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Synaptic plasticity in health and disease: introduction and overview

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We summarize the reviews and research papers submitted by speakers at a discussion meeting on Synaptic Plasticity in Health and Disease held at the Royal Society, London on 2–3 December 2013, and a subsequent satellite meeting convened at the Royal Society/Kavli Centre at Chicheley Hall on 4–5 December 2013. Together, these contributions give an overview of current research and controversies in a vibrant branch of neuroscience with important implications for the understanding of many forms of learning and memory, and a wide spectrum of neurological and cognitive disorders.

Introduction

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This Theme Issue of *Philosophical Transactions* brings together contributions to a discussion meeting held at the Royal Society in London and a separate satellite meeting at the Kavli/Royal Society Centre at Chicheley on Synaptic Plasticity in Health and Disease. The best-known and most intensively studied form of activity-dependent synaptic plasticity remains long-term potentiation (LTP). Together with other forms of activity-dependent synaptic plasticity that include long-term depression (LTD), metaplasticity, homeostatic plasticity, and spike-timing-dependent plasticity (STDP), LTP is widely believed to provide the neural substrate for learning and memory. To provide evidence of such a role remains a principal goal of the field. Ten years ago, on the occasion of the thirtieth anniversary of the publication of the first extended description of LTP, a similar meeting reviewed our understanding of the molecular mechanisms involved in the induction and expression of LTP and its relevance to learning and memory [1]. In the ensuing decade, significant advances have been made in understanding the functional role and molecular basis of LTP and related forms of synaptic plasticity, driven in many cases by the development of new techniques such as multi-photon microscopy.

The papers in this issue, a mixture of reviews and research articles, are divided into three parts. Part I covers the properties and cellular mechanisms of synaptic plasticity. It was realized many years ago that mechanistically distinct forms of LTP can occur at different synapses, when LTP at mossy fibre synapses was found not to be NMDA receptor-dependent, in contrast to LTP at perforant path and Schaffer collateral-commissural (SCC) synapses. There are now many examples of synapses where plasticity differs in more or less subtle ways from the canonical NMDA receptor-dependent hippocampal synapses, and it is highly likely that there exist yet undiscovered forms of plasticity. The contributions to Part I of this issue, devoted to properties and mechanisms of synaptic plasticity, reflect this diversity, though the NMDA receptor remains the major focus. It will also become apparent to the reader that disagreements about mechanisms persist even when experimenters direct their attention to the same synapse. The long-running controversy about whether the expression of LTP at hippocampal SCC synapses is exclusively postsynaptic, or is a combination of pre- and postsynaptic mechanisms, continues unabated. A number of attempts to reconcile the conflicting evidence are made by contributors to this issue. The focus of Part II is on the functional roles of synaptic plasticity, and here the field has been galvanized by the recent

introduction of a reagent that can reverse LTP at arbitrary times after its induction. Part III reflects the growing realization during the past decade that abnormalities in synaptic plasticity contribute to a wide range of neurological and cognitive disorders, most notably Alzheimer's disease (AD), but extending to many other brain disorders, including autism, schizophrenia, addiction, multiple sclerosis (MS) and chronic pain. The developing interest in the role of synaptic plasticity in neural disorders is reflected in the contributions to Part III on synaptic plasticity and brain disorders. In the final section we look to the future, briefly surveying the problems that remain unresolved, and the approaches that will be needed to complete a neurobiological account of memory.

1. Properties and mechanisms of synaptic plasticity

(a) Induction

The essential role played by the NMDA receptor in the induction of LTP at hippocampal SCC synapses was established 30 years ago. The NMDA receptor is also involved in the induction of LTD produced by long low-frequency trains in young rodents. There has been considerable research into the possibility that different NMDA receptor subtypes subserve different roles in the induction of LTP and LTD. This controversial field is comprehensively reviewed by Shipton & Paulsen [2]. One of their conclusions is that GluN2B-containing receptors, linked at their C terminal tail to CaMKII, play a role in the induction of LTP in adult animals.

