Investigating the Effects of Synbiotic Intervention on Working Memory performance in Healthy Young Women

Yeganeh Salimi[1], Behnaz Namdarzadeh[1], Fateme Dehghani-Arani[2], Abdolhossien Vahabi[3,1,4], Ehsan Rezayat[1,4*].

1- Department of Cognitive Sciences, Faculty of Psychology and Education, University of Tehran, Tehran, Iran.
2- Department of Psychology, Faculty of Psychology and Education, University of Tehran, Tehran, Iran.
3- School of Electrical and Computer Engineering, College of Engineering, University of Tehran, Tehran, Iran
4- School of Cognitive Sciences, Institute for Research in Fundamental Sciences (IPM), Niavaran, Tehran, Iran

* Correspondence: rezayat@ut.ac.ir

Abstract

The gut-brain axis (GBA) mediates communication between the gastrointestinal system and the brain, influencing cognitive functions and emotional well-being, with gut microbiota playing a crucial role. While synbiotics and probiotics have shown potential to enhance cognitive function, results remain inconsistent. This study examines the effects of synbiotic supplementation on auditory performance metrics—threshold, sensitivity, accuracy, and reaction time—using a repeated measures design with a control group. Thirty young females (ages 18-32) completed the Positive and Negative Affect Schedule (PANAS) and an auditory working memory task. Although no significant differences were found in auditory thresholds, sensitivity, or accuracy, the synbiotic group exhibited significantly faster reaction times than the control group ($p < 0.00001$), suggesting enhanced cognitive processing speed. These findings underscore the need for further research into the mechanisms through which synbiotics influence cognitive health.

Keyword: Synbiotic, working memory, gut-brain axis

Introduction

GBA is a complex communication network linking the gastrointestinal system and the brain, crucial for maintaining both mental and gut health. It regulates cognitive functions, motivation, and emotional states while also ensuring gastrointestinal homeostasis (Carabotti et al., 2015; Cryan et al., 2019; Eastwood et al., 2021). Central to this axis is the gut microbiota, a diverse community of microorganisms that influences immune development, nutrient metabolism, and the production of essential biomolecules (Cryan et al., 2019; Oriach et al., 2016; Sarkar et al., 2018).

The interactions between microbiota and the host are fundamental to their symbiotic relationship, affecting brain function and behavior through complex signaling pathways. Research has increasingly demonstrated that modulating gut microbiota significantly influences cognitive processes (Cryan et al., 2019; Eastwood et al., 2021; Morais et al., 2021). For instance, specific microbiome profiles have been linked to working memory, and disruptions in these profiles can impair cognitive function (Arnoriaga-Rodriguez et al., 2020; Cryan et al., 2019). Additionally, greater microbiota diversity has been associated with improved connectivity in brain networks related to working memory (Cai et al., 2021).

Both probiotics, which provide health benefits when consumed in adequate amounts, and prebiotics, non-viable components that support beneficial microbes, have shown promising effects on working memory in in both preclinical (Coletto et al., 2022; Griffin et al., 2023; Li et al., 2022; Ohsawa et al., 2015; Yin et al., 2024) and clinical studies (Bloemendaal et al., 2021; Önning et al., 2023; Papalini et al., 2019; Serra et al., 2019). Probiotics focus on the viability and proper dosage of beneficial microorganisms, while prebiotics aim to nurture the growth of these advantageous microbes. Since both probiotics and prebiotics target the gut, it's clear that combining them can enhance their individual benefits and potentially amplify their effects on intestinal health(Ouwehand et al., 2007). This combination, known as a symbiotic, a mix of live microorganisms and specialized substrates that are utilized by these microbes to deliver health benefits to the host(Swanson et al., 2020).

Recent findings indicate that synbiotic supplementation can lead to significant improvements in working memory in animal models (Cruz-Martínez et al., 2024, Parois et al., 2021) and children (Nieto-Ruiz et al., 2022) consuming synbiotics. These investigations collectively underscore the potential of synbiotics to positively influence working memory.

A balanced gut microbiota is crucial for protecting the host from harmful microorganisms and maintaining overall homeostasis (Swanson et al., 2020). However, factors like antibiotic treatments, stress, Western diets, and environmental pollution can disrupt this balance (Cryan et al., 2019). Such disruptions, common even in healthy individuals, can lead to gut dysbiosis, contributing to inflammatory, pathogenic, and metabolic disorders that impair cognitive functions, including working memory (Cryan et al., 2019; Patangia et al., 2022; Zhao et al., 2022; Czajeczny et al., 2023). Therefore, modulating gut microbiota is important for enhancing cognitive function in both individuals with health conditions and the broader population.

This study aims to investigate whether a synbiotic formulation containing Lactobacillus and Bifidobacterium strains, paired with fructooligosaccharides (FOS), (10^9 CFU per capsule), can improve working memory performance in healthy females. We hypothesize that this synbiotic intervention will yield enhancements in this cognitive function.

