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Effects of Prenatal Nicotine Exposure on Short-Term and Long-Term Memory: A Literature Review

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Abstract

Introduction: Prenatal nicotine exposure occurs when pregnant individuals use nicotine products, exposing the fetus to nicotine, which readily crosses the placental and blood-brain barriers, accumulating in fetal circulation and amniotic fluid. As nicotine is a neuroteratogenic agent, prenatal nicotine exposure disrupts fetal brain development, particularly in regions critical for memory and cognition, such as the hippocampus and prefrontal cortex. These disruptions have been shown to have a profound long-term impact on short and long-term memory. This literature review aims to understand how prenatal nicotine exposure affects short- and long-term memory.

Methods: A literature search was performed using Boolean operators to find pre-clinical studies, clinical studies and reviews on the effects of prenatal nicotine exposure on memory published between 2010 and 2024. The databases used were Web of Science, PubMed, EMBASE, and the JAMA Network. After removing duplicates and studies that did not meet inclusion criteria, 22 studies remained.

Results: 12 preclinical studies, 6 clinical studies, and 4 reviews met the inclusion criteria and were included in this review. The studies found the exposed participants did not perform as well as the non-exposed control participants in memory and learning tests. Impaired brain function, hyperactivity, reduced nAChRs, and decreased integrity of the brain and neuronal structures were found in exposed subjects across multiple studies.

Discussion: Prenatal nicotine exposure impairs memory with distinct neural and cognitive implications. It alters brain structures such as the hippocampus, prefrontal cortex, and cerebellum, disrupting cholinergic and glutamatergic pathways critical for memory function. Short-term memory deficits are linked to compensatory neural mechanisms, while long-term memory impairments involve structural changes like reduced hippocampal and cortical volumes. Sex-dependent effects show males experiencing greater spatial memory deficits, while females exhibit heightened exploratory tendencies. Due to impaired development of the brain and/or neuronal regions critical for memory, memory and learning deficits can carry into adolescence and adulthood of exposed participants.

Conclusion: The information summarized in this review can be used to guide future research and aid in public education on the negative effects of maternal smoking. Therapeutic and public health-oriented strategies can be developed to reduce the effects of prenatal nicotine exposure on cognitive development.

Keywords: blood-brain barrier; fetal; hippocampus; long-term memory; nicotine; prenatal exposure; short-term memory

Introduction

Nicotine, a key component of tobacco, smoking and vaping products, poses significant risks when used during pregnancy, exposing the developing fetus to its harmful effects through prenatal nicotine exposure (PNE) [1]. Nicotine readily crosses the placental barrier, entering fetal circulation and causing adverse effects on neurodevelopment such as reductions in brain cell number, size, and surface area [1]. The blood-brain barrier (BBB), a critical structure of the central nervous system (CNS), regulates the brain's microenvironment by restricting the passage of macromolecules and proteins while mediating immune cell trafficking. Damage to the BBB by nicotine exacerbates its impact on brain development through fewer tight junction proteins and altered ion transporter expression which increases permeability, and induces oxidative stress and inflammation, thus affecting the barrier's integrity [2].

Nicotine is a neuroteratogen that crosses both the placental and blood-brain barriers, exposing the fetus and thus impairing the development of brain regions critical to memory, such as the hippocampus and prefrontal cortex [2-4]. These disruptions are mediated by nicotine binding to nicotinic acetylcholine receptors (nAChRs), which are critical for cholinergic neurotransmitter system regulation [1, 4]. nAChRs can begin activating during the

first trimester of pregnancy, and plays a critical role in neurodevelopment [5]. Early activation and subsequent desensitization of nAChRs during neurodevelopment result in long-term neurological consequences. [5, 6]. With nicotine's addictive property and ability to accumulate in amniotic fluid and breast milk, fetal exposure and risks for placental dysfunction, fetal growth restriction, and preterm birth are amplified [3, 4]. Ultimately, these harmful effects of nicotine on fetal brain development can carry into adulthood, creating long-term deficits.

