

Investigating the Joint Effects of Fecal Microbiota Transplant and Diet on Cognitive Function in Alzheimer's Symptoms in Mice (*Mus musculus*): A Research Protocol

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Abstract

Introduction: Alzheimer's disease (AD) is characterized by the buildup of amyloid beta (A β) protein in the hippocampal and temporal regions, causing progressive cognitive and memory decline. Emerging evidence suggests the gut-brain axis influences AD pathophysiology through gut dysbiosis. This protocol aims to investigate how dietary pattern variations of fecal donors improve cognitive deficits caused by Alzheimer's Disease, using fecal microbiota transplants (FMT) as the delivery system.

Methods: Thirty healthy donor mice (wild-type 2 months old) will be fed from one of three diets: an "Standard" diet with standard lab nutrition, a "Moderate-fat" diet with moderate fat and sodium, and a "High-fat" diet with high fat and sodium. After 16 weeks of diet pattern variation, fecal microbiota from each diet group will be transplanted into 30 6-month old 5xFAD model mice via oral gavage. Novel object recognition tests will assess long-term memory. Magnetic Resonance Imaging (MRI) will visualize amyloid-beta plaque deposition in the hippocampus. Gut microbiome composition analysis of donor and recipient mice will be achieved via 16S rRNA sequencing.

Anticipated Results: In the "Standard" diet group, limited composition change is expected, as the mice will have consumed this diet prior to testing. Improved cognitive ability is hypothesized. The "Moderate-fat" diet group may experience some microbe composition change. The "High-fat" diet group will exhibit significant microbiome changes, specifically, higher levels of *Firmicutes* and lower *Bacteroidetes*. The cognitive decline is expected to deteriorate.

Discussion: If the above results are observed, we would determine if diet helps regulate AD pathology. The study combines diets and FMTs as a long-term treatment for Alzheimer's, offering insight into the mechanism causing AD pathology.

Conclusion: This study will allow for direct observation of diet-induced dysbiosis on amyloid beta plaques and neurodegeneration, providing insight on the mechanism of Alzheimer's. Future directions should explore mechanistic effects on lifestyle changes, specifically, diet, and its effect on the gut-brain axis, and should not be translated to humans yet.

Keywords: Alzheimer's Disease; FMT; gut-brain axis; A β plaques

Introduction

Current research regarding the gut-brain axis suggests that the gut microbiome plays a role in the onset of Alzheimer's Disease (AD). AD is a neurodegenerative disease which accounts for 60%-70% of all dementia cases in the world [1]. AD neurodegeneration begins in the hippocampus and progresses to other areas of the brain [1], leading to a decline in cognition and memory. Despite its prevalence, the cause of AD is unknown. Current knowledge suggests that factors like aging and family history of the disease can contribute to its onset; lifestyle factors such as smoking, alcohol consumption, and diet can also influence the onset of AD.

In the 19th century, physicians generally agreed that the gastrointestinal system had an impact on the healthy functioning of the brain. Contrastingly, physicians of the 20th century believed that the brain was responsible for the abnormalities in the gut [2]. Current-day research posits that the brain and the gut microbiome interact in a bi-directional manner. The exact mechanism of this bi-directional communication remains unknown. However, it is known that the bacteria in the gastrointestinal tract communicate with the brain via the secretion of neuroactive substances such as neurotransmitters, short-chain fatty acids, and amino acids [3]. This may explain why

imbalances in the microbiome can influence the onset of neurodegenerative diseases such as AD [4].

