AMPAR Receptors: A Key Piece in the Puzzle of Memory Retrieval

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Retrieval constitutes a highly regulated and dynamic phase in memory processing. Its rapid temporal scales require a coordinated molecular chain of events at the synaptic level that support transient memory trace reactivation. AMPA receptors (AMPAR) drive the majority of excitatory transmission in the brain and its dynamic features match the singular fast timescales of memory retrieval. Here we provide a review on AMPAR contribution to memory retrieval regarding its dynamic movements along the synaptic compartments, its changes in receptor number and subunit composition that take place in activity dependent processes associated with retrieval. We highlight on the differential regulations exerted by AMPAR subunits in plasticity processes and its impact on memory recall.

Keywords: memory retrieval, AMPA receptor, AMPA receptor trafficking, AMPA receptor subunits, memory retrieval mechanisms

INTRODUCTION

The ability to recall past events is a major determinant of survival strategies in all species and is of paramount importance in determining our uniqueness as individuals. Memory retrieval refers to the complex and active process of re-accessing previously stored information and its expression in the brain. Retrieval is critical for memory: without its retrieval it is not possible to ensure we have a given memory. Furthermore, some reports have revealed that some types of amnesia are associated with memory retrieval rather than consolidation failures (Weiskrantz, 1966; Warrington and Weiskrantz, 1968; Roy et al., 2016). Besides, retrieval constitutes a “gateway” process: it could involve memory trace destabilization (Nader et al., 2000b) that can lead to memory reconsolidation or extinction, two critical stages in memory processing (Nader et al., 2000a; Dudai and Eisenberg, 2004; Tronson and Taylor, 2007; Monfils et al., 2009; Kida, 2020). Whether or not memory destabilization takes place depends on the strength and age of the memory as well as the duration of memory retrieval (Suzuki et al., 2004). Even more, retrieval can trigger forgetting of other memory traces that competes with the one being retrieved in a process called “retrieval-induced forgetting” (RIF) (Anderson, 2003; Bekinschtein et al., 2018; Anderson and Hulbert, 2021). For example, in rats, retrieved memories of an object leads to a reduced retention of other objects seen in the same context (Bekinschtein et al., 2018). In humans, some theories point that RIF could be linked to inhibitory mechanisms that reduce the accessibility of non-target items that interfere with the retrieval of target items whereas other theories point to strength-based competition or blocking (Murayama et al., 2014).
Memory recall is a very rapid process, since animals retrieve as soon as they receive, usually without notice, the conditioned stimulus (CS) or other cues, including stimuli reminiscent of the unconditioned stimulus (US) or an emotional context reminiscent of the memory. Indeed, data from human declarative memory studies indicates that the reinstatement of the patterns of activity needed to retrieve is achieved between 500 and 1500 ms (Staresina and Wimber, 2019). This is clearly a very short timescale compared to other memory processes that could take from minutes to hours (synaptic consolidation), to days or even weeks like systems consolidation (Dudai and Morris, 2000; Squire et al., 2015). Strikingly, there are circumstances in which memory retrieval neural circuit activation could occur without the behavioral output associated, leading to the distinction between memory retrieval and memory expression (Delorenzi et al., 2014).

Memory retrieval involves the reactivation of a relevant number of synapses between learning-activated neurons in various regions of the brain. There is a general consensus that the neuronal activity and synapses that are reactivated when the animals are demanded to retrieve are those that have been changed through the molecular processes that underlie memory formation (Frankland et al., 2019). For those who are interested in what is known about the link between memory formation and retrieval, the multiplicity of brain regions involved in memory retrieval, the interactions between putative “engram cells” and retrieval cues, the neural factors that determine retrieval occurrence, and the consequences of recalling, there are several good review articles dedicated to various aspects of the neurobiology of memory retrieval (Izquierdo et al., 2006; Tronson and Taylor, 2007; Tonegawa et al., 2015; Frankland et al., 2019; Josselyn and Tonegawa, 2020).

Retrieval cues lead to partial reinstatement of the original pattern of neural activity elicited at the moment of encoding (Rugg et al., 2015). In this sense, the overlap between encoding and retrieval neural representations has been proposed in both the transfer-appropriate processing (TAP) and cortical reinstatement hypothesis (Rugg et al., 2008). In particular, theta rhythm has been proposed to set the dynamics for encoding and retrieval within cortical circuits although different phases of hippocampal theta rhythm may enable separation between encoding and retrieval (Hasselmo and Stern, 2014).

In contrast to memory formation, the information about the molecular mechanisms of memory retrieval is surprisingly scarce and fragmentary. In this context, the notion that retrieval constitutes a process as active and involving molecular pathways as intricate as other memory phases is new. In this regard, recent work has revealed the requirement of protein synthesis during memory retrieval (Lopez et al., 2015; Pereyra et al., 2018). Since then, fundamental questions have emerged: Which are the synaptic plasticity proteins whose expression is necessary at the time of retrieval?

The molecular mechanisms of memory retrieval take place in systems that are “ready to go” whenever the animal is demanded to retrieve using pre-existing house-keeping molecules, such as receptors or signaling enzymes. In this review, we will focus on the analysis of some of the molecular mechanisms of memory recall and in particular, we highlight the role of different AMPA receptor (AMPAR) subunits in retrieval of stored information.

**MEMORY RETRIEVAL: AN AMPAR STORY**

The most prevalent neurotransmitter in the brain is glutamate, which mostly activates AMPAR. AMPAR consists of four homologous pore-forming subunits (GluA1-4) that generally assemble into heteromers. The presence of GluA2 is of functional importance because it confers calcium impermeability to the AMPAR channel (Isaac et al., 2007). In the CA1 area of the hippocampus, GluA1/GluA2 and GluA2/GluA3 heteromers represent approximately 80 and 20%, respectively, of the postsynaptic response in baseline conditions (Buonarati et al., 2019).

Memory retrieval has been historically associated with changes in AMPAR. In particular, the first works that studied AMPAR role in memory retrieval with pharmacological approaches have addressed AMPAR activation (Table 1; Liang, 1991; Bianchin et al., 1993; Izquierdo et al., 1993, 1997; Kim et al., 1993; Riedel et al., 1999; Szapiro et al., 2000; Yasoshima et al., 2000). Interestingly, these receptors have a very peculiar fast temporal kinetics which lead to a rapid activation that could support recall processes’ brief timescales. Compared to NMDAR, AMPAR are not blocked by Mg2+ and thus they need less depolarization to be activated (Stern and Alberini, 2013). Indeed, AMPAR activation is needed for NMDAR activation.