(b) Expression

The next group of papers addresses a debate that has been continuing with undiminished fervour for over three decades: is the expression of NMDA receptor-dependent LTP (the induction of which is, by general consent, postsynaptic) mediated by presynaptic or postsynaptic mechanisms? While this state of affairs is perplexing ('unbelievably frustrating' as one of our sets of authors writes, 'controversies that have raged far too long' writes another), it has stimulated important advances in our understanding of both presynaptic mechanisms of transmitter release, and the trafficking and mobility of postsynaptic membrane receptors and their ancillary proteins. MacDougall & Fine [3], and Padamsey & Emptage [4] have used multi-photon imaging techniques to monitor synaptic activity at individual synapses in hippocampal slices. The work from their two laboratories has produced strong evidence that LTP at SCC synapses on CA1 pyramidal cells in the hippocampus has a significant and in some cases dominant presynaptic mode of expression. MacDougall and Fine postulate that the additional AMPA receptors slotted into the membrane following the induction of LTP are too far from the active zone to contribute to the potency of the postsynaptic response but these extra slots could be sites for trans-synaptic signalling, leading to an increase in the probability of transmitter release. Padamsey and Emptage take a different approach: they report the results of a meta-analysis of a large number of LTP experiments and conclude that weak LTP-inducing stimulation produces an NMDAR-dependent form of LTP which is postsynaptically expressed, whereas strong stimulation triggers a form of LTP, the induction of which is mediated by Ca^{2+} entering through L-type voltage-gated Ca^{2+} channels and which is presynaptically mediated. 'There are two sides to the synapse', conclude Padamsey and Emptage, 'and both can change'. This is not a statement with which Collingridge and co-workers [5] would disagree. In their survey of the expression literature, they take another look at the distinction between the rapidly decaying phase of LTP often referred to as STP, and the two phases of early- and late-LTP, which are distinguished by their sensitivity to protein synthesis inhibitors. They make the point that all three forms of potentiation can last for at least many hours (in the case of STP, duration depends inversely on the frequency at which synaptic efficacy is sampled after the tetanus). The authors call these three phases LTPa, LTPb and LTPc, and conclude that LTPa is expressed presynaptically, LTPb postsynaptically and LTPc is likely to have both pre- and postsynaptic components. The postsynaptic school is also represented here by Granger and Nicoll [6] who review the very large body of evidence that NMDA receptor-dependent LTP and LTD at SCC synapses involve the movement of AMPA receptors into and out of the postsynaptic membrane. Their uncompromising conclusion is that the expression of LTP at this synapse is postsynaptic.

Isaac and co-workers [7] also nail their colours to the postsynaptic mast. They provide new data to support their idea that the conversion of silent synapses to non-silent, AMPA receptor-expressing synapses following LTP-inducing stimulation to CA1 neurons is a two stage process, involving first the insertion of GluA2-lacking AMPA receptors which are permeable to calcium, and then the replacement of these with GluA2-containing, calcium impermeable receptors. In a theoretical study, Rusakov and co-worker [8] use Monte Carlo methods to ask how many more subsynaptic AMPA receptors would be needed to produce a 50% increase in current at a typical excitatory synapse in the hippocampus. Their surprising finding is that while 100–200% increase in the number of AMPA receptors would be required, reducing the distance between the existing populations of receptors by 30–35% would have a similar effect.

Malinow and co-workers [9] briefly address two controversies in the literature regarding SCC synapses. They report evidence to support their view that the insertion of overexpressed GluA1 subunits occurs only at potentiated synapses, a view challenged by the Nicoll laboratory; and, secondly, evidence supporting their contention that LTD in the hippocampus is not blocked by the NMDA receptor glycine-binding site antagonist 7-chloro kynurenate.

But other synapses have other mechanisms. Glutamatergic synapses onto stratum oriens/stratum lacunosum moleculare (O-LM) interneurons of stratum oriens in area CA1 of the hippocampus have been studied by Nicholson & Kullmann [10]. Here, induction of LTP is also controlled postsynaptically, though independent of the NMDA receptor, and the evidence on expression points consistently to a presynaptic locus. As has been recognized for many years, if induction is postsynaptic and expression is presynaptic, then a retrograde messenger is required to convey information from one side of the synapse to the other. Nicholson and Kullmann investigate two candidates, nitric oxide and the eicosannoid 12-(S)-HPETE, both of which are found wanting.