Methods

A systematic search of databases (Web of Science, PubMed, EMBASE, and the JAMA Network) was conducted to identify relevant studies published between 2010 and 2024. Boolean operators (nicotine) AND (prenatal) AND (memory) yielded 115 studies. After removing duplicates and applying inclusion criteria, 22 pre-clinical studies, clinical studies, and reviews were selected, focusing on cognitive and anatomical outcomes related to memory in both preclinical and clinical models after PNE. Inclusion criteria consisted of peer-reviewed studies that were written in English, included PNE compared to a control, effects on short or long-term memory and/or cognitive function. Studies that did not investigate the anatomical or cognitive impacts of PNE were excluded. Specific effects of polydrug exposure mentioned in a few papers such as Liu et al. (2024) were not included due to possible confounding effects. A secondary search was conducted to supplement the findings using Boolean operators such as (placenta), (placenta) AND (nicotine), and (brain sparing) for additional information included in this review. Moreover, to expand upon specific terms or definitions, simple searches were conducted to consult relevant literature

Results

The literature search identified 12 preclinical studies, 6 clinical studies, and 4 literature reviews. Preclinical studies used rodent models to assess cognition and memory through various behavioural tests, summarized in Table 1, such as the Y-maze test, radial arm maze (RAM), Morris water maze test (MWMT), radial arm water maze (RAWM), novel object recognition test (NORT), object location test (OLT), object recognition test (ORT), open field test (OFT) [2, 7-17]. In these preclinical studies, rodents exposed to prenatal nicotine (PN) were compared to unexposed control counterparts to evaluate the specific impacts of nicotine exposure on cognitive function. Human clinical studies employed methods such as the Back-Task, fMRI analysis, and electroencephalogram (EEG) protocols [18-23], as summarized in Table 2. Both preclinical and clinical studies highlight cognitive deficits. However, clinical research is limited and sometimes fails to control for confounding factors like alcohol, marijuana exposure, or genetics. The studies involving animal and human subjects included relevant ethical considerations such as formal committee approval of utilised procedures.

Table 1. Summary of Findings from Preclinical Studies

Study	Study Model	Nicotine Exposure	Results
Archie et al. (2023) [2]	Adult CD1 female and male mice, PD40-45 and PD90-95 testing	e-Cigarette (ECIG) vapour (2.4% nicotine) from gestational day (GD) 5 to postnatal day (PD) 7 via lactation.	Significantly reduced expression of tight junction proteins (ZO-1, claudin-5, and occludin) of BBB in ECIG-exposed offspring. Slower learning processes were observed for ECIG-exposed male and female mice at adulthood. Decreased short-term recognition memory in exposed offspring for the NORT.
Al-Sawalha et al. (2020) [7]	Wistar rats, 19 weeks postnatal testing	1-hour ECIG aerosol exposure, 18 mg/mL nicotine.	Impairments in long-term memory function in the exposed group through testing with RAM trials after 30 min, 5 hours, and 24 hours.
Church et al. (2020) [8]	CD-1 Mice, 8 weeks postnatal testing	16 mg/mL nicotine, 3 hours/day for 7 days/week from GD 0.5 to GD 17.5.	Delayed escape latency, and reduced probe test performance and increased exploratory behaviours. Significant effects on exploratory and novelty-seeking behaviours in females. Reduced novel object recognition ability and IFNγ in PN-exposed offspring.
Deng et al. (2023) [9]	C57BL/6 Mice and only used male offspring mice in the behavioural experiments, PD60 testing	200 μg/mL nicotine in drinking water with 1% saccharin, beginning 2 weeks before mating and continuing through weaning of the offspring.	Compromised recognition memory in MWMT. Significant hippocampal and prefrontal cortical region changes through Bdnf, pCreb, and Sert gene expression.

