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Xenoestrogens, Cognitive Function, Pain Modulation, and Neuroplasticity: Neuroendocrine Interactions Involving the Prefrontal Cortex and Amygdala

Marco Vinícios de Oliveira Santana[1], Carlos Henrique Marchiori[1*], Klebert de Paula Malheiros[1], Érico Meirelles de Melo[1]

[1]Marco Santana Institute, Goiânia, Goiás, Brazil

Abstract: Xenoestrogens are environmental compounds capable of interfering with endogenous estrogenic signaling through receptor-mediated and non-receptor-mediated mechanisms. Although traditionally studied in relation to reproductive and developmental toxicity, increasing evidence indicates that these compounds may also affect the central nervous system. Estrogen-sensitive pathways participate in synaptic plasticity, neurodevelopment, neuroinflammation, cognition, emotional regulation, and pain modulation. This narrative review synthesizes current evidence on the relationship between xenoestrogens, cognitive function, pain modulation, and neuroplasticity, with emphasis on mechanisms involving the prefrontal cortex and amygdala. The literature indicates that bisphenol A, bisphenol analogs, phthalates, PFAS, parabens, pesticides, and other endocrine-disrupting chemicals may influence neuronal development, dendritic remodeling, neurotransmission, oxidative stress, glial activation, and estrogen receptor signaling. The strongest evidence concerns neurodevelopmental and cognitive outcomes, particularly following prenatal, early-life, or chronic low-dose exposure. Evidence directly linking xenoestrogens to chronic pain remains limited; however, biological plausibility is supported by the involvement of estrogen receptors, neuroimmune pathways, prefrontal descending control, amygdala-mediated emotional salience, and maladaptive plasticity in pain processing. Current limitations include exposure heterogeneity, mixture effects, sex-specific variability, non-linear dose responses, and insufficient integration of neuroimaging, hormonal, inflammatory, cognitive, and pain-related outcomes. Future research should prioritize longitudinal, sex-sensitive, biomarker-based, and mixture-oriented approaches. Overall, xenoestrogens should be considered potential environmental modulators of brain health across the lifespan, with particular relevance to cognition, neuroplasticity, emotional regulation, and pain vulnerability.

Keywords: Amygdala, Cognitive Function, Bisphenol A, Endocrine-Disrupting Chemicals, Estrogen Receptors, Neuroplasticity, Neuroinflammation, Pain Modulation, Prefrontal Cortex, Xenoestrogens.

Research Paper

***Corresponding Author:**
Carlos Henrique Marchiori
Marco Santana Institute, Goiânia, Goiás, Brazil

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1.0. INTRODUCTION

Xenoestrogens are exogenous chemical compounds capable of mimicking, antagonizing, or modifying endogenous estrogenic signaling through genomic and non-genomic pathways. These substances belong to the broader group of endocrine-disrupting chemicals and include bisphenols, phthalates, parabens, pesticides, polychlorinated compounds, and other environmental contaminants. Their relevance to medicine has expanded because estrogen signaling is not restricted to reproductive tissues, but also participates in brain development, synaptic remodeling, neuroimmune regulation, mitochondrial function, and behavioral adaptation. The central nervous system is therefore a critical target for compounds capable of interfering with estrogen receptors and estrogen-sensitive intracellular cascades (Shanle and Xu, 2011; Frye *et al*., 2012).

Estrogens influence brain function through estrogen receptor alpha, estrogen receptor beta, and membrane-associated receptors, including G protein-coupled estrogen receptor pathways. These receptors are distributed in cortical, limbic, hippocampal,

hypothalamic, and brainstem regions involved in cognition, pain modulation, emotional processing, and autonomic regulation. Through these mechanisms, estrogenic signaling can affect dendritic spine density, synaptic transmission, neurotransmitter balance, neurogenesis, and long-term potentiation. Consequently, xenoestrogens may disrupt brain function not only by imitating estradiol, but also by altering receptor expression, intracellular signaling, and the timing of neurodevelopmental events (Watson *et al*., 2011; Hara *et al*., 2015).

The prefrontal cortex is one of the most important neural substrates for executive function, working memory, inhibitory control, decision-making, and top-down regulation of emotional and nociceptive responses. Estrogen-sensitive signaling in this region contributes to synaptic efficiency and cognitive flexibility, while disruption of cortical maturation may impair behavioral regulation and adaptive responses to stress. Experimental studies indicate that bisphenol A and related compounds can modify synaptic structure and function in cortical networks, suggesting a plausible pathway through which xenoestrogens may affect cognition and prefrontal-dependent behavior (Hajszan and Leranth, 2010; Hu *et al*., 2017).

The amygdala is another critical structure for understanding the relationship between xenoestrogens, pain, and cognition. This region integrates threat perception, emotional memory, salience attribution, fear learning, and affective components of pain. Its functional interaction with the prefrontal cortex allows emotional experiences to influence attention, decision-making, and pain perception. During development, the amygdala is particularly sensitive to environmental and hormonal signals, which makes it vulnerable to chemicals capable of interfering with estrogenic and neuroendocrine regulation (Liu *et al*., 2017; Tottenham and Gabard-Durnam, 2017).

Pain is not only a sensory phenomenon, but also a multidimensional experience involving nociceptive transmission, emotional appraisal, attention, memory, and descending modulatory control. Estrogen receptors participate in several levels of pain regulation, including peripheral nociceptors, spinal cord circuits, supraspinal structures, glial activation, and inflammatory signaling. Depending on receptor subtype, sex, hormonal state, tissue context, and timing of exposure, estrogenic mechanisms may produce pronociceptive or antinociceptive effects. This complexity provides an important biological basis for investigating whether xenoestrogens may influence pain sensitivity, central sensitization, and chronic pain vulnerability (Almey *et al*., 2015; Chen *et al*., 2021).

Neuroplasticity represents the central biological bridge connecting cognition, pain, and environmental endocrine disruption. Adaptive plasticity allows the nervous system to respond to learning, stress, injury, hormonal variation, and environmental challenges, whereas maladaptive plasticity may contribute to persistent pain, affective symptoms, and cognitive decline. Estrogenic signaling is involved in synaptic remodeling and neural resilience across the lifespan, and interference by xenoestrogens may disturb the balance between adaptive and pathological plasticity. This is especially relevant for cortical-limbic circuits, where changes in connectivity may modify emotional regulation, pain processing, and cognitive performance (Korol and Pisani, 2015; Price and Duman, 2020).

Early-life exposure to endocrine-disrupting chemicals has become a major concern because prenatal, neonatal, childhood, and adolescent periods are marked by intense neuronal proliferation, migration, synaptogenesis, myelination, and pruning. During these windows, estrogenic signaling contributes to the organization of neural circuits, including those related to cognition, emotion, and stress responsivity. Exposure to bisphenol A, phthalates, and other xenoestrogens during vulnerable developmental stages may therefore produce persistent neurobehavioral consequences. These effects may be expressed later as impairments in attention, executive function, memory, affective regulation, or pain-related vulnerability (Braun, 2017; Minatoya and Kishi, 2021).

Bisphenol A is among the most extensively studied xenoestrogens in relation to brain function. Experimental evidence has associated BPA exposure with alterations in dendritic spines, cortical neurogenesis, neurotransmission, BDNF-related pathways, and synaptic plasticity. Human and translational research also supports concern regarding BPA and bisphenol analogs as potential contributors to neurodevelopmental and behavioral outcomes. Although findings vary across models, doses, exposure windows, and sex, the convergence of epidemiological and experimental evidence supports the need for a focused synthesis of BPA-related effects on neural systems involved in cognition, emotion, and pain (Hyun *et al*., 2022; Li *et al*., 2023; Costa *et al*., 2024).

