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Review Article

The Modulatory Role of Nicotine and Alcohol in State-Dependent Learning and Memory

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Abstract

State-dependent learning occurs when memories formed under specific conditions or drug influence are best retrieved in the same state. Though complex, its mechanisms are not fully understood. Nicotine and ethanol are key substances affecting this process. This review highlights recent findings on state-dependent memory and examines the impact of these substances. Research involved defining questions and searching databases like PubMed, Scopus, and Google Scholar using keywords such as "nicotine," "ethanol," and "state-dependent learning." Both substances influence memory, either enhancing or impairing it through intricate mechanisms. Studies show nicotine and ethanol together can trigger state-dependent learning, involving neurotransmitter interactions in brain regions like the amygdala and hippocampus during memory formation and retrieval.

Keywords: State-dependent learning, State-dependent memory, Nicotine, Ethanol, Neurotransmitters

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Introduction

Nicotine

Nicotine is the major alkaloid of the cigarette, obtained from *Nicotiana tabacum*. Nicotine affects various biochemical and physiological functions.[1,2] The cognition-enhancing effects of nicotine enhance performance in several cognitive functions, including memory, attention, and learning.[3] Nicotine has also been thought to behave like an antioxidant, reducing oxidative stress. Apart from this, nicotine reduces inflammation and prevents neurons from being affected by amyloid-beta (Aβ) through halting its aggregation in the brain. Nicotine activates nicotinic acetylcholine receptors (nAChRs) in the brain, just like an outside substance.[4]

nAChRs and memory function

Both the central and peripheral nervous systems have nicotinic acetylcholine receptors.[4] Each receptor has five identified beta subunits.[5] The structure of nicotinic acetylcholine receptors allows various complexes of potential α subunits and three β subunits.[6] The activation of nicotinic acetylcholine receptors in the brain can influence the release of neurotransmitters such as dopamine, glutamate, serotonin, norepinephrine, and GABA-aminobutyric acid.[6] Changing the number or function of nicotinic acetylcholine receptors can change the release of neurotransmitters and their effects on different brain parts. These neurotransmitters substantially influence the modulation of a range of behaviors, such as locomotion, anxiety, exploration, learning, and memory.[4]

Cholinergic neurons contain nicotinic acetylcholine receptors (nAChRs) of the α7 subtype, which play a crucial role in nicotine's modulation of synaptic plasticity, particularly in state-dependent learning and memory. Studies show that mice lacking α7 nAChRs exhibit increased difficulty in focusing and remembering information. Additionally, mice deficient in α7 nAChRs within their GABAergic neurons display impaired cognitive function and social behavior. [7] Furthermore, α7 nAChR knockout mice struggle with episodic memory, while rats with reduced α7 nAChRs experience deficits in spatial memory.[8] Nicotine exposure also influences nAChR functionality, leading to various behavioral changes in rats depending on the duration of exposure.[9]

Ethanol

Ethanol, or ethyl alcohol, has neurotoxic effects that could induce neurodegeneration, oxidative damage,

and structural changes within the cerebellum and hippocampus when it is abused.[10] It will lead to chronic alcohol consumption, characterized by depression, loss of memory, anxiety disorders, and failures of organs associated with it.[11] This induces various epigenetic modifications that alter the expression of genes in the brain. Neurological impairments due to acute and chronic drinking result in dementia.[11] The effect of ethanol on memory is complex; several studies have indeed suggested that ethanol can enhance memory, while others have reported detrimental effects.[12]

Ethanol impacts cognitive functions like learning and memory, particularly affecting the hippocampus, vital for spatial learning. Intraperitoneal ethanol impairs spatial memory in adult male mice (Morris water maze) and disrupts memory in juvenile female rats without affecting locomotion.[13] Ethanol disrupts spatial learning in juvenile and adult female rats[14], contributes to cognitive decline, increases β-amyloid deposition, and is linked to Alzheimer's disease.[15] Maternal alcohol consumption adversely affects offspring cognition.[16] Long-term ethanol use harms spatial memory, while low doses may improve it. Binge drinking minimally impacts memory, and repeated exposure does not impair spatial learning. In older adults, moderate alcohol intake may lower dementia risk, and chronic exposure could protect against brain damage. Alcohol disrupts memory encoding but enhances consolidation by increasing synaptic dopamine.[17]