Study	Study Model	Nicotine Exposure	Results
Gavini et al. (2021) [10]	C57BL/6 J female mice	200 ug/ml of nicotine through drinking water mixed with 2% saccharin initiated 3 weeks before mating until birth of offspring daily.	Reduction in spatial memory capacity and impairment in object location memory in nicotine-exposed mice from ORT and RAM tests. Decrease in acetylcholine (ACh) and acetylcholinesterase (AChE) in the hippocampus.
Fuentes-Cano et al. (2020) [11]	Albino mice BALB/c, PD30 testing	12 ug/mL of daily oral nicotine consumption initiated 10 days before mating until weaning	Decreased learning efficiency within a 24-hour study period. Impairments in long-term memory after 8 days of learning experience with the exposed mice.
Li et al. (2015) [12]	Pregnant Sprague-Dawley rats, PD70 testing	Nicotine at 6 mg/kg/day with a flow rate of 60 µl/day from GD4 until the end of the pregnancy.	Longer escape latency for PN-exposed offspring in the MWMT. Increased N-methyl-D-aspartic acid receptor protein (NMDAR1) and mRNA expression in PN-exposed offspring's hippocampus. Altered expression of α7 nAChRs and NMDAR during hippocampal development. Decreased α7-nAChRs in the hippocampus of PN-exposed offspring.
Martin et al. (2020) [13]	GAD67-GFP knock-in Swiss Webster female mice, PD60 and PD90 testing	100 or 200 µg/mL of nicotine in drinking water beginning 3 weeks before breeding and until 3 weeks postpartum.	Lower GABA-to-non-GABA neuron ratio in the frontal cortex of the 200 ug/mL nicotine mice group. Increased exploratory and novelty-seeking behaviours in PN-exposed mice found through photobeam motion sensor testing, Y-Maze, and Elevated Plus Maze testing.
McCarthy et al. (2022) [14]	Swiss Webster C57BL/6 female mice, 2-3 months testing	100-200 ug/mL nicotine in drinking water, daily consumption was 600-1200 ug of nicotine.	Decreased GABA-to-non-GABA ratios in PN-exposed mice. Reduction in medial prefrontal cortex volume and microstructural integrity of the ansiform lobule. Increased exploratory behavior in PN-exposed mice.
Polli et al. (2020) [15]	NMRI Mice	300 µg/mL nicotine via drinking water from 7 days before mating until the end of pregnancy. Saccharine (2%) was added to the drinking water.	Behavioural and neurobiological impairments in males. Exhibited hyperactivity in females but were otherwise less affected behaviorally. Results measured through the spontaneous alternation behaviour test, OFT and mRNA analysis for mGlu and NMDA receptors.
Sirasanagandla et al. (2014) [16]	Female Wistar rats, PD40 testing	0.96 mg/kg body weight subcutaneous injections daily dose.	PNE reduced spatial learning and memory performance in rat offspring, tested through the MWMT.
Zhang et al. (2018) [17]	C57Bl/6 female mice, PD30 testing	100 µg/ml of nicotine with 2% saccharin in aqueous solution initiated 3 weeks before mating until 3 weeks postpartum.	Spontaneous alternation (three arm choices without repeated entry) decreased in male mice in the water, saccharin, and nicotine + saccharin (N+S) groups. Object-based attention tests showed significant deficits in male N+S mice.

Table 2. Summary of Findings from Clinical Studies

Study	Nicotine Exposure	Study Size	Age	Results
Bennett et al. (2013) [18]	Mean number of cigarettes is 4.18 with a range of 1-10/per day	n = 18	12 years	Higher fMRI brain activation in the inferior parietal region of the exposed group. Lesser inferior frontal activation in the exposed group.
King et al. (2018) [19]	Smoking rates ranged from 0-20 cigarettes every day for the PN-exposed group	n = 48	3 to 5 months	Reduced orientation to stimulus from infants in the PN-exposed group. Reduced delta activity in K-complexes in the PN-exposed group.
Liu et al. (2024) [20]	Exposure to nicotine through tobacco, quantity, and frequency unspecified	n = 40	13 to 15 years	Reduced palladium volume. Results were confounded with cocaine exposure. Results discussed are related to nicotine exposure.
Longo et al. (2014) [21]	0.03-35 mg/day of nicotine	n = 25	Mean age of 21 years	Greater fMRI brain response in the frontal regions of exposed individuals. Greater activity in the parietal lobule and the left cingulate gyrus.
Madley-Dowd et al. (2024) [22]	Not specified	n = 13 479	8 to 15 years	No significant impacts on intellectual ability. A negative control design with partner smoking did not demonstrate a causal effect between PNE and intellectual disability.
Puga et al. (2024) [23]	Exposure to cigarettes, e-cigarettes, smokeless tobacco, cigars, and hookah	n = 11 448	9 to 12 years	Impairments in picture sequence memory capabilities in the PNE group. Significantly decreased ability in episodic memory.

Short-Term Memory Impacts of PNE

PNE significantly impacted short-term memory by disrupting neural development through genetic and epigenetic alterations and impaired neuronal balances, as evidenced by both clinical and preclinical studies [2]. Specifically, PNE affected the hippocampus, a critical region for memory, through receptor oxidative stress, inflammation, and neurotransmitter imbalances [8, 12-, 14]. Behavioural studies with NORT showed impaired short-term recognition memory in PNE offspring [2, 8, 9]. MWMT also revealed slowed learning in PNE offspring, indicative of deficits in short-term spatial acquisition [2, 8, 9, 12, 16]. The animals showed increased escape latency and difficulty identifying platforms during initial trials. These deficits were accompanied by altered synaptic plasticity, reduced neural connectivity, and disruptions in acetylcholine signalling, which is essential for cognitive processing [24]. As such, the effects of PNE can carry into adulthood, impairing essential cognitive functions.

