It is said that we possess a “second brain”. This term was coined by Dr. Michael Gershon, who pioneered work establishing that serotonin is not only a neurotransmitter in the brain but also in the gut (Gershon, 1998). Dr. Gershon’s years of research led to the discovery that nerve cells in the gut, and its overall neural circuitry, act with the same intelligence as the nerve cells in the brain.

The gut is a highly innervated organ that possesses its own nervous system, known as the enteric nervous system (ENS), which consists of more neurons than those present in the spinal cord or the peripheral nervous system (Furness, 2012). Implanted in its walls, an extensive network of neurons lines the entire gastrointestinal tract and is responsible for regulating all aspects of digestion (Furness, 2012). In addition, and as it will be discussed, the ENS is also responsible for impacting on brain function.

Since Dr. Gershon’s work, much research has been conducted on the now-established bidirectional communication between the brain and the gut. To add to this body of research, a seminal study published in 2004 provided some of the first evidence of bidirectional interaction between gut microbiota and the brain (Sudo et al., 2004). Since then, an extensive amount of research has been carried out on the effects that gut microbiota have on brain function and the impact of this on mood and behaviour.

It is this subject matter—highlighting how the gut is a key player in neuroscience and encompassing insights into the many ways that the gut impacts on brain neurology—that will be discussed here. This includes discussion on the channels of communication between these two nervous systems, the roles of epigenetics and the immune system, and the critical influence of the gut microbiota.

Establishing the Gut–Brain Axis Connection

The recent discovery of the human microbiome, and in particular the gut microbiota (Human Microbiome Project Consortium, 2012), has caused a shift in the way neuroscience is viewed. Gut–brain interaction has been the subject of study for decades, providing a significant amount of information about the close interaction between the gut-associated immune and endocrine systems and the ENS, and how they relate and influence brain function (Cryan, 2016; Cryan & Dinan, 2012; Evrensel & Ceylan, 2015; Fetallov & Déchelotte, 2011; Mayer, 2011). Furthermore, this axis is recognised to play an important role in gastrointestinal pathologies as well as a number of mental health-related morbidities such as depression, obsessive compulsive disorder, Tourette syndrome, anxiety, and autistic spectrum disorder (Evrensel & Ceylan, 2015; Foster & McVey Neufeld, 2013; Mayer, Knight, Mazmanian, Cryan, & Tillish, 2014).

Current research is additionally highlighting the influence of the gastrointestinal microbiota on brain neuroscience and their potential impact on brain pathologies, and recent studies have demonstrated the importance of the gut microbiota on central nervous system (CNS) function (Clarke et al., 2013; Dinan & Cryan, 2012; Forsythe & Kunze, 2013; Heijtz et al., 2011). A growing body of evidence from animal studies, which will be discussed below, further supports the role of the gut microbiota in modulating emotional behaviour.

Although much of the research is primarily based on animal models, initial studies among humans appear to support the idea that there is indeed a relationship between gut microbiota and brain neurology. This relationship involves bidirectional communication along the gut–brain axis, which is to say that gut microbiota...
influence CNS function and that the CNS influences the gut microbiota composition through its effects on the gastrointestinal tract (Evrensel & Ceylan, 2015; Mayer, Tillish, & Gupta, 2015).

The gut–brain axis is a term to collectively describe the interrelationship and biochemical signalling between the brain and the gut (Stilling, Dinan, & Cryan, 2014). It encompasses two nervous systems—the CNS, comprised of the brain and spinal cord, and the nervous system of the gastrointestinal tract, the ENS (Stilling et al., 2014). These two nervous systems are formed at the same time during foetal development and are created from the same tissues (Tortora & Derrickson, 2006).

The gut–brain axis is a term to collectively describe the interrelationship and biochemical signalling between the brain and the gut (Stilling, Dinan, & Cryan, 2014). It encompasses two nervous systems—the CNS, comprised of the brain and spinal cord, and the nervous system of the gastrointestinal tract, the ENS (Stilling et al., 2014). These two nervous systems are formed at the same time during foetal development and are created from the same tissues (Tortora & Derrickson, 2006).

Interestingly many metabolites synthesised by the gut bacteria can act as epigenetic modulators, with research suggesting that microbiota and its metabolites influence genomic reprogramming.

There are several ways in which they connect and communicate: the circulatory system acts as a vehicle for the endocrine and immune systems of the gut to relay messages to the brain via hormones and chemical messengers (Cryan & Dinan, 2012); the vagus nerve (the tenth cranial nerve) conducts bidirectional neural communication through vagal nerve stimulation (Cryan & Dinan, 2012); and, recently, with the discovery of lymphatic vessels in the brain (Louveau et al., 2015), a third route of gut–brain communication suggests that gut-derived signals could conceivably enter the brain directly from the lymph.

