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SUPPLEMENTARY INFORMATION

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The neuroactive potential of the human gut microbiota in quality of life and depression

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Supplementary Information

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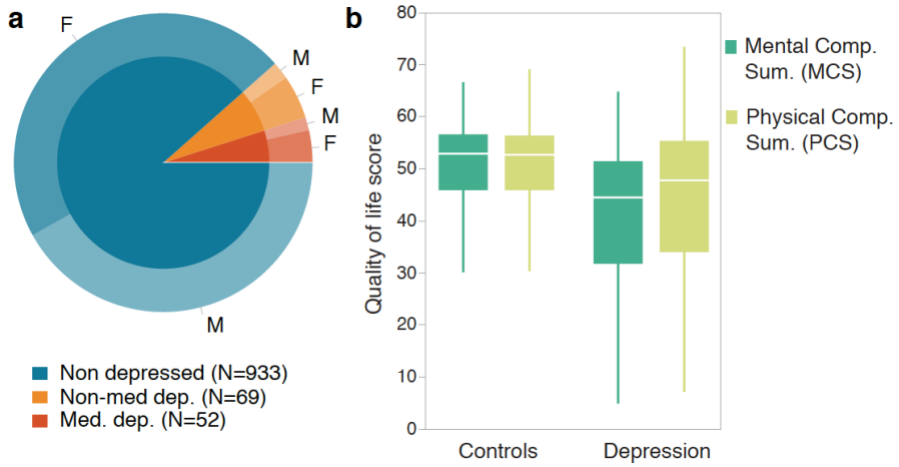
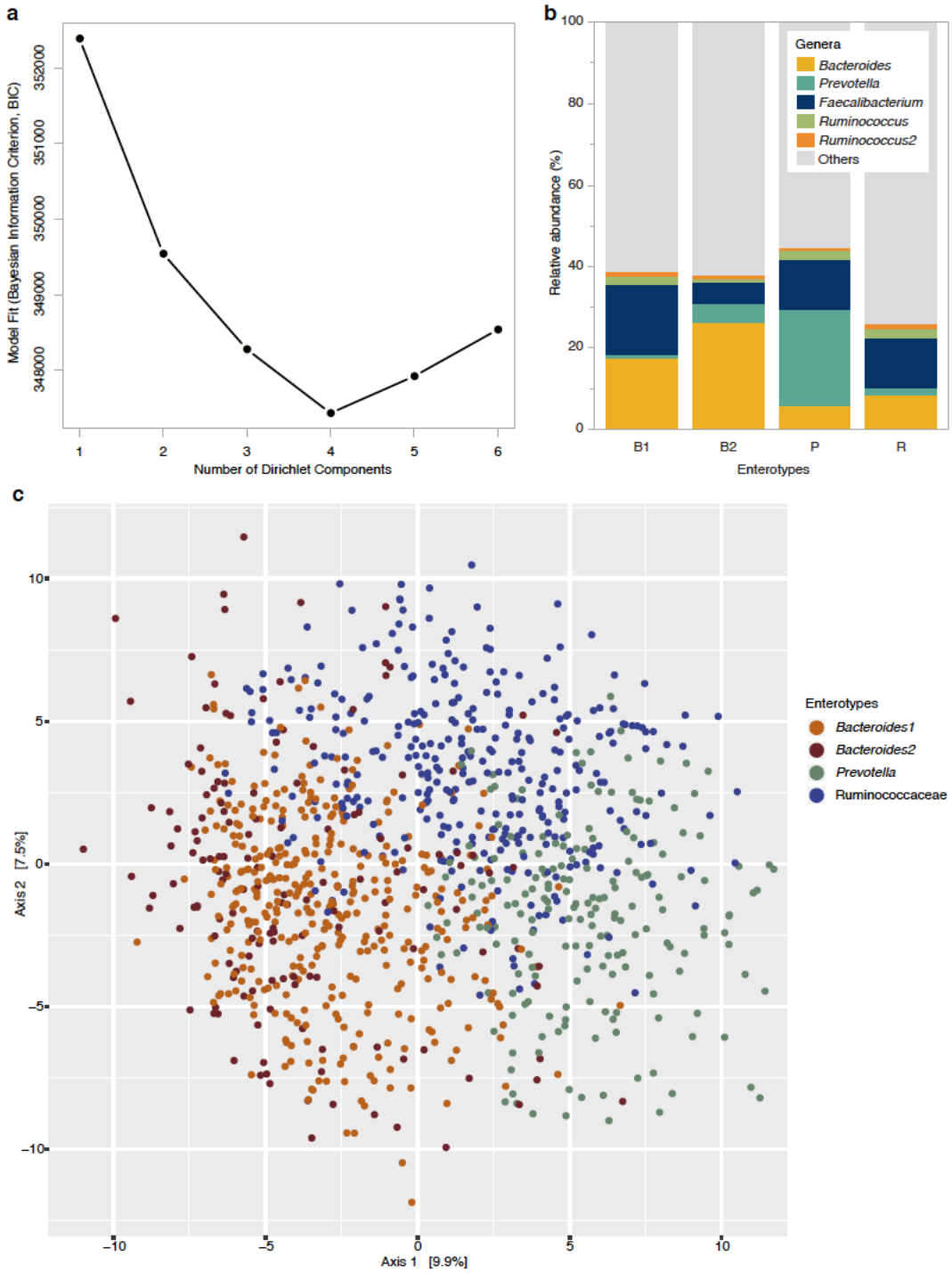
This file includes:
Supplementary Figures 1 to 3
Legends for Supplementary Data 1 and 2
Legends for Supplementary Tables 1 to 18