Materials and methods

Fourthy-eight participants were recruited for the investigation. three individuals voluntarily withdrew from the experiment and 15 didn’t met the inclusion criterial. Participants in this study were excluded if they had a acute or chronic illness, adhered to a specific dietary plan, took any form of medication, had a body mass index (BMI) that fell outside the normal range, were

younger than 18 or older than 40 years, consumed alcohol, had a possibility of being pregnant, showed signs of immunodeficiency, color blindness, vision or hearing impairments, or engaged in substance abuse. In addition, individuals who had used probiotics, synbiotics, or antibiotics in the previous two months were not included. These criteria were used to guarantee that the volunteers were suitable for the study and to minimize confounding variables that may alter the outcomes related to the manipulation of gut microbiota on cognitive performance. Considering to the influence of gender on the variation in gut microbiota, all participants in the study were females and aged between18 and 32 years.

The study reviewed and received approval from the Research Ethics Committees of the Faculty of Psychology and Education at the University of Tehran (Approval ID IR.UT.PSYEDU.REC.1403.041), ensuring ethical conduct of the research. Each participant freely signed their consent and were informed of their freedom to withdraw from the research at any point.

We conducted a study using a repeated measures design that included a control group (Figure 1). Initially, participants were screened for depression and anxiety using the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI). Demographic information was also collected at this stage. During the first session, participants completed the Positive and Negative Affect Schedule (PANAS) questionnaire, followed by a parametric auditory working memory task. After completing these assessments, participants were randomly assigned to either the intervention or control group. Those in the intervention group began taking synbiotic capsules, with instructions to consume one capsule daily for 15 days. We closely monitored adherence to the regimen, excluding participants who missed two or more doses. Both groups were instructed to maintain their usual diet and exercise routines and to avoid other probiotics. Participants were also required to inform the researchers about any need for antibiotics or other medications, which could lead to their exclusion from the study. Intervention group participants were advised to discontinue the capsules and contact the researchers immediately if they experienced any side effects. In the second session, all participants repeated the PANAS questionnaire and the auditory working memory task.

Positive and Negative Affect Schedule

The PANAS questionnaire (Watson et al., 1988) is a self-report tool used to measure positive and negative affect. It comprises a sequence of adjectives describing diverse emotions. Participants are requested to rate the level of intensity at which they have encountered each emotion during a specific period, utilizing a scale ranging from 1 (indicating a minimal) to 5 (indicating an exceptionally high amount). Higher scores on the Positive Affect (PA) scale represent higher levels of positive affect, whereas higher scores on the Negative Affect (NA) scale indicate a higher level of negative affect. Every participant filled out the PANAS questionnaire online through Porsline.com at the start of each session. They responded to each question based on their mood during the previous week.

Parametric auditory working memory test

In this study an auditory delayed comparison task (Akrami et al., 2018) were used (figure 2a). In each trial participants were exposed to pairs of pink noise sounds, each set at one of the following levels: 60, 62, 64, 66, 68, 70, or 72 dB, via noise-cancelling headphones during each trial. The pairs of sounds were assigned randomly. Participants commenced the task by checking out the instructions and carrying out six training trials. During the testing phase, the initial auditory stimulus was simultaneous with the appearance of a green square on the left side of a computer monitor positioned in front of the participant. Following a delay period of either 2 or 6 seconds, as indicated by the word 'WAIT!' displayed on the screen, the second sound was presented with a red square displaying on the right side of the screen. After receiving the second stimulus and the go cue, the participants evaluated the two sounds to determine which one was louder. They indicated their choice by clicking on the corresponding square on the screen using the mouse. Following their decision, participants assessed their level of confidence in their selection using a numerical scale ranging from 0 to 100% for each trial. Feedback regarding the accuracy of their response was displayed on the screen for each individual trial. Every participant completed a total of 150 trials. The code for this test was written in MATLAB (The MathWorks Inc., Massachusetts, US) using the Psychtoolbox.

Supplementation

Synbiotic intake was controlled by administering a commercially available supplement (Familact 2Plus, Zist Takhmir, Iran) containing live bacterial species, including *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus salivarius*, *Lactobacillus reuteri*, *Bifidobacterium lactis*, *Bifidobacterium longum*, and *Bifidobacterium bifidum*, along with FOS as a prebiotic (10^9 CFU per capsule). The supplement was provided in enteric-coated capsules. Participants in the intervention group were instructed to follow the information sheet guidelines, taking one capsule on an empty stomach, 1 hour before a meal, for 15 days. No participants reported any side effects during or after the study.

Statistical Analysis

The study design incorporated a between-subjects factor, consisting of two groups: control and synbiotic, and a within-subjects factor involving two time points: session 1 and session 2. Analyzed trials were conducted for each session and participant using MATLAB.

Due to the binary nature of the accuracy data, we utilized generalized linear models (GLM) for statistical analyses. To assess the probability of selecting the second stimulus (clicking on the right square), we employed psychometric curves and examined measures of sensitivity and threshold. Additionally, we used a linear mixed model estimated through generalized linear mixed models (GLMM) to analyze accuracy, reaction time, sensitivity, and threshold. These models are robust to incomplete data and suitable for our mixed design, enabling us to calculate the effects of each factor and the interaction between time and group.

The Wilcoxon rank-sum test was also employed to analyze participant characteristics, PANAS scores, sensitivity, and threshold between the control and intervention groups, while the Wilcoxon signed-rank test was used to analyze PANAS scores, sensitivity, and threshold within groups.

Result

We included 30 female in our experiment, divided into two groups control (n = 15) and symbiotic (n = 15). Table 1 details the demographic and baseline characteristics of the participants, and there were no significant differences between groups for each characteristic.

