Does spike-timing-dependent synaptic plasticity underlie memory formation?

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Summary

1. Synaptic plasticity is thought to underlie learning and memory formation in the brain. However, how synaptic plasticity is induced during these processes remains controversial. An attractive candidate mechanism for learning at the neuronal level is spike-timing-dependent synaptic plasticity (STDP), which depends on the precise (millisecond) timing of the synaptic input and the postsynaptic action potential. This temporal relationship resembles typical features of associative learning. Here we review recent evidence suggesting that STDP is likely to underlie certain forms of learning.

2. First we discuss the cellular mechanisms of STDP elucidated by *in vitro* experiments. A special focus is put onto aspects known to differ between *in vitro* preparations and the *in vivo* situation.

3. Next we review the experimental induction of STDP *in vivo*, in various systems ranging from *Xenopus* tectum to human motor cortex.

4. The last part of the review addresses the question whether STDP can be induced by activity patterns occurring during normal behaviour.

5. We conclude that STDP is a robust phenomenon *in vivo* and a likely mechanism underlying sensory map plasticity in the neocortex. Further experimental evidence is required to determine whether STDP also has a role in more complex forms of learning.

Introduction

One of the central questions in neuroscience is understanding the mechanisms mediating the enormous information storage capacity of the brain. The discovery of long-term potentiation (LTP) of synaptic transmission[1] and its counterpart, long-term depression (LTD),[2] sparked off an avalanche of research which ultimately led to the hypothesis that activity-dependent synaptic plasticity is both necessary and sufficient for memory formation.[3,4] Although there is still debate about the exact stage(s) of memory formation at which synaptic plasticity is required, it is now generally accepted that synaptic plasticity participates in many forms of learning and memory formation.[3-5]

With this proviso, the present review addresses the question of what mechanisms are likely to underlie induction of synaptic plasticity in the vertebrate brain *in vivo*. Experimentally, synaptic plasticity can be induced by a plethora of protocols, which can loosely be grouped into two groups: frequency-dependent and pairing-dependent. In frequency-dependent protocols, the sign and magnitude of the change in synaptic strength depends on the frequency of synaptic activation. Low-frequency activation as a rule causes LTD, whereas high-frequency activation typically elicits LTP. In contrast, pairing-dependent protocols induce plasticity through coincidence of presynaptic activation and postsynaptic depolarisation. The duration of coincident activation during pairing varies greatly in these protocols, from several hundred milliseconds[6] to just one pre- and postsynaptic action potential in a specific form of synaptic plasticity termed spike-timing-dependent plasticity (STDP). In contrast to frequency-dependent protocols, during STDP the sign and magnitude of the change in synaptic strength depends on the precise timing of pre- and postsynaptic activation.