Phthalates, PFAS, bisphenol substitutes, parabens, and pesticide-related endocrine disruptors are increasingly relevant because real-life exposure rarely occurs through a single chemical agent. Humans are chronically exposed to mixtures of compounds through food packaging, consumer products, contaminated water, cosmetics, household materials, and occupational environments. These combined exposures may interact through additive, synergistic, or antagonistic mechanisms, complicating causal interpretation. For this reason, contemporary research has moved from isolated chemical models toward mixture-based approaches and multi-system evaluation of neuroendocrine disruption (Sellinger *et al*., 2021; Morales-Grahl *et al*., 2024; Sánchez *et al*., 2024).

Sex, age, hormonal status, and life stage are essential modifiers of the neurological effects of xenoestrogens. The female lifespan includes dynamic changes in ovarian hormones, brain estrogen receptor density, and neuroendocrine regulation, while males also depend on estrogenic signaling through aromatization and receptor-mediated pathways. Menopause, aging, puberty, pregnancy, and neurodevelopmental transitions may therefore modify susceptibility to xenoestrogen exposure. The same environmental chemical may produce different consequences depending on receptor distribution, endogenous hormone levels, metabolic capacity, and pre-existing vulnerability of cortical-limbic circuits (Maioli *et al*., 2021; Reddy *et al*., 2022; Mosconi *et al*., 2024).

Despite growing evidence, several gaps remain. The relationship between xenoestrogens and cognition is better studied than the relationship between xenoestrogens and pain. Likewise, many studies focus on neurodevelopmental outcomes, while fewer integrate pain, prefrontal regulation, amygdala reactivity, and adult neuroplasticity within the same framework. Current evidence also remains heterogeneous because of differences in exposure assessment, biological matrices, dose ranges, sex-specific analyses, outcome measures, and experimental models. These limitations justify a narrative review capable of integrating mechanistic, experimental, epidemiological, and clinical perspectives (Hilz *et al*., 2022; Cajachagua-Torres *et al*., 2024).

The objective of this review is to synthesize current evidence on the relationship between xenoestrogens, cognition, pain, and neuroplasticity, with emphasis on estrogen-sensitive mechanisms involving the prefrontal cortex and amygdala. The specific objectives are to describe the main xenoestrogens relevant to neural function; examine their effects on estrogen receptors, synaptic plasticity, neuroinflammation, and neurodevelopment; analyze possible links with cognitive performance, emotional regulation, and pain modulation; identify current methodological limitations; and discuss future perspectives for research, prevention, and translational medicine (Bustamante-Barrientos *et al*., 2021; Patisaul, 2021; Jocsak *et al*., 2026).

2. METHODS

This study was designed as a narrative review aimed at synthesizing current scientific evidence on the relationship between xenoestrogens, cognition, pain, and neuroplasticity, with emphasis on mechanisms involving estrogen-sensitive signaling in the prefrontal cortex and amygdala. A narrative approach was selected because the theme integrates heterogeneous evidence from toxicology, neuroendocrinology, neuroscience, pain medicine, developmental biology, and environmental health. This format allowed conceptual integration of mechanistic, experimental, epidemiological, and translational findings without restricting the analysis to a single outcome or population.

Scientific literature was identified through structured searches in PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. Search terms included combinations of xenoestrogens, endocrine-disrupting chemicals, bisphenol A, bisphenol analogs, phthalates, PFAS, estrogen receptors, neuroplasticity, cognition, pain, chronic pain, nociception, prefrontal cortex, amygdala, neuroinflammation, synaptic plasticity, neurodevelopment, and brain aging. Boolean operators were used to combine chemical exposure terms with neurological and clinical outcomes. The search strategy prioritized publications from 2018 to 2026, while also allowing inclusion of classical studies when they were essential for defining mechanisms, concepts, or historical foundations.

Eligible publications included original experimental studies, epidemiological investigations, clinical observational studies, systematic reviews, meta-analyses, narrative reviews, mechanistic studies, and authoritative scientific statements. Studies were considered relevant when they addressed estrogenic endocrine disruption, brain estrogen receptor signaling, synaptic or structural plasticity, cognitive outcomes, pain modulation, cortical-limbic circuitry, or developmental and adult neurological consequences of xenoestrogen exposure. Articles were excluded when they focused exclusively on reproductive outcomes without neurological relevance, occupational toxicology without central nervous system endpoints, or chemical exposure without a mechanistic or clinical connection to cognition, pain, or neuroplasticity.

Data extraction was performed qualitatively, with emphasis on study design, exposure type, biological mechanism, neural region, population or model studied, and reported neurological outcome. The extracted information was organized into predefined thematic domains: xenoestrogen classes and sources of exposure; estrogen receptor signaling; prefrontal cortex and cognition; amygdala, emotion, and pain; neuroplasticity and synaptic remodeling; neuroinflammation and oxidative stress; developmental vulnerability; sex-specific effects; and current limitations and future perspectives. Because of the heterogeneity of exposure measurements, biological matrices, experimental models, and clinical outcomes, no quantitative meta-analysis was performed.

The synthesis was structured to support a clinically oriented interpretation of the available evidence. Results were organized thematically and summarized in tables to compare chemical classes, mechanisms, neural targets, and potential clinical implications. The discussion was developed to integrate mechanistic plausibility with translational relevance, highlighting the current gaps between experimental

evidence and human clinical outcomes. Particular attention was given to the need for cautious interpretation, since the relationship between xenoestrogens and cognition is more developed than the direct evidence linking xenoestrogens to chronic pain.

3. RESULTS

The literature synthesis identified a heterogeneous but coherent body of evidence linking xenoestrogen exposure to estrogen-sensitive neural mechanisms involved in cognition, pain modulation, and neuroplasticity. The analyzed studies included experimental animal models, in vitro neuronal investigations, epidemiological studies, neurodevelopmental cohorts, systematic reviews, mechanistic papers, and translational analyses. Although the strength of evidence varied according to compound, exposure window, sex, and outcome, the overall findings supported the concept that xenoestrogens may interfere with multiple levels of central nervous system regulation. The main chemical classes identified in the literature included bisphenols, phthalates, PFAS, parabens, pesticides, industrial pollutants, and mixed environmental exposures, each with distinct sources, mechanisms, and neurological implications (Table 1).

Table 1: Main xenoestrogen classes and neurological relevance. This table summarizes the principal compound groups identified in the literature. Potential links with cognition, pain, neuroplasticity, and clinical interpretation are highlighted

Xenoestrogen class	Examples	Exposure sources	Neural target	Potential implication
Bisphenols	BPA	Plastics; food packaging	Cortex; hippocampus	Synaptic plasticity
Bisphenol analogs	BPS; BPF	Thermal paper substitutes	Developing brain	Neurodevelopment
Phthalates	DEHP	PVC; plasticizers	Prefrontal cortex	Executive function
Phthalates	DBP; DEP	Cosmetics; personal care	Attention networks	Behavioral regulation
PFAS	PFOS	Water; industrial products	White matter	Cognitive performance
PFAS	PFOA	Food packaging	Developing brain	Learning outcomes
Parabens	Methylparaben	Cosmetics; preservatives	Estrogen receptors	Hormonal signaling
Pesticides	Organochlorines	Agriculture; residues	Limbic circuits	Emotional regulation
Pesticides	Pyrethroids	Domestic insecticides	Neural excitability	Neurobehavioral effects
PCBs	PCB mixtures	Environmental pollutants	Brain development	Cognitive impairment
Dioxin-like agents	TCDD-related	Industrial contamination	Neuroimmune pathways	Inflammation
Mixed exposure	Multiple agents	Daily environmental contact	Cortical-limbic systems	Combined disruption

Bisphenol A emerged as the most frequently investigated compound in relation to neural function. Experimental studies consistently reported alterations in synaptic development, dendritic spine density, neurotransmission, and cortical maturation following BPA exposure. Several studies also indicated that BPA may affect pathways related to estrogen receptor signaling, BDNF-mediated synaptic support, glutamatergic transmission, oxidative stress, and neuroinflammatory activation. These findings were particularly relevant in models involving prenatal, perinatal, juvenile, and adult exposure. The results suggest that BPA may influence both early brain organization and later-life neural function, especially in regions involved in cognition and behavioral regulation (Table 2).