The term microbiota–gut–brain axis has also been suggested to include the gut microbiota in the interplay as a communication channel that coordinates the behaviour of healthy gut bacteria with brain activity (Dinan & Cryan, 2012). So far, it has been estimated that there are 300 trillion bacteria in the large intestine (Theoharides, 2015). The compilation of some one thousand species of microbes includes one thousand times more cells than exist in the brain and spinal cord, and ten times more than the number of human cells in the entire body (Theoharides, 2015). This has led some to refer to the gut microbiota as an organ that rivals the brain in complexity (Theoharides, 2015).

Resident microbiota colonise the human large intestine shortly after birth and remain throughout life.
et al., 2014; Tsankova, Renthal, Kumar, & Nestler, 2007).

Other functions of intestinal microbiota include: synthesis of vitamins; the maintenance of gastrointestinal barrier integrity (to keep out harmful bacteria, viruses and parasites); assistance with digestion; absorption of nutrients and detoxification; prevention of infections and secretion of potent antibiotic substances such as bacteriocins; influence on local and systemic antioxidant status; decreased production of inflammatory cytokines (immune system cell-signalling proteins); and modulation of cortisol and adrenaline, the stress hormones implicated in affective disorders such as major depression (Bested, Logan, & Selhub, 2013; Brogan, 2016; Dinan & Cryan, 2012).

Many of the beneficial effects of the microbiota in the gut are dependent on vagal activation affecting brain function. While the molecular mechanisms underlying how gut bacteria affect vagal signalling is yet to be fully elucidated, direct neural routes of communication between the ENS and CNS are in part attributed to sensory neurons of the myenteric plexus in the ENS, where they offer the first point of contact for the intestinal microbiota in the gut lumen. These sensory neurons are in close synaptic communication with vagal nerve endings (Foster & McVey Neufeld, 2013; Gershon, 1998).

The brain also obtains information from the gut via the luminal epithelial chemoreceptors, specialised cells that respond and relay information regarding bacterial metabolites, such as neuroactive compounds that are contained within the gastrointestinal lumen and have the potential to be interpreted and acted upon by parts of the brain (Breer, Eberle, Frick, Haid, & Widmayer, 2012). These neuroactive compounds include short-chain fatty acids, and a variety of amino acids, neurotransmitters, and neuregulators such as gamma-aminobutyric acid (GABA), tryptophan, noradrenaline, serotonin, dopamine, acetylcholine, and cytokines (Cryan & Dinan, 2012).

A closer look at gut microbiota and their effects on brain neurology
There is increasing evidence that gut microbiota directly interact with and produce effects on CNS neurophysiology that ultimately influences host behaviour. The ability of gut microbiota to influence behaviour may be due to their ability to produce and recognise neurochemicals that are analogous in structure to those produced by the host’s nervous system.

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serotonin is also used by platelets in haemodynamics, and in the gastrointestinal tract, where 90% of serotonin resides (Keszthelyi, Troost, & Masclee, 2009). This neurotransmitter exerts its effects on gastric secretion, pancreatic secretion, gastrointestinal motility and colonic tone (O’Mahony et al., 2015). Serotonin is not able to cross the blood–brain barrier due to its molecular size, therefore any mood-related effects can most likely be attributed to the serotonin produced in the brain (Birdsall, 1998). Nevertheless, given the gut’s substantial serotonin stores located close to the vagal nerve pathways that link directly to the brain’s affective control centres (Crowell, 2004), the serotonin synthesised in the gut may plausibly affect the brain’s emotional centres, although this has not as yet been determined.

**Gut Microbiota, Tryptophan, and the Serotonergic System**

Aside from its role as a serotonin precursor, tryptophan is also synthesised into other biologically active agents such as niacin, kynurenic acid (KA), 3-hydroxykynurenine (3HK), and quinolinic acid (QA) (Savitz, Drevets, Wurfel, et al., 2015; Schwarcz, Bruno, Muchowski, & Wu, 2012). There is evidence to show that dysregulation of the kynurenine branch of the tryptophan metabolic pathway is associated with a number of conditions in both the brain and the gastrointestinal tract—depression and irritable bowel syndrome, for example (Clarke et al., 2012; O’Mahony et al., 2015). Neurological conditions are characterised by reductions in hippocampal and grey matter volume, dendritic atrophy and/or glial cell loss (Savitz, Drevets, Smith, et al., 2015; Savitz, Drevets, Wurfel, et al., 2015).

