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**Fecal microbiome and hippocampal volume in children**

Syventävien opintojen kirjallinen työ

Kevätlukukausi 2025

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The gastrointestinal (GI) microbiome is not stable immediately after birth. Early GI microbiome composition is influenced by multiple factors, such as early antibiotic use and birthing method. Similarly, the hippocampal volume continues to grow rapidly during the first three years of life. Numerous studies have suggested a correlation between brain development and the GI microbiome.

The purpose of this research was to determine whether there is a significant correlation between the fecal microbiome and hippocampal volume. Specifically, the associations between intestinal microbiome alpha and beta diversity and hippocampal volumes were investigated.

Data for this cross-sectional study was collected from the FinnBrain Birth Cohort study. The participants included families from the city of Turku, nearby municipality of Turku and Åland. The sample included 82 children who delivered a fecal sample at the age of 2,5 months. MRI scans were conducted at 5 years of age.

No statistically significant linear correlation was between alpha diversity and left hippocampal volume ($p = 0.711$) or right hippocampal volume ($p = 0.2617$).

Similarly, there was no significant correlation between beta diversity and left hippocampal volume (F. Model = 0.737, Pr (> F) = 0.76) or between beta diversity and right hippocampal volume (F. Model = 1. 2205, Pr (> F) = 26).

The results differed from previous studies. While prior research has demonstrated associations between alpha diversity and brain development as well as beta diversity and brain, these relationships have not been clearly established at this specific age point. Future studies are needed to achieve better understanding of correlations between brain and GI microbiome.

Key words: alpha diversity, beta diversity, hippocampus, GI microbiome

CONTENTS

## 1. Introduction

The microbiota-gut-brain-axis (MGBA) has interested researchers for a while now. Studies have shown that brain and gut communicate through a bidirectional pathway consisting of the central nervous system (CNS), the enteric nervous system (ENS), the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal-axis (HPA). In this network, signals are transmitted via neural, endocrine, metabolic, and immunological factors. Gut microbiota interacts in this pathway by producing vitamins, neurotransmitters such as GABA, and metabolites like short-chain fatty acids. (Carabotti et al., 2015; Laue et al., 2022.)

Many studies have suggested that microbiota play a role in brain development and functioning. In CNS gut microbiota's signaling products influence microglial cell development and maturation (Erny, De Angelis, et al., 2015). Microglial cells are important for brain development as well as for the immune system. During brain development and adulthood, these microglial cells play a role in synaptic remodeling and pruning. (Erny, de Angelis, et al., 2015.) In germ-free mice, hippocampal neurogenesis is increased, and this is not affected by later microbial colonization of gastrointestinal (GI) tract, suggesting the importance of early GI microbiota in brain development (Ogbonnaya et al., 2015).

Studies have shown that the volume of the hippocampus is positively associated with declarative, verbal, and visual episodic memory (Pohlack et al., 2014; Zammit et al., 2017). Loss of the hippocampal volume has been shown to correlate with many CNS disorders, such as schizophrenia, early-onset psychosis, Alzheimer's disease, and Parkinson's disease (Camicioli et al., 2003; McHugo et al., 2020; Uysal & Ozturk, 2020). Likewise, these disorders have been associated with gut microbiota dysbiosis (Kesika et al., 2021; Wang et al., 2021; Yuan et al., 2022).

The volume of the hippocampus is greatest during preadolescence (Uematsu et al., 2012). In the postnatal period, the hippocampus experiences its most significant growth during the first and second years after birth (Knickmeyer et al., 2008; Utsunomiya et al., 1999; Matsuzawa, J. et al., 2001). Similarly, the gut microbiome is not stable immediately after birth; however, microbiome stability increases during the first three years of life (Koenig et al., 2011; Yatsunenko et al., 2012). Thus, the

development of hippocampal volume and gut microbiome stabilization occur partly at the same time.

Understanding the effects that early GI microbiome has on neurodevelopment is important, as it can be influenced by environmental factors such as birth method and early use of antibiotics (Galazzo et al., 2020). These effects on the brain can be studied through imaging techniques. A few studies have shown that changes in MRI findings are associated with infant GI microbiomes composition, and it has been speculated that this could affect cognitive skills and neurodevelopment. (Carlson et al., 2018; Tamana et al., 2021). There is paucity of research on the effects of infant microbiome on brain development, whereas in adults, the microbiome's association with brain function and brain volume has been more clearly demonstrated in magnetic resonance imagining studies (Bagga et al., 2018; Liang et al., 2022; Zhu et al., 2022).

