animals

IMPACT FACTOR 2.7

Indexed in: PubMed

CITESCORE 4.9

Review

The Relationship between Canine Behavioral Disorders and Gut Microbiome and Future Therapeutic Perspectives

Paula Kiełbik and Olga Witkowska-Piłaszewicz

Special Issue

Advances in Companion Animal Cognition and Behavior

Edited by

Dr. Daniel J. Horschler

MDPI

https://doi.org/10.3390/ani14142048

animals

MDPI

Review

The Relationship between Canine Behavioral Disorders and Gut Microbiome and Future Therapeutic Perspectives

Paula Kiełbik * and Olga Witkowska-Piłaszewicz

Department of Large Animal Diseases and Clinic, Institute of Veterinary Medicine, Warsaw University of Life Sciences, 02-787 Warsaw, Poland
* Correspondence: paula_kielbik@sggw.edu.pl

Simple Summary: Canine behavioral disorders have become one of the most common concerns and challenging issues among dog owners. Therefore, to face this challenge, searching for novel therapeutic methods is highly required. Accumulated data show that mammals' gut microbiome, immune system, and nervous system are in continuous communication and influence animal physiology and behavior. This review aimed to summarize and discuss the most important scientific pieces of evidence on the relationship between mental disorders and gut microbiota in dogs, simultaneously presenting comparable outcomes in humans and rodent models. A comprehensive overview of crucial mechanisms of the gut–brain axis is included. Additionally, the possible effects of the fecal microbiome transplantation procedure as a new tool to manipulate gut microbiota are discussed.

Abstract: Canine behavioral disorders have become one of the most common concerns and challenging issues among dog owners. Thus, there is a great demand for knowledge about various factors affecting dogs' emotions and well-being. Among them, the gut–brain axis seems to be particularly interesting, especially since in many instances the standard treatment or behavioral therapies insufficiently improve animal behavior. Therefore, to face this challenge, the search for novel therapeutic methods is highly required. Existing data show that mammals' gut microbiome, immune system, and nervous system are in continuous communication and influence animal physiology and behavior. This review aimed to summarize and discuss the most important scientific evidence on the relationship between mental disorders and gut microbiota in dogs, simultaneously presenting comparable outcomes in humans and rodent models. A comprehensive overview of crucial mechanisms of the gut–brain axis is included. This refers especially to the neurotransmitters crucial for animal behavior, which are regulated by the gut microbiome, and to the main microbial metabolites—short-chain fatty acids (SCFAs). This review presents summarized data on gut dysbiosis in relation to the inflammation process within the organism, as well as the activation of the hypothalamic–pituitary–adrenal (HPA) axis. All of the above mechanisms are presented in this review in strict correlation with brain and/or behavioral changes in the animal. Additionally, according to human and laboratory animal studies, the gut microbiome appears to be altered in individuals with mental disorders; thus, various strategies to manipulate the gut microbiota are implemented. This refers also to the fecal microbiome transplantation (FMT) method, based on transferring the fecal matter from a donor into the gastrointestinal tract of a recipient in order to modulate the gut microbiota. In this review, the possible effects of the FMT procedure on animal behavioral disorders are discussed.

Keywords: canine behavioral disorders; gut–brain axis; fecal microbiota transplantation; gut dysbiosis; dog behavior

Citation: Kiełbik, P.; Witkowska-Piłaszewicz, O. The Relationship between Canine Behavioral Disorders and Gut Microbiome and Future Therapeutic Perspectives. *Animals* **2024**, *14*, 2048. https://doi.org/10.3390/ani14142048

Academic Editor: Tiffani Josey Howell

Received: 18 June 2024
Revised: 5 July 2024
Accepted: 10 July 2024
Published: 12 July 2024

1. Introduction

Canine behavioral disorders have become one of the most common concerns and challenging issues among dog owners [1–5]. There is growing concern about dogs' emotionality

and welfare, especially since pets are treated as family members and play very important social roles in modern societies [6–8].

Interestingly, according to studies investigating pet owners' experience during the COVID-19 pandemic, dogs became an important social and emotional support for their owners during this time [9,10]. Moreover, in one of the studies, the authors suggest that companion animals can help mitigate the effects of extreme stress and social isolation [11]. Consequently, nowadays, we can observe an increased effort to mitigate not only somatic but also mental issues in companion dogs.

The term "behavioral disorder" describes an animal behavior which appears to be undesirable or unexpected for the owner. Thus, lots of dog actions (classified as problematic for people) seem to be normal and natural activities for domestic canines. This refers to suspiciousness towards strangers, digging, chasing game, and barking, among others. This might be why many dog owners state that their dog expresses some behavioral problem (prevalence around 70–80%). Certainly, diagnosing dog behavioral abnormalities only based on owners' subjective opinions can be misleading.

Nevertheless, even studies regarding the prevalence of canine behavioral problems reported by veterinarians or behaviorists show a high percentage of animals with behavioral issues [12–14]. In fact, canine undesirable behaviors can sorely impact dog–owner relationships, leading to animal relinquishment [14–18] or even euthanasia [19–21]. Moreover, recent studies have shown that pet behavioral problems might lead to poor mental health of the owners [22–25]. In one of the studies, which focused on exploring the experience of people owning problematic dogs, the authors concluded that all the examined owners experienced some level of frustration with their dog's excitable behavior, and the majority of them were very frustrated [26]. Moreover, some canine behavioral disorders (aggressiveness towards people and/or animals) may become serious public health concerns. Especially dog bites are a worldwide public health concern, since they are the main risk factor for human rabies and affect mostly children [27–29]. However, it is worth mentioning that behavioral issues directly affect the welfare of the dog itself [30–32]. Stress, as an integral part of each dog's behavioral disorder, seriously affects the organism, especially when it is prolonged. Impaired growth, reproduction, immune function, and reduced lifespan are examples of the many potential outcomes [33,34]. We can conclude that behavioral disorders in companion dogs may have serious consequences for the quality of life of both dogs and their owners.

2. Gut–Brain Connection

In many instances, standard treatment or behavioral therapies insufficiently improve animal behavior; thus, to face this challenge, searching for novel therapeutic methods is highly required [35,36]. The advanced approaches in this area should involve a detailed recognition of underlying physiological mechanisms, not only those widely recognized, such as neurological and hormonal changes or pain. Among the numerous factors contributing to canine behavioral disorders, the influence of gut-related mechanisms seems to be particularly interesting. This review aimed to summarize and discuss the most important scientific evidence on the relationship between mental disorders and gut microbiota in dogs, along with comparable outcomes observed in humans and rodent models. A comprehensive overview of the crucial mechanisms of the gut–brain axis is included in this review. These mechanisms include the homeostatic balance of the intestinal microbiome and crucial neurotransmitters and metabolites (mainly SCFAs) regulated by the gut microbiome, as well as the influence of the gut microbiome on inflammation and the hypothalamic–pituitary–adrenal (HPA) axis. All of the above mechanisms are presented in this review in strict correlation with brain and/or behavioral changes in the animal. Additionally, the possible effects of the manipulation of the gut microbiome by fecal microbiome transplantation on mental health are discussed.

2.1. Canine Gut Microbiome and Dysbiosis

The term microbiota refers to living microorganisms found in a defined environment, e.g., gut microbiota. These microbial communities are in symbiosis with the host, contributing to homeostasis and acting by regulating the organism's physiological functions [37]. Within various segments of the canine gastrointestinal tract, different microbial communities can be found, but most bacterial sequences belong to the following phyla: Firmicutes, Fusobacteria, Bacteroidetes, Proteobacteria, and Actinobacteria [38]. The composition of gut microbiota differs among individuals, which is related to various diets, age, or geographical locations of the host. Interestingly, studies revealed some level of microbiota sharing between dogs and their owners [39,40]. Thus, the obtained results suggest that direct and frequent contact with our cohabitants may significantly shape the composition of our microbial communities. It is worth remembering that the term microbiome refers not only to microorganism composition but also to specific environmental conditions, microbial structural elements, and metabolites related to microbial activity. Thus, the microbiome creates a dynamic and interactive ecosystem that can change with time and interact with hosts [41].

The homeostatic balance of the intestinal microbiome is exceptionally beneficial to the host. A proper, healthy gut microbiome ensures a beneficial influence on the host's immune system, defense against pathogens, or supply of vitamins and nutrients. Gut dysbiosis has been defined as a disturbance to gut microbiota homeostasis with further changes in their functional composition and metabolic activities [42,43]. Dysbiosis might have serious health consequences, as was proven in dogs as well. The gut microbiome is altered in many gastrointestinal diseases such as diarrhea, chronic enteropathies, and inflammatory bowel disease (IBD) but also in obesity, pancreatic insufficiency, or heart diseases in humans and dogs [44–47]. While the abovementioned diseases have been studied relatively extensively in relation to dysbiosis, there is still limited knowledge of how the gut microbiome influences dogs' mental health, mood, and behavior.

2.2. Gut–Brain Axis

The term gut–brain axis refers to the constant communication between the brain and gastrointestinal tract, and because of this, the enteric nervous system is often called the body's "second brain". This connection is bidirectional and affects various areas of animal life, including mood and behavior. The gut–brain axis is composed of immunological, metabolic, endocrinological, and neuronal mediators [48]. The microbiome can influence the animal central nervous system via the vagus nerve [49], neurotransmitter level regulation [50], the hypothalamic–pituitary–adrenal (HPA) axis [51], influence on the immune system [52], and production of metabolites [53] (Figure 1).

Human studies have shown that people with anxiety disorders and depression have more gastrointestinal symptoms (such as irritable bowel syndrome-like symptoms), compared to healthy individuals [54–56]. Similarly, altered microbiota composition was found to occur more often in other human mental diseases, including anxiety [57–59], schizophrenia [60,61], or posttraumatic stress disorder (PTSD) [62,63].

Similar studies as were conducted on humans have not been conducted as extensively on dog patients with behavioral disorders. The significance of this area of study seems to be high, especially since dogs show numerous physiological similarities to humans [64–66]. This refers also to the gastrointestinal tract. A recent study revealed that the gut microbiome of dogs is more similar to that of humans than that of mice and pigs, especially when lots of dogs eat the same food as their owners [67]. Interestingly, age-related differences were found in dog gut microbiome composition, pointing at a decreased diversity of the gut microbiome and reduced number of lactobacilli in older individuals [68,69]. These results suggest that the dog gut microbiome is likely to vary with age, as occurs in other animals, including humans. Additionally, dogs with better memory performance revealed a lower number of one of the genera of bacteria (*Actinobacteria*) in their fecal samples, which is in agreement with the high abundance of *Actinobacteria* in the gastrointestinal tract of persons

living with Alzheimer's disease [70]. Thus, the changes are similar to those reported in humans.

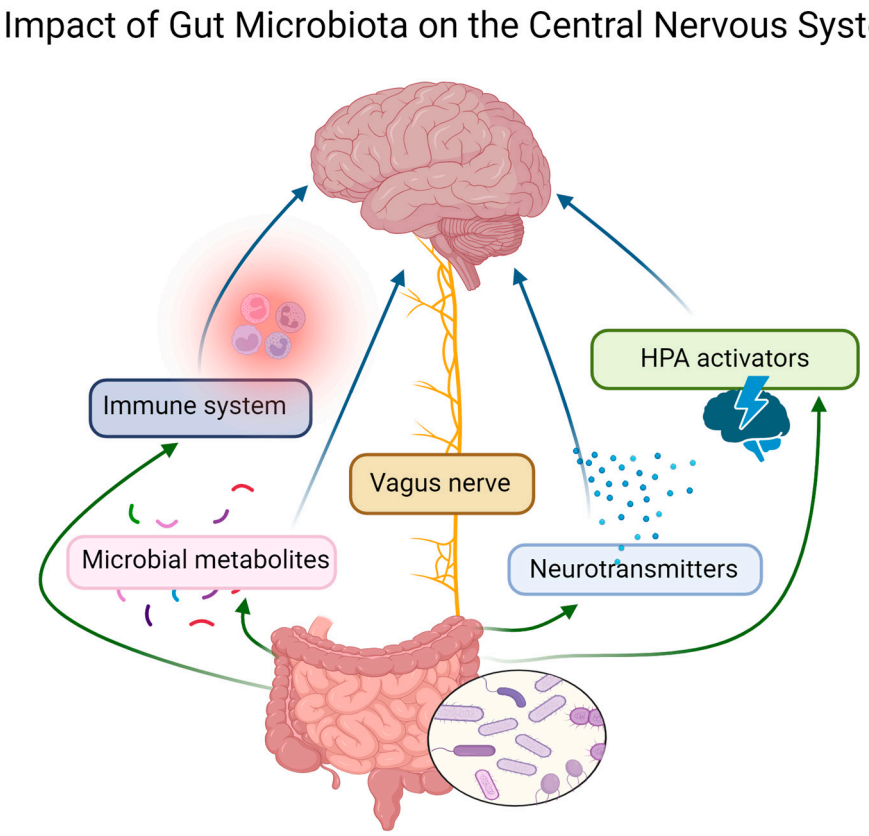

Figure 1. Crucial mechanisms of gut microbiome influence on the central nervous system. The gut microbiota has been found to influence the central nervous system through various mechanisms. This refers to the production/regulation of neurotransmitters, innervation via the vagus nerve, activation of the hypothalamic–pituitary–adrenal (HPA) axis, influence on the immune system, or production of microbiota metabolites.

