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# The developmental stages of synaptic plasticity

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**Abstract** The brain is programmed to drive behaviour by precisely wiring the appropriate neuronal circuits. Wiring and rewiring of neuronal circuits largely depends on the orchestrated changes in the strengths of synaptic contacts. Here, we review how the rules of synaptic plasticity change during development of the brain, from birth to independence. We focus on the changes that occur at the postsynaptic side of excitatory glutamatergic synapses in the rodent hippocampus and neocortex. First we summarize the current data on the structure of synapses and the developmental expression patterns of the key molecular players of synaptic plasticity, *N*-methyl-D-aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, as well as pivotal kinases ( $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II, protein kinase A, protein kinase C) and phosphatases (PP1, PP2A, PP2B). In the second part we relate these findings to important characteristics of the emerging network. We argue that the concerted and gradual shifts in the usage of plasticity molecules comply with the changing need for (re)wiring neuronal circuits.

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## Introduction

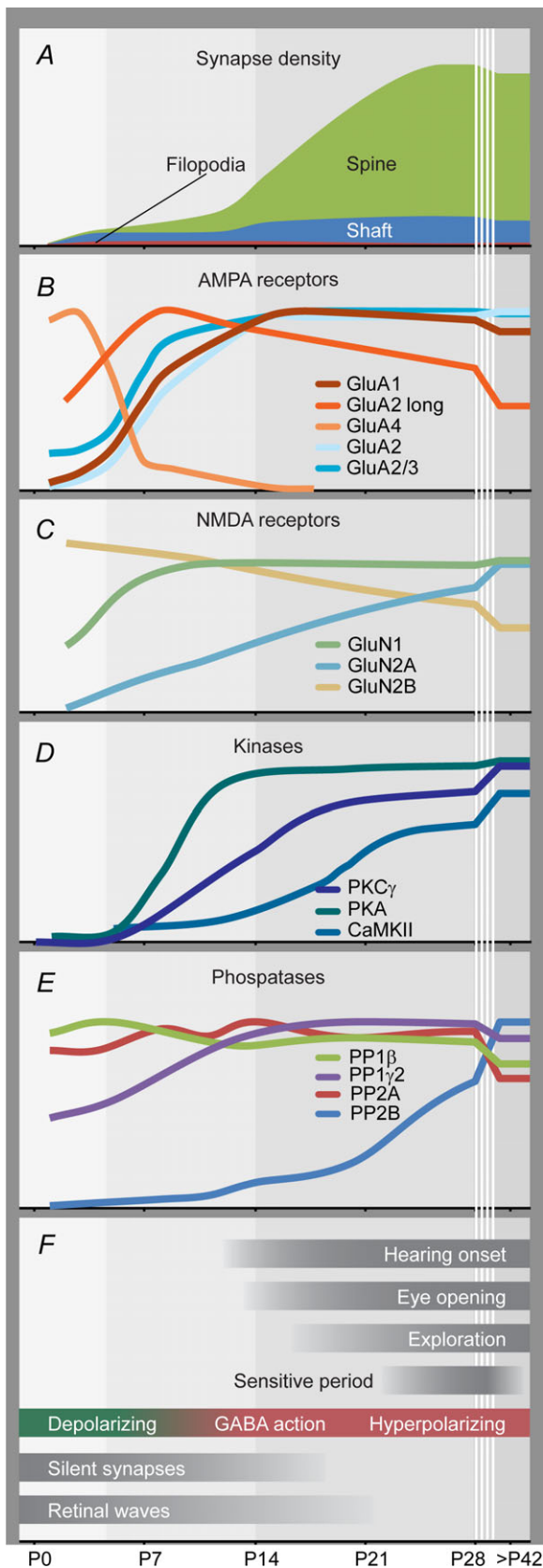
Our brains enable us to perceive and interact with the outer world. Synaptic connections between neurons can be adjusted to respond flexibly to changes in the environment, for example when we learn. In addition, plasticity mechanisms play important roles during early development, even before we are born, to prepare the neuronal circuitry for processing sensory information when we open our eyes. The demands for synaptic plasticity keep changing during the course of a lifetime. At

the first developmental stage of life, neuronal networks are being built in the brain to prepare itself for dealing with the outside world after birth (enabling perceptions and the programming of innate behaviour). To accomplish this, synaptic contacts are being shaped in the absence of sensory input. In the next phase of life, the infant has to absorb and process a great deal of new information in a short time (parents, family, language, cultural behaviour), which demands high levels of synaptic plasticity. At the mature stage the need for synaptic plasticity becomes

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gradually less urgent: a picture of the outside world is made that only incidentally requires adaptation.

Here, we review how the rules of synaptic plasticity change during development of the brain, from birth to independence. The different phases of synaptic plasticity are extensively studied in the rodent brain. Mice and rats open their eyes approximately 2 weeks after birth, and are considered sexually mature at 2 months of age, suggesting that the different phases of synaptic plasticity take place within that time frame. As an attempt to visualize how the demands for plasticity change in the rodent brain, the expression profiles of a number of key synaptic components during the first weeks of the rodent life were gathered from literature and portrayed in Figs 1 and 2. In the first part of this review we will discuss the plasticity changes during the first weeks of the rodent life from the perspective of each individual synaptic component (Fig. 1). In the second part we will discuss the key synaptic plasticity mechanisms from the perspective of each developmental phase (Fig. 2). We focus on the post-synaptic changes that occur at excitatory glutamatergic synapses in the hippocampus and neocortex in rats and mice. Other important aspects of the development of synaptic physiology and plasticity have been reviewed excellently elsewhere (Huang & Scheiffele, 2008; Kerchner & Nicoll, 2008; Feldmeyer & Radnikow, 2009; Groc *et al.* 2009; Oswald & Sigrist, 2009; Sanes & Kotak, 2011; Clarke *et al.* 2012).

### Structural and molecular determinants of synaptic plasticity

The ability of synapses to undergo plastic changes of postsynaptic responses is determined by many factors. First, synaptic structure plays an important role, for example the presence or absence of synaptic spines. Spines represent specialized dendritic compartments that isolate synapses biochemically and electrically from each other and may thus help to confine plasticity events to individual

#### Figure 1. Time course of various synaptic components

Time course of the postnatal development of synapses (A) and postsynaptic plasticity molecules (B–E) in the hippocampus, forebrain or whole brain in comparison with cellular, network and behavioural development (F). Curves in A–E are expressed as a percentage of the maximal density or expression level. Original data were smoothed (running average). Original data: A, synapse density (Fiala *et al.* 1998; Steward & Falk, 1991). Proportion of filopodia, shaft and spine synapses (P1–P12: Fiala *et al.* 1998; P21: Boyer *et al.* 1998; adult: Harris *et al.* 1992). B, GluA1, 2, 2/3, 4 (Zhu *et al.* 2000); GluA2<sub>long</sub> (Kolleker *et al.* 2003). C, GluN1, 2A, 2B (Sans *et al.* 2000). D, PKC $\gamma$  (Roisin & Barbin, 1997); PKA (Kelly, 1982); CaMKII (Kelly & Vernon, 1985). E, PP1 $\beta$ , PP1 $\gamma$ 2 (Strack *et al.* 1999); PP2A, 2B (Takahashi *et al.* 2000).

synapses. Besides synaptic structure, also the molecular machinery within a synapse defines the malleability of synaptic transmission. The basic molecular components that underlie synaptic transmission are the neurotransmitter receptors that transform chemical signals into changes of membrane polarization. These receptors are also an important substrate of synaptic plasticity, because their numbers and functionality can increase or decrease to potentiate or depress synaptic function. Furthermore, intracellular signalling cascades are required to translate specific activity patterns into changes of synaptic strength. Central to many plasticity mechanisms are kinases and phosphatases that mediate or influence synaptic plasticity. Importantly, these molecular components of the synaptic plasticity machinery change in parallel with the changing demands for neuronal adaptation during development.

