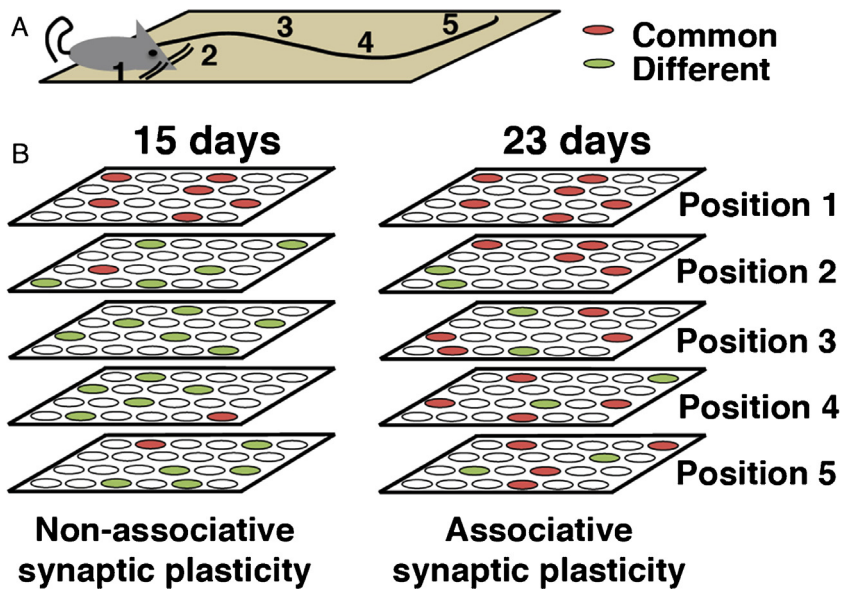
#### 4.2. The reduced threshold for postsynaptic LTP enhances the contribution of associative plasticity to the formation and use of cognitive maps

Combined with the reduction in presynaptic LTP, the late postnatal enhancement of postsynaptic associative LTP likely results in better defined and more stable representations of space. Additionally, associative wiring of hippocampal networks may permit higher-order place cell properties of hippocampal neurons, including trajectory encoding and decoding (Fig. 6). This notion is not novel and numerous models have been generated that link theta rhythms and hippocampal LTP to sequence learning in adult animals (Larson and Lynch, 1989; Melamed et al., 2004; Jensen and Lisman, 2005). It is possible that in animals under 3 weeks of age, the time window for summation is too short to properly encode sequences experienced at the speed of the animal's movement through space. As the summation window increases at the end of the third postnatal week, greater portions of the animal's trajectory can be associated and compressed into a sequence of ensembles (Fig. 7). Alternatively, the duration of synaptic

depolarization may be more closely related to the amount of contextual information that can be encoded at positions that are only briefly visited. In this case, the limited spatial experience of juvenile animals, combined with shorter synaptic depolarization, may create a vague cognitive map that provides insufficient information for navigation purposes. These hypotheses can be tested through delivery of amphetamine drugs or overexpression of GluA3 subunits and TARP combined with unit recording in animals less than 3 weeks of age. One result of the prolonged synaptic depolarization and enhanced associative LTP might be the emergence of transient neuronal discharge patterns that encode and decode the animal's movements and improve spatial navigation.

#### 4.3. Low frequency-dependent inhibition of LTP induction regulates the proportion of synapses that take part in representation of a given context

This means that synapses that are activated at high frequencies during context encoding contribute to creating neuronal ensembles that represent the testing environment. At the same time, synapses that are moderately active do not take part in long-term context encoding and are also prevented from further altering ensemble discharge patterns guided by the adjustments in synaptic weight that occurred during encoding. This might act to provide some degree of network stability or may serve to “save” these unaltered synapses for later use, thereby increasing the processing capacity of the network. As such, hippocampal synapses may be too functionally labile to produce lasting impression of context in animals less than 3 weeks of age because they lack this metaplastic constraint on LTP induction.



**Fig. 7.** Associative synaptic plasticity permits overlap in the neural ensembles that represent adjacent locations in a testing environment. (A) The line on the parallelogram depicts the path of a rat moving across a testing platform. Numbers indicate timepoints when the ensembles below become activated. (B) Small samples of CA1 place cells at the timepoints marked in panel A. At 15 days of age, a preponderance of non-associative synaptic plasticity mechanisms results in minimal overlap in the ensembles that represent adjacent locations on the testing platform. At 23 days of age, waning of non-associative plasticity mechanisms unmasks synaptic alterations due to associative plasticity. The result is an increase in the overlap of ensembles that represent adjacent locations on the testing platform. Red ovals are neurons that are active in two adjacent locations on the platform. Green ovals represent neurons that were active in one position, but not in an adjacent position. Associative synaptic plasticity permits sequential activation of ensembles that depict the past trajectory or future path of the animal.

## 5. Conclusion

Maturation of baseline transmission at SC-CA1 synapses in the hippocampus during the late postnatal period produces numerous forms of metaplasticity. On the presynaptic side, an increase in the baseline probability of transmitter release increases the threshold for induction of presynaptic LTP. Conversely, on the postsynaptic side, replacement of AMPARs containing GluA1 with AMPARs containing GluA3 prolongs AMPAR responses and reduces the threshold for induction of postsynaptic LTP. Additionally, a low frequency-induced increase in the LTP induction threshold becomes apparent only after the end of the third postnatal week. Combined, these metaplastic events, each occurring within the same synaptic population, illustrate the abundance of metaplastic factors involved in the regulation of synaptic maturation. Moreover, these alterations to the constraints for induction of synaptic plasticity may provide the appropriate thresholds and magnitudes for activity-dependent alterations in synaptic efficacy to support the network information processing necessary for spatial learning and memory.

## Conflict of interest statement

The authors report no conflict of interest with respect to the science presented in this review paper.

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