Which induction mechanism is employed *in vivo* will depend on the activity patterns occurring in the brain during learning, and ultimately on how information is represented and processed in the brain. Information theory predicts that information can be coded either exclusively in the rate of action potential firing[7] or using both the rate and timing of action potentials.[8] Mounting evidence suggests that spike-timing is likely to be important for information processing in both invertebrates[9] and vertebrates. *In vivo* whole-cell recordings from the cortex of rats during anaesthesia,[10] quiet wakefulness[11] and free exploration[12] show surprisingly low action potential rates. This suggests that single action potentials have a much higher information content than previously thought; an interpretation which is further supported by the recent finding that the firing of a single cortical neuron can elicit whisking movement.[13] In this study the importance of spike-timing is highlighted by the fact that whisking was phase-locked to the timing of individual action potentials. In summary, there is evidence that at least in some brain areas, such as somatosensory cortex, spike-timing is used to encode information. This makes STDP a prime candidate for induction of synaptic plasticity. In this review we will discuss the cellular mechanisms underlying STDP induction *in vitro* with a focus on how this might differ *in vivo*. We will then review recent evidence suggesting that STDP occurs *in vivo*.
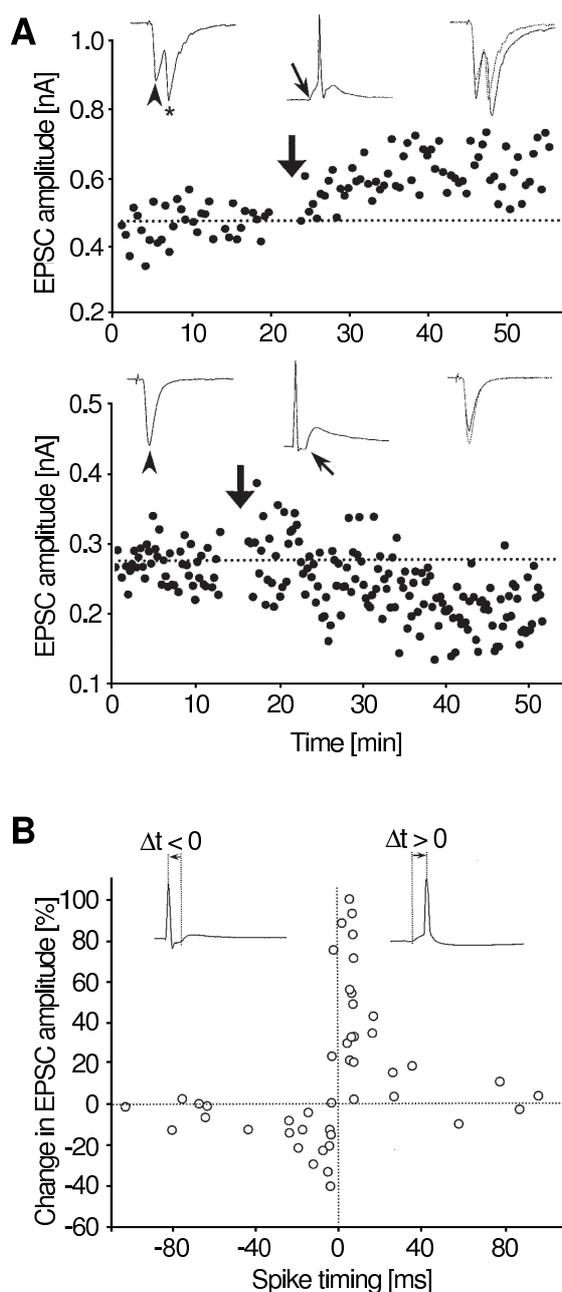
Figure 1. STDP learning rules in vitro. Paired recordings were performed in dissociated cultures of rat hippocampal neurons. A: Stimulation of the presynaptic neuron gives rise to an EPSC (top, left inset, arrowhead). After pairing pre- and postsynaptic action potentials in current clamp (top, large arrow), with the EPSP leading the postsynaptic action potentials by +5 ms (top, middle inset, small arrow indicates EPSP onset), synaptic strength is persistently enhanced. Conversely, LTD is induced if the EPSP follows the postsynaptic action potential during pairing (bottom). B: The full STDP timing curve is characterised by induction of LTP for positive and LTD for negative timings. Note the striking transition from maximal LTP to maximal LTD over the very narrow time window around 0 ms. Reproduced with permission from Bi & Poo,[18] copyright 1998 by the Society for Neuroscience.

Cellular mechanisms underlying spike-timing-dependent plasticity

STDP is a form of bi-directional plasticity in which the temporal order of pre- and postsynaptic action potentials on a precise (millisecond) time scale triggers changes in synaptic strength (reviewed in Dan & Poo, 2004,[14] 2006[15]). The dependence of synaptic plasticity on temporal order was first described in experiments using different stimulation intensities for ipsi- and contralateral projections from the entorhinal cortex to the dentate gyrus.[16] Levy and Steward noted that pairing short stimulus trains of a weak input with a strong input caused timing-dependent plasticity in the weak input, with LTP elicited when the weak input preceded the strong stimulus train, whereas LTD was observed for the reverse order.

A detailed characterisation of the timing-dependence of STDP (see Figure 1) showed that most synapses undergo LTP when the postsynaptic action potential follows the synaptic input (positive timing), whereas LTD is usually observed when the postsynaptic action potential precedes the synaptic input (negative timing).[6,17,18] The functional interpretation of these results is that synaptic inputs that contribute to postsynaptic firing are potentiated, whereas uncorrelated inputs are depressed. This is in essence Hebb's postulate,[19] which is computationally attractive since it directly relates plasticity of an input to its contribution to neuronal output.

