REVIEW
LONG-TERM POTENTIATION AND MEMORY PROCESSES IN THE PSYCHOLOGICAL WORKS OF SIGMUND FREUD AND IN THE FORMATION OF NEUROPSYCHIATRIC SYMPTOMS

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Abstract—Far from disproving the model of mind functioning proposed by psychoanalysis, the recent advances in neuropsychiatrical research confirmed the crucial ideas of Sigmund Freud. The hypothesis that the origin of mental illnesses lies in the impossibility for a subject to erase the long-term effects of a remote adverse event is in tune with the view that several psychiatric disturbances reflect the activation of aberrant unconscious memory processes. Freud’s insights did not stop here, but went on to describe in an extremely precise manner the neural mechanisms of memory formation almost a century before the description of long-term synaptic potentiation. © 2005 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: drug addiction, fear conditioning, OCD, synaptic plasticity, trauma, TMS.

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More than 10 years ago, the American magazine Time wondered if Freud was dead (Gray, 1993). At that time, the progress of cognitive neuroscience seemed to suggest that that model of mind functioning inspired by psychoanalysis was inadequate to account for the experimental data, while the advances in genetics and psychopharmacology were seen as a confirmation that mental disorders have a purely biological origin. Since then, however, something has changed. The rediscovery of Freud’s thought coincided with the reconsideration of the “nature/nurture problem,” as it is increasingly accepted that the two terms do not necessarily conflict. It is now increasingly clear, in fact, that pre-existing conditions may predispose to the development of some psychiatric disorders following an external event. For example, it has been recently shown that individuals with one or two copies of the short allele of the serotonin transporter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele (Caspi et al., 2003). Also, the vulnerability to psychological trauma has been found to be greatly influenced by pre-existing smaller hippocampal volumes (Gilbertson et al., 2002).

On the other hand, evidence exists that relevant life events do induce functional and morphological remodeling of brain circuits, leading to significant changes in behavior. This new perspective originates from basic neurosciences as well as clinical research, and can be summarized in the following terms: mental processes are an expression of brain activity, and environmental factors influence brain functioning by modifying the connectivity among neurons. These changes encode specific forms of experience-dependent learning and give rise to psychic or behavioral events, including symptoms (Kandel, 1999; LeDoux, 2001).

Freud described the relationship between accidental life events and predisposition in terms of co-implication of chance and determinism. For example, in 1910 he stated: “We are all too ready to forget that in fact everything to do with our life is chance . . . chance which nevertheless has a share in the law and necessity of nature, and which merely lacks any connection with our wishes and illusions” (Freud, 1910).

Far from trying to present the whole Freudian theorization on the relationship between accidental events and predisposition in psychic determinism, the aim of this article is to present Freud’s anticipations about the relationship between traumatic events, synaptic plasticity, memory processes, and psychopathology in the light of current...
ideas on the neuronal bases of psychic symptoms and the synaptic substrate of learning and memory.

Over many years, in fact, Freud created many theories, not all integrated, to explain psychological processes. Although many of these theories are not easily mapped onto current neuroscience, several authors agree in considering Freud’s ideas on the synaptic bases of memory and on the salience of unconscious memories in psychopathology remarkably modern (McCrone, 2004).

Trauma, repetition, and memory in Freud’s theory on the origin of neuroses

The notion of psychic determinism is fundamental in Freud’s theory on the functioning of the mind. This principle affirms that behaviors, emotions, and thoughts are determined in each subject by preceding, real or imaginary, psychic events. Clearly, this reflects the ability of the brain to establish associations between temporally distant events and to modify behaviors and choices accordingly, even in the absence of conscious intervention (Kandel, 1999). The brain’s ability to learn by association has been recognized since the pioneering work of Ivan Pavlov (1927), and represents a critical process through which experiences shape personality (LeDoux, 2001).

