Clinical and Experimental Pharmacology and Physiology (2007) **34**, 1070–1076 doi: 10.1111/j.1440-1681.2007.04724.x

Proceedings of the Australian Physiological Society Symposium: Development and Physiological Adaptations of Neuronal Circuits and Synapses-I

DOES SPIKE TIMING-DEPENDENT SYNAPTIC PLASTICITY UNDERLIE MEMORY FORMATION?

Johannes J Letzkus, Björn M Kampa* and Greg J Stuart

Division of Neuroscience, The John Curtin School of Medical Research, Australian National University, Canberra, Australian Capital Territory, Australia

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 (msec) timing of the synaptic input and the post-synaptic 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. Second, 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.

Key words: back-propagating action potential, dendrite, learning, memory, *N*-methyl-D-aspartate (NMDA) receptor, spike timing, synaptic plasticity.

Correspondence: Greg J Stuart, Division of Neuroscience, The John Curtin School of Medical Research, Australian National University, Mills Road, Canberra, ACT 0200, Australia. Email: greg.stuart@anu.edu.au

*Present address: Department of Neurophysiology, Brain Research Institute, University of Zürich, Switzerland.

Presented at the AuPS Symposium Development and Physiological Adaptations of Neuronal Circuits and Synapses-I, September 2006. The papers in these proceedings were peer reviewed under the supervision of the AuPS Editor. The papers are being published with the permission of AuPS and were initially published on the AuPS website http://www.aups.org.au

Received 9 January 2007; revision 6 March 2007; accepted 28 March 2007.

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 an avalanche of research that 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 be loosely grouped into two: 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 post-synaptic depolarization. The duration of coincident activation during pairing varies greatly in these protocols, from several hundred msec[6] to just one pre- and post-synaptic action potential in a specific form of synaptic plasticity termed spike timing-dependent plasticity (STDP). In contrast with frequency dependent protocols, during STDP the sign and magnitude of the change in synaptic strength depends on the precise timing of pre- and post-synaptic activation.

Which induction mechanism is used *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 that is further supported by the recent finding that the firing of a single cortical neuron can elicit whisking movement.[13] In that 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 the somatosensory cortex, spike timing is used to encode information. This makes STDP a prime candidate for induction of synaptic plasticity. In the present review, we discuss the cellular mechanisms underlying STDP induction *in vitro* with a focus on how this may differ *in vivo*. We then review recent evidence suggesting that STDP occurs *in vivo*.

CELLULAR MECHANISMS UNDERLYING STDP

Spike timing-dependent plasticity is a form of bidirectional plasticity in which the temporal order of pre- and post-synaptic action potentials on a precise (msec) time-scale triggers changes in synaptic strength (for reviews, see Dan and Poo[14,15]). 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.[16]

A detailed characterization of the timing dependence of STDP (see Fig. 1) showed that most synapses undergo LTP when the post-synaptic action potential follows the synaptic input (positive timing), whereas LTD is usually observed when the post-synaptic action potential precedes the synaptic input (negative timing).[6,17,18] The functional interpretation of these results is that synaptic inputs that contribute to post-synaptic firing are potentiated, whereas uncorrelated inputs are depressed. This is in essence Hebb's postulate,[19] which is computationally attractive because it directly relates the 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 msec.[21] In addition, STDP also depends on the timing of preceding action potentials,[22,23] the subcellular 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 back-propagation 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 depolarization associated with back-propagating action potentials triggers plasticity via relief of the voltage-dependent block of the *N*-methyl-D-aspartate (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 been shown recently that brief depolarizations 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

