Medical Xpress

Take your time: Neurobiology sheds light on the superiority of spaced vs. massed learning

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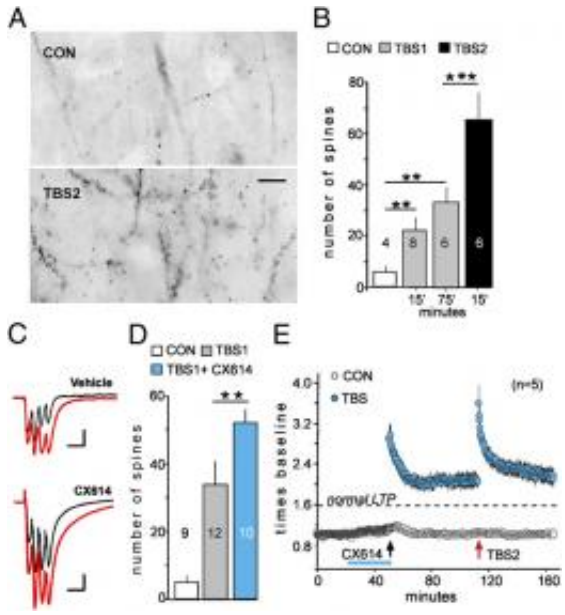

A second theta burst train expands the pool of F-actin-enriched spines. (A) Fluorescent phalloidin labeling in CA1 stratum radiatum. (Scale bar = 10 μm). (B) Counts of densely phalloidin-positive spines in slices collected 15 or 75 min after TBS1 (gray bars) or 15 min after TBS2 delayed by 60 min (black bar). (C) Traces show responses to two successive bursts separated by 200 ms (red for second response). (D) Counts of TBS1-induced phalloidin labeling for vehicle (gray) and CX614-treated (blue) slices. (E) Pretreatment with CX614 (blue line) caused a 70% increase in the magnitude of LTP induced by TBS1; this was accompanied by a loss of TBS2-induced potentiation. Image Copyright © 2012 PNAS, doi: 10.1073/pnas.1120700109

(Medical Xpress) -- College and cramming – often where's there's one, the other is not far behind. That said, however, it has been recognized since the late 1800s that repeated periodic exposure to the same material leads to better retention than does a single en masse session. Nevertheless, the phenomenon's neurobiological processes have remained poorly understood, although activity-dependent synaptic plasticity – notably long-term potentiation (LTP) of glutamatergic transmission – is believed to enable rapid storage of new information. Recently, researchers at the University of California in Irvine and the Scripps Research Institute in Jupiter, Florida determined that hippocampal activity can enhance LTP through theta burst stimulation (TBS) – but only when the affected synapses receive, after a long delay, a secondary TBS. The researchers describe mechanisms that maximize synaptic changes that optimally encode new memory by requiring long delays learning-related TBS activity.

Gavin Rumbaugh (Scripps Research Institute) discussed the challenges he, Gary Lynch (University of California) and their team encountered in the study. "The field is trying to understand the neurobiology of new learning, and in particular, how learning induces an even more complex biology to keep new information in our neural circuits," Rumbaugh tells *Medical Xpress*. "Over the recent decade, it has become clear that plasticity at individual synapses is a way that neural circuits store information. However, it remains unclear how properties of synapses influence key aspects of learning and memory."

The team's study aimed to fill this knowledge gap: They hypothesized that individual synapses have properties that affect a neural network's ability to encode and store new information, and that these properties would be relevant to what we already know about how humans learn best. One such example is spaced versus mass training. "It's clear to anyone who has gone to school that that repetition of information and concepts results in better retention of information," Rumbaugh

illustrates. “This is especially true if the time between repetitions is on the order of days – that is, spaced training. In contrast, the same overall time spent with the information in one bulk cramming session, or mass training, results in poor understanding and retention compared to spaced intervals.” This is why school systems are set up to teach multiple subjects in parallel, with each subject session separated by at least one day, instead of teaching each subject in a massed, linear fashion – for example, 20 days of physics, followed by 20 days of calculus, and so on.