When the concept of psychic determinism is applied to the field of psychopathology, a causal link between psychic symptoms and traumatic experiences emerges. The notion of trauma is central in Freud’s theory of the origin of neuroses. It is defined by Freud himself as “an experience that in a short period of time delivers to psychic life such strong stimuli that cannot be eliminated or processed in the usual way, and so it is unavoidable that permanent disorders appear in the energetic organization of the psyche” (Freud, 1916). In Freud’s thought, the “usual way” to process psychic stimuli consists in their prompt evacuation according to the “principle of constance,” the aim of which is to maintain excitation of the psychic apparatus as low as possible (Freud, 1895a, b, 1909, 1920). At the end of the 19th century, Freud was not alone in borrowing from physics the idea that the psychic apparatus functions in normal conditions to maintain its internal excitation at a constant level. A representation of psychic phenomena of this kind, in fact, was given by Fechner (1873), who tried to confer universal value on his “stability principle.” In Freud’s theory, the principle of constance is coincident with the pleasure principle, as low excitation is experienced as pleasure and strong excitation as displeasure (Freud, 1920).

In Freud’s theory, therefore, a trauma occurs when the principle of constance fails, and gives rise to irreversible, pathological changes in brain functioning (Freud, 1895a, b, 1916, 1920, 1926). In other words, those subjects who experience a trauma are irreversibly marked by that event in their everyday life, given the substantial impossibility to “forget” such an event. This concept makes it possible to understand the sense of the famous Freudian sentence: “The hysterick suffers from reminiscences” (Freud, 1895b, 1909) and of his observation dated 1894: “I only know that such ‘oblivion’ was not reached by the patients I analyzed, but that instead it led to various pathological reactions” (Freud, 1894). Unconscious memories, therefore, can be pathogenic.

This simple scheme on the origin of psychopathological symptoms can be found throughout all Freud’s writings, although variably specified in the different periods of his elaboration. Particularly interesting in this context, however, is that, when referred to the organic substrate of the psychic processes, the long-term effects of a trauma are described by Freud as “facilitation among neurons” (Freud, 1895a, 1920), while its psychopathological manifestation is the “compulsion to repeat” (Freud, 1914, 1920, 1926). Although notably clear in traumatic neuroses in the form of painful re-experiencing phenomena, repetition is discovered by Freud in all psychic symptoms (Freud, 1900, 1914, 1920, 1926). Freud never stopped to note that neurotics infinitely repeat painful acts and scenes even though this repetition is unpleasant or frankly harmful. He noticed that the compulsion to repeat is unexplainable in terms of the pleasure principle and it appears rather as an autonomous mechanism that patients can hardly inhibit, activated when the pleasure principle fails. Freud evocatively describes the impossible oblivion of neurotics as: “the eternal return of the same” (Freud, 1919, 1920).

The connection among the concepts of trauma, facilitation, repetition, memory, and psychopathology is also clearly established by Freud when describing his idea of “fixation to trauma” (Freud, 1909, 1916). With this regard, he wrote: “All hysterics and neurotics not only remember the painful experiences of their distant past, but are also emotionally attached to this; 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” (Freud, 1909).

Psychic symptoms as an expression of aberrant implicit information storage

The most recent views on the intimate nature of psychiatric illnesses confirm Freud’s idea that neurotics suffer from reminiscences. Obsessive–compulsive disorder (OCD), Tourette’s syndrome, eating disorders, gambling, drug addiction, anxiety and phobias are increasingly viewed as diseases of experience-dependent implicit memory storage.

Retaining information from past experiences is essential for reinforcing homeostatic behaviors and for escaping from aversive expositions. Several forms of implicit learning are engaged to this purpose, and allow refining adaptive responses with minimal or even absent voluntary intervention.

Recent studies indicate that several psychopathological conditions rely on the neurobiological mechanisms that underlie unconscious associative memory, as the symptoms typical of these disorders originate from the co-optation of the neural mechanisms normally involved in the formation and consolidation of several forms of implicit adaptive memories. Obsessions, compulsions, avoidance, and addictions have plausible and even ordinary content and motivation, but become pervasive, inaccessible to voluntary stop signals and particularly refractory to devaluation processes even when

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frankly unwanted or harmful. Affected people get trapped in repetitious, self-defeating behaviors, clearly standing beyond the pleasure principle.

