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The Impact of Probiotic Intervention during Developmental Cafeteria Diet Consumption on Social Behavior in Adulthood

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ABSTRACT

This study examines the ramifications of consuming a cafeteria diet during developmental stages and subsequent probiotic therapy on social behavior in adult male Wistar rats. The investigation involves four experimental groups: a control group, a probiotics-only group, a cafeteria diet group, and a cafeteria diet with probiotics supplementation group. From day 21 (weaning) today 56 (the end of the developmental period), the treatments were administered. Social behavior was assessed using a three-chambered apparatus to evaluate the time spent interacting with unfamiliar rats. The results displayed that consuming a cafeteria diet during development significantly altered social behaviors, as demonstrated by decreased interaction times with unfamiliar animals, which suggests increased anxiety or diminished sociability. Conversely, the probiotics-supplemented group, which consumed the cafeteria diet, displayed social behaviors that were more comparable to the cafeteria diet group. These findings indicate that a poor diet during critical growth periods can have detrimental effects on social interaction and suggest that probiotic supplementation may be able to mitigate these negative consequences. The study emphasizes the importance of early dietary interventions and gut microbiota modulation in maintaining social health and reducing the long-term consequences of an unhealthy diet.

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1. INTRODUCTION

A diet rich in processed and calorie-dense foods, often referred to as a cafeteria diet, serves as an established model for investigating the various health impacts that arise from dietary habits [1]. The developmental phases of life are especially susceptible to the influences of such dietary patterns, which can result in profound and lasting health ramifications over time [2]. These dietary habits negatively impact vital organs, including the liver, which plays a crucial role in metabolic processes and detoxification [3]. In Wistar rats, the administration of cafeteria diets during developmental stages rapidly induces obesity, with the effects being more pronounced than those observed with high-fat diets alone. The persistent consumption of foods that are high in calories disrupts the body's energy homeostasis, resulting in significant weight gain and an increase in various metabolic markers, which highlight the potential health hazards associated with such dietary practices [4]. One notable consequence of the cafeteria diet is the marked elevation in leptin levels, which indicates the early stages of leptin resistance, a condition that hampers the body's ability to regulate appetite and energy expenditure effectively. Furthermore, this diet leads to adverse alterations in lipid profiles, including increased cholesterol levels, which are indicative of potential cardiovascular risks. Although the cafeteria diet is designed to replicate the palatability and variety of a typical Western diet, it faces criticism due to the lack of consistency and standardization in its food components, which can lead to variability in experimental outcomes and complicate the interpretation of results [4]. Moreover, the persistent consumption of a cafeteria diet poses significant long-term risks to liver health, potentially predisposing individuals to the development of metabolic diseases in later stages of life [5]. Investigating these connections yields vital insights into the intricate relationships between diet, metabolism, and health outcomes. This research is instrumental in pinpointing therapeutic targets and developing strategies to counteract the detrimental effects of a cafeteria diet on liver function and overall metabolic homeostasis [6]. Additionally, diets rich in processed and high-energy foods can lead to significant disruptions in gut microbiota composition, exacerbate inflammatory responses, and contribute to liver damage. These adverse effects further underscore the potential health risks associated with prolonged consumption of a cafeteria diet [7].

The gut microbiome is essential for digestion and various metabolic functions, exerting a profound influence on the liver and other vital organs. Its role is pivotal in maintaining overall health and metabolic balance [8–11]. The gut microbiome is implicated in the pathogenesis of numerous liver diseases, including oxidative liver injury, chronic hepatitis B, hepatic steatosis, non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma. These associations highlight the critical role of gut microbiota in liver health and disease [12]. Probiotics, which consist of beneficial microorganisms, can significantly ameliorate these liver conditions by modulating the gut microbiota, reducing systemic inflammation, and enhancing the integrity of the gut barrier. Through these mechanisms, probiotics positively influence liver health and contribute to overall metabolic stability [13, 14]. Administering probiotics during developmental stages has the potential to counteract the detrimental effects of a cafeteria diet on liver and metabolic health. These beneficial microorganisms work by modulating the gut microbiota, reducing inflammation, and enhancing gut barrier function, which collectively contribute to improved liver health and metabolic stability. Given the promising benefits of probiotics, future animal studies are of paramount importance. Such research will be essential for identifying potential therapeutic targets and interventions to mitigate the adverse impacts associated with a cafeteria diet. Through these investigations, valuable insights can be gained into the development of effective strategies for preserving liver and metabolic health. Additionally, regular use of probiotics may offer long-term health benefits by offsetting the negative consequences of diets high in processed and calorie-dense foods [15].

