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The Hidden Impact: Exploring Cognitive Consequences of EDCs Through the Lens of Gut Microbiota

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1. INTRODUCTION

The intricate interplay between the gut and the brain has long been recognized by scientists as a fundamental aspect of human physiology and health. As the eminent scientist John F. Cryan remarked, 'The gut is the epicentre of our emotions, highlighting the profound connection between these two vital organs. The human gut-biota can be considered an organ itself, as it possesses more than a thousand microbial species that have 150 times more genes compared to the human genome, regulating various biological processes. The homeostasis between the microbiota and host depends primarily on host factors, including environmental factors, lifestyle, age, and diet, with recent attention being given to the role of diet. (Acharya et al., 2022; Lagier et al., 2016; Z & R, 2015)

The food we consume has emerged as a major source of toxic chemicals, including endocrine-disrupting chemicals (EDCs), which can cause detrimental health effects(Wong & Durrani, 2017a)]. In 2009, The Endocrine Society released its first Scientific Statement, raising concerns about the excessive use and negative health consequences of EDCs. Subsequent studies have provided insights into the influence of EDCs on the intricate interplay between gene-environment interactions, supported by correlative epidemiology data in humans(Gore et al., 2015). These disruptions in endocrine function have been linked to various diseases such as diabetes, cancer, infertility, asthma, and neuro-cognitive disorders.(Lind & Lind, 2018)(Bokobza et al., 2021a)(Dodson et al., 2012)(Kajta & Wójtowicz, 2013)(Arya et al., 2020)(Virant-Klun et al., 2022)(A. Sharma et al., 2020)

EDCs encompass a diverse range of synthetic and natural compounds that interfere with the proper functioning of the endocrine system(Simpson et al., 2012). These compounds are ubiquitous in our environment, found in everyday products such as plastics, pesticides, and personal care items(Wong & Durrani, 2017b). Mounting evidence suggests that exposure to EDCs can disrupt the delicate balance of the gut microbiota, which plays a vital role in digestion, immunity, metabolism, and overall health. This disruption, known as gut dysbiosis, involves alterations in microbial composition and functionality, exerting profound implications on host health. (Velmurugan et al., 2017)(Das & Nair, 2019)

Recent research has highlighted the impact of EDCs on the delicate equilibrium between the gut microbiota and cognition, as the gut microbiota plays a pivotal role in shaping the gut-brain axis, a bidirectional communication pathway between the gastrointestinal tract and the central nervous system(Romijn et al., 2008)(Rosenfeld, 2021). The gut microbiota profoundly influences neurodevelopment, cognition, and behaviour through various mechanisms, including the production of neurotransmitters, regulation of the immune system, and modulation of the neuroendocrine system(Cussotto et al., 2018). Consequently, dysregulation of the gut-brain axis resulting from EDC exposure can have far-reaching consequences for cognitive function, mental health, and overall well-being(Gareau, 2014).

Comprehending the intricate relationship between EDCs, gut biota, and cognition is of utmost importance in the fields of neuroscience and environmental health. By elucidating the underlying mechanisms by which EDCs disrupt the gut microbiota and impact cognition, we can pave the way for potential therapeutic interventions to mitigate these adverse effects. One such promising avenue of research involves the utilization of psychobiotics, a term coined to describe live microorganisms or their byproducts that confer mental health benefits when ingested. (Dinan et al., 2013)

By aiding in understanding this complicated relationship between EDCs, gut biota, and cognition, this review pursues to contribute to the growing body of knowledge surrounding the impact of EDCs on human health. Additionally, we intent to provide valuable understandings into possible interventions that can decrease the adverse effects of EDC exposure on the gut-brain axis, ultimately promoting a healthier and more resilient population.

In this review, we will investigate the current understanding of EDCs and their prevalence in the environment. Subsequently, we will explore the complex relationship between the gut microbiota and the brain, highlighting the intricate communication pathways and the profound impact of dysbiosis caused by EDCs on cognitive function. Furthermore, we will examine the specific mechanisms through which EDCs abnormalize the gut-brain axis, leading to dysbiosis and consequently cognitive dysfunction. At last, we will discuss probable therapeutic interventions, with a particular focus on pharmacological interventions like, faecal microbial transplant (FMT), herbal drugs, as a means to restore gut microbiota homeostasis and restoring the negative cognitive effects caused by EDC exposure.

2. EDCs and cognition

EDCs have become major concern for public health since last few decades due to the wide range of exposure to humans and abundance sources. The name EDCs is self-explanatory as it refers to the chemical that disrupts normal endocrine function that regulates the hormonal homeostasis in body. The looming threat has propelled scientific research on the subject from every field. One area that has gained lot of attention for the EDCs' negative effects is: Cognition

The cruciality of recent times to understand the effects of EDCs on public health and particularly on cognition has provided a much-needed push to clinical and preclinical research on the subject.

