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Neuroscience and Biobehavioral Reviews 152 (2023) 105296

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

The microbiota-gut-brain axis in hippocampus-dependent learning and memory: current state and future challenges

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ARTICLE INFO

Keywords:
Gut microbiota
Microbiota-gut-brain axis
Probiotic
Prebiotic
Dysbiosis
Hippocampus
Learning
Memory
Neurogenesis
Vagus nerve
HPA-axis
Metabolites
Short chain fatty acid
Inflammation

ABSTRACT

A fundamental shift in neuroscience suggests bidirectional interaction of gut microbiota with the healthy and dysfunctional brain. This microbiota-gut-brain axis has mainly been investigated in stress-related psychopathology (e.g. depression, anxiety). The hippocampus, a key structure in both the healthy brain and psychopathologies, is implicated by work in rodents that suggests gut microbiota substantially impact hippocampal-dependent learning and memory. However, understanding microbiota-hippocampus mechanisms in health and disease, and translation to humans, is hampered by the absence of a coherent evaluative approach. We review the current knowledge regarding four main gut microbiota-hippocampus routes in rodents: through the vagus nerve; via the hypothalamus-pituitary-adrenal-axis; by metabolism of neuroactive substances; and through modulation of host inflammation. Next, we suggest an approach including testing (biomarkers of) the four routes as a function of the influence of gut microbiota (composition) on hippocampal-dependent (dys)functioning. We argue that such an approach is necessary to proceed from the current state of preclinical research to beneficial application in humans to optimise microbiota-based strategies to treat and enhance hippocampal-dependent memory (dys)functions.

1. Introduction

Learning and memory are central processes in shaping cognition and behaviour, defining who we are and what we do. These processes crucially depend on synaptic plasticity in the hippocampus, a brain structure that contributes to episodic declarative memory in humans through the establishment of cognitive maps as representations of spatial and episodic contexts (Lisman et al., 2017). A recent fundamental shift in neuroscience, supported by an ever-growing body of studies, suggests a bidirectional interaction of trillions of gut organisms that together constitute the gut microbiota with the brain (Burokas et al., 2015; Cryan and Dinan, 2012; Longo et al., 2023; Mayer et al., 2014). This microbiota-gut-brain axis has mainly been investigated in relation to potential therapeutic effects of the microbiota on well-being, in relation to stress-related psychopathology (e.g. depression, anxiety). Here, the beneficial effects of gut microbial symbiosis, facilitated by pre- and probiotics, and detrimental effects of dysbiosis (e.g. antibiotics-induced) have been established in rodents with evidence of positive translation to humans (Sarkar et al., 2016; Steenbergen et al., 2015; Wang et al., 2016). The role of the hippocampus in both healthy learning and stress regulation, as well as being a key centre in the development of stress-related psychopathologies (Larosa and Wong, 2022; Toda et al., 2019), combined with the emerging influence of the microbiota on these processes (Shoubridge et al., 2022), raises the question of how gut microbiota impact hippocampal-dependent memory and learning mechanisms and how these integrate with affective processing to achieve therapeutic outcomes. However, there is no coherent scientific approach to these gut microbiota-hippocampus interactions. We argue in this narrative review that such an approach is necessary to build bridges between the current state of the microbiota-gut-brain axis field and beneficial application in human hippocampal-dependent functioning in health and psychopathology.

The function and assessment of the hippocampus in rodents and to lesser extent humans is well established. The hippocampus regulates memory encoding and spatial navigation. Hippocampal lesions in both humans and animals result in a failure to learn new episodic memories

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https://doi.org/10.1016/j.neubiorev.2023.105296
Received 27 June 2022; Received in revised form 15 May 2023; Accepted 23 June 2023
Available online 26 June 2023

(Neves et al., 2008). The unique contribution of the hippocampus to declarative learning and memory resides in the capacity of the hippocampus to create and strengthen synaptic contacts i.e., synaptic plasticity (Neves et al., 2008). On a behavioural level, hippocampus-dependent memory function in rodents is typically assessed through memory-guided behavioural tasks probing episodic memory, context-dependent spatial navigation, or non-spatial object recognition memory (Lisman et al., 2017; Moscovitch et al., 2006; Opitz, 2014). This has allowed elucidation of underlying neural mechanisms through molecular markers such as translation of immediate early gene c-Fos, which is upregulated after neuronal activity, and brain-derived neurotrophic factor (BDNF), which can transform synaptic activity into long-term synaptic memories. Furthermore, strengthened neural connections after synaptic activity can directly be assessed through electrophysiological measurements such as long-term potentiation (LTP). In humans, information about the structure and function of the hippocampus was initially gleaned from clinical subjects (Augustinack et al., 2014) but can now be assessed through functional magnetic resonance imaging (fMRI). To date there are few established gut microbiota-hippocampus interactions in humans and we argue these are necessary and feasible. This would allow for novel, microbiota-derived, markers of hippocampal function facilitating translation from rodents to humans.

Evidence for the microbiota effects on hippocampal structure and plasticity and related behaviours comes historically from rodent studies showing effects of antibiotics, probiotics (living organisms with beneficial effects for the host), prebiotics (often fibres that improve the host's health by stimulating growth and/or activity of the host's probiotic strains), synbiotics (combination of pre- and probiotics), and microbiota composition, suggesting a key role for gut microbiota in regulating hippocampus-dependent learning and memory, but findings are preliminary, and mechanisms unclear (for review see (Tang et al., 2020)). In humans, research into the interaction of the microbiota with hippocampal-dependent processing is in its infancy, but prebiotic supplementation has been shown to improve hippocampus-related cognition (for review (Serra et al., 2019)), antibiotic-induced dysbiosis has been found to impair hippocampal function (Çalışkan et al., 2022), and microbiota composition correlates with hippocampal functioning in older adults (Manderino et al., 2017; Renson et al., 2020), to state a few examples. To add, Alzheimer's disease (AD), the most common neurodegenerative disorder resulting in memory loss and eventually dementia, is characterized by changes in hippocampal structure and function and by alterations in gut microbiota. That is, both animal and human studies show significantly altered gut microbial composition in animal models and humans suffering from AD (Tang et al., 2020; Verhaar et al., 2021) and transplanting gut microbiota of AD patients into healthy mice resulted in microglia activation in the hippocampus and severe cognitive impairment: effects that could be rescued by transplantation of healthy human faeces (Shen et al., 2020). Further, patients suffering from irritable bowel syndrome (IBS), characterised by dysfunctional microbiota (Carding et al., 2015), show subtle hippocampal-mediated visuospatial working memory deficits (Kennedy et al., 2014). Conversely, differences in hippocampal-dependent working- or episodic memory in IBS patients are not always apparent (Berrill et al., 2013). And, although one would hypothesize gut microbial interventions may have therapeutic potential for such disorders, probiotic supplementation (*Lactobacillus casei*) in healthy participants unexpectedly impaired episodic memory recall (Benton et al., 2007).

Although gut microbiota is implicated in memory deficits in clinical populations and a wealth of fundamental animal research does indicate a profound effect of gut microbiota on hippocampal functioning in memory and learning (for review see Tang et al., 2020), the discrepancies between rodent and human studies and the equivocal findings and relative paucity of studies in humans demand critical evaluation of preclinical knowledge. Supported by a recent review concluding that gut microbiota intervention-effects on hippocampal functions are preliminary and their mechanisms unclear (Tang et al., 2020), we argue the paradigm shift is currently hampered by a focus on the gut microbiota and the brain, rather than on the 'axis' (or axes, as we will argue). That is, a lack of a more targeted and coherent approach to microbiota-gut-brain interactions hamper fundamental understanding of microbiota-hippocampus effects in health and disease. This in turn impedes evaluation and optimisation of targeting gut microbiota for enhancement and/or treatment of hippocampal-dependent memory performance and dysfunction, and translation of these effects to humans.

