Supporting Information

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SI Materials and Methods

Animals. Adult male BALB/c mice ($n = 36$) were obtained from Harlan. All of the animals were allowed to acclimate for ≥7 d in the housing facility before the experiment. Animals were group-housed (nine animals per cage) in standard conditions (room temperature of 21 °C, with a 12-h light–dark cycle, lights on at 07:00) with access to regular chow and water ad libitum. Cages were cleaned once weekly to avoid excessive handling. Mice were of comparable weight (25–30 g) and age (10–11 wk) at the moment of sacrifice. All experimental procedures were carried out in accordance with the protocols approved by the Ethics Committee, University College Cork under a license issued from the Department of Health and Children [Cruelty to Animal Act 1876, Directive for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (89/609/EEC)]. Experiments conducted in Canada were similarly approved by the Animal Ethics committee of McMaster University.

Treatments and Sacrifice. Animals were orally gavaged with broth without bacteria (broth control group, $n = 16$) or with *L. rhamnosus (JB-1)* [10^9 cfu; *L. rhamnosus (JB-1)* group, $n = 16$]. This procedure was carried out daily between 8:00 and 9:00 for a period of 28 continuous d. Toward the end of the treatment, the animals underwent a series of behavioral testing including SIH, EPM, and fear conditioning. In addition, on the day samples were collected, half of the animals in each group were put in the FST [broth, $n = 8$; *L. rhamnosus (JB-1)*, $n = 8$] to evaluate behavior and also to measure stress-induced levels of corticosterone. All of the animals were killed by cervical dislocation; the head was rapidly removed, and trunk blood was collected into EDTA-containing tubes for separating plasma. Animals that were not used for FST were killed between 8:00 and 9:00, while the FST stressed groups were killed 30 min after the end of the forced swim session (9:30–11:45). For each behavioral test, the experimenter was blinded to the treatment of each animal.

Bacterial Preparation. The bacterial strain used in this study, *L. rhamnosus (JB-1)*, is the same as that used in several published investigations from 2004 to present (1–5) and was previously referred to as *Lactobacillus reuteri*. This strain was recently confirmed as a *L. rhamnosus* by amplified fragment length polymorphism (AFLP) fingerprinting and full genomic analysis. It is distinct from *L. rhamnosus* GG, and according to the Bacteria Collection Laboratory for Microbiology at the University of Ghent (Belgium) in an independent study, it differs from all of the 118 *L. rhamnosus* strains studied by Vancanneyt et al. (6) and cannot be assigned to any of the seven clusters of *L. rhamnosus* they had previously identified (Fig. S6). From frozen stocks (–80 °C), bacteria were suspended in Man–Rogosa–Sharpe liquid medium (MRS broth; Difco Laboratories) plated in MRS agar, cultured anaerobically at 37 °C for 24 h, then inoculated in fresh MRS broth and grown at 37 °C under anaerobic conditions for 48 h in 50-mL tubes. After 2 d, tubes were centrifuged at $850 \times g$ for 15 min at 20 °C and washed twice with sterile PBS to a concentration of 6×10^8 bacteria per mL as determined by a Vitek colorimeter (bioMérieux). Bacterial suspensions were centrifuged in 15-mL tubes at 2,000 rpm for 15 min at 20 °C, supernatants discarded, and bacteria resuspended in MRS broth to give a concentration of 5×10^9 per mL.

Vagotomy Procedure. Mice were anesthetized using gaseous anesthesia with isoflurane using a rodent anesthetics machine. The stomach and lower esophagus were visualized after an upper midline laparotomy. The skin and abdominal wall were incised along the ventral midline, and the intestine was retracted to allow access to the left lateral lobe of the liver (LLL) and the stomach. The LLL was retracted, and a ligature was placed around the esophagus at its entrance to the stomach to allow gentle retraction to clearly expose both vagal trunks. These were dissected and all neural and connective tissue surrounding the esophagus below the diaphragm was removed to transect all small vagal branches. At least a 2-wk recovery period was allowed.