Long-Term Memory Impacts of PNE

3 reviews discussed the effects of PNE on hippocampal neurogenesis, focusing on the effects of long-term memory potentiation and long-term memory such as episodic memory, semantic memory, and muscle memory [25, 26]. These forms of memory play a role in conditioning and testing trials of various memory tests such as NORT. In animal models, persistent autonomic alterations carried into adulthood such as decreased norepinephrine levels and impaired acute cholinergic stimulation [3]. Alterations in the brain's cholinergic neurotransmitter system were discussed as an effect of PNE and a justification for decreased cognitive function [16]. The literature search included only preclinical studies that studied the impact of PNE on long-term memory. Studies claimed that the long-term impacts of PNE include hyperactivity, decreased learning and memory function, increased depression, altered brain development and enhanced hypoxic-ischemic brain injury [2].

Neuropathological Impacts of PNE

Nicotine directly stimulates nAChRs, altering brain cell proliferation, maturation and differentiation [3, 12]. PNE decreases α7-nAChRs in the hippocampus of PN-exposed offspring but no significant difference at the mRNA level, suggesting post-transcriptional changes or cell death rather than gene expression alterations [12]. Moreover, overactivation of NMDAR1 leads to calcium influx, oxidative damage, mitochondrial dysfunction, and neuronal apoptosis, impairing learning and memory [12]. PNE reduces blood oxygen levels and increases pCO_2 and hemoglobin in fetuses which may exacerbate receptor changes through oxidative stress and neuronal apoptosis, contributing to memory impairment [12]. Reduced ACh and AChE activity levels were reduced due to decreased mRNA expression of choline transporters in the hippocampus [10]. PNE has been associated with epigenetic changes, including DNA methylation alterations in placental and fetal tissues, particularly in hippocampal

regions [9, 24]. For instance, studies have identified hypo-methylation in promoter regions of nicotine-metabolizing enzymes like CYP1A1, increasing susceptibility to oxidative damage

Anatomical Effects of PNE

A recurring theme found in the literature highlights areas and regions such as the hippocampus, prefrontal cortex, cingulate gyrus, frontal gyrus, temporal gyrus, medial temporal lobe, cerebellum, and parietal lobe and their roles in the function of spatial, sensory, verbal , picture sequence, declarative, episodic memory and overall consolidation [3, 9, 10, 12, 18, 19, 21, 23, 25, 26]. Specifically, 3 reviews discussed the hippocampus's role in long-term potentiation, episodic and spatial memory, and memory retrieval via synaptic connection to areas responsible for visual memory, auditory memory, and semantic memory [25-27]. Changes in baseline prefrontal cortical function affected short-term memory through an inability to process information. fMRI studies highlighted higher activation in regions, such as the inferior parietal lobe, left middle frontal gyrus, and left dorsolateral prefrontal cortex [14, 18, 21]. These brain regions are involved in short-term memory storage, verbal memory, and memory maintenance and manipulation, respectively, thus critical to the normal function of short-term memory [18, 21]. Decreases in cortical volumes of gray matter such as the medial prefrontal cortex, which is involved in critical regulation of attention, short-term memory, and risk-taking behaviours, were also observed in offspring with PNE [3, 14]. Sex differences were noted in 7 studies, with males exhibiting greater behavioural, molecular, and anatomical impairments related to memory than females [2, 8, 9, 12-15].

Discussion

While differences in gestation timelines exist between humans and animal model studies, rodent studies offer valuable insight into the impacts on brain development and help to nicotine's neuro-teratogenic effects on the CNS despite limitations in replicating the full human gestation period.

Short-Term Memory

Short-term memory, also called active or working memory, involves the temporary storage and processing of information for fast recall [26]. Sensory memory such as echoic or iconic memory precedes and transitions into short-term memory upon processing [26]. PNE impacts the structure and function of brain regions essential for memory such as the hippocampus, prefrontal cortex, parietal lobe, and cingulate gyrus, also inducing structural changes in prefrontal cortex neurons, including increased dendritic length and spine density [4].

fMRI analyses revealed heightened activity in brain regions such as the left middle frontal gyrus and dorsolateral prefrontal cortex in PN-exposed individuals during verbal memory tasks which suggests that exposed individuals expend greater neural effort to achieve comparable task performance to non-exposed counterparts [21]. Increased inferior parietal activation in exposed individuals implies a compensatory mechanism for memory maintenance but highlights inefficiencies compared to controls [21]. It was found that in animal model studies, specifically male mice exposed to PNE demonstrated anxiety- and compulsive-like behaviors, thus providing insight into gender differences within attention deficit hyperactivity disorder (ADHD) development in humans [15]. Exposed individuals exhibit patterns resembling those of ADHD, with impaired short-term memory, compared to age-appropriate frontal region development in unexposed counterparts [21, 25, 26]. When the development of key brain regions like the prefrontal cortex is particularly affected, the likelihood of disorders such as ADHD in PN-exposed individuals increases, becoming more apparent during school age [2, 3].

