Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

# Mechanical transmission at spine synapses: Short-term potentiation and working memory

Haruo Kasai[1,2], Hasan Ucar[1,2], Yuichi Morimoto[1,2], Fumihiro Eto[1,2] and Hitoshi Okazaki[1,2]

**Abstract**

Do dendritic spines, which comprise the postsynaptic component of most excitatory synapses, exist only for their structural dynamics, receptor trafficking, and chemical and electrical compartmentation? The answer is no. Simultaneous investigation of both spine and presynaptic terminals has recently revealed a novel feature of spine synapses. Spine enlargement pushes the presynaptic terminals with muscle-like force and augments the evoked glutamate release for up to 20 min. We now summarize the evidence that such mechanical transmission shares critical features in common with short-term potentiation (STP) and may represent the cellular basis of short-term and working memory. Thus, spine synapses produce the force of learning to leave structural traces for both short and long-term memories.

**Addresses**

[1] International Research Center for Neurointelligence (WPI-IRCN), UTIAS, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

[2] Laboratory of Structural Physiology, Center for Disease Biology and Integrative Medicine, Faculty of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

Corresponding author: Kasai, Haruo (hkasai@m.u-tokyo.ac.jp)

**Current Opinion in Neurobiology** 2023, **80**:102706

This review comes from a themed issue on **Neurobiology of Learning and Plasticity** 2023

Edited by **Muming Poo** and **Thomas John McHugh**

For complete overview of the section, please refer the article collection - Neurobiology of Learning and Plasticity 2023

Available online 15 March 2023

**https://doi.org/10.1016/j.conb.2023.102706**



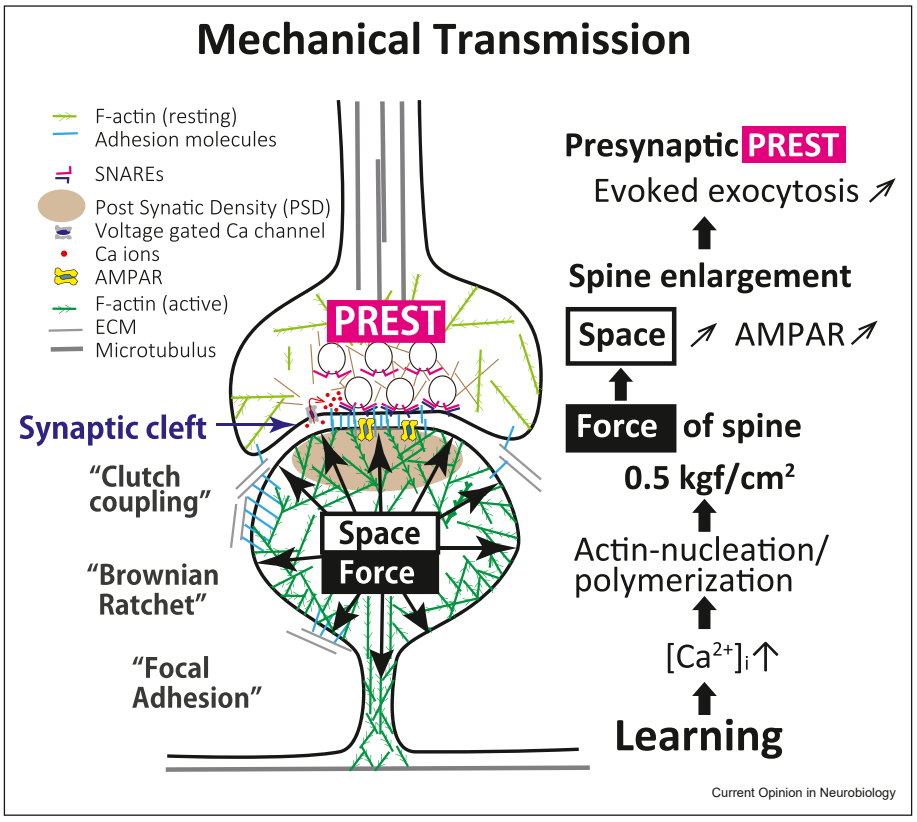
## Introduction

The spiny protrusions on dendrites called dendritic spines form the postsynaptic component of most excitatory synapses. The dendritic spines, however, are not required for excitatory transmission *per se*, as exemplified by excitatory synapses on the smooth dendritic shaft of cortical inhibitory neurons [1,2]. Thus, what is the functional role of spines? Recently, dendritic spines were discovered in a nematode, *Caenorhabditis elegans* [3], where spines have head and neck structures. As in higher-order animals, its spines form synaptic contacts with the head, contain filamentous actin (F-actin), and exhibit dynamic motility as well as $Ca^{2+}$ transients. Thus, the key conserved feature of dendritic spines is their actin-based motility. Spines express the same concentration of F-actin as smooth muscle cells of brain microvessels [4]. They display resting motilities [5–8] and activity-dependent plasticity in the hippocampus [9–11] as well as in the neocortex [12,13] (Figure 1), which can be observed as spine enlargement or shrinkage. Spine enlargement has two phases consisting of a rapid, short-term enlargement (STE) and a slow long-term enlargement (LTE) [9,12,14,15] (Figure 2a and b). During the LTE phase, increases in glutamate sensitivity proportional to the spine volume are observed [9,11,16,17]. Thus, spine enlargement is considered the structural basis for long-term potentiation (LTP) of excitatory synapses [9,18] and is termed structural LTP (sLTP = LTE) [15,18–20]. Although STE is often more pronounced than LTE [9,14,15,21], the increases in glutamate sensitivity are never greater than LTE [9,11,16,22].

It has recently been reported that rapid spine enlargement directly pushes the presynaptic boutons and facilitates evoked neurotransmitter release [23]. This process is referred to as "mechanical transmission" because the force transmits information from post-to presynaptic terminals (Figure 1). Presynaptic terminals are an ideal structure for receiving the force of enlargement as they face the spines and undergo $Ca^{2+}$-dependent exocytosis of neurotransmitters, where $Ca^{2+}$ signaling is sensitive to nano-distances [24] and exocytosis involves nanostructures alterations [25–27]. Thus, spine enlargement can modify presynaptic functions [23,28] as spines push the terminal by 20–130 nm. Presynaptic functions can be rapidly modified also by presynaptic $Ca^{2+}$ signals in the traditional short-term presynaptic plasticity, such as paired-pulse facilitation (PPF), augmentation, depression, and post-tetanic potentiation (PTP) [27,29].

This review will first focus on the mechanical force during synaptic plasticity and its roles in the postsynaptic and presynaptic compartments. The existing lines of evidence for the role of mechanical transmission

**Figure 1**




**Schematic representation of "mechanical transmission."** Learning stimuli activate NMDARs by associative synaptic input to postsynaptic spines, which in turn activates CaMKII and Rho family GTPases, and triggers nucleation, branching, as well as (**a**) polymerization of actin to generate 0.5 kg f/cm$^2$ muscle-like force (arrows), for example, via the "Brownian rachet," "clutch coupling," and "focal adhesion" mechanisms. (**b**) The force primarily expands the spine and utilizes the functional readout of AMPAR and persistent structural modification. (**c**) Next, the force also works on the presynaptic terminal via postsynaptic membranes, adhesion molecules of the synaptic cleft, and presynaptic membrane, and compresses the button as a physical reaction (arrows), which includes closer apposition of vesicles and the plasma membrane. This leads to the enhancement of evoked release of glutamate. We refer to the presynaptic responses as PREST and the spine action on PREST as mechanical transmission.