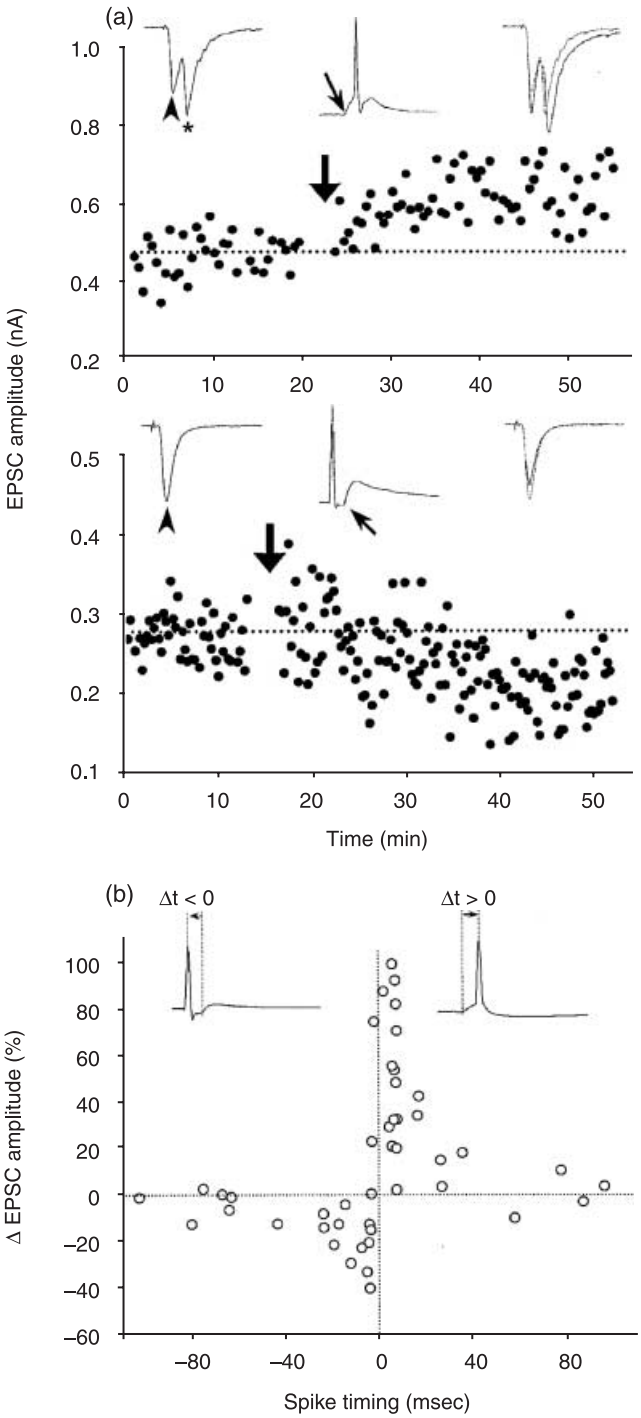

Fig. 1 Spike timing-dependent synaptic plasticity (STDP) learning rules *in vitro*. Paired recordings were performed in dissociated cultures of rat hippocampal neurons. (a) Stimulation of the presynaptic neuron gives rise to an excitatory post-synaptic current (EPSC; top, left inset, arrowhead). After pairing pre- and post-synaptic action potentials in current clamp (top, large arrow), with the EPSP leading the post-synaptic action potentials by +5 msec (top, middle inset; the small arrow indicates EPSP onset), synaptic strength is persistently enhanced. Conversely, long-term depression (LTD) is induced if the EPSP follows the post-synaptic action potential during pairing (bottom). (b) The full STDP timing curve is characterized by induction of long-term potentiation (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 msec. Reproduced with the permission of the Society for Neuroscience from Bi and Poo.[18]

