resulted not only in negative affective behavioral regulation, but also in a marked, selective functional activation of the extended amygdala circuit, a brain network well linked to negative affect (Anderson *et al*, 2013) (Figure 1).

In addition to experimental rodents, DREAMM is now being used in non-human primates and has the potential to be implemented in the future in humans (pending advances in gene-therapy safety/efficacy currently under development). The clinical relevance and translational therapeutics potential of DREAMM holds promise as an application for repeated, longitudinal, non-invasive assessment and monitoring of disease/therapy progression in patients undergoing DREADD-based neuromodulatory therapy. Furthermore, DREAMM would also have the capacity to be utilized alongside advanced cellular genetic engineering approaches such as combined DREADD and cell replacement therapeutics (Dell'Anno *et al*, 2014) to assess the efficient functional integration of such transplanted cells within neuronal networks.

In sum, DREAMM holds significant promise as a powerful, reverse-engineering strategy to visualize *in vivo*-specific neuronal ensemble networks associated with normal and pathologic behavior and to thus enhance knowledge about distinct neuronal circuits relevant to neuropsychiatric disorders.

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More than a Gut Feeling: the Microbiota Regulates Neurodevelopment and Behavior

The realization of the importance of the gut microbiota in health and disease has been one of the most exciting areas in biomedical research over the past 5 years. We are teeming with microrganisms in and on our body, having >150 times more microbial genes (the microbiome) than mammalian genes. Studies are revealing how variations in the composition of the gut microbiota influence all aspects of physiology, including brain function and even behavior. In terms of neuroscience and psychiatric disease the field is still very much in its infancy, but evidence is accumulating that it has a key role. Factors that shape the bacterial landscape include being born by Caesarian delivery, not being breastfed, environment, gestational age, host genetics, exposure to infections (both maternal and infant), and antibiotic usage. Moreover, stress, especially that in early life and prenatally, can have marked effects on microbiota composition (Borre *et al*, 2014).

A variety of strategies have been used to investigate the role of this so-called microbiota–gut–brain axis in health and disease. Germ-free mice (mice that never have been exposed to any bacteria) have been used to show that microbiota is crucial for hypothalamic–pituitary–adrenal axis function. Moreover, these mice have widespread neurodevelopmental changes in the brain, including alterations in monoaminergic neurotransmission and behavioral changes in anxiety (Foster and McVey Neufeld, 2013). More recently, we have shown that these mice also exhibit autism-like traits, such as deficits in sociability, social cognition, and increased repetitive behaviors (Desbonnet *et al*, 2014). Interestingly, as in autism and other neurodevelopmental disorders, these effects are much more pronounced in males than females. Moreover, studies in germ-free mice can be expanded to enable research on the 'humanization' of the gut microbiota, that is, transplanting faecal microbiota from specific human conditions or from animal models. Indeed, it has been shown that behavioral traits can be transplanted between strains of mice (Collins *et al*, 2013).

Administration of various potential probiotic strains in rodents or humans has also been shown to have beneficial effects in rodents. Major strain and species differences occur in terms of their 'psychobiotic' effects. Studies have shown that some *Bifidobacteria* and *Lactobacilli* species as well as *Bacteroides fragilis* can have positive effects on anxiety, depression, cognition, and autism-related behaviors (Hsiao *et al*, 2013). Prebiotics, non-digestible food ingredients that promotes the growth of beneficial gut microorganisms, are also being shown to affect brain BDNF levels. Human studies of prebiotics and probiotics have lagged behind to date, although there is interesting neuroimaging studies emerging clearly showing that such bacterial-based dietary interventions can affect brain function.