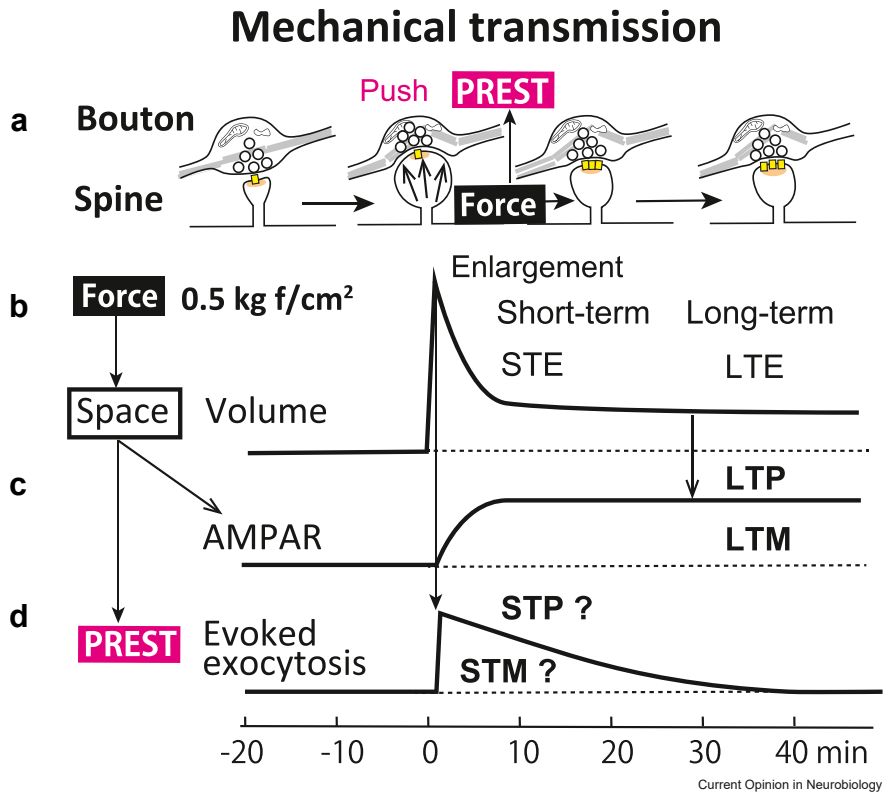
in short-term potentiation (STP) and working memory will then be summarized.

## Mechanical force induces spine enlargement

Activity-dependent spine enlargement was induced via selective stimulation of spines under the associative learning conditions that stimulate N-methyl-D-aspartate (NMDA) receptors in a solution without magnesium or via spike-timing-dependent protocol (STDP) [9–11,17,23]. Considering that the enlargement is generated by a force within a spine and that not all molecular processes are involved in force generation, one can distinguish three physical processes during spine enlargement: 1) Force generation within the spine; 2) utilization of the expanded space in the spine; and 3) pushing of the presynaptic terminal (Figure 1).

Force generation was associated with forming an enlargement pool of F-actin throughout the spine head [30]. This process is primarily induced by activating $Ca^{2+}$/calmodulin-dependent protein kinase II (CaMKII) [9,31–33], the most abundant protein in the postsynaptic density (PSD), which regulates F-actin nucleation and branching [14,34] and phosphorylates LIM domain kinase (LIMK) to prevent severing of actin fibers and promote the formation of additional actin fibers and their elongation [14,19,33,35]. Actin polymerization occurs at the barbed end of F-actin and causes a retrograde flow of F-actin from the leading edge of the plasma membrane toward the cytosol [30]. Polymerization and branching of F-actin happen in all spine-heads [34,36] neck regions [37] and results in force generation [38–40], involving the following mechanisms: 1) The "Brownian ratchet" mechanism, which converts the free energy of actin polymerization into force by clamping a thermal motion of the plasma membrane [38–40]; 2) The "clutch coupling" mechanism, which extracts the force from the retrograde flow of actin fibers by coupling with the extracellular matrix

**Figure 2**




**Pre- and postsynaptic dynamics in short and long-term memory.** (**A**) Mechanical transmission: The actin-based force within the spine induces PREST in the axon terminal. (**B**) The expansive force induces spine enlargement in the short-term (STE) and long-term phases (LTE). They constitute the structural LTP (sLTP = STE + LTE). (**C**) The expansive force strengthens the evoked exocytosis of glutamate (PREST) in the presynaptic terminal, which can last 20 min and possibly give rise to short-term memory (STM).D. The persist phase is accompanied by proportional increases in glutamate sensitivity and is considered to underlie long-term memory (LTM).

(ECM) [41,42]; 3) The cofilin-F-actin (cofilactin) complex formation, which may assist actin polymerization during spine enlargement [15,43,44]; and 4) The "focal adhesion" complexes, which tightly anchor the actin-cytoskeletons to ECM, support enlargement, and prevent the outflow of the enlarged actin pool into the dendritic shaft [30] (Figure 1).

How much force can actin polymerization cause during spine enlargement? The force has been difficult to measure because a presynaptic bouton covers the spine, and there is no way to put a cantilever or a glass pipette within the synaptic cleft. However, a previous study revealed that the presynaptic active zone (AZ) could act as a pressure sensor [23], where the pressure can be read out by the soluble N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) assembly in AZ [45] and the evoked glutamate release [23]. This measurement indicated that the force of spine enlargement equals the osmotic pressure of 20 mM sucrose, which can diffuse into the synaptic cleft and push AZ from the front as the spine does. The osmotic pressure of 20 mOsm is equal to 0.5 kg f/cm$^2$ or 10 nN per the mean synaptic contact area of 0.2 μm$^2$. Thus, the force of the spine enlargement is comparable to that of the isometric contraction of smooth muscle [46]. How is such a strong force generated in the spine? Notably, the actin concentration in the spines was as high as those in smooth muscles of the brain microvasculature [47,48]. Thus, the force-generating mechanisms occur in masses of actin fibers, each generating a force of 20–30 pN per F-actin filament [38–40]. Even though the force is large, spines perform only a small amount of work (= force × distance) as they move a very short distance (~100 nm), unlike muscles.