This research aims to determine whether there is significant correlation between hippocampal volume and the gut microbiome. Regarding microbiota, I will focus on alpha and beta diversity. Alpha diversity describes the number of different species within a single stool sample, whereas beta diversity refers to differences in microbial composition between separate stool samples. I studied the associations between alpha and beta diversity of the early gastrointestinal microbiome and hippocampal volumes at the age of five. This objective has not been previously studied in longitudinal, population-based cohort research or at this specific age point.

## 2. Methods

### 2.1. Subjects

Data was obtained from the FinnBrain Birth Cohort Study (Karlsson et al., 2018). This is transgenerational, prospective observational study including women (n = 3,808), men (n = 2,623) and their children (n = 3,837) from Southwest Finland (Karlsson et al., 2018). FinnBrain investigates how genetic and environmental factors affect children's health. The Ethics Committee of the Hospital District of Southwest Finland has approved this study. Written consent was obtained from the families, and mothers provided consent on behalf of their children.

Fecal samples with analyzed microbiota profiles were available from 445 children. MRI scans were obtained from 173 out of 203. From the main cohort, this study included all subjects who had successfully provided both a fecal sample and an MRI scan, resulting in a total of 82 subjects.

## 2.2. Imaging

MRI scans were taken from 5-year-old children. Magnetic resonance imaging (MRI) is a non-invasive method that captures cross-sectional images of the body. Through MRI, the anatomy, metabolism, and function of the human body can be observed. (Moser et al., 2009) The study group was scanned using Siemens Magnetom Skyra fit 3T with 20 – element head/neck matrix coil. Participants were either awake or in natural sleep during the MRI scan. T1-weighted brain MRIs were processed using FreeSurfer. The MRI recruitment process, exclusion criteria for imaging and image processing are more thoroughly described in Pulli et al., 2022.

## 2.3. Microbiome data

At the time of fecal sample collection, infants had a mean age were 64.5 days (SD = 13.4). Parents were given specific instructions both orally and in written form for collecting the fecal samples at home. Samples were collected in a sterile tube, which included the date and time of collection. The tubes were immediately stored at temperatures below +4°C. Parents were instructed to deliver the samples to the research lab (Turku University Hospital, Clinical Microbiology, Microbiome Biobank) within 24 hours; however, samples delivered within 48 hours were also included in the study. (A. K. Aatsinki et al., 2019)

The samples were analyzed as described in (A. K. Aatsinki et al., 2023). In research lab, samples were homogenized, divided into aliquots, and stored at -75 °C until DNA extraction. Bacterial DNA extraction was performed using the GXT Stool Extraction Kit VER 2.0 (Hain Lifescience GmbH, Nehren, Germany). The extraction procedure followed the manufacturer's instructions, with the sample vortex step replaced by homogenization using the MOBIO PowerLyzer 24 Bench-Top Bead-Based

Homogenizer (Keskitalo et al., 2021). The hypervariable region V4 was amplified, and the samples were sequenced using 16S rRNA sequencing with Illumina MiSeq. Raw sequences from 16S rRNA were processed using the DADA2 pipeline (version 1.14) to obtain exact amplicon sequence variants (AVSs) (Callahan et al., 2016).

The reads from the dataset were shortened to a length of 225 base pairs. All reads containing more than two errors were discarded (maxEE = 2). ASVs were taxonomically assigned using the SILVA taxonomy database (version 138) and the RDP Naive Bayesian Classifier algorithm.

Multiple sequence alignment was performed using the DECIPHER package. After processing, the resulting samples contained between 14,000 – 255,000 reads per sample (mean = 83,000, SD = 57,000).

### 2.4. Statistical analyses

Fecal samples were the source of data for alpha and beta diversity analyses. The numerical data was analyzed using RStudio (version 2022.02.3+492) including the microbiome and vegan packages.

Alpha diversity was assessed using the Shannon and Chao1 indices. In the linear regression model, the Shannon and Chao1 indices were used as dependent variables.

