How long will long-term potentiation last?

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The paramount feature of long-term potentiation (LTP) as a memory mechanism is its characteristic persistence over time. Although the basic phenomenology of LTP persistence was established 30 years ago, new insights have emerged recently about the extent of LTP persistence and its regulation by activity and experience. Thus, it is now evident that LTP, at least in the dentate gyrus, can either be decremental, lasting from hours to weeks, or stable, lasting months or longer. Although mechanisms engaged during the induction of LTP regulate its subsequent persistence, the maintenance of LTP is also governed by activity patterns post-induction, whether induced experimentally or generated by experience. These new findings establish dentate gyrus LTP as a useful model system for studying the mechanisms governing the induction, maintenance and interference with long-term memory, including very long-term memory lasting months or longer. The challenge is to study LTP persistence in other brain areas, and to relate, if possible, the properties and regulation of LTP maintenance to these same properties of the information that is actually stored in those regions.

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Since the pioneering studies performed 30 years ago by Tim Bliss, Terje Lømo and Tony Gardner-Medwin (Bliss & Lømo 1973; Bliss & Gardner-Medwin 1973), LTP has generated enormous interest as a potential memory mechanism. This is because LTP exhibits numerous properties expected of an associative memory mechanism, such as rapid induction, input specificity, associative interactions, persistence, and dependence on correlated pre- and postsynaptic activity. The close similarity between these features and those of the learning rule of Hebb (1949) has added lustre to the LTP phenomenon. In addition, there is important yet complex regulation of LTP by prior synaptic activity (metaplasticity), neighbouring afferents (e.g. synaptic tagging), and state variables such as levels of stress hormones and activity in neuromodulatory transmitter systems (see Martin *et al.* (2000) for a review of these properties of LTP). It can be argued, however, that among all these intriguing and important characteristics, the paramount feature that defines LTP as a potential memory mechanism is its persistence over time. Thus, although short-lasting frequency potentiation of synaptic potentials was described in the hippocampus many years ago, it was not until the discovery of LTP that researchers seriously considered that a model system for studying synaptic mechanisms of mammalian memory had been established. It is curious, therefore, that despite the fundamental importance of LTP maintenance over days and weeks, relatively few studies have addressed its mechanisms and regulation. The purpose of this review is to summarize the data from experiments charting how long LTP can last, and then to address the factors that regulate

how long LTP will in fact persist under various conditions. Finally, I briefly discuss the relation of LTP persistence to memory retention, and pose some key questions for future research on the mechanisms and behavioural relevance of the maintenance of LTP.

1. HOW LONG CAN LTP PERSIST?

(a) *Early studies of LTP persistence*

Bliss & Gardner-Medwin (1973) pioneered the use of field potential recordings in the dentate gyrus of awake animals to investigate the persistence of LTP. This preparation remains the method of choice for studying LTP in freely moving animals, probably because the large isopotential region in the dentate hilus allows a certain tolerance of recording electrode movement over time without significantly affecting the stability of the field recordings. The principal finding of this early report was that one bout of stimulation could induce LTP in the rabbit dentate gyrus lasting up to 3 days. However, it was noted that this might not be the limit, because in one animal, repeated episodes of stimulation resulted in LTP of the population spike lasting 16 weeks. Subsequent studies from several laboratories confirmed in rats that LTP can indeed last from less than a day to many weeks, depending on the stimulation protocol (Barnes 1979; Racine *et al.* 1983; Barnes & McNaughton 1985; de Jonge & Racine 1985; Staubli & Lynch 1987; Jeffery *et al.* 1990; Abraham *et al.* 1993).

More mechanistic studies of LTP persistence, occurring in parallel with the descriptive ones above, showed that LTP has at least two stages of maintenance: early-LTP which is dependent on post-translational modifications and lasts for, at most, a few hours, followed by a late LTP which is dependent on *de novo* gene expression and protein synthesis and which lasts for many hours (Krug *et al.*

One contribution of 30 to a Theme Issue 'Long-term potentiation: enhancing neuroscience for 30 years'.

Figure 1. Dentate gyrus LTP decay curves obtained from a survey of the literature by Abraham & Otani (1991). Three families of curves were identified and calculated to have average decay time constants of 2.1 h, 3.5 days and 20.3 days. They were termed LTP1, LTP2 and LTP3, respectively. LTP1 is protein-synthesis independent, and corresponds to early-phase LTP in the more commonly used terminology. LTP2 and LTP3 both fall in the category of late-phase LTP. These and other data indicate that late LTP may involve more than one set of mechanisms that determine its persistence. (Curves were redrawn from the table of decay constants reported by Abraham & Otani (1991).)