## Postsynaptic actions of mechanical force: spine enlargement and LTP

The expansive force enlarges the spine head to create a new space that may increase molecule mobility and drive spatial reorganizations within the spine (Figure 1). For instance, in a previous study, two-photon fluorescence correlation spectroscopy (FCS) was used to show an increase in the diffusion of cytosolic monomeric enhanced

green fluorescent protein (EGFP) immediately after spine enlargement [49]. The enlarged space and enhanced mobility harness multifarious downstream reactions to yield persistent structural alterations [15,50], including invasion of the spine apparatus, trafficking of α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors through endosomal exocytosis or lateral diffusion [51], local synthesis of component proteins [52], as well as binding of CaMKII and other molecules [49]. Some molecules may function in force generation and space utilization processes, as exemplified for CaMKII. Most importantly, PSDs gradually increase in size following protein synthesis to maintain structural plasticity [15,53,54]. Furthermore, thickening of the spine neck was detected by two-photon [55,56], electron [15], and stimulated emission depletion (STED) microscopy [57], in part due to the integration of the endoplasmic reticulum [58]. Moreover, the spines twitch [23,56,59,60] to make mRNA and RNA protein complexes (RNPs) more accessible to the spine head [61]. Spine twitching and thickening reduce the electrical decay [59,62,63] and avoid saturation of excitatory input [57]. These findings indicate that the mechanical force is the origin of the spine enlargement (STE and LTE) and related cellular processes (Figures 1 and 2).

The spine volume altered by the mechanical force is strongly correlated with the number of functional AMPA receptors [64—68], as well as the ultrastructural [69—71] and biochemical [72] expression of AMPA receptors (Figure 2C, Table 1). This may be ascribed to the binding of AMPAR auxiliary subunits to PSD scaffolding proteins [73]. Furthermore, as glutamate sensitivity gradually increases during spine enlargement [74], spines reinstate the initial structure-function relationship. Spine enlargement can leave traces for a long time and subserve the endurance of spines and memory [8].

## Presynaptic actions of mechanical force: PREST

Pushing of a presynaptic terminal by rapid STE results in an immediate increase in SNARE assembly and glutamate release, both of which continue unabated for 20 min [23] (Figure 2D; Table 1). The pushing force is required for the processes because no such effect is observed when spine enlargement is prevented from pushing the terminals due to the twitching of the spine neck. Upon enlargement, spines elongate by ∼150 nm, and boutons recess by ∼50 nm in full width at half-maximal diameter (FWHM), which is well below the damaging threshold (<120 nm) [23]. The force is active only when synapses are in contact. Thus, the following scenario is envisaged (Figure 1): A spine elongates via actin polymerization, and the spine plasma membrane pushes the presynaptic membrane via the synaptic adhesion molecules from the synaptic cleft. The force physically compresses presynaptic structures, including the active zone, synaptic vesicle clusters, cytoskeletons, and organelles within the presynaptic terminal. The compression of the cytosol induces closer apposition of synaptic vesicle clusters to the plasma membrane, which is sensed by SNARE proteins in the vesicles and presynaptic plasma membrane. These processes can occur rapidly (<10 s or earlier) and persistently (<30 min) as they are mechanical and structural. Slow chemical processes may also come into play [75]. This cellular sensation and mechano-transduction mechanism [76] has been termed 'PREST' (Pressure Sensation and Transduction).

Spine enlargement is considered the major cause of PREST because the deformation of presynaptic structures is the essence of PREST [23]. The change in osmotic pressure caused by membrane impermeable substances in the blood can also induce PREST by fine deformation, but only until volume regulatory mechanisms restore the cytosolic volume [77]. Changes in blood pressure are unlikely to yield PREST as the intact skull confines both the brain tissue and cerebrospinal fluid, and blood pressure generates a static pressure within the skull. The static pressure does not significantly deform the tissue even up to 2100 atm, as evidenced by the high-pressure freezing technique of synapses [78]. Since muscle-like force is required to

**Table 1**

**Comparisons of STP and short-term synaptic plasticity (STSP).**

| | Induction | Expression | Mechanisms | Specificity | Persistence |
|---|---|---|---|---|---|
| LTP | Post | Post | LTE = sLTP | Synaptic | >30 min |
| STP | Post | Pre | STE + PREST | Synaptic | <30 min |
| STSP | Pre | Pre | Na-spike/Ca-signal | Cellular | <1 min |

Repetitive activation of spine NMDAR triggers spine enlargement whose long-term spine phase (LTE = sLTP) induces accumulation of AMPAR. The early short-term phase (STE) causes PREST in the synaptically connected presynaptic button. This review proposes the possibility that STE and PREST may mediate short-term potentiation (STP). In contrast, short-term synaptic plasticity (STSP) comprises paired-pulse facilitation (PPF), depression, augmentation and post-tetanic potentiation and is induced only by electrical stimulation of presynaptic axons and, therefore, occurs along the entire axon (cellular) and dissipates quickly.

induce PREST, spine enlargement must be the only major cause in physiological conditions.

## Mechanical transmission and STP

We reported PREST as a novel consequence of spine enlargement [23]. We noticed afterward that spine enlargement and PREST share the same major properties as the STP process (Table 1) investigated 30 years ago. However, the STP process has nearly disappeared from recent studies [79]. STP can be induced with the same tetanic stimulation as LTP (for example, 100 Hz for 1 s) of presynaptic fibers using a metal electrode and recorded with the slope of the field excitatory postsynaptic potentials (fEPSPs).

1) Induction protocols for pure STP are weaker than for LTP [80–84], as STE and LTE [30].
2) STP persist for 10–30 min [30,83,84], as PREST.
3) Induction of STP and STE require postsynaptic NMDA receptors [9,80,83,85] and can induce associative synapse-specific plasticity, namely Hebbian plasticity, as in LTP and LTE.
4) The expression of STP is considered presynaptic because STP is associated with increases in presynaptic glutamate release [86] and without increases in postsynaptic glutamate sensitivity [79,87], contrary to LTP [88].
5) STP [89–91] and STE [9,14,19,21] are resistant to the effects of kinase inhibitors relative to LTP and LTE. PREST is resistant to the high concentration of K-252a, which non-selectively blocks serine/threonine kinases [23].
6) Both STP [79] and STE [56] are weakened and disappear following whole-cell perfusion of postsynaptic cells (the same for LTP and LTE), likely due to the prevention of cell motility.

In a traditional view, if STP induction is postsynaptic but its expression is presynaptic (Table 1), a retrograde chemical signaling is necessary; however, retrograde chemical messengers, which transfer postsynaptic NMDA signaling to the presynaptic terminals, have been disputed [79,92,93]. This point must have hampered the investigations of STP [79]. Mechanical transmission has removed the obstacle, as it does not require chemical messengers and enables the most intimate and physical communication from the spine to the bouton. It should be noted that STP was elicited and recorded with metal electrodes and readout with fEPSPs, while the mechanical transmission (STE + PREST) was induced with single spine stimulation and monitored with two-photon imaging of the single bouton innervating the spine. Therefore, it is surprising that their key features are the same. Mechanical transmission is likely operated in broader experimental conditions than standard STP, for example, a rapid phase of enlargement by STDP [11], those LTPs which were considered presynaptic at least in part [86,94–97], spontaneous spine motilities [5], and other unknown *in vivo* paradigms for spine enlargement [98].

