

Gut Microbiome Dysbiosis In At-Risk Versus Low-Risk Stroke Adults

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Introduction

Healthy brain aging has been a significant focus in older adults. Lifestyle changes such as diet and exercise have been implemented by adults to avoid brain related disease processes such stroke and Alzheimer's disease. Stroke risk factors such as high BMI, hypertension, diabetes, and the presence of ApoE4 gene have been explored in hopes to find interventions targeted to promote more healthy brain aging. Currently there is a knowledge gap on how interventions can promote healthy brain aging. Targeting the bidirectional gut-brain axis by manipulating the gut microbiome can be a possible intervention to promote brain health.

Methodology

We recruited 30 healthy participants ages 55-85 years old from researchmatch.org and online advertisements. We genotyped their APOE status and obtained their demographical and medical information, including BMI, gender, hypertension and diabetes. Stool samples were collected to measure the gut microbiome with shotgun metagenomic sequencing. We used T1 imaging, magnetic resonance spectroscopy, arterial spin labeling, and diffusion tensor imaging for brain volume, metabolites, cerebral blood flow, and white matter integrity, respectively. Correlational analysis was done using the Lin2 regression package.

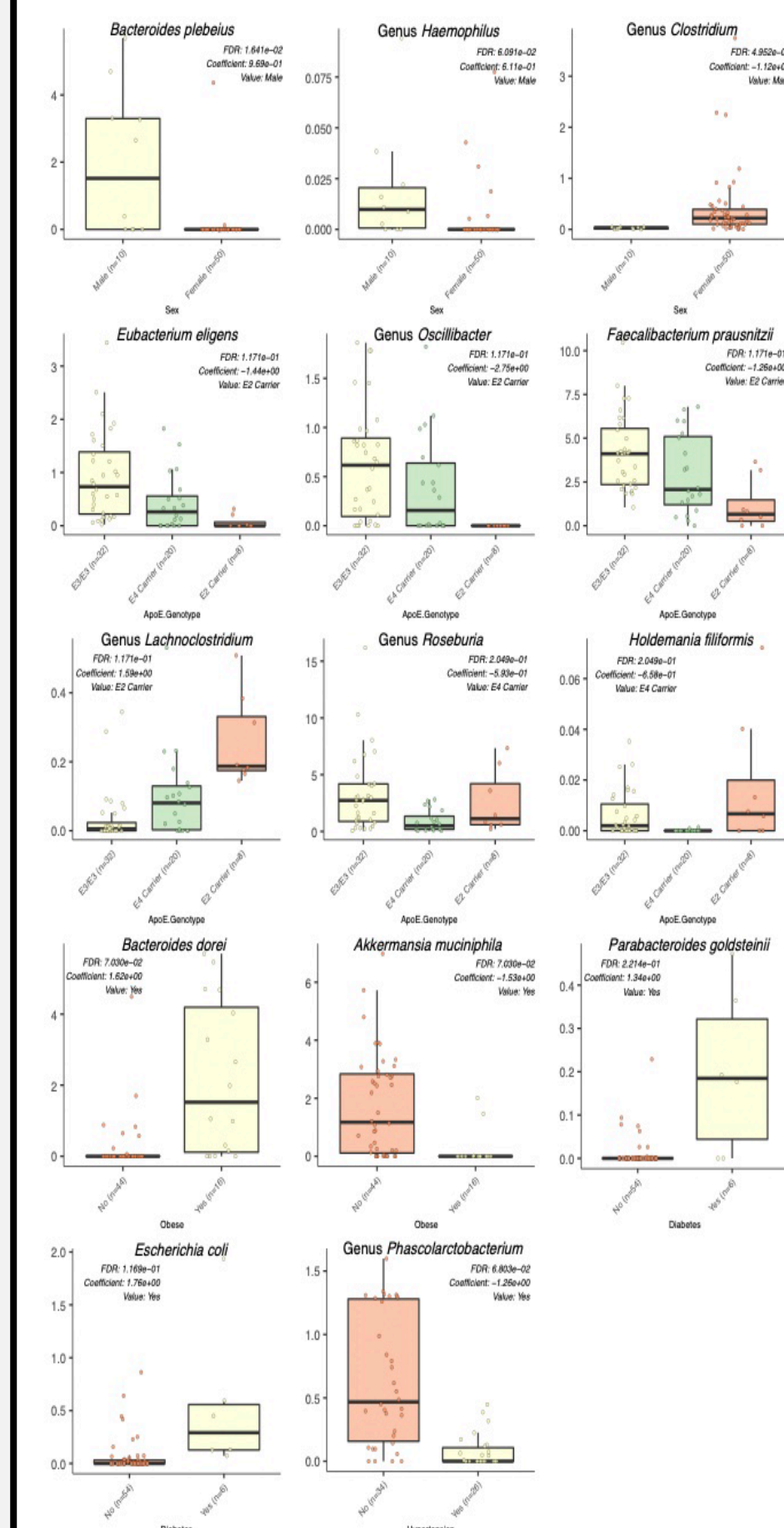
Microbial taxa associated with imaging features

