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Removing Pathogenic Memories

A Neurobiology of Psychotherapy

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Abstract

Experimental research examining the neural bases of nondeclarative memory has offered intriguing insight into how functional and dysfunctional implicit learning affects the brain. Long-term modifications of synaptic transmission, in particular, are currently considered the most plausible mechanism underlying memory trace encoding and compulsions, addiction, anxiety, and phobias. Therefore, an effective psychotherapy must be directed to erase maladaptive implicit memories and aberrant synaptic plasticity.

This article describes the neurobiological bases of pathogenic memory disruption to provide some insight into how psychotherapy works. At least two mechanisms of unwanted memory erasing appear to be implicated in the effects of psychotherapy: inhibition of memory consolidation/reconsolidation and extinction. Behavioral evidence demonstrated that these two ways to forget are profoundly distinct in nature, and it is increasingly clear that their cellular, synaptic, and molecular underpinnings are different. Accordingly, the blockade of consolidation/reconsolidation erases memories by reversing the plasticity associated with memory maintenance, whereas extinction is a totally new form of plasticity that, similar to the plasticity underlying the old memory, requires protein synthesis-dependent synaptic remodeling.

Index Entries: Extinction; forgetting; long-term depression; long-term potentiation; reconsolidation.

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"I only know that such 'oblivion' was not reached by the patients I analysed, but that instead it led to various pathological reactions" (Freud, 1894, The Neuro-Psychoses of Defence).

"The hysteric suffers from reminiscences" (Freud, 1895, Studies on Hysteria. Freud, 1909, Five Lectures on Psycho-Analysis).

Introduction

In Freud's theory on the origin of neuroses, real or imaginary traumatic experiences permanently alter the functioning of the psychic apparatus. Therefore, unconscious memories can be pathogenic: "All hysterics and neurotics remember the painful experiences of their distant past…; they are unable to free themselves from the past and thus neglect reality and the present. This fixation of psychic life for pathogenic traumas is one of the most important characteristics and practically the most significant of neurosis" *(1)*.

It is increasingly accepted that many psychiatric symptoms originate from the formation and consolidation of implicit dysfunctional memories. Implicit, or nondeclarative, learning refers to the ability of the brain to establish unconscious associations between distinct events. Indeed, learning by association is an essential process for retaining information from past experiences to reinforce homeostatic behaviors and escape from aversive conditions *(2–4)*.

Experimental research examining the neural bases of nondeclarative memory (such as habit formation, classical conditioning, and fear conditioning) has offered intriguing insight into how functional and dysfunctional implicit learning affects the brain. Long-term modifications of synaptic transmission in particular, are currently considered the most plausible mechanisms underlying memory trace encoding compulsions, addiction, anxiety, and phobias *(5–7)*. In this line, compulsions and other stereotypies are viewed as pathological habits (nearly automated implicit motor abilities) encoded as aberrant synaptic plasticity in the cortico-basal ganglia loop *(8–11)*. Conversely, addictive drugs abuse the molecular mechanisms of reward-based associative learning by inducing long-term changes in synaptic effectiveness in those brain areas serving basic biological needs, such as feeding and sexual interaction (midbrain dopamine neurons and several brain structures receiving dopamine-releasing axon terminals) *(12–15)*. Finally, anxiety, panic disorder, and phobias are viewed as uncontrolled and repetitive defensive reactions secondary to abnormal fear conditioning (a form of implicit associative learning, encoded as long-term potentiation [LTP] in the lateral amygdala in which emotionally neutral stimuli acquire the capacity to elicit defensive responses after association with an aversive event) *(16–18)*.

Therefore, a main corollary of these considerations is that an effective psychotherapy must be directed to erase maladaptive implicit memories and aberrant synaptic plasticity.

This article discusses the processes of memory disruption following behavioral treatment. The cellular and molecular mechanisms of the process of "forgetting" are also described to provide biological insight into how psychotherapy works.