Based on existing research, we hypothesize that consumption of a cafeteria diet during critical developmental stages will negatively impact social behaviors in adult rats, manifesting as increased anxiety and reduced sociability. Furthermore, we propose that probiotic supplementation during these stages will mitigate these adverse effects by modulating gut microbiota, thereby promoting healthier social interactions and reducing anxiety-related behaviors. This study aims to elucidate the interplay between diet, gut health, and social behavior, offering insights into potential therapeutic strategies for addressing the behavioral consequences of poor dietary habits during development.

2. MATERIAL METHOD

2.1. Animal Studies

Male Wistar rats, 21 days old and recently weaned, were utilized as model organisms for the study. The rats were divided into four groups, each consisting of seven rats: the control group (n=7), the SCD Probiotics group (n=7), the cafeteria diet group (n=7), and the cafeteria diet with SCD Probiotics supplementation group (n=7). Treatments were administered until day 56, marking the end of the developmental period. SCD Probiotics were given orally via gavage at a dose of 3/2 mL (1 × 10^8 CFU) per day. The probiotic supplement used was Liquid Probiotic Supplement (Essential Probiotics XI - 500 ml, H.S. Code: 2206.00.7000) from SCD Probiotics, containing strains such as *Bacillus subtilis, Bifidobacterium bifidum, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus fermentum, Lactobacillus plantarum, Lactococcus lactis, Saccharomyces cerevisiae, and Streptococcus thermophiles* [16]. All animals were provided with a standard rodent diet ad libitum, with the cafeteria diet given in addition to regular feeding, as detailed in Table 1. Weekly measurements of the animals' weights, food consumption, and cafeteria diet content were recorded, ensuring comparable initial average weights across all groups. The groups receiving the cafeteria diet were given identical diet products. Social behavior tests were conducted on both control and experimental groups at the end of the developmental period. All animals were housed in accordance with standard animal care protocols in clear Plexiglas cages (7 rats per cage) under a 12-hour light/dark

cycle at a constant temperature of 21 °C. No rats died or were excluded from the study. The study was approved by the Bingöl University Animal Experiments Local Ethics Committee (meeting date: 29.06.2021, approval number: 2021/03).

2.2. Behavioral Test

2.2.1. Social behavioral test

The social behavior testing apparatus comprises three rectangular Plexiglas chambers, each separated by partitions featuring small openings for accessibility. To begin the experiment, rats were placed in the central chamber with the doors closed, allowing for a 5-minute acclimatization period. Following this initial phase, an unfamiliar rat, matched by strain and sex, was placed inside an inverted wire cup within one of the outer chambers. Conversely, the other outer chamber contained an empty wire cup. The doors to the outer chambers were then opened, granting the experimental rat the freedom to explore all three chambers for a duration of 10 minutes. Throughout this exploration period, a video camera positioned above the apparatus recorded the amount of time the experimental rat spent in each chamber. This setup enabled the assessment of the rat's social interaction tendencies and preferences based on its exploratory behavior in the presence of a novel conspecific and an empty cup.

In the third phase of the test, a second unfamiliar rat (stranger 2) was placed in the previously empty wire cup. The experimental rat was again allowed to explore all three chambers for 10 minutes. The time spent in each chamber was recorded using the same video camera setup. This test was designed to assess the social interaction preferences and novelty response of the experimental rats [17].

2.3. Statistic

To statistical evaluations and graphical representations of the results were conducted using GraphPad Prism 10.0 software (GraphPad, USA). The data analysis involved the application of an unpaired t-test and one-way ANOVA to assess the significance of differences among various groups. These groups included the control group (Cnt), the group receiving SCD Probiotics (Prb), the cafeteria diet group (Cd), and the cafeteria diet group supplemented with SCD Probiotics (CdPrb). The levels of statistical significance were set at $P \leq 0.05$, $P \leq 0.01$, and $P \leq 0.001$. The results are expressed as mean values accompanied by the standard error of the mean (SEM), providing a clear representation of the data variability and reliability. This comprehensive statistical approach ensured robust analysis and accurate interpretation of the experimental outcomes.