It seems clear that both presynaptic and postsynaptic mechanisms are available to synapses within the experimental milieu of the hippocampal slice. The controversy about expression mechanisms is essentially a controversy about

SCC synapses. There is little disagreement that presynaptic mechanisms operate at other synapses (for example, mossy fibres in the hippocampus). Moreover, the mechanisms exploited by the freely moving animal to support memory over days, weeks and years, remain largely unexplored. It is perhaps time to move on from the increasingly sterile debate about expression mechanisms at the SCC synapse and accept that there are many rooms in the mansion of synaptic plasticity.

(c) Long-term depression

During the past 10 years, there has been an increasing emphasis on understanding the mechanisms that support LTD, in particular those triggered by the synaptic activation of NMDA receptors or mGlu receptors, and considerable progress has been made in understanding the signalling cascades used by these two major forms of LTD. Sheng & Ertürk [11] propose a model of NMDAR-LTD in which locally constrained components of the caspase apoptotic pathway, activated by Ca^{2+} entry through NMDA receptors, lead to localized upregulation of GSK-3β and a consequent internalization of synaptic AMPA receptors and reduction in spine size.

(d) Metaplasticity

An intriguing aspect of synaptic plasticity is the fact that past activity can radically alter the properties of plasticity produced by a given stimulus protocol. This impact of past activity is called metaplasticity and it can be expressed in both homosynaptic and heterosynaptic pathways. Abraham & co-workers [12] examine an example of heterosynaptic metaplasticity, in which priming stimulation of afferent fibres projecting to the basal dendrites of CA1 hippocampal pyramidal cells modifies the LTP produced by subsequent tetanic stimulation of fibres projecting to the apical dendrites. The authors find no evidence of the involvement of intracellular messengers, but note that Ca^{2+} concentration in astrocytes in the heterosynaptic domain is elevated following the priming stimulus. Gap junction inhibitors block both the astrocytic Ca^{2+} transient and the subsequent expression of heterosynaptic LTP, suggesting the involvement of an intercellular signalling system in this form of plasticity.

(e) Spike-timing-dependent plasticity

STDP has gained prominence in the past few years as a cellular mechanism by which Hebbian and anti-Hebbian plasticity can be produced at individual synapses by varying the relative timing of pre- and postsynaptic firing. The supposition is that this is more likely to be a physiologically relevant induction event than long trains of high-frequency stimulation. Poo and co-workers [13] provide evidence that the neurotrophin BDNF is required for spike-timing-dependent potentiation in acute slices. Moreover, they show that in neuronal cell cultures expressing BDNF-GFP, repetitively paired iontophoretic pulses of glutamate with appropriately timed spiking in the target neuron result in the release of BDNF into the extracellular environment, suggesting that BDNF may act as retrograde messenger for spike-timing-dependent potentiation.

(f) Molecules of plasticity

A major area of research over the past decade has been to identify the signalling cascades that are activated by NMDARs and lead to alterations in pre- and postsynaptic function. The most exciting molecule to emerge during the past few years has been PKMζ. A peptide inhibitor of PKMζ termed zeta inhibitory peptide (ZIP) is able to reverse pre-established LTP and eliminate stored information, thereby providing direct evidence that LTP-like mechanisms underlie information storage in the brain. Like much of the field, these studies are not without controversy. It has been argued, based on the use of knockouts, that the effects of ZIP are not via PKMζ (though this does not undermine the support that ZIP's amnesic properties lend to the 'LTP = memory' hypothesis). It may be that in PKMζ knockouts, there is compensation by another atypical, ZIP-sensitive PKC isoform (PKMι/λ). In this issue, Sacktor and co-workers [14] provide the first detailed characterization of the cellular and subcellular distribution of PKMζ in rat hippocampus and neocortex, information that gives clues to its functions in the central nervous system.