However, STDP timing requirements differ between cell types and synapses: connections between neocortical spiny stellate neurons display LTD over a wide range of positive and negative timings,[20] whereas hippocampal inhibitory connections potentiate over a symmetrical time window of ± 20 ms.[21] In addition, STDP also depends on the timing of preceding action potentials,[22,23] the sub-cellular location of inputs in the dendritic tree,[24-26] the firing mode during induction,[26-29] and the generation of dendritic spikes.[26,29-32]

Despite cell type and synapse specific differences, there is little doubt that active backpropagation of action potentials into the dendritic tree[33,34] serves as the feedback signal to synapses during STDP induction.[35] The common model of STDP induction assumes that depolarisation associated with backpropagating action potentials triggers plasticity via relief of the voltage-dependent block of the NMDA-receptor by magnesium ions.[36,37] At positive spike timings this leads to substantial calcium influx through synaptic NMDA-receptors, triggering LTP.[38,39] Consistent with this it has recently been shown that brief depolarisations early after glutamate binding are best able to activate NMDA-receptors.[40] In contrast, the moderate NMDA-receptor mediated calcium signal evoked by pairings at negative times is thought to trigger LTD.[14,41-43] However, LTD induction appears to be more heterogeneous since it has also been reported to depend on NMDA-receptor desensitisation,[24] voltage-gated calcium channels,[18] metabotropic glutamate receptors[20,39,44] and

presynaptic NMDA-receptors.[44,45]

Can the requirements for STDP identified *in vitro* be observed *in vivo*? With respect to spike timing there is ample evidence that action potentials in neuronal networks can be activated with precise millisecond timing during physiological stimuli (Figure 2A,B).[46-48] The extent of action potential backpropagation *in vitro* can be regulated by dendritic membrane potential,[49,50] and so is likely to be influenced by the level of excitatory and inhibitory synaptic drive *in vivo*. This would be expected to impact on STDP induction *in vivo* where network activity is thought to be much greater than in the relatively quiescent slice preparation. Recordings from anaesthetised animals frequently show periodical oscillations in membrane potential termed up- and down-states.[51,52] Up-states have been interpreted as 'high-conductance states'[53] (but see Waters & Helmchen[54]), which might compromise action potential backpropagation.[55] In contrast, recent studies have found that action potential backpropagation is similar *in vitro* and *in vivo* (Figure 2C),[56-59] and can actually be boosted *in vivo* during up-states (Figure 2D).[60] A greater understanding of action potential backpropagation *in vivo* under behaviourally relevant conditions (if feasible, see Lee *et al.*[12]) is required to judge whether STDP is likely to be a robust phenomenon *in vivo*.

Another open question is the relative importance of dendritic spikes for *in vivo* plasticity induction. Dendritic spikes are regenerative events in the dendrite which can be elicited by strong extracellular stimulation (e.g. Holthoff *et al.*[31] and Schiller *et al.*[61]) or by high-frequency bursts of backpropagating action potentials (e.g. Larkum, Kaiser & Sakmann[62] and Kampa & Stuart[63]). Both forms of dendritic spikes are able to induce synaptic plasticity *in vitro*,[26,29-31] but their contribution to *in vivo* plasticity is controversial.[64,65] New techniques like two-photon fluorescence imaging that allow high resolution measurements of dendritic calcium signals *in vivo*[66] can be used to detect dendritic spikes in cortical pyramidal neurons during extracellular stimulation or sensory input.[59,67] Further studies will be needed to explore the importance of these dendritic spikes to information processing and induction of synaptic plasticity in the intact brain.

