Special Article

Effects of prebiotics on affect and cognition in human intervention studies

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Studies conducted in rodents have highlighted that neurobiological processes underlying cognition and affect are modulated by the gut microbiota. Certain dietary fibers are able to modulate the composition of gut microbiota and are thus considered prebiotics. A review of the impact of the available prebiotic intervention studies in humans on cognition and affect, addressing the potential mediating role of the microbiota, was conducted. PubMed, Scopus, and PsycINFO were selected as sources. Fourteen articles were eligible for narrative synthesis. Data extraction and quality assessment were performed with characteristics established a priori. Some chronic prebiotic interventions (>28 d) improved affect and verbal episodic memory compared with a placebo. Acute prebiotic interventions (<24 h) were more efficient in improving cognitive variables (eg, verbal episodic memory). Future research should measure microbiota using adequate methodologies and recruit patients with dysbiosis, inflammation, or psychopathology. More research is needed to unravel the conditions required to obtain effects on affect and cognition.

INTRODUCTION

Rationale

Interest in the role played by gut microbiota in health has increased in the last decade.[1] The intestinal tract contains 100 trillion microbes,[2] which is 10-fold the number of human cells.[3] The gut microbiota is essential for health because it influences the immune system, metabolizes xenobiotics and nutrients escaping the digestion in the upper part of the gut, and synthesizes bioactive molecules and vitamins.[1,4] Recent studies have emphasized that some neurobiological processes underlying emotional, cognitive, and behavioral functions seem to be regulated by gut microbiota.[5] However, this evidence comes mostly from studies in rodents. Thus, the extent to which these findings and their explanatory mechanisms can be transferred to humans is not known.[4,5] The arrival of a new generation of technologies (eg, Illumina Genome Analyser [GA] technology) with high-throughput sequencing techniques and specialized microarrays has allowed a better understanding of human gut microbial composition in different conditions.[4,6]

The bidirectional communication between the brain and the gut is called the gut-brain axis.[7] Several reviews describe how the microbiome affects the brain (eg, Cryan and Dinan[7]; Grenham et al[8]; Gaman and Kuo[9]). Three main pathways were distinguished: neural, endocrine, and immune. Microbiota is thought to influence the brain via the vagus nerve[4,5]; the hypothalamic-pituitary-adrenal axis[10]; immune activation[4,11]; tryptophan metabolism[5]; the production of neuroactive compounds such as dopamine or

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noradrenaline[12]; the production of short-chain fatty acids (SCFAs), which have some neuro-active properties[13]; and the regulation of central neurotransmitter levels and receptor expression by bacteria.[5] Furthermore, changes in microbiota are associated with a number of neuropsychiatric disorders, which supports the implication of the microbiota in the central nervous system (CNS).[7] Several strategies have been developed to modulate gut microbiota in order to improve the mental health of the host.[14] For instance, probiotics, also called psychobiotics in this context, could be used in patients with psychiatric illness because they produce neuroactive substances such as serotonin and gamma-aminobutyric acid (GABA).[12]

Diet has long been acknowledged as one of the most important external factors that explains the variance in gut microbiota composition.[1,15] A study in mice has shown that 57% of the total structural variation of the microbiota was explained by diet changes, whereas 12% was explained by genetic mutations.[16] In humans, a major shift in diet, such as a strict animal- or plant-based diet, can modify the microbiota after only a few days.[17] One study has shown that a long-term dietary pattern is a predictor of microbial composition.[18] Proteins and carbohydrates, as well as fat and carbohydrates, predicted in different ways this microbial composition. Nevertheless, the proportion of the total variance in microbiota explained by interventions (eg, $<0.1\%$ with a probiotic intervention) is markedly smaller in humans than in animals.[15]

As part of the diet, prebiotics can modulate the gut microbiota to enhance health.[19] Gibson and Roberfroid[20] first defined a prebiotic as "a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health." Most definitions of prebiotics advocate a selective effect on health-promoting bacteria (essentially bifidobacteria and lactobacilli) in microbiota. However, several arguments are not in favor of this criterion.[21] One of them argues that beneficial and detrimental bacteria cannot yet be discriminated. Improved technologies have also demonstrated that established prebiotics do not seem to be as selective as previously thought.[21] The definition of prebiotics has thus evolved according to increasing data on the role of nutrients on gut microbiota.[21] Lastly, the International Society for the Study of Probiotics and Prebiotics proposed the following definition[22]: "a substrate that is selectively utilized by host microorganisms conferring a health benefit." In this review, the focus is on dietary fibers, which tend to modulate the gut microbiota, and they will therefore be called "prebiotics."[21,23,24]

The most studied prebiotics are inulin type fructans (ITFs), fructooligosaccharides (FOSs), galacto-oligosaccharides (GOSs), trans-galactooligosaccharides (TOSs), and xylo-oligosaccharides (XOSs).[25] They are naturally present in different foods such as artichokes, asparagus, garlic, and bananas (see Appendix S1 in the Supporting Information online for a list).[25,26] Prebiotics are not digested by enzymes; thus they enter the proximal colon and are fermented by bacteria, which gain proliferative advantages due to substrate availability.[27] As a consequence, gases and acidic products, including lactate and SCFAs such as butyrate, acetate, and propionate, will be released.[27] The specific changes in gut microbiota and metabolites profiling may determine the effect prebiotics have on host health.[25]

Prebiotics could beneficially impact the brain via increased gut barrier function, immunity, and production of SCFAs, as well as a reduction of potentially pathogenic microbes.[25] For instance, FOS and GOS can modulate various neurotransmitters, neural growth factors (eg, brain-derived neurotrophic factor [BDNF]), N-methyl-D-aspartate receptor (NMDAR) subunits, and synaptic proteins through the influence of microbiota on the vagus nerve in mice.[28,29] BDNF has been shown to have anxiolytic effects, and NMDAR subunits may modulate cognitive functions.[28] These effects give rise to the possibility for prebiotics to alter neural processes, including mood and cognitive abilities, via the modulation of microbiota.[28] However, a direct effect of prebiotics on the brain without altering microbiota cannot be ruled out.[28] For instance, in mice, GOS and other prebiotics can directly regulate hormones such as plasma peptide YY.[28] In humans, FOS may regulate appetite through its impact on glucagon-like peptide-1 (GLP-1) and peptide YY.[30] Finally, prebiotics may be used to prevent psychological disorders such as depression and anxiety disorders by modulating microbiota.[31] The evidence concerning the influence of prebiotic treatment on psychological variables in humans can therefore be evaluated.