Impact of Synbiotics on Auditory Threshold

We analyzed the probability of selecting the second stimulus, specifically the response of clicking on the right square, using psychometric curves to evaluate sensitivity and threshold measures, applying linear mixed models to account for variability.

The Wilcoxon Signed-Rank Test revealed significant differences in thresholds for both the synbiotic group ($p = 0.025574$) and the control group ($p = 0.021545$). However, the Mann-Whitney U Tests indicated no significant differences in thresholds between the groups, with pretest and posttest p-values of 0.90097 and 0.6783, respectively. Thus, while both groups demonstrated significant changes in their thresholds, no significant differences were found between the synbiotic and control groups.

Impact of Synbiotics on Auditory Sensitivity

The statistical analyses indicated no significant differences in sensitivity between the synbiotic and control groups. The Wilcoxon Signed-Rank Test for the synbiotic group produced a p-value of 0.63867, and for the control group, it was 0.22931, both failing to reject the null hypothesis.

Additionally, the Mann-Whitney U Tests revealed p-values of 0.38373 for the pretest and 0.83571 for the posttest comparisons, suggesting no significant differences in sensitivity between the groups at both time points. Overall, the results indicate that neither the synbiotic intervention nor the control condition led to significant changes in sensitivity.

Controlling the impact of other covariates

We used generalized linear mixed-effects models (GLMM) to investigate the impact other parameter in study. Accuracy was analysis by employing the formula (accuracy ~ 1 + time + group + stimulus diffrence + delay time + group*time + (1|subject)). The interaction effect of group × time, which evaluates the hypothesis by comparing the impact of the intervention between the two groups, was not significant (beta = -0.010801, SE = 0.17998, t(7581) = -0.060013, p = 0.95215). The main effect of test time was also not significant (beta = 0.40013, SE = 0.23256, t(7581) = 1.7205, p = 0.085375). Although there was a trend towards improved accuracy over time, this trend did not reach statistical significance at the conventional alpha level of 0.05. Similarly, the effect of the group alone was not significant (beta = -0.05682, SE = 0.29742, t(7581) = -0.19104, p = 0.8485), indicating that there were no substantial differences in accuracy between the synbiotic and control groups at the initial session.

The interaction between test time and group in reaction time, which evaluates our hypothesis by comparing the effects of the synbiotic intervention across groups, was found to be positive and highly significant (estimate = 0.10395, SE = 0.018962, t(7581) = 5.4822, $p < 0.00001$). This result indicates that, although overall reaction times followed a general pattern, there was a

significant enhancement in reaction time for the synbiotic group compared to the control group from the pretest to the posttest.

As anticipated, the main effect of test time alone did not show a significant impact (estimate = -0.030024, SE = 0.023234, t(7581) = -1.2922, p = 0.19633), suggesting no overall change in reaction time across sessions when considering both groups together. Similarly, the effect of the group alone was significant (estimate = -0.21517, SE = 0.0748, t(7581) = -2.8767, p = 0.0040302), revealing a significant difference in reaction times between the synbiotic and control groups, with the synbiotic group demonstrating quicker reaction.

For thresholds, the effect of time was significant, with an estimated coefficient of -0.4262 (SE = 0.16394, t(56) = -2.5998, p = 0.011906), indicating a substantial negative impact. In contrast, the effect of the group variable was estimated at 0.19226 (SE = 0.26557, t(56) = 0.72398), suggesting no significant differences between groups. Lastly, the interaction between time and group yielded an estimate of 0.032837 (SE = 0.23184, t(56) = 0.14164, p = 0.88788), indicating that this combined effect was not significant.

In sensitivity analysis, the effect of time was estimated at 0.15452 (SE = 0.097253, t(56) = 1.5889, p = 0.11772), indicating no significant change. For the group variable, the estimated coefficient was 0.16658 (SE = 0.16422, t(56) = 1.0143, p = 0.3148), suggesting no substantial differences between the synbiotic and control groups. Additionally, the interaction between time and group produced an estimate of -0.12292 (SE = 0.13754, t(56) = -0.89374, p = 0.37529), indicating that this combined effect did not reach statistical significance.

Discussion

This study evaluated the effects of synbiotic supplementation on auditory working memory performance in young, healthy women. Our findings indicate that working memory was not significantly affected by the synbiotic intervention in terms of accuracy, threshold, or sensitivity. However, we did observe that the synbiotic group demonstrated significantly faster reaction times compared to the control group, suggesting a potential benefit of synbiotics in enhancing processing speed.

First, the analysis of participants' characteristics shows no significant differences between the synbiotic and control groups in terms of age, BMI, years of education, or baseline measures of anxiety, depression, and differences of Positive and Negative Affect Schedule score. This uniformity ensures that the observed effects of synbiotic supplementation are unlikely to be attributed to these variables.

In contrast to our findings, which did not reveal significant effects on either positive or negative mood as measured by PANAS, existing literature presents a more diverse picture. Bagga et al. (2018) reported significant increases in positive affect with a probiotic formulation that included several strains also present in our study, such as *B. bifidum*, *B. lactis*, *B. longum*, *L. acidophilus*, *L. casei*, and *L. salivarius*. Conversely, Boehme et al. (2023) found that *B. longum* led to a lower increase in positive affect compared to placebo and did not significantly impact negative affect. This finding contrasts with both the results of Bagga et al. and our own study, highlighting that

even with *B. longum*, a strain included in our formulation, the effects on mood can vary. These discrepancies underscore that while certain strains overlap between studies, the overall impact on mood, as assessed by PANAS, can be influenced by factors such as the specific strain used, dosage, and the duration of the intervention.