To address these difficulties, rather than reviewing microbiota effects on hippocampal structure, function, and -related behaviour that have been the subject of recent reviews (Tang et al., 2020), we summarize four established main routes through which gut microbiota interact with rodent hippocampal functioning in memory and learning; through 1) modulating tenth cranial or vagus nerve activity, 2) altering the adaptive stress response of the hypothalamus-pituitary-adrenal (HPA)-axis, 3) metabolism of potentially neuroactive substances and 4) affecting host inflammatory tone. It should be noted that microbiota modulation of host gut epithelial and endothelial blood brain barrier is regarded as a separate route of interaction by some researchers. However, we argue both gut and brain barriers should be considered as moderating and/or mediating the four main routes and, as such, do not discuss barrier function as a separate route; the barriers do not provide main routes of interaction themselves. Further, although we report mainly on preclinical rodent research that can seemingly distinguish the routes, we consider the four routes as integrated entities that closely interact and overlap with each other in vivo, see Fig. 1. This complexity is even more evident in humans. After making the case for evaluation of these four main routes and their components in hippocampal-dependent learning and memory, to enhance understanding, optimisation, and translation of microbiota-induced effects on hippocampal-dependent learning and memory in (dys)functioning, we conclude by suggesting a structural approach for future studies.

2. Gut-microbiota hippocampal route 1: tenth cranial or vagus nerve

One direct neuroanatomical route between the gut microbiota and the brain is the vagus nerve (VN; 10th cranial nerve), which coordinates a range of parasympathetic functions, such as respiration, cardiac function, inflammation, and gut motility in digestion. The VN consists of sensory and motor—or afferent and efferent—components in a ratio of 9:1 (Forsythe et al., 2014). The vagal afferent nerves (VANs) can (indirectly) sense microbiota, and transfer gut information into higher CNS structures eventually resulting in autonomic responses, executed by the vagal efferent nerves (for review (Fülling et al., 2019)).

2.1. Microbiota putatively activates gut VANs, affecting upstream hippocampal processing

The importance of the VN in mediating microbiota effects on hippocampal processing is illustrated by studies where faecal microbiota transplantation rescued hippocampal-dependent spatial learning deficits in septic mice, critically dependent on an intact VN signalling (Li et al., 2018). Furthermore, application of probiotic *L. rhamnosus* (JB-1) in an *ex vivo* jejunal segment increased in VAN firing rate (Bharwani et al., 2020), also dependent on an intact VN (Perez-Burgos et al., 2013), and when orally administered in vivo could induce cFOS expression in different brain regions including the ventral, but not dorsal, hippocampus (Bharwani et al., 2020). The VN promotes hippocampal episodic and spatial memory (Suarez et al., 2018) and activating VANs through vagus nerve stimulation (VNS) correlates with activation of hippocampal regions and can enhance memory (Broncel et al., 2018; Clark et al., 1999; Ghacibeh et al., 2006). There is no direct anatomical connection between the VN and the HPC, as the signal enters the brainstem through

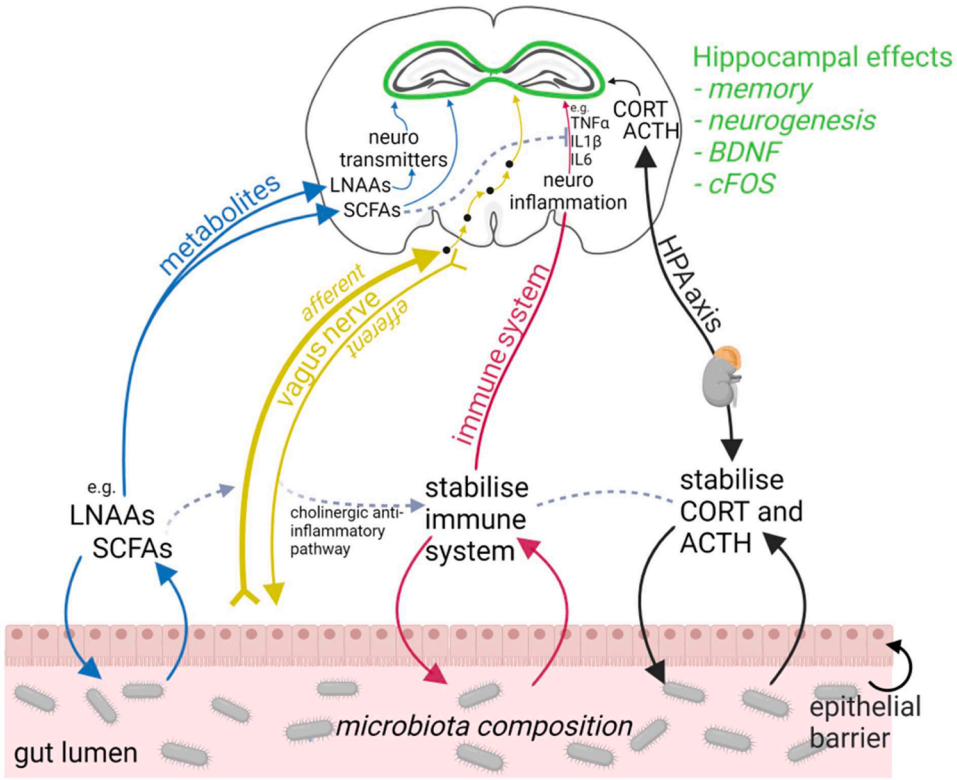

Fig. 1. Microbiota-gut-hippocampus axes. The gut microbiota can interact with the hippocampus through four bidirectional routes. From left to right: through metabolism of neuroactive substances, or their precursors (blue), for example LNAAs (large neutral amino acids) and SCFAs (short chain fatty acids); through the vagus nerve (yellow); via modulation of host inflammation (red) that determines local release of inflammatory factors, for example such as those indicated; and through the hypothalamus-pituitary-adrenal-axis (black). These axes can interact and overlap with each other (examples are indicated by dotted grey lines). Abbreviations: ACTH (adrenocorticotropic hormone); BDNF (brain derived neurotropic factor); CORT (corticosterone); HPA (hypothalamus-pituitary-adrenal); IL1β (interleukin 1β); IL6 (interleukin 6); LNAAs (large neutral amino acids); SCFA (short chain fatty acid); TNFα (tumor necrosis factor α).

the medial nucleus of the solitary tract (mNTS) after which it is relayed through the locus coeruleus (LC) and medial septum (MS) that innervate hippocampal regions (Broncel et al., 2018; Castle et al., 2005; Suarez et al., 2018). Rodent studies have confirmed electrophysiological correlations between VNS and the hippocampus. For example, in urethane-anesthetised rats VNS was shown to enhance hippocampal LTP (Shen et al., 2012; Ura et al., 2013) and to induce a CA1 type II theta rhythm, which is implicated in memory consolidation (Broncel et al., 2017, 2018). In freely moving rats, VNS enhanced LTP in the dentate gyrus (Zuo et al., 2007), as well as hippocampal BDNF, neurogenesis, and epigenetic changes (Biggio et al., 2009; O'Leary et al., 2018; Sanders et al., 2019), which together improved hippocampal memory as assessed by behaviour (A. Liu et al., 2016; Y.-W. Liu et al., 2016; Sanders et al., 2019; Smith et al., 2005). It should be noted that even though external activation of the vagus nerve by VNS enhances memory, and the vagus nerve is a key mediator between the microbiota and hippocampal-dependent memory in septic rodents, the extent to which the microbiota induces vagal activity in vivo has not been tested, nor to what degree VNS is representative of this.

How might microbiota affect vagal activity? VAN activity might be altered by microbiota in healthy conditions through enteroendocrine cells (EECs) (for reviews Bonaz et al., 2018; Yu et al., 2020). EECs make up 1% of the gut epithelium but together are considered one of the largest mammalian endocrine systems (Sternini et al., 2008). Anatomically, EECs are located between the terminal endings of the VANs and the gut lumen where the microbiota resides. EECs can sense microbiota both directly and indirectly through their metabolites. Directly, EEC recognise microbiota through, amongst others, toll-like receptor (TLR) binding of e.g. bacterial lipopolysaccharides (LPS) (Abreu et al., 2005). Indirectly, EECs express an array of members of the G protein-coupled receptor (GPCR) superfamily that can sense microbiota metabolites such as short chain fatty acids (SCFAs), nutrients, and bitter and sweet tastants (for reviews (Sternini et al., 2008; Yu et al., 2020)). EECs are thought to relay this information to the VANs either indirectly via release of signalling molecules, or directly though synapse-like structures. Indirectly, EECs release of a variety of signalling molecules such as serotonin, or gut satiety peptides, such as cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), peptide tyrosine-tyrosine (PYY), and ghrelin (for reviews Han et al., 2022; Kuwahara et al., 2020). Interestingly, of these, ghrelin has been shown to mediate hippocampal contextual episodic memory in a vagal-dependent way (Davis et al., 2020). However, it has not been demonstrated that microbiota produce ghrelin that can exert a similar effect. Secondly, another way of EEC-VN transmission is directly through recently described synapse-like structures that protrude from the EEC basal membrane and connect with the VN; these 'neuropods' release glutamate in response to luminal signals (Kaelberer et al., 2018, for review Liddle, 2019). Taken together, the VN reacts to, at least, certain probiotic strains, such as JB-1, and electrophysiological activity of the VN correlates with hippocampal processing. However, the exact mechanism how the VN receives microbiota-related information and how this all comes together to define the microbiota-VN-hippocampus axis is unknown. Furthermore, how this might differ between strains remains to be characterised.