Over 50% of microbial variations between mice can be explained by diet, and 20% in humans [5, 6]. Despite differences between individual gut-microbiomes, 90% of the composition of healthy gut microbiota is accounted for by *Firmicutes* and *Bacteroidetes* [7]. Diet influences the composition of the gut microbiome [8]. Common diets like the Western Diet (WD), are high in refined substances like simple carbohydrates and saturated fatty acids [8]. The WD has lower intakes of grains, fiber, and mono- and polyunsaturated fatty acids required for a balanced gut microbiome composition [8]. An imbalanced microbiome caused by the nutritional components of the WD is said to be in a state of WD-related dysbiosis [8] which affects absorption and metabolism of nutrients [4]. AD pathophysiology is marked by the accumulation of abnormal proteins in the form of plaques. Such proteins include Amyloid-beta ($A\beta$) peptides and tau neurofibrillary tangles which pose neuro-toxic risks in abnormal amounts [8, 9]. Although past studies make connections between the gut microbiome and AD [10], it is unclear whether diet-induced dysbiosis affects $A\beta$ accumulation. Current AD treatments alleviate the cognitive decline associated with AD, however improperly address AD pathophysiology [11]. To quantify the amyloid-beta deposition, MRI techniques can be used as a non-invasive approach [12].

A 2023 study by Jin et al. demonstrated that the gut is a potential source of $A\beta$ in the brain for both wild-type mice and those genetically predisposed to AD [10]. This study found high levels of $A\beta$ in the gut of both AD mice and humans. They also found that $A\beta$ levels increased with age in wild type and amyloid precursor protein/presenilin (APP/PS1) mice. The gut microbiome of the mice were characterised using 16 sRNA sequencing. Through this, it was found that the compositions of the gut microbiome in aged APP/PS1 mice versus wild-type were significantly different. The same study also suggests that gut microbiota can upregulate the production of $A\beta$ in the gut, potentially contributing to AD development [10]. For instance, one study observed that transferring the microbiome contents of AD-model mice to wild-type mice via FMT upregulates AD progression in the wild-type mice [13].

This proposed protocol will be using mice as the primary subject of study. A generally accepted method to quantify the initial state of a mouse's cognition and behaviour is the novel object recognition (NOR) test which takes place over 3 days: habituation day, training day, and testing day [14]. On training day, the mouse explores 2 identical objects [14]. On test day, one of the objects is replaced with a novel object; mice have an innate preference for novel objects. Due to this preference, the mouse will spend most of its time with the novel object rather than the familiar object. The NOR test will provide this proposed protocol with an understanding of the initial cognitive and behavioural states of the mice.

To study the composition of the taxa found within the gut microbiome, studies typically make use of 16S rRNA gene amplicon sequencing as a technique [15] Prior to manipulating microbial variables in a study, it is good practice to conduct 16S rRNA gene amplicon sequencing as a reference to any changes made by future manipulations.

An anecdotal clinical study of FMT infusion from healthy human donors to patients with AD showed promising results in an AD patient's cognition improvement [16]. Kim et al. found rapid improvements in 82-year-old's cognitive abilities after 2 months of a single FMT infusion using stool from the patient's intellectually acute 85-year-old wife as a donor [16]. Given this anecdotal evidence, it is worth further investigation to better understand the impact of FMT as an effective intervention to delay the cognitive decline in AD [9].

Though evidence links the gut microbiome to Alzheimer's, it is unclear how diet-induced dysbiosis affects cognitive decline and amyloid-beta ($A\beta$) buildup. FMT can improve AD symptoms by regulating the microbiome, but studies have not tested its effectiveness on diet-induced microbiome imbalances. This protocol seeks to test the joint effects of FMT and a healthy diet on AD pathophysiology. By comparing the effects of microbiota from high-fat and low-fat diet donors, this protocol proposes an experiment to uncover whether diet quality enhances the effectiveness of FMT as a therapy for cognitive decline associated with AD. The findings may provide insights into the benefits of combining FMT with dietary interventions to slow cognitive decline in AD patients. As well, the possible outcomes of this study may lead to a better understanding of AD pathophysiology.

It is important to note that since this proposed protocol is to be conducted on mouse models, it would be premature to extrapolate its potential results to human trials. This protocol aims to provide preliminary theory and trials for future studies to better understand the pathophysiology of AD and novel therapies for it.

Methods

This protocol proposes a study which seeks to compare the influence of FMT received from donors with high-fat versus low-fat diet in reducing cognitive decline associated with AD. Cognitive improvement will be measured using NOR. Amyloid-beta levels will be measured using MRI.