Our results indicate that both the synbiotic and control groups experienced significant reductions in auditory thresholds over time; however, no significant differences were observed between groups at either the pretest or posttest stages. This suggests that improvements in auditory detection are likely attributable to practice effects rather than the synbiotic intervention. This interpretation is supported by the GLMM analysis, which revealed a significant main effect of time but no effects for group or the group-by-time interaction. Similarly, sensitivity analyses revealed no significant differences between groups at any time point, with GLMM analysis showing non-significant effects for time, group, and their interaction. These findings imply that synbiotic supplementation did not enhance sensitivity to subtle auditory differences, indicating that any potential cognitive benefits may not extend to auditory sensitivity in this experimental framework.

In line with the results for sensitivity and auditory thresholds, synbiotic supplementation did not significantly enhance accuracy in auditory working memory tasks compared to the control group. Although there was a trend toward improved accuracy over time, this trend did not reach statistical significance, suggesting that neither the intervention nor the passage of time substantially impacted accuracy in this context.

In contrast, the analysis of reaction times showed a significant group-by-time interaction, indicating that the synbiotic group experienced a notable improvement in reaction times from pretest to posttest. This finding suggests a potential benefit of synbiotics in enhancing processing speed, even if their effects on auditory thresholds, sensitivity, and accuracy were not significant.

The impact of synbiotic supplementation on working memory varies across studies, likely due to differences in strains, prebiotics, duration of supplementation, and participant characteristics. For instance, a study evaluating Enterococcus faecium and agave inulin in rats found no significant differences in accuracy between the synbiotic and control groups (Romo-Araiza et al., 2023), consistent with our findings. Conversely, another study using the same synbiotic combination in rats with ischemic stroke reported significantly improved accuracy in an eight-arm radial maze for the synbiotic group (Cruz-Martínez et al., 2024). Additionally, Moloney et al. (2021) investigated the effects of Bifidobacterium longum—a strain included in our intervention—and similarly found no significant improvements in working memory performance, reinforcing our results.

In contrast, our study aligns with research indicating that probiotics can enhance processing speed. A double-blind, randomized trial with Lactobacillus GG in middle-aged and older adults reported significant improvements in mood and cognitive functions, including processing speed (Sanborn et al., 2018). Similarly, daily intake of Lactobacillus casei Shirota improved reaction times in a digit vigilance test among athletes, suggesting enhanced cognitive performance under stress (Adikari et al., 2020). Collectively, these findings support the notion that probiotic

interventions can positively impact processing speed, aligning with the improvements observed in our study.

Several mechanisms may explain how synbiotics improve processing speed. Primarily, synbiotics enhance the production of short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate through the fermentation of dietary fibers by beneficial gut bacteria. These SCFAs help reduce systemic inflammation and support the integrity of the blood-brain barrier (BBB), creating a healthier environment for brain function. Additionally, synbiotics can modulate gut microbiota, influencing the synthesis of key neurotransmitters such as gamma-aminobutyric acid (GABA), serotonin, and dopamine, which are vital for mood regulation and cognitive performance. This modulation also affects the hypothalamic-pituitary-adrenal (HPA) axis, further enhancing cognitive outcomes. Therefore, by boosting SCFA production, maintaining BBB integrity, and regulating neurotransmitter levels, synbiotics collectively support improved cognitive function and mental health (Ansari et al., 2023; Chen et al., 2021; McLoughlin et al., 2017; Silva et al., 2020)

The limited impact of our synbiotic intervention on cognitive outcomes may be attributed to several factors. Individual differences, such as age, diet and systemic inflammation, could influence the effectiveness of probiotics on cognitive function. Furthermore, the inconsistency of cognitive effects across different studies underscores the need for larger trials that consider potential confounding factors, including strain-specific efficacy and individual microbiome characteristics, to better understand the cognitive impacts of synbiotic supplementation in various populations (Czajeczny et al., 2020).

Several limitations must be considered. First, the research exclusively involved female participants, limiting the generalizability of the findings to males. Second, the study had a short intervention period, potentially overlooking the long-term benefits of synbiotics on cognitive function. Future research should explore different dosages of synbiotics and employ longer intervention durations. Additionally, examining changes in microbiome profiles post-intervention would provide valuable insights into the underlying mechanisms, ensuring that observed cognitive changes result from bacterial colonization in the gut rather than from factors like paraprobiotics. By addressing these limitations, future studies could yield more robust evidence of the cognitive benefits of synbiotic supplementation.