Assessment of Vagotomy. A food intake analysis was performed based on the satiety effect of cholecystokinin–octapeptide (CCK-8) (Sigma–Aldrich). Satiety induced by CCK-8 is mediated by the afferent vagus nerve (7). After 20 h of food deprivation, sham-operated and vagotomized mice were treated with CCK at a dose of 8 μg/kg body weight, ip. Food intake was then monitored for 2 h. Only vagotomized animals, which did not show a significant decrease in their food intake when administered CCK were used in the study.

In Situ Hybridization. The in situ hybridization was conducted as described (8–11) using oligodeoxynucleotide (cDNA) probes complementary to GABA$_{A\alpha1}$ mRNA (847–886 bp; NCBI Nucleotide Database reference no. NM_010250.4), GABA$_{A\alpha2}$ mRNA (1,466–1,506 bp; NCBI Nucleotide Database reference no. NM_008066) and GABA$_{B1b}$ mRNA (82–39 bp; NCBI Nucleotide Database reference no. AF120255), labeled with a digoxigenin (DIG) oligonucleotide 3′-OH tailing kit (Roche, Molecular Biochemicals). Briefly, coronal brain sections (10 μm thick) were mounted on glass slides and post fixed for 30 min in 4% paraformaldehyde. After treatment with 0.001% Proteinase K (Sigma), 0.25% acetic anhydride in 0.1 M triethanolamine, the tissues were dehydrated through a graded series of ethanol (70%, 95%, and 100%). Then the samples were delipidated in chloroform for 5 min. Later the tissues were rinsed with ethanol (95%) and air dried before hybridization. The tissues were then incubated overnight at 37 °C with the hybridization solution [formamide 50%, saline and sodium citrate buffer (SSC) 4×, Denhart solution 1× (from a 50× stock: 1% ficoll 400, 1% polivinilpyrrolidone and 1% BSA) sheared salmon DNA 6.25mg/mL, tRNA 125 μg/mL, and cDNA probe at fixed concentration of 100 pmol/mL]. Then, the samples are rinsed with SSC 4×, and blocked with Roche's blocking reagent (Roche, Molecular Biochemicals) Detection was carried out with anti DIG antibody (1:500 dilution prepared in Roche's blocking reagent with 1% FBS, 0.1% Triton X-100), which is conjugated with an alkaline phosphatase (Roche, Molecular Biochemicals). Finally, substrate solution was added (NBT/BCIP. Sigma) and when a violet/blue precipitate was present on the tissues, the reaction was stopped. The slides were then left to air dry, coverslipped, and photographed. In addition, negative controls were generated by using 100-fold excess of the respective unlabeled oligodeoxynucleotide (Fig. S5). For semiquantitative analysis, densitometric measurements of prefrontal cortex, hippocampus, amygdala and *locus coeruleus* (LC) microphotographs were performed using FujiFilm's Science Lab Multi Gauge v2.2 software (Fuji Photo Film Co., Ltd.). Pictures were analyzed in gray scale and values correspond to the intensity of pixels (the darkest staining corresponding to the highest intensity) in a given area (density of pixels). Values for each animal represent the average from four to five brain sections (analyzed on both brain hemispheres). Analysis of the pictures was carried out in a random

fashion and treatments of each animal were blinded to the experimenter to prevent a bias in the analysis.

Behavioral Analysis. *Open field.* Mice were placed individually in a 18×38-cm clear Plexiglas enclosure for a 10 min period. Enclosures were equipped with photo beam sensors to measure total distance traveled, speed, mobility time and time spent in the center of the box (Motor Monitor; Kinder Scientific).