1984; Otani *et al.* 1989; Nguyen *et al.* 1994). However, studies in chronically recorded animals where negative exponential functions have been fitted to the LTP decay data have revealed that, in addition to the early LTP which decays with a time constant of 2–3 h (Racine *et al.* 1983; Abraham & Otani 1991), there are at least two distinct families of late-LTP decay functions, with average decay time constants of *ca.* 3.5 and 25 days, respectively (Abraham & Otani 1991; Abraham *et al.* 1993; figure 1). For convenience, these families of decay functions were termed LTP1, LTP2 and LTP3 (Racine *et al.* 1983; Abraham & Otani 1991), with the suggestion that LTP3 may be more dependent on transcription than the other forms. Regardless of how LTP persistence is best categorized, an important conclusion from these studies, after the first two decades of research, was that LTP in the dentate gyrus was decremental, that is, it eventually returned to baseline even if it took many weeks to do so (figure 1; Abraham & Otani 1991; Abraham *et al.* 1995; Abraham 2000). An identical conclusion was reached for heterosynaptic LTD in the dentate gyrus, which decays in parallel with the LTP induced simultaneously on the stimulated pathway (Abraham *et al.* 1994). Furthermore, the fact that control recordings in non-tetanzated pathways could be stably maintained for the same period of time, and that LTP could be reinstated to the original level with a second bout of HFS meant that the decline of recorded LTP over time was in fact due to its decay, and not due to recording

Figure 2. One year LTP in the dentate gyrus of a single animal given four bouts of five trains (4×5 T) of high-frequency stimulation, spaced 5 min apart. The fEPSP slope values have been normalized with respect to the values obtained in the control non-tetanzated hemisphere. The solid line describes the single negative exponential function fitted to the LTP maintenance data. The asymptote of this function was 10% above the original baseline value. (Data were taken, with permission, from Abraham *et al.* (2002).)

instabilities that sometimes occur during long-term recordings (de Jonge & Racine 1985; Abraham *et al.* 1995).

(b) *Recent developments*

The relatively simple view of LTP persistence outlined above has been challenged in recent years in two ways. First, two forms of LTP intermediate between the early and late phases have been described: one protein synthesis-independent (Winder *et al.* 1998), the other dependent on translational but not transcriptional processes (Raymond *et al.* 2000). The latter study confirmed a previous finding made in anaesthetized animals (Otani *et al.* 1989).

Second, there is evidence that LTP may not necessarily be decremental. Staubli & Lynch (1987) first described non-decremental LTP lasting at least several weeks in area CA1 of the hippocampus. More recently, we have shown that even dentate gyrus synapses, under the right conditions, have the capacity for stable LTP lasting at least many months, and in one case up to a year (Abraham *et al.* 2002; figure 2). These latter studies are particularly important because they demonstrate that LTP has the capacity to be extremely stable, thus expanding the temporal range of memories that can, in principle, be supported by this mechanism (see below for further discussion). Another implication of this growing diversity of LTP persistence functions, however, is that multiple mechanisms undoubtedly contribute to the maintenance of LTP, thus complicating studies of its regulation and its molecular or anatomical expression mechanisms.

(c) *LTP across brain regions*

Although dentate gyrus synapses provide a useful model system for studying LTP properties, it seems likely that the persistence of LTP will vary across brain regions, perhaps according to the information processing requirements of those regions. For example, it has been proposed from computational models that learning-related LTP in the dentate gyrus should be relatively transient under normal circumstances, owing to erasure by heterosynaptic

LTD or depotentiation as elicited by subsequent experiences (Rolls 1996b). In agreement with this idea, most studies have observed decremental LTP in the dentate gyrus, as reviewed above, and heterosynaptic LTD can indeed readily erase LTP in the dentate gyrus of awake animals (cf. figure 3). In contrast, it has been suggested that memory storage, and thus LTP, should be longer lasting in areas CA3 and CA1 of the hippocampus (Granger *et al.* 1996). Furthermore, neocortical LTP is predicted to be even more persistent than hippocampal LTP, because cortically based memories that are dependent on the hippocampus consolidate and lose that dependence over time, presumably because the relevant neocortical representations become sufficiently integrated and stable to permit accurate retrieval without assistance from the hippocampus (Milner 1989; McClelland *et al.* 1995).

