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Neurobiological Mechanisms of State-Dependent Learning

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Abstract

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.

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.

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Conflict of interest

Nothing declared.

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. 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 towards 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 GABAergic drugs to induce SDL is the applied dose. Contrary to the initial assumption that SDL requires high drug doses, Colpaert [43] demonstrated that relatively low, therapeutic doses of the benzodiazepine chlordiazepoxide also give rise to SDL, and that doses required for recall can be much lower than those applied at encoding. This differs from initial observations with pentobarbital, where the highest degree of recall was found with the same dose of drug whereas the amnestic barrier became stronger the more the dose at test deviated from the dose at training [4*]. This could explain some of the inconsistent findings in the field and suggests that research on SDL warrants careful consideration of dose responses for particular drugs and learning tasks.

Studies examining the ability of $GABA_AR$ agonists to substitute for one another in recovering state-dependent memories have revealed that substitution is asymmetrical, suggesting that discrete $GABA_AR$ mechanisms underlie SDL. In general, ethanol, the least specific $GABA_AR$ agonist, could recover memories encoded under the $GABA_AR$ agonists diazepam or muscimol, but neither diazepam nor muscimol were effective when SDL occurred under ethanol [44]. Similarly, amobarbital, which binds to all $GABA_AR$, recovered the memory [45] whereas diazepam, which predominantly binds to synaptic $GABA_AR$ [46], did not yield consistent results [42]. This suggests that extrasynaptic, αβδ $GABA_AR$, could be particularly important for SDL. Unlike most of γ subunit-containing GABA receptors, αβδ receptors have a very low sensitivity to benzodiazepines, but are highly sensitive to low concentrations of alcohol [47] and the drug gaboxadol [48]. These $GABA_AR$ are extrasynaptic, regulating tonic inhibition [49*], and they mediate the sensitivity of mice to the sedative, hypnotic, and anxiolytic effects of neuroactive steroids [50]. In our own work,

gaboxadol strongly supported SDL [25**], and this was shown with the contextual fear conditioning paradigm, in which state-dependent effects are usually difficult to observe.

Bioinformatic analyses have recently revealed that in addition to their regulation by various endogenous and exogenous agents, $GABA_AR$ are also targeted by many microRNAs (miRNA). miRNAs regulate protein levels through the degradation or translation block of their target mRNA. Unlike transcriptional regulation, which causes substantial changes in the protein level, miRNAs cause subtle changes in protein levels and their role is seen more as fine-tuning the amounts of the target proteins [51, 52]. However, although their effect on individual targets is small, their overall physiological effect is strong due to the simultaneous regulation of many functionally related proteins. We have recently found that miR-33, which targets several GABA-related proteins, has a strong influence on the ability of gaboxadol to induce SDL. Unlike miRNAs that directly regulate learning and memory [53], miR-33 increased the threshold for gaboxadol's actions, and shifted the dose-response curve to the right [25**]. Interestingly, the levels of several extrasynaptic $GABA_AR$ and $GABA_AR$-targeting miRNAs, including miR-33, are consistently dysregulated in patients suffering from major psychiatric disorders [54, 55], such as major depression and schizophrenia. It remains to be determined whether the observed molecular abnormalities contribute to the generation and maintenance of state-dependent information processing characteristic of these disorders.

In summary, several neurotransmitter systems, most notably the GABAergic system, support SDL, allowing for the formation of memories that are not readily retrievable. Much work needs to be done to better understand the mechanisms and significance of memory formation under different states. One of the important remaining questions is whether GABAergic mechanisms mediate SDL or, alternatively, whether they induce states that allow for different interpretation of ongoing glutamatergic transmission.

Cellular and circuit mechanisms of SDL

In addition to GABAergic drugs, GABA receptors also mediate the SDL induced by other drugs such as morphine [24]. This is not surprising given that μ opioid receptors are primarily expressed on interneurons [56], and suggests that GABA receptors can be the downstream effectors of other receptor mechanisms involving interneurons. Innervation of pyramidal excitatory neurons by interneurons is domain-specific, allowing for the coordination of multiple glutamatergic inputs on different parts of pyramidal cells [57**]. This is achieved through temporally distinct activity of GABAergic interneurons, which change their firing during different network states [58]. Although interneuron-specific firing has so far been mainly implicated in segregating cell assemblies and establishing the temporal order of assemblies during behaviors, it is also likely that some of these mechanisms contribute to SDL (see below).