While most of the current literature focuses on humans, recent studies have shown differences in the composition of the gut microbiome between dogs with behavioral disorders and healthy individuals. In one of the studies, the gut microbiome structure and adrenocortical activity were investigated in dogs with aggressive and phobic behavioral disorders [71]. The obtained results revealed that aggressive behavioral disorder is characterized by a specific gut microbiome structure with a high biodiversity and enrichment in generally subdominant bacterial genera (*Catenibacterium* and *Megamonas* among others), compared to both phobic and normal behavior groups. On the other hand, phobic dogs were characterized by an enrichment in the *Lactobacillus* genus with well-known probiotic properties. The authors hypothesized that the dysbiotic microbiota of dogs with behavioral disorders (strictly related to long-term stress) can influence the local gut environment by releasing potentially neuroactive microbial by-products [71]. Similarly, another study revealed that the composition of the gut microbiome differs between aggressive and non-aggressive dogs [72]; however, the results are contradictory with those obtained by Mondo et al. [71]. Members of *Lactobacillus* bacteria were more abundant in the gut microbiomes of aggressive dogs [72], whereas in the previously cited study [71], the enrichment in the *Lactobacillus* genus was linked to phobic dogs. This inconsistency may be related to the methodology of canine behavioral disorder classification. Many aggressive behaviors are fear-based; thus, depending on the chosen criteria, animals can be classified as phobic (based on the underlying cause of the unwanted behavior) or aggressive (based on the observable, unwanted behavior) dogs. Nevertheless, further study on the canine gut microbiome role

may certainly help clarify whether or how this can influence canine aggression. Kirchoff et al. also reported higher *Proteobacteria* and *Fusobacteria* abundances in non-aggressive dogs, whereas *Firmicutes* were more abundant in aggressive animals [72]. Craddock et al. characterized the microbiota of working dogs and determined if the composition of the microbiota is associated with behavioral and performance outcomes [73]. The obtained results showed an increased abundance of *Firmicutes* in aggressive dogs, which is in line with findings from Kichoff et al. [72]. The authors also observed increased *Lactobacillus* in association with phobic behavior, as well as the increased richness of gut microbiota among more aggressive individuals, which is consistent with the study of Mondo et al. [71]. Craddock et al. [73] also identified increased *Ruminococcus* abundance in association with increased canine aggression, while Mondo et al. [71] linked this member of the canine gut microbiota with phobic behavior. Other results obtained by Pellowe et al. [74] revealed an increased richness of gut microbiota in both aggressive and anxiety groups of dogs, similar to results obtained by Mondo et al. [71] and Craddock et al. [73]. Studies performed by Pellowe et al. also suggest a strong relationship between the genus *Blautia* and anxiety in domestic dogs [74]. Interestingly, in dogs, a significantly decreased level of genus *Blautia* within intestinal microbiota was observed in dogs with gastrointestinal disease, especially acute hemorrhagic diarrhea [75].

Studies cited in the following review suggest that there is an urgent need to deepen the knowledge on the mechanisms underlying the relationship between canine behavioral disorders and the altered composition of the gut microbiome. Future investigations in this area of study should also consider the individual dog core microbial population in the gut. The biodiversity of the canine gut microbiome may naturally occur in various diet compositions or geographical locations.

2.3. Gut Microbiome and Neurotransmitters

Gut microbiota can influence brain function by regulating crucial animal behavior neurotransmitters such as serotonin (5-HT), gamma-aminobutyric acid (GABA), acetylcholine, dopamine, or norepinephrine [76]. The imbalance of neurotransmitters is one of the reasons responsible for distress and mental disorders; thus, we can hypothesize that the gut microbiome influences mental health, mood, and behavior. Summarized information regarding serotonin, GABA, and dopamine in relation to animal behavior is presented in Table 1.

Serotonin plays a crucial role in animal behavior by regulating an animal's mood, sleep, cognition, social interactions, and anxiety [77]. In general, serotonin is known as the "happiness hormone" produced due to the transformation of tryptophan. According to studies, more than 90% of total body serotonin is produced in the gut by specialized endocrine cells enterochromaffin cells (ECs), mucosal mast cells, and neurons from the enteric nervous system [78]. Serotonin is an important factor acting locally in the gastrointestinal tract by influencing intestinal peristalsis, motility, secretion, vasodilatation, and the absorption of nutrients. The exact mechanism explaining how peripheral serotonin could influence brain functionality is not clear; however, the link between the systemic serotonin system and animal behavior has been recognized [79,80]. The importance of the gut microbiome's role in regulating blood serotonin levels was proven. In germ-free mice (an animal model without microbial colonization), a significant decrease in serum serotonin level was detected [81]. In another study in mice, following 4 weeks of antibiotic treatments, the richness and diversity of intestinal microbiota and serotonin levels decreased significantly [82]. Additionally, in one of the studies, the authors reported reduced levels of serotonin in patients with gut microbiome-related dysbiosis—irritable bowel syndrome (IBS)—compared to healthy controls. Interestingly, this study also revealed a correlation between decreased levels of serotonin and psychological state changes in tested patients [83]. Likewise, a 50% reduction in serotonin in intestine mucosa was found in mice mimicking autism syndrome [84], which is consistent with another study where reduced intestinal serotonin synthesis was found in children with autism spectrum disorder [85]. Therefore,

study evidence (mostly based on mice and humans) shows that mental health disorders may be related with the disturbance in gut-related serotonin metabolism.

In the case of canine behavioral disorders, several studies have reported a relationship between a decreased level of serotonin and undesirable behaviors. Researchers detected significantly lower serum serotonin concentrations in aggressive dogs, compared to non-aggressive individuals [86–88]. To the best of the authors' knowledge, no study has been conducted to investigate the relationship between canine behavioral disorders and the disturbance in gut-related serotonin metabolism. In one of the studies, the effect of a novel nutraceutical supplement (containing 5-HTP—the intermediate metabolite of L-tryptophan in the biosynthesis of serotonin) on the fecal microbiome and stress-related behaviors in dogs was investigated. Serum serotonin levels were not measured in this study; however, supplementation revealed an improvement in both gastrointestinal disturbances (vomiting episodes and diarrhea) and behavioral disorders (aggressiveness, nervousness, alertness, hiding and isolating, fearfulness) [89].

Another example of a neurotransmitter regulated by gut microbial function is dopamine. This catecholamine regulates crucial central and peripheral nervous system functions, including reward and motivation [90–93]. Dopamine is a vital neurotransmitter for mental disorders including depression, which was previously associated only with noradrenergic and serotonergic system dysfunction. Current studies have proven the role of dopaminergic dysfunction in the pathophysiology of major depression [94,95]. It is of great importance that in humans more than 50% of dopamine is synthesized in the gastrointestinal tract and the overall dopamine level is influenced by gut microbiota [96]. In germ-free mice, the level of free dopamine was decreased compared to specific pathogen-free mice. Germ-free mice also exhibited an increased turnover rate of dopamine in the brain [97]. The obtained results indicate that the gut microbiota plays a crucial role in the production of free catecholamines (including dopamine) in the gut lumen. Significant evidence supports the involvement of some key microbial genera in dopamine production, release, and bioavailability. Microbiota dysbiosis can lead to dopaminergic deficits that are related to pathological conditions such as Parkinson's disease [98]. In dogs, lower levels of the urinary dopamine/serotonin ratio have been associated with impulsivity in dogs [99], whereas increased levels of plasma dopamine and serotonin have been detected in anxious dogs [100]. In one study, dogs with ADHD-like behaviors showed lower serotonin and dopamine serum concentrations [101]. Unfortunately, none of the cited studies performed an analysis of the gut microbiota and its potential involvement in dopamine system dysregulation in correlation with dog behavioral disorders.

Gamma-aminobutyric acid (GABA) is a main inhibitory neurotransmitter in the central nervous system with important physiological and behavioral functions such as the regulation of mood, anxiety, sleep, or memory enhancement [102–104]. GABAergic neurotransmission inhibits the amygdala and prevents inappropriate emotional and behavioral responses [105]. Reduced GABA plasma concentrations and GABA concentrations in prefrontal brain regions have been reported in anxiety states, stress-related disorders, and depression in humans [106–108]. A broad diversity of bacteria has been reported to produce/influence GABA in human gut microbiota, and reports suggest that the manipulation of the gut microbiota may impact GABA levels [109]. Moreover, researchers found that oral GABA administration in mice could elevate the production of total SCFAs (short-chain fatty acids), which play a crucial role in intestinal tract health [110]. Promising outcomes in this area of study led to increased research studies into the development of food products containing GABA for calming effects [111–113]. The alleviative effects of administered GABA were also evaluated on behavioral abnormalities in aged dogs. The obtained results revealed an improvement in emotional states, with no adverse effects [114]. Similarly, calming effects were observed in another study, where orally administered GABA reduced activity and urinary cortisol levels in the examined dogs [115]. It seems that GABA can also be influenced by diet in dogs. In one study, dogs on a BARF diet (Feeding Bones and Raw Food) revealed higher levels of GABA in their feces, as well as a different microbial

composition (significantly higher abundance of *Escherichia coli* and *Clostridium*), compared to commercially fed dogs [116].

Table 1. Representative behavior-related neurotransmitters regulated by the gut microbiota. The table presents the probable role of the neurotransmitter in animal behavior, data on the role of the gut microbiota in its regulation, and canine studies in the area of behavioral disorders in connection with the neurotransmitter.

Neurotransmitter	Effect on Animal Behavior	Gut Microbiota Regulation	Canine Behavioral Disorder
Serotonin	Regulates mood, sleep, cognition, social interactions, and anxiety [77]	• Germ-free mice revealed a significant decrease in serum serotonin level [81] • Significant decrease in serum serotonin level after 4 weeks of antibiotic treatments in mice [82] • Reduced serotonin serum level in human patients with IBS [83] • Reduced intestinal serotonin synthesis in children with autism spectrum disorder [85]	Significantly lower serotonin serum level in aggressive dogs [86–88]
Dopamine	Regulates reward-related behavior and motivation [90–93]	• Germ-free mice revealed decreased level of free dopamine and increased turnover rate of dopamine in the brain [97] • Microbiota dysbiosis can potentially lead to dopaminergic deficits (related with Parkinson's disease, among others) [98]	• Lower level of urinary dopamine/serotonin associated with impulsivity in dogs [99] • Increased level of plasma dopamine in anxious dogs [100] and dogs with ADHD-like behaviors [101]
Gamma-aminobutyric acid (GABA)	Regulates mood and anxiety and prevents inappropriate emotional and behavioral responses [102–105]	Various bacteria produce/influence GABA in human gut microbiota, and manipulation of gut microbiota may impact GABA levels [109]	Reduced activity and urinary cortisol level in dogs after orally administered GABA [115]

2.4. Main Microbial Metabolites—Short-Chain Fatty Acids (SCFAs)

Gut microbiota produces metabolites such as short-chain fatty acids (SCFAs), which seem to play a key role in intestinal and overall homeostasis. Acetate, propionate, and butyrate are three major SCFAs derived from the intestinal microbial fermentation of undigested dietary fibers [117–119]. Moreover, since these undigested polysaccharides are fermented by gut microbiota, the analysis of the SCFA levels can directly help to assess the gut microbiota composition. SCFAs act as an energy source for colonic epithelial cells with numerous health benefits, including anti-inflammatory, immunoregulatory, anti-obesity, anti-diabetes, anticancer, cardiovascular protective, and hepatoprotective activity [120]. It is also widely accepted that microbial dysbiosis can lead to the altered production of microbial metabolites, including decreased SCFA levels [121]. This refers to dogs, as well. Acute diarrhea leads to dysbiosis with significant alteration in fecal SCFA profiles, among others. The abundance of SCFA-producing bacteria was reduced in fecal samples of dogs with acute diarrhea [122], chronic enteropathies [123], or inflammatory bowel diseases (IBDs) [124].