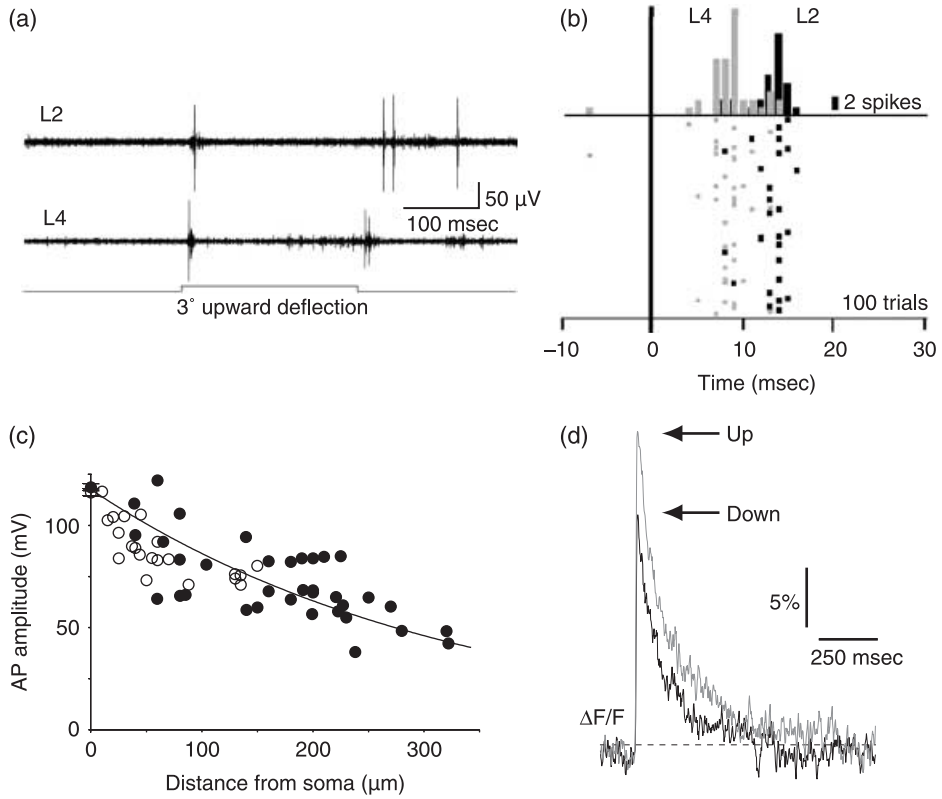

Fig. 2 Temporal fidelity and action potential back-propagation *in vivo*. (a,b) Simultaneous extracellular recordings in layer (L) 4 and L2/3 of rat barrel cortex. (a) Examples of spike trains in response to multiwhisker deflection (bottom). Note the low overall action potential rates. (b) The Raster plot of spikes elicited by 100 whisker deflections shows that L4 neurons consistently fire before L2/3 cells. (c) Back-propagating action potentials (APs) 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 back-propagating 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 back-propagating APs 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 back-propagation is boosted during up-states. Figures with the permission of Macmillan Publishers Ltd from Celikel *et al.*[48] (a,b) and the Society for Neuroscience from Waters *et al.*[59] and Waters and Helmchen[60] (c,d).

heterogeneous because it has also been reported to depend on NMDA receptor desensitization,[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 msec timing during physiological stimuli (Fig. 2a,b).[46–48] The extent of action potential back-propagation *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 anaesthetized 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 and Helmchen[54]), which may compromise action potential back-propagation.[55] In contrast, recent studies have found that action potential back-propagation is similar *in vitro* and *in vivo* (Fig. 2c)[56–59] and can actually be boosted *in vivo* during up-states (Fig. 2d).[60] A greater understanding of action potential back-propagation *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 that can be elicited by strong extracellular stimulation[31,61] or by high-frequency bursts of back-propagating action potentials.[62,63] 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, such as 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 the induction of synaptic plasticity in the intact brain.

EXPERIMENTAL INDUCTION OF STDP *IN VIVO*

The first characterization of STDP induced *in vivo* was provided by Zhang *et al.* 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 because 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] The induction of LTP depended on post-synaptic 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 excitatory post-synaptic potential (EPSP)–action potential pairings. This question was addressed in a recent paper that found that pairing subthreshold visual stimuli with single action potentials evoked in tectal neurons by current injection elicits STDP with