Experimental induction of STDP *in vivo*

The first characterisation of STDP induced *in vivo* was provided by Zhang and co-workers using electrical stimulation of retinotectal afferents in the *Xenopus* tadpole while recording from tectal neurons.[68] Pairing was performed using suprathreshold stimulation of one input combined with subthreshold activation of a second, independent input. This was a landmark study since it provided direct evidence for STDP *in vivo* with timing requirements for induction of LTP and LTD similar to those found *in vitro*. In addition, it provided a plausible mechanism for refinement of the retinotectal map during development. It was subsequently shown that repetitive visual input elicits LTP at retinotectal afferents.[69] LTP induction depended on postsynaptic action potential firing,

NMDA-receptor activation and occluded further potentiation, consistent with STDP observed *in vitro*. However, the light stimulus used typically evoked several action potentials, making it impossible to determine the contribution of single EPSP-action potential pairings. This question was addressed in a recent paper which found that pairing subthreshold visual stimuli with single action potentials evoked in tectal neurons by current injection elicits STDP with conventional timing requirements.[70] In summary, this series of studies strongly supports a critical role for STDP in the activity-dependent refinement of retinotectal afferents in *Xenopus laevis*.

There is also evidence for STDP in the mammalian brain. In the kitten, pairing of orientated gratings of a given orientation with extracellular stimulation of the cortex induced shifts in the orientation preference of this area as assessed by intrinsic optical imaging.[71] The observed effects were consistent with STDP learning rules: when the visual stimulus preceded electrical stimulation of the cortex by approximately 20 ms, the orientation preference was shifted towards the paired orientation. Conversely, if the visual stimulus followed electrical activation by ~10 ms, the orientation preference was shifted away from the paired orientation. A complimentary approach was pursued by Yao and Dan[72] who paired gratings of different orientation while electrically recording the orientation preference of single neurons in primary visual cortex. This caused a shift in the orientation tuning of the recorded neurons away from their initially preferred orientation towards the orientation of the stimulus that was presented first. It was subsequently shown that this shift was most likely mediated by STDP of intracortical connections.[73]

Similar results have been obtained for the representation of visual space.[74] The spike-timing of neurons in primary visual cortex was found to be precisely controlled by visual activation of their receptive field. When the receptive fields of two neurons were activated repeatedly in a defined temporal order, the receptive field was found to shift towards the location which was presented first. A similar displacement of the receptive field has recently been demonstrated at the single cell level using pairing of visual input with precisely timed postsynaptic action potentials,[75] suggesting that STDP is likely to underlie this phenomenon. Taken together, these data provide strong evidence that STDP can be induced experimentally in the visual cortex, both by pairing visual stimuli with electrical stimulation and by pairing two visual stimuli.

