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Review

The Effect of Gut Microbiome, Neurotransmitters, and Digital Insights in Autism

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Abstract: Background: Autism spectrum disorder is a multifactorial phenomenon whose genetic, biological, environmental, and nutritional factors outline the heterogeneous phenotype of the disease. A limitation in social connections with others, stereotyped reactions, and specific interests and preferences characterize the behavioral manifestations of a person with autism. Also, weaknesses are found in emotional, cognitive, and metacognitive development, significantly burdening the individual's quality of life. Lately, it has gained widespread acceptance that the gut microbiome and neurotransmission constitute two decisive etiological factors of autism both in the prenatal period and postnatally. This study aims to investigate data on the interaction between the quantitative and qualitative composition of the gut flora and neurotransmission in humans, as well as their influences on the appearance and progression of the symptoms of autism spectrum disorder. At the same time, it captures the role of digital technology in diagnosing and intervening in autism, which is mainly related to the individual subjects under study. Methods: The current research employs an exploratory review to provide a concise overview of the complex neuronal functions associated with neurotransmitter action and the homeostasis mechanisms that allow the brain and the human body to survive and perform optimally. Results: A review of 111 sources highlighted the connection of dietary habits with synthesizing and releasing neurotransmitters and their influence on the emergence of autism-related behaviors. Conclusions: The literature review's findings revealed the importance and influence of nutritional factors on neurotransmission performance and behavioral, social, and cognitive development among individuals with autism. Moreover, it is noteworthy that combining a healthy lifestyle and the targeted use of digital tools can improve the intensity of autism symptoms.

Keywords: gut microbiome; neurotransmitters; autism spectrum disorders; information and communication technologies

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1. Introduction

The human microbiome is the medium via which genes interact with their surroundings. The study of microbiomes provides insights into the individual's neurodevelopmental course and behavioral phenotypes. This has resulted in a better understanding of factors influencing human cognitive, behavioral, and nutritional development, particularly in neuropsychiatric conditions ranging from affective disorders to autism [1].

A person's eating habits shape the microbial community of the gut, affecting the brain's function and the quality of his life. Research data highlight the critical role of gut microflora in maintaining body homeostasis. Conversely, dysbiosis of the microbiota affects the functioning of the immune system and is related to illnesses of the stomach, neuroendocrine system, and behavior [2].

Gut microorganisms participate in releasing some of the principal neurotransmitters (NTs) of the brain, which act on the gut–brain axis and regulate the organism's food intake and energy balance [3]. In particular, the intestinal microflora, through certain bacteria, can change the levels of precursor substances such as tryptophan, affecting serotonin's synthesis. Also, some species of lactobacilli produce neurotransmitters such as gamma-aminobutyric acid (GABA), dopamine, and acetylcholine, which are not directly involved in brain activity, through the enteric nervous system [4]. Autism spectrum disorder (ASD) is a neurodevelopmental disorder with diverse and complex features involving social communication, restricted interests, and stereotyped repetitive behaviors. Several studies support that nutritional status is of prominent importance in the frequency and severity of the dominant symptoms of autism. Comorbid conditions include gastrointestinal problems associated with significant behavioral challenges such as aggression, self-injury, and rigid, stereotyped attitudes. Consequently, adequate and balanced nutrition contributes to optimal brain function, promoting the prevention of cognitive disorders [5,6].

Since the incidence of gastrointestinal symptoms in children with ASD ranges from 9% to 91%, the gut microbiome (GM) has been a vital factor in studying gastrointestinal disorders in autism compared to its symptomatology. The mode of birth and the age of the mother are factors that influence the composition of the intestinal microflora, influencing the manifestation of autism. However, some research reports that the severity of symptoms in ASD can affect the individual's eating habits and, by extension, the diversity of the intestinal microbiome [7]. Given that autism is represented by a multiplicity of intricate and varied behavioral expressions and a broader heterogeneity in phenotype, one of the primary mechanisms of pathogenesis is the brain's signaling systems' functioning [8].

The assessment of the heterogeneous symptoms of ASD results mainly from behavioral observation, creating the imperative to adopt objective methods in disease assessment [9]. Artificial intelligence applications enhance the analysis of cognitive processes by creating large-scale simulations of the neural mechanisms behind intelligence, improving both the diagnosis and treatment of autism [10,11].

The heterogeneous phenotype of ASD combined with its increasing prevalence has particularly troubled the research community in recent decades. The severe abnormalities in gastrointestinal function and neurotransmission observed in individuals with autism are two crucial etiological factors for the onset of the disease. Therefore, investigating the mutual interaction of diet, gut microflora, and ASD is essential, to identify dominant and individual parameters that influence the onset and progression of autism symptoms.

This research explores the relationship between gut flora's quantitative and qualitative makeup and human neurotransmission. Furthermore, it aims to investigate how these factors may influence the onset and progression of symptoms associated with autism spectrum disorder. In addition, the role of Information and Communication Technologies (ICTs) in the function of certain neurotransmitters and the symptomatology of ASD is recognized. The literature was searched in international databases such as PubMed, Scopus, and Google Scholar using exploratory research that provides patterns and insights into an issue, setting the stage for future research and often generating new hypotheses about old or new subjects [12,13]. This study highlights the link between eating habits and neurotransmitters in autism spectrum disorder behaviors, emphasizing the role of ICTs. It underscores the importance of the gut microbiome and neurotransmission in ASD symptom development and suggests further research on improving dietary habits.

The research topic's theoretical foundation is outlined in three subsections, focusing on gut microbiota, neurotransmitters, and autism spectrum disorder.

1.1. Gut Microbiome

The gut microbiome is an ecosystem of microorganisms that include bacteria, viruses, fungi, protozoa, and archaea that coexist for the benefit of the organism through digestive, endocrine, and immune functions. The metabolic products of the microbiome, including neurotransmitters and neuromodulators, affect the enteric nervous system function and the development and formation of the central nervous system (CNS), justifying the conceptual microbiota–gut–brain connection [14].

The enteric nervous system is characterized as the "second brain", compared to the brain, by its size, complexity, and similarity—in neurotransmitters and signaling molecules [15].

The structural composition of the gut microflora appears to be significantly influenced but also determined by factors such as lifestyle or diet [16]. The establishment of the gut microbiome begins during the prenatal period, continues with the birth of the infant, and evolves into adolescence and adulthood. Diet and antibiotics are the main factors influencing the composition of the gut microflora throughout human life. However, the gut microbiome diverges over time, restoring dysfunctions [17].

Changes in the gut microbiome can trigger epigenetic changes, affecting brain function and behavioral manifestations. Furthermore, human epidemiological studies report a co-occurrence of gastrointestinal disturbances in patients with ASD, reflecting the association of gut dysbiosis with ASD [18,19]. Consequently, maintaining gastrointestinal balance affects a person's emotional state, motivation, behavior, and cognitive functions. It is a crucial element in controlling brain chemistry through its communication with the CNS, influencing the neuro-endocrine systems linked to stress, anxiety, and memory function [20,21].

1.2. Neurotransmitters

Man develops mental, emotional, and independent brain activities because of the interaction of 100 billion neurons, nerve cells, and structural and functional units of the nervous system. Each neuron makes approximately 1000 complex, asymmetric, dynamic, and specialized synapses and contacts other neurons [22].

The nervous system controls behavior, as thoughts, feelings, and behaviors are created after biochemical processes that occur in neurons, the cells of the nervous system. Neurotransmitters are information providers between neurons, which receive and send chemical and electrical signals, promoting neuroplasticity. The cellular structure includes the cell body, dendrites, axons that carry information to other neurons, and synapses, microscopic and specialized structures that form contact points between cells [23,24] (Figure 1).

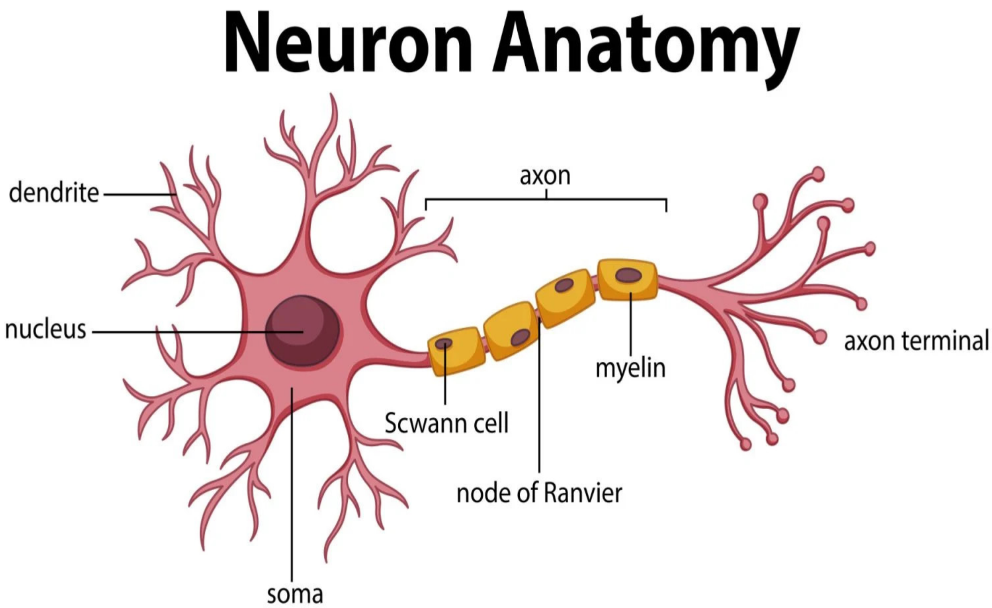

Figure 1. The structure of a neuron [25].

The fundamental structural elements of the neuron employ this particular formation. Thus, a neuron consists of the following components: the cell body, which serves as the nucleus of the cell; the axon, a nerve fiber; the dendrites receiving signals from other neurons and transferring them to the cell body; the terminal ends of the neuron transmitting signals to other neurons; and the myelin sheath, which envelops the neuron's axons [23–25].

The categorization of a neuroactive compound as a neurotransmitter requires the following: (a) production and release to be made by the same neuron, while storage takes place in the presynaptic terminal; (b) the creation of a specific behavior in the postsynaptic neuron; (c) its exogenous administration having the same effect; and (d) a specific mechanism to stop its induced action on the postsynaptic cell [26].

A neurotransmitter is a chemical compound released presynaptically from a neuron at a nerve synapse, affecting the postsynaptic neuron in a specific way. In transmitting information, neurotransmitters can increase nerve transmission, causing an excitatory effect, or decrease it, creating an inhibitory effect. Once produced, neurotransmitters are stored in synaptic vesicles, the terminal endings of the neuronal axon that releases them [23].

Natural sources of NTs exist as byproducts of essential metabolic processes and ecological interactions, or they can be synthesized artificially. However, the natural way of composing them in the daily diet limits neuropsychiatric, neurodevelopmental, and neurological dysfunctions. A healthy diet affects the synthesis, production, and release of neurotransmitters and mostly the person's general state of health. Both trace elements and vitamins are essential for neurotransmitters and affect the central nervous system [27].

Neurotransmission is a crucial process for organisms, enabling the transmission of information along the nervous system upon receiving a stimulus. Specifically, a void appears between two neurons, a synaptic cleft that allows them to communicate. The synapse is a microscopic structure essential to the information's transit from one neuron to another through the substances secreted, the neurotransmitters. Axon stimulation activates the synaptic vesicles of the presynaptic neuron that release the neurotransmitter across the synaptic cleft. Following this, the chemical is absorbed by the postsynaptic neuron's receptors, resulting in neurotransmission [23–25,28] (Figure 2).

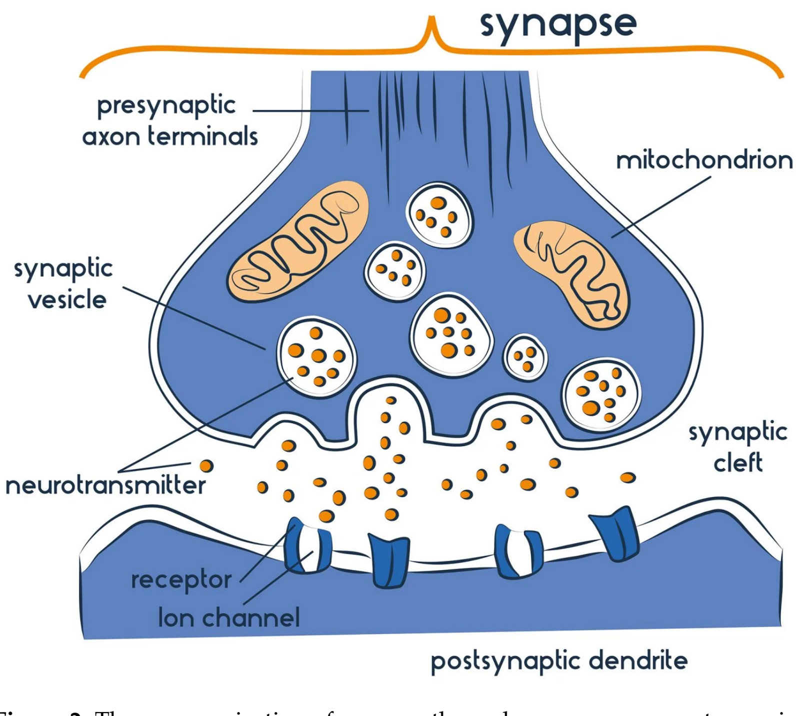

Figure 2. The communication of neurons through synapses—neurotransmission [28].