A key property of LTP is the specificity of the process to individual, or small groups, of synapses. But some components of LTP involve nuclear protein synthesis (for example, the products of immediate early genes such as *cfos* and *zif268*). This poses the problem of how input specificity is maintained at individual synapses in the face of cell-wide distribution of new proteins. An idea, known as the synaptic tag and capture hypothesis, has been advanced to explain this conundrum. The idea is that activated synapses are tagged by appropriate local activity to sequester neuron-wide plasticity-related proteins. Bito and co-workers [15] review the extensive literature and posit that a key pathway involves calcium calmodulin-dependent kinases (CaMKs) and the transcription factor CREB. They also describe how the immediate early gene *Arc* may function in a reverse tagging phenomenon that weakens inactive synapses. Israely and co-workers [16] also discuss the role of protein synthesis in synapse strengthening and weakening, with an emphasis on the consequences for structural plasticity. Their work illustrates how the multi-photon confocal microscope is complementing more traditional intracellular and patch recording techniques to help to realize a sense of how things may be changing structurally.

One of the first, and arguably the most widely studied, kinases in the context of LTP is CaMKII. Another key molecule involved in the stabilization of glutamate receptors at synapses, and which is important for both LTP and LTD, is the scaffolding protein PSD-95. Turrigiano and co-worker [17] present new data concerning the co-localization and mobility of these two important proteins at synapses. The Shank proteins are also scaffolding proteins that indirectly link ionotropic to metabotropic glutamate receptors. The three Shank proteins have become the focus of intense research because mutations in each are associated with neurodevelopmental and psychiatric disorders, such as schizophrenia and autism. In this volume, Schuman and co-workers [18] describe the localization, expression levels and stability of the three Shank proteins in CA1 neurons.

2. Functional roles of synaptic plasticity

The idea that alterations in the strength of connections between neurons could be the basis of learning and memory has a long history, extending back at least to Ramón y Cajal and arguably

earlier. Cajal himself referred to the idea in his Croonian Lecture to the Royal Society in 1894 [19]. There are numerous reasons for favouring a synaptic mechanism of storage, not the least being the greater storage potential of such a mechanism compared with cell-wide changes in excitability or even local changes in dendritic integration. However, all of these and yet other mechanisms are candidates for information storage in the nervous system. Their role has to be decided by the evidence—and this requires experimental techniques that couple what we know about the molecular mechanisms (Part I) with behavioural studies.

Morris and co-workers [20] provide a summary of what they call the 'generic' synaptic plasticity and memory (SPM) hypothesis, and take us through some of the more recent tests of this idea with reference to criteria such as detectability, anterograde alteration, retrograde alteration and mimicry. A key aspect of their argument is to remind readers that there are qualitatively different forms of learning and memory, and that the role that activity-dependent synaptic plasticity plays in each type of memory could differ. They also summarize new approaches to the synaptic tagging and capture idea.

In a similar vein, Mayford [21] argues that understanding the molecular and cellular changes underlying complex forms of memory represents 'a major difficulty' and goes on to identify a parallel set of criteria that need to be met. These are: (i) identify a learning-induced molecular and corresponding functional cellular change in a specific subset of neurons; (ii) block the identified molecular/cellular change and prevent memory formation; (iii) induce the identified molecular/cellular change in the identified subset of neurons or synapses and produce a memory independent of behavioural training; (iv) determine how the learning-induced cellular changes function within the circuit to produce recognition (e.g. recruit specific neural representations) and alter behavioural output. He then discusses recent approaches using powerful new tools for calcium imaging (GCAMP) and neuronal manipulation (optogenetics and designer receptors exclusively activated by designer drugs (DREADDS)).

