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Review

Exercise, diet and stress as modulators of gut microbiota: Implications for neurodegenerative diseases

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ABSTRACT

The last decade has witnessed an exponentially growing interest in gut microbiota and the gut-brain axis in health and disease. Accumulating evidence from preclinical and clinical research indicate that gut microbiota, and their associated microbiomes, may influence pathogenic processes and thus the onset and progression of various diseases, including neurological and psychiatric disorders. In fact, gut dysbiosis (microbiota dysregulation) has been associated with a range of neurodegenerative diseases, including Alzheimer's, Parkinson's, Huntington's and motor neuron disease, as well as multiple sclerosis. The gut microbiota constitutes a dynamic microbial system constantly challenged by many biological variables, including environmental factors. Since the gut microbiota constitute a changeable and experience-dependent ecosystem, they provide potential therapeutic targets that can be modulated as new interventions for dysbiosis-related disorders, including neurodegenerative diseases. This article reviews the evidence for environmental modulation of gut microbiota and its relevance to brain disorders, exploring in particular the implications for neurodegenerative diseases. We will focus on three major environmental factors that are known to influence the onset and progression of those diseases, namely exercise, diet and stress. Further exploration of environmental modulation, acting via both peripheral (e.g. gut microbiota and associated metabolic dysfunction or 'metabolopathy') and central (e.g. direct effects on CNS neurons and glia) mechanisms, may lead to the development of novel therapeutic approaches, such as enviromimetics, for a wide range of neurological and psychiatric disorders.

1. Introduction

1.1. The gut-brain axis

The estimation of the density of bacterial cells in the colon is around 10^{13} to 10^{14} per millilitre, making it one of the most densely populated microbial habitats on earth (Sender et al., 2016). When compared with approximately one trillion cells in the human body, bacterial cells constitute an even greater number of cells, residing within (and on) the body. Whilst these bacteria have largely evolved to have symbiotic relationships with their host organisms, they can also engage in parasitic and pathological relationships. Furthermore, the gut microbiome incorporates more than 150 times the number of genes than that which exist in the human genome (MetaHIT Consortium et al., 2010). Those impressive numbers reflect the complexity of community composition, diversity, metabolite production, interaction with the host, and ultimately the relationship between health and disease.

The fast progress of DNA sequencing approaches, such as shotgun-sequencing metagenomics, and bioinformatics techniques has resulted in the sequencing of the entire collection of DNA in microbial samples, leading to the comprehensive phylogenetic identification of gut communities of bacteria, as well as other microbes such as fungi and viruses. Furthermore, high-throughput and less expensive approaches, such as 16S rRNA amplicon sequencing, have allowed rapid uptake of these approaches in fields as diverse as biomedicine, agriculture and ecology. These breakthroughs in metagenomics and bioinformatics have been revolutionary, transforming not only microbiology but also our understanding of the myriad microbiomes which symbiose with all animal species (Knight et al., 2018). The last decade has thus witnessed an exponentially growing interest in the gut microbiome and more specifically, the gut-brain axis, including proposed modulatory roles in neurodevelopment, brain function and neurodegenerative diseases (recently reviewed by (Cenit et al., 2017; Dinan and Cryan, 2017; Moos et al., 2016; Spielman et al., 2018; Stefano et al., 2018)).

One hypothesis arising from these recent discoveries is that an 'unhealthy gut' can lead to an 'unhealthy brain', although this remains

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to be systematically tested (Spielman et al., 2018). In that context, some recent neurological and psychiatric research has investigated gut microbial population imbalance (also called gut dysbiosis), especially focusing on pathogenic imbalance (Keightley et al., 2015; Skolnick and Greig, 2019). A more diverse gut microbiome is generally considered to be healthy (in the absence of elevated pathogenic bacterial species) and has been associated with improved learning/memory and behavioural flexibility and, conversely, low microbial diversity is connected with impairment of cognitive abilities (reviewed by (Davidson et al., 2018)).

The diversity and composition of gut microbiota is crucial for many different reasons. Gut bacteria are regulators of basic processes such as digestion along the gastrointestinal tract, mediating nutrient and metabolite extraction, synthesis and absorption. Also, by competition for nutrients, producing bacteriocins and maintaining the intestinal epithelium integrity, commensal bacteria promote a first immune response against pathogenic bacteria (Rinninella et al., 2019). Furthermore, gut bacteria diversity and composition determines the abundance of microbiota-derived metabolites, neurotransmitters and the short-chain fatty acids (SCFAs, e.g. butyrate, propionate and acetate), which are major end-products of microbial fermentation in the gut (Campbell et al., 2016). The balance between those SCFAs are vital for gut health. Butyrate concentration, for example, is related to mucin production, has anti-inflammatory effects and increases tight-junction protein levels, ultimately promoting the maintenance of the intestinal barrier and reducing mucosal gut permeability (Campbell et al., 2016; Matsumoto et al., 2008). Imbalance in the aforementioned processes is associated with impairment in gut integrity and functionality, ultimately resulting in altered intestinal permeability and gut inflammation, establishing an aberrant gut environment. This profile generates a milieu of signaling molecules that ultimately can communicate with the brain through neural communication (vagal nerve), endocrine signaling (including the hypothalamus-pituitary–adrenal (HPA) axis) and the immune system (cytokines) (Westfall et al., 2017), modulating brain function, behaviour and, most remarkably, cognition (Gareau, 2016) (schematized in Fig. 1).

