Faecalibacterium prausnitzii and *Blautia faecis* improve motor and cognitive phenotypes through microglial and metabolic reprogramming in the 3KL synucleinopathy model

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Background

Emerging evidence implicates the gut microbiome in the pathogenesis and progression of Parkinson's disease and related synucleinopathies. Notably, butyrate-producing bacteria are consistently reduced in these disorders. This study aimed to investigate the role of two key butyrate-producing commensals, *F. prausni*tzii and *B. faecis*, in synucleinopathy.

1. Study design

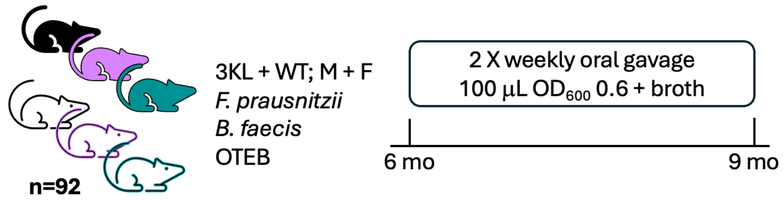

Figure 1. Male and female, α-synuclein 3KL and WT mice were gavaged live bacterial suspensions in culture media (including supernatant) of either *F. prausnitzii*, *B. faceis,* or OTEB broth twice per week for three months, from 6-9 months of age.

2. *F. prausnitzii* and *B. faecis* improve motor and cognitive phenotypes in male 3KL mice

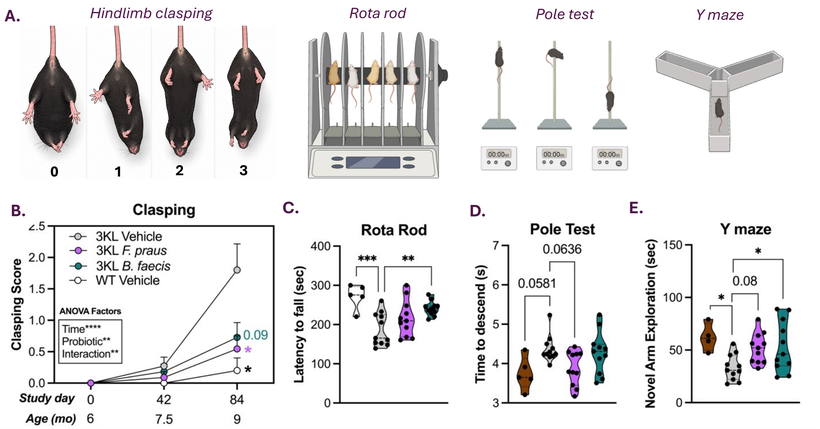

Figure 2. ***F. prausnitzii* and *B. faecis* improve motor and cognitive phenotype. A)** Caroon rendering of behavior tests **B)** Hindlimb clasping phenotype measured longitudinally. Analysis performed by two-way ANOVA with Tukey's MTC. **C)** Motor endurance and coordination measured by latency to fall on the rota rod. **D)** Fine motor coordination measured by pole test. **E)** Spatial memory analyzed by novel arm radial Y-maze. Analysis for B-D measured by one-way ANOVA with Tukey's MTC. *P<0.05, **P<0.01, ***P<0.001.