The kynurenine metabolic pathway is tightly controlled by the immune system and is catalysed by either indoleamine 2,3-dioxygenase or the hepatic enzyme tryptophan 2,3-dioxygenase (Schwarcz et al., 2012). The activity of both enzymes can be activated by inflammatory mediators and corticosteroids (Savitz, Drevets, Wurfel, et al., 2015). An under- or over-production of certain metabolites, including KA (neuroprotective) and 3HK and QA (both neurotoxic), is associated with neurodegenerative and other neurological disorders, as well as psychiatric diseases such as depression and schizophrenia, due to their effect on hippocampal neurons, the amygdala, and striatum (Schwarcz et al., 2012). Dysregulation of tryptophan metabolism is thus a key player in impacting mood and other functions of the CNS (Clarke et al., 2012).

Gut microbiota have been shown to influence the serotonergic system via their effect on tryptophan metabolism and serotonin production with implications in both CNS and ENS function. Gut microbiota have been shown to influence the serotonergic system via their effect on tryptophan metabolism and serotonin production, with implications for both CNS and ENS function (O’Mahony et al., 2015). Certain strains of microbiota (*Bifidobacterium infantis* 35624) have been demonstrated to positively affect tryptophan metabolism and availability via inhibition of inflammatory pathways that trigger the enzymes involved in the kynurenine pathway (Desbonnet et al., 2010). Subsequent positive impacts include the availability and modulation of serotonin in the prefrontal cortex, which has been associated with positive influences on mood (Albert, Vahid-Ansari, & Luckhart, 2014; Desbonnet, Garret, Clarke, Bienenstock, & Dinan, 2008).

On the topic of gut bacteria influencing certain areas of the brain involved in mood, a number of studies have been carried out to investigate the influence of probiotics on affective disorders. The term *psychobiotic*, defined as “a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering...
from psychiatric illness” (Dinan, Stanton, & Cryan, 2013, p. 720), has been used to describe these probiotics. In this regard, scientific evidence suggests that certain probiotics confer modulatory antidepressant-like behaviours by reducing pro-inflammatory cytokines (Maes et al., 2009). Further evidence comes from a study that showed the use of specific probiotics significantly decreased anxiety-like behaviour in animal models and reduced psychological distress in humans (Messaoudi et al., 2011). And in another study, the presence of a particular strain of bacteria known as *Bifidobacterium longum* NCC3001 eliminated anxiety-like behaviour in mice (Bercik, Park, et al., 2011).

In addition to communicating with the brain via the immune system, gut microbiota also influence CNS neurology and function directly via activation of vagal nerve signalling pathways and alterations in the hypothalamic–pituitary–adrenal (HPA) axis (Foster & McVey Neufeld, 2013; Leonard, 2007; Neufeld, Kang, Bienenstock, & Foster, 2011a; Neufeld, Kang, Bienenstock, & Foster, 2011b). This is the case for both commensal and pathogenic bacteria, with studies showing an increased stress response leading to worsening of symptoms (e.g., anxiety) associated with pathogenic bacteria (Dinan & Cryan, 2012; Goehler, Park, Opitz, Lyte, & Gaykema, 2008). In contrast, administration of probiotics has been shown to reverse anxiety-like behaviour in animal models (Stilling et al., 2014).

There is further evidence showing that gut microbiota also have an influence on neuroplasticity—the ability of the brain to reorganise and create new neural pathways (Jung, Jung, Kim, Han, & Kim 2012). The creation of new neural pathways between neurons is of particular significance in relation to behaviour modification (Olsen 2011). One potent stimulator of neuroplasticity in the brain is brain-derived neurotrophic factor (BDNF), and animal studies have demonstrated that alterations to gut microbiota due to pathogenic infection lead to a

There is evidence to show that gut microbiota also has an influence on neuroplasticity—the ability of the brain to reorganise and create new neural pathways.
reduction in hippocampal BDNF and altered brain biochemistry, with subsequent anxiety-like behaviour (Bercik et al., 2010; Bercik, Denou, et al., 2011; Cryan, & Dinan 2012; Goehler et al., 2008). For example, germ-free mice (lacking gut microbiota) have decreased levels of BDNF in the hippocampus (Bercik, Denou, et al., 2011), and hippocampal BDNF is similarly decreased in mice following antibiotic administration (Bercik, Denou, et al., 2011). These studies also demonstrate a reversal of behavioural changes associated with a return to control levels of BDNF following the administration of probiotics (Bercik et al., 2010; Bercik, Denou, et al., 2011).