Since mechanical transmission was only recently discovered in 2021, it requires further studies and clarifications. One key issue is that although PPF occurs promptly [29], knowledge of the onset speed of STP and STE is limited (Table 1). This is because 1) the rapid components of presynaptic plasticity (e.g., PTP) ambiguated the results [85]; 2) whole-cell clamping inevitably perfuses the cytosol and greatly slows down and reduces spine motility [56,79]; and 3) the characterization of STE has been unattractive for researchers as the functional role of STE was unclear, unlike sLTP (or LTE) [15,18–20]. As strong evidence that STE induces PREST emerged, the onset of early spine enlargement and STP will become a focus for future research.

## Short-term and working memory

Since LTP associated with LTE are involved in long-term memory (LTM) formation [20,44], it follows that STP associated with STE may be involved in short-term memory (STM) formation (Figure 2). STM can be divided into "short-term memory" which is a capacity to hold information in an active, readily available state for a short time interval, and "working memory" which does so for further processing purposes and decision making. Both types of STM are stored in an associative fashion [99–101] and play a crucial role in the execution of a wide range of cognitive tasks. In the delayed response paradigm, a stimulus that is briefly presented to an animal must be maintained for several seconds until the execution of the task. Enhanced stimulus-specific spiking activity has been observed during the delay period and is regarded as the neuronal correlate of STM [99,102]. The involvement of synaptic plasticity was suggested because the increase in the activity sometimes disappears completely during the delay period (activity-silent working memory) [103–105] and because STM is associative memory. Moreover, STM gradually transforms to LTM [99,106], as STP does to LTP and STE to LTE.

The involvement of STP in working memory has been proposed. STP was significantly reduced in a mutant mouse line (GluA1 KO mice with unknown mechanisms) [107–109], where working memory was impaired [110], while maintaining intact spatial reference learning of maze tasks [110,111], which was partly restored by overexpression of GluA1 [112,113]. Likewise, NMDA receptor inhibitors blocked STP, resulting in working memory deficits [114,115]. NMDARs containing NR2A are required for working memory in mice, but not spatial reference memory [116]. NR2A, but not the NR2B subunit in the prefrontal cortex, is required for working

memory in aged rats [117]. It is noteworthy that GluA1 and NR2A are listed in the 108 loci which are most susceptible to schizophrenia in genome-wide association studies (GWAS) [118] because impairment of working memory is a core cognitive symptom. Other genes related to long-term synaptic plasticity [8,119] may also affect STP. Impairments in PREST would account for STM deficits in schizophrenic patients and other subjects [100] with relatively intact LTM. In schizophrenic patients, there is a reduction in the number of synaptic vesicles [120] and synapsin II expression [121]. A computational neuronal network model mimicking STP is constructed to explain how prefrontal cortex could maintain and update novel associations [122].

Traditional short-term synaptic plasticities (STSP), such as PPF, depression, augmentation, and PTP, is also presynaptic and proposed to support working memory (Table 1) [123–125]. In fact, simulation studies suggest that STSP helps a neuronal network focus on already acquired long-term memory, and such activity is readily updated and short-lasting, as is often the case with working memory in humans [126]. However, STSP does not show associativity and synaptic selectivity and occurs along the entire axon (Table 1). Thus, it is questionable whether STSP can account for a new working memory involving association, for example, between a novel scenery and an image that is remembered. Furthermore, although working memory can be transferred to LTM if repeated [101,127,128], STSP cannot generate LTM because it does not cause LTP (Table 1). Moreover, unlike STP, there is no mutant or pharmacological evidence for the involvenet of STSP in working memory, unlike STP. However, there are kinetic differences between STP and STSP, and it will be important to clarify how STP (or mechanical transmission) and STSP differentially and cooperatively support activity-silent working memory.

## Conclusions

Simultaneous investigation of both pre-and postsynaptic sites of the same spine synapse has revealed that the generation of muscle-like force underlies spine enlargement. Although spine synapses usually operate under electrochemical mechanisms, they generate mechanical force during associative learning to leave their traces for some time. In the early phase, the force is transmitted to the presynaptic terminal. Since the transmission is physical, it can be rapid, intimate, flexible, and mnemonic, representing a hidden basis of dynamic working memory.

## Author contributions

Conceptualization: H. Kasai, H. Ucar, H. Okazaki. Writing: H. Kasai, H. Ucar, Y. Morimoto, F. Eto.

## Conflict of interest

Nothing declared.

## Data availability

No data was used for the research described in the article.

## Acknowledgments

The authors thank G. Augustine, H. Murakoshi, and T. Watanabe for their helpful discussions. This work was supported by Grants-in-Aid (20H05685 to H.K.; 21K15203 to H.U.; 21K20682 to Y.M.) from the Japan Society for the Promotion of Science; the World Premier International Research Center Initiative from the Japan Ministry of Education, Culture, Sports, Science and Technology (MEXT); and Core Research for Evolutional Science and Technology (JPMJCR1652 to H.K.) from the Japan Science and Technology Agency, a grant-in-aid of The Fugaku Trust for Medical Research (to H.K.) and Takeda Science Foundation (to H.O.).

## References

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Somogyi P, Kisvarday ZF, Martin KA, Whitteridge D: **Synaptic connections of morphologically identified and physiologically characterized large basket cells in the striate cortex of cat**. *Neuroscience* 1983, **10**:261–294.

2. Goldberg JH, Tamas G, Aronov D, Yuste R: **Calcium microdomains in aspiny dendrites**. *Neuron* 2003, **40**:807–821.

3. • Cuentas-Condori A, Mulcahy B, He S, Palumbos S, Zhen M, Miller 3rd DM: **C. elegans neurons have functional dendritic spines**. *Elife* 2019, **8**.

Dendritic spines in *C. elegans* were functionally identified based on the actin cytoskeleton, resting motilities, the position in the presynaptic active zone, and dynamic $Ca^{2+}$ transients by cholinergic input.

4. Matus A: **Actin-based plasticity in dendritic spines**. *Science* 2000, **290**:754–758.

5. Fischer M, Kaech S, Wagner U, Brinkhaus H, Matus A: **Glutamate receptors regulate actin-based plasticity in dendritic spines**. *Nat Neurosci* 2000, **3**:887–894.

6. Yasumatsu N, Matsuzaki M, Miyazaki T, Noguchi J, Kasai H: **Principles of long-term dynamics of dendritic spines**. *J Neurosci* 2008, **28**:13592–13608.

7. Minerbi A, Kahana R, Goldfeld L, Kaufman M, Marom S, Ziv NE: **Long-term relationships between synaptic tenacity, synaptic remodeling, and network activity**. *PLoS Biol* 2009, **7**, e1000136.

8. Kasai H, Ziv NE, Okazaki H, Yagishita S, Toyoizumi T: **Spine dynamics in the brain, mental disorders and artificial neural networks**. *Nat Rev Neurosci* 2021, **22**:407–422.

9. Matsuzaki M, Honkura N, Ellis-Davies GC, Kasai H: **Structural basis of long-term potentiation in single dendritic spines**. *Nature* 2004, **429**:761–766.

