

Review

Through the Intestines to the Head? That Is, How the Gastrointestinal Microbiota Affects the Behavior of Companion Animals

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Abstract: Microbiome research has become significantly advanced in recent years, both in human and veterinary medicine. The development of DNA sequencing technology has enabled a deeper understanding of the diversity of microorganisms inhabiting animal bodies. It has given clinicians, scientists, and behaviorists a chance of better understanding the impact that a proper microbial population has on the individual, enabling a much more holistic view of the animals' health and welfare. Current knowledge is increasingly based on analyses of the impact of microorganisms present in the gastrointestinal tract on the neurobiology and behavior of the host. This review presents research results, indicating potential implications for fields such as ethology and veterinary medicine. Understanding the role of the microbiome in shaping animal behavior could open up new therapeutic opportunities and lead to more sustainable animal husbandry practices.

Keywords: microbiome; behavior; canine; feline; gut; microbiota; dysbiosis



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1. Microbiome—A Brief Characteristic

The gastrointestinal tract of cats and dogs contains an abundant ecosystem in various colonizing microorganisms such as bacteria, fungi, protozoa, and viruses [1]. In mammals, the gastrointestinal tract colonization starts during parturition: the mother's vaginal and fecal microbes are transmitted to the infant's gut [2,3]. It is now suspected that, in mammals, the way of delivering the offspring may not significantly reflect on the initial acquisition of the microbes in newborns [3]. In dogs, however, there are reports suggesting that the process of colonization of the microbiome likely begins before birth, as evidenced by the presence of microbes in the placenta and meconium of newborn puppies [4]. The type of delivery (e.g., natural birth vs. cesarean section) appears to influence the puppies' weight gain, indicating that the mode of delivery might affect the initial microbial colonization and subsequent health outcomes. After birth, in mammals, the microbial community then undergoes maturation in response to changes in health, development, and the environment, but is also shaped by microbial transmission from the mother [5]. Interestingly, adult littermates have been found to present a more similar microbiome composition than unrelated dogs [6].

Fecal samples in canines show a reliable representation of the most relevant taxa [3]. In dogs, the majority of microbiota belong mainly to the phyla Firmicutes (Clostridia, Bacilli—mostly of the genera *Streptococcus* and *Lactobacillus*; Erysipelotrichi—mainly comprising the genera *Turicibacter*, *Catenibacterium*, and *Coprobaillus*), Fusobacteria, Bacteroidetes (genera *Bacteroides*, *Prevotella*, and *Megamonas*), Proteobacteria, and Actinobacteria. The microbiome is rather stable in healthy animals [7,8]. As for the phylum and genus in each part of the gastrointestinal tract,

the stomach is mostly colonized by the phyla Firmicutes and Proteobacteria, and the genera *Lactobacillus* and *Helicobacter*; the small intestine by the phyla Firmicutes, Proteobacteria, Bacteroidetes, Spirochaetes, Fusobacteria, and Actinobacteria, and the genera *Lactobacillus* and *Staphylococcus*; and the large intestine by the phyla Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, and Actinobacteria, and the genera *Lactobacillus*, *Staphylococcus*, *Streptococcus*, *Pediococcus*, *Enterococcus*, and *Bifidobacterium* [1]. The microbiota of dogs with no behavioral issues is abundant with Firmicutes and Bacteroidetes and poor in Actinobacteria, Fusobacteria, and Proteobacteria [9]. Regarding microbiome changes in aging dogs, Masuoka et al., 2017 [10], showed in a study conducted on 50 dogs divided into five different age groups (10 animals per group) that *Lactobacillus* and *Bifidobacterium* decreased in elderly dogs.

Felines are obligate carnivores. However their gut microbiome, in terms of microbial phylogeny and gene content, reflects the one in omnivores [11]. In cats, the most abundant core genera are *Prevotella*, *Bacteroides*, *Collinsella*, *Blautia*, and *Megasphaera*. The most prevalent core genera are *Bacteroides*, *Blautia*, *Lachnospirillum*, *Sutterella*, and *Ruminococcus gnavus* [12]. Other sources claim that the major phyla in the feline fecal microbiota are Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria [13,14]. Regarding the phyla and genera in each part of the gastrointestinal tract (the GI tract), the stomach is mostly colonized by the genus *Helicobacter*; the small intestine by the phyla Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, and Actinobacteria, and the genera *Lactobacillus*, *Streptococcus*, *Bacteroides*, *Clostridium*, *Enterococcus*, *Fusobacteria*, and *Eubacteria*; the large intestine by the phyla Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, and Actinobacteria, and the genera *Lactobacillus*, *Bacteroides*, *Fusobacterium*, and *Prevotella* [13,15].

Bacteria can be categorized into different groups based on the impact on the host organisms. These groups include pathogenic bacteria, beneficial (commensal and mutualistic) bacteria (*Lactobacillus* (Firmicutes), *Bifidobacterium* (Actinobacteria), *Prevotella* (Bacteroidetes), *Bacteroides* (Bacteroidetes), *Collinsella* (Actinobacteria), *Blautia* (Firmicutes), *Megasphaera* (Firmicutes), *Lachnospirillum* (Firmicutes), *Sutterella* (Proteobacteria), and *Ruminococcus gnavus* (Firmicutes)); and opportunistic bacteria (*Enterobacteriaceae* (Proteobacteria), *Clostridium* (Firmicutes), *Helicobacter* (Proteobacteria), *Streptococcus* (Firmicutes), *Staphylococcus* (Firmicutes), *Pediococcus* (Firmicutes), *Enterococcus* (Firmicutes), and *Fusobacterium* (Fusobacteria)) [16]. Opportunistic bacteria can become pathogenic in various situations, including immune suppression, disruption of the normal microbiome, damage to mucosal barriers, and age [17].

2. The Role of the Microbiome

The gastrointestinal microbiome influences the host's physiology both directly and indirectly [3,18]. Microbes affect the metabolism, modulate the immune system, provide protection from pathogens, and take part in energy acquisition, vitamin synthesis (vitamin K, vitamins of group B), digestion, and neurobehavioral development [14,19].

Part of the occupation of the bacteria in the GI tract includes fermentation of alcohols and carbohydrates that are not digestible to the host. That process enables the production of short-chain fatty acids (SCFAs), which reduce intestinal pH. Furthermore, SCFAs absorption through the intestine allows reabsorption of Na⁺ or K⁺ ions. The microbiome creates an environment for the absorption of dietary fats and liposoluble vitamins in the gut through transformation of primary and secondary bile acids [19,20].

Furthermore, the intestinal mucosa is an interface between the external environment and the immune system. Germ-free (GF) animals (microbiota-deficient) raised in a sterile environment have a lower density of lymphoid cells in the intestinal mucosa and a lower quantity of immunoglobulins (Ig) in serum [19,21]. Importantly, systemic inflammation caused by dysbiosis during early life development may begin hyperreactivity of the immune system and cause dysregulation in the hypothalamic–pituitary–adrenal axis (HPA). Moreover, dysbiosis may lead to impoverishment of the immune system and possession of fewer and smaller lymph nodes [9].

The microbiome acting on enteroendocrine cells affects metabolism. Changes in the gut microbiome induce inflammation and obesity by affecting intestinal epithelial cells and enteroendocrine cells and the secretion of gut hormones: glucagon-like peptides 1 and 2 (GLP-1 and GLP-2). GLP-1 stimulates insulin secretion, delays the passage of food through the stomach, and causes satiety and weight loss; GLP-2 increases glucose transport from the intestines and reduces the permeability of the intestinal wall [22].

In healthy individuals, there is a homeostatic balance between the host and microbes inhabiting its GI tract. The host supplies the microbes with an environment supporting undisturbed reproduction. Among other effects, the bacteria enhance protective systems for the host, and both the host and the microbes provide each other with nutrients to sustain life [9]. Eubiosis occurs when the gut remains well, free from pathogenic bacteria and overgrowth. Disruption of this homeostasis may lead to dysbiosis, which is a term used to describe changes in microbiome structure, functioning, and/or diversity [1]. Mondo et al. [16] divide dysbiosis into three categories: reduction in bacterial diversity, loss of beneficial bacteria, and overgrowth of pathogens. Any changes in the gut microbiome may lead to increased permeability, digestion dysfunction, metabolic syndromes, inflammation of the GI tract, obesity, and mood disorders [18,19]. Importantly, systemic inflammation caused by dysbiosis during early life development may begin hyperreactivity of the immune system and cause dysregulation in the HPA axis. The given information applies to mammals as a taxonomic group and is not exclusive to dogs and cats.