Pearson’s correlation was used to test the linear correlation between hippocampal volumes and alpha diversity. The correlation between beta diversity and hippocampal volumes was tested using PERMANOVA with the adonis function and Bray - Curtis dissimilarity. Beta diversity was visualized using principal coordinates analysis (PCoA).

## 3. Results

### 3.1. Alpha diversity

Pearson's correlation test indicated that there was no statistically significant linear correlation between alpha diversity and left hippocampal volume (p = 0.711, df = 79, correlation factor = 0.0418) (Figure 1) or right hippocampal volume (p = 0.2617, df = 79, correlation factor = -0.126) (Figure 2).

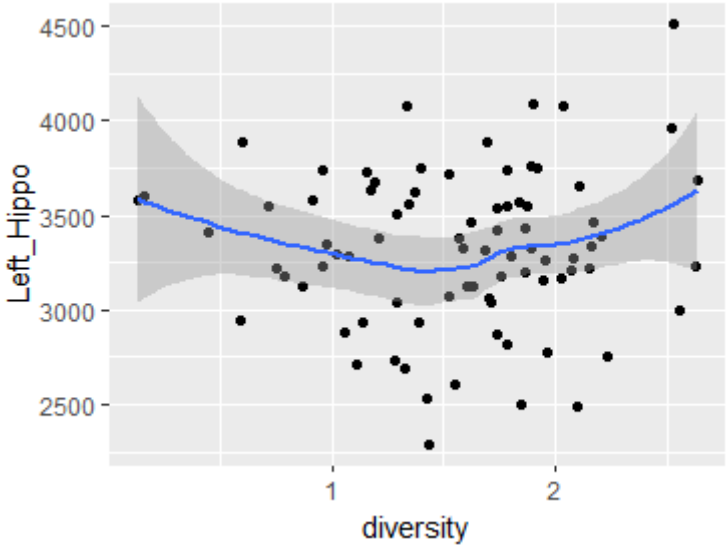


Figure 1. Linear correlation between left hippocampal volume and alpha diversity

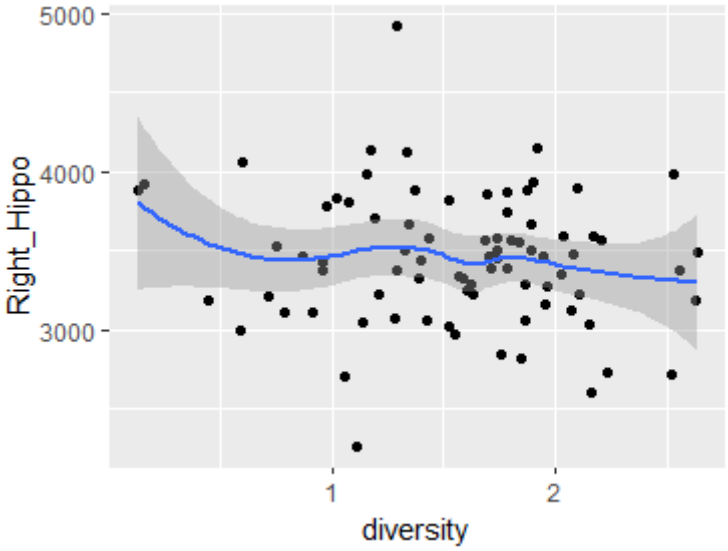


Figure 2. Linear correlation between right hippocampal volume and alpha diversity

## 3.2. Beta diversity

There was no significant association between beta diversity and left hippocampal volume (F. Model = 0.737, Pr (> F) = 0.76) (Figure 3). Similarly, there was no

significant association between beta diversity and right hippocampal volume (F. Model = 1. 2205, Pr (> F) = 26) (Figure 4).

