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Synaptic Plasticity: The Role of Learning and Unlearning in Addiction and Beyond

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> Love is so short, forgetting is so long.
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> Pablo Neruda, *Twenty Love Poems and a Song of Despair* (1)

Our ability to remember and our ability to forget–and the precarious balance between these opposing forces–reflects the essence of what makes us human. Why is it that some memories are so easily forgotten while others persist and even haunt us?

Long before modern neuroscience, even before the concept of neurons or cells, the Greek philosopher Plato described the brain as "a wax block, that may vary in size, cleanliness, and consistency in different individuals" (2). individuals with softer wax could learn quickly but memories were easily erased, whereas those with harder wax learned slowly but also had a more difficult time erasing memories. Today, the vernacular we use to describe changes occurring in the brain during learning and memory are not that different.

Both in scientific writing and in the media, it has become commonplace to refer to the brain as "plastic." The term has been applied to a number of diverse neurologic and psychiatric phenomena, anywhere from explaining the effects of meditation on the brain, to describing the neural changes that take place when a person falls in love. Yet, whereas Plato used "wax" metaphorically, nowadays when we say the brain is plastic we are referring to actual processes occurring in neurons. At its most basic level, plasticity refers to the ability of the brain to physically change. Although this may sound trivial today, the idea is relatively new from a historical perspective and did not come into common use until around the 1950s. Before then, the brain was thought to be completely formed–and static–by the time we reached adolescence.

Today we know that the capacity of the brain to physically change throughout our lifetime is the basis of all adaptation, learning, and memory. Every time we read something new and remember it, our brain is physically changing. Whereas large-scale changes such as the growth of new neurons or dendrites can occur (e.g., as seen in the rewiring of the brain after a stroke), these types of changes are relatively rare. In contrast, minute-to-minute changes

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are continuously happening at the level of microscale connections between neurons. These changes in neuronal connections are the primary mechanism for learning and memory and are known as “synaptic plasticity.”

The idea of synaptic plasticity first emerged in 1894. Based on the belief that the number of neurons in the brain remained stable throughout life, the Spanish neuroanatomist Santiago Ramon y Cajal proposed that memories must therefore be formed by the strengthening of existing neuronal connections (3). The psychologist Donald Hebb later elaborated on this idea, suggesting that perhaps neurons that “fire together, wire together,” which is to say that if two cells consistently fire at the same time, then the strength of the connection between them will grow stronger (4). (This model is often referred to as Hebbian learning.)

It was not until 1970 when elegant experiments by Eric Kandel’s group first established a clear connection between the physical changes that occur at individual synapses and behavioral evidence of learning and memory (5). Studying *Aplysia californica*, a giant sea slug, they showed that as the animal learned to withdraw its gills to noxious stimuli, the strength of the synapses (as measured by electrophysiology) involved in this process became stronger. Conversely, as the *Aplysia* became desensitized to an innocuous stimulus, those same synapses became weaker. In 1973, evidence for a similar type of “activity-dependent” strengthening of synapses was discovered in mammals and referred to as long-term potentiation (LTP) (6). A key question remained: what molecular processes enabled this increase to occur?

A critical finding came from studying the interplay of two postsynaptic receptors: α-amino-3-hydroxy-5-methyl-4-isoxazo-lepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) (7). Both receptors are activated by glutamate. However, whereas the AMPA receptor is a simple ionotropic channel, the NMDA receptor has a unique feature: when the cell is at resting potential, the channel is blocked by a magnesium ion that prevents it from opening. Only when the cell is slightly depolarized–as can happen with co-occurring AMPA activation–is the magnesium ion displaced, thereby allowing the channel to open. This NMDA receptor activation triggers a complex signaling cascade, beginning with the influx of calcium, that leads to the eventual incorporation of more AMPA receptors in the postsynaptic membrane (Figure 1). This increase in AMPA receptors increases the size of the excitatory current, so that next time that synapse is activated, the postsynaptic neuron will be more likely to fire. Working in tandem, AMPA and NMDA receptors offer a direct mechanism by which Hebbian learning can occur and demonstrate how cofiring of neurons can lead to an increase in the strength of the synapse.