Based on how they act, neurotransmitters are classified into three categories: (A) Excitatory neurotransmitters (glutamate or glutamic acid, histamine) activate the target cells to take action. (B) Inhibitory neurotransmitters (gamma-aminobutyric acid—GABA, serotonin) cause an inhibitory effect on the receiving neuron. (C) Modulatory neurotransmitters (acetylcholine, norepinephrine, dopamine) simultaneously send a message to different neurons, affecting the action of other neurotransmitters [29].

Catecholamines [CATs], also known as "stress hormones", are a set of monoamines that interact with the endocrine and nervous systems and function as hormones and neurotransmitters. Norepinephrine (noradrenaline), epinephrine (adrenaline), and dopamine carry signals in the body and brain. They act on the gastrointestinal tract, enhancing nutrient absorption, immunity, and the microbiome [30]. Foods such as lean meat, fish, eggs, legumes, nuts, leafy greens, vegetables, whole grains, dairy, low-sugar fruits, seafood, olive oil, etc., increase the levels of norepinephrine and epinephrine in the body [29].

Dopamine regulates movement and emotional responses, influencing sleep, memory, learning, concentration, adaptability, decision-making, pleasure, and mood. It also aids in the unlearning of phobic associations [29,31]. Eating foods rich in tyrosine (a precursor substance), such as apples, oranges, bananas, cheese, nuts, peas, broccoli, and cauliflower, increases the amount of dopamine [29].

GABA is considered the foremost inhibitory neurotransmitter of the central nervous system. Foods that strengthen the body with a significant amount of GABA are cereals, lupine, tomato, sweet potato, and spinach [29]. It regulates the sleep–wake cycle, motor activity, and memorization, aids brain cell metabolism, and enhances concentration, thinking efficiency, and memory. Research reports that any disturbance in the microflora of the gastrointestinal system can affect and limit microbial GABA synthesis [32].

Glutamic acid or glutamate is an excitatory neurotransmitter, crucial for brain function. In foods, glutamate occurs in two forms—as "bound glutamate" with another amino acid to trigger protein synthesis (mushrooms, seafood, stews), contributing to learning and memory, and as "free glutamate", which creates various problems such as hyperstimulation in the digestive–nervous system and neurodevelopmental disorders. Low levels of glutamate in the body can cause anxiety, decreased energy, insomnia, memory loss, and depression, while eating foods high in glutamate causes increased levels of excitotoxicity [29].

Serotonin is a neurotransmitter that controls most brain functions. Dysregulation of the serotonergic system is related to the pathogenesis of several neuropsychiatric disorders [33]. It is produced in the gut and brain and is considered a natural mood stabilizer. Tryptophan is the precursor to serotonin, and foods (seafood, cheese, milk, poultry) rich in the amino acid tryptophan increase the serotonin level. Decreased levels of serotonin lead to depression, stress, unexplained irritability, panic attacks, obsessions, and deficits in episodic memory [29].

The release of **acetylcholine**, which comes from the parasympathetic nervous system and is involved in muscle contraction in the neuromuscular system, marks the first identification of a neurotransmitter in the peripheral nervous system. Acetylcholine plays a crucial role in the central nervous system (CNS) by influencing memory, attention, sleep, and learning. In addition, as a neuromodulating agent, it works on cognitive and motor functions [26]. Consuming foods rich in choline, such as breast milk, eggplant, spinach, beans, broccoli, egg meat, etc., its precursor substance, can increase acetylcholine levels [29].

1.3. Autism Spectrum Disorders

Autism is a neurodevelopmental disorder characterized by deficits in social communication, repetitive, persistent behavior, and restricted interests, with impacts on the individual's quality of life [34]. Moreover, ASD is marked by mitochondrial dysfunction, oxidative stress, and neurotransmitter imbalance in the cortex, hippocampus, and cerebellum, influencing language, personality, social interaction, self-control, planning, and executive function [21].

The incidence of ASD has increased remarkably in recent years, reaching 1–1.5% of the world's population, with research results indicating that one in 36 to 68 children has autism. The interaction of genetic and environmental factors is the core etiology, where 20% of ASD cases are related to alterations in the genetic mechanism. The high age of the parents, pesticides, premature birth, the exposure of the pregnant woman to infections or drugs during pregnancy, and polluted air, constitute some environmental parameters with an increased risk of ASD [35]. Especially when combined postnatally with oxidative stress and the appearance of inflammation, they significantly affect the neurodevelopment and neurotransmission of the individual [36].

Early infancy is a time when children's behavior is most closely associated with the onset of ASD symptoms. During this time, their brains develop in response to environmental cues, learning, and diet. In the early postnatal period of children with ASD, a different development of the cortex, cerebellum, hippocampus, and amygdala is observed [11,24,37].

ASD is most often associated with gastrointestinal symptoms, anxiety, and immune dysregulation. Some of the gastrointestinal symptoms experienced by people with autism are diarrhea, abdominal pain, discomfort, and gastric reflux. Additionally, postmortem studies of individuals with autism show an increased gut permeability, highlighting the association of gut dysbiosis with the pathophysiology of the disease [38]. Recent research explores the gut microbiota's role in autism, highlighting its potential health and disease implications, noting that changes in its composition can disrupt brain–gut coordination [34].

The following three sections relate to the connection of the gut microbiota with neurotransmission and their impact on ASD, the connection of certain neurotransmitters with the development of the disorder, and the contribution of ICT to the overall development of the disease. Finally, the study concludes with Sections 5 and 6 concerning the discussion and conclusions of the research.

2. Gut Microflora and Its Connection to NTs in ASD

2.1. Eating Habits in ASD

The causes of limited prevention in children with ASD are related to various biological and environmental factors such as gastrointestinal concerns, behavioral rigidity, reinforcement patterns, and family-promoted dietary restrictions [39].

Eating disorders are disorders in which there is an inability or refusal to consume sufficient nutritious food, necessary for the survival of the individual. Research has proven that a large percentage of children with ASD show feeding problems, with negative consequences at social, psychological, and developmental levels. The dietary selectivity demonstrated by children with autism is most often due to the sensory sensitivity that characterizes them, which is why they defend themselves by refusing the intake of various foods [40]. Several times their nutritional difficulties have been linked to problems in the gastrointestinal system, in sensory processing (tactile, visual, and auditory sensitivities), but also with problematic behaviors such as anxiety, irritability, and emotional instability [41].

Parents of children with autism describe their children's unusual eating behavior, which affects both the adequate intake of necessary nutrients and their development. Specifically, they argue that their diet is framed by the selective consumption of specific foods such as carbohydrates and sugary foods, their ritual attitude, or even the refusal to feed [42]. The food's color, texture, form, and temperature belong to the factors considered in the selection process. The combination of these criteria, with the rejection of enough fruits, vegetables, or proteins and the parallel preference for processed foods and starches, leads to weight gain. In addition, children with ASD show gastrointestinal problems (such as constipation, diarrhea, cramps, and gastroesophageal reflux), food allergies, and metabolic abnormalities, with effects on their neurobiological, social, and cognitive development [43].

The poor diet in children with autism is a vital cause of emotional problems, especially when it concerns the consumption of foods that contain dyes, artificial flavors, and preservatives. Chemical substances added to the food production procedure, to improve its taste or overall image, most often have carcinogenic effects or cause intolerance and allergies [44].

2.2. Effects of Selective Nutrition of Children with Autism on NTs

The causes of autism are not clearly defined. The role of the gut microflora in autism is gaining more and more interest from the scientific community. The gut microbiota is crucial to human health. Any alteration in its composition can affect the balance in the communication between gastrointestinal microflora and the brain [34].

Gut bacteria influence cells in the gastrointestinal tract that produce neurotransmitters and digestive hormones in the gut, which affect the brain and behavioral response. Factors that can differentiate gut bacteria, such as diet, environment, probiotics, and antibiotics, influence the function of the vagus nerve, which is the communication channel between the brain and the gastrointestinal system and the main component of the parasympathetic nervous system [45].

The study by Fouquier et al. [46] is regarded as the first to establish a connection between the severity of behavioral symptoms at various times and the makeup of the gut microbiome in people with ASD. In particular, they argue that the composition of gut microbes has a causal role in autism symptoms such as social withdrawal or inappropriate speech. Consequently, the gut microbiome constitutes a prime therapeutic target in autism. In addition, it is emphasized that interindividual variation in the gut microbiome may lead to different phenotypes in individuals, reinforcing the heterogeneous nature of ASD.

The quality of nutrition seems to influence the manifestation of symptoms in people with ASD and consequently their quality of life. Foods such as processed sugar, complex carbohydrates, fast food, high-carbohydrate foods, animal fat, and unsaturated fatty acids are factors associated with inflammation and intestinal disorders [47].

Gut microbes create essential neurochemical substances affecting behavior, social development, and cognitive function. Therefore, they are part of the unconscious system that impacts behavior control and coping with stressors. Notably, the absence of microbes can cause disturbances in the organism's development, such as in the functioning of the serotonergic system related to emotional regulation. Furthermore, researchers have noted that rodents that were not bred with bacteria display limited sociability, with distinct autistic behavioral patterns [4].

Metabolites produced by the gut microbiota affect neural processes, brain structure, and function [34,38]. Intestinal short-chain fatty acids (SCFAs) are generated by the bacterial fermentation of dietary carbohydrates and are considered key signaling molecules. Some of them are acetic acid (AA), butyric acid (BA), and propionic acid (PPA), which have an effect on the digestive tract and a regulatory role in the intestinal neuroendocrine process [48]. Short-chain fatty acids can influence the neurotransmitter phenotype, as increased or decreased levels of SCFAs have been observed in children with autism. In particular, SCFAs can cross the blood–brain barrier, modulating neurotransmission and behavior. More specifically, they have an impact on the biosynthesis of catecholamines, changing cerebral function and causing behavior characterized by anxiety and cardiovascular instability, symptoms seen in autism [34,48,49].

2.3. Dysbiosis Prevention–Treatment in ASD

Traditional Chinese, Ayurvedic, and Hippocratic medicine have recognized the importance of nutrition and the functioning of the digestive system in mental process regulation. Studies of modern medicine indicate the role played by stress and emotional and cognitive factors in the overall functioning of the organism [38]. Maintaining the balance of microbial composition is referred to as eubiosis. Gut microbes have an essential role in gut motility, the maintenance of gut integrity, the regulation of the immune system, and the absorption and production of nutrients, as well as intestinal barrier homeostasis [35].

The term "dysbiosis" describes the decrease in helpful bacteria and the rise in pathogens that limits the diversity of microbes in the small intestine [50]. The impact of this on individual health has been linked to the development of diseases like inflammatory bowel disease, obesity, diabetes, asthma, and autism [35].

According to studies, exposing the fetus to a balanced diet is especially important, as it can significantly moderate the effect of environmental chemicals and toxic substances. Specifically, a prenatal diet rich in folate and folic acid, omega-3 fatty acids, B vitamins, and vitamin D can limit or neutralize environmental toxins while providing antioxidant properties. Consequently, it differentiates the interaction of ecological chemicals, ASD, and the broader neurodevelopmental course prenatally and postnatally [36].

Folic acid is recommended for pregnant women due to its potential to protect against ASD deficits, improve social skills and executive functioning, and alleviate hyperactivity and language delay symptoms. Additionally, the child's behavioral, motor, and cognitive development, particularly in communication skills, is significantly influenced by the inclusion of iron, vitamin D, and specific eating habits [43].

In addition, the combination of prebiotics and probiotic supplements in sufficient quantities positively affects bowel function. In particular, prebiotics are plant fibers or complex proteins that contribute to gut homeostasis and improve metabolic, endocrine, immune, and nervous functions. Probiotics are live bacteria that are an emerging therapeutic approach in ASD, as they can reduce the inflammatory state of the gut, enhance microbial flora, and improve behavior in children with ASD [51].

According to various research studies, nutrition supplements act adjunctively with other interventions and can improve various symptoms of autism. Some supplements given with positive results in the symptoms of ASD are omega-3 fatty acids, probiotics, vitamin B6 with magnesium, B12, vitamins C, A, and D, iron, and folic acid. In particular, it has been established that a lack of omega-3 fatty acids can affect the development of the nervous system in childhood, presenting deficits in concentration, hyperactivity, dyslexia, dyspraxia, and symptoms of autism. In addition, the controlled administration of vitamins may enhance the interaction of neurotransmitters in the brain, subsequently influencing the autistic person's behavior and cognitive development [44].

The role of amino acids is especially significant to the body's functioning. Jennings and Basiri [5] characteristically state that certain amino acids used in protein synthesis, called essential amino acids, are taken in with food, while those that are not considered essential amino acids are synthesized in the human body. However, those amino acids, whose intake is through a healthy diet, possess a noteworthy impact on the CNS, controlling the body and mind. In addition, some of them help regulate CNS neurotransmitters such as serotonin and dopamine. Examples include tryptophan and tyrosine, which respectively increase serotonin and dopamine levels.

