DURABLE LEARNING SEMINAR SERIES

The Neuroscience of Learning

A Supplemental Resource for Medical Educators

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An overview of major brain neurotransmitters, brain-derived neurotrophic factor, and other important components that impact learning and memory

Section 1

Neurotransmitters and Their Effects on Learning

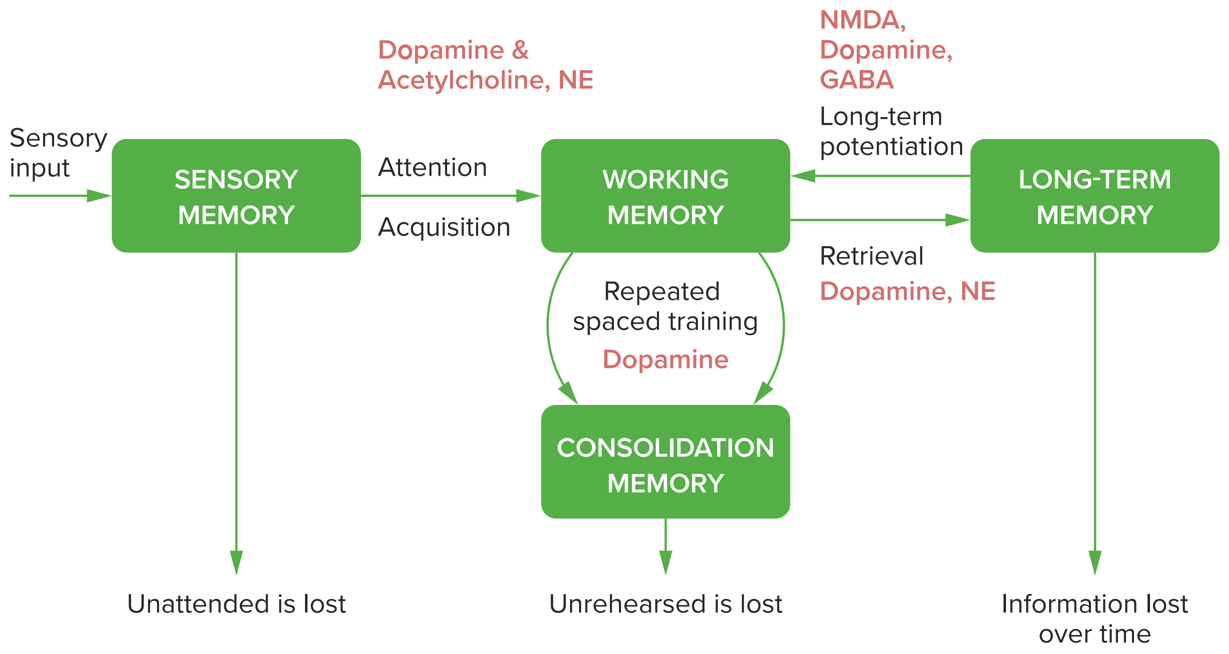

Figure 1. The relationship between neurotransmitters and memory processes* (1)
*NE: Norepinephrine; NMDA: N-methyl-D-aspartate; GABA: Gamma-aminobutyric acid

Which brain neurotransmitters are relevant to learning?

The literature is still evolving at this point, but five general neurotransmitters (NTs) are considered to play a significant role in learning. These include **acetylcholine (ACh)**, **dopamine (DA)**, **norepinephrine (NE)**, **gamma-aminobutyric acid (GABA)**, and **N-methyl-D-aspartate (NMDA)** and **Glutamate**.(1) There are other neurotransmitters that are also relevant for learning, but they will not be discussed in this document.

What are the major actions of these neurotransmitters on learning and memory?