One area of controversy highlighted by Mayford concerns the role that NMDA receptors may play in learning. An early idea was that, in hippocampus, they would be crucial functionally because they would provide the mechanism of signalling an association between pre- and postsynaptic activity, so providing a molecular basis for Hebbian synaptic plasticity. New work by Bannerman and co-workers [22] using mutant mice questions this assumption, with data suggesting that spatial learning can be quite normal in animals with GluN1 deleted in CA1 and the dentate gyrus—though these mice do show a deficit in spatial reversal learning. They suggest that 'hippocampal NMDARs, particularly in CA1, act as part of a comparator system to detect and resolve conflicts arising when two competing, behavioural response options are evoked concurrently, through activation of a behavioural inhibition system'. Bannerman and Morris, using pharmacological techniques, had in earlier work together raised the question of whether NMDA receptors are necessary for long-term spatial learning. Their views have now diverged with Bannerman raising the idea of a role in selecting between different behavioural outputs, while Morris asserts that NMDA receptors are vital and that the critical role of CA1 and CA3 NMDA receptors is in enabling one-shot episodic-like memory encoding.

Tonegawa *et al*. [23] take to the field in the exciting new territory of false memory. It has long been known that memory is not always veridical and that people may, under certain circumstances, believe that something happened in the past when in fact it did not. This is an interesting test case of the synaptic plasticity and memory idea as the ability of multiple synaptic changes to 'mimic' a memory would satisfy an important prediction of the hypothesis. The Tonegawa group goes on to describe how they have used optogenetics in conjunction with context fear conditioning to train animals to behave as afraid in a neutral situation in which nothing untoward has happened. Their paper describes how the intellectual context of their work is very much in the spirit of identifying and manipulating hippocampal engrams, as outlined by Mayford, although both approaches involve direct manipulation of cells rather than synapses.

Wang and co-workers [24] also provide a fresh perspective on an old problem. It has long been appreciated that a memory trace may be formed but that is no guarantee that it will last, leading to the many studies of 'consolidation'. This is the process that somehow stabilizes memory traces. The lateral thinking they bring to this issue is to raise the spectre that forgetting itself may not be a passive process, but one involving the active removal of AMPA receptors from the postsynaptic density. Focusing here on early- and late-LTP, they provide evidence that even consolidated changes in synaptic potentiation (i.e. late-LTP) can be subjected to active forgetting and that blocking the process of AMPA receptor endocytosis can make potentiation last longer. It will be interesting to see whether the same intervention prolongs memories.

In a similar vein, but focusing more on consolidation, Laroche and co-workers [25] describe the work in which they specifically induce Zif268 overexpression in forebrain neurons of mice, and then examine the impact on recognition memory and hippocampal synaptic transmission and plasticity. The memory for objects in a testing arena did not change, but regional-specific Zif268 overexpression enhanced the capacity to form a long-term memory of the spatial location of the objects. This enhancement was paralleled by increased LTP in the dentate gyrus of the hippocampus.

To date, LTP has been examined *in vivo* or *in vitro* either with microelectrodes, or by examining synapses, single cells or small groups of cells with multi-photon microscopy. Canals and co-workers [26] take us into a new era by asking whether the induction of LTP causes measureable changes in the BOLD signal as measured in fMRI. Combining high-resolution fMRI and *in vivo* electrophysiology in rats, Canals and co-workers had previously reported a functional remodelling of long-range hippocampal networks induced by LTP of synaptic plasticity in the perforant pathway. By long range, they mean and include changes occurring in the prefrontal cortex that, of course, are not normally monitored in a conventional study with a single recording electrode in a single synaptic zone. Their new results reveal an increased bilateral coupling in the hippocampus—specifically supported by the mossy cell commissural/associational pathway in response to LTP. This exciting use of fMRI brings a fresh 'systems' perspective to thinking about the functions of hippocampal LTP.

Neuroscientists rightly honour Ramón y Cajal, but they also look upon Donald Hebb as a visionary with his ideas about the physiological circumstances in which potentiation would occur and his concept of the 'cell-assembly'. Cooke and co-worker [27] revisit the very area of the brain that

Hebb had in mind, the visual cortex, and present evidence that both LTD (during the developmental fine-tuning of connections) and LTP (in the form of selective response potentiation and perceptual learning) play an important role. However, they qualify their assertion by noting that a full understanding of the role of plasticity in visual cortex will require an appreciation of intrinsic microcircuits in which other forms of plasticity may prevail.

3. Synaptic plasticity and brain disorders

A hugely important development over the past decade or so has been the realization that aberrant synaptic plasticity may lie at the heart of many brain disorders. Consequently, the study of synaptic plasticity in disease models offers a promising route by which improved treatments for neurological and psychiatric conditions may be developed.