Table 1: the demographic and baseline characteristics of the participants

characteristics	Synbiotic group Mean(SD)	Cotrol group Mean(SD)	P-value
Age	25.26(3.14)	23.07(3.19)	0.13
BMI	24.43(3.74)	23.45(4.25)	0.62
Years of Education	18.28(1.72)	17.14(1.02)	0.053
BAI	8.57(4.34)	8.71(4.13)	0.74
BDI	8.21(3.42)	8.21(4.06)	0.94
ΔPANAS Positive	0.14(8.86)	0.07(6.79)	0.94
ΔPANAS negative	3.21(7.93)	-2.64(8.72)	0.14

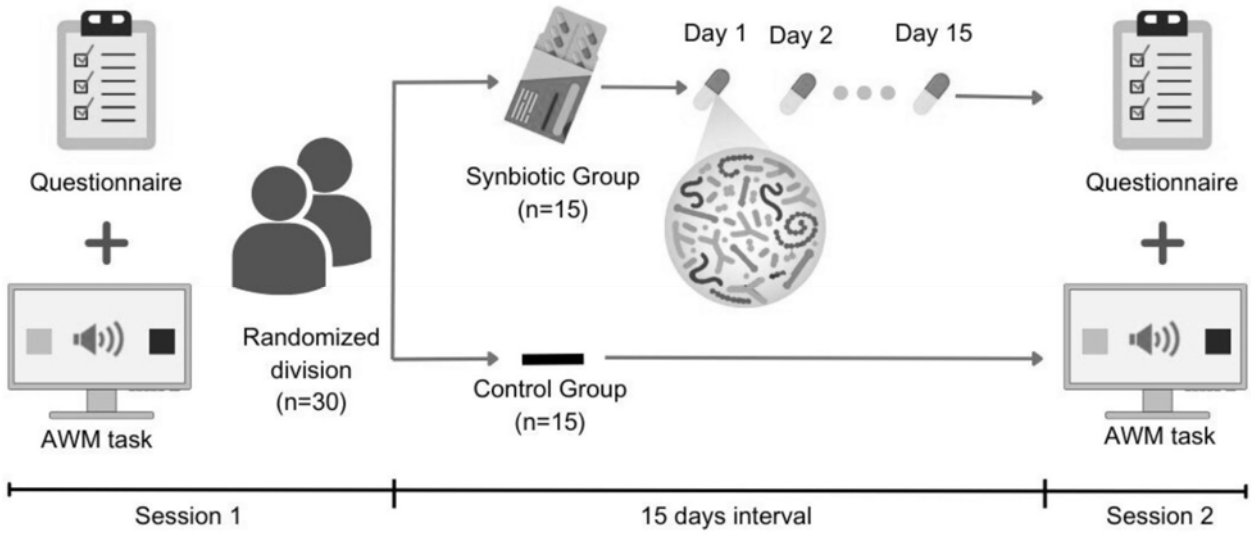

Figure 1: Experimental Design. The figure illustrates the repeated measures design, including the main procedures for both experimental sessions. It outlines the screening, random assignment to the intervention or control group, and the synbiotic capsule protocol followed by participants over 15 days.

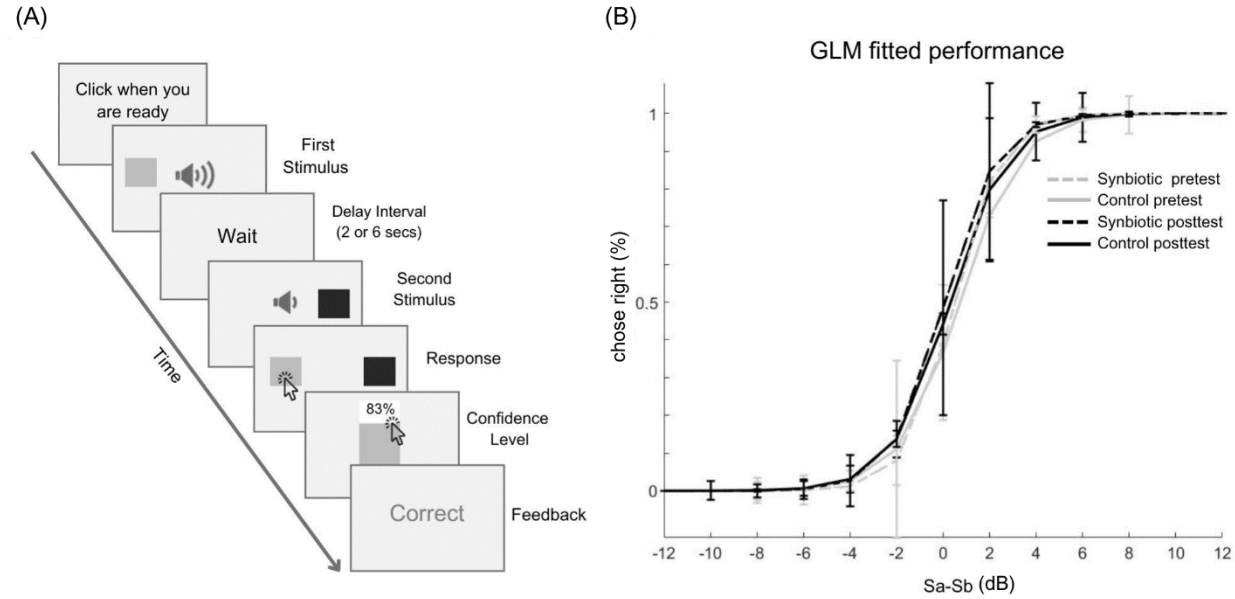

Figure 2: Parametric Auditory Working Memory. **A**, The figure shows the auditory delayed comparison task. Participants compared the loudness of two pink noise sounds, presented with a delay and marked by colored squares. They indicated their choice and confidence, with feedback provided after each of the trials. **B**, The figure shows GLM-fitted psychometric curves for both groups, depicting the probability of choosing the second stimulus (rightward) based on the dB difference between the first and second stimuli. The y-axis represents the percentage of rightward choices, and the x-axis indicates the stimuli difference.