Acetylcholine (cholinergic system)

This neurotransmitter originates mainly from the basal forebrain and the mesopontine tegmentum of the brain.[2] Involving both nicotinic and muscarinic receptors, ACh augments the encoding of memories in response to sensory stimuli and has been shown to converge with the dopaminergic system to affect the neocortex and hippocampus in modulating learning and memory.[1] The absence of either ACh or DA led to impairment in working memory tasks in animal studies. [1]

Dopamine (dopaminergic system)

DA is produced in the ventral tegmental area (VTA) and is received by the nucleus accumbens and prefrontal cortex. Commonly known as a precursor to NE, DA also acts as an NT in some parts of the brain. DA is essential for retrieving information from long-term memory, to consolidate acquired short-term memory, and is related to motivation and declarative memory concerned with reward.[1,3] DA often correlates with ACh in promoting learning and has a role in forgetting through the signaling of DAMB, a dopamine receptor.[1] As a result of unexpected rewards, levels of DA increase which can augment synaptic plasticity.[4] This transient increase of DA produces a pleasurable sensation, which can positively influence motivation.[5]

Norepinephrine

Originating in the VTA and locus coeruleus, NE is produced together and works incredibly closely with DA to affect learning.[6] NE affects memory in that it is associated with stronger emotions and is also implicated in reward learning.[6,7] In animal studies, high levels of stress (which increases NE levels) led to higher anxiety, shorter attention spans, lower concentration, and reduced focused performance, but moderate levels of stress facilitated behavioral performance accuracy (see Figure 2).[8,9]

GABA (gabaergic system)

GABA, an amino acid occurring mainly in the CNS, is ubiquitous and is produced in the presynaptic neurons in the body from its precursor, glutamate.[10] In the Central Nervous System (CNS), GABA serves as the primary inhibitory neurotransmitter.[1,10] GABA plays a role in long-term memory creation through the long-term potentiation (LTP) process, supports the development of conditioned inhibition, and contributes to the regulation of vigilance and anxiety.[11,12] In some animal and human studies, higher levels of baseline GABA in the hippocampus have been associated with stronger retrieval performance, whereas very high levels of GABA are often associated with impaired memory performance.[11] Sleep deprivation in mice brains has been shown to cause increased levels of GABA [13]. Balanced GABA and glutamate levels in the brain can thus be inferred to be required for the optimal performance of memory consolidation, acquisition, and potentiation.

NMDA and glutamate

(glutamatergic pathways)

NMDA is an amino acid that acts on the NMDA receptor and mimics the effects of glutamate, one of the main excitatory NTs in the brain.[1] Its receptors are among the most well-researched receptors in the brain, and it is closely associated with the role of GABA in LTP in the hippocampus, amygdala, and medial septum. NMDA also contributes to the general formation of long-term memories.[14,15] Furthermore, NMDA has been shown to have an effect on different kinds of learning and memory, such as spatial learning, working and reference memory, and reversal learning.[15] Commonly implicated in the fields of psychiatry and neurology for the treatment of neurodegenerative diseases, memory impairments, and depression, NMDA receptors (and by extension NMDA and glutamate) are affected by acute and chronic stress.[16] Acute stress causes an increase in glutamate and leads to excitotoxicity and atrophy of neurons in the medial prefrontal cortex and hippocampus.[16]

Key takeaways

In medical education, knowledge of NT can be relevant in multiple ways. The main recommendation for educators is to create a favorable learning environment by ensuring that positive conditions conducive to dopamine and acetylcholine production are maintained and that high-stress environments that promote NT imbalances are kept to a minimum so that they do not extend past their usefulness. Considering the body of evidence linking sleep deprivation to learning difficulties (see below), medical educators should also strive to avoid a culture of excessive work overload and consequent sleep inadequacy in their learning institutions in order to optimize learning.