2.1 Mechanisms Underlying the Cognitive Effects of EDCs

The negative effects that have been found to be related to EDCs exposure has raised an urgent need to decipher the mechanisms by which it effects the various organs and functions in the human body. Understanding the mechanisms by which the EDCs cause the impairment might aid in the process of safeguarding from its harmful impacts. In this section of the review, we will discuss the mechanisms by which the EDCs exserts its effect on cognition.

1. Disruption of Hormone Signalling

Endocrine is one of the major systems that can be manipulated negatively by the EDCs. Hormone homeostasis is one the most important system in the body. The major effect of hormones on the cognition stems from the initial stages of life as Hormones play important roles in brain development, synaptic plasticity, and cognitive processes. EDCs can disturb hormone production, transport, breakdown, and binding, resulting in the imbalances that can have profound effects on cognitive function.

Addition to their role in metabolism Thyroid hormones, such as thyroxine (T4) and triiodothyronine (T3), are found to be important for brain development and cognitive function. One of the most common EDC, BPA has been found to impair the cognitive function via the altered expression of genes involved thyroid hormone signalling. And impaired spatial learning and memory in rats. ((Smith, 2002)) and in humans, BPA exposure during pregnancy is related to reduced thyroid stimulating hormone (TSH) in neonates resulting in altered development (Chevrier et al., 2013)) (X. Xu et al., 2019).

Along with thyroid hormones, sex hormones, such as estrogen and testosterone, are also speculated to play a role in cognitive function. EDCs can interfere with the production and metabolism of sex hormones, leading to disparities that can influence brain development and function. For instance, studies have shown that exposure to phthalates, such as di(2-ethylhexyl) phthalate (DEHP), can disrupt estrogen signalling and impair learning and memory in animal models through decreased activity of ERK1/2, and the down-regulated D2 and ERβ in striatum(Hamson et al., 2016) (Schantz & Widholm, 2001) (Wang et al., 2016).

EDCs can also affect the hypothalamic-pituitary-adrenal (HPA) axis, which is vital for stress response through glucocorticoid hormones. Chronic activation of the HPA axis due to EDC exposure can lead to increased cortisol levels, which have been associated with cognitive impairments, including deficits in memory and attention. (Raymond et al., 2018) (Graceli et al., 2020)

2. Oxidative Stress

Even though oxygen is one of the most important molecules for life to prosper it also need to be in equilibrium. Disturbance in the that might cause oxidative stress, characterized by an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defence system. It has been speculated as one of the fundamental mechanisms underlying the cognitive effects of EDCs. EDCs can generate ROS directly or indirectly through the disruption of cellular processes, resulting in oxidative damage to neurons (Burton & Jauniaux, 2011).

Hippocampus, Brain region crucial for memory and learning has been found to have increased oxidative stress when exposed to BPA and Polychlorinated biphenyls in rats. Which might cause impairments in spatial learning and memory tasks. Similarly, exposure to organophosphate pesticides has been shown to induce neurotoxicity probably by the oxidative stress in the brain. (Khadrawy et al., 2016) (Naughton & Terry, 2018) (Selvakumar et al., 2013a).

Oxidative stress can result in oxidation of lipids, proteins, and DNA, affecting cellular integrity and function. Also, it can disturb redox-sensitive signalling pathways involved in neuronal survival, synaptic plasticity, and neurotransmitter release, further contributing to cognitive deficits as found in an observational study of aging healthy adults. ((Hajjar et al., 2018))

3. Inflammation

EDCs can also cause neuroinflammation by the activation of immune cells and the release of pro-inflammatory cytokines. Chronic neuroinflammation has been associated with cognitive impairments and neurodegenerative diseases. ((Ferraz da Silva et al., 2018))

As mentioned earlier BPA has been found to cause cognitive and behavioural impairments in animal models which has been the result of the characteristic of BPA to cause neuroinflammation. (Khan et al., 2019)(Ni et al., 2021a) also Phthalates and polychlorinated biphenyls (PCBs), others widely spread EDCs has been found to cause the cognitive and memory impairments. ((Y. Yu et al., 2023)) ((Selvakumar et al., 2013b))

4. Epigenetic Modifications

Epigenetic alterations, like, DNA methylation, histone modifications, and microRNA expression, have arose as possible mechanisms arbitrating the cognitive effects of EDCs. Epigenetic changes can moderate gene expression patterns without changing the DNA sequence, leading to continuing alterations in cellular function. ((Alavian-Ghavanini & Rüegg, 2018)).

In a Swedish study the children exposed to BPF prenatally were found to have association with lower IQ as well as difficulty in verbal comprehension and perceptual reasoning in boys, while not significant association was found in girls. ((Engdahl et al., 2021) Additionally, animal studies have elucidated the effects of EDCs in the cognition via the epigenetic modifications (Raja et al., 2022) like, prenatal exposure to phthalates was associated with altered DNA methylation patterns in genes related to neuronal development and cognitive function in children.(Zhang et al., 2019)

Histone modifications, such as acetylation and methylation, might be affected by EDCs and can influence gene expression and chromatin structure. This alteration can affect synaptic plasticity and neuronal communication, ultimately leading to cognitive function alterations. For example, studies have shown that BPA exposure can alter histone acetylation patterns, leading to impaired spatial memory in animals (Jiang et al., 2016).