Inhibition of Consolidation/ Reconsolidation and Extinction Are Two Distinct Ways to Forget

Over the past decade, remarkable progress has been made toward our understanding of the mechanisms of memory formation and consolidation. More recently, attention has also focused on the process of forgetfulness. The emerging scenario is particularly interesting, because it is increasingly clear that forgetting does not simply result from the passive degradation of the plasticity associated with memory acquisition; rather, it represents a very complex process that actively counters the learning course.

At least two mechanisms of unwanted memory disruption might be implicated in the effects of psychotherapy: inhibition of memory

consolidation/reconsolidation and extinction. Both processes must be clearly distinguished from repression, a process by which unaccepted memories are kept out of consciousness and, therefore, are not properly forgotten. Proposed by Freud more than a century ago, the psychological process of memory repression has come to be clarified only in recent years, based on the demonstration of a series of psychological inhibitory mechanisms actively recruited to prevent unwanted memories from entering awareness *(19)*.

Inhibition of Memory Consolidation/Reconsolidation

It has long been recognized that long-term information storage involves a process by which a labile short-term memory is converted into a stable, fixed trace that is particularly impervious to amnesic treatments *(20–22)*. This view was originally proposed based on evidence that treatments such as electroconvulsive shock that produce amnesia shortly after learning have no effect when delivered several hours later *(23)*. The transition from short- to long-term memory is called consolidation and is believed to follow the transformation of temporary alterations in synaptic transmission into persistent modifications of synaptic architecture in specific brain areas *(7,24–26)*. This model, which is more than 100 yr old *(27,28)*, was initially challenged in a 1968 study showing that although electroconvulsive shock was ineffective in disrupting memory hours after the learning process, it could induce amnesia if a fully consolidated and stable long-term memory was re-activated by a reminder process prior to amnesic treatments *(29)*. Therefore, this finding indicates that old memory re-activation returns it to a labile state, which undergoes another round of consolidation similar to that occurring after new learning. This process has been referred to as reconsolidation *(30,31)*. In recent years, the process of reconsolidation was clearly demonstrated by using a large number of behavioral paradigms and amnesic agents; it is now increasingly accepted that it represents a phenomenon shared by different types of memories *(28)*. Thus, instead of occurring only once, memory storage is a process that is reiterated with each use of the memory.

These discoveries substantially contributed to revision of the concept that long-term memories are irreversibly stored in the wiring of the brain and, rather, indicated that memories can be continually updated, modified, and even erased. Incidentally, the susceptibility of the reconsolidation process to interference may account for the occurrence of false (including pathogenic) memories. Specifically, during re-activation of a memory trace, its content can be changed through suggestion or other means *(32)*.

If the original memory traces become susceptible to changes each time the memory is retrieved and this is true also for pathogenic memories, the psychotherapy treatment (which enables patients to recall and re-elaborate past traumatic experiences) can help to extinguish their pathogenic potential by interfering with the reconsolidation process. Notably, since the very beginning of his theorization, Freud discovered that memory re-activation and re-elaboration can be beneficial. In *Recollection, Repetition and Working Through* (1914), he wrote: "We know therefore that the patient in analysis repeats instead of remembering…From repetitive reactions, the known paths (psychoanalytical therapy) lead to the reawakening of memories" *(33)*. In other terms, the pathogenic effects of dysfunctional unconscious memories, which are responsible for repetition typical of neurotic symptoms, can be overcome by a process or memory trace retrieval and re-elaboration.

Memory Extinction

Although the inhibition of reconsolidation is a process of interference with the mechanism of memory restorage that follows the reminder, extinction is a completely different phenomenon. Accordingly, inhibition of consolidation as well as reconsolidation tends to render a

certain memory "unlearnt," whereas extinction is a new learning process that does not disrupt previously acquired plasticity but, rather, triggers additional plasticity. Experimentally, extinction consists in the progressive decrease and eventual disappearance of a conditioned response (CR; e.g., fear) when a neutral conditioned stimulus (CS; e.g., a light) predictive of a certain significant event (unconditioned stimulus [US]; e.g., a footshock) is repeatedly presented alone.

