

# Gut microbial communities modulating brain development and function

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**Keywords:** brain development, gut microbiota, behavior, probiotics, microbiota-gut-brain axis

Mammalian brain development is initiated in utero and internal and external environmental signals can affect this process all the way until adulthood. Recent observations suggest that one such external cue is the indigenous microbiota which has been shown to affect developmental programming of the brain. This may have consequences for brain maturation and function that impact on cognitive functions later in life. This review discusses these recent findings from a developmental perspective.

## Gut Microbiota

The gut contains an immense and complex microbial ecosystem, comprising a myriad of bacteria, of which most are strict anaerobes.<sup>1</sup> The term “gut microbiome” is used to describe the constituents of the microbiota, ranging from its bacterial genes to their proteins and metabolites.<sup>2</sup> While the gut microbiome is assumed to be similar between family members,<sup>3</sup> recent data suggest that the human microbiome may be subgrouped into ‘enterotypes’ depending on bacterial prevalence.<sup>4</sup> Gut microbiota serve the host by protecting against pathogens, participating in the intake of dietary nutrients, metabolizing certain drugs and carcinogens, and influencing the absorption and distribution of fat.<sup>5</sup> The influence of the microbiota extends beyond the gastrointestinal (GI) tract; contributing to, for example, pain perception in the skin<sup>6</sup> and fat deposition in the liver.<sup>7,8</sup> Disruption of the symbiotic relationship between the microbiota and the GI tract<sup>9</sup> perturbs host functions and, in some cases, will contribute to a “leaky” gut-immune barrier<sup>10</sup> leading to malfunction and illness such as inflammatory bowel disease (IBD) and *Clostridium difficile* colitis.<sup>11</sup>

Although it is known that a bi-directional communication between the GI tract and the central nervous system (CNS) occurs, less is known on how microbiota can influence this gut-to-brain communication. Recent data, however, have begun to shed some light on the ability of microbiota to influence behavior

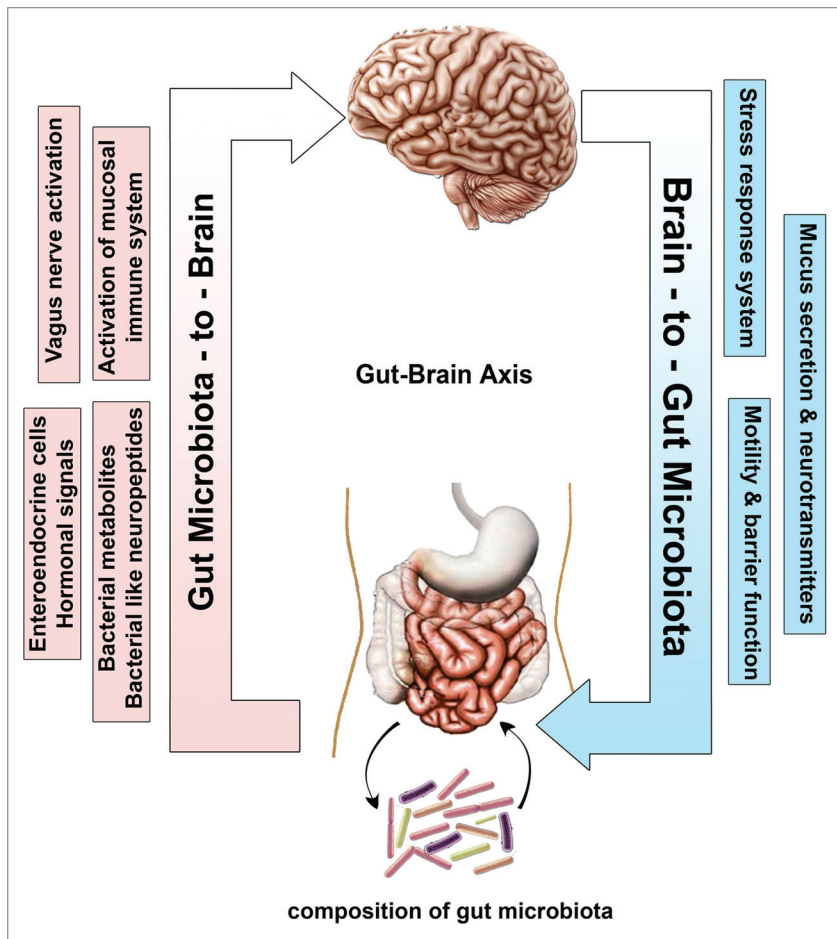
in mice.<sup>12-15</sup> The mechanisms are essentially unknown but are currently subject to intense investigation.