Also, another epigenetic regulator, microRNAs (miRNAs) a small RNA molecule that regulate gene expression post-transcriptionally, can be changed by EDCs resulting in altered miRNA expression patterns, thereby manipulating the expression of target genes involved in neuronal development and function. Disruptions in miRNA-mediated gene regulation have been associated with cognitive impairments induced by EDC exposure (Kaur et al., 2021)

Overall, the cognitive effects of EDCs are intertwined with the various complex mechanisms which might be interrelated with each other further aggregating the deleterious effects of EDCs based on the duration of exposure, individuals' susceptibility and type of EDC.

2.2 Preclinical and epidemiological evidences.

Animal studies have played a critical role in elucidating the cognitive effects of EDC exposure. Researchers have exposed animals to various EDCs, including bisphenol A (BPA), phthalates, and organophosphate pesticides, during critical periods of brain development. These studies have demonstrated that EDC exposure leads to cognitive impairments in animals, mimicking the effects observed in humans. EDCs' effects on the neuronal development and cognition it has been suggested that EDCs effects brain development prenatally and postnatally.

A study revealed that pubertal exposure to fenvalerate, a widely used pyrethroid insecticide, impairs cognitive, spatial learning and behavioural development in mice. Interestingly, the impairment caused by fenvalerate was more severe in female mice than in males, suggesting gender-specific impacts on spatial learning and memory. (Meng et al., 2011) Contradicting human trial on pre-pubertal children. That used a Virtual Morris Water Task, researchers observed that pre-pubertal boys outperformed girls in spatial tasks. These differences indicate that early-life hormonal effects and distinct learning strategies in boys and girls may contribute to disparities in spatial abilities. Demonstrating that sex differences in spatial learning and memory exist prior to puberty and do not appear to require the effects of sex hormones at puberty. (NEWHOUSE et al., 2007) directing that early-life hormonal effects and distinct learning strategies in boys and girls may contribute to disparities in spatial abilities.

Female rats were exposed to BPA during pregnancy and lactation at 40mg\kg, a dose below currently accepted daily intake. BPA exposed mid-adolescent offspring of animal had significantly altered spatial memory regardless of the sex. While anxiety like behaviours were more prominent in female. Probably driven by the corticosterone manipulation by the BPA (Poimenova et al., 2010) and estrogen or oestradiol receptors as it has been found to alter the neurobehavioral traits in female mice especially maternal behaviour by altering critical growth events during brain development (Palanza et al., 2008) (Rubin et al., 2006) also, the relation of EDCs with other systems of the body and alteration of the homeostasis can contribute to cause the cognitive deficiency such as reduced the production of SCFAs altered diversity and structure of the gut microbiota, damaged intestinal barrier function and the disruption in BBB, increased neuroinflammation and colonic inflammation. (Wu et al., 2020).

There are complicated relations between sex, effects of EDC and cognition and memory. Sex hormones are speculated to play a critical role in the learning and memory as steroid hormones are recognized for their beneficial effects on learning and memory. Disruption of these hormones due to exposure to EDCs has been linked to the development of cognitive and neurobehavioral deficits, similar to those observed in autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD), as reported in epidemiological studies. Impairments in attention, activity, and impulse control are inherently associated with poor learning and memory outcomes and hence cognition. Notably, ADHD is more commonly diagnosed in adolescent males, and in rodent models, males consistently exhibit higher levels of impulsive behaviour compared to females thus, alteration in testosterone hormone in serum and diminished ERα and ERβ mRNA in colon and hippocampus in male mice might also cause disruption in memory and cognition. (Ni et al., 2021b) there's thought to be evolutionary difference between male and female learning patterns as female rodents perform better in learning related to operantly (pressing the button, pulling lever on ques. Etc.) task while male outperform female in spatial tasks which might be reason for the sex dependent cognition alteration by EDCs.(Hilz & Gore, 2022)

Epidemiological studies also aid the hypothesis of EDCs causing cognitive impairment exposure to polychlorinated biphenyl-153 (PCB-153), dichlorodiphenyldichloroethylene (DDE), or hexachlorobenzene (HCB) post-natal via breast milk. Increasing concentrations of PCB-153 during prenatal development were associated with poorer mental and psychomotor scores, with statistical significance observed specifically for psychomotor. Notably, the impact of PCB-153 exposure on neurodevelopment gradually diminished as postnatal life progressed. The findings suggest that while breastfeeding may increase children's blood levels of persistent organic pollutants (POPs) during postnatal life, the detrimental effects of PCB-153 on neuropsychological development are primarily attributed to prenatal exposure.(Gascon et al., 2013)

