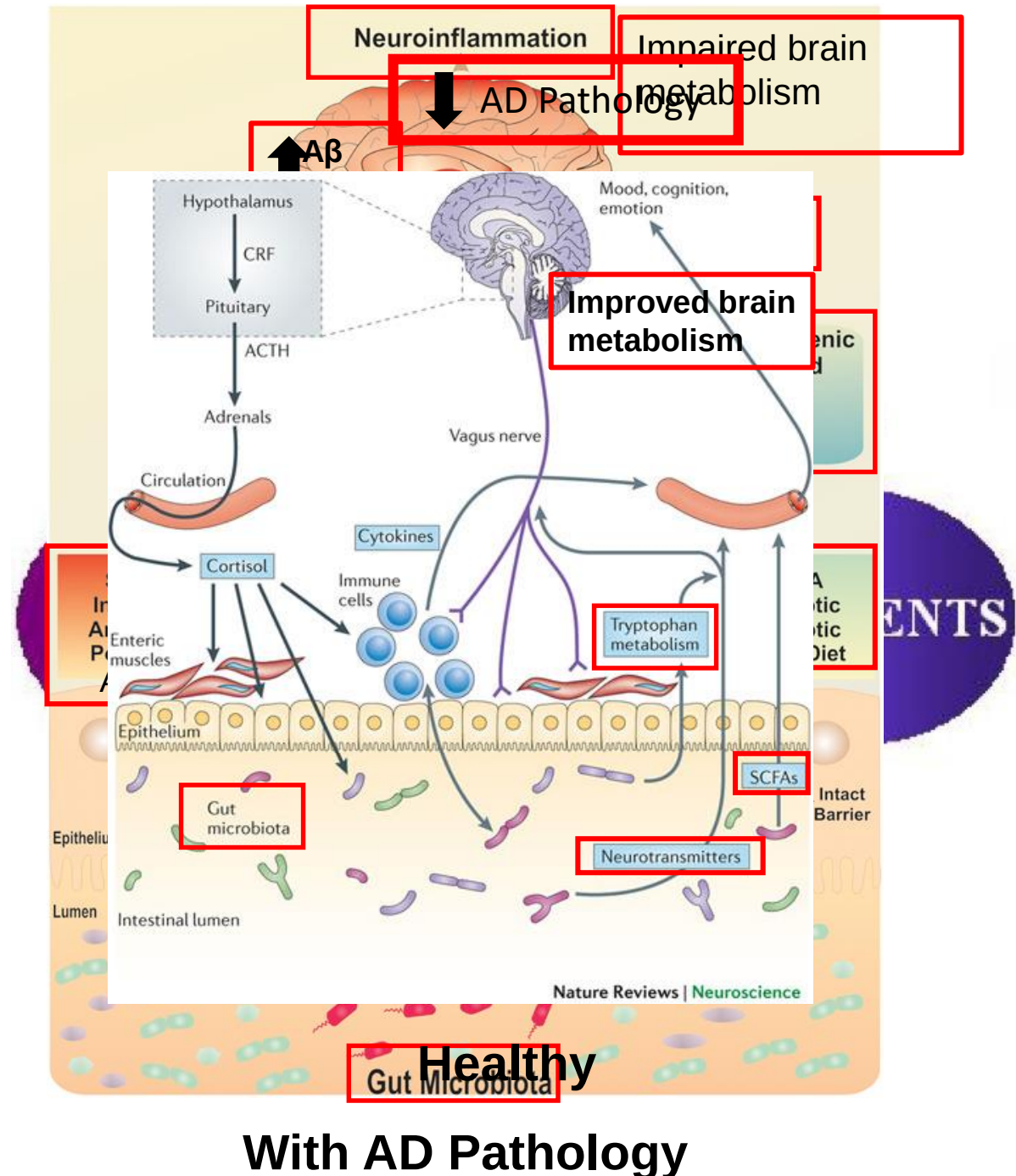


Apolipoprotein E genotype- dependent nutrigenetic effects to prebiotic inulin for reducing risk for Alzheimer's disease in mice via gut-brain axis