Experience-triggered neuroadaptive changes involve use-dependent remodeling of neuronal connectivity in specific brain areas. In this respect, long-term potentiation (LTP) is a form of synaptic plasticity in which hyperstimulation connects neurons by making synapses more responsive to future activation (Bliss and Collingridge, 1993), and is a major candidate for representing both implicit, unconscious memory and the neural correlate of phobias, compulsions, and addictions. According to the classical Pavlovian conditioning, in fact, if the activity of cell A is part of the representation of a neutral stimulus (for example 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. Due to this kind of associations, phobic patients perceive danger in situations that are not dangerous, obsessive patients repeat habitual acts in apparently neutral situations, addicted individuals take drugs despite efforts to abstain.

Basic research into the mechanisms of LTP and its role in physiological and pathological conditions proposed that this synaptic phenomenon has important functional roles in many brain areas and under many circumstances. LTP, however, must be considered as only one of the repertoire of synaptic plasticity mechanisms that contribute to neural circuit remodeling following experience, so that LTP induction in a given brain area should not be viewed as the only neural response to a given physiological or pathological stimulus, but rather as a phenomenon which concurs with other forms of synaptic plasticity, in the same or in other brain structures, to retain information. It is generally accepted, however, that specific experiences preferentially trigger synaptic changes in specific areas (Maleanka, 2003).

**LTP and compulsion to repeat in OCD**

A pathology of habit-forming systems seems to underlie OCD and tic disorders (Calabresi et al., 1997; Graybiel and Rauch, 2000; Leckman and Riddle, 2001). Habits are adaptive, nearly automated behaviors encoded as implicit motor memories in the cortico-basal ganglia circuits. Habit learning is characterized by the progressively smoother execution of a particular action or behavioral sequence in response to specific sensory cues. The incremental learning of implicit associations is also a feature of habit acquisition (Knowlton et al., 1996). Use-dependent changes in the efficacy of corticostriatal transmission are believed to underlie motor learning and habit formation (Calabresi et al., 1997; Jog et al., 1999), and are thought to be excessively facilitated in some psychiatric disorders (Canales and Graybiel, 2000; Graybiel and Rauch, 2000; Leckman and Riddle, 2000). This facilitation might explain the compulsive nature of tics and obsessions, but also of bulimia, gambling, kleptomania, trichotillomania (compulsive hair-pulling), and other impulse-control and intermittent explosive disorders (Helmut, 2001; Holden, 2001). Compulsions and several other forms of pathological stereotypies, therefore, may be seen as the repetitive execution of habitual acts triggered by abnormally represented perceptual cues.

**LTP and compulsion to repeat in drug addiction**

A pathological usurpation of the neuronal mechanisms involved in the reinforcement of rewarding behaviors is believed to underlie drug addiction (Berke and Hyman, 2000; Nestler, 2001). In this perspective, addiction reflects the control of behavior by pharmacological actions on brain circuitry that serves basic biological needs, such as feeding and sexual interaction. Dopamine-dependent neuronal adaptations are critical for retaining implicit information about reward-predicting environmental stimuli, and, consequently, to direct behavior toward homeostatic responses (Schultz, 2002). During reward-predicting associative learning processes, the activation of the dopamine system drives synaptic plasticity in the so-called “reward circuitry,” which includes midbrain dopamine neurons themselves and several brain structures receiving dopamine-releasing axon terminals. Interestingly, while the full diversity of pharmacological effects is mediated by multiple neurotransmitters acting in multiple brain regions, addictive drugs share the common property of increasing dopamine concentrations in the reward circuitry, thereby mimicking (or potentiating) the physiological response of dopamine neurons during reward-based implicit learning processes (Nestler, 2001; Schultz, 2002). Addictive drugs, therefore, abuse the molecular mechanisms of associative learning and reward (Berke and Hyman, 2000), and induce long-term changes in synaptic effectiveness in critical brain areas (Dani et al., 2001; Thomas et al., 2001; Ungless et al., 2001; Saal et al., 2003). Thus, compulsive drug-seeking and drug-taking behaviors result from the consolidation of maladaptive memories in the form of homeostatic information.