Our thinking on AMPAR role on synaptic plasticity have been traditionally focused on receptor activity and integrity. However, new technical approaches development has expanded this historical view. In the last three decades, findings coming from advances in labeling postsynaptic surface components (Fujimoto, 1995; Masugi-Tokita et al., 2007) as well as single molecule detection has provided enough evidence about AMPAR mobility between different synaptic compartments and its implications in learning and memory processes (Choquet and Triller, 2013; Penn et al., 2017; Zhang et al., 2018). Also, once inserted in the postsynaptic density (PSD) membrane, AMPAR exhibits a singular clustered aggregation in nanodomains in precise alignment with presynaptic sites that account for efficient synaptic transmission (MacGillavry et al., 2013; Nair et al., 2013). The fact that AMPAR could be exchanged between intra and extrasynaptic compartments (Borgdorff and Choquet, 2002; Petrini et al., 2009; Choquet, 2018) in a fast way made these receptors excellent candidates to underlie the processes involved in memory retrieval that may occur in seconds timescale. Indeed, AMPAR resides as the most mobile among all receptors (Borgdorff and Choquet, 2002). Moreover, modulating AMPAR surface diffusion has been shown to restore memory expression in Huntington Disease model (Zhang et al., 2018).

In the last few years, the focus of AMPAR research has shifted from its mere activation toward its dynamic movements between synapse compartments. A special emphasis has been directed to the role of AMPAR endocytosis (Carroll et al., 2001) in the postsynapse where most surface AMPAR resides (Table 1;...
| S. no. | AMPAR feature engaged in memory retrieval | Animal model | Approach | Task | Brain area | References |
|--------|-----------------------------------------|-------------|----------|------|------------|------------|
| 1      | AMPAR activation                         | Rat         | Pharmacological | Inhibitory avoidance | Amygdala | Liang, 1991 |
| 2      | AMPAR activation                         | Rat         | Pharmacological | Fear-potentiated startle | Amygdala | Kim et al., 1993 |
| 3      | AMPAR activation                         | Rat         | Pharmacological | Inhibitory avoidance and habituation to a novel environment | Hippocampus and amygdala | Bianchin et al., 1993 |
| 4      | AMPAR activation                         | Rat         | Pharmacological | Inhibitory avoidance and habituation to a novel environment | Hippocampus and amygdala | Izquierdo et al., 1993 |
| 5      | AMPAR activation                         | Rat         | Pharmacological | Inhibitory avoidance | Hippocampus, amygdala, entorhinal cortex, parietal cortex | Izquierdo et al., 1997 |
| 6      | AMPAR activation                         | Rat         | Pharmacological | Open-field water maze | Hippocampus | Riedel et al., 1999 |
| 7      | AMPAR activation                         | Rat         | Pharmacological | Inhibitory avoidance | Hippocampus | Szapiro et al., 2000 |
| 8      | AMPAR activation                         | Rat         | Pharmacological | Conditioned taste aversion | Basolateral amygdala | Yasoshima et al., 2000 |
| 9      | AMPAR activation | Rat | Pharmacological | Paired associated learning (food and its spatial location) | Hippocampus | Wyatt et al., 2003 |
| 10     | AMPAR activation                         | Rat         | Pharmacological | Spontaneous object recognition | Perirhinal cortex | Winters and Bussey, 2005 |
| 11     | AMPAR activation                         | Rat         | Pharmacological | Auditory fear conditioning | Basolateral, amygdala | Mamou et al., 2006 |
| 12     | AMPAR activation and endocytosis         | Rat         | Pharmacological | Object recognition | Perirhinal cortex | Cazakoff and Howland, 2011 |
| 13     | AMPAR activation, endocytosis            | Mice        | Biochemical, pharmacological | Contextual fear conditioning | Hippocampus | Rao-Ruiz et al., 2011 |
| 14     | AMPAR activation                         | Rat         | Pharmacological | Conditioned taste aversion | Amygdala | Rodriguez-Ortiz et al., 2012 |
| 15     | Exchange of calcium impermeable to calcium-permeable AMPAR | Rat | Pharmacological, electrophysiological | Auditory cue fear conditioning | Lateral amygdala | Hong et al., 2013 |
| 16     | AMPAR activation                         | Rat         | Pharmacological | Conditioned taste aversion | Basolateral amygdala | Garcia-del-Torre et al., 2014 |
| 17     | AMPAR trafficking                        | Rat         | Pharmacological | Auditory fear conditioning | Amygdala | Lopez et al., 2015 |
| 18     | AMPAR activation                         | Rat         | Pharmacological | Conditioned taste aversion | Insular cortex and amygdala | Osorio-Gómez et al., 2017 |
| 19     | AMPAR activation and endocytosis         | Rat         | Pharmacological | Morris water maze | Hippocampus | Wang et al., 2017 |
| 20     | GluA2-containing AMPAR endocytosis       | Rat         | Pharmacological | Contextual fear conditioning | Amygdala | Ferrara et al., 2019 |
| 21     | GluA2-containing AMPAR endocytosis and AMPAR expression | Rat | Pharmacological | Morphine conditioned place preference | Ventromedial prefrontal cortex | Sun et al., 2019 |
| 22     | S845 GluA1 AMPAR phosphorylation        | Mice        | Genetic engineering | Contextual fear conditioning, social recognition | Hippocampus | Hasegawa et al., 2019 |
Cazakoff and Howland, 2011; Rao-Ruiz et al., 2011; Wang et al., 2017; Ferrara et al., 2019; Sun et al., 2019; Ashourpour et al., 2020; Pereyra et al., 2021). AMPAR activity-dependent trafficking allows subtle changes in number and localization of these postsynaptic receptors, which in turn shapes neural plasticity processes. Since the relatively low number of AMPAR in spines, even a mild alteration in AMPAR internalization could have a great impact on neuronal homeostasis and transmission and hence in behavior (Matsuzaki et al., 2001; Tanaka et al., 2005).

