The Microbiome in Psychology and Cognitive Neuroscience

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Keywords: microbiome, microbiota, gut-brain axis, hypothalamic-pituitary-adrenal axis, interkingdom signalling, prebiotics, probiotics, antibiotics, psychobiotics, commensal bacteria

Abstract: Psychology and microbiology make unlikely friends, but the last decade has witnessed striking bidirectional relationships between intrinsic gut microbes and the brain, relationships with largely untested psychological implications. Though microbe-brain relationships are receiving a great deal of attention in biomedicine and neuroscience, psychologists have yet to join this journey. Here, we illustrate microbial associations with emotion, cognition, and social behaviour. Despite considerable enthusiasm and potential, technical and conceptual limitations including low statistical power and lack of mechanistic descriptions, prevent a nuanced understanding of microbiome-brain-behaviour relationships and pose barriers to translation. Our goal is to describe microbial effects in domains of cognitive significance and the associated challenges, in order to stimulate interdisciplinary research on this hidden kingdom's contribution to psychological processes.

The Hidden Kingdom

Psychology and microbiology make for an unconventional pairing, belonging to disparate disciplines, and encompassing different methodologies and levels of analysis. What benefit might emerge from attempting to connect them? Is such a connection even possible? In this review, we illustrate new evidence of the associations between our bacterial colonisers and psychological processes.

The gut hosts a hidden kingdom, an enormous array of microorganisms (predominantly bacteria), that form an ecosystem of immense complexity and genetic diversity (see Box 1). The gut microbiome is defined as the totality of these **commensal microorganisms** (see Glossary) and their genomes that reside in the intestinal tracts. The importance of gut microbes to general health was first perceived by the Russian biologist Élie Metchnikoff early in the 20th century, who observed that villagers in a certain region of Bulgaria lived unusually long lives, a phenomenon he ultimately attributed to the presence of microorganisms in their dairy products[1]. Since then, bacteria have been found to be strongly correlated with the host's metabolism[2], adiposity[3], and immunity[4]. A great deal of interest has also emerged around the ingestion of **probiotics** and **prebiotics**, which appear to confer a range of health benefits, including inhibition of diet-induced obesity[5], regulation of cardiovascular function and blood pressure[6], and even as potential adjuvant therapies for cancer[7].

In contrast to more established roles of commensal microbes in general health and varied physiological processes, investigations of bacterial contributions to neural processes - just over a decade old- are comparatively new entries on the mainstream research agenda. Yet despite the youth of this field, the emergence of bacteria-brain relationships, mediated by the **gut-brain axis**, is heralded as a paradigm shift in neuroscience[8]. While many of the bacteria-brain findings are currently understood in terms of correlation rather than causation, a burgeoning research literature employing several experimental formats conducive to causal

inference (see Table 1) indicates with ever greater confidence that gut microbes exert meaningful influences on the nervous system (see Box 2).

A frontier that is now rapidly sliding into focus is the contribution of gut microbes to psychological processes, and there is presently a great deal of interest in the association between the microbiome and host behaviour[9]. Although the microbiome has not traditionally been considered in psychological analysis, there is much to be gained from the participation of psychologists and psychiatrists in these explorations.

In this review, we focus almost entirely on bacteria (the dominant microbial lifeform in the host) All commensal microbes share a lifelong symbiotic relationship with the host. More generally, multicellular life has hosted unicellular life throughout evolutionary history[10]. Humans and other hominids have been evolving and diversifying in concert with their gut bacteria for at least 15 million years[11]. This close bacteria-host **mutualism** suggests the possibility that many of the host's biological and psychological characteristics may receive input from the symbiotic relationship with its commensal bacteria[12,13]. Importantly, gut bacteria are not known to have any direct communication with the brain, and remain within the intestinal tracts. Rather, a range of physiological systems act in concert to mediate bacteria-brain signalling along the gut-brain axis (these communication pathways are described in Box 3, and several of these processes are illustrated in Figure 1).

Our primary aim in this review is to call for a closer consideration of the microbiome in mainstream psychological science. To that extent, we describe microbial contributions to four core phenomena of interest to cognitive scientists and psychologists, including 1) stress and emotion, 2) learning and memory, 3) social behaviour, and 4) autism.

Microbial Associations with Emotion and Stress

One of the major areas of investigation in the bacteria-brain relationship is the role of the microbiome in emotional experience, and particularly anxiety and depression[14]. Indeed, it

was the causal effects of bacteria on stress and anxiety (see below) that first alerted researchers to the possibility of bacterial contributions to psychological processes. More recently, research efforts have expanded to study the effects of **psychobiotics**.

Rodent Germ-free Studies on Emotion and Stress

The report that triggered widespread interest in bacterial contributions to neurodevelopment described abnormal activation of the **hypothalamic-pituitary-adrenal axis** (HPA-axis) in **germ-free** mice[15], which are born and develop entirely in the absence of microorganisms (see Table 1). In comparison to normally colonised mice, germ-free mice exposed to stress-inducing physical restraint displayed exaggerated endocrine reactivity (elevations in biomarkers of stress, such as plasma adrenocorticotropic hormone and corticosterone). Germ-free mice also displayed reduced levels of hippocampal and cortical **brain-derived neurotrophic factor** (BDNF), a protein closely associated with neuroplasticity, learning, and memory[16].

These findings provided the first indications of a causal role for bacteria in the emergence and regulation of stress neurocircuitry and neural growth factors. Importantly, different groups of mice were also recolonized with a conventional microbiome at different ages. Microbial recolonization reduced HPA-axis hyperreactivity at six weeks of age, but was less effective in this regard at 14 weeks of age. This time-sensitive efficacy of bacterial reconstitution hinted at the existence of critical **neurodevelopmental windows** within which the abnormalities associated with an absent **microbiota** could be reversed through time-dependent bacterial colonisation. Neurodevelopmental windows have now become an important feature of germ-free research[17]. This was also the first study to show that recolonization of germ-free animals with individual strains of microbes (a process referred to as monoassociation) was able to selectively influence reactivity of the HPA-axis[15]. This observation suggested roles for specific bacteria in the modulation of the stress circuit.

The discovery of a causal effect of gut microbes on the development of the HPA-axis has motivated a range of investigations into the bacteria-dependent aspects of stress physiology. For example, subsequent studies have shown that exaggerated biological reactions occur when germ-free mice and rats are exposed to stress, mostly in terms of elevated glucocorticoid levels[18-21], replicating the original observation[15]. More recently, these investigations have been extended into the bacteria-dependence of host psychology. The bulk of research focussing on the psychological effects of gut bacteria in both rodents and humans have clustered largely around the experience of negative emotional states such as stress, anxiety, and depression. For example, behavioural despair in rodents is indexed by an insufficient struggle to escape from noxious stimuli and aversive situations. Anxiety is inferred from the extent to which the rodent is willing to explore unfamiliar environments, such as the centre of a large open space. Time spent exploring unfamiliar environments is a key behavioural feature of approach-orientation, and is necessary for adapting to novel situations. Negative emotional states such as stress and anxiety are strongly correlated with reductions in exploration and approach-orientation[22,23].

Somewhat counterintuitively, behavioural assays of anxiety have provided consistent evidence that germ-free mice display decreased anxiety (e.g., greater rates of exploratory behaviour)[20,21,24-27]. These impairments in experiencing anxiety in germ-free rodents can be mitigated via recolonization with a normal microbiome[20,25,26]. The cognitive mechanism underlying these reductions in anxious behaviour observed in germ-free mice remain mostly unknown. However, a recent investigation has shown that germ-free mice display impairments in maintaining the associations involved in normal fear conditioning, and therefore show reduced fear behaviour in response to contextual cues preceding noxious stimuli[28]. In other words, it appears that gut bacteria are necessary for the normal development of fear-learning processes. This behavioural profile was regulated by altered gene

expression in the amygdala, and was partially mitigated by recolonization with a conventional microbiome.

Bacterial effects on amygdalar anatomy and physiology may underlie many of the emotional and stress-related outcomes that have been attributed to the microbiome. The is crucially involved in the generation, experience, and processing of emotional information[29]. A number of studies have shown changes in the amygdalar concentration of various brain chemicals and receptors, including BDNF and N-methyl-D-aspartate receptors, in germ-free and antibiotic treated mice[20,26,30-32]. Analysis of gene expression in germ-free mice is suggestive of an overall increase in neural hyperactivity in the amygdala[28,32]. For example, **early-immediate genes** and genes associated with cholinergic and dopaminergic neurotransmission (known to be involved in amygdala-related learning and extinction) are upregulated in germ-free mice. Furthermore, germ-free status also predicts enhanced volume of amygdalar subregions, such as the basolateral amygdala, which also displayed evidence of **dendritic hypertrophy**[33].

Taken together, these results suggest that the microbiome both modulates general approach-orientation by inhibiting exploratory behaviour and also governs psychophysiological reactions to stressors. The cognitive mechanism underlying both these effects appears to be the formation and maintenance of the stimulus-response associations entailed in fear conditioning.

Emotional Effects of Faecal Microbiota Transplantation

Converging evidence of bacterial influence on stress and emotion also derives from the striking effects of faecal transplants (see Table 1). Microbiota transfers via faecal transplants are effective in treating bacterial infections in humans[34]. Faecal transplants have also been proposed as a potential means of treating irritable bowel syndrome and disorders of the central nervous system, including conditions such as multiple sclerosis, Parkinson’s disease, and

chronic fatigue syndrome[35,36], all of which have well-known psychological sequelae

Transferring faecal content from an innately stress-sensitive mouse strain to non-anxious mice was sufficient to trigger anxiety-like phenotypes (i.e., reduced exploratory behaviour) in the recipients, alongside reductions in hippocampal BDNF[31]. Colonisation triggered by transferring bacteria from non-anxious mice to innately anxious recipients caused the latter to display reduced anxiety (as indexed by increased exploratory behaviour)[31]. A similar pattern was also observed in rats that received faecal transplants from depressed or healthy humans[37]. Such results[27,31,37], taken together, further suggest that the microbiome contributes to the pathophysiology of anxiety and depression.

While these findings provide precedent for the use of faecal transplants in the treatment of psychological disorders in humans, to our knowledge there are as yet no studies that have attempted to establish a comprehensive psychological profile of the effects of such transplants in adults (though see the section on autism, where a preliminary effort in this direction is described). Reports of faecal transfers for the treatment of anxiety and depression in humans have not yet been published, but it is an important direction to consider. Once the mechanisms of bacteria-brain communication are better understood, faecal transplants may show some promise in the treatment of anxiety and depression.

Bacteria, Emotions, and Inflammation

Inflammation is an adaptive physiological response orchestrated by the immune system to pathogens and injury which protects the organism against infection. Amongst the biological changes associated with inflammation is the activity of **cytokines**, proteins that modulate inflammation[38]. Pro-inflammatory cytokines increase inflammation, and include, for example, interleukin-1, interleukin-12, tumour necrosis factor-alpha, and interferon-gamma. Anti-inflammatory cytokines reduce inflammation, and include interleukin-4, interleukin-10, and interleukin-13. Some cytokines, such as interleukin-6, may have anti- or

pro-inflammatory properties depending on the context in which they are secreted[39]. While normal immunological activity requires a balance between both forms of cytokines, depression has been frequently associated with elevations in pro-inflammatory cytokines and general inflammation[40,41]. More generally, the link between the immune system and behaviour has emerged as an important area of research[41], especially in the context of immunological contributions to psychiatric conditions such as depression [41,42]. The evolutionary underpinnings of the effects of the immune system on behaviour remain largely unknown. Stereotypical "sickness" behavior (e.g., social isolation, depression, apathy, attentional impairments) may simply be a by-product of immune activation, or an adaptation favoured by the positive effects that social isolation has on the **inclusive fitness** of the sick individual. Inflammation is also triggered by impairment in gut barrier function (often referred to as "leaky gut"), wherein the host's gut barrier confining intestinal content becomes weakened, allowing bacteria or bacterial products to infiltrate into systemic circulation[43]. Many bacteria themselves have pro-inflammatory elements which directly raise inflammation. The host's immune system also detects potentially pathogenic bacteria and triggers further pro-inflammatory responses. Reductions in barrier integrity, and increases in bacterial translocation and attendant inflammation, have been linked to the pathophysiology of depression and other psychiatric conditions in humans[43-45].

A mechanism underlying the psychobiotic effect on emotion likely entails a reduction in pro-inflammatory cytokines and an increase in anti-inflammatory cytokines, which reduce general inflammation both independently, and in interaction with one another. Ingestion of **probiotics** (e.g., from the *Bifidobacterium* and *Lactobacillus* genera) and **prebiotics** (e.g., oligosaccharides) reduce pro-inflammatory cytokines[46-53] and also increase anti-inflammatory cytokines[52,54,55]. Probiotics can also reduce inflammation by enhancing the integrity of the gut barrier, thereby preventing further bacterial translocation[56,57].

Overall, these changes indicate a general shift toward lower levels of inflammation which may underlie the affective benefits associated with the ingestion of prebiotics and probiotics. Some studies, however, have found emotional benefits of psychobiotics in the absence of any changes in cytokine concentrations[58]. This suggests – reasonably - that alterations in inflammation are a partial rather than a total mediator of these effects.

Psychobiotic Effects on Emotion and Stress in Humans

Psychobiotic administration in humans has shown promise in modulating emotional processing in humans. We have reviewed the emotional effects of psychobiotics in rodents and humans elsewhere[59]. Here, we focus only on the human studies. Several results appear to converge on the general pattern that, relative to a placebo, consuming probiotics from the *Bifidobacterium* and *Lactobacillus* genera reduces negative mood and emotion in healthy populations[60-66]. In these studies, affective changes have been noted in self-reports[60,62,66]. At the physiological level, probiotic consumption is often attended by reductions in cortisol relative to placebo[60,62,64], while other studies have reported increases in faecal serotonin concentrations[64] or reductions in natural killer cells[65].

The neurocognitive mechanism underlying these emotional changes may be a general reduction in affective reactivity (i.e., the strength of the psychophysiological response to emotional stimuli). For example, one research group found that ingestion of a probiotic mixture, relative to placebo, reduced self-reported reactivity to sad mood, a change that was ascribed specifically to reductions in aggression and rumination[66]. Similarly, another group administered a probiotic mixture to female participants over several weeks[67]. After the regime, participants viewed emotional stimuli (faces) while undergoing functional magnetic resonance imaging. Relative to controls, individuals who consumed the probiotic showed reduced activation in brain regions that have been implicated in the processing of emotional information, including the insula, the somatosensory cortex, and the periaqueductal grey. Thus,

probiotic ingestion may alter the processing of emotional information at a network level[59,67]. Finally, it has also been shown that consuming the prebiotic galacto-oligosaccharide reduced waking cortisol levels and attenuated emotional vigilance to fearful stimuli[68]. Both waking cortisol and sensitivity to fearful stimuli have been studied as markers of depression and anxiety[69-71], and their mitigation by prebiotics shows several similarities to the effects of prebiotics in rodents[46]. More broadly, these three human studies provide preliminary but converging evidence from multiple modalities (self-reports, neuroimaging data, cortisol concentrations, and reaction times) for the hypothesis that psychobiotics exert their effects by reducing emotional reactivity. The strongest support for such a hypothesis would arise from convergent evidence using different methodologies, but also with larger direct replications of some of the key studies described here. There is, however, an important caveat to consider: If indeed psychobiotics can reduce emotional reactivity, then aside from potential benefits in terms of reductions in negative affect, there may be some costs in terms of reduced positive affect as well. Reduced emotional reactivity may not in itself, therefore, be beneficial.