10. Okamoto K, Nagai T, Miyawaki A, Hayashi Y: **Rapid and persistent modulation of actin dynamics regulates postsynaptic reorganization underlying bidirectional plasticity**. *Nat Neurosci* 2004, **7**:1104–1112.

11. Harvey CD, Svoboda K: **Locally dynamic synaptic learning rules in pyramidal neuron dendrites**. *Nature* 2007, **450**:1195–1200.

12. • Noguchi J, Nagaoka A, Hayama T, Ucar H, Yagishita S, Takahashi N, Kasai H: **Bidirectional in vivo structural dendritic spine plasticity revealed by two-photon glutamate uncaging in the mouse neocortex**. *Sci Rep* 2019, **9**:13922.

The authors examined spine enlargement in adult mouse neocortex *in vivo* using two-photon glutamate uncaging. They showed similar properties as in the hippocampus but in a smaller subset (22%) of spines than that in the hippocampus (95%), thus, suggesting a protection mechanism in the cortex.

13. • Hedrick NG, Lu Z, Bushong E, Singhi S, Nguyen P, Magaña Y, Jilani S, Lim BK, Ellisman M, Komiyama T: **Learning binds new inputs into functional synaptic clusters via spinogenesis**. *Nat Neurosci* 2022, **25**:726–737.

*In vivo* time-lapse imaging study of the motor cortex demonstrated the clustered spine enlargement that arose beside newly generated filopodia. The authors did not measure the real-time dynamics of spine enlargement since a stepwise volume change induced by each bout of STDP was below the threshold for detection.

14. Murakoshi H, Wang H, Yasuda R: **Local, persistent activation of Rho GTPases during plasticity of single dendritic spines**. *Nature* 2011, **472**:100–104.

15. Bosch M, Castro J, Saneyoshi T, Matsuno H, Sur M, Hayashi Y: **Structural and molecular remodeling of dendritic spine substructures during long-term potentiation**. *Neuron* 2014, **82**: 444–459.

16. Harvey CD, Yasuda R, Zhong H, Svoboda K: **The spread of Ras activity triggered by activation of a single dendritic spine**. *Science* 2008, **321**:136–140.

17. Yagishita S, Hayashi-Takagi A, Ellis-Davies GC, Urakubo H, Ishii S, Kasai H: **A critical time window for dopamine actions on the structural plasticity of dendritic spines**. *Science* 2014, **345**:1616–1620.

18. Nicoll RA: **A brief history of long-term potentiation**. *Neuron* 2017, **93**:281–290.

19. Hedrick NG, Harward SC, Hall CE, Murakoshi H, McNamara JO, Yasuda R: **Rho GTPase complementation underlies BDNF-dependent homo- and heterosynaptic plasticity**. *Nature* 2016, **538**:104–108.

20. Yang Y, Liu J-J: **Structural LTP: signal transduction, actin cytoskeleton reorganization, and membrane remodeling of dendritic spines**. *Curr Opin Neurobiol* 2022, **74**:102434.

21. Lee SJ, Escobedo-Lozoya Y, Szatmari EM, Yasuda R: **Activation of CaMKII in single dendritic spines during long-term potentiation**. *Nature* 2009, **458**:299–304.

22. Herring BE, Nicoll RA: **Long-term potentiation: from CaMKII to AMPA receptor trafficking**. *Annu Rev Physiol* 2016, **78**: 351–365.

23. •• Ucar H, Watanabe S, Noguchi J, Morimoto Y, Iino Y, Yagishita S, Takahashi N, Kasai H: **Mechanical actions of dendritic-spine enlargement on presynaptic exocytosis**. *Nature* 2021, **600**: 686–689.

Spine enlargement pushed the presynaptic terminal, facilitated SNARE pre-assembly, and enhanced evoked glutamate release. The same actions were missed when the spine twitched and did not push despite enlargement but could be induced by direct pushing by a glass pipette and a mild hyperosmotic solution, indicating that the pressure of spine enlargement was 0.5 kgf/cm$^2$.

24. Augustine GJ: **How does calcium trigger neurotransmitter release?** *Curr Opin Neurobiol* 2001, **11**:320–326.

25. Jahn R, Scheller RH: **SNAREs–engines for membrane fusion**. *Nat Rev Mol Cell Biol* 2006, **7**:631–643.

26. Kasai H, Takahashi N, Tokumaru H: **Distinct initial SNARE configurations underlying the diversity of exocytosis**. *Physiol Rev* 2012, **92**:1915–1964.

27. Kusick GF, Ogunmowo TH, Watanabe S: **Transient docking of synaptic vesicles: implications and mechanisms**. *Curr Opin Neurobiol* 2022, **74**:102535.

28. Kasai H, Fukuda M, Watanabe S, Hayashi-Takagi A, Noguchi J: **Structural dynamics of dendritic spines in memory and cognition**. *Trends Neurosci* 2010, **33**:121–129.

29. Zucker RS, Regehr WG: **Short-term synaptic plasticity**. *Annu Rev Physiol* 2002, **64**:355–405.

30. Honkura N, Matsuzaki M, Noguchi J, Ellis-Davies GC, Kasai H: **The subspine organization of actin fibers regulates the structure and plasticity of dendritic spines**. *Neuron* 2008, **57**: 719–729.

31. Zhang YP, Holbro N, Oertner TG: **Optical induction of plasticity at single synapses reveals input-specific accumulation of alphaCaMKII**. *Proc Natl Acad Sci U S A* 2008, **105**: 12039–12044.

32. Rossetti T, Banerjee S, Kim C, Leubner M, Lamar C, Gupta P, Lee B, Neve R, Lisman J: **Memory erasure experiments indicate a critical role of CaMKII in memory storage**. *Neuron* 2017, **96**:207–216 e202.

33. Saneyoshi T, Matsuno H, Suzuki A, Murakoshi H, Hedrick NG, Agnello E, O'Connell R, Stratton MM, Yasuda R, Hayashi Y: **Reciprocal activation within a kinase-effector complex underlying persistence of structural LTP**. *Neuron* 2019, **102**: 1199–1210.

34. Kim IH, Racz B, Wang H, Burianek L, Weinberg R, Yasuda R, Wetsel WC, Soderling SH: **Disruption of arp2/3 results in asymmetric structural plasticity of dendritic spines and progressive synaptic and behavioral abnormalities**. *J Neurosci* 2013, **33**:6081–6092.

35. •• Shibata ACE, Ueda HH, Eto K, Onda M, Sato A, Ohba T, Nabekura J, Murakoshi H: **Photoactivatable CaMKII induces synaptic plasticity in single synapses**. *Nat Commun* 2021, **12**: 751.

The authors constructed a photoactivatable CaMKII using the LOV2 domain and induced spine enlargement to a similar degree as glutamate uncaging based on amplitude, time-course, Rho GTPase activation, association with LTP, and protein synthesis in young hippocampal slices. The paCaMKII optogenetic probe could also efficiently induce spine enlargement in the adult neocortex *in vivo*.