Table 1. The ingredients of the cafeteria diet

Energy and Food Ingredients (100)	Total (kcal)	Total fat (g)	Total Carbohydrate (g)	Protein (g)	Sugar (g)
Control Diet					
SC 7001 (Harley)	382	4	54	25	0
CAF Diet					
Crackers					
Çay Keyfi (Eti)	462	20.4	67.8	5.8	28.5
Cookies					
Hoşbeş (Eti)	493	24.5	63.9	7.6	28.5
Hanımeller (Ülker)	427	18.1	62.1	3.9	25.0
Nestlé Crunch	500	26	67	5	55
Cereals					
Nesquik mısır gevreği (Nestle)	372	4.1	76.1	7.6	30.7
Chips					
Lays Wavy (Frito-Lay)	536	36	54	7	0
Lays Klasik (Frito-Lay)	529	33	51	7.0	0
Doritos (Frito-Lay)	491	24.5	60.5	7.2	2.3

3. RESULTS

3.1. The Second Phase of the Test

3.1.1. Comparison of time spent in the empty cage between control and experimental groups

In the first phase of this test, each rat was placed in a test apparatus with three chambers: an empty cage, a cage with an unfamiliar rat, and a central chamber. The focus of the graph is on the time spent by the rats in the 'empty' cage compared to the cage with the first unfamiliar animal (Figure 1).

The control rats (Cnt), which received a standard diet, spent a certain amount of time in the empty cage, providing a baseline for comparison against the other groups. Rats supplemented with probiotics (Prb) in addition to their standard diet may show differences in the time spent in the empty cage, reflecting the potential influence of probiotics on social behavior and curiosity. Rats fed a cafeteria diet (Cd), which is high in processed and energy-dense foods, are likely to exhibit altered behavior due to the dietary impact on their development. The time spent in the empty cage for this group may indicate decreased social interaction or increased anxiety. The group received a cafeteria diet supplemented with probiotics (CdPrb). The comparison of time spent in the empty cage for this group is critical to understanding the mitigating effects of probiotics on the adverse impacts of a cafeteria diet.

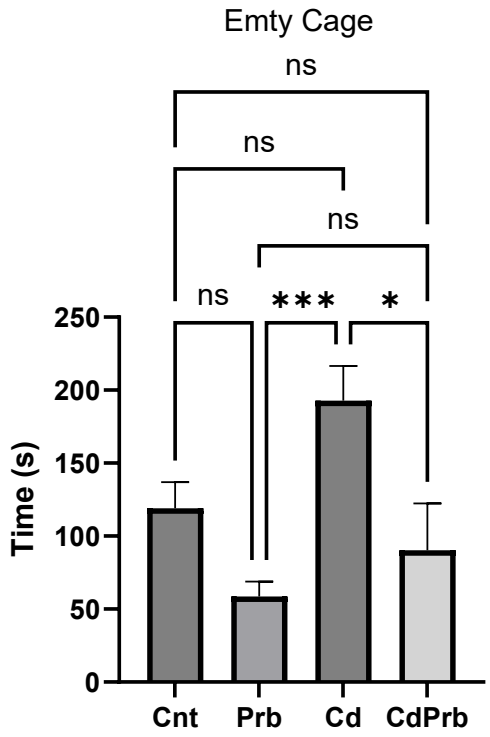

Figure 1. The impact of a cafeteria diet, SCD Probiotics supplementation, and the combined effect of SCD Probiotics during a cafeteria diet on social behavior was evaluated through a social behavioral test. Comparison of time spent in the empty cage. The data were analyzed using One-way ANOVA was conducted to analyze the data. Values were expressed as mean ± SEM, with n = 7 per group. Statistical significance was determined at $p \leq 0.05$* and $p \leq 0.001$***, with ns indicating non-significant results. The groups included were Cnt (control), Prb (SCD Probiotics), Cd (Cafeteria diet), and CdPrb (cafeteria diet with SCD Probiotics supplementation).