The contributions of the microbiome to emotion will also play a role in the emerging field of nutritional psychiatry, which is dedicated to analysing the (often profound) effects of diet on mental health[72]. Many nutritionally-derived mental health benefits may be mediated by the microbiome[73]. Indeed, given the extraordinary responsiveness of the microbiome to nutrition intake, diet may be the most potent psychobiotic of all (see Box 4).

Microbial Associations with Cognition

There is now growing interest in the role of bacteria in cognition. In general, this is a smaller and less well-developed literature in comparison to studies of bacterial effects on emotion. However, a number of recent results are pointing toward a bacteria-cognition link that should be rigorously explored.

Rodent Research on Learning and Memory

Germ-free and psychobiotic supplementation studies in rodents have found significant bacterial effects on cognitive processes, most notably learning and memory. An early demonstration of the bacteria-cognition relationship showed impairments in tests of memory and reductions in hippocampal BDNF in germ-free mice compared to normally colonised mice[74]. More recent work has shown that exposure to antibiotics also modulates learning and memory (see Table 1 for the utility of the antibiotic approach). For example, rats administered ampicillin showed decreased spatial learning performance (and heightened anxiety)[75].

A number of studies have investigated prebiotic effects on cognitive processes. For instance, compared to vehicle-treated rodents, mice and rats exposed to human milk oligosaccharides (a prebiotic) showed enhanced performance on a range of learning and memory tests, including working memory, spatial learning and memory, and learning via reinforcement[76]. These cognitive benefits were associated with several neurophysiological changes, including enhanced long-term potentiation and increased concentrations of BDNF. Investigations on infant rats showed similar effects of human milk oligosaccharides on novel object recognition, place and spatial memory, and long-term potentiation, benefits that were visible even a year after initial exposure to the prebiotic[77].

Probiotics comprising bacterial strains or consortia of strains have also been shown to exert beneficial effects on cognitive processes in rodents. For example, mice administered a probiotic displayed enhanced performance on a battery of cognitive tasks designed to test learning and memory, compared to a sterile vehicle, including better object-recognition and maze learning[78]. Interestingly, probiotic treated mice displayed improved stimulus associations in fear conditioning but showed extinction profiles similar to vehicle-fed mice. Probiotics are also effective in mitigating cognitive dysfunction induced by exposure to medical and dietary changes. For example, mice fed high-fat diets displayed impaired spatial

memory, and this deficit was corrected via probiotic ingestion[79]. Rats treated with antibiotics displayed poorer spatial memory and greater anxiety, changes that were again mitigated via consuming probiotics[75]. A recent study has suggested that gut microbiota may also influence executive functions supported by the prefrontal cortex. Rats that had been supplemented with a prebiotic for 3 weeks demonstrated greater cognitive flexibility (indexed by the attentional-set shifting paradigm) compared to controls[80]. Prebiotic intake also elevated neuronal NMDA receptor responses, which corroborated the participation of glutamate signalling in the psychotropic effects of enteric bacteria[81]. In a preliminary examination, this study also suggested that the short-chain fatty acid acetate (a metabolite of the prebiotic used) may have mediated the observed behavioural and neurophysiological effects[80].

Rodent research also suggests that the hippocampus may be a neurobiological mediator underlying the bacteria-cognition link. The hippocampus plays a critical role in learning and memory, and its function in the generation and maintenance of spatial maps is especially well-described in rodents[82]. A consistent finding in studies examining bacterial effects on the hippocampus is an alteration in the expression of BDNF. For instance, in rodents, hippocampal BDNF increases in response to both prebiotics[46,76,81, 83] and probiotics[47]. The effect of antibiotics has been inconsistent, however, as hippocampal BDNF in rodents has both increased[31]) and decreased[84] in response to antibiotics. These differences may be attributable to the nature and effects of the specific molecules that characterise different antibiotics. Germ-free mice show lower levels of hippocampal BDNF[25,26], elevated levels of hippocampal serotonin[25], and variations in hippocampal morphology[33].

Importantly, psychobiotic effects on cognition may not always be beneficial, or may have both positive and negative effects simultaneously. A recent study of healthy rats examined the interactions between probiotic administration and consumption of a **cafeteria diet**[85]. Rats fed the cafeteria diet showed deficits in place memory, a diet-induced effect that was mitigated

by probiotic supplementation. However, probiotic administration also impaired object memory, regardless of diet.

Human Research on Learning and Memory

The question that follows on the observation of microbial effects on cognition in rodents is whether such effects may occur in humans. There is some evidence of this possibility. For example, infection of humans with Chlorovirus ATCV-1, an algae-derived virus, has been associated with a broad range of cognitive changes, including decreased performance on psychological assessments of visual processing and visual motor speed, effects that were replicated in mice[86].

There is also some research on microbiome-cognition associations in human adults. For example, studies of obese individuals[87] found an association with microbiome composition and performance on the Trail Making Test (a psychometric assessment of motor speed, attention, and cognitive flexibility[88]). This study[87] also found that greater diversity of gut bacterial populations (i.e., the number of different species of gut bacteria at a site) were associated with greater variation in brain microstructure, including the hippocampus, the hypothalamus, and the caudate nucleus.

Gut bacterial diversity may not always be beneficial, however. A recent longitudinal study on one-year old human infants found that gut bacterial diversity were linked to visual reception and language acquisition at two years of age[89]. Interestingly, lower gut bacterial diversity was associated with better cognitive performance. As studies frequently find that increased bacterial diversity is associated with desirable outcomes, these results[89] suggest that higher levels of diversity may not always predict benefits. Nonetheless, this finding highlights potential associations between the microbiome and human cognitive development.

A question of particular interest is whether psychobiotics can be used as a form of cognitive enhancement. Psychobiotic administration in humans has yielded mixed results in

terms of cognitive changes. Probiotics administered to a sample of elderly participants produced some improvements in sustained attention and working memory relative to participants administered a placebo[90]. A more recent investigation employed a repeated measures design to investigate probiotic benefits[60]. Consistent with the cognitive effects noted in mice[78], probiotic ingestion produced a small improvement on a paired-associate learning task. An electrophysiological profile consistent with improved cognitive performance was also observed, characterised by greater frontal midline oscillatory activity. The use of electrophysiology in studying bacteria-brain-cognition relationships is relatively uncommon, and more widespread implementation of this technique in both animals and human research would generate important insights about bacteria-induced changes in brain function.

However, human findings have also pointed in the opposite direction – toward potential cognitive impairments. An early study found that probiotic consumption produced a small decline in performance on an episodic memory task and some aspects of long-term memory[61]. While the authors discuss that this negative effect may be due to chance, it does leave open the possibility that probiotics may exert cognitive costs[59]. However, other investigations that have administered probiotics to humans did not find any costs to learning and memory[63,91]. At the same time, while no cognitive cost was observed, there was also no evidence of a benefit. Therefore, it is currently far from clear whether psychobiotics can exert any consistent effects on cognition in humans. The possibility of psychobiotic-induced cognitive impairments also prefigures recent rodent work showing that probiotics impaired object memory in healthy rats[85], described in the preceding section.

Our overview of several key results in this area demonstrates a lack of conclusive results and multiple sources of discrepancy. These include variation in the bacterial strains used, the operationalisation of cognitive constructs, and the age of participants. It remains difficult to predict what benefits (or costs) will arise in which conditions, and this uncertainty,

alongside issues of statistical power, both reduce the replicability of published results and increase the difficulty of generating precise test implications. Quantification of the nature and scope of cognitive effects of psychobiotics in humans is therefore an important area of investigation. For researchers interested in the potential of psychobiotics as a cognitive enhancer, identifying the conditions under which psychobiotics may be most effective is a crucial step[59].

Are Cognitive Benefits of Psychobiotics an Epiphenomenon of Peripheral Changes in Glucocorticoids and Inflammation?

The microbiome-cognition link also requires greater conceptual and mechanistic elucidation. For instance, an important point of ambiguity is the relationship between bacterial modulation of stress and immunological activity on the one hand, and learning and memory on the other. In particular, many of the bacterial benefits in learning and memory occur alongside reductions in biomarkers of stress (glucocorticoids) or inflammation (pro-inflammatory cytokines)[46,60,75]. Both glucocorticoids and pro-inflammatory cytokines impair cognitive performance under numerous (but not all) conditions[92,93]. Therefore, are the cognitive effects that follow psychobiotic administration independent bacterial effects, or are they entirely due to bacteria-mediated reductions in glucocorticoids and pro-inflammatory cytokines? While neurophysiological changes in brain structures such as the hippocampus suggest that cognitive improvements occur independent of systemic physiological changes, it should be noted that the hippocampus itself is highly sensitive to glucocorticoids[94]. Thus, hippocampal changes supporting improved cognitive performance may reflect a general bacteria-induced reduction in systemic glucocorticoids, rather than a separate neural process.

Published research does allow for a cautious inference that these might be independent processes. For example, one report showed that ingestion of antimicrobials increased hippocampal BDNF expression in the absence of other peripheral changes in mice[31]. Another

investigation found that germ-free mice displayed impaired cognitive performance in the absence of clear increases in anxiety[74]. Finally, one study found that mice treated with probiotics showed enhanced object recognition and spatial memory in the absence of a decrease in glucocorticoids[78]. Jointly, results such as these provide some evidence that bacterial effects on cognition may be separable from effects on peripheral physiology and emotion. However, these are post-hoc interpretations of published data. Experimentally establishing the relative independence (or lack thereof) of the stress- and immune-related effects of bacteria on the one hand and their cognitive effects on the other will be an important step toward understanding bacterial contributions to cognition.

Microbial Associations with Social Behaviour

Evidence is now emerging that gut microbes (and especially bacteria) may be necessary for the development of normal social functioning (see also the following section on autism). On balance, the bacteria-behaviour link is likely to be fairly subtle in mammals (see Box 5 for some remarkable cases of microbial behavioural control of mammalian hosts).

Foetal programming of social behaviour also occurs in response to antibiotic-induced alterations in the mother's microbiome. A recent investigation has shown that the offspring of rats exposed to antibiotics during pregnancy demonstrate marked social dysfunction in comparison to conspecific controls[95]. Social behaviours such as playing, grooming, and sniffing were greatly reduced in the offspring of rats exposed to antibiotics, both in terms of the number of social interactions and the time spent in social interactions. This finding may have important implications for the administration of antibiotics in human pregnancy as well. Another study examined the effect of bacterial transplantation on social behaviour[96]. The authors found that exposure to a physical stressor triggered social avoidance behaviour in mice. Transplanting faecal matter from these mice to a separate strain of innately stress-sensitive mice was sufficient to trigger social avoidance in the recipients reminiscent of behaviour

observed in the donors.

Germ-free studies have also provided evidence of the causal role of gut bacteria in social behaviour. For instance, compared to normally colonised rats, germ-free rats showed reduced interest in a conspecific (indexed by sniffing behaviour) in the first two minutes of a ten minute interaction[18]. These results are conceptually similar to the behaviour of germ-free mice in the three-chamber sociability test[97], a test of rodent social preference. The mouse is placed in the middle of three interconnected chambers. In the first phase of the experiment, the adjacent chambers contain a novel mouse or a novel object. Sociability is indexed by the mouse's preference to interact with the novel mouse over the novel object. In the second phase of the experiment, the adjacent chambers contain a familiar mouse or an unfamiliar mouse. Social novelty is indexed by the mouse's preference to interact with the unfamiliar mouse over the familiar mouse. Normal social behaviour entails a greater tendency to interact with the mouse over the object in the first phase, and with the unfamiliar mouse over the familiar mouse in the second. In comparison to normally colonised mice, germ-free mice demonstrated substantial reductions in sociability and preference for social novelty[97,98]. Bacterial colonisation was sufficient to increase sociability, but did not increase preference for social novelty, suggesting that some aspects of sociality may be more sensitive to bacterial modulation than others[97]. Interestingly, another germ-free project that utilised significantly older mice of a different strain found the opposite result in the three-chamber test: germ-free mice showed greater sociability than normally colonised mice[30]. These opposing results present an intriguing and unresolved puzzle. One cause for this difference, discussed by the authors, may be the greater age of the mice they used. The social neurocircuitry would have had substantially longer to develop, and greater age may therefore result in significant behavioural variations.

Of the published reports on bacteria-sociality relationships in rodents, the general trend

appears to be that major disruptions to the gut microbiome reduce social interaction[18,49,95-98], suggesting that bacteria contribute to the motivation for and maintenance of sociality. However, there has been a report that germ-free mice may also display *increased* sociability[30]. One interpretation of this is that the mice are attempting to acquire microbes from others. That is, the absence of a microbiome is triggering behaviours to develop a normal microbiome. Microbial acquisition would be facilitated by seeking out and interacting with others. Indeed, such behaviour would be analogous to the searching behaviour noted in the insect *Megacopta cribraria*. Females will leave microbe-containing pellets near their eggs. On hatching, *Megacopta cribraria* will consume these pellets, thereby gaining a normal microbiome[99]. However, in the absence of these pellets, the insects will display enhanced exploratory behaviour, likely in search of this initial "dose" of microbes[99]. Such an explanation for increased sociability in some germ-free mice[30] would also be consistent with the increased exploratory behaviour observed in rodents in other germ-free studies [20,21,24-27].

Explanations for both increased or decreased sociability in germ-free mice are broadly but independently consistent with the evolutionary hypotheses concerning bacterial transmission via social interaction. However, juxtaposed as the findings are (i.e. some germ-free rodents show decreased sociability, while others show increased sociability), the interpretation is no longer as straightforward. Overall, while these studies suggest that gut bacteria play a role in social behaviour, the direction of effects is at best uncertain and likely depends on a variety of moderators.

Microbial Associations with Autism

Autism is one of the most striking examples of bacterial associations with neurodevelopment and social behaviour. Autism is a complex condition characterised by two core behavioural features: deficits in social interaction and communication, and highly rigid,

repetitive behaviours[100,101]. Whilst these behavioural patterns are used to formally detect autism, there is increasing interest in the cognitive, neurobiological, and genetic correlates of this condition.

Autism has also been linked to gastroenterological and immunological dysregulation, as well as variation in microbial content[102-107]. Both gastroenterological and immunological processes also interact with the gut microbiome. Rodent models of autism and humans with autism differ from neurotypical controls in terms of gut bacterial profiles. The detection of such differences has led researchers to hypothesise a functional connection between gut bacteria and autism[108]. In murine models of autism, for example, *in utero* exposure to valproic acid triggers behavioural patterns that mimic autistic traits in humans (e.g., impaired sociability, repetitive behaviour) and produces marked shifts in microbiome profiles[109,110]. Human studies have revealed several bacterial differences between autistic and non-autistic individuals[111-115]. At the same time, there is also considerable variation and discrepancy in identifying bacterial markers of autism, with ratios of bacterial phyla being inconsistent and even contradictory across studies[111,115-118]. Understanding the causes and circumstances of these inconsistencies must be incorporated into the wider research programme of determining the causal contributions of bacteria to autism.