Prenatal exposure to organophosphate (OP) pesticides has been consistently associated with poorer neurodevelopment and behaviours related to autism spectrum disorders (ASD) in previous studies. This association was particularly evident in the Centre for Health Assessment of Mothers and Children of Salinas (CHAMACOS) study, which focused on a birth cohort residing in the agriculturally intensive Salinas Valley in California. Explaining the relationship between prenatal OP pesticide exposure and ASD-related traits during childhood and adolescence within the CHAMACOS cohort. OP exposure during pregnancy was assessed by measuring di-alkyl phosphates (DAP) metabolites in urine, while the proximity of residential locations to OP usage during pregnancy was determined using California's Pesticide Use Reporting (PUR) data. The results indicated that prenatal DAP levels were significantly associated with poorer social behaviour as reported by both parents and teachers. Specifically, a ten-fold increase in DAP concentration corresponded to a 2.7-point increase in parent-reported Social Responsiveness Scale, Version 2, T-scores at age 14. However, no conclusive evidence was found regarding the associations between residential proximity to OP usage during pregnancy and ASD-related traits. (Sagiv et al., 2018) Overall, these findings contribute to the existing body of evidence linking prenatal OP pesticide exposure to developmental disorders such as ASD. Importantly, even subtle effects of pesticide exposure on ASD-related traits, particularly within a population

characterized by ubiquitous exposure, could potentially contribute to an increased incidence of clinically diagnosed ASD cases.

Attention-deficit hyperactivity disorder (ADHD), a disorder which alters the cognition by disruption in learning and memory processes, affects approximately 7% of school-aged children, a case-control study was conducted involving 76 clinically diagnosed ADHD cases and 98 controls aged 4 to 15 years. The study assessed the concentrations of urinary metabolites of acrylamide, acrolein, nonylphenol, phthalates, and organophosphate pesticides, as well as biomarkers. The results revealed significant positive dose-response relationships between ADHD and specific compounds. 4-hydroxy-2-nonenal-mercapturic acid (HNE-MA) showed a significant association with cognitive decline these findings indicate that children with ADHD may have an increased susceptibility to the burden of EDCs, even at lower levels of exposure. Among the compounds examined, organophosphate pesticides appear to be the main risk factor. The biomarker HNE-MA, indicative of lipid peroxidation, is recommended for further investigations into the role of oxidative stress in the aetiology of ADHD. Overall, this study highlights the potential contributions of specific compounds and oxidative stress in the development of ADHD, shedding light on the complex interactions between environmental factors and neurodevelopmental disorders. ((Waits et al., 2022))

Similar to other EDCs nonylphenol exposure has been speculated to effect cognition adversely. Significant association between higher urinary nonylphenol levels and an increased risk of ADHD was found. Children with ADHD exhibit significantly higher levels of nonylphenol compared to the control group. Moreover, there is a dose-response relationship, indicating that higher nonylphenol exposure is associated with a greater likelihood of ADHD diagnosis.

Higher nonylphenol levels were correlated with poorer performance in tasks related to attention, executive function, and working memory. These cognitive deficits are characteristic of ADHD symptoms and suggest a potential mechanism through which nonylphenol may impact cognitive development.

The results emphasize the role of EDCs, specifically nonylphenol, in the aetiology of ADHD and its impact on cognitive functioning in Taiwanese children. However, it is important to note that this study is observational in nature, limiting the ability to establish a causal relationship between nonylphenol exposure and ADHD. (C.-J. Yu et al., 2016)

3. Gut-Brain Axis and Cognition

The connection between the gut microbiota and the brain has emerged as one of the most intriguing research areas in recent years. The gut, often referred to as the "second brain," houses a diverse community of microorganisms that play a crucial role in our body's overall well-being and are closely connected to our emotions(Young, 2012). The term "gut feeling" likely originated from the intimate relationship between our gut and intuition, highlighting the complex interplay between our intestine, behaviour, and cognition.

Recent developments in the field have revealed that the intestine has features beyond digestion and metabolism, extending to human health, immune function, behaviour, and even cognition. Cognition, being particularly intriguing, has been extensively explored, and the research community has been able to establish connections between the gut and cognition through the gut-brain axis. (Proctor et al., 2017)(Escobar et al., 2022)

Cognition encompasses mental processes involved in understanding, knowledge acquisition, and reasoning. It involves a wide range of functions, including attention, memory, learning, and decision-making. Cognition can significantly impact a person's quality of life and is associated with various neuro-psychiatric disorders such as Alzheimer's disease, Parkinson's disease, ASD (autism spectrum disorders), anxiety, and depression. Human beings have been striving to combat cognitive impairments throughout history, with the recent focus cantered around the gut-brain axis.