Methods

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was performed using a systematic approach across multiple academic databases, including PubMed, PsycINFO, Web of Science, OvidSP, Scopus, and ScienceDirect, to identify relevant scientific studies. Additionally, Persian-language databases such as the National Publications Database (Magiran), the Scientific Information Database (SID), the Research Institute of Information Science and Technology of Iran (IranDoc), and the Barkat Knowledge System (IranMedex) were thoroughly explored. To ensure accuracy and minimize potential bias, two researchers independently reviewed and assessed the articles during both the search and quality evaluation stages. In cases of disagreement, a third researcher was consulted to achieve a consensus.

Search strategy

The search strategy was developed using Medical Subject Headings (MeSH) to identify relevant papers in English-language databases. Keywords such as "learning," "memory," "alcohol," "nicotine," and "modulation," along with their plural forms, were included to ensure comprehensive coverage. Boolean operators "OR" and "AND" were employed to combine these terms effectively, as outlined in Table 1. There were no restrictions on publication dates, and all related studies published up to January 10, 2024, were considered. Additionally, reference lists of shortlisted articles were manually screened to identify other relevant sources. A detailed overview of the comprehensive search strategy applied across the databases is provided in Table 1.

Inclusion and exclusion criteria

This systematic review included observational studies (cross-sectional, prospective cohort, retrospective cohort, and case-control) that investigated the effects of nicotine and alcohol on learning and memory across various populations worldwide. To ensure methodological rigor, only studies reporting accurate sample sizes and clearly defined outcomes were considered. Studies with unreliable data reporting or those limited to conference abstracts without full-text availability were excluded.

Results

Nicotine, cognitive function, and suggested mechanisms

Nicotine exerts both positive (Figure 1) and negative effects (Figure 2) on memory and cognition, with these outcomes varying based on dose, method of administration, and duration of exposure.[18] Levin et al. (2006), observed that acute nicotine administration enhanced cognitive performance in rats by stimulating memory and attention tasks through nicotinic acetylcholine receptors.[19] Furthermore, their research indicated that nicotine could counteract cognitive deficits caused by nicotinic receptor antagonists, suggesting its potential therapeutic role in addressing cognitive impairments linked to cholinergic dysfunction.

However, not all findings are uniformly positive. Acute nicotine doses have been associated with impaired performance on cancellous memory tasks in aged female rats, even in conjunction with reduced levels of nerve growth factor in the hippocampus.[20] On the other hand, nicotine has also been found to facilitate contextual fear conditioning and enhance memory reconsolidation in rats.[21] In human studies, a clinical trial involving non-smoking participants with late-life depression revealed that nicotine injections improved texture discrimination and working memory performance.[22] These findings collectively highlight nicotine's complex and multifaceted effects on cognitive function, warranting further exploration into its mechanisms and therapeutic potential. On the contrary, nicotine may be one of the risks associated with intrusive memories and the development of post-traumatic stress disorder (PTSD).[21] Nicotinic acetylcholine receptors, particularly α7, exist mainly in the hippocampus and prefrontal cortex and are involved in the regulation of learning and memory and higher-order cognitive processes.[23] Alhowail (2021) mentioned that nicotine's positive effects on memory function are mediated through mechanisms that inhibit histone deacetylases (HDAC) – key regulators of synaptic plasticity – and activate histone acetyltransferases (HAT).[24] Through the modulation of α7 nicotinic acetylcholine receptors along with other epigenetic mechanisms, nicotine was found