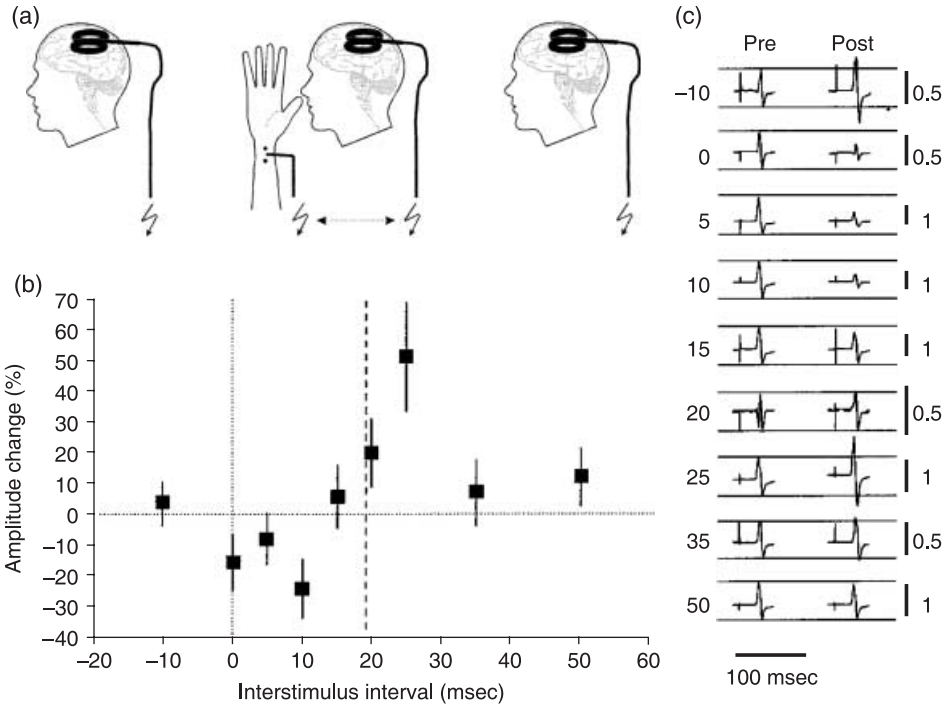

Fig. 3 Spike timing-dependent synaptic plasticity (STDP) induction in human motor cortex. (a) Motor evoked potentials (MEPs) were elicted by transcranial magnetic stimulation (TMS) of the motor cortex. Pairing was performed between TMS and electrical stimulation of the median nerve in the periphery (middle). (b) The effect of pairing depends on interstimulus interval: stimulation of the peripheral nerve 10 msec before TMS (+10 msec) depresses MEPs, whereas MEPs are potentiated at +25 msec. The full timing curve has striking similarity with the STDP curves observed *in vitro* (Fig. 1), but is offset by +20 msec, which is approximately the time required for excitation from the peripheral nerve to reach the motor cortex. (c) Examples of MEPs before (Pre) and after (Post) pairing at the timings indicated on the left. Calibration bars on the right are in mV. Reproduced with permission from Wolters *et al*.[78]

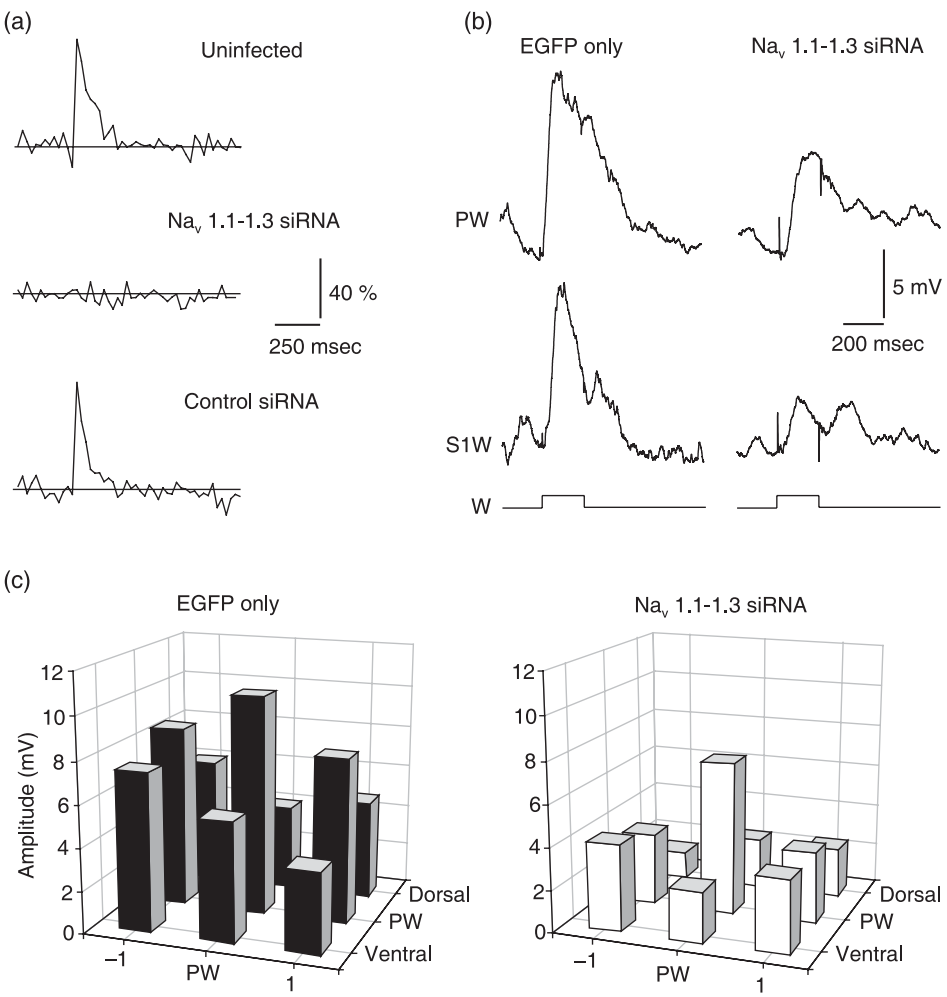

Fig. 4 Action potential back-propagation is required for normal developmental strengthening of sensory responses in barrel cortex. (a) *In vivo* imaging of action potential-evoked calcium transients in the apical dendrite of layer 2/3 pyramidal neurons in rat barrel cortex. Neurons infected with a viral vector carrying short interfering RNAs (siRNAs) targeting voltage-gated sodium channel subunits (Na_v 1.1–1.3) displayed no back-propagation (middle), whereas infection with enhanced green fluorescent protein (EGFP) alone had no effect (control siRNA). (b) Examples of sensory responses evoked by deflection (W; bottom) 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 PW and surround whiskers (+/–1: ventral, dorsal), suggesting that action potential back-propagation is crucial for synapse maturation. Reproduced with permission of Macmillan Publishers Ltd from Komai *et al*.[83]

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 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 msec, the orientation preference was shifted towards the paired orientation. Conversely, if the visual stimulus followed electrical activation by approximately 10 msec, 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 the 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 that 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 post-synaptic 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] That study reported a persistent enhancement of motor-evoked potentials when nerve stimulation precedes TMS-evoked cortical activation by 25 msec (Fig. 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 msec.[78]

CAN STDP BE EVOKED *IN VIVO* BY PHYSIOLOGICALLY RELEVANT INPUTS?