3. Microbiome and the Central Nervous System

It is certain that microbiome influences the central nervous system (CNS) and can be affected by the brain’s activity. Microbial metabolites act via the blood–brain barrier (BBB) and the vagus nerve, and may modulate the HPA axis and the immune system. Conversely, the brain can impact gut secretion, motility, and permeability, thus affecting the microbiota. This bidirectional interaction is termed the gut–brain axis (GBA), with serotonin as a main signaling molecule both in the CNS and in the enteric nervous system (ENS) [9,21]. The GBA is composed of endocrinological, immunological, and neural mediators [23].

Probiotic bacteria can interfere with the CNS by three different mechanisms. Firstly, bacteria produce neuroactive substances that influence the GBA, such as glucocorticoids, sex steroids, neuropeptides, and monoamines. Some of them are neurotransmitters and their precursors that have the potential to influence emotions and modulate behavior [9]. Secondly, SCFAs and secondary bile acids have the ability to interact with host cells, which regulate production of signaling molecules. Thirdly, inactive signaling molecules can be turned into their active forms by the process of bacterially mediated enzymatic deconjugation [2].

Microbes have been described to manufacture or contribute to concentration of dopamine, serotonin, tryptophan, gamma-aminobutyric acid (GABA), acetylcholine, glutamate, and norepinephrine. Detailed information is included in Table 1.

Table 1. List of selected bacteria derived neurotransmitters or their precursors.

Substance	Physiological Function	Behavioral Function	Microbial Origin	Additional Information
Dopamine	Control of the motor functions and coordination, regulation of cardiovascular and renal function [24].	An important role in the reward system and may also facilitate social bonding [25].	Secreted in the gut by <i>Bacillus</i> spp. and <i>Serratia</i> spp. [2,9].	Microbiome can influence central dopaminergic signaling, e.g., by converting levodopa into dopamine, which may lead to reduced central dopamine availability in the brain. Peripheral dopamine cannot cross the blood-brain barrier (BBB) in contrast to its precursor, levodopa [2,25].

Table 1. *Cont.*

Substance	Physiological Function	Behavioral Function	Microbial Origin	Additional Information
Gamma-Aminobutyric Acid (Gaba)	By mechanisms of pre- and postsynaptic inhibition suppresses synaptic transmission [26].	Important inhibitory neurotransmitter that behaviorally has a calming effect [27].	Manufactured by <i>Lactobacillus</i> spp. and <i>Bifidobacterium</i> spp. [28].	
Serotonin	Regulation of the gastrointestinal, excretory, cardiovascular functions [2], affects vasoconstriction, platelet aggregation, uterine contractions, intestinal peristalsis, and bronchoconstriction [29].	A role in emotion regulation, social behavior and cognition, aggression, sleep, sexual functions [29].	Produced by <i>Escherichia</i> spp., <i>Enterococcus</i> spp., <i>Candida</i> spp., and <i>Streptococcus</i> spp. [9].	
Norepinephrine	Blood pressure regulation, increasing blood glucose levels.	Affects alertness, fear, anger, and stress [30].	Produced by <i>Escherichia</i> spp., <i>Bacillus</i> spp., and <i>Saccharomyces</i> spp. [28].	
Acetylcholine	Regulation of blood pressure, glandular secretion, intestinal peristalsis and cardiac contractions [31].	Enabling learning and memorizing [9]; plays a role in arousal, attention, and behavioral activity.	Produced by <i>Lactobacillus</i> spp. [9].	
Tryptophan	A precursor to serotonin.	Tryptophan and its metabolites can cross the BBB increasing the concentration of serotonin in the central nervous system; indole (tryptophan metabolite) decreases pro-inflammatory responses from astrocytes [32].	Fabricated by <i>Clostridium</i> spp., <i>Bacteroides</i> spp., <i>Escherichia</i> spp., <i>Burkholderia</i> spp., <i>Streptomyces</i> spp., <i>Pseudomonas</i> spp., and <i>Bacillus</i> spp. [9].	

Neurotransmitters created by the microbes in the GI tract cannot cross the BBB, although they act on enteroendocrine cells, which provide a synapse with the vagus nerve. In this way, the signal is transmitted to the brain. Neurotransmitter precursors (phenylalanine, tryptophan, tyrosine, etc.) have the ability to cross the BBB and become functional neurotransmitters [32].

The GI tract bacteria play a major role in the growth and maturation of specific parts of neurological white matter [9]. Research conducted on GF animals provides data on the essentiality of gut microbiota in the normal development of the brain and behavior, as much as impinging on tryptophan and serotonin [21]. There is a need for further in-depth research specifically involving pets. The knowledge gained from laboratory animals cannot be directly applied to dogs and cats. Nevertheless, these findings provide a suggestion and a starting point for further exploration of the topic. Studies available on humans may prove useful in the context of dogs, due to the similarities between the human and canine microbiomes [33]. The microbiome affects brain development and functioning, influencing such regions as the hippocampus, amygdala, and prefrontal cortex (PFC) [2].

3.1. Amygdala

The amygdala enables acquisition and storage of a memory of the conditioning experience, and plays a role in the expression of fear responses, implicit learning, emotion processing and social behavior, emotional modulation of memory, emotional influence on perception and attention, facilitation attention to salient stimuli, inhibition and regulation of emotions, emotional regulation, and coping [34]. A study conducted on 26 mice in total (conventionally colonized and GF; kept under ethically approved conditions) showed that, in GF mice, the lateral, the basolateral amygdala, and the central nuclei of the amygdala have a greater volume compared to those in normally colonized animals in the control group. Moreover, in GF mice, dendritic hypertrophy in the basolateral amygdala (dendrites

of aspiny interneurons and pyramidal neurons) had been observed [35]. Those structural changes in the brain may be related to the lack of microbiota in prenatal or postnatal life. Due to these discoveries, the question arises about the importance of the microbiome in the proper development of the brain structure. Structural brain changes in GF mice may result from the lack of microbiota during embryogenesis and pregnancy, when maternal hormones influence brain development. Alternatively, changes may occur postnatally, requiring further studies comparing different stages of development and the possibility of correlation between animal species. It is crucial to establish whether the changes in microbiota that alter the amygdala structure happen pre- or postnatally, and how the stress stimuli that the pregnant mother is subjected to correlates with microbial acquisition and brain structural development. As has already been shown, prenatal stress influences HPA axis gene expression through epigenetic changes, which may lead to altered stress responses in adulthood in offspring, and social stress experienced by mothers prenatally programs neuroendocrine and behavioral responses to stress in adult offspring, with sex-dependent effects [36]. Another important aspect is the reversibility of structural changes in the amygdala and the time in which it is possible to reverse them through pre-, pro- or synbiotic therapy. Further research should focus on answering the arising questions.

3.2. Prefrontal Cortex

The PFC is a structure involved in cognitive behavior, social motivation, recognition, and decision making [37]. In GF mice, the thickness of the myelin sheath was enhanced and the upregulation of genes associated with myelination on myelin plasticity was observed [38]. The research utilized GF mice, which lack microbiota, comparing them to conventionally raised (CON) mice and ex-GF mice (GF mice colonized with microbiota post-weaning). The absence of microbiota leads to reduced myelination in the PFC. The microbiota plays a significant role during critical periods of brain development, impacting the formation and maintenance of myelin in the PFC.

Furthermore, microbial transfers from stressed mice trigger prefrontal demyelination and social avoidance in healthy recipients. The PFC might be sensitive to probiotics, as the supply of the *L. rhamnosus* in mice showed reduced GABAA α 2 mRNA in the PFC [39]. The experiment involved male BALB/c mice ($n = 36$). These mice were divided into two groups: one receiving *Lactobacillus rhamnosus* JB-1 and a control group not receiving the bacteria. Mice treated with *Lactobacillus rhamnosus* exhibited reduced anxiety and depression-like behaviors. These mice showed changes in central GABA receptor expression, particularly in the brain regions associated with emotion and stress. The beneficial effects were abolished when the vagus nerve was severed, indicating its crucial role in mediating the microbiota–brain interaction. The study suggests potential therapeutic strategies for managing anxiety and depression through modulation of gut bacteria.