Since the pioneering studies of Pavlov, extinction has been studied in several experimental paradigms, including eyeblink conditioning, several appetitive paradigms, and fear conditioning *(34,35)*. Incidentally, the experimental protocol used to induce fear extinction in animals—that is, the iterative presentation of the CS in the absence of the US—is very similar to the psychotherapeutic approach employed to treat fear disorders in humans, which commonly involves exposure to the feared object in the absence of any overt danger.

Several observations indicate that extinction does not result from the progressive weakening and ultimate degradation of the original CS–US association. For example, extinction does not occur following simple passage of time but, conversely, is the extinction process that tends to dissipate, as indicated by the progressive re-appearance of the extinguished CRs over time *(36)*. Similarly, an extinguished CR re-appears when an animal *(37)* or a human *(38)* is tested in a context different from that in which the extinction training occurred or when unsignaled US are presented following the completion of the extinction training.

Together, these data indicate that extinction does not permanently erase the ability of a CS to drive a CR; rather, it triggers a second learning process that inhibits the expression of the CR without destroying the old memory, although it suppresses its expression *(34)*. In other words, extinction is a process that generates a further inhibitory association between the CS and US, which actively counters to the tendency of the CS to activate US representation. Notably, the inhibitory association at the basis of extinction is generally more labile than the excitatory one, indicating why the extinguished response tends to re-appear with time or changing the environmental context *(34,36–38)*. Therefore, the high rate of relapse observed in patients treated with behavioral therapy might rely on this peculiar feature of the learning process that is activated by extinction.

Although distinct in nature, it is likely that the inhibition of consolidation/reconsolidation and extinction occur simultaneously during disruption of maladaptive memories. In fact, based on several behavioral findings, it has been proposed that reconsolidation (which favors memory maintenance) and extinction (which facilitates memory inhibition) are two processes competing for their expression following memory re-activation. For example, it has been reported that far from inducing a reconsolidation of the learned behavior, reiteration of the CS alone solely causes extinction of learned fear *(39)*. Therefore, when extinction is favored, reconsolidation is invariably inhibited *(28,34,39,40)*. Although the study of the factors favoring the emergence of a process over the other is still at its infancy, a recent report proposed that reminder duration is a major determinant dictating whether reconsolidation or extinction is preferentially activated *(41)*.

Molecular and Synaptic Bases of Forgetfulness

When studied at the molecular level, blockade of consolidation/reconsolidation and extinction appear as two completely different phenomena. Intriguingly, although pharmacological inhibition of protein synthesis favors the blockade of both consolidation and reconsolidation, this treatment prevents extinction. These findings are generally interpreted as confirmation that the blockade of reconsolidation erases memories by reversing the plasticity associated with memory maintenance, whereas, extinction is a totally new form of plasticity requiring protein synthesis-dependent synaptic re-arrangements (similar

to the plasticity underlying the old memory) *(28,34,39–41)*.

Long-Term Potentiation of Excitatory Transmission As a Synaptic Correlate of Memory

In 1973, Bliss and Lømo *(42)* reported the first finding that repetitive synaptic activation induced a long-lasting increase in the efficacy of excitatory transmission in the hippocampus, a brain area known to be involved in learning and memory processes. This phenomenon, known as LTP, essentially consists of the enduring facilitation of the communication between two neurons in response to the sustained activation of the synapses by which they are interconnected. Several subsequent scientific discoveries have made it possible to correlate this synaptic phenomenon with learning and memory *(6,7,43)*. Notably, LTP has now been described at several other excitatory synapses of the central nervous system, including those of brain areas important for implicit memory encoding.

Molecular and Synaptic Correlates of the Inhibition of Consolidation/Reconsolidation

If LTP subserves memory formation and consolidation, then it is likely that depotentiation represents the synaptic underpinning of the process of inhibition of memory reconsolidation. Depotentiation is a recently described synaptic phenomenon consisting of the possibility to reverse a previously induced LTP by an appropriate protocol of synaptic stimulation *(44–47)*. Although depotentiation exhibits some similarities to long-term depression (LTD) of synaptic transmission, it represents a completely different phenomenon because the commonly employed depotentiation protocol is unable to depress nonpotentiated synapses *(43,47)*.