Lucille M. Yanckello, Ya-Hsuan Chang, Jared D. Hoffman, Penghui Lin
Geetika Nehra, George Chlipala, Scott D. McCulloch, Tyler C.
Hammond, Andrew T. Yackzan, Andrew N. Lane, Stefan J. Green, Anika
M.S. Hartz, Ai-Ling Lin

Introduction

- APOE4 gene is the highest genetic risk factor for Alzheimer's Disease
 - In the brains of APOE4 carriers we see
 - Altered glucose & lipid metabolism
 - Mitochondrial dysfunction
 - Pentose Phosphate Pathway alterations
- Not seen in APOE3 carriers
- How do these genes affect the processing of nutrients?
- **How is Alzheimer's Disease related to the gut brain axis?**



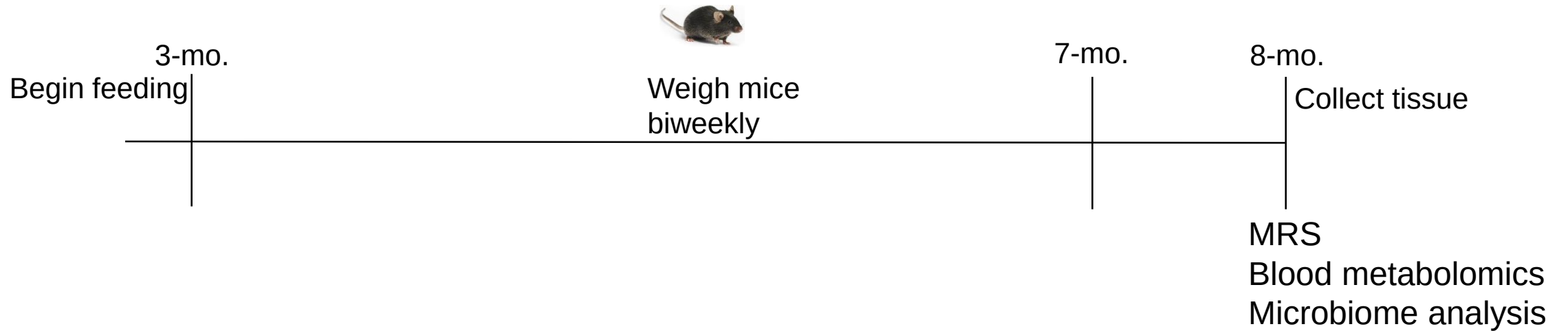
Goal of the study:

To determine whether responses to inulin are *APOE* genotype-dependent

Hypothesis:

Inulin will be processed differently by each genotype leading to distinctions in systemic and brain metabolism and gut microbiome structure