36. Chazeau A, Mehidi A, Nair D, Gautier JJ, Leduc C, Chamma I, Kage F, Kechkar A, Thoumine O, Rottner K, *et al.*: **Nanoscale segregation of actin nucleation and elongation factors determines dendritic spine protrusion**. *EMBO J* 2014, **33**: 2745–2764.

37. Frost NA, Shroff H, Kong H, Betzig E, Blanpied TA: **Single-molecule discrimination of discrete perisynaptic and distributed sites of actin filament assembly within dendritic spines**. *Neuron* 2010, **67**:86–99.

38. Peskin CS, Odell GM, Oster GF: **Cellular motions and thermal fluctuations: the Brownian ratchet**. *Biophys J* 1993, **65**: 316–324.

39. Mogilner A, Oster G: **Force generation by actin polymerization II: the elastic ratchet and tethered filaments**. *Biophys J* 2003, **84**:1591–1605.

40. Pollard TD, Borisy GG: **Cellular motility driven by assembly and disassembly of actin filaments**. *Cell* 2003, **112**: 453–465.

41. Suter DM, Forscher P: **Substrate-cytoskeletal coupling as a mechanism for the regulation of growth cone motility and guidance**. *J Neurobiol* 2000, **44**:97–113.

42. Minegishi T, Kastian RF, Inagaki N: **Mechanical regulation of synapse formation and plasticity**. *Semin Cell Dev Biol* 2023, **140**:82–89.

43. Andrianantoandro E, Pollard TD: **Mechanism of actin filament turnover by severing and nucleation at different concentrations of ADF/cofilin**. *Mol Cell* 2006, **24**:13–23.

44. • Goto A, Bota A, Miya K, Wang J, Tsukamoto S, Jiang X, Hirai D, Murayama M, Matsuda T, McHugh TJ, *et al.*: **Stepwise synaptic plasticity events drive the early phase of memory consolidation**. *Science* 2021, **374**:857–863.

Cofilin fused with photosensitizer SuperNova (SN) erased spine enlargement if light-activation was within 30 min after the onset of enlargement. Inhibitory avoidance behavior was similarly erased by light-activation of cofilin-SN in the hippocampus. Its behavioral stabilization was impaired by light-activation of cofilin-SN in the anterior cingulate cortex during sleep.

45. • Takahashi N, Sawada W, Noguchi J, Watanabe S, Ucar H, Hayashi-Takagi A, Yagishita S, Ohno M, Tokumaru H, Kasai H: **Two-photon fluorescence lifetime imaging of primed SNARE complexes in presynaptic terminals and β cells**. *Nat Commun* 2015, **6**:8531.

FRET-FLIM fluorescent probes for intermolecular SNARE assembly reported the*trans*-SNARE pre-assembly in the active zone but not in secretory cells. The SNARE probes could also visualize *cis*-SNARE formation by exocytosis.

46. Iino M: **Tension responses of chemically skinned fibre bundles of the Guinea-pig taenia caeci under varied ionic environments**. *J Physiol* 1981, **320**:449–467.

47. Matus A, Ackermann M, Pehling G, Byers HR, Fujiwara K: **High actin concentrations in brain dendritic spines and postsynaptic densities**. *Proc. Natl. Acad. Sci. U.S.A* 1982, **79**: 7590–7594.

48. Korobova F, Svitkina T: **Molecular architecture of synaptic actin cytoskeleton in hippocampal neurons reveals a mechanism of dendritic spine morphogenesis**. *Mol Biol Cell* 2010, **21**:165–176.

49. •• Obashi K, Matsuda A, Inoue Y, Okabe S: **Precise temporal regulation of molecular diffusion within dendritic spines by actin polymers during structural plasticity**. *Cell Rep* 2019, **27**: 1503–1515 e1508.

During the initial phase of spine enlargement, diffusion of molecules <100 kDa was transiently enhanced, and molecular interactions were facilitated, revealed using two-photon correlation spectroscopy (FCS) and fluorescence recovery after photobleaching (FRAP).

50. Obashi K, Taraska JW, Okabe S: **The role of molecular diffusion within dendritic spines in synaptic function**. *J Gen Physiol* 2021:153.

51. Penn AC, Zhang CL, Georges F, Royer L, Breillat C, Hosy E, Petersen JD, Humeau Y, Choquet D: **Hippocampal LTP and contextual learning require surface diffusion of AMPA receptors**. *Nature* 2017, **549**:384–388.

52. tom Dieck S, Kochen L, Hanus C, Heumuller M, Bartnik I, Nassim-Assir B, Merk K, Mosler T, Garg S, Bunse S, *et al.*: **Direct visualization of newly synthesized target proteins in situ**. *Nat Methods* 2015, **12**:411–414.

53. Meyer D, Bonhoeffer T, Scheuss V: **Balance and stability of synaptic structures during synaptic plasticity**. *Neuron* 2014, **82**:430–443.

54. Sun Y, Smirnov M, Kamasawa N, Yasuda R: **Rapid ultrastructural changes in the PSD and surrounding membrane after induction of structural LTP in single dendritic spines**. *J Neurosci* 2021, **41**:7003–7014.

55. Noguchi J, Matsuzaki M, Ellis-Davies GC, Kasai H: **Spine-neck geometry determines NMDA receptor-dependent Ca2+ signaling in dendrites**. *Neuron* 2005, **46**:609–622.

56. Tanaka J, Horiike Y, Matsuzaki M, Miyazaki T, Ellis-Davies GCR, Kasai H: **Protein synthesis and neurotrophin-dependent structural plasticity of single dendritic spines**. *Science* 2008, **319**:1683–1687.

57. Tonnesen J, Katona G, Rozsa B, Nagerl UV: **Spine neck plasticity regulates compartmentalization of synapses**. *Nat Neurosci* 2014, **17**:678–685.

58. Perez-Alvarez A, Yin S, Schulze C, Hammer JA, Wagner W, Oertner TG: **Endoplasmic reticulum visits highly active spines and prevents runaway potentiation of synapses**. *Nat Commun* 2020, **11**:5083.

59. Crick F: **Do dendritic spines twitch?** *Trends Neurosci* 1982, **5**: 44–46.

60. Hayama T, Noguchi J, Watanabe S, Takahashi N, Hayashi-Takagi A, Ellis-Davies GC, Matsuzaki M, Kasai H: **GABA promotes the competitive selection of dendritic spines by controlling local Ca2+ signaling**. *Nat Neurosci* 2013, **16**: 1409–1416.

61. Zhang G, Neubert TA, Jordan BA: **RNA binding proteins accumulate at the postsynaptic density with synaptic activity**. *J Neurosci* 2012, **32**:599–609.

62. Beaulieu-Laroche L, Harnett MT: **Dendritic spines prevent synaptic voltage clamp**. *Neuron* 2018, **97**:75–82 e73.

63. Cornejo VH, Ofer N, Yuste R: **Voltage compartmentalization in dendritic spines in vivo**. *Science* 2022, **375**:82–86.

64. Matsuzaki M, Ellis-Davies GCR, Nemoto T, Miyashita Y, Iino M, Kasai H: **Dendritic spine geometry is critical for AMPA receptor expression in hippocampal CA1 pyramidal neurons**. *Nat Neurosci* 2001, **4**:1086–1092.