Other important AMPAR features concern its subunit composition. AMPARs consist of four homologous pore-forming subunits (GluA1-4) that generally assemble into heteromers (Rossmann et al., 2011). Different GluA subunits are related with distinctive properties to AMPAR. The presence of GluA2 is of functional importance because it confers calcium impermeability to the AMPAR channel (Isaac et al., 2007). Most AMPARs described in the brain contain GluA2 subunit (Wenthold et al., 1996; Sans et al., 2003; Lu et al., 2009; Rozov et al., 2012). Nevertheless, a small group of AMPAR lacking GluA2 or lacking GluA2 specific editing, have been described as calcium permeable (CP) AMPAR (Shi et al., 2001; Hong et al., 2013). This exchange is known to occur through endocytosis involving the C-terminal tail of GluA2 (Collingridge et al., 2010).

AMPA receptors number, composition and mobility are related to the two major forms of plasticity that underlie memory, long-term potentiation (LTP) and long-term depression (LTD). LTP induces recruitment of AMPAR while LTD is accompanied by internalization of AMPAR (Yuste and Bonhoeffer, 2001; Malinow and Malenka, 2003; Diering and Huganir, 2018). It has been shown that optical LTD stimulation can impair memory recall in lateral amygdala whereas LTP stimulation delivery can restore the recall of memory, respectively (Nabavi et al., 2014). Moreover, KIBRA, a gene related with human memory performance has been shown to regulate AMPAR trafficking potentially by affecting LTP and LTD processes (Makuch et al., 2011).

### TABLE 1 | (Continued)

| S. no. | AMPAR feature engaged in memory retrieval | Animal model | Approach | Task | Brain area | References |
|--------|----------------------------------------|--------------|----------|------|------------|------------|
| 23     | Calcium-permeable AMPAR activity       | Rat          | Pharmacological | Auditory fear conditioning, contextual fear conditioning | Basolateral amygdala and hippocampus | Torquatto et al., 2019 |
| 24     | AMPAR endocytosis                      | Rat          | Pharmacological | Morris water maze | Hippocampus | Ashourpour et al., 2020 |
| 25     | AMPAR expression                       | Rat          | Pharmacological | Contextual fear conditioning | Basolateral amygdala | Guo et al., 2020 |
| 26     | AMPAR expression and endocytosis       | Rat          | Pharmacological | Inhibitory avoidance | Hippocampus | Pereyra et al., 2021 |
| 27     | AMPAR-Gria2 transcription              | Mice         | Monosynaptic tracing, electrophysiology, immunohistochemistry, and optogenetics | Two choice spatial discrimination | Hippocampus (DG) | Li et al., 2021 |
| 28     | AMPAR trafficking                      | Mice         | Freeze fracture replica immunolabeling | Auditory fear conditioning | Amygdala | Seewald et al., 2021 |

### MEMORY RETRIEVAL AND AMPAR SUBUNITS: A MATTER OF TIMING

Neuron ensembles recruited by learning in the CA1 area of the hippocampus exhibit key synaptic changes such as AMPAR insertion (Whitlock et al., 2006). Among AMPAR subunits, GluA1 is delivered in a very fast mode compared to GluA2 and GluA3 upon field stimulation (Tanaka and Hirano, 2012). Considering the similar neural activation pattern between
FIGURE 1 | Proposed AMPAR events associated with memory retrieval. (A) In a memory trace latent state, GluA1-containing AMPAR are not enough represented at the postsynaptic density and memory recall does not take place. (B) GluA1 subunit synthesis is needed for memory retrieval to occur (mediated by mTORC1 pathway as we previously reported), which could favor transient GluA1-containing AMPAR formation (especially GluA1 homomers AMPAR) and surface expression which replaces GluA2-containing AMPAR in the postsynaptic density. (C) Alternatively, enhanced GluA1-containing exocytosis may occur in response to activity regulated GluA1-containing AMPAR recruitment. (D) Regulated levels of GluA2-containing AMPAR endocytosis may also account for a greater representation of GluA1-containing AMPAR at the synapse. In all the cases, the proposed AMPAR subunit point alterations lead to GluA2 to GluA1 subunit composition shift during memory retrieval. GluA2 synthesis is also required for memory retrieval although GluA2-containing AMPAR seem to have a support role at the time of retrieval.
encoding and retrieval and given the fast temporal course of memory retrieval, it is logical to think that GluA1 insertion (Figure 1A) could be considered a critical step for memory retrieval. In this regard, there is a consensus on the need for stable GluA1 levels at the synapse at the time of retrieval (Lopez et al., 2015; Pereyra et al., 2021). Whether these stable levels are achieved by ongoing GluA1 protein synthesis (Lopez et al., 2015; Pereyra et al., 2021) and/or if they are a result of GluA1-AMPAR trafficking (Lopez et al., 2015) or different regulations on GluA1-trafficking, such as phosphorylation of GluA1 on Ser 845 by PKA (Man et al., 2007; Hasegawa et al., 2019) or exchange between CI to CP AMPAR (Hong et al., 2013; Torquatto et al., 2019) remains to be elucidated (Figures 1B,C). Moreover, a recent report has demonstrated that Gria2 (the gene that encodes for GluA2 subunit) transcription reduced the efficacy of memory retrieval, likely by promoting a genetic switch from CP to CI-AMPAR (Li et al., 2021). To dissect the role of GluA1-containing AMPAR synthesis and insertion in memory retrieval (Figures 1B,C), it would be useful to use GluR1CT, an interference peptide that selectively disrupts GluA1-containing AMPAR exocytosis (Yu et al., 2008; Cui et al., 2011).

We have demonstrated the need of GluA2 subunit ongoing synthesis during memory retrieval (Pereyra et al., 2021). Whether these GluA2 subunits form GluA2-containing AMPAR to be inserted at the moment of retrieval or if they are needed right after memory retrieval to replenish appropriate levels of GluA2-containing AMPAR at the synapse remains to be further elucidated. In any case, it seems logical that GluA2-containing AMPAR have a supporting rather than a plasticity drive role at the time of retrieval. Various reports indicate that the infusion of Tat-GluR23y (a selective GluA2-containing AMPAR endocytosis blocker) rescued several memory retrieval deficits (Lopez et al., 2015; Pereyra et al., 2021) (Figure 1D). The memory retrieval rescue effect induced by preventing GluA2-containing AMPAR removal remains to be further evaluated. Are these extra retained GluA2-containing AMPAR acting as a reserve pool that then move along the membrane to be recruited in the PSD? Or do they contribute to maintaining a balance between different AMPAR subtypes or between AMPAR across different synaptic compartments? Also, the contribution of GluA3-containing AMPAR to plasticity has been less explored (Kessels and Malinow, 2009; Schwenk et al., 2014; Renner et al., 2017) and a differential role evaluation of GluA1/2 and GluA2/3 in memory retrieval has not yet been addressed.