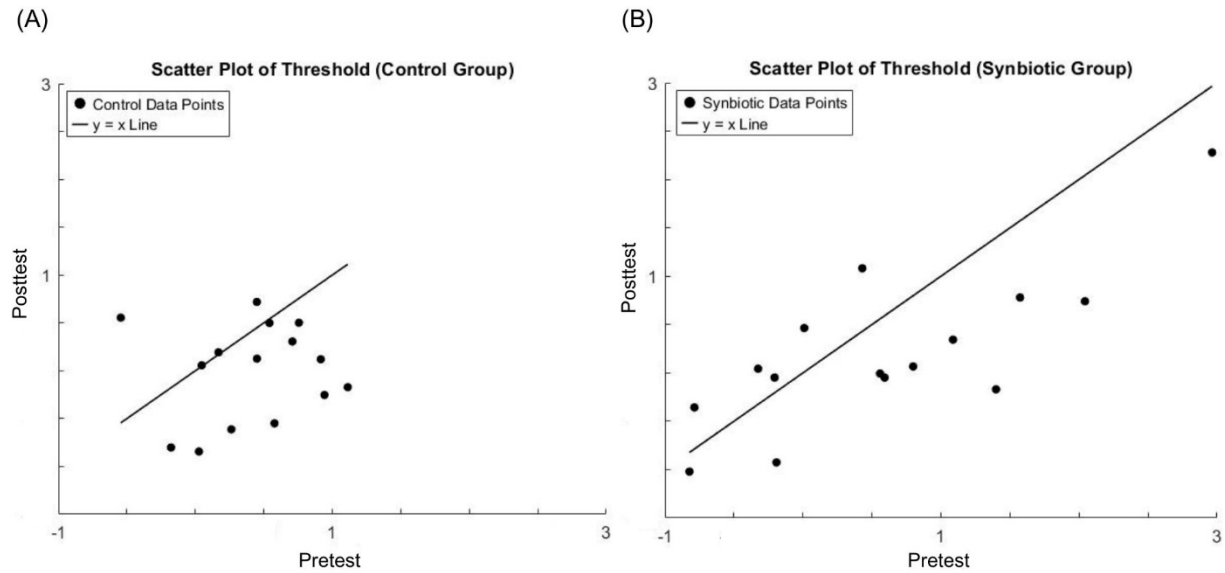

Figure 3: Threshold. Scatter plots of pretest and posttest auditory threshold scores for the control group (A) and the synbiotic group (B). Each point represents an individual score, with the solid line indicating equality (y = x). Positive correlations were observed in both the control and synbiotic groups.

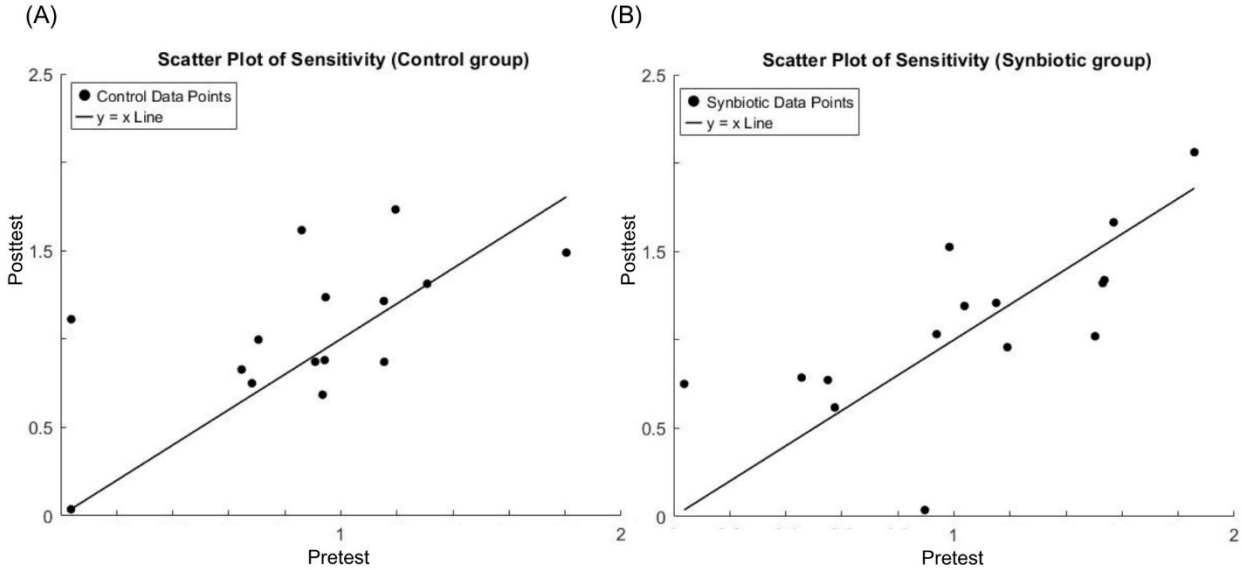

Figure 4: Sensitivity. Scatter plots of pretest and posttest sensitivity scores for the control group (A) and synbiotic group (B). Each point represents an individual score, with the solid line indicating equality (y = x). Both groups exhibit positive correlations.

References

Adikari, A., Appukutty, M., & Kuan, G. (2020). Effects of daily probiotics supplementation on anxiety induced physiological parameters among competitive football players. *Nutrients*, *12*(7), 1920.