Fecal Donor Preparation: The gut microbiome of 30 age-matched healthy donor mice initially receiving the AIN-93M diet will be analyzed before diet manipulation using 16S rRNA gene amplicon sequencing [17]. This commonly used sequencing technique utilizes the 16S rRNA gene as a marker to identify and quantify microbiota species in the gut [15]. The gene is amplified and sequenced are compared to reference sequences from public databases [18]. Mice will be placed in individual enclosures without bedding and naturally defecated fecal samples collected with sterile toothpicks [19]. Samples not

immediately processed will be stored at -80°C [19, 20]. To extract the bacterial DNA, samples will be added to 250 μL of Extraction solution, heated, and added to 250 μL of Dilution solution according to the protocol by Segni et al. [20]. Samples will undergo PCR and will be run on a 1% agarose gel stained with ethium bromide [20]. Amplicons of 375-425 bp shown under UV light will be considered high-quality and will be used [20]. Bands will be extracted, diluted and sequenced [20].

Next, donor mice will be blindly divided into one of three groups: the standard, moderate-fat, or high-fat diet group. Each group will receive their respective diet for 16 weeks to allow for bacterial engraftment [21]. A previous study by Kulecka et al. show that gut microbiomes of mice fed regular diets and high fat diets show significant differences by week 12 of diet regimen [22]. Other studies show that longer term diet changes show larger differences in gut microbiota [23]. It is imperative that fecal donor mice engraft their respective new microbiomes from their diets to observe the effects of their microbiota on

FMT. The standard diet group will continue to receive the standard AIN-93M diet for laboratory mice, consisting of 76.80% carbohydrates, 13.70% protein, 5.30% fiber in the form of cellulose and 4.0% fats (Fig. 1A) [24]. The remaining two diets are modeled after diets used in a study by Więckowska-Gacek, Mietelska-Porowska, Wydrych, and Wojda, and will build on the standard diet, with increasing ratios of fat and salt and much less fiber [8]. The "Moderate-fat" diet will have a moderate increase in fat and salt up to 10% total composition, and a decrease in fiber to 3.10% (Fig. 1B). The "High-fat" diet will drastically increase fat and salt to 51.10% and 1.00% respectively, and no significant amount of fiber (Fig. 1C). Mice will receive 3.5 g of their assigned diet per day, as this has been shown to be the average amount consumed per mouse per day [24]. After the diet treatments, fecal samples will be collected and analyzed to confirm a significant change in the microbiome through 16s rRNA sequencing.

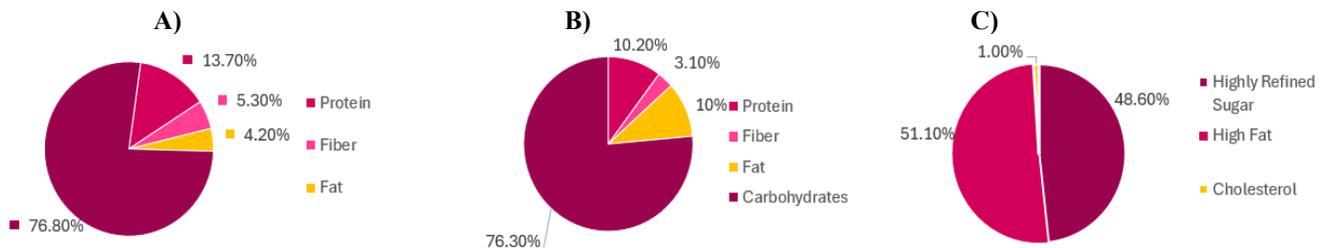


Figure 1. Composition of Diets. Figure A) shows the standard diet, B) shows the moderate-fat diet, C) shows the high-fat diet. Figures were generated using Excel [25].

