Microbiome in brain function and mental health

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A R T I C L E   I N F O

Article history:
Received 7 August 2015
Received in revised form 29 March 2016
Accepted 2 May 2016
Available online xxxx

Keywords:
Microbiota-gut-brain axis
Gut microbiota
Brain function
Psychiatric disorder
Mental health
Functional food

A B S T R A C T

Background: Over recent years it has become evident that the physiological influence of the gut microbiota extends beyond the periphery to the central nervous system (CNS). Current data derived from preclinical studies indicate that the gut microbiota can influence CNS function. Despite limited attempts to translate these findings to clinical populations, emerging evidence suggests that alterations in the composition of the gut microbiota, across the lifespan, may have a fundamental role in the pathophysiology of a number of mental health disorders. Moreover, accumulating evidence demonstrates the central role of food consumed in programming gut microbiota composition, diversity and functionality throughout life.

Scope and approach: In this review, we outline what is considered a healthy infant and adult gut microbiota composition followed by describing how the gut microbiota can influence the CNS via signalling pathways of the microbiota-gut-brain axis. Current findings from preclinical investigations, observation and intervention studies in humans, indicating the gut microbiota in brain function and mental health are reviewed. Finally, we consider microbiota-targeted functional food interventions with potential application in promoting normal brain function.

Key findings and conclusions: Much work is yet to be performed in determining the role of the gut microbiota in brain function and behaviour in human populations. Nevertheless, the potential for microbiota-targeted functional food interventions is evident. As new findings emerge in this rapidly developing field, it is envisaged that a greater understanding of microbe-brain interactions will herald a new era of psychotropic therapies to promote normal brain function and mental health.

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1. Introduction

Although a key role for gut bacteria (the gut microbiota) in specific aspects of health and disease, such as regulating immune function and metabolic activity, has been recognised for some time (Sampson & Mazmanian, 2015), only recently has it become apparent that the physiological influence of the microbiota extends beyond the periphery to the central nervous system (CNS). Clinically, the phenomenon of hepatic encephalopathy which, in the extreme, is characterised by dementia like symptoms that can be ameliorated by treatment with antibiotics (Strauss & da Costa, 1998), is often cited as a unique example of how perturbing the microbiota can influence brain function. It has also long been recognised that the acute phase reaction to microbial infection is accompanied by a number of neuro-immune mediated behavioural symptoms such as depressed mood and cognitive impairment (Dantzer, 2009). However, the realisation that not only pathogenic microorganisms, but the commensal/symbiotic gut bacteria can influence CNS activity, has led to a 'Paradigm Shift' in brain and behavioural research (Mayer, Knight, Mazmanian, Cryan, & Tillisch, 2014). Moreover, recent discoveries in microbe-brain interactions have revolutionised our approach to investigating psychopathology, and spurred the development of microbiota-targeted interventions (psychobiotics) which hold great potential as a new therapeutic approach in mental health disorders (Dinan, Stanton, &
In this review, we first provide an outline of what is, conceptually, considered a healthy infant and adult gut microbiota composition, followed by a description of the key pathways by which the gut microbiota signal to the brain to influence brain function and behaviour. Next, we review current evidence demonstrating a role for the gut microbiota in brain function and mental health, incorporating both preclinical and clinical studies. Finally, we discuss potential food-based microbiota-targeted approaches which have shown promise or have potential in the management of mental health.

2. Healthy gut microbiota composition

Despite large variation in composition between healthy individuals due to a variety of environmental, physiological, genetic and psychological factors, a ‘core’ or ‘normal’ gut microbiota composition is emerging, and despite large taxonomic diversity between individuals, colonization trends can be observed in both infants and adults.

Until recently, it was assumed that the infant gut was colonized during delivery, either from contact with the vaginal and faecal bacteria from the mother during standard vaginal delivery (SVD) or, in the case of caesarean section (CS) delivery, from the hospital environment and maternal skin microbes (Borre et al., 2014).

However, it has become apparent that this is not the case, as it has been reported that low counts of bacteria can be isolated from the amniotic fluid, placenta and meconium of healthy new-borns before breast-feeding (Rodríguez et al., 2015). Culture based studies have shown that at birth the healthy infant gut is initially colonised by facultative anaerobes such as Enterobacteriaceae, and once oxygen has been depleted and an anaerobic environment is present, strict anaerobes such as **Bifidobacterium** and **Bacteroides** appear (Adlerberth & Wold, 2009). Recently, improvements in 16S rRNA sequencing have led to a more accurate description of the gut microbiota composition, inclusive of the substantial number of unculturable bacteria found in the gut. In healthy, vaginally delivered infants, the most prevalent initial bacterial groups include **Staphylococcus**, **Lactococcus**, Enterobacteriaceae and **Bifidobacterium**, followed by later increases in the abundance of **Veillonella** and **Lachnospiraceae** and a decline in **Staphylococcus** (Palmer, Blak DiGiulio, Relman, & Brown, 2007). During infancy, the composition of the gut microbial community is unstable and dynamic and undergoes a variety of changes before resembling an adult gut microbiota at approximately two years of age, after the introduction of solid foods (Borre et al., 2014).

What constitutes a ‘healthy gut microbiota’ in adults is not entirely clear and indeed may be person specific. Nevertheless, many advances have been made in defining a healthy phylogenetic core, which have led to a consensus that the healthy adult gut is dominated by Firmicutes, Bacteroidetes, Actinobacteria, and **Verrucomicrobia** (Human Microbiome Project Consortium, 2012). Within these phyla, there is still large inter-individual diversity, with each person harbouring a unique microbiota profile.

It has been proposed that the gut microbiota can be categorised into three core clusters or enterotypes (Arumugam et al., 2011). These are broad clusters which are defined by the presence of a particular bacterial genus – **Bacteroides**, **Prevotella** or **Ruminococcus**. However, this approach to defining the gut microbiota composition is the subject of ongoing debate, and it is questionable when considering that over the course of a year, a healthy individual’s microbiota can vary between clusters and is not strictly defined within one enterotype (Knights et al., 2014). Alternatively, rather than a taxonomic core, the composition may be viewed as a core set of functional profiles, in which some key bacterial species may contribute significantly to the functional profile, and play an important role in health and disease (Flint, Scott, Louis, & Duncan, 2012).

