The role of short-chain fatty acids in microbiota–gut–brain communication

*Boushra Dalile[1], Lukas Van Oudenhove[1], Bram Vervliet[2] and Kristin Verbeke[1]**

Abstract | Short-chain fatty acids (SCFAs), the main metabolites produced by bacterial fermentation of dietary fibre in the gastrointestinal tract, are speculated to have a key role in microbiota–gut–brain crosstalk. However, the pathways through which SCFAs might influence psychological functioning, including affective and cognitive processes and their neural basis, have not been fully elucidated. Furthermore, research directly exploring the role of SCFAs as potential mediators of the effects of microbiota-targeted interventions on affective and cognitive functioning is sparse, especially in humans. This Review summarizes existing knowledge on the potential of SCFAs to directly or indirectly mediate microbiota–gut–brain interactions. The effects of SCFAs on cellular systems and their interaction with gut–brain signalling pathways including immune, endocrine, neural and humoral routes are described. The effects of microbiota-targeted interventions such as prebiotics, probiotics and diet on psychological functioning and the putative mediating role of SCFA signalling will also be discussed, as well as the relationship between SCFAs and psychobiological processes. Finally, future directions to facilitate direct investigation of the effect of SCFAs on psychological functioning are outlined.

The gut–brain axis refers to the bidirectional signalling mechanisms between the gastrointestinal tract and the central nervous system (CNS)[1]. Through complex neurohumoral pathways, signals from the brain can alter the sensorimotor and secretory functions of the gut, and conversely, visceral afferent signals originating in the gastrointestinal tract can modulate brain function. The gut microbiota is the ecological community of symbiotic and pathogenic microorganisms present in the gut, some of which can be critically involved in gut–brain communication[2]. Imbalances in the microbial composition of the gut are present in gastrointestinal disorders such as IBS and coeliac disease, and metabolic disorders such as obesity and diabetes[3], as well as in mental illnesses such as eating disorders[4], autism spectrum disorder (ASD)[5] and mood and anxiety disorders[6]. Microbiota–gut–brain (MGB) communication can theoretically occur through multiple systems comprising the gut–brain axis (including the autonomic nervous system and enteric nervous system), neuroendocrine systems and the immune system. Nevertheless, the specific mechanisms of this communication and its putative effects on human brain development, behaviour, cognition and mood are largely unknown.

To explore the influence of the gut microbiome on psychological functioning, the microbiome can be modified by means of prebiotic, probiotic and dietary interventions. Experimental studies adopting this approach have demonstrated modulation of stress reactivity, affective and cognitive processes and behaviour in animals and, to a lesser extent, humans[7]. Although the biological mediators driving these effects remain largely unknown, short-chain fatty acids (SCFAs), which are microbial metabolites that constitute the major products from bacterial fermentation of dietary fibre in the intestines, are often considered key candidate mediators. SCFAs might be directly or indirectly involved in communication along the MGB axis owing to their neuroactive properties and their effects on other gut–brain signalling pathways including the immune and endocrine systems[8,9]. However, research directly exploring the role of SCFAs as potential mediators of the effects of microbiota-targeted interventions on affective and cognitive functioning is sparse, especially in humans. In this Review, we summarize the existing knowledge on the potential of SCFAs to mediate MGB interactions. We review the effect of microbiota-targeted interventions on psychological functioning and the putative mediating role of SCFA signalling therein. We also discuss the literature that examines the relationship between SCFAs and psychobiological processes, and finally, we outline future research directions to facilitate investigation of the effects of SCFAs on psychological functioning.

[1]*Translational Research Center in Gastrointestinal Disorders (TARGID), Department of Chronic Diseases, Metabolism, and Ageing, Faculty of Medicine, KU Leuven, Leuven, Belgium.*

[2]*Laboratory of Biological Psychology, Brain & Cognition, Faculty of Psychology and Educational Sciences, KU Leuven, Leuven, Belgium.*

**e-mail: kristin.verbeke@kuleuven.be*

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Key points

- Short-chain fatty acids (SCFAs) are speculated to have a mediational role in the microbiota–gut–brain axis crosstalk.
- SCFAs might influence psychological functioning via interactions with G protein-coupled receptors or histone deacetylases and exert their effects on the brain via direct humoral effects, indirect hormonal and immune pathways and neural routes.
- Dietary intervention studies indirectly implicate a mediational role for SCFAs in cognition and emotion.
- Animal studies provide direct evidence of the effects of SCFAs on neuropsychiatric disorders and psychological functioning, whereas human studies are sparse, suffer from methodological limitations and offer inconsistent conclusions.
- SCFAs should be quantified in the systemic circulation in dietary intervention studies, in which the effects on psychological functioning and psychopathology are an outcome of interest.
- SCFAs could ultimately be used as interventional substances to target microbiota–gut–brain interactions in humans.

Metabolism and local effects of SCFAs

SCFAs are saturated fatty acids with a chain length ranging from one to six carbon atoms and are the main products from the fermentation of dietary fibre in the colon[10]. Approximately 500–600 mmol of SCFAs are produced in the gut per day depending on the fibre content of the diet[11]. Acetate (C2), propionate (C3) and butyrate (C4) are the most abundant SCFAs in the human body and the most abundant anions in the colon[12]. They are responsible for the drop in pH when progressing from the terminal ileum to the proximal colon. Other SCFAs, namely, formate, valerate and caproate, are produced in lesser amounts[12]. Acetate, propionate and butyrate are present in the colon in an approximate molar ratio of 60:20:20, respectively[13], although the amount and relative proportion of each SCFA depend on the substrate, the microbiota composition and gut transit time[12] (TABLE 1). Following their production in the colon, SCFAs are rapidly absorbed by colonocytes, mainly via active transport mediated by monocarboxylate transporters (MCTs) (FIG. 1). MCT1 transports SCFAs in an H^+-dependent, electroneutral manner, whereas SCFA anion transport occurs via the electrogenic, sodium-dependent monocarboxylate transporter 1 (SMCT1; also known as SLC5A8). A comprehensive list of all known SCFA transporters is shown in TABLE 2. Absorption of undissociated SCFAs from the colon by passive diffusion is probably quantitatively less important, as is exchange for HCO_3^- via SLC26A3 (also known as downregulated-in-adenoma (DRA))[14].

After absorption by colonocytes, SCFAs enter the citric acid cycle in the mitochondria to generate ATP and energy for the cells[15]. SCFAs that are not metabolized in the colonocytes are transported into the portal circulation, where concentrations of SCFAs in humans have been reported to be, on average, 260 μM, 30 μM and 30 μM for acetate, propionate and butyrate, respectively[16]. In the liver, all three SCFAs are used as energy substrates for hepatocytes[15]. In addition, acetate is a substrate for cholesterol and fatty acid synthesis[17–19]. Propionate is a known precursor for the synthesis of glucose in the liver, at least in ruminants[20], but gluconeogenesis from propionate in the human liver is quantitatively less important[17]. Consequently, only a minor fraction of the colon-derived acetate, propionate and butyrate (36%, 9% and 2%, respectively[21]) reaches the systemic circulation and peripheral tissues. Plasma concentrations of acetate, propionate and butyrate have been reported in ranges of 25–250 μM, 1.4–13.4 μM and 0.5–14.2 μM, respectively[13]. Other sources of plasma acetate include endogenous production from fatty acid oxidation and amino acid metabolism[22,23], ketogenesis in hepatocytes[23] or oxidation of ethanol by microsomal cytochrome P450 enzymes[24]. Bovine milk fats also provide a source of butyrate, as 5–10% of the triacylglycerides mixture in bovine milk contains butyrate, which is then released in mammals by gastric lipase[25].

SCFAs can reach the brain, as they were shown to cross the blood–brain barrier (BBB) in a cell culture model[26], possibly owing to the abundant expression of MCTs on endothelial cells[27,28]. Brain uptake of SCFAs across the BBB in rats following injection of ^{14}C-SCFA in the carotid artery is in the relative order of butyrate (highest), propionate and acetate[29]. In human brain tissues, average concentrations of 17.0 pmol/mg of brain tissue for butyrate and 18.8 pmol/mg for propionate have been reported[30]. Using PET imaging, it was shown that ~3% of intravenously infused ^{11}C-acetate was immediately taken up in rat brain, whereas ~2% was taken up in the brain 20 minutes following colonic infusion[31]. However, brain uptake of ^{11}C-labelled butyrate in primates was limited to only 0.006% of the injected dose[32]. In human PET studies, no measurable brain uptake of ^{11}C-acetate was detected[33,34] up to 76 min after intravenous injection[34]. In summary, despite being able to cross the BBB, brain uptake of SCFAs appears to be minimal.

SCFAs exert a number of effects locally to improve gut health. For instance, SCFAs maintain intestinal barrier integrity and protect from intestinal inflammation[35]. The intestinal barrier is a physical barrier composed of epithelial cells connected via intercellular junctions, which facilitates the absorption of nutrients and prevents paracellular passage of harmful intraluminal substances and pathogens. Butyrate, in particular, is able to enhance intestinal barrier function by regulating the expression of tight junction proteins, and this effect might be mediated by the activation of AMP-activated protein kinase (AMPK)[36] or the downregulation of claudin 2 expression (a cation-selective pore)[37].

SCFAs also affect mucous production in the gastrointestinal tract. Mucus acts as a biological lubricant, decreasing the interaction between the epithelial cells and luminal microorganisms and toxic agents and protecting these cells from the fluctuating acidity during digestion[38,39]. Acetate and butyrate, but not propionate, increased mucin secretion following intraluminal administration in an isolated rat colon loop[40]. Butyrate stimulated mucin production in the mouse colon by affecting MUC2 gene expression[41]. Nevertheless, daily administration of butyrate enemas for 2 weeks did not affect MUC2 expression in colonic biopsy samples from healthy individuals or patients with ulcerative colitis in remission[42].