Stress-induced hyperthermia. The stress-induced hyperthermia (SIH) test was conducted as described (12, 13). Briefly, mice were singly housed in smaller cages 24 h before testing. In this procedure, two rectal temperature measurements are taken. This first measurement (T1) serves as the basal value and provides the initial stressor. The second rectal temperature (T2) of each mouse is measured 15 min after T1. SIH was defined as the difference between the second measurement and the first measurement (SIH = T2–T1). Rectal temperature was measured to the nearest 0.1 °C by inserting a lubricated thermistor probe (model PRA-22002-A; ELLAB) 2.2 mm diameter 20 mm into the rectum, connected to an ELLAB instruments thermometer (Model DM 852).

Elevated plus maze. The elevated plus maze (EPM) was carried out as described (14–16). The apparatus comprised two open arms (30×5 cm) and two enclosed arms ($30 \times 5 \times 15$ cm), which extended from a common central platform (5×5 cm). The configuration formed the shape of a plus sign, with like arms arranged opposite one another, and the apparatus was elevated 60 cm above floor level on a central pedestal. The maze floor and end walls of the enclosed arms were made of gray Plexiglas. Grip on the edges of open arms was facilitated by inclusion of a small raised edge (0.25 cm) around their perimeter. Procedure was carried out under red light, with each open arm illuminated by 9 lx light. Animals were transported from the holding room to the testing room at least 1 h before testing. Mice were placed onto the central platform facing an open arm. A 5-min trial was performed and, between subjects, the maze was thoroughly cleaned. Test sessions were recorded by a video camera positioned directly above the apparatus, and behavioral determinations were made by an observer blind to the experiment following conventional parameters: number of open and closed arm entries (arm entry defined as all four paws entering an arm) and time spent on open arms (excluding the central platform).

Fear conditioning. This procedure was adapted from Brinks et al. (17). This fear conditioning paradigm allows differentiating between context and context/cue related behavioral responses in the same setting. Training (day 1) involved 3 min of baseline recording, followed by 6 light/tone conditioned stimulus (CS) and shock [unconditioned stimulus (US)] pairings with an interval of 1 min. Pairings consisted of the cue [e.g., a combined light (260 lx) and tone exposure (70 dB)] for 20 s and an electric footshock (0.4 mA) during the last 2 s of the cue. Mice were returned to their home-cage 2 min after the last pairing. At 24 and 48 h after conditioning (days 2 and 3, respectively), the same experimental procedure was repeated in absence of shocks to test for memory and extinction of the conditioned fear response. The procedure lasted 12 min per mouse per day and was performed between 8.00 and 13.00 h in an experimental room different to the housing room.

Open field. Mice were placed individually in a 18×38-cm clear Plexiglas enclosure for a 10 min period. Enclosures were equipped with photo beam sensors to measure total distance traveled, speed, mobility time and time spent in the center of the box (Motor Monitor, Kinder Scientific).

Forced swim test. Forced swim test (FST) was conducted as described (18–20). Briefly, mice were individually placed into glass cylinders (50 cm high × 21 cm internal diameter) filled with water (24–25 °C) to a depth of 15 cm. Test sessions were recorded by a video camera positioned directly above the cylinders. A well-trained observer, blinded to the treatment groups, scored these videotapes for the duration of mouse immobility during the last 4 min of the 6 min test period. A mouse was judged to be immobile when making only those movements necessary to keep its head above water.

AFLP methods for comparison of L. rhamnosus (JB-1) and L. rhamnosus GG. The *L. rhamnosus GG* strain used as a comparator to *L. rhamnosus (JB-1)* in AFLP analysis is a subculture of ATCC 53103 (Gorbach–Goldin strain).

DNA was extracted using the method of Gevers et al. (21). Purified total DNA was digested by two restriction enzymes, a 4-base cutter and a 6-base cutter. In this way, only a limited number of fragments with two different ends and of suitable size for efficient PCR are obtained. Small dsDNA molecules (15–20 bp) containing one compatible end were ligated to the appropriate sticky end of the restriction fragments. Both adaptors are restriction halfsite-specific and have different sequences. These adaptors serve as binding sites for PCR primers.