Table 1. Search strategy in databases

	Search date the most recent search took place on January 10, 2024			
	Search strategy		**Number of articles retrieved**	**Search Filters**
Database	Science Direct	Humans/female/male Long-term potentiation/physiology Nicotine/pharmacology Brain/drug brain/drug effects Cognition/drug effects Alcohol/ethanol/nicotine/pharmacology Alcohol/ethanol/nicotinic Agonists/pharmacology Smoking/pathology Smoking/physiopathology Hippocampus/drug effects Hippocampus/physiopathology Illicit drugs / adverse effects Learning/drug learning/drug effects Learning/physiology learning/physiology Memory/drug memory/drug effect Memory/physiology Neuronal plasticity/drug effects Neuronal plasticity/physiology Substance-related disorders/psychopathology Adrenergic uptake inhibitors/pharmacology Avoidance learning/drug learning/drug effects Avoidance learning/physiology Learning/psychology CA1 region: hippocampal/drug effects CA1 Region, hippocampal/metabolism	139 results	✓ Year of publication: any time ✓ Sort by relevance ✓ Keywords in the title of the article
	PubMed		457 results	✓ Article Language: English, Persian
	PsycINFO		77 Results	✓ Entire site
	Web of Science		154 results	✓ Scholarly journals
	Scopus		156 results	✓ No search filters were applied.
	Magian		16 results	✓ Article type: research article ✓ Keywords in the abstract
	IranDoc		15 results	✓ Keywords in the abstract
	SID		230 results	✓ In medical journals
	Iran MEDEX		14 results	✓ No search filters were applied.
Search engine Google Scholar		Central nervous system Depressants/pharmacology Dose-response relationship, drug Motor activity/drug activity/drug effects Motor activity/physiology Activity/physiology N-methyl-3,4-methylenedioxyamphetamine/pharmacology Nicotinic agonists/pharmacology Receptors, nicotinic/metabolism	406 results	✓ Year of publication: any time ✓ Sort by relevance ✓ Keywords in the title of the article