Preclinical rodent studies suggest that SCFAs can also influence gastrointestinal motility[43]. These effects

Table 1 | **Fibre substrates, their dietary source and SCFA-producing bacteria**

Substrates	Dietary source	Fermenting genera
Resistant starch	Cashew, green banana, white beans, oat and potato	• *Ruminococcus* • *Bacteroides*
Cellulose	Seaweed and cereal bran	• *Bacteroides* • *Ruminococcus*
Hemi-celluloses (xylan and arabinoxylan)	Cereal bran	• *Bacteroides* • *Roseburia* • *Prevotella*
Pectin	Apples, apricots, cherries, oranges and carrots	• *Eubacterium* • *Bacteroides* • *Faecalibacterium*
Fructans (inulin and fructooligosaccharides)	Asparagus, leek, onions, banana, wheat, garlic, chicory and artichoke	• *Bacteroides* • *Faecalibacterium*
Milk oligosaccharides	Breast milk	*Bifidobacterium*
Lactose (only in lactose-intolerant people)	Milk, yogurt, buttermilk and cheese	*Bifidobacterium*
β-Glucan	Oat, barley, wheat, rye, mushrooms and seaweed	• *Eubacterium* • *Atopobium* • *Enterococcus* • *Lactobacillus* • *Prevotella* • *Clostridium* cluster XIVa
Gum arabic	Acacia tree and prepared food additive	• *Bifidobacterium* • *Lactobacillus* • *Ruminococcus*
Guar gum	Guar bean and prepared food additive	• *Bifidobacterium* • *Ruminococcus*
Laminarin	Seaweed	*Prevotella*
Galacto-oligosaccharides	Artichoke, beans, beetroot, broccoli, chickpeas, fennel, lentils, lettuce, radicchio and onion	*Bifidobacterium*
Raffinose and stachyose	Cottonseed flour, soy flour, onions, chickpeas, beans, peas and lentils	• *Bifidobacterium* • *Lactobacillus*

SCFA, short-chain fatty acid. Data from REF.[252] and REF.[264].

might be mediated by activation of SCFA receptors[44], the release of gut hormone peptide YY (PYY)[43] or SCFA-induced serotonin release from enterochromaffin cells[45]. In humans, caecal infusion of SCFAs was found to relax the proximal stomach[46]; however, no evidence indicates their effect on human colonic motility[47].

Finally, butyrate has long been known to exhibit inhibitory effects on tumorigenesis and might play a role in reducing the risk of colorectal cancer (extensively reviewed elsewhere[48,49]). The mechanisms involved in its anti-carcinogenic effects include decreasing cell proliferation, inhibiting migration of neoplastic cells, promoting differentiation and cell death, supressing angiogenesis, metastasis and survival of tumour cells and exhibiting anti-inflammatory and immunomodulatory properties[50]. The anti-inflammatory effects of butyrate and other SCFAs are discussed later in this Review.

SCFAs in gut–brain signalling

In addition to exerting local effects in the colon, SCFAs act as endogenous ligands for orphan G protein-coupled receptors (GPCRs), and intracellular SCFAs affect gene expression by inhibiting histone deacetylases (HDACs). Additionally, SCFAs affect inflammation and hormonal regulation and interact with vagal afferents. In this section, we outline the interactions of SCFAs with specific cellular systems and gut–brain signalling pathways, arguing for a potential key role of SCFAs in MGB communication (FIG. 2).

Effects on cellular systems

SCFA receptors. The best-studied SCFA receptors are GPR43 and GPR41, which were later renamed as free fatty acid receptor 2 (FFAR2) and FFAR3, respectively. These receptors are activated by SCFA anions such as formate, acetate, propionate and butyrate although with differing specificity for carbon chain length[51]. FFAR2 is expressed mainly in enteroendocrine L cells, the vasculature and immune cells, including lymphocytes, neutrophils and monocytes[52,53]. FFAR3 is expressed in the colon, kidneys, sympathetic nervous system and blood vessels[54–56]. G protein-coupled receptor 109 A (GPR109A; also known as HCAR2), initially identified as a receptor for niacin present on adipocytes, immune cells and colonocytes, is activated by butyrate and β-D-hydroxy butyrate[57,58]. Other receptors activated by SCFAs are listed in TABLE 3.

Evidence exists for the presence of functional SCFA receptors in the CNS and peripheral nervous system (PNS). FFAR3 is highly expressed in rat brain tissue[59] and in sympathetic ganglia, specifically the superior cervical ganglion, in adult mice[60]. The expression of FFAR3 in the sympathetic ganglia seems important in controlling sympathetic nerve activity, as reduced activity was observed in *Ffar3*$^{-/-}$ mice[60]. Furthermore, intraperitoneal administration of propionate (1 g/kg) resulted in increased heart rate in wild-type and *Ffar2*$^{-/-}$ mice but not in *Ffar3*$^{-/-}$ mice. The expression of FFAR3 was confirmed in mice in the superior cervical ganglion and in the sympathetic ganglia of the thoracic and lumbar sympathetic trunk, as well as in both autonomic and sensory ganglia, such as the vagal ganglion, spinal dorsal root ganglion and trigeminal ganglion[55]. Contrary to the evidence from rats[59], however, FFAR3 was not found in the brain or spinal cord of mice[55].

FFAR3 signalling is implicated in propionate-induced intestinal glucogenesis via gut–brain neurocircuitry. Both propionate and butyrate increase intestinal glucose production; however, butyrate does so directly by upregulating intestinal glucogenesis genes (*G6PC* and *PCK1*), whereas propionate does so indirectly. Propionate receptor FFAR3 is present in the nerve fibres of the portal vein wall and is necessary for in vivo propionate-induced intestinal glucogenesis[61]. Propionate feeding also affected CNS regions implicated in receiving signals from the portal area via the vagal and spinal pathways. Specifically, this study found FOS activation (a marker for neuronal activation) following propionate feeding in all areas of the dorsal vagal complex, the C1 segment of the spinal cord and the parabrachial nucleus. Hypothalamic areas, namely, the paraventricular nucleus, the lateral hypothalamus and the arcuate nucleus, which receive input from the parabrachial nucleus, also exhibited FOS activation in response to

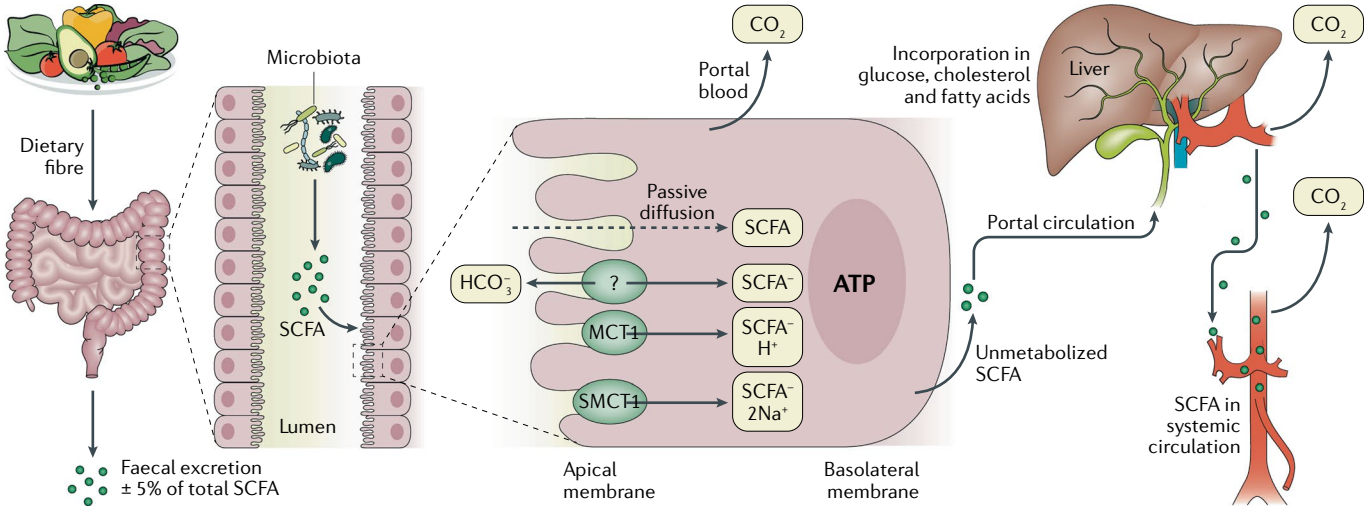

Fig. 1 | **Metabolism of SCFAs from dietary fibre to systemic circulation.** Fermentation of dietary fibre by commensal gut bacteria in the colon leads to the production of short-chain fatty acids (SCFAs), which are rapidly absorbed by colonic cells via monocarboxylate transporters, passive diffusion or exchange with bicarbonate (HCO_3^-) via an exchanger of unknown identity and then partly oxidized to CO_2, producing energy for the cells in the form of ATP. SCFAs that are not metabolized by colonic cells travel via the basolateral membrane into the portal circulation to the liver, providing an energy substrate for hepatocytes via oxidation. SCFAs are also incorporated in hepatocytes during the biosynthesis of glucose, cholesterol and fatty acids. Thus, only small amounts of the colonically produced SCFAs reach systemic circulation. MCT1, monocarboxylate transporter 1; SMCT1, sodium-dependent monocarboxylate transporter 1.

propionate feeding[61]. These findings indicate that propionate acts via FFAR3 on the periportal afferent neural system, which subsequently signals to peripheral and CNS areas, to induce intestinal gluconeogenesis. Together, these findings suggest that, through binding of GPCRs, SCFAs might affect the CNS and PNS, which is a prerequisite for their putative effects on psychological processes.