Importantly, not all studies indicating a protective effect of microbiota on hippocampal-dependent learning suggest that this is exclusively vagally mediated (Mayer et al., 2015; Sarkar et al., 2016). For example, the protective effects of *Lactobacillus rhamnosus* and *Bifidobacterium infantis* on intestinal inflammation—of which the detrimental effects on hippocampal-dependent learning will discussed in Section 4—have also been shown to be independent of an intact vagal nerve in a model of dextran sulfate sodium colitis (van der Kleij et al., 2008).

2.2. Microbiota-gut-VN-hippocampus axis in humans

Human studies indicating memory-improving effects of pre- and probiotics rarely assess the contribution of vagal activity. This may be explained by the fact that to date there are no direct non-invasive measures for afferent (ascending gut-to-brain) vagal activity (but see (Usami et al., 2013)), despite the ability to assess efferent vagal tone using heart reflexes (Schrezenmaier et al., 2007) and heart rate

variability (Thayer and Lane, 2000). One case study with recordings from an implanted intracranial electrode into the hippocampus of a 17-year-old epileptic patient reported that VNS can affect hippocampal electrophysiology in an intensity-dependent way, although memory function was not assessed (Olejniczak et al., 2001). Scalp-recorded vagus evoked potentials may provide a potential marker for ascending gut-to-brain vagal tone (de Gurtubay et al., 2021; Usami et al., 2013). To our knowledge, very limited studies have evaluated the relation between gut microbiota composition and such vagus-evoked potentials, although ascending vagal activity, as measured by 24 h cardiac vagal activity, correlated with microbiota composition in an exploratory pilot (Mörkl et al., 2022).

VN effects on human hippocampal functions have however been reported. For example, hippocampal hyperactivity is a biomarker of cognitive dysfunction in schizophrenia patients, and VNS seems to decrease this hyperactivity across clinical and healthy populations, putatively enhancing cognition (Smucny et al., 2015) (for review see (Vonck et al., 2014)). In epileptic patients, short term VNS enhances declarative and verbal recognition memory (Clark et al., 1999; Ghacibeh et al., 2006), potentially in part through enhancement of hippocampal long term potentiation (LTP). Although there is no consensus on the effect of chronic VNS on cognition across clinical populations, it seems to enhance cognition in AD patients (Vonck et al., 2014). Importantly, non-invasive VN stimulation by transcutaneous VNS (tVNS) in patients with mild cognitive impairment, an early stage of AD, modified amongst others hippocampal functional activity (Murphy et al., 2023), and subtly increased explicit recollection-based memory performance in healthy participants (Giraudier et al., 2020; see for review Colzato and Beste, 2020). Overall, stimulating the VN seems to be particularly beneficial for improving hippocampal impairments in clinical populations, but how the microbiota might tap into this remains poorly understood.

2.3. Summarising microbiota-gut-VN-hippocampus effects

Taken together, rodent and human studies support the premise that the microbiota can enhance hippocampal memory, and this may be achieved through activating VANs. Indeed, VNS to depolarise VANs induces characteristic electrophysiological changes of hippocampal-dependent memory, at least in rodents. It must be noted that microbiota-induced vagal activity is poorly defined, and it is unknown to what extent VNS might be representative of this, and both are avenues for future research. Comparing in vivo hippocampal electrophysiology in animals performing hippocampal-dependent behavioural memory tasks where the microbiota may be manipulated in combination with VNS or vagotomy, using an improved protocol (Diepenbroek et al., 2017), should give profound insights. Importantly, the positive effect of the microbiota on hippocampal function is not always crucially vagal-dependent, indicating the participation of non-vagal mechanisms (Sarkar et al., 2016).

3. Gut-microbiota hippocampal route 2: HPA-axis: adaptive stress response

Stress can either be induced by threats to homeostasis (i.e., stressors) or by the absence of safety signals (Brosschot et al., 2018) and can be observed behaviourally and physiologically at the affective level as well as in cellular and molecular changes. The stress response consists broadly of disinhibition of two main adaptive systems: (i) the fast-acting sympathetic system, and (ii) the slower acting hypothalamic-pituitary-adrenal (HPA) axis that culminates in the release of adrenal glucocorticoid hormone (cortisol in humans, corticosterone (CORT) in rodents) into the systemic circulation. Glucocorticoids can cross the blood-brain barrier (BBB) and exert relatively fast non-genomic actions as well as slower genomic effects (Joëls and Baram, 2009). Chronic stress and glucocorticoid exposure, which might both be induced by and result in dysbiosis and infection (Bermúdez-Humarán et al., 2019; Dinan and Cryan, 2012), usually impairs memory and depends on reversible structural neuronal remodelling (McEwen et al., 2016).

3.1. Microbiota plays a key role in normal HPA axis functioning: lessons from psychopathology

Important lessons can be learned from the influence of the microbiota on the (dysfunctional) HPA response in studies of stress-related psychopathology, which gives a starting point to hypothesise on putative altered hippocampal functioning in learning and memory. In 2004, seminal work by Sudo and colleagues demonstrated early-life microbe exposure is essential for adaptive HPA-axis development; germ-free mice exhibit an exaggerated HPA stress response and an altered limbic system, including the prefrontal cortex, hippocampus, and amygdala (Sudo et al., 2004). Furthermore, the effect of gut microbiota on HPA axis functioning is not confined to early life, but extends into adulthood (Eutamene and Bueno, 2007). These effects are not limited to stressed populations: supplementation of the probiotic JB-1 to non-stressed mice downregulated HPA-axis activity, whilst differentially affecting GABA expression over different brain regions including the hippocampus (Bravo et al., 2011). Taken together, these studies indicate robust effects of gut microbiota in the establishment and maintenance of the normal stress response, mediated by the HPA-axis and the limbic system including the hippocampus (for review see (Foster et al., 2017)).

3.2. Microbiota affects cognitive functioning and memory through stress-related mechanisms

Hippocampal functioning is sensitive to alterations of the HPA-axis (Farrell et al., 2015), which is not surprising given the high density of glucocorticoid and mineralocorticoid receptors (GR and MRs, respectively) in the hippocampus (Reul and de Kloet, 1985). Specifically, hippocampal pyramidal cells, which have a crucial role in the systems consolidation of long term memory, highly express GRs, which can be downregulated by chronic microbiota depletion (Hoban et al., 2016). Furthermore, GR and MR function is modulated by chronic exposure to glucocorticoids (Kim et al., 2006; Krugers et al., 2010), and the gut microbiota can affect serum glucocorticoid concentrations. Several probiotics, especially *Lactobacillus* strains, have been shown to reduce both levels of serum CORT (Bravo et al., 2011; Gareau et al., 2011; Liang et al., 2015; Wang et al., 2015) (however, see also (Barrera-Bugueño et al., 2017; Kelly et al., 2017)) and adrenocorticotropic hormone (ACTH) (Liang et al., 2015; Wang et al., 2015), which was associated with improved hippocampal-dependent spatial (Ohland et al., 2013; Wang et al., 2015) and non-spatial memory (Gareau et al., 2011; Liang et al., 2015). *Bifidobacterium* supplementation can also decrease serum CORT levels (H.M. Jang et al., 2018; S.-E. Jang et al., 2018; Moya-Pérez et al., 2017; Desbonnet et al., 2010, Tian et al., 2019, 2020), normalise anxious behaviour (Desbonnet et al., 2010; H.M. Jang et al., 2018; S.-E. Jang et al., 2018; Moya-Pérez et al., 2017; Savignac et al., 2014; Tian et al., 2019, 2020), and improve both spatial and non-spatial memory (Savignac et al., 2015) although not replicated for all *Bifidobacteria* strains (Savignac et al., 2014).