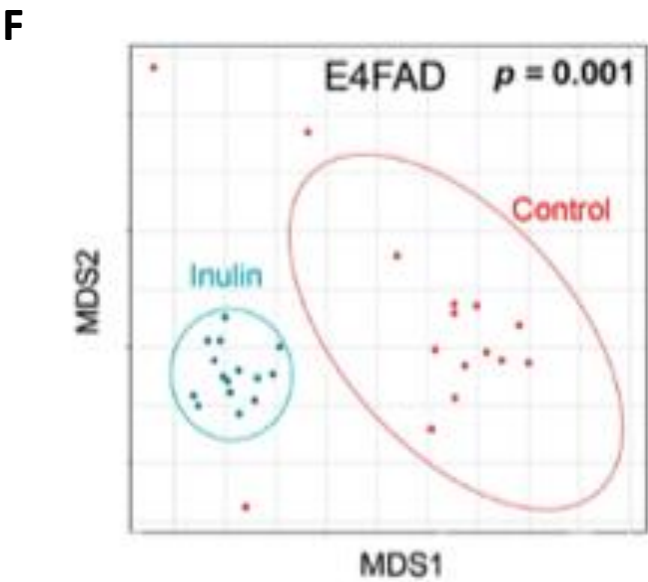
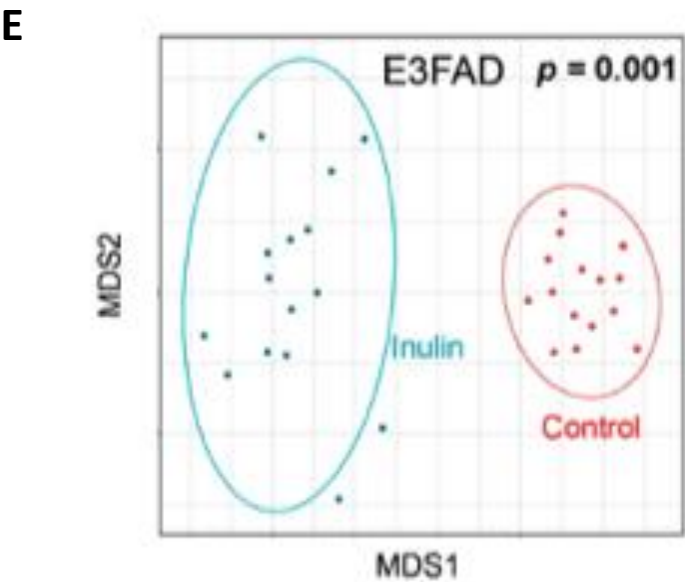
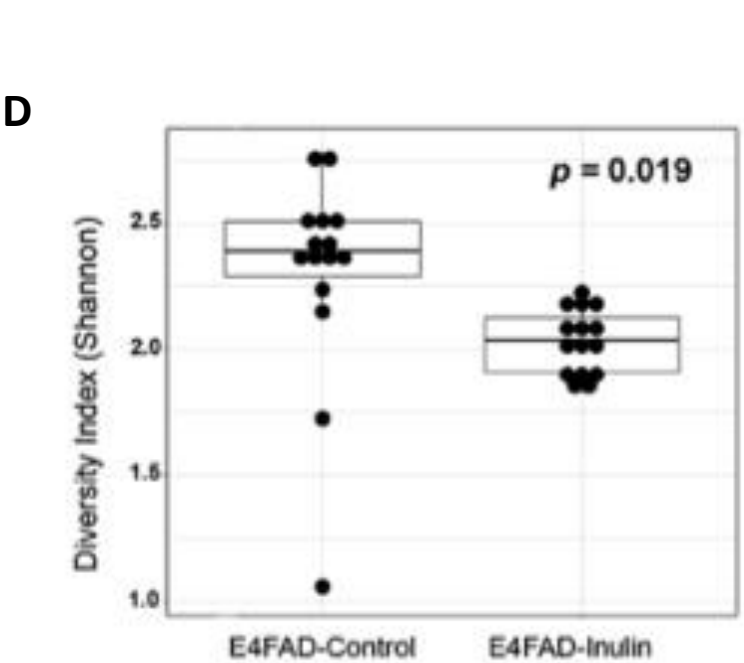
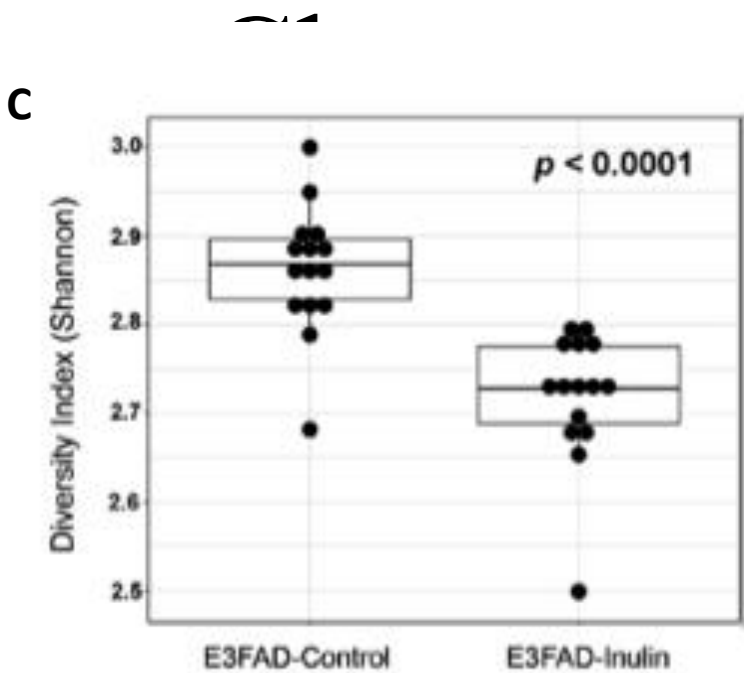
Study Design