### Synaptic structure (Fig. 1A)

During the first weeks of development neurons undergo substantial structural alterations: dendrites and axons grow at a fast rate and establish new synaptic contacts. Furthermore, the fine structure of synapses changes dramatically. At birth the number of synapses is low and most are located on dendritic shafts or small protrusions called filopodia (Fiala *et al.* 1998). In the third week after birth the number of synapses increases sharply (De Felipe *et al.* 1997; Steward & Falk, 1991) and the great majority of newly generated synapses are located on dendritic spines (Boyer *et al.* 1998). During the fourth week the generation of synapses and spines slows down and reaches mature levels in the cortex and hippocampus. The absolute number of shaft synapses in the hippocampus does not change much during development after the first post-natal week and therefore only a small minority (<10%) of excitatory synapses are located on shafts in mature hippocampal neurons (Harris *et al.* 1992; Boyer *et al.* 1998). The relative number of filopodial synapses also decreases during maturation and is very low in the adult. Although in the mature brain synaptic structures can still be dynamic, for example during learning, overall synaptic efficacies remain stationary, and average spine density and spine size are constant or become slightly reduced (Steward & Falk, 1991; De Felipe *et al.* 1997; Holtmaat *et al.* 2005; Loewenstein *et al.* 2011).

That the developmental increase in spine synapses coincides with a relative decrease in shaft synapses led to the hypothesis that shaft synapses are precursors to spine synapses (Fiala *et al.* 1998; Ethell & Pasquale, 2005). However, long-term live imaging showed that newly emerging dendritic protrusions occur adjacent to shaft synapses and that new spines turn into functional postsynaptic compartments only after their emergence (Nagerl *et al.* 2007; Zito *et al.* 2009; Kwon & Sabatini, 2011).

A shaft-to-spiny synapse transition was never observed. In addition, spine growth was shown to precede synapse formation (Knott *et al.* 2006). Several lines of evidence suggest that shaft synapses and spine synapses represent different types of synapses: they are of different size (the postsynaptic densities of shaft synapses are on average 2-fold larger; Rusakov *et al.* 1998), they are differentially regulated (Geinisman *et al.* 1996; Helmeke *et al.* 2001; Zha *et al.* 2005; Aoto *et al.* 2007; Nedelescu *et al.* 2010), and can receive input from different sources (e.g. in the amygdala; Dong *et al.* 2010).

There are several advantages for having a synapse located on a spine, and these can be of chemical (Muller & Connor, 1991; Koch *et al.* 1992; Koch & Zador, 1993; Yuste & Denk, 1995; Sabatini *et al.* 2002), electrical (Araya *et al.* 2006a,b; Grunditz *et al.* 2008; Bloodgood *et al.* 2009; Yuste, 2011; Gullledge *et al.* 2012; Harnett *et al.* 2012) and spatial (Chklovskii, 2004) nature. The influx of cations, and in particular calcium, during synaptic activation is more restricted within the head compartment of a spine. The signal transduction pathways that are activated by the increase in calcium are therefore more local, too, because the likelihood that calcium or second messengers diffuse to neighbouring synapses is low. Secondly, the spine necks form electrical filters that amplify voltage changes in the spine head. Thirdly, the presence of dendritic spines maximizes connectivity within the available volume of tissue.

If there are all these advantages for having synapses located on dendritic spines, why are dendrites in early development lacking them? The requirement of spatial optimization may be less stringent during early development where interstitial space is abundant. Whether there is less need for chemical or electrical isolation of synapses is unknown. Perhaps with shaft synapses there is a higher degree of flexibility: it may be less costly to rearrange shaft synapses than those on spines. It is also possible that chemical or electrical isolation of synapses is less desirable during early development. We speculate that there is a need for neighbouring synapses to be influenced by each other chemically or electrically to facilitate clustering of synchronized inputs (Kleindienst *et al.* 2011; Takahashi *et al.* 2012).

### AMPA receptor composition (Fig. 1B)

Most synapses use  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors (AMPA receptors) for fast transmission of signals across the synapse. The efficacy by which signals are transmitted across the synapse depends on the number of AMPARs at the postsynaptic site. Long-term potentiation (LTP) and long-term depression (LTD) of synaptic strength are expressed by the addition and removal of synaptic



AMPA receptors (Shepherd & Huganir, 2007; Malinow & Malenka, 2002; Bassani *et al.* 2013), processes that play a role in the rewiring of neuronal circuits and the adaptation of behaviour (Kessels & Malinow, 2009). AMPARs are tetrameric molecules, consisting of four AMPAR subunits. There are four different AMPAR genes, *Gria1*, *Gria2*, *Gria3* and *Gria4*, which encode for AMPAR subunits GluA1, GluA2, GluA3 and GluA4 respectively. These AMPAR subunits are most distinctively different in the structure of their cytoplasmic regions. GluA1, GluA4 and a splice variant of GluA2 named GluA2<sub>long</sub> have long cytoplasmic tails, while the c-tails of GluA2 and GluA3 are short and similarly structured.

Before birth and in the first postnatal week GluA4 is expressed in excitatory neurons of the hippocampus and cortex. Since the levels of the other subunits are low at this time, AMPARs at this early stage probably consist predominantly of GluA4. Entry of GluA4 homomers into synapses is activity dependent and a low level of activity (i.e. spontaneous activity) is sufficient for trafficking of GluA4 into synapses (Zhu *et al.* 2000). Soon after birth the expression levels of GluA4 decline as a consequence of increased neuronal activity (Akaneya, 2007). When GluA4 levels drop, another developmental AMPAR rises: GluA2<sub>long</sub>. GluA2<sub>long</sub> is an alternatively spliced isoform of GluA2 with a long cytoplasmic tail that is similar in structure to that of GluA4. The expression levels of GluA2<sub>long</sub> suggest that it is specialized in mediating synaptic strengthening during development: its expression peaks in the second week after birth, and is low in the mature hippocampus (Kolleker *et al.* 2003). The activity patterns that trigger GluA2<sub>long</sub> insertion into synapses are thought to lie between those of GluA4 and GluA1: both spontaneous activity and LTP-inducing activity patterns mediate synaptic insertion of GluA2<sub>long</sub> homomers (Kolleker *et al.* 2003).