The graph illustrates the behavioral tendencies of the rats, specifically focusing on their preference for the empty cage over the cage with an unfamiliar rat. Significant differences between the groups would suggest that diet and probiotic supplementation during development have profound effects on social behavior in adulthood. For example, a higher time spent in the empty cage by the Cd group compared to the Cnt group might indicate reduced sociability or increased stress levels due to the cafeteria diet. Conversely, if the CdPrb group shows a similar time spent in the empty cage as the Cnt group, it could indicate that probiotics counteract the negative effects of the cafeteria diet.

3.1.2. Comparison of time spent in cage with the first unfamiliar animal between control and experimental groups

This comparison focuses on the time spent by rats in the cage containing the first unfamiliar animal, relative to the empty cage and the central chamber (**Figure 2**). The purpose of this comparison is to understand how different diets and probiotic supplementation influence social interaction behaviors. Control rats (Cnt) are expected to display baseline social interaction behaviors, spending a balanced amount of time exploring the cage with the unfamiliar animal, indicating normal curiosity and social behavior. Probiotic-supplemented rats (Prb) may exhibit increased or more balanced social interactions due to the potential positive effects of probiotics on gut health and behavior. The time spent in the cage with the unfamiliar animal will highlight these effects. Rats on a cafeteria diet (Cd) might show altered social behaviors, potentially spending less time in the cage with the unfamiliar animal due to the diet's impact on anxiety and sociability. This group provides insight into how an unhealthy diet affects social interaction. Cafeteria diet with probiotics group's (CdPrb) behavior is crucial in understanding whether probiotics can mitigate the negative effects of a cafeteria diet on social behavior. An increase in time spent in the cage with the unfamiliar animal compared to the Cd group would suggest that probiotics help maintain or restore normal social behaviors.

This comparative analysis helps in understanding how early dietary interventions, combined with probiotic supplementation, influence social behaviors and potentially mitigate negative developmental impacts caused by poor diets.

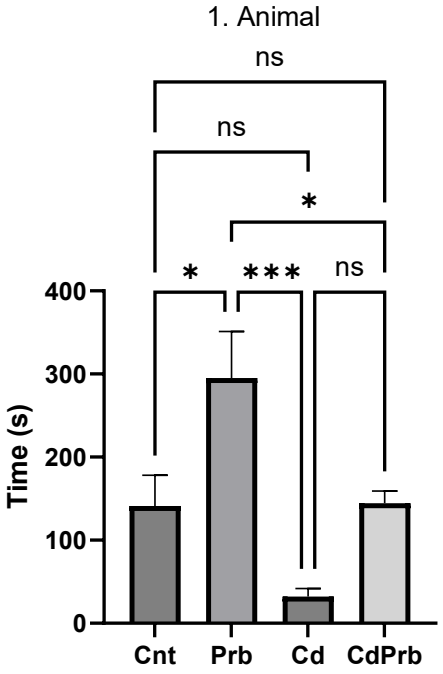

Figure 2. The impact of a cafeteria diet, SCD Probiotics supplementation, and the combined effect of SCD Probiotics during a cafeteria diet on social behavior was evaluated through a social behavioral test. Comparison of time spent in cage with the first unfamiliar animal. One-way ANOVA was conducted to analyze the data. Values were expressed as mean ± SEM, with n = 7 per group. Statistical significance was determined at $p \leq 0.05$* and $p \leq 0.001$***, with ns indicating non-significant results. The groups included were Cnt (control), Prb (SCD Probiotics), Cd (Cafeteria diet), and CdPrb (cafeteria diet with SCD Probiotics supplementation).

The comparison in the graph demonstrates the rats' social preferences and willingness to interact with an unfamiliar animal. Significant differences between groups indicate how early dietary interventions and probiotic supplementation impact social behavior in adulthood. If the Cd group spends significantly less time with the unfamiliar animal than the Cnt group, it would suggest increased anxiety or reduced sociability due to the cafeteria diet. Conversely, if the CdPrb group spends more time with the unfamiliar animal than the Cd group, it would indicate that probiotics mitigate the adverse effects of the cafeteria diet.