It is worth mentioning that SCFAs also play a crucial role in the communication between the brain and gastrointestinal tract, however, the underlying mechanisms through which SCFAs influence the brain and behavior have not been fully clarified. These compounds are involved in maintaining integrity of the intestinal barrier and preventing the translocation of bacterial products, which can lead to increased production of cytokines and affect the blood–brain barrier (BBB) [125]. Likewise, SCFAs regulate microglia functions and BBB integrity. Increased permeability of BBB is related to various neurological disorders

such as neuroinflammation or neurodegeneration [126]. Impaired integrity of BBB, caused as a consequence of altered SCFA concentrations, can lead to the hypothalamic–pituitary–adrenal (HPA) axis activation or systemic inflammation and indirectly affect animal mood and behavior [127].

Studies have shown that changed gut microbiota with altered SCFAs production is related to mental and neurologic pathologies, including Parkinson's disease [128], Alzheimer's disease [129], and autism spectrum disorder [130]. The potential interactions between the abundance of SCFA-producing bacteria and behavioral pathologies were also considered. In one study, the authors concluded that gastrointestinal illnesses or any disruptions related to the gut microbiome (such as IBD) are often worsened during stressful periods [131]. Similarly, an association between fecal SCFA levels and depressive symptoms among women was indicated [132]. A study on the non-human primate model of depression also revealed that peripheral (serum) and central (cerebrospinal fluid) SCFAs are implicated in the onset of depression [133]. An interesting experiment was recently performed on mice with a depleted microbiome. The authors of the study revealed that orally administered SCFAs decreased anxiety-like behavior in the tested mice [134]. Similar studies were not conducted on dogs; however, a deeper understanding of the interaction between SCFA levels and canine behavioral disorders is exceedingly required.

2.5. Gut Dysbiosis and Inflammation

A healthy microbiome protects the body against excessive inflammatory reactions, simultaneously inducing intestinal immune responses during the invasion of pathogens. Thus, we can conclude that a properly functioning microbiome may have both pro- and anti-inflammatory effects, depending on the situation [135]. Changes in the gut microbial composition and/or overall organism homeostatic imbalance result in a pro-inflammatory state induced by gut microbiota. In response, the body produces effector molecules (cytokines and other mediators) to initiate an inflammatory response [136–138]. Chronic inflammation and gut dysbiosis underlay many chronic multisystem conditions in dogs, including chronic inflammatory enteropathy [139,140], IBD [141,142], cardiovascular diseases [143,144], and arthritis [145]. Increasing evidence also indicates the role of ongoing inflammation in behavioral disorders. Elevated levels of pro-inflammatory cytokines (including Tumor Necrosis Factor-alpha (TNF-alpha) and Interleukin 6 (IL-6)) influence brain function, leading to depression, anxiety, and anger in humans [146–148]. The addition of probiotics to the standard medications used for mental disorder treatment can decrease the level of pro-inflammatory cytokines, as was proven in human patients [149] and mice [150] suffering from chronic inflammation. In one study, the inhibition of pro-inflammatory cytokines was achieved by introducing Lactobacillus mucosae NK41 and Bifidobacterium longum NK46 to mice with induced anxiety-like/depressive behaviors [151]. The obtained results revealed that the administered gut bacteria can alleviate anxiety/depression and colitis by suppressing gut dysbiosis.

The human and mouse studies indicate that depression and anxiety disorders are associated with chronic inflammation and gut dysbiosis. In the case of canine behavioral disorders, no similar studies were performed. Inflammatory processes have been widely studied in relation to diet and its possible anti-inflammatory effect [152–154]. In one study, the authors tested the hypothesis that an elevation in inflammatory markers (C-reactive protein, IL-6) could be associated with the presence of aggressive behavior in dogs. The obtained results showed higher levels of inflammatory markers in dogs with aggression, compared to non-aggressive individuals [155]. However, possible interactions between gut dysbiosis, inflammation, and behavior were not explored in dogs.

2.6. Gut Dysbiosis and Hypothalamic–Pituitary–Adrenal (HPA) Axis

Another important mechanism involved in the crosstalk between the gut microbiota and brain is through the modulation of the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis is the main physiological system that modulates a wide variety of behavioral

processes, especially body stress response, but also rewarding behaviors, learning, and memory [156–158]. Stressful situations lead to the activation of the HPA axis, invoking corticotrophin-releasing hormone (CRH) release from the hypothalamus and the secretion of adrenocorticotropic hormone (ACTH). Circulating ACTH stimulates glucocorticoid hormone synthesis and secretion from the adrenal glands [159,160]. Since the activation of the HPA axis is essential for survival during stressful situations, the chronic elevation of stress hormones can lead to multiple organ systems' dysregulation and has clinical consequences [161].

It is of great importance that increased activity and dysregulation of the HPA axis are observed in human patients with mental disorders [162]. Increased cortisol levels are also associated with cognitive impairment, which can affect behavior [163]. Stressful situations, with further activation of the HPA axis, can also lead to changes in the gut microbiome. Altered microbiota composition has been observed following exposure to various stressors (including physical restraint, noise, or maternal separation) in animal models. Until now, various mechanisms have been proposed to clarify the link between the gut microbiota and HPA axis. As was mentioned above, gut dysbiosis may contribute to the enhanced production of pro-inflammatory cytokines. Some of these small bioactive molecules (including TNF-alpha and IL-6) might cross the blood–brain barrier (BBB) and act as activators of the HPA axis [164]. The activation of the HPA axis contributes to an increased intestinal permeability, which results in an alteration in the intestinal microbial composition and neurotransmitter production (including serotonin), as well as bacterial migration (Figure 2).

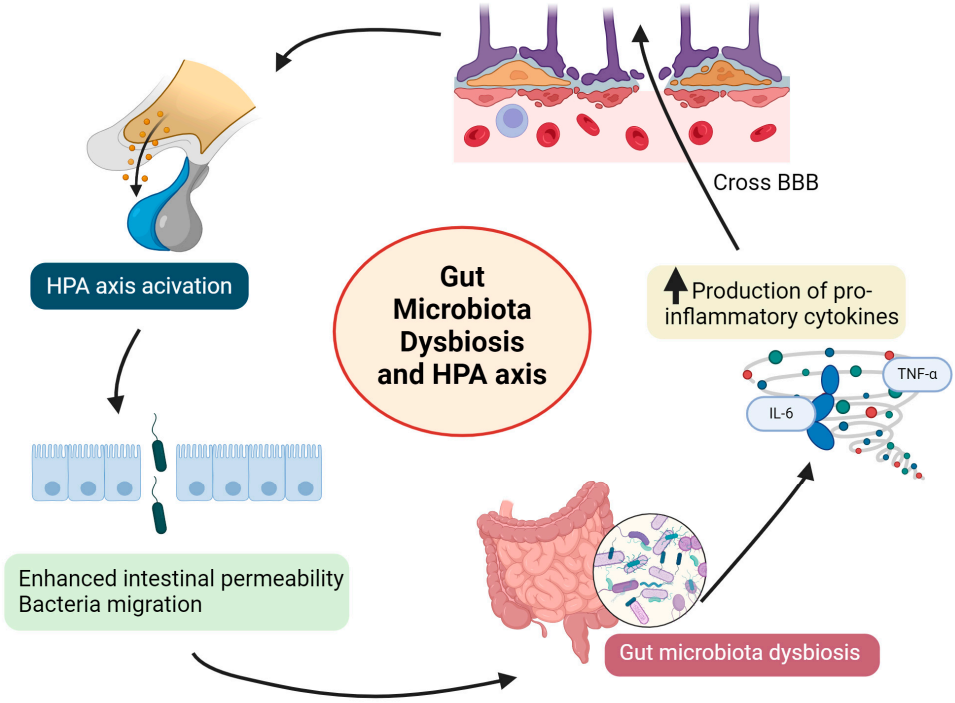

Figure 2. Modulation of the hypothalamic–pituitary–adrenal (HPA) axis by gut microbiota dysbiosis. The figure shows one of the proposed mechanisms linking gut microbiota dysbiosis and the HPA axis. Gut dysbiosis may contribute to the enhanced production of pro-inflammatory cytokines, and some of these molecules (including TNF-alpha and IL-6) might cross the blood–brain barrier (BBB) and act as activators of the HPA axis. The activation of the HPA axis leads to an increased intestinal permeability, with further bacterial migration and additional alteration in the gut microbial composition.

The HPA axis can be also activated by a bacterial endotoxin lipopolysaccharide (LPS), which stimulates systemic inflammation and translocates from the gut to the brain via the leaky mucosal barrier. Oral administration of *Escherichia coli*-derived LPS induced abnormal

behavior and increased glucocorticoid receptor pathway genes in mice [165]. Similarly, *Escherichia coli* colonization in germ-free mice enhanced the HPA axis response to stressful situations [166]. Taken together, emerging evidence has indicated that changes in the gut microbiome can influence brain functions, which results in HPA axis dysregulation, chronic systemic inflammation, neurotransmitter imbalance, and finally, behavioral disorders.

The HPA axis is generally considered to be the main mechanism of the canine stress response, and plasma levels of cortisol have been widely used as measures of stress in dogs [167–169]. In one study, the authors focused on the comparison of the gut microbiota between dogs exhibiting aggressive, phobic, or normal behavior, with specific associations with adrenocortical activity. The obtained results revealed the specific gut microbiome composition of aggressive dogs, compared to phobic and normal individuals, with no differences in fecal cortisol levels [71]. These contradictory results (aggressive dogs are well known to have higher blood concentrations of cortisol) may be related to the methodology of the experiment since cortisol levels were tested in fecal samples, not within the blood. This necessitates further experimental study to deeply investigate the mechanisms underlying the relationship between the gut microbiome, the activity of the HPA axis, and canine behavioral disorders.

3. Fecal Microbiota Transplantation (FMT)

Accumulated data show that mammals' gut microbiome, immune system, and nervous system are in continuous communication and influence animal physiology and behavior. According to human studies, the gut microbiome appears to be altered in people with depression disorders [54–56], anxiety [57–59], schizophrenia [60,61], posttraumatic stress disorder (PTSD) [62,63], or Alzheimer's disease [70]. A different composition of the gut microbiota is also related with behavioral disorders in dogs, including aggressive and phobic behavioral disorders [71–74]. Thus, the modification of the gut microbiome can potentially be a helpful tool for treating mental health disorders. There are various strategies to manipulate gut microbiota, such as dietary changes, the administration of prebiotics, probiotics, or postbiotics, or fecal microbiome transplantation (FMT) [170–172]. The FMT method is based on transferring the fecal matter from a donor into the gastrointestinal tract of a recipient in order to modulate the gut microbiota. FMT is currently indicated for the treatment of debilitating gastrointestinal infections [173]. Preclinical and clinical data suggest that FMT is a promising strategy to meliorate psychiatric disorder symptoms [170]. Studies showed that transplanting the fecal microbiome from depressed humans to microbiota-depleted rats and mice can induce depressive-like and anxiety behaviors in recipients [174–176]. FMT was also used to correct intestinal flora and intestinal barrier damage in rats with stress-induced depressive-like behavior. Animals in this study were exposed to different stressors (including social isolation, heat stress, and restraint stress) for 4 weeks. Subsequently, the FMT procedure was performed by using fresh fecal samples from the control group. The obtained results revealed an improvement in depressive-like behavior, serotonin concentration, intestinal flora dysregulation, and the mucosal barrier in rats following FMT [177]. Similar studies were also performed on human patients with major depressive disorder. The FMT method was used as an add-on therapy and showed correction of patients' depressive symptoms after 4 weeks following transplantation [178]. These beneficial therapeutic effects of FMT were also visible in patients with irritable bowel syndrome and co-occurring psychiatric symptoms (anxiety and depression behaviors) [179,180]. Although the research in this field is far from complete, the potential use of FMT treatment to alleviate anxiety and depression behaviors in human patients is promising.