Several diets that have shown promise when used with individuals with ASD are the ketogenic diet, the Mediterranean diet, the gluten- and casein-free diets, the specific carbohydrate diet, and the low-oxalate diet [47]. However, considering that children with autism are particularly picky eaters, restrictive diets could cause a further restriction of variety in food intake and macronutrient and micronutrient deficiencies. Therefore, adopting a gluten- or casein-free diet presupposes individual measurements to rule out further aggravating factors. In contrast, the Mediterranean diet effectively improves gut microflora and neurobehavioral and cardiovascular diseases [51]. However, a healthy diet at the individual level should include factors directly related to the individual's lifestyle and concerns, genetic data, the gut microbiome, personal characteristics and habits, dietary preferences, medical history, the possibility of physical exercise, and environmental conditions [52].

Integrating daily activities like exercise, yoga, and meditation boosts the brain circulation. This enhanced blood flow helps the brain absorb essential micronutrients, improving neurotransmitter function and overall cognitive performance [53,54].

2.4. Gut Microbiome and Neurotransmitters

Neurotransmitter imbalance is involved in a variety of diseases, including anxiety, depression, insomnia, autism, multiple sclerosis, and functional gastrointestinal disorders. The complex two-way communication network between the CNS and the gut, called the gut–brain axis, includes the autonomic nervous system, the enteric nervous system, the endocrine system, the hypothalamic–pituitary–adrenal axis (HPA), the immune system, and the microflora and its metabolites [30,33,50]. Gut dysbiosis affects the gut–brain axis [GBA], which relates the function of the gastrointestinal tract to a set of functions and emotional–cognitive brain regions, such as the limbic system, the prefrontal cortex, and the hypothalamus. This results in the creation of a predisposition to disorders such as ASD [55].

Numerous research works discuss the two-way communication between the gut, the central nervous system (CNS), and its microbiome—the BGM system. Three routes of communication—neuronal, endocrine, and immunoregulatory mechanisms—connect the gut microbiota to the brain [38,56]. The CNS influences the composition and function of the gut microbiota through the autonomic nervous system. This is achieved indirectly through the gastrointestinal (GI) tract, mucus secretion, intestinal barrier permeability, and neurotransmitter release [38].

Research in recent years points to the role of gut microflora in mood disorders and neuropsychiatric diseases. The ability of gut microorganisms to create a variety of neurotransmitters, including acetylcholine, noradrenaline, dopamine, and serotonin, is highlighted. Therefore, an insufficient gut microbiome can impact neurotransmitter synthesis and production, affecting an individual's emotional and cognitive development. As an example, we mention that the altered levels of serotonin, dopamine, and noradrenaline can adversely impact one's emotional and behavioral condition through neuroendocrine pathways, causing symptoms of depression in people with ASD [50]. Certain types of bacteria produce molecules that affect the metabolism of the nervous system, directly or indirectly, characterizing this process as chemical signaling [35].

The human body's homeostasis, with a focus on gastrointestinal (GI) physiology, is significantly influenced by neurotransmitters such as serotonin and catecholamines. Norepinephrine (NE), epinephrine (E), dopamine (DA), and serotonin act to regulate and control blood flow, gut functionality, nutrient absorption, the immune system, and the microbiome. Although it was frequently held that monoamines solely functioned as neurotransmitters and neuromodulators in the central nervous system, science has highlighted their essential contribution to the gut microbiome. Because of this, their indirect role in brain regulation and the cognitive mechanism is underlined [57].

Human nutrition strengthens mental and physical health; on that account, it is necessary to include daily foods rich in vitamins, minerals, trace elements, and fatty acids. Amino acids that the body takes in through the diet, such as tryptophan, tyrosine, and phenylalanine (which contributes to the production of tyrosine), act as precursors for the production of neurotransmitters. In addition, they are a source of energy for cell development and survival, and their lack can affect a person's cognitive function, mood, and emotional state [58–61].

First and foremost, neurotrophins are a class of proteins that have been revealed to play a crucial part in the nervous system's operation, but they additionally exert an influence over other functional areas. Notably, they control the regulation, generation, maintenance, differentiation, proliferation, and death of neurons in the peripheral and central nervous system. In addition, they were found to contribute to the angiogenesis mechanism and immune and reproductive system functions, such as those of brain-derived neurotrophic factor [62].

Brain-derived neurotrophic factor (BDNF) is a neurotrophin (protein) that supports the survival of existing neurons, while promoting the growth and differentiation of new neurons and synapses. It contributes to the formation of dendritic structure and synaptic transmission, positively impacting neuroplasticity. In addition, it exhibits increased activity in the hippocampus and cerebral cortex, enhancing learning, memory, and the higher cognitive mechanism. Studies report that changes in the gut microbiota affect levels of BDNF, while studies indicate increased levels in children with ASD, causing effects on mood, pain, and cognitive function [4,33,63,64].

3. Composition of the Gut Microbiota in ASD

The microbiota, a crucial mediator of risk factors in ASD, is influenced by genetic background and environmental factors like feeding patterns, age, infection, and antibiotic treatment. Clinical studies reveal altered gut microbiota profiles in subjects with ASD compared to neurotypical controls. Colonized during birth, the human gut contains 100 trillion microorganisms, affecting the appearance and development of ASD. Extensive oral antibiotic treatment in ASD-affected children before 3 years of age may cause anaerobic bacteria proliferation, destabilize gut microbiota, and open opportunities for pathogens that contribute to ASD. *Bacteroidetes*, *Clostridia*, and *Desulfovibrio* are common bacteria that can cause gastrointestinal symptoms and autistic behaviors by altering the intestinal immune system and producing neurotoxins [65].

The neurological mechanisms underlying ASD could be greatly affected by metabolic imbalances resulting from changes in gut flora. Specifically, the microbiota's production of chemicals like short-chain fatty acids (SCFAs), propionate, and butyrate can influence brain function, potentially contributing to immune and mitochondrial dysfunction, potentially leading to ASD. Zou et al. [66] found that children with autism spectrum disorder have unique gut bacterial compositions and greater species diversity and richness than their non-ASD peers. This suggests their gut microbiota may contain harmful bacteria that could worsen their symptoms. Therefore, addressing these microbial imbalances is essential for improving their well-being and quality of life.

The adult gut microbiota comprises four key bacterial groups that make up over 90% of the total bacterial population. These groups are as follows: (a) *Bacteroidetes*: Gram-negative bacteria, including the genera Bacteroides and Prevotella. (b) *Firmicutes*: Gram-positive bacteria, both aerobic and anaerobic, such as *Lactobacillus*, *Clostridium*, and *Ruminococcus*. (c) *Proteobacteria*: this group includes species like Entero-bacter. (d) *Actinobacteria*: notably represented *by Bifidobacterium*. In addition to these, the gut microbiota also includes *Fusobacteria* and *Verrucomicrobia* [67].

The gut microbiota profile affects immunological, metabolic, and neurological systems and varies by person, age, lifestyle, and nutrition. Balance and diversity are crucial for proper functioning. Dysbiosis, a condition where the number of beneficial bacteria decreases, can lead to harmful bacteria colonizing the intestinal tract, causing gastrointestinal issues and potentially extra-intestinal physiological complications [68].

Recent studies suggest that alterations in the gut microbiota in early life can influence emotional and cognitive development. At the same time, the diversity of the gut microbiota is a determining factor for the effective use of behavioral abilities and brain development [69]. According to Kang et al. [70], gut problems are linked to ASD symptoms in humans and animal models, with gut microbes and their metabolites potentially causing gastrointestinal distress and ASD behavioral symptoms.

Mihailovich et al. [71] report that the gut microbiome is a dynamic ecosystem in which the phyla Firmicutes and Bacteroidetes are the most abundant in healthy adults. In contrast, *Actinobacteria*, *Fusobacteria*, *Proteobacteria*, and *Verrucomicrobiota* are less prevalent. Study [72] had similar results, finding that the main gut microbiota components in children with ASD and healthy control groups were *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*. The most abundant bacterial classes in both groups were *Clostridia*, *Bacteroides*, and unidentified *Actinobacteria*, with no significant differences identified.

The research indicates that autistic symptoms are associated with a less diverse gut microbiome, characterized by a lower abundance of specific bacteria such as *Prevotella*, *Coprococcus*, and *Veillonellaceae*. Additionally, ASD-related differences in the microbiota composition may lead to the loss of crucial microbial interactions, resulting in reduced diversity and functionality [73].

Vernocchi et al. [74] state that the *Pasteurellaceae* family is linked to ASD patients. It promotes intestinal inflammation due to dysregulated innate immune responses, as demonstrated in mice models with varying adaptive immunity genotypes. Moreover, Bacteroidetes were primarily associated with gastrointestinal symptoms linked to autism severity. Bacteroides fragilis, despite its high propionic acid concentrations, which could potentially cause toxic effects, has been connected to detrimental impacts in neurodevelopmental processes, including autism spectrum disorders (ASDs). Also, *Roseburia*, a genus of bacteria found in higher abundance in ASD patients, is known to degrade starch, contributing to the synthesis of short-chain fatty acids. Additionally, the study showed that patients with ASD exhibited higher levels of *Prevotella*, *Sutterella*, and *Lactobacillus* than those with neurotypical development. Conversely, useful microorganisms like Bifidobacterium decreased in all ASD subjects, potentially causing the reorganization of important microbes and contributing to some ASD symptoms.

In another study, Ye et al. [65] found a higher abundance of microorganisms such as *Ruminococcus* and *Faecalibacterium* in children with ASD. *Faecalibacterium* is associated with interferon-gamma, which is involved in brain plasticity and synapse formation. In addition, they observed lower levels of protective bacteria, such as Bifidobacterium, alongside increased levels of *Faecalibacterium* (the butyrate producer) and *Klebsiella* (known to cause infections).

More specifically, the research shows that children with autism spectrum disorder (ASD) have lower levels of Bifidobacteria in their stools compared to neurotypical children. This difference is related to changes in key metabolites derived from tryptophan metabolism. Importantly, dietary interventions containing *Bifidobacterium* strains or other bacterial compounds have been shown to enhance gut health and reduce the severity of ASD [75].

Morton et al. [76] identified a stable core microbiome comprised of *Bacteroides*, *Prevotella*, *Bifidobacteria*, *Desulfovibrio*, and butyrate producers, indicating a potential causal link to autism symptoms. Study [77] highlighted the importance of examining confounding variables in comparing the gut bacterial profiles associated with ASD and neurotypical development, thereby identifying robust microbial signatures across cohorts. In particular, it highlights the importance of controlling for and consistently assessing age, gender, and gut function when evaluating ASD datasets across studies.

The research indicates that children with ASD often exhibit a lower Bacteroidetes/Firmicutes ratio. However, it is important to note that this ratio is not a definitive marker and can sometimes remain stable or even increase in these children. This highlights the complexity of understanding the gut microbiome of ASD, underscoring the need for further investigation into these microbial patterns [78].

Stratis et al. [79] reported an altered microbial community at both the bacterial and fungal levels. Furthermore, they observed a significant increase in the *Firmicutes/Bacteroidetes* ratio in autistic individuals due to a substantial decrease in *Bactermites*. Inflammatory conditions like inflammatory bowel disease and obesity were associated with a rise in the ratio of *Firmicutes* to *Bacterodites*. In addition, the gut microbiota of autistic individuals showed an increased abundance of *Collinsella*, *Corynebacterium*, *Dorea*, and *Lactobacillus*, with a decreased abundance of *Alistipes*, *Bilophila*, *Dialister*, *Parabacteroids*, and *Veillonella*. According to the studies, the prolonged use of antibiotics alters the bacterial microflora of the gut, preventing community reconstitution and leading to an altered abundance of *Bacteroidetes, Lactobacilli*, *Ruminococcus*, and *Lachnospiraceae*.

Yang et al. [80] point out that a significant 9% to 91% of individuals with ASD report gastrointestinal symptoms, including diarrhea, constipation, and abdominal pain. These gastrointestinal issues are not just common; they are closely linked to disruptions in the gut microbiota and may significantly influence the intensity of ASD clinical symptoms. Addressing these gut health concerns could be crucial for improving overall well-being in individuals with ASD.

According to the findings of studies [66–68,72–75,78,80], we summarize in the figure below (Figure 3) the composition of the intestinal microflora in ASD compared to individuals with neurotypical development. Specifically, it includes bacterial phyla more abundant in ASD (black color), bacterial genera more prevalent in ASD (left column of bacteria), bacterial genera less prevalent in ASD (right column of bacteria), and bacterial phyla with no difference between ASD and the control group (purple color).