3.3. Hippocampus

Hippocampus plays an important role in information foraging and memory function, such as memory retrieval and long-term memory function and spatial navigation [40]. The research that involved GF mice and specific-pathogen-free (SPF) mice demonstrated that the absence of gut microbiota in GF mice led to increased hippocampal neurogenesis compared to SPF mice. GF mice showed reduced dendritic spine density and decreased levels of hippocampal brain-derived neurotrophic factor (BDNF) and BDNF mRNA. BDNF is a protein that takes part in neuroplasticity and memory. Microbiome may regulate the adult neurogenesis in the hippocampus [41].

It is now known that the canine microbiome is more similar to the human microbiome than to the rodent's [23]. The feline microbiome is almost one of a kind and making any comparisons is risky. However, the microbial influence on brain development and functioning in mice is worth stating for the purpose of future research. The link between cognitive performance and microbiome composition was described in dogs [42]. The study involved 29 pet dogs of various breeds, diets, and life histories. The researchers found

a negative correlation between the abundance of the *Fusobacteria* phylum and the dogs' chronological age. Dogs with poorer memory performance (more memory test mistakes) had higher levels of *Actinobacteria* in their gut microbiome. The study of the link between cognitive performance and microbiome composition in dogs can be related to the hippocampus, a brain region critical for memory and cognitive function, in several ways: the hippocampus plays a crucial role in memory formation and spatial navigation. The study found correlations between gut microbiome composition and memory performance in dogs, suggesting that changes in gut microbiota could affect hippocampal function. Changes in gut microbiota composition, such as increased levels of *Actinobacteria*, can lead to systemic inflammation, which might negatively affect the hippocampus [42]. Chronic inflammation is known to impair hippocampal neurogenesis and has been linked to neurodegenerative conditions such as Alzheimer's disease in humans, where hippocampal dysfunction is a key feature [43].

3.4. The Olfactory System

The diverse role of the olfactory system is extended to inter- and intraspecific communication, feeding, foraging, environmental recognition, exploration, territorial marking, predation and avoidance of predators, mating, and reproduction [44]. The olfactory receptors are widely distributed along the whole organism and host-associated microbes are capable of creating odorants that bind to some receptors, such as classical odorant receptors, trace-amine-associated receptors, and formyl peptide receptors. Signaling molecules produced microbially may also regulate the host odor profiles and scent-based markings; however, the whole theme needs to be further investigated [2,45]. Research into the olfactory system and its connection to the microbiome–gut–brain axis has revealed significant interactions that influence both physiological and behavioral processes [46]. The gut microbiome can impact the CNS through various mechanisms, including the production of neurotransmitters and metabolites that influence brain function and behavior. The olfactory system, responsible for detecting and processing smells, is closely linked to the brain's limbic system, which governs emotions and memory. Changes in the gut microbiome can, therefore, affect olfactory function and subsequently influence mood, cognition, and behavior. Studies using GF mice, which lack a microbiome, have shown that these mice exhibit altered olfactory functions and behavioral changes. Introducing specific bacterial strains can restore normal behavior and olfactory processing, highlighting the microbiome's role in these processes [47]. Administering probiotics to animals has been found to improve olfactory function and modulate behavior, indicating the potential for microbiome-targeted therapies in treating olfactory and cognitive disorders [48]. Overall, the interplay between the microbiome and olfactory and semiochemical communication systems underscores the importance of microbial communities in animal behavior and ecology. This growing body of research offers new insights into the mechanisms underlying animal communication and the potential for microbiome-targeted interventions to modulate these processes.

4. Microbiome Alteration

As there is more and more innovative research concerning canine and feline microbiomes, better knowledge is being gathered of what influences the microbiota and how this is done.

Microbial composition may be influenced by diet, probiotics, fecal microbiota transplantation, prebiotics, psychobiotics (pro- and prebiotics affecting the microbiome–gut–brain axis) [2], structural changes in the intestine, stress, drugs (e.g., antibiotics and chemotherapeutics), inflammation in the gut, and many more factors to yet be discovered [1]. It is worth stating that recently a tool allowing quantifying gut dysbiosis has been developed via a PCR-based algorithm, called the Dysbiosis Index (DI). The DI also allows disease monitoring and observing the organism's response to treatment [49].

4.1. Drugs

Microbial manipulations are often a part of treating GI diseases. Antibiotics rapidly and significantly induce a drop in taxonomic richness, evenness, and diversity of the microbiome [3]. Abundant usage of antibiotics may result in the reduction in the beneficial bacteria population, advance antimicrobial resistance, ease the increase in the population of pathogens or potential pathogens, modify the GI microbial composition, and contribute to dysbiosis [19]. Antimicrobial-induced dysbiosis is a term used in cases of dysbiosis caused by antibiotics usage and describes processes such as loss of beneficial bacteria, alterations in the metabolic functions and end-products of the microbiota, decreases in microbial richness and diversity, and blooms of intestinal pathogens [50]. There are currently not enough data about the long-term consequences of canine and feline antibiotic-induced dysbiosis and whether that state may consistently contribute to clinical morbidity [51].

Some drugs interfere with both the microbiome and behavior. A study conducted on 12 dogs (10 males, 2 females) diagnosed with idiopathic epilepsy threw light on that matter. Idiopathic epilepsy (IE) is a common neurological disorder in dogs, characterized by recurrent seizures of unknown origin. All dogs included in the study had a confirmed diagnosis of idiopathic epilepsy and were prescribed phenobarbital (PB) as a treatment regimen, with a dose of 2.3 ± 0.4 mg/kg administered every 12 h. Behavioral assessments were conducted to evaluate the impact of phenobarbital treatment on the dogs' behavior. This included monitoring for signs of aggression, anxiety, and other behavioral changes (the Canine Behavioral Assessment & Research Questionnaire—cBARQ; Attention Deficit Hyperactivity Disorder—ADHD; and Canine Cognitive Dysfunction Rating Scale—CCDR values). PB treatment was associated with improvements in stranger-directed fear, non-social fear, and trainability in dogs with IE. There was no significant difference in behavioral improvements between PB-responders (PB-R) and PB-non-responders (PB-NR), indicating that the behavioral benefits of PB might be independent of its antiseizure efficacy. PB treatment resulted in a significant decrease in the bacterial order Clostridiales. This change inversely correlated with an increase in SCFAs, particularly butyrate and propionate. Regarding the microbiome, the reduction in Clostridiales has been observed. This may be due to changes in specific bacteria within this order that are not SCFA producers. Total SCFA concentrations, including of butyrate and propionate, increased with PB treatment. SCFAs are known to have beneficial effects on gut and brain health and can cross the BBB. The study suggests that phenobarbital treatment in dogs with idiopathic epilepsy can lead to behavioral improvements and changes in the gut microbiome, particularly an increase in beneficial SCFAs. These findings indicate a potential link between gut health and epilepsy, highlighting the importance of considering both pharmacological and microbiological aspects in the management of epilepsy and its comorbidities. Further research is needed to fully elucidate these interactions and their implications for treatment strategies [52].

4.2. Diet

Dietary components are divided into nutrients and non-nutrients. Nutrients are substances that the body needs to function properly, grow, and maintain health. They can be divided into macronutrients (carbohydrates, proteins, fats) and micronutrients (vitamins, minerals) [53]. Non-nutrients are compounds that are not essential for survival but can still have health benefits. They include phytochemicals, antioxidants, and dietary fiber. Phytochemicals are plant-based compounds with antioxidant properties; examples are flavonoids and carotenoids. Dietary fiber aids in digestion and prevents constipation; examples are cellulose and lignin. Antioxidants protect cells from oxidative damage; examples and polyphenols, and vitamins C and E [54].

There happens to be a suggestion that dietary components may have an impact on heart diseases, neurological disorders [1], diabetes, allergies, weight management, oral health, and kidney disease through changes in the gut microbiome of cats and dogs [55].