Unfortunately, there are few studies of LTP persistence outside the dentate gyrus by which to test the above predictions. The Schaffer collateral synapses in area CA1 have generally been reported to show decremental LTP (Buzsáki 1980; Leung & Shen 1995), but they do appear to have the capacity for stable LTP lasting for weeks (Staubli & Lynch 1987), even when induced by relatively mild HFS such as theta-burst stimulation. Interestingly, in our investigations, such stimulation fails to elicit any LTP at all in the dentate gyrus of awake animals (Abraham & Logan 2000). It is possible, therefore, that CA1 has a lower threshold for exhibiting stable LTP, and this may reflect differences in the normal information storage functions of these regions. Curiously, there have been no studies of LTP persistence in area CA3 of the hippocampus, despite its prominence as an auto-associative memory store in many models (McClelland *et al.* 1995; Rolls 1996a,b).

The persistence of neocortical LTP has been studied by Racine and colleagues, using callosal projections to sensorimotor cortex in awake animals as a model system. In this preparation, persistent LTP appears to require multiple stimulation episodes delivered across many days (Racine *et al.* 1995). This LTP, once established, lasts for many weeks, although the full scope of its persistence has not yet been charted (Trepel & Racine 1998). None the less, the data are at least superficially consistent with views that the neocortex is a slow learner, requiring repeated training or stimulation episodes for long-term synaptic change (Marr 1971; Milner 1989; McClelland *et al.* 1995). It is notable too, that visual cortical synapses can utilize LTP-like mechanisms to adapt to altered visual experience during early development, and that these synaptic connections then become relatively 'hard-wired' and resistant to change once the developmental sensitive period finishes (Olson & Freeman 1980; Wiesel 1982). Insofar as LTP indeed contributes to such experience-dependent plasticity, the extreme persistence of the changes suggests that LTP in the neocortex has a remarkable capacity for durability. One caveat of the LTP studies, however, is that white matter stimulation is less efficacious at inducing neocortical synaptic plasticity *in vitro* than intracortical stimulation, which can generate robust LTP after a single HFS (Kirkwood *et al.* 1993). Thus, neocortical synapses may also have the capacity for rapid plasticity, and therefore rapid learning. Verifying whether rapid LTP occurs *in vivo* may require the devel-

opment of new stimulation protocols in this preparation, although evidence from other conditioning paradigms already suggests this is indeed the case (Frégnac *et al.* 1998).

2. HOW LONG WILL LTP PERSIST?

The diversity of LTP persistence across protocols and brain areas indicates that this key property of LTP is likely to be under complex regulation. Indeed, despite what the capacity for LTP maintenance may be under optimal conditions, the actual persistence of LTP is, in fact, sensitive to a host of regulatory events occurring not only during the induction protocol, but also preceding and following LTP establishment. Those regulatory events that specifically affect the late phase(s) of LTP will be reviewed below, and where known, the mechanisms underlying this regulation will be outlined.

(a) *Protocol and state variables affecting the induction of persistent LTP*

One key protocol variable that determines how long LTP in the dentate gyrus will persist is the number of HFS trains delivered. Repetition of trains on one day, or across consecutive days, increases the persistence of LTP (Bliss & Gardner-Medwin 1973; Barnes 1979; Jeffery *et al.* 1990; Abraham *et al.* 1993; Abraham *et al.* 2002), although there may be a limit to the duration of LTP that can be generated by repetition of a particular HFS protocol (Abraham *et al.* 1995). The frequency at which multiple trains are delivered is another key variable, as delivery of the trains spaced at 5–10 min intervals generates more persistent LTP than massed delivery (Huang & Kandel 1994; Abraham *et al.* 2002). Repetition of the HFS prolongs LTP maintenance by promoting activation of the protein synthesis processes for late-phase LTP (Huang & Kandel 1994), but the reason why these processes are sensitive to the number and timing of the stimulus trains remains unclear.