Section 2

Stress and Its Effects on Learning

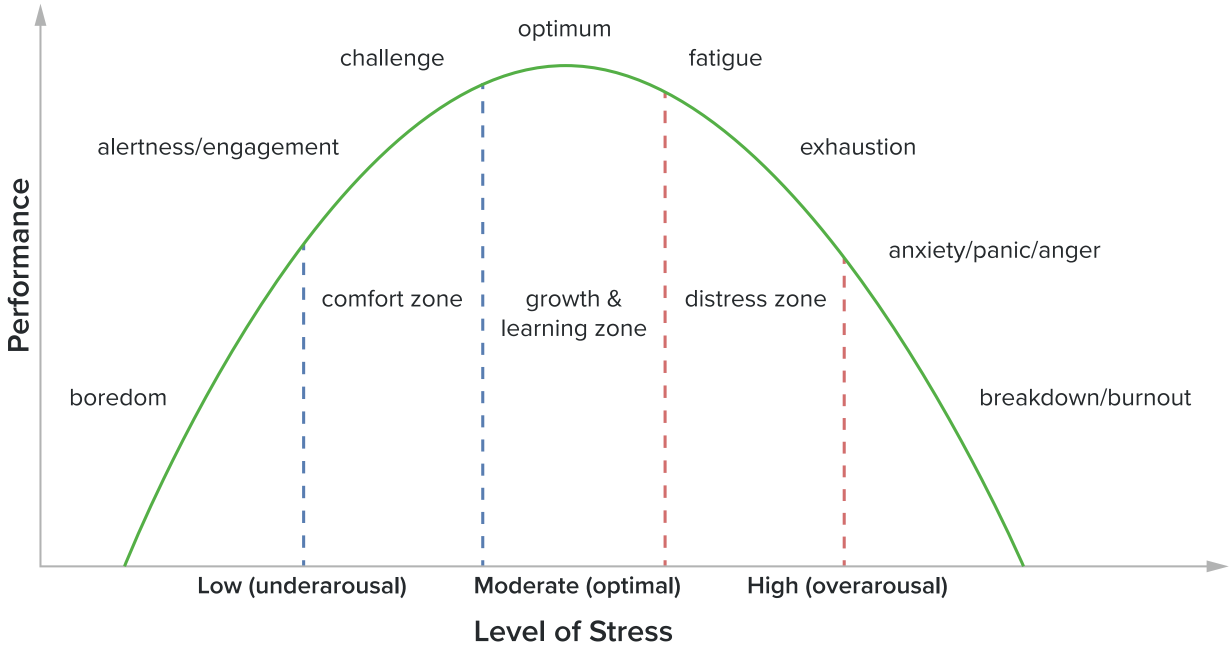

Figure 2. Graphical representation of the Yerkes-Dodson Law (17)

What is stress, and how does it affect the brain?

Stress is an umbrella term that describes a force contrary to the body's homeostasis, which can be psychological or biological in nature.[18,19] Understanding the effect of stress on the brain and, by extension, on learning and memory can be challenging, considering its multiple, seemingly opposite effects that have been documented.[18] Stress, both acute and chronic, leads to alterations of neurotransmitter and hormonal levels in the body. This may, in turn, lead to structural changes in the brain that predispose one to different states of learning and performance.[8,9,16,18] Biological changes that result from unchecked stress include the reduction of brain-derived neurotrophic factor (BDNF) expression (proved in animal studies),[20] atrophy of neurons in the medial Prefrontal Cortex and hippocampus due to glutamate excitotoxicity,[16] and NT imbalances that may in turn also lead to structural alteration and suboptimal performance in learning.[8,9,16,18] Some research has also shown that timing matters when it comes to stress.

What do medical students perceive as stress?

A plethora of things may be perceived as stress by medical students. Stress is not limited to things that can be controlled within a classroom or practical environment, but includes personal stressors in a student's life. This may be why the commonly held Yerkes-Dodson theory of optimal stress, or the inverted-U theory, has been shown by research to be a poor prediction model in medical education.[21] An interesting study reviewing the experiences of students and educators in an OB-GYN rotation identified several main stressors perceived by students. These included the context of the rotation (e.g., the working pace, logistical realities, the sensitive nature of certain procedures, and unpredictability of the field), communication in the rotation (e.g., unfamiliar terminology and difficulty in communicating with the team), clinical scenarios (e.g., crisis and emergency situations in the rotation and patients refusing medical student participation).[22] A more general study evaluated the stressors of millennial medical students through a combination of quantitative and qualitative means.[23] Quantitatively, commonly stated stressors such as high workload, time management, peer relations, work–life balance, and health and financial concerns were confirmed by the results of the study, variations related to the participants' year in medical school and their gender.[(23)] Qualitatively, common themes were identified: the workload level, pressure to succeed, administrative and personnel issues, time management and work-life balance, negative peer and social relationships, the negative impact on health of the demands of medical school, career planning, and financial concerns.[(23)]

How can stress be optimally used in teaching?