Taken together, specific probiotic strains may plausibly improve hippocampal-dependent memory by reducing plasma stress hormone levels. Left untreated, psychological or dietary stress can negatively alter the gastrointestinal microbiota (Bailey et al., 2011; Bailey and Coe, 1999; Lyte et al., 2011; Park et al., 2013; Tannock and Savage, 1974; Vlisidou et al., 2004). Furthermore, elevated levels of corticosterone can affect gut permeability by changing the intestinal mucosal barrier (Santos et al., 2001; Söderholm and Perdue, 2001), potentially exacerbating microbiota dysbiosis (Bailey et al., 2011; O'Mahony et al., 2009), which can induce hippocampal dysfunction (H.M. Jang et al., 2018; S.-E. Jang et al., 2018). For example, dietary stress induced by infection of the gut with *C rodentium* exacerbates corticosterone levels induced by

behavioural stress, which impairs c-Fos and BDNF expression in the CA1-region of the hippocampus, and disrupts non-spatial hippocampal-dependent memory, all of which could be rescued by probiotics (Gareau et al., 2011).

3.3. Microbiota-gut-HPA-hippocampus axis in humans

Translation from rodents to humans of how microbiota-induced effects on the HPA-axis influence cognitive performance has met with difficulties (for review see Reis et al., 2018). One study trying to replicate the ameliorating effects of *Lactobacillus rhamnosus* (JB-1) which reduced stress-induced HPA activity and anxiety- and depression-related behaviour in rodents (Bravo et al., 2011) failed to reproduce improvement of the HPA-axis and anxiolytic effects of JB-1 in humans (Kelly et al., 2017). This could potentially be due to the anxiolytic effects of probiotics being only effective in anxious populations, as suggested in rodent studies by the strain specificity of JB-1, which was effective in innately anxious BALB/c (Bravo et al., 2011), but not in non-anxious Swiss Webster mice (Neufeld et al., 2018).

To our best knowledge, only two studies have investigated the influence of microbiota on hippocampal-dependent cognition through HPA-mediated mechanisms in healthy humans. The first showed that four weeks of multi-strain probiotic supplementation could buffer against acute stress impairment of working memory (Papalini et al., 2018). In the second, Allen and colleagues reported beneficial effects of the probiotic *Bifidobacterium longum 1714*, which reduced stress to an acute stressor and improved performance on the hippocampal-dependent Paired Associate Learning task (Allen et al., 2016). Considering probiotics can improve hippocampal-dependent memory by normalising the HPA-response to heightened stress, and the hippocampus playing a key role in establishing therapeutic efficacy in stress-related disorders (Toda et al., 2018), the paucity of studies using probiotics to enhance hippocampus-dependent memory in anxious patients is surprising.

3.4. Summarising microbiota-gut-HPA-hippocampus effects

Taken together, gut microbes play a key role in the establishment and maintenance of the normal stress response in rodents. Certain bacterial strains can enhance or decrease CORT and/or ACTH levels in later life, which modulates hippocampal learning processes. Furthermore, the causality between bacterial strains and HPA-axis activity seems to be bidirectional with the composition of the microbiota itself being sensitive to CORT and ACTH levels. In humans, the study of probiotic effects on the hippocampus through stress-related mechanisms is still in its infancy. The state of study subjects, whether rodent or human, appears important in understanding microbial effects; either being stressed (e.g. by study design) or exhibiting altered stress responsivity (e.g. by psychopathology) which suggests that microbiota (probiotics) can control the (hyper)active adaptive stress response. On a final note, it is currently unknown how microbiota affect the hippocampus through stress-related mechanisms over time, which would benefit from rodent in vivo electrophysiological probe approaches.

4. Gut-microbiota hippocampal route 3: gut microbiota metabolism

One of the principal roles of the gut microbiota is to metabolise host-indigestible nutritional substances. Notably, as the diversity of the gut microbiota composition is highly dependent on the diet it is supplied with (Bibbò et al., 2016) and microbial disbalances are associated with metabolic disorders (Santacruz et al., 2009). The gut microbiota is essential for the metabolism of several neuroactive substances, such as short-chain fatty acids (SCFAs) and neurotransmitter precursors (for reviews see e.g. (Flint et al., 2015; Nicholson et al., 2012; Tremaroli and Bäckhed, 2012)).

4.1. Short-chain fatty acids (SCFAs)

SCFAs are small organic monocarboxylic acids with a carbon chain up to six carbon atoms that are produced through anaerobic fermentation of dietary fibres and resistant starch, such as oligo- and polysaccharides, by a range of anaerobic commensal bacteria in the gut (Koh et al., 2016; Morrison and Preston, 2016; Pascale et al., 2018). The three main SCFAs are acetate, butyrate, and propionate (Cummings et al., 1987). Acetate and propionate are produced by e.g. *Bacteriodetes*, whereas e.g. *Firmicutes, Bifidobacterium, Lactobacillus,* and *Clostridium* produce butyrate (LeBlanc et al., 2017; Macfarlane and Macfarlane, 2012). SCFAs can influence the CNS and the hippocampus through two main routes: first, by interacting with gut mucosal enteroendocrine cells to release gut hormones such as PYY, GLP-1, and ghrelin of which the vagal-dependent satiety inducing and putative mnemonic effects have previously been described, and secondly, by directly affecting the CNS after crossing the BBB via endothelial monocarboxylate transporters (Oldendorf, 1973; see for review Silva et al., 2020).

SCFAs in the CNS are considered to exert a direct effect on memory by enhancing BNDF and modulating histone lysine (de)acetylase. Hippocampal BDNF is associated with neurogenesis and is critically implied in memory, as hippocampus-specific deletion of BDNF in mice impairs both novel object recognition and spatial learning (Heldt et al., 2007). BDNF is sensitive to microbiota changes, as its levels are decreased by antibiotic treatment-induced dysbiosis (Bistoletti et al., 2019; Desbonnet et al., 2015) and enhanced by supplementation of probiotics, especially *Bifidobacterium longum* (Leung and Thuret, 2015). SCFAs, specifically butyrate, mediate these effects. For example, an interesting study supplemented germ-free mice with gut microbiota from either older donors or from their peers and found that donation from older donors increased BDNF and neurogenesis, an effect specifically attributed to enrichment of butyrate-producing microbes following exposure to older donor microbiota (Kundu et al., 2019). Furthermore, probiotic administration of *Clostridium butyricum* increases butyrate, enhances CA1 BNDF, and can counteract cognitive decline (Liu et al., 2015). Synbiotic treatment of a probiotic (*E. faecium*) and a prebiotic (agave inulin) enhances butyrate production and improves specifically hippocampal-dependent performance in the Morris water maze, whilst not affecting a hippocampal-independent Pavlovian autoshaping procedure (Romo-Araiza et al., 2018), implying hippocampal sensitivity for synbiotic-induced butyrate.

Butyrate can also influence BDNF levels by inhibiting the inflammatory agent NF-κβ, which can disrupt BDNF concentrations through regulation of IL-1β (Carlos et al., 2017). In addition, rats subjected to bilateral common carotid artery occlusion to induce compromised cognition and gut barrier function, demonstrated decreased abundance of SCFA producers along with decreased hippocampal SCFAs. Recolonizing these rats using faecal microbiota transplantation improved gut barrier function and levels of hippocampal SCFAs, along with improving cognitive impairments (Xiao et al., 2022). Anti-inflammatory interactions with hippocampal functioning are further discussed in Section 5.

In addition to enhancing BDNF, butyrate also inhibits histone lysine deacetylase, which can enhance memory through manipulation of the epigenome (Gräff and Tsai, 2013; Reddy et al., 2018). The epigenome regulates the expression of genes, including those that encode proteins involved in memory processes. Intrahippocampal butyrate promotes both consolidation and reconsolidation of spatial memory in mice through these acetylating properties (Villain et al., 2016) and has been found to enhance long term contextual fear memory (Blank et al., 2014, 2015; Garcez et al., 2018; Levenson et al., 2004; Zhong et al., 2014) (however, see (Castellano et al., 2014)). A recent study further demonstrated that histone lysine acetylation was altered in germ-free mice, contributing to mitochondrial dysfunction in the hippocampus which may play a key role in regulating brain function and behaviour (Yu et al., 2021). In addition, Keogh and colleagues reported

antibiotic-induced dysbiosis administered at birth caused anxiolytic behaviour in adulthood, possibly explained by the reported dysregulated myelination in the PFC and decreased hippocampal neurogenesis. Interestingly, butyrate administration reversed disturbances in myelination and behavioural impairments (Keogh et al., 2021).