Histone deacetylase inhibition. Gene expression can be regulated by modulating the coiling of the DNA around histones, mostly via acetylation of the histones[62]. Acetylated histones exhibit less compact and more transcriptionally active chromatin. Conversely, removal of the acetyl groups by HDACs leads to condensed and transcriptionally silenced chromatin[62]. Studies show that intracellular butyrate and propionate[63], as well as acetate[64], inhibit the activity of HDACs, promoting hyperacetylation of histones. HDACs are involved in brain development and a range of neuropsychiatric diseases including depression, schizophrenia, Alzheimer disease and addiction[65]. Furthermore, preclinical studies in rodents suggest that HDAC inhibitors act as cognitive enhancers in fear, anxiety and trauma-related processes and might be used in conjunction with psychotherapy to promote long-term positive treatment outcomes and relapse prevention[66].

Evidence demonstrating SCFA-mediated HDAC inhibition and its effects on the brain mostly comes from animal research with sodium butyrate. Chronic (28 days) and acute systemic administration of butyrate (0.6 g/kg) combined with fluoxetine (10 mg/kg) (a selective serotonin reuptake inhibitor antidepressant) substantially decreased behavioural despair in mice in comparison with fluoxetine alone[67], with the acute administration resulting in upregulation of brain-derived neurotrophic factor (BDNF) transcript levels, suggesting that upregulation of BDNF expression might be important for the observed effect. Notably, histone hyperacetylation following systemic injection of a single dose of sodium butyrate (1.2 g/kg) was observed in the hippocampus and frontal cortex and might explain the superior antidepressant effects of the combined treatment over fluoxetine alone. Chronic inhibition of HDACs by intraperitoneal injection of sodium butyrate (1.2 g/kg daily for 4 weeks) also improved learning and memory in wild-type mice and in mice with brain atrophy[68]. Furthermore, systemic (1.2 g/kg) and intrahippocampal (55 mmol/l) injection of sodium butyrate in mice induced enhanced and persistent extinction of fear[69]. For a more extensive summary on the effects of butyrate administration on brain physiology and function, the reader is directed elsewhere[8].

Although studies in mice solely used butyrate, propionate and acetate are also capable of inhibiting HDACs, albeit to a lesser extent[64,70]. In a rat hepatoma cell line, propionate administration resulted in build-up of acetylated forms of histones[70]. Furthermore, using purified calf thymus HDACs, propionate inhibited HDACs in vitro to a similar extent as butyrate[70]. Acetate increases histone acetylation not only by inhibiting deacetylation but also by stimulating acetylation. Acetate supplementation using a single dose of glyceryl triacetate (6 g/kg) in rats increased acetylation in brain histones, possibly via inhibition of HDAC2, as increased brain histone acetylases temporally coincided with decreases in HDAC2 protein levels, and acetate supplementation had no effect on histone acetyltransferases[64]. By contrast, long-term acetate supplementation in rats did not affect total brain HDAC levels and had variable effects on class I

and II HDACs, but increased histone acetylation by increasing brain levels of histone acetyltransferases[71], suggesting that HDAC inhibition might become desensitized in the long term and that other transcription processes could be at play.

The dose of SCFAs, particularly butyrate, might be critical in determining the effects on behavioural and psychophysiological processes. Intraperitoneal injection of sodium butyrate (100 mg/kg daily for 10 days) attenuated social deficits in a mouse model for ASD with no adverse effects on locomotor and anxiety-related behaviours[72]. However, intraperitoneal injection of the dose normally used to induce HDAC inhibition (1.2 g/kg) did not affect the examined social behaviours[72]. The high dose of butyrate induced global changes in histone acetylation, whereas the low dose selectively modified the expression of genes involved in excitatory and inhibitory pathways in the prefrontal cortex. In another study, the dose of 1.2 g/kg of sodium butyrate acted as a pharmacological stressor, increasing plasma levels of the stress markers corticosterone and adrenocorticotropic hormone (ACTH), as well as glucose[73], whereas a low dose (200 mg/kg) only slightly increased ACTH. As argued by Stilling et al.[8], butyrate is usually administered at supraphysiological concentrations in animal studies. Consequently, it is currently unclear whether butyrate at physiological concentrations (10 μM in mouse plasma[74] and 0.5–14.2 μM in human plasma[13]) does influence the brain through a different mechanism than HDAC inhibition, still influences the brain through HDAC inhibition or does not influence the brain at all. The last possibility is questionable, as a physiological oral dose of butyrate affected brain metabolism and hippocampal neurogenesis in pigs[75]. Some studies also showed that diet modifies histone acetylation[76] and that SCFAs are at least partially responsible for this modification[77]. Together, these findings suggest that butyrate, and perhaps other SCFAs, do play a part in diet-induced chromatin changes, but whether these changes also occur directly in the brain, or reach the brain indirectly (for example, via expression of genes associated with immune function), remains to be demonstrated.

Other histone modifications including crotonylation, butyrylation and hydroxybutyrylation have been identified over the past decade, but their functional importance remains unclear. Histone crotonylation positively correlates with gene expression and promotes histone acetylation, but it might have a more direct role in promoting transcription than histone acetylation[78]. Moreover, crotonyl-coenzyme A, an intermediate in the fermentation of butyrate, increased histone crotonylation and subsequently transcription in vivo and in vitro[78]. One study found that histone crotonylation is abundant in both the intestinal epithelium and the brain in mice[79]. Notably, the gut microbiota and SCFAs were important to histone crotonylation, with butyrate specifically promoting histone crotonylation in intestinal cell culture and organoid culture[79]. As SCFAs can enter the brain via the BBB, they might induce CNS histone crotonylation, thereby influencing brain functions[79].

In summary, SCFAs might influence brain function via interaction with FFARs and/or inhibition of HDACs (FIG. 2). However, studies exploring SCFA interactions with these cellular systems are lacking in humans. Exploration of the dose–response effect of individual SCFAs on HDAC inhibition and post-translational modifications is needed. Specifically, it will be critical to determine whether an SCFA dose produces a global, potentially unfavourable HDAC inhibition versus a more specific HDAC inhibition that modulates a psychological response in the desired direction.

Table 2 | **Overview of SCFA transporters and their localization in the body and the brain**

Transporter	Localization in the body	Localization in the CNS and/or brain	SCFA substrate	Refs
MCT1 (SLC16A1)	Ubiquitous; apical membrane and basolateral membrane of colonic epithelium and small intestine	Ubiquitous; brain endothelial cells, astrocytes, ependymocytes and some neurons in rats	Acetate, propionate and butyrate; butyrate uptake mainly involves this transporter	265–267
SMCT1 (SLC5A8)	Entire large intestine (apical membrane), kidney and retina	Neurons	Acetate, propionate and butyrate; butyrate faster than propionate and acetate	268–270
SMCT2 (SLC5A12)	Apical membrane of colonic epithelium and small intestine, kidney and retina	Astrocytes and glia	Low affinity for propionate and butyrate	268,271,272
SLC26A3	Apical site of colonocytes and basolateral site of colonocytes	ND	Acetate, propionate and butyrate	14
MCT2 (SLC16A7)	Stomach and small intestine	• Ubiquitous but strong expression in cortex, hippocampus and cerebellum • Neurons and some astrocytes in rats	Probably low affinity for acetate, propionate and butyrate	265–267
MCT4 (SLC16A3)	Basolateral membrane of colonic epithelium, small intestine skeletal muscle, brain, kidney, placenta, leukocytes, heart, lung and chondrocytes	• Ubiquitous, but strong expression in cortex, hippocampus and cerebellum • Astrocytes	High affinity for butyrate	28,265–267
OAT7 (SLC22A9)	Liver and sinusoidal membrane of hepatocytes	ND	Butyrate	273,274
OAT2 (SLC22a7)	Kidney and liver	ND	Propionate (other SCFAs ND)	274,275

CNS, central nervous system; MCT, monocarboxylate transporter; ND, not determined; OAT, organic anion transporter; SCFA, short-chain fatty acid; SMCT, sodium-dependent monocarboxylate transporter. Data from (REF.[27]).

Effects on gut–brain pathways

Immune pathways. Immune responses and inflammation might be involved in the pathogenesis of psychiatric disorders[80,81] (FIG. 3). CNS–cytokine interactions influence neural processes, thereby affecting the function of neurocircuits that regulate mood, motor activity and motivation[82]. Microglia dysregulation was reported in a range of psychiatric disorders including major depression, schizophrenia, ASD and obsessive–compulsive disorder[83]. The effects of SCFAs on intestinal mucosal immunity are well documented[84], yet SCFAs might also affect the peripheral immune system to modulate brain function. Systemic inflammation might be reduced indirectly by improving the intestinal barrier and preventing translocation of bacteria and bacterial products or by direct interaction between SCFAs and immune cells, which might, in turn, reduce neuroinflammation in the brain.

SCFAs directly affect immune cells and immune modulators to maintain homeostasis[84]. SCFAs regulate the differentiation, recruitment and activation of neutrophils, dendritic cells (DCs), macrophages and monocytes, and T cells[84]. Neutrophils originate from the bone marrow and are the most abundant type of granulocytes, forming an essential part of the innate immune system. They are the first to arrive at the site of inflammation and recruit other cells, including macrophages, via the production of cytokines[85]. SCFAs directly affect neutrophils by regulating the production of inflammatory cytokines such as TNF, possibly through HDAC inhibition, and act as neutrophil chemoattractants by regulating the production of chemokines such as CXCL1 and CXCL8 (REF.[85]). SCFAs affect neutrophil chemotaxis by activating FFAR2, which is present on these cells[85].

Monocytes are large phagocytic white bloods cells that play a critical role in adaptive immune responses. Upon infection of a tissue or an organ, monocytes leave the bloodstream and differentiate into macrophages and DCs as they enter the affected site. SCFAs inhibit the maturation of monocytes, macrophages and DCs, altering their abilities to capture antigens and reducing their ability to produce pro-inflammatory cytokines such as IL-12 and TNF[84,86]. SCFAs seem to affect these cells by inhibiting HDACs, which in turn suppresses the expression of important transcription factors[86].