Because of its prevalence and severity, the most pressing disorder to understand is AD. In the UK alone, it is predicted that by 2021 there will be a million people with dementia, of which AD is the most common form. It is an incurable chronic condition which accordingly places a heavy socio-economic burden on society. The current treatments—anticholinesterase inhibitors and the NMDAR antagonist memantine—offer only modest, short-term benefit and then only in some patients, and improved treatments are urgently needed. A major breakthrough in the understanding of AD was the discovery by the Trinity College Dublin team led by Michael Rowan and Roger Anwyl that oligomeric species of Aβ inhibits LTP and promotes LTD in the hippocampus. Rowan and co-workers [28] here present new data concerning the ability of Aβ to inhibit LTP in the anaesthetized rat. Remarkably they find that a single injection of a brain extract containing stable Aβ dimers can inhibit LTP evoked a week later. In addition, they report Aβ inhibition of NMDAR-independent LTP. Cholinergic modulation is complex: a form of LTP induced by endogenous activation of muscarinic receptors is resistant to Aβ while endogenous activation of nicotinic receptors protects against the Aβ inhibition of NMDAR-LTP.

A key question is how Aβ triggers neurodegeneration. Using the acute Aβ inhibition of LTP as a model of AD, Cho and co-workers had identified a crucial role of GSK-3β, and Paulsen and co-workers had found a requirement for tau. GSK-3β is known to be responsible for the hyperphosphorylation of tau that leads to the formation of tangles in AD but whether tau has a physiological function in synaptic plasticity was unknown. Cho and co-workers [29] here provide evidence that tau does indeed play an obligatory role in LTD. They show that NMDAR-LTD is absent in the tau knockout and when tau is knocked down by RNAi. Furthermore, they show that LTD is associated with the GSK-3-dependent phosphorylation of tau on the PHF epitope. The finding that both GSK-3β and tau, molecules closely associated with AD, are part of the LTD process supports the emerging idea that AD is caused by a dysregulation of LTD.

NMDAR-LTD is associated with both the removal of AMPARs and the shrinkage of spines. In this issue, Kim and co-workers [30] address the role of a cell adhesion molecule, netrin-G ligand-3 (NGL-3) in these processes. They report that LTD is associated with the cleavage of NGL-3 via a mechanism that requires both matrix metalloproteinases and presenilin/gamma-secretase. The latter observation is interesting in the context of AD, as gain of function mutations in presenilin genes are the cause of some forms of early onset AD. It is tempting to speculate that overactive presenilin may facilitate the generation of LTD by the cleavage of cell adhesion molecules, for example NGL-3, leading to the aberrant elimination of synapses. NMDA receptor-dependent LTD could be a point of convergence of many of the risk factors for AD. Recently, it was found that the JAK/STAT pathway, an effector of many cytokines and hormones, is involved in this form of LTD. In complementary research, Irving & Harvey [31] here review the evidence that leptin, a hormone involved in energy homeostasis that signals via JAK/STAT, regulates both LTP and LTD, and suggest that leptin-based agents are potential therapeutic targets in the treatment of AD.

The NMDA receptor is central to many forms of synaptic plasticity. Not surprisingly, therefore, mutations in proteins that are associated with NMDARs can lead to alterations in NMDAR-dependent synaptic plasticity and can constitute risk factors for brain disorders. This is exemplified by the Shank proteins. These proteins link NMDARs, via intermediary scaffolds, to other components of the synapse that are important for synaptic plasticity, for example mGlu5 receptors. Mutations in all three Shank isoforms can predispose to autism. Kaang and co-workers [32] review the literature concerning Shank mutant mice as animal models of autism.

NMDA receptor-dependent LTP is also modulated by a wide variety of external factors. For example, it has been known for a long time that chronic stress can severely impair NMDAR-LTP in the hippocampus. Here, Chattarji and co-workers [33] describe work from their laboratory that shows how chronic stress has the opposite effect on NMDAR-LTP in the amygdala. Through the formation of silent synapses, chronic stress leads to enhanced LTP and associated fear memory.