**Gut-brain axis.** The brain and the gut are highly integrated organs, with communication occurring in a bidirectional manner via passive and active mechanisms including neural, immunological and endocrine pathways as well as through hypothalamic-pituitary-adrenal (HPA) stress axis<sup>16-18</sup> (Fig. 1). Research on gut-brain axis has focused on top-down communication on how the brain affects GI motility, blood flow and secretion, and on the bottom-up effects of intestinal activity on visceral perception and CNS activity. The neuroanatomy of the gut-brain axis has been reviewed elsewhere.<sup>19,20</sup>

**Gut microbiota-to-brain.** Over the years, the ability of microbiota to impact on brain function has been subject to an intense debate following the observation that administration of oral antibiotics and laxatives resulted in a dramatic improvement in patients with hepatic encephalopathy.<sup>21,22</sup> The observation that common categories of GI diseases (functional and inflammatory) often display correlation with psychiatric comorbidity that includes depression and anxiety in up to 80% of patients, supports the possibility that alteration of microbiota can affect CNS function.<sup>23,24</sup> These clinical findings are supported by results from animal studies showing that certain pathogenic enteric bacteria, during the initial phase of infection, can induce an anxiety-like behavior.<sup>25</sup> Furthermore, microbiota has also been shown to modulate the levels of adreno-corticotrophic hormone (ACTH) in mice.<sup>13</sup> Hence, the term: “gut feelings” and its role in intuitive decision making has perhaps some bearing and the Asian understanding of the gut being the “location of the soul and the center of spiritual and physical strength” and not only a simple digestive system are in support of these findings.<sup>26,27</sup> These findings were recently corroborated by us<sup>28</sup> and others<sup>14,29</sup> in which it was shown that germ free (GF) mice display (1) increased motor activity and reduced anxiety (2) decreased N-methyl-D-aspartate receptor subunit NR2B mRNA expression in the amygdale, (3) decreased 5HT-1A receptor in the hippocampus and (4) increased expression of brain-derived neurotrophic factor (BDNF) in the hippocampus.<sup>14,28-30</sup>

Modification of microbiota by a combination of probiotics (*Lactobacillus helveticus* and *Bifidobacterium longum*) has been shown to reduce anxiety in animals and bring beneficial psychological effects with a decrease in serum cortisol in patients.<sup>31</sup>

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Submitted: 07/04/11; Revised: 06/17/12; Accepted: 06/27/12  
<http://dx.doi.org/10.4161/gmic.21287>



**Figure 1.** Bidirectional communication between the gut microbiota and the central nervous system (CNS). The composition of gut microbiota could modulate the function of CNS through various communication means including neural (vagus nerve activation), hormonal (enteroendocrine cells and bacterial neuropeptides), humeral (bacterial metabolites) and immunological (activation of mucosal immune system). The brain-to-gut microbiota axis is mediated via stress factors, alteration in intestinal permeability and motility and through release of neurotransmitters and mucus.

Furthermore, Bravo et al. showed that long lasting treatment of mice with the probiotic bacterium *Lactobacillus rhamnosus* appears to impact on emotional behavior and the expression of the neurotransmitter GABA ( $\gamma$ -aminobutyric acid) in the CNS in a region-dependent manner.<sup>32</sup> Likewise, *Lactobacillus rhamnosus* treatment may be associated with a decrease in corticosterone levels as well as anxiety- and stress-related behavior. These alterations were not observed in vagotomized mice, indicating the vagus nerve may be part of the communication pathways that allow communication between the gut and the brain.<sup>32</sup> By analogy, Li et al., have observed a temporal association between diet-induced alterations in intestinal microbiota diversity and changes in working and reference memories.<sup>15</sup> Consistent with Li's findings, Gareau et al., showed that memory dysfunction in *Citrobacter rodentium* infected mice was prevented by daily treatment with probiotics.<sup>33</sup> The study also showed a deficit in non-spatial and working memory in GF mice even in the absence of stress. While several mechanisms have been proposed, including

the release of bacterial metabolites, neuropeptides or directly by activating vagal pathways at the level,<sup>33</sup> the precise pathways remain to be identified (Fig. 1).