The gut-brain axis represents the bidirectional communication pathway between the gut and the brain, enabling constant signalling and interaction between these two organs. This communication is believed to occur through three major mechanisms: neural, endocrine, and immune pathways. In all three mechanisms, the gut microbiota plays a key role and has been found to have a modulatory effect on the gut-brain axis, controlling behaviour and cognition. (Berding et al., 2021).

3.1 Bidirectional Communication Pathways of gut brain axis.

The bidirectional communication pathways between the gut and the brain form the foundation of the gut-brain axis. This intricate network allows for constant signalling and interaction between these two organs, playing a crucial role in maintaining homeostasis and influencing various physiological processes, including cognition. The microbiota-gut-brain axis involves endocrine, neural, and immune pathways.

1. Neural Pathways

Neural pathways are one of the key mechanisms through which the gut and the brain communicate. The enteric nervous system (ENS) consists of millions of neurons that extend throughout the gastrointestinal tract, functioning independently of the central nervous system (CNS). However, it also communicates bidirectionally with the brain via the vagus nerve (Dickson, 2020).

The vagus nerve, the longest cranial nerve, connects the brainstem to various organs, including the gut. Gut microbes and their metabolites directly signal to the vagus nerve via specialized enteroendocrine cells called "neuropods," serving as a major conduit for communication between the gut and the brain. Conversely, the brain can send signals down the vagus nerve to modulate gut functions. In conditions such as "leaky gut," where the intestinal barrier is compromised, antigens can enter the blood circulation, causing inflammation and neuroinflammation. The vagus nerve modulates the cholinergic anti-inflammatory pathway (CAIP), attenuating inflammation and decreasing intestinal permeability (Mörkl et al., 2023). In a study involving the transplantation of faecal material from older individuals into mice with colitis, certain microorganisms were found to impair cognition. However, when the mice underwent vagotomy (vagus nerve severance), the cognitive impairment was inhibited. (Lee et al., 2020a)

This neural communication pathway allows for the transmission of information about gut motility, nutrient availability, and immune responses to the brain. It also enables the brain to regulate gastrointestinal functions, including gastric secretion, gut motility, and intestinal permeability. Agitations in this neural pathway have been implicated in gastrointestinal disorders such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), which are often associated with cognitive impairments. (Karakan et al., 2021)(Bonaz et al., 2018)(Décarie-Spain et al., 2023)

2. Endocrine Pathways

The endocrine system, which contains various hormones, plays a vital role in the bidirectional communication between the gut and the brain. The gut produces and releases a diverse array of hormones, including cholecystokinin (CCK), peptide YY (PYY), and glucagon-like peptide-1 (GLP-1), in response to food intake. These hormones not only affect metabolism but also act as signalling molecules in the brain. For example, high levels of CCK, GLP-1, and PYY can be observed after a meal for several hours. A diet rich in protein induces CCK production, which gives a feeling of fullness by acting on the brain, pancreas, and central nervous system (Cabou & Burcelin, 2011). High CCK levels have been associated with increased anxiety.

During fasting, the stomach releases the hunger hormone ghrelin, which crosses the blood-brain barrier to activate the production of neuropeptide Y (NPY) and agouti-related peptide (AgRP) in the brain's arcuate nucleus. NPY, in conjunction with neurotransmitters like GABA and glutamate, stimulates hunger, regulates fat storage, and reduces anxiety, stress, and pain. AgRP induces the secretion of stress hormone cortisol and prolactin.

The brain can also influence gut functions through the release of hormones. Stress, for instance, triggers the release of stress hormones such as cortisol and adrenaline, which can impact gut motility, permeability, and microbial composition. Stress is known to be associated with dysbiosis.(V. Sharma et al., 2021)

3. Immune Pathways

Microbes in the gut stimulate the growth and maturation of immune cells, ensuring an appropriate immune response to pathogens while maintaining tolerance to harmless antigens. Dysfunction of this immune-microbiota interaction can lead to immune dysfunction and chronic inflammation, which have been implicated in the pathogenesis of cognitive disorders. The immune system has been well proven to be maintained by the gut biota it regulates the immune system after the birth till the maturation of the system. The alterations of immune system in the germfree mice which is corelated to many autoimmune disorders. The composition of the microbiota differs between healthy individuals and those affected by neurodegenerative disorders such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), as well as neuropsychiatric disorders, including major depressive and mood disorders. According to studies , the altered microbiota in patients has the potential to transmit the disease from a human host to a mouse host. (Rutsch et al., 2020)(Lee et al., 2020b)

In gut is largest population of immune cells in the body resides, which form the gut-associated lymphoid tissue (GALT). These immune cells continually examine gut for pathogens and maintain immune homeostasis. Inflammatory molecules, cytokines and chemokines are produced in gut which can directly or indirectly affect brain function. They can cross the BBB and trigger neural and endocrine pathways to effect neuronal activity, synaptic plasticity, and neuroinflammation. Chronic inflammation in the gut has been associated with cognitive decline and an increased risk of neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. Thus, immune system gut and brain are in communication with each other

directly and indirectly and the gut biota disruption can manifest negative impacts on the host health (Rutsch et al., 2020b)(Stokes et al., 2017)(S. Liu et al., 2020).