The diet composition, especially large macronutrient differences, reflects on the gut microbiome profiles. In dogs, the origin of the ingredients seems to be less important than

the overall macronutrient composition [3]. Furthermore, research shows that the richness of *Firmicutes*, and the genera *Bacteroides* and *Prevotella*, happens to decrease in dogs fed raw diets. The same studies detected an increase in the abundance of the genera *Lactobacillus* and *Clostridium*, and the genus *Fusobacterium*, in dogs fed biologically appropriate raw food (BARF) [56,57]. Raw diets (BARF) might also have a role in increasing fecal levels of GABA and its precursor, gamma-hydroxybutyric acid [3]. However, the research must be continued on greater groups of animals to determine whether that is an overall rule. In another study, the raw meat diet was associated with a higher diversity of gut bacteria in both dogs and cats compared to those fed conventional dry food. A diverse microbiome is generally considered beneficial for gut health and resilience against pathogens. In cats and dogs fed raw meat, the gut microbiome showed an increase in certain bacterial genera. In particular, the study noted an increase in *Lactobacillus* and *Bifidobacterium*, both of which are known for their beneficial effects on gut health, including the production of SCFAs and modulation of the immune system. The results suggest that raw meat diets might promote a more natural and beneficial gut microbiome in pets, similar to that seen in their wild counterparts. However, the potential increase in pathogenic bacteria (*Clostridium perfringens* and *Escherichia coli*) also indicates that careful management and preparation of raw diets are crucial to prevent health risks [58]. Dogs fed high-protein diets showed an increased abundance of the *Fusobacterium* genus, which plays a key role in protein fermentation. Diets rich in fiber led to a higher abundance of *Bacteroidetes*, specifically *Prevotella*, which are efficient in breaking down complex carbohydrates and fibers into SCFAs [59]. In felines fed a high-protein diet, the gut microbiome is enriched with bacteria that specialize in protein fermentation. Key bacterial genera associated with this diet included *Clostridium* and *Peptostreptococcus*, which are involved in the breakdown of amino acids and protein byproducts. In contrast, a high-carbohydrate diet resulted in an increased abundance of bacteria capable of carbohydrate fermentation. Notable genera observed in this group included *Bacteroides* and *Prevotella*, which are known for breaking down complex carbohydrates into simpler sugars and fermentation products [60]. Feeding cats diets that closely match their natural high-protein intake could help maintain a gut microbiome that supports their overall health and metabolic functions, reducing the risk of diet-related disorders.

Diet plays a significant role in shaping the behavior and cognitive function of dogs and cats. A balanced diet with appropriate levels of amino acids, fatty acids, vitamins, and minerals is essential for maintaining optimal mental health and behavior. Specific dietary interventions, like increased tryptophan or Omega-3 fatty acids, can be used to address behavioral issues such as aggression, anxiety, and hyperactivity. In a study conducted on 24 elderly beagle dogs, it was demonstrated that medium-chain triglyceride (MCT) supplementation in healthy senior dogs led to a significant increase in blood ketone bodies under fed conditions, without restricting dietary carbohydrates and proteins. Notably, dogs fed the MCT diet outperformed those fed the control diet in three cognitive tests. These findings indicate that MCT supplementation substantially enhances cognitive abilities in senior dogs, improving attention, memory, spatial learning, and executive functions such as concept learning and trainability [61].

4.3. Prebiotics, Probiotics

A prebiotic is a “nondigestible compound that, through its metabolization by microorganisms in the gut, modulates composition and/or activity of the gut microbiota, thus conferring a beneficial physiological effect on the host” [62]. It has been shown that prebiotics have a beneficial role in modulating GI microbiota, e.g., in canines, 1.5% inulin intake [63] may reduce fecal pH and expand the *Bifidobacteria* population. Supplementation of fructooligosaccharide (FOS) also has a positive input in *Bifidobacteria* growth [64]. Beet pulp enlarges the phylum *Firmicutes*, with increased abundance of class *Clostridia*, and decreases in *Erysipelotrichi* and the phylum *Fusobacteria*. Potato fiber and soybean husk enrich *Firmicutes*. Along with potato fiber and soybean husk, inulin-type fructans increase

SCFA [65]. The yeast cell wall supports the growth of the genus *Bifidobacterium* [3]. In felines, the high-protein diet influences growth in fecal *Clostridium*. FOS dietary supplementation enlarges the *Bifidobacteria* population and lessens the *Escherichia coli* population. Addition of pectin increases the *Clostridium perfringens* and Lactobacilli concentrations [19].

Probiotics “are exogenous live bacteria introduced into the host gut via direct ingestion or oral gavage” [2]. Another definition by FAO/WHO, 2001, describes them as “live microorganisms that when administered in adequate amounts confer a health benefit on the host”. The usage of probiotics in companion animals is still developing. Probiotic bacteria are shown to only slightly enhance microbial diversity or, typically, not to be able to colonize the gut owing to rivalry with already existing microbiota [6]. The benefits of probiotics intake include diarrhea prevention, prolonging a steady and healthy GI microbiome, and coping with small bacterial overgrowth and mild enteropathies [19].

In a study involving 45 dogs with behavioral issues—including aggression, hyperattachment, vocalization, destructiveness, house-soiling when left alone, compulsive disorders, and excessive barking—it was found that dogs receiving *Lactiplantibacillus plantarum* PS128 experienced a significant reduction in aggressive behaviors [66]. The probiotic also helped alleviate symptoms of separation anxiety; dogs showed less distress and fewer anxiety-related behaviors when left alone, indicating an overall improvement in their emotional well-being. A 14-day administration of PS128 appeared to stabilize the emotional status of the dogs, and it was observed that PS128 reduced the plasma serotonin turnover ratio in dogs with separation anxiety. In another study, the probiotic strain of *Saccharomyces boulardii* was found to lower fecal calprotectin, IgA, and cortisol levels in dogs, suggesting it may alleviate intestinal inflammation and reduce stress hormone secretion [67].

Dietary components, including both nutrients and non-nutrients, interact closely with pre-, pro-, syn-, and postbiotics to promote gut health and overall well-being. Nutrients such as vitamins and minerals can enhance the growth and activity of probiotics, while non-nutrients like dietary fibers act as prebiotics, feeding beneficial gut bacteria. Probiotics utilize these prebiotics to produce postbiotics, which are bioactive compounds that confer additional health benefits. Synbiotics combine probiotics and prebiotics to synergistically improve the survival and effectiveness of beneficial bacteria in the gut. Together, these dietary components and biotics form a comprehensive system that supports digestion, immune function, and disease prevention [68].

4.4. Obesity

Research that focused on evaluation of the composition of the fecal microbiota in lean and obese pet dogs was conducted to determine whether there is a significant change in the microbiota in lean and obese dogs. The results showed that the mean abundance of *Actinobacteria* and the genus *Roseburia* increased in the obese group. The overall abundance of *Clostridiales* was greater in the obese pet dogs fed ad libitum. The richness of *Bacillales* and *Fusobacteriales* was less in the obese group compared to the lean group. To summarize, there were no significantly major changes in the fecal microbiota between obese and lean dogs in that certain group [14].

Obesity in dogs and cats significantly impacts their behavior, reducing physical activity, altering feeding patterns, and potentially causing psychological distress. It can lead to a cycle of decreased activity and increased weight gain, further impacting their physical and mental health. Addressing obesity through proper diet, exercise, and veterinary care can improve both the physical health and behavior of pets, enhancing their overall quality of life [69,70].

4.5. Stress

A state of disruption, or its possibility, in homeostasis caused by an external or internal stimulus, or the prediction of such a stimulus occurring, and the requirement of psychological, physiological, and/or behavioral efforts to manage the event and its outcomes, is called stress [71]. Motility and visceral perception can be modulated by the stress

response via GBA interactions [21]. The association between stress, various gastrointestinal diseases, and the GI microbiome is being actively studied. At present, there are not enough data to definitely state the results of stress itself on the gut microbiome. Research shows, however, that acute or chronic stress may induce alteration in the stress response plasticity. Corticotropin-releasing factor (CRF) is a mediator of the central stress response. There are two described CRF receptor subtypes and it has been shown that in response to stress, they mediate increased colonic motor activity and slowed gastric emptying [72].