In neurotransmitter systems, GABAergic signalling is also affected by certain gut bacteria, with research showing altered expression of GABA receptors in certain brain regions involved in the regulation of emotional behaviour, such as the prefrontal cortex, amygdala, hippocampus, paraventricular nucleus, the bed nucleus of the stria terminalis, and locus coeruleus (Bravo et al., 2011). GABA is a major inhibitory neurotransmitter in the CNS and is significantly involved in the regulation of a number of physiological and psychological processes.

Collectively these studies suggest that microbiota manipulation could be a valid therapeutic strategy to modulate CNS signalling and improve mood (Cryan & O’Mahony, 2011). While the majority of the research reviewed was from animal studies, and cautions should be made before extrapolating data to humans, the demonstrated mechanism of action by certain gut bacteria on CNS offers promising insight into how gut microbiota communicate with brain neurology. Equally, while the use of probiotics has consistently demonstrated an impact on anxiety and depression (Bravo et al., 2011).

Alterations in CNS–GABA receptor expression are implicated in the pathogenesis of anxiety and depression (Cryan & O’Mahony, 2011). Collectively these studies suggest that microbiota manipulation could be a valid therapeutic strategy to modulate CNS signalling and improve mood (Cryan & O’Mahony, 2011). While the majority of the research reviewed was from animal studies, and cautions should be made before extrapolating data to humans, the demonstrated mechanism of action by certain gut bacteria on CNS offers promising insight into how gut microbiota communicate with brain neurology. Equally, while the use of probiotics has consistently demonstrated an impact on anxiety and depression-like behaviour, the evidence from human studies is still limited. Recently, however, studies investigating the use of probiotics for the relief of depression and anxiety in humans show promise that intestinal bacteria could be targeted for their therapeutic potential (Dickerson et al., 2014; Messaoudi et al., 2016; Steenbergen, Sellaro, van Hemert, Bosch, & Colzato, 2015; Tomasik, Yolken, Bahn, & Dickerson, 2015).

Gut microbiota metabolites as neuroactive substances

Neuroactive substances produced by the gut microbiota include microbial metabolites such as short-chain fatty acids (SCFA). SCFAs confer neuroactive actions via their ability to penetrate the selectively permeable blood–brain barrier (MacFabe, Cain, Boon, Ossenkopp, & Cain 2011; Thomas et al., 2012). SCFAs readily cross the blood–brain barrier via both passive and active channels where they can exert alterations in multiple neurophysiological processes, including neurotransmitter synthesis and release (involving glutamate, dopamine, noradrenaline, and serotonin), gene expression of neurons, mitochondrial function, immune modulation, gap junction gating, and, ultimately, behaviour and mood (MacFabe et al., 2011). In addition, butyrate also confers significant effects on behaviour and mood in animal models (Huuskonen, Suuronen, Nuutinen, Kyrölenko, & Salminen, 2004; Schroeder, Lin, Crusio, & Akbarian, 2007).

Immune system communication and effects on brain neurology

Further communication from the gut microbiota to the brain occurs via direct stimulation of the immune cells in the gut itself. The majority of the immune system, 80% of it, is located in the gut, and is called gut-associated lymphoid tissue, or GALT (Lee & Mazmanian, 2010). This component of the immune system does not operate in isolation and is in constant communication with other immune system cells throughout the body, including the brain, via chemical messengers that signal when it is time to mount up a response against pathogens and potentially harmful substances (Lee & Mazmanian, 2010). Certain immune molecules, the cytokines, are used to communicate with the brain and travel through the blood or reach the brain in the form of nerve signals (Berk et al. 2013; Leonard, 2007). Thus, inflammation that originates in the gut can affect the brain: for example, cytokines that cross the blood–brain barrier activate the brain’s resident immune cells, the microglia cells. As inflammatory signals from the gut persist, the inflammation in the brain increases (Kharrazian, 2013). Inflammation can interfere with the neu-
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Inflammation can interfere with the neurological functions of the brain, causing decreased and slower nerve conduction that negatively affects the HPA axis and manifests as increased stress response, depression, or anxiety.