A range of factors are known to disrupt the infant and adult gut microbiota composition, which have been extensively reviewed elsewhere (Rodríguez et al., 2015), and include mode of delivery at birth, antibiotic treatment, diet, stress, infection and host genetics. The extent to which each of these factors influences brain function and mental health via disrupting the gut microbiota composition is not entirely clear and is currently an area of intensive investigation. Nevertheless, the following sections integrate current findings in which these factors are implicated in brain function and behaviour, via interactions with the gut microbiota.

3. The microbiota-gut-brain axis

The microbiota-gut-brain axis is a bi-directional communication network encompassing the central nervous system (CNS), sympathetic and parasympathetic branches of the autonomic nervous system (ANS), the enteric nervous system (ENS), neuroendocrine and neuroimmune pathways, and the gut microbiota (See Fig. 1; Cryan & Dinan, 2012). A complex reflexive network of efferent fibres projecting to the gastrointestinal (GI) tract and afferent fibres that project to a number of interconnected regions of the CNS facilitate communication within the axis (Dinan, Stilling, Stanton, & Cryan, 2015). Bidirectional communication along neural, hormonal and immune pathways thus enable the brain to influence secretory, sensory, and motor functions of the GI tract, and conversely, signals arising from the viscer a to influence CNS activity (Aziz & Thompson, 1998). Although interactions between the brain and enteric nervous system have been the focus of intense study over the past two decades, particularly in the context of functional GI disorders such as irritable bowel syndrome, over recent years there has been growing recognition that the gut microbiota has a dominant influence on signalling along this axis (Cryan & Dinan, 2012; Mayer et al., 2014; Sampson & Mazmanian, 2015).

4. Microbe to brain signalling pathways

4.1. The vagus nerve

The vagus is the major nerve mediating parasympathetic activity of the autonomic nervous system. Vagal afferent sensory neurons relay information from the GI tract to the nucleus of the solitary tract, which projects to the thalamus, hypothalamus, locus coeruleus, amygdala and periaqueductal grey (Aziz & Thompson, 1998). A number of preclinical studies have demonstrated afferent pathways of the vagus nerve are fundamental in mediating the effects of the gut microbiota on brain function and behaviour. For example, in a landmark preclinical study with conventional mice, treatment with the probiotic **Lactobacillus rhamnosus** (JB1) reduced anxiety and depressive-like behaviour and stress-induced corticosterone levels, however, these behavioural effects were not evident in vagotimized mice (Bravo et al., 2011). Despite the importance of vagal pathways, it must be noted that vagotomy does not mediate all effects of the microbiota on brain function and behaviour (Bercik et al., 2011), and the mechanisms underlying vagal mediated microbiota-brain interactions have not yet been determined (Cryan & Dinan, 2012).

4.2. Microbial regulation of neuro-immune signalling

Bacterial colonization of the gut during early life influences normal development and maturation of the immune system, and across the lifespan, the gut microbiota regulate innate and adaptive immune responses (Shanahan & Quigley, 2014). A recent ground-
Breaking report has elegantly demonstrated that maturation and function of microglia—the tissue macrophages of the CNS—are under control of the gut microbiota (Erny et al., 2015). Of note, this effect was demonstrated in both germ-free (GF) and conventional mice following ablation of the gut microbiota with antibiotics. Microglia have been implicated in the pathophysiology of a host of neurodegenerative and psychiatric disorders and as such, this study has major implications for our understanding of how the microbiota interact with CNS immune activity to affect brain function and mental health. Finally, proinflammatory cytokines released from macrophages following immune activation can act on receptors of afferent pathways of the vagus nerve to signal to the CNS, or if released systemically following a GI immune response, they may influence the hypothalamic-pituitary-adrenal (HPA) axis at the anterior pituitary or hypothalamus, active transport via saturable transport molecules, passage through leaky portions of the BBB or by activation of endothelial cells (Dantzer, 2009).

4.3. Microbiota-mediated tryptophan metabolism

Tryptophan is an essential amino acid which is the precursor to serotonin (5-HT), kynurenine, and metabolites of the kynurenine pathway (Clarke, McKernan, et al., 2012). Despite a focus on the 5-HT system in brain-gut axis and psychiatric disorders, only around 5% of systemic tryptophan is metabolised into 5-HT, whilst around 90% is metabolised along the kynurenine pathway (O’Mahony, Dancin, & Cryan, 2015). The rate of tryptophan metabolism along the kynurenine pathway is dependent on expression of indoleamine-2,3-dioxygenase (IDO), which is localised to the liver (Clarke, McKernan, et al., 2012). IDO expression can be induced by the action of inflammatory cytokines (Interferon-γ in particular), and TDO expression by glucocorticoids (O’Mahony et al., 2015). As noted previously, the microbiota regulate host immune function, and as will be discussed below, can modulate HPA axis activity and the production of glucocorticoids (Dinan & Cryan, 2012). Thus, the gut microbiota may affect the rate of tryptophan metabolism along the kynurenine pathway. Indeed, an informative study conducted in GF animals indicates that peripheral tryptophan levels are under microbial control (Clarke, Grenham, et al., 2012). Moreover, the probiotic Bifidobacteria infantis was found to increase plasma tryptophan and kynurenine levels in a preclinical study in rats (Desbonnet, Garrett, Clarke, Bienenstock, & Dinan, 2008). This has important implications for brain function and behaviour; downstream metabolites of the kynurenine pathway—quinolinic and kynurenic acid—have been shown to be neuroactive and can act on N-methyl-D-aspartate receptors and nicotinic receptors in the CNS, and as such, there is increased interest in the role of the kynurenine pathway in psychiatric disorders and neurodegenerative disease (O’Mahony et al., 2015).

The mechanisms by which the gut microbiota regulate tryptophan metabolism have not been fully elucidated. However, delineating this process may be pivotal in understanding microbiota-brain interactions in brain function and mental health.