There is growing evidence that impairments in synaptic plasticity are central to conditions that involve cognitive disability. Loss of function mutations of Oligophrenin-1 (OPHN1) leads to cognitive disabilities in humans. Lüthi and colleagues [34] describe the effects of the constitutive lack of OPHN1 in mice. There is a complete lack of PKA-dependent presynaptic forms of LTP in both the hippocampus and amygdala, and there are associated learning problems. Intriguingly, the learning deficits could be fully rescued by Fasudil, a ROCK/PKA kinase inhibitor. These forms of LTP, that may rely on kainate receptor activation rather than NMDAR activation and are expressed presynaptically, have been less studied than the prototypical NMDAR-LTP. It will be interesting to see the extent to which alterations in these presynaptic, non-canonical forms of LTP also contribute to brain disorders.

The diverse array of conditions involving cognitive dysfunction that are attributable to altered synaptic plasticity is further exemplified by the contribution from Nisticò and his colleagues [35], who review recent work on mouse models of MS. These authors found enhanced LTP and a reduction in LTD in a model of experimental autoimmune encephalomyelitis; both effects can be replicated by application of the pro-inflammatory cytokine IL-1β. They propose that the release of cytokines from infiltrating lymphocytes and activated macrophages is responsible for the alterations in synaptic plasticity and the associated cognitive deficits in such conditions.

An area where there is particularly strong evidence for a functional role of synaptic plasticity is in chronic pain. Zhuo [36] concludes the issue with a review of the evidence for the importance of LTP and LTD in the anterior cingulate

cortex in the perception of pain. It is now readily apparent that the same types of LTP and LTD mechanisms that exist in the hippocampus for the storage of, for example, episodic memories are engaged in this cortical structure to encode chronic pain. Thus, treatments that can reverse pre-established NMDAR-LTP, for example the PKM inhibitor ZIP, offer the potential for treating chronic pain if they can be appropriately targeted.

4. Looking ahead

The crystal ball is an uncertain tool with which to peer into the future. Had we speculated about the future 10 years ago, we would not have imagined that miniature optic fibres penetrating the brain with blue, green and yellow light would be activating and deactivating neurons and, in the process, revealing so much about those aspects of neuronal activity that are causal of behavioural and other processes. So who is to know what is round the next corner?

Key conceptual issues remain with us through all the new developments of technology in the neurosciences. We have seen how the big question of pre- versus postsynaptic expression of NMDA receptor-dependent LTP has been with us for many years and remains unresolved. It would be a relief if closure on this key issue could be achieved and attempts are made in this issue to do just that. Understanding the signalling pathways of LTD, metaplasticity, STDP and homeostatic plasticity is currently a very active area of research and an important one as insights are emerging that are directly relevant to aspects of neuropathology.

With respect to function, the likely role of activity-dependent changes in synaptic efficacy in learning now feels much more secure than it did 10 years ago when sceptics were still relatively easy to find. The main predictions of the SPM hypothesis have by and large been confirmed. The recent 'mimicry' experiments are particularly encouraging with respect to establishing the existence of hippocampal engrams, that these can affect behaviour, and that they can be selectively re-activated through the use of molecular tools. However, an experiment in which spatial patterns of synaptic change are activated or re-activated, as distinct from the neurons within which these patterns are expressed, remains unachieved. Presently this seems a long way off. But with the plethora of new tools at hand, many of which have contributed to the results described or reviewed in this volume, it feels more than ever an exciting time to be in the field.

Finally, it is becoming increasingly apparent that there is more to LTP and its variants than their importance in unravelling the synaptic basis of learning and memory. It is now established beyond reasonable doubt that LTP and LTD are central to many physiological functions and that their dysregulation contributes, and in many cases may be causal for, a number of brain disorders. Among those implicated are autism, schizophrenia, AD and other dementias, mental retardation, addiction, MS and chronic pain. Understanding LTP and other forms of synaptic plasticity, both the NMDAR-dependent and NMDAR-independent varieties, thus provides hope for the development of more effective treatments for some of mankind's greatest afflictions.

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