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# Hypothesis on Remote Memory Forming from Heterosynaptic LTD-Mediated Neuronal Degeneration

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## Abstract

In this article, it is hypothesized a new mechanism for the formation of stable remote memory in brain comprising the important memory acquired during childhood and the common words in language. It has been demonstrated that the memory forms concurrently at both homosynaptic long term potentiation (LTP) and heterosynaptic long term depression (LTD). It is pointed out that the repeated LTD may result in neuronal degeneration as evidenced at molecular and cellular level, becoming long lasting throughout the lifespan. Besides, it is further supported by the consequent storage of remote memory directly on the information pathway, as evidenced by the degenerative ocular dominance plasticity and the storage of common words/grammar within the linguistic areas of brain. Accordingly, it is herein completed the hypothesis on the formation of remote memory from the heterosynaptic LTD-mediated neuronal degeneration in brain so long as the homosynaptic pathway does not degenerate from such causes as aging and so on, while supplementing a new form of neuronal plasticity for memory in addition to the contemporary LTP and LTD.

## Subject Areas

Cell Biology, Developmental Biology, Linguistics, Neuroscience

## Keywords

Remote Memory, Homosynaptic LTP, Heterosynaptic LTD, Neuronal Degeneration

## 1. Introduction

Declarative memory is the memory for facts and episodes, while procedural

memory is the memory for skills and habits [1] [2] [3] [4]. Short-term memory is the precedent memory within minutes or seconds, while long-term memory is the memory of them more than hours or days ago [1] [2] [3]. Remote memory refers to the stable memory more than many years [1] [2] [3] [4].

It is common knowledge that the important memory acquired during childhood can be stored for decades of years as stable remote memory [3] [4]. More importantly, the common linguistic words are stored as remote declarative memories [5] [6], while the linguistic grammar stored as procedural memories [5] [6]. Due to the very importance of remote memory, it is certainly necessary to figure out its underlying neural mechanisms.

It has been an enigma to scientists that the remote memory is so stable that some of which can even last long for the whole span of life. It is widely accepted that the memory exists as synaptic plasticity at cellular level [7]. However, the two types of synaptic plasticity, the long term potentiation (LTP) and the long term depression (LTD), can both be reversed in experiments [8] [9], implicating that they can be forgotten naturally before lasting decades of years to become remote memory. In this regard, it is interesting to find out the alternative molecular and cellular mechanisms for the formation of stable remote memory in the brain.

## 2. Method

To deal with such an important but big topic, there was no better and more convincing way than integration of various progressions from all relevant fields of studies. It is necessary to point out that meta-analysis fits investigation of a specific topic in a well-studied subfield, but not for integrative summarization from several fields. Citing updated relevant reviews or, if not available, salient and repeated experimental result in subfields was the best method.

Papers were searched out from Pubmed and Baidu Xueshu. The updated relevant reviews in subfields were given priority to cite. If not available, the relevant reviews are cited. If still unavailable, the salient and repeated experimental results of original articles in subfields were cited. The papers written by the author were cited with the priority above all of these so as to demonstrate the expertise of the author to write this theoretical article.

## 3. Memory as Concurrent Homosynaptic LTP and Heterosynaptic LTD

At the cellular level, memory exists as neuronal synaptic plasticity [7], as LTP or LTD. Many electrophysiological experiments have revealed that the mnemonic synaptic plasticity is present concurrently as both homosynaptic LTP and heterosynaptic LTD in response to electrical stimulation [8] [9] [10] [11], demonstrating that the memory is stored as both homosynaptic LTP and heterosynaptic LTD in brain. The homosynaptic neuronal activation was shown to be required for the generation of heterosynaptic LTD [12] [13]. Recently, it was re-

ported that the formation of such heterosynaptic LTD may be mediated by ATP released from astrocytes [14]. More investigations are required for demonstrating the detailed underlying mechanisms how the memory forms as the concurrent homosynaptic LTP and heterosynaptic LTD.

The memory as the concurrent homosynaptic LTP and heterosynaptic LTD may occur in many places in brain. It has been shown to be concurrently present in the hippocampal dentate gyrus with the perforant afferents [10] [13], while as well in the hippocampal CA1 region [14]. Besides, it has further been reported that the concurrent homosynaptic LTP and heterosynaptic LTD also occur in visual cortex [15]. These are all important regions in brain for memory.

The homosynaptic LTP and heterosynaptic LTD can both be reversed by manipulations in experiments [8] [9], implicating that they are unstable, dynamic, and characterized as continuous learning, memory and forgetting in the brain.

It is necessary to point out that the newly acquired memory would undergo consolidation and retrieval, in such mechanism as proposed by the coupling of descending limbic system to the four ascending reticular systems of noradrenaline (NA), serotonin (5-HT), dopamine (DA) and acetylcholine (ACh) [1] [2]. These neurotransmitters exert complex effects on both LTP and LTD. For instance, DA was shown to facilitate the heterosynaptic inhibitory LTD in the prefrontal cortex [16], while stimulation of Locus coeruleus rich in NA could facilitate LTD in the hippocampal dentate gyrus via $\beta$-adrenergic receptors [17]. Besides, nicotine was reported to facilitate LTD in layer V pyramidal neurons of the mouse insular cortex via $\beta$2-containing nicotinic acetylcholine receptors (nAChRs) [18]. Due to the diversity and complexity, more investigations are obviously required in related fields in future.

