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Neurobiological mechanisms of state-dependent learning

Jelena Radulovic, Vladimir Jovasevic and Mariah AA Meyer

State-dependent learning (SDL) is a phenomenon relating to information storage and retrieval restricted to discrete states. While extensively studied using psychopharmacological approaches, SDL has not been subjected to rigorous neuroscientific study. Here we present an overview of approaches historically used to induce SDL, and highlight some of the known neurobiological mechanisms, in particular those related to inhibitory neurotransmission and its regulation by microRNAs (miR). We also propose novel cellular and circuit mechanisms as contributing factors. Lastly, we discuss the implications of advancing our knowledge on SDL, both for most fundamental processes of learning and memory as well as for development and maintenance of psychopathology.

Address
Department of Psychiatry and Behavioral Sciences, The Asher Center for Study and Treatment of Depressive Disorders, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA

Corresponding author: Radulovic, Jelena (j-radulovic@northwestern.edu)

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Introduction

SDL is a phenomenon related to information processing wherein information acquired in a certain state requires a similar state for best recall. Because such information cannot be reliably accessed under baseline conditions, SDL is manifested as a memory retrieval deficit, however this deficit can be reversed with techniques that reinstate the conditions that were present at encoding.

The phenomenon of SDL was first demonstrated by Girden and Culler [1••], who noticed that leg flexion conditioned in dogs under curare could only be elicited when the animals were drugged with curare again. However, when the reflex was conditioned in the non drugged state, it disappeared under curare, and reappeared under a non drugged state. They also referred to the phenomenon as 'dissociation of learning' to indicate the separation of memory encoding and recall between the drugged and non-drugged state.

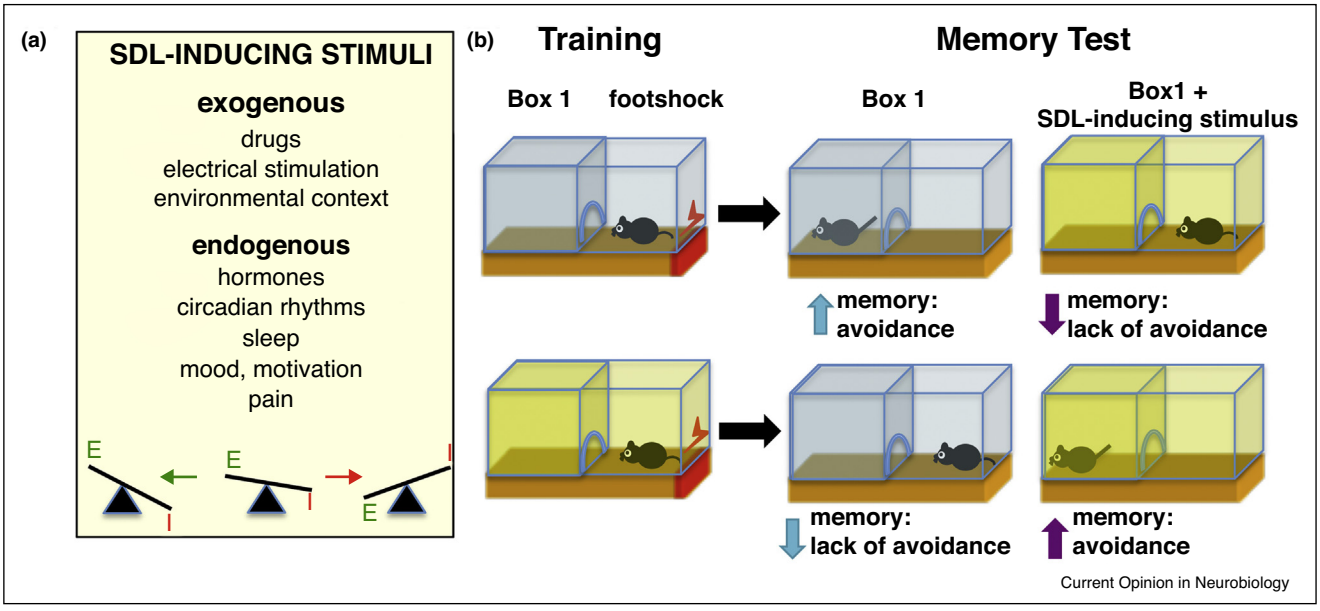
SDL has since been demonstrated in a wide variety of organisms, including invertebrates, goldfish, mice, rats, rabbits, cats, dogs, monkeys, and man [2•,3,4•,5••]. Furthermore, in addition to drugs [6–8], a number of exogenous and endogenous stimuli have proved capable of supporting SDL [9]. These include electrical stimulation (*e.g.*, electroconvulsive seizures, cortical spreading depression) [10,11], hormones [12], mood and motivation [13,14], circadian rhythms [15], sleep [16], pain [17], and environmental contexts [18]. With this in mind, it is reasonable to suppose that as a result of affective states, implicit and explicit motives, and interaction with the environment, all memories are to some degree state-dependent (Figure 1).