FMT is also a recently adapted therapeutic approach in dogs; however, studies on its application are limited (Table 2).

Table 2. Summarized data on fecal microbiome transplantation (FMT) procedures performed in dogs with various diseases cited in the current review. The table shows studies using the FMT procedure as a treatment targeting various canine diseases, with the number of recipients enrolled in the study, the FMT method performed, and observed effects.

Fecal Microbiome Transplantation (FMT) Procedure in Dogs			
Recipient	**No of Recipients**	**FMT Method**	**Effects**
Dogs with acute hemorrhagic diarrhea syndrome [181]	8	Endoscopic	No clinical benefit; however, increased abundance of SCFA-producing bacteria (beneficial for the organism) was observed
Dogs with acute diarrhea [182]	11	Rectal enema	Fecal consistency significantly improved in all dogs, with proper microbial (based on dysbiosis index) and metabolic profiles (in contrast to dogs treated with metronidazole)
Dogs with inflammatory bowel diseases [183,184]	16 [183]; 9 [184]	Oral/endoscopic [183]; rectal enema [184]	Clinical improvement in most of dogs [183]; improvement in canine inflammatory bowel disease activity index in all dogs [184]
Dogs with chronic enteropathies (FMT used as add-on therapy) [185]	41	Rectal enema	Thirty-one dogs responded to treatment, resulting in improved fecal quality and/or activity level
Dogs with atopic dermatitis [186]	12	Oral	Eleven dogs presented significantly decreased skin lesions and pruritus scores and beneficially changed gut microbiota

In one study on dogs with acute hemorrhagic diarrhea syndrome, the FMT treatment did not have any clinical benefit [181]. On the other hand, a study in dogs with acute diarrhea treated with either fecal microbiota transplantation or metronidazole revealed beneficial effects of the FMT procedure. Dogs treated with metronidazole did not show proper microbial and metabolic profiles 28 days after, whereas the FMT treatment effectively stabilized microbiome parameters 7 days following the treatment [182]. Fecal transplantation has recently been tested as a treatment for canine IBD. The FMT procedure was performed in 16 dogs with an idiopathic IBD, unresponsive to common therapies. The results showed a clinical improvement in most of the patients after transplantation (by oral and endoscopic methods) [183]. Similarly, another study examining the FMT method as a treatment for canine IBD showed an improvement in clinical signs (including vomiting, diarrhea, and weight loss) after fecal implantation. According to the authors, the observed improvements were related to the changes in microbiota composition, especially the increase in *Fusobacterium* [184]. The effects of FMT as an adjunctive therapy were also evaluated in dogs with chronic enteropathies. The obtained results showed good clinical outcomes and suggest that FMT can be useful as an additive to standard therapy in dogs with chronic enteropathy [185]. Additionally, the FMT therapy has been recently recognized as a possible new therapeutic approach for canine atopic dermatitis [186].

Although the FMT procedure has been tested as a novel therapeutic approach targeting various canine somatic disorders, there is no study investigating the possible effect of this procedure on meliorating behavioral disorder symptoms.

4. Conclusions

Canine behavioral disorders have become one of the most common concerns and challenging issues among dog owners nowadays. It seems important to investigate the etiopathogenesis of canine mental disorders and look for more effective therapeutic agents

or medical interventions to improve the mental health of dogs and, at the same time, the comfort of life of their caregivers.

Recently, scientific attention has been paid to the gut microbiota as a target in the treatment and prevention of abnormal behaviors. The exact mechanisms by which the gut microbiota modulates mental health are not fully understood. However, it is well known that the gut microbiome can influence the animal central nervous system via various mechanisms such as the vagus nerve, neurotransmitter level regulation (serotonin and dopamine, among others), production of metabolites (especially short-chain fatty acids), and the modulation of the HPA axis or inflammatory state within the organism. All of these factors sorely impact not only the somatic condition of the dog but also its mood and behavior.

However, currently, the influence of the gut microbiota on behavioral disorders is more recognized in human medicine compared to canine studies. The possible relationship between altered levels of crucial mental health neurotransmitters (such as serotonin, dopamine, and GABA), undesirable canine behaviors, and the condition of the gut microbiota should be examined. In particular, according to human and rodent studies, fecal microbiome transplantation could be a beneficial tool for treating mental health disorders also in canine patients.

In conclusion, future studies investigating the relationship between the brain–gut axis and canine behavioral disorders should incorporate a wider set of biomarkers, neurotransmitters, metabolites, and laboratory methods to test various interactions between the brain and the microbiome.

Author Contributions: Writing and original draft preparation and visualization, P.K.; writing—review and editing, O.W.-P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding. Open access funding was provided by the Department of Large Animal Diseases and Clinic, Institute of Veterinary Medicine, Warsaw University of Life Sciences.

Data Availability Statement: Data sharing is not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Campbell, W.E. The prevalence of behavioural problems in American dogs. *Mod. Vet. Pract.* **1986**, *67*, 28–31.
2. Dinwoodie, I.R.; Dwyer, B.; Zottola, V.; Gleason, D.; Dodman, N.H. Demographics and comorbidity of behavior problems in dogs. *J. Vet. Behav. Clin. Appl. Res.* **2019**, *32*, 62–71. [CrossRef]
3. Salonen, M.; Sulkama, S.; Mikkola, S.; Puurunen, J.; Hakanen, E.; Tiira, K.; Araujo, C.; Lohi, H. Prevalence, comorbidity, and breed differences in canine anxiety in 13,700 Finnish pet dogs. *Sci. Rep.* **2020**, *10*, 2962. [CrossRef] [PubMed]
4. Yang, J.; Langford, F.; Kiddie, J. Risk factors for aggressive behaviour in domestic dogs (*Canis familiaris*), as reported by owners in mainland China. *Appl. Anim. Behav. Sci.* **2021**, *234*, 105211. [CrossRef]
5. Yamada, R.; Kuze-Arata, S.; Kiyokawa, Y.; Takeuchi, Y. Prevalence of 25 canine behavioral problems and relevant factors of each behavior in Japan. *J. Vet. Med. Sci.* **2019**, *81*, 1090–1096. [CrossRef] [PubMed]
6. Mcconnell, A.R.; Paige Lloyd, E.; Humphrey, B.T. We Are Family: Viewing Pets as Family Members Improves Wellbeing. *Anthrozoös* **2019**, *32*, 459–470. [CrossRef]
7. Charles, N. Post-Human Families? Dog-Human Relations in the Domestic Sphere. *Sociol. Res. Online* **2016**, *21*, 83–94. [CrossRef]
8. Barker, S.B.; Barker, R.T. The human-canine bond: Closer than family ties? *J. Ment. Health Couns.* **1988**, *10*, 46–56.
9. Ratschen, E.; Shoesmith, E.; Shahab, L.; Silva, K.; Kale, D.; Toner, P.; Reeve, C.; Mills, D.S. Human-animal relationships and interactions during the COVID-19 lockdown phase in the UK: Investigating links with mental health and loneliness. *PLoS ONE* **2020**, *15*, e0239397. [CrossRef]
10. Bussolari, C.; Currin-McCulloch, J.; Packman, W.; Kogan, L.; Erdman, P. "I Couldn't Have Asked for a Better Quarantine Partner!": Experiences with Companion Dogs during COVID-19. *Animals* **2021**, *11*, 330. [CrossRef]
11. Kogan, L.R.; Currin-McCulloch, J.; Bussolari, C.; Packman, W.; Erdman, P. The Psychosocial Influence of Companion Animals on Positive and Negative Affect during the COVID-19 Pandemic. *Animals* **2021**, *11*, 2084. [CrossRef] [PubMed]
12. Fatjó, J.; Ruiz-de-la-Torre, J.; Manteca, X. The epidemiology of behavioural problems in dogs and cats: A survey of veterinary practitioners. *Anim. Welf.* **2006**, *15*, 179–185. [CrossRef]

13. Cannas, S.; Talamonti, Z.; Mazzola, S.; Minero, M.; Picciolini, A.; Palestrini, C. Factors associated with dog behavioral problems referred to a behavior clinic. *J. Vet. Behav. Clin. Appl. Res.* **2018**, *24*, 42–47. [CrossRef]
14. Normando, S.; Di Raimondo, G.; Bellaio, E. An investigation using different data gathering methods into the prevalence of behavior problems in shelter dogs—A pilot study. *J. Vet. Behav. Clin. Appl. Res.* **2019**, *30*, 1–8. [CrossRef]
15. Eagan, B.H.; Gordon, E.; Protopopova, A. Reasons for Guardian-Relinquishment of Dogs to Shelters: Animal and Regional Predictors in British Columbia, Canada. *Front. Vet. Sci.* **2022**, *9*, 857634. [CrossRef] [PubMed]
16. Weiss, E.; Slater, M.; Garrison, L.; Drain, N.; Dolan, E.; Scarlett, J.M.; Zawistowski, S.L. Large Dog Relinquishment to Two Municipal Facilities in New York City and Washington, D.C.: Identifying Targets for Intervention. *Animals* **2014**, *4*, 409–433. [CrossRef] [PubMed]
17. Shore, E.R. Returning a recently adopted companion animal: Adopters' reasons for and reactions to the failed adoption experience. *J. Appl. Anim. Welf. Sci.* **2005**, *8*, 187–198. [CrossRef]
18. Kwan, J.Y.; Bain, M.J. Owner attachment and problem behaviors related to relinquishment and training techniques of dogs. *J. Appl. Anim. Welf. Sci.* **2013**, *16*, 168–183. [CrossRef]
19. Scarlett, J.M.; Salman, M.D.; New, J.G.; Kass, P.H. The role of veterinary practitioners in reducing dog and cat relinquishments and euthanasias. *J. Am. Vet. Med. Assoc.* **2002**, *3*, 306–311. [CrossRef]
20. Kass, P.H.; New, J.C., Jr.; Scarlett, J.M.; Salman, M.D. Understanding animal companion surplus in the United States: Relinquishment of nonadoptables to animal shelters for euthanasia. *J. Appl. Anim. Welf. Sci.* **2001**, *4*, 237–248. [CrossRef]
21. Siracusa, C.; Provoost, L.R.; Reisner, I. Dog- and owner-related risk factors for consideration of euthanasia or rehoming before a referral behavioral consultation and for euthanizing or rehoming the dog after the consultation. *J. Vet. Behav. Clin. Appl. Res.* **2017**, *22*, 46–56. [CrossRef]
22. Barcelos, A.M.; Kargas, N.; Assheton, P.; Maltby, J.; Hall, S.; Mills, D.S. Dog owner mental health is associated with dog behavioural problems, dog care and dog-facilitated social interaction: A prospective cohort study. *Sci. Rep.* **2023**, *13*, 21734. [CrossRef]
23. Barcelos, A.M.; Kargas, N.; Maltby, J.; Hall, S.; Mills, D.S. A framework for understanding how activities associated with dog ownership relate to human well-being. *Sci. Rep.* **2020**, *10*, 11363. [CrossRef] [PubMed]
24. Enders-Slegers, M.; Hediger, K. Pet ownership and human–animal interaction in an aging population: Rewards and challenges. *Anthrozoös* **2019**, *32*, 255–265. [CrossRef]
25. Kuntz, K.; Ballantyne, K.C.; Cousins, E.; Spitznagel, M.B. Assessment of caregiver burden in owners of dogs with behavioral problems and factors related to its presence. *J. Vet. Behav.* **2023**, *64–65*, 41–46. [CrossRef]
26. Shabelansky, A.; Dowling-Guyer, S. Characteristics of Excitable Dog Behavior Based on Owners' Report from a Self-Selected Study. *Animals* **2016**, *6*, 22. [CrossRef]
27. De Keuster, T.; Lamoureux, J.; Kahn, A. Epidemiology of dog bites: A Belgian experience of canine behaviour and public health concerns. *Vet. J.* **2006**, *172*, 482–487. [CrossRef] [PubMed]
28. Ishaya, N.; Habib, T.; Van Rooyen, C.; Steinberg, W.J. Profile of dog bite injuries in patients presenting at Kimberley Hospital Complex's emergency and gateway centres, 2015 to 2017. *Afr. J. Prim Health Care Fam. Med.* **2020**, *12*, a2301. [CrossRef]
29. Kaye, A.E.; Belz, J.M.; Kirschner, R.E. Pediatric dog bite injuries: A 5-year review of the experience at the Children's Hospital of Philadelphia. *Plast. Reconstr. Surg.* **2009**, *124*, 551–558. [CrossRef]
30. Wormald, D.; Lawrence, A.J.; Carter, G.; Fisher, A.D. Reduced heart rate variability in pet dogs affected by anxiety-related behaviour problems. *Physiol. Behav.* **2017**, *168*, 122–127. [CrossRef]
31. Luño, I.; Palacio, J.; García-Belenguer, S.; González-Martínez, Á.; Rosado, B. Perception of Canine Welfare Concerns among Veterinary Students, Practitioners, and Behavior Specialists in Spain. *J. Vet. Med. Educ.* **2017**, *44*, 217–222. [CrossRef] [PubMed]
32. Malkani, R.; Paramasivam, S.; Wolfensohn, S. A Multidimensional Evaluation of the Factors in the Animal Welfare Assessment Grid (AWAG) That Are Associated with, and Predictive of, Behaviour Disorders in Dogs. *Animals* **2024**, *14*, 528. [CrossRef] [PubMed]
33. Barnett, J.L.; Hemsworth, P.H. The validity of physiological and behavioural measures of animal welfare. *Appl. Anim. Behav. Sci.* **1990**, *25*, 177–187. [CrossRef]
34. Protopopova, A. Effects of sheltering on physiology, immune function, behavior, and the welfare of dogs. *Physiol. Behav.* **2016**, *159*, 95–103. [CrossRef] [PubMed]
35. Dinwoodie, I.R.; Zottola, V.; Dodman, N.H. An investigation into the effectiveness of various professionals and behavior modification programs, with or without medication, for the treatment of canine aggression. *J. Vet. Behav.* **2021**, *43*, 46–53. [CrossRef]
36. Dodman, N.H.; Smith, A.; Holmes, D. Comparison of the efficacy of remote consultations and personal consultations for the treatment of dogs which are aggressive towards their owners. *Vet. Rec.* **2005**, *156*, 168–170. [CrossRef] [PubMed]
37. Hou, K.; Wu, Z.X.; Chen, X.Y.; Wang, J.Q.; Zhang, D.; Xiao, C.; Zhu, D.; Koya, J.B.; Wei, L.; Li, J.; et al. Microbiota in health and diseases. *Sig Transduct. Target. Ther.* **2022**, *7*, 135. [CrossRef] [PubMed]
38. Honneffer, J.B.; Steiner, J.M.; Lidbury, J.A.; Suchodolski, J.S. Variation of the microbiota and metabolome along the canine gastrointestinal tract. *Metabolomics* **2017**, *13*, 26. [CrossRef]