In the second postnatal week the expression levels of GluA1, GluA2 and GluA3 start to rise in parallel and reach the high levels seen in adults by the third postnatal week. A unique feature of GluA2 is that its RNA is edited such that it has a positively charged arginine in its transmembrane region (Sommer *et al.* 1991). As a result, GluA2 homomers are unstable (Greger *et al.* 2002) and thus GluA2 predominantly forms heteromers with the other subunits (Greger *et al.* 2003). At the mature stage, three types of AMPARs are formed in excitatory neurons of the hippocampus and cortex: GluA1/2 heteromers, GluA2/3 heteromers and a smaller population of GluA1 homomers (Wenthold *et al.* 1996). The relative amounts of AMPAR subunits GluA1, GluA2 and GluA3 in hippocampal dendrites are estimated to be at a ratio of 1:2:1 (Kessels *et al.* 2009), suggesting that GluA1/2 and GluA2/3 are present in equivalent amounts. To determine the AMPAR subunit composition in synapses,

synapse strength was measured after deletion of either GluA1 or GluA3 during the first weeks of development. GluA1-deficient neurons were 80% decreased in synaptic AMPAR currents, while currents in GluA3-deficient synapses were reduced by 15%, suggesting that the majority of synaptic AMPARs are GluA1/2s (Lu *et al.* 2009). However, the expression of an AMPAR subunit may not be the only factor that determines synaptic strength. GluA1-lacking neurons have very few functional AMPARs on their extrasynaptic surface (Andrasfalvy *et al.* 2003), and as extrasynaptic AMPARs are the main source of receptors for obtaining LTP (Makino & Malinow, 2009; Patterson *et al.* 2010), GluA1-deficient neurons have a major impairment in LTP (Zamanillo *et al.* 1999; Granger *et al.* 2013). While LTD is intact (Selcher *et al.* 2012), the lack of LTP probably contributes to the large decrease in average synapse strength compared with GluA1-expressing neurons. In GluA3-deficient neurons LTP is not impaired (Meng *et al.* 2003), which may explain their modest decrease in synapse strength. The notion that synaptic currents depend not only on AMPAR expression levels is supported by the observation that the acute expression of GluA1 in GluA1-deficient neurons did not result in a change in synaptic strength (Kessels *et al.* 2009). A more definitive estimation of AMPAR subunit usage in synapses awaits experimentation without AMPAR manipulation.

The population of GluA2-lacking AMPARs (i.e. GluA1 homomers) can vary in size, and is regulated by the level of RNA editing of GluA2 (Seeburg & Hartner, 2003; Kwak & Weiss, 2006) or by changing the relative expression levels of GluA1 and GluA2 (Ju *et al.* 2004; Grooms *et al.* 2006; Mameli *et al.* 2007). Neurons that are highly active tend to increase their production of GluA2, while activity blockade selectively increases GluA1 production (Sutton & Schuman, 2006; Mameli *et al.* 2007; Liu *et al.* 2010). Since the GluA2-lacking AMPARs are Ca<sup>2+</sup> permeable, their presence at the synapse can boost Ca<sup>2+</sup> influx upon synaptic activation and thereby lower the threshold for synaptic plasticity (Liu *et al.* 2006). This suggests that GluA2-lacking AMPARs are involved in a form of homeostatic plasticity (Isaac *et al.* 2007): an overactive neuron will gradually impede strengthening of its synapses by decreasing its levels of Ca<sup>2+</sup>-permeable AMPARs, while vice versa a quiet neuron will increase its levels of Ca<sup>2+</sup>-permeable AMPARs to promote synaptic strengthening. Endogenous GluA2-lacking AMPARs can be transiently inserted into synapses upon LTP induction (Plant *et al.* 2006), although this is not always detected (Adesnik & Nicoll, 2007). GluA2-lacking AMPARs can also be found enriched in synapses after *in vivo* experience in the cortex (Clem & Barth, 2006) or memory formation in the hippocampus (Clem & Huganir, 2010).

The role of GluA1-containing AMPARs in LTP was studied by overexpressing GluA1 in hippocampal neurons,

which mostly produces GluA1 homomers (Hayashi *et al.* 2000). Upon overexpression of a subunit, the total AMPAR levels are less than ~50% above endogenous levels, indicating that the GluA1 homomers largely replace the existing dendritic AMPAR pool without overloading the dendritic AMPAR delivery machinery (Kessels *et al.* 2009). Under basal conditions these GluA1 homomers are excluded from entering the synapse. Upon stimulation with high-frequency activity, synapses are strengthened through the synaptic insertion of GluA1 homomers (Shi *et al.* 1999; Hayashi *et al.* 2000). This LTP-dependent synaptic trafficking of GluA1 is controlled by protein interactions at its c-terminal tail. While a small mutation in the c-terminal PDZ domain of overexpressed GluA1 prevents synaptic delivery (Hayashi *et al.* 2000; Passafaro *et al.* 2001), a larger PDZ mutation in a knock-in model did not affect trafficking (Kim *et al.* 2005). These differences were not a consequence of differences in experimental models, but point towards a mechanism of competitive protein interactions at the GluA1 PDZ domain that regulates GluA1 synaptic delivery (Boehm *et al.* 2006a). The activity-dependent synaptic delivery of recombinantly expressed GluA1 homomers was shown to also take place *in vivo* upon amygdala-dependent associative short-term memory formation (Rumpel *et al.* 2005), hippocampus-dependent short-term contextual memory formation (Mitsushima *et al.* 2011) and barrel cortex-dependent whisker experience (Takahashi *et al.* 2003). Notably, GluA1 homomers were shown to behave the same as GluA1/2 heteromers in the whisker experience-dependent synaptic trafficking (Makino & Malinow, 2011). Combined, these studies suggest that GluA1 c-tail-containing AMPARs traffic into synapses in an activity-dependent manner.

As a model for GluA1-lacking AMPARs, overexpression of unedited GluA2 was used. In the absence of a GluA1 c-tail, these GluA2 homomers traffic into synapses independently of activity and without a change in synaptic strength (Shi *et al.* 2001; Makino & Malinow, 2011). In the barrel cortex synaptic trafficking of GluA2 homomers takes place independently of whisker experience (Takahashi *et al.* 2003) and mirrors the trafficking of GluA2/3 heteromers (Shi *et al.* 2001; Makino & Malinow, 2011). GluA2/3s constitutively replace synaptic AMPARs, potentially to keep synaptic strength stable in the face of continuous protein turnover. The replacement of overexpressed GluA1 homomers inserted into hippocampal synapses upon LTP induction or cortical synapses after whisker experience has been shown to not require activity and to take approximately 24 h (Takahashi *et al.* 2003; McCormack *et al.* 2006). Whether GluA2/3s are also used for synaptic strengthening during LTP is currently a matter of debate. A recent paper showed that in principle any type of receptor (independent of the c-tail) can be driven into synapses to achieve LTP