Already in some of the first SDL studies, it was shown that brain regions differently support SDL. For example, for the caudate nucleus and hippocampus, low intensity electrical stimulation is sufficient for SDL, whereas the amygdala produces SDL effects only after strong stimulation that induces overt seizures [59].

In their early work on SDL, Girden and Culler, [1] suggested that conditioning under curare is subcortical in nature and does not require, or is even suppressed by cortical activity. The first study to address this question was by Girden [60]. He found that bilateral ablation of the auditory cortex in dogs eliminated dissociation between a curare- induced drug state and the nondrug state. However, this was not replicated by Bliss, Sledjeski, and Leiman [61] who demonstrated intact SDL when monkeys with bilateral dorsolateral frontal ablation were on pentobarbital. Robust circuit effects were next shown with the finding of lateralization of state-dependency in split brain rats, but not in intact rats [62]. In our own lab, we have examined the role of the extended hippocampal circuit in gaboxadol-induced SDL. Normally, contextual fear conditioning depends on the hippocampus as well as the retrosplenial cortex [63], but as predicted by Girden and Culler, SDL under gaboxadol was independent of this cortical area, and even showed enhancement following retrosplenial cortical inactivation [25**]. Analyses of suppressed cortical and elevated subcortical activation of immediate early genes further support this view [25**] and suggest that changes of neuronal states also involve changes of the routing of neuronal signals within broader brain circuits.

Brain states supporting learning processes are often defined by the rhythmic neuronal activity of various frequencies [64**]. Many drugs that give rise to SDL also induce changes of the electroencephalogram (EEG), as first reported for phentobarbital [65]. Subsequently, Sadowski and Longo [66] found that the synchronization of the EEG after injection of scopolamine closely paralleled the disruption of a response learned under the nondrug state. Leiman, Bliss, Powers, and Rosenzweig [67] showed that when rats were injected with pentobarbital at a dosage capable of producing dissociation, the EEG activity changed from the normal arousal portrait of low-voltage desynchronized activity to high-amplitude synchronized waves. It is now well established that most drugs that support SDL, including gaboxadol, scopolamine, and opiates, induce changes of oscillatory neuronal activity, measured by EEG or local field potentials [68–70]. These large changes in electrical activity may well be correlated with the behavioral findings of drug dissociation. Thus, a process initiated at a molecular level, such as activation of extrasynaptic $GABA_AR$, could change local and global network activity that enables state-dependent encoding and retrieval of memories (Figure 2).

Conclusion and implications of SDL

The SDL phenomenon has received little recent attention, which is somewhat surprising given that a number of advantages will accrue from a better understanding of the neurobiology of SDL. These relate to (i) the fundamental principles of information processing, (ii) the impact of inaccessible memories on behavior, (iii) the role of SDL in transition to and maintenance of psychopathology, and (iv) information processing under psychiatric conditions.

Although, in research settings, SDL is most frequently studied using drugs, it may well be a routine aspect of information processing. Recent work is exploring the idea that spatiotemporal patterns of synchronized spontaneous activity in neuronal networks serve as memories [71], and it has recently been suggested that state-dependency accounts for the

variety of such patterns [72**]. From an evolutionary perspective, SDL has also been conceptualized as a way to organize memories so that they can influence decision-making only under constrained conditions when access to specific information is particularly advantageous [5]. Finally, SDL is regarded as a protective mechanism that helps to temporarily avoid negative affect triggered by distressing memories [73].