39. Song, S.J.; Lauber, C.; Costello, E.K.; Lozupone, C.A.; Humphrey, G.; Berg-Lyons, D.; Caporaso, J.G.; Knights, D.; Clemente, J.C.; Nakielny, S.; et al. Cohabiting family members share microbiota with one another and with their dogs. *eLife* **2013**, *2*, e00458. [CrossRef]
40. Wipler, J.; Čermáková, Z.; Hanzálek, T.; Horáková, H.; Žemličková, H. Sharing bacterial microbiota between owners and their pets (dogs, cats). *Klin. Mikrobiol. Infekc. Lek.* **2017**, *23*, 48–57.
41. Berg, G.; Rybakova, D.; Fischer, D.; Cernava, T.; Vergès, M.C.; Charles, T.; Chen, X.; Cocolin, L.; Eversole, K.; Corral, G.H.; et al. Microbiome definition re-visited: Old concepts and new challenges. *Microbiome* **2020**, *8*, 103. [CrossRef]
42. Bien, J.; Palagani, V.; Bozko, P. The intestinal microbiota dysbiosis and *Clostridium difficile* infection: Is there a relationship with inflammatory bowel disease? *Therap Adv. Gastroenterol.* **2013**, *6*, 53–68. [CrossRef]
43. DeGruttola, A.K.; Low, D.; Mizoguchi, A.; Mizoguchi, E. Current Understanding of Dysbiosis in Disease in Human and Animal Models. *Inflamm. Bowel Dis.* **2016**, *22*, 1137–1150. [CrossRef] [PubMed]
44. Suchodolski, J.S.; Dowd, S.E.; Wilke, V.; Steiner, J.M.; Jergens, A.E. 16S rRNA gene pyrosequencing reveals bacterial dysbiosis in the duodenum of dogs with idiopathic inflammatory bowel disease. *PLoS ONE* **2012**, *7*, e39333. [CrossRef] [PubMed]
45. Park, H.J.; Lee, S.E.; Kim, H.B.; Isaacson, R.E.; Seo, K.W.; Song, K.H. Association of obesity with serum leptin, adiponectin, and serotonin and gut microflora in beagle dogs. *J. Vet. Intern. Med.* **2015**, *29*, 43–50. [CrossRef]
46. Isaiah, A.; Parambeth, J.C.; Steiner, J.M.; Lidbury, J.A.; Suchodolski, J.S. The fecal microbiome of dogs with exocrine pancreatic insufficiency. *Anaerobe* **2017**, *45*, 50–58. [CrossRef]
47. Li, Q.; Larouche-Lebel, É.; Loughran, K.A.; Huh, T.P.; Suchodolski, J.S.; Oyama, M.A. Metabolomics Analysis Reveals Deranged Energy Metabolism and Amino Acid Metabolic Reprogramming in Dogs with Myxomatous Mitral Valve Disease. *J. Am. Heart Assoc.* **2021**, *10*, e018923. [CrossRef]
48. Rhee, S.H.; Pothoulakis, C.; Mayer, E.A. Principles and clinical implications of the brain-gut-enteric microbiota axis. *Nat. Rev. Gastroenterol. Hepatol.* **2009**, *6*, 306–314. [CrossRef] [PubMed]
49. Bonaz, B.; Bazin, T.; Pellissier, S. The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. *Front. Neurosci.* **2018**, *12*, 49. [CrossRef]
50. Murphy, D.L.; Andrew, A.M.; Wichems, C.H.; Li, Q.; Tohda, M.; Greenberg, B. Brain serotonin neurotransmission: An overview and update with an emphasis on serotonin subsystem heterogeneity, multiple receptors, interactions with other neurotransmitter systems, and consequent implications for understanding the actions of serotonergic drugs. *J. Clin. Psychiatry* **1998**, *59* (Suppl. S15), 4–12.
51. Misiak, B.; Łoniewski, I.; Marlicz, W.; Frydecka, D.; Szulc, A.; Rudzki, L.; Samochowiec, J. The HPA axis dysregulation in severe mental illness: Can we shift the blame to gut microbiota? *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2020**, *102*, 109951. [CrossRef] [PubMed]
52. Cussotto, S.; Sandhu, K.V.; Dinan, T.G.; Cryan, J.F. The Neuroendocrinology of the Microbiota-Gut-Brain Axis: A Behavioural Perspective. *Front. Neuroendocrinol.* **2018**, *51*, 80–101. [CrossRef] [PubMed]
53. Pilla, R.; Suchodolski, J.S. The Gut Microbiome of Dogs and Cats, and the Influence of Diet. *Vet. Clin. N. Am. Small Anim. Pract.* **2021**, *51*, 605–621. [CrossRef] [PubMed]
54. MacQueen, G.; Surette, M.; Moayyedi, P. The gut microbiota and psychiatric illness. *J. Psychiatry Neurosci.* **2017**, *42*, 75–77. [CrossRef] [PubMed]
55. Jiang, H.; Ling, Z.; Zhang, Y.; Mao, H.; Ma, Z.; Yin, Y.; Wang, W.; Tang, W.; Tan, Z.; Shi, J.; et al. Altered fecal microbiota composition in patients with major depressive disorder. *Brain Behav. Immun.* **2015**, *48*, 186–194. [CrossRef] [PubMed]
56. Naseribafrouei, A.; Hestad, K.; Avershina, E.; Sekelja, M.; Linløkken, A.; Wilson, R.; Rudi, K. Correlation between the human fecal microbiota and depression. *Neurogastroenterol. Motil.* **2014**, *26*, 1155–1162. [CrossRef] [PubMed]
57. Kim, C.S.; Shin, G.E.; Cheong, Y.; Shin, J.H.; Shin, D.M.; Chun, W.Y. Experiencing social exclusion changes gut microbiota composition. *Transl. Psychiatry* **2022**, *12*, 254. [CrossRef] [PubMed]
58. Malan-Müller, S.; Valles-Colomer, M.; Palomo, T.; Leza, J.C. The gut-microbiota-brain axis in a Spanish population in the aftermath of the COVID-19 pandemic: Microbiota composition linked to anxiety, trauma, and depression profiles. *Gut Microbes* **2023**, *15*, 2162306. [CrossRef] [PubMed]
59. Yuan, X.; Chen, B.; Duan, Z.; Xia, Z.; Ding, Y.; Chen, T.; Liu, H.; Wang, B.; Yang, B.; Wang, X.; et al. Depression and anxiety in patients with active ulcerative colitis: Crosstalk of gut microbiota, metabolomics and proteomics. *Gut Microbes* **2021**, *13*, 1987779. [CrossRef]
60. Li, S.; Zhuo, M.; Huang, X.; Huang, Y.; Zhou, J.; Xiong, D.; Li, J.; Liu, Y.; Pan, Z.; Li, H.; et al. Altered gut microbiota associated with symptom severity in schizophrenia. *PeerJ* **2020**, *8*, e9574. [CrossRef]
61. Zhang, X.; Pan, L.Y.; Zhang, Z.; Zhou, Y.Y.; Jiang, H.Y.; Ruan, B. Analysis of gut mycobiota in first-episode, drug-naïve Chinese patients with schizophrenia: A pilot study. *Behav. Brain Res.* **2020**, *379*, 112374. [CrossRef]
62. Gao, F.; Guo, R.; Ma, Q.; Li, Y.; Wang, W.; Fan, Y.; Ju, Y.; Zhao, B.; Gao, Y.; Qian, L.; et al. Stressful events induce long-term gut microbiota dysbiosis and associated post-traumatic stress symptoms in healthcare workers fighting against COVID-19. *J. Affect. Disord.* **2022**, *303*, 187–195. [CrossRef] [PubMed]
63. Malan-Muller, S.; Valles-Colomer, M.; Foxx, C.L.; Vieira-Silva, S.; van den Heuvel, L.L.; Raes, J.; Seedat, S.; Lowry, C.A.; Hemmings, S.M.J. Exploring the relationship between the gut microbiome and mental health outcomes in a posttraumatic stress disorder cohort relative to trauma-exposed controls. *Eur. Neuropsychopharmacol.* **2022**, *56*, 24–38. [CrossRef]