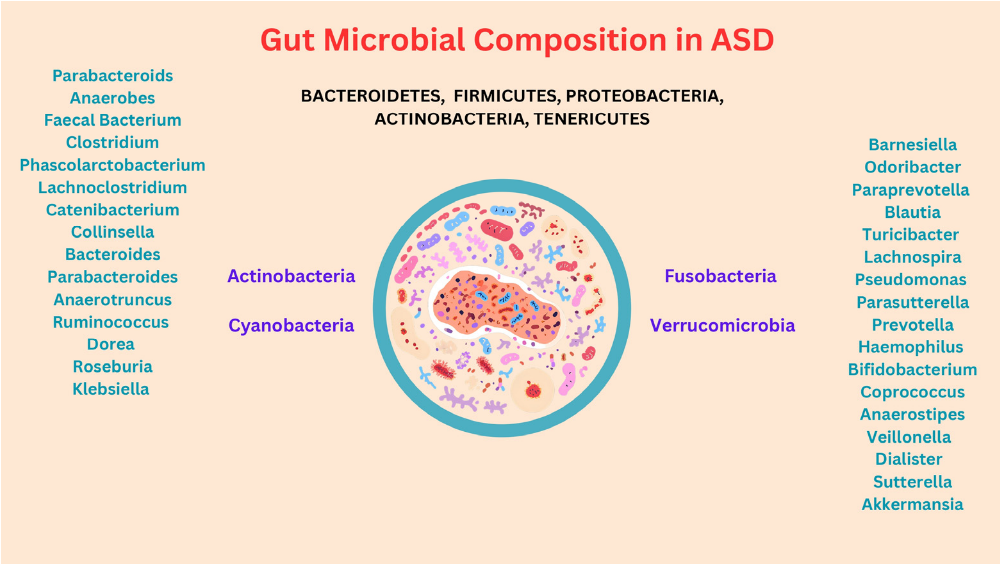

Figure 3. The composition of the gut microbiota in ASD.

4. ASD and NTs

ASD is a neurodevelopmental disorder characterized by limited communication and social interaction, stereotyped repetitive behaviors and interests, and a particular sensory responsiveness. The increase in prevalence observed, with apparent symptoms in the first months of children's life, indicates the existence of neurochemical factors that affect the development of the central nervous system. The results of molecular imaging studies and genetic data highlight the connection of neurotransmitters with the course of autism development [81]. Chemical substances such as neuropeptides, hormones, hormone-like substances, and neurotransmitters (serotonin, norepinephrine, dopamine) act as messengers of messages in the brain's neuronal network. Some of those are closely associated with interpreting social cues, mainly due to their action with the amygdala and hippocampus, facilitating cognitive development. Therefore, when any disorder occurs in their composition or action, it can lead to social behaviors analogous to ASD [64].

The gut microbiota influences the structure and function of the enteric and central nervous systems, with implications for human behavior and brain regulation. The number of bacteria in the gut affects both the stimulation and the function of the vagus nerve. The enteric nervous system, also known as the second brain, constitutes the greatest system of neurons and protective cells (glia) after the central nervous system [82]. In addition, the intestinal dysbiosis seen in people with autism can cause an increase in intestinal permeability to neurotoxic substances, with effects on the body. These may occur as microorganisms from the gastrointestinal tract enter the bloodstream, with corresponding effects on the CNS [83].

The essential neurotransmitters that significantly affect the brain and behavior are acetylcholine, catecholamines, serotonin, and the amino acids glutamic acid and GABA [84]. Autism spectrum disorders are associated with alterations in the brain's structural and functional mechanisms as well as in neurotransmitters, which play a regulatory role in several neurodevelopmental processes. Specifically, deviations in glutamatergic, glutamatergic, GABAergic, serotonergic, dopaminergic, and oxytocinergic signaling are observed in individuals with ASD. Among these abnormalities in neurotransmission, the most chemically and imaging-confirmed is the case of serotonin, where numerous studies support blood hyperserotonemia in a large percentage of cases, up to approximately 45%. Data from studies indicate that peripheral 5HT dysfunction indicates central deviations, influencing brain architecture, mainly during the developmental period [85].

Maintaining the function and homeostasis of the central nervous system [CNS] requires the balance of the excitation and inhibition of nerve cells [86]. Since serotonin and catecholamines are associated with many physiological processes, any change in their composition or action can cause brain disorders. One of them is autism, where individuals with ASD show qualitative and quantitative differences in the gut microflora [57].

According to the findings of studies [26,29,31,33,84,85,87,88], we summarize in the following figure the association of certain neurotransmitters with ASD. Specifically, this refers to central neurotransmitters, where any alteration in their synthesis and release leads to dysfunctions that reflect symptoms of autism (Figure 4).

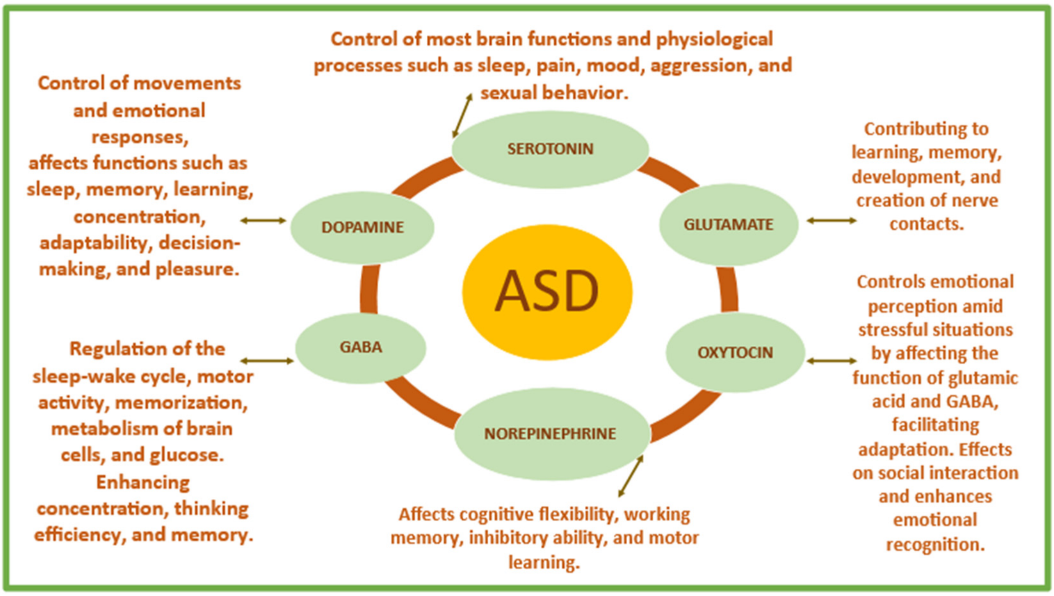

Figure 4. ASD etiology is linked to modifications in NT production and release.

4.1. Serotonin

Several studies emphasize the role of serotonin in ASD, mainly through the gut–brain axis. The central and peripheral serotonin systems are involved in ASD mechanisms, and the function of the peripheral serotonergic system appears to act as a link in the brain–gut axis in autism [89].

The gut produces around 95% of serotonin. Tryptophan is a precursor chemical required for its production and release. However, individuals with autism exhibit a weakening of their metabolism because of the lower expression of genes encoding the molecules involved in it. It leads to abnormal serotonin signaling, which exacerbates the repetitive behaviors associated with ASD. The insufficient functioning of the serotonergic system creates developmental alterations in cortical morphogenesis. As a result, alterations in neural network connections may lead to autism [90]. In addition, serotonin directly influences other neurotransmitters, inhibiting dopamine and glutamate release in the frontal cortex, modulating glutamate and GABA transmission, and promoting glutamate transmission in the prefrontal cortex [26].

4.2. Norepinephrine or Noradrenaline

Norepinephrine or noradrenaline is a critical component of the arousal mechanism that can influence cognitive flexibility, working memory, inhibitory ability, and motor learning. Study findings report increased noradrenergic activity in ASD, associated with elevated plasma epinephrine and norepinephrine levels, as well as altered urinary excretion of some catecholaminergic metabolites [91]. According to Gevi et al. [92], a data analysis of the urine of children with autism showed a significant percentage of altered metabolites. Specifically, higher dopamine levels were identified, along with a reduced activity of the enzyme dopamine β-hydroxylase, an enzyme necessary for the metabolism of catecholamines and responsible for converting dopamine into noradrenaline. Lower levels of noradrenaline and adrenaline in the urine of children with ASD were linked to deficits in attention and memory and learning difficulties.

4.3. Dopamine

According to Saha, the dopamine (DA) system has a functional role in ASD by regulating motor activity, goal-directed behaviors, and cognitive processes such as working memory, attention, and perception. Changes in dopaminergic signaling pathways cause decreased reward system activation, with consequences for decision-making [26]. Findings from studies involving individuals with ASD have shown neuroanatomical defects in the basal ganglia, frontal/prefrontal cortices, and dorsal striatum, areas associated with dopaminergic signaling. Research highlights the connection of dopamine receptor D4 (DRD4) with various neurobehavioral disorders. In particular, the DA 4 receptor is mainly expressed in the prefrontal cortex, where higher cognitive functions such as the reaction to several situations, inhibitory control, and other cognitive processes are involved, which are often deficient in individuals with autism [93].

Several studies indicate the importance of dopaminergic dysfunction in ASD, since dopamine signaling disturbances in the midbrain dopaminergic regulatory systems can cause social deficits and stereotyped behavior [94]. Studies of the dopamine system in ASD have found an increase in one of its metabolites in the cerebrospinal fluid of patients. Further research links the pathogenesis of ASD to evidence of genetic variation in dopamine signaling genes, its receptors, and genes involved in its transport [85].

4.4. Oxytocin

Oxytocin is a hormone produced in the hypothalamus. It has a neuromodulatory role in the central nervous system and peripheral tissues. According to various studies, oxytocin controls how a person reacts in respect to specific social cues involving the maintenance instinct. Others point to its beneficial effect on social interaction, a sense of trust in others, and enhanced emotional recognition after its administration, particularly in cases of autism. Oxytocin plays an indirect role in activating the action of several neurotransmitters [87].

Specifically, oxytocin modulates inhibitory neurotransmission. Specifically, it contributes to preserving the equilibrium of the inhibitory–stimulatory system, which is linked to social dysfunction, playing a crucial part in regulating social cognition and behavior [85]. More precisely, oxytocin controls emotional perception amid stressful situations by affecting the function of glutamic acid and GABA, facilitating adaptation. In addition, it has a neuroprotective effect by increasing the resistance of neurons to toxins. What matters is its effectiveness on serotonergic transmission by activating the immediate release of serotonin, as it acts on serotonergic receptors. In addition, serotonin and its precursor molecule, a metabolite of the amino acid tryptophan, stimulate oxytocin release [87].

4.5. GABA–Glutamate

Excitatory/inhibitory (E/I) imbalance refers to the lack of balance between excitatory (glutamatergic) and inhibitory (GABAergic) systems as a causative factor for the onset of autism symptoms [95]. The imbalance between excitatory and inhibitory neuronal function suggests an alteration in synaptic excitation and inhibition, characterized by a deficient glutamatergic and GABAergic (gamma-aminobutyric acid) metabolism that causes hyperexcitability in the cerebral cortex. Overstimulation in the brain creates excessive inhibition in certain areas, which may be related to increased levels of GABA in the prefrontal cortex. According to the studies, an immoderate or unstable excitatory metabolism can lead to hyperinhibition, which can affect the recognition of emotions, empathy, social communication, and the appearance of stereotypic behavior, areas that in autism are underperforming [96,97]. It is emphasized that GABA is a critical neurotransmitter that is excitatory during early developmental stages and is inhibitory in the mature central nervous system. This function is mediated by the expression of chloride/cation transporters, which are involved in neurogenesis processes [98,99].

Several researchers focusing on the genetic cause of autism have discovered common genetic variants associated with autism. These genes are involved in transporters, glutamate and GABA receptors, and protein coding. Hollestein et al. [95] studied the possible genetic basis of excitation/inhibition imbalance, various behavioral phenotypes, and brain structure in autism. Combining the study's genetic, phenotypic, and structural results, they concluded that the balanced excitation/inhibition disorder varies across ASD phenotypes and brain regions. Additionally, their study revealed that glutamate genes are associated with the behavioral features of autism, while GABA genes are primarily associated with sensory processing.

Glutamic acid is found in the brain's nerve cells and is the dominant excitatory neurotransmitter, providing a protective action on cognitive function and neural plasticity. However, elevated glutamate levels are neurotoxic, causing damage to other neurons as well as neuroinflammation linked to autism [100]. Specifically, increased blood glutamate is associated with limited social skills. In addition, glutamate is converted to GABA, whose dysfunction is reported in ASD, involving glutamate and GABA receptors [85].

Neurotransmitters are crucial for neuronal network communication, brain development, memory performance, motor function, and behavior manifestation. Consequently, the dysregulation of neurotransmitter function is causally related to ASD, as it affects neuronal cell differentiation and communication, synaptogenesis, and the neurobiological development of the brain [86].

5. The Contribution of Digital Technology

The rapid development of sciences and technologies inevitably led to the gradual establishment of digital health. Digital health presupposes the interaction of advanced medical technologies and digital communication, combined with disruptive innovative ideas to deliver healthcare in the best possible way. Furthermore, "digital health" could be defined as the cultural transformation of innovative technologies, where digital and objective data are available to doctors, patients, and caregivers to collaborate in shared decision-making and optimal care [101].

Digital health refers to individual fields such as wearable technology, telemedicine, personalized medicine, and mobile health (mHealth). Digital technology has a pivotal role in healthcare. Digital capabilities significantly enhance clinical assessment and decision-making for medical scientists, leading to more accurate diagnoses and effective patient treatment. Therefore, in health and education, artificial intelligence constructively uses machine learning, digital platforms, software, sensors, wearable devices, computer networks, and robots [60].