4.4. Microbial control of neuroendocrine function

A seminal report by Sudo and colleagues was the first to demonstrate that the HPA axis, the core neuroendocrine system in...
humans and rodents, is under microbial control (Sudo et al., 2004). GF mice exhibited an exaggerated corticosterone and ACTH response to mild-restraint stress in comparison to specific pathogen-free controls (Sudo et al., 2004). Importantly, the exaggerated HPA axis response in GF mice could be partly normalized by reconstitution with fecal matter from specific pathogen free mice, and fully normalized, in a time-dependent manner, by monoassociation with *Bifidobacterium infantis* (Sudo et al., 2004). In addition to elegantly demonstrating the intricate interplay between microbes and neuroendocrine function, this study also highlights two critical points; that a microbiota during development is essential for normal HPA axis function in later life; and that there are critical neurodevelopmental time-windows during which microbes must colonize the gut for development of a normal stress response (Dinan et al., 2015). This finding has subsequently been replicated by independent investigators (Clarke et al., 2013). These findings are important when considering that HPA axis dysfunction is a key factor in the pathophysiology of psychiatric disorders such as depression (O’Brien, Scott, & Dinan, 2004) and functional GI disorders with marked psychiatric co-morbidity, such as irritable bowel syndrome (IBS) (Kennedy, Cryan, Dinan, & Clarke, 2014). However, to date, it is unknown if microbiota targeted interventions have positive effects on HPA axis function in psychiatric populations. Nevertheless, promising results from preclinical studies with healthy control participants indicate that pre and probiotic interventions can modulate HPA axis functioning (Messaoudi et al., 2011; Schmidt et al., 2015).

4.5. Microbial neuro-metabolite production

Gut bacteria can produce a number of neuroactive compounds which have potential to influence brain function and mental health (Dinan et al., 2013). For example, *in vitro* studies have demonstrated that *Candida*, *Streptococcus*, *Escherichia* and *Enterococcus* species produce 5-HT; *Bacillus* and *Serratia* species produce Dopamine; *Escherichia*, *Bacillus*, *Saccharomyces* species produce noradrenaline; *Lactobacillus* species produce Acetylcholine (Lyte, 2011) and *Lactobacillus* and *Bifidobacterium* secrete GABA (Barrett, Ross, O'Toole, Fitzgerald, & Stanton, 2012). Given the key role of these neurotransmitters in all aspects of brain function and behaviour, that gut bacteria secrete these is a striking finding. However, replicating this *in-vivo* still poses a significant challenge and the mechanism(s) by which neurotransmitters secreted by gut bacteria can influence the CNS is unclear at present, as some neurotransmitters such as GABA do not cross the blood brain barrier (Hyland & Cryan, 2010). Nevertheless, utilizing neuro-active metabolite secreting bacteria to promote normal brain function and mental health is a promising avenue of investigation.

4.6. Microbial short-chain fatty acid production and brain function

Short-chain fatty acids (SCFAs), such as butyric, acetic and propionic acid are produced by microbial fermentation of complex carbohydrates in the GI tract (Macfarlane & Macfarlane, 2003). SCFAs can cross the blood brain barrier (BBB) and have been shown to possess some neuro-active properties (Sampson & Mazmanian, 2015). For example, a high dose of propionic acid administered direct to the CNS (MacFabe, Cain, Boon, Ossenkopp, & Cain, 2011) or peripherally (Foley, Ossenkopp, Kavaliers, & MacFabe, 2014) in rats, induces a range of behavioural alterations relevant to neurodevelopmental disorders. Butyrate on the other hand, has potential pro-cognitive and beneficial behavioural properties via epigenetic mechanisms, due to potent inhibition of histone deacetylase (Stilling, Dinan, & Cryan, 2014). SCFAs also regulate immune activity locally in the GI tract which may have downstream effects on CNS function (Dantzer, 2009). Moreover, the recent study by Enry and colleagues which reported that maturation of microglia within the CNS of GF animals was impaired, also demonstrated that treatment with a mix of SCFAs could rescue microglial function in the same manner as re-colonization of a complex microbiota (Enry et al., 2015).

4.7. Microbes, neurotransmitters & neurophysiology

Clear mechanistic links between microbiota-mediated processes of peripheral biochemical parameters and central neurobiological changes are difficult to establish. Nevertheless, it is clear that the microbiota, and specific bacterial species, can regulate central neurotransmitter levels and receptor expression. For example, GF mice have decreased 5-HT levels and 5-HT1A receptor expression in the amygdala and hippocampus (Bercik et al., 2011; Clarke et al., 2013; Diaz Heijtz et al., 2011; Neufeld, Kang, Bienenstock, & Foster, 2011), increased 5-HT, noradrenaline and dopamine turnover in the striatum (Diaz Heijtz et al., 2011), and increased activity-related transcriptional pathways in the amygdala (Stillig et al., 2015). In conventional mice, treatment with the probiotic *Lactobacillus rhamnosus* (JB-1) led to a number of brain region specific changes in GABA receptor expression; GABA<sub>γ</sub> mRNA was increased in cortical regions, but reduced in the hippocampus, amygdala, and locus coeruleus; GABA<sub>α2</sub> mRNA expression was reduced in the prefrontal cortex and amygdala, but increased in the hippocampus (Bravo et al., 2011). Many of these neurochemical changes likely regulate numerous neurophysiological processes which are thought to underlie key aspects of brain function and behaviour, such as hippocampal neurogenesis (Ogbonnaya et al., 2015).

In summary, there is clear evidence that the gut microbiota can signal to the CNS and also regulate many neurobiological processes that underlie the full spectrum of behaviour, emotional and cognitive functions. Much of this evidence is by necessity, gleaned from preclinical studies in rodents and the extent to which the mechanisms described above, through which the gut microbiota influence brain function and behaviour translate to human physiology is not yet fully understood. Nevertheless, the following sections outline what is currently understood with respect to microbiota-brain interactions in healthy individuals and clinical populations.

5. The microbiota in brain-gut axis and psychiatric disorders

5.1. Irritable bowel syndrome (IBS): the prototypical brain-gut axis disorder

IBS is a stress-related, brain-gut axis disorder in which GI symptoms are accompanied by functional and structural brain abnormalities, HPA axis dysfunction, subtle cognitive impairment and significant psychiatric co-morbidity (Kennedy et al., 2014). The role of the microbiota in the pathogenesis of GI and extra-intestinal symptoms in IBS has received significant attention over recent years, with a growing body of evidence that the diversity, stability and metabolic activity of the gut microbiome is altered in IBS compared to healthy individuals (Jeffery, Quigley, Ohman, Simrén, & O’Toole, 2012). At the phylum level, a relatively consistent finding across studies determining the gut microbiota composition in IBS is decreased abundance of Bacteroidetes and increased Firmicutes (Jeffery, O’Toole, et al., 2012). Although the functional relevance of alterations in the composition of specific microbial species in IBS is not clear, correlational studies have documented a relationship between *Ruminococcus-torques* related bacterial phylotype and Firmicutes, *Gammaproteobacteria* and *Verrucomicrobia*.
Major depression is a highly prevalent, debilitating, mental health condition, affecting up to one in five adults and is associated with examinations of anxiety, sleep, pain, role impairment and substantial socioeconomic cost (Kessler et al., 2002). Major depression is rarely a principal diagnosis and with marked symptom severity, chronicity, role impairment and to the dexmethasone challenge test (O'Brien et al., 2004). In addition, elevated plasma proinflammatory cytokines levels have been documented by a number of studies in individuals with depression (Clarke et al., 2004), in addition to other physiological processes involved in depression and anxiety such as tryptophan metabolism (Dantzer, 2009), a prominent role for the microbiota in depressive and anxiety disorders has been proposed (Dinan et al., 2013).