In contrast to these generally beneficial effects, relying on SDL as a predominant learning strategy has many adverse consequences partly because memories and their associated emotions are not properly integrated at encoding. This could place individuals at risk for a wide variety of psychiatric disorders, especially dissociative disorders and post-traumatic stress-disorder [74], because despite the fact that state-dependent (often traumatic) memories cannot be fully retrieved, they nevertheless strongly influence social and affective behavior [75, 76]. Accordingly, emotion processing, an important domain of social cognition, is state-dependent in patients with schizophrenia [77*]. SDL has been implicated in the persistence of drug addiction, because being on drugs can be a strategy for gaining better access to information learned while in a drug state [78]. This putative role of SDL may prove of particular relevance given the widespread and increasing use and abuse of recreational and prescription drugs. Taken together, understanding the mechanisms of SDL could help us to better understand both the phenomenology of psychiatric states and actions of psychotropic drugs. By facilitating transfer of information across different states, we might be able to generate more effective treatment approaches for various psychiatric and neurological disorders.

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Highlights

- SDL can be induced by a variety of endogenous and exogenous stimuli
- Many drugs supporting SDL converge on GABAergic transmission
- GABAergic induction of SDL is regulated by microRNAs
- SDL entails changes of circuit and global network activities
- SDL is a fundamental mechanism of learning and a gateway to psychopathology

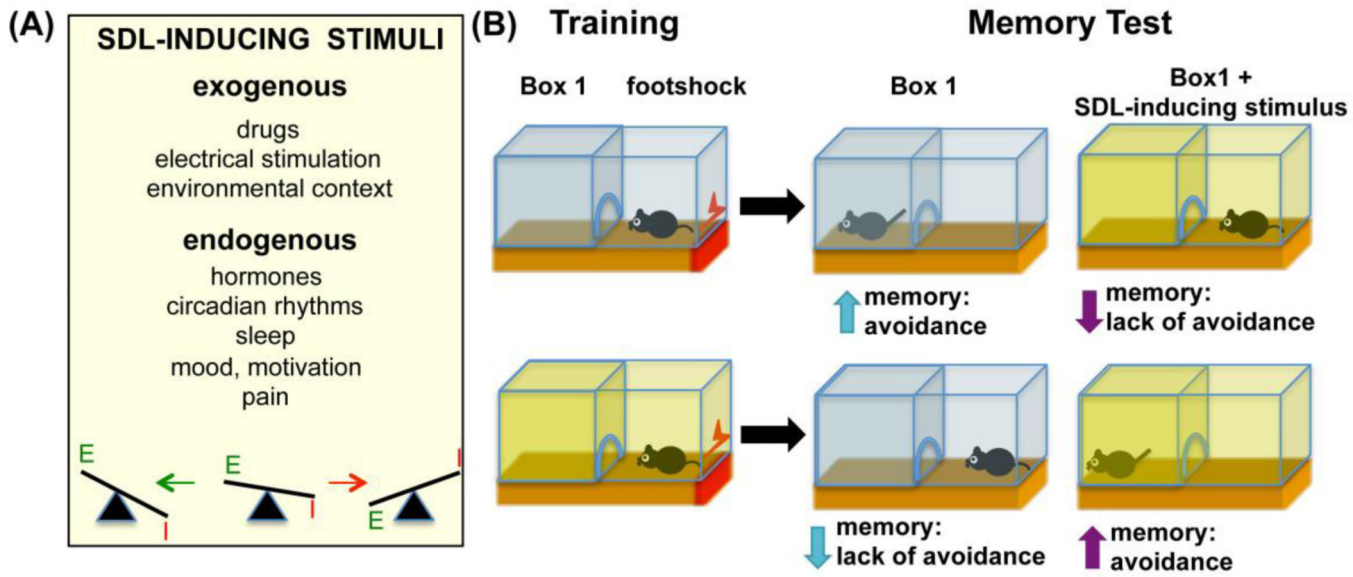

Figure 1.

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.