65. Beique JC, Lin DT, Kang MG, Aizawa H, Takamiya K, Huganir RL: **Synapse-specific regulation of AMPA receptor function by PSD-95**. *Proc Natl Acad Sci U S A* 2006, **103**: 19535–19540.

66. Zito K, Scheuss V, Knott G, Hill T, Svoboda K: **Rapid functional maturation of nascent dendritic spines**. *Neuron* 2009, **61**: 247–258.

67. Noguchi J, Nagaoka A, Watanabe S, Ellis-Davies GCR, Kitamura K, Kano M, Matsuzaki M, Kasai H: **In vivo two-photon uncaging of glutamate revealing the structure-function relationships of dendritic spines in the neocortex of adult mice**. *J Physiol* 2011, **589**:2447–2457.

68. •• Holler S, Kostinger G, Martin KAC, Schuhknecht GFP, Stratford KJ: **Structure and function of a neocortical synapse**. *Nature* 2021, **591**:111–116.

Paired electrophysiological quantal analysis followed by EM serial section reconstruction revealed the proportional relationship between spine volumes and EPSC amplitudes. In contrast, the relationship between bouton sizes and release probability was weakly correlated with a significant y-section. Thus, they suggest that postsynaptic spines adapt to longer-term memory while presynaptic terminals adapt to shorter-term memory.

69. Takumi Y, Ramirez-Leon V, Laake P, Rinvik E, Ottersen OP: **Different modes of expression of AMPA and NMDA receptors in hippocampal synapses**. *Nat Neurosci* 1999, **2**:618–624.

70. Nusser Z, Lujan R, Laube G, Roberts JD, Molnar E, Somogyi P: **Cell type and pathway dependence of synaptic AMPA receptor number and variability in the hippocampus**. *Neuron* 1998, **21**:545–559.

71. Hruska M, Cain RE, Dalva MB: **Nanoscale rules governing the organization of glutamate receptors in spine synapses are subunit specific**. *Nat Commun* 2022, **13**:920.

72. Zhang Y, Cudmore RH, Lin DT, Linden DJ, Huganir RL: **Visualization of NMDA receptor-dependent AMPA receptor synaptic plasticity in vivo**. *Nat Neurosci* 2015, **18**:402–407.

73. Diaz-Alonso J, Nicoll RA: **AMPA receptor trafficking and LTP: carboxy-termini, amino-termini and TARPs**. *Neuropharmacology* 2021, **197**:108710.

74. Kopec CD, Li B, Wei W, Boehm J, Malinow R: **Glutamate receptor exocytosis and spine enlargement during chemically induced long-term potentiation**. *J Neurosci* 2006, **26**:2000–2009.

75. Kilinc D: **The emerging role of mechanics in synapse formation and plasticity**. *Front Cell Neurosci* 2018, **12**:483.

76. Hannezo E, Heisenberg CP: **Mechanochemical feedback loops in development and disease**. *Cell* 2019, **178**:12–25.

77. Okada Y: **Ion channels and transporters involved in cell volume regulation and sensor mechanisms**. *Cell Biochem Biophys* 2004, **41**:233–258.

78. • Kusick GF, Chin M, Raychaudhuri S, Lippmann K, Adula KP, Hujber EJ, Vu T, Davis MW, Jorgensen EM, Watanabe S: **Synaptic vesicles transiently dock to refill release sites**. *Nat Neurosci* 2020, **23**:1329–1338.

The authors used the zap-and-freeze technique in dissociated culture preparations to quantify vesicle dynamics by population comparisons. Single zap triggered ultrafast exocytosis and facilitated docking of vesicles during PPF; thus, suggesting that the short-term plasticity may be nano-structural.

79. Lauri SE, Palmer M, Segerstrale M, Vesikansa A, Taira T, Collingridge GL: **Presynaptic mechanisms involved in the expression of STP and LTP at CA1 synapses in the hippocampus**. *Neuropharmacology* 2007, **52**:1–11.

80. Kauer JA, Malenka RC, Nicoll RA: **NMDA application potentiates synaptic transmission in the hippocampus**. *Nature* 1988, **334**:250–252.

81. Racine RJ, Milgram NW: **Short-term potentiation phenomena in the rat limbic forebrain**. *Brain Res* 1983, **260**:201–216.

82. McNaughton BL: **Long-term synaptic enhancement and short-term potentiation in rat fascia dentata act through different mechanisms**. *J Physiol* 1982, **324**:249–262.

83. Malenka RC: **Postsynaptic factors control the duration of synaptic enhancement in area CA1 of the hippocampus**. *Neuron* 1991, **6**:53–60.

84. Schulz PE, Fitzgibbons JC: **Differing mechanisms of expression for short- and long-term potentiation**. *J Neurophysiol* 1997, **78**:321–334.

85. Hanse E, Gustafsson B: **Onset and stabilization of NMDA receptor-dependent hippocampal long-term potentiation**. *Neurosci Res* 1994, **20**:15–25.

86. Dolphin AC, Errington ML, Bliss TV: **Long-term potentiation of the perforant path in vivo is associated with increased glutamate release**. *Nature* 1982, **297**:496–498.

87. Davies SN, Lester RA, Reymann KG, Collingridge GL: **Temporally distinct pre- and post-synaptic mechanisms maintain long-term potentiation**. *Nature* 1989, **338**:500–503.

88. Volianskis A, France G, Jensen MS, Bortolotto ZA, Jane DE, Collingridge GL: **Long-term potentiation and the role of N-methyl-D-aspartate receptors**. *Brain Res* 2015, **1621**:5–16.

89. Malenka RC, Kauer JA, Perkel DJ, Mauk MD, Kelly PT, Nicoll RA, Waxham MN: **An essential role for postsynaptic calmodulin and protein kinase activity in long-term potentiation**. *Nature* 1989, **340**:554–557.

90. O'Dell TJ, Kandel ER, Grant SG: **Long-term potentiation in the hippocampus is blocked by tyrosine kinase inhibitors**. *Nature* 1991, **353**:558–560.

91. Schuman EM, Madison DV: **A requirement for the intercellular messenger nitric oxide in long-term potentiation**. *Science* 1991, **254**:1503–1506.

92. Sanes JR, Lichtman JW: **Can molecules explain long-term potentiation?** *Nat Neurosci* 1999, **2**:597–604.

93. Padamsey Z, Emptage N: **Two sides to long-term potentiation: a view towards reconciliation**. *Philos Trans R Soc Lond B Biol Sci* 2014, **369**:20130154.

94. Kullmann DM, Erdemli G, Asztely F: **LTP of AMPA and NMDA receptor-mediated signals: evidence for presynaptic expression and extrasynaptic glutamate spill-over**. *Neuron* 1996, **17**:461–474.

95. Zakharenko SS, Zablow L, Siegelbaum SA: **Visualization of changes in presynaptic function during long-term synaptic plasticity**. *Nat Neurosci* 2001, **4**:711–717.