Nevertheless, researchers have made important strides in bringing the microbiome into the mainstream analysis of autism, and there have been two remarkable attempts at manipulating the bacteria-autism association in mice. In one study, autistic behaviours were triggered in mice during prenatal development using **maternal immune activation**[49]. The offspring demonstrated reliable behavioural markers of autism, including reduced social interaction and communication, and increased repetitive behaviour, along with aberrations in gut bacterial composition. Probiotic treatment significantly ameliorated some (but not all) behavioural deficits, and also normalised gut bacterial composition. Another study triggered

autistic traits in offspring by exposing pregnant mice to high-fat diets[98]. In addition to behavioural and microbiome abnormalities associated with autism, the researchers found that autistic-type mice showed deficits in long-term potentiation in the ventral tegmental area that followed social interaction in normal mice, as well as reduced numbers of hypothalamic **oxytocin immunoreactive neurons**. Furthermore, microbiota transplants from the offspring of mice fed high-fat diets to normal mice triggered similar tendencies in the recipients, providing further evidence of the causal role of gut bacteria in the development of autistic phenotypes. Treatment with probiotics attenuated these behavioural and neural abnormalities.

There has also been some exciting (though preliminary) progress in humans. A crossover study in which autistic children were administered probiotics did not find any improvements in behavioural deficits, but did show changes in microbial composition[119]. Numerous potential moderators make it difficult to interpret why a null result was observed for behavioural symptoms. On the other hand, treatment with antibiotics such as vancomycin has shown at least short-term benefits in reducing autistic tendencies in children[120,121], an effect that may be attributed to reductions in neurotoxin-producing indigenous bacteria. Recently, an open-label pilot trial involving 18 children diagnosed with autism investigated the impact of faecal transplants from healthy controls on behavioural and gastrointestinal symptoms in recipients with encouraging results[122]. In particular, the improvements in behavioural symptoms persisted even eight weeks after the cessation of treatment. Microbiota transplants exert wider changes on an individual's microbiome than psychobiotic ingestion, and this large-scale introduction of new bacteria may be one reason that this effort is showing initial success.

Overall, this is an extremely important area of investigation that, once better explored, may yield at least some therapeutic benefits for individuals diagnosed with autism, especially where subtypes, comorbidities, and severity are carefully specified.

The appeal of a potential psychobiotic therapy for autism lies, of course, in the concept

of reversibility. The detection of clear bacterial profiles underlying autism facilitates intervention attempts that are not possible with other putative causes of autism, such as genetic polymorphisms or prenatal exposure to elevated levels of steroid hormones[123], whose neurodevelopmental effects have already occurred and in that sense are permanent. Microbial composition, however, is amenable to exogenous manipulation. We are certainly not suggesting that a clear bacterial signature underlying autism (even if it existed) would imply a psychobiotic route to reversing this condition. However, approaching the microbiome as a therapeutic target does make the task of providing some therapies for autism more tractable than many current models permit, and is a promising direction for future research.

Psychologists in the Hidden Kingdom

In addition to the four areas we have outlined, we describe three further points of intersection between microbiome science and cognitive science that will enrich our understanding of the microbiome-brain-behaviour pathway. While there are important grounds for scepticism as well[124], we hope that our discussion will provide new opportunities for rigorous, cross-disciplinary collaboration.

The Search for Bacterial Signatures

One theme in this review has been the possibility of finding the bacterial signatures of psychological profiles and traits. If such signatures exist, finding them is likely to require large-scale collaborations and multi-site data collection. How each bacterial component in a putative bacterial signature contributes to the onset and maintenance of a disorder or trait is unknown. More broadly, it is a matter of debate whether it is even possible to determine a consistent signature or profile of any psychological profile in terms of the differences bacterial communities, a problem compounded by the known effects of age, sex, diet, medication use, and a variety of others moderators that would affect the microbiome. Overall, a bacterial signal might be very difficult to detect amidst the noise.

Psychologists will be able to contribute detailed knowledge of the behavioural and cognitive features associated with different psychological conditions and traits, which may help us better understand how microbial effects on host physiology influence particular aspects of a broader psychological profile (and vice versa).

A major focus in the area of signatures has been on depression, though the psychological implications of variation in bacterial communities for emotional disorders remain unclear. At present, there is some evidence of such microbial patterns associated with various psychological states. For instance, depression has recently been associated with changes in the relative abundance of several bacterial communities, though the results are often inconsistent or contrary when compared across studies[27,125-127]. Interestingly, in some cases, concentrations of particular bacterial communities may correlate with the severity of depression[126].

It is also unclear whether bacterial signatures may accompany variation in stress and emotion in healthy populations. For example, a recent investigation found correlations between microbial composition and personality traits, including conscientiousness and neuroticism[128]. However, in another (smaller) study of healthy females, there were no associations detected between bacterial diversity and measures of subclinical depression, anxiety, and stress[129].

Though we have focussed on autism, depression, and anxiety in this review, these are far from the only psychological disorders in which the microbiome is implicated. For example, an emerging area of inquiry is linking the microbiome to disorders characterised by psychosis, such as schizophrenia[130]. Psychosis refers to a diminished capacity to perceive and engage with reality (most notably delusions and hallucinations). Psychosis is usually a prominent feature of schizophrenia. Researchers have been interested in an infection-schizophrenia link since at least the 1920s, when an increase in schizophrenic symptoms was observed following

the 1918 influenza epidemic[131]. Relatively recently, researchers have also studied the link between *toxoplasma gondii* infection and psychosis in humans[132], though in some cases the evidence for this association has been mixed[133].

More generally, immune dysregulation has been widely implicated in biological models of psychosis[134], and individuals with schizophrenia consistently show elevations in pro-inflammatory cytokines and inflammation[130]. Furthermore, the recently discovered lymphatic vessels subserving the central nervous system[135] may act as a delivery mechanism for pro-inflammatory cytokines and other immune molecules into the brain. Given the role of bacteria in regulating the development and function of the immune system (including levels of pro-inflammatory cytokines), a bacterial component underlying psychosis may be biologically plausible. To this effect, a recent preliminary investigation has found that individuals treated for first episode psychosis showed differences in gut bacterial composition compared to healthy controls[136]. Importantly, the magnitude of these bacterial differences was negatively associated with the efficacy of antipsychotic treatment. As with autism and depression, we are not suggesting that there is a pure, reversible bacterial signature of schizophrenia in humans. However, this is a promising line of inquiry, and further mechanistic elucidation will facilitate the development of theoretical frameworks to account for the physiological aspects of psychosis, and possible therapies for at least a subset of individuals.

Clearly, issues of statistical power and enormous variance will complicate the search for microbial signatures. Nonetheless, large-scale data collection efforts with much greater power to detect effects (e.g., the American Gut Project, the ElderMet Project, the Human Microbiome Project) may provide scope for optimism in the discovery of more specific bacterial underpinnings of at least some psychological disorders and traits. Active involvement of psychologists in new, large-scale initiatives of this type as they are established will provide further valuable insights. In these cases, psychologists will be able to provide expertise on

psychometric assessments that can be added onto data collection, and which can subsequently be examined for the microbial correlates of a variety of behavioural and cognitive features.

Senescence, Cognitive Decline, and Alzheimer's Disease

Ageing places heavy and lasting socioeconomic burdens on communities and societies[137]. Ageing confers greater risk for diabetes and cancer, heightened pro-inflammatory activity, generalised cognitive impairments, and greater likelihood of developing neurological conditions such as Alzheimer's disease. Maintenance of cognitive health during ageing has recently emerged as a prominent public health goal, and incorporation of the microbiome into research programmes may yield important translational benefits.

Alongside molecular and cellular changes occurring in the host, the composition of the microbiome also changes with increasing age. For example, gut bacterial diversity shows a negative association with frailty and cognitive dysfunction[138]. While cause and effect remain unclear, the existence of associations between bacterial communities and longevity provide fruitful ground for future longitudinal investigations, which would provide stronger causal evidence. Psychobiotic supplementation also serves as a point of entry into the bacteria-senescence loop and can provide insights into causality, and the development of translational medicine. For instance, ageing rats fed probiotics displayed normalisation of age-related impairments in long-term-potentiation compared to ageing rats fed a neutral vehicle substance[139]. Probiotic ingestion has also been shown to enhance attention and memory in elderly humans[90]. Probiotics are also being examined for their capacity to reduce physical weakness and muscle-wasting in ageing populations, with promising early rodent evidence[140].

Another important area of investigation is the association between the microbiome and Alzheimer's disease. There appear to be Alzheimer's-associated alterations in gut microbiota composition in both rodents and humans[141], but identifying consistent bacterial profiles

associated with the condition remains elusive. A prominent correlate of Alzheimer's disease is amyloidosis, or deposition and accumulation of the peptide amyloid-β in the brain[142]. An initial human study has correlated increased rates of amyloidosis and cognitive impairment to changes in gut microbial profiles[143]. A recent investigation using a rat model of Alzheimer's disease has shown preliminary benefits of prebiotic ingestion[50]. These findings yield early insights for the development of further psychobiotic interventions for neurodegenerative disorders.

In general, the psychological implications of bacterial contributions to lifespan development, ageing, and dementia remain largely unknown. Psychologists are well placed to answer key questions in this area. There is already some evidence that individuals with low bacterial diversity also display lower cognitive functioning[138], inferred from poorer scores from the Mini-Mental Status Examination[144]. However, there are few such studies overall. Moreover, there are numerous behavioural markers of neuropsychological functioning in ageing, such as reduced error-awareness[145], working memory deficits[146], and impaired multi-tasking[147]. Such assessments will provide more precise estimates of bacterial effects, if any, on the cognitive status of elderly individuals.

Fine-Grained Measures of Psychological Processes and Executive Function

With a few exceptions[68], most human psychobiotic studies have not employed more fine-grained measures of psychological function. Subtle, bacteria-induced changes in perception, attention, and information processing are important but largely unexplored areas of investigation. A reliance on self-reports for the assessment of mood assumes that participants will be able to detect shifts in their own emotional states. While self-reports have been successful in some studies on the bacterial effects on emotion[62,66], they have failed to detect such effects in others[148]. Self-reports are unlikely to capture subtle differences in information processing, and this lack of nuance in measurement poses a high risk of producing

false negative results. For example, a computerised test of working memory performance at the millisecond-level may be more conducive to detecting bacterial effects that could not be captured on a gross measure of total accuracy on a memory inventory. Reaction times, which are a hallmark behavioural measure in cognitive psychology, have not yet been widely deployed in elucidating the bacteria-cognition link. A shift toward information processing approaches that incorporate behavioural performance such as reaction times[68] are likely to provide more sensitive measures of the emotional and cognitive effects of gut bacteria, especially combined with electrophysiology[60] and neuroimaging[67,88].

Concluding Remarks

We have described microbial associations (largely bacterial) with emotion, cognition, and behaviour, as well as described how psychologists might contribute to the generation of new knowledge. As noted earlier[59,116], reviews and research reports often express tremendous optimism in the potential of the bacteria-brain relationship. Though our view is enthusiastic, we must acknowledge that the evidence-enthusiasm ratio is far from 1:1, and optimism not tempered by scepticism risks being misleading. Indeed, a recent issue is the potential overselling of the microbiome both to researchers and to the public[124], which is likely to occlude nuanced interpretations of the microbiome's psychophysiological contributions. Researchers must also contend with a range of inconsistent results on a prominent future application of psychobiotics- their effects on human psychological processes, especially emotions and neuropsychiatric conditions (See Boxes 6 and 7). Furthermore, statistical power to detect effects and a lack of direct replications of several key findings remain important issues, similar to many other subdisciplines in psychology, neuroscience, and medicine. Another significant challenge lies in enhancing translation (see Box 7).

Aside from psychologists becoming more involved in exploring the research questions described here (see also the Outstanding Questions), a longer-term view might incorporate

elementary discussions of the microbiota-gut-brain axis in undergraduate and graduate biopsychology teaching. This will allow at least a glimpse of the microbiome-cognition link and highlight the need to investigate it, perhaps building interest in this emerging area at an earlier stage of training.

Overall, greater participation of psychologists in microbiome-brain research will yield two mutually reinforcing benefits. First, psychologists will be able to widen their scope of analysis, generating richer theories that encompass the neurocognitive effects of previously unconsidered biological variables: gut microbes. Second, though some broad patterns of the psychological associations with gut microbes are emerging, more precise predictions remain elusive. There are many links in the chain from microbes to the gut to the nervous system to psychological experience. Of these, perhaps the least understood are the cognitive and behavioural aspects. Psychologists will be able to provide much needed input on more sophisticated explorations of the psychological contributions of this hidden kingdom.

Box 1: Features of the Gut Microbiota

Size and Complexity: Gut-based microbes form an extremely large and diverse ecological community. Microbial genes are over 100 times more abundant than those of the human genome[149]. General estimates of the bacterial population size in humans vary widely. The intestines are estimated to harbour 10^{13}-10^{14} microorganisms (10 times that of the cells in the body), though more recent approximations point to a ratio of host-to-bacterial cells much closer to 1:1[150]. This ecosystem includes archaea, bacteria, fungi, protozoa, and viruses[151]. Bacteria dominate the microbiome, including at least 1,000 distinct species and 7,000 strains[152,153]. Anaerobic bacteria, mainly *Firmicutes* and *Bacteroidetes*, comprise approximately 70-75% of this community[154,155], along with smaller concentrations of *Actinobacteria, Fusobacteria*, *Proteobacteria*, and *Verrucomicrobia*[156].

Beneficial Bacteria: Bacterial genera frequently exploited as probiotics include *Bifidobacterium* and *Lactobacillus*. Prebiotics such as galactooligosaccharides and fructooligosaccharides support the growth of intrinsic *Bifidobacterium* and *Lactobacillus*. Unlike pathogenic genera (e.g., *Salmonella*), the cell walls of harmless bacteria do not possess pro-inflammatory lipopolysaccharide coatings. Therefore, their propagation in the gut does not trigger full-fledged immunological reactions. These bacteria train the immune system to distinguish to between pro- and anti-inflammatory entities and develop appropriate immunogenic responses[157].

Origin and Development: Microbiome composition is age-sensitive, and humans show marked differences in microbial profiles during infancy, adolescence, adulthood, and ageing[158]. These changes correspond closely to changes in health status, medication use, diet[159] and potentially even the occurrence of early life trauma[160]. Mounting evidence suggests that some maternal microbial transmission also occurs during foetal development, which was previously considered a strictly germ-free process[161]. Colonisation of the infant gut accelerates during parturition, which carries a maternal imprint shaped by mode of delivery. Vaginal delivery predicts infant gut bacteria compositions resembling the mother's faecal and vaginal microbiota, while caesarean delivery predicts gut microbial profiles corresponding more closely to the mother's skin[162]. Maternal stress also exerts bacteria-driven neurodevelopmental changes in the offspring, via changes in the mother's vaginal microbiome[164,165].

The infant microbiome receives continuous environmental input, and resembles adult-level complexity and richness within the first three years[156,159]. Major disruptions to the microbiome trigger lasting changes to the composition of gut bacterial communities and the central nervous system. In rodents, for example, antibiotic treatment during foetal development and infancy shifts microbial profiles, increases cytokine expression in the brain and impairs

normal behaviour[165], induces visceral hypersensitivity in adulthood[166], and alters metabolism[167]. In humans, early evidence indicates that antibiotic ingestion in the first year of life is correlated with signs of depression[168].

Box 2: Microbial Influences on the Nervous System and Neurometabolite Production

Germ-free studies in rodents reveal widespread microbial contributions to the development and function of the host's nervous system[169]. These include microbial effects on central glial development[170], development of the enteric nervous system that controls the entire gastrointestinal tract[171], and normal development of the brain[26]. Recent efforts have also identified microbial contributions to adult hippocampal **neurogenesis**[172]. The microbiome even appears to be critical for the normal development of the blood-brain barrier[173]. Furthermore, gut microbes contribute causally to the production of a substantial proportion of potentially neuroactive molecules, including serotonin[174,175] and oxytocin[98,176], which exert well-documented psychological effects.