Although all 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 (for a review, see Feldman and Brecht[79]). The barrel cortex is ideally suited for these studies because it contains an ordered, somatotopic map representing the animal's facial whiskers (for a review, see 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 experimental regimen 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 post-synaptic 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 anaesthetized animals. When all whiskers where deflected simultaneously, spike timing was precise, with L4 neurons spiking several msec before L2/3 neurons (Fig. 2a,b). Acute deprivation of the principal whisker caused an immediate reversal of firing order and a marked 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 back-propagation, which is mediated by dendritic voltage-gated sodium channels.[33] Komai *et al.*[83] used lentivirus-based knock-down of voltage-gated sodium channel subunits by short interfering RNAs (siRNAs) *in vivo* to assess the role of post-synaptic, somatodendritic excitability in cortical maturation. The knock-down effectively abolished action potential back-propagation, as assessed by calcium imaging (Fig. 4a), and would also have compromised dendritic spike generation while leaving action potential threshold unaltered. After approximately 1 week of normal behaviour, this caused a marked reduction in the amplitude of sensory post-synaptic potentials evoked by deflection of the principal whisker and the adjacent surrounding whiskers (Fig. 4b,c). The strength of this approach is that only a small number of neurons was infected, which left the network virtually unaltered. Therefore, the observed effect is only dependent on the excitability of the post-synaptic neuron, which strongly suggests that STDP is crucial during normal development of the barrel cortex.

CONCLUSIONS AND OUTLOOK

Over the past 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,[6,17,18,84] as well as 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, because such learning paradigms are remarkably similar to pairing of pre- and post-synaptic action potentials during induction of STDP. However, it has been pointed out that the time-scale of the two processes is markedly different:[86] STDP occurs within a time window of tens of milliseconds, whereas classical conditioning takes place over tens of seconds. Simulations suggest that this apparent discrepancy can be resolved if the sensory stimuli elicit sustained responses that 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.

ACKNOWLEDGEMENT

The authors thank Maarten Kole (Division of Neuroscience, The John Curtin School of Medical Research, Australian National University) for helpful comments on the manuscript.