**Brain-to-gut microbiota.** Whereas the focus of current research is mainly on studying the influence of gut microbiota on the brain, there are also data to suggest that descending signals from CNS can alter the composition and function of the gut microbiota in rodents<sup>34,35</sup> and primates.<sup>36,37</sup> For example, while acute stress increased colonic paracellular permeability involving overproduction of IFN- $\gamma$  and a decrease in mRNA expression of ZO-2 and occludin,<sup>38</sup> stress induced secretion of norepinephrine favored overgrowth of non-pathogenic isolates of *Escherichia coli* as well as the pathogenic *E. coli* 0157:H7.<sup>39,40</sup> Other mechanisms such as changes in mucus secretion<sup>41</sup> and in GI motility<sup>42</sup> have also been shown to affect gut microbiome composition (Fig. 1).

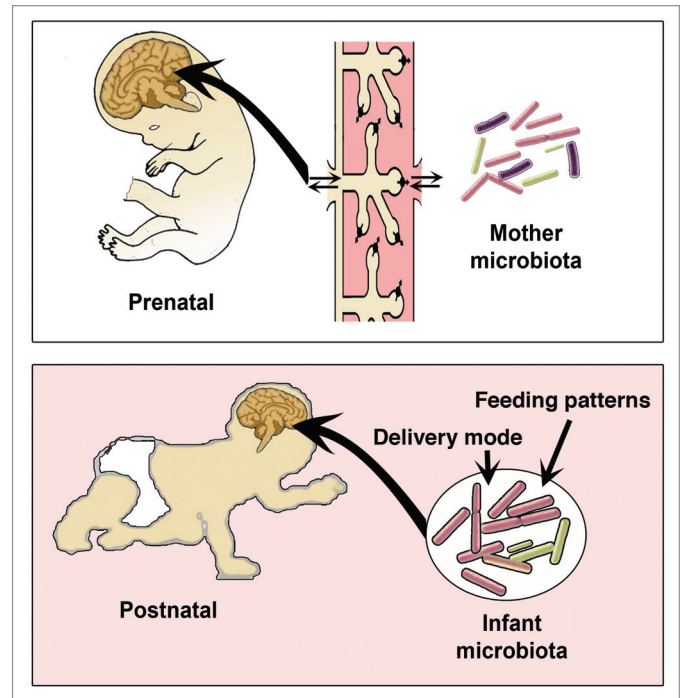
### Gut Microbiota and Brain Development (Prenatal and Postnatal)

The prenatal and postnatal periods in mammalian development are characterized by rapid changes in neuronal organization, thus providing a critical window of opportunity during which environmental factors could have long-term influences on brain and behavior. During the last few years, a number of studies pointed to an ability of microbiota to influence the fine maturation of the brain which have long lasting effects on functions of the brain.<sup>13,28</sup>

**Prenatal.** A rapidly growing body of empirical evidence supports the Barker hypothesis regarding the influence of the intrauterine environment on fetal development and susceptibility to a wide range of metabolic, neurodevelopmental and psychiatric diseases later in life.<sup>43</sup> The developing brain has been shown to be susceptible to both internal and external environmental cues during prenatal life. Epidemiological data have indicated a possible common link between neurodevelopmental disorders, such as autism and schizophrenia, and microbial pathogen infections during the prenatal period.<sup>44-46</sup> Experimental studies in rodents further support these findings, demonstrating that exposure to microbial pathogens during similar developmental periods results in behavioral abnormalities, including anxiety-like behavior and impaired cognitive function.<sup>47-49</sup> The role of gut microbiota in modulating mood and behavior has been the focus of many research studies.<sup>14,28,29</sup> As mentioned above, GF mice display increased motor activity and decreased anxiety compared with conventionally raised mice. Notably, colonizing adult GF mice with a whole microbiota failed to normalize the behavior of GF mice. On the other hand, colonizing the mother for at least 30 d before mating