The technological developments of the last decades have led to the application of new neuroimaging methods, including positron emission tomography (PET) and single positron emission computed tomography (SPECT), in combination with structural and functional magnetic resonance imaging (MRI), to investigate the neural anatomical, functional, and molecular bases of individuals with autism. Specific molecular imaging techniques have allowed the study of biological processes in vivo at the cellular and molecular level, pointing out that the alterations in the serotonergic, dopaminergic, glutamatergic, and GABAergic systems are related to the appearance of disorders in the neuronal network of ASD. In addition, neuroimaging investigations help evaluate the effective treatment of autism, providing objective biomarkers that will aid in creating and assessing suitable treatment strategies for the disease [102].

Detecting and diagnosing gastrointestinal problems in ASD is not an easy process, given the limited social skills children display. In addition, several symptom manifestations might not receive much attention, since they are part of the general behavior of children with autism. Artificial intelligence (AI) helps diagnose and treat autism spectrum disorder (ASD) by enhancing children's cognitive, social-emotional, and communicative abilities. In addition, AI is a reliable complementary method in the disorder detection of the gastrointestinal system, creating the possibility of personalizing the diet and improving the intestinal microbiome [103].

Specifically, artificial intelligence allows the gathering and analyzing of a complex dataset of dietary responses using electronic health records, biosensors, wearable devices, and nutritional assessments to provide personalized dietary recommendations. To achieve the ongoing tracking of energy intake and expenditure, we cite the example of "smart" dietary follow-up equipment like smartwatches and smartphones, which also include activity data [52].

The National Institutes of Health, following advances in artificial intelligence in the analysis and management of complex data in individual nutritional adaptations, created the Nutrition for Precision Health program, supported by the All of Us Research Program (see https://commonfund.nih.gov/nutritionforprecisionhealth accessed on 5 November 2024). The project aims to develop algorithms that predict individual reactions to dietary patterns and foods impacting everyday life [52].

Kaur et al. [45] highlight that machine learning can effectively integrate phenotypic, genotypic, epigenetic, and microbiome information through a thorough data collection and analysis. As a result, it paves the way for the growth of effective personalized interventions for brain disorders.

Data science and digital health technologies enable long-term support for people with ASD. For example, we mention smartphones that can process long-term and complex physical and mental health data for utilization in diagnosis and monitoring. Additionally, it is possible to analyze complex information using machine learning to predict and access digital health interventions through software, video conferencing, chatbots, or virtual reality [104].

The contribution of ICTs to the development of self-control and the promotion of healthy eating habits is noteworthy. With plenty of interactive tools at its disposal, digital learning highlights its importance and acts as a set of compensatory elements for the inadequacies students have shown, while also offering vital support to special education. In particular, the use of mobile learning technologies (tablets, smartphones) in the educational process of children with autism is effective mainly through the innovative methods used, while promoting students' flexibility, autonomy, and adaptability [105,106].

In particular, smartphone applications or techniques that utilize distance education can influence people's dietary choices, directing their attention and interest to a healthy way of eating. That is achieved through the individual's interaction with digital tools, which promote continuous encouragement, self-evaluation, and positive reinforcement [107].

In addition, digital technologies play a dominant role in the educational process. Specifically, they enhance social-emotional, cognitive, and metacognitive skills, emphasizing the strengthening of emotional intelligence and the executive mechanism, especially in people with increased educational needs [108–111].

Virtual reality (VR) has shown promise in ASD assessment and treatment. The application of virtual environments in the educational process reduces anxiety, enhances the development of social skills and the expression and management of emotions, and strengthens the cognitive mechanism [111]. Moreover, the utilization of metacognitive processes, with an emphasis on mindfulness practices, combined with virtual reality highlights the enhancement in the release of neurotransmitters related to the regulation of stress, relaxation, self-control, and behavioral adaptability [112]. Simultaneously, memory, attention, and executive functioning can be assessed using specific virtual reality apps. Nonetheless, its application has to be focused on preventing unfavorable outcomes [111].

The use of digital games is particularly effective in the field of learning, where depending on the emotions they cause and the mental processes they activate, they can affect the release and levels of neurotransmitters, influencing behavior and cognitive development accordingly [113]. In particular, more and more studies are turning their attention to the use of serious games (SGs) as an innovative form of intervention in the management of the neurobehavioral and cognitive disorders of children with neurodevelopmental disorders such as ASD and ADHD. Their efficacious application is attained through training cognitive skills such as memory, concentration, inhibitory control, and the recognition and expression of emotions, utilizing computer platforms, mobile applications, software, and video game consoles. Additionally, this can enhance the formation and restructuring of neurobiological pathways, especially in children, since they show greater neuroplasticity compared to adults [114].

In addition, applications of modern technology such as 3D animations, collaborative virtual environments, and the 3D avatars, what is more, in many web apps help significantly in the development of social skills of children with autism [115]. Notable in this respect are the findings of experimental neuroscience studies, which report that human–robot interaction promotes interactive social cues, including social praise. When the student receives social praise from the robot, dopamine, a neurotransmitter linked to pleasure, is released, elevating the learner's self-esteem [116].

The application of serious games plays a fundamental role in the education of children with autism, which is extensive in special education, by combining auditory, visual, tactile, and intellectual stimuli to create internal motivation in students. In addition, it enhances individualized learning and autonomy and promotes the development of many skills, such as information processing, problem-solving, communication, memory, attention, and cognitive flexibility [117]. Electronic educational games support the educational process by building knowledge, improving weaknesses, and turning abilities into skills [118].

Consequently, using a variety of ICT applications improves autism diagnosis and intervention, along with accessibility to schooling. Essentially, it raises the standard of the learning environment and learning, turning it into an engaging, active process connected to real life [119–121].

6. General Discussion

Genetic studies in patients with autism report the existence of a variety of genetic mutations, which have a wide range of variability, with effects on brain function and the individual's immune status. Deficits in sensory processing and social compliance in children with autism exacerbate their feeding disorders. This can result in the consolidation of food intolerance and the creation of intense stress for the parents, with the adoption of negative feeding patterns [103].

An integral component of microbial activities and neurochemical processes is a person's diet, which could be considered a principal form of therapy in combating the neurodevelopmental disorders caused by ASD [51]. Early colonization, antibiotic use, stress, and fiber fermentation can affect the gut microbiota and the development of autism. Dysbiosis and colonization by pathogenic microbes can produce neurotoxins, affecting CNS function [122]. Gut microbial dysregulation appears to alter a person's immune response, negatively affecting their social and cognitive performance. Several studies demonstrate that symptoms associated with neurodevelopmental disorders, including autism, can be controlled and improved by remodeling dietary habits and the aftermath of the gut microbiome composition [53,78]. Ther gut microflora influences the differentiation of cells in the gastrointestinal space, releasing hormones and neurotransmitters that affect the brain and the cognitive–social manifestation of the individual, such as in autism. Consequently, the microbiome–gut–brain axis links the emotional and cognitive regions of the brain with the peripheral gut machinery and is implicated in the pathogenesis of autism [43].

The data show a strong link between dietary intake, neurodevelopment, and cognitive function in healthy children, with dietary components significantly influencing central nervous system mechanisms. Studies indicate that ASD often coexists with dysbiosis in children, with autism being attributed to the limited diversity of the microflora. The gut microflora's influence is attributed to the hormones and metabolites produced by bacteria, although the exact causes are unknown [49,72]. The research suggests that FDA-approved probiotics and metabolites can improve ASD symptoms by enhancing the bacterial composition. Furthermore, culturing a specific combination of bacteria and fecal microbial transplantation offer an alternative to microbial transplantation, rebuilding the gut microbiota, protecting it, and treating autism symptoms [122,123]. An adequate nutritional intake promotes brain development during the prenatal and postnatal period and enhances the formation of a functionally complete brain structure. The importance of eating food lies in the intake of energy and the possibility of producing neurotransmitters, as foods contain natural chemicals that contribute to the smooth functioning of the human neurological system [27].

The gut's intricate nervous system influences brain function, affecting mood, behavior, and cognitive function. Its millions of neurons act as a second brain controlling the gastrointestinal system [34]. The cells located along the intestinal tract are the largest producers of hormones and neurotransmitters in the body, such as histamine, serotonin, and catecholamines (dopamine, noradrenaline, and adrenalin) [82].

Gut microbial composition changes, impacting the byproducts and neurotransmitters produced by gut microbes, affecting the human brain and neurochemistry. Microorganisms produce several important neurotransmitters, including GABA, norepinephrine, dopamine, acetylcholine, and serotonin [84,124]. Our diet impacts brain processes, regulating the central and peripheral nervous systems. Primary components (proteins, carbohydrates, fats) and secondary components (minerals, vitamins) provide energy and precursors for neurotransmitters. Consequently, eating habits contribute to mental and physical well-being and act as a synthetic neurotransmitter [29].

Several studies emphasizing the importance of microbial metabolism during the postnatal period point out that neuroactive compounds produced by the gut microflora can affect synaptogenesis and synaptic function in the developing brain. It is particularly noticeable in people with genetic mutations that affect synaptic components or neurotransmitters that function at various synapses [1]. Later research indicates that the gut microbiome can regulate brain function by influencing the production, expression, and renewal of neurotransmitters like serotonin, dopamine, norepinephrine, and epinephrine. Additionally, it may affect the brain through bacteria or their metabolites, since they function as signaling molecules in specific cell types within the mucosa [125]. Researchers report that gut microbes can subliminally generate interoceptive inputs that influence memory, emotional arousal, and behavioral expression in various emotional states [15,124]. Consequently, the functioning of the nervous system is related to the composition and diversity of the intestinal microflora [126]. Focusing on the function of neurotransmitters linked to brain processes can directly alter the reaction of the brain mechanism. Specifically, the differentiation (increase–decrease) of the precursors needed for synthesizing and releasing neurotransmitters might produce the intended effects [127].

Considering the importance of neurotransmitters in the state of the brain, we can draw conclusions about the gravity of their disturbed homeostasis and limited neurotransmission in the functioning of the human body. Imbalanced levels of neurotransmitters (glutamate, GABA, dopamine, serotonin, norepinephrine, acetylcholine, and histamine) are associated with the pathophysiology of various disorders–diseases, such as ASD, sleep disorders, schizophrenia, Parkinson's disease, Alzheimer's disease, and depression. Because of this, it is especially crucial to detect and investigate the mechanisms of action of neurotransmitters and the availability of the tools required to keep them at physiological levels [26].

The environment can act as a causative factor when it accumulates harmful elements that pre-exist autism. However, some factors can be protective and reverse or limit the onset of ASD symptoms. The support of an appropriate psychosocial environment, combined with healthy nutritional habits prenatally and postnatally, is of crucial significance for the progression of the disease. It is pointed out that a balanced maternal diet during pregnancy is vital, as it strengthens fetal programming and brings about positive results in its development [128]. In addition, a healthy diet that includes a balanced intake of long-chain polyunsaturated fatty acids, amino acids, carbohydrates, and minerals contributes to the development of the neural circuits of the brain that strengthen cognitive performance and emotional competence [61].

Artificial intelligence and neuroscience are interrelated fields of knowledge that contribute to each other's progress through interactive research studies. Artificial intelligence has significantly improved our ability to identify neurological and neurodevelopmental disorders [10]. It is worth noting that the use of artificial intelligence in medicine allows the management, processing, and integration of data resulting from a range of complex medical evaluations, for the benefit of a precise and personalized intervention. Its inventiveness stems from its ability to overcome obstacles like a limited workforce, insufficient primary care, complex assessment procedures, increased waiting lists, and demographic biases [9].

Specifically, the application of artificial intelligence to cases of healthy individuals and patients can highlight nutritional risks related to genetic, behavioral, and environmental factors or disease characteristics. The discovery of these data allows the creation of valid adapted dietary recommendations, which prevent disease or work therapeutically against its development [52,74]. Additionally, artificial intelligence (AI) and technology have been successfully involved in the education sector, making it accessible for students with special needs. Moreover, the application of assistive technologies empowers people to work toward inclusive education and encourages its advancement [129].

In conclusion, the combination of alternative forms of addressing deficits in ASD, when possible, including a nutritious diet, emerges more effectively, especially during the first years of the child's life, as opposed to taking medication, which concentrates on treating symptoms and has adverse effects. In addition, giving priority to the utilization of ICTs as autism intervention tools enables children's social and cognitive development and paves the way to their autonomy through engaging, structured audio-visual experiences [11].

7. Conclusions

In summary, the quality of a person's diet determines the diversity of the gut microbiome, which affects the synthesis and production of neurotransmitters, whose healthy operation is required to preserve the body's equilibrium. Consequently, considering the communication and interaction of the enteric nervous system with the mechanism of the brain, any alterations in neurotransmission affect the organism's overall health. In particular, this is evident in various cases of individuals with neurobiological disorders, including ASD, where chemical messenger disturbances impact the behavioral, social, cognitive, and metacognitive development of individuals with autism. Moreover, the gut microbiota's makeup significantly influences the severity of autistic symptoms. By conducting a further analysis, we can unlock the potential for tailored dietary interventions that may greatly benefit individuals on the autism spectrum. However, the change to a healthy way of living that includes appropriate nutrition, exercise, and education, when applicable, combining the usage of digital technologies, can result in a substantial improvement and the elimination of ASD symptoms.