1.2. The gut-brain axis in neurodegenerative diseases

There is growing evidence that such gut dysbiosis may influence pathogenic processes and thus the onset and progression of various disorders, including neurological diseases (Catanzaro et al., 2015; Patterson et al., 2016). In fact, preclinical and clinical data have associated gut dysbiosis with a range of neurodegenerative diseases, including Alzheimer's disease (AD) (Hu et al., 2016; Wu et al., 2017), Parkinson's disease (PD) (Bedarf et al., 2017; Fields et al., 2018; Hill-Burns et al., 2017; Keshavarzian et al., 2015), amyotrophic lateral sclerosis (ALS; the most common form of motor neuron disease) (Wright et al., 2018) and more recently, Huntington's disease (HD) (Kong et al., 2018). Studies in germ-free mice have demonstrated significant cognitive deficits due to the absence of microbes, corroborating the critical link the gut-brain axis has to cognition and its modulation (Gareau et al., 2011).

1.3. Environmental factors affect gut microbiota

Modulation of human gut microbiota by environmental factors has been suggested since before the advent of metagenomics, when the study of microorganisms was restricted to only those microorganisms able to be cultured (Phillips, 2009; Tannock and Savage, 1974). Considering that the gut microbial community has a high level of complexity, it can be assumed that each human subject hosts a unique gut microbiome. In addition, the functionality, diversity, stability and resilience of the human gut microbiota vary between individuals, and in health and disease (recently reviewed by (Rinninella et al., 2019)). The gut microbiota thus constitute a changeable ecosystem constantly challenged by many variables, including environmental factors such as exercise, diet, stress, altitude, temperature, toxicants/pollutants and noise (recently reviewed by (Karl et al., 2018)). In this review we will focus on three major environmental factors that are known to influence the onset and progression of neurodegenerative diseases, namely exercise, diet and stress.

Since gut microbiota constitute a changeable ecosystem, they provide potential therapeutic targets that can be modulated as new treatments for dysbiosis-related disorders, including neurodegenerative diseases. Thus, this article reviews the environmental modulation of gut microbiota and its relevance to brain disorders, exploring in particular the implications for neurodegenerative diseases.

2. Exercise

2.1. Exercise, a protective intervention for neurodegenerative diseases

There is compelling evidence that many different types of exercise can promote enhanced cognitive functions both in health and disease, with a promising role for neurodegenerative diseases (Barnes, 2015; Hamilton and Rhodes, 2015). A recent meta-analysis demonstrated that regular exercise performed by elderly people is protective against AD (Santos-Lozano et al., 2016), slowing down the decline of cognition (Du et al., 2018). Besides improving cognitive performance, it was already reported that exercise could also improve amyloid-β levels and slow disease progression (Brini et al., 2018). Also, a systematic review showed an inverse association between physical activity and risk of AD, corroborating with other evidence of a protective role of exercise (Stephen et al., 2017). Therefore, exercise has been considered by some researchers to be an intervention for AD, which can be used concurrently with pharmacotherapy, and also a cost-effective prevention strategy (Cui et al., 2018).

The beneficial cognitive effects promoted by exercise have also been suggested for PD, demonstrated in preclinical studies (Crowley et al., 2018) and randomized controlled clinical trials (da Silva et al., 2018). Exercise also showed benefits in improving physical capacities, such as gait, and importantly, cognitive improvements in PD patients (reviewed by (Intzandt et al., 2018; Lauzé et al., 2016)). Even for genetically determined diseases such as Huntington's disease, there is preclinical and clinical support for the exercise benefits in terms of motor function, gait and cognitive outcomes (reviewed by (Fritz et al., 2017; Mo et al., 2015).

The mechanisms behind those effects promoted by exercise are not well understood. The knowledge has been based on preclinical studies and particularly in the cognitive outcomes which lead to a focus on the cerebral cortex, especially the hippocampus. Indeed, there is substantial evidence that exercise increases levels of neurotrophic factors (e.g. BDNF, NGF, VEGF), hippocampal neurogenesis and hippocampal volume, identifying exercise as a neuroplasticity promoter (reviewed by (Cass, 2017; Hamilton and Rhodes, 2015; Hirsch et al., 2016; Ma et al., 2017; Paillard et al., 2015)). Another significant mechanistic role has been explored in terms of epigenetic modifications, with promising outcomes (Grazioli et al., 2017). Although the aforementioned studies point out important related mechanisms, due to the potential to become a prescribed non-pharmacological therapy, a better understanding of the beneficial role of exercise on neurodegenerative diseases is required. To complete the picture, we require new insights into brain–body interactions, including the gut microbiome as a mediator, as discussed below.