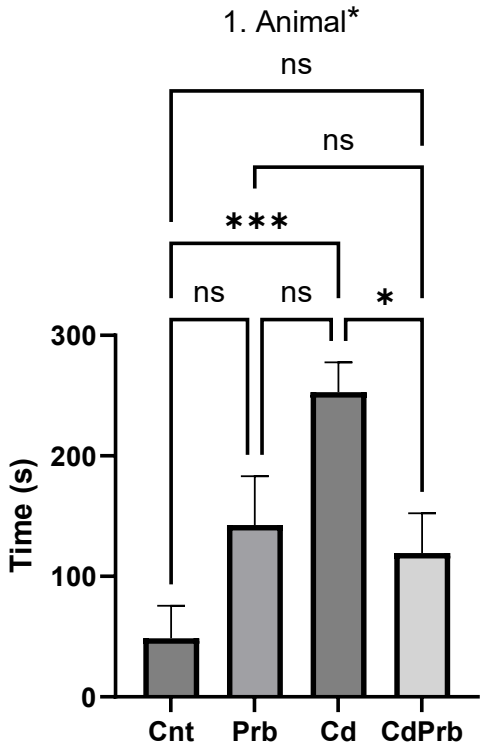

Figure 3. The impact of a cafeteria diet, SCD Probiotics supplementation, and the combined effect of SCD Probiotics during a cafeteria diet on social behavior was evaluated through a social behavioral test. Comparison of time spent in cage with the first unfamiliar animal in the third phase of the test. One-way ANOVA was conducted to analyze the data. Values were expressed as mean ± SEM, with n = 7 per group. Statistical significance was determined at $p \leq 0.05$* and $p \leq 0.001$***, with ns indicating non-significant results. The groups included were Cnt (control), Prb (SCD Probiotics), Cd (Cafeteria diet), and CdPrb (cafeteria diet with SCD Probiotics supplementation).

3.2. The Third Phase of the Test

3.2.1. Comparison of time spent in cage with the first unfamiliar animal between control and experimental groups

In the third phase of the test, the time spent by the rats in the cages containing either the first unfamiliar animal (introduced in the initial phase) or a new, second unfamiliar animal is measured (**Figure 3**). This comparison aims to determine whether the rats prefer to spend more time with an animal they have already encountered or with a completely new animal. The control group rats' behavior serves as a baseline for normal social interaction. The time spent in the cage with the first unfamiliar animal versus the second unfamiliar animal will indicate their preference for familiarity or novelty. Rats in the probiotic group (Prb) may exhibit different social preferences due to the influence of probiotics on gut health and behavior. Comparing their time spent with the first unfamiliar animal to the second can highlight the effects of probiotics on social memory and preference. The cafeteria diet group (Cd) is expected to show altered social behavior due to the diet's impact on their development. The preference for the first unfamiliar animal versus the second can provide insights into how an unhealthy diet affects social interaction and memory. Cafeteria diet with probiotics group (CdPrb) is crucial in understanding whether probiotics can mitigate the negative effects of a cafeteria diet on social behavior. If these rats spend more time with the first unfamiliar animal compared to the second, similar to the control group, it would suggest a positive impact of probiotics.

The graph illustrates the time each group of rats spends in the cage with the first unfamiliar animal during the second phase of the test. Significant differences between groups can indicate the impact of diet and probiotic supplementation on social preferences. For example, if the Cd group spends less time with the first unfamiliar animal compared to the Cnt group, it suggests a reduced preference for familiarity, potentially due to increased anxiety or impaired social memory. Conversely, if the CdPrb group shows a similar pattern to the Cnt group, it suggests that probiotics help restore normal social behavior despite the cafeteria diet.