Evidence for STDP in the human brain

Remarkably, psychophysical experiments suggest that pairing different visual stimuli can have similar effects on both the orientation preference[72] and the spatial representation[74] in humans. In addition, a timing-dependent form of plasticity can be induced in the human brain during pairing of transcranial magnetic stimulation (TMS) of the motor cortex with peripheral nerve stimulation.[76] This study reported a persistent enhancement of motor evoked
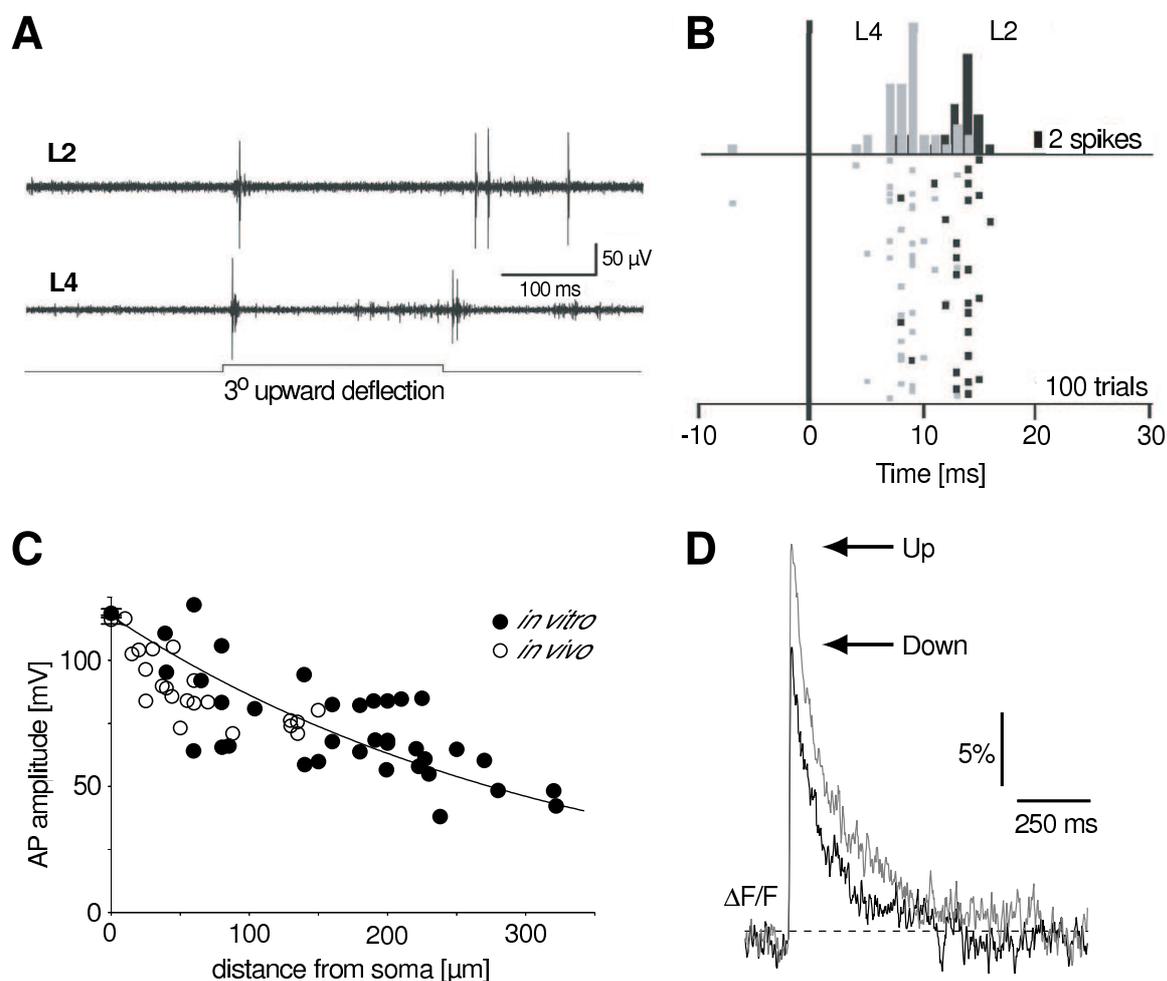
***Figure 2. Temporal fidelity and action potential backpropagation** in vivo. **A,B:** Simultaneous extracellular recordings in layer 4 and layer 2/3 of rat barrel cortex. **A:** Example spike trains in response to multi-whisker deflection (bottom). Note the low overall action potential rates. **B:** Raster plot of spikes elicited by 100 whisker deflections shows that layer 4 neurons consistently fire before layer 2/3 cells. **C:** Backpropagating action potentials were recorded at different locations on the apical dendrite of neocortical L2/3 pyramidal neurons in brain slices (in vitro) and in vivo. The amplitude of backpropagating APs declines with distance from the soma to a similar extent* in vitro *and* in vivo*. **D:** Two-photon imaging of calcium transients evoked by backpropagating action potentials in the apical dendrite of L2/3 pyramidal neurons* in vivo*. Action potentials fired from an up state ("Up") elicit larger calcium transients, suggesting that backpropagation is boosted during up states. **A,B** reproduced with permission from Celikel, Szostak & Feldman.[48] **C,D** reproduced with permission from Waters* et al.[59] *and Waters & Helmchen,[60] copyright 2003 and 2004 by the Society for Neuroscience.*

potentials when nerve stimulation precedes TMS-evoked cortical activation by 25 ms (Figure 3). This potentiation is thought to be expressed in motor cortex, is long-lasting (up to 60 min) and depends on NMDA-receptor activation.[77] A later extension of the pairing intervals showed that motor evoked potentials can also be depressed by this paradigm, revealing a timing curve with striking similarity to classical STDP learning rules but offset by approximately +20 ms.[78]

Can STDP be evoked *in vivo* by physiologically relevant inputs?