Although previous reviews have described the influence of gut microbiota on health, brain functions, and/or behavior, as well as microbiota-targeted interventions in animals and humans,[4,5,25,31–36] they have not exhaustively reported on the effect of prebiotic interventions on human affective and cognitive processes. Collins and Reid's review[25] reported the most studies (ie, 7) addressing this question. These authors summarized findings from prebiotic interventions in humans on bone density or immune function and reported the effects of prebiotics on memory, attention, learning, and mood. They summarized a wide range of variables influenced by prebiotics and explored mechanisms of action, as well as potential practical

applications. Nevertheless, the present review takes into account the whole range of published interventions (n = 14) with prebiotics focusing on cognition and affect. Moreover, a quality assessment was performed for included studies in order to draw reliable conclusions. Indeed, a poorly constructed design can result in bias that could be the primary reason for observed effects.[37] Because a quality assessment evaluates the robustness of studies, its results can be used to guide prevention, treatment, or policy decisions and to inform standards for future studies.[37]

Objective of the study and definition of the context

The objective of this review—taking into account the criteria of quality reported before[37]—is to examine the effects of prebiotics on affect (mood, emotions, well-being, depression, and anxiety) and cognitive dimensions (memory, attention, perception, and executive functions) in intervention studies with prebiotics conducted on humans. It will also investigate the conditions under which the effects of prebiotics on these dependent variables are found and the extent to which the microbiota is involved in these effects. Given the heterogeneity of the included studies due to the use of different types of interventions, types of prebiotics, and outcomes, a narrative synthesis is more appropriate than a meta-analysis.[37] Although a narrative synthesis is more subjective, it will still allow us to provide a detailed view of the effects found, together with an examination of potential moderators and conditions under which the effects are found.

METHODS

Eligibility criteria

The selection of articles for this review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (see Table 1).[38] The selected studies needed to include an intervention with prebiotics on humans. The specific focus is on dietary fibers, which tend to modulate the gut microbiota. Outcome variables were related to affect and cognition. Affect includes emotion, mood, psychological well-being, anxiety, and depression. Cognition involves memory, attention, perception, and executive functions. Heterogeneity across studies was allowed in order to widen the scope and discover potential moderators of prebiotic effects. There were no restrictions regarding the comparator of the treatment or the placebo condition, the length of the intervention, the design, and the type of participants. Only studies with children (aged <10 y) were excluded because the behavioral measures used in these studies were too different from the ones that are used in studies on adults. Finally, a quality assessment was performed, but because the total number of articles was limited, low quality was not considered to be a criterion for exclusion.

Table 1 **PICOS criteria for inclusion and exclusion of studies**

Population	Humans
Intervention	Prebiotics (dietary fibers)
Comparator	No restriction
Outcomes	Affective dimension: mood, emotion, psychological well-being, anxiety, and depression. Cognitive dimension: memory, attention, perception, and executive functions
Setting	No restriction

Information sources

A systematic literature search was performed on PubMed, Scopus, and PsycINFO between February 20 and March 20, 2017. The reference lists of the papers identified in the literature search and in relevant books[19,39] were also checked to find potential missing studies. The books were chosen because they were recent and clearly related to the research question.

Search

The following search terms were used for all databases (see Appendix S2 in the Supporting Information online): (Dietary fibre* OR dietary fiber* OR inulin OR prebiotic* OR fructan* OR fructo-oligosaccharide* OR oligofructose OR galacto-oligosaccharide* OR oligosaccharide*) AND (mood OR emot* OR affective OR well-being OR wellbeing OR depress* OR anxiety OR attent* OR memory OR percept* OR executive function* OR cognit*).

Search strategies were peer reviewed by all authors to reach a consensus. Prebiotics related to other dietary fibers, such as arabinoxylan, arabinoxylan-oligosaccharides, and nondigestible carbohydrates, were also considered. They were added as key words in the literature search. However, no study considering the effects of these dietary fibers on affect or cognition in humans was found. Finally, English was the only language used for keywords, which means that only articles published in English were considered.

Study selection

The titles of all articles were screened. When an article seemed to be relevant, the abstract was read and the article was selected for full-text reading. When a specific

type of population, prebiotic, or dependent variable was used, at least four authors discussed the article in order to have a consensus on its eligibility.

Data collection process

The relevant information to extract was defined based on discussions among the authors. For each included study, the type of intervention, including the type of prebiotic, the dose and the duration, the type and number of participants, the design, the exclusion and inclusion criteria, the location of studies, the comparator or the placebo, the moderators, the outcomes, and the effect size when it was reported were extracted.

Quality assessment

A quality assessment of the included studies was performed (see Table 2) using an adapted quality assessment scale (see Appendix S3 in the Supporting Information online), originally developed by Downs and Black.[40] Additional items were added to the quality assessment to adapt it to the included studies. For instance, a question regarding the presence of a control group was added because a study that did not have one was included. The main categories (reporting, external validity, risk of bias, confounding, and power) were kept. Given that studies were not excluded on the basis of their design, the scale developed by Downs and Black[40] was chosen because it allows for both randomized and nonrandomized trials. Three authors independently assessed the studies, then met to cross-check these independent evaluations. Divergences were resolved by discussions and consensus. Publication bias was not quantitatively investigated because a meta-analysis was not performed.

RESULTS

Study selection

The search on PubMed, Scopus, and PsycINFO databases resulted in 2630 articles (see Figure 1). Only 30 articles remained relevant on the basis of the title and the abstract. Nonrelevant articles did not comply with the inclusion and exclusion criteria. In addition to the databases, the references of included studies and books were searched. This search provided 9 additional articles that met the eligibility criteria. Thus 39 articles remained after this first screening. Four articles were discarded because they considered a trans-sectional design. After the full-text assessment, 14 studies were eligible for a narrative synthesis. The 25 other studies were rejected because they were literature reviews or correlational studies, or the interventions or dependent variables differed too much from the scope of the review, or because the type of dietary fibers examined was not specified. A poster was also excluded due to a lack of available information.[41] Correlational studies were excluded because they did not fulfill the criteria of being an intervention. The dependent variables that qualified as being too different were gastrointestinal well-being (eg, vomiting, flatulence, wind, reflux)[42,43]; physical symptoms related to quality of life[44,45]; infant fussing, crying, and irritability[46]; and emotional distress related to fatigue.[47] Two intervention studies were also excluded because they included dietary fibers that were not specified.[47,48] Not every dietary fiber has a prebiotic effect,[23] so it is important to specify the type of fiber. Finally, 1 intervention was excluded because it concerned milk fortified with vitamins, minerals, and inulin, so the effects cannot be attributed to the prebiotic only.[49]

Study characteristics

Design.