Glutamatergic neurons and GABAergic neurons, also known as GABA, are found to be recruited as associative memory cells in the brain [27]. Significant dose-dependent reductions to GABA-to-non-GABA neuron ratios were observed in preclinical studies, suggesting that PNE targets neural networks associated with GABA transmission and results in an imbalance between excitatory and inhibitory signalling through a reduction in frontal cortical inhibitory tone [14].

Long-Term Memory

Long-term memory stores information indefinitely, thus differing from short-term in storage capacity and duration [26]. Declarative memory, a subset of long-term memory, includes semantic memory (general knowledge) and episodic memory (past personal experiences) [26]. PNE significantly impairs episodic memory, with deficits linked to parahippocampal area reduction [23]. Structural and functional changes due to PNE in the hippocampus and cerebellum, critical for long-term and motor memory, further hinder memory consolidation [20, 25, 26, 28]. PNE compromises BBB integrity through the downregulation of tight-junction proteins like ZO-1 and occludin, impacting nervous tissue and behaviour [2].

A reduction in hippocampus-associated short-term and object location memory correlated with a decrease in ACh and AChe levels and an altered cholinergic function critical for normal memory function [13, 29]. Reductions in hippocampal choline transporter mRNA translation disrupt the regulation of hippocampal circuits [29]. ACh modulation of memory function is most prominent in the hippocampus where its role with declarative memory is independent of the modulation of implicit memory [29]. Nonetheless, a decrease in ACh levels align with the impairments observed [13]. Additionally, an absence of IFNγ in memory-related

brain regions was associated with altered performance in tasks on memory function [8, 10, 28].

Smaller cortical volumes in the posterior cingulate and entorhinal cortex, both critical for episodic memory processing, and reduced pallidum volume in adolescents exposed to PNE further underscores long-term structural impacts [19, 20]. Disrupted K-complex delta activity during sleep in PNE groups suggested impaired memory consolidation processes, particularly for declarative memory [19]. Overall, the clinical studies indicated that PNE does not manifest as overt cognitive deficits but rather, induces compensatory neural strategies and structural changes, with lasting implications for memory and cognitive function.These compensatory strategies likely aim to mitigate cognitive deficits as it has been discussed that human subjects challenged with harder tasks, and prenatally exposed to greater amounts of nicotine, may have more difficulty compensating, thus resulting in performance impairment [21].

Age Effects

It is important to consider the function of memory amongst age groups participating in clinical studies as memory function continues to change and develop after birth. Short-term and long-term object recognition peaks during adolescence [30]. Amongst the 6 clinical studies discussed, 1 study involved an age group of young adults, while the others studies age groups of adolescent participants or younger [18-23]. Longo et al. discussed greater brain responses in the brain's frontal regions of PNE individuals while Bennett et al. discussed lesser inferior frontal region brain activation in PNE individuals, suggesting changes in efficient usage of neural resources from adolescence to young adulthood to complete cognitive tasks [18, 21]. Both clinical studies utilised Back-Task performance results as a metric for short-term and long-term object recognition [18, 21]. No prominent trends were identified between the mice's ages and the impacts of PNE.

Sex Differences

PNE exhibits sex-dependent effects on cognition and behaviour in animal models. Nicotine-exposed male offspring exhibited more significant deficits in spatial memory and object-based attention with tasks such as the NORT, revealing increased errors and impaired recognition memory. These deficits may be linked to altered glutamatergic signalling, particularly affecting mGlu and NMDA receptor subunits in the prefrontal cortex, which may underlie behavioural deficits such as hyperactivity and increased escape latency in memory tasks [2, 9, 15]. However, nicotine-exposed females showed higher exploratory behaviour, hyperactivity, and novelty-seeking tendencies, possibly linked to estrogen receptor signalling and the hypothalamic-pituitary axis [8, 13, 14].