(Granger *et al.* 2013). However, when both long-tailed and short-tailed AMPARs are present, the long-tailed ones appear to be preferentially used for synaptic strengthening. This was shown for recombinantly expressed AMPARs (Jia *et al.* 1996; Hayashi *et al.* 2000; Shi *et al.* 2001; Lee *et al.* 2003; Kopec *et al.* 2006; Makino & Malinow, 2009; Makino *et al.* 2011; Tanaka & Hirano, 2012), as well as for endogenous AMPARs in amygdala synapses upon learning (Nedelescu *et al.* 2010). In addition, targeted *in vivo* mutations of AMPAR subunits demonstrate that the protein interactions and phosphorylations at the c-tail control their synaptic targeting (Lee *et al.* 2003; Steinberg *et al.* 2006). Thus, the long c-tail seems to give AMPARs a competitive advantage to be inserted into synapses upon synaptic strengthening (Sheng *et al.* 2013). The function of GluA2/3s in memory formation or information processing remains largely unclear. Mice that lack GluA2/3s (i.e. GluA3-knockout mice) have few behavioural deficits (Adamczyk *et al.* 2012) and create fear memories normally (Humeau *et al.* 2007). GluA2/3s have been implicated to play a role in the homeostatic scaling of synapse strength (Rial Verde *et al.* 2006; Gainey *et al.* 2009; Makino & Malinow, 2011). It is tempting to speculate that the increased propensity of GluA3-deficient mice to develop seizures (Steenland *et al.* 2008) is due to a defect in synaptic scaling.

### NMDA receptor composition (Fig. 1C)

NMDARs are ionotropic receptors that – by transmitting calcium ions – mediate multiple forms of synaptic plasticity (Malenka & Nicoll, 1993). Furthermore, NMDARs serve a structural role and can stabilize synapses (Alvarez *et al.* 2007). Mechanistically important is their sophisticated regulation of the ion pore. Under resting conditions the channel is blocked by magnesium ions, even in the presence of the endogenous agonist glutamate. Only upon significant depolarization from the resting potential is the magnesium block removed. As a consequence, NMDARs function as coincidence detectors: they only open their channels when presynaptic glutamate release and a postsynaptic depolarization precisely coincide. In most synapses, NMDARs are the major mediators of calcium influx. Therefore, the activity of NMDARs is crucial for the activation of Ca<sup>2+</sup>-dependent signalling pathways. For example, NMDAR activation and a subsequent intracellular rise in Ca<sup>2+</sup> are required for the induction of LTP. Also, LTD is triggered by NMDARs and a long held view postulates that NMDAR activation leads to LTD when low amounts of Ca<sup>2+</sup> enter the synapse (Cummings *et al.* 1996). However, a recent study demonstrated that NMDAR-dependent LTD does not depend on calcium influx (Nabavi *et al.* 2013). Instead, NMDARs also have metabotropic functions beyond their

role as ion channels: persistent glutamate binding to the NMDAR in the absence of channel opening activates a signalling pathway that leads to synaptic depression (Kessels *et al.* 2013; Nabavi *et al.* 2013).

NMDARs are tetramers, which are composed of two GluN1 subunits and two GluN2 subunits. There are four types of GluN2 subunits, GluN2A–D, which are differentially expressed across brain regions and developmental stages (Cull-Candy *et al.* 2001; Paoletti *et al.* 2013). The different GluN2 subunits confer strikingly variable characteristics on the functional receptors, including their kinetics, magnesium sensitivity, ion conductance, molecular interaction partners and – as a consequence – role in synaptic plasticity. As GluN2A and GluN2B predominate in hippocampal and cortical neurons (GluN2C is mainly found in cerebellum and GluN2D is only sparsely expressed) we will discuss the development of these two subspecies of NMDARs (Ewald & Cline, 2009).

NMDAR subunit composition changes during development. GluN2B expression levels are high before birth and in the first 2 weeks after birth. Thereafter, the expression levels of GluN2B decrease (Kirson *et al.* 1999; Sans *et al.* 2000). In contrast, GluN2A occurs later during development and the expression of GluN2A increases steadily throughout the first month after birth (Monyer *et al.* 1994; Sheng *et al.* 1994; Sans *et al.* 2000). As a consequence, the ratio of GluN2B to GluN2A in synapses increases during development in an activity-dependent fashion (Carmignoto & Vicini, 1992; Quinlan *et al.* 1999; Bellone & Nicoll, 2007). The GluN2B and GluN2A subunits differ in several functional aspects. (1) GluN2Bs have a higher affinity for glutamate (Laurie & Seeburg, 1994) and deactivate and desensitize more slowly than GluN2As (Flint *et al.* 1997; Vicini *et al.* 1998). (2) The voltage-dependent gating is slightly slower in GluN2B-containing NMDARs (Erreger *et al.* 2005; Clarke *et al.* 2013). (3) GluN2B-containing NMDARs traffic more rapidly in the cell membrane than those containing GluN2A, suggesting that in mature neurons NMDARs are more stably anchored (Groc *et al.* 2006). (4) The structure of the c-terminal region, with which they recruit cytoplasmic proteins to the synapse, differs between GluN2B and GluN2A. For instance, the GluN2B c-tail has a higher affinity for Ca<sup>2+</sup>/calmodulin-dependent protein kinase II (CaMKII) than the GluN2A c-tail (Strack & Colbran, 1998; Leonard *et al.* 1999), a protein that is crucial for the induction of LTP (see below). As a consequence, the presence of the GluN2B c-tail at a synapse facilitates LTP induction (Barria & Malinow, 2005; Foster *et al.* 2010; Ryan *et al.* 2013). GluN2B-rich synapses are therefore more plastic than synapses that are rich in GluN2A; they have a lower threshold for both LTP (Tang *et al.* 1999; Clayton *et al.* 2002) and LTD (Cui *et al.* 2013). In the mature hippocampus GluN2A

eventually outnumbers GluN2B in synapses. Synaptic NMDARs in mature neurons consist of GluN1/GluN2A or GluN1/GluN2A/GluN2B heteromers (Rauner & Kohr, 2011), while GluN1/GluN2B receptors can mostly be found outside synapses (Petralia *et al.* 2009). Therefore, mature synapses have a reduced ability to undergo plasticity compared with young synapses (Yashiro & Philpot, 2008; Lee *et al.* 2010b).

### Kinases (Fig. 1D) and phosphatases (Fig. 1E)

Synaptic plasticity events are mediated by altering protein interactions through phosphorylation. The phosphorylation targets comprise a myriad of synaptic proteins – including NMDARs and AMPARs. The majority of these phosphorylations take place on serine or threonine residues and a minority on tyrosine residues. There are many types of kinases and phosphatases that differ in substrate selectivity and regulation mechanisms and many of them have roles in synaptic plasticity. Here, we focus on those Ser/Thr kinases/phosphatases that are classically considered the most important for synaptic plasticity: the kinases protein kinase A (PKA), protein kinase C (PKC) and CaMKII, and the phosphatases PP1, PP2A and calcineurin (PP2B).