Using a number of approaches, it has been shown in preclinical studies with some consistency, that the gut microbiota leverages a significant influence on depressive and anxiety like behaviour. For example, GF mice exhibit both decreased (Clarke et al., 2013; Diaz Hejtz et al., 2011; Neufeld et al., 2011) and increased (Bercik et al., 2011) anxiety-like behaviour, which can be normalized by bacterial colonization prior to critical neurodevelopmental time windows (Clarke et al., 2013). Treatment with the probiotic *Bifidobacterium breve* 1205 (Savigac et al., 2014), or ablation of the gut microbiota through administration of an antibiotic cocktail (Desbonnet et al., 2015) reduces anxiety-like behaviour in conventional mice. Moreover, it has been shown that an anxiety-like behavioural phenotype can be transferred from one mouse strain to another via fecal microbiota transplantation (Bercik et al., 2011). Finally, studies examining the role of the gut microbiota in depressive-like behaviour in rodents indicate that specific probiotic strains such as *B. infantis* (Desbonnet et al., 2008), *L. rhamnosus* (Bravo et al., 2011) and a cocktail of *Lactobacillus helveticus* and *Bifidobacterium longum* (Messaud et al., 2011) possess potential anti-depressant properties. Investigations with healthy human volunteers lend some support to these preclinical data indicating a microbial influence on mood and anxiety. For example, probiotic treatment has been shown to reduce self-reported depression (Messaud et al., 2011), increase self-reported happiness in participants with low baseline mood (Benton et al., 2007) and decrease ruminative thinking (Steenbergen et al., 2015). Moreover, intervention with a probiotic combination of *L. helveticus* and *B. longum* reduced 24 h urinary cortisol output (Messaud et al., 2011) and four week treatment with a probiotic reduced the cortisol awakening response (Schmidt et al., 2015) in healthy volunteers. Finally, at the cognitive level, a probiotic intervention increased response time to positive versus negative stimuli in an emotional attention task (Schmidt et al., 2015) whilst a brain imaging study showed that four week intake of a fermented milk product containing probiotic modulates functional brain activity during a similar task (Tillisch et al., 2013).

To date, only two studies have directly measured the gut microbiota composition in individuals with depression. In a Norwegian sample of 37 patients with a diagnosis of major depression and 18 healthy control participants, no significant group difference in overall gut microbial diversity or richness was found, but an underrepresentation of Bacteroides was associated with depression (Naseribafrouei et al., 2014). In contrast, an independent report documented increased bacterial α-diversity in patients with major depression who were ‘actively’ depressed (Hamilton Rating Scale for Depression (HAMDS) score ≥20), in comparison to patients who had responded to treatment (HAMDS score ≥20 at baseline with a 50% reduction after 4 weeks) and healthy controls (Jiang et al., 2015). At the phylum level, reduced levels of Firmicutes and increased Bacteroidetes, Proteobacteria, and Actinobacteria were found in patients with major depression, regardless of treatment status. Furthermore, differences in specific genera were documented, with increased Enterobacteriaceae and Alistipes, but decreased abundance of *Faecalibacterium* which negatively correlated with HAMDS scores (Jiang et al., 2015).

With limited data available in clinical populations, it is not yet possible to draw meaningful conclusions as to the nature of microbiota alterations in patients with depressive and anxiety disorders. Moreover, conflicting findings between studies is perhaps not surprising as considering major depression or anxiety disorders as singular clinical entities does not capture the breadth and inter-individual variability of symptoms that patients may experience. Future studies with well phenotyped patient cohorts are needed to fully determine if mood and anxiety disorders are characterised by an altered gut microbiota composition in general, and if particular microbial compositions are associated with specific symptomatology.

### 5.3. Microbiota, social behaviour and autism

Autism spectrum disorders (ASD) are neurodevelopmental disorders typified by marked deficits in reciprocal social interaction, communication and language development, and restricted, repetitive patterns of activities and behaviours (Dinan et al., 2015). A role for the gut microbiota in neurodevelopmental disorders such as ASD has become a topic of significant interest over recent years (Borre et al., 2014). Clinically, this interest has been spurred by the recognition that a subset of individuals with ASD suffer problematic GI symptoms, an altered composition of the gut microbiota and increased intestinal permeability (Julio-Peiper et al., 2014).

In parallel, preclinical studies with GF animals have demonstrated that in the complete absence of a microbiota, rodents exhibit impairments in social behaviours (Desbonnet et al., 2008). This effect is also observed in the hyperactive sample of 37 patients with a diagnosis of major depression (Borre et al., 2014). It is noteworthy that in rodents, perturbing the gut microbiota with antibiotic treatment in early life can induce visceral hypersensitivity (O’Mahony et al., 2014), whilst probiotic strains such as *Bifidobacteria infantis* 35624 can alleviate hypersensitivity (O’Mahony et al., 2014).
types of behaviour such as anxiety and stress responsiveness, studies with GF animals suggest that the presence or absence of the gut microbiota during critical neurodevelopmental windows can modulate the expression of normal or abnormal social behaviours in later life.

Maternal infection during pregnancy is a known risk factor for ASD (Atladottir et al., 2010), and the maternal immune activation (MIA) mouse model produces adult offspring exhibiting both ASD-like behavioural deficits and GI disturbances, including increased gut permeability and an altered gut microbiota (Malkova, Yu, Hsiiao, Moore, & Patterson, 2012). Interestingly, in this model, treatment with Bacteroides fragilis was shown to repair intestinal barrier function and normalize deficits in communicative, stereotyped and anxiety-like behaviours (Hsiao et al., 2013).