Both sexes experience reductions in GABA-to-non-GABA neuron ratios in the frontal cortex, leading to disrupted excitation-inhibition balance, though females exhibit greater exploratory tendencies compared to males [8, 12, 13]. PNE impacts the medial prefrontal cortex and cerebellum, contributing to deficits in short-term memory and attention regulation; these effects were more pronounced in males, resulting in cognitive impairments during memory retention phases [8, 9, 14]. The sex-dependent differences of PNE can be attributed to the varying impacts of nicotine on neurotransmitter systems, including glutamatergic and cholinergic pathways, as well as sex-dependent epigenetic regulation during fetal development. Moreover, the effects of nicotine may be less pronounced in females due to faster metabolism of nicotine [2].Another possible reason for the sex differences is BBB integrity. Research suggested that PNE males exhibit greater reductions in tight junction proteins like ZO-1 and claudin-5, which are crucial for maintaining BBB function. Disruptions in BBB permeability may enhance the passage of neuroinflammatory agents into the brain, exacerbating cognitive deficits in males. Female offspring, on the other hand, tend to have stronger BBB integrity due to higher baseline expression of tight junction proteins, as observed in preclinical studies comparing male and female endothelial cells [2]. These differences in BBB regulation may contribute to the more severe cognitive and behavioural impairments seen in males, particularly in tasks related to memory retention and attention [2].

Fetal Growth Restriction

PNE disrupts fetal brain development through placental dysfunction, compensatory fetal brain responses, and fetal growth restriction, which often results in a premature birth [2, 12, 24]. Chronic fetal hypoxia caused by placental dysfunction triggers brain sparing, which redirects oxygen-rich blood to the brain, but prolonged activation during later stages of gestation disrupts cerebral vasculature, hindering normal brain development [12, 24, 31, 32]. Fetal growth restriction and preterm delivery further reduce brain volume in white and gray matter, increasing the risk of neurobehavioral challenges, motor learning difficulties, and cognitive impairments in school-aged children, particularly in brain regions critical for attention and learning [3, 32].

Limitations

Through the literature review, it was determined that PNE correlated with negative impacts on memory. However, there remains a gap in the literature for studies that investigated impacts of PNE on long-term memory, specifically in human models. Future research can be driven towards longitudinal clinical study designs with human participants to investigate the structural, biochemical and cognitive impacts of PNE. While existing studies primarily focused on the overall effects of PNE, they did not extensively investigate the underlying sex-specific mechanisms, highlighting the need for future research on

hormonal and genetic influences. Future research may also include investigations into alternate exposure mechanisms such as that of second-hand exposure to smoke from nicotine sources.

Conclusions

This review highlighted the effects of PNE on memory, emphasizing its impact on brain structures, molecular pathways, and behaviour crucial to memory development and function. Alterations in the hippocampus, cerebellum, blood-brain barrier, and prefrontal cortex result in cognitive deficits like impaired object-based attention, spatial working memory, and locomotor activity, increasing the risk of conditions like ADHD, particularly in males. While evidence points to the detrimental effects of PNE, gaps remain in understanding its long-term memory impacts in humans. These findings stress the need for public health initiatives to reduce nicotine use during pregnancy and prevent enduring cognitive impairments in offspring.

List of Abbreviations

ACh: acetylcholine
AChE: acetylcholinesterase
ADHD: attention deficit hyperactivity disorder
BBB: blood-brain barrier
CNS: central nervous system
ECIG: e-cigarette
EEG: electroencephalogram
fMRI: functional magnetic resonance imaging
GD: gestational day
MWMT: morris water maze test
nAChR: nicotinic acetylcholine receptors
NORT: novel object recognition test
OFT: open field test
OLT: open location test
PD: postnatal day
PNE: prenatal nicotine exposure
RAM: radial arm maze
RAWM: radial arm water maze

Conflicts of Interest

The authors declare that they have no conflict of interest.

Ethics Approval and/or Participant Consent

As this was a literature review, no ethical concerns or consent needed to be considered.

Authors' Contributions

PB: made equal contributions to the entirety of this manuscript as well as the conception and design of the work and is to be held equally accountable for all aspects including drafting the manuscript, critically examining it for its content, and collectively approving the final version to be submitted.

EP: made equal contributions to the entirety of this manuscript as well as the conception and design of the work and is to be held equally accountable for all aspects including drafting the manuscript, critically examining it for its content, and collectively approving the final version to be submitted.