3. *F. prausnitzii* and *B. faecis* alter microglial transcriptional profiles

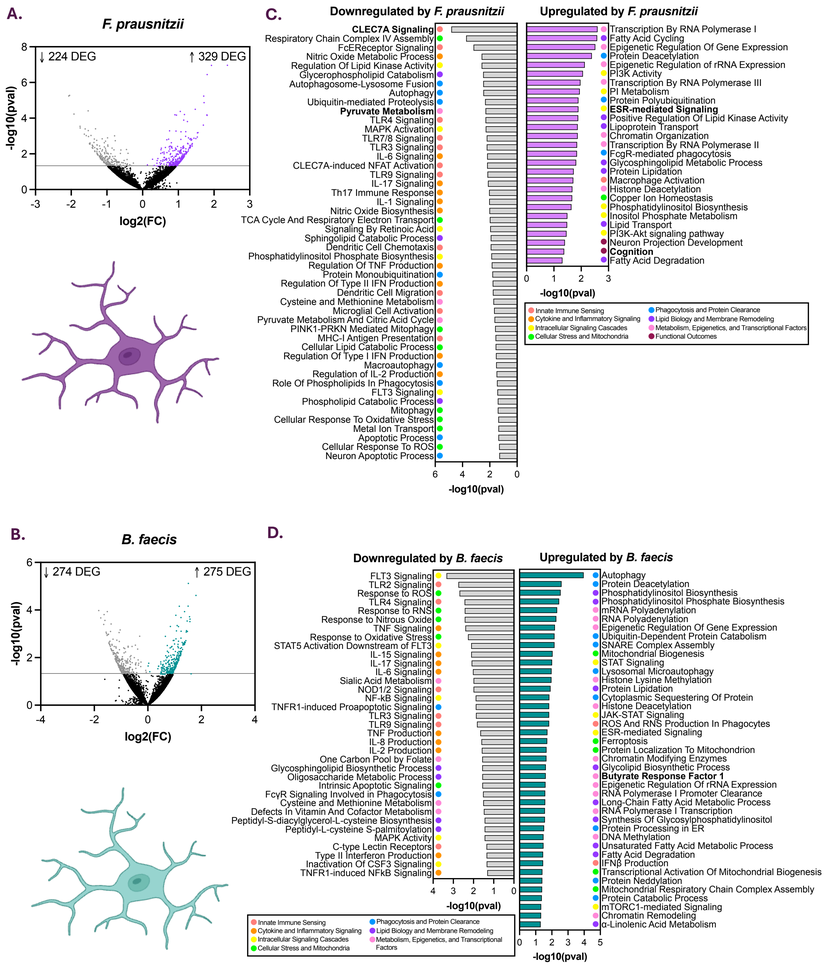

Figure 3. ***F. prausnitzii* and *B. faecis* alter microglial transcriptional profiles in male 3KL mice.** Volcano plot of differentially expressed genes significantly altered by **A)** *F. prausnitzii* and **B)** *B. faecis* by bulk RNA sequencing of isolated microglia. Ingenuity Pathway Analysis revealed changes in canonical pathways including **C)** downregulation of inflammatory signaling pathways in response to *F. prausnitzii* and **D)** increased butyrate response genes and lipid metabolism in response to *B. faecis*. All pathways shown are statistically significant (P<0.05), two-sided Wald test using the DESeq2 package in R.

4. *F. prausnitzii* and *B. faecis* produce multiple SCFAs

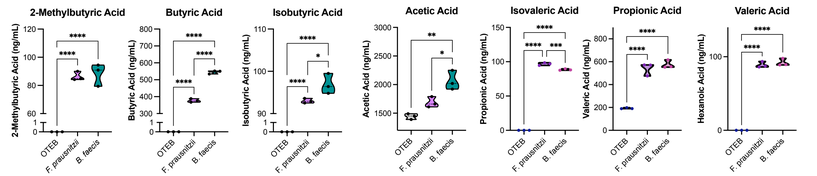

Figure 4. Short chain fatty analysis. *B. faecis* produces more butyric and isobutyric acid than *F. prausnitzii*

5. *F. prausnitzii* and *B. faecis* alter host metabolomic profiles

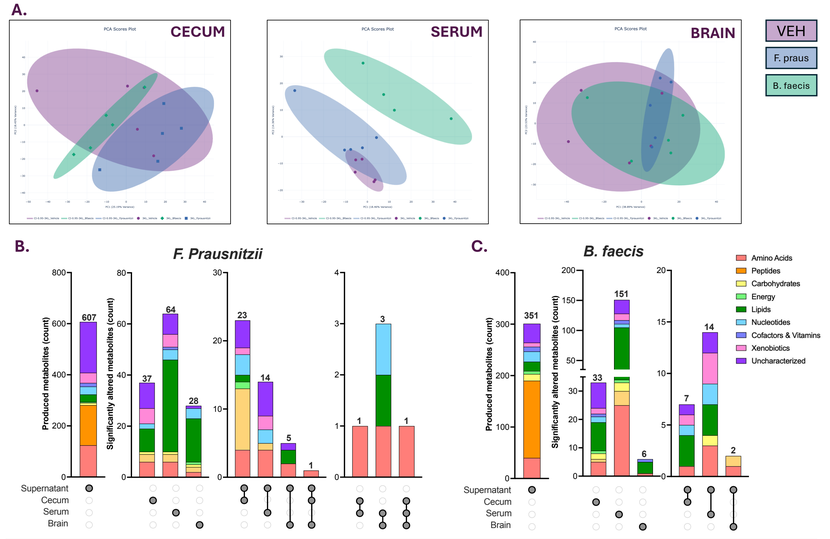

Figure 5. ***F. prausnitzii* and *B. faecis* altered host metabolites. A)** PCoA plots of cecum, serum, and brain metabolites from 3KL male mice treated with *F. prausnitzii* (blue), *B. faecis* (green) and OTEB (purple). Stacked histograms of metabolites produced by and in response to **B)** *F. prausnitzii* and **C)** *B. faecis* categorized by metabolic super pathways.

Conclusions

These findings demonstrate that *F. prausnitzii* and *B. faecis* improve motor and cognitive function in a model of synucleinopathy through microglial and metabolic reprogramming. Distinct microbial metabolites, including betaine and unsaturated fatty acid–related compounds, were detected in recipient mouse brains, supporting a gut–brain mechanistic link. Together, these results highlight beneficial commensal microbes as modulators of neuroinflammation and metabolism and targeting the gut microbiome may represent a therapeutic strategy for synucleinopathies. This work is funded by the **Susan and Charles Berghoff Foundation.**