Summarising these studies provide evidence that microbiota-derived SCFAs can exert powerful mnemonic effects through distinct mechanisms but human studies are lacking, which may be explained by experimental SCFA doses being excessively higher than any dietary fibre induced SCFA-change used in preclinical research (Kim et al., 2013; Stilling et al., 2016). Nevertheless, some indirect evidence links SCFAs with hippocampal functioning, as patients suffering from major depressive disorder (MDD) show faecal alterations in butyrate-producing bacteria (Jiang et al., 2015; Zheng et al., 2016), as well as decreased hippocampal volume and functioning (Travis et al., 2015). On a final note, it is important to mention that conversely, SCFAs can modulate microbiota composition. Dietary produced SCFAs lower the pH which promotes certain *Clostridia* and impairs *Bacteroidetes spp,* which are associated with a dysbiotic and healthy composition, respectively (Duncan et al., 2009). It remains to be addressed how microbiota regulates this, and whether and when harmful effects of low-pH induced dysbiosis counterbalance the protective effects of SCFAs on hippocampal-dependent memory.

4.2. Neurotransmitters

Certain microbiota strains produce large quantities of substances identified as neurotransmitters, or their precursors, used in many multicellular organisms (Strandwitz, 2018). Microbiota-generated neurotransmitters in the lumen mainly interact with the host ENS. These substances are typically unable to cross the BBB, and lumen-produced neurotransmitters have often not been assessed for CNS effects. However, microbiota-derived neurotransmitter precursors could have an impact on CNS neurotransmitter synthesis. Indeed, seminal work indicated that germ-free mice show an elevated turnover of norepinephrine, dopamine, and serotonin in the striatum compared to SPF mice, however, no hippocampal differences were found and the origin (i.e. lumen or CNS) of neurotransmitters was not assessed (Diaz Heijtz et al., 2011). Recent interest has focussed on large neutral amino acids (LNAA) which are derived from many high-protein foods (Portune et al., 2016), such as tryptophan, a serotonin (5-HT) precursor; tyrosine, a catecholamine precursor; and glutamine, the precursor of glutamate and GABA.

4.2.1. Tryptophan and serotonin

The microbiota are considered to play a major role in tryptophan and serotonin metabolism (Yano et al., 2015) and early serotonergic CNS development (for review (Gao et al., 2018)). The microbiota can modulate tryptophan metabolism which dictates the amount of circulating tryptophan and metabolites. Dietary-derived tryptophan can cross the BBB through the large amino acid transporter and participate in the synthesis of serotonin (5-HT) and also melatonin (Mawe and Hoffman, 2013; Ruddick et al., 2006). Dysbiosis can decrease hippocampal 5-HT levels and impairs specifically hippocampal-dependent spatial memory (Hoban et al., 2016). Furthermore, tryptophan that accesses the CNS via the BBB can also exert neuroactive effects though the tryptophan-kynurenine pathway. Its metabolites act upon the N-methyl-D-aspartate (NMDA) receptor, which mediates excitatory neurotransmission. Tryptophan-kynurenine metabolites, such as quinolinic acid (a neurotoxic NMDAR agonist) and kynurenic acid (a neuroprotective NMDAR antagonist) can directly affect neuronal excitability through their NMDAR-modulating properties (O'Mahony et al., 2015; Schwarcz and Stone, 2017), which has been loosely associated with hippocampal functioning (Zwilling et al., 2011). Interestingly, LPS-induced inflammatory tone has been associated with the neurotoxic branch of kynurenine metabolism, impairing non-spatial recognition memory (Heisler and O'Connor, 2015), which makes it tempting to speculate that inflammatory tone induced by dysbiosis might exert similar memory-impairing effects through neurotoxic kynurenine metabolites, at least in part. Conversely, probiotics can exert beneficial effects through tryptophan metabolites: *Bifidobacterium* can enhance plasma tryptophan and kynurenic acid (Desbonnet et al., 2008), which can enhance hippocampal-dependent learning (Haider et al., 2007; Yousefzadeh et al., 2020), and *L. helveticus* has been shown to restore hippocampal 5-HT in chronically stressed animals (Liang et al., 2015).

In humans, several clinical populations show alterations in tryptophan metabolism. Patients with irritable bowel syndrome (IBS), characterised by dysfunctional microbiota (Carding et al., 2015), are reported to have enhanced tryptophan degradation to kynurenine (Clarke et al., 2009), and interestingly, acutely depleting peripheral tryptophan enhances episodic visuospatial hippocampal-dependent memory in female IBS patients, but not in healthy controls (Kennedy et al., 2015). In patients with bipolar disorder, a higher kynurenic acid/3-hydroxykynurenine ratio, which is assumed to be neuroprotective, correlates with enhanced verbal memory (Platzer et al., 2017). In patients with depression, this ratio correlates with enhanced memory recall and less activity in the left hippocampus, indicating increased hippocampal efficiency (Young et al., 2016). In summary, neuroprotective tryptophan metabolites show memory-enhancing potential in human clinical populations, however, therapeutic effects of probiotics remain to be assessed.

4.2.2. Tyrosine and catecholamines

Tyrosine is a catecholamine precursor, and can be produced by gut microbiota, in addition to many high-protein foods (Portune et al., 2016). After crossing the BBB, tyrosine can be converted in catecholaminergic neurons to L-DOPA which can be decarboxylated to dopamine, which can be further metabolised into norepinephrine (NE) in the locus coeruleus (Fernstrom, 2013). Both dopamine and NE are implicated in hippocampal functioning.

The dopaminergic system is well known for its role in fine motor control and reward-motivated behaviour, but dopaminergic signalling in the prefrontal cortex and hippocampus is also critically implicated in spatial working memory (Wilkerson and Levin, 1999), and is sensitive to microbiota (for review (González-Arancibia et al., 2019)). Microbiota present during early life is considered to be important for hippocampal dopaminergic development, although there is no consensus on the exact effects (Diaz Heijtz et al., 2011; Pan et al., 2019). In adult life, dysbiosis by chronic antibiotics induces a 2.5-fold L-DOPA increase in rats, associated with decreased hippocampal-dependent spatial memory (Hoban et al., 2016). However, it remains elusive through what mechanism the microbiota affects dopaminergic neurochemistry.

Noradrenergic neurons, whose cell bodies are mainly localised to the locus coeruleus, project densely to the hippocampus, facilitating spatial learning (Hansen and Manahan-Vaughan, 2015) (for review (Borodovitsyna et al., 2017)). Research on microbiota effects in learning through NE-mechanisms has been minimal, but one study indicated that probiotics (*L. helveticus*) can restore hippocampal NE in chronically stressed animals (Liang et al., 2015). It is important to determine to what extent the microbiota can influence human hippocampal memory through dopaminergic and NE mechanisms, as these are implicated in several psychopathologies, such as addiction and schizophrenia, respectively.

4.2.3. Glutamine and glutamate and gamma-aminobutyric acid (GABA)

Glutamine is the most prevalent non-essential amino acid in the human body, and is found in high concentrations in the gut. Humans can synthesise glutamine, notably in the muscles, but it can also be diet-derived, or produced by bacteria, mainly by *Firmicutes* (Ma and Ma, 2019). The effects of microbiota-derived glutamine have received scant attention, but oral glutamine supplementation can positively affect microbiota composition, suppress inflammation, and enhance gut apical tight junctions (for review (Rao and Samak, 2012)). Thus, it could be

speculated that synbiotic supplementation targeted at enhancing glutamine could also exert rescuing effects in dysbiosis, potentially rescuing the possible associated impaired hippocampal processing.