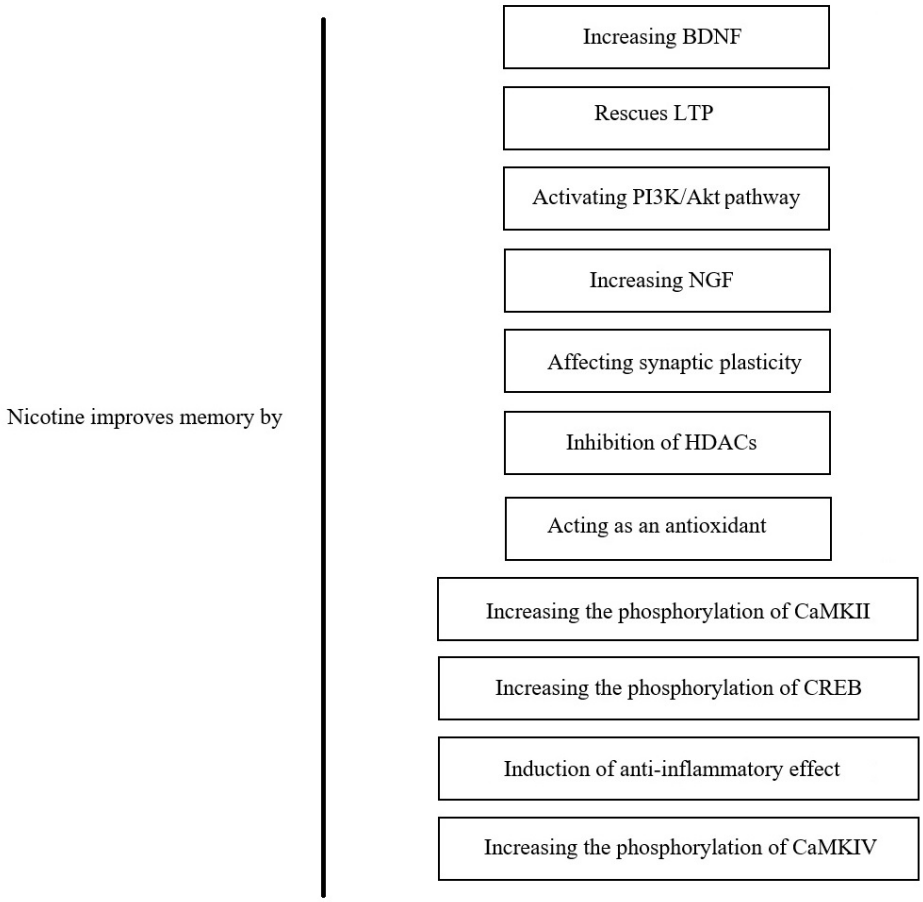

Figure 1. Mechanisms involved in the improvement effect of nicotine on memory performance. (BDNF: Brain-Derived Neurotrophic Factor; LTP: Long-Term Potentiation; PI3K: Phosphoinositide 3-Kinase; Akt: Protein Kinase B; NGF: Nerve Growth Factor; HDACs: Histone Deacetylase; CaMKII: Calcium/Calmodulin-Dependent Protein Kinase II; CREB: cAMP Response Element-Binding)

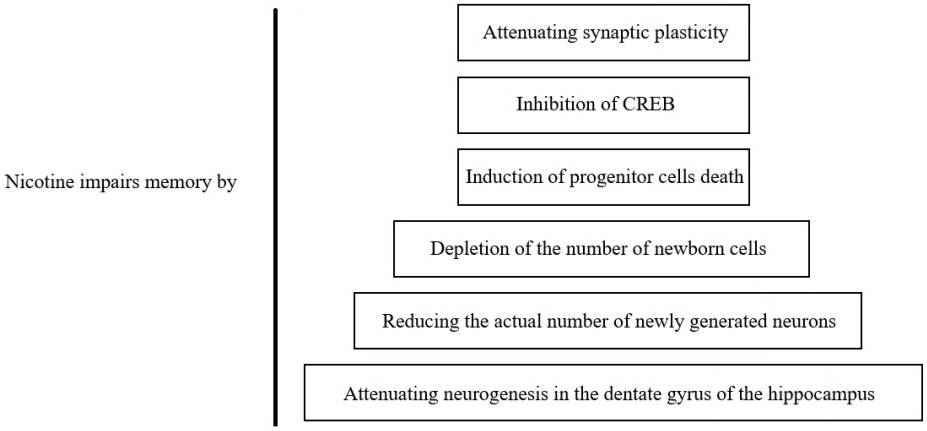

Figure 2. Mechanisms involved in the impairment effect of nicotine on memory performance. (CREB: cAMP Response Element-Binding)

to enhance synaptic plasticity and cognitive function in animal models of Alzheimer's disease and chronic stress.[25] Long-term exposure to nicotine decreases the potential to generate new neurons in the hippocampus and is associated with a decline in hippocampal plasticity.[26] Additionally, nicotine can trigger the death of progenitor cells and cause behavioral deficits in the offspring of exposed mothers.[27] Acute nicotine exposure makes it harder for male mice to forget contextual fear memories. This means they do not experience the expected drop in fear during extinction trials, but their freezing behavior remains unchanged. Nicotine exposure also enhances the spontaneous recovery of extinguished contextual fear.[28] Nicotine addiction makes contextual fear last longer, and this effect lasts during withdrawal, which coincides with the upregulation of nicotinic acetylcholine in the hippocampus.[29] Both genders exhibit negative effects of acute nicotine exposure on extinction, though males may demonstrate greater sensitivity. This suggests a potential protective mechanism in females, possibly influenced by estrogen levels.[30] Since acetylcholine plays a role in learning, the effect of estrogen on memory could account for the observed gender differences in nicotine-related effects on extinction.[31]

Figure 2 illustrates the mechanisms by which nicotine impairs memory function.