A protocol variable that appears to regulate whether stable LTP will last stably over months is the amount of time the animal spends in the recording chamber before and after HFS. As far as can be ascertained, the previous studies reporting decremental LTP in the dentate gyrus, including our own, kept animals in the recording chambers for *ca.* 10–20 min before and after HFS. By contrast, in a recent study of stable LTP carried out in my laboratory, animals were given at least 30 min in the recording chamber before HFS, and 60 min after, before being returned to their home cage (Abraham *et al.* 2002). A direct comparison of such short- and long-baseline protocols revealed this to be an important factor determining whether stable LTP was generated. This comparison also revealed that HFS in the longer baseline protocol was more efficient at causing phosphorylation of CREB on serine133, although the expression of another LTP-related inducible transcription factor, Zif268, was not affected (Abraham *et al.* 2002). This finding is consistent with other evidence that CREB phosphorylation is a key intermediate step in activating the transcriptional processes necessary for late-phase LTP (Bourtchouladze *et al.* 1994; Davis *et al.* 2000). Unfortunately, it is not yet clear why the length of time in the recording chamber should make

such a difference to CREB phosphorylation and the maintenance of LTP. It is tempting to speculate that, despite the animals being well habituated to the handling and movement associated with making recordings, the small stress or behavioural arousal associated with these procedures was enough to affect the mechanisms of LTP consolidation when experienced shortly before, or after, HFS. However, further investigation is required before deciding whether this is the critical intervening variable.

A key state variable at the time of induction that affects subsequent LTP persistence is the level of activity in neuromodulatory inputs to the hippocampus, such as the dopaminergic and noradrenergic afferents. Several studies have shown that generation of the late-phase of CA1 LTP is critically dependent on activation of D1/D5 dopamine receptors, both *in vitro* and *in vivo* (Frey *et al.* 1990; Swanson-Park *et al.* 1999). Whether activation of D1/D5 receptors is *sufficient* to induce late-phase LTP is more debatable (Huang & Kandel 1995; Swanson-Park *et al.* 1999), and it is likely that late-phase LTP requires coactivation of both dopamine and NMDA receptors. Because D1/D5 receptors couple to G_s -proteins, one such coincidence detector could be Type I adenylyl cyclase, which is activated by both calcium and G_s -proteins. Gene transcription and protein synthesis could then be triggered through the cAMP, protein kinase A, phosphoCREB pathway. Interestingly, D1/D5 receptors do not regulate LTP persistence in the dentate gyrus. Instead this role appears to be played by activation of β -adrenergic receptors, although this action can be obscured by the fact that β -adrenergic receptors also regulate the induction of early-phase LTP (Swanson-Park *et al.* 1999). None the less, treatments that specifically lead to more persistent LTP in the dentate gyrus, such as stimulation of the basolateral amygdala and the behavioural access to reinforcing or punishing stimuli, have been shown to act through stimulation of β -adrenergic receptors (Seidenbecher *et al.* 1997; Frey *et al.* 2001). This activation needs to occur within a fairly narrow time-window flanking the induction of LTP. It is possible that it is through downregulation of these neuromodulatory transmitter systems that the general anaesthetic pentobarbital, when administered just during the time of HFS, reduces both gene expression and LTP maintenance (Jeffery *et al.* 1990).

(b) *Anterograde regulation of LTP persistence*

Both positive and negative regulation of LTP persistence can be generated by synaptic activation occurring before the induction of LTP. For example, activation of synapses by a low-frequency (5 Hz) train of 900 pulses has been shown, in CA1 slices, to selectively inhibit the subsequent induction of late-phase LTP by multi-train HFS, without affecting the early phase (Woo & Nguyen 2002). This represents an interesting form of metaplasticity, i.e., the regulation of plasticity by prior activity (Abraham & Bear 1996), in that it selectively downregulates the late-phase. This regulation requires activation of NMDA receptors during the LFS followed by upregulation of protein phosphatase 1/2a activity (Woo & Nguyen 2002). The downstream effect of increased phosphatase activity may be to prevent or reverse CREB phosphorylation, which is PP1 sensitive (Hagiwara *et al.* 1992), although phosphatase modulation of other key signalling

molecules such as extracellular signal-related kinase ERK or protein kinase C may also be important.

Heterosynaptic upregulation of LTP persistence by prior activity has also been reported. Thus, when strong HFS sufficient to induce late-phase LTP is delivered to one afferent pathway in CA1, the induction of late-phase LTP is then primed for all other synapses on the same cell. This means that subsequent delivery to a second pathway of a weak HFS that normally generates only early-phase LTP will elicit late-phase LTP instead (Frey & Morris 1997). The priming effect can persist for at least 30 min, and the postulated mechanism is that the weakly activated synapses are tagged in such a way that they can somehow capture the proteins previously synthesized in response to strong activation of other synapses for use in establishing their own late-phase LTP. This interpretation has been termed the synaptic tag hypothesis (Frey & Morris 1997).