PKA expression starts after the first week of development and reaches mature levels in the second postnatal week. PKA is a tetrameric molecule with two regulating domains that inhibit the two catalytic domains (Francis & Corbin, 1994). Upon binding of cyclic AMP to the regulatory domain, the catalytic domain is released to phosphorylate its substrates. PKA has a wide range of targets, amongst which are *N*-methyl-D-aspartate receptors (NMDARs) and AMPARs. Early during development, the PKA-mediated phosphorylation of GluA4 is sufficient for synaptic potentiation (Esteban *et al.* 2003). At later stages when GluA1 is expressed, PKA phosphorylation of GluA1-containing AMPARs increases their surface levels (Man *et al.* 2007) and lowers the threshold for LTP (Esteban *et al.* 2003; Hu *et al.* 2007; Man *et al.* 2007; Seol *et al.* 2007; Lee *et al.* 2010a).

The PKC family of isozymes is a Ca<sup>2+</sup>-dependent phospholipid-sensitive group of Ser/Thr kinases. PKC is present in neuronal tissue in high concentration and participates in various neuronal functions including synaptic plasticity (Malenka *et al.* 1986; Malinow *et al.* 1989). Phosphorylation of long-tailed AMPARs GluA4 and GluA1 by PKC promotes their surface expression (Gomes *et al.* 2007; Lin *et al.* 2009) and LTP (Boehm *et al.* 2006b). PKC also phosphorylates the short c-tail of GluA2, but with an opposite effect: it leads to internalization of GluA2-containing AMPARs and LTD of synaptic strength (Chung *et al.* 2003; Seidenman *et al.* 2003; Lu



& Ziff, 2005; Steinberg *et al.* 2006). The outcome of PKC phosphorylation on synaptic strength therefore probably depends on the AMPAR subunit usage of a synapse. PKC isoforms alpha, beta, epsilon and zeta are expressed both during development and in adults (Roisin & Barbin, 1997). The most abundant isoform in hippocampus, cortex and cerebellum is the neuron-specific PKC $\gamma$  (Saito & Shirai, 2002). PKC $\gamma$  expression starts relatively late in comparison with PKA, in the second postnatal week, and reaches adult levels after 3 weeks (Roisin & Barbin, 1997).

CaMKII is crucial for the induction of LTP (Lisman *et al.* 2012). CaMKII is a circular holoenzyme that consists of 12 (alpha or beta) subunits. Upon LTP induction, calcium influx through the NMDAR channel leads to Ca<sup>2+</sup>-calmodulin binding to CaMKII and the activation of its catalytic kinase domain. A major phosphorylation target of CaMKII is CaMKII itself. LTP-induced autophosphorylation between neighbouring subunits can keep the CaMKII complex in an active state for up to 1 min after calcium levels have dropped (Miller & Kennedy, 1986; Lee *et al.* 2009). Upon autophosphorylation CaMKII translocates to the synapse (Shen & Meyer, 1999), where it can bind the GluN2B subunit of the NMDARs (Strack & Colbran, 1998; Leonard *et al.* 1999), thereby locking CaMKII in an active state (Bayer *et al.* 2001). Once activated and translocated to the synapse, CaMKII induces spine growth independent of its kinase activity (Pi *et al.* 2010), suggesting that CaMKII has a crucial structural role during LTP. The CaMKII–GluN2B interaction is vital for the induction of LTP (Barria & Malinow, 2005), and is either reversible or permanent depending on the level and duration of synaptic stimulation (Bayer *et al.* 2006). After LTP induction CaMKII can reside at the synapse for prolonged periods of time (Otmakhov *et al.* 2004), where its presence is required for the maintenance of synaptic strength (Sanhueza *et al.* 2011). Activation of CaMKII is sufficient to induce synaptic strengthening through the addition of GluA1-containing AMPARs to synapses (Hayashi *et al.* 2000). Besides its autophosphorylation required for LTP induction, CaMKII phosphorylation of GluA1 (Barria *et al.* 1997; Lu *et al.* 2010,*b*) and its auxiliary subunits (Tomita *et al.* 2005; Opazo *et al.* 2010) facilitate AMPAR insertion into synapses. It is possible that these phosphorylation events may only indirectly promote synaptic AMPAR trafficking by preventing AMPAR degradation and increasing their cell surface levels (Hayashi *et al.* 2000; He *et al.* 2009; Kessels *et al.* 2009). CaMKII phosphorylation events on GluA1 complexes also contribute to LTP by increasing AMPAR single-channel conductance (Derkach *et al.* 1999; Kristensen *et al.* 2011). CaMKII-dependent synaptic strengthening is common in adult neurons, but not during early development. In relation to this, CaMKII expression is relatively low during the first 2 weeks of development and increases in the

third and fourth week of development (Kelly & Vernon, 1985).

In contrast to LTP, NMDAR-dependent LTD depends largely on phosphatase activity (Malenka & Bear, 2004). LTD is prevented by inhibiting the phosphatases calcineurin (PP2B; Mulkey *et al.* 1994), PP1 (Mulkey *et al.* 1993; Kirkwood & Bear, 1994) or PP2A (Nicholls *et al.* 2008; Mauna *et al.* 2011). Calcineurin is a Ca<sup>2+</sup>-calmodulin dependent Ser/Thr phosphatase, is one of the most abundant phosphatases in the nervous system and acts on multiple substrates (Baumgartel & Mansuy, 2012). Calcineurin has a high affinity for Ca<sup>2+</sup>/calmodulin, and is already active under basal conditions when free Ca<sup>2+</sup> levels within the neuron are low, thereby constitutively inhibiting the insertion of GluA1-containing AMPARs into synapses and providing the force to generate LTD (Nabavi *et al.* 2013). An alternative route to achieve synaptic potentiation is lowering intracellular calcium levels or blocking calcineurin activity (Wang & Kelly, 1997; Nabavi *et al.* 2013). Previously identified types of synaptic potentiation that involve prolonged silencing or loss of Ca<sup>2+</sup> channels (Turrigiano *et al.* 1998; Ultanir *et al.* 2007; Adesnik *et al.* 2008) could potentially be driven by reduced calcineurin activity as a consequence of a drop in intracellular Ca<sup>2+</sup>. Calcineurin expression starts late during development: expression levels are low during the first 2 weeks of development, and gradually increase during the third and fourth weeks. In contrast, PP1 and PP2A are expressed at maximal levels from birth onwards (Strack *et al.* 1999; Takahashi *et al.* 2000) and therefore may control synaptic depression during early stages. Phosphatase activity of PP1 and PP2A is not Ca<sup>2+</sup>-dependent, but it is regulated through binding of accessory proteins or through their phosphorylation (Munton *et al.* 2004).