## 4. Remote Memory from Heterosynaptic LTD-Mediated Neuronal Degeneration

The homosynaptic LTP and heterosynaptic LTD in brain are unstable, dynamic, and undergo continuous change during learning, memory, and forgetting, as evidenced by that they can both be reversed by manipulations in experiments [8] [9]. Accordingly, they are not the suitable candidates for the stable cellular mechanisms underlying the remote memory lasting long for many years and even the while life span [1] [2] [3] [4].

However, LTD resembles the effect of neuronal degeneration in that both of them decrease the synaptic transmission. Whereas, neuronal degeneration cannot be reversed, and can last long for many years up to the while life span. If the repeated LTD can transform into the neuronal degeneration, then the memory repeatedly stored as the heterosynaptic LTD can transform into the stable remote memory.

The molecular and cellular progressions in memory reveal that the repeated LTD can really transform into the neuronal degeneration, becoming irreversible and stable decrease in neuronal connection. For instance, it was reported in vis-

ual cortex that both the NMDAR-dependent LTD *in vitro* and ocular dominance plasticity *in vivo* as morphological degeneration shared the common metabotropic glutamate receptor signaling [19]. It was also demonstrated that there was a unifying molecular mechanism related to Arc gene for the age-/activity-dependent modulation of LTD and degenerative ocular dominance plasticity *in vivo* [20].

It is noted that this link of LTD to neuronal degeneration to form remote memory would result in the storage of remote memory exactly in the loci of LTD initially acquired during learning without translocation of mnemonic traces. The morphological degeneration in deprived visual cortex [19] [20] supports this memory storage at the early stage of processing pathway of visual information. Besides, the linguistic common words and grammar are both stored as remote memories [5] [6], and are both stored within the linguistic areas of brain [5] [6], also supporting that the memory storage and processing would share the same brain location.

It is also necessary to point out that the slow wave sleep (SWS) may as well facilitate LTD in various areas in cortex [21] [22]. Obviously, the LTDs facilitated during SWS contribute to the consolidation of the acquired memories [23] [24]. Whether SWS concurrently facilitates the LTD-mediated neuronal degeneration and the formation of remote memory requires further investigations.

## 5. Discussions

The remote memory consists of the important memories acquired during childhood [3] [4] and the common words in language [5] [6], and is an important form of stable memory able to last for decades of years [3] [4]. Accordingly, it is important to reveal its underlying neural mechanisms.

In this article, it is demonstrated that the heterosynaptic LTD-mediated neuronal degeneration forms the stable remote memory in brain. From the literatures searched out in "Method", there has not been the same hypothesis explicitly expressing the similar theory as in this paper. Two lines of evidences support this new hypothesis. One is that the memory is formed concurrently as both homosynaptic LTP and heterosynaptic LTD [8] [9] [10] [11], while another is the link of LTD to neuronal degeneration at the molecular and cellular level [19] [20].

As long as the homosynaptic pathway does not degenerate from such causes as aging and so on, this mechanism of remote memory from heterosynaptic LTD-mediated neuronal degeneration would last long for decades of years and even throughout the lifespan.

This mechanism of heterosynaptic LTD-mediated neuronal degeneration stores the remote memory directly on the information pathway. It is supported by the degenerative ocular dominance plasticity *in vivo* [19] [20] as well as the common words and grammar stored within the linguistic areas of brain [5] [6]. This mechanism of remote memory does not require the feeling of familiarity to facilitate its formation. It is still not clear in detail mechanism how the repeated

LTD can result in the neuronal degeneration for remote memory. More investigations are required for the detailed molecular mechanisms and processes underlying the LTD-mediated neuronal degeneration. This is a very prospective field for investigations in future.

It is noted that this heterosynaptic LTD-mediated neuronal degeneration supplements a new form of neuronal plasticity for memory in addition to the contemporary LTP and LTD. Both homosynaptic LTP and heterosynaptic LTD can be reversed by manipulations in experiments [8] [9]. They are unstable, dynamic, and characterized as continuous learning, memory, and forgetting in brain. Whereas, the heterosynaptic LTD-mediated neuronal degeneration would last long for decades of years as remote memory so long as the homosynaptic pathway does not degenerate during the period.

It has widely been speculated by the people in television that the "athorny" pyramid cells, which mediates the hippocampal sharp-wave [25], may also be the homosynaptic cells storing the remote memory with its heterosynaptic LTD neurons already degenerating out.

It is also noted that this mechanism may be useful in the consideration of pathology of some diseases in which remote memory is impaired, such as dementia and so on. The LTD pathways can be excluded from the pathology of the diseases with remote memory cleared because the LTD neurons have already degenerated in remote memory. Whereas, the homosynaptic LTP may be relevant to the pathology of these diseases.

## 6. Conclusion

In this article, a new hypothesis is demonstrated on the formation of stable remote memory in brain. Many experiments have shown that the memory forms concurrently at both homosynaptic LTP and heterosynaptic LTD. Besides, the repeated LTD may result in neuronal degeneration as evidenced by the NMDAR-dependent or Arc-related mechanism shared by both LTD and morphological degeneration in deprived visual cortex. The remote memory formed in this way can last long throughout the lifespan, so long as the homosynaptic pathway does not degenerate from such causes as aging and so on. The storage of remote memory directly on the information pathway, as evidenced by the degenerative ocular dominance plasticity *in vivo* as well as the storage of common words and grammar within the linguistic areas of brain, can also support this hypothesis. This heterosynaptic LTD-mediated neuronal degeneration for remote memory supplements a new form of neuronal plasticity for memory in addition to the contemporary LTP and LTD.

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## Conflicts of Interest

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