was successful in reverting the behavioral phenotype in the offspring.<sup>28</sup> This interesting finding hints to a crucial role of the microbiota on the mother during pregnancy that might have programming effects later in life. The fetus lives in an almost sterile environment<sup>50-53</sup> and communicates with the mother through the placenta<sup>54</sup> (Fig. 2). It is possible that maternal microbial metabolites could reach the growing fetus through the placenta and affect fetal brain development. Several recent studies indicate an important role of the placenta in shaping the fetus development. The placenta, nicknamed the fetal armor,<sup>55</sup> has been shown to protect the fetus from damage when the mother is deprived of food by breaking down its own tissue (placental autophagy) to nourish energy demanding organs like the fetal brain.<sup>56</sup> The placenta appears also to provide the hormone serotonin essential for fetal forebrain development.<sup>57</sup> Using a novel ex vivo preparation, the authors demonstrated that the placenta could convert maternal tryptophan into the neurotransmitter serotonin (5-hydroxytryptophan; 5-HT), providing the primary source of 5-HT for the developing mouse forebrain at midgestation.<sup>57</sup> The hormonal interaction between the placenta and the fetal hypothalamus-pituitary-adrenal axis (HPA) was shown to be involved in regulating fetal brain development especially during stress. In rodents, prenatal stress had programming effects that extended to adulthood. These effects included elevation of stress-induced HPA axis activity,<sup>58,59</sup> increased anxiety and behavioral reactivity/fearfulness,<sup>60-62</sup> decreased hippocampal glucocorticoid binding capacity<sup>58,63</sup> and a decline in cognitive performance.<sup>64</sup> Several studies pointed to the effect of microbiota in modulating the activity of HPA axis. Prenatally, maternal probiotic supplementation during pregnancy and lactation normalized the high corticosterone concentrations and restored corticotrophin-releasing hormone seen in maternally separated neonates.<sup>65</sup> The mechanism whereby microbiota influences brain prenatally is yet to be determined, but the placenta is one of several possibilities.

**Postnatal.** The postnatal period is another critical period for brain development. For most vertebrates, the majority of organs and tissue development occurs during embryogenesis, and postnatal changes are primarily concerned with growth. However, the CNS is different in that a considerable amount of morphological development, cell differentiation and acquisition of function, takes place during postnatal development.<sup>66</sup> Colonization of the GI tract with microbiota begins postnatally at birth, overlapping with this critical period of brain development. Microbiota colonization is actually influenced to a great degree by mode of delivery<sup>67</sup> and feeding patterns<sup>68</sup> (Fig. 2). Clinical studies have shown that breast-fed infants have better neurodevelopment outcomes and higher scores on intelligence tests.<sup>69,70</sup> The microbiota of breast-fed infants appear to be more diverse and heterogeneous than the formula-fed according to a recent metagenomic study.<sup>71</sup> However, the effect of breastfeeding on the composition of the infant gut microbiota, more specifically on the predominance of bifidobacteria is still controversial. Several reports<sup>72,73</sup> found no difference for bifidobacteria between breast- and formula-fed infants. Interestingly the strains of bifidobacteria that colonize the infant intestine are different from adult predominating mainly with *Bifidobacterium longum* and *Bifidobacterium bifidum*. These



**Figure 2.** Gut microbiota-to-Brain communications during prenatal and postnatal development.

two strains are then replaced with *Bifidobacterium adolescentis* and by other strains of the same species.<sup>74</sup> Using bifidobacteria “of human infant intestinal origin” in probiotics may have beneficial effects on depression in rats exposed to maternal separation stress in early life.<sup>12</sup> Recently, Stanton and coworkers showed that feeding mice with two forms of bifidobacteria isolated from infant feces could influence brain fatty acid composition.<sup>75</sup> These studies show the ability of infant microbiota to reset and influence neurophysiological parameters.

Gut microbiota also synthesize vitamins that are essential for human survival such as vitamins K2 and B12. Vitamin B12 or cobalamin is produced mainly by *Lactobacillus reuteri*<sup>76</sup> and is important for development of the nervous system.<sup>77,78</sup>

Further evidence for the role of microbiota on postnatal brain development came from animal studies on GF mice. The activity of the HPA axis<sup>13</sup> and more recently the hippocampal serotonergic system<sup>79</sup> are altered in GF mice with elevation in corticosterone and serotonin levels. Colonisation of GF mice post weaning was insufficient to reverse the CNS neurochemical consequences<sup>79</sup> and had no effect on the HPA axis,<sup>13</sup> introducing the notion of a critical time window very early in life. These finding gives support to the microflora hypothesis<sup>80</sup>—an extension of the hygiene hypothesis which suggests that insufficient exposure to microbiota early in life may affect the composition and maturation of the adult microbiota that, in turn, skews the immune development in a way that increases susceptibility to contract allergic, and immune related diseases. The microflora hypothesis may also be considered in the etiology of autism<sup>81</sup>—a neurodevelopment disorder of unknown etiology that starts to develop in the late postnatal period. Numerous reports have pointed to a possible role