REFERENCES

1. Bliss TVL, Lømo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J. Physiol*. 1973; **232**: 331–56.
2. Lynch GS, Dunwiddie T, Gribkoff V. Heterosynaptic depression: A postsynaptic correlate of long-term potentiation. *Nature* 1977; **266**: 737–9.
3. Martin SJ, Grimwood PD, Morris RG. Synaptic plasticity and memory: An evaluation of the hypothesis. *Annu. Rev. Neurosci*. 2000; **23**: 649–711.
4. Morris RG, Moser EI, Riedel G *et al*. Elements of a neurobiological theory of the hippocampus: The role of activity-dependent synaptic plasticity in memory. *Philos. Trans. R. Soc. Lond. B Biol. Sci*. 2003; **358**: 773–86.
5. Whitlock JR, Heynen AJ, Shuler MG, Bear MF. Learning induces long-term potentiation in the hippocampus. *Science* 2006; **313**: 1093–7.
6. Debanne D, Gahwiler BH, Thompson SM. Long-term synaptic plasticity between pairs of individual CA3 pyramidal cells in rat hippocampal slice cultures. *J. Physiol*. 1998; **507**: 237–47.
7. Sanger TD. Neural population codes. *Curr. Opin. Neurobiol*. 2003; **13**: 238–49.
8. Petersen RS, Panzeri S, Diamond ME. Population coding in somatosensory cortex. *Curr. Opin. Neurobiol*. 2002; **12**: 441–7.
9. Perez-Orive J, Bazhenov M, Laurent G. Intrinsic and circuit properties favor coincidence detection for decoding oscillatory input. *J. Neurosci*. 2004; **24**: 6037–47.
10. Manns ID, Sakmann B, Brecht M. Sub- and suprathreshold receptive field properties of pyramidal neurones in layers 5A and 5B of rat somatosensory barrel cortex. *J. Physiol*. 2004; **556**: 601–22.
11. Margrie TW, Brecht M, Sakmann B. *In vivo*, low-resistance, whole-cell recordings from neurons in the anaesthetized and awake mammalian brain. *Pflügers Arch*. 2002; **444**: 491–8.
12. Lee AK, Manns ID, Sakmann B, Brecht M. Whole-cell recordings in freely moving rats. *Neuron* 2006; **51**: 399–407.
13. Brecht M, Schneider M, Sakmann B, Margrie TW. Whisker movements evoked by stimulation of single pyramidal cells in rat motor cortex. *Nature* 2004; **427**: 704–10.
14. Dan Y, Poo MM. Spike timing-dependent plasticity of neural circuits. *Neuron* 2004; **44**: 23–30.
15. Dan Y, Poo MM. Spike timing-dependent plasticity: From synapse to perception. *Physiol. Rev*. 2006; **86**: 1033–48.
16. Levy WB, Steward O. Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus. *Neuroscience* 1983; **8**: 791–7.
17. Markram H, Lubke J, Frotscher M, Sakmann B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* 1997; **275**: 213–15.
18. Bi GQ, Poo MM. Synaptic modifications in cultured hippocampal neurons: Dependence on spike timing, synaptic strength, and post-synaptic cell type. *J. Neurosci*. 1998; **18**: 10464–72.
19. Hebb D. *The Organization of Behavior: A Neuropsychological Theory*. Wiley, New York. 1949.
20. Egger V, Feldmeyer D, Sakmann B. Coincidence detection and changes of synaptic efficacy in spiny stellate neurons in rat barrel cortex. *Nat. Neurosci*. 1999; **2**: 1098–105.
21. Woodin MA, Ganguly K, Poo MM. Coincident pre- and postsynaptic activity modifies GABAergic synapses by postsynaptic changes in Cl^- transporter activity. *Neuron* 2003; **39**: 807–20.
22. Froemke RC, Dan Y. Spike-timing-dependent synaptic modification induced by natural spike trains. *Nature* 2002; **416**: 433–8.
23. Wang HX, Gerkin RC, Nauen DW, Bi GQ. Coactivation and timing-dependent integration of synaptic potentiation and depression. *Nat. Neurosci*. 2005; **8**: 187–93.
24. Froemke RC, Poo MM, Dan Y. Spike-timing-dependent synaptic plasticity depends on dendritic location. *Nature* 2005; **434**: 221–5.
25. Sjostrom PJ, Hausser M. A cooperative switch determines the sign of synaptic plasticity in distal dendrites of neocortical pyramidal neurons. *Neuron* 2006; **51**: 227–38.
26. Letzkus JJ, Kampa BM, Stuart GJ. Learning rules for spike timing-dependent plasticity depend on dendritic synapse location. *J. Neurosci*. 2006; **26**: 10420–9.
27. Pike FG, Meredith RM, Olding AW, Paulsen O. Rapid report: Post-synaptic bursting is essential for 'Hebbian' induction of associative long-term potentiation at excitatory synapses in rat hippocampus. *J. Physiol*. 1999; **518**: 571–6.
28. Birtoli B, Ulrich D. Firing mode-dependent synaptic plasticity in rat neocortical pyramidal neurons. *J. Neurosci*. 2004; **24**: 4935–40.
29. Kampa BM, Letzkus JJ, Stuart GJ. Requirement of dendritic calcium spikes for induction of spike-timing-dependent synaptic plasticity. *J. Physiol*. 2006; **574**: 283–90.
30. Golding NL, Staff NP, Spruston N. Dendritic spikes as a mechanism for cooperative long-term potentiation. *Nature* 2002; **418**: 326–31.
31. Holthoff K, Kovalchuk Y, Yuste R, Konnerth A. Single-shock LTD by local dendritic spikes in pyramidal neurons of mouse visual cortex. *J. Physiol*. 2004; **560**: 27–36.
32. Humeau Y, Luthi A. Dendritic calcium spikes induce bi-directional synaptic plasticity in the lateral amygdala. *Neuropharmacology* 2007; **52**: 234–43.
33. Stuart GJ, Sakmann B. Active propagation of somatic action potentials into neocortical pyramidal cell dendrites. *Nature* 1994; **367**: 69–72.
34. Spruston N, Schiller Y, Stuart G, Sakmann B. Activity-dependent action potential invasion and calcium influx into hippocampal CA1 dendrites. *Science* 1995; **268**: 297–300.
35. Magee JC, Johnston D. A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* 1997; **275**: 209–13.
36. Mayer ML, Westbrook GL, Guthrie PB. Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurones. *Nature* 1984; **309**: 261–3.
37. Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A. Magnesium gates glutamate-activated channels in mouse central neurones. *Nature* 1984; **307**: 462–5.
38. Koester HJ, Sakmann B. Calcium dynamics in single spines during coincident pre- and postsynaptic activity depend on relative timing of back-propagating action potentials and subthreshold excitatory postsynaptic potentials. *Proc. Natl Acad. Sci. USA* 1998; **95**: 9596–601.
39. Nevian T, Sakmann B. Spine Ca^{2+} signaling in spike-timing-dependent plasticity. *J. Neurosci*. 2006; **26**: 11 001–13.
40. Kampa BM, Clements J, Jonas P, Stuart GJ. Kinetics of Mg^{2+} unblock of NMDA receptors: Implications for spike-timing dependent synaptic plasticity. *J. Physiol*. 2004; **556**: 337–45.