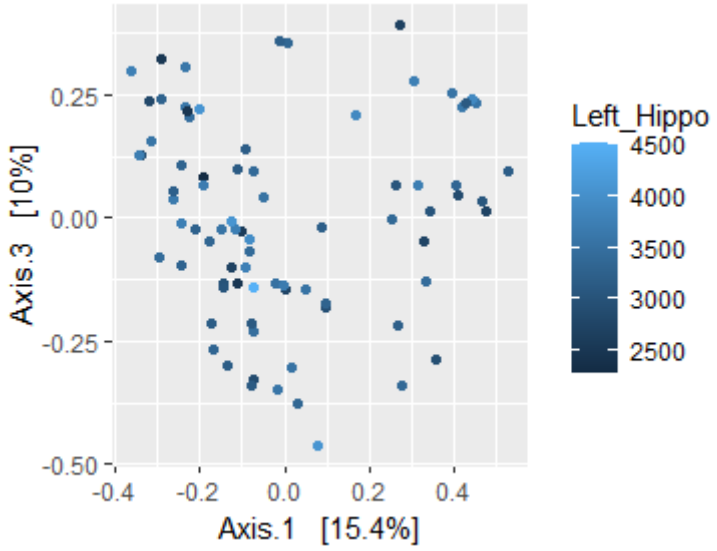


Figure 3. PCoA of left hippocampal volume compared to beta diversity

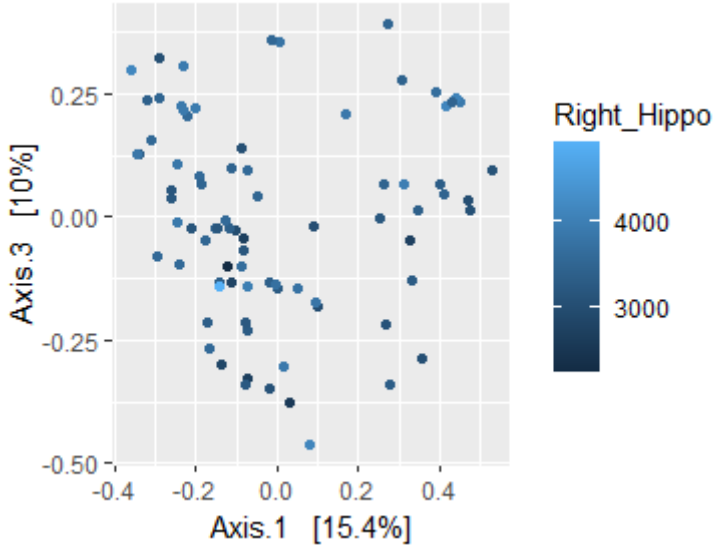


Figure 4. PCoA of right hippocampal volume compared to beta diversity

## 4. Discussion

In this study, the association between the early GI microbiome and later childhood hippocampal volume was examined. Microbial data was derived from stool samples collected around two months of age. Hippocampal volumes were measured at five years of age from the same participants who had provided stool samples in infancy.

Hippocampal volumes were then compared to the alpha and beta diversity of the GI microbiome.

No significant correlation was found between alpha diversity and hippocampal volume. However, the link between alpha diversity and the brain has been widely demonstrated in previous research. A recent study on adult patients with geriatric depression found a significant correlation between alpha diversity of the GI microbiomes alpha and hippocampal volume (Melanie Lee et al., 2022). Additionally, in schizophrenic adult patients, alpha diversity showed a clear linear correlation with gray matter volume (Li et al., 2021). Nevertheless, children remain an underrepresented study population in research examining alpha diversity and neurodevelopment.

Concerning beta diversity, there wasn't significant correlation between beta diversity and hippocampal volumes. Conversely, in a mouse study, hippocampal connectivity was decreased in mice that had received GI microbiota from ADHD patients compared to a healthy control group (Tengeler et al., 2020). Similarly, in human studies, differences in GI microbiome composition and hippocampal functional activity have been observed when comparing depressed patients to healthy controls (Xiao et al., 2024).

Contradictory findings across studies may stem from methodological limitations. The sample size in this study was relatively small compared to large-scale studies, making the results more susceptible to selection bias. Additionally, a smaller dataset may limit the ability to detect infrequent but significant correlations that could be observed in larger samples. Moreover, microbial and MRI data at this specific age point have been minimally analyzed in previous research. Future studies with larger cohorts and longitudinal designs may help confirm or refine the findings presented here.

## 5. Conclusion

This research examined the association between infant GI microbiota diversity and childhood hippocampal volume. No significant correlation was found between alpha

or beta diversity and volumes of hippocampus. For future studies, a larger sample size is recommended, as it may help identify less frequent but potentially significant correlations.

## 6. Sources


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