Finally, SCFAs are able to modulate adaptive immune responses by direct or indirect modulation of T cell differentiation and proliferation. SCFAs indirectly modulate T cell differentiation by inhibiting DC maturation and modulating their production of immune mediators[87]. These effects might be due to activation of GPR109A present on DCs[88]. Exposing DCs to butyrate also resulted in the expression of the enzymes indoleamine 2,3-dioxygenase 1 and aldehyde dehydrogenase 1A2, which exhibit immunosuppressive properties and promote the conversion of naive T cells into forkhead box P3 (FOXP3)$^{+}$ regulatory T cells rather than pro-inflammatory IFNγ-producing cells[89]. It has been suggested that HDAC inhibition mediates the effect of SCFA on DCs[89]. Alternatively, SCFAs can also directly affect T cells by promoting the generation of T helper 1 (T_H1) cells and T_H17 cells[87,90]. Conversion of acetate into acetyl-CoA leads to the integration of SCFAs into cellular metabolism, which boosts mTOR activation. This process in turn facilitates the differentiation of T cells into T_H1 cells, T_H17 cells and IL-10^{+} T cells[91,92]. HDAC inhibition by SCFAs in T cells increased mTOR activity and the subsequent differentiation into T helper cells[93]. SCFA receptors FFAR3 and FFAR2 do not appear to mediate SCFA-induced T cell differentiation[93].

As SCFAs can reach the bloodstream, they have the potential to modulate immune cell function in the systemic circulation and potentially influence brain and neuronal function. For example, oral administration of butyrate and propionate promoted peripheral regulatory T cell generation in mice[94]. Furthermore, acetate or FFAR2-specific and FFAR3-specific synthetic agonists modulate human, but not mouse, monocyte inflammatory responses in vitro via activation of FFAR2 and FFAR3, resulting in increased p38 phosphorylation and decreased pro-inflammatory cytokine expression[95]. One study suggested that LY6C^{hi} monocytes might be important for hippocampal neurogenesis[96]. Specifically, hippocampal neurogenesis and memory retention were

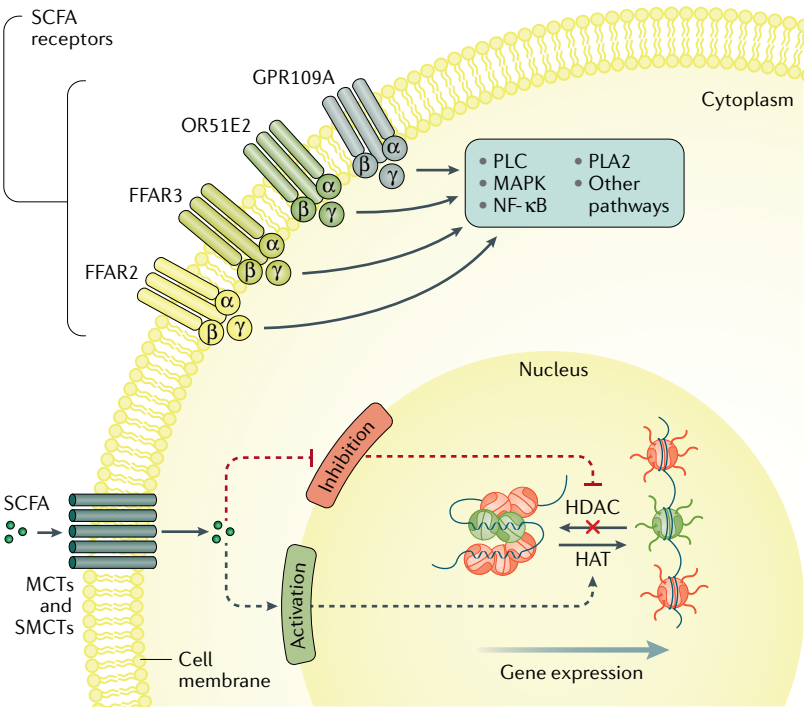

Fig. 2 | **SCFA cellular signalling pathways.** Short-chain fatty acids (SCFAs) might influence microbiota–gut–brain interactions by signalling to the host via free fatty acid receptors (FFARs) FFAR2 and FFAR3, as well as G protein-coupled receptor 109A (GPR109A) and olfactory receptor 51E2 (OR51E2; also known as OLFR78 in mice), which, once activated, result in further signalling cascades that include phospholipase C (PLC), mitogen-activated protein kinases (MAPKs), phospholipase A2 (PLA2) and nuclear factor-κB (NF-κB) pathways (see TABLE 3). Intracellular SCFAs can also influence acetylation and deacetylation of histones, thereby promoting gene transcription. This process occurs either via inhibiting the activity of histone deacetylases (HDACs), resulting in more transcriptionally active chromatin, or by increasing the activity of histone acetyltransferases (HATs), thereby stimulating acetylation. These processes can occur in colonocytes but also possibly in every cell within a tissue that is accessible by SCFAs, either indirectly via FFARs or directly via monocarboxylate transporters (MCTs) and sodium-dependent monocarboxylate transporters (SMCTs). Adapted from REF.[84], CC-BY-4.0.

Table 3 | **Overview of SCFA receptors and their localization in the body and the brain**

Receptor	Name	Localization in the body	Localization in the CNS, PNS and/or brain	SCFA substrate	Refs
FFAR2 (GPR43)	Free fatty acid receptor 2 (G protein-coupled receptor 43)	Colonic epithelium, enteroendocrine cells, mast cells, neutrophils, macrophages, monocytes, regulatory T cells, B lymphocytes, polymorphonuclear cells, eosinophils, adipocytes, small intestinal epithelium, leukocytes (eosinophils, basophils, neutrophils, monocytes and dendritic cells), skeletal muscle, heart and spleen	ND	Acetate and propionate	51,53,60, 114,276–278
FFAR3 (GPR41)	Free fatty acid receptor 3 (G protein-coupled receptor 41)	Colonic epithelium, enteroendocrine cells, small intestinal epithelium, mast cells, spleen, pancreas, bone marrow, lymph nodes, adipose tissue, peripheral blood mononuclear cells and periportal afferent system	Sympathetic ganglia, vagal and dorsal root and trigeminal ganglia	Acetate, propionate and butyrate	51,55,56, 60,61,148
GPR109A	G protein-coupled receptor 109A	Apical membrane of colonic and/or small intestinal epithelium, macrophages, monocytes, neutrophils, dendritic cells, adipocytes, epidermal Langerhans cells and retinal pigment epithelium	Rostral ventrolateral medulla and PC12 cells	Butyrate	57,88,279
OR51E1 (GPR164)	Olfactory receptor 51E1 (G protein-coupled receptor 164)	Cardiac, fundic, pyloric, duodenal, jejunal, ileal, caecal, colonic and rectal mucosa	ND	Butyrate	280
OR51E2 (Olfr78)	Olfactory receptor 51E2 (Olfactory receptor 78)	Kidney: renal juxtaglomerular apparatus; smooth muscle cells of other arteries and a subset of nerves in the heart and in the gut, blood vessels and melanocytes	Neurons: ganglia of the autonomic nervous system and sphenopalatine ganglion	Propionate and acetate	281,282
GPR42	G protein-coupled receptor 42	Human colon	Human abdominal sympathetic ganglia and rat superior sympathetic neurons	Propionate	283,284

CNS, central nervous system; ND, not determined; PNS, peripheral nervous system; SCFA, short-chain fatty acid. Data from (REF.[285]).

decreased following antibiotic treatment in mice and restored upon reconstitution of a normal gut microbiota combined with probiotics or physical exercise. These mice had higher numbers of LY6C^{hi} monocytes in the brain than antibiotic-treated mice, and depletion of these monocytes decreased neurogenesis in the brain, whereas adoptive transfer of LY6C^{hi} monocytes rescued neurogenesis in antibiotic-treated mice, demonstrating that these monocytes are important messengers signalling from the periphery to restore brain homeostasis[96]. Thus, monocytes can probably be regulated via microbially derived SCFAs, and after subsequently reaching the bloodstream and the brain, the monocytes might then influence neural structure and function and higher-order brain functions.

Human studies on the modulation of systemic inflammation by SCFAs are scarce and have yielded inconsistent results. In a systematic review[97], only two of five studies administering SCFAs showed statistically significant decreases in serum inflammatory markers. Plasma TNF levels significantly ($P < 0.04$) decreased in hyperinsulinaemic female individuals after intravenous or rectal administration of acetate[98]. In the second study in overweight or obese normoglycaemic men, fasting levels of IL-1β significantly decreased ($P < 0.05$) following colonic infusion of an SCFA mixture high in acetate (24 mmol sodium acetate, 8 mmol sodium propionate and 8 mmol sodium butyrate) in comparison with an SCFA mixture high in propionate (18 mmol sodium acetate, 14 mmol sodium propionate and 8 mmol sodium butyrate), with the acetate mixture inducing nonsignificantly lower IL-1β levels than placebo (40 mmol sodium chloride)[99]. The studies that failed to demonstrate an effect of SCFAs on systemic inflammation administered SCFAs for periods between 3 and 20 days[100–102], suggesting that the effects of SCFAs on pro-inflammatory cytokines might be observable only after acute administration. However, it remains difficult to compare these studies given the small sample sizes (<16 participants) and the heterogeneity of the study populations. Comparatively, 29 and 26 studies have investigated the effects of prebiotic and synbiotic (mixtures of prebiotics and probiotics) supplementation on systemic inflammation, respectively[97]. Inflammatory markers were decreased in 48% of the prebiotic studies and 53% of the synbiotic studies, with no effect on inflammation in the remaining studies, and in a few studies, even an increase in inflammation was observed. Although the meta-analysis did not take into account changes in SCFA levels reported in some of the prebiotic or synbiotic studies (only 5 out of 55 studies)[103–107], SCFAs were suggested to drive the effects on systemic inflammation on the basis of the administered substrate and/or changes in gut microbiota composition[97].