Long-term stress can lead to the development of behavioral problems such as aggression, anxiety disorders, and phobias. Research indicates that dogs exhibit specific stress behaviors such as yawning, lip licking, and avoiding eye contact when exposed to stressful stimuli. A study by Dreschel and Granger [73], has found that dogs' cortisol levels and stress behaviors increased significantly during kenneling compared to their home environment. Another study, conducted by Carlstead et al. [74], found that cats in shelters showed higher levels of stress-related behaviors and cortisol compared to those in a home environment. Overall, behavioral indicators of stress in dogs are increased barking, whining, destructive behavior, excessive licking or grooming, changes in appetite, and withdrawal from social interactions [73]; in cats, indicators are hiding, excessive grooming, spraying or urinating outside the litter box, aggression, and changes in eating or sleeping patterns [74].

It is worth noting that stress and obesity often coexist, with each condition potentially contributing to the development of the other [75]. Some pets may eat more when they are stressed. This behavior, often driven by the pet seeking comfort or distraction, can lead to overeating and, eventually, obesity. Moreover, stress may induce reduction in a pet's activity, leading to weight gain. Once a pet becomes obese, the extra weight itself can be a source of stress [76]. Overweight animals may experience joint pain, difficulty breathing, and reduced mobility, which can lead to frustration, anxiety, and further inactivity [77]. Obesity and stress can form a vicious cycle in companion animals, where each condition exacerbates the other. Effective management requires addressing both the physical and emotional well-being of the pet, ensuring a balanced diet and regular exercise, and minimizing environmental stressors.

5. Microbiome's Correlation with Behavior

It is possible that the GI microbiome influences the host's behavior through interacting with the organism's physiology [78]. For this to occur, study of GF animals is needed. Research on GF mice showed that they have visible deficits in social development, and exhibit different anxiety levels abnormal stress reactions in comparison to control groups, i.e., normally colonized animals. Furthermore, GF mice had significantly elevated corticosterone levels in response to stress compared to normally colonized animals; in comparison to normally colonized controls, they tended to have an enlarged lateral amygdala and basolateral amygdala, and a larger central nucleus of the amygdala, a greater volume of certain hippocampal regions, and a reduced level of BDNF [2]. Although there is much more evidence every day of the compound relationship between the gut microbiota, immune system, and behavior in animals, the current literature is still limited.

In dogs, the composition of the microbiome differs in healthy animals and in those with behavioral issues. Data suggest that an elevated abundance of *Firmicutes* was visible in dogs with behavioral disorders such as phobias, separation anxiety, and aggression. In addition, in phobic dogs, the genus *Lactobacillus* and the family *Rikenellaceae* were enriched; in animals behaving aggressively, *Bacteroides*, *Sutterella*, *Peptostreptococcus*, *Oscillospira* were reduced, and an increase in the abundance of *Catenibacterium*, *Megamonas*, and *Eubacterium* was present [9]. In a comparative study of fecal microbiota in aggressive and non-aggressive dogs, the results showed that *Firmicutes*, *Fusobacteria*, *Bacteroidetes*, and *Proteobacteria* were the dominant phyla in all fecal samples; *Proteobacteria* and *Fusobacteria* were relatively more abundant in non-aggressive dogs; and the family *Lactobaccillaceae* was richer in aggressive dogs of that particular participating animal group. Moreover, the authors sug-

gest there might be an association between aggression and an increase in specific lineages of *Lactobacillus* and *Paraprevotellaceae* [78].

In a study conducted on rats, fecal microbiota transplants from patients diagnosed with depression (donors) to microbiota-depleted individuals made the recipients behave anxiously [79]. The study was conducted on 28 adult male Sprague-Dawley rats. They were divided into control ($n = 15$) and depressed groups ($n = 14$) [79]. This suggests that transferring GI microbiota impacts the mood and thus the behavior of the receiving animal, and that when transplanting microbes, the mood of the donor is also transferred [8].

The pilot study by Watanangura et al., 2024 [80], explored the potential benefits of fecal microbiota transplantation (FMT) for treating behavioral comorbidities in dogs with drug-resistant epilepsy (DRE). The study aimed to assess the impact of FMT on behavioral issues associated with epilepsy, such as anxiety, cognitive dysfunction, and ADHD-like behavior. Post-FMT, the dogs exhibited notable improvements in ADHD-like behavior, fear- and anxiety-like behavior, and overall quality of life. There were significant decreases in the excitatory neurotransmitters aspartate and glutamate, alongside an increase in the inhibitory neurotransmitter GABA and the GABA/glutamate ratio. Minor taxonomic changes in the gut microbiota were observed, including a reduction in *Firmicutes* and *Blautia_A* species and an increase in a *Ruminococcus* species. However, functional gene analysis, SCFA concentrations, and blood parameters remained largely unchanged.

Poor nutrition and gastrointestinal conditions are important factors to developing some of the behavioral disorders, such as restlessness, polyphagia, pica, unsettled sleep, anxiety, aggression, stereotypies, and hyperalertness [9]. Both of those factors (GI conditions and poor nutrition) are also associated with gut dysbiosis [1] and stress. Dysbiosis correlated with altered SCFA concentration may lead to a syndrome called the “leaky gut”, which involves impaired gut permeability, intestinal inflammation, and translocation of antigens, enteric corticosterone, and microbial metabolites into the systemic circulation. The mentioned molecules are able to either cross the BBB or modulate the vagus nerve, thus causing the stress response via activating the HPA axis or inducing systemic inflammation [8]. The general impact of stress on the animals’ mental health includes:

- chronic frustration, social anxiety, decreased food intake, inhibition of exploratory and social behaviors, learned helplessness, and stereotypies [81];
- other effects on dogs: deleterious psychological effects of raised levels of glucocorticoids, nervousness and/or restlessness, increased startle responses, food guarding, increased avoidance responses including irritable aggression and increased barking, tail chasing, flank sucking in Dobermans, tail chasing and spinning in German shepherds and bull terriers, and aggressive behavior toward family members or toward dogs living in the same household;
- other effects on cats: wool sucking in Oriental cat breeds [82], urine marking, fecal marking, house soiling problems, anorexia, reduced play and exploration, increased vigilance, anorexia, aggression, and hiding [83].

Dysbiosis during early life development has been shown to affect both the immune and nervous systems, thus influencing the evolution of behavioral and cognitive disorders [9].

6. Discussion

Specific mechanisms and biological pathways enabling the microbiome to influence the host’s physiology and the behavior itself remain poorly understood and are yet to be fully clarified. The beginning of understanding the intricate relationship between the gut microbiome and behavior in companion animals opens new avenues for therapeutic interventions. Future research should focus on long-term studies and larger sample sizes to better elucidate these interactions and their potential for improving the mental health and behavior of pets. Integrating microbiome management into veterinary practices could enhance the overall quality of life for companion animals. While discussing the impact of the GI microbiome on companion animals’ behavior, a few questions need to be asked: What is the role of the stress response in the whole process? Is the alteration in behavior

due to microbial change or secondary to the stress? Does the altered microbiota impact the development of behavioral disorders in animals or does the mental status predispose to microbial changes via altering the physiological status of the animal? New techniques of studying the microbiome have been established, enabling its precise profiling and raising the possibility of scientific answers to those questions. Moreover, the prospects of FMTs and nutraceutical therapy in influencing behavior through microbial changes are promising but require further investigation. FMTs offer a direct approach to restoring gut health, which can have immediate behavioral benefits. Nutraceuticals provide a more gradual and potentially sustainable method for modulating the gut microbiome. Both therapies highlight the importance of the GBA in maintaining mental health and behavior, introducing novel approaches for holistic and integrative treatments in veterinary medicine.

Studies across various species have demonstrated that microbial communities can affect a wide range of behaviors, from social interactions and stress responses to feeding patterns and reproductive strategies. For example, alterations in the gut microbiota have been linked to anxiety-like behaviors in mice, aggressive behavior in dogs, and stress resilience in fish. These findings suggest that the microbiome not only reflects an animal's health status, but also actively participates in shaping behavioral phenotypes.