“Our current study demonstrates that the timing of information coming into a memory circuit – specifically, CA1 hippocampus – is critical for optimal encoding of new information,” he continues. “When similar patterns of information are separated by at least an hour – a typical classroom session – there is a dramatically enhanced encoding of this info. The key challenge to realizing this discovery was actually linking electrical properties of the circuit, which is done by physiological recordings, to physical, morphological and anatomical properties of the circuit, which is done by high-resolution imaging of synapses before and after stimulation.”

This ability to combine circuit structure and function allowed the researchers to understand which synapses were potentiated by each round of similar stimulations, and then assess how timing impacted both aspects of information storage. ‘Specifically,” Rumbaugh explains, “we were able to induce information storage – LTP1 – by electrical stimulation and then specifically label the synapses in the circuit that encoded the enhanced transmission arising from the original round of stimulation. When we reactivated the circuit, after waiting at least one hour, we greatly increased information storage in the circuit – LTP2 – as measured in our electrical recordings.” Using the imaging methods mentioned above, the team then found that LTP2 induced changes in synapses neighboring the synapses that originally stored LTP1.

"This clustering of information at neighboring synapses was unexpected," notes Rumbaugh. "To better understand how this information might cluster in a neuron, we exploited a novel technology where we're able to induce information storage at a single synapse of our choosing by stimulating the synapse with a specially-designed near IR laser, and then observing the synapse physically grow using time-lapse multiphoton imaging in a living brain slice. While it's already known that this synapse growth is key to learning, we found that in the adult rodent hippocampus, most synapses are refractory to storing information – but synapses neighboring an already potentiated synapse were much more likely to participate encoding a second bout of similar stimulation patterns."

Therefore, they reasoned, a key feature of learning, spaced training, appears to be a result of properties that exist at individual synapses – so properties of synapses can affect the way networks encode and store information. "This finding has real implications for persons with learning disabilities," Rumbaugh points out, "since these features are of greatest benefit to understanding how learning disabilities arise – especially in neurodevelopmental disorders such as Intellectual Disability, or ID, which was formerly called Mental Retardation. We've realized over the past few years that a common feature of ID is dysfunction of synaptic plasticity in which the neural basis of information encoding is disrupted." Now that the team has found that individual synapses govern the efficacy of learning at the network level, they're confident that they can hypothesize that ID arises from a disruption in still-unknown synaptic processes that govern spaced learning.

"In fact, my laboratory is working on a novel rodent model of ID, and we will certainly apply these principles to this model. For instance," he explains, "we will definitely test the idea that the timing of repeated stimulations in our model of ID is abnormal. Once we understand how

the rules are different in this ID model, we can then determine two things: First, if there exists a different timing that results in optimal information storage – and if so, this could inform special education providers. Second, and perhaps more importantly, we could begin to understand at the molecular level how the timing rules are impaired – that is, what's wrong, at the molecular level, at synapses that prevent them from encoding spaced information. Once these deficient molecular events are understood, we'll be on the path to fixing the molecular perturbation through pharmacological interventions."

Stated another way, they would target this putative broken molecular process with a drug-like chemical compound capable of restoring the normal timing rules of spaced plasticity in a network preparation. If successful, the ultimate goal would be to test the idea that learning disabled patients would improve after application of this hypothetical compound.

Might it be possible to transition to in silico modeling? "Yes, absolutely," Rumbaugh affirms. "Modelers need basic rules to set up a simulation. With these rules, they can then test any number of variables, which could influence a system in interesting ways. Any model of neural network learning should include a rule where each individual unit of storage – a synapse – is unlikely to store information after an initial stimulation. It should also contain a rule," he concludes, "that a similar stimulation of the circuit should result in efficient storage of information by synapses neighboring the original location of storage only if the stimulations are separated by an appropriate time period."

More information: Synaptic evidence for the efficacy of spaced learning, *PNAS* March 12, 2012, Published online before print, doi: 10.1073/pnas.1120700109

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