Among the 14 studies selected, 5 were randomized, crossover trials, 3 of which were double-blind[50–52] and 2 of which were nonblinded studies.[53,54] Seven were randomized, double-blind, parallel, controlled trials.[55–61] One study was a randomized, simple-blind, controlled, parallel, and crossover trial.[62] Finally, 1 study did not have a control group.[63]

Intervention.

The duration of the interventions ranged from 10 minutes to 13 weeks, with administrations of prebiotics that ranged from 5 mg[52] to 10 g.[54] Some interventions included well-known prebiotics such as oligofructose-enriched inulin,[54] inulin,[52] FOS,[60] Bimuno-galactooligosaccharides (B-GOS),[60] trans-galactooligosaccharide,[62] short chain of fructooligosaccharides,[55,59] and xylo-oligosaccharides.[50] Other interventions were performed with mixtures, including, namely, potential prebiotics: agave fructan[51]; beta-glucan[61]; a mixture of nonstarch polysaccharides (Ambrotose Complex) containing larch arabinogalactan, rice starch, aloe vera gel extract, ghatti gum, glucosamine hydrogen chloride, and tragacanth gum[56–58]; cereals containing at least 5.4 g of fiber (3.5 g of wheat bran)[63]; and a breakfast with a high or a low ratio of simple (mono and di)/complex (polysaccharides) carbohydrates.[53] The majority of studies used maltodextrin in powder as a placebo.[50–52,55,59,60,62] Other studies used rice flour,[57,58,61] sucrose,[57] stevia,[56] simple carbohydrates,[53] or did not specify.[54]

Table 2 **Quality ranking of selected studies**

References	Reporting[a]	External validity[b]	Risk of bias[c]	Confounding[d]	Power[e]	Total[f]
Childs et al (2014)[50]	12	1	8	6	1	28
Azpiroz et al (2017)[55]	12	1	8	5	1	27
Ramnani et al (2015)[51]	11	1	9	4	1	26
Best et al (2009)[58]	11	1	9	5	0	26
Buigues et al (2016)[59]	11	1	8	3	1	24
Best et al (2015)[57]	9	1	8	5	0	23
Best et al (2008)[56]	11	1	8	3	0	23
Talbott and Talbott (2009)[61]	8	1	8	5	0	22
Smith et al (2015)[52]	9	1	9	2	1	22
Schmidt et al (2015)[60]	10	1	8	3	0	22
Pasman et al (2003)[53]	10	1	7	3	0	21
Silk et al (2009)[62]	10	1	8	1	1	21
Lawton et al (2013)[63]	11	1	4	3	0	19
Smith (2005)[54]	7	1	6	2	0	16

[a]Scale of 0–12.
[b]Scale of 0–3.
[c]Scale of 0–9.
[d]Scale of 0–6.
[e]For power, 1 indicates that a power analysis was performed, whereas 0 indicates a power analysis was not performed.
[f]Scale of 0–31.

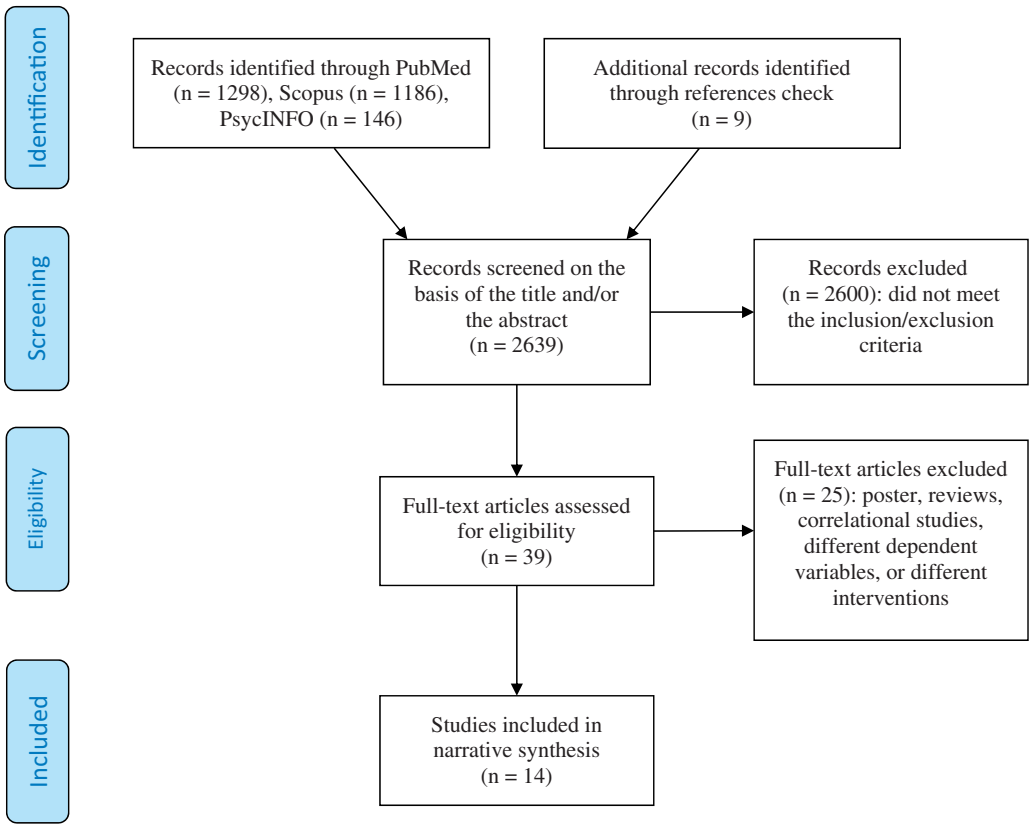

Figure 1 **Flow diagram of the literature search process.**

Participants.