## Developmental phases of synaptic plasticity

The expression levels of the key molecules underlying synaptic plasticity change during the first 4 weeks of mouse and rat development. Even though these changes are gradual, they can be placed roughly into three developmental and one mature phase (Fig. 2). Interestingly, these phases are also associated with specific developmental stages beyond the structure and molecular composition of excitatory synapses. These comprise the presence of silent synapses, the switch from depolarization to hyperpolarization at GABAergic synapses, the onset of vision, hearing and active exploration when evoked activity adds to spontaneous activity in shaping circuitry, and finally the critical period after which brain function is usually considered to be mature (Fig. 1*F*). In the following we describe these developmental stages and analyse how the changes on the molecular and physiological levels



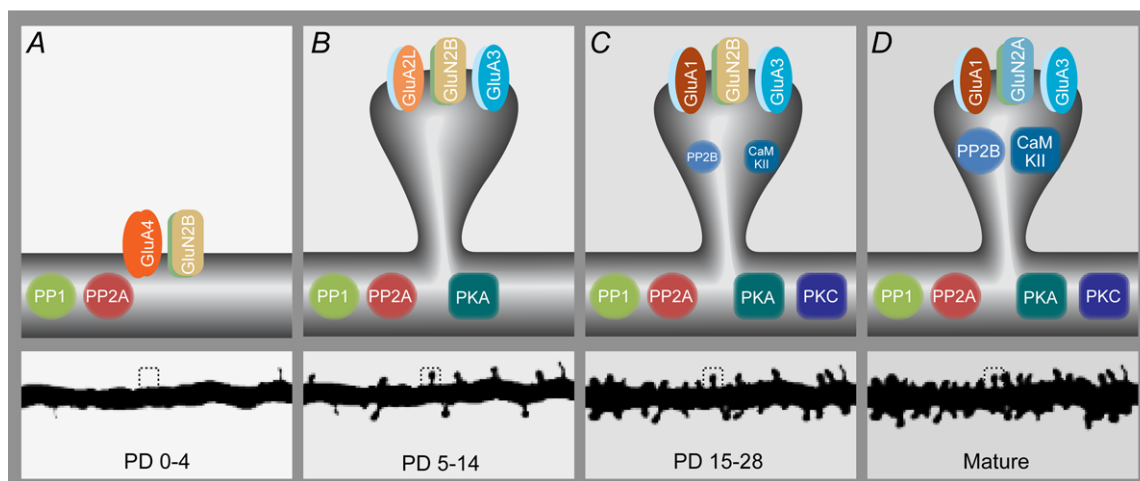
may help shape the networks that eventually direct behaviour.

### Early postnatal stages of synapse development, PD 0–4 (Fig. 2A)

The behaviour of the newborn rodent is based largely on reflexes. For instance, the suckling reflex requires olfaction and tactile sensation, and is mediated by the brainstem. The hippocampus and cortex receive only limited experiential sensory input during the first days of life (Akerman *et al.* 2002; Leinekugel *et al.* 2002; Khazipov *et al.* 2004; Colonnese *et al.* 2010). The density of synapses is still very low in hippocampus (Steward & Falk, 1991; Fiala *et al.* 1998) and cortex (De Felipe *et al.* 1997), and they are predominantly located on dendritic shafts or filopodia. However, the occurrence of dendrite–axon contacts increases during this period of development. Early steps of synaptic partner selection that are based on cellular recognition mechanisms during the formation of these contacts involve calcium signalling, but occur independently of neuronal activity (Lohmann & Bonhoeffer, 2008; Lohmann, 2009).

Despite the low numbers of functional synapses that are present at this age, spontaneous network activity is prevalent (Allene & Cossart, 2010; Blankenship & Feller, 2010). The transmission of early spontaneous network activity is mediated through gap junctions

(Kandler & Katz, 1995; Khazipov & Luhmann, 2006; Niculescu & Lohmann, 2013), transmembrane channels that directly connect the cytoplasm of adjacent cells. Gap junctions mediate both electrical and metabolic coupling of neurons by allowing the passage of ions and small signalling molecules. Through this they coordinate transcriptional activities in developing neurons (Meyer, 1991; Kandler & Katz, 1995; Roerig & Feller, 2000) and contribute to synchronized spontaneous activity. The incidence of gap junction coupling decreases during postnatal weeks 1–3 of the rat hippocampus (Strata *et al.* 1997) and neocortex (Connors *et al.* 1983; Peinado *et al.* 1993). This developmental uncoupling coincides with the major period of synaptogenesis and increased synaptic activity (Kandler & Katz, 1998). Spontaneous activity plays an important role in the establishment of early connections (Katz & Shatz, 1996; Feller, 1999) and can trigger synaptic plasticity in developing networks. For example, pairing spontaneous bursts of network activity with Schaffer collateral stimulation potentiates CA3 to CA1 synapses in a brain-derived neurotrophic factor (BDNF) and extracellular signal-regulated kinase (ERK) pathway-dependent fashion (Kasyanov *et al.* 2004; Mohajerani *et al.* 2007). Such correlation-based plasticity mechanisms act on quite long time scales at these ages (several hundred milliseconds; Lee *et al.* 2002; Kasyanov *et al.* 2004; Butts *et al.* 2007; Gjorgjieva *et al.* 2009) matching the duration of spontaneous bursts. It is likely that the presence of the GluN2B subunit of the



**Figure 2. Schematic of the structure and plasticity molecules of glutamatergic synapses at four fundamental stages of development**

A, between postnatal day 0 and 5 most synapses are located on the dendritic shaft, AMPARs only consist of GluA4 and NMDARs have all GluN2B. Phosphatases PP1 and PP2A are present, but the prime kinases are still absent. B, between postnatal days 5 and 14 synapses are still scarce but start occurring on spines, GluA2<sub>long</sub> is temporarily the dominant long-tailed AMPAR subunit, while short-tailed AMPAR subunits GluA2/3 also start being expressed. C, in the third and fourth weeks after birth spine numbers increase exponentially. PKA is becoming the dominant kinase. D, when the rodent is mature, spine numbers maximize, the developmental switch of GluN2B to GluN2A has occurred and CaMKII and calcineurin (PP2B) have reached maximal levels.

NMDAR at this developmental stage, which deactivates and desensitizes more slowly than GluN2As (Flint *et al.* 1997; Vicini *et al.* 1998), underlies the ability to integrate correlations across entire bursts of activity.

Furthermore, spontaneous activity is important for an even finer scale of connection specificity: both action potential firing and NMDAR activation are required for sorting synapses on dendrites of hippocampal pyramidal cells in dependence of their presynaptic activity patterns, i.e. the functional clustering of synaptic inputs (Kleindienst *et al.* 2011). However, how this early plasticity relates to classical LTP mechanisms is unclear, as the critical molecular players involved are either absent or present only at low levels. Furthermore, LTP-inducing protocols trigger postsynaptic depolarizations less efficiently and thus young neurons show higher thresholds for LTP induction (Liao & Malinow, 1996).