Glutamine can cross the BBB through multiple transporters, that are thought to include system A, L, and N transporters (Albrecht and Zielińska, 2019; Xiang et al., 2003). In the CNS it can be converted into glutamate, the main excitatory neurotransmitter of the CNS with major involvement in memory mechanisms. In humans, preliminary evidence was found using magnetic resonance spectroscopy that IBS patients suffering from dysbiosis have a reduced hippocampal glutamate/glutamine (Glx) ratio (Niddam et al., 2011), and higher Glx intensity has been correlated with better performance on a hippocampal-dependent word recall test, specifically in older adults (Nikolova et al., 2017). While intriguing, these observations do not demonstrate a causal relationship and more work is needed to obtain a clear understanding of the mechanistic impact of microbiota-derived glutamine.

In the brain, somewhat paradoxically, glutamate is the precursor of GABA, the main inhibitory neurotransmitter of the CNS. GABA is implicated in stress-related psychopathologies and epilepsy, as well as having important roles in hippocampal-dependent learning (Sibbe and Kulik, 2017). GABA is not a dietary amino acid so its synthesis from glutamate is paramount. However, certain probiotic species, including *Lactobacillus, Bifidobacterium*, and *Bacteroides,* can produce GABA in the gut (Barrett et al., 2012; Strandwitz et al., 2019), but it is debated whether peripheral GABA can cross the BBB (for review (Boonstra et al., 2015)). What is known is that the expression of the receptors to which GABA binds in the CNS can be modulated by microbiota, as probiotic supplementation of JB-1 altered hippocampal GABA-Aα2 and GABA-B1b mRNA expression (Bravo et al., 2011). Furthermore, another study showed that early life gut dysbiosis decreased hippocampal expression of GABA-A receptor α5 and δ subunits, and spatial memory in rodents, both of which could be rescued by a probiotic mix of *Lactobacillus rhamnosus* and *Bifidobacterium longum* (Liang et al., 2017). On a final note, a dietary supplement of GABA with a meal has been shown to activate vagal afferent nerves in mice (Nakamura et al., 2022), putatively providing an unexplored alternative route of microbiota-derived GABA on hippocampal functions.

4.3. Summarising microbiota-metabolites-hippocampus effects

The key message from this section is that microbes in the gut can produce a wide array of potentially neuroactive substances or their precursors. For some, such as SCFAs, the contribution of the microbiota and their mnemonic properties are starting to become relatively well described. For others, such as LNAAs—the precursors of certain important neurotransmitters—their production depends, at least in part, on microbiota composition, but precise neuroactive properties of specifically microbiota-derived LNAAs remain unknown. Furthermore, this is not an exhaustive list as other potentially neuroactive microbiota-generated substances may be recognised. Concluding, the ability of microbiota-derived substances to influence rodent hippocampal function, either directly or via developmental effects, is intriguing. Compelling evidence of how, and to what extent, they may affect human hippocampal-dependent learning and memory remains to be addressed.

5. Gut-microbiota hippocampal route 4: host immunity and inflammation

The gut, and therefore the microbiota, is close to the mucosal immune system and key for systemic immune system development (Fung et al., 2017). In fact, germ-free mice show immature mucosal and systemic immune systems with reduced expression of B- and T-lymphocytes (Macpherson and Harris, 2004). This is accompanied by significant behavioural consequences that can often be attributed to altered hippocampal function (for a review see (Foster et al., 2017)). For example, immunodeficient mice show impaired hippocampal learning (Brynskikh et al., 2008; Smith et al., 2014) which can be ameliorated by early life probiotics (Smith et al., 2014). This may not be surprising given that microbiota and the immune systems serve to recognize potential pathogens and evoke an adaptive (i.e., restoring homeostasis) inflammatory response by eliminating the pathogenic source; which can extend into an inflammatory response within the brain, including the hippocampus (for review see (Domínguez-Rivas et al., 2021)). Furthermore, the importance of brain inflammation in the pathogenesis of cognitive decline in AD has become well-established (Green et al., 2020). These, together with other findings, have established a gut microbiota-immune-brain axis that is potentially relevant to hippocampal learning and memory (for a detailed review see also (Tang et al., 2020)).

5.1. Microbiota supports immune system and memory function

Commensal microbes play a crucial role in immune system development and this effect is mediated by SCFAs, as discussed in Section 3.1 (Erny et al., 2015; Furusawa et al., 2013). Once fully mature, the immune system is activated after recognising microbial pathogens through specific Toll-like receptors (TLRs). TLRs are expressed on macrophages and dendritic cells and detect conserved molecular motifs of microorganisms, such as lipopolysaccharide (LPS), which trigger the TLR-MyD88 signalling pathway, initiating the inflammatory response and result in antigen-specific immunity (Takeda et al., 2003). More specifically, in both human patient populations and rodents, TLR2 and TLR4 have been identified as key factors in recognizing microbial components of Gram-positive bacteria and LPS of Gram-negative bacteria, respectively (Cario, 2005; Takeuchi et al., 1999). Interestingly, inhibiting TLR2 and TLR4 expression in the hippocampus of rodents results in improved memory function (Kwilasz et al., 2021), indicating that neuroinflammatory responses can impair hippocampal functioning.

Under normal steady-state conditions, the low-grade inflammatory tone maintained by commensal bacteria is crucial for baseline epithelial homeostasis and host protection (Rakoff-Nahoum et al., 2004; Yirmiya and Goshen, 2011). Of particular relevance to hippocampal function, gut bacteria stimulate the gut mucosal immune system, activate T lymphocyte function (i.e., regulate T cells) (Gaboriau-Routhiau et al., 2009; Talham et al., 1999; Umesaki et al., 1995, 1999), and promote maturation, morphology, and function of microglia, which are the resident macrophages of the CNS and are critically implicated in hippocampal functioning and neuroinflammation (Rodríguez-Iglesias et al., 2019). As a result, gut microbiota and mucosal- and neuroinflammation are closely related. That is, mucosal T cell activation is associated with microglial activation (Nakajima et al., 2021) and microglia in the hippocampus can release inflammatory cytokines, including TNFα and IL1β, which contribute to neurodegeneration as for example implicated in AD (Fang et al., 2019; Leng and Edison, 2021).

The immunologic effects of commensal bacteria extend to the general systemic immune system, as, for example, the microbiota can enhance systemic T cell responses (Hooper et al., 2012) which can control hippocampal LTP, neurogenesis, and memory by inducing cytokine activity, most notably IL6, IL1β, and TNFα (del Rey et al., 2013; Derecki et al., 2010; Wolf et al., 2009; for review see Tang et al., 2020). In the absence of infection, a low physiological baseline immune response activation supports hippocampal function through balancing levels of hippocampal excitability, plasticity-related factors, and neurogenesis (Yirmiya and Goshen, 2011).

5.2. Gut dysbiosis can induce inflammation which ultimately can impair memory

Dysbiosis can lead to the impairment of hippocampal-dependent memory by inducing neuroinflammation through extensive mucosal-systemic-neuroimmunological interactions. Dysbiosis combined with inflammation is a hallmark of inflammatory bowel disease (IBD), such as ulcerative colitis and Crohn's disease, that includes ulcers and bleeding

of the gut. IBD is closely related but distinct from IBS, which is a functional disorder of the gastrointestinal tract with seemingly normal mucosa (Spiller and Major, 2016). A rodent model of IBD exhibited reduced hippocampal adult neurogenesis both acutely (Takahashi et al., 2019) as chronically (Zonis et al., 2015) but see also (Gampierakis et al., 2020). Dysbiosis, caused by disease and/or stress (Bailey et al., 2011), can induce inflammation and macrophage dysfunction, which contribute to pathogenesis through inefficient clearance of pathogenic microbial products, dysfunctional pro- and anti-inflammatory responses, and loss of the intestinal barrier integrity (Fung et al., 2017), through which potentially pathological LPS can enter the systemic circulation (DeGruttola et al., 2016). This further induces the peripheral immune response, culminating in systemic inflammation and further gut dysfunction (Borre et al., 2014), which can ultimately induce neuroinflammation (Baizabal-Carvallo and Alonso-Juarez, 2020; Sharon et al., 2016) and affect hippocampal-dependent memory (Emge et al., 2016) (however, see also (Fröhlich et al., 2016)). Mimicking dysbiosis by stimulating the peripheral innate immune system with LPS induces cytokines such as IL1β (Bilbo et al., 2005) and activates microglia through TLR4 signalling (Jiamvoraphong et al., 2017; Lyman et al., 2014; Zhang et al., 2018). This inflammatory response impairs hippocampal-dependent LTP (Yirmiya and Goshen, 2011) and memory (Bilbo et al., 2005; Pugh et al., 1998; Sell et al., 2001; Zhang et al., 2018). Importantly, the immune response is furthermore shaped by the HPA-axis: LPS-induced hippocampal neuroinflammation can be modulated by glucocorticoids (for review (Bolshakov et al., 2021)). The detrimental effects of neuroinflammation seem to be especially evident in aged animals, as these show increased inflammatory cytokine mRNA expression in hippocampal regions and exhibit impaired spatial memory (Chen et al., 2008).