The microbiome is also an important site for the production of short-chain fatty acids

(SCFAs, or fatty acids possessing two to six carbon atoms, produced from the fermentation of dietary fibres). These include acetate, butyrate, lactate, and propionate which are generated via bacterial fermentation of otherwise indigestible fibres such as plant polysaccharides[177,178]. These SCFAs enter systemic circulation and have been shown to regulate the activity of the sympathetic nervous system[179]. The interactions between the microbiome, SCFAs, and the brain, and the behaviour arising from these interactions, has generated much interest in areas such as appetite control and nutrient intake[177]. There is also particular interest in the role of SCFAs in models of psychiatric illness. For example, butyrate has been implicated in depression and anxiety[180,181], and there is evidence of antidepressant effects of systemic sodium butyrate administered to rodents[182].

It is now necessary to gather data on two fronts. First, the generation of neuroactive compounds does not necessarily mean that those compounds always become involved in regulating neurotransmission[116], and further direct evidence of such interactions is necessary. Second, closely related to this issue, it is unclear at present how bacterially-derived neurometabolites and SCFAs influence the brain and subsequent behaviour. We have speculated that they are likely to modulate activity in the proximal neurons of the enteric nervous system, which would alter its communication with the brain[59].

Box 3: Bacteria-Gut-Brain Communication Pathways

Immunological and Cytokine Activity: The brain and immune system communicate bidirectionally[183]. Bacteria can both enhance or inhibit the secretion of pro- and anti-inflammatory cytokines. Intrinsic beneficial bacteria can stimulate the release of anti-inflammatory cytokines, while others trigger pro-inflammatory cytokine expression. Probiotics and prebiotics can also physically bind to pattern-recognition receptors, inhibiting the release of pro-inflammatory cytokines and enhancing the expression of anti-inflammatory cytokines[184,185].

Central Lymphatic Vessels: It has recently been discovered that the central nervous system is drained by a network of lymphatic vessels which communicate bidirectionally with the brain[135]. It is therefore possible that immune molecules such as cytokines may interact

more directly with central nervous tissue than previously appreciated. Bacterial modulation of immunological activity may affect the entry of inflammatory mediators into the central nervous system.

Vagal Connections: The vagus is the tenth cranial nerve, coordinating a range of parasympathetic activities, including cardiac function, gut motility, and respiration. The majority of nerve fibres are sensory, enabling the brain to monitor the state of all vagally innervated organs. Vagal stimulation exerts potent anti-inflammatory effects[186], and is applied in treating depression and anxiety. Psychopharmacological molecules also alter vagal activity[187]. The vagus nerve is able to distinguish between pathogenic and beneficial bacteria in the gut[188], and responds rapidly to the exogenous introduction of beneficial bacteria[189]. The specific mechanism through which this interaction occurs requires elucidation. Severing the vagus nerve (vagotomy) has been shown to abolishes psychobiotic effects, providing evidence of vagal mediation of the probiotic-brain relationship[190]. However, vagotomy has also failed to attenuate bacteria-brain communication in some cases[31], implying that non-vagal communication mechanisms also operate.

Tryptophan-Kynurenine Metabolism: The balance between the processing of tryptophan into its metabolites kynurenine and serotonin is considered to play an important role in bacteria-brain signalling[191]. The bulk of the body's systemic tryptophan is metabolised into kynurenine, a reaction regulated by the enzymes tryptophan dioxygenase and indoleamine 2,3-dioxygenase[192]. The action of these enzymes can be triggered by increases in pro-inflammatory cytokines and corticosteroids[192]. Elevated kynurenine generation is associated with depression and reduced neuroprotection[193]. Gut bacteria intervene in the metabolism of tryptophan into kynurenine, and can both increase or decrease kynurenine biosynthesis, depending on which bacteria are involved. Both prebiotics and probiotics have been shown to reduce kynurenine levels[46,47]. The mechanistic component underlying bacterial effects on

kynurenine levels may be an inhibition of the enzymes that contribute to its biosynthesis[194].

Box 4: The Microbiome, Diet, and Ingestive Behaviour

Plasticity: The microbiome quickly and efficiently adapts to the host's diet, accompanied by changes in metabolism. In humans, for example, microbiota composition is associated both with long-term diet[195] and with short-term dietary changes[196]. Indeed, microbial composition changes as early as the day after a dietary change[195,197]. Long-term nutritional patterns, such as high-sugar, high-fat Western diets, can also result in gut bacterial extinctions in mice[198].

Ingestive Behaviour and Obesity: The microbiome influences host appetite[199], including the generation of gut-based satiety hormones such as glucagon-like peptide 1 (GLP-1) and peptide tyrosine tyrosine (PYY)[200]. In humans, prebiotic supplementation enhances plasma concentrations of short-chain fatty acids arising from microbial fermentation of dietary

fibres can also induce satiety and regulate energy intake[201].

Disruptions to these processes are well-illustrated by obesity. A key behavioural feature of obesity is excessive energy intake. In humans and mice, obesity is associated with abnormal bacterial compositions[202]. Obese mice have an enhanced, bacteria-dependent capacity for extracting energy from nutrition, and transferring the microbiota from obese to lean mice increases body fat in the recipients, suggesting causal contributions of gut bacteria to obesity[3].

Probiotics can reduce diet-induced obesity and inflammation[5]. Recent efforts have uncovered a microbiome-brain-pancreas signalling mechanism mediated by the SCFA acetate[177]. Microbiota-induced increases in acetate alter parasympathetic activity, which stimulates the production of insulin and ghrelin, in turn affecting both metabolism and appetite.

Culture and Geography: Humans inhabit diverse geographies associated with lifestyle and dietary variation, which are in turn associated with gut microbial variation. Initial evidence of geographical differences in microbiota composition arose from comparisons between children from America, Venezuela, and Malawi[203]. Geographical differences in microbial composition specifically attributable to dietary differences have been noted between European and African children[204]. Cultural and diet-based differences in bacterial composition reflect adaptations to specific environmental demands, and may lead to metabolic, immunological, and endocrine variation. The psychological consequences of these differences, if any, remain to be explored.

Box 5: Cases of Extraordinary Microbial Control of Mammalian Behaviour

It is unlikely that microbial contributions to host behaviour are uniform throughout the animal kingdom. Rather, we speculate that the "net" role of gut bacteria in psychological processes may covary negatively with brain size and complexity of the host. Animals with more complex brains, such as mammals, exhibit a wide repertoire of behaviours, each of which may or may not be susceptible to microbial influence. Although microbes affect some mammalian behaviours, such as the rodent behaviours described in this article, these influences are most likely less pronounced than those of the symbionts of less complex hosts. For example, some pathogenic fungi can gain total control of the motility of their insect hosts, such as ants infected by *Ophiocordyceps unilateralis.* Infected ants will leave the colony and fix themselves to locations ideal for the growth of the fungus, and will remain there until death, while the

fungus uses the corpse to develop and disperse its spores[205].

Such strong microbial control in mammalian hosts is unlikely. Microbial signals are expected to join the general stream of interoceptive information that the brain receives from the periphery[12]. However, there are several examples of mammalian microbes that have profound and multi-faceted behavioural effects on their hosts.

One well-known case is the intracellular parasite *Toxoplasma gondii,* which manipulates the behaviour of its intermediate host, the rat, to enhance rates of transmission to its primary host, the cat. Infection with this parasite abolishes the rat's innate fear of cats, and may even lead to sexual attraction toward cats[206,207]. *Toxoplasma gondii* abolishes the mouse fear of cat urine, an effect that, intriguingly, persists beyond parasite clearance[208]. Another widely known example is the rabies virus. Rabies triggers acute inflammation in the brain, and precipitates a suite of abnormal behaviours such as extreme aggression and hydrophobia in a diversity of placental mammals, including humans, non-human primates, and dogs.

Overall, therefore, while microbial control of mammalian behaviour is in general relatively subtle, there are cases in which this control can be extraordinarily strong and wide-ranging. Though fatal for the host, the microbe-induced behavioural modifications enhance the probability of transmission to new hosts. In the case of *Toxoplasma gondii* (warping perceptions of predation-risk) and rabies (hydrophobia), these behavioural effects are powerful enough to even override evolutionary survival instincts.

Box 6: Inconsistent Results in Human Research on Psychobiotic Treatment of Anxiety and Depression

While psychobiotic effects on human emotional experience seem broadly in line with psychobiotic effects in rodents, it is also important to note null effects. For instance, some human studies suggest promising mood-based benefits or reductions in cortisol[62], whilst others do not[61,91].

Two recent randomised controlled trials investigating the effect of psychobiotics on major depressive disorder have yielded discrepant results. Both studies administered similar psychobiotics over an eight-week period. One study found significant positive psychobiotic effects on self-reported indicators of depression[209]. The second study[148], which utilised a

larger sample, found no effect of psychobiotic ingestion on any psychological outcome measure and no improvement in depressive symptoms. However, the psychobiotic effect appeared to be moderated by baseline vitamin D levels, which affects immune function[210]. Participants with higher vitamin D experienced greater improvements in mood compared to those with lower vitamin D. This suggests that vitamin D (and therefore other diet-derived organic compounds) could moderate the effects of psychobiotics in humans.

Systematic quantitative reviews examining psychiatric benefits of psychobiotic ingestion in humans in experimental settings have also yielded inconsistent conclusions. One systematic review found no evidence that probiotic consumption produced antidepressant effects[211], while two later quantitative reviews did find consistent evidence of probiotic-induced alleviations of depression[212,213]. A recent quantitative review has also found a positive probiotic effect on depression, pointing toward reductions in inflammation (primarily a reduction in pro-inflammatory cytokines) and an increase in serotonin as the likely physiological mechanisms underlying these improvements[214].

Two observational studies have also yielded mixed evidence. One study found that consumption of probiotic-containing fermented foods predicted lower social anxiety in individuals with high trait neuroticism[215]. Another investigation of a national dataset examined probiotic consumption over time found lower odds of depression amongst individuals reporting greater probiotic consumption, but the effect was attenuated with the introduction of other relevant factors, suggesting, in this case, no unique role for probiotic consumption[216]. Furthermore, the quality, viability, and efficacy of many commercially available probiotics has been questioned[217], warranting further research in this area.

These inconsistencies should not dampen translational efforts toward psychobiotic development. Rather, they highlight the need for mechanistic elucidation, greater statistical power, and consideration of moderators. If effectively developed, and after side-effects and

long-term effects are either understood or ruled out, psychobiotics may serve as valuable adjuvants alongside traditional antidepressants and anxiolytics[59]. Psychobiotics may also serve as a post-treatment intervention following cessation of antidepressants or anxiolytics.

Box 7: Toward Successful Animal-Human Translations

The majority of the experimental research in this area has been performed on rodents. Studies on nonhuman primates and humans, are limited. Aside from the inevitable ethical issues associated with human intervention studies, several crucial factors hinder effective rodent-to-human translation. For example, certain mouse strains on which psychobiotics have proved beneficial are considered innately anxious, and psychotropic benefits may have been a function of baseline differences. This pertains to the larger and ever-present issue of noise in human research. Variance is much lower in genetically identical rodents, in a controlled environment, receiving indistinguishable diets, and displaying congruent behavioural deficits. Baseline differences in biological and cognitive profiles of human participants, which are likely to influence study outcomes, are extremely difficult to control.

This is not to say, however, that it is impossible to control for environmental, dietary, and psychological profiles in humans, and there are some crude ways of doing so. Increasing sample size is the most obvious form of decreasing the effects of individual differences. Researchers might also consider testing individuals from the same (small) communities who arguably share comparable environments and perhaps diets (e.g., a particular neighbourhood or school). Perhaps the best designs are placebo controlled cross-over studies, which allow within-subjects analysis, thereby providing a substantial boost to statistical power.

Another important issue that affects translation concerns dose. Many probiotic experiments in mice have used 1×10^9 bacteria[190], a dose that is also used in humans[90]. In terms of the actual number of ingested bacteria per unit of body weight, there is an enormous difference. It may be that animal studies are misleading because the doses are very high, or that human studies fail to show consistent effects because the dose is very low. Researchers must consider whether larger doses are safe and feasible in humans.

A further important issue, of course, relates to causality in the microbiome-disease relationship. Prospective cohort studies could track microbial composition in large groups before the manifestation of a neurocognitive condition. For psychosis and Alzheimer's disease, there may be individuals with prodromal symptoms (or other "at risk" individuals) whose gut microbiota can be monitored. If microbial communities across prodromal individuals are similar, but not all individuals go on to develop the condition, then the involvement of the microbiome on the pathophysiology of the condition can be refuted. However, if prodromal individuals displayed differential microbial profiles before they manifest a disorder, compared with those who do not develop a condition, then it is likelier that microbial communities do influence the onset of brain dysfunction.

Finally, there are substantial differences between rodent and human brains, without estimates of which effects are species-specific. Primate-based investigations will enhance

clarity here. There are already a few some promising experimental findings from monkeys[218-220]. Primate research is much more resource-intensive and logistically challenging than rodent models (especially germ-free studies), but the insights derived are more likely to be translatable to humans than rodent models.

Glossary

Adult Neurogenesis: The biological phenomenon of new neurons emerging in the adult brain. For much of the history of neuroscience, neurogenesis was believed to occur exclusively in very early development. However, significant recent evidence points toward the birth of new neurons in mammalian brains, including rodents and primates. Evidence of adult neurogenesis in humans is less conclusive.

Brain-derived Neurotrophic Factor: A nerve growth protein that is involved in the survival of neurons. The expression of this protein has been associated with enhanced learning and memory.

Cafeteria Diet: Similar to but distinct from the typical high-fat rodent diet. The cafeteria diet is dense in energy and more closely resembles unhealthy human energy intake. It is characterised by elements such as high concentrations of fat, salt, and sugar, and low levels of fibre content.

Commensal microorganisms: The intrinsic microbes (mostly bacteria) that reside in the host. These microbes inhabit not only the gut (the largest such community) but are distributed across the host. Indeed, there are commensal microbial communities associated with the skin, the oral cavity, the nasal passage, the lungs, and the vagina.

Cytokines: Soluble proteins that regulate inflammation and lymphocyte responses.

Dendritic hypertrophy: Enlargement of a neuron’s dendrites.

Early-immediate genes: Genes that respond rapidly to alterations in the cellular environment,

prior to protein synthesis.

Germ-free: An artificially induced biological state in which an organism (e.g., mouse, rat, zebrafish) is born and reared in a strictly sterile environment. The animal therefore cannot be colonised by any microbes. Because all known multicellular organisms have always been colonised by microbes throughout evolutionary history, the germ-free state is useful for observing how host physiology and behaviour differ in their absence.

Gut-brain Axis: The multidirectional biological system comprising the gastrointestinal tract, the enteric nervous system, and the brain. The interactions between these systems contribute to the organism's health and homeostasis by regulating functions such as digestion, metabolism, and immunity.

Hypothalamic-pituitary-adrenal axis: The biological system governing the endocrine reaction to stress. One of its key roles is the regulation of the glucocorticoid response. Glucocorticoids such as cortisol (in humans) and corticosterone (in rodents) serve to metabolise sugars, and play an important role in preparing the organism for uncertainty. HPA-axis dysregulation is associated with depression and anxiety.

Inclusive fitness: The survival and reproductive success of an individual and its kin, with each relative contributing in proportion to its relatedness to the individual (e.g., siblings contribute twice the amount that cousins contribute).