Other Supplementary material for this manuscript include:
Supplementary Data 1
Supplementary Data 2 (Excel file containing Supplementary Tables 1 to 18)

Supplementary Figures and Legends

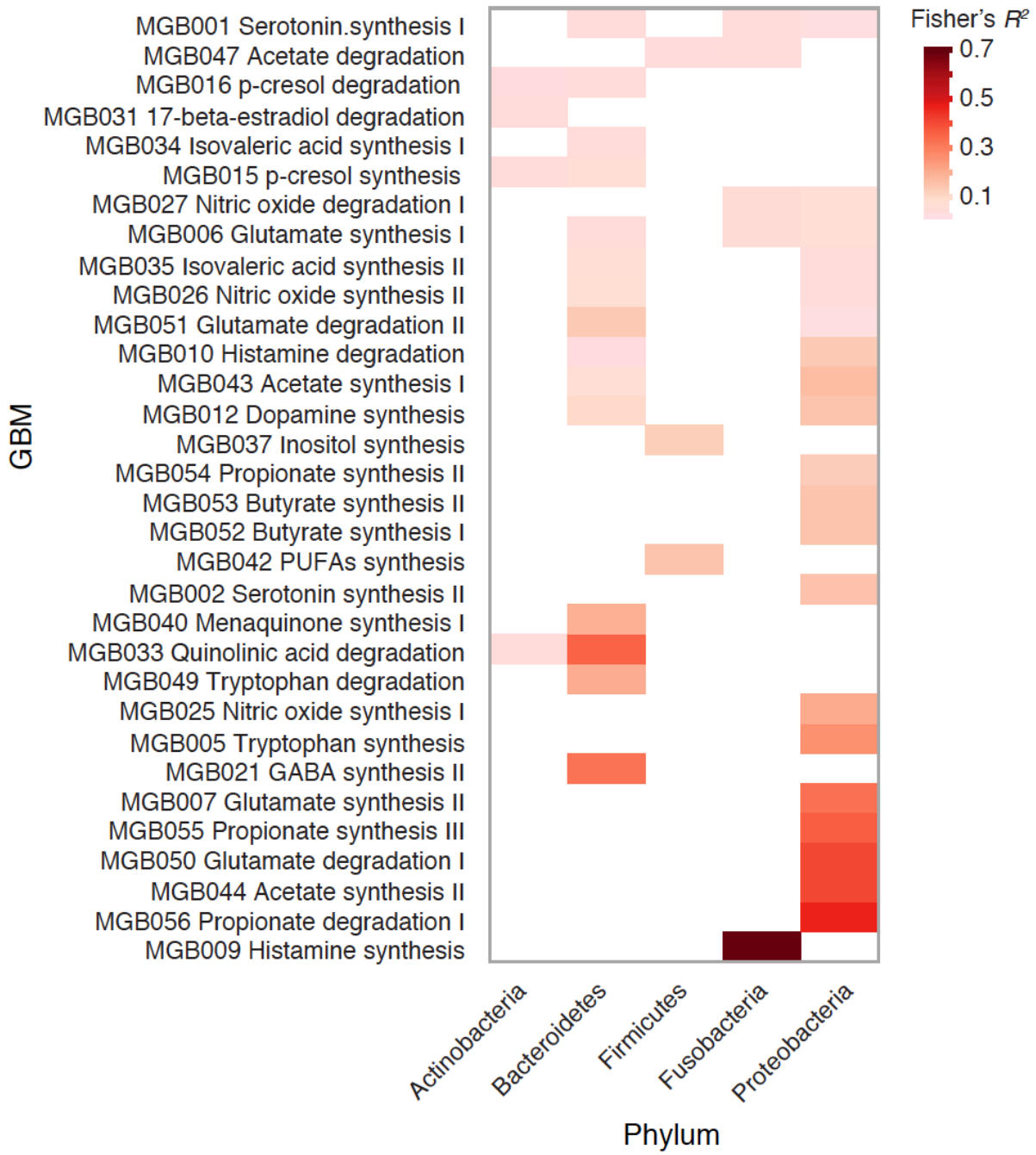


Supplementary Figure 1. Depression prevalence and association with QoL in the FGFP dataset (N=1054). (a) Prevalence of depression and proportion of individuals taking antidepressant medication. F: females, M: males. (b) QoL scores in controls (N=933) *vs* individuals with GP-reported depression (N=121); all scores were lower in individuals with depression (two-sided Wilcoxon rank-sum test, FDR<0.1; Supplementary Table 3). For simplicity only the mental and physical summary scores are shown. The body of the box plot represents the first and third quartiles of the distribution, and the median line. The whiskers extend from the quartiles to the last data point within 1.5×IQR, with outliers beyond.



Supplementary Figure 2. Community type stratification of the FGFP cohort. (a) Identification of the optimal number of clusters (Dirichlet components) in the FGFP cohort (N=1054) based on the Bayesian Information Criterion (BIC). The optimal number of clusters (minimum BIC=347431.6) is four. (b) Barplot representation of the average relative abundance of a few representative genera split into the four enterotypes identified by DMM community typing on the FGFP cohort (N=1054). (c) Genus-level microbiota community variation represented

by principal coordinates analysis (Aitchison distance PCoA; N=1054). Samples are coloured by enterotype.



Supplementary Figure 3. GBM phylogenetic inertia. Phylum-level associations (only phyla with ≥5 genome representatives; Fisher's test, FDR<0.1) of GBMs displaying phylogenetic inertia (GBM presence in gut genomes [N=532] correlated to phylogenetic tree topology; Pagel's lambda, FDR<0.1). Colour intensity is proportional to Fisher's test R^2 of GBM-phyla associations.