of microbiota in the development of autism: (1) most children with autism often experience a range of GI disorders, (2) onset of the disease usually follows antimicrobial therapy, (3) a significant percentage of children with late-onset autism (18–24 mo of age) have a history of extensive antibiotic use and (4) oral vancomycin treatment showed a decrease in autistic symptoms, while relapse occurs following cessation of treatment.<sup>45,82</sup> Real time qPCR<sup>83</sup> and culture-based microbiota<sup>45</sup> profiling techniques support the possibility that alteration in microbiota may contribute to disease phenotype. For example, a 10-fold increase in certain clusters of *Clostridium* spp in stool samples from autistic children compared with healthy controls has been observed. The authors further speculated on the possibility that exposure to trimethoprim/sulfamethoxazole antibiotics were more likely to precede diagnosis of late-onset autism than exposure to any other antibiotic regimen because trimethoprim/sulfamethoxazole are not effective against *Clostridium* spp, while oral vancomycin specifically targets Gram positive organisms which include *Clostridium* spp.<sup>45</sup> It has also been suggested that *Clostridia* spores could be one reason for the high rates of autism seen among siblings.<sup>84</sup> Additional mechanisms are of course equally possible and great caution needs to be exercised in the interpretation of these data on autism and it could very well be a chicken-and-egg situation whereby symptoms observed in autistic children were the result of their autism rather than the cause.

### Putative Mechanisms Underlying Microbiota Brain Axis

**Bacterial metabolites and bacterial neuro-like peptides.** Dietary carbohydrates can be digested in colon by gut microbiota into short chain fatty acids (SCFA) such as butyrate, acetate and propionate.<sup>85</sup> SCFA are sensed by G protein coupled receptors (GPRs), GPR41 and GPR43, which induce colonic motility, regulate appetite<sup>86</sup> and suppress colon cancer.<sup>87</sup> Butyrate can be directly used by colonocytes as an energy source, whereas propionate and acetate are taken up directly to the blood stream and transported to various organs.<sup>88,89</sup> Butyrate as well as propionate are strong inhibitors of histone deacetylases (HDACs), whereas acetate is not able to block HDAC functions.<sup>90</sup> Oral administration of acetate<sup>91</sup> or butyrate<sup>92</sup> was able to ameliorate the disease phenotype in DSS-induced colitis model in mice. SCFAs can interact with nerve cells by stimulating sympathetic nervous system<sup>93</sup> and butyrate in particular has been suggested to influence memory and learning processes via HDAC inhibition.<sup>94,95</sup> Moreover systemic injection of butyrate exerted a potential antidepressant effect by inducing histone hyperacetylation in mice that had increased BDNF transcripts in the frontal cortex.<sup>96</sup> On the same treatment regime another SCFA, propionate, has been reported not only to accelerate an autism-like behavior in rodents<sup>97</sup> but also to impair specific object recognition and social behavior in rats exposed to propionate compared with controls.<sup>98</sup>

Modulation of transmitters (e.g., serotonin, melatonin, gamma-aminobutyric acid, histamines and acetylcholine) within the gut is yet another possible mechanism of action that could mediate the effects of the gut microbiota. For example, metabolic

profiling of GF and conventionalized mice have revealed that conventionalization of GF mice by gut microbiota results in a 2.8-fold increase in plasma serotonin levels.<sup>99</sup> In line with this study, administration of the commensal bacteria, *Bifidobacteria infantis*, increased the plasma concentration of tryptophan, suggesting that the normal microbiota can influence the precursor pool for serotonin (5-HT).<sup>12</sup> It has been reported that microbiota may express and secrete neuropeptide like molecules proposed to influence behavior and emotion.<sup>100</sup>