Systemic inflammation is highly important in brain immunity and can modulate neuroinflammation[108,109]. Butyrate decreased lipopolysaccharide (LPS)-induced inflammation in rat primary microglia, hippocampal

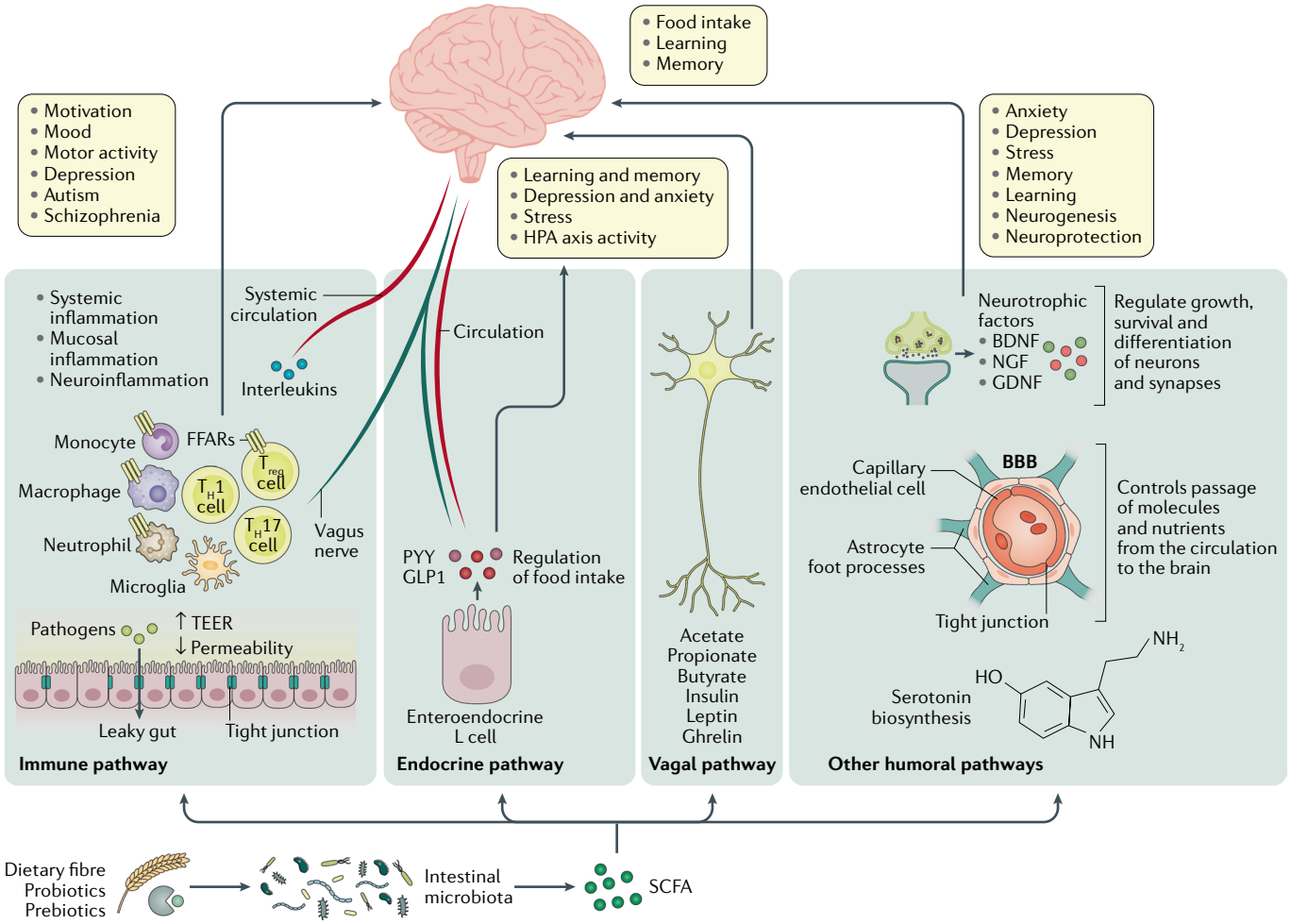

Fig. 3 | **Potential gut–brain pathways through which SCFAs might modulate brain function.** Fermentable dietary fibre, prebiotics and probiotics contribute to increases in short-chain fatty acids (SCFAs) via proliferation of beneficial SCFA-producing bacteria or fermentation of complex carbohydrates. SCFAs might influence gut–brain communication and brain function directly or indirectly through immune, endocrine, vagal and other humoral pathways. Via the immune route, SCFAs locally interact with intestinal epithelial cells and immune cells, such as monocytes and neutrophils, by activating free fatty acid receptors (FFARs) or by inhibiting histone deacetylases. In turn, these processes can influence intestinal mucosal immunity and barrier function. SCFAs can also enhance barrier integrity by upregulating the expression of tight junction proteins and augmenting transepithelial electrical resistance (TEER). Peripherally, SCFAs influence systemic inflammation by regulating the secretion of interleukins. SCFAs also influence neuroinflammation by affecting microglia cell morphology and function, thereby potentially affecting emotion, cognition and pathophysiology of mental disorders. Via the endocrine pathway, SCFA interaction with their receptors on colonocytes promotes indirect signalling to the brain via the systemic circulation or vagal pathways by inducing the secretion of gut hormones such as glucagon-like peptide 1 (GLP1) and peptide YY (PYY) from the enteroendocrine L cells. These hormones can in turn influence learning, memory and mood. SCFAs can directly activate vagal afferents via FFARs, thereby signalling to the brain. Finally, SCFAs can cross the blood–brain barrier (BBB) via monocarboxylate transporters located on endothelial cells and influence BBB integrity by inhibiting pathways associated with inflammatory responses. They also modulate levels of neurotrophic factors centrally via histone acetylation and can contribute to the biosynthesis of serotonin. Together, interaction of SCFAs with these gut–brain pathways can directly or indirectly modulate processes associated with neural functioning, learning, memory and mood. BDNF, brain-derived neurotrophic factor; GDNF, glial cell line-derived neurotrophic factor; HPA, hypothalamus–pituitary–adrenal; NGF, nerve growth factor; T_H1, T helper 1; T_H17, T helper 17; T_{reg} cell, regulatory T cell.

slice cultures and co-cultures of rat cerebellar granule neurons, astrocytes and microglial cells[110]. However, in murine N9 microglia cells, which have been stimulated with an extracellular ATP challenge and transformed into amoeba-like cells, butyrate and propionate had a pro-inflammatory effect[110]. In another study, the microbiota was found to influence homeostasis, maturation and the function of microglia in the CNS[111]. Specifically, germ-free mice exhibited compromised innate immune responses owing to microglia-related defects. When challenged with LPS and lymphocytic choriomeningitis virus, the microglial innate immune response of the germ-free mice was severely reduced compared with that of specific pathogen-free mice. Furthermore,

microbiota depletion via antibiotic administration in specific pathogen-free mice severely compromised microglia homeostasis, resembling that in germ-free mice[111]. Notably, 4-week oral administration of an SCFA mix in the drinking water of germ-free mice resulted in restored microglial cell morphology and reversed microglial immaturity. In further support of a crucial role of SCFAs, SCFA-treated *Ffar2*$^{-/-}$ mice continued to exhibit malformed microglia in terms of major alterations of dendrite length, number of segments, branching points, terminal points and increased cell volumes[111].

Prebiotic treatment also altered neuroimmune responses, potentially via SCFAs. Mice fed the prebiotic β-galacto-oligosaccharides (BGOS) showed reduced anxiety following LPS-induced inflammation compared with control mice[112]. Furthermore, LPS-induced increases in IL-1β levels and 5-HT2AR (also known as 5-HT2) expression in the frontal cortex were lower in the BGOS group than in the control group. These attenuated neuroimmune responses were attributed to fermentation of BGOS into SCFAs.

Taken together, these results suggest that the gut microbiota might affect systemic inflammation and central neuroimmune function, with SCFAs being candidate mediators of these effects. SCFAs interact with a variety of immune cells, influencing systemic inflammation and affecting microglia structural and functional integrity and microglia-related activation involved in neuroinflammation. Studies of prebiotic interventions that result in decreased systemic inflammation could benefit from concurrent measurement of plasma SCFAs to confirm a potential mediational effect of SCFAs on pro-inflammatory and anti-inflammatory markers. Results from mouse studies seem promising, but translation to, and replication in, humans is lacking but might be possible in vivo using PET imaging.

Endocrine pathways. SCFAs can also exert their effects on the gut–brain axis by modulating secretion of gut hormones (FIG. 3). In humans, supplementation of fermentable polysaccharides increased plasma levels of PYY and glucagon-like peptide 1 (GLP1)[113]. The mechanism underlying the production of these gut hormones is the activation of GPCRs by SCFAs in the colon, which stimulates the release of GLP1 and PYY from enteroendocrine L cells[114–116]. This process might in turn activate a signalling cascade affecting brain circuits involved in appetite and food intake regulation, either through the systemic circulation[98] or through vagal afferents[117].

GLP1 is best known as an incretin hormone that enhances glucose-dependent insulin secretion. However, it is also secreted in the nucleus tractus solitarius of the brainstem[118]. GLP1 can influence brain function via humoral and neural pathways[119], and its receptors are widespread across the body, including in the pancreas, intestines, heart and lungs, as well as the CNS and PNS[120]. Administration of GLP1 or a GLP1 receptor agonist affected responses to food pictures in reward-related brain regions in participants with obesity[121], had anxiogenic effects under acute administration and antidepressant effects under chronic administration in rats[122] and increased ACTH and cortisol levels in animals and humans[123]. In mice, GLP1 was involved in improved learning and memory[124,125], improved neuroprotection and neuroplasticity in the hippocampus[126,127] and reduced β-amyloid plaques and microglia activation in animal models of Alzheimer disease[126].