Inflammation: Local or systemic immune system reaction, which restores normal physiological functioning after tissue injury. Typically includes accumulation of leukocytes at the site of damage, vascular dilation, and increased leakage of proteins and fluid into the tissue. Chronic low-grade inflammation refers to a continuous secretion of low levels of inflammatory substances such as cytokines, without actual physical damage, and is observed in coronary heart disease, type 2 diabetes, and depression.

Maternal immune activation: Triggering a pro-inflammatory response in a pregnant rodent

via exposure to compounds such as polyinosinic:polycytidylic acid, which mimics viral infection. The enhanced inflammatory environment of the mother increases the probability that the offspring will display phenotypes of autism or other neurodevelopmental disorders.

Microbiota: The collection of microbes inhabiting a particular site (e.g., the gut). "Microbiota" is frequently used interchangeably with "microbiome", though the latter refers formally to the totality of the microbial genes at a particular site.

Mutualism: In broad terms, mutually beneficial, cooperative interactions between species.

Neurodevelopmental Windows: Instances in an organism's developmental trajectory that are characterised by sensitivity and plasticity of particular systems. These are critical periods of rapid development during which developmental milestones are reached. These may be biological (e.g., brain development during infancy) or psychological (e.g., core language learning in humans occurs during childhood, which is a critical period for the development of linguistic competence). The extent of the relevant development is either slower or non-existent outside of these windows.

Oxytocin Immunoreactive Neurons: Oxytocin-containing neurons that are visualized through the binding of a specific antibody raised against the neuropeptide

Probiotics: Beneficial bacteria, such as *lactobacilli* and *bifidobacteria* that are exogenously added to the gut microbiome via ingestion.

Prebiotics: Organic compounds, often fibres, that act as nutrients for commensal bacteria. They are fermented by the gut bacteria.

Psychobiotics: The subset of prebiotics and probiotics that exert psychological effects. We have argued that researchers should consider expanding the "psychobiotic" label to include other substances that may exert psychological effects via the microbiome (e.g., antibiotics, antidepressants, antipsychotics).

Figure Legend

Figure 1: Bacteria-Brain-Behaviour Relationships – Gut bacteria communicate with the brain through various channels (see also Boxes 2 and 3). The vagus nerve enables bidirectional communication between the gut and the brain. Bacteria produce neurotransmitters as metabolites, and these are likely able to regulate activity in the proximal neurons of the enteric nervous system. Bacteria also produce short-chain fatty acids (SCFAs) via fermentation of non-digestible dietary fibres. SCFAs can modulate neural activity in the host directly, but they also stimulate the release of gut hormones such as glucagon-like peptide 1 (GLP-1) and peptide tyrosine tyrosine (PYY), which control host appetite and satiety. Beneficial bacteria can also trigger the release of anti-inflammatory cytokines, which decrease systemic inflammation. However, pathogenic bacteria migrating out of the gut (through a weakened gut barrier) trigger pro-inflammatory cytokine release. Higher levels of inflammation are correlated with depression, and "leaky gut" is associated with both conditions. Furthermore, experiencing stress – and the attendant glucocorticoid response – can also weaken the gut barrier, potentially worsening the inflammatory pathophysiology of emotional disorders. Diet and the use of drugs and antibiotics also directly modulate composition of the gut bacteria, which in turn alter the

physiological signal generated by the bacteria. Overall, these bacterially-generated signals modulate the central nervous system, and affect emotion, cognition, and behaviour.

Tables

Table 1: Research Designs to Investigate Bacteria-Brain-Behaviour Relationships

Format	Method	Comparison Group	Applicable to Humans?	Strengths	Limitations
Germ-Free Studies	Model animals, typically rodents, which are raised in sterile environments and cannot become hosts to microorganisms.	Normally colonised control animals free of any pathogenic microorganisms (i.e., specific pathogen free animals).	No	Enables causal statements about the necessity of gut bacteria for specific psychological and physiological processes.	Absence of the gut microbiota in germ-free studies is assumed to be the major cause of differences observed in subjects. However, the method cannot be used to identify the effects of absence of any specific bacteria, or body site-specific bacterial communities, only the microbiota as a whole. Logistically challenging. Human-relevant inferences must be made with caution.

Antibiotic Administration Studies	Administration of antibiotics to either alter gut bacteria composition or deplete the gut bacteria over time.	Control animals exposed to a neutral vehicle substance/ placebo.	No, in general. Under certain conditions an antibiotic regime may be in progress for bacterial infection and limited data collection may be possible. Some single-dose or short-term studies may also be possible.	Different antibiotics have different psychological and physiological effects, enabling more accurate descriptions of how antibiotic molecules interact with commensal bacteria. More logistically straightforward than germ-free studies.	Total ablation into a complete and permanent germ-free state may not be possible. Less informative than germ-free research about influence of bacteria on neurodevelopmental processes, because antibiotics are typically administered after those processes are already underway. Not all antibiotic effects occur via bacterial depletion. Some antibiotic molecules interact directly with host tissue to alter physiological and psychological processes[86].
Recolonisation and Microbiota Transplant Studies	Transfer of complete microbial content (e.g., via faecal transplant) from one organism (the donor) into another (the recipient), and examination of	Control animals (or humans) that do not receive microbial transplants.	Yes, for therapeutic purposes or clinical research.	Enables causal statements about the role of gut bacteria in the physiological and behavioural phenotypes of specific psychiatric conditions.	No information on which bacteria or which molecules cause changes in recipient physiology or behaviour.

	subsequent physiological or psychological changes in the recipient, which typically resemble those of the donor.			Transplants can be carried out between species (i.e., humans to mice).	
Psychobiotic Studies	Ingestion of prebiotics (organic substances, such as fructans, that support the growth of commensal bacteria) or probiotics (live bacteria). Ingestion of prebiotics and probiotics occurs over several weeks rather than a single dose. Other potential psychobiotics include antibiotics, antipsychotics, antidepressants and anxiolytics and other exogenous modulators of gut bacteria.	Control animals (or humans) exposed to either a neutral vehicle substance/placebo, other psychobiotics, or other drugs.	Yes	Enables some causal inferences about the contributions of particular bacteria to psychological and physiological processes. Viable for investigation as adjunct therapies alongside mainstream antidepressants and anxiolytics. High naturalistic appeal in humans may facilitate participant recruitment Logistically straightforward. Investigating animal-human translation is more straightforward	Limited or no information on dose-response functions, effect longevity, side-effects, time-course, and potential moderators (e.g., diet, genotype, sex). It should not be assumed that the effects following exogenous addition of bacteria to the gut microbiota necessarily mean that the intrinsic counterparts of those bacteria function in the same way[116].

				than other techniques.	

Acknowledgements
The authors thank Arjun Dutta, Andrea Tracy, Kathrin Cohen Kadosh, and Paul Warchuk for valuable feedback on earlier drafts of this manuscript. The authors also extend their gratitude to the four anonymous reviewers who served as the referees of this manuscript, and whose feedback has significantly improved this review. The editor Dr. Lindsey Drayton and the former editor Dr. Rebecca Schwarzlose have both provided extensive guidance, advice, and insight throughout the preparation of this manuscript, and their input has greatly enhanced the clarity and focus of this manuscript. AS, SH, SML, AHM, and RIMD declare no competing biomedical interests, financial or otherwise. JFC and TGD conduct research at the APC Microbiome Institute (University College Cork, Ireland), which is supported by Science Foundation Ireland (SFI). Relevant findings covered in this review have originated from research enabled by Science Foundation Ireland (SFI/12/RC/2273). JFC and TGD were also supported by the Health Research Board through Health Research Awards (including HRA_POR/2011/23; HRA_POR/2012/32, HRAPOR-2-14-647) and through EU grant 613979 (MYNEWGUT FP7-KBBE-2013-7). JFC and TGD are conducting research in collaboration with Mead Johnson, Alimentary Health, DuPont, Nutricia, 4D-Pharma, Cremo & Suntory Wellness. PWJB is in receipt of research funds from the Biotechnology, Biological Sciences Research Council (BBSRC), UK, [BB/N010035/1], and Clasado BioSciences Ltd, UK.

References

1. Podolsky, S. H. (2012). Metchnikoff and the microbiome. *The Lancet, 380*, 1810-1811.
2. Le Chatelier, E., Nielsen, T., Qin, J., Prifti, E., Hildebrand, F., Falony, G., ... & Leonard, P. (2013). Richness of human gut microbiome correlates with metabolic markers. *Nature, 500*, 541-546.
3. Turnbaugh, P. J., Ley, R. E., Mahowald, M. A., Magrini, V., Mardis, E. R., & Gordon, J. I. (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature, 444*, 1027-131.
4. Hooper, L. V., Littman, D. R., & Macpherson, A. J. (2012). Interactions between the microbiota and the immune system. *Science, 336*, 1268-1273.
5. Poutahidis, T., Kleinewietfeld, M., Smillie, C., Levkovich, T., Perrotta, A., Bhela, S., ... & Chatzigiagkos, A. (2013). Microbial reprogramming inhibits Western diet-associated obesity. *PloS One, 8*, e68596.
6. Marques, F. Z., Mackay, C. R., & Kaye, D. M. (2018). Beyond gut feelings: how the gut microbiota regulates blood pressure. *Nature Reviews Cardiology, 15*, 20.
7. Erdman, S. E. (2016). Gut microbiota: Microbes offer engineering strategies to combat cancer. *Nature Reviews Gastroenterology and Hepatology, 13*, 125.
8. Mayer, E. A., Knight, R., Mazmanian, S. K., Cryan, J. F., & Tillisch, K. (2014). Gut microbes and the brain: Paradigm shift in neuroscience. *Journal of Neuroscience, 34*, 15490-15496.
9. Vuong, H. E., Yano, J. M., Fung, T. C., & Hsiao, E. Y. (2017). The microbiome and host behavior. *Annual review of neuroscience, 40*, 21-49.
10. McFall-Ngai, M., Hadfield, M. G., Bosch, T. C., Carey, H. V., Domazet-Lošo, T., Douglas, A. E., ... & Hentschel, U. (2013). Animals in a bacterial world, a new imperative for the life sciences. *Proceedings of the National Academy of Sciences, 110*, 3229-3236.
11. Moeller, A. H., Caro-Quintero, A., Mjungu, D., Georgiev, A. V., Lonsdorf, E. V., Muller, M. N., ... & Ochman, H. (2016). Cospeciation of gut microbiota with hominids. *Science, 353*, 380-382.
12. Allen, A. P., Dinan, T. G., Clarke, G., & Cryan, J. F. (2017). A psychology of the human

brain–gut–microbiome axis. *Social and personality psychology compass*, *11*.
13. Stilling, R. M., Bordenstein, S. R., Dinan, T. G., & Cryan, J. F. (2014). Friends with social benefits: host-microbe interactions as a driver of brain evolution and development?. Frontiers in Cellular and Infection Microbiology, 4.
14. Foster, J. A., & Neufeld, K. A. M. (2013). Gut–brain axis: how the microbiome influences anxiety and depression. *Trends in Neurosciences*, *36*, 305-312.
15. Sudo, N., Chida, Y., Aiba, Y., Sonoda, J., Oyama, N., Yu, X. N., ... & Koga, Y. (2004). Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. *The Journal of Physiology*, *558*, 263-275.
16. Yamada, K., Mizuno, M., & Nabeshima, T. (2002). Role for brain-derived neurotrophic factor in learning and memory. *Life Sciences*, *70*, 735-744.
17. Borre, Y. E., O'Keeffe, G. W., Clarke, G., Stanton, C., Dinan, T. G., & Cryan, J. F. (2014). Microbiota and neurodevelopmental windows: implications for brain disorders. *Trends in Molecular Medicine*, *20*, 509-518.
18. Crumeyrolle-Arias, M., Jaglin, M., Bruneau, A., Vancassel, S., Cardona, A., Daugé, V., ... & Rabot, S. (2014). Absence of the gut microbiota enhances anxiety-like behavior and neuroendocrine response to acute stress in rats. *Psychoneuroendocrinology*, *42*, 207-217.
19. Desbonnet, L., Clarke, G., Traplin, A., O'Sullivan, O., Crispie, F., Moloney, R. D., ... & Cryan, J. F. (2015). Gut microbiota depletion from early adolescence in mice: Implications for brain and behaviour. *Brain, Behavior, and Immunity*, *48*, 165-173.
20. Neufeld, K. M., Kang, N., Bienenstock, J., & Foster, J. A. (2011). Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterology & Motility*, *23*, 255.
21. Neufeld, K. M., Kang, N., Bienenstock, J., & Foster, J. A. (2011). Effects of intestinal microbiota on anxiety-like behavior. *Communicative & Integrative Biology*, *4*, 492-494.
22. Carobrez, A. P., & Bertoglio, L. J. (2005). Ethological and temporal analyses of anxiety-like behavior: The elevated plus-maze model 20 years on. *Neuroscience & Biobehavioral Reviews*, *29*, 1193-1205.
23. Walf, A. A., & Frye, C. A. (2007). The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. *Nature Protocols*, *2*, 322-328.
24. Campos, A. C., Rocha, N. P., Nicoli, J. R., Vieira, L. Q., Teixeira, M. M., & Teixeira, A. L. (2016). Absence of gut microbiota influences lipopolysaccharide-induced behavioral changes in mice. *Behavioural Brain Research*, *312*, 186-194.
25. Clarke, G., Grenham, S., Scully, P., Fitzgerald, P., Moloney, R. D., Shanahan, F., ... & Cryan, J. F. (2013). The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Molecular Psychiatry*, *18*, 666-673.
26. Heijtz, R. D., Wang, S., Anuar, F., Qian, Y., Björkholm, B., Samuelsson, A., ... & Pettersson, S. (2011). Normal gut microbiota modulates brain development and behavior. *Proceedings of the National Academy of Sciences*, *108*, 3047-3052.
27. Zheng, P., Zeng, B., Zhou, C., Liu, M., Fang, Z., Xu, X., ... & Zhang, X. (2016). Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. *Molecular Psychiatry*, *21*, 786-796.
28. Hoban, A. E., Stilling, R. M., Moloney, G., Shanahan, F., Dinan, T. G., Clarke, G., & Cryan, J. F. (2017). The microbiome regulates amygdala-dependent fear recall. *Molecular Psychiatry*.
29. Phelps, E. A., & LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron*, *48*, 175-187.