Table 2: Main neurological mechanisms associated with bisphenol A exposure. This table summarizes mechanisms commonly described in BPA-related neural studies. The mechanisms are organized by pathway, consequence, brain region, and clinical relevance

Mechanism	Pathway	Neural consequence	Region involved	Clinical relevance
ER signaling	Genomic/non-genomic	Hormonal disruption	Cortex; limbic system	Cognition; emotion
Spine density	Dendritic remodeling	Reduced connectivity	Prefrontal cortex	Executive impairment
BDNF signaling	Trophic support	Synaptic maturation changes	Cortex; hippocampus	Learning vulnerability
Glutamate balance	Excitatory transmission	Altered plasticity	Cortical networks	Cognitive dysfunction
GABA balance	Inhibitory tone	Network instability	Limbic circuits	Anxiety; reactivity
Oxidative stress	Redox imbalance	Cellular injury	Neurons; glia	Neural vulnerability

Mechanism	Pathway	Neural consequence	Region involved	Clinical relevance
Neuroinflammation	Cytokine signaling	Glial activation	Brain-wide	Pain; behavior
Mitochondria	Energy metabolism	Reduced resilience	High-demand circuits	Fatigue; dysfunction
Epigenetics	Gene expression	Persistent changes	Developing brain	Long-term outcomes
Neurogenesis	Cell production	Altered maturation	Cortex; hippocampus	Developmental risk
Monoamines	Dopamine/serotonin	Behavioral modulation	Prefrontal-limbic	Mood; attention
Synaptogenesis	Circuit formation	Network reorganization	Cortical neurons	Neurodevelopment

Evidence related to developmental windows indicated that timing of exposure is a major determinant of neurological outcome. Prenatal and early postnatal periods were associated with vulnerability in neurogenesis, synaptogenesis, hormonal programming, and limbic-cortical organization. Childhood and adolescence were linked to effects on attention networks, myelination, executive maturation, and emotional regulation. Adult and aging periods were more often associated with altered synaptic remodeling, neuroimmune balance, brain estrogen receptor changes, and cognitive resilience. This temporal pattern supports the interpretation that xenoestrogens may produce different outcomes depending on the maturational stage of the nervous system at the time of exposure (Table 3).

Table 3: Xenoestrogen-related outcomes across developmental stages. This table summarizes neurological vulnerability according to the timing of exposure. The developmental window is linked with neural processes, regions, outcomes, and clinical concerns

Exposure window	Main neural process	Vulnerable region	Possible outcome	Clinical concern
Preconception	Gamete programming	Epigenetic marks	Inherited susceptibility	Intergenerational risk
First trimester	Neural tube; migration	Primitive brain	Early organization change	Developmental delay
Second trimester	Neurogenesis	Cortex	Cell number alteration	Cognitive risk
Third trimester	Synaptogenesis	Limbic circuits	Emotional programming	Stress sensitivity
Neonatal period	Sensory integration	Amygdala; hypothalamus	Affective change	Regulation problems
Infancy	Rapid synapse growth	Cortex; hippocampus	Learning changes	Delayed milestones
Childhood	Myelination	Attention networks	Executive weakness	School performance
Adolescence	Synaptic pruning	Prefrontal cortex	Risk-taking; impulsivity	Behavioral vulnerability
Adult life	Synaptic remodeling	Cortical-limbic circuits	Adaptation changes	Cognition; pain
Pregnancy	Hormonal adaptation	Maternal brain	Neuroendocrine change	Exposure transfer
Menopause	ER reorganization	Brain networks	Cognitive vulnerability	Brain aging
Older age	Neuroimmune balance	White matter; cortex	Reduced resilience	Cognitive decline

The prefrontal cortex appeared as a central region for interpreting the cognitive consequences of xenoestrogen exposure. Studies involving BPA, phthalates, and related endocrine-disrupting chemicals reported changes in cortical neuron number, synaptic formation, cognitive flexibility, working memory, and stress-related behavioral responses. Because the prefrontal cortex exerts top-down control over attention, emotion, and pain modulation, disruption of this region may produce broad neurological effects. The findings suggest that xenoestrogen exposure may weaken regulatory control over limbic and nociceptive systems, particularly when exposure occurs during periods of cortical maturation (Table 4).

Table 4: Prefrontal cortex functions potentially affected by xenoestrogens. This table summarizes prefrontal domains relevant to cognition, emotion, and pain control. Potential endocrine-disrupting effects are related to mechanisms, behavior, and clinical interpretation

Prefrontal domain	Potential disruption	Mechanism	Behavioral expression	Clinical implication
Working memory	Reduced efficiency	Synaptic weakening	Forgetfulness	Cognitive impairment
Inhibitory control	Poor filtering	Maturation change	Impulsivity	Behavioral dysregulation
Cognitive flexibility	Rigid responses	Dopamine imbalance	Poor adaptation	Executive dysfunction
Attention	Network instability	Neurotransmitter change	Distractibility	Learning difficulty
Decision-making	Altered valuation	Cortical-limbic imbalance	Risk choices	Maladaptive behavior
Emotion regulation	Weaker control	Top-down failure	Anxiety sensitivity	Affective symptoms
Stress adaptation	Hormonal dysregulation	HPA interaction	Hyperreactivity	Somatic burden
Pain inhibition	Reduced descending control	Prefrontal output change	Pain persistence	Chronic pain risk
Social cognition	Altered appraisal	Connectivity changes	Misinterpretation	Functional impairment
Reward processing	Dopamine disruption	Motivational change	Anhedonia	Mood vulnerability
Planning	Reduced organization	Executive load	Poor goal setting	Daily dysfunction
Metacognition	Impaired self-monitoring	Network disruption	Poor insight	Treatment challenge

The amygdala was identified as an important limbic structure connecting xenoestrogen exposure with emotional salience, fear learning, stress reactivity, and the affective dimension of pain. Although direct studies on xenoestrogens and amygdala-mediated pain remain limited, the available evidence supports biological plausibility through estrogen-sensitive developmental and synaptic mechanisms. Altered amygdala-prefrontal communication may influence pain perception by increasing threat appraisal, emotional memory, and hypervigilance. This relationship is particularly relevant because chronic pain often involves enhanced limbic reactivity and reduced cortical regulation, forming a neural pattern that may be susceptible to endocrine and environmental modulation (Table 5).