Proposed mechanisms for ethanol in the regulation of memory processes

The mechanisms behind alcohol-induced memory impairment are not yet fully understood, but heightened oxidative stress appears to play a significant role in causing neural damage.[32] Acute exposure to ethanol reduces the activity of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase. This increases hippocampal malondialdehyde (MDA) levels and connects oxidative stress to memory loss.[33] Exposure to ethanol can decrease glutathione (GSH) and the GSH/GSSG ratio, increasing lipid peroxidation and protein oxidation and impairing memory formation.[34] Coenzyme Q10 reduces anxiety and depression-like behaviors derived from chronic opioid use and increases GDNF expression in the hippocampus of morphine-dependent rats. These findings suggest an effect on neurotrophic factors that may underlie cognitive deficits related to the hippocampus, such as learning and memory deficits.[35] Changes resulting from oxidative stress can perturb cellular mechanisms that are necessary for synaptic plasticity and memory consolidation within the hippocampus.[36] Alcohol inhibits NMDA receptors, essential for memory and learning, impairing brain function and contributing to ethanol tolerance and dependence.[37,38]

Loss of cholinergic neurons in the basal forebrain and CA3 and CA1 neurons in the hippocampus compromises the integrity of the CAL system. These projections extend to the hypothalamus and cerebral cortex.[39] In rodents, postnatal ethanol exposure during a developmental period comparable to the human third trimester impairs hippocampal neurodevelopment and reduces dendritic spine density, LTP, and neurogenesis.[40] Being exposed to alcohol during pregnancy hurts NMDA receptor-related LTP in the CA1 region and dentate gyrus.[41] Studies have shown that exposing newborns to ethanol makes it harder for dentate gyrus cells to work and changes the plasticity of synapses, which impairs their ability to think and learn.[42] Notably, prenatal ethanol exposure affects both LTP and long-term depression (LTD), with males experiencing reductions in both, while females only show changes in LTP.[43] Ethanol can also lead to memory blackouts by weakening recall ability. These cognitive issues might be caused by cells that are not as sensitive as mature hippocampal slices. This is because immature hippocampal slices have more significant drops in LTP and NMDA receptor-dependent EPSPs than mature slices.[44] Generally, the blocking of LTP disrupts learning and memory acquisition.[45] Alcohol affects the brain's BDNF signaling, a key regulator of neuronal excitability, synaptic plasticity, and memory.[46] It potentiates NMDA receptor function and changes LTD and LTP processes in the hippocampus.[47] Ethanol exposure suppresses CREB expression and levels of BDNF, thereby causing defects in the memory of object location in rats.

Perinatal ethanol exposure impairs memory by reducing hippocampal BDNF mRNA, with stronger effects in male

rats.[48] Transcutaneous auricular vagus nerve stimulation reverses cognitive deficits in morphine-withdrawn rats by boosting BDNF and glial activity in the hippocampus.[49] Reduced BDNF may hinder synaptic plasticity and memory, but downstream effects, especially regarding cell death in female rats, remain unclear.[50]

Figure 3 illustrates the mechanisms through which ethanol disrupts memory function.

"State-dependent" learning/memory: The role of ethanol and nicotine

State-dependent learning occurs when information learned in a specific state, emotion, or under certain medications is best recalled in that same state. First studied by Garden and Culler with dogs conditioned under anesthesia, responses were retrievable only under similar anesthetic conditions. Various substances, including anesthetics, stimulants, anxiolytics, and drugs of abuse like ethanol, nicotine, cannabinoids, and morphine, have been shown to induce state-dependent memory.[51] Ethanol may hinder recovery when consumed before exercise, but can improve memory formation if administered before a memory test following induced amnesia.[52] The mechanisms underlying state-dependent learning and memory involve a complex interplay among several brain regions, including the hippocampus, prefrontal cortex, and amygdala.[53] These regions contribute to the processes of encoding, consolidating, and retrieving memories tied to context-dependent cues, utilizing time-sensitive mechanisms governed by cholinergic and dopaminergic systems.[54]