Akrami, A., Kopec, C. D., Diamond, M. E., & Brody, C. D. (2018). Posterior parietal cortex represents sensory history and mediates its effects on behaviour. *Nature*, *554*(7692), 368-372.

Ansari, F., Neshat, M., Pourjafar, H., Jafari, S. M., Samakkhah, S. A., & Mirzakhani, E. (2023). The role of probiotics and prebiotics in modulating of the gut-brain axis. *Frontiers in nutrition*, *10*, 1173660.

Arnoriaga-Rodriguez, M., Mayneris-Perxachs, J., Burokas, A., Contreras-Rodriguez, O., Blasco, G., Coll, C., Biarnes, C., Miranda-Olivos, R., Latorre, J., & Moreno-Navarrete, J.-M. (2020). Obesity impairs short-term and working memory through gut microbial metabolism of aromatic amino acids. *Cell metabolism*, *32*(4), 548-560. e547.

Bagga, D., Reichert, J. L., Koschutnig, K., Aigner, C. S., Holzer, P., Koskinen, K., Moissl-Eichinger, C., & Schöpf, V. (2018). Probiotics drive gut microbiome triggering emotional brain signatures. *Gut Microbes*, *9*(6), 486-496.

Bloemendaal, M., Szopinska-Tokov, J., Belzer, C., Boverhoff, D., Papalini, S., Michels, F., van Hemert, S., Arias Vasquez, A., & Aarts, E. (2021). Probiotics-induced changes in gut microbial composition and its effects on cognitive performance after stress: exploratory analyses. *Translational psychiatry*, *11*(1), 300.

Boehme, M., Rémond-Derbez, N., Lerond, C., Lavalle, L., Keddani, S., Steinmann, M., Rytz, A., Dalile, B., Verbeke, K., & Van Oudenhove, L. (2023). Bifidobacterium longum subsp. longum reduces perceived psychological stress in healthy adults: an exploratory clinical trial. *Nutrients*, *15*(14), 3122.

Cai, H., Wang, C., Qian, Y., Zhang, S., Zhang, C., Zhao, W., Zhang, T., Zhang, B., Chen, J., & Liu, S. (2021). Large□scale functional network connectivity mediate the associations of gut microbiota with sleep quality and executive functions. *Human Brain Mapping*, *42*(10), 3088-3101.

Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Annals of gastroenterology: quarterly publication of the Hellenic Society of Gastroenterology*, *28*(2), 203.

Chen, Y., Xu, J., & Chen, Y. (2021). Regulation of neurotransmitters by the gut microbiota and effects on cognition in neurological disorders. *Nutrients*, *13*(6), 2099.

Coletto, E., Latousakis, D., Pontifex, M. G., Crost, E. H., Vaux, L., Perez Santamarina, E., Goldson, A., Brion, A., Hajihosseini, M. K., & Vauzour, D. (2022). The role of the mucin-glycan foraging Ruminococcus gnavus in the communication between the gut and the brain. *Gut Microbes*, *14*(1), 2073784.

Cruz-Martínez, Y., Aguilar-Ponce, L., Romo-Araiza, A., Chávez-Guerra, A., Martiñón, S., Ibarra-García, A. P., Arias-Santiago, S., Gálvez-Susano, V., & Ibarra, A. (2024). Supplementation with a Symbiotic Induced Neuroprotection and Improved Memory in Rats with Ischemic Stroke. *Biomedicines*, *12*(1), 209.

Cryan, J. F., O'Riordan, K. J., Cowan, C. S., Sandhu, K. V., Bastiaanssen, T. F., Boehme, M., Codagnone, M. G., Cussotto, S., Fulling, C., & Golubeva, A. V. (2019). The microbiota-gut-brain axis. *Physiological reviews*.

Czajeczny, D., Kabzińska, K., & Wójciak, R. W. (2023). Effects of Bifidobacterium Lactis BS01 and Lactobacillus Acidophilus LA02 on cognitive functioning in healthy women. *Applied Neuropsychology: Adult*, *30*(5), 552-560.

Eastwood, J., Walton, G., Van Hemert, S., Williams, C., & Lamport, D. (2021). The effect of probiotics on cognitive function across the human lifespan: A systematic review. *Neurosci Biobehav Rev*, *128*, 311-327.

Griffin, S. M., Lehtinen, M. J., Meunier, J., Ceolin, L., Roman, F. J., & Patterson, E. (2023). Restorative effects of probiotics on memory impairment in sleep-deprived mice. *Nutritional neuroscience*, *26*(3), 254-264.

Li, Y., Sun, H., Huang, Y., Yin, A., Zhang, L., Han, J., Lyu, Y., Xu, X., Zhai, Y., & Sun, H. (2022). Gut metagenomic characteristics of ADHD reveal low Bacteroides ovatus-associated host cognitive impairment. *Gut Microbes*, *14*(1), 2125747.

McLoughlin, R. F., Berthon, B. S., Jensen, M. E., Baines, K. J., & Wood, L. G. (2017). Short-chain fatty acids, prebiotics, synbiotics, and systemic inflammation: a systematic review and meta-analysis. *The American journal of clinical nutrition*, *106*(3), 930-945.