Limitations and Suggestions for Future Research

The gut microflora is essential in ASD development symptoms, affecting neurotransmitter efficiency, neuronal cell differentiation, synaptogenesis, and brain neuroplasticity [24]. Consequently, higher-order activities are affected, combining different neural networks' cooperation in the executive system [130–132]. Furthermore, executive function is directly related to the cognitive and metacognitive development of the individual, including cases with ASD [11,37]. The present study did not investigate the interaction impact of the gut microbiome and neurotransmitters on the development of metacognition. However, because the development of metacognitive function enhances cognitive and socioemotional factors, it is appropriate to motivate future research [11]. In addition, the study limitation of a lack of an age demographic focus does not allow for a comprehensive investigation of gut microbiota and neurotransmission effects in different age groups, providing the stimulus for further studies.

Future studies must focus longitudinally on the bidirectional influence of ASD individuals' diet and neurotransmitter generation. Additionally, the potential for the modulation of gut–brain axis neurotransmission in autism is noteworthy. Therefore, it is of utmost importance that preclinical investigations prioritize the search for individual diagnostic biomarkers that cause dysbiosis and affect the synthesis and release of chemical substances. In addition, it would be highly beneficial when selecting a therapy strategy to pursue an in-depth investigation of the interaction between the gut microflora, the regulation of the CNS, and the appearance of ASD symptoms.

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References

1. Gonzalez, A.; Stombaugh, J.; Lozupone, C.; Turnbaugh, P.J.; Gordon, J.I.; Knight, R. The mind-body-microbial continuum. *Dialogues Clin. Neurosci.* **2011**, *13*, 55–62. [CrossRef]
2. El Aidy, S.; Dinan, T.G.; Cryan, J.F. Gut Microbiota: The Conductor in the Orchestra of Immune-Neuroendocrine Communication. *Clin. Ther.* **2015**, *37*, 954–967. [CrossRef] [PubMed]
3. Thakur, A.K.; Shakya, A.; Husain, G.M.; Emerald, M.; Kumar, V. Gut-Microbiota and Mental Health: Current and Future Perspectives. *J. Pharmacol. Clin. Toxicol.* **2014**, *2*, 1016. Available online: https://www.researchgate.net/publication/260425062 (accessed on 28 October 2024).
4. Dinan, T.G.; Cryan, J.F. The Microbiome-Gut-Brain Axis in Health and Disease. *Gastroenterol. Clin. N. Am.* **2017**, *46*, 77–89. [CrossRef] [PubMed]
5. Jennings, L.; Basiri, R. Amino Acids, B Vitamins, and Choline May Independently and Collaboratively Influence the Incidence and Core Symptoms of Autism Spectrum Disorder. *Nutrients* **2022**, *14*, 2896. [CrossRef] [PubMed]
6. Israelyan, N.; Margolis, K.G. Reprint of: Serotonin as a Link between the Gut-Brain-Microbiome Axis in Autism Spectrum Disorders. *Pharmacol. Res.* **2019**, *140*, 115–120. [CrossRef] [PubMed]
7. De Sales-Millán, A.; Aguirre-Garrido, J.F.; González-Cervantes, R.M.; Velázquez-Aragón, J.A. Microbiome–Gut–Mucosal–Immune–Brain Axis and Autism Spectrum Disorder (ASD): A Novel Proposal of the Role of the Gut Microbiome in ASD Aetiology. *Behav. Sci.* **2023**, *13*, 548. [CrossRef] [PubMed]
8. Di, J.; Li, J.; O'Hara, B.; Alberts, I.; Xiong, L.; Li, J.; Li, X. The Role of GABAergic Neural Circuits in the Pathogenesis of Autism Spectrum Disorder. *Int. J. Dev. Neurosci.* **2020**, *80*, 73–85. [CrossRef]
9. Shannon, J.; Salomon, C.; Chettiath, T.; Abbas, H.; Taraman, S. Autism spectrum disorder and the promise of artificial intelligence. *J. Child Adolesc. Behav.* **2022**, *10*, 428.
10. Surianarayanan, C.; Lawrence, J.J.; Chelliah, P.R.; Prakash, E.; Hewage, C. Convergence of Artificial Intelligence and Neuroscience towards the Diagnosis of Neurological Disorders—A Scoping Review. *Sensors* **2023**, *23*, 3062. [CrossRef] [PubMed]
11. Bamicha, V.; Drigas, A. ToM & ASD: The Interconnection of Theory of Mind with the Social-Emotional, Cognitive Development of Children with Autism Spectrum Disorder. The Use of ICTs as an Alternative Form of Intervention in ASD. *Tech. Soc. Sci. J.* **2022**, *33*, 42–72. [CrossRef]
12. Hussain, S.J.; Cohen, L.G. Exploratory studies: A crucial step towards better hypothesis-driven confirmatory research in brain stimulation. *J. Physiol.* **2017**, *595*, 1013–1014. [CrossRef]
13. Swedberg, R. Exploratory Research. In *The Production of Knowledge: Enhancing Progress in Social Science*; Cambridge University Press: Cambridge, UK, 2020; pp. 17–41. [CrossRef]
14. Quigley, E.M.M. Basic Definitions and Concepts: Organization of the Gut Microbiome. *Gastroenterol. Clin. N. Am.* **2017**, *46*, 1–8. [CrossRef]
15. Mayer, E.A. Gut Feelings: The Emerging Biology of Gut–Brain Communication. *Nat. Rev. Neurosci.* **2011**, *12*, 453–466. [CrossRef] [PubMed]
16. Garcia-Gutierrez, E.; Narbad, A.; Rodríguez, J.M. Autism Spectrum Disorder Associated with Gut Microbiota at Immune, Metabolomic, and Neuroactive Level. *Front. Neurosci.* **2020**, *14*, 578666. [CrossRef] [PubMed]
17. Alharthi, A.; Alhazmi, S.; Alburae, N.; Bahieldin, A. The Human Gut Microbiome as a Potential Factor in Autism Spectrum Disorder. *Int. J. Mol. Sci.* **2022**, *23*, 1363. [CrossRef]

18. Rosenfeld, C.S. Microbiome Disturbances and Autism Spectrum Disorders. *Drug Metab. Dispos.* **2015**, *43*, 1557–1571. [CrossRef] [PubMed]
19. Sideraki, A.; Papageorgiou, E.; Tsiava, M.; Drigas, A. Stress, Hormones & the role of ICT in autism. *Tech. BioChemMed* **2022**, *3*, 42–59.
20. Carabotti, M.; Scirocco, A.; Maselli, M.A.; Severi, C. The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. *Ann. Gastroenterol.* **2015**, *28*, 203–209.
21. Bamicha, V.; Salapata, Y. LLLT Applications May Enhance ASD Aspects Related to Disturbances in the Gut Microbiome, Mitochondrial Activity, and Neural Network Function. *Braz. J. Sci.* **2023**, *3*, 140–158. [CrossRef]
22. Duman, J.G.; Tu, Y.-K.; Tolias, K.F. Emerging Roles of BAI Adhesion-GPCRs in Synapse Development and Plasticity. *Neural Plast.* **2016**, *2016*, 8301737. [CrossRef] [PubMed]
23. Barnfield, A. Role of Neurotransmitters. In *Encyclopedia of Personality and Individual Differences*; Zeigler-Hill, V., Shackelford, T., Eds.; Springer: Cham, Switzerland, 2019; pp. 1–7. [CrossRef]
24. Poornimai Abirami, G.P.; Radhakrishnan, R.K.; Johnson, E.; Roshan, S.A.; Yesudhas, A.; Parveen, S.; Biswas, A.; Ravichandran, V.R.; Muthuswamy, A.; Kandasamy, M. The Regulation of Reactive Neuroblastosis, Neuroplasticity, and Nutraceuticals for Effective Management of Autism Spectrum Disorder. *Adv. Neurobiol.* **2020**, *24*, 207–222. [CrossRef] [PubMed]
25. Guy-Evans, O. An Easy Guide to Neuron Anatomy with Diagrams. Available online: https://www.simplypsychology.org/neuron.html# (accessed on 1 September 2024).
26. Teleanu, R.I.; Niculescu, A.-G.; Roza, E.; Vladâcenco, O.; Grumezescu, A.M.; Teleanu, D.M. Neurotransmitters—Key Factors in Neurological and Neurodegenerative Disorders of the Central Nervous System. *Int. J. Mol. Sci.* **2022**, *23*, 5954. [CrossRef]
27. Kumar, S.; Mishra, T.; Prajapati, A.; Sethi, P. Nutrition, Neurotransmitters, and Behavior. In *Nutrition and Psychiatric Disorders*; Mohamed, W., Kobeissy, F., Eds.; Springer: Singapore, 2022; pp. 89–108. [CrossRef]
28. Guy-Evans, O. What Happens at The Synapse Between Two Neurons? Available online: https://www.simplypsychology.org/synapse.html (accessed on 1 September 2024).
29. Dhailappan, A.; Samiappan, S. Impact of Diet on Neurotransmitters. In *Role of Nutrients in Neurological Disorders*; Rajagopal, S., Ramachandran, S., Sundararaman, G., Gadde Venkata, S., Eds.; Springer: Singapore, 2022; pp. 363–383. [CrossRef]
30. LaGreca, M.; Hutchinson, D.R.; Skehan, L. The Microbiome and Neurotransmitter Activity. *J. Sci. Med.* **2021**, *3*. [CrossRef]
31. Drigas, A.; Mitsea, E. Metacognition, Stress—Relaxation Balance & Related Hormones. *Int. J. Recent Contrib. Eng. Sci. IT* **2021**, *9*, 4. [CrossRef]
32. Oleskin, A.V.; Shenderov, B.A.; Rogovsky, V.S. Role of Neurochemicals in the Interaction between the Microbiota and the Immune and the Nervous System of the Host Organism. *Probiotics Antimicrob. Proteins* **2017**, *9*, 215–234. [CrossRef]
33. Rieder, R.; Wisniewski, P.J.; Alderman, B.L.; Campbell, S.C. Microbes and Mental Health: A Review. *Brain Behav. Immun.* **2017**, *66*, 9–17. [CrossRef]
34. Mehra, A.; Arora, G.; Sahni, G.; Kaur, M.; Singh, H.; Singh, B.; Kaur, S. Gut Microbiota and Autism Spectrum Disorder: From Pathogenesis to Potential Therapeutic Perspectives. *J. Tradit. Complement. Med.* **2022**, *13*, 135–149. [CrossRef] [PubMed]
35. Eicher, T.P.; Mohajeri, M.H. Overlapping Mechanisms of Action of Brain-Active Bacteria and Bacterial Metabolites in the Pathogenesis of Common Brain Diseases. *Nutrients* **2022**, *14*, 2661. [CrossRef] [PubMed]
36. Bragg, M.; Chavarro, J.E.; Hamra, G.B.; Hart, J.E.; Tabb, L.P.; Weisskopf, M.G.; Volk, H.E.; Lyall, K. Prenatal Diet as a Modifier of Environmental Risk Factors for Autism and Related Neurodevelopmental Outcomes. *Curr. Environ. Health Rep.* **2022**, *9*, 324–338. [CrossRef] [PubMed]
37. Bamicha, V.; Drigas, A. The Evolutionary Course of Theory of Mind—Factors That Facilitate or Inhibit Its Operation & the Role of ICTs. *Tech. Soc. Sci. J.* **2022**, *30*, 138–158. [CrossRef]
38. Horn, J.; Mayer, D.E.; Chen, S.; Mayer, E.A. Role of Diet and Its Effects on the Gut Microbiome in the Pathophysiology of Mental Disorders. *Transl. Psychiatry* **2022**, *12*, 164. [CrossRef] [PubMed]
39. Sharp, W.G.; Berry, R.C.; McElhanon, B.O.; Jaquess, D.L. Dietary Diversity in Children with Autism. In *Comprehensive Guide to Autism*; Patel, V., Preedy, V., Martin, C., Eds.; Springer: New York, NY, USA, 2014; pp. 2077–2097. [CrossRef]
40. Leader, G.; Tuohy, E.; Chen, J.L.; Mannion, A.; Gilroy, S.P. Feeding Problems, Gastrointestinal Symptoms, Challenging Behavior and Sensory Issues in Children and Adolescents with Autism Spectrum Disorder. *J. Autism Dev. Disord.* **2020**, *50*, 1401–1410. [CrossRef] [PubMed]
41. Malhi, P.; Saini, S.; Bharti, B.; Attri, S.; Sankhyan, N. Sensory Processing Dysfunction and Mealtime Behavior Problems in Children with Autism. *Indian Pediatr.* **2021**, *58*, 842–845. [CrossRef]
42. Mahmoud, N.F.; Abdelhameed, R.S.; Abdelmonam, S.A.; Abdelmonem, A.A.; Khalil, D.M.; Bakia, S.A.S. Parent-Reported Feeding Characteristics in Children with ASD vs. Children Who Are Typically Developing. *Egypt. J. Otolaryngol.* **2021**, *37*, 110. [CrossRef]
43. Peretti, S.; Mariano, M.; Mazzocchetti, C.; Mazza, M.; Pino, M.C.; Verrotti Di Pianella, A.; Valenti, M. Diet: The Keystone of Autism Spectrum Disorder? *Nutr. Neurosci.* **2018**, *22*, 825–839. [CrossRef]
44. Kawicka, A.; Regulska-Ilow, B. How nutritional status, diet and dietary supplements can affect autism. A review. *Rocz. Panstw. Zakl. Hig.* **2013**, *64*, 1–12. [PubMed]
45. Kaur, H.; Singh, Y.; Singh, S.; Singh, R.B. Gut Microbiome Mediated Epigenetic Regulation of Brain Disorder and Application of Machine Learning for Multi-Omics Data Analysis. *Genome* **2020**, *64*, 355–371. [CrossRef] [PubMed]