3.2 Microbiota, Neurotransmitters and cognition.

The intricate interplay between the gut and the brain is mediated by various mechanisms, including the production of neurotransmitters such as serotonin, dopamine, and gamma-aminobutyric acid (GABA) (T. Liu et al., 2020).(O'Donnell et al., 2020) (X. Yu et al., 2021)These neurotransmitters play essential roles not only in behaviour and signalling but also in cognition. The gut microbiota, which has a significant role in this process, can influence the immune system and neuroinflammation.

Research has demonstrated that alterations in the composition of the gut microbiota can lead to dysregulated immune responses and chronic inflammation. Neuroinflammation, characterized by the activation of immune cells in the brain, has been implicated in the development and progression of neurological disorders, including Alzheimer's disease. (Bairamian et al., 2022)(Cerovic et al., 2019)(Bokobza et al., 2021b)

The gut microbiota modulates immune function, exerting both protective and detrimental effects on cognitive health. This modulation involves the direct production of neurotransmitters and the production of intermediate metabolites that can cross the blood-brain barrier and be converted into neurotransmitters in the brain(Strandwitz et al., 2018a). (Zhu et al., 2020). The gut microbiota also secretes enzymes that aid in the conversion of these metabolites into neurotransmitters. While most neurotransmitters are amino acids that can be transported to the brain via active transport, larger molecules may not be able to cross the blood-brain barrier. Research findings have suggested that the gut microbiota can influence neurotransmitter synthesis. (Gao et al., 2018a) Additionally, some signalling molecules produced by the gut microbiota may provide signals for the synthesis or release of neurotransmitters. (Yano et al., 2015a)(Luqman et al., 2018)(Williams et al., 2014)

Understanding the interplay between the gut microbiota and neurotransmitters is essential for unravelling the pathophysiology of cognitive disorders and developing novel therapeutic strategies to promote cognitive health.

Research conducted on Germ-Free (GF) mice, which are mice delivered through C-section and raised in aseptic conditions without contact with microorganisms, suggested that these mice exhibited muscle atrophy and lower levels of serum choline, a precursor of acetylcholine (ACh). ACh is a neurotransmitter that plays a crucial role in neuromuscular transduction. However, when the GF mice were treated with Faecal Microbiota Transplantation (FMT) and Short Chain Fatty Acids, their muscle function was restored. (Jameson & Hsiao, 2018)

The altered composition of the gut microbiota in GF mice, which is less diverse than that of normal control mice, has been associated with changes in Brain-derived neurotrophic factor (BDNF) and 5-hydroxytryptamine (5-HT, serotonin) levels, both of which are crucial for cognition and neurodevelopment. Approximately 80% of serotonin is produced in the gastrointestinal tract (GIT) by enterochromaffin cells. Serotonin has also been linked to cognitive ability in animals and humans, including patients with psychotic disorders like schizophrenia (Schmitt et al., 2006) (Bacqué-Cazenave et al., 2020)(Roth et al., 2004). These cells absorb tryptophan from dietary protein, which is then transported to the brain, where it is synthesized into serotonin. (O'Mahony et al., 2015a)The synthesis of serotonin is regulated by the bacterial kynurenine synthesis pathway. (O'Mahony et al., 2015b) Furthermore, serotonin treatment has been found to reverse neuronal dysfunction in GF mice. (Glavin & Szabo, 1990)(De Vadder et al., 2018).

In addition to serotonin, there are other neurotransmitters produced by the gut microbiota that have implications for cognition. Glutamate, an essential neurotransmitter for cognition, is produced by enteroendocrine cells to transmit rapid signals to the brain. The gut microbiota also includes microbial communities that produce γ-aminobutyric acid (GABA) and dopamine, both of which are important neurotransmitters. (Kaelberer et al., 2018a)(Strandwitz et al., 2018b)(Horiuchi et al., 2003a)

Furthermore, antibiotic use has been found to reduce the levels of aromatic amino acids and their downstream neurotransmitters, such as serotonin and dopamine, in faeces, blood, and the hypothalamus. This reduction is likely due to dysbiosis caused by antibiotics.(Gao et al., 2018b) (M.-T. Liu et al., 2009)(Yano et al., 2015b)

Dopamine: Dopamine is a neurotransmitter associated with reward and plays a crucial role in behaviour modulation, cognition, voluntary movement, motivation, and more. More than 50% of dopamine is produced in the gut. Some *Bacillus and Serratia* species in the gastrointestinal tract also contribute to dopamine production. The gut microbiota has been shown to impact neurotransmitter function, as observed in studies involving individuals with Parkinson's disease. The metabolism of levodopa, a precursor of dopamine, by gut microbiota can reduce its availability, leading to unwanted side effects. Future psychiatric treatments may

involve considering the gut microbiota to optimize drug selection (Eisenhofer et al., 1997)(Hamamah et al., 2022)(Asano et al., 2012)(González-Arancibia et al., 2019).