Lipopolysaccharides (LPS) are a potent inducer of the inflammatory response that are associated with the production of inflammatory markers linked to depression.
LPS are a combination of lipids and sugars found on the outer membrane of certain gram-negative bacteria that occur naturally in the gut (Maes, Kubera, & Leunis 2008; Maes, Kubera, Leunis, & Berk, 2012; Maes et al., 2013). The role of LPS is to protect these bacteria from being digested by bile acids released by the gall bladder. LPS are not supposed to travel beyond the gut lumen, and in healthy individuals they cannot gain entrance into the bloodstream. However, when the cells of the intestine are damaged and the tight junctions are compromised, LPS are able to gain access into the systemic circulation and provoke an immune response, inducing inflammation and causing dysregulation of the HPA axis via the cortisol receptors (Maes et al., 2008; Maes at al., 2012). Damage to the cells of the gut wall can occur for a number of reasons—for example, poor diet and alcohol, food intolerances or allergies, overgrowth of pathogenic bacteria, stress (emotional, mental or physical), and certain medications (Brogan, 2016; Gareau, Silva, & Perdue, 2008; Teitelbaum, Gareau, Jury, Yang, & Perdue, 2008). LPS can also penetrate the blood–brain barrier, causing an inflammatory response to be induced in the brain as well (Feng, Xia, Garcia, Hwang, & Wilson, 1995).

**Manipulation of gut microbiota: The use of prebiotics to improve mental health**

On a last note, the capacity of gut microbiota to produce neuroactive substances is dependent on the availability of suitable substrates. Therefore, the role of diet and dietary modifications must be a consideration when evaluating the capacity for the microbiota to produce neuroactive substances that may act on the CNS, and they are paramount in any successful manipulation of gut microbiota.

A potential strategy for modulating the microbiota–gut–brain axis is the use of prebiotics. Prebiotics are fermented ingredients that can effect changes in both the composition and/or activity of the gastrointestinal microbiota that confer benefits upon host well-being and health (MacFarlane, Steed, & Macfarlane, 2008). Specific prebiotics, namely fructooligosaccharides, a type of soluble fibre found in fruits and vegetables (Sabater-Molina, Larqué, Torrella, & Zamora, 2009), and galactooligosaccharides, produced from lactose and naturally found in human milk (Niittynen, Kajander, & Korpela, 2007; Torres, Gonçalves, Teixeira, & Rodrigues 2010), have been associated with increases in levels of BDNF in certain regions of the hippocampus (Savignac et al., 2013).

Different microbes have a preference for different dietary substrates. Many gut bacteria have a broad selection and can grow on a variety of substrates; typically, however, they prefer one substrate to another (Wu et al., 2011), and individual genera of bacteria have been shown to have particular preferences. For example, *Bacteroidetes* appear to have a preference for particular fats, *Prevotella* ideally proliferate on a carbohydrate...
source, and *Bifidobacteria* are able to outcompete others in the presence of dietary fibre (González-Rodriguez, Ruiz, Geimonde, Margolles, & Sánchez, 2013; Wu et al., 2011). Some microbes, such as *Akkermansia muciniphila*, do not depend on dietary substrates at all and instead thrive on the carbohydrate of the mucus layer secreted by host gut epithelial cells (Reunanen et al., 2015).

The advantage of using prebiotics to modify gut bacteria composition and reap the health benefits is that, unlike probiotics that may have to compete against established colonic communities and often confer benefits only while being administered, prebiotics target bacteria that are already commensal to the large intestine. As a consequence, prebiotics may be a more practical and efficient way to manipulate the gut microbiota than probiotics, provided the appropriate health-promoting species are already present in the bowel (Macfarlane et al., 2008). While it is beyond the scope of this paper to delve into specific prebiotic foods and their unique properties, it is worth noting that these foods include plant fibre found in fruits, vegetables, nuts, legumes, and wholegrains (Roberfroid, 2007).

In summary, it has been well established that the gut impacts and influences brain neurology, and that it is a key player in neuroscience with profound implications for psychiatric conditions. In particular, the role of the gut microbiota in gut–brain axis communication has offered a number of insights into the mechanisms by which the gut communicates with the brain. These comprise various means that include the endocrine, immune, and neuronal systems. The ability to target the brain via the gut has the potential to introduce a paradigm shift in neuroscience to now include the ENS as part of the study of how brain neurology drives behaviour and emotion. As neuroscientists, psychiatrists, therapists and anyone with an interest in mental health, we should question how the gut is contributing to the presentation of a neurological or psychiatric disease—because the gut is indeed the second brain.

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Micaela has also studied mind–body nutrition, the psychology of eating, and counselling techniques. She finds that incorporating these principles and techniques into her work helps to bring about positive change in her clients and restore health in many aspects of their lives.

Other areas of interest, which Micaela believes can also have a significant impact on mental health, include stress management, sleep issues, fatigue syndromes, female and male hormonal imbalances, thyroid conditions, cognitive issues, immune dysfunction (including food allergies/intolerances, autoimmune conditions), digestive complaints, eating challenges (overeating, binge eating, body image, chronic dieting) and weight management.

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