Recent epidemiological data suggest that mode of delivery at birth (C-section vs. vaginal) may also influence normal CNS development leading to cognitive and motor problems during infancy (Al Khalaf et al., 2015). Furthermore, CS delivery has been associated with an increased risk of developing ASD (Curran, O’Neill, et al., 2015). However, this association may be better accounted for by genetic or environmental factors than birth by C-section (Curran, Dalman, Kearney, & et al., 2015).

Taken together, the preclinical and clinical evidence suggest that the gut microbiota may influence neurodevelopment and may have a role in the pathophysiology of ASD. However, as with other mental health disorders, clinical studies to determine the efficacy of microbiota targeted therapies in ASD are lacking. Over a decade ago, it was shown in a small sample of children with regressive-onset autism, that treatment with oral vancomycin could improve symptoms (Sandler et al., 2000). The beneficial effect of this antibiotic was not apparent following the cessation of treatment at follow-up, and of course, long-term antibiotic treatment is not a viable therapeutic strategy in ASD. Nevertheless, when taken with the preclinical work which has been conducted to date, developing safer approaches to targeting the gut microbiota through food-based approaches to ameliorate symptoms in ASD has potential, and presents an exciting and hopeful prospect in new treatment approaches for these individuals.

5.4. The gut microbiota and age-related cognitive decline

As the world’s ageing population is rapidly expanding, it has become a major societal goal to promote health and wellbeing in later life, and a number of innovative European strategies have been implemented over recent years (Rechel et al., 2013). A prominent consequence of ageing is a steady decline in a number of cognitive functions including the ability to encode new episodic memories, working memory/executive functions and processing speed (Deary et al., 2009). Ageing is accompanied by a plethora of age-related neurobiological changes, including altered HPA axis function, decreased neurotransmitter/neuropathology concentration and receptor expression, and increased oxidative stress (Prenderville, Kennedy, Dinan, & Cryan, 2015). Moreover, the concept of inflamm-ageing, indicating a general increase of inflammatory tone during ageing, has been championed as a key process mediating some aspects of cognitive function (Dinan et al., 2015), and a recent double-blind randomised controlled trial in a small sample of healthy elderly adults revealed that treatment with a Lactobacillus helveticus probiotic strain had some positive effects on attentional performance (Chung et al., 2014).

Clearly, further clinical interventions studies are needed to determine the potential pro-cognitive effects of microbiota-targeted interventions in elderly individuals, either in healthy or clinical populations. Nevertheless, as preclinical data indicate that the gut microbiota may mediate various aspects of cognitive performance, there is potential for microbial targeted prophylactic interventions to tackle age-related cognitive decline and promote normal cognitive function in later life.

6. Microbiota-targeted functional foods for brain health

6.1. Prebiotics and probiotics

As the studies reviewed above indicate, modulation of the gut microbiota using dietary intervention, in particular with prebiotics and probiotics is a promising intervention strategy in promoting normal brain function and mental health (See Table 1). However, to progress the field, it is of great importance to understand the mechanisms by which prebiotics and probiotic species exert their effect on brain function and behaviour. Prebiotics may exert a beneficial brain effect through improving host immunity, enhancing SCFA production, reducing potentially pathogenic microbes and improving gut barrier function (Slavin, 2013). Lactobacillus spp. and Bifidobacterium spp. are the most commonly used probiotics and may act via a number of mechanisms to alter the gut microbiota of the host in order to improve brain health, including production of antimicrobial compounds, reduction of the luminal pH through the production of SCFA, competitive exclusion (which involves preventing other microbes from adhering to epithelial cells), production of growth substrates such as vitamins and exopolysaccharides, enhanced barrier function, and modulation of immune responses (Power, O’Toole, Stanton, Ross, & Fitzgerald, 2014). Future studies to more fully understand the mechanism of effect of pre and probiotic interventions for brain function and behaviour are needed to determine which species may have potential application in mental health disorders.

6.2. Polyphenols

Polyphenols are a large group of compounds naturally occurring in plants and a variety of foods, including citrus fruits, cocoa, red wine, tea and coffee (Gomez-Pinilla & Tyagi, 2013). Based on their structure, the main classes of polyphenols are phenolic acids, flavonoids, lignans, and stilbenes (Valdes et al., 2015). Large-scale epidemiological investigations suggest that a diet rich in polyphenols may help maintain normal brain function and mental health (Letenneur, Proust-Lima, Le Gouge, Dartigues, & Barberger-Gateau, 2007). Interventional studies in humans provide some supportive evidence for this epidemiological data (see Table 2). Although a number of mechanisms, including anti-inflammatory, anti-oxidant and modulation of enzyme activity have been proposed to account for the positive CNS effects of polyphenols (Letenneur et al., 2007), these actions are presumed to be indirect, as bio-availability of native polyphenols is low (Crozier, Jaganath, & Clifford, 2009). Approximately 90–95% of total dietary polyphenols accumulate in the large intestine where they are broken down into
A major characteristic of the modern Western diet is an increased consumption of proinflammatory omega-6 fatty acids; such consumption may significantly affect gut microbiota composition which may in turn affect polyphenol bioefficacy (Selma et al., 2009). Furthermore, it is not entirely clear which specific constituents of polyphenol rich food exert beneficial effects on brain function. Nevertheless, future studies to determine the positive effects of polyphenol-microbe interactions on brain function and mental health may prove to be a fruitful therapeutic approach.

6.3. Omega-3 polyunsaturated fatty acids

A major characteristic of the modern Western diet is an increased consumption of proinflammatory omega-6 fatty acids; such consumption may significantly affect gut microbiota composition which may in turn affect polyphenol bioefficacy (Selma et al., 2009). Furthermore, it is not entirely clear which specific constituents of polyphenol rich food exert beneficial effects on brain function. Nevertheless, future studies to determine the positive effects of polyphenol-microbe interactions on brain function and mental health may prove to be a fruitful therapeutic approach.