Although the investigation of the effects of dysbiosis in experimental animals achieved by peripheral LPS exposure has provided key insights, it may not be fully representative of clinical dysbiosis; for example it does not mimic the altered epithelial dysregulation and metabolism. Inducing dysbiosis by a high-fructose diet addresses these limitations and causes alteration of the gut microbiome along with epithelial dysfunction (Kawabata et al., 2019) triggering hippocampal neuroinflammation and hippocampal-dependent place recognition (Fierros-Campuzano et al., 2022; Hsu et al., 2015). Interestingly, diet-induced memory deficits correlated with both microbiota composition and hippocampal expression of inflammatory markers such as IL1β and TLR4 (Beilharz et al., 2016). Furthermore, high-fructose diet-induced hippocampal neuroinflammation and associated memory impairment could be rescued by SCFAs (Li et al., 2019). It must be noted that effects of a high-fructose diet on hippocampal-dependent recognition memory as assessed by the Morris Water Maze are still equivocal, as one study found an impairment (Cisternas et al., 2015), whilst others found no effect (Li et al., 2019; Sangüesa et al., 2018; Woodie and Blythe, 2018). These discrepancies might arise through subtle protocol and strain differences. In summary, however, it seems that gut dysbiosis can trigger systemic inflammation, which when left untreated can escalate into neuroinflammatory cytokine infiltration and/or expression in the hippocampus, with impairment of hippocampal functioning.

5.3. Prebiotics and probiotics can enhance immune function and learning

Probiotics can produce beneficial immunomodulatory effects in health and disease, overall enhancing memory. Supplementation of probiotics, e.g. from strains of *Bifidobacterium* and/or *Lactobacillus,* decreases pro-inflammatory markers through systemic mechanisms (Cazzola et al., 2010; Groeger et al., 2013; Wagar et al., 2009), and rescue epithelial dysfunction (Ait-Belgnaoui et al., 2012; Hsiao et al., 2013; Miyauchi et al., 2012) (for review (Yousefi et al., 2019)). This may, in turn, reduce the inflammatory response within the hippocampus and improve related cognition and behaviour. For example, a specific *Bifidobacterium* strain was found to reduce TLR2 expression in the hippocampus of obese mice (Agusti et al., 2018). Probiotic administration or TLR stimulation can normalise dysbiosis and rescue hippocampal memory through cytokines across disease models, such as hyperammonaemia-induced neuroinflammation (Luo et al., 2014) and AD (Pourbadie et al., 2018). In addition, prebiotics (Su et al., 2018) or synbiotics (Romo-Araiza et al., 2018) can reduce inflammatory markers and enhance hippocampal-dependent memory.

Furthermore, anti-inflammatory effects have been found to be induced by efferent VN activity on a systemic and local level through activation of the "cholinergic anti-inflammatory pathway" of the efferent VN. The active VN stimulates acetylcholine (ACh) release in efferent vagal neurons, that interacts with α7 nicotinic ACh receptors on macrophages to inhibit the release of pro-inflammatory cytokines, mainly tumor necrosis factor-α (TNF α) and interleukin 1β (IL1β) (Alen, 2022; Borovikova et al., 2000; Mizrachi et al., 2021). To our best knowledge, the interaction of VN activity with specifically microbiota composition and subsequent memory effects have not been described. But taken together, it seems likely that certain probiotic strains, such as JB-1 (Bercik et al., 2011; Bravo et al., 2011; Perez-Burgos et al., 2013), will decrease pro-inflammatory cytokines and thus tend to normalise systemic inflammation (Bonaz et al., 2018) by enhancing vagal efferent tone. Normalisation of inflammatory tone could enhance the gut epithelial apical junctional complex (Bonaz et al., 2018; Bruewer et al., 2003; Yu et al., 2012), and potentially rescue both immune-driven dysbiosis (Hooper et al., 2012), and related impaired hippocampal-dependent memory (H.M. Jang et al., 2018; S.-E. Jang et al., 2018). These hypotheses warrant further studies to assess the contribution of probiotic strains, such as JB-1, to hippocampal-dependent learning mediated by the cholinergic anti-inflammatory pathway.

Lastly, 'inflammaging', i.e., age-related increases in inflammatory activity (Franceschi et al., 2018) and -related spatial memory deficits have been found to be reversed by probiotics (e.g., a mixture of *L. plantarum* and *L. curvatus* (Jeong et al., 2015)). Indeed, antibiotic dysbiosis-induced negative effects on hippocampal neurogenesis and hippocampal-dependent novel object recognition can be rescued by a combination of exercise and a probiotic mixture, (partially) mediated by brain-residing Ly6C^{hi} monocytes of the innate immune system (Möhle et al., 2016). These studies indicate enticing probiotic-immune-memory enhancing effects; however, the exact mechanistic pathways remain to be identified. A potential mechanism could involve a reduction in hippocampal expression of IL1β and TNFα by probiotics: a herbal extract of New Zealand spinach reportedly prevented increases in hippocampal IL1β and TNFα mRNA expression in a rat model of AD, as well as modulating BDNF and ciliary neurotrophic factor (CNTF) (Kim et al., 2020).

5.4. Microbiota-gut-immune-hippocampus axis in humans

A clinical population exhibiting pathological alterations in microbiota, inflammation, and impaired hippocampal-dependent learning includes humans defined as obese (Beilharz et al., 2015; Das, 2001). Microbiota composition is drastically altered in obese patients: a healthy human gut is dominated by a high *Bacteriodetes:Firmicutes* ratio, whereas obese patients show an inverse ratio (Jumpertz et al., 2011). Obesity is associated with a dysbiosis-induced inflammatory tone, which can have developmental impact with obese children having a decreased hippocampal volume (Bauer et al., 2015) and also increases probability of developing cognitive decline such as dementia and Alzheimer's disease (AD) in later life (Bruce-Keller et al., 2009). The profound effect of dysbiosis is emphasised by a study showing that post mortem AD patients show three times more bacteria-derived LPS in their hippocampus, with more advanced cases exhibiting up to a 26-fold increases compared to age-matched controls (Zhao et al., 2017). Furthermore, patients suffering from irritable bowel syndrome (IBS) show microbial dysbiosis, increased gut permeability, and low-grade mucosal inflammation

(Holtmann et al., 2016) and lower hippocampal volumes (Labus et al., 2014). Even in healthy humans, the medial temporal lobe (where the hippocampus is located) may be especially susceptible to bacterial-induced inflammation, as systemic inflammation induced by the *Salmonella typhi* vaccine decreases parahippocampal glucose metabolism and impairs object location memory (Harrison et al., 2014). Taken together microbiota disruption in humans can induce systemic inflammation, which can profoundly affect hippocampal functioning through the inflammatory response. Potential immune-normalising and memory-protective effects of probiotics remain to be addressed.

5.5. Summarising microbiota-gut-immune-hippocampus effects

It is evident that pathologic or therapeutic microbiota compositions, by dysbiosis or probiotics respectively, influence the immune system on different levels. In normal conditions, the microbiota plays a key role in maintaining immune system homeostasis, supporting normal hippocampal-dependent learning and memory. Deviations through dysbiosis can result in epithelial dysfunction and systemic translocation of bacterial products, such as LPS, enhancing inflammatory tone, which when left untreated can culminate in neuroinflammation, impairing hippocampal-dependent memory. Interestingly, probiotic supplementation can exert rescuing effects, and through immune-normalising effects, improve hippocampal function. The exact underlying mechanisms are unknown but TLR2 and TLR4 and cytokines such as IL6, IL1β and TNF-α (see Tang et al., 2020), are proposed to play a key role in the complex dialogue between beneficial microbiota, immune function, epithelial integrity, neural inflammation, and neuronal plasticity.