Table 5: Amygdala-related mechanisms potentially involved in xenoestrogen effects. This table summarizes limbic mechanisms connecting endocrine disruption with emotion and pain. Amygdala functions are linked with possible effects, circuit interactions, and consequences

Amygdala function	Possible effect	Circuit interaction	Pain/cognition link	Consequence
Threat detection	Increased salience	Amygdala-cortex	Attention bias	Hypervigilance
Fear learning	Altered conditioning	Hippocampus	Pain memory	Avoidance
Stress response	Enhanced reactivity	HPA axis	Somatic arousal	Stress sensitivity
Pain affect	Greater unpleasantness	Insula; ACC	Pain amplification	Chronic vulnerability
Emotional memory	Persistent encoding	Hippocampus	Pain recall	Rumination
Reward aversion	Negative valuation	Striatum	Motivation loss	Affective burden
Social threat	Misread cues	Prefrontal cortex	Social stress	Anxiety symptoms
Autonomic output	Sympathetic bias	Brainstem	Body vigilance	Somatic distress
Development	Limbic programming	Cortical maturation	Emotional traits	Long-term risk
Neuroimmune response	Cytokine sensitivity	Glia	Pain sensitization	Inflammation
Connectivity	Reduced regulation	PFC-amygdala	Poor inhibition	Emotional dyscontrol
Extinction	Delayed safety learning	Prefrontal circuits	Persistent fear	Pain avoidance

Neuroplasticity was the main integrative domain across the reviewed literature. Xenoestrogens were associated with alterations in synaptic remodeling, dendritic architecture, neurogenesis, receptor expression, neurotransmitter balance, epigenetic regulation, and glial adaptation. These mechanisms were observed across different experimental systems, including cortical neurons, hippocampal circuits, and developmental models. The results suggest that xenoestrogens may not produce a single neurological phenotype, but rather

modify the biological conditions under which neural circuits adapt to experience, stress, inflammation, and hormonal variation. This plasticity-centered interpretation helps connect apparently separate outcomes, including cognitive impairment, affective symptoms, and pain modulation (Table 6).

Table 6: Neuroplastic mechanisms linking xenoestrogens to neurological outcomes. This table summarizes plasticity pathways through which environmental estrogenic agents may act. Mechanisms are connected with the direction of disruption, target system, and possible outcomes

Plasticity mechanism	Direction of disruption	Target system	Functional domain	Possible outcome
Dendritic remodeling	Abnormal spine density	Cortical neurons	Learning	Memory change
Synaptogenesis	Altered formation	Developing circuits	Neurodevelopment	Developmental dysfunction
LTP	Reduced strengthening	Hippocampus; cortex	Memory	Poor retention
LTD	Imbalanced pruning	Cortical networks	Adaptation	Rigid behavior
Neurogenesis	Modified production	Hippocampus	Plasticity	Mood/cognition change
Myelination	White matter change	Association tracts	Processing speed	Cognitive slowing
Epigenetic regulation	Persistent expression	Genome-wide	Development	Long-term vulnerability
Receptor expression	ER redistribution	Hormonal circuits	Sensitivity	Altered responses
Glial plasticity	Reactive activation	Microglia; astrocytes	Neuroimmune support	Pain/mood interaction
Network connectivity	Altered balance	PFC-amygdala	Regulation	Emotional symptoms
Neurotransmission	Excitation/inhibition shift	Cortical-limbic	Information flow	Behavioral instability
Metaplasticity	Changed plastic threshold	Multiple circuits	Learning capacity	Reduced resilience

Neuroinflammation and oxidative stress appeared repeatedly as intermediate mechanisms between xenoestrogen exposure and nervous system dysfunction. Several studies suggested that endocrine-disrupting chemicals may activate glial cells, increase inflammatory mediators, impair mitochondrial function, alter redox balance, and disturb cellular survival pathways. These mechanisms are relevant because neuroinflammation participates in both cognitive decline and chronic pain states. In this context, xenoestrogens may act not only through receptor-mediated estrogenic effects, but also through broader cellular stress pathways. This dual action may help explain why the same compounds can influence neurodevelopment, adult behavior, synaptic function, and possibly pain-related sensitization (Table 7).

Table 7: Cellular stress pathways associated with xenoestrogen exposure. This table summarizes inflammatory, oxidative, and metabolic pathways relevant to neural dysfunction. Each pathway is related to a biological effect, neural level, and possible clinical consequence

Pathway	Biological effect	Neural level	Associated process	Clinical consequence
Microglial activation	Inflammatory signaling	Glia	Neuroimmune response	Pain sensitization
Astrocyte reactivity	Altered support	Synapse environment	Network regulation	Cognitive change
Cytokine release	Immune imbalance	Brain parenchyma	Inflammation	Mood/pain modulation
Oxidative stress	Cellular damage	Neurons	Redox imbalance	Synaptic dysfunction
Mitochondrial impairment	Low energy efficiency	High-demand circuits	Metabolic stress	Neural fatigue
Pyroptosis signaling	Inflammatory cell death	Neuronal/glial cells	Cell injury	Tissue vulnerability
BBB disruption	Permeability change	Vascular interface	Toxic access	Neurotoxic risk
Calcium imbalance	Signal instability	Synapses	Excitability	Sensitization

Pathway	Biological effect	Neural level	Associated process	Clinical consequence
Endoplasmic stress	Protein-folding burden	Cells	Stress response	Cell dysfunction
DNA damage	Repair activation	Nucleus	Genotoxic stress	Long-term risk
Lipid peroxidation	Membrane injury	Cell membranes	Oxidative injury	Reduced resilience
Apoptotic signaling	Programmed cell loss	Neural tissue	Developmental injury	Functional deficit

The relationship between xenoestrogens and pain was less directly established than the relationship between xenoestrogens and cognition or neurodevelopment. However, the literature revealed several indirect pathways through which xenoestrogens may influence pain mechanisms. These included estrogen receptor signaling, neuroimmune activation, oxidative stress, synaptic plasticity, emotional regulation, descending pain modulation, and cortical-limbic connectivity. The evidence therefore supports a cautious interpretation: xenoestrogens should not yet be considered established direct causes of chronic pain, but they may represent environmental modulators of biological systems that participate in pain vulnerability and persistence (Table 8).

Table 8: Possible pathways linking xenoestrogens with pain modulation. This table summarizes indirect mechanisms through which estrogenic disruptors may influence pain. The pathways include peripheral, spinal, supraspinal, emotional, and descending components

Pathway	Neural level	Potential mechanism	Pain implication	Evidence strength
ER signaling	Peripheral/central	Receptor modulation	Sensitivity change	Moderate
Neuroinflammation	Glia/cytokines	Immune activation	Central sensitization	Indirect
Oxidative stress	Cellular metabolism	Excitability change	Hyperalgesia risk	Indirect
Prefrontal dysfunction	Supraspinal	Reduced top-down control	Poor inhibition	Plausible
Amygdala reactivity	Limbic	Threat amplification	Pain unpleasantness	Plausible
Hippocampal memory	Limbic	Pain memory encoding	Persistence	Indirect
Descending control	Brainstem pathways	Modulatory imbalance	Low analgesia	Plausible
Spinal sensitization	Dorsal horn	Synaptic gain	Allodynia	Limited
Peripheral nociceptors	Sensory neurons	Threshold change	Nociception	Limited
Stress axis	Neuroendocrine	HPA dysregulation	Pain amplification	Plausible
Sex hormones	Systemic	Hormonal interaction	Sex-specific pain	Moderate
Epigenetic changes	Gene regulation	Persistent expression	Chronicity	Emerging

Sex-specific effects were a recurrent finding across the reviewed evidence. Differences in receptor expression, endogenous hormone levels, developmental timing, metabolism, and brain circuit organization may alter vulnerability to xenoestrogen exposure. Some experimental findings showed sex-dependent effects on cortical structure, monoaminergic systems, behavior, and synaptic outcomes. In human studies, sex-stratified analyses were not always available, which limited interpretation. Nevertheless, the available data indicate that sex should be treated as a core biological variable in studies of xenoestrogens, cognition, pain, and neuroplasticity rather than as a secondary adjustment factor (Table 9).