Among the potential upstream modulators of AMPAR movements at the synapse, mTORC1 has been proposed to play a pivotal role in memory processes (Bekinschtein et al., 2007; Lopez et al., 2015; Pereyra et al., 2021). mTORC1 regulates local protein translation in dendrites (Tang et al., 2002; Hay and Sonenberg, 2004; Hoeffer and Klann, 2010; Raab-Graham and Niere, 2017) and its blockade is associated with downregulation of GluA1 levels during memory retrieval in the PSD (Lopez et al., 2015; Pereyra et al., 2021) (Figure 1B). In the hippocampus, but not in the amygdala, downregulation of GluA1 levels is also observed in the synaptic plasma membrane fraction in rapamycin (selective mTORC1 inhibitor)-treated animals (Lopez et al., 2015; Pereyra et al., 2021). Infusion of Tat-GluR23y rescued mTORC1 blockade effects on memory retrieval while showing no effect on memory retrieval alone (Lopez et al., 2015; Pereyra et al., 2021). Nevertheless, a work has shown that infusion of Tat-GluR23y in the perirhinal cortex impaired object recognition memory retrieval (Cazakoff and Howland, 2011). Further questions in this direction are still unsolved: are AMPAR-mediated retrieval mechanisms brain region and/or memory valence specific? mTORC1 local control of AMPAR subunit translation seems compatible on a temporal scale with the memory retrieval molecular events that occur in the synapse and could provide a rapid synthesis rate that assures AMPAR pools that could be recruited in an activity dependent way.

Another factor to take into account when analyzing AMPAR exchanges lies in the stability of the tetratures once inserted in the membrane. A study that uses single molecule imaging has reported that AMPAR membrane tetratures would be metastable complexes that are in dynamic equilibrium with their respective monomers and dimers (Morise et al., 2019). This would imply dissociations of the AMPARs that allow changes in subunit composition at a very fast rate. Finally, different characteristics and regulatory mechanisms of the different AMPAR subunits (Hirano, 2018) can influence the assembly, insertion, lateral diffusion, and endocytosis rate of AMPAR and thus the associated molecular events that account for memory retrieval.

It is also interesting to evaluate the different AMPAR subunits role in some types of memory forgetting that usually represents a reversible memory retrieval disruption (Li et al., 2014; Guskjolen, 2016; Roy et al., 2016). For example, GluA2-containing AMPAR endocytosis mediates memory forgetting (Hardt et al., 2014; Dong et al., 2015; Migues et al., 2016) while blocking this phenomenon reverses memory retrieval deficits (Lopez et al., 2015; Pereyra et al., 2021). Besides, GluA2-containing AMPAR removal has been proposed to contribute to neuron excitability decrease inducing forgetting (Frankland et al., 2013).

CONCLUDING REMARKS

In this review, we have mainly focused on findings coming from rodent studies. Understanding the molecular basis of memory retrieval is extremely important to fulfill the gap between basic and clinical research. Potential clinical applications include the development of new or more precise targets for the treatment of human memory retrieval pathologies or dysfunction. Memory recall represents an attractive therapeutic time window for potential translational interventions. Retrieval enables both memory updating and weakening. In this regard, involuntary memory retrieval of a traumatic event is one hallmark symptom of posttraumatic stress disorder (American Psychiatric Association, 2013). Also, memory retrieval deficit has been reported in early stages of Alzheimer mouse model (Roy et al., 2016). On the other hand, there are few reports that address memory retrieval enhancement (Izquierdo et al., 2001, 2003; Barros et al., 2002, 2003; Stern and Alberini, 2013).

Regarding potential memory retrieval enhancement, ampakines, small molecules that positively regulate AMPAR,
have been widely evaluated in a variety of rodent models and human studies as a therapeutic avenue for treating memory disorders and to enhance cognitive function (Lynch and Gall, 2006; Lynch et al., 2011, 2014; Seese et al., 2020). For instance, CX-691, a specific ampakine, has been shown to improve memory in a rodent model of Alzheimer (Mozafari et al., 2018). In humans, CX-691 has been shown to acutely improve short-term memory in healthy elderly volunteers (Wezenberg et al., 2007). CX-691, a specific ampakine, has been shown to improve memory disorders and to enhance cognitive function (Lynch and Gall, 2013).

Further comprehension on AMPAR-mediated plasticity mechanisms will shed light on more selective potential targets (Zhang and Bramham, 2020) regarding memory retrieval deficits associated with neurological diseases.

REFERENCES

American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Virginia, VA: APA.

Anderson, M. C. (2003). Rethinking interference theory: executive control and the mechanisms of forgetting. J. Memory Lang. 49, 415–445.

Anderson, M. C., and Hubert, J. C. (2021). Active forgetting: adaptation of memory by prefrontal control. Annu. Rev. Psychol. 72, 1–36. doi: 10.1146/annurev-psych-072720-094140

Ashourpour, F., Jafari, A., and Babaei, P. (2020). Co-treatment of AMPA endocytosis inhibitor and GluN2B antagonist facilitate consolidation and retrieval of memory impaired by β amyloid peptide. Int. J. Neurosci. doi: 10.1080/02707454.2020.1837800 Online ahead of print.

Barros, D. M., Izquierdo, L. A., Medina, J. H., and Izquierdo, I. (2002). Supraptop and sertraline enhance retrieval of recent and remote long-term memory in rats. Behav. Pharmacol. 13, 215–220. doi: 10.1097/00008877-200205000-02005004

Barros, D. M., Izquierdo, L. A., Medina, J. H., and Izquierdo, I. (2003). Pharmacological findings contribute to the understanding of the main physiological mechanisms of memory retrieval. Curr. Drug Targets-CNS Neurol. Disorders 2, 81–94. doi: 10.2174/15680703348931

Bekinschtein, P., Katche, C., Slipczuk, L. N., Igaz, L. M., Cammarota, M., Izquierdo, I., et al. (2007). mTOR signaling in the hippocampus is necessary for memory formation. Neurobiol. Learn. Mem. 87, 303–307. doi: 10.1016/j.nlm.2006.08.007

Bekinschtein, P., Weissstaub, N. V., Gallo, F., Renner, M., and Anderson, M. C. (2018). A retrieval-specific mechanism of adaptive forgetting in the mammalian brain. Nat. Commun. 9:4660. doi: 10.1038/s41467-018-07128-7127