6. Future challenges

In this review we have attempted to demonstrate considerable evidence for multiple gut-immune-brain axes that impact on hippocampal function. What is apparent from this body of work is the limited mechanistic detail, paucity of human studies and lack of substantive evidence of how this interaction could be promoted for positive or therapeutic effects. However, based on current state of knowledge, we argue that the most promising strategy to enhance hippocampal learning and memory by manipulating the microbiota would hypothetically be to provide a synbiotic combination that enhances multiple—preferably all—routes described above, capitalising on enhancing vagal tone, normalising the HPA-axis, increasing SCFAs, especially butyrate, and decreasing inflammation. Based on interventions that improve hippocampal-dependent memory through these routes—that is pre-, probiotics, and VNS—a combination of intake of dietary fibre, *Lactobacillus, Bifidobacterium* (Allen et al., 2016), and (t)VNS would be hypothesized to have promising potential. Although this is easily testable, the scientific field would benefit from studies evaluating more than just intervention-outcome effects.

That is, to understand, evaluate, optimise, and translate the microbiota-gut-brain axis in hippocampal-dependent memory (dys) functioning, future clinical and preclinical studies would benefit from a more coherent and structured approach. Based on the above, three major challenges in microbiota-hippocampus research seem to hamper progress: 1) heterogeneity of individuals with respect to microbiota composition and/or function and the variation this may produce in distribution between routes; 2) a relatively poor understanding, especially in humans, of the complex dialogue between composition, routes of interaction, and hippocampal functioning for specific microbiota-based interventions, and, as a consequence, 3) overall small effect sizes of microbiota-based interventions (i.e. variance in behavioural outcome measure explained by intervention).

First, in current approaches, individual variability along each of the above 4 summarized pathways is seen as something that needs to be controlled for. But to eventually establish strategies for microbiota-based memory enhancement across individuals, perhaps individual variability in composition and the four routes is in fact the key. That is, current studies often only assess the effect of, for example, probiotic supplementation on hippocampal memory, but ignore two major intermediate steps: effect on microbiota composition and/or function, and modulation of the four routes. We argue that these two steps should be assessed per intervention. Specific antibiotic, prebiotic, or probiotic effects on alteration of microbiota composition could non-invasively be estimated using faecal next-generation sequencing methods, such as whole genome shotgun sequencing (Ranjan et al., 2016).

Secondly, but related, future studies should specifically address how an intervention affects each of the four proposed routes of interaction. Although not each route has easily obtainable markers, and routes may interact: based on rodent studies plasma can be monitored throughout the intervention for stress response, such as cortisol/corticosterone, metabolic markers, especially butyrate, 5-HT and kynurenine metabolites, and host immune system by expression of TLR2 and TLR4 and pro- and anti-inflammatory markers, such as IL-1β, IL-6, and TNFα. To the best of our knowledge, there are no robust plasma biomarkers for vagal tone, but a molecular candidate could be pancreatic polypeptide, as this exclusively enteroendocrine cell (EEC)-expressed peptide is critically regulated by the vagus (Holzer et al., 2012; Schwartz et al., 1978). A robust alternative in rodents would be to measure tone invasively in vivo or *ex vivo* (e.g. as per (Buckley and O'Malley, 2018)). In humans, efferent (i.e., descending) vagal tone can be monitored non-invasively, albeit indirectly, by heart rate variability (e.g. as per (Pellissier et al., 2014)). Afferent (i.e., ascending gut-to-brain) vagal tone may be marked by scalp-recorded vagus-evoked potentials (Usami et al., 2013). Overall, these biomarkers should be confirmed, and establishing a plasma biomarker for vagal tone over time would be particularly practical. Combining information per specific microbiota-based intervention on changes of gut composition, route-markers, and performance of a battery of hippocampal-dependent cognitive tests would not only aid in allowing more variation in outcome measures to be explained, but also aid in the establishment of pre- and probiotics as personalised medicine based on composition and route-markers at baseline.

A note on diet. Contrary to cage-kept rodents, human diet is difficult to assess and/or control reliably. On the one hand, a standardised uniform diet enhances comparability between studies and labs for rodent studies, but on the other, uniform nutrition can be argued to impair translation to humans, who typically follow diverse eating habits. Importantly, diet significantly affects both microbiota composition (Bibbò et al., 2016; Magnusson et al., 2015) and hippocampal functioning (Magnusson et al., 2015; Proctor et al., 2017; Provensi et al., 2019; Pyndt Jørgensen et al., 2014), thus unvarying provision of a standard diet can be regarded as a restricting factor. For example, mice fed with 50% lean ground beef show increased microbiota diversity, physical activity, and hippocampal-dependent memory performance (Li et al., 2009) and even the beneficial effects of probiotics can be diet-dependent (Beilharz et al., 2018; Ohland et al., 2013).

The characterisation of the effects of specific dietary variations is an important challenge for future research and could help establish a standardised diet that includes variety. A standardised yet diverse diet would enhance the translatability of rodent microbe-gut-brain studies whilst ensuring comparability between labs. Whilst this is no easy endeavour, diet is an intrinsic part of the microbiota-gut-brain axis paradigm shift, and hence we argue that the time is overdue for discussing the standardisation of a diverse diet within microbiota-hippocampus animal research. In fact, diet and food-related behaviour may be key to understanding *why* gut microbiota would affect learning and memory. For example, taking an evolutionary perspective, if one assumes microbiota are sensitive to dietary changes (Conlon and Bird, 2014; Scott et al., 2013), such changes will logically enhance hippocampal-dependent episodic and spatial memory as this would improve remembering beneficial food-predicting cues and food source locations, which are essential to survival.

6.1. Conclusion

The human brain, with its 86 • 10^9 neurons, is considered the most complex structure in the universe. The incredible amount of 100 • 10^{12} prokaryotic organisms colonising the human gut, which across individuals consists of tens of thousands of different species that together express 10 million genes, appears to be serious competition. Converging evidence indicates that these two highly complex systems interact. In studies of psychopathology, the beneficial effects of probiotics, and detrimental effects of dysbiosis have generally translated relatively well to humans (Sarkar et al., 2016; Wang et al., 2016). Interestingly, capitalising specifically on hippocampal memory and learning, animal studies have also provided evidence that overall, memory can be enhanced or impaired by pre- and probiotics or dysbiosis, respectively.

However, this interaction is poorly understood, which hampers optimisation of microbiota-based memory enhancing effects and translation of these effects to humans. This review aimed to provide a structured understanding of microbe-hippocampus interaction and argue that this should be understood in four main routes in rodents: through the tenth cranial or vagus nerve, modulation of the adaptive stress hypothalamus-pituitary-adrenal axis, through production of neuroactive substances and their precursors, and by modulation of host immunity and inflammation. These routes should not be interpreted as isolated concepts, as processes and key molecules can overlap, painting an overall complex and variable picture, see Fig. 1. Importantly, major questions as to specific underlying mechanisms and interactions between these routes, and microbiota-strain specific effects, which might critically depend on host-specific characteristics (e.g. psychopathology, but also microbiota composition at baseline and diet), remain to be answered. And even though enthusiasm and optimism for beneficial effects of microbiota-based interventions are likely well-placed, important questions as to the precise underlying mechanisms, avenues for optimisation, and true translational value remain to be addressed in order to ultimately develop tailored strategies for microbiota-based enhancement of hippocampal-dependent memory and learning across human populations.

Funding

The work by Laura Steenbergen was supported by a Veni grant from the Netherlands Organization for Scientific Research (NWO, 016.Veni.198.030). The funding source had no further role in the work reported in this review.

CRediT authorship contribution statement

EJK conceived this article, performed literature search, and the prepared the first draft of this review. LS critically revised the manuscript; performed additional literature search and restructured and updated our review accordingly. Both contributed to the article and approved this final version.

Declaration of Competing Interest

The authors report no declarations of interest.

Data Availability

No data was used for the research described in the article.

Acknowledgements

The authors would like to acknowledge Dr. Jeroen Maljaars from the Leiden University Medical Centre for his valuable feedback on an earlier version, and Prof. Sue Wonnacott from the University of Bath for her valuable feedback on a later version of this review. The graphical abstract and figure were created with BioRender.com.

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