The included studies involved 988 participants in total and had sample sizes ranging from 26[53] to 153.[54,63] Among them, there were 60 participants aged >65 years[59] and 123 patients with irritable bowel syndrome (IBS).[55,62] The main exclusion criteria (see Appendix S4 in the Supporting Information online) were participants that 1) have a disease, 2) take medication, 3) have had major surgery, 4) engage in drug use, 5) consume a high amount of fiber, 6) have allergies, or 7) have participated in a clinical study. Half of the included studies were conducted in the United Kingdom (n = 7 of 14;

n = 521 participants). Other studies were conducted in France and Spain (n = 79 participants), Spain only (n = 60 participants), the United States (n = 75 participants), Australia (n = 227 participants), or the Netherlands (n = 26 participants).

Outcomes of interest

Affective variables.

Mood was often examined across studies[48,50–54,57,58,61] and is defined as a diffuse affect state affecting experiences and behaviors, characterized by subjective feelings, not related to any clear trigger, generally of low intensity, and lasting for a few hours or days.[64] Related to mood, feelings of joy,[52] alertness,[51] and energy[51] were also investigated. Other affective variables measured were well-being,[63] an experience of high levels of pleasant affect and low levels of negative affect[65]; stress,[51,58,60] "a response characterized by physiological arousal and negative affect"[66]; and anxiety,[55,58,60,62] an autonomic arousal associated with somatic symptoms and feelings of fear, tension, panic, and worry.[67] Depression was investigated in 2 studies[55,62] using the Hospital Anxiety and Depression scale (HADS) with the depression scale focused on anhedonia (diminished pleasure or interest).[68] All of these measures were self-reported. Only 1 study considered emotion scores based on task performance. It included the Emotional Test Battery (ETB), attentional dot-probe task, face expression task, and tasks of emotional memory and emotional categorization.[60]

Cognitive variables.

Several cognitive dimensions were considered in the studies reviewed. Processing speed, which is the capacity to process (encoding, transforming, retrieving) information within working memory,[69] was assessed with psychomotor tasks (eg, simple reaction time and choice reaction time).[52,54,58] Two types of attention were evaluated: 1) selective attention,[54,58] which is the capacity to use resources to process relevant elements while inhibiting distractors,[70] and 2) sustained attention,[52,54] "the subject's readiness to detect rarely and unpredictably occurring signals over prolonged periods of time."[71] The studies also included measures of long-term memory such as episodic memory (direct recall, delayed recall and/or recognition), which is the capacity to remember events that were personally lived in a specific spatial and temporal context,[70] and semantic memory,[54] which is the general and conceptual knowledge people have about the world that allows them to reason, solve problems, and understand their environment and language.[70] Short-term memory,[56] which is the ability to retain information for a short period of time,[70] and working memory,[54,56,58] which is "the ability to maintain and process information simultaneously during the performance of a cognitive task,"[72] were other measured outcomes. Finally, the studies investigated logical reasoning,[52] cognitive difficulties,[52] and general cognitive abilities,[56,58,59] which were measured by inductive reasoning tasks or general verbal abilities. One study used the cognitive demand battery (CDB), which evaluates speed, accuracy, and mental fatigue related to performance.[57]

The microbiota.

Of 14 studies, 4 measured fecal microbiota.[50,51,55,62] Among these 4, 2 studies examined SCFAs.[50,51]

The secondary outcomes were also extracted from the selected studies (see Appendix S5 in the Supporting Information online).

Quality assessment of included studies

The results of the quality assessement can be found in Table 2.[50–63]

Syntheses of results

The results of individuals studies have been summarized in Table 3 and and the PICOS criteria in Table S1 in the Supporting Information online.[50–63]

For the syntheses of results, studies were categorized according to the length of the intervention. Those classified as chronic studies lasted for at least 28 days, where those classified as acute interventions lasted <1 day. Some authors have proposed that, due to the transit time, acute interventions are less likely to have an effect on microbiota.[17] A study demonstrated that nondigestible carbohydrates are able to alter microbial composition of humans within 3–4 days.[73] Other data showed that changes in the composition of microbiota were detectable within 24 hours of consumption of a high-fat/low-fiber or low-fat/high-fiber diet in humans.[18] Some authors claim that prebiotics could alter the microbial composition before entering the colon because microbes are already present in the mouth.[74] In the same vein, more and more attention is being paid to microbiota present in the upper part of the gut when host–microbe interactions and the impact of nutrition on health are being evaluated.[75]

A distinction was also made between the results of studies that included healthy participants and those that included patients presenting a pathology. This distinction is useful to highlight the influence of individual differences on the relationship between prebiotics and dependent variables (eg, mood). The effect of prebiotics could be different in a clinical sample with patients with