Table 9: Factors modifying neurological responses to xenoestrogen exposure. This table summarizes biological and methodological variables that may influence outcomes. Modifiers are linked with their effects and implications for future research design

Modifier	Influence on outcome	Affected domain	Interpretation issue	Research implication
Sex	Hormonal context	Brain receptors	Different vulnerability	Stratified analysis
Age	Developmental stage	Neural maturation	Window-specific effects	Age-based models
Dose	Non-linear response	Endocrine signaling	Low-dose complexity	Dose-response testing
Mixtures	Combined action	Multiple pathways	Single-agent limits	Mixture designs
Duration	Cumulative burden	Plasticity	Acute vs chronic	Longitudinal data
Timing	Critical windows	Neurodevelopment	Sensitive periods	Precise exposure mapping
Biological matrix	Measurement variability	Exposure assessment	Comparability limits	Standardized sampling

Modifier	Influence on outcome	Affected domain	Interpretation issue	Research implication
Genetics	Susceptibility	Metabolism/receptors	Individual differences	Risk profiling
Epigenetics	Persistent regulation	Gene expression	Delayed effects	Molecular endpoints
Nutrition	Detoxification capacity	Metabolism	Confounding	Dietary assessment
Comorbidity	Baseline vulnerability	Pain/cognition	Mixed causality	Clinical adjustment
Socioenvironmental	Exposure clustering	Population risk	Residual confounding	Contextual models

The evidence also highlighted important methodological limitations. Exposure assessment varied substantially across studies, including differences in biological matrices, timing of sampling, chemical metabolites, and analytical methods. Many experimental studies used exposure conditions that may not fully reflect chronic low-dose human exposure. Human studies often faced residual confounding, mixture complexity, reverse causality, and limited longitudinal follow-up. In addition, cognitive outcomes were more frequently measured than pain outcomes, and few studies integrated neuroimaging, inflammatory biomarkers, hormonal assessment, and clinical pain evaluation in the same design. These limitations reduce causal certainty but identify clear priorities for future investigation (Table 10).

Table 10: Current limitations and future priorities in xenoestrogen neurobiology. This table summarizes methodological gaps that reduce causal certainty in current research. Future priorities are presented to guide studies on cognition, pain, and neuroplasticity

Current limitation	Consequence	Affected outcome	Future priority	Expected gain
Heterogeneous exposure	Difficult comparison	All outcomes	Standard biomonitoring	Better reproducibility
Single-chemical focus	Poor realism	Mixture effects	Mixture studies	Real-life validity
Few pain endpoints	Weak direct evidence	Pain	Pain-specific measures	Clinical relevance
Short follow-up	Unclear persistence	Development/aging	Longitudinal cohorts	Temporal inference
Limited sex analysis	Missed differences	Cognition/pain	Sex-stratified reporting	Biological precision
Variable cognitive tests	Outcome inconsistency	Cognition	Harmonized tools	Comparable findings
Sparse neuroimaging	Limited circuit data	PFC/amygdala	Imaging biomarkers	Mechanistic insight
Few biomarkers	Weak mechanisms	Inflammation/hormones	Integrated panels	Causal plausibility
Animal-human gap	Translation limits	Clinical outcomes	Translational models	Applicability
Confounding	Uncertain causality	Epidemiology	Robust adjustment	Stronger inference
Low-dose complexity	Hidden effects	Endocrine outcomes	Sensitive assays	Risk detection
Limited intervention data	No prevention proof	Public health	Reduction trials	Preventive guidance

Overall, the results support a multidimensional model in which xenoestrogens may influence cognition, pain, and neuroplasticity through overlapping estrogenic, inflammatory, synaptic, developmental, and cortical-limbic mechanisms. The strongest evidence was observed for neurodevelopmental and cognitive effects, especially in relation to BPA, phthalates, PFAS, and early-life exposure. Evidence for pain was more indirect but biologically plausible, particularly through estrogen receptor signaling, neuroinflammation, amygdala reactivity, and prefrontal modulation. These findings justify a discussion focused on mechanisms, current problems, translational relevance, and future research directions, especially regarding how environmental endocrine disruption may interact with brain plasticity and chronic pain vulnerability.

4.0. DISCUSSION

The findings of this review support the interpretation that xenoestrogens should be understood as neuroendocrine modulators rather than isolated reproductive toxicants. Their biological relevance derives from the capacity to interfere with estrogen receptor signaling, intracellular cascades, synaptic architecture, inflammatory balance, and developmental programming. This broader interpretation is consistent with the current view that endocrine-disrupting chemicals may affect the nervous system through multiple pathways, including receptor-dependent and receptor-independent mechanisms. In this context, cognition, pain, and neuroplasticity represent interconnected outcomes rather than independent domains, because they share cortical-limbic networks, neuroimmune regulation, and hormone-sensitive synaptic mechanisms (Vaiserman, 2014; Gore *et al*., 2015; Wang *et al*., 2021).

Figure 1 illustrates a proposed conceptual model in which xenoestrogen exposure interacts with estrogen receptors, neuroinflammatory pathways, oxidative stress, and synaptic remodeling. These mechanisms may converge on the prefrontal cortex, amygdala, hippocampus, and descending pain modulatory systems. Although the

clinical expression may vary, the same biological network can theoretically contribute to executive dysfunction, emotional dysregulation, altered pain perception, and maladaptive plasticity. This model is useful because it connects environmental exposure with brain function through shared mechanisms rather than through a single linear pathway (Eilam-Stock *et al*., 2012; Sadowski *et al*., 2014; Brann *et al*., 2022).