While all of the studies reviewed above have demonstrated that experimental induction of STDP is

possible *in vivo*, a question of equal importance is whether the activity patterns occurring during normal behaviour are able to induce STDP. This question was addressed by recent papers investigating the synaptic mechanisms underlying map plasticity due to sensory deprivation in rat barrel cortex (reviewed in Feldman & Brecht[79]). The barrel cortex is ideally suited for these studies since it contains an ordered, somatotopic map representing the animal's facial whiskers (reviewed in Petersen[80]). This makes it possible to perform sensory deprivation by plucking a row of whiskers and, after several days during which the animal is exposed to its normal environment, the corresponding cortical columns can be identified *in vitro* in a slice preparation.[81] This
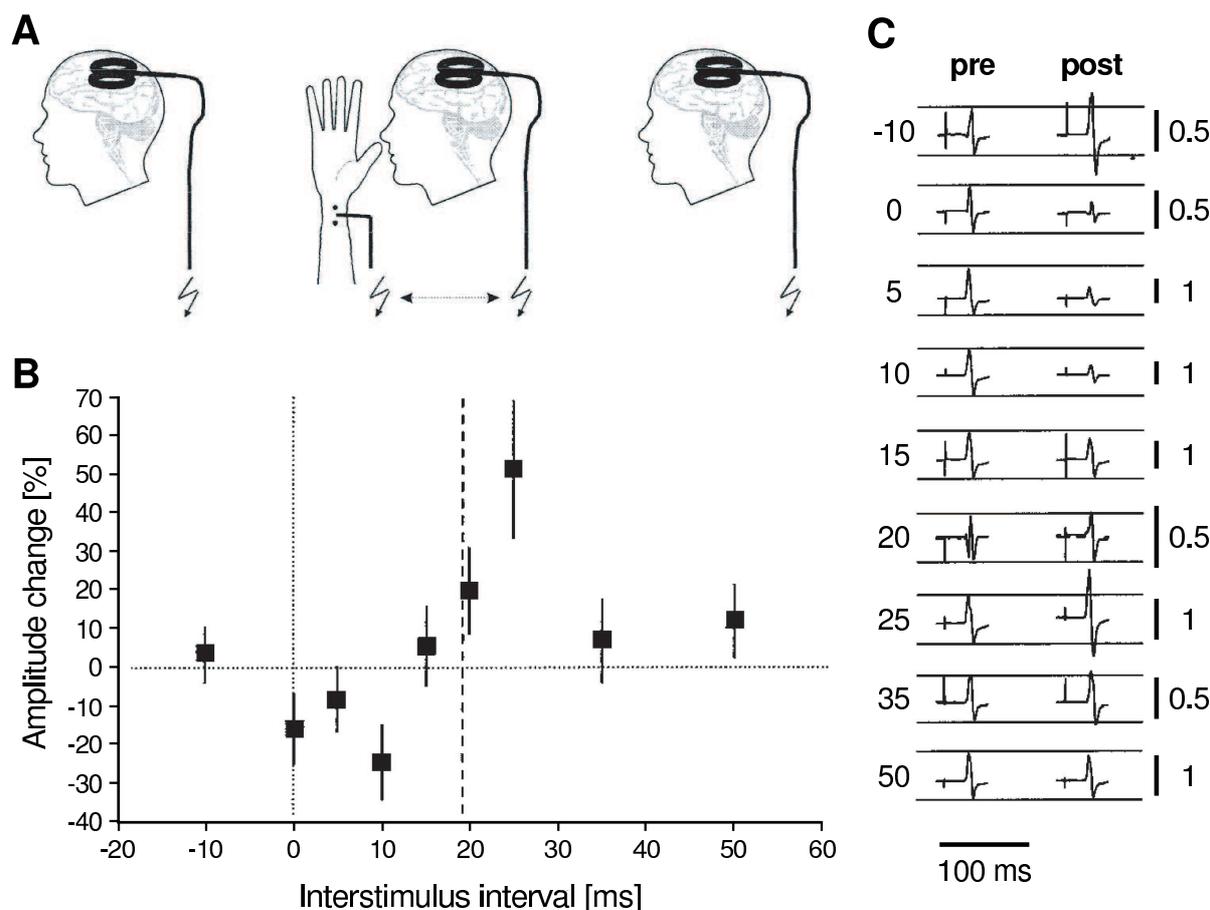
Figure 3. STDP induction in human motor cortex. A: *Motor evoked potentials (MEPs) were evoked by transcranial magnetic stimulation (TMS) of the motor cortex. Pairing was carried out between TMS and electrical stimulation of the median nerve in the periphery (middle).* **B:** *The effect of pairing depends on inter-stimulus interval: stimulation of the peripheral nerve 10 ms before TMS (+10 ms) depresses MEPs, whereas MEPs are potentiated at +25 ms. The full timing curve has striking similarity to STDP curves observed* in vitro *(Figure 1), but is offset by +20 ms, which is approximately the time required for excitation from the peripheral nerve to reach the motor cortex.* **C:** *Example MEPs before and after pairing at the timings indicated on the left. Calibration bars on the right are in mV. Reproduced with permission from Wolters* et al.*.[78]*