Bianchin, M., Walz, R., Ruschel, A. C., Zanatta, M. S., Da Silva, R. C., e Silva, M. B., et al. (1993). Memory expression is blocked by the infusion of CNQX into the brain. Behav. Pharmacol. 59, 83–86. doi: 10.1016/0163-1047(93)90782-d

Borgdorff, A. J., and Choquet, D. (2002). Regulation of AMPA receptor lateral movements. Nature 417, 649–653. doi: 10.1038/nature00780

Brusa, R., Zimmermann, F., Koh, D. S., Feldmeyer, D., Gass, P., Seeburg, P. H., et al. (1995). Early-onset epilepsy and postnatal lethality associated with an editing-deficient Glur-B allele in mice. Science 270, 1677–1680. doi: 10.1126/science.270.5242.1677

Buonarati, O. R., Hammes, E. A., Watson, J. F., Greger, I. H., and Hell, J. W. (2019). Mechanisms of postsynaptic localization of AMPA-type glutamate receptor and their regulation during long-term potentiation. Sci. Signal. 12(624):eaar6889. doi: 10.1126/scisignal.aear6889

Carroll, R. C., Beattie, E. C., von Zastrow, M., and Malenka, R. C. (2001). Role of AMPA receptor endocytosis in synaptic plasticity. Nat. Rev. Neurosci. 2, 315–324. doi: 10.1038/sj.nrn2500

Cazakoff, B. N., and Howland, J. G. (2011). AMPA receptor endocytosis in rat perirhinal cortex underlies retrieval of object memory. Learn. Memory 18, 688–692. doi: 10.1101/lm.2312711

Choquet, D. (2018). Linking nanoscale dynamics of AMPA receptor organization to plasticity of excitatory synapses and learning. J. Neurosci. 38, 9318–9329. doi: 10.1523/JNEUROSCI.2119-18.2018

Choquet, D., and Triller, A. (2013). The dynamic synapse. Neuron 80, 691–703. doi: 10.1016/j.neuron.2013.10.013

Collingridge, G. L., Peineau, S., Howland, J. G., and Wang, Y. T. (2010). Long-term depression in the CNS. Nat. Rev. Neurosci. 11, 459–473. doi: 10.1038/nrn2867

Cui, W., Darby-King, A., Grimes, M. T., Howland, J. G., Wang, Y. T., McLean, J. H., et al. (2011). Odor preference learning and memory modify GluA1 phosphorylation and GluA1 distribution in the neonate rat olfactory bulb: testing the AMPA receptor hypothesis in an appetitive learning model. Learn. Memory 18, 283–291. doi: 10.1016/j.nlm.1987711

Day, M., Langston, R., and Morris, R. G. (2003). Glutamate-receptor-mediated encoding and retrieval of paired-associate learning. Nature 424, 205–209. doi: 10.1038/nature01769

Delorenzi, A., Maza, F. J., Suárez, L. D., Barreiro, K., Molina, V. A., and Stehberg, J. (2014). Memory beyond expression. J. Physiology-Paris 108, 307–322. doi: 10.1016/j.jphysparis.2014.07.002

Díaz-Alonso, J., Morishita, W., Incontro, S., Simms, J., Holtzman, J., Gill, M., et al. (2020). Long-term potentiation is independent of the C-tail of the GluA1 AMPA receptor subunit. eLife 9:e58042. doi: 10.7554/eLife.58042

Diering, G. H., and Huganir, R. L. (2018). The AMPA receptor code of synaptic plasticity. Neuron 100, 314–329. doi: 10.1016/j.neuron.2018.10.018

Dong, H., O’Brien, R. I., Fung, E. T., Lanahan, A. A., Worley, P. F., and Huganir, R. L. (1997). GRIP: a synaptic PDZ domain-containing protein that interacts with AMPA receptors. Nature 386, 279–284. doi: 10.1038/386279a0

Dong, Z., Han, H., Li, H., Bai, Y., Wang, W., Tu, M., et al. (2015). Long-term potentiation decay and memory loss are mediated by AMPAR endocytosis. J. Clin. Invest. 125, 234–247. doi: 10.1172/JCI77888

Dudai, Y., and Eisenberg, M. (2004). Rites of passage of the engram: reconsolidation and the lingering consolidation hypothesis. Neuron 44, 93–100. doi: 10.1016/j.neuron.2004.09.003

Dudai, Y., and Morris, R. G. (2000). “To consolidate or not to consolidate: what are the questions?,” in Brain Perception Memory Advances in Cognitive Neuroscience, ed. J. J. Bulhuis (Oxford: Oxford University Press), 149–162.

Ferrara, N. C., Jarome, T. J., Cullen, P. K., Orsi, S. A., Kwapis, J. L., Trask, S., et al. (2019). GluR2 endocytosis-dependent protein degradation in the amygdala mediates memory updating. Sci. Rep. 9:5180. doi: 10.1038/s41598-019-41526-41521

Frankland, P. W., Josselyn, S. A., and Köhler, S. (2019). The neurobiological foundation of memory retrieval. Nat. Neurosci. 22, 1576–1585. doi: 10.1038/s41598-019-41526-41521

Frankland, P. W., Köhler, S., and Josselyn, S. A. (2013). Hippocampal neurogenesis and forgetting. Trends Neurosci. 36, 497–503. doi: 10.1016/j.tins.2013.05.002

Fujimoto, K. (1995). Freeze-fracture replica electron microscopy combined with SDS digestion for cytochemical labeling of integral membrane proteins.

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application to the immunogold labeling of intercellular junctional complexes. J. Cell Sci. 108, 3443–3449.