Selective amplification of some of the restriction fragments: PCR primers were specifically hybridized with the adaptor ends of the restriction fragments. Since the primers contain at their 3′ end one or more so-called selective bases that extend beyond the restriction site into the fragment, only those restriction fragments that have the appropriate complementary sequence adjacent to the restriction site will be amplified.

The following primer combinations were used:

E01: 5′-GACTGCGTACCAATTCA-3′
T11: 5′-GTTTCTTATGAGTCCTGACCGAA-3′
E01: 5′-GACTGCGTACCAATTCA-3′
T13: 5′-GTTTCTTATGAGTCCTGACCGA**G**-3′

PCR products were separated according to their length using an ABI Prism 3130XL Genetic Analyzer (Applied Biosystems). Fragments that contain an adaptor specific for the restriction halfsite created by the 6-bp cutter are visualized due to the 5′-end labeling of the corresponding primer with the fluorescent dye FAM. The resulting electrophoretic patterns were normalized and subjected to a band pattern recognition procedure using the GeneMapper 4.0 software (Applera). Normalized tables of peaks, containing fragments of 20–600 base pairs, were transferred into the BioNumerics 4.61 software (Applied Maths). For numerical analysis, a data interval was delineated between the 40- and 580-bp bands of the internal size standard. The E01/T11 AFLP™ DNA fingerprints were compared with the E01/T11 reference AFLP™ DNA fingerprints of the lactic acid bacteria taxa (including bifidobacteria) as currently available in the Belgian Coordinated Collections of Microorganisms (BCCM) database. Clustering of the patterns was achieved using the Dice coefficient and the UPGMA algorithm. The PCR products of *L. rhamnosus (JB-1)* and *L. Rhamnosus* GG were generated in a single PCR run from DNA extracted and prepared in parallel. They were also separated on the same day. This strategy was followed to minimize the variation inherent to the technique.

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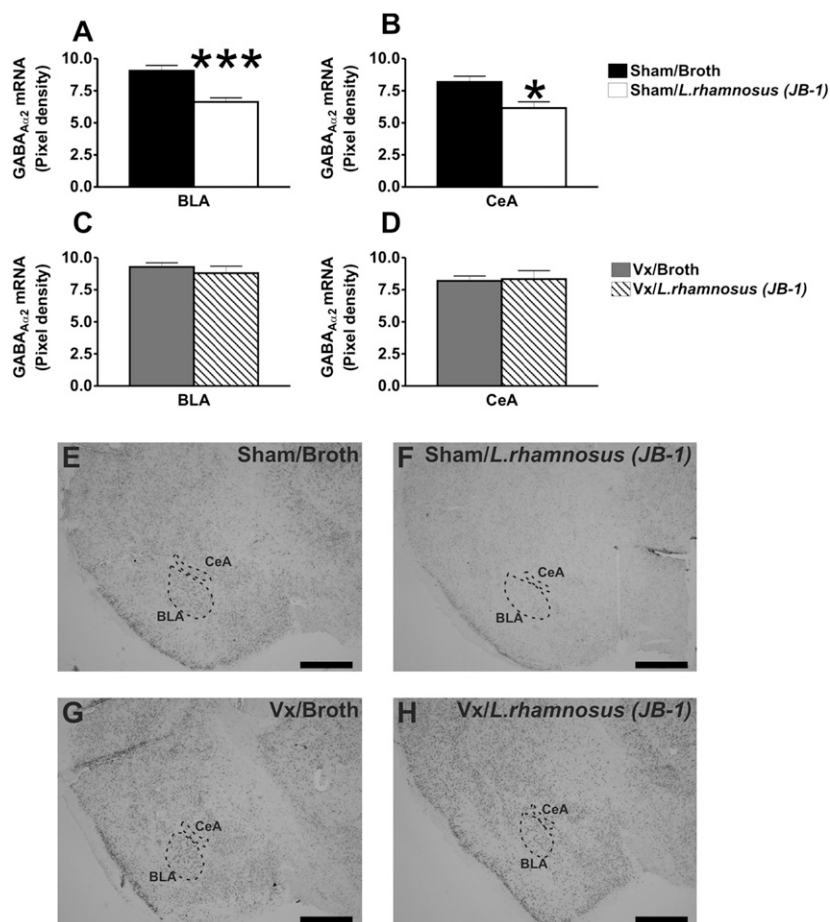
Fig. S1. Effect of vagotomy (Vx) on GABA$_{A\alpha2}$ mRNA expression in the amygdala of animals treated with *L. rhamnosus* (*JB-1*). (*A* and *B*) Sham operated animals treated with *L. rhamnosus* (*JB-1*) ($n = 6$) had significantly lower levels of GABA$_{A\alpha2}$ mRNA expression in the basolateral amygdala (BLA) (*A*) and central amygdala (CeA) (*B*) in comparison with sham operated mice fed with broth ($n = 6$; ***$P < 0.001$ and *$P < 0.05$, respectively). (*C* and *D*) In addition, Vx prevented the effect of *L. rhamnosus* (*JB-1*) on GABA$_{A\alpha2}$ mRNA expression in the BLA (*C*) and CeA (*D*), as the levels of the transcript in broth-fed ($n = 6$) and *L. rhamnosus* (*JB-1*)-fed ($n = 6$) animals are not different from control sham operated animals. (*E–H*) Representative microphotographs of the analyzed areas of sham animal fed with broth (*E*); sham operated animal treated with *L. rhamnosus* (*JB-1*) (*F*); vagotomized animal fed with broth (*G*); and vagotomized animal treated with *L. rhamnosus* (*JB-1*) (*H*). (Scale bar: 1 mm.)