**LTP and compulsion to repeat in panic disorder**

Abnormal fear conditioning is thought to underlie panic disorder, phobias and anxiety. Fear conditioning is a form of implicit associative learning in which emotionally neutral stimuli acquire the capacity to elicit defensive responses after association with an aversive event. During fear conditioning, the information from both neutral (conditioned) stimulus and aversive (unconditioned) stimulus converge in the lateral amygdala, where association between the two stimuli is formed and stored (Maren, 2001). Once the connection has been established, arousal, freezing, startle reaction, and avoidance behavior follow the presentation of innocuous stimuli that have the property of anticipating environmental threats. There is strong evidence that LTP in the lateral amygdala encodes fear memory, as both fear conditioning and LTP lead to the emergence of behavioral fear responses (Rogan et al., 1997); are sensitive to the same stimulus contingencies (Bauer et al., 2001); and fear conditioning occludes the subsequent induction of LTP at cortico-amygdala synapses (Tsvetkov et al., 2002). Anxiety, panic disorder and phobias can be viewed as disorders of fear conditioning, characterized by uncontrolled and repetitive activation of defensive reactions secondary
Evidence that LTP-like phenomena underlie psychiatric disorders in humans

Experimental data in patients seem to confirm the idea that unregulated excitation of specific neuronal aggregates plays a role in many psychiatric conditions (Silbersweig et al., 1995; Greenberg et al., 2000; Wasserman et al., 2001; Shaw et al., 2002). Such a focal brain hyperexcitability has been correlated with the occurrence of regional LTP-like phenomena on the basis of the beneficial effects reported with slow (\(<1\) Hz) repetitive transcranial magnetic stimulation (rTMS) in posttraumatic stress disorder (Grisaru et al., 1998; McCann et al., 1998), OCD (Alonso et al., 2001), depression (Klein et al., 1999), and auditory hallucinations (Hoffman et al., 2000; Schoenfeldt-Lecuona et al., 2001). Accordingly, reversal of LTP is generally believed to underlie the therapeutic effects of slow rTMS in human pathology (Hoffman and Cavus, 2002). There are, in fact, many parallels between the slow rTMS administered to humans as a therapeutic tool and the low-frequency stimulation protocol used to induce synaptic depotentiation in rodents (Stäubli and Scafidi, 1999; Picconii et al., 2003) and also in humans (Chen et al., 1996). Interestingly, synaptic depotentiation consists in the possibility to reverse a previously induced LTP by a low-frequency stimulation paradigm, which is unable, however, to inhibit non-potentiated synapses (Stäubli and Scafidi, 1999; Picconii et al., 2003). It follows, therefore, that those psychiatric conditions responsive to rTMS should rely on aberrant expression of LTP in critical brain areas.

Freud’s anticipation of LTP-memory connection theory

Thanks to the practice of psychoanalysis, Freud grasped very soon the salience of memory processes for the formation of the conscious and unconscious part of the ego and for the genesis of neurotic symptoms. This explains his early interest in the neural bases of memory and his attempt to elaborate in 1895 a model of memory formation based upon the sensational discoveries of Camillo Golgi and Ramon y Cajal on the histological organization of the nervous system. In 1873, Golgi had perfected a method of coloration of nervous tissue that allowed for a microscopic visualization of single neurons, with the cell body and its principal processes, the dendrites and axon. Cajal demonstrated that the nervous system is composed of distinct cell types, which are morphologically polarized and are connected in a specific way to the other neurons. Ramon y Cajal’s first important histological study of the theory of the neuron was published in 1892, and certainly drew the attention of the young Freud (Ramon y Cajal, 1892).

In 1895, in a book entitled Project for a Scientific Psychology, Freud made a clear reference to these modern theories in the attempt to build a scientific theory of mind functioning. He declared:“An essential element of this new knowledge is that the nervous system consists of distinct neurons, which are in contact with each other by means of an extraneous substance, and one terminates in the other as in parts of extraneous tissue, in which certain lines of conduction are predetermined, inasmuch as they receive [excitation] through the continuation of the cells [or dendrites] and replace [it] through the axon” (Freud, 1895a). Most notably, in his Project Freud theorized about the possibility of representing memory at the synaptic level as “a permanent alteration following an event” (Freud, 1895a), almost a century before the description of LTP. Accordingly, in chapter 3 of this book, Freud wrote: “We assume that these neurons are permanently altered by the flux of excitation; or rather, if we introduce the contact barrier theory, that their contact barriers are in a state of

To unconscious, dysfunctional associative memory storage (Maren, 2001).
permanent alteration... this alteration must depend on the fact that the contact barriers become more capable of conduction and less impermeable. ... We shall describe this situation of the contact barriers as their degree of facilitation. We may therefore state that memory is represented by facilitations that exist between the neurons” (Freud, 1895a).