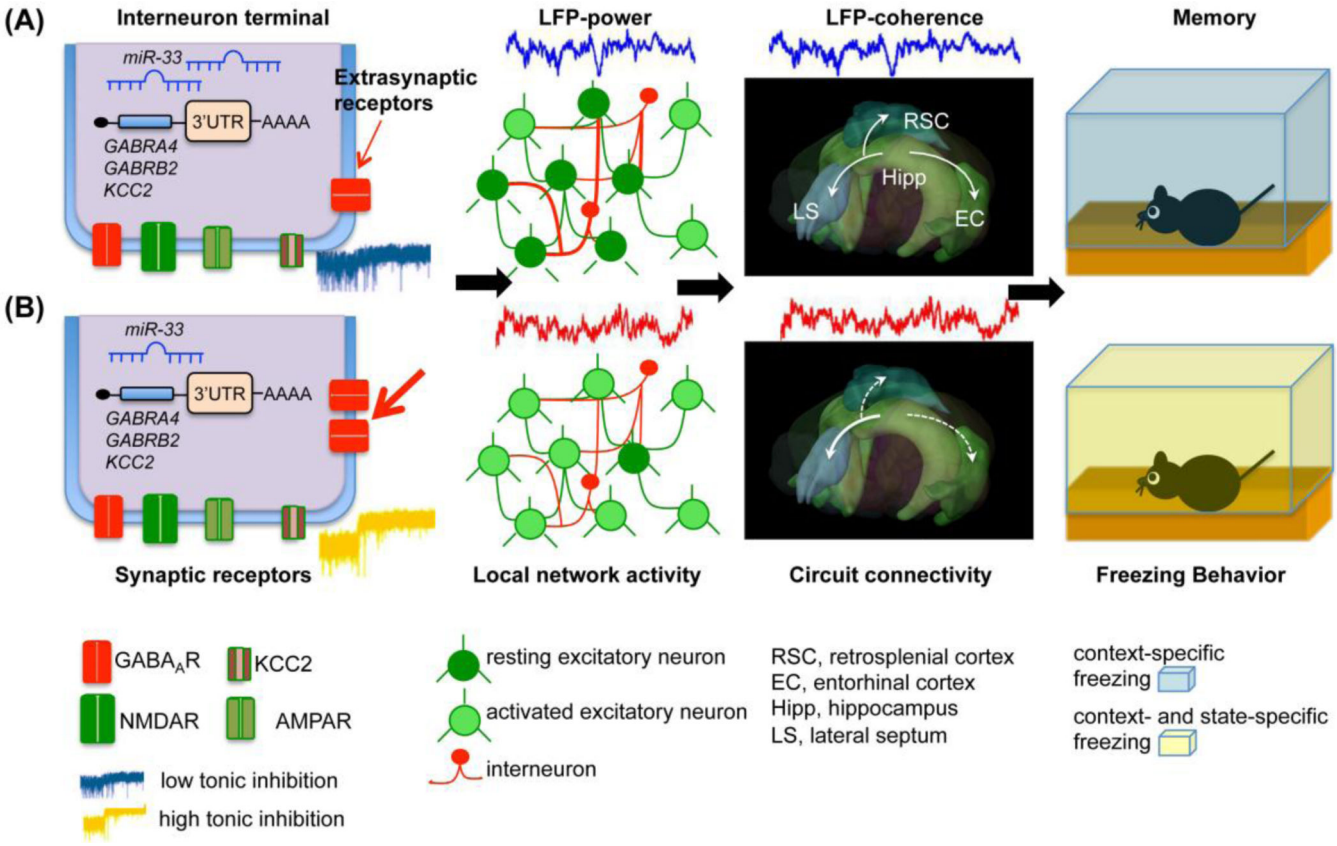

Figure 2.

Molecular, cellular, and circuit mechanisms of SDL. A model of SDL based on activation of extrasynaptic GABA$_A$R on hippocampal dentate gyrus interneurons [28**]. (A) Conditions reflecting normal tonic inhibition (thin red arrow) allow for activation of some excitatory granule cells and induce changes of local network activity as well as coherent activity between the hippocampus and its cortical and subcortical targets. These changes are correlated with successful memory retrieval in a contextual fear conditioning paradigm, revealed as freezing behavior during a memory test. (B) Increasing tonic inhibition *via* extrasynaptic GABA$_A$R (thick red arrow) on interneurons increases the number of active granule cells via disinhibition, and induces changes of local and global oscillatory activities. This results in disrupted hippocampal-cortical and enhanced hippocampal subcortical processing of context memories. Such memories are best retrieved when extrasynaptic GABA$_A$R are reactivated, recreating the state at encoding. KCC2, chloride symporter.