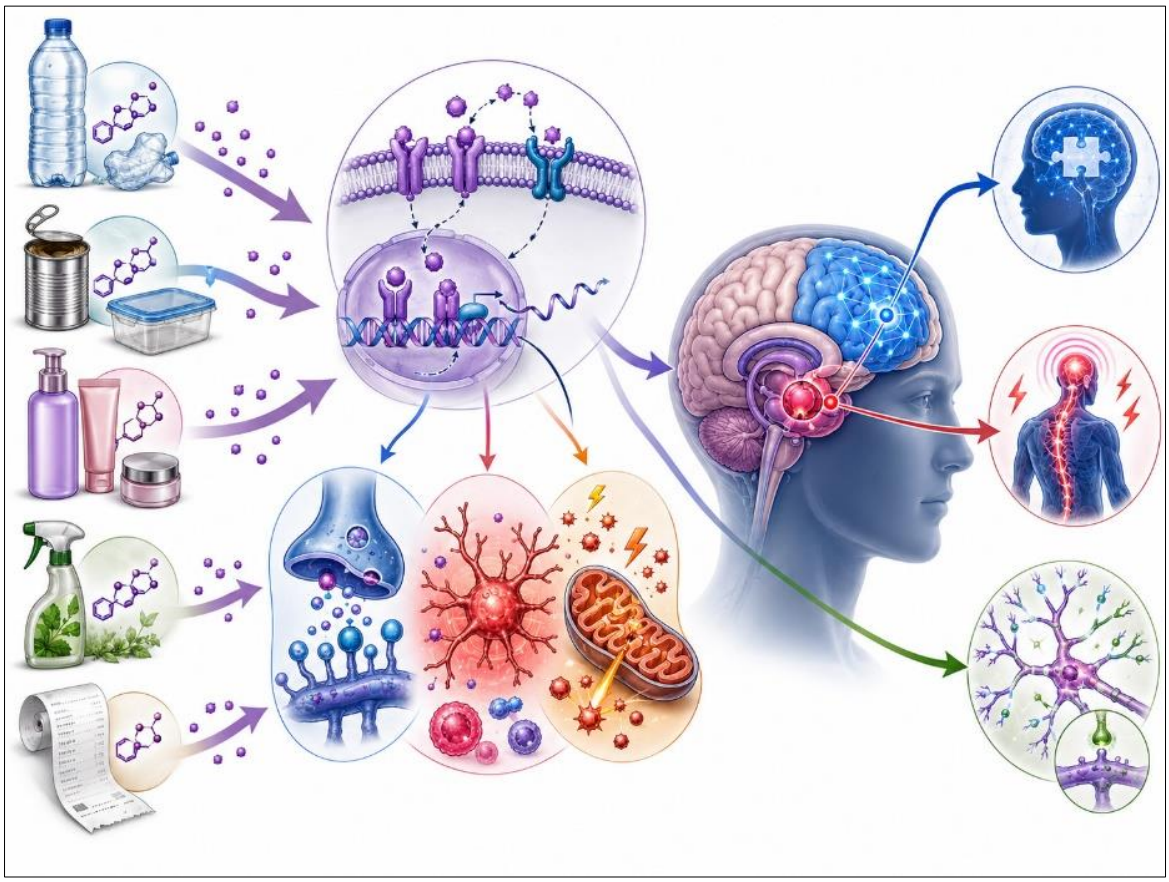

Figure 1: Proposed neuroendocrine model linking xenoestrogens, estrogen receptors, and brain function. This figure summarizes how environmental estrogenic compounds may interfere with receptor signaling, synaptic remodeling, neuroinflammation, and oxidative stress. These mechanisms converge on cortical-limbic networks involved in cognition, pain regulation, and neuroplastic adaptation

The prefrontal cortex is a particularly relevant region in this model because it provides executive control over attention, working memory, inhibition, emotion, and descending pain regulation. Disruption of prefrontal maturation or synaptic efficiency may therefore produce effects that are simultaneously cognitive, affective, and somatic. The developmental vulnerability of this region is important because prefrontal circuits mature slowly and remain sensitive to hormonal, inflammatory, and environmental influences throughout childhood and adolescence. Altered prefrontal regulation may also reduce the capacity to inhibit limbic and nociceptive amplification, creating a plausible link between endocrine disruption and pain vulnerability (Catenaccio *et al*., 2016; Yuen *et al*., 2016; Kolk and Rakic, 2022).

The amygdala contributes to this relationship by assigning emotional salience to sensory and internal bodily signals. In chronic pain states, amygdala activity may amplify fear, threat anticipation, hypervigilance, and the affective unpleasantness of pain. Xenoestrogens may not need to act directly on nociceptive neurons to influence pain; they may instead modify emotional learning, stress responsiveness, and cortical-limbic balance. Such a mechanism is clinically relevant because chronic pain frequently involves persistent interaction among sensory input, memory, mood, and threat appraisal. Therefore, altered estrogen-sensitive amygdala-prefrontal communication may represent one of the most plausible pathways linking xenoestrogen exposure to pain-related outcomes (Luine, 2020; Hwang *et al*., 2021).

Figure 2 presents the interaction between the prefrontal cortex and amygdala as a regulatory axis. Under physiological conditions, prefrontal networks exert inhibitory and contextual control over amygdala responses. When synaptic plasticity, receptor signaling, or neuroimmune balance is disrupted, this regulatory system may become less efficient. The result may be increased emotional reactivity, impaired cognitive

control, and reduced modulation of pain-related signals. This interpretation is particularly relevant for conditions in which cognitive symptoms, anxiety, fatigue, and chronic pain coexist without a single structural lesion explaining the full clinical picture (Marzola *et al*., 2023; Ruehr *et al*., 2025).

Figure 2: Prefrontal-amygdala axis in cognition, emotion, and pain modulation. This figure shows the reciprocal interaction between prefrontal executive control and amygdala emotional salience. Xenoestrogen-related disruption of this axis may contribute to altered cognition, emotional regulation, and pain amplification

One of the strongest areas of evidence concerns early-life exposure. Prenatal and childhood periods are characterized by rapid synaptogenesis, neuronal migration, myelination, hormonal programming, and circuit refinement. Exposure to endocrine-disrupting chemicals during these stages may produce persistent consequences because small molecular changes can be amplified across developmental time. This is especially important for compounds with short biological half-lives but repeated daily exposure, such as bisphenols and phthalates. The developmental model also explains why neurological outcomes may appear years after the initial exposure, when affected circuits are later recruited for executive, affective, or pain-related functions (Boberg *et al*., 2020; Lauby *et al*., 2024; Toledano *et al*., 2024).

Human neurodevelopmental evidence remains complex but increasingly important. Some studies associate endocrine-disrupting chemical exposure with attention, behavior, cognitive performance, and brain structural outcomes. However, variability in exposure timing, biological matrices, socioeconomic confounding, sex-specific responses, and co-exposure to multiple chemicals makes interpretation difficult. The most defensible conclusion is not that a single xenoestrogen determines a specific disorder, but that environmental estrogenic disruption may contribute to vulnerability within a multifactorial neurodevelopmental context. This interpretation supports preventive research without overstating causality (Yesildemir *et al*., 2023; Yang *et al*., 2024; Zoppé *et al*., 2024).

Bisphenol A remains the most informative compound for mechanistic interpretation because it has been studied in neuronal cultures, animal models, and human observational contexts. Evidence suggests that BPA can affect synaptic density, cortical development, inflammatory responses, and neuronal function. Importantly, BPA substitutes such as BPS and BPF should not automatically be considered neurologically safe, because structural similarity may preserve endocrine activity. The concept of regrettable substitution is therefore relevant to medical toxicology and public health, since replacement chemicals may reduce exposure to one compound while maintaining similar biological risks through related pathways (Welch *et al*., 2022; Jiang *et al*., 2024; Carrese *et al*., 2025).

Figure 3 summarizes the possible cellular mechanisms through which bisphenols may influence neural function. These include changes in estrogen receptor signaling, BDNF-related pathways, dendritic

spine remodeling, glutamatergic balance, oxidative stress, and inflammatory activation. These mechanisms are not mutually exclusive and may interact across time. For example, early oxidative stress may alter synaptic maturation, while later neuroinflammation may reinforce maladaptive plasticity. This layered mechanism helps explain why exposure may be associated with different outcomes according to age, sex, dose, and the neural system being evaluated (Baek *et al*., 2024; Al-Shami *et al*., 2025).