García-delatorre, P., Pérez-Sánchez, C., Guzmán-Ramos, K., and Bermúdez-Rattoni, F. (2014). Role of glutamate receptors of central and basolateral amygdala nuclei on retrieval and consolidation of taste averse memory. Neurobiol. Learn. Mem. 111, 35–40. doi: 10.1016/j.nlm.2014.03.003

Guo, H., Yuan, K., Zhang, Z., Xue, Y., Yan, W., Meng, S., et al. (2020). P4iKIIa regulates unconditioned stimulus-retrieval-induced fear memory consolidation through endosomal trafficking of AMPA receptors. *siscience* 23:100895. doi: 10.1016/j.siscience.2020.100895

Guskjolen, A. J. (2016). Losing connections, losing memory: ampa receptor endocytosis as a neurobiological mechanism of forgetting. *J. Neurosci.* 36, 7559–7561. doi: 10.1523/JNEUROSCI.1445-16.2016

Hardt, O., Nader, K., and Wang, Y. T. (2014). GluA2-dependent AMPA receptor endocytosis and the decay of early and late long-term potentiation: possible mechanisms for forgetting of short-and long-term memories. *Philos. Trans. R. Soc. B: Biol. Sci.* 369:20130141. doi: 10.1098/rstb.2013.0141

Hasegawa, S., Fukushima, H., Hosoda, H., Serita, T., Ishikawa, R., Rokukawa, T., et al. (2019). Hippocampal clock regulates memory retrieval via dopamine and PKA-induced GluA1 phosphorylation. *Nat. Commun.* 10:5766. doi: 10.1038/s41467-019-13554-y

Hasselmø, M. E., and Stern, C. E. (2014). Theta rhythm and the encoding and retrieval of space and time. *Neuroimage* 85, 656–666. doi: 10.1016/j.neuroimage.2013.06.022

Hay, N., and Sonenberg, N. (2004). Upstream and downstream of mTOR. *Annu. Rev. Neurosci.* 27, 103–137. doi: 10.1146/annurev.neuro.27.070203.144020

Hirano, T. (2018). Visualization of exo- and endocytosis of AMPA receptors during hippocampal synaptic plasticity around postsynaptic-like membrane formed on glass surface. *Front. Cell. Neurosci.* 12:442. doi: 10.3389/fncel.2018.00442

Hoefeer, C. A., and Klann, E. (2010). mTOR signaling: at the crossroads of plasticity, memory and disease. *Trends Neurosci.* 33, 67–75. doi: 10.1016/j.tins.2009.11.003

Hong, I., Kim, J., Kim, J., Lee, S., Ko, H. G., Nader, K., et al. (2013). AMPA receptor expression underlies transient memory destabilization on retrieval. *Proc. Natl. Acad. Sci. U S A.* 110, 8218–8223. doi: 10.1073/pnas.1305235110

Huganir, R. L., and Nicoll, R. A. (2013). AMPARs and synaptic plasticity: the last path to cognitive enhancement. *Pharmacol. Biochem. Behav.* 99, 116–129. doi: 10.1016/j.phbb.2010.12.024

Lynch, G., Cox, C. D., and Gall, C. M. (2014). Pharmacological enhancement of memory or cognition in normal subjects. *Front. Systems Neurosci.* 8:90. doi: 10.3389/fnsys.2014.00090

Lynch, G., and Gall, C. M. (2006). Ampakines and the threelfold path to cognitive enhancement. *Trends Neurosci.* 29, 554–562. doi: 10.1016/j.tins.2006.07.007

Lynch, G., Palmer, L. C., and Gall, C. M. (2011). The likelihood of cognitive enhancement. *Pharmacol. Biochem. Behav.* 99, 116–129. doi: 10.1016/j.phbb.2010.11.017

MacGillivray, H. D., Song, Y., Raghavachari, S., and Blanpied, T. A. (2013). Nanoscale scaffolding domains within the postsynaptic density concentrate synaptic AMPA receptors. *Neuron* 78, 615–622. doi: 10.1016/j.neuron.2013.03.009

Makino, H., and Malinow, R. (2009). AMPA receptor incorporation into synapses during LTP: the role of lateral movement and exocytosis. *Nature* 46, 381–390. doi: 10.1038/nature08035

Makuch, L., Volk, L., Anggono, V., Johnson, R. C., Yu, Y., Duning, K., Sprengel, R., et al. (2009). Subunit composition of synaptic AMPA receptors revealed by a single-cell genetic approach. *Neuron* 62, 254–268. doi: 10.1016/j.neuron.2009.02.027

Makino, H., and Malenka, R. C. (2002). AMPA receptor trafficking through PKA-induced GluA1 phosphorylation. *Neuron* 34, 67–75. doi: 10.1016/s0896-6273(02)00066-0

MacGillivray, H. D., Song, Y., Raghavachari, S., and Blanpied, T. A. (2013). Nanoscale scaffolding domains within the postsynaptic density concentrate synaptic AMPA receptors. *Neuron* 78, 615–622. doi: 10.1016/j.neuron.2013.03.009

Makino, H., and Malinow, R. (2009). AMPA receptor incorporation into synapses during LTP: the role of lateral movement and exocytosis. *Nature* 46, 381–390. doi: 10.1038/nature08035

Makuch, L., Volk, L., Anggono, V., Johnson, R. C., Yu, Y., Duning, K., et al. (2011). Regulation of AMPA receptor function by the human memory-associated gene KIBRA. *Neuron* 71, 1022–1029. doi: 10.1016/j.neuron.2011.08.017

Malinow, R., and Malenka, R. C. (2002). AMPA receptor trafficking through PKA-induced GluA1 phosphorylation. *Neuron* 34, 67–75. doi: 10.1016/s0896-6273(02)00066-0

Makino, H., and Malinow, R. (2009). AMPA receptor incorporation into synapses during LTP: the role of lateral movement and exocytosis. *Nature* 46, 381–390. doi: 10.1038/nature08035

Makuch, L., Volk, L., Anggono, V., Johnson, R. C., Yu, Y., Duning, K., et al. (2011). Regulation of AMPA receptor function by the human memory-associated gene KIBRA. *Neuron* 71, 1022–1029. doi: 10.1016/j.neuron.2011.08.017

Malinow, R., and Malenka, R. C. (2002). AMPA receptor trafficking through PKA-induced GluA1 phosphorylation. *Neuron* 34, 67–75. doi: 10.1016/s0896-6273(02)00066-0

Makino, H., and Malinow, R. (2009). AMPA receptor incorporation into synapses during LTP: the role of lateral movement and exocytosis. *Nature* 46, 381–390. doi: 10.1038/nature08035

Man, H. Y., Sekine-Aizawa, Y., and Huganir, R. L. (2007). Regulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor trafficking through PKA phosphorylation of the GluR1 subunit. *Proc. Natl. Acad. Sci. U S A.* 104, 3579–3584. doi: 10.1073/pnas.0611698104

Matsuzaki, M., Ellis-Davies, G. C., Nemoto, T., Miyashita, Y., Inoue, M., and Kasai, H. (2001). Dendritic spine geometry is critical for AMPA receptor expression in hippocampal CA1 pyramidal neurons. *Nat. Neurosci.* 4, 1086–1092.
Matsuzaki, M., Honkura, N., Ellis-Davies, G. C., and Kasai, H. (2004). Structural basis of long-term potentiation in single dendritic spines. *Nature* 429, 761–766. doi: 10.1038/nature02617