PYY is another anorexic neuropeptide that inhibits gastric motility and reduces appetite. In addition to its secretion from L cells in the distal gastrointestinal tract (ileum and colon), PYY is expressed in various regions of the human brain with the highest concentrations found in the hypothalamus and the pituitary gland[128]. The most common form of circulating PYY is the truncated form, $PYY_{3\text{-}36}$, which preferentially binds to the Y2 neuropeptide Y receptor[129]. Animal studies suggest that PYY influences appetite and brain function through mechanisms involving either crossing the BBB[130] or transmitting to the brainstem by activating vagal afferent pathways that extend to the myenteric plexus and lamina propria layers of the gut wall[131,132]. PYY influences affective state, but evidence regarding the nature of its effects is contradictory. Knockout of the gene encoding PYY exacerbated both depressive-like and anxiety-like behaviour in mice[133], whereas in another study, depressive-like but not anxiety-like behaviour was exacerbated[134]. Knockout of Y2 receptors enhanced ability to cope with stress and reduced anxiety in mice[135], while stimulating the receptors increased anxiety-like and depressive behaviour[136].

The extent to which SCFA-induced changes in GLP1 and PYY mediate brain function is not well investigated. One study found that increased colonic propionate produced by consumption of an inulin–propionate ester influenced brain anticipatory reward responses in the caudate and nucleus accumbens during a functional MRI food picture evaluation task in non-obese men[137]. In parallel, decreases in the subjective appeal of high-energy food pictures and reduced energy intake during an ad libitum meal were also observed[137]. However, no changes in plasma PYY and GLP1 levels were observed. In another study using the same propionate-delivery method, however, acute supplementation increased plasma PYY and GLP1 levels, but long-term supplementation did not[138], suggesting that gut hormones might be differently involved in SCFA brain effects in the long versus short term. Studies that have examined the direct effect of PYY and GLP1 on the brain render it difficult to judge whether intravenous injection of GLP1 and PYY induces similar psychological changes to those seen when they are produced by the enteroendocrine L cells. In addition, it is unclear whether SCFA-induced GLP1 and PYY production in the enteroendocrine L cells would attenuate or exacerbate stress, anxiety and depressive-like behaviour.

Other metabolic hormones that influence brain function and that are affected by SCFAs include leptin, ghrelin and insulin; however, these hormones have been studied less extensively than PYY and GLP1. Leptin is an anorexigenic hormone predominantly secreted from adipose cells[139] and is mainly known for its regulatory role in energy balance by activating its hypothalamic receptors to express orexigenic and anorexigenic neuropeptides such as neuropeptide Y and α-melanocyte-stimulating hormone, thereby inhibiting food intake[140]. All SCFAs

seem to regulate leptin production, but the directionality and mechanisms are not clear[141]. Acetate and propionate increased leptin expression in adipocytes[142–145], and whereas one study[146] found that butyrate had no effect on leptin secretion, another found that fasting leptin levels were significantly reduced following chronic supplementation of all SCFAs separately, including butyrate[147]. Furthermore, although an involvement of FFAR2 in SCFA-induced leptin regulation is implicated by some studies[143,145,146], others suggest that FFAR3 is involved[142,148], and one study found no effect of SCFAs or expression of FFARs in relation to leptin[149]. The BBB and the vagus nerve have been implicated in the effect of leptin on the brain, although transport-related and receptor-related mechanisms are not clear[150–154]. Leptin signalling also influences non-hypothalamic areas such as the cortex and the hippocampus, thereby potentially modulating a range of brain functions involved in reward, motivation and cognition, as well as brain structure, neuronal and synaptic function and neuronal plasticity[155]. Disruption in leptin signalling has been associated with Alzheimer disease, depression, bipolar disorder and schizophrenia[156].

Ghrelin, the main orexigenic hormone, is produced by ghrelin cells that are mainly present in the stomach and duodenum and functions as a neuropeptide in the CNS[157]. Ghrelin influences the brain through the vagus nerve[158] or by crossing the BBB[159] and acts on the hypothalamus to increase hunger and prepare the body for food intake[160]. Plasma ghrelin concentrations decreased after injection of SCFAs in wethers (castrated rams)[161] independently of circulating glucose and insulin concentrations. Furthermore, ingestion of inulin increased serum SCFA levels and reduced ghrelin in lean and obese individuals[162,163]. The mechanisms that mediate this inverse relationship between SCFAs and ghrelin are not clear. However, ghrelin modulates a number of brain functions. Specifically, intravenous administration of ghrelin in humans activated brain regions (including the amygdala and the orbitofrontal cortex) implicated in reward and the incentive value of food cues[164], suggesting modulation of hedonic, as opposed to solely homeostatic, responses to food. In mice, ghrelin modulated neuronal and synaptic function in the hippocampus, which was paralleled by enhanced learning and memory[165,166]. Furthermore, ghrelin modulated stress, depression and anxiety via the hypothalamus–pituitary–adrenal (HPA) axis, the serotonergic system and the sympathetic nervous system[167].

Insulin is a hormone produced by the pancreas that enables the body to maintain stable blood sugar levels, preventing hyperglycaemia and hypoglycaemia[168]. Earlier work found that infusion of propionate and butyrate, but not acetate, in sheep increased plasma insulin levels 4-fold and 14-fold, respectively, without affecting plasma glucose. These effects were also found in cows but not in non-ruminant species (rats, rabbits or pigs)[169,170]. In humans, supplementation (30 g per day for 4 weeks) of resistant starch, which is fermented into SCFAs, increased both SCFAs and systemic and muscle insulin sensitivity despite decreased insulin levels[171]. Insulin is also a CNS regulatory peptide, and peripheral insulin can be taken up by the brain, but the mechanisms remain a matter of debate[172]. Insulin might influence the brain from the periphery, following intravenous administration, or centrally, following intranasal and intracerebroventricular routes to the CNS[172] or intracranial or intrathecal transplantation of pancreatic islets[173]. A large body of literature suggests that insulin availability and/or alterations in insulin receptor sensitivity or availability are relevant to brain function. This observation has been made in relation to cognitive function and mood in Alzheimer disease[174–177] and bipolar disorder[178] but not in major depressive disorder[179]. However, a neural circuit involving the ventral striatum, insula and anterior mid-cingulate cortex linked increased insulin resistance with depressed mood in healthy humans[180]. Intranasal administration of insulin to a healthy population improved learning and memory, as well as responses to psychosocial stress[181,182].

More research is needed to discern whether there is a direct effect of SCFAs on leptin, ghrelin and insulin and the mechanisms underpinning these effects. Surprisingly, in mice, chronic intragastric acetate infusion doubled acetate turnover in the brain during high-fat diet consumption in comparison with chow diet and increased insulin and ghrelin secretion, caloric intake and weight gain. These effects were prevented by vagotomy, suggesting that the effect of chronic acetate administration is mediated by parasympathetic activation[183]. Whether SCFA-prompted release of these hormones has positive or negative effects on the brain and its psychobiological functions is difficult to predict. Nonetheless, studies suggest that SCFAs increase the production of some hormones in the gastrointestinal tract and that these hormones influence mood and cognition. Thus, investigating whether these gastrointestinal hormones might be a mechanism through which SCFAs affect psychological functioning would be worthwhile.

Vagal pathways. The vagus nerve contains 80% afferent and 20% efferent fibres and innervates almost all the digestive tract. Vagal afferent nerve terminals innervate various layers of the gastrointestinal wall, with the mucosal afferents terminating within the lamina propria of the intestinal mucosa[132]. Vagal afferents are not in direct contact with the gut microbiota or luminal content but can indirectly sense luminal signals through diffusion across the gastrointestinal barrier of bacterial compounds or metabolites[184] such as serotonin and gut hormones released from the enteroendocrine cells[185,186]. Electric stimulation of vagal afferents modulates neurotransmitter levels in the brain[187], and certain bacterial strains and products such as LPS[188] can also indirectly stimulate vagal afferents, thereby affecting brain function. For instance, chronic treatment of mice with *Lactobacillus rhamnosus* JB1 attenuated stress-induced corticosterone levels and depressive-like and anxiety-like behaviours, normalized BDNF levels in the hippocampus and resulted in changes in GABA mRNA expression in the brain[189]. Similarly, chronic treatment with *Bifidobacterium longum* NCC3001 ameliorated anxiety-like symptoms induced by chronic gut inflammation[190]. Damaging the integrity of the vagus nerve by

means of vagotomy abolished the effects observed in these studies[189,190].

SCFAs might directly activate vagal afferents. Luminal perfusion of sodium butyrate (10 mM) in the jejunum of anaesthetized male rats evoked vagal afferent nerve discharge that was abolished following subdiaphragmatic vagotomy[191]. Importantly, butyrate probably acted directly on vagal afferent terminals, at least independent of CCK-A receptors present on vagal afferents. In 2018, intraperitoneal injection of acetate, propionate and butyrate (separately, each at 6 mmol/kg) was shown to suppress food intake in mice in the relative order of butyrate (highest), propionate and acetate[192]. This effect was attenuated following desensitization of vagal afferents by systemic capsaicin treatment and via hepatic branch vagotomy. Butyrate also directly interacted with single neurons isolated from the mouse nodose ganglion and increased intracellular Ca^{2+} signalling[192]. As FFAR3 is expressed in nodose ganglion neurons[55], the effect of SCFAs on appetite suppression via the vagus nerve might be mediated by FFAR3 (REF.[184]). More research is needed to examine SCFA–vagal interactions and the potential mediating role of the vagus nerve in SCFA-induced psychobiological changes related to depressive-like and anxiety-like behaviour.

Other direct humoral pathways. An intact BBB is critical to brain development and the preservation of CNS homeostasis, as it ensures a controlled passage of molecules and nutrients from the circulation to the brain (FIG. 3). As mentioned earlier, SCFAs can cross the BBB, but their uptake in the brain appears to be minimal.