(c) *Retrograde regulation of LTP persistence*

Once triggered, the induction process for LTP occurs within seconds (Gustafsson *et al.* 1989). However, the biochemical and morphological processes that render LTP persistent continue for hours and possibly days post-induction (Abraham *et al.* 1993; Meberg *et al.* 1993; Frey & Morris 1997; Williams *et al.* 1998). Several studies have shown that, early after induction, LTP is rather sensitive to reversal (depotentialiation) when studied *in vitro*. Treatments such as hypoxia and adenosine receptor activation readily reverse LTP, particularly in the first few minutes after its induction (Arai *et al.* 1990; Huang *et al.* 1999). Prolonged LFS will also readily reverse LTP up to an hour post-HFS, but after that depotentialiation appears to be harder to obtain (Fujii *et al.* 1991; O'Dell & Kandel 1994; Staubli & Chun 1996; but see Bashir & Collingridge 1994). This time dependence may reflect a particular resistance by late-phase LTP to reversal by homosynaptic stimulation (Woo & Nguyen 2002). Intriguingly, a selective disruption of late-phase LTP can be caused by soluble amyloid- β peptide (Chen *et al.* 2002), an effect that may underlie some of the memory deficits observed in Alzheimer's disease. In freely moving animals, LTP in the dentate gyrus is also resistant to reversal by homosynaptic stimulation (Errington *et al.* 1995; Abraham *et al.* 1996; but see Kulla *et al.* 1999), but it can be readily reversed by heterosynaptic stimulation (Doyère *et al.* 1997). Interestingly, soon after its induction, LTP in CA1 is sensitive to reversal by experience. Thus, exposure to a stressful novel environment will promote LTP reversal, when experienced at 1 h post-HFS but not at 24 h (Xu *et al.* 1998; Manahan-Vaughan & Braunewell 1999). The mechanisms underlying these diverse means of reversing LTP may be equally diverse, but it is interesting to note that a block of memory retention by exposure to novel stimuli shortly after training was associated with a reduction in subsequent CREB phosphorylation (Viola *et al.* 2000).

An important but relatively unstudied issue is whether the maintenance of late-phase LTP is actively regulated or whether it passively follows a time-course set by the initial processes of induction and consolidation. Two recent studies indicate that LTP persistence over days is in fact subject to ongoing regulation. In one study, LTP

Figure 3. Induction, reversal and reinstatement of stable LTP. (a) LTP at lateral perforant path synapses was induced by combined medial and lateral HFS on three consecutive days (to saturate LTP). The LTP met our criteria for stability (Abraham *et al.* 2002) in all six cases. LTP was completely reversed by heterosynaptic HFS of the medial path alone, but could be reinstated to its original level 2 weeks later by another combined HFS. Lateral path waveforms are averages of 30 sweeps taken before the initial HFS (control), 60 min following the third combined HFS (d0), day 21 post-HFS (d21), 2 weeks following LTP reversal, and 60 min following LTP reinstatement, for an individual animal. Data are mean $\pm$ s.e.m. Scale bars: 5 mV, 5 ms. (b) Lateral path data for four animals that showed stable LTP following a single combined HFS. At 108 days post-HFS, tetanization of the medial path alone caused reversal of the lateral path LTP. Two weeks later, stable LTP was reinstated by combined stimulation of the medial and lateral paths. Lateral path waveforms are averages of 30 sweeps taken from an individual animal. Averages were taken just prior to tetanization (control), and on days 1, 60 and 108 post-HFS, day 1 post-reversal and day 14 post-reinstatement. Data are mean $\pm$ s.e.m. Scale bars: 5 mV, 5 ms.

that was normally decremental over 7 days post-HFS was made stable when the NMDA receptor antagonist (RS)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid

(CPP) was injected once daily (Villarrreal *et al.* 2001). This treatment also prevented forgetting a learned spatial task. It is not certain, unfortunately, whether the LTP reversal in control animals was due to normal behavioural experiences or whether it was induced by the daily injection procedure, as a non-injected control group was not included. None the less, the data do appear to support the view that LTP can be caused to decay by an active NMDA receptor-dependent process in the days following induction.