To date, SDL has most extensively been studied using drugs, which has led to the identification of many conditions that support SDL, as well as some constraints. Under some drugs such as phentobarbital, dissociation or state-dependency can be complete, meaning that there is no information transfer between the drug and non drug states, however, such transfer can occur among drug-induced states which share similarities [4•]. In animal experiments, recovery of memory has also been found during increased arousal [19], with the presentation of a salient reminder [20], or after overtraining [21]. Examples of recovery in humans can also arise as a result of experimental cueing or prompting [7,8].

State-dependency of learning and memory under various psychoactive drugs has been extensively reported with rodent models of reinforcement learning and passive avoidance [22••,23,24]. However, many of these drugs, such as benzodiazepines, NMDAR antagonists, amphetamine, and scopolamine have, until recently [25••], proved ineffective in fear conditioning [26–29]. The reasons for these task-related differences are not known, but some possibilities will be discussed below.

Extensive research in the 1960s–1980s resulted in an impressive breath but limited depth of our knowledge of SDL both in respect to the definition of a state as well as to the underlying neurobiological mechanisms. The term 'state' has been broadly used to describe a condition of the brain, the mind, or individual as a whole.

Figure 1



Inducing SDL by stimuli that change the excitatory/inhibitory balance. **(a)** Exogenous and endogenous stimuli known to induce SDL. **(b)** SDL in an example of a passive avoidance paradigm, where the presence of memory is reflected by avoidance of the shock compartment at test. Top, memories learned under normal conditions are easily retrieved under similar conditions, but not if SDL-inducing stimuli are applied before the test. Bottom, memories learnt under SDL-inducing stimuli are not accessible for retrieval under normal conditions but can be retrieved if the same stimuli are reapplied. E, excitation; I, inhibition.

Nevertheless, at the most fundamental level it refers to changes of timing and routing of neuronal firing within specific networks [4•]. These changes can alter the processing of distinct stimulus features at encoding [30,31], and possibly the function of neuronal comparators (whose role is to match sensory inputs with encoded information) at retrieval [32]. When it comes to candidate mechanisms of SDL, there are all kinds of possibilities because state-dependency is inherent to every component of neuronal activity, from molecular, cellular, circuit, and global network activity, to consciousness itself [33]. Therefore, determinants of discrete neuronal states will likely be found at all of these levels. This may best be illustrated with the example of sleep, an altered state of information processing, which entails well-defined changes of the balance among key neurotransmitter systems, redistribution of activity within subcortical and cortical circuits, and generation of slow oscillatory rhythms [34•]. Similar levels of analyses applied to SDL are likely to identify the defining features of the various brain states that support the encoding and retrieval of long-term memories.

Molecular mechanisms of SDL

Under normal awake conditions, memory processes predominantly depend on excitatory transmission, in particular *N*-methyl-D-aspartate receptor (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), whose activity somewhat predominates in the overall excitatory/inhibitory balance. However, changes of this balance in either direction can support SDL. For example, cholinergic mechanisms of SDL involve both blocking cholinergic function with scopolamine and increasing cholinergic function with physostigmine [35]. In humans and rodents, SDL is frequently reported with psychostimulants, such as, amphetamine [6], meprobamate [36], cocaine [37], and caffeine [38]. Opiates also support SDL and of all classes of opioid receptors, morphine-activated μ receptors seem to be the most effective [39].

Notwithstanding the above, most of the evidence for SDL comes from activation of GABAergic transmission and shifting the excitatory/inhibitory balance toward inhibition. The ionotropic $GABA_AR$ is a pentamer composed of two α, two β, and one γ or δ subunit. Many drugs bind to $GABA_AR$ and alter its conductance for chloride ions, which regulates the degree of neuronal inhibition. However, drug effects are also unique because they bind to distinct sites of the receptor complex. In rodents, SDL has been found with a variety of $GABA_AR$ agonists and positive allosteric modulators, including barbiturates [9]. $GABA_BR$ agonists, such as baclofen are ineffective [40•], supporting the view that SDL is primarily $GABA_AR$-mediated phenomenon. Similar effects have been found in humans [2•,6,41] except that diazepam's actions were less clear [42]. An important condition for the ability of