GABA (γ-aminobutyric acid) and Glutamate: GABA is an inhibitory neurotransmitter that plays a vital role in cognition. Disruptions in GABA levels or signalling have been associated with cognitive processes such as learning, memory, and attention. Specific gut microbiota has been found to modulate GABAergic signalling, influencing anxiety and depression symptoms. *Lactobacillus rhamnosus JB-1*, for example, has been shown to alter GABA receptor expression, leading to a reduction in anxiety and depression. Additionally, gut microbiota can produce acetate, which can cross the blood-brain barrier and affect GABA neuroglial cycling pathways in the hypothalamus. Other gut microbiota, such as *Akkermansia muciniphila*, *Parabacteroides merdae*, and *Parabacteroides distasonis*, may influence GABA regulation by altering GABA/glutamate ratios and increasing brain glutamate levels (Strandwitz et al., 2018c).(Horiuchi et al., 2003b) (de J.R. De-Paula et al., 2018)Glutamate the other neurotransmitter found essential for the cognition is in a study found to be produced by the enteroendocrine cells to transfer the rapid signals to the brain.

Norepinephrine: Norepinephrine, also known as noradrenaline, is a neurotransmitter involved in behaviour, cognition, memory, learning, and attention. It also plays a role in inflammation and modulates autonomic nervous system responses. Certain bacterial species can produce norepinephrine as part of their quorum sensing mechanisms. Germ-free mice have shown reduced norepinephrine levels, but colonization with specific bacteria can restore these levels. These findings highlight the involvement of norepinephrine and gut microbiota in modulating cognitive processes and bacterial interactions. (Sudo, 2019)(Kaelberer et al., 2018b).

3.3 BDNF Gut Biota and Cognition

BDNF is a crucial protein involved in the development, maintenance, and plasticity of the nervous system. It plays a significant role in neuronal survival, growth, and differentiation, particularly in brain regions associated with learning and memory. BDNF is essential for various cognitive processes, including synaptic plasticity, neuronal connectivity, and neurogenesis. Dysfunctions or alterations in BDNF levels have been linked to neurological and psychiatric disorders, emphasizing its importance in cognition and brain function. (Siuda et al., 2017)

Studies have reported reduced serum levels of BDNF in patients with cognitive impairment and higher neuropsychiatric activity in healthy individuals with higher serum levels (Laske et al., 2006)(Gunstad et al., 2008). Interestingly, the gut microbiota has also been implicated in the regulation of BDNF. Dysbiosis, characterized by an imbalance in gut microbial composition, has been associated with altered BDNF levels, leading to disruptions in the central signal-to-noise ratio and aberrant synaptic behaviour, ultimately resulting in cognitive deficits (Maqsood & Stone, 2016). Alcohol consumption-induced dysbiosis has also been linked to diminished BDNF levels and neuropsychiatric behaviours (Z. Xu et al., 2019).The vagus nerve is thought to be serving as the bridge between the brain and the gut, is believed to regulate BDNF levels and may have a close relationship with the gut microbiota. Studies have shown that vagotomised animals, which have undergone vagus nerve severance, exhibit lower BDNF levels in the hippocampus and reduced neuronal survival. (O'Leary et al., 2018).

3.4 Gut biota and cognition clinical and preclinical evidences

Recent research has shed light on the impact of gut biota on cognitive function. In this section we will discuss current scientific evidences regarding the relationship between gut microbiota and cognition by understanding insights from clinical and preclinical studies.

Increasing interest of scientific community in deciphering the complex relation between gut microbiota and cognition has probed many studies in the field and is being explored extensively. A study in 2015 found that an increase in the abundance of a pro-inflammatory GMB taxon, *Escherichia/Shigella*, and a reduction in the abundance of an anti-inflammatory taxon, *Eubacterium rectale*, are possibly associated with a peripheral inflammatory state in patients with cognitive impairment and brain amyloidosis. This finding lead to the hypothesis that the GMB composition may drive peripheral inflammation, contributing to brain amyloidosis and, possibly, neurodegeneration and cognitive symptoms in AD. (Cattaneo et al., 2017a) Animal studies done on transgenic mice have obtained similar results where the alteration in microbiota was associated with the amyloid deposition. (Lee et al., 2020c)(Qian et al., 2022)(Bo et al., 2020)

A study also indicated that when the mice were transplanted with *Paenalcaligenes hominis* and *Escherichia coli* from elderly individuals they found to have developed cognition impairment (Cattaneo et al., 2017b). These findings hypothesise the strong effect of gut biota on the host's neurotransmitter regulation and plasticity of the brain. study investigated the effects of preventing coprophagy in voles, a phenomenon where

the animal consumes own faeces to meet the nutritional requirements (the ingestion of faeces) on the gut microbiome, metabolism, neurochemistry, and cognitive behaviour in a small mammal. The study found that when coprophagy was prevented, there were significant changes in the gut microbiome composition, metabolism, and neurotransmitter levels, associated with altered cognitive behaviour which was ameliorated when the animals were given short chain fatty acid (SCFAs) acetates the probable reason being the SCFAs, which have been shown to influence brain function. SCFAs are the byproducts of microbial fermentation of dietary fibre in the gut. They have been found to have anti-inflammatory properties and can enhance blood-brain barrier integrity, thereby protecting the brain from harmful substances. SCFAs also act as signalling molecules, influencing neuronal activity and synaptic plasticity, both of which are crucial for learning and memory (Minter et al., 2016)(Harach et al., 2017).