30. Arentsen, T., Raith, H., Qian, Y., Forssberg, H., & Heijtz, R. D. (2015). Host microbiota modulates development of social preference in mice. *Microbial Ecology in health and Disease*, *26*, 29719.
31. Bercik, P., Denou, E., Collins, J., Jackson, W., Lu, J., Jury, J., ... & Verdu, E. F. (2011). The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. *Gastroenterology*, *141*, 599-609.
32. Stilling, R. M., Ryan, F. J., Hoban, A. E., Shanahan, F., Clarke, G., Claesson, M. J., ... & Cryan, J. F. (2015). Microbes & neurodevelopment–Absence of microbiota during early life increases activity-related transcriptional pathways in the amygdala. *Brain, Behavior, and Immunity*, *50*, 209-220.
33. Luczynski, P., Whelan, S. O., O'sullivan, C., Clarke, G., Shanahan, F., Dinan, T. G., & Cryan, J. F. (2016). Adult microbiota-deficient mice have distinct dendritic morphological changes: differential effects in the amygdala and hippocampus. *European Journal of Neuroscience*, *44*, 2654-2666.
34. Cammarota, G., Ianiro, G., & Gasbarrini, A. (2014). Fecal microbiota transplantation for the treatment of Clostridium difficile infection: a systematic review. *Journal of Clinical Gastroenterology*, *48*, 693-702.
35. Collins, S. M., Kassam, Z., & Bercik, P. (2013). The adoptive transfer of behavioral phenotype via the intestinal microbiota: experimental evidence and clinical implications. *Current Opinion in Microbiology*, *16*, 240-245.
36. Smits, L. P., Bouter, K. E., de Vos, W. M., Borody, T. J., & Nieuwdorp, M. (2013). Therapeutic potential of fecal microbiota transplantation. *Gastroenterology*, *145*, 946-953.
37. Kelly, J. R., Borre, Y., O'Brien, C., Patterson, E., El Aidy, S., Deane, J., ... & Hoban, A. E. (2016). Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. *Journal of Psychiatric Research*, *82*, 109-118.
38. Turner, M. D., Nedjai, B., Hurst, T., & Pennington, D. J. (2014). Cytokines and chemokines: at the crossroads of cell signalling and inflammatory disease. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, *1843*, 2563-2582.
39. Scheller, J., Chalaris, A., Schmidt-Arras, D., & Rose-John, S. (2011). The pro-and anti-inflammatory properties of the cytokine interleukin-6. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, *1813*, 878-888.
40. Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry*, *67*, 446-457.
41. Maier, S. F., & Watkins, L. R. (1998). Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychological Review*, *105*, 83-107.
42. Eisenberger, N. I., Moieni, M., Inagaki, T. K., Muscatell, K. A., & Irwin, M. R. (2017). In sickness and in health: the co-regulation of inflammation and social behavior. *Neuropsychopharmacology*, *42*(1), 242.
43. Kelly, J. R., Kennedy, P. J., Cryan, J. F., Dinan, T. G., Clarke, G., & Hyland, N. P. (2015). Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Frontiers in Cellular Neuroscience*, *9*, 392.
44. Mass, M., Kubera, M., & Leunis, J. C. (2008). The gut-brain barrier in major depression: Intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. *Neuroendocrinology Letters*, *29*, 117-124.
45. Slyepchenko, A., Maes, M., Jacka, F. N., Köhler, C. A., Barichello, T., McIntyre, R. S., ... & Carvalho, A. F. (2017). Gut microbiota, bacterial translocation, and interactions

with diet: Pathophysiological links between major depressive disorder and non-communicable medical comorbidities. *Psychotherapy and Psychosomatics*, *86*, 31-46.

46. Burokas, A., Arboleya, S., Moloney, R. D., Peterson, V. L., Murphy, K., Clarke, G., ... & Cryan, J. F. (2017). Targeting the microbiota-gut-brain axis: Prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. *Biological Psychiatry*.
47. Desbonnet, L., Garrett, L., Clarke, G., Bienenstock, J., & Dinan, T. G. (2008). The probiotic *Bifidobacteria infantis*: An assessment of potential antidepressant properties in the rat. *Journal of Psychiatric Research, 43*, 164-174.
48. Desbonnet, L., Garrett, L., Clarke, G., Kiely, B., Cryan, J. F., & Dinan, T. G. (2010). Effects of the probiotic *Bifidobacterium infantis* in the maternal separation model of depression. *Neuroscience*, *170*, 1179-1188.
49. Hsiao, E. Y., McBride, S. W., Hsien, S., Sharon, G., Hyde, E. R., McCue, T., ... & Patterson, P. H. (2013). Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell*, *155*, 1451-1463.
50. Jia, S., Lu, Z., Gao, Z., An, J., Wu, X., Li, X., ... & Sun, Y. (2016). Chitosan oligosaccharides alleviate cognitive deficits in an amyloid-β 1–42-induced rat model of Alzheimer's disease. *International Journal of Biological Macromolecules*, *83*, 416-425.
51. Luo, J., Wang, T., Liang, S., Hu, X., Li, W., & Jin, F. (2014). Ingestion of *Lactobacillus* strain reduces anxiety and improves cognitive function in the hyperammonemia rat. *Science China. Life sciences*, *57*, 327-335.
52. Rodrigues, D. M., Sousa, A. J., Johnson-Henry, K. C., Sherman, P. M., & Gareau, M. G. (2012). Probiotics are effective for the prevention and treatment of Citrobacter rodentium–induced colitis in mice. *The Journal of Infectious Diseases*, *206*, 99-109.
53. Savignac, H. M., Couch, Y., Stratford, M., Bannerman, D. M., Tzortzis, G., Anthony, D. C., & Burnet, P. W. (2016). Prebiotic administration normalizes lipopolysaccharide (LPS)-induced anxiety and cortical 5-HT2A receptor and IL1-β levels in male mice. *Brain, Behavior, and Immunity*, *52*, 120-131.
54. O'Mahony, L., McCarthy, J., Kelly, P., Hurley, G., Luo, F., Chen, K., ... & Quigley, E. M. (2005). Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*, *128*, 541-551.
55. Pessi, T., Sütas, Y., Hurme, M., & Isolauri, E. (2000). Interleukin-10 generation in atopic children following oral *Lactobacillus rhamnosus* GG. *Clinical & Experimental Allergy*, *30*, 1804-1808.
56. Ait-Belgnaoui, A., Durand, H., Cartier, C., Chaumaz, G., Eutamene, H., Ferrier, L., ... & Theodorou, V. (2012). Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology*, *37*, 1885-1895.
57. Zareie, M., Johnson-Henry, K., Jury, J., Yang, P. C., Ngan, B. Y., McKay, D. M., ... & Sherman, P. M. (2006). Probiotics prevent bacterial translocation and improve intestinal barrier function in rats following chronic psychological stress. *Gut*, *55*, 1553-1560.
58. Bercik, P., Verdu, E. F., Foster, J. A., Macri, J., Potter, M., Huang, X., ... & Lu, J. (2010). Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice. *Gastroenterology*, *139*, 2102-2112.
59. Sarkar, A., Lehto, S. M., Harty, S., Dinan, T. G., Cryan, J. F., & Burnet, P. W. (2016). Psychobiotics and the manipulation of bacteria–gut–brain signals. *Trends in Neurosciences*, *39*, 763-781.
60. Allen, A. P., Hutch, W., Borre, Y. E., Kennedy, P. J., Temko, A., Boylan, G., ... &

Clarke, G. (2016). *Bifidobacterium longum* 1714 as a translational psychobiotic: Modulation of stress, electrophysiology and neurocognition in healthy volunteers. *Translational Psychiatry*, *6*, e939.

61. Benton, D., Williams, C., & Brown, A. (2007). Impact of consuming a milk drink containing a probiotic on mood and cognition. *European Journal of Clinical Nutrition*, *61*, 355-361.
62. Messaoudi, M., Lalonde, R., Violle, N., Javelot, H., Desor, D., Nejdi, A., ... & Cazaubiel, J. M. (2011). Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R0052 *and Bifidobacterium longum* R0175) in rats and human subjects. *British Journal of Nutrition*, *105*, 755-764.
63. Messaoudi, M., Violle, N., Bisson, J. F., Desor, D., Javelot, H., & Rougeot, C. (2011). Beneficial psychological effects of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in healthy human volunteers. *Gut Microbes*, *2*, 256-261.
64. Kato-Kataoka, A., Nishida, K., Takada, M., Kawai, M., Kikuchi-Hayakawa, H., Suda, K., ... & Kushiro, A. (2016). Fermented milk containing *Lactobacillus casei* strain *Shirota* preserves the diversity of the gut microbiota and relieves abdominal dysfunction in healthy medical students exposed to academic stress. *Applied and Environmental Microbiology*, *82*, 3649-3658.
65. Sashihara, T., Nagata, M., Mori, T., Ikegami, S., Gotoh, M., Okubo, K., ... & Itoh, H. (2013). Effects of *Lactobacillus gasseri* OLL2809 and α-lactalbumin on university-student athletes: A randomized, double-blind, placebo-controlled clinical trial. *Applied Physiology, Nutrition, and Metabolism*, *38*, 1228-1235.
66. Steenbergen, L., Sellaro, R., van Hemert, S., Bosch, J. A., & Colzato, L. S. (2015). A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. *Brain, Behavior, and Immunity*, *48*, 258-264.
67. Tillisch, K., Labus, J., Kilpatrick, L., Jiang, Z., Stains, J., Ebrat, B., ... & Mayer, E. A. (2013). Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology*, *144*, 1394-1401.
68. Schmidt, K., Cowen, P. J., Harmer, C. J., Tzortzis, G., Errington, S., & Burnet, P. W. (2015). Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. *Psychopharmacology*, *232*, 1793-1801.
69. Beck, A. T. (Ed.). (1979). *Cognitive therapy of depression*. Guilford press.
70. Bhagwagar, Z., Hafizi, S., & Cowen, P. J. (2005). Increased salivary cortisol after waking in depression. *Psychopharmacology*, *182*, 54-57.
71. Ironside, M., O'Shea, J., Cowen, P. J., & Harmer, C. J. (2016). Frontal cortex and stimulation reduces vigilance to threat: implications for the treatment of depression anxiety. *Biological Psychiatry*, *79*, 823-830.
72. Sarris, J., Logan, A. C., Akbaraly, T. N., Amminger, G. P., Balanzá-Martínez, V., Freeman, M. P., ... & Nanri, A. (2015). Nutritional medicine as mainstream in psychiatry. *The Lancet Psychiatry*, *2*, 271-274.
73. Dash, S., Clarke, G., Berk, M., & Jacka, F. N. (2015). The gut microbiome and diet in psychiatry: Focus on depression. *Current Opinion in Psychiatry*, *28*, 1-6.
74. Gareau, M. G., Wine, E., Rodrigues, D. M., Cho, J. H., Whary, M. T., Philpott, D. J., ... & Sherman, P. M. (2010). Bacterial infection causes stress-induced memory dysfunction in mice. *Gut*, *60*, 307-317.
75. Wang, T., Hu, X., Liang, S., Li, W., Wu, X., Wang, L., & Jin, F. (2015). *Lactobacillus fermentum* NS9 restores the antibiotic induced physiological and psychological abnormalities in rats. *Beneficial Microbes*, *6*, 707-717.
76. Vázquez, E., Barranco, A., Ramírez, M., Gruart, A., Delgado-García, J. M., Martínez-

Lara, E., ... & Prieto, P. (2015). Effects of a human milk oligosaccharide, 2′-fucosyllactose, on hippocampal long-term potentiation and learning capabilities in rodents. *The Journal of Nutritional Biochemistry, 26*, 455-465.

77. Oliveros, E., Ramirez, M., Vazquez, E., Barranco, A., Gruart, A., Delgado-Garcia, J. M., ... & Martin, M. J. (2016). Oral supplementation of 2′-fucosyllactose during lactation improves memory and learning in rats. *The Journal of Nutritional Biochemistry*, *31*, 20-27.
78. Savignac, H. M., Tramullas, M., Kiely, B., Dinan, T. G., & Cryan, J. F. (2015). *Bifidobacteria* modulate cognitive processes in an anxious mouse strain. *Behavioural Brain Research*, *287*, 59-72.
79. Ohland, C. L., Kish, L., Bell, H., Thiesen, A., Hotte, N., Pankiv, E., & Madsen, K. L. (2013). Effects of Lactobacillus helveticus on murine behavior are dependent on diet and genotype and correlate with alterations in the gut microbiome. *Psychoneuroendocrinology*, *38*, 1738-1747.
80. Gronier, B., Savignac, H. M., Di Miceli, M., Idriss, S. M., Tzortzis, G., Anthony, D., & Burnet, P. W. (2017). Increased cortical neuronal responses to NMDA and improved attentional set-shifting performance in rats following prebiotic (B-GOS®) ingestion. *European Neuropsychopharmacology*.
81. Savignac, H. M., Corona, G., Mills, H., Chen, L., Spencer, J. P., Tzortzis, G., & Burnet, P. W. (2013). Prebiotic feeding elevates central brain derived neurotrophic factor, N-methyl-d-aspartate receptor subunits and d-serine. *Neurochemistry International, 63*, 756-764.
82. O'Keefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Research, 34*, 171-175.
83. Williams, S., Chen, L., Savignac, H. M., Tzortzis, G., Anthony, D. C., & Burnet, P. W. (2016). Neonatal prebiotic (BGOS) supplementation increases the levels of synaptophysin, GluN2A-subunits and BDNF proteins in the adult rat hippocampus. *Synapse, 70*, 121-124.
84. Fröhlich, E. E., Farzi, A., Mayerhofer, R., Reichmann, F., Jačan, A., Wagner, B., ... & Kashofer, K. (2016). Cognitive impairment by antibiotic-induced gut dysbiosis: analysis of gut microbiota-brain communication. *Brain, Behavior, and Immunity, 56*, 140-155.
85. Beilharz, J. E., Kaakoush, N. O., Maniam, J., & Morris, M. J. (2017). Cafeteria diet and probiotic therapy: cross talk among memory, neuroplasticity, serotonin receptors and gut microbiota in the rat. *Molecular psychiatry*.
86. Yolken, R. H., Jones-Brando, L., Dunigan, D. D., Kannan, G., Dickerson, F., Severance, E., ... & Agarkova, I. V. (2014). Chlorovirus ATCV-1 is part of the human oropharyngeal virome and is associated with changes in cognitive functions in humans and mice. *Proceedings of the National Academy of Sciences*, *111*(45), 16106-16111.
87. Fernandez-Real, J. M., Serino, M., Blasco, G., Puig, J., Daunis-i-Estadella, J., Ricart, W., ... & Portero-Otin, M. (2015). Gut microbiota interacts with brain microstructure and function. *The Journal of Clinical Endocrinology & Metabolism, 100*, 4505-4513.
88. Tombaugh, T. N. (2004). Trail Making Test A and B: normative data stratified by age and education. *Archives of Clinical Neuropsychology*, *19*, 203-214.
89. Carlson, A. L., Xia, K., Azcarate-Peril, M. A., Goldman, B. D., Ahn, M., Styner, M. A., ... & Knickmeyer, R. C. (2017). Infant gut microbiome associated with cognitive development. *Biological Psychiatry*.
90. Chung, Y. C., Jin, H. M., Cui, Y., Kim, D. S., Jung, J. M., Park, J. I., ... & Chae, S. W. (2014). Fermented milk of Lactobacillus helveticus IDCC3801 improves cognitive functioning during cognitive fatigue tests in healthy older adults. *Journal of Functional*