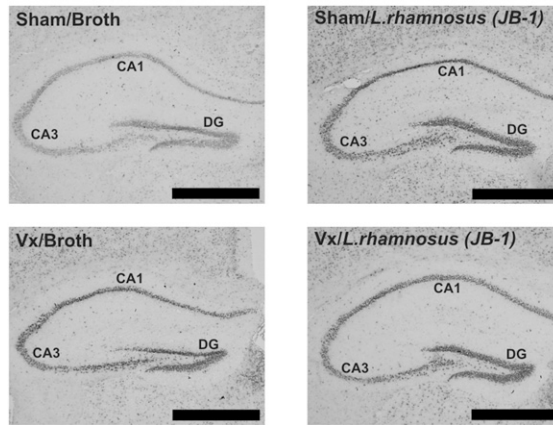# GABA$_{A\alpha2}$

Fig. S2. Representative images of hippocampal expression of GABA$_{A\alpha2}$ mRNA expression. (*Upper, Left*) Representative image of a sham vagotomised animal fed with broth. (*Upper, Right*) Representative image of a sham vagotomised animal fed with *L. rhamnosus* (*JB-1*). (*Lower, Left*) Representative image of a vagotomised animal fed with broth. (*Lower, Right*) representative image of a vagotomised animal fed with *L. rhamnosus* (*JB-1*). (Scale bar: 1mm.)
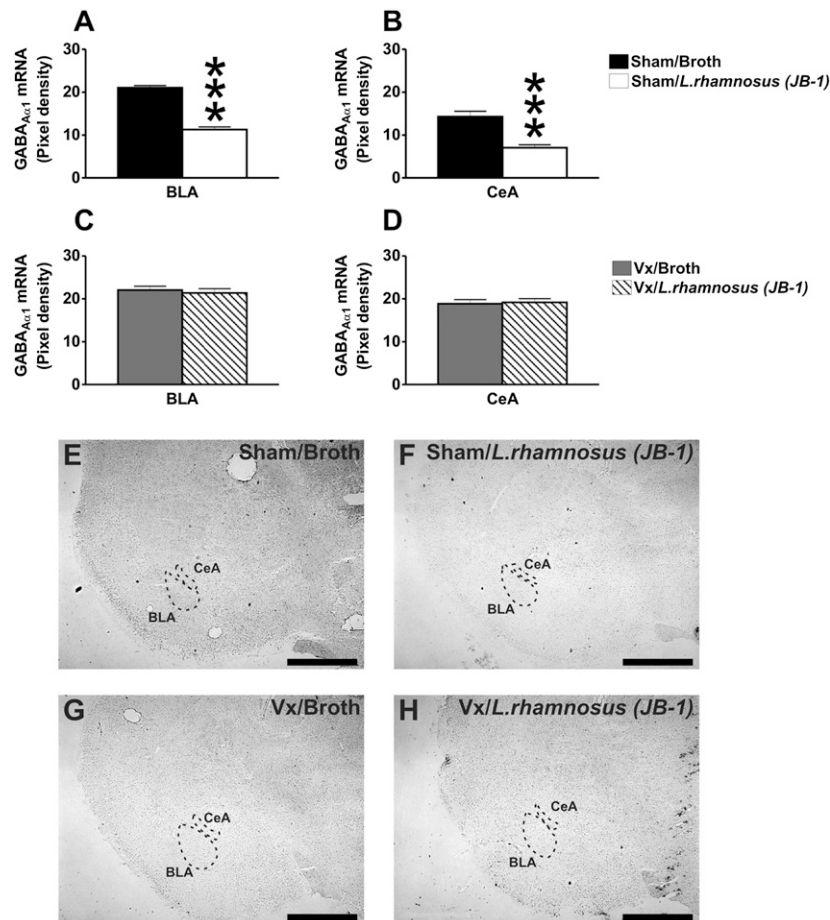

Fig. S3. Effect of Vx on GABA$_{A\alpha1}$ mRNA expression in the amygdala of animals treated with *L. rhamnosus* (*JB-1*). (*A* and *B*) Sham operated animals treated with *L. rhamnosus* (*JB-1*) (*n* = 6) had significantly lower levels of GABA$_{A\alpha1}$ mRNA expression in the BLA (*A*) and CeA (*B*) in comparison with sham operated mice fed with broth (*n* = 6; ***$P < 0.001$ in both cases). (*C* and *D*) In addition, Vx prevented the effect of *L. rhamnosus* (*JB-1*) on GABA$_{A\alpha1}$ mRNA expression in the BLA (*C*) and CeA (*D*) as the levels of the transcript in broth-fed (*n* = 6) and *L. rhamnosus* (*JB-1*)-fed (*n* = 6) animals were not different from control sham operated animals. (*E–H*) Representative microphotographs of the analyzed areas of sham animal fed with broth (*E*); sham operated animal treated with *L. rhamnosus* (*JB-1*) (*F*); vagotomized animal fed with broth (*G*); and vagotomized animal treated with *L. rhamnosus* (*JB-1*) (*H*). (Scale bar: 1 mm.)
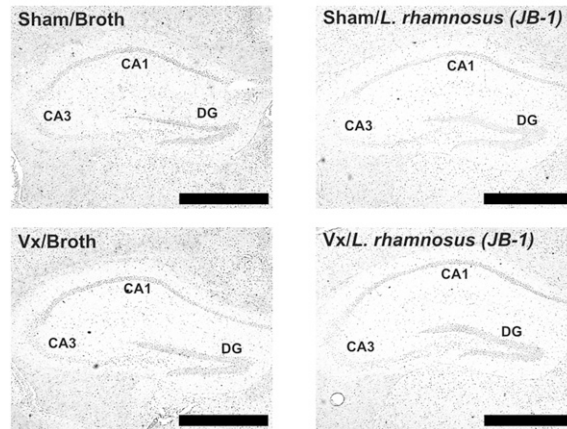
GABA$_{A\alpha1}$