Nonetheless, compared with normal mice, germ-free mice have increased BBB permeability, and butyrate treatment decreases BBB permeability to a level similar to that of pathogen-free mice that had a normal gut microbiota[193]. Propionate also protected BBB integrity, as exposure of a human cerebromicrovascular endothelial cell line (hCMEC/D3) to 1 μM propionate for 24 h led to the inhibition of a number of pathways associated with nonspecific inflammatory responses to microbial infections in vitro[194]. For example, exposure of hCMEC/D3 monolayers for 12 h to physiological concentrations of propionate (1 μM) and butyrate (1 μM), but not acetate (65 μM), attenuated the permeabilizing effect of LPS derived from *Escherichia coli*[194]. Propionate also protected the BBB from oxidative stress via NFE2L2 (also known as NFE2-related factor 2) signalling and protected against LPS-induced disruptions in the tight junction proteins occludin, claudin 5 and zona occludens 1. Given the low brain and systemic SCFA concentrations[17], it is unlikely that colonic-derived SCFAs affect brain function through uptake in the brain, but the limited evidence in mice does not completely rule out this possibility.

Some evidence shows that SCFAs that cross into the CNS have neuroactive properties. In mice, acetate taken up through the BBB altered the levels of the neurotransmitters glutamate, glutamine and GABA in the hypothalamus and increased anorexigenic neuropeptide expression[31]. Propionic acid induced the expression of tryptophan 5-hydroxylase 1, the enzyme involved in synthesis of serotonin, in a pheochromocytoma cell line. Furthermore, propionate and butyrate also induced tyrosine hydroxylase gene transcription[195], which is involved in a rate-limiting step in the biosynthesis of dopamine, noradrenaline and adrenaline[196].

The mechanisms by which dietary fibre and butyrate affect the brain might involve neurotrophic factors, such as nerve growth factor (NGF), BDNF and glial cell line-derived neurotrophic factor (GDNF). These small proteins regulate the growth, survival and differentiation of neurons and synapses in the CNS and PNS[197], playing important parts in learning, memory and a range of brain disorders. Fructo-oligosaccharide and BGOS feeding in rats elevated hippocampal BDNF and *N*-methyl-D-aspartate (NMDA) receptor subunits, which are important for synaptic plasticity and memory formation[198]. These effects might be mediated by butyrate, as butyrate injection enhanced levels of neurotrophic factors alongside positive effects on mood-related behaviours in rats[199] and mice[200]. The effects of butyrate on neurotrophic factors also benefit learning and memory in mice. Upregulation of hippocampal BDNF, following exercise and intraperitoneal administration of butyrate, was necessary to transform a weak learning event into long-term memory in sedentary mice[201]. Similarly, butyrate prevented memory impairment and reversed levels of hippocampal BDNF and GDNF in a mouse model of pneumococcal meningitis[202]. Finally, effects of butyrate on neurogenesis[203] and neuroprotection[204] might be due to increasing neurotrophic factor mRNA levels or promoter activity via HDAC inhibition.

Serotonin biosynthesis constitutes another humoral gut–brain communication pathway that might be affected by SCFAs. Serotonin (5-hydroxytryptamine (5-HT)) is derived from tryptophan and functions as a neurotransmitter in the CNS and in the periphery. More than 90% of 5-HT in the body is synthesized in the enterochromaffin cells in the gastrointestinal tract, where it regulates diverse gastrointestinal functions such as motility and secretory reflexes[205]. The remainder is synthesized in the CNS in the raphe nuclei located in the brainstem, the ascending projections of which are involved in regulation of mood, appetite, memory, learning and sleep[206]. Intraluminal administration of physiological concentrations of SCFAs into the proximal colon of rats stimulated the release of 5-HT from enterochromaffin cells[45]. One study found that acetate and butyrate promoted tryptophan hydroxylase 1 (the rate-limiting enzyme for mucosal 5-HT synthesis) transcription in a human-derived enterochromaffin cell model, suggesting that SCFAs might be crucially involved in enteric 5-HT production and homeostasis[207]. Similarly, Yano et al.[208] found that specific microbial metabolites, including butyrate and propionate, have a critical role in promoting host 5-HT biosynthesis, regulating both colon and serum levels of 5-HT. Taken together, these findings suggest that SCFAs might modulate the peripheral levels of serotonin, which might, in turn, regulate brain function by influencing the immune system[209] or fetal brain development[210,211] or signalling to the brain via 5-HT receptors on vagal afferent fibres[212].

In summary, SCFAs might directly influence the brain by crossing the BBB, reinforcing BBB integrity, modulating neurotransmission, influencing levels of neurotrophic factors and promoting serotonin biosynthesis. Owing to the invasive nature of these studies, research into the direct humoral effects of SCFAs on brain function is limited to in vitro and animal studies. Importantly, it remains to be established whether alterations in microbiota-derived SCFAs exert similar effects on the BBB, neurotransmission and neurotrophins and whether microbiota-derived SCFAs reach physiologically relevant concentrations in the human CNS.

Modulation of SCFA production

SCFA production can be indirectly modulated by manipulating the intestinal microbiota via the ingestion of live beneficial bacteria, known as probiotics[179,213]. An alternative strategy is the intake of prebiotics, which are defined as "a substrate that is selectively utilized by host microorganisms, conferring a health benefit"[214]. Prebiotics act as a substrate for bacteria in the colon, which in turn ferment them into SCFAs. Diet substantially influences gut health and its microbial composition. For example, increased consumption of plant-based food, as found in a Mediterranean diet, increases the availability of fermentable substrates for advantageous bacteria, thereby modulating SCFA formation[215]. Ample evidence exists that intervention with prebiotics[13,216–219] and probiotics[220,221] or adherence to a Mediterranean diet[222–224] increases colonic SCFA production. Additionally, the number of studies in animals and humans demonstrating positive effects of prebiotics, probiotics and adherence to a Mediterranean diet on psychological functioning is increasing[225]. End points in such studies include depressive-like and anxiety-like behaviour, stress-related behaviour and cognitive functioning. An overview of these studies is provided in Supplementary Tables 1 and 2. However, less than a handful of studies on the psychological effects of these dietary interventions quantified SCFAs.

In rodents, a few studies have shown changes in SCFA levels and brain function following administration of prebiotics and probiotics. Administration of *Clostridium butyricum* in mice increased butyrate levels in faeces and in the brain in a model of vascular dementia and resulted in significant attenuation of cognitive impairment and histopathological changes in the hippocampus of mice, as well as activated BDNF–PI3K–AKT pathway-related proteins in the hippocampus[226]. A 3-week supplementation of the diet with fructo-oligosaccharides and galacto-oligosaccharides in mice attenuated stress-induced corticosterone release, reduced pro-inflammatory cytokine levels, modified gene expression in the hippocampus and hypothalamus, increased caecal acetate and propionate and reduced caecal isobutyrate concentration. Importantly, changes in caecal SCFA levels correlated with reduced depression-like and anxiety-like behaviours[227]. Studies in rats showed that prebiotic BGOS increased plasma acetate levels, increased brain NMDA receptor levels and improved cognitive flexibility in an attentional set-shifting task[228,229]. In addition, BGOS also induced increases in cortical GluN2B subunits (involved in glutamate neurotransmission) and acetyl-CoA carboxylase mRNA, all of which were also evident following direct acetate supplementation by gavage[229]. Altogether, these findings encourage future investigation of the mediational role of SCFAs in brain and behavioural changes induced by probiotic and prebiotic interventions.

SCFAs and psychopathological processes

Despite the knowledge of multiple pathways that support a potential key role of SCFAs in MGB axis signalling, studies linking SCFAs directly with one or more aspects of psychological functioning are currently sparse and heterogeneous in terms of study design and study population and yield conflicting results. Notwithstanding these limitations, SCFAs have been implicated in a range of neuropsychiatric disorders, such as the controversial role of SCFAs in Parkinson disease. Patients with Parkinson disease have a lower abundance of SCFA-producing bacteria than healthy controls[230–233] and have lower faecal SCFA concentrations than age-matched healthy controls[234]. Butyrate administration in animal models of Parkinson disease improved motor impairment and dopamine deficiency[235–237]. However, in one mouse model of Parkinson disease where the protein α-synuclein (αSyn) is overexpressed, orally administered SCFA mixtures promoted neuroinflammation and motor deficits in comparison with germ-free or antibiotic-treated mice[238], suggesting that, under genetic predisposition, SCFAs might exacerbate symptoms associated with Parkinson disease.

Key neuropathological processes underlying Alzheimer disease might also be modulated by SCFAs. Butyrate administration recovered memory function and increased expression of genes implicated in associative learning in a mouse model of Alzheimer disease via HDAC inhibition[239]. In another study, valeric acid, butyric acid and propionic acid interfered with protein–protein interactions between amyloid-β peptides, thereby disrupting their assembly into neurotoxic oligomers[240].

The role of SCFAs in ASD is also controversial. Children with ASD have been reported to have both lower[241] and higher[242] faecal SCFA levels than controls. However, altered faecal SCFA levels in children with ASD might be due to fibre intake, changes in gut microbiota composition or variability in gut transit time[241]. Higher levels of butyrate have been detected in the caecum of offspring in a valproic acid mouse model of ASD than in mice exposed to PBS[243], but another study with the BTBR mouse model of ASD demonstrated that treatment with butyrate attenuated social behaviour deficits via modulation of GABA signalling and of inhibitory and/or excitatory gene transcription in the frontal cortex[72]. Finally, treating rodents with SCFAs (predominantly propionate) via various methods of administration (intracerebroventricular, intraperitoneal, subcutaneous and oral) has been suggested to induce behavioural and brain alterations consistent with those exhibited in patients with ASD[244]. This evidence highlights the difficulty in drawing conclusions on the role of SCFAs in ASD and the need for more research in patients with ASD. Rodent models of ASD should be systematically evaluated to determine which models best recapitulate the behavioural, immune and metabolic profiles

found in most patients with ASD and which model(s) might be superior to others in subsets of patients with ASD with differing pathophysiological profiles.