The fact that LTP can be stably maintained (Staubli & Lynch 1987; Abraham *et al.* 2002) indicates that decay is not obligatory, although it should be cautioned that the LTP in these studies may simply have exhibited a very slow time-course of decay. None the less, even if such LTP is in fact non-decremental, it does not reflect a permanent synaptic change because it is still subject to regulation. For example, an otherwise stable LTP can be actively reversed by heterosynaptic stimulation given 3 weeks post-induction. In these experiments, we induced robust and saturated stable LTP in lateral perforant path synapses of freely moving animals by combined medial and lateral path HFS, repeated on three consecutive days. Three weeks later, medial path HFS alone caused an immediate and dramatic heterosynaptic reversal of lateral path LTP (from 54% LTP to -4% below original baseline $n=6$; figure 3a). LTP remained stably reversed for 2 weeks, after which it was reinstated to its original level by one bout of combined medial and lateral HFS.

To test whether stable LTP is also sensitive to behavioural activation of hippocampal pathways, we induced stable LTP in perforant path synapses and then 2 weeks later we gave the animals, which are normally singly housed under stimulus-poor conditions, repeated exposures to a CE that involved a novel larger cage containing multiple objects and 1–2 other animals (Abraham *et al.* 2002). Significant, albeit incomplete, reversal of LTP gradually occurred as a result of 1 h per day of CE for 3 weeks, beginning 2 weeks post-HFS (figure 4a). When the 'dose' of exposure to the CE was increased to 14 h per day (i.e. overnight exposure), complete depotentiation rapidly occurred within a week (figure 4b). It remains to be determined whether the depotentiation of LTP by CE is due to homosynaptic activity at the potentiated synapses, heterosynaptic activity in neighbouring synapses, or both. Interestingly, reversal of LTP by CE did not occur when exposure commenced 90 days post-induction (Abraham *et al.* 2002), suggesting that there is a long-term consolidation process that takes weeks to complete, at least in the dentate gyrus. Nevertheless, this does not mean that LTP becomes so stabilized that it is completely impervious to new patterns of activity. Thus, LTP that is allowed to stabilize over 120 days can still be rapidly reversed by heterosynaptic HFS of the medial perforant path (figure 3b).

Taken together, the above data indicate that LTP is only maintained stably in the hippocampus under particular induction and maintenance conditions. Establishment of the late-phase does not fully protect the LTP against subsequent reversal, even though it may render it more resistant to certain depotentiating stimuli. Instead, there are patterns of neural activity, such as heterosynaptic stimulation and the activity generated by repeated exposure to novel and complex environments, which can efficiently reverse the LTP, possibly working via NMDA

Figure 4. Reversal of dentate gyrus LTP by exposure to complex environments (CE). (a) Comparison of LTP maintenance for two groups: home cage controls (HC, $n = 5$) and animals receiving CE exposure for 1 h day^{-1} for 3 weeks (CE, $n = 5$). The CE group showed a lasting partial reversal of LTP. Data are corrected for changes in the control hemisphere, which have also been plotted for the CE group ($n = 4$). The smooth curve is the fitted negative exponential function to the HC data; asymptote = 13% LTP. (b) Comparison of LTP maintenance for two groups: HC controls ($n = 6$) and animals receiving CE exposure overnight for 7 days beginning 14 days post-HFS (CE, $n = 5$). The HC group showed LTP with an average asymptote of 18%, but the CE group showed a rapid and lasting reversal of LTP, confirming the sensitivity of LTP maintenance in the dentate gyrus to behavioural experiences. Data are corrected for changes in the control hemisphere, which have also been plotted for the CE group ($n = 5$). Key: open circles, HC; filled circles, CE; open triangles, CE control hemisphere. 50 T, 50 trains of high-frequency stimulation. (Data are taken with permission from Abraham *et al.* (2002).)

receptor-dependent mechanisms. Such LTP reversal paradigms may provide useful model systems for studying the biological mechanisms underlying the psychological phenomenon of retrograde interference, i.e. the impairment of memory recall by newly learned information.