Notably, one of the long-tail glutamate receptor subunits, GluA4, is maximally expressed during this period. As GluA4-containing AMPARs can be incorporated into synapses during early steps of synapse formation (Sia *et al.* 2007), the question emerges as to whether GluA4 may support some form of early synaptic potentiation. Interestingly, GluA4 can be targeted to synapses through a mechanism that requires spontaneous activity in slightly older neurons (P5–7, see below; Zhu *et al.* 2000). Therefore, it is likely that during the first few days of rodent life the dominant mechanism for AMPAR recruitment to synapses is this spontaneous activity-driven GluA4 trafficking. The GluA4-driven synapse strengthening may play an important role in the initial establishment of the functional circuitry. Interestingly, the GluA4-knockout mouse displays behavioural deficits that mimic aspects of schizophrenia-like behaviour (Sagata *et al.* 2010). Altered brain development at the fetal or neonatal stage can indeed be the origin of schizophrenia. Whether schizophrenia can originate from mutations in GluA4 is unclear; an association between polymorphisms in the GluA4 gene *Gria4* and susceptibility for schizophrenia was found among a Japanese population (Makino *et al.* 2003), but not in a Chinese or Korean population (Guo *et al.* 2004; Crisafulli *et al.* 2012).

### Synapse development before onset of visual and auditory experience, PD5–14 (Fig. 2B)

The second postnatal phase of brain development leads up to the moment when mice and rats open their eyes, begin hearing and start interacting with the environment at the end of the second postnatal week. Synapse numbers increase steadily, at a sub-maximal rate in the hippocampus (Steward & Falk, 1991; Fiala *et al.* 1998) and almost maximally in the cortex (De Felipe *et al.* 1997). While some sensory inputs can be measured, for

example in central somatosensory and visual pathways (Akerman *et al.* 2002; Khazipov *et al.* 2004; Colonnese *et al.* 2010), spontaneously generated activity still dominates the emerging networks (Leinekugel *et al.* 2002; Demas *et al.* 2003; Allene *et al.* 2008; Golshani *et al.* 2009; Rochefort *et al.* 2009; Colonnese *et al.* 2010; Ackman *et al.* 2012; Siegel *et al.* 2012). Besides glutamatergic and gap junction signalling (see below), GABAergic transmission is required for normal spontaneous network activity at these ages (Khazipov & Luhmann, 2006; Ben Ari *et al.* 2007; Allene & Cossart, 2010). Counterintuitively, GABA acts as a depolarizing transmitter during the first postnatal week and becomes inhibitory only during the second week. The cause of the shift from depolarizing to hyperpolarizing action of GABA is a reduction in the intracellular chloride concentration during the second postnatal week, which is mediated in turn by changes in chloride transporter expression (Rivera *et al.* 1999; Sipilä *et al.* 2006). Importantly, depolarizations at GABAergic synapses can remove the magnesium block of NMDARs during this stage of development (Leinekugel *et al.* 1997) and may therefore contribute directly to the plasticity or unsilencing of excitatory synapses (Chancey *et al.* 2013).

The progression of spontaneous activity across brain regions requires, besides chemical synapses, gap junctions during the first week of postnatal development in several rodent brain structures, for example the retina and the cortex (Syed *et al.* 2004; Dupont *et al.* 2006; Siegel *et al.* 2012). Furthermore, recent studies suggest that early gap junction coupling is required for wiring neurons into emerging circuits (Li *et al.* 2012; Yu *et al.* 2012). During the first postnatal week, clonally related neurons in the visual cortex are highly connected with each other via gap junctions, but not with other nearby neurons. Later in life, these clones are still highly interconnected, although not through gap junctions, but rather by functional synapses. Remarkably, early electrical coupling is necessary for the formation of chemical synapses between sister neurons later on (Yu *et al.* 2012) and for the establishment of similar receptive fields among them after eye opening (Li *et al.* 2012). An intriguing possibility is that gap junctions facilitate simultaneous firing of electrically coupled neurons and thus increase the occurrence of LTP in their common inputs (Yu *et al.* 2012; Ko *et al.* 2013).

While the initiation of LTP is not fully developed at the end of the first postnatal week, 1 week later the ability to undergo potentiation is already maximal at hippocampal synapses (Harris & Teyler, 1984; Liao & Malinow, 1996). This correlates with an increase in the number of spine synapses and – on the molecular level – the expression of the key kinases PKA and PKC during the second postnatal week. CaMKII is still expressed at low levels (Kelly & Vernon, 1985) and is, in contrast to PKA, not required for LTP before P14 (Yasuda *et al.* 2003). The dependence of LTP on PKA during the second week of

development correlates with a change in AMPAR subunit usage. Between the first and the second postnatal week, the expression of the long-tailed AMPAR subunits GluA4, GluA2<sub>long</sub> and GluA1 peaks sequentially (Zhu *et al.* 2000; Kollerker *et al.* 2003). The two early expressed subunits, GluA4 and GluA2<sub>long</sub>, are targeted to synapses by spontaneous activity (Zhu *et al.* 2000; Kollerker *et al.* 2003). Also, PKA activation is sufficient to target GluA4 to synapses through phosphorylation of its c-tail (Esteban *et al.* 2003). As the structures of the GluA4 and GluA2<sub>long</sub> c-tail are highly conserved around the PKA phosphorylation site, it is possible that PKA phosphorylation of the GluA2<sub>long</sub> c-tail suffices, too. In contrast, for GluA1, which is expressed later, spontaneous activity or PKA activation is insufficient; GluA1 requires more elaborate activity patterns and CaMKII activation to be inserted into synapses during LTP (Hayashi *et al.* 2000). The question of whether the evolving changes in AMPAR usage reflect differences in demands for LTP was addressed in a study in the barrel cortex of the rat (Miyazaki *et al.* 2012). Whisker experience leads to GluA4 synaptic targeting at P8–10 when CaMKII levels are still low. A few days later, at P12–14, the preference is reversed: GluA1 subunits are inserted into synapses upon whisker experience and not GluA4 subunits. Thus, the developmental change in plasticity mechanisms (e.g. PKA or CaMKII driven) coincides with the preference for AMPAR subtype to be used for synaptic insertion.

At the end of the second postnatal week, mice and rats open their eyes and start interacting with their environment. This moment seems to be critical in hippocampal and cortical development. In developmental disorders, errors in connectivity become frequently apparent at this age. For example, SynGAP mutant mice, a model of intellectual disability and autism, exhibit premature spine structure and synaptic function at P14. And even though spines and synapse function appear to be normal at later stages, the behavioural abnormalities are permanent (Clement *et al.* 2012).

### Synapse development after activation of sensory inputs, P15–28 (Fig. 2C)

During the next 2 weeks when young animals start exploring their environment synapse density increases fast in the cortex and hippocampus (Steward & Falk, 1991; De Felipe *et al.* 1997). This increase is almost exclusively driven by the emergence of spine synapses, and is critically dependent on NMDAR function (Ultanir *et al.* 2007). During the third week of development, when spines are very dynamic and synapse numbers increase rapidly, synaptic NMDARs are dominantly composed of GluN2B. In neurons in which GluN2B is selectively knocked-out the number of synapses is increased, suggesting that GluN2B

mediates the loss of synapses that lack correlated activity (Gray *et al.* 2011). The expression levels of GluN2A gradually increase at this stage and the GluN2B to GluN2A ratio in synapses decreases. As a consequence of this GluN2B to GluN2A switch, functional and structural changes in spines become more difficult and synapse numbers stabilize (Gambrill & Barria, 2011; Gray *et al.* 2011). Synapse density reaches a maximum at the end of the fourth week (Steward & Falk, 1991; De Felipe *et al.* 1997).