Migues, P. V., Liu, L., Archbold, G. E., Einarsson, E. Ö, Wong, J., Bonasia, K., et al. (2016). Blocking synaptic removal of GluA2-containing AMPA receptors prevents the natural forgetting of long-term memories. *J. Neurosci*. 36, 3481–3494. doi: 10.1523/JNEUROSCI.3333-15.2016

Monfils, M. H., Cowansage, K. K., Klann, E., and LeDoux, J. E. (2009). Extinction-reconsolidation boundaries: key to persistent attenuation of fear memories. *Science* 324, 951–955. doi: 10.1126/science.1167975

Morise, J., Suzuki, K. G., Kitagawa, A., Wakazono, Y., Takamiya, N., Nissen, W., Szabo, A., Somogyi, J., Somogyi, P., and Lamsa, K. P. (2010). Cell Nishimune, A., Isaac, J. T., Molnar, E., Noel, J., Nash, S. R., Tagaya, M., et al. (2016). Blocking synaptic removal of GluA2-containing AMPA receptors underlies adaptive reconsolidation of contextual fear. *Nat. Neurosci*. 14, 1302. doi: 10.1038/nn.2907

Renner, M. C., Albers, E. H., Gutierrez-Castellanos, N., Reinders, N. R., van Huijstee, A. N., Xiong, H., et al. (2017). Synthetic plasticity through activation of GluA3-containing AMPA receptors. *Nat. Rev. Neurosci*. 2, 898–905. doi: 10.1038/nrn.2013202

Rodriguez-Ortiz, C. J., Balderas, J., García-DeLaTorre, P., and Bermúdez-Rattoni, F. (2012). Taste aversion memory reconsolidation is independent of its retrieval. *Neurobiol. Learn. Mem.* 98, 215–219. doi: 10.1016/j.nlm.2012.08.002

Rossmann, M., Sukumaran, M., Penn, A. C., Veprintsev, D. B., Babu, M. M., and Greger, I. H. (2011). Subunit-selective N-terminal domain associations organize the formation of AMPA receptor heteromers. *EMBO J.* 30, 959–971. doi: 10.1038/emboj.2011.16

Roy, D. S., Arons, A., Mitchell, T. I., Pignatelli, M., Ryan, T. J., and Tonegawa, S. (2016). Memory retrieval by activating engramp cells in mouse models of early Alzheimer’s disease. *Nature* 531, 508–512. doi: 10.1038/nature17172

Rozov, A., Sprengel, R., and Seeburg, P. H. (2012). GluA2-lacking AMPA receptors in hippocampal CA1 cell synapses: evidence from gene-targeted mice. *Front. Mol. Neurosci.* 5, 222. doi: 10.3389/fnmol.2012.00222

Rugg, M. D., Johnson, J. D., Park, H., and Uncapher, M. R. (2008). Encoding-retrieval overlap in human episodic memory: a functional neuroimaging perspective. *Prog. Brain Res.* 169, 339–352. doi: 10.1016/S0079-6123(07)00201-20

Rugg, M. D., Johnson, J. D., and Uncapher, M. R. (2015). “Encoding and retrieval in episodic memory,” in *The Wiley Handbook on the Cognitive Neuroscience of Memory*, Eds. D. R. Addis, M. Barense, and A. Duarte (Hoboken, NJ: Wiley-Blackwell), 84–107.

Saglietti, L., Dequidt, C., Kamieniara, K., Rouset, M. C., Valnegri, P., Thoumine, O., et al. (2007). Extracellular interactions between GluR2 and N-cadherin in spine regulation. *Nature* 54, 461–477. doi: 10.1038/nn.984

San, N., Vissel, B., Petralia, R. S., Wang, Y. X., Chang, K., Royle, G. A., et al. (2003). A TrkB agonist and ampakine rescue synaptic plasticity and multiple forms of memory in a mouse model of mitochondrial disease. *Neuron* 38, 41–54. doi: 10.1016/j.neuron.2003.08.044

Seese, R. R., Le, A. A., Wang, K., Cox, D. C., Lynch, G., and Gall, C. M. (2020). A TrkB agonist and ampakine rescue synaptic plasticity and multiple forms of memory in a mouse model of mitochondrial disability. *Neurobiol. Dis.* 134:104604. doi: 10.1016/j.nbd.2019.10.4604

Seewald, A., Schönherr, S., Hörttagl, H., Ehrlich, I., Schmuckermann, C., and Ferraguti, F. (2021). Fear memory retrieval is associated with a reduction in AMPA receptor density at thalamic to amygdala intercalated cell synapses. *Front. Synaptic Neurosci.* 13:634558. doi: 10.3389/fnsyn.2021.634558

Shi, S. H., Hayashi, Y., Esteban, J. A., and Malinow, R. (2001). Subunit-specific rules of AMPA receptor expression requirement during long-term memory retrieval and its association with mTORC1 signaling. *Mot. Neurosci.* 58, 1711–1722. doi: 10.1016/s0092-8674(01)00321-x

Sommer, B., Kohler, M., Sprengel, R., and Seeburg, P. H. (1991). RNA editing in brain controls a determinant of ion flow in glutamate-gated channels. *Cell* 67, 11–19. doi: 10.1016/0092-8674(91)90568-j

Squire, L. R., Genzel, L., Wixted, J. T., and Morris, R. G. (2015). Memory consolidation. *Cold Spring Harb. Perspect. Biol.* 7:a01766. doi: 10.1101/cshperspect.a01766

Staresina, B. P., and Wimber, M. (2019). A neural chronometry of memory recall. Trends Cogn. Sci. 23, 1071–1085. doi: 10.1016/j.tics.2019.09.011

Stern, A. S., and Alberini, C. M. (2013). Mechanisms of memory enhancement. *Wiley Interdisciplinary Rev. Systems Biol. Med.* 5, 37–53. doi: 10.1002/wsbm.1196

Raab-Graham, K. F., and Niere, F. (2017). mTOR refrees memory and disease through mRNA repression and competition. *FEBS Lett.* 591, 1540–1554. doi: 10.1016/s0014-5793(17)34675-7