Moloney, G. M., Long-Smith, C. M., Murphy, A., Dorland, D., Hojabri, S. F., Ramirez, L. O., Marin, D. C., Bastiaanssen, T. F., Cusack, A.-M., & Berding, K. (2021). Improvements in sleep indices during exam stress due to consumption of a Bifidobacterium longum. *Brain, Behavior, & Immunity-Health*, *10*, 100174.

Morais, L. H., Schreiber IV, H. L., & Mazmanian, S. K. (2021). The gut microbiota–brain axis in behaviour and brain disorders. *Nature Reviews Microbiology*, *19*(4), 241-255.

Nieto-Ruiz, A., García-Santos, J. A., Verdejo-Román, J., Diéguez, E., Sepúlveda-Valbuena, N., Herrmann, F., Cerdó, T., De-Castellar, R., Jiménez, J., & Bermúdez, M. G. (2022). Infant formula supplemented with milk fat

globule membrane, long-chain polyunsaturated fatty acids, and synbiotics is associated with neurocognitive function and brain structure of healthy children aged 6 years: the COGNIS study. *Frontiers in nutrition*, *9*, 820224.

Ohsawa, K., Uchida, N., Ohki, K., Nakamura, Y., & Yokogoshi, H. (2015). Lactobacillus helveticus–fermented milk improves learning and memory in mice. *Nutritional neuroscience*, *18*(5), 232-240.

Önning, G., Montelius, C., Hillman, M., & Larsson, N. (2023). Intake of Lactiplantibacillus plantarum HEAL9 improves cognition in moderately stressed subjects: a randomized controlled study. *Nutrients*, *15*(15), 3466.

Oriach, C. S., Robertson, R. C., Stanton, C., Cryan, J. F., & Dinan, T. G. (2016). Food for thought: The role of nutrition in the microbiota-gut–brain axis. *Clinical Nutrition Experimental*, *6*, 25-38.

Ouwehand, A., Tiihonen, K., Mäkivuokko, H., & Rautonen, N. (2007). Synbiotics: combining the benefits of pre- and probiotics. In *Functional dairy products* (pp. 195-213). Elsevier.

Papalini, S., Michels, F., Kohn, N., Wegman, J., van Hemert, S., Roelofs, K., Arias-Vasquez, A., & Aarts, E. (2019). Stress matters: randomized controlled trial on the effect of probiotics on neurocognition. *Neurobiology of stress*, *10*, 100141.

Parois, S. P., Eicher, S. D., Lindemann, S. R., & Marchant, J. N. (2021). Potential improvements of the cognition of piglets through a synbiotic supplementation from 1 to 28 days via the gut microbiota. *Scientific Reports*, *11*(1), 24113.

Patangia, D. V., Anthony Ryan, C., Dempsey, E., Paul Ross, R., & Stanton, C. (2022). Impact of antibiotics on the human microbiome and consequences for host health. *Microbiologyopen*, *11*(1), e1260.

Romo-Araiza, A., Picazo-Aguilar, R. I., Griego, E., Márquez, L. A., Galván, E. J., Cruz, Y., Fernández-Presas, A. M., Chávez-Guerra, A., Rodríguez-Barrera, R., & Azpiri-Cardós, A. P. (2023). Symbiotic supplementation (E. faecium and Agave Inulin) improves spatial memory and increases plasticity in the hippocampus of obese rats: a proof-of-concept study. *Cell Transplantation*, *32*, 09636897231177357.

Sanborn, V., Azcarate-Peril, M. A., Updegraff, J., Manderino, L. M., & Gunstad, J. (2018). A randomized clinical trial examining the impact of LGG probiotic supplementation on psychological status in middle-aged and older adults. *Contemporary clinical trials communications*, *12*, 192-197.

Sarkar, A., Harty, S., Lehto, S. M., Moeller, A. H., Dinan, T. G., Dunbar, R. I., Cryan, J. F., & Burnet, P. W. (2018). The microbiome in psychology and cognitive neuroscience. *Trends in cognitive sciences*, *22*(7), 611-636.

Serra, M. C., Nocera, J. R., Kelleher, J. L., & Addison, O. (2019). Prebiotic intake in older adults: effects on brain function and behavior. *Current Nutrition Reports*, *8*, 66-73.

Silva, Y. P., Bernardi, A., & Frozza, R. L. (2020). The role of short-chain fatty acids from gut microbiota in gut-brain communication. *Frontiers in endocrinology*, *11*, 508738.

Swanson, K. S., Gibson, G. R., Hutkins, R., Reimer, R. A., Reid, G., Verbeke, K., Scott, K. P., Holscher, H. D., Azad, M. B., & Delzenne, N. M. (2020). The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nature reviews Gastroenterology & hepatology*, *17*(11), 687-701.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of personality and social psychology*, *54*(6), 1063.

Yin, X., Liu, W., Feng, H., Huang, J., Wang, Q., Zhang, Q., He, J., & Wang, R. (2024). Bifidobacterium animalis subsp. lactis A6 attenuates hippocampal damage and memory impairments in an ADHD rat model. *Food & Function*, *15*(5), 2668-2678.

Zhao, Z., Cui, D., Wu, G., Ren, H., Zhu, X., Xie, W., Zhang, Y., Yang, L., Peng, W., & Lai, C. (2022). Disrupted gut microbiota aggravates working memory dysfunction induced by high-altitude exposure in mice. *Frontiers in Microbiology*, *13*, 1054504.