7. Conclusions

Environmental factors such as diet, habitat, and social interactions significantly influence the composition of the microbiome, which in turn can alter behavior. This bidirectional relationship highlights the importance of considering both microbial and environmental influences when studying animal behavior. Additionally, the potential for microbiome manipulation, through diet or probiotics, offers exciting possibilities for modifying behavior in domestic and wild animals, with applications in animal welfare, conservation, and even human–animal interactions.

The study of the microbiome–behavior relationship is essential for a holistic understanding of animal biology. Future research should aim to unravel the specific microbial mechanisms underlying behavioral changes, the evolutionary significance of these interactions, and the potential for microbiome-targeted interventions to improve animal health and behavior. As our understanding deepens, it is clear that the microbiome is not just a passive passenger, but an active player in the complex orchestra of animal life.

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References

1. Suchodolski, J.S. Analysis of the gut microbiome in dogs and cats. *Vet. Clin. Pathol.* **2021**, *50*, 6–17. [[CrossRef](#)] [[PubMed](#)]
2. Sarkar, A.; Harty, S.; Johnson, K.V.A.; Moeller, A.H.; Carmody, R.N.; Lehto, S.M.; Erdman, S.E.; Dunbar, R.I.; Burnet, P.W. The role of the microbiome in the neurobiology of social behaviour. *Biol. Rev.* **2020**, *95*, 1131–1160. [[CrossRef](#)] [[PubMed](#)]
3. Pilla, R.; Suchodolski, J.S. The Role of the Canine Gut Microbiome and Metabolome in Health and Gastrointestinal Disease. *Front. Vet. Sci.* **2020**, *7*, 582809. [[CrossRef](#)]
4. Zakošek Pipan, M.; Kajdič, L.; Kalin, A.; Plavec, T.; Zdovc, I. Do newborn puppies have their own microbiota at birth? Influence of type of birth on newborn puppy microbiota. *Theriogenology* **2020**, *152*, 18–28. [[CrossRef](#)]

5. Ferretti, P.; Pasolli, E.; Tett, A.; Asnicar, F.; Gorfer, V.; Fedi, S.; Armanini, F.; Truong, D.T.; Manara, S.; Zolfo, M.; et al. Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. *Cell Host Microbe* **2018**, *24*, 133–145. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Hand, D.; Wallis, C.; Colyer, A.; Penn, C.W. Pyrosequencing the canine fecal microbiota: Breadth and depth of biodiversity. *PLoS ONE* **2013**, *8*, e53115. [\[CrossRef\]](#)
7. Garcia-Mazcorro, J.F.; Dowd, S.E.; Poulsen, J.; Steiner, J.M.; Suchodolski, J.S. Abundance and short-term temporal variability of fecal microbiota in healthy dogs. *MicrobiologyOpen* **2012**, *1*, 340–347. [\[CrossRef\]](#)
8. Tuniyazi, M.; Hu, X.; Fu, Y.; Zhang, N. Canine Fecal Microbiota Transplantation: Current Application and Possible Mechanisms. *Vet. Sci.* **2022**, *9*, 396. [\[CrossRef\]](#)
9. Homer, B.; Judd, J.; Dehcheshmeh, M.M.; Ebrahimie, E.; Trott, D.J. Gut Microbiota and Behavioural Issues in Production, Performance, and Companion Animals: A Systematic Review. *Animals* **2023**, *13*, 1458. [\[CrossRef\]](#)
10. Masuoka, H.; Shimada, K.; Kiyosue-Yasuda, T.; Kiyosue, M.; Oishi, Y.; Kimura, S.; Ohashi, Y.; Fujisawa, T.; Hotta, K.; Yamada, A.; et al. Transition of the intestinal microbiota of cats with age. *PLoS ONE* **2017**, *12*, e0178467. [\[CrossRef\]](#)
11. Barry, K.A.; Middelbos, I.S.; Vester Boler, B.M.; Dowd, S.E.; Suchodolski, J.S.; Henrissat, B.; Coutinho, P.M.; White, B.A.; Fahey, G.C., Jr.; Swanson, K.S. Effects of dietary fiber on the feline gastrointestinal metagenome. *J. Proteome Res.* **2012**, *11*, 2381–2391. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Ganz, H.H.; Jospin, G.; Rojas, C.A.; Martin, A.L.; Dahlhausen, K.; Kingsbury, D.D.; Osborne, C.X.; Entrolezo, Z.; Redner, S.; Ramirez, B.; et al. The Kitty Microbiome Project: Defining the Healthy Fecal “Core Microbiome” in Pet Domestic Cats. *Vet. Sci.* **2022**, *9*, 635. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Minamoto, Y.; Hooda, S.; Swanson, K.S.; Suchodolski, J.S. Feline gastrointestinal microbiota. *Anim. Health Res. Rev.* **2012**, *13*, 64–77. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Handl, S.; German, A.J.; Holden, S.L.; Dowd, S.E.; Steiner, J.M.; Heilmann, R.M.; Grant, R.W.; Swanson, K.S.; Suchodolski, J.S. Faecal microbiota in lean and obese dogs. *FEMS Microbiol. Ecol.* **2013**, *84*, 332–343. [\[CrossRef\]](#)
15. Lee, D.; Goh, T.W.; Kang, M.G.; Choi, H.J.; Yeo, S.Y.; Yang, J.; Huh, C.S.; Kim, Y.Y.; Kim, Y. Perspectives and advances in probiotics and the gut microbiome in companion animals. *J. Anim. Sci. Technol.* **2022**, *64*, 197–217. [\[CrossRef\]](#)
16. Hornef, M. Pathogens, Commensal Symbionts, and Pathobionts: Discovery and Functional Effects on the Host. *ILAR J.* **2015**, *56*, 159–162. [\[CrossRef\]](#)
17. Parke, J.L.; Gurian-Sherman, D. Diversity of the Burkholderia cepacia complex and implications for risk assessment of biological control strains. *Annu. Rev. Phytopathol.* **2001**, *39*, 225–258. [\[CrossRef\]](#)
18. Zhang, Y.; Si, X.; Yang, L.; Wang, H.; Sun, Y.; Liu, N. Association between intestinal microbiota and inflammatory bowel disease. *Anim. Models Exp. Med.* **2022**, *5*, 311–322. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Mondo, E.; Marliani, G.; Accorsi, P.A.; Cocchi, M.; Di Leone, A. Role of gut microbiota in dog and cat’s health and diseases. *Open Vet. J.* **2019**, *9*, 253–258. [\[CrossRef\]](#)
20. Rhimi, S.; Kriaa, A.; Mariaule, V.; Saidi, A.; Drut, A.; Jablaoui, A.; Akermi, N.; Maguin, E.; Hernandez, J.; Rhimi, M. The Nexus of Diet, Gut Microbiota and Inflammatory Bowel Diseases in Dogs. *Metabolites* **2022**, *12*, 1176. [\[CrossRef\]](#)
21. O’Mahony, S.M.; Clarke, G.; Borre, Y.E.; Dinan, T.G.; Cryan, J.F. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behav. Brain Res.* **2015**, *277*, 32–48. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Gliński, Z.; Kostro, K. Mikrobiom—Charakterystyka i znaczenie. *Życie Weterynaryjne* **2015**, *90*, 7.
23. Ambrosini, Y.M.; Borchering, D.; Kanthasamy, A.; Kim, H.J.; Willette, A.A.; Jergens, A.; Allenspach, K.; Mochel, J.P. The Gut-Brain Axis in Neurodegenerative Diseases and Relevance of the Canine Model: A Review. *Front. Aging Neurosci.* **2019**, *11*, 156. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Wise, R.A. Dopamine, learning and motivation. *Nat. Rev. Neurosci.* **2004**, *5*, 483–494. [\[CrossRef\]](#)
25. Baron, A.B.; Søvik, E.; Cornish, J.L. The Roles of Dopamine and Related Compounds in Reward-Seeking Behavior Across Animal Phyla. *Front. Behav. Neurosci.* **2010**, *4*, 163. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Kidskin-Conhaim, L. Physiological and morphological changes in developing peripheral nerves of rat embryos. *Brain Res.* **1988**, *470*, 15–28. [\[CrossRef\]](#)
27. Kania, B.F. The role of gamma-aminobutyric acid (GABA) in animals aggression. *Życie Weterynaryjne* **2017**, *92*, 277–279.
28. Halverson, T.; Alagiakrishnan, K. Gut microbes in neurocognitive and mental health disorders. *Ann. Med.* **2020**, *52*, 423–443. [\[CrossRef\]](#)
29. Crowell-Davis, S.L.; Poggiagliolmi, S. Understanding behavior: Serotonin syndrome. *Compend. Contin. Educ. Pract. Vet.* **2008**, *30*, 490–493.
30. Stanley, A.T.; Post, M.R.; Lacefield, C.; Sulzer, D.; Miniaci, M.C. Norepinephrine release in the cerebellum contributes to aversive learning. *Nat. Commun.* **2023**, *14*, 4852. [\[CrossRef\]](#)
31. Powledge, T.L. Acetylcholine and Its Role in Synaptic Plasticity, Learning, and Memory. *Compr. Physiol.* **2012**, *2*, 2553–2580. [\[CrossRef\]](#)
32. Makris, A.P.; Karianaki, M.; Tsamis, K.I.; Paschou, S.A. The role of the gut-brain axis in depression: Endocrine, neural, and immune pathways. *Hormones* **2021**, *20*, 1–12. [\[CrossRef\]](#) [\[PubMed\]](#)