46. Fouquier, J.; Moreno Huizar, N.; Donnelly, J.; Glickman, C.; Kang, D.-W.; Maldonado, J.; Jones, R.A.; Johnson, K.; Adams, J.B.; Krajmalnik-Brown, R.; et al. The Gut Microbiome in Autism: Study-Site Effects and Longitudinal Analysis of Behavior Change. *mSystems* **2021**, *6*, e00848-20. [CrossRef]
47. Rodop, B.B.; Başkaya, E.; Altuntaş, İ.; Erbaş, O. Nutrition Effect on Autism Spectrum Disorders. *J. Exp. Basic Med. Sci.* **2021**, *2*, 7–17. [CrossRef]
48. MacFabe, D.F. Enteric Short-Chain Fatty Acids: Microbial Messengers of Metabolism, Mitochondria, and Mind: Implications in Autism Spectrum Disorders. *Microb. Ecol. Health Dis.* **2015**, *26*, 28177. [CrossRef] [PubMed]
49. Berding, K.; Donovan, S.M. Microbiome and Nutrition in Autism Spectrum Disorder: Current Knowledge and Research Needs. *Nutr. Rev.* **2016**, *74*, 723–736. [CrossRef]
50. Shanmugam, H.; Ganguly, S.; Priya, B. Plant Food Bioactives and Its Effects on Gut Microbiota Profile Modulation for Better Brain Health and Functioning in Autism Spectrum Disorder Individuals: A Review. *Food Front.* **2022**, *3*, 124–141. [CrossRef]
51. Shah, F.; Dwivedi, M. Pathophysiological Role of Gut Microbiota Affecting Gut–Brain Axis and Intervention of Probiotics and Prebiotics in Autism Spectrum Disorder. In *Probiotic Research in Therapeutics*; Deol, P.K., Sandhu, S.K., Eds.; Springer: Singapore, 2022; pp. 69–115. [CrossRef]
52. Cohen, Y.; Valdés-Mas, R.; Elinav, E. The Role of Artificial Intelligence in Deciphering Diet–Disease Relationships: Case Studies. *Annu. Rev. Nutr.* **2023**, *43*, 225–250. [CrossRef] [PubMed]
53. Moos, W.H.; Faller, D.V.; Harpp, D.N.; Kanara, I.; Pernokas, J.; Powers, W.R.; Steliou, K. Microbiota and Neurological Disorders: A Gut Feeling. *BioResearch Open Access* **2016**, *5*, 137–145. [CrossRef] [PubMed]
54. Drigas, A.; Bamicha, V. PoM & ToM—Harnessing the Power of Mind in Theory of Mind by Shaping Beneficial Mental States in Preschoolers and the ICT's Role. *Res. Soc.* **2023**, *12*, e13212541590. [CrossRef]
55. Davies, C.; Mishra, D.; Eshraghi, R.S.; Mittal, J.; Sinha, R.; Bulut, E.; Mittal, R.; Eshraghi, A.A. Altering the Gut Microbiome to Potentially Modulate Behavioral Manifestations in Autism Spectrum Disorders: A Systematic Review. *Neurosci. Biobehav. Rev.* **2021**, *128*, 549–557. [CrossRef]
56. Capuco, A.; Urits, I.; Hasoon, J.; Chun, R.; Gerald, B.; Wang, J.K.; Kassem, H.; Ngo, A.L.; Abd-Elsayed, A.; Simopoulos, T.; et al. Current Perspectives on Gut Microbiome Dysbiosis and Depression. *Adv. Ther.* **2020**, *37*, 1328–1346. [CrossRef]
57. Mittal, R.; Debs, L.H.; Patel, A.P.; Nguyen, D.; Patel, K.; O'Connor, G.; Grati, M.; Mittal, J.; Yan, D.; Eshraghi, A.A.; et al. Neurotransmitters: The Critical Modulators Regulating Gut-Brain Axis. *J. Cell. Physiol.* **2017**, *232*, 2359–2372. [CrossRef]
58. Zavitsanou, A.; Salapata, Y.; Stathopoulou, A. Special Nutrition for Students with Special Education Needs, and the ICT's Role for Their Health Education. *TechHub J.* **2022**, *2*, 82–97. Available online: https://techhubresearch.com/index.php/journal/article/view/77 (accessed on 2 November 2024).
59. Zavitsanou, A.; Drigas, A. Nutrition in Mental and Physical Health. *Tech. Soc. Sci. J.* **2021**, *23*, 67–77. [CrossRef]
60. Driga, A.M.; Zavitsanou, A.; Drigas, A. Heavy Metals, Halogens, Carbon and Nitrogen Oxides, and Autism the Important Role of Digital Technologies in Health Education, Prevention and Digital Health. *GSC Adv. Res. Rev.* **2023**, *16*, 50–60. [CrossRef]
61. Javadpour, P.; Askari, S.; Ghasemi, R. Nutrition, Cognitive Functions, and Emotions. In *Nutrition and Psychiatric Disorders. Nutritional Neurosciences*; Mohamed, W., Kobeissy, F., Eds.; Springer: Singapore, 2022; pp. 27–50. [CrossRef]
62. Sahay, A.S.; Sundrani, D.P.; Joshi, S.R. Neurotrophins. In *Neurotrophins: Role in Placental Growth and Development. Vitamins and Hormones*; Gerald, L., Ed.; Academic Press: Cambridge, MA, USA, 2017; pp. 243–261. [CrossRef]
63. Hennessy, M.; Hamblin, M.R. Photobiomodulation and the Brain: A New Paradigm. *J. Opt.* **2017**, *19*, 013003. [CrossRef] [PubMed]
64. De Luca, F. Endocrinological Abnormalities in Autism. *Semin. Pediatr. Neurol.* **2020**, *35*, 100582. [CrossRef] [PubMed]
65. Ye, F.; Gao, X.; Wang, Z.; Cao, S.; Liang, G.; He, D.; Lv, Z.; Wang, L.; Xu, P.; Zhang, Q. Comparison of Gut Microbiota in Autism Spectrum Disorders and Neurotypical Boys in China: A Case-Control Study. *Synth. Syst. Biotechnol.* **2021**, *6*, 120–126. [CrossRef] [PubMed]
66. Zou, R.; Xu, F.; Wang, Y.; Duan, M.; Guo, M.; Zhang, Q.; Zhao, H.; Zheng, H. Changes in the Gut Microbiota of Children with Autism Spectrum Disorder. *Autism Res.* **2020**, *13*, 1614–1625. [CrossRef]
67. Fattorusso, A.; Di Genova, L.; Dell'Isola, G.; Mencaroni, E.; Esposito, S. Autism Spectrum Disorders and the Gut Microbiota. *Nutrients* **2019**, *11*, 521. [CrossRef]
68. Iglesias-Vázquez, L.; Van Ginkel Riba, G.; Arija, V.; Canals, J. Composition of Gut Microbiota in Children with Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. *Nutrients* **2020**, *12*, 792. [CrossRef]
69. Jendraszak, M.; Gałęcka, M.; Kotwicka, M.; Regdos, A.; Pazgrat-Patan, M.; Andrusiewicz, M. Commercial Microbiota Test Revealed Differences in the Composition of Intestinal Microorganisms between Children with Autism Spectrum Disorders and Neurotypical Peers. *Sci. Rep.* **2021**, *11*, 24274. [CrossRef]
70. Kang, D.-W.; Ilhan, Z.E.; Isern, N.G.; Hoyt, D.W.; Howsmon, D.P.; Shaffer, M.; Lozupone, C.A.; Hahn, J.; Adams, J.B.; Krajmalnik-Brown, R. Differences in Fecal Microbial Metabolites and Microbiota of Children with Autism Spectrum Disorders. *Anaerobe* **2018**, *49*, 121–131. [CrossRef]
71. Mihailovich, M.; Tolinački, M.; Bajić, S.S.; Lestarevic, S.; Pejovic-Milovancevic, M.; Golić, N. The Microbiome–Genetics Axis in Autism Spectrum Disorders: A Probiotic Perspective. *Int. J. Mol. Sci.* **2024**, *25*, 12407. [CrossRef] [PubMed]
72. Ding, X.; Xu, Y.; Zhang, X.; Zhang, L.; Duan, G.; Song, C.; Li, Z.; Yang, Y.; Wang, Y.; Wang, X.; et al. Gut Microbiota Changes in Patients with Autism Spectrum Disorders. *J. Psychiatr. Res.* **2020**, *129*, 149–159. [CrossRef]

73. Krajmalnik-Brown, R.; Lozupone, C.; Kang, D.-W.; Adams, J.B. Gut Bacteria in Children with Autism Spectrum Disorders: Challenges and Promise of Studying How a Complex Community Influences a Complex Disease. *Microb. Ecol. Health Dis.* **2015**, *26*, 26914. [CrossRef] [PubMed]
74. Vernocchi, P.; Ristori, M.V.; Guerrera, S.; Guarrasi, V.; Conte, F.; Russo, A.; Lupi, E.; Albitar-Nehme, S.; Gardini, S.; Paci, P.; et al. Gut Microbiota Ecology and Inferred Functions in Children with ASD Compared to Neurotypical Subjects. *Front. Microbiol.* **2022**, *13*, 871086. [CrossRef] [PubMed]
75. Peralta-Marzal, L.N.; Rojas-Velazquez, D.; Rigters, D.; Prince, N.; Garssen, J.; Kraneveld, A.D.; Perez-Pardo, P.; Lopez-Rincon, A. A Robust Microbiome Signature for Autism Spectrum Disorder across Different Studies Using Machine Learning. *Sci. Rep.* **2024**, *14*, 814. [CrossRef] [PubMed]
76. Morton, J.T.; Jin, D.-M.; Mills, R.H.; Shao, Y.; Rahman, G.; McDonald, D.; Zhu, Q.; Balaban, M.; Jiang, Y.; Cantrell, K.; et al. Multi-Level Analysis of the Gut–Brain Axis Shows Autism Spectrum Disorder-Associated Molecular and Microbial Profiles. *Nat. Neurosci.* **2023**, *26*, 1208–1217. [CrossRef] [PubMed]
77. West, K.A.; Yin, X.; Rutherford, E.M.; Wee, B.; Choi, J.; Chrisman, B.S.; Dunlap, K.L.; Hannibal, R.L.; Hartono, W.; Lin, M.; et al. Multi-Angle Meta-Analysis of the Gut Microbiome in Autism Spectrum Disorder: A Step toward Understanding Patient Subgroups. *Sci. Rep.* **2022**, *12*, 17034. [CrossRef]
78. Nakazawa-Miklasevica, M.; Daneberga, Z.; Murmane, D.; Kroica, J.; Cupane, L.; Isarova, D.; Berga-Svitina, E.; Masinska, M.; Miklasevics, E. Alterations of Gut Microbiota among Children with Autism Spectrum Disorder. *Mol. Genet. Microbiol. Virol.* **2021**, *36*, S29–S36. [CrossRef]
79. Strati, F.; Cavalieri, D.; Albanese, D.; De Felice, C.; Donati, C.; Hayek, J.; Jousson, O.; Leoncini, S.; Renzi, D.; Calabrò, A.; et al. New Evidences on the Altered Gut Microbiota in Autism Spectrum Disorders. *Microbiome* **2017**, *5*, 24. [CrossRef] [PubMed]
80. Yang, C.; Xiao, H.; Zhu, H.; Du, Y.; Wang, L. Revealing the Gut Microbiome Mystery: A Meta-Analysis Revealing Differences between Individuals with Autism Spectrum Disorder and Neurotypical Children. *BioSci. Trends* **2024**, *18*, 233–249. [CrossRef]
81. Marotta, R.; Risoleo, M.C.; Messina, G.; Parisi, L.; Carotenuto, M.; Vetri, L.; Roccella, M. The Neurochemistry of Autism. *Brain Sci.* **2020**, *10*, 163. [CrossRef] [PubMed]
82. Larroya-García, A.; Navas-Carrillo, D.; Orenes-Piñero, E. Impact of Gut Microbiota on Neurological Diseases: Diet Composition and Novel Treatments. *Crit. Rev. Food Sci. Nutr.* **2019**, *59*, 3102–3116. [CrossRef] [PubMed]
83. Ristori, M.V.; Quagliariello, A.; Reddel, S.; Ianiro, G.; Vicari, S.; Gasbarrini, A.; Putignani, L. Autism, Gastrointestinal Symptoms and Modulation of Gut Microbiota by Nutritional Interventions. *Nutrients* **2019**, *11*, 2812. [CrossRef] [PubMed]
84. Wu, W.; Kong, Q.; Tian, P.; Zhai, Q.; Wang, G.; Liu, X.; Zhao, J.; Zhang, H.; Lee, Y.K.; Chen, W. Targeting Gut Microbiota Dysbiosis: Potential Intervention Strategies for Neurological Disorders. *Engineering* **2020**, *6*, 415–423. [CrossRef]
85. Fernández, M.; Mollinedo-Gajate, I.; Peñagarikano, O. Neural Circuits for Social Cognition: Implications for Autism. *Neuroscience* **2018**, *370*, 148–162. [CrossRef]
86. Cetin, F.H.; Tunca, H.; Güney, E.; Iseri, E. *Neurotransmitter Systems in Autism Spectrum Disorder*; InTech: Houston, TX, USA, 2015; pp. 15–30. [CrossRef]
87. Florea, T.; Palimariciuc, M.; Cristofor, A.C.; Dobrin, I.; Chiriță, R.; Bîrsan, M.; Dobrin, R.P.; Pădurariu, M. Oxytocin: Narrative Expert Review of Current Perspectives on the Relationship with Other Neurotransmitters and the Impact on the Main Psychiatric Disorders. *Medicina* **2022**, *58*, 923. [CrossRef] [PubMed]
88. Mitsea, E.; Drigas, A.; Skianis, C. Mindfulness for Anxiety Management and Happiness: The Role of VR, Metacognition, and Hormones. *Technium BioChemMed* **2022**, *3*, 37–52. [CrossRef]
89. Rodnyy, A.Y.; Kondaurova, E.M.; Tsybko, A.S.; Popova, N.K.; Kudlay, D.A.; Naumenko, V.S. The Brain Serotonin System in Autism. *Rev. Neurosci.* **2023**, *35*, 1–20. [CrossRef]
90. Yang, C.-J.; Tan, H.-P.; Du, Y.-J. The Developmental Disruptions of Serotonin Signaling May Involved in Autism during Early Brain Development. *Neuroscience* **2014**, *267*, 1–10. [CrossRef]
91. Beversdorf, D.Q. The Role of the Noradrenergic System in Autism Spectrum Disorders, Implications for Treatment. *Semin. Pediatr. Neurol.* **2020**, *35*, 100834. [CrossRef] [PubMed]
92. Gevi, F.; Belardo, A.; Zolla, L. A Metabolomics Approach to Investigate Urine Levels of Neurotransmitters and Related Metabolites in Autistic Children. *Biochim. Biophys. Acta* **2020**, *1866*, 165859. [CrossRef]
93. Saha, S.; Chatterjee, M.; Dutta, N.; Sinha, S.; Mukhopadhyay, K. Analysis of Neurotransmitters Validates the Importance of the Dopaminergic System in Autism Spectrum Disorder. *World J. Pediatr.* **2023**, *19*, 770–781. [CrossRef]
94. Pavăl, D. A dopamine hypothesis of autism spectrum disorder. *Dev. Neurosci.* **2017**, *39*, 355–360. [CrossRef] [PubMed]
95. Hollestein, V.; Poelmans, G.; Forde, N.J.; Beckmann, C.F.; Ecker, C.; Mann, C.; Schäfer, T.; Moessnang, C.; Baumeister, S.; Banaschewski, T.; et al. Excitatory/Inhibitory Imbalance in Autism: The Role of Glutamate and GABA Gene-Sets in Symptoms and Cortical Brain Structure. *Transl. Psychiatry* **2023**, *13*, 18. [CrossRef]
96. Maier, S.; Düppers, A.L.; Runge, K.; Dacko, M.; Lange, T.; Fangmeier, T.; Riedel, A.; Ebert, D.; Endres, D.; Domschke, K.; et al. Increased Prefrontal GABA Concentrations in Adults with Autism Spectrum Disorders. *Autism Res.* **2022**, *15*, 1222–1236. [CrossRef] [PubMed]
97. Bernardino, I.; Dionísio, A.; Violante, I.R.; Monteiro, R.; Castelo-Branco, M. Motor Cortex Excitation/Inhibition Imbalance in Young Adults with Autism Spectrum Disorder: A MRS-TMS Approach. *Front. Psychiatry* **2022**, *13*, 860448. [CrossRef] [PubMed]