Moreover, intervention studies have provided further evidence for the influence of gut microbiota on cognition. A randomized controlled trial by Tillisch et al. in 2013 investigated the effects of probiotic supplementation on brain activity and found that individuals who consumed a probiotic yogurt exhibited altered connectivity patterns in brain regions associated with changes in midbrain connectivity, which could explain the observed differences in activity of brain regions that control central processing of emotion and sensation measured during the study task. (Tillisch et al., 2013). Another systemic review, demonstrated that dietary modification, such as a Mediterranean-style diet, led to improvements in cognitive performance and alterations in the gut microbiota composition resulted from low adherence to Mediterranean diet which was corelated with the AD and PD. (Solch et al., 2022). A randomized double blinded control trial a rather challenging but most reliable form of clinical trial has also provided similar results were in healthy men *Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI (1 × 109 CFU/d) for 12 weeks was given and The probiotics group showed greater improvement in mental flexibility test and stress score than the placebo group, improving cognitive and mental health in community-dwelling healthy elderly with changes in gut microbial composition with increase observed in BDNF levels of supplement group (Neufeld et al., 2011). In a separate systemic review, it was observed that 9 out of 10 studies showed improvement in cognitive function when patients were given supplement of probiotics.

Furthermore, preclinical studies have explored the potential mechanisms through which gut microbiota influences cognition. For example, Bravo et al. in study from 2011 demonstrated that administration of specific strains of beneficial probiotics bacteria, improved cognitive function and reduced anxiety-like behaviour in mice. The probiotics thought to exerted their effects by modulating neurochemical pathways, including the synthesis of neurotransmitters like gamma-aminobutyric acid (GABA).

Germ-free mice, lacking a gut microbiota, have been used to demonstrate the impact of microbial colonization on cognitive outcomes. For instance, Neufeld et al. showed that germ-free mice displayed deficits in spatial learning and memory compared to conventionally raised mice. However, colonization with a complex gut microbiota restored cognitive function, highlighting the essential role of gut microbiota in cognitive processes(Sampson et al., 2016a).

Importantly, preclinical studies have also investigated the impact of gut dysbiosis on cognitive impairments and neurodegenerative diseases. Sampson et al. showed that mice with gut dysbiosis exhibited increased neuroinflammation and impaired memory compared to control mice. Moreover, recent research has suggested a potential role for the gut microbiota in neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. gut microbiota alterations can precede the development of neuropathological features in a mouse model of Alzheimer's disease, supporting the concept of the gut-brain axis in neurodegenerative processes. (Sampson et al., 2020)(Kim et al., 2021)(Handajani et al., 2023)

Data from both clinical and preclinical studies provide persuasive evidence for the intricate relationship between gut microbiota and cognition. The findings propose that alterations in gut microbiota composition can impact cognitive function, while interventions targeting the gut microbiota hold potential for improving cognitive outcomes. The research in the field of psychobiotics and other intervention for improvement of cognition through the gut brain axis has gained a huge interest and is one of the emerging areas which we will cover in the next section of this review.

4. Conclusion:

Increase in the knowledge about the EDCs and it's deleterious effects has lead to exploration of its effects in various physiological aspects and gut biota has been indicated to be playing a crucial role according to Clinical and Preclinical evidences from various studies. The link between and gut biota and cognition has been well established and the dysbiosis caused by the EDCs might also impact the cognition is a relevant and widely explored area in recent times. The effects of EDCs on the cognition depends in various factors and vary with individual, gender, socioeconomical background, Gut biota, diet , type of EDCs, exposure time as well as

other physiological and environmental factors. When it comes to mechanisms which exserts the cognition declines by EDCs via the Gut – Brain axis many comes to play from the molecular signalling pathways to the vagus nerve hypothesis. Exploring these aspects gives a future direction for the exploration of various interventions that can be utilised for mitigation of the detrimental effects of EDCs. For instance, the exploration Faecal Microbial Transplant (FMT), Psychobiotics and Short Chain Fatty Acids (SCFAs) are being studied as a pharmacological intervention to restore the lost in gut biota caused by EDCs. Exploration of various physiological in harmony with other systems can give us deep understanding of the intricacies and window of opportunity to utilise it for the betterment of lives.

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