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References

[1] Jacobsen LK, Slotkin TA, Westerveld M, Mencl WE, Pugh KR. Visuospatial memory deficits emerging during nicotine withdrawal in adolescents with prenatal exposure to active maternal smoking. Neuropsychopharmacology. 2005 Dec 7;31(7):1550–61. https://doi.org/10.1038/sj.npp.1300981

[2] Archie SR, Sifat AE, Zhang Y, Villalba H, Sharma S, Nozohouri S, et al. Maternal e-cigarette use can disrupt postnatal blood-brain barrier (BBB) integrity and deteriorates motor, learning and memory function: Influence of sex and age. Fluids and Barriers of the CNS. 2023 Mar 10;20(1). https://doi.org/10.1186/s12987-023-00416-5

[3] Blood-Siegfried J, Rende EK. The long-term effects of prenatal nicotine exposure on neurologic development. Journal of Midwifery & Women's Health. 2010 Mar 4;55(2):143–52. http://doi.org/10.1016/j.jmwh.2009.05.006

[4] National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. Nicotine. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. [Internet]. Centers for Disease Control and Prevention (US); 2014. Chapter [5], Nicotine. [cited 2024 Nov 16]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK294308/

[5] Dwyer JB, McQuown SC, Leslie FM. The dynamic effects of nicotine on the developing brain. Pharmacology & Therapeutics. 2009 Mar 5;122(2):125–39. https://doi.org/10.1016/j.pharmthera.2009.02.003

[6] Wittenberg RE, Wolfman SL, De Biasi M, Dani JA. Nicotinic acetylcholine receptors and nicotine addiction: A brief introduction. Neuropharmacology. 2020 Jul 29;177:108256. https://doi.org/10.1016/j.neuropharm.2020.108256

[7] Al-Sawalha N, Alzoubi K, Khabour O, Karaoghlanian N, Ismail Z, Shihadeh A, et al. Effect of electronic cigarette aerosol exposure during gestation and lactation on learning and memory of adult male offspring rats. Physiology & Behavior. 2021 Jul 1;221: 112911. https://doi.org/10.1016/j.physbeh.2020.112911

[8] Church JS, Chace-Donahue F, Blum JL, Ratner JR, Zelikoff JT, Schwartzer JJ. Neuroinflammatory and behavioral outcomes measured in adult offspring of mice exposed prenatally to e-cigarette aerosols. Environmental Health Perspectives. 2020 Apr 15;128 (4). https://doi.org/10.1289/EHP6067

[9] Deng L, Wang Q, Lou Y. Maternal nicotine intoxication before pregnancy induces depressive- and anxiety-like behaviors as well as cognitive deficits in male offspring and correlates with neurobiological changes. Brain and Behavior. 2023 May 9;13(7). https://doi.org/10.1002/brb3.3052

[10] Gavini K, Yang E, Parameshwaran K. Developmental nicotine exposure impairs memory and reduces acetylcholine levels in the hippocampus of mice. Brain Research Bulletin. 2021 Nov;176:1–7. https://doi.org/10.1016/j.brainresbull.2021.07.030

[11] Fuentes-Cano MA, Bustamante-Valdez DJ, Durán P. Perinatal exposure to nicotine disrupts circadian locomotor and learning efficiency rhythms in juvenile mice. Brain Structure and Function. 2020 Aug 13; 225 (7);2287–97. https://doi.org/10.1007/s00429-020-02126-2

[12] Li J, Bo L, Zhang P, Gao Q, Li L, Tang J, et al. Exposure to nicotine during pregnancy and altered learning and memory in the rat offspring. Nicotine & Tobacco Research. 2014 Sept 19;17(6):661–6. https://doi.org/10.1093/ntr/ntu178

[13] Martin MM, McCarthy DM, Schatschneider, C, Trupiano, MX, Jones, SK, Kalluri A, et al. Effects of developmental nicotine exposure on frontal cortical GABA-to-non-GABA neuron ratio and novelty-seeking behavior. Cerebral Cortex. 2019 Oct 10;30(3): 1830–1842. https://doi.org/10.1093/cercor/bhz207

[14] McCarthy DM, Zhang L, Wilkes BJ, Vaillancourt, DE, Biederman J, Bhide PG. Nicotine and the developing brain: Insights from preclinical models. Pharmacology Biochemistry and Behavior. 2022 Mar; 214:173355. https://doi.org/10.1016/j.pbb.2022.173355

[15] Polli FS, Scharff MB, Ipsen TH, Aznar S, Kohlmeier KA, Andreasen JT. Prenatal nicotine exposure in mice induces sex-dependent anxiety-like behavior, cognitive deficits, hyperactivity, and changes in the expression of glutamate receptor associated-genes in the prefrontal cortex. Pharmacology Biochemistry and Behavior. 2020 Aug;195:172951. https://doi.org/10.1016/j.pbb.2020.172951

[16] Sirasanagandla S, Rooben, Rajkumar, Narayanan SN, Jetti R. Ascorbic acid ameliorates nicotine exposure induced impaired spatial memory performances in rats. West Indian Medical Journal. 2014 Feb 24;63(4):318-24. https://doi.org/10.7727/wimj.2013.089