A definitive demonstration of the correlation between inhibition of consolidation/reconsolidation and depotentiation is lacking, but in our opinion, some considerations exist for this association. First, consolidation and reconsolidation are inhibited *(48)*, and depotentiation is favored *(26,49)* by blocking the transcription factor cyclic adenine monophosphate-response-element binding protein. Second, memory trace and LTP are susceptible to erasing processes (inhibition of reconsolidation and synaptic depotentiation, respectively) for only a short time following memory acquisition (or retrieval) *(28)* and LTP induction *(45,46)*. Finally, the process of extinction-independent forgetting is facilitated *(50)* in the same way as depotentiation *(47,51)* by the activity of protein phosphatase 1, an enzyme critical for the removal of phosphate groups from target proteins *(52)*. Notably, the stimulation of several protein kinases, which conversely add phosphate groups on the same target proteins, enables LTP formation *(7)*.

Depotentiation can apparently reset synaptic transmission to the naïve state, implying that memory trace disappears entirely following inhibition of consolidation/reconsolidation. However, recent studies have challenged this view, indicating that the plasticity history of a synapse is as important as its current physiological state in determining its response to a given stimulation. An interesting study demonstrated that excitatory synapses can occupy as many as seven distinct states (silent, active, depressed, recently potentiated, recently depotentiated, recently unsilenced, and remotely unsilenced) and that the lasting response to the same stimulation protocol differs among them *(53)*. With respect to the plastic potential of a naïve and of a depotentiated synapse, low-frequency stimulation was found to induce LTD in both cases, but the depression observed in depotentiated synapses was significantly smaller in amplitude *(53)*. Therefore, depotentiated synapses tend to prefer the potentiated, rather than the depressed, state *(54)*. This evidence indicates that once employed for information storage, synapses indefinitely retain a trace of this experience, even after LTP and memory erasing. This might provide an explanation for the evidence that memory disruption produced by blockade of

reconsolidation can recover *(55)* and for the clinical experience that treated symptoms tend to re-appear. Freud evocatively described the impossible oblivion of many neurotics as: "the eternal return of the same" *(56,57)*.

Molecular and Synaptic Correlates of Extinction

As reported earlier, general agreement exists regarding the fact that extinction is a new learning process. Not surprisingly, therefore, the molecular determinants of memory extinction parallel those of synaptic plasticity and memory formation. For example, the stimulation of *N*-methyl-D-aspartate (NMDA) glutamate receptors is a critical requirement for amygdalal LTP *(58,59)* and fear memory acquisition *(60–63)*; however, it has also been found to be crucial for fear extinction *(60,64,65)*. Additionally, the postreceptor events initiated by NMDA receptor stimulation and mediating LTP and memory formation are substantially identical to those involved in extinction. Accordingly, protein kinase A, calcium/calmodulin-dependent protein kinase II, and mitogen-activated protein kinase are all required for LTP *(43,66–69)* as well as memory formation *(68,70,71)* and extinction *(65,72)*. Finally, extinction, similarly to memory consolidation *(28)* and the late phase of LTP *(7)*, requires new protein synthesis *(34)*.

Although these data are all suggestive of the fact that extinction recapitulates the molecular and synaptic events at the basis of memory and plasticity of glutamatergic synapses, an attractive alternative hypothesis is that extinction-associated plasticity does not involve glutamatergic transmission but, rather, γ-aminobutyric acid (GABA)ergic inhibitory synapses. A recent study showed that impairment of fear extinction is associated with the disruption of LTD of GABAergic transmission (iLTD) in the basolateral amygdala *(73)*, implying this form of synaptic plasticity in aversive memory elimination.