State-dependent learning mechanisms remain unclear, but neurotransmitter systems are crucial. Ethanol reduces acetylcholine release in the hippocampus, while salbutamol may enhance recall by activating cholinergic neurons.[55] GABA-A receptor-mediated processes, influenced by ethanol as a GABA-A receptor agonist, aid state-dependent memory retrieval via hippocampal circuits.[56] Differences in GABA receptor subtypes highlight their distinct roles in memory consolidation and retrieval.[57]

Key brain regions involved in state-dependent learning

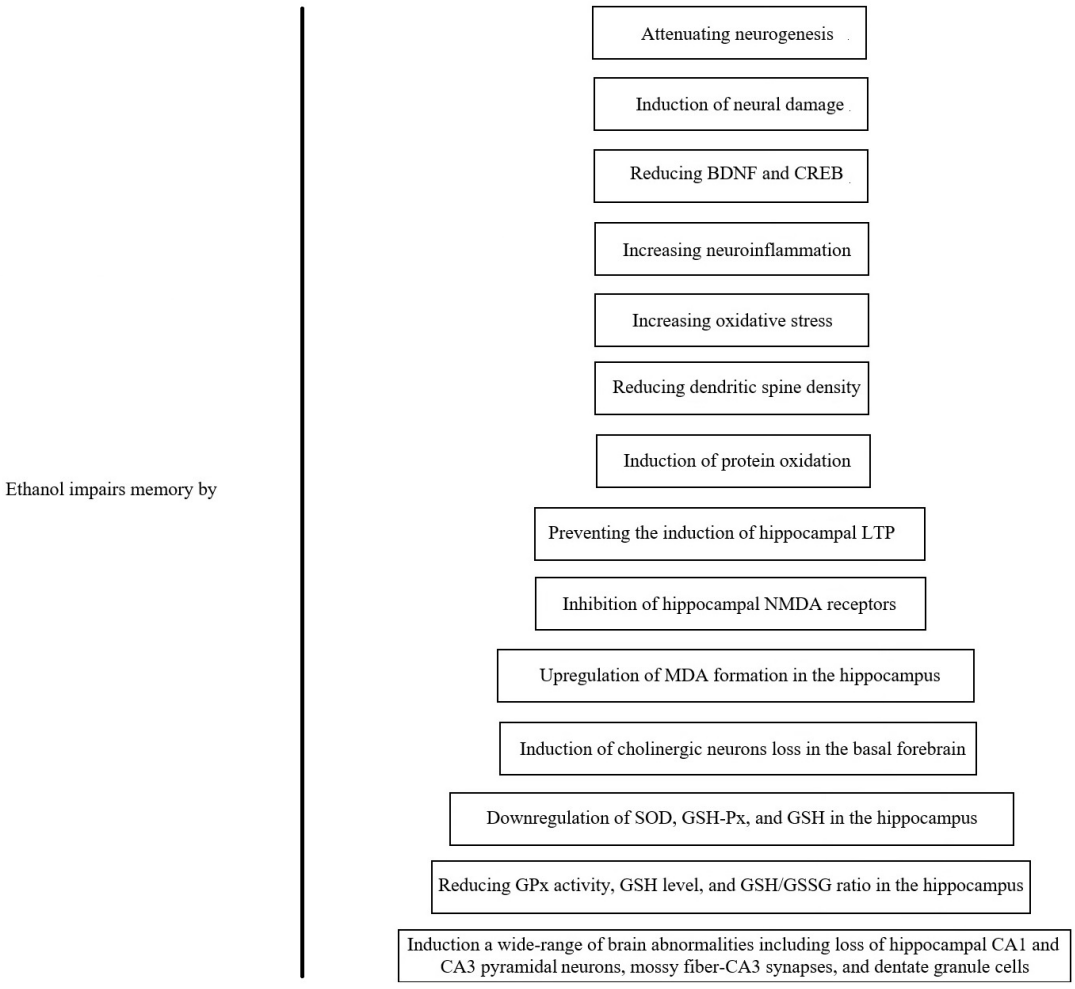

Figure 3. Mechanisms involved in the impairment effect of ethanol on memory performance. (BDNF: Brain-Derived Neurotrophic Factor; CREB: cAMP Response Element Binding; LTP: Long-Term Potentiation; NMDA: N-Methyl-D-Aspartate; MDA: Malondialdehyde; SOD: Superoxide Dismutase; GSH: Glutathione; GSH-Px: Glutathione Peroxidase; GSSG: Oxidized GSH)

include the hippocampus, amygdala, nucleus accumbens (NAC), and ventral tegmental area (VTA), along with the noradrenergic, [6] dopaminergic, [58] and endocannabinoid systems. [53] These intricate interactions underscore the gaps in our understanding of state-dependent learning. The following section explores cross-state-dependent memory and the influence of drugs on learning.

Figure 4 illustrates the brain regions and neurotransmitters playing a role in facilitating state-dependent memory.

Cross-state-dependent learning/memory

Research frequently associates the rewarding effects of substances such as nicotine, ethanol, and morphine with cross-state-dependent learning. [59] For example, nicotine has been shown to counteract the memory-impairing effects caused by morphine and ethanol, highlighting a potential interaction among these substances that may impact learning and memory processes. [60] Studies have demonstrated that both tramadol and morphine stimulate μ-opioid receptors in the CA1 region of the hippocampus, a mechanism that facilitates cross-state-dependent memory.[61]

Discussion