3. NEUROGENESIS AND LTP

It is an odd twist of fate that the dentate gyrus has been the focus of most LTP persistence studies, yet it is also one of the few brain regions that shows a significant degree of ongoing neurogenesis (Kaplan & Hinds 1977; Van Praag *et al.* 1999). In most studies, neurogenesis is prob-

ably not a major complicating factor for the tracking of LTP maintenance because animals are singly housed in impoverished environments, and under these conditions the birth of new neurons occurs at a slow rate. The fact that stable recordings of both potentiated and non-potentiated synapses can be made for months under these conditions supports this view (Abraham *et al.* 1995, 2002). But what of the reversal of LTP by exposure to complex environments? Under these conditions, both the neurogenesis rate and the survival rate of neurons should be high, potentially leading to a net accumulation of granule cells (Gould *et al.* 1999; Young *et al.* 1999). Such architecture changes could distort the field potential recordings and degrade the measurements of LTP. It is interesting to note, therefore, that exposure of adult animals to complex environments does not affect the fEPSP measurement for non-potentiated pathways (Sharp *et al.* 1987; Abraham *et al.* 2002; figure 4). Furthermore, the reversal of LTP by complex environments is time dependent, and occurs within days of exposure to the complex environment, at a time before the new neurons could have fully differentiated and formed viable synapses. Thus, although it is conceivable that an increase in new neurons and overall synaptic number could dilute the contribution of potentiated synapses to the overall field potential recording, and make a stable LTP appear to decline, the timing of the neurogenesis process does not appear to be able to account for a rapid and complete loss of LTP. None the less, it is still important to note that the dentate gyrus has a much greater range of ages among its neurons than elsewhere in the brain, and thus the properties of LTP observed in this region may be heterogeneous and not easily extrapolated (Wang *et al.* 2000).

4. LTP MAINTENANCE AS A MODEL FOR MEMORY

Most studies have shown that late-phase LTP decrements over days or weeks. This has been a more than sufficient duration to warrant extensive molecular and behavioural studies of LTP as a putative memory mechanism. But is such plasticity persistent enough to account for long-term information storage? This remains a pertinent question despite the demonstrations of stable or very slowly decrementing LTP, because such persistent LTP may be an artefact of having the experimental animals live in an impoverished environment (figure 4). Thus, there remain lingering doubts about the usefulness of LTP as a mechanism underlying very long-term memory storage (Abraham 2000), because memories can persist longer than a few weeks, even in rats (Maren *et al.* 1999; Kubie *et al.* 1999; Clark *et al.* 2002). However, there are several theoretical and experimental considerations that can reconcile differences between LTP maintenance and memory retention. First, memories can be subject to reactivation and rehearsal, and these processes may preserve that memory by refreshing what would otherwise be decaying synaptic weight changes. By contrast, the maintenance of one-shot LTP may not be subject to such reactivation effects because of its artificial nature, and thus its persistence may not accurately model the maintenance of real memories. Secondly, LTP persistence may vary between brain regions, and conclusions drawn from one brain region may not be generalizable to others. At the present

time, LTP persistence has only been extensively studied in the hippocampus, a structure that does not store information for long periods of time, according to many experimental studies and computational models (Squire 1986; McClelland *et al.* 1995; but see Nadel & Moscovitch 1997; Cipolotti *et al.* 2000). Thus, structures that are believed to store very long-term memories, such as the neocortex, may be capable of showing much longer-lasting LTP. Third, in certain neural network models of sequential learning, synaptic weights at individual synapses can shift dramatically as a result of new learning and yet the network can retain an originally stored memory (Robins & Frean 1998). Thus, memories may outlast LTP, or LTD, at any particular set of synapses under study.

5. QUESTIONS FOR THE FUTURE

Despite the above caveats about the persistence of LTP *vis à vis* memory, the physiological properties of LTP continue to play a critical role in bridging the molecular and behavioural levels of analysis. A thorough understanding of the basic properties of LTP persistence and how it is regulated will help inform the thinking and experimental planning at these other levels of analysis. However, despite the recent progress that has been made, there is still a sense that we are chipping away at the tip of the iceberg of factors controlling LTP maintenance. Below are some of the key questions are raised requiring future study.

(a) *Do NMDA receptor-dependent and receptor-independent LTP have different maintenance mechanisms and persistence properties?*

So far, studies of LTP have focused on NMDA receptor-dependent LTP (Jeffery *et al.* 1990; Abraham *et al.* 2002). However, it has been suggested that LTP induced by activation of VDCCs may have different underlying induction and early-phase maintenance mechanisms (Grover & Teyler 1990, 1995), although this view is not easily reconciled with reports that the late-phase of NMDA receptor-dependent LTP requires VDCC activation, at least in hippocampal slices (Impey *et al.* 1996). It is important therefore to establish for how long VDCC-specific LTP can last, and whether the mechanisms of maintaining this LTP overlap with those for NMDA receptor-dependent LTP.