33. Coelho, L.P.; Kulima, J.R.; Costea, P.I.; Fournier, C.; Pan, Y.; Czarnecki-Maulden, G.; Hayward, M.R.; Forslund, S.K.; Schmidt, T.S.B.; Descombes, P.; et al. Similarity of the dog and human gut microbiomes in gene content and response to diet. *Microbiome* **2018**, *6*, 72. [[CrossRef](#)] [[PubMed](#)]
34. Phelps, E.A.; LeDoux, J.E. Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron* **2005**, *48*, 175–187. [[CrossRef](#)] [[PubMed](#)]
35. Luczynski, P.; Whelan, S.O.; O'Sullivan, C.; Clarke, G.; Shanahan, F.; Dinan, T.G.; Cryan, J.F. Adult microbiota-deficient mice have distinct dendritic morphological changes: Differential effects in the amygdala and hippocampus. *Eur. J. Neurosci.* **2016**, *44*, 2783–2795. [[CrossRef](#)]
36. Herba, C.M.; Glover, V. The Developmental Effects of Prenatal Maternal Stress: Evolutionary Explanations. In *Prenatal Stress and Child Development*; Wazana, A., Székely, E., Oberlander, T.F., Eds.; Springer: Berlin/Heidelberg, Germany, 2021; pp. 23–52.
37. Mohapatra, A.N.; Wagner, S. The role of the prefrontal cortex in social interactions of animal models and the implications for autism spectrum disorder. *Front. Psychiatry* **2023**, *14*, 1205199. [[CrossRef](#)]
38. Hoban, A.E.; Stilling, R.M.; Ryan, F.J.; Shanahan, F.; Dinan, T.G.; Claesson, M.J.; Clarke, G.; Cryan, J.F. Regulation of prefrontal cortex myelination by the microbiota. *Transl. Psychiatry* **2016**, *6*, 774. [[CrossRef](#)]
39. Bravo, J.A.; Forsythe, P.; Chew, M.V.; Wscavage, E.; Savignac, H.M.; Dinan, T.G.; Bienenstock, J.; Cryan, J.F. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 16050–16055. [[CrossRef](#)]
40. Johnson, A.; Varberg, Z.; Benhardys, J.; Maahs, A.; Schrater, P. The hippocampus and exploration: Dynamically evolving behavior and neural representations. *Front. Hum. Neurosci.* **2012**, *6*, 216. [[CrossRef](#)]
41. Ogbonnaya, E.S.; Clarke, G.; Shanahan, F.; Dinan, T.G.; Cryan, J.F.; O'Leary, O.F. Adult hippocampal neurogenesis is regulated by the microbiome. *Biol. Psychiatry* **2015**, *78*, e7–e9. [[CrossRef](#)]
42. Kubinyi, E.; Bel Rhali, S.; Sándor, S.; Szabó, A.; Felföldi, T. Gut microbiome composition is associated with age and memory performance in pet dogs. *Animals* **2020**, *10*, 1488. [[CrossRef](#)] [[PubMed](#)]
43. Zonis, S.; Pechnick, R.N.; Ljubimov, V.A.; Mahgerefteh, M.; Wawrosky, K.; Michelsen, K.S.; Chesnokova, V. Chronic intestinal inflammation alters hippocampal neurogenesis. *J. Neuroinflamm.* **2015**, *12*, 65. [[CrossRef](#)] [[PubMed](#)]
44. Alvites, R.; Caine, A.; Cherubini, G.B.; Prada, J.; Varejao, A.S.P.; Mauricio, A.C. The olfactory bulb in companion animals—Anatomy, physiology, and clinical importance. *Brain Sci.* **2023**, *13*, 713. [[CrossRef](#)] [[PubMed](#)]
45. Archie, E.A.; Tung, J. Social behavior and the microbiome. *Curr. Opin. Behav. Sci.* **2015**, *6*, 28–34. [[CrossRef](#)]
46. Bienenstock, J.; Kunze, W.A.; Forsythe, P. Disruptive physiology: Olfaction and the microbiome-gut-brain axis. *Biol. Rev. Camb. Philos. Soc.* **2018**, *93* (Suppl. 1), 390–403. [[CrossRef](#)]
47. Rinanda, T.; Riani, C.; Sasongko, L. Correlation between gut microbiota composition, enteric infections and linear growth impairment: A case-control study in childhood stunting in Pidie, Aceh, Indonesia. *Gut Pathog.* **2023**, *15*, 54. [[CrossRef](#)]
48. Schiano Moriello, A.; Di Marzo, V.; Petrosino, S. Mutual links between the endocannabinoidome and the gut microbiome, with special reference to companion animals: A nutritional viewpoint. *Animals* **2022**, *12*, 348. [[CrossRef](#)] [[PubMed](#)]
49. AlShawaqfeh, M.K.; Wajid, B.; Minamoto, Y.; Markel, M.; Lidbury, J.A.; Steiner, J.M.; Serpedin, E.; Suchodolski, J.S. A dysbiosis index to assess microbial changes in fecal samples of dogs with chronic inflammatory enteropathy. *FEMS Microbiol. Ecol.* **2017**, *93*. [[CrossRef](#)]
50. Levy, M.; Kolodziejczyk, A.A.; Thais, C.A.; Elinav, E. Dysbiosis and the immune system. *Nat. Rev. Immunol.* **2017**, *17*, 219–232. [[CrossRef](#)]
51. Stavroulaki, E.M.; Suchodolski, J.S.; Xenoulis, P.G. Effects of antimicrobials on the gastrointestinal microbiota of dogs and cats. *Vet. J.* **2023**, *291*, 105929. [[CrossRef](#)]
52. Watanangura, A.; Meller, S.; Suchodolski, J.S.; Pilla, R.; Khattab, M.R.; Loderstedt, S.; Becker, L.F.; Bathen-Nöthen, A.; Mazzuoli-Weber, G.; Volk, H.A. The effect of phenobarbital treatment on behavioral comorbidities and on the composition and function of the fecal microbiome in dogs with idiopathic epilepsy. *Front. Vet. Sci.* **2022**, *9*, 933905. [[CrossRef](#)] [[PubMed](#)]
53. Whitney, E.; Rolfes, S.R. *Understanding Nutrition*; Cengage Learning: Singapore, 2018.
54. Kris-Etherton, P.M.; Hecker, K.D.; Bonanome, A.; Coval, S.M.; Binkoski, A.E.; Hilpert, K.F.; Etherton, T.D. Bioactive compounds in foods: Their role in the prevention of cardiovascular disease and cancer. *Am. J. Med.* **2002**, *113*, 71–88. [[CrossRef](#)] [[PubMed](#)]
55. Wernimont, S.M.; Radosevich, J.; Jackson, M.I.; Ephraim, E.; Badri, D.V.; MacLeay, J.M.; Jewell, D.E.; Suchodolski, J.S. The effects of nutrition on the gastrointestinal microbiome of cats and dogs: Impact on health and disease. *Front. Microbiol.* **2020**, *11*, 1266. [[CrossRef](#)] [[PubMed](#)]
56. Butowski, C.F.; Moon, C.D.; Thomas, D.G.; Young, W.; Bermingham, E.N. The effects of raw-meat diets on the gastrointestinal microbiota of the cat and dog: A review. *N. Z. Vet J.* **2022**, *70*, 1–9. [[CrossRef](#)]
57. Handl, S.; Dowd, S.E.; Garcia-Mazcorro, J.F.; Steiner, J.M.; Suchodolski, J.S. Massive parallel 16S rDNA sequencing highlights influences of age, diet, and environment on canine intestinal microbiome. *PLoS ONE* **2011**, *6*, e26659. [[CrossRef](#)]
58. Badri, D.V.; Jackson, M.I.; Jewell, D.E. Dietary Protein and Carbohydrate Levels Affect the Gut Microbiota and Clinical Assessment in Healthy Adult Cats. *J. Nutr.* **2021**, *151*, 3637–3650. [[CrossRef](#)]
59. Bermingham, E.N.; Maclean, P.; Thomas, D.G.; Cave, N.J.; Young, W. Key bacterial families (Clostridiaceae, Erysipelotrichaceae and Bacteroidaceae) are related to the digestion of protein and energy in dogs. *PeerJ* **2017**, *5*, e3019. [[CrossRef](#)]