Foods, *10*, 465-474
91. Kelly, J. R., Allen, A. P., Temko, A., Hutch, W., Kennedy, P. J., Farid, N., ... & Clarke, G. (2017). Lost in translation? The potential psychobiotic Lactobacillus rhamnosus (JB-1) fails to modulate stress or cognitive performance in healthy male subjects. *Brain, Behavior, and Immunity*, *61*, 50-59.
92. Dominique, J. F., Roozendaal, B., & McGaugh, J. L. (1998). Stress and glucocorticoids impair retrieval of long-term spatial memory. *Nature*, *394*, 787-790.
93. Donzis, E. J., & Tronson, N. C. (2014). Modulation of learning and memory by cytokines: Signaling mechanisms and long term consequences. *Neurobiology of Learning and Memory*, *115*, 68-77.
94. Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*, 434-445.
95. Degroote, S., Hunting, D. J., Baccarelli, A. A., & Takser, L. (2016). Maternal gut and fetal brain connection: Increased anxiety and reduced social interactions in Wistar rat offspring following peri-conceptional antibiotic exposure. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *71*, 76-82.
96. Gacias, M., Gaspari, S., Santos, P. M. G., Tamburini, S., Andrade, M., Zhang, F., ... & Zachariou, V. (2016). Microbiota-driven transcriptional changes in prefrontal cortex override genetic differences in social behavior. *Elife*, *5*.
97. Desbonnet, L., Clarke, G., Shanahan, F., Dinan, T. G., & Cryan, J. F. (2014). Microbiota is essential for social development in the mouse. *Molecular Psychiatry*, *19*, 146-148.
98. Buffington, S. A., Di Prisco, G. V., Auchtung, T. A., Ajami, N. J., Petrosino, J. F., & Costa-Mattioli, M. (2016). Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. *Cell*, *165*, 1762-1775.
99. Hosokawa, T., Kikuchi, Y., Shimada, M., & Fukatsu, T. (2008). Symbiont acquisition alters behaviour of stinkbug nymphs. *Biology Letters*, *4*, 45-48.
100. Baron-Cohen, S., & Belmonte, M. K. (2005). Autism: a window onto the development of the social and the analytic brain. *Annual Review Neuroscience, 28*, 109-126.
101. Happé, F., Ronald, A., & Plomin, R. (2006). Time to give up on a single explanation for autism. *Nature Neuroscience*, *9*, 1218-1220.
102. Adams, J. B., Johansen, L. J., Powell, L. D., Quig, D., & Rubin, R. A. (2011). Gastrointestinal flora and gastrointestinal status in children with autism–comparisons to typical children and correlation with autism severity. *BMC gastroenterology*, *11*, 22.
103. Ashwood, P., Wills, S., & Van de Water, J. (2006). The immune response in autism: A new frontier for autism research. *Journal of Leukocyte Biology*, *80*, 1-15.
104. Ashwood, P., Krakowiak, P., Hertz-Picciotto, I., Hansen, R., Pessah, I., & Van de Water, J. (2011). Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. *Brain, Behavior, and Immunity*, *25*, 40-45.
105. Finegold, S. M., Molitoris, D., Song, Y., Liu, C., Vaisanen, M. L., Bolte, E., ... & Collins, M. D. (2002). Gastrointestinal microflora studies in late-onset autism. *Clinical Infectious Diseases*, *35*.
106. Li, X., Chauhan, A., Sheikh, A. M., Patil, S., Chauhan, V., Li, X. M., ... & Malik, M. (2009). Elevated immune response in the brain of autistic patients. *Journal of Neuroimmunology*, *207*, 111-116.
107. Gorrindo, P., Williams, K. C., Lee, E. B., Walker, L. S., McGrew, S. G., & Levitt, P. (2012). Gastrointestinal dysfunction in autism: Parental report, clinical

evaluation, and associated factors. *Autism Research*, *5*, 101-108.

108. Vuong, H. E., & Hsiao, E. Y. (2017). Emerging roles for the gut microbiome in autism spectrum disorder. *Biological Psychiatry*, *81*, 411-423.

109. Coretti, L., Cristiano, C., Florio, E., Scala, G., Lama, A., Keller, S., ... & Raso, G. M. (2017). Sex-related alterations of gut microbiota composition in the BTBR mouse model of autism spectrum disorder. *Scientific Reports*, *7*.

110. de Theije, C. G., Wopereis, H., Ramadan, M., van Eijndthoven, T., Lambert, J., Knol, J., ... & Oozeer, R. (2014). Altered gut microbiota and activity in a murine model of autism spectrum disorders. *Brain, Behavior, and Immunity*, *37*, 197-206.

111. Finegold, S. M., Dowd, S. E., Gontcharova, V., Liu, C., Henley, K. E., Wolcott, R. D., ... & Liu, M. (2010). Pyrosequencing study of fecal microflora of autistic and control children. *Anaerobe*, *16*(4), 444-453.

112. Parracho, H. M., Bingham, M. O., Gibson, G. R., & McCartney, A. L. (2005). Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. *Journal of Medical Microbiology*, *54*, 987-991.

113. Song, Y., Liu, C., & Finegold, S. M. (2004). Real-time PCR quantitation of clostridia in feces of autistic children. *Applied and Environmental Microbiology*, *70*, 6459-6465.

114. Wang, L., Christophersen, C. T., Sorich, M. J., Gerber, J. P., Angley, M. T., & Conlon, M. A. (2013). Increased abundance of *Sutterella* spp. and *Ruminococcus torques* in feces of children with autism spectrum disorder. *Molecular Autism*, *4*, 42.

115. Williams, B. L., Hornig, M., Buie, T., Bauman, M. L., Paik, M. C., Wick, I., ... & Lipkin, W. I. (2011). Impaired carbohydrate digestion and transport and mucosal dysbiosis in the intestines of children with autism and gastrointestinal disturbances. *PloS One*, *6*, e24585.

116. Forsythe, P., Kunze, W., & Bienenstock, J. (2016). Moody microbes or fecal phrenology: What do we know about the microbiota-gut-brain axis?. *BMC Medicine*, *14*, 58.

117. Kang, D. W., Park, J. G., Ilhan, Z. E., Wallstrom, G., LaBaer, J., Adams, J. B., & Krajmalnik-Brown, R. (2013). Reduced incidence of Prevotella and other fermenters in intestinal microflora of autistic children. *PloS One*, *8*, e68322.

118. Son, J. S., Zheng, L. J., Rowehl, L. M., Tian, X., Zhang, Y., Zhu, W., ... & Ir, D. (2015). Comparison of fecal microbiota in children with autism spectrum disorders and neurotypical siblings in the Simons simplex collection. *PLoS One*, *10*, e0137725.

119. Parracho, H. M., Gibson, G. R., Knott, F., Bosscher, D., Kleerebezem, M., & McCartney, A. L. (2010). A double-blind, placebo-controlled, crossover-designed probiotic feeding study in children diagnosed with autistic spectrum disorders. *International Journal of Probiotics & Prebiotics*, *5*, 69-74.

120. Krajmalnik-Brown, R., Lozupone, C., Kang, D. W., & Adams, J. B. (2015). Gut bacteria in children with autism spectrum disorders: challenges and promise of studying how a complex community influences a complex disease. *Microbial Ecology in Health and Disease*, *26*, 26914.

121. Sandler, R. H., Finegold, S. M., Bolte, E. R., Buchanan, C. P., Maxwell, A. P., Väisänen, M. L., ... & Wexler, H. M. (2000). Short-term benefit from oral vancomycin treatment of regressive-onset autism. *Journal of Child Neurology*, *15*, 429-435.

122. Kang, D. W., Adams, J. B., Gregory, A. C., Borody, T., Chittick, L., Fasano, A., ... & Pollard, E. L. (2017). Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. *Microbiome*, *5*, 10.

123. Baron-Cohen, S., Auyeung, B., Nørgaard-Pedersen, B., Hougaard, D. M., Abdallah, M. W., Melgaard, L., ... & Lombardo, M. V. (2015). Elevated fetal steroidogenic activity in autism. *Molecular Psychiatry*, *20*, 369.
124. Hanage, W. P. (2014). Microbiome science needs a healthy dose of scepticism: to guard against hype, those interpreting research on the body's microscopic communities should ask five questions. *Nature*, *512*, 247-249.
125. Lin, P., Ding, B., Feng, C., Yin, S., Zhang, T., Qi, X., ... & Li, Q. (2017). *Prevotella* and *Klebsiella* proportions in fecal microbial communities are potential characteristic parameters for patients with major depressive disorder. *Journal of affective Disorders*, *207*, 300-304.
126. Jiang, H., Ling, Z., Zhang, Y., Mao, H., Ma, Z., Yin, Y., ... & Li, L. (2015). Altered fecal microbiota composition in patients with major depressive disorder. *Brain, Behavior, and Immunity*, *48*, 186-194.
127. Naseribafrouei, A., Hestad, K., Avershina, E., Sekelja, M., Linløkken, A., Wilson, R., & Rudi, K. (2014). Correlation between the human fecal microbiota and depression. *Neurogastroenterology & Motility*, *26*, 1155-1162.
128. Kim, H. N., Yun, Y., Ryu, S., Chang, Y., Kwon, M. J., Cho, J., ... & Kim, H. L. (2017). Correlation between gut microbiota and personality in adults: a cross-sectional study. *Brain, Behavior, and Immunity*.
129. Kleiman, S. C., Bulik-Sullivan, E. C., Glenny, E. M., Zerwas, S. C., Huh, E. Y., Tsilimigras, M. C., ... & Carroll, I. M. (2017). The gut-brain axis in healthy females: Lack of significant association between microbial composition and diversity with psychiatric measures. *PloS one*, *12*, e0170208.
130. Rogers, G. B., Keating, D. J., Young, R. L., Wong, M. L., Licinio, J., & Wesselingh, S. (2016). From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Molecular psychiatry*, *21*(6), 738.
131. Meninger, K. A. (1926). Influenza and schizophrenia. An analysis of post-influenza “dementia praecox” as of 1918 and five years later. *Am J Psychiatry*, *5*, 469-529.
132. Sutterland, A. L., Fond, G., Kuin, A., Koeter, M. W. J., Lutter, R., Gool, T., ... & Haan, L. (2015). Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, *132*, 161-179.
133. Yolken, R., Torrey, E. F., & Dickerson, F. (2017). Evidence of increased exposure to Toxoplasma gondii in individuals with recent onset psychosis but not with established schizophrenia. *PLoS neglected tropical diseases*, *11*, e0006040.
134. Khandaker, G. M., Cousins, L., Deakin, J., Lennox, B. R., Yolken, R., & Jones, P. B. (2015). Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. *The Lancet Psychiatry*, *2*, 258-270.
135. Louveau, A., Smirnov, I., Keyes, T. J., Eccles, J. D., Rouhani, S. J., Peske, J. D., ... & Harris, T. H. (2015). Structural and functional features of central nervous system lymphatic vessels. *Nature*, *523*, 337-341.
136. Schwarz, E., Maukonen, J., Hyytiäinen, T., Kieseppä, T., Orešič, M., Sabunciyan, S., ... & Suvisaari, J. (2017). Analysis of microbiota in first episode psychosis identifies preliminary associations with symptom severity and treatment response. *Schizophrenia Research*.
137. Harper, S. (2014). Economic and social implications of aging societies. *Science*, *346*, 587-591.
138. Claesson, M. J., Jeffery, I. B., Conde, S., Power, S. E., O’Connor, E. M., Cusack, S., ... & Fitzgerald, G. F. (2012). Gut microbiota composition correlates with

diet and health in the elderly. *Nature*, *488*, 178-184.
139. Distrutti, E., O'Reilly, J. A., McDonald, C., Cipriani, S., Renga, B., Lynch, M. A., & Fiorucci, S. (2014). Modulation of intestinal microbiota by the probiotic VSL# 3 resets brain gene expression and ameliorates the age-related deficit in LTP. *PloS One*, *9*, e106503.
140. Varian, B. J., Goureshetti, S., Poutahidis, T., Lakritz, J. R., Levkovich, T., Kwok, C., ... & Erdman, S. E. (2016). Beneficial bacteria inhibit cachexia. *Oncotarget*, *7*(11), 11803.
141. Hill, J. M., Clement, C., Pogue, A. I., Bhattacharjee, S., Zhao, Y., & Lukiw, W. J. (2014). Pathogenic microbes, the microbiome, and Alzheimer's disease (AD). *Frontiers in Aging Neuroscience*, *6*.303.
142. Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science*, *297*, 353-356.
143. Cattaneo, A., Cattane, N., Galluzzi, S., Provasi, S., Lopizzo, N., Festari, C., ... & Bianchetti, A. (2017). Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiology of Aging*, *49*, 60-68.
144. Tombaugh, T. N., & McIntyre, N. J. (1992). The mini-mental state examination: A comprehensive review. *Journal of the American Geriatrics Society*, *40*, 922-935.
145. Harty, S., O'Connell, R. G., Hester, R., & Robertson, I. H. (2013). Older adults have diminished awareness of errors in the laboratory and daily life. *Psychology and Aging*, *28*, 1032-1041.
146. Gazzaley, A., Cooney, J. W., Rissman, J., & D'esposito, M. (2005). Top-down suppression deficit underlies working memory impairment in normal aging. *Nature Neuroscience*, *8*, 1298-1300.
147. Anguera, J. A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., Janowich, J., ... & Gazzaley, A. (2013). Video game training enhances cognitive control in older adults. *Nature*, *501*, 97-101.
148. Romijn, A. R., Rucklidge, J. J., Kuijer, R. G., & Frampton, C. (2017). A double-blind, randomized, placebo-controlled trial of Lactobacillus helveticus and Bifidobacterium longum for the symptoms of depression. *Australian & New Zealand Journal of Psychiatry*.
149. Hamady, M., & Knight, R. (2009). Microbial community profiling for human microbiome projects: Tools, techniques, and challenges. *Genome Research*, *19*, 1141-1152.
150. Sender, R., Fuchs, S., & Milo, R. (2016). Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. *Cell*, *164*, 337-340.
151. Dinan, T. G., Stanton, C., & Cryan, J. F. (2013). Psychobiotics: A novel class of psychotropic. *Biological Psychiatry*, *74*, 720-726.
152. de Vos, W. M., & de Vos, E. A. (2012). Role of the intestinal microbiome in health and disease: From correlation to causation. *Nutrition Reviews*, *70*, S45-S56.
153. Lozupone, C. A., Stombaugh, J. I., Gordon, J. I., Jansson, J. K., & Knight, R. (2012). Diversity, stability and resilience of the human gut microbiota. *Nature*, *489*, 220-230.
154. Eckburg, P. B., Bik, E. M., Bernstein, C. N., Purdom, E., Dethlefsen, L., Sargent, M., ... & Relman, D. A. (2005). Diversity of the human intestinal microbial flora. *Science*, *308*, 1635-1638.
155. Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K. S., Manichanh, C., ... & Mende, D.R. (2010). A human gut microbial gene catalogue established by metagenomics sequencing. *Nature*, *464*, 59-65.