Strong synaptic stimulation was proposed by Freud as the essential requirement for the generation of synaptic potentiation. Accordingly, Freud singled out the factor that makes the induction of synaptic facilitation possible in a "quantity" that he defined as $Q\eta$, which "passes through the neuron during the process of excitation... The higher the $Q\eta$ during the course of excitation, the greater the facilitation" (Freud, 1895a).

Although formulated half a century earlier, the description of LTP contained in the Project is not far from the one supplied in 1949 by Donald Hebb, who is also to be credited for identifying the importance of spike timing of pre- and postsynaptic neurons for synaptic potentiation (Sejnowski, 1999). He wrote: "when an axon of cell A is near enough to excite cell B repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased" (Hebb, 1949).

Freud, in any case, not only anticipated LTP and its correlation to memory, but described with precision basic properties of this synaptic phenomenon, such as the input specificity of the potentiation. This term describes the fact that facilitation of the synaptic transmission is only established on that specific synapse activated by the conditioning stimulus (Bliss and Collingridge, 1993). Freud stated: "It is necessary for every neuron to have several connection paths with other neurons, that is, various contact barriers. ... It is therefore clear that the facilitation situation of every contact barrier must be independent from that of all the others that are part of the same neuron” (Freud, 1895a). And also: "If we assume that all the contact barriers have facilitations of equal degrees or, what is the same, offered equal resistance, the characteristics of memory would not result evident. ... Therefore it would be more correct to say that memory is represented by the differences of facilitations existing among the neurons” (Freud, 1895a). In Freud’s thoughts, therefore, one specific neuronal group in a network, or even the same postsynaptic neuron, must be capable of accurately selecting the synapses to potentiate in response to the appropriate stimulation, and this capability is critical for memory storage. This concept is in line with the recent evidence that information is better stored and retained when there is a variable degree of permeability among synapses existing in a given neuronal network (Hancock et al., 1991).

Concluding remarks

From the letters to Wilhelm Fliess, we know that Sigmund Freud wrote the Project in an attempt to provide neurobiological bases to psychological functions. His initial enthusiasm, however, soon turned into frustration, so that he decided not to finish the book and even wanted his manuscript to be destroyed. This explains why this book was unpublished until 1950, when the ideas of Hebb (1949) on synaptic plasticity already had a certain diffusion. Although Freud’s main interests in the following years turned to the investigation of unconscious processes, he never revised his original intuition that the capability to undergo plastic modifications is a fundamental property of the nervous system. On the contrary, this idea proved essential for explaining the functioning of the unconscious and the formation of psychic symptoms. The link existing between unconscious and use-dependent brain plasticity is again affirmed in 1920 in Beyond the Pleasure Principle, where Freud proposed a neurophysiological explanation of unconscious memory processes and their role in psychic determinism. Similarly to what he had suggested 25 years earlier, Freud wrote "It can hypothesized that in its passage from one element to another, excitation must overcome a resistance, and that this decrease in resistance indeed produces a permanent trace of excitation (that is, it produces a facilitation). ... We can assign excitations "traumatic" that come from the outside and are strong enough to penetrate the protective shield “ (Freud, 1920).

In the same book, Freud further stated: “The deficiencies in our description would probably vanish if we were already in a position to replace the psychological terms with physiological or chemical ones. ... We may expect [physiology and chemistry] to give the most surprising information and we cannot guess what answers it will return in a few dozen years of questions we have put to it. They may be of a kind that will blow away the whole of our artificial structure of hypothesis” (Freud, 1920). More than 80 years later, many answers have emerged from the scientific study of how the human brain works, but indeed they did not blow away Freud’s structure of hypothesis.

REFERENCES


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