Table 3 **PICOS criteria of included studies**

References	Population	Intervention	Comparator	Outcomes	Design
Smith (2005)[54]	Healthy participants	Oligofructose-enriched inulin	Placebo	Decrease in simple and choice reaction time	Placebo-controlled, crossover design
Schmidt et al (2015)[60]	Healthy participants	Fructooligosaccharides (FOS) or Bimuno-galactooligosaccharide (B-GOS)	Placebo (maltodextrin)	GOS : less salivary cortisol and a decrease in attentional vigilance toward negative stimuli vs positive in the unmasked condition (no correlation between attentional vigilance and cortisol)	Randomized, double-blind, placebo-controlled, parallel design
Ramnani et al (2015)[51]	Healthy participants	Agave fructan (5 g/d)	Placebo (maltodextrin)	Increase in fecal bifidobacteria and lactobacilli but no change regarding mood	Randomized, double-blind, placebo-controlled, crossover design
Childs et al (2014)[50]	Healthy participants	Xylooligosaccharides (XOS), *Bifidobacterium animalis* subsp. *lactis* (Bi-07), or combined	Placebo (maltodextrin)	XOS: increase in vitality, joy, fecal bifidobacteria (not different from the control group) and cetic and butyric concentrations	Randomized, double-blind, placebo-controlled, crossover design
Talbott et al (2009)[61]	Marathon athletes	BETA-GLUCAN 250 mg/d or 500 mg/d	Placebo (rice flour)	Significant and dose-dependent improvement of confusion (decrease), fatigue (decrease), vigor (increase), tension (decrease), and anger (decrease)	Double-blind, placebo-controlled design
Best et al (2009)[58]	Middle-aged healthy participants	Combination of plant polysaccharides (Ambrotose Complex)	Placebo (rice flour starch)	Improvement in verbal free recall and recognition; decrease in depression-dejection and anger-hostility subscales of the Profile of Mood States (POMS)	Randomized, double-blind, placebo-controlled design
Lawton et al (2013)[63]	Healthy participants but low consumers of fibers	Cereals (5.4 g of fibers with 3.5 g of wheat bran)	No comparator	Increase in vigilance, subjective slimness, happiness, and energy. Decrease in stress, mental fatigue, feeling of being fat, difficulty concentrating, physical fatigue	Intrasubject design with unique center, multisite, and open (no control group)
Silk et al (2009)[62]	Patients with irritable bowel syndrome	Trans-galactooligosaccharide (3, 5 or 7 g/d)	Placebo (maltodextrin)	Increase in fecal bifidobacteria and decrease in anxiety	Randomized, simple blind (patients), placebo-controlled, parallel, and crossover design
Azpiroz et al (2017)[55]	Patients with irritable bowel syndrome	Short-chain fructooligosaccharides	Placebo (maltodextrin)	Increase in fecal bifidobacteria and decrease in anxiety and in the global score of Hospital Anxiety Depression (HAD)	Randomized, double-blind, placebo-controlled
Buigues et al (2016)[59]	Elderly participants (from aged 65 y) with frailty syndrome	Inulin plus fructooligosaccharides (Darmocare Pre)	Placebo (maltodextrin)	Improvement in exhaustion and muscle strength and less fatigue	Randomized, simple blind, placebo-controlled, parallel design
Smith et al (2015)[52]	Healthy participants	Inulin	Placebo (maltodextrin)	Happier, more recalled words (direct and delayed) and better recognition (but slower)	Randomized, placebo-controlled, crossover design

(continued)

Table 3 **Continued**

References	Population	Intervention	Comparator	Outcomes	Design
Best et al (2015)[57]	Middle-aged healthy participants	Combination of plant polysaccharides (Ambrotose Complex)	Placebo (rice flour) or saccharose	Increase in working memory and recognition (not due to glucose levels)	Randomized, double-blind, placebo-controlled, parallel design
Pasman et al (2003)[53]	Healthy men	Breakfast with a high ratio of simple (monosaccharides and disaccharides)/complex (polysaccharides) carbohydrates	Breakfast with a low ratio of simple (monosaccharides and disaccharides)/complex (polysaccharides) carbohydrates	No effect besides less fatigue	Randomized, open trial, crossover design
Best et al (2008)[56]	Healthy participants (aged 40 to 63 y)	Combination of plant polysaccharides (Ambrotose Complex)	Glucose or placebo (stevia)	No significant difference	Randomized, double-blind, placebo-controlled, parallel design

IBS, for which the microbiota has a different composition.[76] The scores on affect and cognition at baseline could also modulate the strength of the effect of prebiotics. Finally, affective and cognitive outcomes were considered separately.

Chronic studies

Healthy participants.

Affective variables. Among the 6 chronic studies that investigated affective variables and were conducted on healthy participants, 4 found an effect of prebiotics on affect.[50,58,61,63]

The first study found that 8 g/day of XOSs for 21 days significantly improved mood in terms of vitality ($P = 0.003$) and happiness ($P = 0.034$), but not stress ($P = 0.319$) and alertness ($P = 0.131$), compared with a placebo (maltodextrin).[50] Moreover, there were significantly more fecal bifidobacteria after XOS intake compared with baseline ($P = 0.008$), but this was not significantly different from the placebo condition ($P > 0.05$).[50] Finally, XOS seemed to have immunostimulatory effects and increase Th1 responses.[50] This type of immune response is mainly developed following infection by some types of viruses and intracellular bacteria.[77] The link between inflammation and behavior—including the gut microbiota as a component—is now considered important, as suggested by studies performed in alcohol-dependent patients that link activation of proinflammatory pathways, gut microbial dysbiosis, and depression symptoms.[78,79] However, in this study, the mechanism by which mood was influenced is not clear and the extent to which immunity was implicated is not known.

The second study was a randomized controlled trial that provided healthy participants with 3.6 g of a combination of polysaccharides (Ambrotose Complex) or a placebo for 12 weeks.[58] This intervention resulted in a significant decrease in scores on the depression-dejection ($P < 0.05$) and anger-hostility subscales ($P < 0.05$) (2 of 6 subscales) of the Profile of Mood States (POMS).[58] Although the use of the Positive and Negative Affect Schedule (PANAS) is more common nowadays, a study found high correlations (ranging from 0.85 to 0.91) between the PANAS-X (60 items) and POMS dimensions.[80]

The third study was a pre/post intervention study without a control group that investigated the effect of a breakfast high in wheat bran fiber (3.5 g of wheat bran) for 14 days on the psychological well-being of healthy, habitual low-fiber consumers.[63] This intervention significantly ($P < 0.0001$) increased self-reported happiness, mental alertness, energy, and subjective slimness.[63] Significant ($P < 0.0001$) decreases in stress,

the feeling of being fat, difficulty in concentrating, mental tiredness, physical tiredness, and headaches were also reported.[63] Wheat bran contains arabinoxylan oligosaccharides, which are considered potential prebiotics.[81]

The fourth study was a postmarathon trial where athletes took 250 mg or 500 mg of beta-glucan or a placebo for 29 days.[61] The authors chose the postmarathon period for their intervention because they investigated the protective effects of prebiotics on immunity and psychological well-being, which is altered 2 weeks following a marathon. Compared with the control group, those in the intervention group had significantly ($P < 0.05$) increased vigor and decreased confusion, fatigue, tension, and anger (as assessed by the POMS) in a dose-dependent manner.[61] However, no difference was found for depression. Although there is no consensus, beta-glucan is considered a prebiotic by Hyland and Stanton.[19]