Alzheimer's Model Preparation: The 30 6-month old 5xFAD Alzheimer's mouse model will be used for this study due to its rapid amyloid- β plaque formation and cognitive impairment levels at 6 months of age (Fig. 2) [26]. Our models will be fed the standard diet in the same amount per day as the donors. This colony will be obtained by crossbreeding female C57B/6J and male 5xFAD mice for maintenance, and only transgenic offspring will be used [27]. Both male and female mice will be used to observe potential sex differences and kept in individual enclosures with 12 hour light cycles [28]. The models will have their initial gut microbiome composition analyzed using gene amplicon sequencing. A hippocampal MRI will be performed to record the initial amount of amyloid- β plaques in the hippocampus

of the mouse models [12]. MRIs are a non-invasive imaging technique commonly used to detect the presence of amyloid- β plaques and neurodegeneration in both small-animal and human studies [12]. Additionally, the NOR test will be done to measure initial cognitive abilities [29]. The models will then receive general antibiotics to eliminate competition from native microbes and help the transplanted microbes grow [21]. A study by Fourati et al. used 1g/L of Amoxicillin, 0.5g/L of Vancomycin, 80mg/ml of Gentamycin, and 0.5% of Metronidazole [21]. Drugs were administered daily, starting 5 days before the transplant and ending 3 days before [21] This schedule will be replicated in our study. AD mouse models will then be randomly and blindly assigned to different fecal donor diet groups.

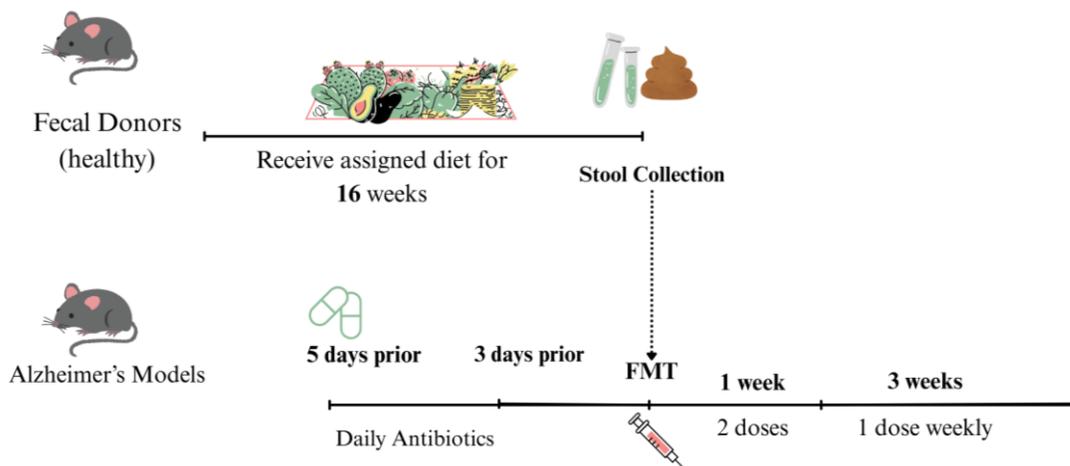


Figure 2. Timeline for healthy fecal donors' stool collection and preparation for Alzheimer's models FMT. Figures were generated on Canva [30].

FMT: Fecal collection from healthy donors will occur at 11 AM to maximize bacterial load, as shown by Bokoliya, Dorsett, Panier, and Zhou who reviewed several studies and determined several optimal time points, most of which varied during early morning hours [31]. Samples will be cryoprotected in trehalose and maltodextrin to maintain viability after exposure to freezing and oxygen, in accordance with the procedure presented by Bokoliya, Dorsett, Panier, and Zhou [31].

Before the transplant, these samples will be suspended in a sterile phosphate-buffered saline solution [31]. They will then be defrosted and preserved using an L-cysteine medium [31]. These samples will then be filtered and centrifuged to concentrate the microbes [31]. In the first week, AD models will receive two 250 ul doses via FMT oral gavage from their respective "diet donors" [31]. We will use the oral gavage technique, as it is the most common and effective way of administering an FMT [31]. For the following 3 weeks, models will receive one dose. Bokoliya, Dorsett, Panier, and Zhou show that this schedule maximizes bacterial engraftment [31]. A group of control 5xFAD model mice will be handled in the same way as the treatment groups, using saline rather than fecal samples. Following the FMT treatments, model mice will undergo gene amplicon sequencing once more to observe changes in microbe composition. Models will repeat the spatial memory ability task and MRI imaging to further observe cognitive changes. T-tests will be conducted to measure statistical significance between groups.