**Stimulation of afferent system to CNS.** Another possible mechanism mediating the gut-brain communication may be via established neuronal circuits. Microbiota can elicit signals via the vagal nerve to the brain and vice versa.<sup>101,102</sup> Several reports showed or supported a direct link between microbiota and the ENS. Oral ingestion of *Lactobacillus rhamnosus* has been shown to reduce stress-induced corticosterone and anxiety- and depression-related behavior in mice via the vagal nerve.<sup>32</sup> Moreover, using another *Lactobacillus* strain, *Lactobacillus reuteri*, Kunze and colleagues observed activation in calcium-dependent potassium channels in a specific subset of enteric neurons in the colonic mesenteric plexus of Sprague Dawley rats,<sup>103</sup> thus pointing to a direct link between microbiota and the ENS. Another study showed that treatment of *Trichur muris* infected mice with a specific probiotic *Bifidobacterium longum* was effective in normalizing anxiety-like behavior exhibited by the infected mice. This effect of *Bifidobacterium longum* required an intact vagus nerve and was not accompanied by changes in gut immune functions.<sup>104</sup>

**Activation of the mucosal immune system.** The gut is patrolled by a variety of immune cells such as T-regulatory cells and antigen presenting cells (APC) which could traffic from the gut associated immune cells (GALT) to other peripheral lymphoid sites including the CNS. Recent studies established that GALT is shaped by components of the gut microbiota, some supporting the differentiation of interleukin (IL)-17-producing TH17 cells,<sup>105-107</sup> while others the generation of regulatory T lymphocytes (Treg).<sup>108</sup> Immune cell populations induced within the gut could cross the blood-brain barrier and within the CNS be reactivated by the appropriate resident APC.<sup>109</sup>

**Endocrine mechanisms.** Enteroendocrine cells (EEC) form the basis of the largest endocrine system in the body. They secrete gut hormones such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), oxyntomodulin, gut peptide YY (PYY) which control food intake and energy homeostasis. The brain receives hormonal signals from the EEC via two main mechanisms either by a paracrine effect on proximate cells (notably vagal afferent fibers), or by a classical endocrine fashion through the circulation acting mainly on the hypothalamus where the blood-brain barrier is leaky or absent. Gut microbiota have been reported to regulate EEC and influence the release of gut hormones.<sup>110</sup> Furthermore, the presence of gut microbiota is necessary for the differentiation of EEC in zebrafish.<sup>111</sup> Cani et al. in a series of studies showed a connection between gut microbiota and levels of two gut hormones GLP-1 and GLP-2. GLP-1 promotes satiety and weight loss<sup>112</sup> while GLP-2 stimulates intestinal glucose transport and reduces gut permeability.<sup>113</sup> In rats, oligofructose treatment, which increases the proportion of

Bifidobacteria has been associated with an increase in GLP-1 secreting EEC in the colon.<sup>110</sup> *Ob/ob* mice treated with a prebiotic had an altered gut microbiome and higher levels of GLP-1 and GLP-2.<sup>114</sup> Another evidence for the role of gut microbiota in modulating gut hormones comes from studies after gastric bypass surgery which showed a large shift in the bacterial population of the gut. Firmicutes which were dominant in normal weight and obese individuals, decreased significantly in individuals after gastric bypass surgery.<sup>115</sup> As we know, gut hormones are able to reduce appetite and weight loss after gastric bypass surgery.<sup>116,117</sup> Interestingly, administration of probiotics after surgery induced an accelerated weight loss,<sup>118</sup> thus supporting the notion that gut microbiota could indeed modulate gut hormones.

### Summary/Conclusion

Considerable progress has already been made in understanding the bi-directional crosstalk governing the gut-brain axis, however we are only just beginning to realize the physiological impact of the microbiota on this process. The finding that microbiota can modulate behavior raises the prospect of its involvement in developmental programming. How does microbiota-to-brain

signaling affect brain development? How beneficial it is to supply mothers during pregnancy with probiotics or prebiotics to shape neural development of the fetus? One of the great advantages in addressing these questions is the fact that we have the tools and techniques to study the microbiota-gut-brain axis. This include mechanistic studies in rodents and in piglets which can be translated into the human situation. Germ free animals such as rodents and piglets are a tremendous tool to study such interactions. Stool samples for metagenomic sequencing and gut tissue that can be easily obtained by endoscopic biopsies for analysis of signaling mechanisms. With the rapid expansion of non-invasive techniques to monitor brain structure, function and signaling, we are quite hopeful that we will see a rapid and significant progress in unlocking the mysterious black box of Gut. Thus, by modulating microbiota, you may modulate the mind.

### Acknowledgments

We would like to thank Qatar University for the PhD funding of M.A. The authors and their works are supported by grants from VR, Cancerfonden, EU-project TORNADO and Singapore Millenium Foundation. We are also grateful for valuable comments from Velmurugesan Arulampalam.

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