Microbial Taxa	Taxa Key Characteristics	Imaging Feature Volume	Coef	Q Value
<i>Bacteroides ovatus</i>	Induces IgA Promotes IL-22	Thalamus	-0.672	0.169
<i>Bacteroides uniformis</i>	Butyrate Producer	White Matter Hypointensities	-0.376	0.1578
Family <i>Acidaminococcaceae</i>	SCFA Producer	Corpus Callosum Mid Posterior	0.364	0.2157

Results

There were several bacterial taxa associated with BMI, diabetes, sex, hypertension, and ApoE genotypes. For instance, the ApoE e3/e4 genotype showed decreased *roseburia*, which is an important butyrate producer. Butyrate producers are associated with thalamus and corpus callosum volumes. Also, *Bacteroides ovatus* and *Bacteroides uniformis* were associated with thalamus volume and white matter hyperintensities, respectively. We found that *Collinsella aerofaciens* was negatively correlated with GABA, the main inhibitory neurotransmitter in brains.

Microbial taxa associated with demographic features



Microbial Taxa associated with Demographic Features

Demographic Feature	Bacterial Taxa	Taxa Key Characteristics	β	Q-Value
Age	None			
	<i>Bacteroides plebeius</i>	Metabolizes agarose	0.969	0.01641
Sex (Male)	<i>Genus Clostridium</i>	Also inhabits female reproductive tract	-1.12	0.04952
	<i>Genus Haemophilus</i>	Infectious, inversely associated with plant-based diet	0.611	0.06091
Race	None			
	<i>Eubacterium eligens</i>	Anti-inflammatory	-1.44	0.1697
	<i>Blautia producta</i>		0.587	0.0827
	<i>Genus Lachnospirillum</i>		1.59	0.1171
ApoE e2 carriers	<i>Genus Oscillibacter</i>		-2.75	0.1808
	<i>Faecalibacterium prausnitzii</i>	Anti-inflammatory	-1.26	0.1808
	<i>Genus Roseburia</i>	Butyrate producer	-0.638	0.2134
ApoE e4 carriers	<i>Holdemania filiformis</i>		-0.658	0.2049
	None			
Obese	<i>Akkermansia muciniphila</i>	Decreased in obesity	-0.663	0.1205
	<i>Bacteroides dorei</i>	Anti-inflammatory	1.62	0.0703
Diabetes	<i>Escherichia coli</i>	Normal gut commensal with capacity to cause extraintestinal infections	1.76	0.1169
	<i>Parabacteroides goldsteinii</i>	Anti-inflammatory	1.34	0.2214
Hypertension	<i>Genus Phascolarctobacterium</i>	Produce SCFAs	-1.26	0.06803
Hyperlipidemia	None			

Microbial taxa associated with brain metabolites

Microbial Taxa	Taxa Key Characteristics	Metabolite	Coef	Q Value
<i>Collinsella aerofaciens</i>	Proinflammatory Bile-Acid Conjugator	GABA	-0.357	0.06152
<i>Parasutterella excrementihominis</i>		GABA	0.703	0.07391
<i>Alistipes putredinis</i>		GPC	0.956	0.2127
Family <i>Acidaminococcaceae</i>	SCFA Producer	GPC	0.338	0.2127
<i>Ruminococcus lactaris</i>	Butyrate Producer	NAA+NAAG	0.653	0.09658
	Inhibits IL-8	MM09	0.688	0.03519
		MM12	0.612	0.09160
<i>Streptococcus thermophilus</i>	Decreases uremic toxins	MM09	0.526	0.1315
		MM12	0.547	0.07143
<i>Eubacterium eligens</i>	Anti-inflammatory	MM14+Lip13a+ Lip13b+MM12	0.484	0.2314