Fig. S4. Representative images of hippocampal expression of GABA$_{A\alpha1}$ mRNA expression. (*Upper*, *Left*) Representative image of a sham vagotomised animal fed with broth. (*Upper*, *Right*) Representative image of a sham vagotomised animal fed with *L. rhamnosus* (*JB-1*). (*Lower*, *Left*) Representative image of a vagotomised animal fed with broth. (*Lower*, *Right*) Representative image of a vagotomised animal fed with *L. rhamnosus* (*JB-1*). (Scale bar: 1mm.)
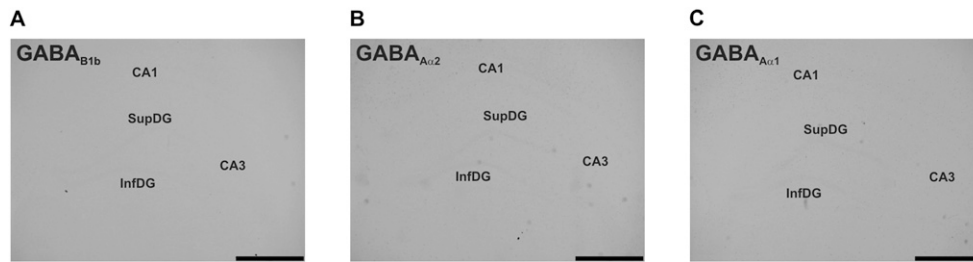

Fig. S5. In situ hybridization negative controls. Representative pictures for GABA$_{B1b}$ (*A*), GABA$_{A\alpha2}$ (*B*), and GABA$_{A\alpha1}$ (*C*) negative controls are shown. DG, dentate gyrus; CA3, cornus