64. Dressman, J.B. Comparison of canine and human gastrointestinal physiology. *Pharm. Res.* **1986**, *3*, 123–131. [CrossRef] [PubMed]
65. Yong, M.H.; Ruffman, T. Emotional contagion: Dogs and humans show a similar physiological response to human infant crying. *Behav. Processes.* **2014**, *108*, 155–165. [CrossRef]
66. Kujala, M.V.; Kujala, J.; Carlson, S.; Hari, R. Dog experts' brains distinguish socially relevant body postures similarly in dogs and humans. *PLoS ONE* **2012**, *7*, e39145. [CrossRef] [PubMed]
67. Coelho, L.P.; Kultima, 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]
68. Mizukami, K.; Uchiyama, J.; Igarashi, H.; Murakami, H.; Osumi, T.; Shima, A.; Ishiahra, G.; Nasukawa, T.; Une, Y.; Sakaguchi, M. Age-related analysis of the gut microbiome in a purebred dog colony. *FEMS Microbiol. Lett.* **2019**, *366*, fnz095. [CrossRef]
69. Masuoka, H.; Shimada, K.; Kiyosue-Yasuda, T.; Kiyosue, M.; Oishi, Y.; Kimura, S.; Yamada, A.; Hirayama, K. Transition of the intestinal microbiota of dogs with age. *Biosci. Microbiota Food Health* **2017**, *36*, 27–31. [CrossRef]
70. 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]
71. Mondo, E.; Barone, M.; Soverini, M.; D'Amico, F.; Cocchi, M.; Petrulli, C.; Mattioli, M.; Marliani, G.; Candela, M.; Accorsi, P.A. Gut microbiome structure and adrenocortical activity in dogs with aggressive and phobic behavioral disorders. *Heliyon* **2020**, *6*, e03311. [CrossRef] [PubMed]
72. 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] [PubMed]
73. Craddock, H.A.; Godneva, A.; Rothschild, D.; Motro, Y.; Grinstein, D.; Lotem-Michaeli, Y.; Narkiss, T.; Segal, E.; Moran-Gilad, J. Phenotypic correlates of the working dog microbiome. *NPJ Biofilms Microbiomes* **2022**, *8*, 66. [CrossRef] [PubMed]
74. Pellowe, S.D.; Zhang, A.; Bignell, A.R.D.; Peña-Castillo, L.; Walsh, C.J. Gut microbiome composition is related to anxiety and aggression score in companion dogs. *Res. Sq.* **2023**. [CrossRef]
75. Suchodolski, J.S.; Markel, M.E.; Garcia-Mazcorro, J.F.; Unterer, S.; Heilmann, R.M.; Dowd, S.E.; Kachroo, P.; Ivanov, I.; Minamoto, Y.; Dillman, E.M.; et al. The fecal microbiome in dogs with acute diarrhea and idiopathic inflammatory bowel disease. *PLoS ONE* **2012**, *7*, e51907. [CrossRef] [PubMed]
76. 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] [PubMed]
77. Berger, M.; Gray, J.A.; Roth, B.L. The expanded biology of serotonin. *Annu. Rev. Med.* **2009**, *60*, 355–366. [CrossRef] [PubMed]
78. Gershon, M.D.; Tack, J. The serotonin signaling system: From basic understanding to drug development for functional GI disorders. *Gastroenterology* **2007**, *132*, 397–414. [CrossRef]
79. Sbrini, G.; Hanswijk, S.I.; Brivio, P.; Middelman, A.; Bader, M.; Fumagalli, F.; Alenina, N.; Homberg, J.R.; Calabrese, F. Peripheral Serotonin Deficiency Affects Anxiety-like Behavior and the Molecular Response to an Acute Challenge in Rats. *Int. J. Mol. Sci.* **2022**, *23*, 4941. [CrossRef]
80. Nanthakumaran, S.; Sridharan, S.; Somagutta, M.R.; Arnold, A.A.; May, V.; Pagad, S.; Malik, B.H. The Gut-Brain Axis and Its Role in Depression. *Cureus.* **2020**, *12*, e10280. [CrossRef]
81. Sjögren, K.; Engdahl, C.; Henning, P.; Lerner, U.H.; Tremaroli, V.; Lagerquist, M.K.; Bäckhed, F.; Ohlsson, C. The gut microbiota regulates bone mass in mice. *J. Bone Miner. Res.* **2012**, *27*, 1357–1367. [CrossRef] [PubMed]
82. Ge, X.; Ding, C.; Zhao, W.; Xu, L.; Tian, H.; Gong, J.; Zhu, M.; Li, J.; Li, N. Antibiotics-induced depletion of mice microbiota induces changes in host serotonin biosynthesis and intestinal motility. *J. Transl. Med.* **2017**, *15*, 13. [CrossRef] [PubMed]
83. Keszthelyi, D.; Troost, F.J.; Jonkers, D.M.; Kruimel, J.W.; Leue, C.; Masclee, A.A. Decreased levels of kynurenic acid in the intestinal mucosa of IBS patients: Relation to serotonin and psychological state. *J. Psychosom. Res.* **2013**, *74*, 501–504. [CrossRef] [PubMed]
84. Golubeva, A.V.; Joyce, S.A.; Moloney, G.; Burokas, A.; Sherwin, E.; Arboleya, S.; Flynn, I.; Khochanskiy, D.; Moya-Pérez, A.; Peterson, V.; et al. Microbiota-related Changes in Bile Acid & Tryptophan Metabolism are Associated with Gastrointestinal Dysfunction in a Mouse Model of Autism. *eBioMedicine* **2017**, *24*, 166–178. [CrossRef] [PubMed]
85. Lim, C.K.; Essa, M.M.; de Paula Martins, R.; Lovejoy, D.B.; Bilgin, A.A.; Waly, M.I.; Al-Farsi, Y.M.; Al-Sharbati, M.; Al-Shaffae, M.A.; Guillemin, G.J. Altered kynurenine pathway metabolism in autism: Implication for immune-induced glutamatergic activity. *Autism Res.* **2016**, *9*, 621–631. [CrossRef]
86. Rosado, B.; García-Belenguer, S.; León, M.; Chacón, G.; Villegas, A.; Palacio, J. Blood concentrations of serotonin, cortisol and dehydroepiandrosterone in aggressive dogs. *Appl. Anim. Behav. Sci.* **2010**, *123*, 124–130. [CrossRef]
87. Amat, M.; Le Brech, S.; Camps, T.; Torrente, C.; Mariotti, V.M.; Ruiz, J.L.; Manteca, X. Differences in serotonin serum concentration between aggressive English cocker spaniels and aggressive dogs of other breeds. *J. Vet. Behav.* **2013**, *8*, 19–25. [CrossRef]
88. León, M.; Rosado, B.; García-Belenguer, S.; Chacón, G.; Villegas, A.; Palacio, J. Assessment of serotonin in serum, plasma, and platelets of aggressive dogs. *J. Vet. Behav.* **2012**, *7*, 348–352. [CrossRef]
89. Cannas, S.; Tonini, B.; Bela, B.; Di Prinzio, R.; Pignataro, G.; Di Simone, D.; Gramenzi, A. Effect of a novel nutraceutical supplement (Relaxigen Pet dog) on the fecal microbiome and stress-related behaviors in dogs: A pilot study. *J. Vet. Behav.* **2021**, *42*, 37–47. [CrossRef]

90. Bardo, M.T. Neuropharmacological mechanisms of drug reward: Beyond dopamine in the nucleus accumbens. *Crit. Rev. Neurobiol.* **1998**, *12*, 37–67. [CrossRef]
91. Baik, J.H. Dopamine signaling in reward-related behaviors. *Front. Neural Circuits* **2013**, *7*, 152. [CrossRef] [PubMed]
92. Beninger, R.J.; Miller, R. Dopamine D1-like receptors and reward-related incentive learning. *Neurosci. Biobehav. Rev.* **1998**, *22*, 335–345. [CrossRef] [PubMed]
93. Lewis, R.G.; Florio, E.; Punzo, D.; Borrelli, E. The Brain's Reward System in Health and Disease. *Adv. Exp. Med. Biol.* **2021**, *1344*, 57–69. [CrossRef] [PubMed]
94. Yadid, G.; Friedman, A. Dynamics of the dopaminergic system as a key component to the understanding of depression. *Prog. Brain Res.* **2008**, *172*, 265–286. [CrossRef]
95. Sittipo, P.; Choi, J.; Lee, S.; Lee, Y.K. The function of gut microbiota in immune-related neurological disorders: A review. *J. Neuroinflamm.* **2022**, *19*, 154. [CrossRef] [PubMed]
96. Eisenhofer, G.; Aneman, A.; Friberg, P.; Hooper, D.; Fåndriks, L.; Lonroth, H.; Hunyady, B.; Mezey, E. Substantial production of dopamine in the human gastrointestinal tract. *J. Clin. Endocrinol. Metab.* **1997**, *82*, 3864–3871. [CrossRef] [PubMed]
97. Asano, Y.; Hiramoto, T.; Nishino, R.; Aiba, Y.; Kimura, T.; Yoshihara, K.; Koga, Y.; Sudo, N. Critical role of gut microbiota in the production of biologically active, free catecholamines in the gut lumen of mice. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2012**, *303*, G1288–G1295. [CrossRef] [PubMed]
98. Hamamah, S.; Aghazarian, A.; Nazaryan, A.; Hajnal, A.; Covasa, M. Role of Microbiota-Gut-Brain Axis in Regulating Dopaminergic Signaling. *Biomedicines* **2022**, *10*, 436. [CrossRef]
99. Wright, H.F.; Mills, D.S.; Pollux, P.M. Behavioural and physiological correlates of impulsivity in the domestic dog (*Canis familiaris*). *Physiol. Behav.* **2012**, *105*, 676–682. [CrossRef]
100. Riva, J.; Bondiolotti, G.; Michelazzi, M.; Verga, M.; Carenzi, C. Anxiety related behavioural disorders and neurotransmitters in dogs. *Appl. Anim. Behav. Sci.* **2008**, *114*, 168–181. [CrossRef]
101. González-Martínez, Á.; Muñiz de Miguel, S.; Graña, N.; Costas, X.; Diéguez, F.J. Serotonin and Dopamine Blood Levels in ADHD-like Dogs. *Animals* **2023**, *13*, 1037. [CrossRef] [PubMed]
102. Hou, D.; Tang, J.; Feng, Q.; Niu, Z.; Shen, Q.; Wang, L.; Zhou, S. Gamma-aminobutyric acid (GABA): A comprehensive review of dietary sources, enrichment technologies, processing effects, health benefits, and its applications. *Crit. Rev. Food Sci. Nutr.* **2023**, 1–23. [CrossRef] [PubMed]
103. Li, H.; Heise, K.F.; Chalavi, S.; Puts, N.A.J.; Edden, R.A.E.; Swinnen, S.P. The role of MRS-assessed GABA in human behavioral performance. *Prog. Neurobiol.* **2022**, *212*, 102247. [CrossRef] [PubMed]
104. Hepsomali, P.; Groeger, J.A.; Nishihira, J.; Scholey, A. Effects of Oral Gamma-Aminobutyric Acid (GABA) Administration on Stress and Sleep in Humans: A Systematic Review. *Front. Neurosci.* **2020**, *14*, 923. [CrossRef] [PubMed]
105. Jie, F.; Yin, G.; Yang, W.; Yang, M.; Gao, S.; Lv, J.; Li, B. Stress in Regulation of GABA Amygdala System and Relevance to Neuropsychiatric Diseases. *Front. Neurosci.* **2018**, *12*, 562. [CrossRef] [PubMed]
106. Hasler, G.; van der Veen, J.W.; Tumonis, T.; Meyers, N.; Shen, J.; Drevets, W.C. Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Arch. Gen. Psychiatry* **2007**, *64*, 193–200. [CrossRef] [PubMed]
107. Goddard, A.W.; Narayan, M.; Woods, S.W.; Germine, M.; Kramer, G.L.; Davis, L.L.; Petty, F. Plasma levels of gamma-aminobutyric acid and panic disorder. *Psychiatry Res.* **1996**, *63*, 223–225. [CrossRef] [PubMed]
108. Dolfen, N.; Veldman, M.P.; Gann, M.A.; von Leupoldt, A.; Puts, N.A.J.; Edden, R.A.E.; Mikkelsen, M.; Swinnen, S.; Schwabe, L.; Albouy, G.; et al. A role for GABA in the modulation of striatal and hippocampal systems under stress. *Commun. Biol.* **2021**, *4*, 1033. [CrossRef] [PubMed]
109. Strandwitz, P. Neurotransmitter modulation by the gut microbiota. *Brain Res.* **2018**, *1693*, 128–133. [CrossRef]
110. Xie, M.; Chen, H.H.; Nie, S.P.; Yin, J.Y.; Xie, M.Y. Gamma-Aminobutyric Acid Increases the Production of Short-Chain Fatty Acids and Decreases pH Values in Mouse Colon. *Molecules* **2017**, *22*, 653. [CrossRef]
111. Park, K.B.; Oh, S.H. Production of yogurt with enhanced levels of gamma-aminobutyric acid and valuable nutrients using lactic acid bacteria and germinated soybean extract. *Bioresour. Technol.* **2007**, *98*, 1675–1679. [CrossRef] [PubMed]
112. Boonstra, E.; de Kleijn, R.; Colzato, L.S.; Alkemade, A.; Forstmann, B.U.; Nieuwenhuis, S. Neurotransmitters as food supplements: The effects of GABA on brain and behavior. *Front. Psychol.* **2015**, *6*, 1520. [CrossRef]
113. Barrett, E.; Ross, R.P.; O'Toole, P.W.; Fitzgerald, G.F.; Stanton, C. γ-Aminobutyric acid production by culturable bacteria from the human intestine. *J. Appl. Microbiol.* **2012**, *113*, 411–417. [CrossRef] [PubMed]
114. Inagawa, K.; Seki, S.; Bannai, M.; Takeuchi, Y.; Mori, Y.; Takahashi, M. Alleviative effects of gamma-aminobutyric acid (GABA) on behavioral abnormalities in aged dogs. *J. Vet. Med. Sci.* **2005**, *67*, 1063–1066. [CrossRef] [PubMed]
115. Uetake, K.; Okumoto, A.; Tani, N.; Goto, A.; Tanaka, T. Calming effect of orally administered γ-aminobutyric acid in Shih Tzu dogs. *Anim. Sci. J.* **2012**, *83*, 796–798. [CrossRef] [PubMed]
116. 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] [PubMed]
117. Nicholson, J.K.; Holmes, E.; Kinross, J.; Burcelin, R.; Gibson, G.; Jia, W.; Pettersson, S. Host-gut microbiota metabolic interactions. *Science* **2012**, *336*, 1262–1267. [CrossRef] [PubMed]