Synaptic plasticity of GABA synapses has been reported to occur in several other regions of the brain, including the hippocampus, cortex, cerebellum, deep cerebellar nucleus, lateral superior olive, and brain stem *(74)*; however, a direct link between GABAergic plasticity and behavioral modifications was still missing. Several findings support the concept that iLTD lies at the basis of the extinction process. For example, NMDA glutamate receptor activation is required for both extinction *(34,60,64,65)* and iLTD *(74,75)*. Additionally, the recent evidence that extinction of cocaine-seeking behavior is associated with upregulation of α-amino-*3*-hydroxy-*5*-methyl-*4*-isoxazole propionic acid glutamate receptors *(76)* is also consistent with the finding that these receptors mediate the initial depolarization during the conditioning protocol of iLTD *(77)*. Finally, pharmacological agents that reduce the effectiveness of GABA transmission (such iLTD) have been found to facilitate the extinction process *(78)*.

The idea that long-term inhibition of GABA transmission is a synaptic correlate of extinction also helps to explain the critical role played by endocannabinoids in this process. Pharmacological or genetic inactivation of cannabinoid CB1 receptors prevents fear extinction, whereas the levels of two major endocannabinoids, anandamide and 2-arachidonylglycerol, increase significantly in the basolateral amygdala during fear extinction training *(73)*. Therefore, evidence exists that behavioral treatment of aversive memories results in the activation of the endocannabinoid system, which, in turn, facilitates memory extinction by stimulating cannabinoid CB1 receptors in the amygdala. Notably, among the different effects of endocannabinoids in central neurons, the short- and long-term inhibition of GABAergic transmission is particularly relevant. Cannabinoid CB1 receptors are abundantly expressed on GABAergic nerve terminals in the brain, where they reduce transmitter release *(79,80)*. Endocannabinoids participate in the inhibitory control of GABA transmission by acting as retrograde messengers—that is, they are released from the somatodendritic region of the postsynaptic neuron and back propagate to inhibit presynaptic GABA-releasing nerve

terminals *(81)*. This mechanism of action has been proposed to explain two distinct synaptic phenomena: depolarization-induced suppression of inhibition (DSI) and iLTD. Whereas DSI consists in a transient inhibition of GABA release triggered by sustained depolarization of the postsynaptic neuron *(82,83)*, iLTD is a long-lasting phenomenon *(74)*. The different time-courses of these two processes likely reflect the duration of endocannabinoid release. Accordingly, whereas DSI is presumably triggered by a brief (a few seconds) release of endocannabinoids *(83,84)*, cannabinoid CB1 receptors must be activated for minutes to trigger iLTD *(85)*. This is consistent with the finding that fear-extinction-triggered iLTD in the amygdala is associated with an increase in endocannabinoids detectable even after the killing of the experimental animals and brain removal *(73)*.

Conclusion

Many psychiatric symptoms follow abnormalities of brain's representation of the outside world as a consequence of dysfunctional unconscious associations between external stimuli. At the end of the 19th century, Ramon and Cajal *(86)* and Freud *(87)* proposed that information could be stored by modifying interneuronal connections—a principle formalized by Hebb 50 yr later: "When an axon of cell A is near enough to excite a cell B and repeatedly and persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficacy, as one of the cells firing B, is increased" *(20)*.

Indeed, Hebb's rule is believed to account for the associations of neural events. In fact, with respect to the classical Pavlovian conditioning, if the activity of cell A is part of the representation of a neutral stimulus (e.g., a sound) and the activity of cell B signals food, once the connection between A and B has been strengthened, each time A is activated by the sound, the representation of food will appear. Because of this kind of association, anxious patients perceive danger in situations that are not dangerous; paranoid patients may misconstrue situations in terms of being deceived or attacked; depressed patients see evidence of personal defect in situations that offer no objective reasons for self-deprecation. In other words, once connected, two or more distinct representations proceed together and behave as one.

Therefore, in the face of the diverse technical approaches, the progressive dissolution of such pathogenic associations should be the purpose of all psychotherapeutic treatments. Notably, in 1922, Freud, in defining psychoanalytic treatment, wrote: "The patient's symptoms and pathological manifestations—like all his psychic activities—are of a highly composite character […]. But the patient is either unaware of these factors or has only an insufficient knowledge of them. Therefore, we teach him to understand the composition of these very complicated psychic formations […], that is, we act like a chemist who isolates a simple substance or chemical 'element' from the salt in which it has combined with other elements and thus become unrecognisable" *(1)*.

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