Table 1

<table>
<thead>
<tr>
<th>Probiotic/ prebiotic delivery</th>
<th>Objectives</th>
<th>Study design</th>
<th>Sample size</th>
<th>Participant age (years)</th>
<th>Probiotic delivery</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bifidobacterium bifidum</strong></td>
<td>Investigate whether a multispecies probiotic may reduce cognitive reactivity in non-depressed individuals</td>
<td>-Triple-blind, placebo-controlled, randomised, pre- and post-intervention assessment</td>
<td>40</td>
<td>20.2 ± 2.4</td>
<td>-2g/day freeze dried powder</td>
<td>-Participants who received the multispecies probiotic showed reduced overall cognitive reactivity to sad mood</td>
<td>(Steenbergen et al., 2015)</td>
</tr>
<tr>
<td><strong>Bifidobacterium lactis</strong></td>
<td>-Participant who consumed inulin felt happier, had less indigestion and were less hungry. They also showed reduced aggression and ruminative thoughts in response to sad mood</td>
<td>-55</td>
<td>30–60</td>
<td>1.5 g/day probiotic stick</td>
<td>-Probiotic treatment showed a beneficial effect on general signs of anxiety and depression</td>
<td></td>
<td>(Messaoudi et al., 2011)</td>
</tr>
<tr>
<td><strong>Lactobacillus acidophilus</strong></td>
<td>Effects of the probiotic formulation on anxiety, stress, depression and coping strategies in healthy individuals</td>
<td>-Double-blind, placebo-controlled, randomised, parallel 30 day intervention</td>
<td>36</td>
<td>18–55</td>
<td>-125 g per day consumed twice daily</td>
<td>-Intake of fermented milk product with probiotic affected brain activity in regions controlling central processing of emotion and sensation</td>
<td>(Tillsch et al., 2013)</td>
</tr>
<tr>
<td><strong>Bifidobacterium lactis</strong></td>
<td>Investigate whether consumption of a fermented milk product with probiotic alters brain intrinsic connectivity or responses to emotional attention tasks in healthy women</td>
<td>-Single centre, placebo-controlled, parallel-arm design</td>
<td>124</td>
<td>48–79</td>
<td>-65 ml pots 10^8 CFU/ml</td>
<td>-Probiotic consumption improved mood in participants whose mood was initially poor</td>
<td></td>
</tr>
<tr>
<td><strong>Streptococcus thermophilus</strong></td>
<td>Effect of consumption of a probiotic containing milk drink on mood and memory</td>
<td>-Double-blind, placebo-controlled, randomised, parallel 3 week intervention</td>
<td>35</td>
<td>18–65</td>
<td>-Sachet containing 8 x 10^8 CFU</td>
<td>-Increase in Lactobacillus and Bifidobacterium in participants taking the probiotic</td>
<td></td>
</tr>
<tr>
<td><strong>Lactobacillus casei Shirota</strong></td>
<td>Effect of probiotic intervention on symptoms of depression and anxiety in adults with chronic fatigue syndrome</td>
<td>-Double-blind, placebo-controlled, randomised, parallel 8 week intervention</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Table 2

<table>
<thead>
<tr>
<th>Source of polyphenol</th>
<th>Major polyphenols</th>
<th>Study aims</th>
<th>Study design</th>
<th>Sample size</th>
<th>Mean age (years)</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concord grape juice</td>
<td>Proanthocyanins, Anthocyanins</td>
<td>Effect of Concord grape juice on memory performance in older adults with age-related memory decline</td>
<td>Double-blind, randomised, placebo-controlled</td>
<td>12</td>
<td>78.2 ± 5</td>
<td>Significant improvement in verbal learning with trends toward improved spatial memory</td>
<td>(Krikorian, Nash, Shidler, Shukitt-Hale, &amp; Joseph, 2010)</td>
</tr>
<tr>
<td>Blueberry juice</td>
<td>Hydroxycinnamic acid ester, Chlorogenic acid, Cyanidin 3-glucoside</td>
<td>Effect of blueberry juice on memory performance in older adults with age-related memory decline</td>
<td>Single-blind, placebo-controlled</td>
<td>16</td>
<td>80.2 ± 6.3</td>
<td>Paired associate learning and word list recall were significantly improved. Trends toward reduced depressive symptoms were seen</td>
<td>(Krikorian, Shidler, et al., 2010)</td>
</tr>
<tr>
<td>Dark chocolate drink</td>
<td>Cocoa polyphenols - Epicatechin, Catechin</td>
<td>Effects of cocoa polyphenols on cognition and mood in healthy middle-aged adults</td>
<td>Double-blind, randomised, placebo-controlled</td>
<td>72</td>
<td>40–65</td>
<td>No improvement in cognition seen for any group</td>
<td>(Pase et al., 2013)</td>
</tr>
<tr>
<td>Dark chocolate</td>
<td>Cocoa flavanols (CF)</td>
<td>Investigated whether visual and cognitive function is influenced by an acute dose of CF in young adults</td>
<td>Single-blind, randomised, crossover</td>
<td>30</td>
<td>18–25</td>
<td>Improvements in visual function, spatial memory and performance in individuals after CF consumption</td>
<td>(Field, Williams, &amp; Butler, 2011)</td>
</tr>
<tr>
<td>Cocoa drink</td>
<td>Cocoa flavanols (CF)</td>
<td>Impact of cocoa flavanol (CF) consumption on cognitive function in elderly individuals with mild cognitive impairment</td>
<td>Double-blind, randomised, parallel</td>
<td>90</td>
<td>65–82</td>
<td>Improvements in cognitive performance were seen in individuals give either high or intermediate doses of CF but not in the group given the low dose</td>
<td>(Desideri et al., 2012)</td>
</tr>
<tr>
<td>Tablet form</td>
<td>Isoflavones</td>
<td>Effects of isoflavones on mood and cognitive function in postmenopausal women</td>
<td>Double-blind, randomised, crossover, placebo-controlled</td>
<td>78</td>
<td>49–50</td>
<td>Better cognitive performance compared to placebo</td>
<td>(Casini et al., 2006)</td>
</tr>
<tr>
<td>Cocoa drink</td>
<td>Cocoa flavanols (CF)</td>
<td>Investigate the relationship between cerebral blood flow and a single acute dose of flavanol-rich cocoa in young adults</td>
<td>Double-blind, randomised, placebo-controlled</td>
<td>16</td>
<td>18–30</td>
<td>High flavanol consumption was seen to increase the cerebral blood flow to grey matter</td>
<td>(Francis, Head, Morris, &amp; Macdonald, 2006)</td>
</tr>
<tr>
<td>Tablet form</td>
<td>Restaverol and piperine</td>
<td>Investigate whether piperine is capable of enhancing the bioeficacy of resveratrol</td>
<td>Double-blind, randomised, crossover, placebo-controlled</td>
<td>23</td>
<td>19–34</td>
<td>Participants given 250 mg trans-resveratrol showed no changes in cerebral blood flow during cognitive tests</td>
<td>(Wightman et al., 2014)</td>
</tr>
</tbody>
</table>
polysaturated fatty acids (PUFA) relative to anti-inflammatory omega-3 PUFA (Simopoulos, 2002). A such, a diet consisting of a greater intake of omega-6 PUFA than omega-3 PUFA has been associated with a number of inflammatory related diseases (Simopoulos, 2002). Dietary intake of omega-3 PUFA, in particular, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been studied in the context of almost every aspect of brain function and mental health, from neurodevelopment to age-related cognitive decline, and the manifestation and treatment of all the major psychiatric disorders (Freeman et al., 2006).