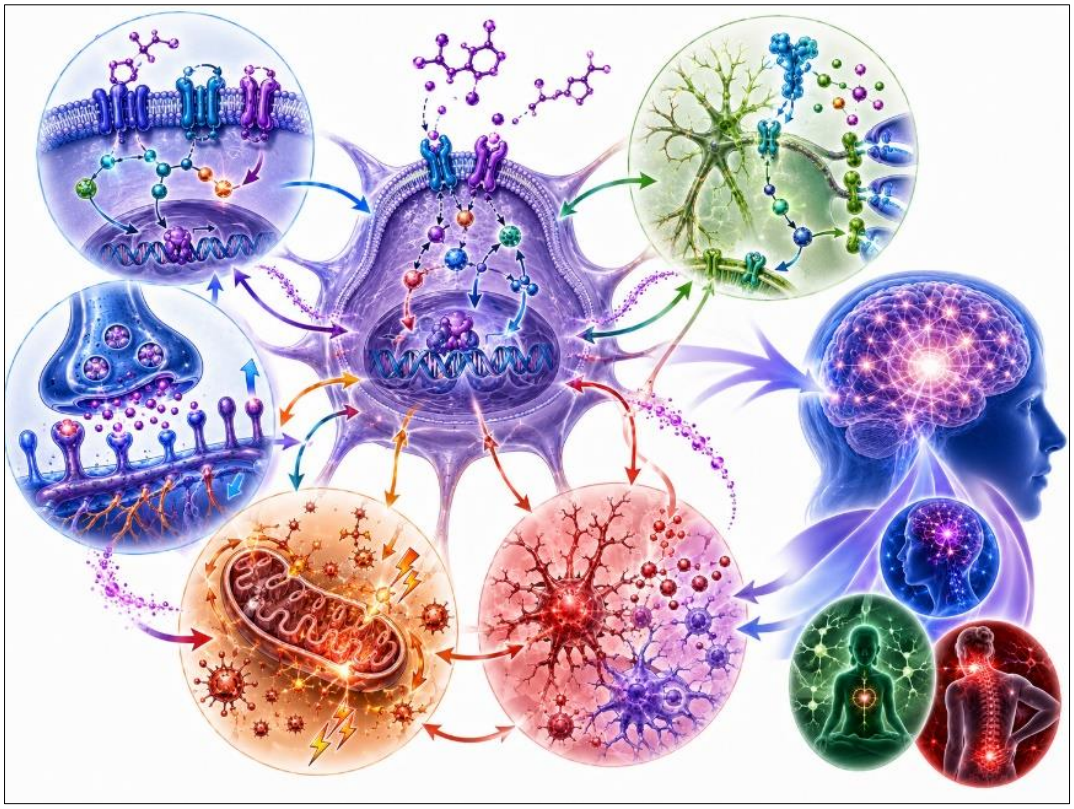

Figure 3: Cellular pathways potentially affected by bisphenols in neural tissue. This figure illustrates receptor signaling, synaptic remodeling, BDNF-related mechanisms, oxidative stress, and inflammatory activation. These pathways may interact to influence cognition, emotional regulation, and pain-related neuroplasticity

The evidence for phthalates, PFAS, and other chemical classes expands the discussion beyond BPA. These compounds may affect neurodevelopment, white matter integrity, hormonal signaling, immune regulation, and cognitive outcomes. Their importance lies not only in individual toxicity but in their presence as part of real-world exposure mixtures. Humans are rarely exposed to one endocrine disruptor in isolation; instead, exposure occurs through food, water, air, packaging, cosmetics, household materials, and occupational contexts. This mixture reality challenges classical toxicological models based on single compounds and highlights the need for cumulative exposure assessment (Sotelo-Orozco *et al*., 2024; Di Credico *et al*., 2025; Wang *et al*., 2025).

Pain remains the most underexplored component of the triad proposed in this review. The current literature provides stronger direct evidence for xenoestrogens and cognitive or developmental outcomes than for xenoestrogens and chronic pain. Nevertheless, pain is regulated by estrogen-sensitive systems, neuroimmune pathways, stress circuits, and synaptic plasticity. Therefore, the absence of extensive direct clinical evidence should not be interpreted as absence of biological plausibility. Rather, it identifies a research gap: future studies should evaluate pain thresholds, central sensitization, descending inhibition, inflammatory biomarkers, and cortical-limbic connectivity in relation to measured xenoestrogen exposure (Ramli *et al*., 2023; Shaw *et al*., 2025).

Figure 4 proposes a pain-focused pathway. Xenoestrogens may alter peripheral and central estrogen receptor signaling, increase neuroimmune activation, affect prefrontal descending control, and enhance amygdala-related emotional amplification. These effects may not independently cause chronic pain, but they may lower resilience in individuals exposed to stress, inflammation, injury, hormonal transition, or genetic vulnerability. This framework may be particularly relevant to disorders characterized by widespread pain, fatigue, cognitive complaints, and emotional symptoms, where central sensitization and neuroimmune mechanisms are already considered important components (Zheng *et al*., 2022; Zsarnovszky *et al*., 2024).

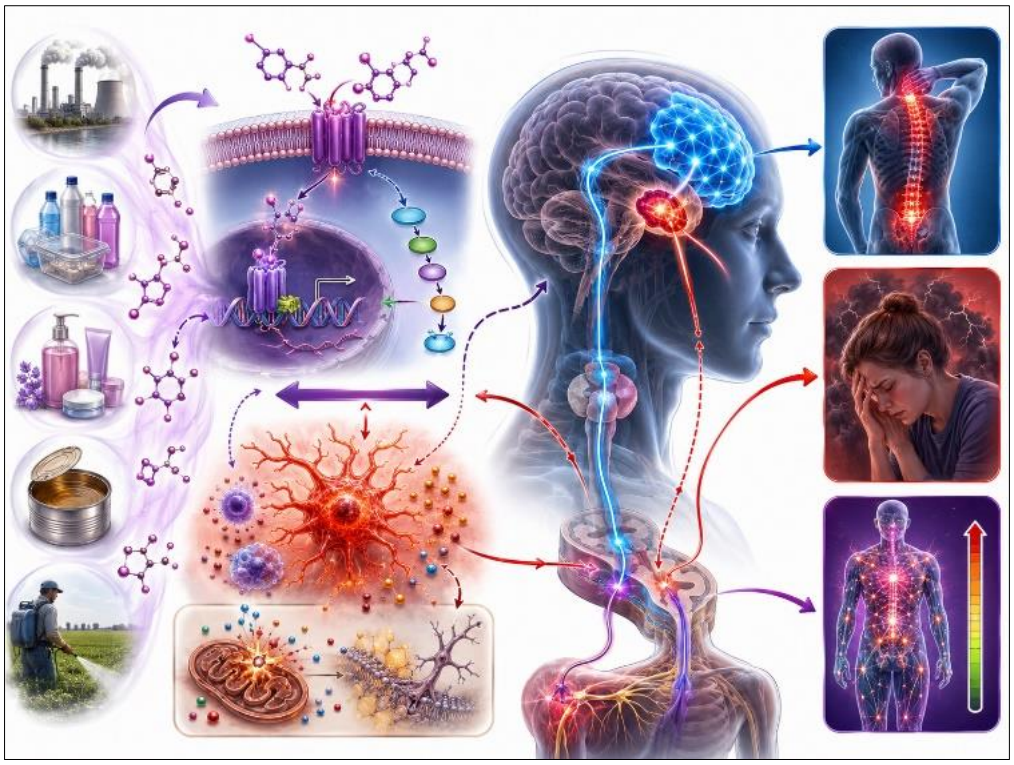

Figure 4: Hypothetical pathway linking xenoestrogens to pain modulation. This figure shows how endocrine disruption may influence nociception through estrogen receptors, neuroinflammation, prefrontal descending control, and amygdala-mediated pain affect. The pathway emphasizes modulation of vulnerability rather than direct causality

A major current problem is methodological heterogeneity. Studies vary in exposure assessment, timing of measurement, tissue or biological matrix, chemical metabolites, statistical adjustment, and outcome definitions. Many xenoestrogens also show non-monotonic dose-response relationships, meaning that low-dose effects may not follow classical toxicological assumptions. In addition, animal studies may not fully represent chronic low-dose human exposure, while human studies may be limited by residual confounding and reverse causality. These problems make it difficult to establish direct clinical causation, especially for complex outcomes such as cognition and pain (Al-Shami *et al*., 2025; Sultan *et al*., 2025).