Supplementary Data 1. Gut-brain module (GBM) description, containing module input and output compounds and database and literature references used to assemble each module. Each line corresponds to one module step. Tabs separate alternative orthologs (OR operator), while commas correspond to orthologs being subunits of enzymatic complexes (AND operator). For the latter, all subunits of a complex need to be detected in other to consider it present.
Format: Text File
Size: 12 KB

Supplementary Data 2. Excel file containing Supplementary Tables 1 to 18 and their legends.
Format: Excel File
Size: 304 KB

Supplementary Table 1. Metadata overview of the datasets used in this study (FGFP, N=1054; LLD, N=1063; TR-MDD, N=7).

Supplementary Table 2. RAND score distribution in the FGFP cohort (N=1054).

Supplementary Table 3. RAND score distribution in heathy individuals (N=933), individuals with depression taking antidepressants (N=52), and individuals not taking antidepressant medication (N=69) in the FGFP cohort. Two-sided Wilcoxon rank-sum test, FDR by Benjamini-Hochberg.

Supplementary Table 4. Associations between RAND scores and anthropometrics (age, sex, and BMI) and gastrointestinal parameters (BSS, gastrointestinal diseases) in the FGFP cohort (N=1054; two-sided Wilcoxon rank-sum test/Spearman tests, FDR by Benjamini-Hochberg).

Supplementary Table 5. Cumulative and independent contribution of metadata variables to microbiome variation (dbRDA and stepwise dbRDA; FDR by Benjamini-Hochberg) in the FGFP cohort (N=1054). Cumulative explanatory power and significance level of the included variables are reported.

Supplementary Table 6. Associations between RAND scores and relative abundances of microbial genera in the FGFP cohort (N=1054) and LLD validation dataset (N=1063), GLMs partialling out anthropometric and gastrointestinal covariate contribution, FDR by Benjamini-Hochberg.

Supplementary Table 7. Microbial genera associated with depression in the FGFP cohort (N=1054) and the LLD validation dataset (N=1063), GLMs partialling out anthropometric and gastrointestinal covariate contribution, FDR by Benjamini-Hochberg.

Supplementary Table 8. Replication of genus-level associations with depression from published case-control studies in the FGFP cohort (N=1054; GLMs partialling out anthropometric and gastrointestinal covariate contribution).

Supplementary Table 9. Enterotype distribution in QoL and depression in the FGFP cohort (N=1054; Kruskal-Wallis test with post-hoc Dunn tests or Chi-squared test with post-hoc pairwise Chi-squared tests, FDR by Benjamini-Hochberg).

Supplementary Table 10. GBM framework overview.

Supplementary Table 11. Evaluation of the GBM framework in gut microbial reference genomes (N=532).

Supplementary Table 12. GBM distribution in genomes of human gut-associated microorganisms (N=532).

Supplementary Table 13. GBM distribution in genomes of free-living (N=1501) vs human gut-associated microorganisms (N=532; Chi-squared test), and GBM phylogenetic inertia (Pagel's lambda and one-sided Fisher's test), FDR by Benjamini-Hochberg.

Supplementary Table 14. GBMs in plasmids of microbial species (N=1150).

Supplementary Table 15. Associations between RAND scores and GBM relative abundances in the FGFP cohort (N=150) and LLD validation dataset (N=1063), Spearman test and GLMs partialling out anthropometric and gastrointestinal covariate contribution, FDR by Benjamini-Hochberg.

Supplementary Table 16. GBM association with depression in the FGFP cohort (N=150) and LLD (N=1063) and TR-MDD (N=7) validation datasets, two-sided Wilcoxon signed-rank test and and GLMs partialling out anthropometric and gastrointestinal covariate contribution, FDR by Benjamini-Hochberg.

Supplementary Table 17. Association between GBMs and enterotype distribution in the FGFP cohort (N=150; Kruskal-Wallis test with post-hoc Dunn tests or Chi-squared test with post-hoc pairwise Chi-squared tests, FDR by Benjamini-Hochberg).

Supplementary Table 18. Association between GBMs and genera abundances in the FGFP cohort (N=150) and LLD validation dataset (N=1063).