Epidemiological data suggest that dietary intake of omega-3 is protective against unipolar and bipolar depression (Freeman et al., 2006) and dementia (Huang et al., 2005). Although concern has been raised over the methodological quality of clinical trials conducted in this field (Bloch & Hamestad, 2012), EPA and DHA have purportedly shown some efficacy when used as adjunct therapy in patients with major depression and schizophrenia (Freeman et al., 2006). In addition, a recent meta-analysis indicates that omega-3 intervention is beneficial in preventing age-related cognitive decline (Zhang, Hou, Li, & Tang, 2015). Preclinical studies have outlined a number of potential mechanisms by which omega-3 PUFAs may act in the CNS to promote normal brain function and mental health. These include regulation of monoaminergic neurotransmission and brain-derived neurotrophic factor (BDNF) levels, modulating HPA axis activity and reducing peripheral and central inflammatory activity (PuSecedu et al., 2015). Many of these central effects may be mediated by the gut microbiota. For example, in-vitro and animal studies suggest that PUFA can promote the growth of Lactobacillus strains and conversely Lactobacillus can modulate PUFA absorption (Laparra & Sanz, 2010). Interestingly, it has been shown that oral administration of conventional mice with B. breve NCIMB 702258 increases brain levels of DHA (Wall et al., 2012). In support of this preclinical data, supplementing infant formula with Bifidobacterium Bb-12 increased plasma alpha-linolenic acid in a small sample of infants with atopic eczema (Kankaanpää, Yang, Kallio, Isolauri, & Salminen, 2002).

In summary, the evidence indicates that PUFA may have a number of physiological effects beneficial to brain function and mental health, which may be mediated via interactions with the gut microbiota. (see Table 3).

7. Other dietary factors that may impact brain and behaviour by modulating the gut microbiota

Recent evidence indicates that food additives such as emulsifiers and food colorants may alter the gut microbiota composition and impact negatively on host health (He, Marco, & Slupsky, 2013). For example, administration of the food emulsifiers, carboxymethylcellulose (CMC) and polysorbate-80 (P80) to normal mice induced low-grade inflammation, metabolic syndrome, and induced colitis when administered to a genetically predisposed mouse strain (Il10−/− and Tlr5−/−) (Chassaing et al., 2015). Moreover, administration of CMC and P80 altered the gut microbial composition in normal mice, and FMT from normal mice induced metabolic syndrome and low-grade inflammation in GF animals (Chassaing et al., 2015) thus demonstrating that changes in the gut microbiota were necessary for the metabolic changes to occur following CMC and P80 treatment. It is yet to be determined if this startling finding translates to humans. Nevertheless, it will be important to understand if these emulsifiers in food, such as CMC and P80 impact not only on metabolic function, but also on brain function and behaviour. Although the impact of other food additives such as colorants on the gut microbiota have not been extensively studied, there is some evidence that some may alter the microbial composition (Pan, Feng, He, Cerniglia, & Chen, 2012). It is of note then, that symptoms of the neurodevelopmental disorder attention deficit hyperactivity disorder (ADHD), show a modest response to dietary exclusion of food colorants (Sonuga-Barke et al., 2013). This raises the intriguing possibility that food colorants may induce symptoms in ADHD via modulation of pathways of the microbiota-gut-brain axis. However, this speculation clearly needs much further investigation.

Emerging evidence that food additives can alter the composition of the gut microbiota must be considered in the context of how these microbial changes might impact on brain function and behaviour. Exclusion of such additives from an individual’s diet should be considered in complement to additions of functional foods which are beneficial for microbial composition and thus brain function and behaviour.

8. Future trends & conclusions

As the growing body of evidence outlined herein indicates, the gut microbiota can influence mammalian brain development and function, ultimately affecting numerous psychological processes such as mood, emotion, social interaction and cognitive function. The preclinical data are strong in this regard, and studies in rodents will continue to be fundamental in providing a mechanistic understanding of microbiota-brain interactions. Despite limited attempts to translate these findings to humans, emerging data suggest that the microbiota can regulate certain aspects of emotional and neuropsychological functioning.

Pre and probiotic interventions in healthy human adults have demonstrated that some bacterial species exert positive effects on emotion, cognition and HPA axis function. Whilst these data are encouraging, such studies have been limited in their scope of psychological assessment (e.g. mood, emotion, cognition), are confounded by lack of specific controls (e.g. diet) and are without a comprehensive analysis of a range of biological parameters (e.g. faecal microbiota, metabolomic analysis, inflammatory markers) to provide a mechanistic account of the physiological processes mediating the gut microbiota influence on brain function. Future intervention studies in healthy participants, which are adequately powered, must rigorously employ a range of biological and psychological measures so as to fully determine the effects of pre or probiotic species on specific aspects of brain function and behaviour.

In clinical populations, current observational data indicate that gut microbiota composition is altered in individuals with depression, ASD and IBS. Future studies are needed to clearly define the nature of gut microbiota changes in these disorders, and to
understand if these disorders are characterised by specific microbial signatures. Such studies will help to narrow the search for bacterial species that can be targeted for therapeutic benefit. Determining cause and effect will be problematic in defining a microbial signature in any mental health disorder, i.e. is the altered microbiota composition a cause or a consequence of mental health problems? As such, randomised controlled trials with well-phenotyped psychiatric populations are clearly warranted.

Developing our understanding of how the gut microbiota influence brain function and behaviour at the extremes of life is a key priority of ongoing and future research. Preclinical studies with GF rodents have demonstrated that the composition of the gut microbiota in early life can significantly influence neurodevelopment and subsequent cognitive and behavioural function. In parallel, there is supporting evidence from epidemiological studies that environmental factors which disrupt the gut microbiota in early life, such as birth by C-section, are associated with related cognitive decline is in

Table 3
Human trials investigating the effects of omega-3 PUFA interventions on brain health and cognition.