Another unresolved issue is sex-specific vulnerability. Estrogenic signaling is relevant in both females and males, but its effects depend on receptor distribution, endogenous hormone levels, developmental stage, and local aromatization. Female hormonal transitions, including puberty, pregnancy, postpartum adaptation, menopause, and aging, may modify susceptibility to xenoestrogens. Male brains may also be affected through estrogen receptor signaling and developmental programming. Future research should therefore avoid treating sex merely as a confounder and should instead analyze sex as a biological variable central to the interpretation of endocrine disruption in brain function (Ruehr *et al*., 2025; Sultan *et al*., 2025).

Future perspectives should prioritize integrative human studies combining biomonitoring, endocrine markers, neuroimaging, cognitive testing, pain phenotyping, and inflammatory or epigenetic biomarkers. Longitudinal cohorts are especially needed to clarify whether early-life exposure predicts later changes in executive function, emotional regulation, pain sensitivity, or brain connectivity. Experimental studies should also use exposure levels and mixtures closer to real-life conditions. Translational models that integrate prefrontal-amygdala circuitry, glial activation, and estrogen receptor signaling may help bridge the gap between molecular toxicology and clinical medicine (Di Credico *et al*., 2025; Wang *et al*., 2025).

Figure 5 integrates the principal mechanisms and neurological outcomes discussed throughout this review. It illustrates how xenoestrogen exposure may converge on estrogen receptor signaling, synaptic remodeling, BDNF-related pathways, neuroinflammation, oxidative stress, and prefrontal-amygdala circuitry. These interacting mechanisms provide a multidimensional framework connecting developmental vulnerability, cognitive dysfunction, emotional dysregulation, altered pain modulation, and maladaptive neuroplasticity.

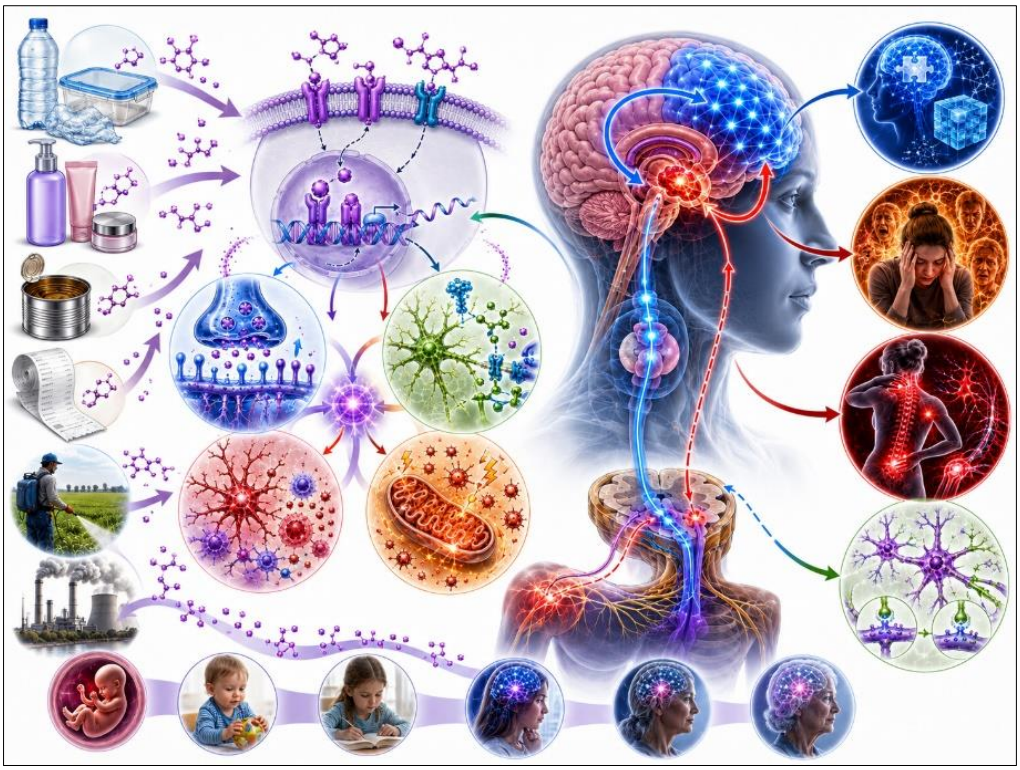

Figure 5: Integrative model of xenoestrogen exposure, neuroendocrine disruption, and brain outcomes. This figure summarizes how environmental xenoestrogens may converge on estrogen receptor signaling, synaptic remodeling, BDNF-related pathways, neuroinflammation, and oxidative stress. These mechanisms interact with prefrontal-amygdala circuits, descending pain modulation, developmental vulnerability, cognition, emotional regulation, and pain-related neuroplasticity

In summary, the discussion supports a cautious but clinically relevant interpretation: xenoestrogens may act as environmental modulators of neuroplasticity, cognition, emotion, and pain-related vulnerability. The strongest evidence concerns neurodevelopmental and cognitive effects, while the pain-related evidence remains indirect but biologically plausible. The prefrontal cortex and amygdala provide a useful anatomical framework because they integrate executive control, emotional salience, stress regulation, and pain modulation. Future research should move beyond single-chemical associations and adopt longitudinal, sex-sensitive, mixture-based, and biomarker-integrated approaches capable of clarifying how environmental endocrine disruption may shape brain health across the lifespan (Baek *et al*., 2024; Zsarnovszky *et al*., 2024; Shaw *et al*., 2025).

5.0. CONCLUSION

This review highlights that xenoestrogens represent a relevant environmental and neuroendocrine concern because their biological activity extends beyond classical reproductive disruption. By interfering with estrogen-sensitive pathways, these compounds may influence synaptic plasticity, neurodevelopment, neuroinflammation, oxidative stress, and cortical-limbic regulation. The available evidence indicates that cognition and neurodevelopment are the most consistently documented neurological domains, especially in relation to bisphenol A, bisphenol analogs, phthalates, PFAS, and early-life exposure. These findings reinforce the importance of considering the brain as a major target of endocrine-disrupting chemicals.

The relationship between xenoestrogens and pain remains less directly established, but the biological plausibility is significant. Pain is regulated by estrogen receptors, neuroimmune pathways, descending prefrontal control, amygdala-mediated emotional salience, and synaptic mechanisms involved in central sensitization. Therefore, xenoestrogens may not act as isolated causes of chronic pain, but they may function as environmental modulators of vulnerability, especially in individuals exposed during critical developmental windows or during hormonal transitions such as puberty, pregnancy, menopause, and aging. This interpretation supports a cautious but clinically meaningful framework linking environmental exposure, neuroplasticity, cognition, emotion, and pain.

Future research should prioritize longitudinal, sex-sensitive, and mixture-based studies integrating biomonitoring, hormonal assessment, neuroimaging, cognitive testing, pain phenotyping, inflammatory markers, and epigenetic analysis. Such approaches are necessary to clarify dose-response relationships, exposure windows, causal pathways, and clinical

relevance. Interdisciplinary collaboration among toxicology, endocrinology, neuroscience, pain medicine, public health, and environmental medicine will be essential to advance prevention strategies and identify populations at greater risk. Overall, xenoestrogens should be considered potential modulators of brain health across the lifespan, with particular relevance to neuroplasticity, cognitive function, emotional regulation, and pain-related vulnerability.

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