Numerous controlled experimental studies have investigated the impact of nicotine and alcohol on state-dependent learning and memory.[56] The findings indicate that these substances influence memory retrieval processes by interacting with specific neurotransmitter systems, such as the nicotinic acetylcholine and GABA systems, in brain regions associated with learning and memory. The rewarding effects of drug abuse may be linked to drug state-dependent memory. [62] As highlighted earlier, WIN is known to cause memory impairments; however, administering nicotine or ethanol during testing can mitigate these impairments, suggesting the potential for state-dependent memory retrieval. WIN or ethanol may support this retrieval by inducing similar pleasurable effects. Supporting this idea, prior research has shown that WIN enhances the activity of dopaminergic neurons in the mesocortical-limbic system. [63] This enhancement occurs via the activation of CB1 receptors, which play a crucial role in regulating dopaminergic and glutamatergic neurotransmission in brain regions associated with reward processing. Similarly, nicotine and alcohol activate the same reward pathways in the brain, promoting dopamine release. Despite these findings, the exact mechanisms driving this process remain unclear.

Dopaminergic neurotransmission is key to controlling internal physiological states, building memories that depend on the current state, and creating memory effects that go beyond state boundaries. Addictive substances like ethanol, nicotine, and morphine activate the mesolimbic dopaminergic system, specifically via activation of the dopamine receptor in the nucleus accumbens. Activation of the mesolimbic dopaminergic system leads to increased release of dopamine, which contributes to the reinforcing effects associated with the impetus to seek drugs and the building of tolerance seen in addiction.[64] Dopaminergic agonists enhance the impact of ethanol and morphine on state-dependent memory, a phenomenon where memory retrieval is facilitated when the internal state during recall matches the state during encoding. In contrast, dopaminergic antagonists diminish this effect, further highlighting the critical role of the dopaminergic system in regulating memory processes.[56] State-dependent memory alterations caused by morphine or ethanol also rely on nicotinic cholinergic transmission. For instance, the state-dependent memory effects of morphine and ethanol can be reversed when nAChRs are inhibited using antagonists.[65] The reversal of state-dependent memory