Several lines of research have made it clear that a certain amount of stress is not only tolerable but also beneficial for learning. One of the more popular ones is that of desirable difficulty, suggested by Robert B. Björk in 1994, according to which an appropriate level of difficulty is desirable because it potentiates encoding and retrieval that is conducive to learning.[(24,25)] The level of desirability varies according to the level of knowledge of the learner: When learning occurs without sufficient background knowledge and background skill to solve the presented problem, difficulty becomes undesirable and no longer potentiates learning.[(25)] Another relevant theory is the Yerkes-Dodson Law, developed by Robert M. Yerkes and John D. Dodson, which illustrates the relationship between pressure and performance and postulates that, after a certain point, extreme pressure reduces performance.[(26)] In animal studies, this law has been corroborated to some extent through observation of animals' performance and behavior when simulated with too high a concentration of stress-related NTs such as NE.[(8,9)] As mentioned, the Yerkes-Dodson Law itself may not be directly applicable as a prediction model for the behavior of medical students or clinicians when confronted with stress;[(21)] however, we still believe that it could still be adopted as a rule of thumb regarding medical education.

There are many ways through which we can apply the beneficial effects of stress in learning, including science-based learning techniques such as interleaving.[(27)] Interleaving is the act of mixing different but related concepts together when learning. It imparts desirable difficulty in the form of contextual interference, through the postulated forgetting reconstruction mechanism (switching to different tasks induced forgetting, and when subsequent sessions include the same knowledge, this knowledge is then rebuilt) and the elaborative-distinctive mechanism (learning multiple things at once allows the students to compare and contrast the knowledge and create a stronger memory representation).[(28,29)] Other strategies that have been proved to work include spaced retrieval, spaced learning, and elaboration.[(30)]

Key takeaways

Stress in medical education is more often than not an avoidable reality considering the high-stakes nature of the field and the density of information that a medical student needs to master. However, reiterating the point made in the previous section, there is such a thing as an environment conducive to studying. In relation to stress, this means maintaining or fostering an optimal frequency or degree of stress exposure that is useful for learning. Echoing a conclusion from a review paper summarizing evidence on the effect of stress on neural activity: "Average is good, extremes are bad."[(31)] Too little stress understimulates students, while too much stress creates burnout and poor knowledge transfer.

Considering these points, we recommend treading the middle ground through the use of evidence-based techniques that impart desirable difficulty and stress in a way that has been consistently proved to work. Please see the final page of this document for relevant past references we have created on this topic.

Section 3

BDNF and its Effect on Learning

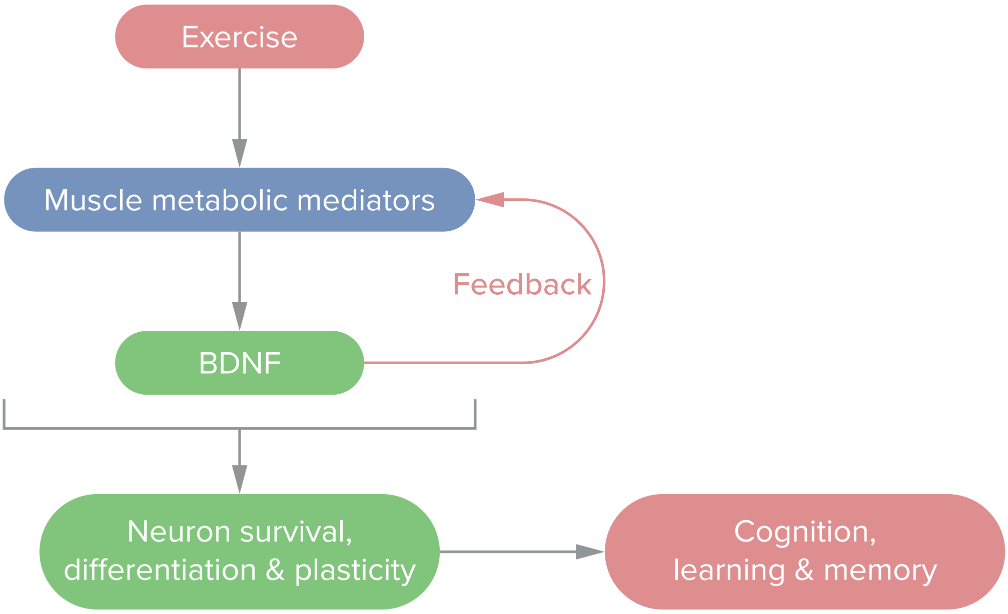

Figure 3. The impact of exercise on BDNF's role in learning (14)

What is BDNF, and how is it related to learning?