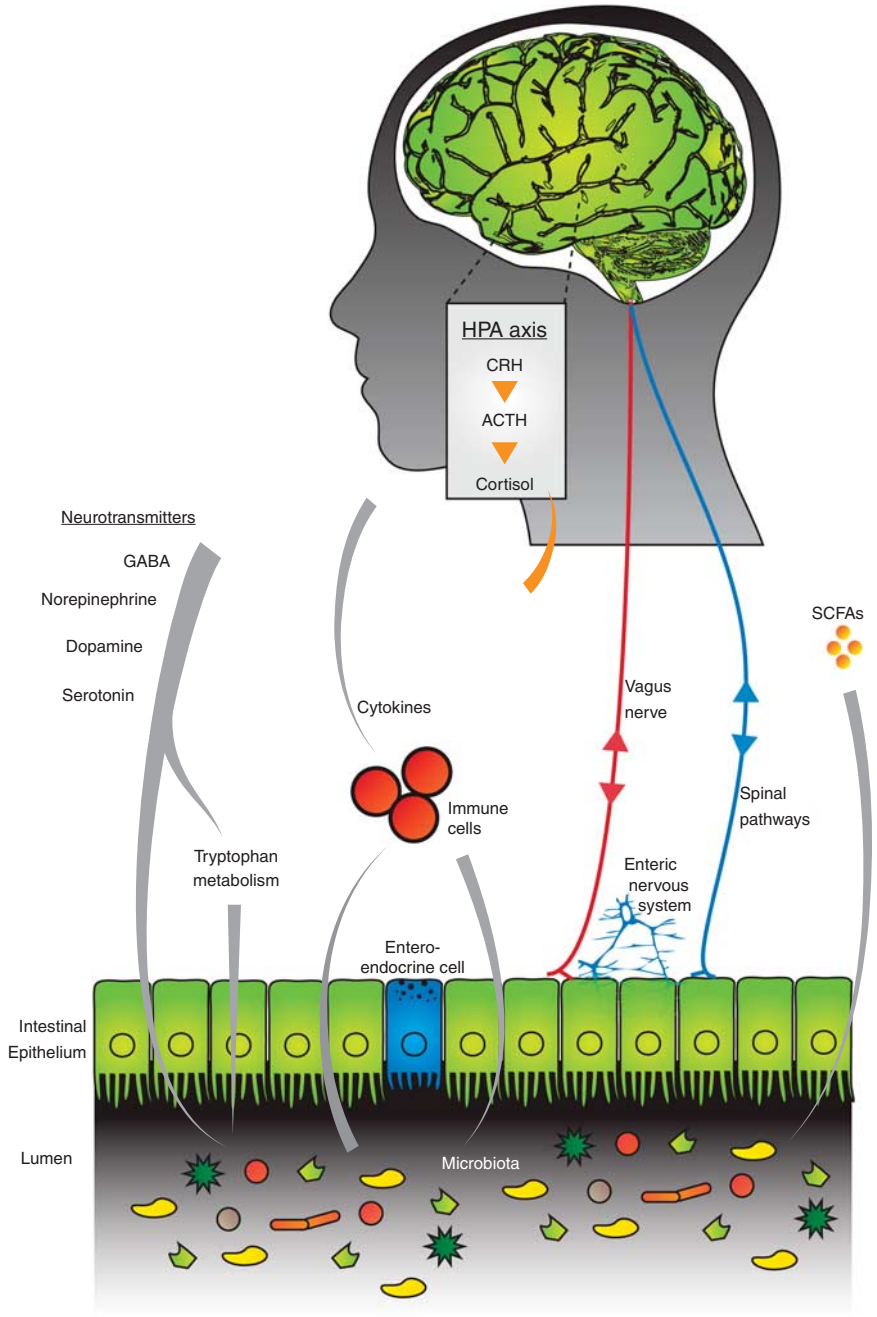

Figure 1. Key pathways involved in microbiota–gut–brain signaling. There are many potential direct and indirect pathways exist through which the gut microbiota can modulate the gut–brain axis. They include endocrine (cortisol), immune (cytokines), and neural (vagus and enteric nervous system) pathways. The gut microbiota and probiotic agents can alter the levels of circulating cytokines, and this can have a marked effect on brain function. Both the vagus nerve and modulation of systemic tryptophan levels are strongly implicated in relaying the influence of the gut microbiota to the brain. In addition, short-chain fatty acids (SCFAs) are neuroactive bacterial metabolites of dietary fibers that can also modulate brain and behavior. Harnessing such pathways may provide a novel approach to treat various brain disorders.

Finally, perturbation of the microbiota by administration of antimicrobial drugs can allow for a temporally controlled and more clinically relevant tool to assess the role of the gut microbiota on behavior. Antibiotics in adulthood and early-life can reverse both antipsychotic-induced obesity (Davey *et al*, 2013) and increase visceral pain (O'Mahony *et al*, 2014) responses, respectively. Further studies focused on the mechanisms on how these gut microbiota signal to the brain are now warranted. To date, it is clear that the vagus nerve, immune signaling, and the production of bioactive metabolites are strongly implicated in communication across the microbiota–gut–brain axis (Figure 1).

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