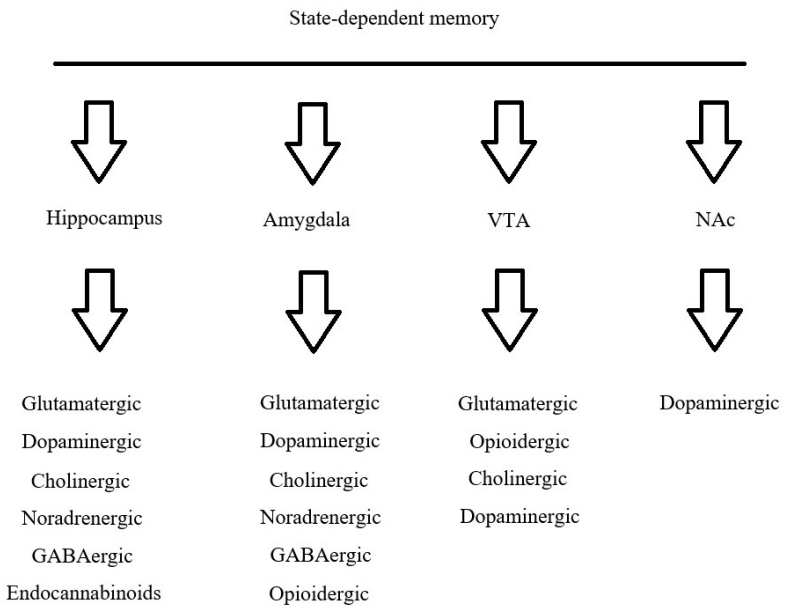

Figure 4. Brain regions and neurotransmitters involved in mediating state-dependent memory. (VTA: ventral tegmental area; NAc: nucleus accumbens)

modifications occurs in the dorsal hippocampus when nAChRs are inhibited by mecamylamine.[66] Furthermore, state-dependent and cross-state-dependent memory are thought to be supported by distinct neural architectures involving specific brain regions. State-dependent learning refers to memory retrieval facilitated by the presence of a single drug state, while cross-state learning involves memory retrieval supported by a different but internally similar drug state. These processes are influenced by activity and transmission within the medial septum, dorsal hippocampus, VTA, and amygdala.[53]

Cholinergic transmission within the dorsal hippocampus is essential for modulating both state-dependent and cross-state-dependent memory functions.[67] Administration of nicotine or physostigmine into the IntraCA1 region or hippocampus significantly mitigates ethanol-induced memory deficits.[68] Similarly, suboptimal doses of cholinergic antagonists, such as atropine (muscarinic) or mecamylamine (nicotinic, in the CA1 area of the dorsal hippocampus demonstrate comparable effects in counteracting ethanol's impact on memory consolidation. Notably, nicotine-induced memory alterations in the dorsal hippocampus and medial septum are mediated through the activation of specific nicotinic acetylcholine receptors (nAChRs.[69]

This review encountered several limitations, such as restricting studies to English and Persian, limited access to full texts, and inconsistencies in study designs, tools, and outcomes, which impeded meta-analysis and thorough synthesis.

Conclusion

Nicotine and ethanol exhibit complex, dual effects on memory, capable of both enhancing and impairing learning processes. They impact various neurobiological pathways and neurotransmitter systems, particularly in crucial brain regions like the hippocampus and amygdala, which are central to memory formation. The interaction between these substances and state-dependent learning underscores the importance of further research on receptor modulation and synaptic plasticity. Gaining deeper insights into these mechanisms may pave the way for advancements in addiction treatments and innovative therapies for conditions such as depression and PTSD.

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Competing Interests

The authors declare that they have no conflict of interest.

Consent to Participate

Not applicable.

Consent to Publish

Not applicable.

Data Availability Statement

The data will be made available upon request.

Ethical Approval

All procedures in this study received approval from the Ethics Committee of Mazandaran University of Medical Sciences for laboratory animals (IR.MAZUMS..REC.1400.11703).

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