3.2.2. Comparison of time spent in cage with the second unfamiliar animal between control and experimental groups

In the third phase of the test, the time spent by the rats in the cage containing the second unfamiliar animal, which they encounter for the first time during this phase, is measured (Figure 4). This comparison aims to assess the rats' inclination towards novelty and their social interaction behaviors in the presence of a new animal. The control group (Cnt) rats provide a baseline for normal exploratory and social behaviors. Their time spent in the cage with the second unfamiliar animal indicates their natural tendency to interact with new conspecifics. Rats in the probiotic group (Prb) may exhibit enhanced social behaviors and curiosity due to the positive effects of probiotics on gut-brain interaction. Their time spent with the second unfamiliar animal will highlight these potential behavioral changes. The cafeteria diet group (Cd) might show decreased social interaction or increased anxiety, reflected in their time spent with the second unfamiliar animal. This comparison provides insight into the impact of an unhealthy diet on novelty preference and social behavior. Cafeteria diet with probiotics group (CdPrb) is critical for understanding whether probiotics can mitigate the negative effects of a cafeteria diet on social behavior. If these rats spend more time with the second unfamiliar animal compared to the Cd group, it suggests that probiotics help maintain or restore healthy social behaviors despite the dietary intervention.

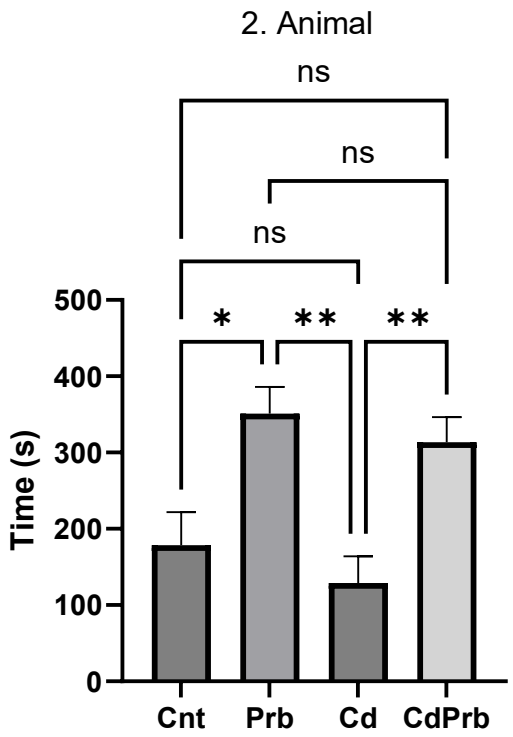

Figure 4. The impact of a cafeteria diet, SCD Probiotics supplementation, and the combined effect of SCD Probiotics during a cafeteria diet on social behavior was evaluated through a social behavioral test. Comparison of time spent in cage with the second unfamiliar animal. One-way ANOVA was conducted to analyze the data. Values were expressed as mean ± SEM, with n = 7 per group. Statistical significance was determined at $p \leq 0.05$* and $p \leq 0.001$***, with ns indicating non-significant results. The groups included were Cnt (control), Prb (SCD Probiotics), Cd (Cafeteria diet), and CdPrb (cafeteria diet with SCD Probiotics supplementation).

The graph demonstrates the time each group of rats spends in the cage with the second unfamiliar animal during the second phase of the test. Significant differences between groups can indicate the impact of diet and probiotic supplementation on novelty preference and social interaction. For example, if the Cd group spends significantly less time with the second unfamiliar animal than the Cnt group, it may suggest increased anxiety or reduced interest in social novelty due to the cafeteria diet. Conversely, if the CdPrb group shows similar behaviors to the Cnt group, it suggests that probiotics help counteract the negative effects of the cafeteria diet on social behavior.

4. DISCUSSION

The present study intended to examine the consequences of a cafeteria diet consumed during developmental stages and the subsequent impact of probiotic therapy on social behaviors in adult Wistar rats. The results indicate that a cafeteria diet, which is rich in processed and energy-dense foods, has a significant negative effect on social interactions, as evidenced by a decrease in time spent with unfamiliar rats and an increase in anxiety-related behaviors. These findings are consistent with previous research that has shown the detrimental effects of high-calorie, nutrient-poor diets on cognitive and social functions. It is worth noting that probiotic supplementation during development appears to mitigate these adverse outcomes, suggesting a protective role for probiotics in maintaining social behavior and reducing anxiety. This study emphasizes the importance of early dietary interventions and supports the potential therapeutic benefits of probiotics in counteracting the negative effects of poor dietary habits on social and behavioral health.