<table>
<thead>
<tr>
<th>Omega 3 PUFA</th>
<th>Objectives</th>
<th>Study design</th>
<th>Sample size</th>
<th>Participant age (years)</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish oil capsules</td>
<td>Effect of omega-3 supplementation on cognition and physiology in healthy participants</td>
<td>Double-blind, placebo controlled, randomised</td>
<td>33</td>
<td>22–51</td>
<td>Omega 3 supplementation associated with improvements in reactivity, attention and cognitive performances</td>
<td>(Fontani et al., 2005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 day intervention</td>
<td></td>
<td></td>
<td>-Improvements in mood state were also seen in the treatment group</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment group consumed</td>
<td></td>
<td></td>
<td>-4 g of fish oil per day containing 2.8 g omega-3 PUFA (1.6 g EPA and 0.8 g DHA and 0.4 g other types of omega-3 PUFA: alpha linolenic, stearidonic, eicosatetraenonic and docosapentaenonic)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment group given 2 g/day EPA</td>
<td></td>
<td></td>
<td>-Patients were still given conventional anti-psychotic medication if this was necessary</td>
<td></td>
</tr>
<tr>
<td>EPA-enriched oil capsules</td>
<td>Investigate the efficacy of EPA as a treatment for schizophrenia</td>
<td>Double-blind, placebo controlled, randomised</td>
<td>30</td>
<td>34.4 ± 8.5 – treatment group</td>
<td>-In the placebo group, all patients required conventional antipsychotic medication at the end of the study while 6 patients in the treatment group were not taking medication</td>
<td>(Peet, Brind, Ramchand, Shah, &amp; Vankar, 2001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36.7 ± 8.1 – placebo group</td>
<td></td>
<td></td>
<td>-Treatment group also had significantly lower scores on the Positive and Negative Syndrome Scale (PANSS)</td>
<td></td>
</tr>
<tr>
<td>Fish oil capsules</td>
<td>Assess the effects of omega-3 long chain PUFA supplementation during pregnancy on infants</td>
<td>Double-blind, placebo controlled, randomised</td>
<td>72 infants</td>
<td>Infants: 2.5 Mothers: 30.9 ± 3.7 – treatment group</td>
<td>-Significant positive correlation between the eye and hand coordination score at 34 months and omega-3 PUFA composition of cord blood erythrocytes</td>
<td>(Dunstan, Simmer, Dixon, &amp; Prescott, 2008)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>83 mothers</td>
<td></td>
<td>32.6 ± 3.6 – placebo group</td>
<td>-Omega-6 levels negatively correlated with eye and hand coordination</td>
<td></td>
</tr>
<tr>
<td>Fish oil capsules</td>
<td>Investigate the effects of omega-3 supplementation on depression-relevant cognitive functioning in healthy individuals</td>
<td>Double-blind, placebo controlled, randomised</td>
<td>54</td>
<td>22.2 ± 3.6 – treatment group</td>
<td>-Treatment group made fewer risk-averse decisions compared with the placebo</td>
<td>(Antypa, Van derDoes, Snelt, &amp; Rogers, 2009)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22.6 ± 4.1 – placebo group</td>
<td></td>
<td></td>
<td>-Participants in treatment group also showed improved scores on a control/perfectionism scale of cognitive reactivity measure</td>
<td></td>
</tr>
<tr>
<td>Fish oil capsules</td>
<td>Determine whether long chain omega-3 PUFA can reduce the rate of progression to first-episode psychotic disorder in young adults at ultra-high risk of psychosis</td>
<td>Double-blind, placebo controlled, randomised</td>
<td>76</td>
<td>13–25</td>
<td>-Treatment group showed reduction in rate of transition to psychosis accompanied by symptomatic and functional improvements during the 40 week monitoring period</td>
<td>(Amninner, Schäfer, Papageorgiou, &amp; et al., 2010)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 week intervention period</td>
<td></td>
<td></td>
<td>-By the end of the monitoring period, 2 of 41 participants in the treatment group transitioned to psychosis compared with 11 of 40 in the placebo group</td>
<td></td>
</tr>
<tr>
<td>Fish oil capsules</td>
<td>Examine whether omega-3 supplementation can attenuate loneliness-related episodic memory problems</td>
<td>Placebo controlled, randomised</td>
<td>138</td>
<td>40–85</td>
<td>-Lonelier participants consuming the higher dose supplement had better verbal episodic memory compared with lonelier participants consuming the placebo</td>
<td>(Jaremka et al., 2014)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5 g/day of omega-3, or 2.50 g/day</td>
<td></td>
<td></td>
<td>-Improvements in plasma omega-6:omega-3 ratio were related to better immediate and long-delay free recall</td>
<td></td>
</tr>
</tbody>
</table>
composition indicates that microbiota-targeted therapies may prove to be of great importance in promoting healthy brain ageing. 

Finally, the extent to which functional foods (prebiotics, probiotics, omega-3 PUFAs and polyphenols) can be employed as stand-alone nutritional solutions to promote normal brain function and mental health, or will be most effective as adjunct to current therapeutic approaches, will be important to determine in future studies with clinical populations, as will identifying the potential negative impact of particular food additives such as emulsifiers and colorants.

As a rapidly developing field, new findings are continually emerging which bolster our knowledge of how the gut microbiota influence brain function and behaviour. Despite significant gains over the past decade in understanding the mechanisms underlying the development and manifestation of most major psychiatric disorders, fewer advances have been made in the discovery of novel CNs acting agents. As such, psychobiotic interventions, which target pathways of microbiota-gut-brain axis, represent a new era in psychotropic therapies and hold great promise in promoting normal brain function and mental health across the lifespan.

Conflict of interest

None.

Acknowledgments

The authors have received funding from the European Community’s Seventh Framework Programme Grant MyNew Gut (FP7-KBBE/2013–2018, grant agreement no 613979) and Dept Agriculture, Food & the Marine, Ireland funded SMARTFood: Science Based ‘Intelligent/Functional and Medical Foods’ for Optimum Brain Health, Targeting Depression and Cognition ([2013–2017] and are supported in part by a research grant from Science Foundation Ireland (SFI) under Grant Number SFI/12/RC/2273.

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Please cite this article in press as: Kennedy, P. J., et al., Microbiome in brain function and mental health, Trends in Food Science & Technology (2016), http://dx.doi.org/10.1016/j.tifs.2016.05.001


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