The 2 other studies used 5.5 g of FOSs or B-GOSs for 21 days[60] and 5 g of the prebiotic agave fructan for 21 days.[51] Compared with a placebo, these interventions failed to influence mood, alertness, hedonic tone, anxiety, energy, and stress.[50,51] One of the interventions showed, however, a significant increase of fecal bifidobacteria ($P < 0.001$) and lactobacilli ($P < 0.0001$) following the intervention compared with placebo.[51] Indeed, agave fructan seems to have a prebiotic effect[82] and is more able to stimulate the growth of *Bifidobacterium breve* and *Lactobacillus casei* than most commercial inulins.[83]

The only study that used objective measures regarding affective variables revealed a significant decrease of attentional vigilance to negative versus positive stimuli following B-GOS intake compared with a placebo ($P = 0.05$).[60] In other words, individuals paid less attention to negative stimuli and more to positive ones after the intervention. This effect was only seen in the unmasked condition of the attentional dot-probe task, where participants are aware of the stimuli.[60] This result indicates that prebiotics enhanced the capacity to disengage attention from negative stimuli, which has been altered in depression.[60] There was also a significant decrease in salivary cortisol, but this effect was not associated with performance ($P < 0.05$). This does not support the involvement of the hypothalamic–pituitary–adrenal axis in the attentional effect seen.

Cognitive variables. Only 2 long intervention studies with healthy participants measured the effect of prebiotics on cognition.[54,58] Ten grams of oligofructose-enriched inulin for 14 days did not influence selective attention, sustained attention, episodic memory, semantic memory, or working memory.[54] Although participants in the intervention group were significantly faster than those in the placebo group at responding to targets shown in the same location as the previous trial and faster at incompatible responses following the intervention ($P < 0.05$), the authors warned that these results could reflect a possible chance effect due to a large number of dependent variables.[54] However, participants that were administered Ambrotose Complex showed significantly increased scores on 2 of 5 trials of the verbal memory task for the immediate recall trial and recognition memory (Rey Auditory Verbal Learning Test; RAVLT) in comparison with the placebo ($P < 0.05$).[58] Nevertheless, no significant intervention effects were observed for visuospatial memory, working memory, attention, speed processing, and general cognitive abilities ($P > 0.05$).[58]

Clinical groups.

Affective variables. Two studies explored the effect of prebiotics compared with a placebo on patients with IBS.[55,62] The intervention of Silk et al[62] concerned the ingestion of trans-galactooligosaccharide (3.5 g or 7 g) for 12 weeks. The study of Azpiroz et al[55] consisted of the intake of 5 g of short-chain fructooligosaccharides for 28 days. Compared with a placebo, both interventions succeeded in significantly decreasing anxiety ($P < 0.05$), but not depression ($P > 0.05$), assessed by the Hospital Anxiety and Depression (HAD) scale. In the study of Silk et al[62] only the 7 g dose of trans-galactooligosaccharides had an effect significantly different from a placebo ($P < 0.05$). This effect was accompanied by an increase of fecal bifidobacteria in both studies.[55,62]

Cognitive variables. Another study was performed on elderly (aged >65 y) participants that received Darmocare Pre containing inulin plus FOSs (7.5 g) or a placebo for 13 weeks.[59] The authors measured frailty, which is a geriatric syndrome with functional and physical decline. General cognitive abilities (as measured by the Mini-Mental Examination Score) and sleep quality did not significantly differ between intervention and control groups ($P > 0.05$).

Acute studies

The next 4 studies explored the acute effect of prebiotics on affect and cognition.[52,53,56,57] The interventions ranged from 10 minutes to 4 hours. Data related to gut microbiota analysis were not reported for any of those studies. Therefore, the implication of gut microbial changes in the observed effect cannot be ruled out.

Affective variables.

Three studies explored the acute prebiotic effect on affective variables, but, in general, they did not find any effect compared with a placebo.[52,53,57] Indeed, the only significant effect of the prebiotics was found on happiness. Five milligrams of oligofructose-enriched inulin, which is a very low dose compared with what is generally administered, significantly enhanced happiness after 4 hours compared with a placebo ($P < 0.05$).[52] The other scores of mood, such as depression, fatigue, subjective energy, stress and anxiety, did not significantly change compared with a placebo group ($P > 0.05$).[52]

Best et al[57] used 4 g of a proprietary mixture of nonstarch polysaccharides (NSPs) (Ambrotose Complex), a placebo (rice flour), or a sucrose control for 30 minutes of effortful and mentally fatiguing tasks. Compared with a control group, this intervention had no effect on anxiety, alertness, contentedness, or calmness.[57] Similar results were observed in an intervention that included a breakfast with complex carbohydrates (6.5 g of fibers) compared with a simple carbohydrate breakfast for 4 hours.[53] Compared with a placebo, this intervention significantly reduced fatigue (measured by a subscale of the POMS) ($P = 0.03$),[53] whereas, depression, anger, vigor, and tension did not differ significantly between groups ($P > 0.05$).

Cognitive variables.

In the intervention of Smith et al[52] more words were recalled correctly and fewer incorrect words were recalled in the inulin condition. For the recognition part, a better accuracy score was found, but reaction times were slower.[52] However, inulin did not have an effect on spatial memory, semantic processing, logical reasoning, psychomotor tasks, or sustained attention.

Best et al[57] found that 4 g of Ambrotose Complex for 30 minutes of effortful and mentally fatiguing conditions significantly increased the number of words recognized compared with the sucrose condition ($P = 0.004$), but not compared with the control group ($P = 0.07$). Regarding the performance on the CDB, a significant greater number of correct responses was recorded during the second cycle of a task measuring working memory and executive functions abilities for those in the polysaccharide condition, compared with those in the placebo condition ($P = 0.02$).[57] Statistical analysis showed these effects cannot be explained by blood glucose levels. However, another study that used 7 g of Ambrotose Complex or 25 g of glucose for 10 minutes showed no effect on memory, such as immediate and delayed recall, recognition, short-term and working memory, and general cognitive ability.[56]

DISCUSSION

Summary of evidence

The aim of this review was to examine intervention studies in humans that investigated the effects of fibers susceptible to changing the gut microbiota (prebiotics) on affective and cognitive variables. Four of the 6 studies that investigated prebiotic effect on self-reported affect showed improved outcomes.[50,58,61,63] Although too few studies are available to draw conclusions, it is possible that a combination of high dose (8 g) and long-term intervention (21 days) (none of the other studies included both conditions),[50] a very long-term intervention (12 wk),[58] or the type of prebiotic (eg, XOS) is responsible for the positive effects seen.