41. Yang SN, Tang YG, Zucker RS. Selective induction of LTP and LTD by postsynaptic $[Ca^{2+}]_i$ elevation. *J. Neurophysiol*. 1999; **81**: 781–7.
42. Cho K, Aggleton JP, Brown MW, Bashir ZI. An experimental test of the role of postsynaptic calcium levels in determining synaptic strength using perirhinal cortex of rat. *J. Physiol*. 2001; **532**: 459–66.
43. Cormier RJ, Greenwood AC, Connor JA. Bidirectional synaptic plasticity correlated with the magnitude of dendritic calcium transients above a threshold. *J. Neurophysiol*. 2001; **85**: 399–406.
44. Bender VA, Bender KJ, Brasier DJ, Feldman DE. Two coincidence detectors for spike timing-dependent plasticity in somatosensory cortex. *J. Neurosci*. 2006; **26**: 4166–77.
45. Sjostrom PJ, Turrigiano GG, Nelson SB. Neocortical LTD via coincident activation of presynaptic NMDA and cannabinoid receptors. *Neuron* 2003; **39**: 641–54.
46. Riehle A, Grun S, Diesmann M, Aertsen A. Spike synchronization and rate modulation differentially involved in motor cortical function. *Science* 1997; **278**: 1950–3.
47. Prut Y, Vaadia E, Bergman H, Haalman I, Slovin H, Abeles M. Spatiotemporal structure of cortical activity: Properties and behavioral relevance. *J. Neurophysiol*. 1998; **79**: 2857–74.
48. Celikel T, Szostak VA, Feldman DE. Modulation of spike timing by sensory deprivation during induction of cortical map plasticity. *Nat. Neurosci*. 2004; **7**: 534–41.
49. Stuart GJ, Hausser M. Dendritic coincidence detection of EPSPs and action potentials. *Nat. Neurosci*. 2001; **4**: 63–71.
50. Larkum ME, Zhu JJ, Sakmann B. Dendritic mechanisms underlying the coupling of the dendritic with the axonal action potential initiation zone of adult rat layer 5 pyramidal neurons. *J. Physiol*. 2001; **533**: 447–66.
51. Steriade M, Nunez A, Amzica F. A novel slow (< 1 Hz) oscillation of neocortical neurons *in vivo*: Depolarizing and hyperpolarizing components. *J. Neurosci*. 1993; **13**: 3252–65.
52. Steriade M, Timofeev I, Grenier F. Natural waking and sleep states: A view from inside neocortical neurons. *J. Neurophysiol*. 2001; **85**: 1969–85.
53. Destexhe A, Rudolph M, Pare D. The high-conductance state of neocortical neurons *in vivo*. *Nat. Rev. Neurosci*. 2003; **4**: 739–51.
54. Waters J, Helmchen F. Background synaptic activity is sparse in neocortex. *J. Neurosci*. 2006; **26**: 8267–77.
55. Williams SR. Spatial compartmentalization and functional impact of conductance in pyramidal neurons. *Nat. Neurosci*. 2004; **7**: 961–7.
56. Buzsaki G, Kandel A. Somadendritic backpropagation of action potentials in cortical pyramidal cells of the awake rat. *J. Neurophysiol*. 1998; **79**: 1587–91.
57. Charpak S, Mertz J, Beaurepaire E, Moreaux L, Delaney K. Odor-evoked calcium signals in dendrites of rat mitral cells. *Proc. Natl Acad. Sci. USA* 2001; **98**: 1230–4.
58. Quirk MC, Blum KI, Wilson MA. Experience-dependent changes in extracellular spike amplitude may reflect regulation of dendritic action potential back-propagation in rat hippocampal pyramidal cells. *J. Neurosci*. 2001; **21**: 240–8.
59. Waters J, Larkum M, Sakmann B, Helmchen F. Supralinear Ca^{2+} influx into dendritic tufts of layer 2/3 neocortical pyramidal neurons *in vitro* and *in vivo*. *J. Neurosci*. 2003; **23**: 8558–67.
60. Waters J, Helmchen F. Boosting of action potential backpropagation by neocortical network activity *in vivo*. *J. Neurosci*. 2004; **24**: 11 127–36.
61. Schiller J, Schiller Y, Stuart G, Sakmann B. Calcium action potentials restricted to distal apical dendrites of rat neocortical pyramidal neurons. *J. Physiol*. 1997; **505**: 605–16.