Diet	Prebiotic Diet	Control Diet
Protein %	18.2	18.2
Carbohydrate %	67.8	60.2
Fat %	7.1	7.1
Fiber %	8.0 (Inulin)	8.0 (Cellulose)
Energy (kcal/g)	4.08	3.78

Gut Microbi

Taxonomy	Food
Alpha and	
Beta	
Butyrate	
Lactobacillus	
Prevotella	
Escherichia	
Coli	
(E. Coli)	
Bifidobacterium	



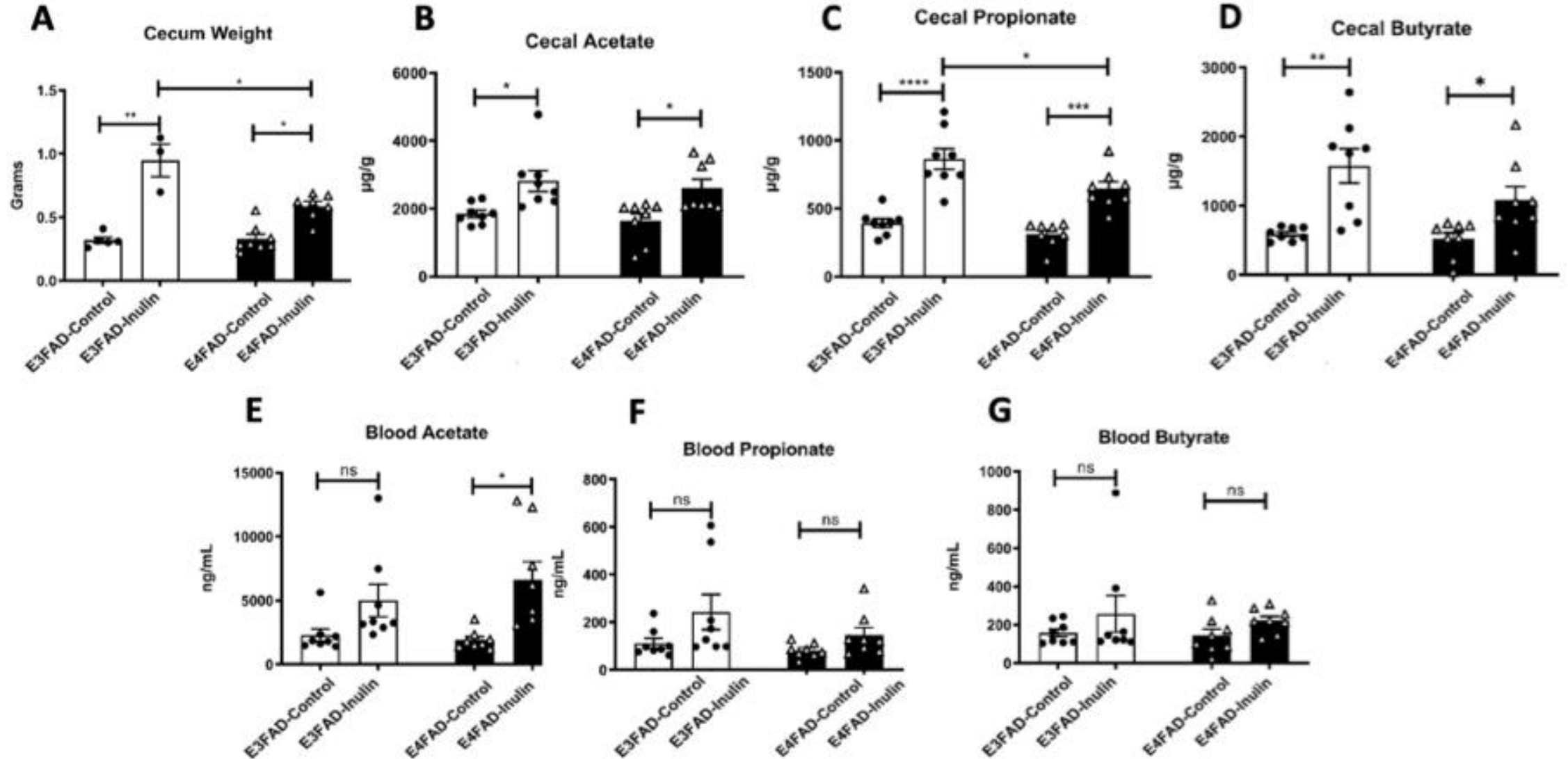
2.10

2.20E-00

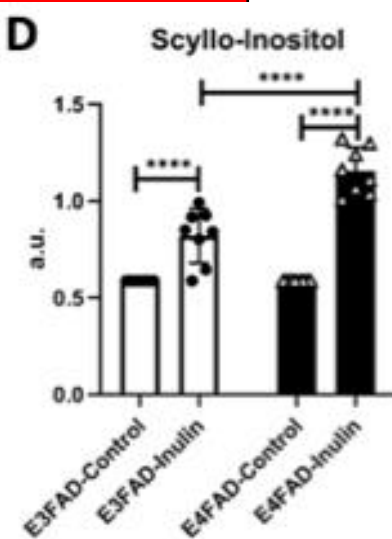
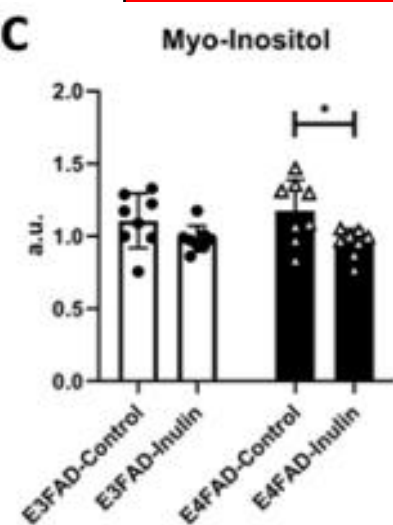
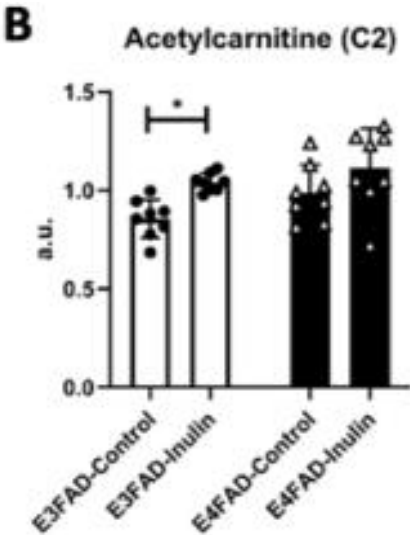
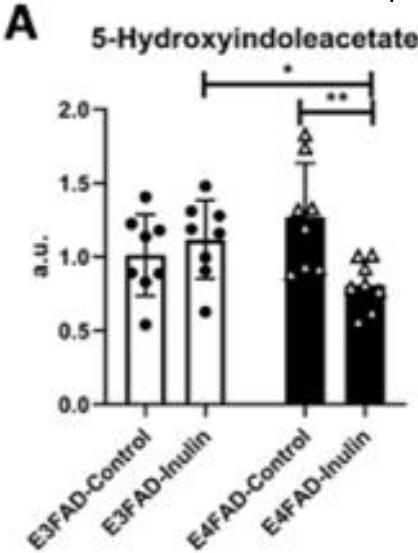
0.11

