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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	16S sequence data was collected and analyzed using QIIME (v 1.8.0). fMRI data was collected using AFNI (v17.0.03) and FSL (v5.0)
Data analysis	Several programs were used throughout this study to analyze the data. Genome assembly and annotation of KLE1738 -- Edena (v3.131028) and RAST (v2.0); GABA quantification in spent mediums of potential GABA producers – ChemStation (Agilient); Metabolic modeling of candidate GABA modulating bacteria – Kbase v 3.0; Transcriptomic Analysis – Prodigal (v2.6.1); 16S sequencing from the American Gut – Deblur v1.0.2; fMRI imaging analysis – AFNI (v17.0.03) and FSL (v5.0).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The 16S rRNA sequence and genome for KLE1738 are available from NCBI (MH636586 and PRJNA482656, respectively). The American Gut sequence data is in EBI under accession ERP012803. fMRI data is available at the discretion of author M.D. All other data that support the findings of this study are available from the corresponding author upon request. Reprints and permissions information is available at www.nature.com/reprints. Correspondence and requests for materials should be addressed to K.L. (k.lewis@neu.edu).

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	For the Major Depression Disorder cohort 23 subjects were recruited as a pilot effort. Given no such cohort (combining microbiome and brain imaging in depressed patients) has existed prior to this one, we had no prior cohorts to compare to for sample size. Nonetheless, a sample size of n=23 was large enough to reach significance between an association of GABA producing Bacteroides and fMRI brain signatures of depression (Figure 3A,B; p=0.0005), suggesting we reached appropriate power.
Data exclusions	No data was excluded.
Replication	GABA dependency phenotypes of KLE1738 was repeated in trplicate, and GABA production capabilities of all reported strains were validated in at least two biological replicates, with the exception of media exclusion experiments (Supplemental Data Table 2), C13 feeding experiments, which were both performed as a single experiment. All details on sample sizes can be found in the figure legends. No variation was observed to change the conclusions of the study.
Randomization	The human cohort was observatory, so we did not have experimental groups.
Blinding	Blinding was not performed for the MDD cohort as all patients had MDD and no intervention was being performed.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	For cultivation experiments, a single adult male donor provided fecal samples. For the MDD cohort, 23 currently depressed subjects between the ages of 19 and 65 (15 female) participated in fMRI imaging component of the study. Subjects were eligible for inclusion if they met DSM-5 criteria for Major Depressive Disorder and a current major depressive episode. Subjects were

required to have a minimum score of 17 on the 21-item Hamilton Depression Rating Scale (HAMD-21) and were permitted to be currently taking psychotropic medications (medication list can be found in Supplemental Information Table 8). Potential subjects were excluded from the study if they presented with a history of claustrophobia, seizure disorder or other neurological disorder, head injury resulting in loss of consciousness, metal implants, pacemakers, intrauterine contraceptive devices, or braces, or if they were currently pregnant or lactating. Potential subjects were also excluded if they had a psychotic disorder, were actively suicidal with plan or intent, had been in their current episode for longer than 3 years, had a history of clinically significant personality disorder as established in the diagnostic interview, or had substance abuse disorder or substance dependence within the past 3 years.

Recruitment

Subjects were recruited through referral from the outpatient clinic in the Department of Psychiatry at Weill Cornell Medical College. Subjects were also self-referred by directly contacting our mood disorders research program or from the local community via flyers, outreach at local events, or direct contact. The recruitment procedure and all other aspects of our experimental protocol were approved by the Institutional Review Board of Weill Cornell Medical College, and all experiments were conducted in accordance with institutional guidelines and regulations. A potential bias to this cohort is that the patients we recruited from the local area -- expansion of this cohort into other regions will help build confidence of the associations.