ammonis region 3; CA1, cornus ammonis region 1. (Scale bar: 1 mm.) Negative controls were generated by using 100-fold excess of unlabeled oligodeoxynucleotide in the presence of 1× of the respectively labeled oligodeoxynucleotide, therefore displacing any specific binding that could be generated by the labeled oligodeoxynucleotide.
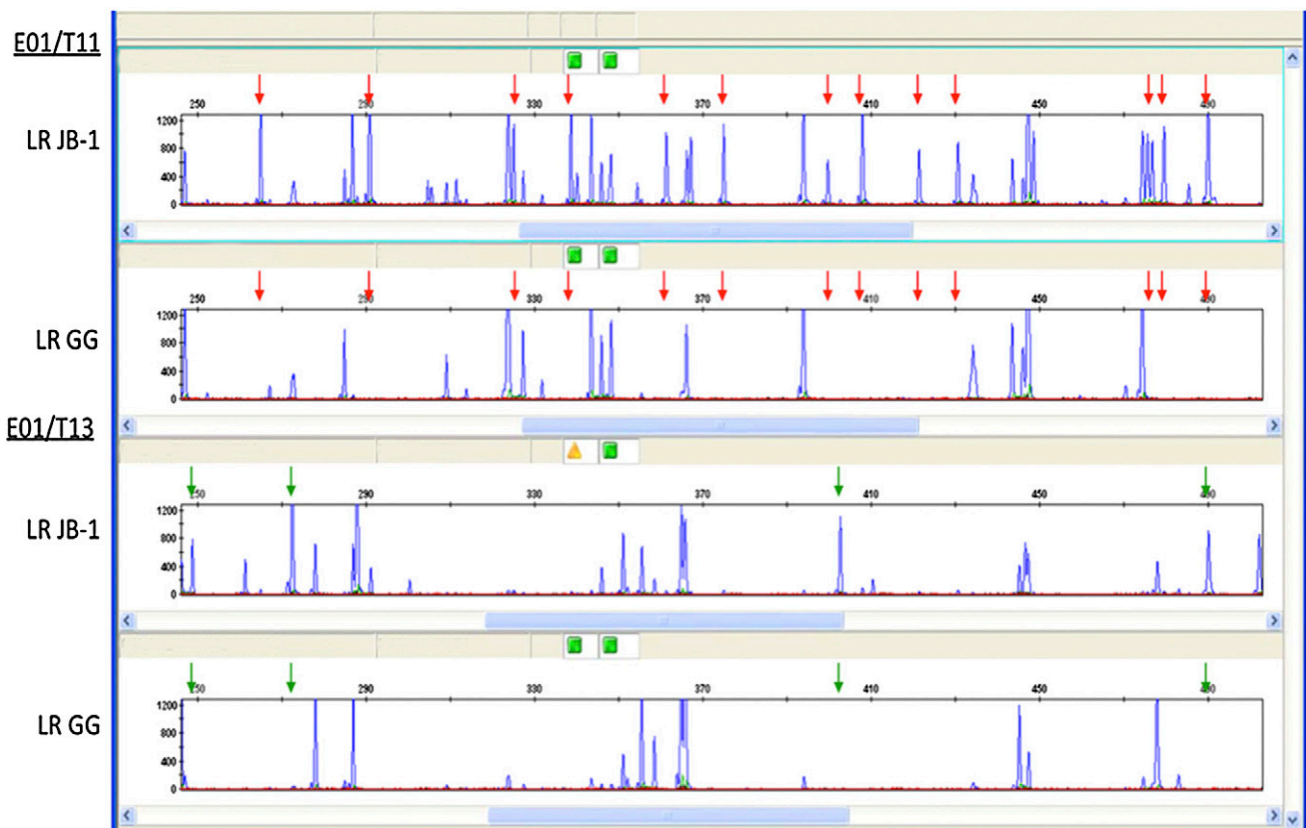
Fig. S6. AFLP analysis of *L. rhamnosus* (*JB-1*) and *L. rhamnosus* GG. A section of the detailed comparison of the E01/T11 and E01/T13 AFLP DNA fingerprints of *L. rhamnosus* (*JB-1*) (LR JB-1) and *L. rhamnosus* GG (LR GG) using the GeneMapper 4.0 software (Applera). There are clear differences in peak positions between strains (indicated by arrows).