62. Larkum ME, Kaiser KM, Sakmann B. Calcium electrogenesis in distal apical dendrites of layer 5 pyramidal cells at a critical frequency of back-propagating action potentials. *Proc. Natl Acad. Sci. USA* 1999; **96**: 14 600–4.
63. Kampa BM, Stuart GJ. Calcium spikes in basal dendrites of layer 5 pyramidal neurons during action potential bursts. *J. Neurosci*. 2006; **26**: 7424–32.
64. Goldberg J, Holthoff K, Yuste R. A problem with Hebb and local spikes. *Trends Neurosci*. 2002; **25**: 433–5.
65. Lisman J, Spruston N. Postsynaptic depolarization requirements for LTP and LTD. A critique of spike timing-dependent plasticity. *Nat. Neurosci*. 2005; **8**: 839–41.
66. Svoboda K, Denk W, Kleinfeld D, Tank DW. *In vivo* dendritic calcium dynamics in neocortical pyramidal neurons. *Nature* 1997; **385**: 161–5.
67. Helmchen F, Svoboda K, Denk W, Tank DW. *In vivo* dendritic calcium dynamics in deep-layer cortical pyramidal neurons. *Nat. Neurosci*. 1999; **2**: 989–96.
68. Zhang LI, Tao HW, Holt CE, Harris WA, Poo M. A critical window for cooperation and competition among developing retinotectal synapses. *Nature* 1998; **395**: 37–44.
69. Zhang LI, Tao HW, Poo M. Visual input induces long-term potentiation of developing retinotectal synapses. *Nat. Neurosci*. 2000; **3**: 708–15.
70. Mu Y, Poo MM. Spike timing-dependent LTP/LTD mediates visual experience-dependent plasticity in a developing retinotectal system. *Neuron* 2006; **50**: 115–25.
71. Schuett S, Bonhoeffer T, Hubener M. Pairing-induced changes of orientation maps in cat visual cortex. *Neuron* 2001; **32**: 325–37.
72. Yao H, Dan Y. Stimulus timing-dependent plasticity in cortical processing of orientation. *Neuron* 2001; **32**: 315–23.
73. Yao H, Shen Y, Dan Y. Intracortical mechanism of stimulus-timing-dependent plasticity in visual cortical orientation tuning. *Proc. Natl Acad. Sci. USA* 2004; **101**: 5081–6.
74. Fu YX, Djupsund K, Gao H, Hayden B, Shen K, Dan Y. Temporal specificity in the cortical plasticity of visual space representation. *Science* 2002; **296**: 1999–2003.
75. Meliza CD, Dan Y. Receptive-field modification in rat visual cortex induced by paired visual stimulation and single-cell spiking. *Neuron* 2006; **49**: 183–9.
76. Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain* 2000; **123**: 572–84.
77. Stefan K, Kunesch E, Benecke R, Cohen LG, Classen J. Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. *J. Physiol*. 2002; **543**: 699–708.
78. Wolters A, Sandbrink F, Schlottmann A *et al*. A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. *J. Neurophysiol*. 2003; **89**: 2339–45.
79. Feldman DE, Brecht M. Map plasticity in somatosensory cortex. *Science* 2005; **310**: 810–15.
80. Petersen CC. The barrel cortex–integrating molecular, cellular and systems physiology. *Pflügers Arch*. 2003; **447**: 126–34.
81. Finnerty GT, Roberts LS, Connors BW. Sensory experience modifies the short-term dynamics of neocortical synapses. *Nature* 1999; **400**: 367–71.
82. Allen CB, Celikel T, Feldman DE. Long-term depression induced by sensory deprivation during cortical map plasticity *in vivo*. *Nat. Neurosci*. 2003; **6**: 291–9.
83. Komai S, Licznerski P, Cetin A *et al*. Postsynaptic excitability is necessary for strengthening of cortical sensory responses during experience-dependent development. *Nat. Neurosci*. 2006; **9**: 1125–33.
84. Sjostrom PJ, Turrigiano GG, Nelson SB. Rate, timing, and cooperativity jointly determine cortical synaptic plasticity. *Neuron* 2001; **32**: 1149–64.
85. Haas JS, Nowotny T, Abarbanel HD. Spike-timing-dependent plasticity of inhibitory synapses in the entorhinal cortex. *J. Neurophysiol*. 2006; **96**: 3305–13.
86. Drew PJ, Abbott LF. Extending the effects of spike-timing-dependent plasticity to behavioral timescales. *Proc. Natl Acad. Sci. USA* 2006; **103**: 8876–81.