It is now recognized that there are many forms of LTP and also of its reverse process, long-term depression (LTD), each of which relies on different neurotransmitters (e.g., glutamate, gamma-aminobutyric acid, glycine, cannabinoids), different postsynaptic receptors (e.g., NMDA, AMPA, metabotropic glutamate receptor 2), and different secondary messengers (e.g., Ca++, Ca++/calmodulin-dependent protein kinase II, cyclic adenosine monophosphate). A feature central to nearly all forms of synaptic plasticity is the eventual incorporation or removal of postsynaptic receptors. The more receptors incorporated at the membrane, the stronger the synapse and vice versa. Moreover, LTP and LTD occur at nearly

every synapse and neural circuit in the cortex, and they are important for more than just learning and memory.

One especially important area of focus has been on understanding the role of LTP and LTD in the process of drug addiction. Addiction has been identified as a public health crisis with 21.5 million Americans (8.1%) meeting criteria for a substance use disorder in 2014 (8). Although effective treatment approaches exist, relapse rates remain extremely high, even among individuals who are committed to sobriety. Studies estimate that as many as 40% to 60% of patients discharged from treatment subsequently relapse within a year (9). In many ways, addiction may be seen as an archetypal example of aberrant learning: associations formed during the course of drug use are extremely strong and remain in the brain for many years (despite the benefit that would come from forgetting these associations). In fact, vulnerability to cue-induced drug craving for some drugs actually increases over time even after prolonged periods of abstinence (10).

The article by Scheyer *et al.* (10) in this issue of *Biological Psychiatry* highlights these exact principles and the important role of plasticity in addiction and cue-induced craving and drug relapse. The investigators demonstrate that at the basic molecular level, changes in plasticity drive cue-induced craving. They show that AMPA receptor–mediated LTP in the nucleus accumbens (often reductively described in the lay media as “the pleasure center” of the brain) is central to long-lasting cravings and relapse in rodents who have become addicted to methamphetamine. What is even more exciting about this work is that the investigators demonstrate that it is possible to reverse this process. By inducing long-term depression in the nucleus accumbens using a synthetic molecule (SYN119), they are able to eliminate cue-induced cravings in these rodents.

These results add to the growing literature on plasticity, they underscore the importance of this process in addiction, and they give hope to patients struggling with recovery. For example, one imagines a future in which an individual recovering from substance dependence might be able to take a medication such as SYN119 to reduce his or her cue-induced drug cravings and thereby prevent relapse. More importantly, the study highlights the possibility of focusing on LTP and LTD as potential targets for novel therapeutic interventions in treating psychiatric conditions.

It is clear that synaptic plasticity is central to all behavioral modification–from the way we form our earliest attachments to the process of habit formation. We are constantly responding to the world around us by tuning up and down synapses, and this leads to the question of what role this process may play in psychiatric illnesses. There are many ways in which this process can go awry, with individuals struggling either to learn or unlearn critical information or behaviors. Perhaps lessons learned here will have implications for other psychiatric syndromes such as posttraumatic stress disorder and obsessive compulsive disorder that may also reflect difficulty in unlearning or overlearning.