60. Schmidt, M.; Unterer, S.; Suchodolski, J.S.; Honneffer, J.B.; Guard, B.C.; Lidbury, J.A.; Steiner, J.M.; Fritz, J.; Kölle, P. The fecal microbiome and metabolome differs between dogs fed Bones and Raw Food (BARF) diets and dogs fed commercial diets. *PLoS ONE* **2018**, *13*, e0201279. [\[CrossRef\]](#)
61. Pan, Y. Enhancing brain functions in senior dogs: A new nutritional approach. *Top. Companion Anim. Med.* **2011**, *16*, 10–16. [\[CrossRef\]](#)
62. Bindels, L.A.; Delzenne, N.M.; Cani, P.D.; Walter, J. Towards a more comprehensive concept for prebiotics. *Nat. Rev. Gastroenterol. Hepatol.* **2015**, *12*, 380–388. [\[CrossRef\]](#)
63. Alexander, C.; Cross, T.L.; Devendran, S.; Neumer, F.; Theis, S.; Ridlon, J.M.; de Godoy, M.R.C.; Swanson, K.S. Effects of prebiotic inulin-type fructans on blood metabolite and hormone concentrations and fecal microbiota and metabolites in overweight dogs. *Br. J. Nutr.* **2018**, *120*, 711–720. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Zentek, J.; Marquart, B.; Pietrzak, T.; Ballevre, O.; Rochat, F. Dietary effects on bifidobacteria and *Clostridium perfringens* in the canine intestinal tract. *J. Anim. Physiol. Anim. Nutr.* **2003**, *87*, 397–407. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Pinna, C.; Vecchiato, C.G.; Bolduan, C.; Grandi, M.; Stefanelli, C.; Windish, W.; Zaghini, G.; Biagi, G. Influence of dietary protein and fructooligosaccharides on fecal fermentative end-products, fecal bacterial populations, and apparent total tract digestibility in dogs. *BMC Vet. Res.* **2018**, *14*, 106. [\[CrossRef\]](#)
66. Yeh, Y.-M.; Lye, X.Y.; Lin, H.Y.; Yi, W.J. Effects of *Lactiplantibacillus plantarum* PS128 on alleviating canine aggression and separation anxiety. *Appl. Anim. Behav. Sci.* **2022**, *247*, 105569. [\[CrossRef\]](#)
67. Meinieri, G.; Martello, E.; Atuahene, D.; Miretti, S.; Stefanon, B.; Sandri, M.; Biasato, I.; Corvaglia, M.R.; Ferrocino, I.; Cocolin, L.S. Effects of *Saccharomyces boulardii* supplementation on nutritional status, fecal parameters, microbiota, and mycobiota in breeding adult dogs. *Vet. Sci.* **2022**, *9*, 389. [\[CrossRef\]](#)
68. Gibson, G.R.; Hutkins, R.; Sanders, M.E.; Prescott, S.L.; Reimer, R.A.; Salminen, S.J.; Scott, K.; Stanton, C.; Swanson, K.S.; Cani, P.D.; et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat. Rev. Gastroenterol. Hepatol.* **2017**, *14*, 491–502. [\[CrossRef\]](#) [\[PubMed\]](#)
69. German, A.J. The growing problem of obesity in dogs and cats. *J. Nutr.* **2006**, *136*, 1940S–1946S. [\[CrossRef\]](#)
70. Laflamme, D.P. Understanding and managing obesity in dogs and cats. *Vet. Clin. N. Am. Small Anim. Pract.* **2006**, *36*, 1283–1295. [\[CrossRef\]](#) [\[PubMed\]](#)
71. Lazarus, R.S.; Folkman, S. *Stress, Appraisal and Coping*; Springer: New York, NY, USA, 1984.
72. Bueno, L.P.; Fioramonti, J. Effects of corticotropin-releasing factor, corticotropin, and cortisol on gastrointestinal motility in dogs. *Peptides* **1986**, *7*, 73–77. [\[CrossRef\]](#)
73. Dreschel, N.A.; Granger, D.A. Methods of collection for salivary cortisol measurement in dogs: Effect on salivary cortisol and its applicability in behavioral research. *Physiol. Behav.* **2009**, *97*, 609–614. [\[CrossRef\]](#)
74. Carlstead, K.; Brown, J.L.; Strawn, W. Behavioral and physiological correlates of stress in laboratory cats. *Appl. Anim. Behav. Sci.* **1993**, *38*, 143–158. [\[CrossRef\]](#)
75. German, A. Obesity in companion animals. *Clin. Pract.* **2010**, *32*, 42–50. [\[CrossRef\]](#)
76. Chandler, M.; Cunningham, S.A.; Lund, E.M.; Khanna, C. Obesity and associated comorbidities in people and companion animals: A One Health perspective. *J. Comp. Pathol.* **2017**, *156*, 296–309. [\[CrossRef\]](#) [\[PubMed\]](#)
77. Laflamme, D.P. Obesity in dogs and cats: What is wrong with being fat? *J. Anim. Sci.* **2012**, *90*, 1653–1662. [\[CrossRef\]](#)
78. Kirchoff, N.S.; Udell, M.A.R.; Sharpton, T.J. The gut microbiome correlates with conspecific aggression in a small population of rescued dogs (*Canis familiaris*). *PeerJ* **2019**, *7*, e6103. [\[CrossRef\]](#)
79. Kelly, J.R.; Borre, Y.; O'Brien, C.; Patterson, E.; El Aidy, S.; Deane, J.; Kennedy, P.J.; Beers, S.; Scott, K.; Moloney, G.; et al. Transferring the blues: Depression-associated gut microbiota induces neurobehavioral changes in the rat. *J. Psychiatr. Res.* **2016**, *82*, 109–118. [\[CrossRef\]](#)
80. Watanangura, A.; Meller, S.; Farhat, N.; Suchodolski, J.S.; Pilla, R.; Khattab, M.R.; Lopes, B.C.; Bathen-Nöthen, A.; Fischer, A.; Busch-Hahn, K.; et al. Behavioral comorbidities treatment by fecal microbiota transplantation in canine epilepsy: A pilot study of a novel therapeutic approach. *Front. Vet. Sci.* **2024**, *11*, 1385469. [\[CrossRef\]](#)
81. Stella, J.L.; Croney, C.C. Environmental aspects of domestic cat care and management: Implications for cat welfare. *Sci. World J.* **2016**, *2016*, 6296315. [\[CrossRef\]](#)
82. Mills, D.S.; Karagiannis, C.; Zulch, H. Stress—Its effects on health and behavior: A guide for practitioners. *Vet. Clin. N. Am. Small Anim. Pract.* **2014**, *44*, 525–541. [\[CrossRef\]](#)
83. Zhang, L.; Bian, Z.; Liu, Q.; Deng, B. Dealing with stress in cats: What is new about the olfactory strategy? *Front. Vet. Sci.* **2022**, *9*, 928943. [\[CrossRef\]](#)

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