Microbial Taxa associated with Cerebral Blood Flow

Microbial Taxa	Taxa Key Characteristics	Perfusion Imaging Feature	Coef	Q Value
Family <i>Eggerthellaceae</i>	Equol Producers	Banks of Superior Temporal Sulcus	-0.364	0.1261
		Left Pars Triangularis	-0.219	0.09265
<i>Adlercreutzia equolifaciens</i>	Equol Producer	Banks of Superior Temporal Sulcus	-0.551	0.1261
		Total Middle Temporal Cortex	-0.356	0.2146
		Left Pars Triangularis	-0.355	0.09821
		Total Banks of Superior Temporal Sulcus	-0.573	0.07049
<i>Assacharobacter celatus</i>	Equol Producer	Left Middle Temporal Cortex	-0.595	0.0489
		Total Middle Temporal Cortex	-0.652	0.01391
		Left Pars Triangularis Cortex	-0.518	0.09265
		Orbita Pars Opercularis Cortex	-0.638	0.02800
<i>Gordonibacter pamelaiae</i>	Equol Producer	Total Pars Opercularis Cortex	-0.591	0.08749
		Total Putamen	-0.577	0.08859
		Left Pars Triangularis Cortex	-0.525	0.09265
		Left Posterior Cingulate Cortex	-0.594	0.1455
<i>Collinsella stercoris</i>	Bile-Acid Conjugator	Right Banks of Superior Temporal Sulcus	0.460	0.00409
		Total Middle Temporal Cortex	0.340	0.1678
		Left Pars Triangularis	0.327	0.09401
		Left Transverse Temporal	0.339	0.2095
<i>Genus Alistipes</i>	SCFA Producer	Left Putamen	-0.485	0.01734
		Total Putamen	-0.386	0.08859
		Left Accumbens area	-0.406	0.1063
<i>Genus Parabacteroides</i>	Alters dopaminergic signaling	Right Hippocampus	-0.753	0.00210
Phylum <i>Firmicutes</i>		Left Transverse Temporal Cortex	-0.894	0.2098
	Order <i>Clostridiales</i>		-0.900	0.2098
<i>Eubacterium siraeum</i>	Positively correlated with HDL cholesterol levels	Total Middle Temporal Cortex	-0.715	0.1352
		Right Caudal Middle Frontal Cortex	-0.770	0.1239
		Right Post Central Cortex	-0.674	0.1691
		Total Post Central Cortex	-0.704	0.1758
<i>Genus Haemophilus</i>	Infectious, inversely associated with plant-based diet	Right Rostral Anterior Cingulate	0.250	0.2167
		Total Rostral Anterior Cingulate	0.267	0.09848
		Total Posterior Cingulate Cortex	0.240	0.1928
Family <i>Haemophilus parvotifluensae</i>		Right Entorhinal	0.281	0.02571
Family <i>Deafalfovibrionaceae</i>	Sulfate reducers	Right Entorhinal Cortex	-0.449	0.1875

Microbial taxa associated with white matter integrity

Microbial Taxa	Taxa Key Characteristics	White Matter Integrity Imaging Feature	Coef	Q Value
Family <i>Eggerthellaceae</i>	Equol Producers	Middle Cerebellar Peduncle	0.245	0.05163
		Left External Capsule	0.252	0.09284
<i>Gordonibacter pamelaiae</i>	Equol Producer	Middle Cerebellar Peduncle	0.720	0.004926
		Pontine Crossing Tract	0.646	0.05013
		Left Corticospinal Tract	0.613	0.1115
		Total Corticospinal Tract	0.590	0.2075
<i>Assacharobacter celatus</i>	Equol Producer	Left Tapetum	0.662	0.02824
		Tapetum	0.611	0.04985
<i>Adlercreutzia equolifaciens</i>	Equol Producer	Left Corticospinal Tract	0.468	0.1821
		Left Corticospinal Tract	0.324	0.2284
<i>Genus Bifidobacterium</i>	SCFA Producer	Left Fornix	0.396	0.1751
		Left Inferior Frontal Occipital Fasciculus	0.437	0.06521
<i>Coprobacter fastidiosus</i>	Butyrate Producer	Right Corticospinal Tract	-0.547	0.1115
<i>Bacteroides uniformis</i>	Butyrate Producer	Right Superior Longitudinal Fasciculus	-0.473	0.2484
		Right Tapetum	0.469	0.03213
<i>Eubacterium siraeum</i>	Positively correlated with HDL cholesterol	Tapetum	0.437	0.03961
		Middle Cerebellar Peduncle	0.645	0.1392
<i>Clostridium innocuum</i>	Infectious	Left Corticospinal Tract	0.423	0.2468
<i>Genus Lactobacillus</i>	Strengthen gut barrier	Left Medial Lemniscus	0.380	0.2285
<i>Lachnospira pectinocitiza</i>	Degrades pectin	Left Medial Lemniscus	0.296	0.2285
<i>Roseburia hominis</i>	Butyrate Producer	Left Cingulum	0.544	0.09441
		Cingulum	0.541	0.1044
<i>Streptococcus thermophilus</i>	Decreases uremic toxins	Left Inferior Frontal Occipital Fasciculus	0.503	0.06636
		Right Superior Longitudinal Fasciculus	-0.426	0.2491
<i>Monoglobus pectinilyticus</i>	Degrades pectin	Right Superior Longitudinal Fasciculus	0.609	0.2484
		Superior Longitudinal Fasciculus	0.656	0.2047
<i>Clostridium citroniae</i>		Right Superior Longitudinal Fasciculus	0.626	0.1934
		Tapetum	0.384	0.2484
<i>Genus Flavonifractor</i>		Right Superior Longitudinal Fasciculus	0.369	0.2484
<i>Gemmiger fornicilis</i>		Right Superior Longitudinal Fasciculus	-0.453	0.2484
		Superior Longitudinal Fasciculus	-0.447	0.2047

Conclusion

The variables associated with increased risk of stroke such as high BMI, hypertension, diabetes, ApoE4 gene are correlated to gut dysbiosis. The gut is therapeutically easier to target than the brain due to the blood brain barrier as well as the skull; thus, interventions targeted at the gut microbiome may be of use for aging adults. Further research must be done to explore the mechanisms of association.

Reference

Hammond, Tyler, "EVALUATING THE MICROBIOME TO BOOST RECOVERY FROM STROKE: THE EMBRS STUDY" (2022). Theses and Dissertations--Neuroscience. 28. https://uknowledge.uky.edu/neurobio_etds/28

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