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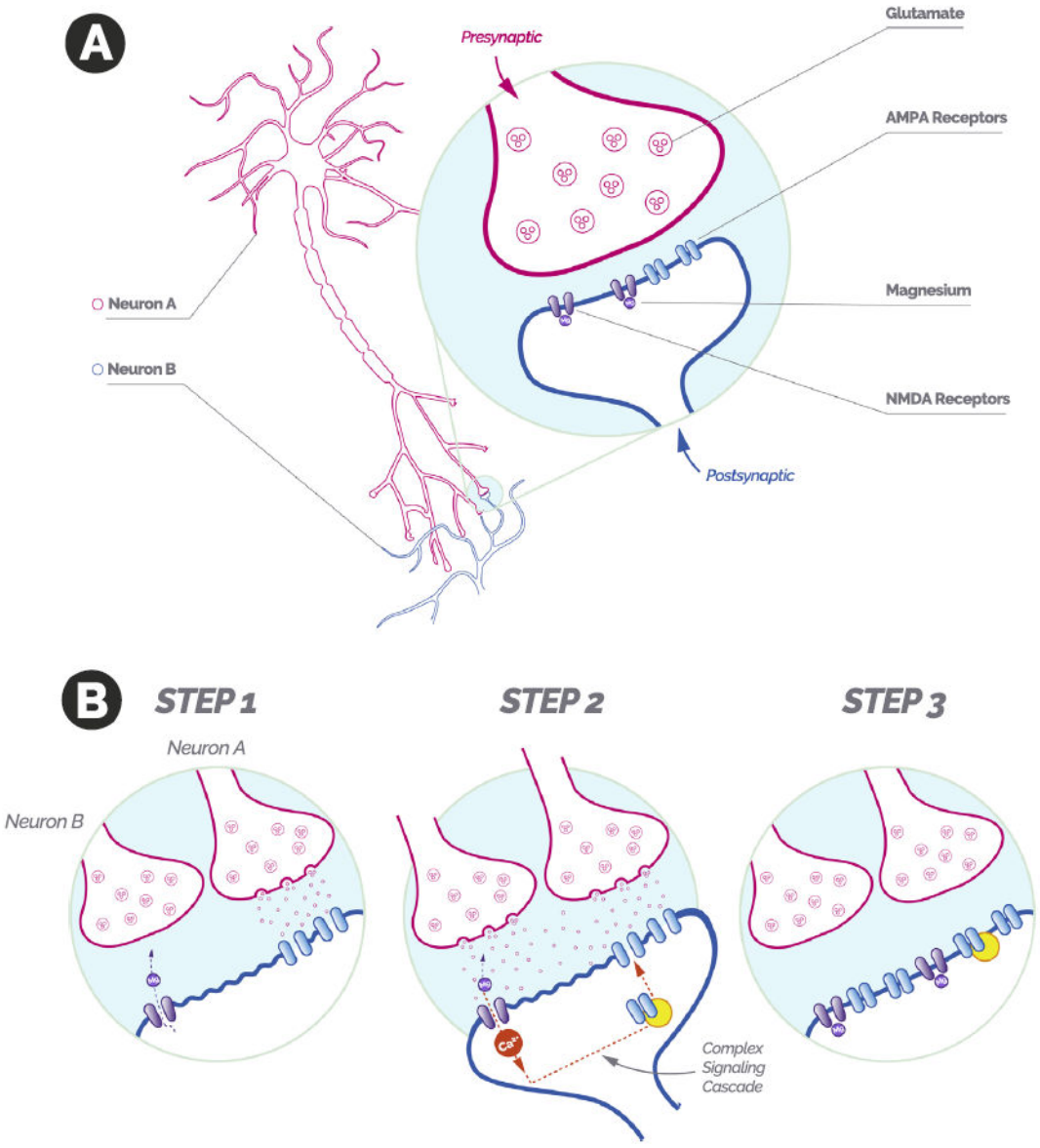

Figure 1.

(A) Anatomy of a synapse: axons from neuron A connect to dendrites from neuron B at microscopic connections called a synapse, shown magnified at right. Components of the presynaptic bouton (red) include neurotransmitter glutamate packaged into vesicles. The postsynaptic membrane (blue) has both α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors. **(B)** Long-term potentiation. Step 1: neuron A fires and releases glutamate, which then opens AMPA receptors, depolarizing the postsynaptic membrane. Magnesium is repulsed from NMDA receptors, priming them for activation. Step 2: neuron B fires and releases glutamate, which then opens NMDA receptors allowing calcium to enter the postsynaptic neuron. Calcium leads to a complex signaling cascade and the eventual incorporation of more AMPA receptors at the

postsynaptic membrane. Step 3: with more AMPA receptors at the postsynaptic membrane, the synapse is potentiated. Next time neuron B fires, the response at the postsynaptic membrane will be stronger.