It is worth highlighting some limitations of these studies. The study of Lawton and colleagues[63] did not have a control group, so the conclusions that can be drawn are limited because confounding factors cannot be excluded. The study that included athlete participants was conducted after heavy exercise,[61] which makes the comparison with other studies difficult. This is because after such exercise, inflammation markers are elevated, and prebiotics reduce these markers,[61] which is not the case with healthy participants of other studies.

The role of microbiota was only evaluated in studies that investigated the effect of prebiotics on affect. In healthy individuals, the results were inconsistent. In 1 study, an increase in bifidobacteria, which was not significantly different from the placebo group ($P > 0.05$), occurred while mood improved.[50] In another study, fecal bifidobacteria and lactobacilli increased, whereas mood did not change.[51] In patients with IBS, the decrease seen in anxiety was associated with an increase in fecal bifidobacteria.[55,62] None of these studies assessed fecal microbiota and affect at multiple times during the treatment to test whether microbial composition changes occur before affect changes. Indeed, this last criterion was proposed to establish mechanisms of action.[84]

In the study conducted by Schmidt et al,[60] which is often cited among other reviews, B-GOS, but not FOS, significantly decreased attentional vigilance to negative versus positive stimuli compared with a placebo ($P = 0.05$). This result must, however, be interpreted with caution because the other objective measures of emotional processing, such as the masked condition of the attentional dot-probe task, the emotional processing tasks, the facial expression recognition task, and the emotional and memory categorization, were not impacted by GOS.[60] A large number of variables was considered, the sample size was small (n = 45 across 3 conditions), and the authors mentioned a correction for

multiple tests regarding the effect of cortisol only. The significant ($P = 0.05$) results observed could thus reflect a chance effect.

Regarding patients with IBS, 2 studies showed the same pattern of results, which is promising. Indeed, prebiotics had an effect on anxiety, but not depression, compared with a placebo.[55,62] Contrary to healthy participants, patients with IBS could have dysbiosis[13] at baseline, a state where the composition and functions of the microbiota are deleterious to the host's health,[4] which allows the prebiotic supplementation to positively modulate the microbiota. Moreover, the absence of an effect on depression could be due to the medium score of depression at baseline versus higher anxiety scores.[55] In fact, anxiety scores were almost clinically significant in both studies.[55,62] If these findings are confirmed, null findings in healthy participants could be partly due to floor and ceiling effects in the processes underlying affect changes. Indeed, it is more likely that a healthy person has a less altered microbiota than a patient with IBS[85] and lower levels of inflammation[86] and more serotonin in the synaptic cleft[87] than a patient with depression, as well as less negative attentional bias than an anxious person.[88] Therefore, prebiotics may have less of an effect on these outcomes in a healthy person. Another explanation could be that, as can be seen with medications, symptoms of depression take longer to improve than those of anxiety.

There is no evidence of prebiotic effect on cognition in a clinical group. Indeed, the study conducted on older participants did not show any influence on scores of the Mini-Mental State Examination.[59] The authors proposed that this test was not sensitive enough to detect minor changes in cognition.[59]

Only 2 chronic studies investigated prebiotic effect on cognition.[54,58] Smith[54] did not find convincing results, but Best et al[58] found an improved verbal episodic memory (immediate recall and recognition) in the group with Ambrotose Complex in comparison with the placebo group. As can be seen in the quality assessment, the Best et al study[58] has less risk of bias and confounding variables than the Smith study.[54] Thus more weight would be given to the former. Even if Ambrotose Complex enhances some dimensions of mood and verbal memory, the authors of the study mentioned that the large number of variables could give rise to significant ($P < 0.05$) results by chance.[58] Moreover, the authors did not examine the mediation of the microbiota. Regarding the effects on mood, they proposed a possible direct effect of saccharides on the brain through the modulation of serotonin, which is involved in mood regulation.[58] For cognition, they postulated a direct effect of saccharides on the brain via an improvement of the cellular activity in the hippocampus, which is implicated in memory formation.[58] However, the effects of microbiota in vivo cannot be ruled out. Changes in gut microbiota could be relevant because an increase in Lactobacilli and Bifidobacteria has been demonstrated in in vitro studies with the Ambrotose Complex.[89]

Regarding acute prebiotic interventions, there is no evidence for modification of the affect variables. Indeed, only happiness and fatigue improved compared with a placebo.[52,53] However, cognition was impacted by acute prebiotic interventions. In the study conducted by Smith et al[52] the number of words recalled correctly and the accuracy of recognition increased after prebiotic intake compared with placebo intake.[52] Nine of 27 variables showed a significant difference between groups ($P < 0.05$). But the authors did not correct for multiple tests ($P = 0.05$), which means that a chance effect cannot be ruled out for at least 1 variable. Another study that used 7 g of Ambrotose Complex did not influence the memory in terms of immediate and delayed recall, recognition, short-term and working memory, or general cognitive abilities after 10 minutes.[56] However, Best et al[57] found that 4 g of Ambrotose Complex enhanced working memory and executive functions compared with a placebo after 30 minutes.[57] The duration of the interventions could explain this inconsistent finding. Importantly, the study of Best et al[56] seemed to lack power and to have more risk of bias, as the quality assessment indicates. This would suggest that more weight should be given to the second study of Best et al.[57] Finally, potential changes in the gut microbiota were not reported for acute studies. Thus, these results could also indicate a direct and reversible effect of prebiotics on the brain through an improvement of hippocampus cellular activity.[58]