experimental regime was found to induce LTD of evoked field potentials at L4 to L2/3 feed-forward synapses in deprived barrels,[82] occluding further LTD induction and enhancing induction of LTP. This *in vivo* induction of synaptic plasticity could be due to sensory deprivation affecting either average action potential firing rates or the relative timing of pre- and postsynaptic action potentials. This question was addressed using simultaneous extracellular recordings in L4 and L2/3 of the same barrel in freely behaving rats.[48] Acute whisker deprivation caused only a modest reduction in average action potential frequency. The authors then assessed relative spike-timing between L4 and L2/3 in anaesthetised animals. When all whiskers where deflected simultaneously, spike-timing was precise, with L4 neurons spiking several milliseconds before L2/3 neurons (Figure 2A,B). Acute deprivation of the principal whisker caused an immediate reversal of firing order and a drastic decorrelation of spike trains in the two layers, effects that are known to drive synaptic depression

during STDP.

Additional evidence that STDP underlies the development of sensory responses in barrel cortex was recently provided.[83] As mentioned above, induction of STDP presumably depends on active action potential backpropagation, which is mediated by dendritic voltage-gated sodium channels.[33] Komai and colleagues[83] employed lentivirus-based knock down of voltage-gated sodium channel subunits by siRNAs *in vivo* to assess the role of postsynaptic, somatodendritic excitability in cortical maturation. The knock down effectively abolished action potential backpropagation as assessed by calcium imaging (Figure 4A), and would also have compromised dendritic spike generation while leaving action potential threshold unaltered. After approximately one week of normal behaviour, this caused a marked reduction in the amplitude of sensory postsynaptic potentials evoked by deflection of the principal whisker and the adjacent surround whiskers (Figure 4B,C). The strength of this approach is that only a
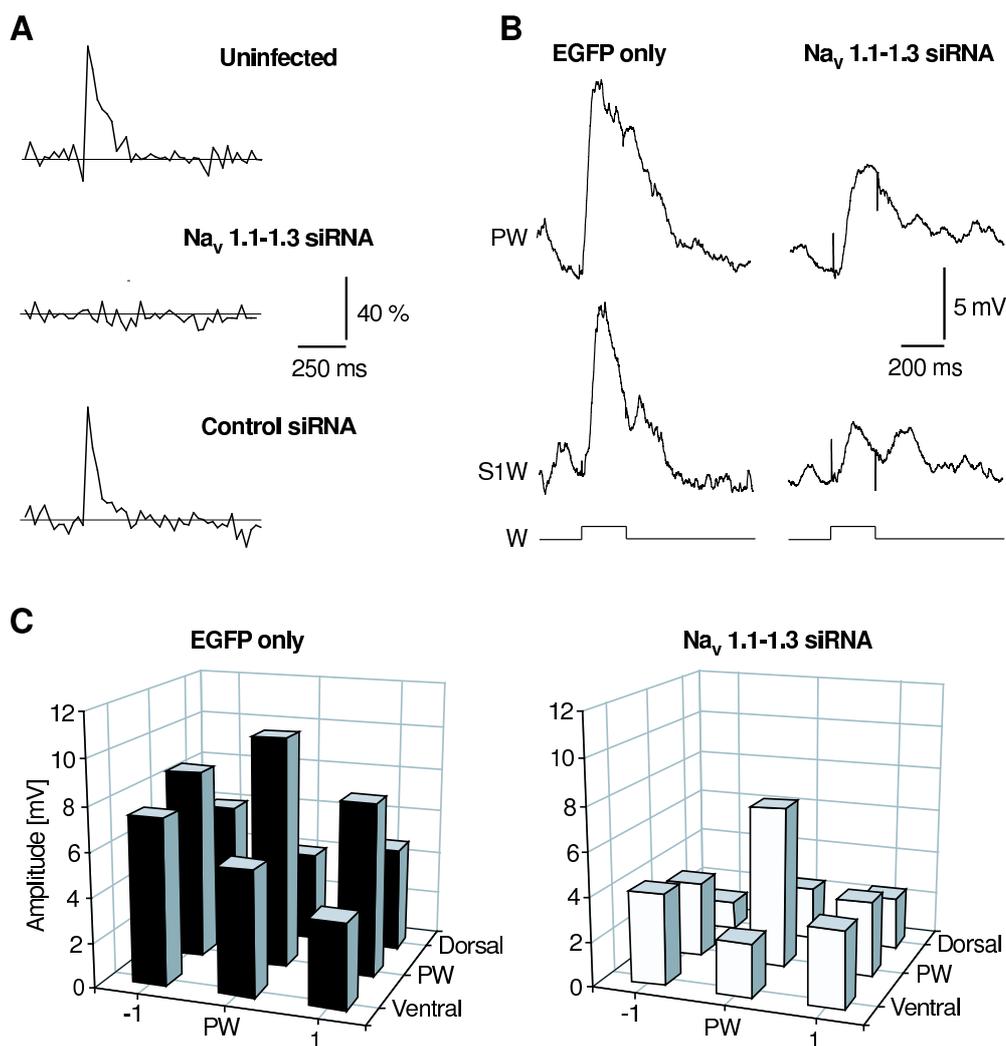