(b) *Does LTD last as long as LTP, and is it regulated by the same factors?*

Because many groups have found homosynaptic LTD difficult to observe *in vivo*, little is known about this issue. Homosynaptic LTD can persist across days (Doyère *et al.* 1996), and is protein-synthesis dependent (Manahan-Vaughan *et al.* 2000), but it is not known how long it can be maintained. Also, as for LTP, there may be important differences between NMDA receptor-dependent and receptor-independent LTD that have not yet been explored. By contrast, heterosynaptic LTD in the dentate gyrus lasts for as long as simultaneously induced LTP, and their decay rates are highly correlated (Abraham *et al.* 1994). Whether LTD maintenance is as sensitive to behavioural variables as LTP is an important question that is currently under investigation.

(c) *Does LTP or LTD vary in its persistence across brain regions, as predicted by theoretical models?*

Based on the retrograde amnesia gradients that are commonly observed after hippocampal lesions, it is the conventional view that the hippocampus is involved only transiently in the representation of episodic information until the representations in neocortex become sufficiently elaborated to independently sustain long-term retention (Marr 1971; Squire 1986; Milner 1989; McClelland *et al.* 1995). One key issue then is how persistent is neocortical LTP? The prediction based on these conventional theories is that neocortical LTP should be capable of stable expression. Furthermore, it should be much more resistant to behavioural interference than hippocampal LTP. Racine and colleagues have begun to address these issues, as noted above, but a fuller description of LTP persistence properties is still required. Of course, as LTP can be observed in most areas of the brain, these same issues are pertinent to many other brain regions.

(d) *How long can synaptic plasticity persist in animals living continuously in a complex environment?*

Most experiments on LTP persistence are conducted in animals living in stimulus-poor environments, including individual housing. Despite being adult animals, their synapses may be in an immature state through lack of stimulation, and thus show different LTP induction and maintenance properties than synapses of animals living in more complex or naturalistic environments. We may get a very different view of the properties of plasticity in various brain regions if studies are done in animals living constantly in enriched environments. Such studies, if combined with behavioural experiments, may modify our views of the contributions made by different brain regions to long-term memory consolidation and storage.

(e) *Do the factors that regulate the maintenance of LTP or LTD equally regulate the persistence of long-term memory?*

It is an underlying assumption, or perhaps merely hope, that understanding the regulation of LTP maintenance will help us understand the properties of long-term memory storage in the corresponding brain regions. Although it is potentially misleading to compare the properties of monosynaptic LTP with the properties of memory stored in a network of synapses, none the less the theory has a certain appeal that will seed experimental tests. Indeed, a recent study reported that a treatment that prolonged LTP retention in the dentate gyrus also prolonged memory retention for a hippocampus-dependent spatial memory task (Villarréal *et al.* 2001). Conversely, reduction of LTP maintenance in *zif268*-knock out mice was associated with reduced retention on several diverse memory tasks (Jones *et al.* 2001). Another approach would be to focus on those brain areas in which experience-dependent LTP can be observed, such as the amygdala or neocortex (Rogan *et al.* 1997; Rioult-Pedotti *et al.* 2000). Regulation of LTP persistence in these models should be directly correlated with the maintenance of the associated memory.

6. SUMMARY AND CONCLUSIONS

Although most properties of a network-based memory do not need to be reflected in the plasticity properties of individual synapses in the network, the retention of memory appears to require a certain stability of the underlying synaptic plasticity. Studies of LTP persistence have shown that it has the capacity, in principle, to underlie memories ranging from short-term to very long-term. Stable LTP is of particular interest given the brain's capacity to retain memories over very long periods of time, but our understanding of the factors regulating its induction, maintenance and distribution in the brain is at a very early stage, and it is vital that these issues are addressed. Ultimately, rodent models may not be able to address key issues regarding very long-term memory in humans, given the differences in lifespan between species. Thus it is still pertinent to ask, as in the title of this paper: 'how long will LTP last?' At this stage in our research efforts, perhaps the response is to adapt a sentiment expressed by Tim Bliss some time ago: 30 years and going strong.

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GLOSSARY

- CE: complex environment
 CREB: cyclic AMP response element binding protein
 fEPSP: field excitatory postsynaptic potential
 HFS: high-frequency stimulation
 LFS: low-frequency stimulation
 LTD: long-term depression
 LTP: long-term potentiation
 NMDA: N-methyl-D-aspartate
 VDCC: voltage-dependent calcium channels