96. Emptage NJ, Reid CA, Fine A, Bliss TV: **Optical quantal analysis reveals a presynaptic component of LTP at hippocampal Schaffer-associational synapses**. *Neuron* 2003, **38**:797–804.

97. Costa RP, Padamsey Z, D'Amour JA, Emptage NJ, Froemke RC, Vogels TP: **Synaptic transmission optimization predicts expression loci of long-term plasticity**. *Neuron* 2017, **96**:177–189 e177.

98. Bittner KC, Milstein AD, Grienberger C, Romani S, Magee JC: **Behavioral time scale synaptic plasticity underlies CA1 place fields**. *Science* 2017, **357**:1033–1036.

99. Miyashita Y, Chang HS: **Neuronal correlate of pictorial short-term memory in the primate temporal cortex**. *Nature* 1988, **331**:68–70.

100. Baddeley A: **The episodic buffer: a new component of working memory?** *Trends Cognit Sci* 2000, **4**:417–423.

101. Tian Y, Yang C, Cui Y, Su F, Wang Y, Wang Y, Yuan P, Shang S, Li H, Zhao J, *et al.*: **An excitatory neural assembly encodes short-term memory in the prefrontal cortex**. *Cell Rep* 2018, **22**:1734–1744.

102. Goldman-Rakic PS: **Cellular basis of working memory**. *Neuron* 1995, **14**:477–485.

103. Rainer G, Miller EK: **Timecourse of object-related neural activity in the primate prefrontal cortex during a short-term memory task**. *Eur J Neurosci* 2002, **15**:1244–1254.

104. Sreenivasan KK, Curtis CE, D'Esposito M: **Revisiting the role of persistent neural activity during working memory**. *Trends Cognit Sci* 2014, **18**:82–89.

105. Stokes MG: **Activity-silent' working memory in prefrontal cortex: a dynamic coding framework**. *Trends Cognit Sci* 2015, **19**:394–405.

106. Ranganath C, Blumenfeld RS: **Doubts about double dissociations between short- and long-term memory**. *Trends Cognit Sci* 2005, **9**:374–380.

107. Romberg C, Raffel J, Martin L, Sprengel R, Seeburg PH, Rawlins JN, Bannerman DM, Paulsen O: **Induction and expression of GluA1 (GluR-A)-independent LTP in the hippocampus**. *Eur J Neurosci* 2009, **29**:1141–1152.

108. Erickson MA, Maramara LA, Lisman J: **A single brief burst induces GluR1-dependent associative short-term potentiation: a potential mechanism for short-term memory**. *J Cognit Neurosci* 2010, **22**:2530–2540.

109. Hoffman DA, Sprengel R, Sakmann B: **Molecular dissection of hippocampal theta-burst pairing potentiation**. *Proc Natl Acad Sci U S A* 2002, **99**:7740–7745.

110. Reisel D, Bannerman DM, Schmitt WB, Deacon RM, Flint J, Borchardt T, Seeburg PH, Rawlins JN: **Spatial memory dissociations in mice lacking GluR1**. *Nat Neurosci* 2002, **5**:868–873.

111. Zamanillo D, Sprengel R, Hvalby O, Jensen V, Burnashev N, Rozov A, Kaiser KM, Koster HJ, Borchardt T, Worley P, *et al.*: **Importance of AMPA receptors for hippocampal synaptic plasticity but not for spatial learning**. *Science* 1999, **284**:1805–1811.

112. Freudenberg F, Resnik E, Kolleker A, Celikel T, Sprengel R, Seeburg PH: **Hippocampal GluA1 expression in Gria1(-/-) mice only partially restores spatial memory performance deficits**. *Neurobiol Learn Mem* 2016, **135**:83–90.

113. Shimshek DR, Bus T, Schupp B, Jensen V, Marx V, Layer LE, Kohr G, Sprengel R: **Different forms of AMPA receptor mediated LTP and their correlation to the spatial working memory formation**. *Front Mol Neurosci* 2017, **10**:214.

114. Fletcher PC, Honey GD: **Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits**. *Trends Cognit Sci* 2006, **10**:167–174.

115. Bannerman DM: **Fractionating spatial memory with glutamate receptor subunit-knockout mice**. *Biochem Soc Trans* 2009, **37**:1323–1327.

116. Bannerman DM, Niewoehner B, Lyon L, Romberg C, Schmitt WB, Taylor A, Sanderson DJ, Cottam J, Sprengel R, Seeburg PH, *et al.*: **NMDA receptor subunit NR2A is required for rapidly acquired spatial working memory but not incremental spatial reference memory**. *J Neurosci* 2008, **28**:3623–3630.

117. McQuail JA, Beas BS, Kelly KB, Simpson KL, Frazier CJ, Setlow B, Bizon JL: **NR2A-containing NMDARs in the prefrontal cortex are required for working memory and associated with age-related cognitive decline**. *J Neurosci* 2016, **36**:12537–12548.

118. Schizophrenia Working Group of the Psychiatric Genomics C: **Biological insights from 108 schizophrenia-associated genetic loci**. *Nature* 2014, **511**:421–427.

119. Hayashi-Takagi A: **Synapse pathology and translational applications for schizophrenia**. *Neurosci Res* 2017, **114**:3–8.

120. Radhakrishnan R, Skosnik PD, Ranganathan M, Naganawa M, Toyonaga T, Finnema S, Hillmer AT, Esterlis I, Huang Y, Nabulsi N, *et al.*: **In vivo evidence of lower synaptic vesicle density in schizophrenia**. *Mol Psychiatr* 2021:7690–7698.

121. Molinaro L, Hui P, Tan M, Mishra RK: **Role of presynaptic phosphoprotein synapsin II in schizophrenia**. *World J Psychiatr* 2015, **5**:260–272.

122. Fiebig F, Herman P, Lansner A: **An indexing theory for working memory based on fast Hebbian plasticity**. *eNeuro* 2020, **7**.

A computational neuronal network model incorporating Hebbian STP and LTP is constructed using a spike-based Bayesian Confidence Propagation Neural Network (BCPNN). The model explains how PFC could associate, maintain, and update multimodal LTM representations.

123. Wang Y, Markram H, Goodman PH, Berger TK, Ma J, Goldman-Rakic PS: **Heterogeneity in the pyramidal network of the medial prefrontal cortex**. *Nat Neurosci* 2006, **9**:534–542.

124. Mongillo G, Barak O, Tsodyks M: **Synaptic theory of working memory**. *Science* 2008, **319**:1543–1546.

125. Kozachkov L, Tauber J, Lundqvist M, Brincat S, Slotine J, Miller E: **Robust working memory through short-term synaptic plasticity**. *bioRxiv* 2022.

126. Mi Y, Katkov M, Tsodyks M: **Synaptic correlates of working memory capacity**. *Neuron* 2017, **93**:323–330.

127. Miyashita Y: **Neuronal correlate of visual associative long-term memory in the primate temporal cortex**. *Nature* 1988, **335**:817–820.

128. Sederberg PB, Howard MW, Kahana MJ: **A context-based theory of recency and contiguity in free recall**. *Psychol Rev* 2008, **115**:893–912.