Table S1. Summary of changes in brain expression of GABA subunit receptor transcripts and its relation to behavioral changes

	GABA$_{B1b}$	GABA$_{A\alpha2}$	GABA$_{A\alpha2}$*	GABA$_{A\alpha1}$*	Behavioral findings	Background literature
CG1	↑	↓				• GABA$_B$ receptor expression in frontal cortices is reduced in animal models of depression (1, 2)
PrL	↑	↓			• *L. rhamnosus* (*JB-1*) treatment has an anxiolytic effect (Fig. 1A, Center) with no effect on motor activity (Fig. 1A)	• GABA$_{B1b}$ is necessary for fear extinction (3)
IL	-	↓				
BLA	↓	↓	↓	↓	• *L.rhamnosus* (*JB-1*) treatment has an antidepressant effect (Fig. 1A, Right)	• The use of GABA$_B$ receptor antagonists mediates antidepressant-like behaviors (4)
CeA	↓	↓	↓	↓		
LC	↓	-				
DG	↓	↑	↑	↓	• Animals treated with *L. rhamnosus* (*JB-1*) have an enhanced emotional response towards an unconditioned stimulus, and also *L. rhamnosus* (*JB-1*) treatment allows fear extinction (Fig. 1B)	• GABA$_{A\alpha2}$ subunit mediates the anxiolytic effect of benzodiazepines while GABA$_{A\alpha1}$ subunits mediate the amnesic and sedative effects of these compounds (5, 6)
CA3	↓	-	↑	↓		
CA1	↓	-	-	↓		• Genetic ablation of the GABA$_{A\alpha1}$ subunit in mice enhances freezing behavior (6)

Arrows indicate the change in relation to their respective control(s): ↑, Higher mRNA expression in comparison to control; ↓, Reduced mRNA expression in comparison to control; -, No difference between experimental groups.
*Comparison between sham/broth v sham/*L .rhamnosus* (*JB-1*) (no differences between Vx/broth and Vx/*L.rhamnosus* (*JB-1*) groups. See Fig. 4 and Figs. S1 and S3 for details).

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