Understanding gut feelings: Probiotics and cognition

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Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46368

Source
ToetsingOnline

Brief title
Probiotics and cognition

Condition

- Other condition

Synonym
not applicable

Health condition

niet van toepassing op een aandoening

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit van Amsterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: affect regulation, cognition, probiotics

Outcome measures

Primary outcome

Participants* mood is assessed through standardized questionnaires. Mood is measured through standardized self-report scales. We refer to the study protocol for a more detailed description of the primary parameters.

Secondary outcome

Cognitive and affective functioning will be measured through standardized cognitive computer tasks. Blood plasma is assessed for amino acid metabolism, markers of barrier functions and inflammation. HPA-functioning is assessed by repeated saliva samples. We emphasize that measurements will only be used to evaluate the effects of the intervention, but not for diagnostic purposes. Information about age, gender, and level of education will be collected in order to assess whether groups match on these background variables. Furthermore, non-verbal IQ, burnout complaints, alexithymia, interpersonal reactivity, autism spectrum symptoms, sleep quality, fatigue severity, state affect, anthropomorphic and physical measures (weight, BMI, fat%, musle%, heart rate, blood pressure) and bowel complaints will be assessed. These will mainly serve as covariates in the analyses of the primary parameters.

Study description

Background summary

In 2004, a seminal study demonstrated that germ-free mice show enhanced reactivity to stress (Sudo et al., 2004). This study spurred research into what is nowadays called the microbiota-gut-brain axis; i.e, the proposition that microorganisms living in the gut may affect functioning of the central nervous system (e.g. Foster & McVey Neufeld, 2013). Many animal studies have followed confirming that gut-brain interactions have behavioural and mood effects (Cryan & O*Mahony, 2011; Foster, Rinaman, & Cryan, 2017). For example, it was shown that transplanting gut bacteria from a highly explorative mouse strain to a more passive strain, and vice versa, altered behaviour in each mouse strain showed that, together with the gut-microbiota, also behavioural traits had swapped (Bercik et al., 2011). Other animal studies demonstrated, amongst others, antidepressant properties of probiotic bacteria. Moreover, probiotics administered to rats positively affected gut barrier integrity, cytokine activity, and central HPA- and monoaminergic activity; biological processes that have been implicated in depression (e.g. Gareau et al., 2007; Desbonnet et al., 2008; Bravo et al., 2011; Gilbert et al., 2013, for a review see Desbonnet et al., 2010).

Human studies have remained sparse, but a recent meta-analysis of 9 human studies (Evrensel & Ceylan, 2015) provided support that manipulation of the *microbiota-gut-brain axis* through the intake of probiotic food supplements has anti-depressant effects, by reducing symptoms depression in healthy non-depressed individuals. The fact that these effects are already observed in non-depressed individuals is important, and dove-tails with recommendation of the World Health Organization (2012) regarding the need for preventive strategies for depression (Huang, Wang, & Hu, 2016).

A major limitation of the human literature on probiotic supplementation, however, is that it has remained elusive by which mechanism probiotics yield their beneficial effects. While a number of potential mechanisms have been proposed on the basis of animal research, these mechanisms have received little to no scrutiny in humans.

Study objective

Translating these animal findings to humans is one of the aims of the current study. The proposed project aims to replicate the aforementioned preliminary findings (Evrensel & Ceylan, 2015; Steenbergen et al., 2015; de Noos et al., 2015; Cryan & O*Mahony, 2011; Foster, Rinaman, & Cryan, 2017) and extend these to include an investigation of the biological- and cognitive mechanisms by which a probiotic intervention may have beneficial effects on mood.

Hence, the proposed study aims to:
1) Determine effects of probiotics on cognitive processes thought to signify vulnerability to depression;
2) Test potentially mediating biological pathways herein.
Regarding aim 1, the study will focus on four cognitive domains.
a) cognitive reactivity/perseverance (CR; see above)
b) positive re-biasing in negative attentional processing; a mechanism counteracting negative attentional bias.
c) Motivation (wanting) and reward (liking)-related learning (Felger & Treadway, 2016)
d) affect recognition; recognition of affect-laden facial expressions has been found to predict depression vulnerability (Pizzagalli, 2014; Bistricky, Ingram, & Atchly, 2011; Boruke, Douglas, & Porter, 2010).
Regarding aim 2, the study will investigate four potential pathways identified in animal studies (Cryan & Dinan, 2012; Desbonnet et al., 2008,2010), but which received little scrutiny in humans:
a) gut permeability (GP), i.e., markers of leakage of bacterial products into the circulation.
b) Through GP, and other routes, probiotics may affect inflammatory activity (Mass, Kubera, & Leunis, 2008)
c) dysregulate activity of the hypothalamic-pituitary-adrenal (HPA) axis, which both have been implicated in depression and cognitive functioning (Foster & Neufeld, 2013; Pariante & Lightman, 2008).
d) Animal studies show that gut microbiota can increase amino acid metabolism (Desbonnet et al., 2008, 2010), which may enhance brain neurotransmitter availability (Silber & Schmidt, 2010).