118. Wang, M.; Wichienchot, S.; He, X.; Fu, X.; Huang, Q.; Zhang, B. In vitro colonic fermentation of dietary fibers: Fermentation rate, short-chain fatty acid production and changes in microbiota. *Trends Food Sci. Technol.* **2019**, *88*, 1–9. [CrossRef]
119. Pascale, A.; Marchesi, N.; Marelli, C.; Coppola, A.; Luzi, L.; Govoni, S.; Giustina, A.; Gazzaruso, C. Microbiota and metabolic diseases. *Endocrine* **2018**, *61*, 357–371. [CrossRef]
120. Xiong, R.G.; Zhou, D.D.; Wu, S.X.; Huang, S.Y.; Saimaiti, A.; Yang, Z.J.; Shang, A.; Zhao, C.N.; Gan, R.Y.; Li, H.B. Health Benefits and Side Effects of Short-Chain Fatty Acids. *Foods* **2022**, *11*, 2863. [CrossRef]
121. Kim, C.H. Complex regulatory effects of gut microbial short-chain fatty acids on immune tolerance and autoimmunity. *Cell. Mol. Immunol.* **2023**, *20*, 341–350. [CrossRef] [PubMed]
122. Guard, B.C.; Barr, J.W.; Reddivari, L.; Klemashevich, C.; Jayaraman, A.; Steiner, J.M.; Vanamala, J.; Suchodolski, J.S. Characterization of microbial dysbiosis and metabolomic changes in dogs with acute diarrhea. *PLoS ONE* **2015**, *10*, e0127259. [CrossRef] [PubMed]
123. Minamoto, Y.; Minamoto, T.; Isaiah, A.; Sattasathuchana, P.; Buono, A.; Rangachari, V.R.; McNeely, I.H.; Lidbury, J.; Steiner, J.M.; Suchodolski, J.S. Fecal short-chain fatty acid concentrations and dysbiosis in dogs with chronic enteropathy. *J. Vet. Intern. Med.* **2019**, *33*, 1608–1618. [CrossRef]
124. Parada Venegas, D.; De la Fuente, M.K.; Landskron, G.; González, M.J.; Quera, R.; Dijkstra, G.; Harmsen, H.J.M.; Faber, K.N.; Hermoso, M.A. Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. *Front Immunol.* **2019**, *10*, 277. [CrossRef]
125. Dinan, T.G.; Cryan, J.F. The microbiome-gut-brain axis in health and disease. *Gastroenterol. Clin. N. Am.* **2017**, *46*, 77–89. [CrossRef]
126. Fock, E.; Parnova, R. Mechanisms of Blood-Brain Barrier Protection by Microbiota-Derived Short-Chain Fatty Acids. *Cells* **2023**, *12*, 657. [CrossRef]
127. Rusch, J.A.; Layden, B.T.; Dugas, L.R. Signalling cognition: The gut microbiota and hypothalamic-pituitary-adrenal axis. *Front. Endocrinol.* **2023**, *14*, 1130689. [CrossRef]
128. Unger, M.M.; Spiegel, J.; Dillmann, K.U.; Grundmann, D.; Philippeit, H.; Bürmann, J.; Faßbender, K.; Schwiertz, A.; Schäfer, K.H. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. *Park. Relat. Disord.* **2016**, *32*, 66–72. [CrossRef]
129. Chen, H.; Meng, L.; Shen, L. Multiple roles of short-chain fatty acids in Alzheimer disease. *Nutrition* **2022**, *93*, 111499. [CrossRef] [PubMed]
130. Liu, S.; Li, E.; Sun, Z.; Fu, D.; Duan, G.; Jiang, M.; Yu, Y.; Mei, L.; Yang, P.; Tang, Y.; et al. Altered gut microbiota and short chain fatty acids in Chinese children with autism spectrum disorder. *Sci. Rep.* **2019**, *9*, 287. [CrossRef] [PubMed]
131. Maltz, R.M.; Keirsey, J.; Kim, S.C.; Mackos, A.R.; Gharaibeh, R.Z.; Moore, C.C.; Xu, J.; Somogyi, A.; Bailey, M.T. Social Stress Affects Colonic Inflammation, the Gut Microbiome, and Short-chain Fatty Acid Levels and Receptors. *J. Pediatr. Gastroenterol. Nutr.* **2019**, *68*, 533–540. [CrossRef] [PubMed]
132. Skonieczna-Żydecka, K.; Grochans, E.; Maciejewska, D.; Szkup, M.; Schneider-Matyka, D.; Jurczak, A.; Łoniewski, I.; Kaczmarczyk, M.; Marlicz, W.; Czerwińska-Rogowska, M.; et al. Faecal Short Chain Fatty Acids Profile is Changed in Polish Depressive Women. *Nutrients* **2018**, *10*, 1939. [CrossRef] [PubMed]
133. Deng, F.L.; Pan, J.X.; Zheng, P.; Xia, J.J.; Yin, B.M.; Liang, W.W.; Li, Y.F.; Wu, J.; Xu, F.; Wu, Q.Y.; et al. Metabonomics reveals peripheral and central short-chain fatty acid and amino acid dysfunction in a naturally occurring depressive model of macaques. *Neuropsychiatr. Dis. Treat.* **2019**, *15*, 1077–1088. [CrossRef] [PubMed]
134. Wu, J.T.; Sun, C.L.; Lai, T.T.; Liou, C.W.; Lin, Y.Y.; Xue, J.Y.; Wang, H.W.; Chai, L.M.X.; Lee, Y.J.; Chen, S.L.; et al. Oral short-chain fatty acids administration regulates innate anxiety in adult microbiome-depleted mice. *Neuropharmacology* **2022**, *214*, 109140. [CrossRef] [PubMed]
135. Tizard, I.R.; Jones, S.W. The Microbiota Regulates Immunity and Immunologic Diseases in Dogs and Cats. *Vet. Clin. N. Am. Small Anim. Pract.* **2018**, *48*, 307–322. [CrossRef] [PubMed]
136. Feng, Q.; Chen, W.D.; Wang, Y.D. Gut microbiota: An integral moderator in health and disease. *Front. Microbiol.* **2018**, *9*, 151. [CrossRef] [PubMed]
137. Hakansson, A.; Molin, G. Gut microbiota and inflammation. *Nutrients* **2011**, *3*, 637–682. [CrossRef]
138. Al Bander, Z.; Nitert, M.D.; Mousa, A.; Naderpoor, N. The Gut Microbiota and Inflammation: An Overview. *Int. J. Environ. Res. Public Health* **2020**, *17*, 7618. [CrossRef]
139. Giaretta, P.R.; Rech, R.R.; Guard, B.C.; Blake, A.B.; Blick, A.K.; Steiner, J.M.; Lidbury, J.A.; Cook, A.K.; Hanifeh, M.; Spillmann, T.; et al. Comparison of intestinal expression of the apical sodium-dependent bile acid transporter between dogs with and without chronic inflammatory enteropathy. *J. Vet. Intern. Med.* **2018**, *32*, 1918–1926. [CrossRef]
140. Guard, B.C.; Honneffer, J.B.; Jergens, A.E.; Jonika, M.M.; Toresson, L.; Lawrence, Y.A.; Webb, C.B.; Hill, S.; Lidbury, J.A.; Steiner, J.M.; et al. Longitudinal assessment of microbial dysbiosis, fecal unconjugated bile acid concentrations, and disease activity in dogs with steroid-responsive chronic inflammatory enteropathy. *J. Vet. Intern. Med.* **2019**, *33*, 1295–1305. [CrossRef]
141. Minamoto, Y.; Otoni, C.C.; Steelman, S.M.; Büyükleblebici, O.; Steiner, J.M.; Jergens, A.E.; Suchodolski, J.S. Alteration of the fecal microbiota and serum metabolite profiles in dogs with idiopathic inflammatory bowel disease. *Gut Microbes* **2015**, *6*, 33–47. [CrossRef]
142. Blake, A.B.; Guard, B.C.; Honneffer, J.B.; Lidbury, J.A.; Steiner, J.M.; Suchodolski, J.S. Altered microbiota, fecal lactate, and fecal bile acids in dogs with gastrointestinal disease. *PLoS ONE* **2019**, *14*, e0224454. [CrossRef]