Adequate microbiota measurement is crucial because several mechanisms of action could explain the effects of prebiotics. In fact, the mechanisms of action by which dietary fibers, called prebiotics, such as some complex saccharides, impact brain functions in humans are largely unknown.[34] Given this limited knowledge, rodent intervention studies may suggest some hypotheses. These studies indicate that the central mediator of prebiotic effects on the brain may be SCFAs, the products of prebiotics fermentation. Short-chain fatty acids influence brain functions either directly or via the gut immune and endocrine systems.[90] For instance, SCFA production influences the secretion of peptide tyrosine-tyrosine and GLP-1, which inhibits neurotransmitter release and, consequently, influences learning and memory processes[91] and antidepressant behavior, respectively.[92] Moreover, prebiotics have anti-inflammatory and proinflammatory effects, which have recognized influences on brain functions such as affect

and cognition.[34,90] However, the possibility that prebiotics alter brain signaling independently of the gut microbiota cannot be ruled out. Prebiotics could, for instance, directly interact with the gut mucosa and consequently influence the response of the immune system, which may impact brain functions.[28] Furthermore, in the colon, indigestible dietary fibers are largely transported by the vagus nerve, whose effects on different brain areas, such as the dentate gyrus and the hippocampus, could influence affect and cognition.[34] It is also worth noting that side effects, such as discomfort due to flatulence, could counteract beneficial prebiotic effects.[52,54] In acute interventions, prebiotic consumption could also influence levels of blood glucose, which could lead to a more positive mood and a better verbal memory[93] and modify glucose metabolism, including glucose intolerance and insulin resistance, which are known to influence cognition.[94] Future studies should thus control for blood glucose and glucose metabolism parameters. Finally, some studies included in this review used nutriments that are less prone to prebiotic effects, such as wheat bran. Indeed, although wheat bran contains arabinoxylan oligosaccharides that are considered potential prebiotics,[81] it is mainly composed of insoluble fibers that are poorly fermented.[95]

An analysis of the gut-brain axis that takes into account the gut microbiota requires innovative and adequate methodological approaches.[96] Characterizing the gut microbiome from a taxonomic and functional point of view now requires high-throughput metagenomic, metatranscriptomic, and metaproteomic analysis. Several small molecules are produced by the gut microbiota and are prone to act on brain functions, either directly or indirectly. Metabolomic approaches such as highly sensitive gas or liquid chromatography coupled with mass spectrometry allow the unraveling of changes of key metabolites in biological fluids, and imaging mass spectroscopy will be a key technique in the future to better understand how the gut microbes dialogue with the brain in patho-physiological conditions. Although most of the studies analyzing gut microbiota composition are performed on fecal samples, one cannot ignore the increasing interest in the microbiota activity in the upper part of the gut, which could require more invasive sampling in humans but would be relevant in many cases, namely, in conditions in which the gut barrier is altered.

Limitations

This review focused on dietary fibers recognized as prebiotics,[21] but other potential prebiotics that fit the definition proposed by the International Society for the Study of Probiotics and Prebiotics[22] were not included. Lactulose, conjugated linoleic acid (CLA), polyunsaturated fatty acid, mannanoligosaccharide, and plant polyphenols can be cited. Also, certain potential prebiotics that were included in this review need to be more researched in humans to show that their health benefits are linked to microbiota changes, as recommended by Gibson and colleagues.[22] Moreover, microbiota measurement performed by fluorescent in situ hybridization techniques or by selected measurement of selected bacteria by quantitative polymerase chain reaction of 16S ribosomal DNA were reported for only 4 included studies.[50,51,55,62] This means that there is almost no direct evidence that microbiota mediates the effect of prebiotics on cognition and affect in humans. Indeed, to examine this issue, microbiota measurement should be taken because prebiotics could influence the brain through other mechanisms, such as the direct regulation of plasma peptide YY.[28] Further studies would require (metagenomics) sequencing of the microbiome and metabolomics approaches that would be helpful to unravel which bacterial consortia or functions could be implicated in the gut-brain axis in this context. In addition, these 4 studies never measured levels of microbiota between the start of the invention and the measurement of psychological variables, which does not allow one to see whether microbiota changes occurred before the changes observed in psychological variables. Furthermore, the review is not fully systematic because preregistration and a standardized extraction of data were not performed. However, almost all other Cochrane criteria were met (see Appendix S6 in the Supporting Information online for the PRISMA checklist). Another limitation was that the investigation of a probable publication bias was not realized because a meta-analysis was not performed. In this case, a meta-analysis was not possible because of high heterogeneity across studies.[37] This heterogeneity also precludes the authors from making generalizable conclusions because the studies were not conducted under comparable conditions. Finally, the risk of bias was often low in the studies (eg, adequate blinding, control group, statistical analysis; see Appendix S3 in the Supporting Information online), but confounding variables were not sufficiently controlled in more than half of the included studies (scores between 1 to 3 out of 6) relative to the other half (scores between 4 to 6 out of 6). This suggests that variables other than those manipulated by the intervention could have led to the observed effects.

CONCLUSION

Although the studies included in this review were very heterogeneous, some important results and guidelines for future studies can be emphasized. In chronic

studies, the effects on cognition, although less investigated, were quite limited, whereas affect was more consistently influenced.[50,58,61,63] In acute studies, however, changes in cognitive tasks were more often observed than changes in affect after prebiotic interventions.[52,53,56,57] One important limitation is that the majority of affective measures were self-reported in both chronic and acute studies. Future studies should also take objective measures of emotional changes, such as autonomic nervous system activity (eg, cortisol),[97] and use affective tasks assessing emotional processing (eg, emotional Stroop task)[98] and memory[60] that are not influenced by the subjective evaluations of participants.

The two IBS studies suggest that higher doses of prebiotics are necessary for obtaining changes in affect. Given the consistency across these 2 studies, more studies considering clinical groups need to be performed. This includes patients with dysbiosis, negative attentional bias (eg, anxious patients),[88] few monoamines (eg, depressed patients),[99] or higher levels of inflammation (eg, interferon alpha–treated patients and patients presenting depression associated with dysbiosis and inflammation, such as alcohol-dependent patients).[78,86]

The quality assessment also provided important information for conducting future studies. It underlines the need to include more control variables that may account for the pattern of results. The large number of variables included will also require larger sample sizes and the need to correct for multiple tests to limit the risk of false-positives. The use of more sensitive cognitive tasks is also recommended.

Strong conclusions regarding the effects of prebiotics on human cognition and affect cannot be drawn due to the great heterogeneity of variables investigated and the lack of replications. The extent to which microbiota is involved in the observed effects is also not known because too few studies included microbiota analyses. The present results are, however, promising, and suggest that there is a need for more studies examining the effectiveness of prebiotics on human cognition and affect.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1. **Foods in which prebiotics can be found**

Appendix S2. **Search strategy in PubMed**

Appendix S3. **Checklist for measuring study quality**

Appendix S4. **Exclusion criteria**

Appendix S5. **Secondary and additional outcomes**

Appendix S6. **PRISMA checklist**

Table S1. **Extensive summary table of included studies**

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