In addition, we will account for factors known to affect or be affected by these domains and pathways, specifically cognitive ability, fatigue, sleep quality, dietary pattern, physical characteristics, microbiome profile, stool characteristics, interaction between these factors, and changes herein (see also Sections 8.1.2 and 8.1.3; Secondary and other parameters; Sandhu et al., 2017; Budree et al., 2017).

Study design

The proposed study will follow a double-blind randomized, placebo-controlled, between-subject design. A sample of 140 adults (18-75 years old) will be included. All questionnaires and tasks, with the exception of a five-week mood diary, a weekly food questionnaire, and the collection of a fecal sample, will be completed during lab visits by the participants before and after the intervention period of 35 days, during which participants will be asked to take either 2 grams of Ecologic®Barrier (probiotics) or 2 grams of a neutral placebo (standard carrier). For a detailed description of the study*s procedures, we would like to refer to section 8.3. Participants (N=140, following Huang, Wang, & Hu, 2016; see also section 4.3 for a detailed power analysis) will be randomly assigned to either the probiotics (n=70) or the control (placebo)

group (n=70). Subjects will be treated according to the international convention governing drug studies in human volunteers; i.e. the declaration of Helsinki (1964) and its subsequent amendments.

Intervention

Following Steenbergen and colleagues (2015) and de Noos and colleagues (2015), the probiotic group will receive 2 grams freeze-dried powder of the probiotic mixture Ecologic®Barrier daily for 35 days. (Winclove probiotics, the Netherlands). Ecologic®Barrier (2.5 × 109 cfu/gram) contains the following bacterial strains: Bifidobacterium bifidum W23, Bifidobacterium lactis W51 and W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, Lactococcus lactis W19 and Lactococcus lactis W58. The placebo group will only receive the standard carrier used for the probiotic product: i.e., 2 grams of maize starch for the same intervention period. Participants in both groups will be asked to dissolve the carrier products in lukewarm water before ingestion.

Study burden and risks

The burden of participation is modest and consists of one phone interview (to screen for in- and exclusion criteria) and 2 visits to the laboratory, 35 days apart. Each testing session will take no longer than 2.5 hours during which questionnaires will be filled out and cognitive tests will be performed. At both visits an 18 ml blood sample will be taken by a trained nurse or phlebotomist, and supervised by a medical doctor. Standard measurements will include heart rate and blood pressure (using an automated monitor) and assessment of anthropomorphic characteristics (i.e., weight, height, skin-folds, waist- and hip circumference). Participants will collect (self-produced) fecal matter in a specially designed collection system that requires very little effort from the participants. Between visits, participants will be asked to keep a diary and to take the required food supplement. The dosage of Ecologic*Barrier (the brand name of the probiotic supplement utilized) is deemed safe ; all strains hold qualified presumption of safety (QPS) status and are approved by the European Food Safety Authority (EFSA). This food supplement is freely accessible to consumers on the market and the negligible health risks in the general population have been well-established.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Healthy adult participants
- aged 18-75 years
- Females taking hormonal contraceptives; with the exception of females post-me nopause (In case of oral contraceptives, we will test participants in the weeks they commence the pill, i.e. at the end of the stop week. This way, we will ensure that hormone patterns are similar between the two test sessions.
- Willingness to travel to the laboratory site, perform tasks and fill out questionnaires and adhere to the study intervention.
- Fluency in Dutch language
- written informed consent before inclusion

Exclusion criteria

- Implementing or planning major changes in diet; e.g. attending a weight-loss program or changing to a vegetarian or vegan diet, or initiating new food supplements (including pro- or pre-biotics).
- Current or past cardiac- (including high blood pressure), inflammatory- or auto-Immune-, gastrointestinal-, hepatic-, renal-, neurological- or psychiatric disorders or diseases, based on

self-reported medical diagnosis and medication use.
- excessive alcohol intake, defined as drinking more than 21 glasses of alcohol per week;
- history of drug abuse or addiction;
- Not using hormonal contraceptives (with the exception of post-menopause females)
- Antibiotic use 3 months prior to the study
- age below 18 or above 75.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-10-2017
Enrollment:	140
Type:	Actual

Ethics review

Approved WMO Date:	29-09-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 28892
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL62568.018.17
OMON	NL-OMON28892