156. Grenham, S., Clarke, G., Cryan, J. F., & Dinan, T. G. (2011). Brain–gut–microbe communication in health and disease. *Frontiers in Physiology*, *2*.
157. Sansonetti, P. J., & Medzhitov, R. (2009). Learning tolerance while fighting ignorance. *Cell*, *138*, 416-420.
158. Kundu, P., Blacher, E., Elinav, E., & Pettersson, S. (2017). Our Gut Microbiome: The Evolving Inner Self. *Cell*, *171*(7), 1481-1493.
159. Koenig, J. E., Spor, A., Scalfone, N., Fricker, A. D., Stombaugh, J., Knight, R., ... & Ley, R. E. (2011). Succession of microbial consortia in the developing infant gut microbiome. *Proceedings of the National Academy of Sciences*, *108*, 4578-4585.
160. Labus, J. S., Hollister, E. B., Jacobs, J., Kirbach, K., Oezguen, N., Gupta, A., ... & Savidge, T. (2017). Differences in gut microbial composition correlate with regional brain volumes in irritable bowel syndrome. *Microbiome*, *5*.
161. Funkhouser, L. J., & Bordenstein, S. R. (2013). Mom knows best: the universality of maternal microbial transmission. *PLoS Biology*, *11*, e1001631.
162. Dominguez-Bello, M. G., Costello, E. K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., & Knight, R. (2010). Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proceedings of the National Academy of Sciences*, *107*, 11971-11975.
163. Jašarević, E., Howerton, C. L., Howard, C. D., & Bale, T. L. (2015). Alterations in the vaginal microbiome by maternal stress are associated with metabolic reprogramming of the offspring gut and brain. *Endocrinology*, *156*, 3265-3276.
164. Jašarević, E., Howard, C. D., Misic, A. M., Beiting, D. P., & Bale, T. L. (2017). Stress during pregnancy alters temporal and spatial dynamics of the maternal and offspring microbiome in a sex-specific manner. *Scientific Reports*, *7*, 44182.
165. Leclercq, S., Mian, F. M., Stanisz, A. M., Bindels, L. B., Cambier, E., Ben-Amram, H., ... & Bienenstock, J. (2017). Low-dose penicillin in early life induces long-term changes in murine gut microbiota, brain cytokines and behavior. *Nature Communications*, *8*.
166. O'Mahony, S. M., Felice, V. D., Nally, K., Savignac, H. M., Claesson, M. J., Scully, P., ... & Marchesi, J. R. (2014). Disturbance of the gut microbiota in early-life selectively affects visceral pain in adulthood without impacting cognitive or anxiety-related behaviors in male rats. *Neuroscience*, *277*, 885-901.
167. Cho, I., Yamanishi, S., Cox, L., Methé, B. A., Zavadil, J., Li, K., ... & Li, H. (2012). Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature*, *488*, 621-626.
168. Slykerman, R. F., Thompson, J., Waldie, K. E., Murphy, R., Wall, C., & Mitchell, E. A. (2017). Antibiotics in the first year of life and subsequent neurocognitive outcomes. *Acta Paediatrica*, *106*, 87-94.
169. Sharon, G., Sampson, T. R., Geschwind, D. H., & Mazmanian, S. K. (2016). The central nervous system and the gut microbiome. *Cell*, *167*, 915-932.
170. Erny, D., de Angelis, A. L. H., Jaitin, D., Wieghofer, P., Staszewski, O., David, E., ... & Schwierzeck, V. (2015). Host microbiota constantly control maturation and function of microglia in the CNS. *Nature Neuroscience*, *18*, 965-977.
171. Kunze, W. A., Mao, Y. K., Wang, B., Huizinga, J. D., Ma, X., Forsythe, P., & Bienenstock, J. (2009). Lactobacillus reuteri enhances excitability of colonic AH neurons by inhibiting calcium-dependent potassium channel opening. *Journal of Cellular and Molecular Medicine*, *13*, 2261-2270.
172. Ogbonnaya, E. S., Clarke, G., Shanahan, F., Dinan, T. G., Cryan, J. F., & O'Leary, O. F. (2015). Adult hippocampal neurogenesis is regulated by the microbiome. *Biological Psychiatry*, *78*, e7-e9.

173. Braniste, V., Al-Asmakh, M., Kowal, C., Anuar, F., Abbaspour, A., Tóth, M., ... & Gulyás, B. (2014). The gut microbiota influences blood-brain barrier permeability in mice. *Science Translational Medicine*, *6*, 263ra158.
174. Wikoff, W. R., Anfora, A. T., Liu, J., Schultz, P. G., Lesley, S. A., Peters, E. C., & Siuzdak, G. (2009). Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proceedings of the National Academy of Sciences*, *106*, 3698-3703.
175. Yano, J. M., Yu, K., Donaldson, G. P., Shastri, G. G., Ann, P., Ma, L., ... & Hsiao, E. Y. (2015). Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell*, *161*, 264-276.
176. Varian, B. J., Poutahidis, T., DiBenedictis, B. T., Levkovich, T., Ibrahim, Y., Didyk, E., ... & Kolandaivelu, K. (2017). Microbial lysate upregulates host oxytocin. *Brain, Behavior, and Immunity*, *61*, 36-49.
177. Perry, R. J., Peng, L., Barry, N. A., Cline, G. W., Zhang, D., Cardone, R. L., ... & Shulman, G. I. (2016). Acetate mediates a microbiome–brain–β-cell axis to promote metabolic syndrome. *Nature*, *534*, 213-217.
178. Puertollano, E., Kolida, S., & Yaqoob, P. (2014). Biological significance of short-chain fatty acid metabolism by the intestinal microbiome. *Current Opinion in Clinical Nutrition & Metabolic Care*, *17*, 139-144.
179. Kimura, I., Inoue, D., Maeda, T., Hara, T., Ichimura, A., Miyauchi, S., ... & Tsujimoto, G. (2011). Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *Proceedings of the National Academy of Sciences*, *108*, 8030-8035.
180. Gundersen, B. B., & Blendy, J. A. (2009). Effects of the histone deacetylase inhibitor sodium butyrate in models of depression and anxiety. *Neuropharmacology*, *57*, 67-74.
181. Resende, W. R., Valvassori, S. S., Reus, G. Z., Varela, R. B., Arent, C. O., Ribeiro, K. F., ... & Quevedo, J. (2013). Effects of sodium butyrate in animal models of mania and depression: Implications as a new mood stabilizer. *Behavioural Pharmacology*, *24*, 569-579.
182. Schroeder, F. A., Lin, C. L., Crusio, W. E., & Akbarian, S. (2007). Antidepressant-like effects of the histone deacetylase inhibitor, sodium butyrate, in the mouse. *Biological Psychiatry*, *62*, 55-64.
183. Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience*, *9*, 46-56.
184. Eiwegger, T., Stahl, B., Haidl, P., Schmitt, J., Boehm, G., Dehlink, E., ... & Szépfalusi, Z. (2010). Prebiotic oligosaccharides: In vitro evidence for gastrointestinal epithelial transfer and immunomodulatory properties. *Pediatric Allergy and Immunology*, *21*, 1179-1188.
185. Zhou, W., Lv, H., Li, M. X., Su, H., Huang, L. G., Li, J., & Yuan, W. M. (2015). Protective effects of bifidobacteria on intestines in newborn rats with necrotizing enterocolitis and its regulation on TLR2 and TLR4. *Genetics and Molecular Research*, *14*, 11505-14.
186. Borovikova, L. V., Ivanova, S., Zhang, M., Yang, H., Botchkina, G. I., Watkins, L. R., ... & Tracey, K. J. (2000). Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*, *405*, 458-462.
187. Smith, R., Allen, J. J., Thayer, J. F., Fort, C., & Lane, R. D. (2014). Increased association over time between regional frontal lobe BOLD change magnitude and cardiac vagal control with sertraline treatment for major depression. *Psychiatry*

Research: Neuroimaging, *224*, 225-233.

188. Perez-Burgos, A., Mao, Y. K., Bienenstock, J., & Kunze, W. A. (2014). The gut-brain axis rewired: Adding a functional vagal nicotinic "sensory synapse". *The FASEB Journal*, *28*, 3064-3074.

189. Perez-Burgos, A., Wang, B., Mao, Y. K., Mistry, B., Neufeld, K. A. M., Bienenstock, J., & Kunze, W. (2013). Psychoactive bacteria Lactobacillus rhamnosus (JB-1) elicits rapid frequency facilitation in vagal afferents. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *304*, G211-G220.

190. Bravo, J. A., Forsythe, P., Chew, M. V., Escaravage, E., Savignac, H. M., Dinan, T. G., ...& Cryan, J. F. (2011). Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceedings of the National Academy of Sciences*, *108*, 16050-16055.

191. O'Mahony, S. M., Clarke, G., Borre, Y. E., Dinan, T. G., & Cryan, J. F. (2015). Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behavioural Brain Research*, *277*, 32-48.

192. Ruddick, J. P., Evans, A. K., Nutt, D. J., Lightman, S. L., Rook, G. A., & Lowry, C. A. (2006). Tryptophan metabolism in the central nervous system: Medical implications. *Expert Reviews in Molecular Medicine*, *8*, 1-27.

193. Myint, A. M., Kim, Y. K., Verkerk, R., Scharpé, S., Steinbusch, H., & Leonard, B. (2007). Kynurenine pathway in major depression: Evidence of impaired neuroprotection. *Journal of Affective Disorders*, *98*, 143-151.

194. Valladares, R., Bojilova, L., Potts, A. H., Cameron, E., Gardner, C., Lorca, G., & Gonzalez, C. F. (2013). *Lactobacillus johnsonii* inhibits indoleamine 2, 3-dioxygenase and alters tryptophan metabolite levels in BioBreeding rats. *The FASEB Journal*, *27*, 1711-1720.

195. Wu, G. D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y. Y., Keilbaugh, S. A., ... & Sinha, R. (2011). Linking long-term dietary patterns with gut microbial enterotypes. *Science*, *334*, 105-108.

196. David, L. A., Maurice, C. F., Carmody, R. N., Gootenberg, D. B., Button, J. E., Wolfe, B. E., ... & Biddinger, S. B. (2014). Diet rapidly and reproducibly alters the human gut microbiome. *Nature*, *505*, 559-563.

197. David, L. A., Materna, A. C., Friedman, J., Campos-Baptista, M. I., Blackburn, M. C., Perrotta, A., ... & Alm, E. J. (2014). Host lifestyle affects human microbiota on daily timescales. *Genome Biology*, *15*, R89.

198. Sonnenburg, E. D., Smits, S. A., Tikhonov, M., Higginbottom, S. K., Wingreen, N. S., & Sonnenburg, J. L. (2016). Diet-induced extinctions in the gut microbiota compound over generations. *Nature*, *529*, 212-215.

199. Fetissov, S. O. (2017). Role of the gut microbiota in host appetite control: Bacterial growth to animal feeding behaviour. *Nature Reviews Endocrinology*, *13*, 11-25.

200. Cani, P. D., Lecourt, E., Dewulf, E. M., Sohet, F. M., Pachikian, B. D., Naslain, D., ... & Delzenne, N. M. (2009). Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. *The American Journal of Clinical Nutrition*, *90*, 1236-1243.

201. Frost, G., Sleeth, M. L., Sahuri-Arisoylu, M., Lizarbe, B., Cerdan, S., Brody, L., ... & Carling, D. (2014). The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. *Nature Communications*, *5*.

202. Ley, R. E., Turnbaugh, P. J., Klein, S., & Gordon, J. I. (2006). Microbial ecology: Human gut microbes associated with obesity. *Nature*, *444*, 1022-1023.

203. Yatsunenko, T., Rey, F. E., Manary, M. J., Trehan, I., Dominguez-Bello, M. G., Contreras, M., ... & Heath, A. C. (2012). Human gut microbiome viewed across age and geography. *Nature*, *486*, 222-227.
204. De Filippo, C., Cavalieri, D., Di Paola, M., Ramazzotti, M., Poullet, J. B., Massart, S., ... & Lionetti, P. (2010). Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proceedings of the National Academy of Sciences*, *107*, 14691-14696.
205. Mongkolsamrit, S., Kobmoo, N., Tasanathai, K., Khonsanit, A., Noisripoom, W., Srikitikulchai, P., ... & Luangsa-ard, J. J. (2012). Life cycle, host range and temporal variation of Ophiocordyceps unilateralis/Hirsutella formicarum on Formicine ants. *Journal of Invertebrate Pathology*, *111*, 217-224.
206. Berdoy, M., Webster, J. P., & Macdonald, D. W. (2000). Fatal attraction in rats infected with Toxoplasma gondii. *Proceedings of the Royal Society of London B: Biological Sciences*, *267*(1452), 1591-1594.
207. House, P. K., Vyas, A., & Sapolsky, R. (2011). Predator cat odors activate sexual arousal pathways in brains of Toxoplasma gondii infected rats. *PloS One*, *6*, e23277.
208. Ingram, W. M., Goodrich, L. M., Robey, E. A., & Eisen, M. B. (2013). Mice infected with low-virulence strains of Toxoplasma gondii lose their innate aversion to cat urine, even after extensive parasite clearance. *PloS One*, *8*, e75246.
209. Akkasheh, G., Kashani-Poor, Z., Tajabadi-Ebrahimi, M., Jafari, P., Akbari, H., Taghizadeh, M., ... & Esmaillzadeh, A. (2016). Clinical and metabolic response to probiotic administration in patients with major depressive disorder: a randomized, double-blind, placebo-controlled trial. *Nutrition*, *32*, 315-320.
210. Kamen, D. L., & Tangpricha, V. (2010). Vitamin D and molecular actions on the immune system: Modulation of innate and autoimmunity. *Journal of Molecular Medicine*, *88*, 441-450.
211. Romijn, A. R., & Rucklidge, J. J. (2015). Systematic review of evidence to support the theory of psychobiotics. *Nutrition Reviews*, *73*, 675-693.
212. Huang, R., Wang, K., & Hu, J. (2016). Effect of probiotics on depression: A systematic review and meta-analysis of randomized controlled trials. *Nutrients*, *8*, 483.
213. Pirbaglou, M., Katz, J., de Souza, R. J., Stearns, J. C., Motamed, M., & Ritvo, P. (2016). Probiotic supplementation can positively affect anxiety and depressive symptoms: A systematic review of randomized controlled trials. *Nutrition Research*, *36*, 889-898.
214. Wallace, C. J., & Milev, R. (2017). The effects of probiotics on depressive symptoms in humans: A systematic review. *Annals of General Psychiatry*, *16*, 14.
215. Hilimire, M. R., DeVylder, J. E., & Forestell, C. A. (2015). Fermented foods, neuroticism, and social anxiety: An interaction model. *Psychiatry Research*, *228*, 203-208.
216. Cepeda, M. S., Katz, E. G., & Blacketer, C. (2016). Microbiome-gut-brain axis: probiotics and their association with depression. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *29*, 39-44.
217. Fredua-Agyeman, M., & Gaisford, S. (2014). Comparative survival of commercial probiotic formulations: tests in biorelevant gastric fluids and real-time measurements using microcalorimetry. *Beneficial Microbes*, *6*, 141-151.
218. Bailey, M. T., & Coe, C. L. (1999). Maternal separation disrupts the integrity of the intestinal microflora in infant rhesus monkeys. *Developmental Psychobiology*, *35*, 146-155.
219. Bailey, M. T., Lubach, G. R., & Coe, C. L. (2004). Prenatal stress alters bacterial

colonization of the gut in infant monkeys. *Journal of pediatric gastroenterology and nutrition*, *38*, 414-421.

220. Ma, J., Prince, A. L., Bader, D., Hu, M., Ganu, R., Baquero, K., ... & Aagaard, K. M. (2014). High-fat maternal diet during pregnancy persistently alters the offspring microbiome in a primate model. *Nature Communications*, *5*, 3889.

221. Pisa, D., Alonso, R., Rábano, A., Rodal, I., & Carrasco, L. (2015). Different brain regions are infected with fungi in Alzheimer's disease. *Scientific Reports*, *5*, 15015.

222. Carter, C. J. (2008). Schizophrenia susceptibility genes directly implicated in the life cycles of pathogens: cytomegalovirus, influenza, herpes simplex, rubella, and Toxoplasma gondii. *Schizophrenia Bulletin*, *35*, 1163-1182.

223. Kramer, P., & Bressan, P. (2015). Humans as superorganisms: How microbes, viruses, imprinted genes, and other selfish entities shape our behavior. *Perspectives on Psychological Science*, *10*, 464-481.

224. Hallmayer, J., Cleveland, S., Torres, A., Phillips, J., Cohen, B., Torigoe, T., ... & Lotspeich, L. (2011). Genetic heritability and shared environmental factors among twin pairs with autism. *Archives of General Psychiatry*, *68*, 1095-1102.

225. Goodrich, J. K., Waters, J. L., Poole, A. C., Sutter, J. L., Koren, O., Blekhman, R., ... & Spector, T. D. (2014). Human genetics shape the gut microbiome. *Cell*, *159*, 789-799.