143. Li, Q. Metabolic Reprogramming, Gut Dysbiosis, and Nutrition Intervention in Canine Heart Disease. *Front. Vet. Sci.* **2022**, *9*, 791754. [CrossRef] [PubMed]
144. Seo, J.; Matthewman, L.; Xia, D.; Wilshaw, J.; Chang, Y.M.; Connolly, D.J. The gut microbiome in dogs with congestive heart failure: A pilot study. *Sci. Rep.* **2020**, *10*, 13777. [CrossRef]
145. Cintio, M.; Scarsella, E.; Sgorlon, S.; Sandri, M.; Stefanon, B. Gut Microbiome of Healthy and Arthritic Dogs. *Vet. Sci.* **2020**, *7*, 92. [CrossRef] [PubMed]
146. Muscatello, M.R.; Bruno, A.; Scimeca, G.; Pandolfo, G.; Zoccali, R.A. Role of negative affects in pathophysiology and clinical expression of irritable bowel syndrome. *World J. Gastroenterol.* **2014**, *20*, 7570–7586. [CrossRef]
147. Gądek-Michalska, A.; Tadeusz, J.; Rachwalska, P.; Bugajski, J. Cytokines, prostaglandins and nitric oxide in the regulation of stress-response systems. *Pharmacol. Rep.* **2013**, *65*, 1655–1662. [CrossRef] [PubMed]
148. Berk, M.; Williams, L.J.; Jacka, F.N.; O'Neil, A.; Pasco, J.A.; Moylan, S.; Allen, N.B.; Stuart, A.L.; Hayley, A.C.; Byrne, M.L.; et al. So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med.* **2013**, *11*, 200. [CrossRef]
149. O'Mahony, L.; McCarthy, J.; Kelly, P.; Hurley, G.; Luo, F.; Chen, K.; O'Sullivan, G.C.; Kiely, B.; Collins, J.K.; Shanahan, F.; et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: Symptom responses and relationship to cytokine profiles. *Gastroenterology* **2005**, *128*, 541–551. [CrossRef]
150. D'Mello, C.; Ronaghan, N.; Zaheer, R.; Dicay, M.; Le, T.; MacNaughton, W.K.; Surrette, M.G.; Swain, M.G. Probiotics Improve Inflammation-Associated Sickness Behavior by Altering Communication between the Peripheral Immune System and the Brain. *J. Neurosci.* **2015**, *35*, 10821–10830. [CrossRef]
151. Han, S.K.; Kim, D.H. Lactobacillus mucosae and Bifidobacterium longum Synergistically Alleviate Immobilization Stress-Induced Anxiety/Depression in Mice by Suppressing Gut Dysbiosis. *J. Microbiol. Biotechnol.* **2019**, *29*, 1369–1374. [CrossRef] [PubMed]
152. Sechi, S.; Di Cerbo, A.; Canello, S.; Guidetti, G.; Chiavolelli, F.; Fiore, F.; Cocco, R. Effects in dogs with behavioural disorders of a commercial nutraceutical diet on stress and neuroendocrine parameters. *Vet. Rec.* **2017**, *180*, 18. [CrossRef] [PubMed]
153. Di Cerbo, A.; Centenaro, S.; Beribè, F.; Laus, F.; Cerquetella, M.; Spaterna, A.; Guidetti, G.; Canello, S.; Terrazzano, G. Clinical evaluation of an antiinflammatory and antioxidant diet effect in 30 dogs affected by chronic otitis externa: Preliminary results. *Vet. Res. Commun.* **2016**, *40*, 29–38. [CrossRef] [PubMed]
154. Lee, H.Y.; Park, Y.M.; Hwang, H.M.; Shin, D.Y.; Jeong, H.N.; Kim, J.G.; Park, H.Y.; Kim, D.S.; Yoo, J.J.; Kim, M.S.; et al. The Effect of the Mixed Extract of *Kalopanax pictus* Nakai and *Achyranthes japonica* Nakai on the Improvement of Degenerative Osteoarthritis through Inflammation Inhibition in the Monosodium Iodoacetate-Induced Mouse Model. *Curr. Issues Mol. Biol.* **2023**, *45*, 6395–6414. [CrossRef] [PubMed]
155. Re, S.; Zanoletti, M.; Emanuele, E. Association of inflammatory markers elevation with aggressive behavior in domestic dogs. *J. Ethol.* **2009**, *27*, 31–33. [CrossRef]
156. Merchenthaler, I. Corticotropin releasing factor (CRF)-like immunoreactivity in the rat central nervous system. Extrahypothalamic distribution. *Peptides* **1984**, *5* (Suppl. S1), 53–69. [CrossRef] [PubMed]
157. Packard, A.E.; Egan, A.E.; Ulrich-Lai, Y.M. HPA Axis Interactions with Behavioral Systems. *Compr. Physiol.* **2016**, *6*, 1897–1934. [CrossRef] [PubMed]
158. Walker, S.E.; Papilloud, A.; Huzard, D.; Sandi, C. The link between aberrant hypothalamic-pituitary-adrenal axis activity during development and the emergence of aggression-Animal studies. *Neurosci. Biobehav. Rev.* **2018**, *91*, 138–152. [CrossRef]
159. Herman, J.P.; McKlveen, J.M.; Ghosal, S.; Kopp, B.; Wulsin, A.; Makinson, R.; Scheimann, J.; Myers, B. Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. *Compr. Physiol.* **2016**, *6*, 603–621. [CrossRef]
160. Smith, S.M.; Vale, W.W. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues Clin. Neurosci.* **2006**, *8*, 383–395. [CrossRef]
161. Mikulska, J.; Juszczyk, G.; Gawrońska-Grzywacz, M.; Herbet, M. HPA Axis in the Pathomechanism of Depression and Schizophrenia: New Therapeutic Strategies Based on Its Participation. *Brain Sci.* **2021**, *11*, 1298. [CrossRef] [PubMed]
162. Cubała, W.J.; Landowski, J. Serotoninergic system and limbic-hypothalamic-pituitary-adrenal axis (LHPA axis) in depression. *Psychiatr. Pol.* **2006**, *40*, 415–430. [PubMed]
163. Du, X.; Pang, T.Y. Is Dysregulation of the HPA-Axis a Core Pathophysiology Mediating Co-Morbid Depression in Neurodegenerative Diseases? *Front. Psychiatry* **2015**, *6*, 32. [CrossRef] [PubMed]
164. Banks, W.A. Blood-brain barrier transport of cytokines: A mechanism for neuropathology. *Curr. Pharm. Des.* **2005**, *11*, 973–984. [CrossRef] [PubMed]
165. Luo, Y.; Zeng, B.; Zeng, L.; Du, X.; Li, B.; Huo, R.; Liu, L.; Wang, H.; Dong, M.; Pan, J.; et al. Gut microbiota regulates mouse behaviors through glucocorticoid receptor pathway genes in the hippocampus. *Transl. Psychiatry* **2018**, *8*, 187. [CrossRef] [PubMed]
166. Sudo, N.; Chida, Y.; Aiba, Y.; Sonoda, J.; Oyama, N.; Yu, X.N.; Kubo, C.; Koga, Y. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J. Physiol.* **2004**, *558*, 263–275. [CrossRef]
167. Markovszky, A.K.; Weber, C.; Biksi, O.; Danes, M.; Dumitrescu, E.; Muselin, F.; Tufarelli, V.; Puvača, N.; Cristina, R.T. Is ECLIA Serum Cortisol Concentration Measurement, an Accurate Indicator of Pain Severity in Dogs with Locomotor Pain? *Animals* **2020**, *10*, 2036. [CrossRef]
168. d'Angelo, D.; d'Ingeo, S.; Ciani, F.; Visone, M.; Sacchettino, L.; Avallone, L.; Quaranta, A. Cortisol Levels of Shelter Dogs in Animal Assisted Interventions in a Prison: An Exploratory Study. *Animals* **2021**, *11*, 345. [CrossRef] [PubMed]

169. Lensen, R.C.M.M.; Moons, C.P.H.; Diederich, C. Physiological stress reactivity and recovery related to behavioral traits in dogs (*Canis familiaris*). *PLoS ONE* **2019**, *14*, e0222581. [CrossRef]
170. Chudzik, A.; Orzyłowska, A.; Rola, R.; Stanisz, G.J. Probiotics, prebiotics and postbiotics on mitigation of depression symptoms: Modulation of the brain-gut-microbiome axis. *Biomolecules* **2021**, *11*, 1000. [CrossRef]
171. Nigam, M.; Panwar, A.S.; Singh, R.K. Orchestrating the fecal microbiota transplantation: Current technological advancements and potential biomedical application. *Front. Med. Technol.* **2022**, *4*, 961569. [CrossRef] [PubMed]
172. Settanni, C.R.; Ianiro, G.; Bibbò, S.; Cammarota, G.; Gasbarrini, A. Gut microbiota alteration and modulation in psychiatric disorders: Current evidence on fecal microbiota transplantation. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2021**, *109*, 110258. [CrossRef]
173. Borody, T.J.; Paramsothy, S.; Agrawal, G. Fecal microbiota transplantation: Indications, methods, evidence, and future directions. *Curr. Gastroenterol. Rep.* **2013**, *15*, 337. [CrossRef] [PubMed]
174. 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 neurobehavioural changes in the rat. *J. Psychiatr. Res.* **2016**, *82*, 109–118. [CrossRef] [PubMed]
175. Zheng, P.; Zeng, B.; Zhou, C.; Liu, M.; Fang, Z.; Xu, X.; Zeng, L.; Chen, J.; Fan, S.; Du, X.; et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. *Mol. Psychiatry* **2016**, *21*, 786–796. [CrossRef] [PubMed]
176. Knudsen, J.K.; Michaelsen, T.Y.; Bundgaard-Nielsen, C.; Nielsen, R.E.; Hjerrild, S.; Leutscher, P.; Wegener, G.; Sørensen, S. Faecal microbiota transplantation from patients with depression or healthy individuals into rats modulates mood-related behaviour. *Sci. Rep.* **2021**, *11*, 21869. [CrossRef] [PubMed]
177. Rao, J.; Xie, R.; Lin, L.; Jiang, J.; Du, L.; Zeng, X.; Li, G.; Wang, C.; Qiao, Y. Fecal microbiota transplantation ameliorates gut microbiota imbalance and intestinal barrier damage in rats with stress-induced depressive-like behavior. *Eur. J. Neurosci.* **2021**, *53*, 3598–3611. [CrossRef] [PubMed]
178. Doll, J.P.K.; Vázquez-Castellanos, J.F.; Schaub, A.C.; Schweinfurth, N.; Kettelhack, C.; Schneider, E.; Yamanbaeva, G.; Mählmann, L.; Brand, S.; Beglinger, C.; et al. Fecal Microbiota Transplantation (FMT) as an Adjunctive Therapy for Depression-Case Report. *Front. Psychiatry* **2022**, *13*, 815422. [CrossRef] [PubMed]
179. Lin, H.; Guo, Q.; Wen, Z.; Tan, S.; Chen, J.; Lin, L.; Chen, P.; He, J.; Wen, J.; Chen, Y. The multiple effects of fecal microbiota transplantation on diarrhea-predominant irritable bowel syndrome (IBS-D) patients with anxiety and depression behaviors. *Microb. Cell Factories* **2021**, *20*, 233. [CrossRef]
180. Kurokawa, S.; Kishimoto, T.; Mizuno, S.; Masaoka, T.; Naganuma, M.; Liang, K.C.; Kitazawa, M.; Nakashima, M.; Shindo, C.; Suda, W.; et al. The effect of fecal microbiota transplantation on psychiatric symptoms among patients with irritable bowel syndrome, functional diarrhea and functional constipation: An open-label observational study. *J. Affect. Disord.* **2018**, *235*, 506–512. [CrossRef]
181. Gal, A.; Barko, P.C.; Biggs, P.J.; Gedye, K.R.; Midwinter, A.C.; Williams, D.A.; Burchell, R.K.; Pazzi, P. One dog's waste is another dog's wealth: A pilot study of fecal microbiota transplantation in dogs with acute hemorrhagic diarrhea syndrome. *PLoS ONE* **2021**, *16*, e0250344. [CrossRef] [PubMed]
182. Chaitman, J.; Ziese, A.L.; Pilla, R.; Minamoto, Y.; Blake, A.B.; Guard, B.C.; Isaiah, A.; Lidbury, J.A.; Steiner, J.M.; Unterer, S.; et al. Fecal Microbial and Metabolic Profiles in Dogs with Acute Diarrhea Receiving Either Fecal Microbiota Transplantation or Oral Metronidazole. *Front. Vet. Sci.* **2020**, *7*, 192. [CrossRef] [PubMed]
183. Bottero, E.; Benvenuti, E.; Ruggiero, P. Faecal Microbiota Transplantation in 16 Dogs with Idiopathic Inflammatory Bowel Disease. *Veterinaria* **2017**, *31*, 31–45.
184. Niina, A.; Kibe, R.; Suzuki, R.; Yuchi, Y.; Teshima, T.; Matsumoto, H.; Kataoka, Y.; Koyama, H. Fecal microbiota transplantation as a new treatment for canine inflammatory bowel disease. *Biosci. Microbiota Food Health* **2021**, *40*, 98–104. [CrossRef] [PubMed]
185. Toresson, L.; Spillmann, T.; Pilla, R.; Ludvigsson, U.; Hellgren, J.; Olmedal, G.; Suchodolski, J.S. Clinical Effects of Faecal Microbiota Transplantation as Adjunctive Therapy in Dogs with Chronic Enteropathies—A Retrospective Case Series of 41 Dogs. *Vet. Sci.* **2023**, *10*, 271. [CrossRef]
186. Sugita, K.; Shima, A.; Takahashi, K.; Ishihara, G.; Kawano, K.; Ohmori, K. Pilot evaluation of a single oral fecal microbiota transplantation for canine atopic dermatitis. *Sci. Rep.* **2023**, *13*, 8824. [CrossRef]