Our research results show that a diet consisting of cafeteria food during developmental stages has a significant negative impact on social behaviors in adult Wistar rats. However, the use of probiotic supplements can mitigate these adverse effects. The SCD Probiotics supplement, which contains strains such as *Bacillus subtilis*, *Bifidobacterium bifidum*, and various species of *Lactobacillus*, appears to play a crucial role in this improvement. This finding aligns with the growing body of literature that emphasizes the significant role of gut microbiota in shaping brain function and behavior. Probiotics are known to affect the gut-brain axis, which in turn influences behavior and cognitive functions [18]. In addition, in a recent study conducted by our team, it was demonstrated that the combined administration of SCD Probiotics and Tauroursodeoxycholic Acid (TUDCA) is more effective in alleviating anxiety-like behavior in aged rats [19]. The inclusion of *Bacillus subtilis* in our probiotic formulation is particularly noteworthy, as this bacterium has been shown to improve gut health and immune responses. *Bacillus subtilis* also produces bioactive compounds that can modulate the central nervous system, which could explain the observed improvement in social behaviors in our study [20]. Specifically, *Bacillus subtilis* can produce neurotransmitter-like substances that may directly or indirectly affect brain function, leading to enhanced social interactions and reduced anxiety.

Emerging evidence highlights the critical role of gut microbiota in modulating host behavior, particularly through the gut-brain axis, influencing cognitive functions, emotional regulation, and responses to stress [21]. *Bifidobacterium bifidum* is a vital component of the SCD Probiotics, as evidenced by previous research demonstrating its ability to reduce inflammation and improve gut barrier function, which are crucial factors for overall health and behavior [22]. *Bifidobacterium bifidum*'s anti-inflammatory properties may contribute to the observed reduction in anxiety-like behaviors in the probiotic-supplemented groups [23]. By reducing systemic inflammation, *Bifidobacterium bifidum* may also help create a more favorable environment for neurodevelopment, thereby positively impacting social behavior.

Lactobacillus species, including L. acidophilus, L. bulgaricus, L. casei, L. fermentum, and *L. plantarum*, which are present in the SCD Probiotics, have been extensively studied for their positive effects on mental health and behavior. *L. rhamnosus*, for example, has been shown to reduce anxiety and depression-related behaviors in mice, possibly through modulation of GABA receptors [24]. Although our study did not specifically include *L. rhamnosus*, the presence of related *Lactobacillus* species suggests similar mechanisms may be at

play, contributing to the enhanced social behaviors observed in the CdPrb group. The presence of multiple Lactobacillus species may create a synergistic effect, enhancing the overall efficacy of the probiotic supplementation in improving social behavior. Additionally, a recent study found that the reduction of specific Lactobacillus species, which play a key role in T cell differentiation to support the host immune system, contributes to stress-induced social-avoidance behavior [25].

The period of development is of paramount importance for the establishment of long-lasting health and behavior patterns. Our findings are consistent with those reported by Ait-Belgnaoui et al. (2012), who found that early probiotic intervention during critical periods can positively impact brain development and function [26]. More recent studies further support this, showing that probiotics can modulate the gut microbiota to reduce social avoidance behaviors induced by stress [27-28-29]. Another study found that probiotic supplementation during development improved social behavior by increasing the abundance of beneficial bacteria and promoting gut-brain communication [30]. Our study reinforces the notion that modulating the gut microbiota during this crucial phase can have lasting effects on social behavior, providing a preventive strategy against the deleterious effects of poor dietary habits. These results highlight the significance of early dietary interventions and suggest that probiotics could serve as a valuable tool in fostering healthy neurodevelopment and social behavior.

5. CONCLUSION

In conclusion, the SCD Probiotics supplement appears to mitigate the adverse effects of a cafeteria diet on social behavior in adult rats, likely due to the combined actions of its constituent bacterial strains. These findings underscore the significance of gut health in influencing behavioral outcomes and highlight the therapeutic potential of probiotics in counteracting the negative impacts of unhealthy diets during critical developmental periods. Further research is needed to elucidate the specific mechanisms involved and to investigate the potential of probiotic interventions in human populations. Gaining a deeper understanding of the precise interactions between diet, probiotics, and neurodevelopment could pave the way for new strategies in the prevention and treatment of diet-related behavioral disorders.

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