98. Wu, C.; Sun, D. GABA Receptors in Brain Development, Function, and Injury. *Metab. Brain Dis.* **2014**, *30*, 367–379. [CrossRef] [PubMed]
99. Cellot, G.; Cherubini, E. Functional Role of Ambient GABA in Refining Neuronal Circuits Early in Postnatal Development. *Front. Neural Circuits* **2013**, *7*, 136. [CrossRef]
100. Begum, P.S.; Razak, M.A.; Rajagopal, S. Influence of Amino Acids on Autism and Attention-Deficit Hyperactive Disorder. In *Proteins Associated with Neurodevelopmental Disorders. Nutritional Neurosciences*; Qoronfleh, M.W., Essa, M.M., Saravana Babu, C., Eds.; Springer: Singapore, 2022; pp. 257–276. [CrossRef]
101. Meskó, B.; Drobni, Z.; Bényei, É.; Gergely, B.; Győrffy, Z. Digital Health Is a Cultural Transformation of Traditional Healthcare. *mHealth* **2017**, *3*, 38. [CrossRef] [PubMed]
102. Li, X.; Zhang, K.; He, X.; Zhou, J.; Jin, C.; Shen, L.; Gao, Y.; Tian, M.; Zhang, H. Structural, Functional, and Molecular Imaging of Autism Spectrum Disorder. *Neurosci. Bull.* **2021**, *37*, 1051–1071. [CrossRef]
103. Al-Biltagi, M.; Saeed, N.K.; Qaraghuli, S. Gastrointestinal Disorders in Children with Autism: Could Artificial Intelligence Help? *AIG Artif. Intell. Gastroenterol.* **2022**, *3*, 1–12. [CrossRef]
104. Green, J.; Leadbitter, K.; Ainsworth, J.; Bucci, S. An Integrated Early Care Pathway for Autism. *Lancet Child Adolesc. Health* **2022**, *6*, 335–344. [CrossRef] [PubMed]
105. Stathopoulou, A.; Loukeris, D.; Karabatzaki, Z.; Politi, E.; Salapata, Y.; Drigas, A. Evaluation of Mobile Apps Effectiveness in Children with Autism Social Training via Digital Social Stories. *Int. J. Interact. Mob. Technol.* **2020**, *14*, 5. [CrossRef]
106. Kyriakaki, E.; Karabatzaki, Z.; Salapata, Y. Mobile Applications for Autism. *Eximia* **2023**, *8*, 51–66.
107. Drigas, A.; Karyotaki, M. E-Learning and ICTs Applications in Nutrition Science. *Int. J. Recent Contrib. Eng. Sci. IT* **2013**, *1*, 4–10. [CrossRef]
108. Bravou, V.; Driga, A.M.S.; Drigas, A. Emotion Regulation, the Function of Stress Hormones & Digital Technologies. *Tech. BioChemMed* **2022**, *3*, 27–33. [CrossRef]
109. Bamicha, V.; Drigas, A. Consciousness Influences in ToM and Metacognition Functioning—An Artificial Intelligence Perspective. *Res. Soc. Dev.* **2023**, *12*, e13012340420. [CrossRef]
110. Bamicha, V.; Drigas, A. Theory of Mind in Relation to Metacognition and ICTs. A Metacognitive Approach to ToM. *Sci. Electron. Arch.* **2023**, *16*. [CrossRef]
111. Kourtesis, P.; Kouklari, E.-C.; Roussos, P.; Mantas, V.; Papanikolaou, K.; Skaloumbakas, C.; Pehlivanidis, A. Virtual Reality Training of Social Skills in Adults with Autism Spectrum Disorder: An Examination of Acceptability, Usability, User Experience, Social Skills, and Executive Functions. *Behav. Sci.* **2023**, *13*, 336. [CrossRef] [PubMed]
112. Mitsea, E.; Drigas, A.; Skianis, C. Digitally Assisted Mindfulness in Training Self-Regulation Skills for Sustainable Mental Health: A Systematic Review. *Behav. Sci.* **2023**, *13*, 1008. [CrossRef] [PubMed]
113. Mitsea, E.; Drigas, A.; Skianis, C. Effects of Digital Games Training on Hormonal Responses and Brain Plasticity. *Res. Soc. Dev.* **2023**, *12*, e20512239568. [CrossRef]
114. Vacca, R.A.; Augello, A.; Gallo, L.; Caggianese, G.; Malizia, V.; La Grutta, S.; Murero, M.; Valenti, D.; Tullo, A.; Balech, B.; et al. Serious Games in the New Era of Digital-Health Interventions: A Narrative Review of Their Therapeutic Applications to Manage Neurobehavior in Neurodevelopmental Disorders. *Neurosci. Biobehav. Rev.* **2023**, *149*, 105156. [CrossRef] [PubMed]
115. Moraiti, I.; Fotoglou, A.; Drigas, A. Digital and Mobile Applications for Autism Inclusion. *Int. J. Online Biomed. Eng.* **2023**, *19*, 83. [CrossRef]
116. Ghazali, A.S.; Ham, J.; Barakova, E.; Markopoulos, P. Assessing the Effect of Persuasive Robots Interactive Social Cues on Users' Psychological Reactance, Liking, Trusting Beliefs and Compliance. *Adv. Robot.* **2019**, *33*, 325–337. [CrossRef]
117. Papanastasiou, G.; Drigas, A.; Skianis, C. Serious Games: How Do They Impact Special Education Needs Children. *Tech. Educ. Humanit.* **2022**, *2*, 41–58. [CrossRef]
118. Chaidi, I.; Drigas, A. Digital Games & Special Education. *Tech. Soc. Sci. J.* **2022**, *34*, 214–236. [CrossRef]
119. Aktaruzzaman, M.; Shamim, M.; Clement, C.K. Trends and issues to integrate ICT in teaching learning for the future world of education. *Int. J. Eng. Sci. Technol.* **2011**, *11*, 114–119.
120. Pergantis, P.; Drigas, A. Sensory Integration Therapy as Enabler for Developing Emotional Intelligence in Children with Autism Spectrum Disorder and the ICT's Role. *Braz. J. Sci.* **2023**, *2*, 53–65. [CrossRef]
121. Pergantis, P.; Drigas, A. Assistive Technology for Autism Spectrum Disorder Children That Experiences Stress and Anxiety. *Braz. J. Sci.* **2023**, *2*, 77–93. [CrossRef]
122. Taniya, M.A.; Chung, H.-J.; Al Mamun, A.; Alam, S.; Aziz, M.A.; Emon, N.U.; Islam, M.M.; Hong, S.-T.; Podder, B.R.; Ara Mimi, A.; et al. Role of Gut Microbiome in Autism Spectrum Disorder and Its Therapeutic Regulation. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 915701. [CrossRef] [PubMed]
123. Li, N.; Chen, H.; Cheng, Y.; Xu, F.; Ruan, G.; Ying, S.; Tang, W.; Chen, L.; Chen, M.; Lv, L.; et al. Fecal Microbiota Transplantation Relieves Gastrointestinal and Autism Symptoms by Improving the Gut Microbiota in an Open-Label Study. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 759435. [CrossRef]
124. Halverson, T.; Alagiakrishnan, K. Gut Microbes in Neurocognitive and Mental Health Disorders. *Ann. Med.* **2020**, *52*, 423–443. [CrossRef]

125. Yang, J.; Fu, X.; Liao, X.; Li, Y. Effects of Gut Microbial-Based Treatments on Gut Microbiota, Behavioral Symptoms, and Gastrointestinal Symptoms in Children with Autism Spectrum Disorder: A Systematic Review. *Psychiatry Res.* **2020**, *293*, 113471. [CrossRef] [PubMed]
126. Sideraki, A.; Drigas, A. The Role of Cortisol and Microbiome in the Anxiety of People with ASD and the Use of ICTs for Regulation. *World J. Biol. Pharm. Health Sci.* **2023**, *14*, 137–148. [CrossRef]
127. Kapalka, G.M. Substances Involved in Neurotransmission. In *Practical Resources for the Mental Health Professional, Nutritional and Herbal Therapies for Children and Adolescents*; Kapalka, G.M., Ed.; Academic Press: Cambridge, MA, USA; Elsevier: San Diego, CA, USA, 2010; pp. 71–99. [CrossRef]
128. Bölte, S.; Girdler, S.; Marschik, P.B. The Contribution of Environmental Exposure to the Etiology of Autism Spectrum Disorder. *Cell Mol. Life Sci.* **2018**, *76*, 1275–1297. [CrossRef]
129. Garg, S.; Sharma, S. Impact of Artificial Intelligence in Special Need Education to Promote Inclusive Pedagogy. *Int. J. Inf. Educ. Technol.* **2020**, *10*, 523–527. [CrossRef]
130. Mitrofanis, J.; Henderson, L. How and Why Does Photobiomodulation Change Brain Activity? *Neural Regen. Res.* **2020**, *15*, 2243. [CrossRef] [PubMed]
131. Hamilton, C.; Liebert, A.; Pang, V.; Magistretti, P.; Mitrofanis, J. Lights on for Autism: Exploring Photobiomodulation as an Effective Therapeutic Option. *Neurol. Int.* **2022**, *14*, 884–893. [CrossRef] [PubMed]
132. Guang, S.; Pang, N.; Deng, X.; Yang, L.; He, F.; Wu, L.; Chen, C.; Yin, F.; Peng, J. Synaptopathology Involved in Autism Spectrum Disorder. *Front. Cell. Neurosci.* **2018**, *12*, 470. [CrossRef] [PubMed]