Figure 4. Action potential backpropagation is required for normal developmental strengthening of sensory responses in barrel cortex. A: In vivo *imaging of action potential evoked calcium transients in the apical dendrite of layer 2/3 pyramidal neurons in rat barrel cortex. Neurons infected with a viral vector carrying short interfering RNAs (siRNAs) targeting voltage-gated sodium channel subunits ($Na_v1.1$-1.3) displayed no backpropagation (middle), while infection with enhanced GFP alone had no effect (control siRNA).* **B:** *Example of sensory responses evoked by deflection of the principal whisker (PW) and surround whiskers (S1W) in neurons with (Na_v 1.1-1.3 siRNA) and without sodium channel knock down (EGFP only).* **C:** *Sodium channel knock down significantly reduces the sensory responses to both principal whiskers (PW) and surround whiskers (±1, ventral, dorsal), suggesting that action potential backpropagation is crucial for synapse maturation. Reproduced with permission from Komai* et al.[83]

small number of neurons was infected, which left the network virtually unaltered. The observed effect is therefore only dependent on the excitability of the postsynaptic neuron, which strongly suggests that STDP is crucial during normal development of the barrel cortex.

Conclusions and outlook

Over the last decade, evidence has mounted suggesting that STDP is a common mechanism shaping synaptic strength during learning and development. It is readily induced *in vitro* in several different species and brain areas[6,17,18,68,84] and in both glutamatergic (see above)

and GABAergic synapses.[21,85] *In vivo*, orientation preference in visual cortex and map plasticity in barrel cortex is likely to be controlled by STDP learning rules. Could STDP also have a role in more complex learning tasks such as classical conditioning performed by pairing an unconditioned stimulus with a conditioned stimulus? This seems likely, as such learning paradigms are remarkably similar to pairing of presynaptic and postsynaptic action potentials during induction of STDP. It has been pointed out, however, that the timescale of the two processes is drastically different:[86] STDP occurs within a time window of tens of milliseconds, while classical conditioning takes place over tens of seconds. Simulations suggest that this

apparent discrepancy can be resolved if the sensory stimuli elicit sustained responses which decay slowly.[86] Further experiments incorporating STDP learning rules in behavioural studies will be required to investigate how information storage and modulation of neural circuits can occur on the basis of a spike-timing based neural code.

Acknowledgements

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