In regard to affective symptomatology, faecal SCFA concentrations were lower in patients with depression than in controls in two studies[245,246] but not in another[247]. Moreover, faecal microbiota transplantation from patients with depression to microbiota-depleted rats transmitted the anxiety-like behaviour but resulted in higher faecal SCFA concentrations than in rats receiving donor faeces from healthy controls[247]. In another study, faecal butyrate correlated with reported emotional problems in children[248]. In animal models of mania, sodium butyrate reversed behavioural hyperactivity and restored hypoactivity of mitochondrial respiratory chain complexes in the prefrontal cortex, hippocampus, striatum and amygdala[249], and reversed depressive-like and manic-like behaviours in rats[250]. In relation to addiction-related behaviour, administration of SCFAs normalized reward responses to cocaine in mice with antibiotic-induced depletion of gut microbiota[251]. Although these studies reveal correlations between affective behaviour and SCFAs, the discrepant findings across the studies are probably due to the quantification of SCFA in faeces, which, in this context, is probably biologically irrelevant (see the next section for further discussion).

In addition to the putative direct influences outlined above, the role of SCFAs in neuropsychiatric disorders might also be indirect, such that instead of alleviating (or exacerbating) symptoms per se, they might alleviate (or exacerbate) symptoms of comorbid physical or psychological symptoms, thereby indirectly reducing (or exacerbating) severity of the primary neuropsychiatric illness. For instance, enriching SCFAs in patients with schizophrenia indirectly via Mediterranean diet-based interventions has been suggested to improve immune and cardiovascular outcomes associated with increased mortality in these patients[252].

Functional brain imaging studies investigating the effects of SCFAs in relation to food reward, cognitive function and brain functional connectivity have been conducted. As mentioned above, one functional MRI study showed attenuated responses to high-energy food pictures in brain regions involved in reward processing following treatment with propionate[137]. In another study with mice with high-fat diet-induced obesity, supplementation of the diet with 5% butyrate for 2 months restored metabolic adaptions, neuroinflammation (decreased number of activated microglia in hippocampus and thalamus, but no changes in levels of TNF, IL-6 or IL-1β) and impairments in spatial memory, systolic blood pressure, cerebral blood flow and functional connectivity to levels seen in chow-fed non-obese mice. Butyrate-related changes in microbiota were also shown to correlate with changes in neuroinflammation[253].

Limitations and future directions

The studies discussed above suggest that SCFAs might indeed have a role in a range of neurological and neuropsychiatric conditions, as well as psychological functioning in general. However, it is premature to decide whether their effects are favourable or unfavourable. A major commonality across these studies is the quantification of faecal SCFAs in both observational and experimental studies. Faecal SCFAs, however, provide information on non-absorbed SCFAs but do not reflect in situ production rates, absorption and interaction with other biologically relevant molecules or cell types[219]. This lack of understanding hampers our ability to understand the influence of SCFAs on psychological and biological functions. This gap in our knowledge stems from an inability to sample the intestinal content to quantify SCFAs during fermentation, the extensive absorption and metabolism of SCFAs in the splanchnic area (small intestine, liver and colon) that result in low plasma SCFA concentrations, and analytical challenges in quantifying low plasma SCFA levels[254]. Knowledge of the systemic availability — that is, the fraction of the administered dose of unchanged compound that reaches the systemic circulation — of SCFAs is critical to understanding their full biological relevance and to deciphering the extent to which systemic SCFAs mediate gut–brain communication through the MGB axis. In 2017, the systemic availability and metabolism of colonic-derived SCFAs were quantified in healthy individuals using stable isotope technology[17]. Known amounts of either ^{13}C-labelled acetate, propionate or butyrate were directly administered to the colon using colon delivery capsules, after which the concentrations of ^{13}C-labelled SCFAs were quantified in plasma. The use of stable isotopes enabled selective and sensitive quantification of the SCFAs originating from the colon. On average, 36% of the administered acetate, 9% of the administered propionate and 2% of the administered butyrate were recovered in the systemic circulation.

Nevertheless, quantification of circulating SCFAs only will not solve the discrepancies seen between findings in animals and humans regarding the role of SCFAs in neuropsychiatric disorders or the intraspecies discrepancies. Animal models of psychiatric disorders in MGB axis research must overcome two major challenges: to adequately model the human microbiome and gastrointestinal tract and to recapitulate the symptom or phenotype of interest. In regard to the former, it should be emphasized that the majority of cited research in this Review is based on rodent models. Important discrepancies between human and rodent microbiota might render translation to humans challenging[255]. For example, the dominant bacterial genera and their relative abundance in mice and humans are different. Furthermore, the differing gastrointestinal tract anatomy between mice and humans, such as the large relative size of the caecum in mice, suggests that anatomical differences might make comparisons difficult, including microbiota composition across the gastrointestinal tract, fibre fermentation and metabolism and absorption of SCFAs[255]. Better models for animal and human gastrointestinal tract and gut microbiota are the pig[256] and the chimpanzee[257], owing to a better resemblance of the human gastrointestinal tract anatomy, physiology and immunology and their similarity to humans in gut microbiota composition. However, practical and ethical considerations restrict their use in MGB axis studies.

It is well established that modelling complex human psychiatric disorders in animals is extremely challenging,

Box 1 | **Future directions in the study of SCFAs in microbiota–gut–brain axis**

- Quantification of systemic concentrations of short-chain fatty acids (SCFAs) in probiotic, prebiotic and dietary intervention studies.
- Use of mediation analysis to determine the extent to which SCFAs mediate the effects of interventions on the psychological outcome of interest.
- Utilize SCFAs as intervention substances and directly test their effects on psychological functions in humans.
- Quantification of systemic concentrations of SCFAs as opposed to faecal SCFAs to correlate with psychopathological processes.
- Examine whether changes in other relevant microbiota–gut–brain interaction pathways, including the immune and endocrine systems, are driven by changes in SCFA production.

and some argue that it cannot mirror the multifaceted nature of any given psychiatric disorder[258]. Inherent limitations lie in using Diagnostic and Statistical Manual of Mental Disorders criteria to construct animal models, as in humans, multiple symptom combinations can result in the same diagnosis of depressive disorder. In addition, the boundaries between multiple psychiatric disorders, as well as between normality and disorder, are quite arbitrary in humans[258], and the phenomenology of certain symptoms such as sadness and guilt in animals are impossible to validate. Finally, an animal model of a neuropsychiatric disorder based on pathophysiological mutations usually consists of a single mutation that might associate with multiple disorders, as was the case with a *DISC1* mutation that resulted in major depressive disorder, bipolar disorder and schizophrenia in a single family[259]. Although animal models are invaluable for studying highly specified molecular, cellular, genetic or neural abnormalities in a given neuropsychiatric disorder, no model can sufficiently recapitulate all the aetiological factors, developmental processes and temporal dynamics that occur with a human psychiatric patient. Currently, it is advised to regard animal models of psychiatric disorders as endophenotype-based or symptom-based models and consider them a "biological system representing a distinct pathological process, but not a nosological entity"[260]. Thus, modelling all interdependent dimensions of a disorder should be avoided, and instead, the model should be restricted to a single symptom, provided that its various dimensions or endophenotypes are adequately distinct and separable[260,261].

In summary, animal studies are instrumental in advancing our understanding of the neurobiological underpinnings of psychiatric disorders and have unquestionably enabled the exploration of molecular mechanisms that are impossible, or at best unethical, to reveal in humans. Future animal studies on the role of SCFAs in the MGB axis should, therefore, draw on models that adequately mirror the gastrointestinal tract and gut microbiome and focus on a single endophenotype of a given psychiatric disorder. Difficulty in satisfying these conditions might, for instance, partially account for failing to translate the effect of *L. rhamnosus* (JB1) on emotional behaviour from animals[189] to humans[262], where no effects on stress response, HPA axis activity, inflammation or cognition were observed in humans in response to *L. rhamnosus* (JB1) probiotic treatment. The true importance of findings in animal models is their translatability in humans, so advancing methodologies for studying the role of SCFAs in the MGB axis in humans is needed. SCFAs can be directly administered to humans orally, intravenously, via enema or by using an esterified fibre to facilitate colonic SCFA delivery[138,263]. Although no single method is perfect, findings from such studies would complement animal studies to increase our understanding of the different pathways through which SCFAs might influence brain and behaviour. Finally, in humans, multiple factors such as dietary fibre intake, microbiota composition and gut transit time can contribute to SCFA production, and along the gastrointestinal tract, absorption rates can vary at different sites, thereby affecting incorporation of SCFAs into relevant biological processes. We hypothesize that the variability of the interrelations between these mechanisms might be larger in humans with gastrointestinal and neuropsychiatric disorders than in healthy populations. Thus, drawing conclusions on the role of SCFAs in the MGB axis of patients might be an unsurmountable challenge if knowledge of their role in healthy humans is not systematically established first. A set of recommendations to better address the role of SCFAs in the MGB axis is summarized in BOX 1.

Conclusion

This Review synthesizes literature that supports a role for SCFAs as mediators of MGB interactions. Through their putative effects on brain function via various gut–brain signalling pathways, they can act as mediators of the effects of probiotics, prebiotics and dietary interventions on a range of psychological functions. The link between SCFAs and psychological functioning is slowly solidifying in animal research, but there is a dearth of human research and little convergence in human and animal studies. Interventions using direct SCFA administration in humans should therefore be carried out. Before making claims on a mechanistic role of SCFAs in the MGB axis, information on dose–effect relationships with respect to various psychological functions is needed. Further knowledge regarding the individual contributions of each of the major SCFAs to such effects is also required.

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