[17] Zhang L, Spencer TJ, Biederman J, Bhide PG. Attention and working memory deficits in a perinatal nicotine exposure mouse model. PLOS ONE. 2018 May 24;13(5). https://doi.org/10.1371/journal.pone.0198064

[18] Bennett DS, Mohamed FB, Carmody DP, Malik M, Faro SH, Lewis M. Prenatal tobacco exposure predicts differential brain function during working memory in early adolescence: A preliminary investigation. Brain Imaging and Behavior. 2012 Jul 21; 7(1), 49–59. https://doi.org/10.1007/s11682-012-9192-1

[19] King E, Campbell A, Belger A, Grewen K. Prenatal nicotine exposure disrupts infant neural markers of orienting. Nicotine & Tobacco Research. 2017 Aug 17;20(7):897–902. https://doi.org/10.1093/ntr/ntx177

[20] Liu J, Lester BM, Neyzi N, Sheinkopf SJ, Gracia L, Kekatpure M, et al. Regional brain morphometry and impulsivity in adolescents following prenatal exposure to cocaine and tobacco. JAMA Pediatrics. 2013 Apr 1; 167(4):348. https://doi.org/10.1001/jamapediatrics.2013.550

[21] Longo CA, Fried PA, Cameron I, Smith AM. The long-term effects of prenatal nicotine exposure on verbal working memory: An fmri study of Young Adults. Drug and Alcohol Dependence. 2014 Nov 1;144:61–9. https://doi.org/10.1016/j.drugalcdep.2014.08.006

[22] Madley-Dowd P, Thomas R, Boyd A, Zammit S, Heron J, Rai D. Maternal smoking during pregnancy and offspring risk of intellectual disability: A UK-based Cohort Study. Frontiers in Psychiatry. 2024 Jun 25;15. https://doi.org/10.3389/fpsyt.2024.1352077

[23] Puga TB, Dai HD, Wang Y, Theye E. Maternal tobacco use during pregnancy and child neurocognitive development. JAMA Network Open. 2024 Feb 13;7(2). https://doi.org/10.1001/jamanetworkopen.2023.55952

[24] Nielsen CH, Larsen A, Nielsen AL. DNA methylation alterations in response to prenatal exposure of maternal cigarette smoking: A persistent epigenetic impact on health from maternal lifestyle? Archives of Toxicology. 2014 Dec 6;90(2):231–45. https://doi.org/10.1007/s00204-014-1426-0

[25] Sridhar S, Khamaj A, Asthana, MK. Cognitive Neuroscience Perspective on memory: Overview and summary. Frontiers in Human Neuroscience. 2023 Jul 26;17. https://doi.org/10.3389/fnhum.2023.1217093

[26] Cascella M, Al Khalili Y. Short-term memory impairment [Internet]. StatsPearls Publishing; 2024. [cited 2024 Nov 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545136/
[27] Wang JH, Wang D, Gao Z, Chen N, Lei Z, Cui S, et al. Both glutamatergic and Gabaergic neurons are recruited to be associative memory cells. Biophysical Journal. 2016 Feb 16;110(3). https://doi.org/10.1016/j.bpj.2015.11.2571
[28] Monteiro S, Ferreira FM, Pinto V, Roque S, Morais M, de Sá-Calçada D, et al. Absence of IFNΓ promotes hippocampal plasticity and enhances cognitive performance. Translational Psychiatry. 2016 Jan 5;6(1). https://doi.org/10.1038/tp.2015.194
[29] Haam J, Yakel JL. Cholinergic modulation of the hippocampal region and memory function. Journal of Neurochemistry. 2017 Aug 1;142(S2):111–21. https://doi.org/10.1111/jnc.14052
[30] Skalaban LJ, Cohen AO, Conley MI, Lin Q, Schwartz GN, Ruiz-Huidobro NA, et al. Adolescent-specific memory effects: Evidence from working memory, immediate and long-term recognition memory performance in 8–30 Yr Olds. Learning & Memory. 2022 Aug;29(8):223–33. https://doi.org/10.1101/lm.053539.121
[31] Miller SL. Huppi PS, Mallard C. The consequences of fetal growth restriction on brain structure and neurodevelopmental outcome. The Journal of Physiology. 2016 Jan 5;594(4):807–23. https://doi.org/10.1113/JP271402
[32] Cohen E, Baerts W, van Bel F. Brain-sparing in intrauterine growth restriction: Considerations for the Neonatologist. Neonatology. 2015 Aug 15;108(4):269–76. https://doi.org/10.1159/000438451

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