Developing a psychobiotic for stress

Ted Dinan
APC Microbiome Ireland
Psychobiotics: A Novel Class of Psychotropic

Timothy G. Dinan, Catherine Stanton, and John F. Cryan

Here, we define a psychobiotic as a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness. As a class of probiotic, these bacteria are capable of producing and delivering neuroactive substances such as gamma-aminobutyric acid and serotonin, which act on the brain-gut axis. Preclinical evaluation in rodents suggests that certain psychobiotics possess antidepressant or anxiolytic activity. Effects may be mediated via the vagus nerve, spinal cord, or neuroendocrine systems. So far, psychobiotics have been most extensively studied in a liaison psychiatric setting in patients with irritable bowel syndrome, where positive benefits have been reported for a number of organisms including *Bifidobacterium infantis*. Evidence is emerging of benefits in alleviating symptoms of depression and in chronic fatigue syndrome. Such benefits may be related to the anti-inflammatory actions of certain psychobiotics and a capacity to reduce hypothalamic-pituitary-adrenal axis activity. Results from large-scale placebo-controlled studies are awaited.
L. Rhamnosus (JB1): impact on stress

Probiotic Reduces Stress-induced Corticosterone Levels
Cognitive testing and EEG

Paired Associates Learning (PAL)  
(visuospatial episodic memory)

- Conditional learning of pattern-location associations
- List memory
- List Learning

Prefrontal cortex
Temporal lobes
Socially evaluated cold pressor test
Immune measures

**Extracellular compartment**

- **TLR1**: Binds to specific bacterial lipopeptides and to GPI-anchorage proteins in parasites.
- **TLR2**: Binds to lipoteichoic acid from gram-positive bacteria and to zymosan, produced by fungi.
- **TLR6**: Binds to LPS from gram-negative bacteria.
- **TLR5**: Binds to flagelin in the tails of motile bacteria.

**Endosome**

- **TLR3**: Binds to double-stranded viral RNA.
- **TLR4**: Binds to single-stranded viral RNA.
- **TLR7**: Binds to single-stranded viral RNA.
- **TLR8**: Binds to single-stranded viral RNA.
- **TLR9**: Binds to CpG DNA from bacteria or viruses.

**Cytoplasm**
Subjective Stress Measures

(A) Beck Depression
(B) Beck Anxiety
(C) Perceived Stress Scale
(D) Symptom Checklist-90

(E) Trait Anxiety
(F) State Anxiety
(G) Sleep Quality
(H) Coping Checklist

Coping Checklist:
- Baseline
- Placebo
- Probiotic

Trait Anxiety Score
State Anxiety Score
PSQI Score
Percent Score
Wish
Positive
Escape
Advice
Blame

* Significant difference
L. Rhamnosus and cognitive performance

**Paired Associates Learning**
- Total errors (A)
- Total errors (B shape) (B)
- Mean trials to success (C)

**Attention Switching Task**
- % Correct (D)
- Correct latency (E)

**Rapid Visual Information Processing**
- Total Correct Hits (F)
- Total false alarms (G)
- Reaction time (H)

**Emotional Stroop**
- % correct (neutral) (I)
- Reaction Time (neutral) (J)

**Emotion Recognition Task**
- % Correctly Identified (K)
- Response Time (L)
Acute Stress response to the Socially Evaluated Cold Pressor Test (SECPT)

(A) Primary Appraisal  (B) Secondary Appraisal  (C) Control Expectancy  (D) Self Control  (E) Threat  (F) Challenge  (G) Stress Index

HPC Response

(H) Baseline Placebo Probiotic

(I) Salivary Cortisol (nmol/l) vs Time (minutes)

(J) AUCg

(K) Delta nmol/l
L. Rhamnosus immune response

Basal Cytokines

TLR4 stimulated cytokines
B. Longum 1714 preclinical observations

Defensive Marble Burying

Savignac et al., Neurogastro & Motility 2014

Barnes Maze

Savignac et al., Behav Brain Res 2015
Effects of *B. Longum* on Stress & Cognition

Cohen perceived stress scale

Awaking Cortisol

![Graph showing comparison between Placebo and Probiotic groups for Cohen perceived stress and awake Cortisol levels.](image-url)
Effects of *B. longum* on Stress and Cognition
**B. longum** on stress resilience and cognitive performance during chronic exam stress in healthy individuals

**Study Outline**

N = 20

Male

Recruitment

Screening

Randomisation

Group I: Placebo

Group II: Probiotic

Intervention period 1

8 weeks

Group I: Probiotic

Group II: Placebo

Intervention period 2

8 weeks

Visit 1

Visit 2

Visit 3

Visit 4

Visit 5

Visit 6

Samples

Cognition

Exam Stress
Microbiome Influence on Energy Balance and Brain Development and/or Function Put into Action to Tackle Diet-Related Diseases has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration. Grant Agreement no: 613979

Paul Kennedy
Amy Murphy
John Kelly
Andrew Allan
Carol Anne O’Shea
Anne Marie Cusack
Aoife Collery
Caitriona Long-Smith
Niamh Wyley
Danielle Dorland
Sara Hojabri