Rao-Ruiz, P., Rotaru, D. C., van der Loo, R. J., Mansvelder, H. D., Stiedl, O., Smit, A. B., et al. (2011). Retrieval-specific endocytosis of GluA2-AMPA receptors underlies adaptive reconsolidation of contextual fear. *Nat. Neurosci.* 14:1302. doi: 10.1038/nn.2907
Wezenberg, E., Verkes, R. J., Ruigt, G. S., Hulstijn, W., and Sabbe, B. G. (2004). Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *J. Neurosci.* 24, 4787–4795. doi: 10.1523/JNEUROSCI.5491-03.2004

Szapiro, G., Iziwerdo, L. A., Alonso, M., Barros, D., Paratcha, G., Ardenghi, P., et al. (2000). Participation of hippocampal metabotropic glutamate receptors, protein kinase A and mitogen-activated protein kinases in memory retrieval. *Neuroscience* 99, 1–5. doi: 10.1016/s0306-4522(00)00236-2

Tanaka, H., and Hirano, T. (2012). Visualization of subunit-specific delivery of glutamate receptors to postsynaptic membrane during hippocampal long-term potentiation. *Cell Rep.* 1, 291–298.

Tanaka, J. I., Matsuzaki, M., Tarusawa, E., Momiyama, A., Molnar, E., Kasai, H., et al. (2005). Number and density of AMPA receptors in single synapses in immature cerebellum. *J. Neurosci.* 25, 799–807. doi: 10.1523/JNEUROSCI.4256-04.2005

Tang, S. I., Reis, G., Kang, H., Gingras, A. C., Sonenberg, N., and Schuman, E. M. (2002). A rapamycin-sensitive signaling pathway contributes to long-term synaptic plasticity in the hippocampus. *Proc. Natl. Acad. Sci. U.S.A.* 99, 467–472. doi: 10.1073/pnas.012605299

Tonegawa, S., Pignatelli, M., Roy, D. S., and Ryan, T. J. (2015). Memory engram storage and retrieval. *Curr. Opin. Neurobiol.* 35, 101–109. doi: 10.1016/j.conb.2015.07.009

Torquatto, K. I., Menegolla, A. P., Popik, B., Casagrande, M. A., and de Oliveira Alves, L. (2019). Role of calcium-permeable AMPA receptors in memory consolidation, retrieval and updating. *Neuropsychopharmacology* 144, 312–318. doi: 10.1016/j.nuepro.2018.10.030

Tronche, C., Lestage, P., Louis, C., Carrie, I., and Bécaud, D. (2010). Pharmacological modulation of contextual “episodic-like” memory in aged mice. *Behav. Brain Res.* 215, 255–260. doi: 10.1016/j.bbr.2010.04.009

Tronson, N. C., and Taylor, J. R. (2007). Molecular mechanisms of memory reconsolidation. *Nat. Rev. Neurosci.* 8, 262–275. doi: 10.1038/nrn2090

Wang, G., Li, S., Gilbert, J., Gritton, H. J., Wang, Z., Li, Z., et al. (2017). Crucial roles for SIRT2 and AMPA receptor acetylation in synaptic plasticity and memory. *Cell Rep.* 20, 1335–1347. doi: 10.1016/j.celrep.2017.07.030

Warrington, E. K., and Weiskrantz, L. (1968). New method of testing long-term retention with special reference to amnesic patients. *Nature* 217, 972–974. doi: 10.1038/217972a0

Weiskrantz, L. (1966). “Experimental studies of amnesia,” in *Amnesia*, eds C. W. M. Whitty and O. L. Zangwill (London: Butterworths).

Wenthold, R. J., Petralia, R. S., and Niedzielski, A. S. (1996). Evidence for multiple AMPA receptor complexes in hippocampal CA1/CA2 neurons. *J. Neurosci.* 16, 1982–1989. doi: 10.1523/JNEUROSCI.16-06-01982.1996

Wezenberg, E., Verkes, R. J., Ruigt, G. S., Hulstijn, W., and Sabbe, B. G. (2007). Acute effects of the ampakine farampator on memory and information processing in healthy elderly volunteers. *Neuropsychopharmacology* 32, 1272–1283. doi: 10.1038/sj.npp.1301257

Whitlock, J. R., Heynen, A. J., Shuler, M. G., and Bear, M. F. (2006). Learning induces long-term potentiation in the hippocampus. *Science* 313, 1093–1097. doi: 10.1126/science.1128134

Winters, B. D., and Bussey, T. J. (2005). Glutamate receptors in perirhinal cortex mediate encoding, retrieval, and consolidation of object recognition memory. *J. Neurosci.* 25, 4243–4251. doi: 10.1523/JNEUROSCI.0480-05.2005

Yasoshima, Y., Morimoto, T., and Yamamoto, T. (2000). Different disruptive effects on the acquisition and expression of conditioned taste aversion by blockades of amygdalar ionotropic and metabotropic glutamatergic receptor subtypes in rats. *Brain Res.* 869, 15–24. doi: 10.1016/s0006-8993(00)02397-2

Yu, S. Y., Wu, D. C., Liu, L., Ge, Y., and Wang, Y. T. (2008). Role of AMPA receptor trafficking in NMDA receptor-dependent synaptic plasticity in the rat lateral amygdala. *J. Neurochem.* 106, 889–899. doi: 10.1111/j.1471-4159.2008.05461.x

Yuste, R., and Bonhoeffer, T. (2001). Morphological changes in dendritic spines associated with long-term synaptic plasticity. *Annu. Rev. Neurosci.* 24, 1071–1089. doi: 10.1146/annurev.neuro.24.1.1071

Zhang, H., and Bramham, C. R. (2020). Bidirectional dysregulation of AMPA receptor-mediated synaptic transmission and plasticity in brain disorders. *Front. Synaptic Neurosci.* 12:26. doi: 10.3389/fnsyn.2020.00026

Zhang, H., Zhang, C., Vincent, J., Zala, D., Benstaelli, C., Sainiolas, M., et al. (2018). Modulation of AMPA receptor surface diffusion restores hippocampal plasticity and memory in Huntington’s disease models. *Nat. Commun.* 9:4272. doi: 10.1038/s41467-018-06675-6

Zhou, Z., Liu, A., Xia, S., Leung, C., Qi, J., Meng, Y., et al. (2018). The C-terminal tails of endogenous GluA1 and GluA2 differentially contribute to hippocampal synaptic plasticity and learning. *Nat. Neurosci.* 21, 50–62. doi: 10.1038/s41593-017-0030-z

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