On the molecular level, the expression of several late occurring, but central, components of the synaptic plasticity machinery increases steadily until P28. Besides the NMDAR subunit GluN2A, the most important molecular factors are the kinase CaMKII and the phosphatase calcineurin (PP2B). In the third week of development, LTP is only partly dependent on PKA and becomes increasingly dependent on CaMKII, which starts to be expressed in hippocampal neurons at this time. At the end of the fourth postnatal week LTP is fully CaMKII dependent (Yasuda *et al.* 2003). The increasing expression of calcineurin during the third and fourth weeks of development impedes long-tailed AMPAR entry into synapses (Nabavi *et al.* 2013), which may raise the threshold for LTP induction. Indeed, whereas in young rats (P12–14) whisker experience is sufficient to drive GluA1-containing AMPARs into synapses, at the third week (P21–23) when functional reorganization of the whisker-barrel map is complete, whisking is insufficient (Jitsuki *et al.* 2011).

### Plasticity in the mature brain, P28 and onwards (Fig. 2D)

Between P28 and P32, synaptic plasticity is temporally enhanced in the mouse visual cortex, and is known to be the critical period for ocular dominance plasticity (Espinosa & Stryker, 2012; Levelt & Hübener, 2012). During this period, a frequently employed plasticity paradigm, monocular deprivation, leads to decreased responses from the deprived eye and increased responses from the open eye and these functional changes are associated with significant rearrangements of synaptic connections. As absolute synapse numbers have reached a maximum by now and are in fact slightly reduced after this period (Steward & Falk, 1991; De Felipe *et al.* 1997), synapse elimination is probably contributing to refining network connections. The late plasticity molecules, CaMKII, calcineurin and GluN2A, approach adult levels during the critical period, at the end of the fourth week of life. While GluN2A is not required for ocular dominance plasticity in general (Fagiolini *et al.* 2003; Cho *et al.* 2009), the relative contribution of LTP is increased whereas LTD is decreased in GluN2A-knockout mice (Cho *et al.* 2009),

suggesting very specific contributions of GluN2A- and GluN2B-mediated synaptic plasticity in adaptations of the visual system during the critical period. In addition, altered plasticity at inhibitory synapses (van Versendaal *et al.* 2012; Chen *et al.* 2012) plays a prominent role in the observed differences in visual plasticity during and after the critical period. After the critical period the threshold for plasticity in the visual system is reduced, but it is still possible and previous experience-induced plasticity (during the critical period) reduces the threshold for plasticity in adults (Hofer *et al.* 2006, 2009). A reduction in structural plasticity might prevent large-scale reorganization of connections after the critical period (Levelt & Hübener, 2012).

When mature, several types of hippocampal learning and cortical information processing depend on the NMDAR-dependent, CaMKII-mediated synaptic strengthening through the insertion of GluA1-containing AMPARs (Kessels & Malinow, 2009; Mayford *et al.* 2012). The ability to have synaptic plasticity is reduced in the mature nervous system, partly caused by an increased GluN2A to GluN2B ratio at the level of individual synapses. The adult rodent is capable of having synaptic plasticity, but this is largely absent under basal conditions and requires special circumstances. For instance, in mature mice whisking does not lead to synaptic strengthening at layer 2/3 pyramidal synapses under normal conditions. However, when surrounding whiskers are removed, stimulation of the remaining whisker does lead to synaptic strengthening through deprivation-mediated disinhibition (Gambino & Holtmaat, 2012). The most important factor that facilitates synaptic plasticity in the mature brain is emotion. An emotionally charged experience induces the release of modulatory neurotransmitters such as dopamine, serotonin, noradrenaline and glucocorticoids, which can facilitate plasticity through multiple signalling pathways, including synaptic AMPAR trafficking (Hu *et al.* 2007; Krugers *et al.* 2010; Jitsuki *et al.* 2011). For instance, both dopamine and noradrenaline signalling lead to PKA phosphorylation of AMPAR subunit GluA1 (Vanhoose & Winder, 2003; Mangiavacchi & Wolf, 2004), and neurons from mature mice depend more on this phosphorylation event to obtain LTP compared with neurons from young animals (Lee *et al.* 2003; Lu *et al.* 2007). The noradrenaline-induced phosphorylation of GluA1 indeed promotes memory formation of a fearful event (Hu *et al.* 2007).

## Conclusion

We have discussed here how the synapses in the brain adapt to the changing requirements for synaptic plasticity. While the emergence of synapse structure and function is gradual during development, we show that it can be

divided roughly into four phases based on the expression levels of key plasticity molecules as illustrated in Figs 1 and 2. Early in rodent development, synaptic plasticity mechanisms are employed to create the synaptic network. In the second developmental phase synaptic connections are being fine-tuned to optimally prepare the brain for interpreting and responding to the outside world. During the third phase, synaptic plasticity is used to process, interpret and encode all this new information in the brain. In phase four, the mature hippocampus and cortex use synaptic plasticity to learn, adapt behaviour and create memories. We hope that this overview may serve as a 'seed crystal' to establish a framework of the molecular and physiological stages of synapse development. It will be important to investigate whether the expression levels of other developmentally regulated plasticity molecules, in particular those that are involved in presynaptic, dendritic or axonal plasticity mechanisms, correlate with the developmental phases as defined in Fig. 1.

In the rodent brain the developmental phases of synaptic plasticity are completed within 6 weeks after birth. The human brain develops in a much different time frame compared with rodents. First, while rodents are blind until P4–5 and open their eyes at P14, human babies have a functional visual system already at gestational week 20 and open their eyes immediately after birth. This may mean that the first two phases after rodent birth are actually accomplished in the human brain before birth. After birth, however, the human brain takes a much longer and slower path to maturity. It will be interesting to establish how the expression levels of the key synaptic plasticity proteins as shown in Fig. 1 develop in humans.

It is clear that synaptic plasticity mechanisms are important for establishment of the neuronal circuitry. Therefore, disruptions of developmental plasticity mechanisms have long-lasting consequences for cognition and behaviour (Zoghbi, 2003; Sudhof, 2008; Bhakar *et al.* 2012; Castren *et al.* 2012). Developmental disorders and other neuropsychiatric illnesses such as autism, schizophrenia, attention deficit hyperactivity disorder (ADHD), anxiety disorders, depression or addiction can be caused genetically (Vorstman & Ophoff, 2013), through physical, hormonal or pharmacological impact during gestation or birth, and through stressful events during birth or early childhood (Insel & Fernald, 2004). Therefore, the mapping of active plasticity mechanisms during the phases of development may provide insights into the specific causes of developmental disorders. Further research integrating molecular, physiological and behavioural aspects will provide a more complete map of synaptic plasticity mechanisms during the different phases of brain development and may inform us at what stage the brain is particularly sensitive to errors in mechanisms of synaptic plasticity and how interventions may prevent cognitive deficits.



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## Additional information

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