BDNF is a protein that is known to be foundational for neuron survival and development, as well as an essential element for neural plasticity.[32,33] LTP is associated with stronger synaptic connections, which lead to improved synaptic transmission of neuronal links. BDNF appears to be one of the essential components of the molecular mechanisms responsible for this synaptic plasticity.[33] This is thought to be a way that the brain creates morphological changes associated with learning and memory. BDNF, a type of neurotrophic growth factor, is involved in multiple intracellular signaling pathways and is thought to be released primarily by stimulated neurons and possibly endothelial cells in the cerebrum.[34,35] There is evidence that BDNF modifies synaptic transmission in the hippocampus and neocortex.[33,36] BDNF protein expression is believed to be part of the mechanism that leads to dendritic spine formation associated with establishment of neural networks.[37] Myelination of brain neurons is critically important to neural transmission, adjusting the speed at which nerve impulses arrive at synapses and thus coordinating neural link communication in different areas of the brain.[38] There is significant evidence that BDNF is a key molecule involved in the myelination process in the CNS, although a precise understanding of the underlying cellular and molecular signaling is not yet clear.[39,40] Learning strategies such as retrieval are hypothesized to be important events behind the changes in synaptic connections that lead to the establishment of long-term retention.[34] More research is needed to elucidate the exact mechanism of BDNF's effects on LTP, myelination, and learning.[40]

What is the relationship between BDNF and exercise?

Exercise has been shown to have multiple cognitive benefits, and there is evidence that BDNF from exercise is involved in hippocampal neurogenesis.[41,42] In addition, exercise has been shown to increase dendritic spine formation, which can enhance stronger neural connections associated with learning and memory.[43] Even a modest amount of aerobic exercise has been shown to increase BDNF levels in the brain.[44] Endurance exercise has been found to increase levels of muscle proteins and metabolic mediators that resulted in elevated levels of BDNF in the hippocampi of mice.[45] In human studies, physical exercise increased BDNF levels in the brains of elderly people with depression, adding to the extensive list of the benefits of exercise to the brain.[46]

What is the relationship between BDNF and sleep?

Researchers found decreased dendritic spine formation and decreased levels of BDNF in the hippocampi of rats placed under chronically stressful conditions.[20] The interplay between sleep, learning, and memory has not been clearly defined, but the research suggests that a sleep-deprived person cannot focus attention and therefore has a diminished ability to learn.[47] Moreover, it is known that sleep plays an important role in the generation of new dendritic spines[48] and the selectively pruning of other synapses[49], both of which are essential in the consolidation process of neural connections.[50] Because sleep plays such an essential role in consolidation, utilizing learning strategies such as spacing enhances learning.[51] Sleep deprivation is shown to decrease BDNF levels, but its specific correlation with stress and sleep needs further study.[52]

Key takeaways

Medical educators should encourage their students to learn about BDNF and its effects on creating physical changes to neurons that enhance synaptic plasticity and learning. Exercise increases BDNF levels in the brain, while sleep deprivation and stress decrease BDNF levels. This scientific evidence should be foundational for implementing institution-wide initiatives for establishing norms for sleep and exercise in medical education.

Section 4

Further Resources

- **Online seminar library for medical educators:**
  https://www.lecturio.com/re-envision/online-seminars/
- **Educational webinars for medical students:**
  https://www.lecturio.com/medical/global-student-events-on-demand/
- **Articles:**
  https://www.lecturio.com/pulse/understanding-memory-to-enhance-learning-in-medical-education/
  https://www.lecturio.com/pulse/how-to-apply-evidence-to-tackle-misconceptions-in-medical-education/
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