0.22

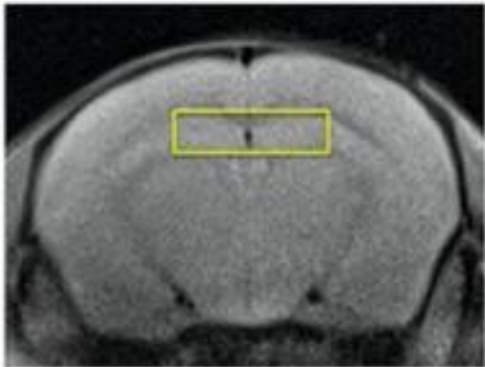
Short Chain Fatty Acid Changes



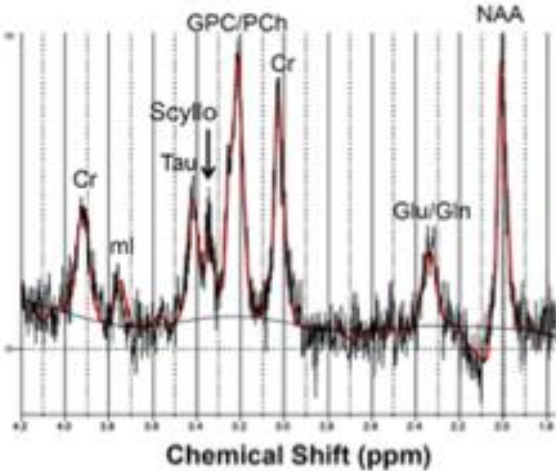
Systemic Metabolic Changes		Fold Change	
		Inulin	
		Ctrl	
Pathway	Biochemical Name	E3FAD	E4FAD
	indoleacrylate	2.91	5.68
	indolepropionate	6.42	9.68
Tryptophan	5-Hydroxyindoleacetate		1.29
	Acetylcarnitine (C2)		0.65
Tyrosine	Myo-Inositol		0.81
	Scyllo-Inositol		0.87
Pentose Metabolism			2.11
			0.14
			1.41
			2.01
			2.08
			1.37
			2.67
			1.36
			1.68
			1.73
Primary Lipids			2.53
			2
			1.6
			1.44
			10.92
			16.81
			8.78
			32.41
			32.44
			22.69
Secondary Lipids	ursocholate	1.76	



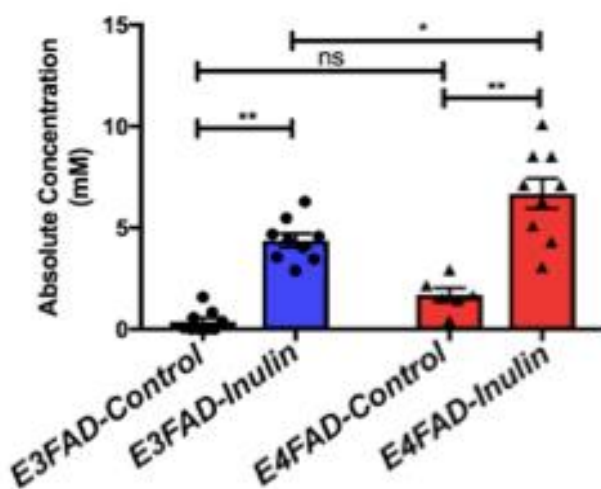
E ¹H-MRS voxel on hippocampus



F ¹H-MRS spectrum



G Scyllo-Inositol in Hippocampus



E3FAD

E4FAD

- Altered metabolic pathways in periphery related to tryptophan and tyrosine
- Increased abundance of *E. Coli*
- Increased abundance of *Bifidobacterium*
- Increased levels of Scyllo-inositol in plasma samples
- Increased levels of acetylcarnitine (C2) in the brain

- **Altered diversity**
- **Increased abundance of *Lactobacillus* and *Prevotella***
- **Reduced abundance of *Tuicibacter***
- **Enlarged cecum size**
- **Increased levels of cecal SCFAs**
- **Increased scyllo-inositol level in vivo (hippocampus) and in the brain tissue**

- Altered metabolic pathways related to TCA, PPP and bile acids
- Decreased abundance of *E. Coli*
- Decreased level of 5-hydroxyindoleacetate in the brain
- Reduced level of myo-inositol in the brain