Anticipated Results

Fecal Donor Microbiome: We anticipate different levels of change in fecal donor microbiome composition after diet alteration. In the "Standard" diet group, we predict that 16s rRNA sequencing will show limited composition change, as the mice will have already

consumed this diet prior to testing. The "Moderate-fat" diet group may experience some microbe composition change, whereas the "High-fat" diet group will have significant microbiome changes. Specifically, we anticipate higher levels of *Firmicutes* and lower *Bacteroidetes*, two microbial shifts that are commonly associated in those who consume high-fat diets [32].

AD Model Microbiome and Cognitive Ability: We anticipate different results for each model mouse group from different fecal donors. We expect that the gut composition of all model mice will resemble that of their respective donors. Additionally, we expect that models receiving transplants from "Standard" diet donor mice will likely improve NOR performance with better discrimination between objects [29], and have significantly less A β plaques in the hippocampal MRI ($p < 0.05$). Models receiving from "Moderate-fat" diet donors may experience similar NOR performance and A β plaque quantity. We predict that models receiving fecal samples from "High-fat" diet donors will have poorer discrimination abilities between objects in the NOR test and more A β plaque [29].

Discussion

The anticipated results suggest that AD development is influenced by gut microbial balance, with donor diet for FMTs being the determinant. Similar to published studies, murine models receiving the 'Standard' diet FMTs are expected to show decreases in amyloid beta plaque deposition and cognitive deficits associated with AD [10]. Using 16sRNA sequencing, the gut microbiome composition in the high-fat diet is expected to have higher levels of *Firmicutes* and lower *Bacteroidetes* compared to the 'Standard' diet [32]. Unlike published studies, this proposal emphasizes diet pattern variation as the primary determinant in shaping the gut microbiome and treatment outcome. By investigating diet, this study combines the

mechanism behind the gut microbial balance and FMTs as a therapeutic approach to AD.

This study has strengths and limitations. Current treatments alleviate AD symptoms through neurotransmitter regulation, but rarely addresses AD pathophysiology [11]. The study proposes an alternative to improve cognitive function by changing the gut microbiome. The research will offer insight into microbial composition and its regulation on neurodegenerative processes. While published studies support the gut microbial regulation on AD, outcomes may differ if the diet pattern variation does not translate across different species. The study observes murine models which lacks generalizability as human models require a different 'Standard' diet composition and possess a different gut microbiome. Therefore, the results would require further testing before considering human clinical trials. Nevertheless, these results could have implications in how AD is treated and understood, providing a research pathway that utilizes the benefits of both healthy diets and FMT treatments.

Conclusions

This experiment intends to investigate the relationship between the gut-brain axis and the progression of Alzheimer's by testing diet changes on the gut microbiome through fecal microbiota transplant. We aim to assert the benefits of two studied treatment methods: diet change and FMT. Combining these treatments could maximize the microbial benefits of a healthy diet. Doing so could allow for a new treatment pathway in Alzheimer's disease research.

List of Abbreviations

AD: Alzheimer's Disease

A β : amyloid-beta

FMT: Fecal Microbiota Transplant

NOR: novel object recognition

WD: Western Diet

Conflicts of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

If this experiment were to be performed, we would seek approval from McMaster's Animal Research Ethics Board (AREB) [33]. This proposal does not require participant consent.

Authors' Contributions

AL: made substantial contributions to the conception of the study, wrote and revised the abstract and introduction, constructed figures, assisted in the acquisition of preliminary research and background research, and gave final approval of the version to be published.

JM: made substantial contributions to the method design of the study, wrote the methods, revised the manuscript

critically, and gave final approval of the version to be published.

LE: made substantial contributions to the conception of the study, wrote and revised the introduction, acquired preliminary and background research, revised the manuscript critically, and gave final approval of the version to be published.

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