2.2. Exercise modulates gut microbiota

The effect of exercise on microbiota has been extensively studied, and has been a focus of several recent reviews (Campbell et al., 2016; Cerdá et al., 2016; Cronin et al., 2017; Hamasaki, 2017; Mitchell et al., 2018; Monda et al., 2017). In general, positive effects have been reported, mainly in order to enhance colon health, increasing the

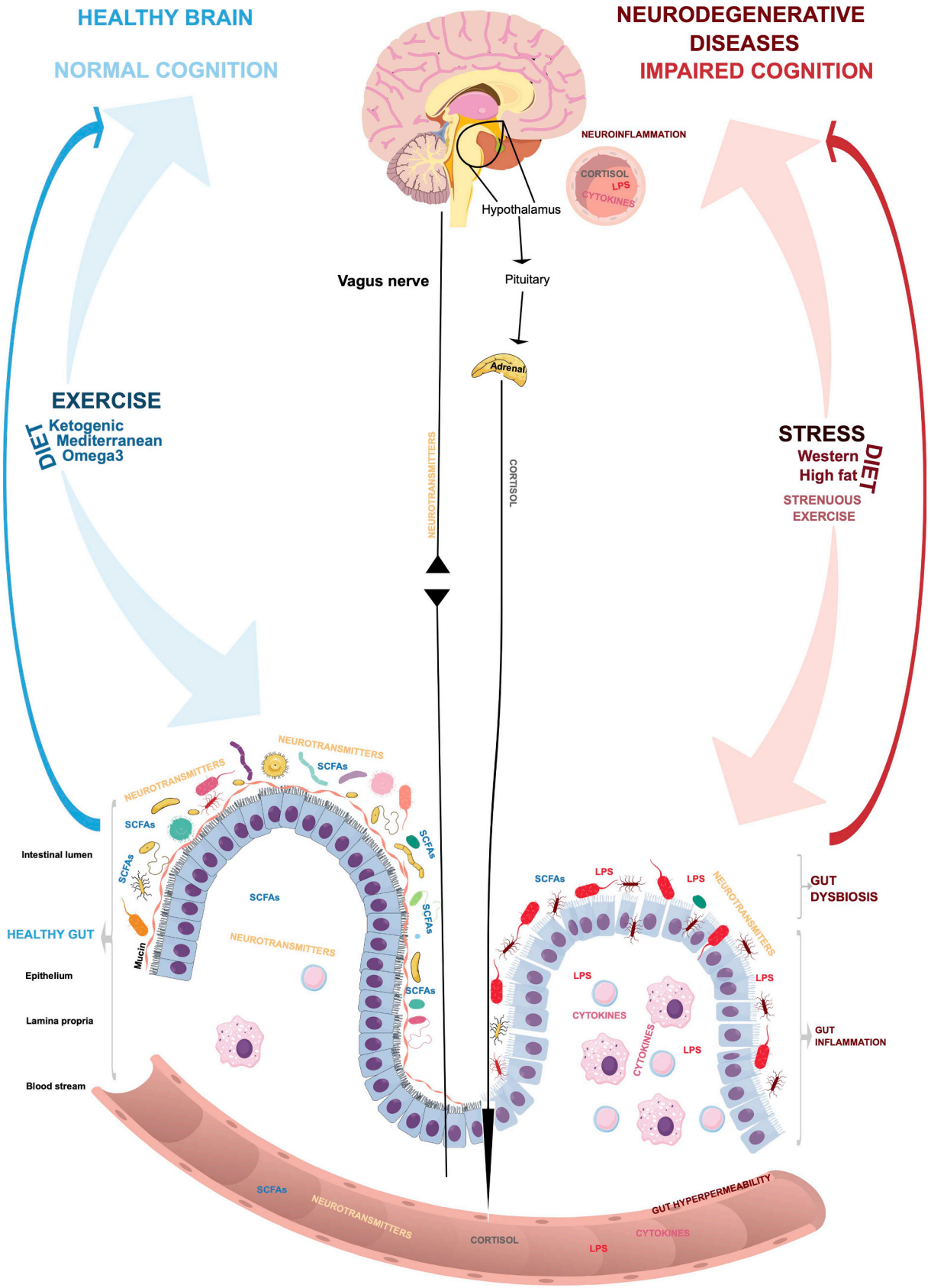

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Figure 1. Schema of environmental modulation of gut microbiota and associated impacts on neurodegeneration and cognition.
A healthy gut is associated with high microbiota diversity and with a positive balance between commensal and pathogenic bacteria. This environment results in the normal production of neurotransmitters and SCFAs, and in an intact mucin layer and intestinal barrier. The gut can communicate with the brain through neural communication (vagal nerve), endocrine signaling (hypothalamus-pituitary–adrenal (HPA) axis) and the immune system (cytokines) modulating brain function, behaviour and, more remarkably, cognition. Some environmental factors have been demonstrated to positively modulate these systems and their bidirectional communication, such as exercise and specific diets, including ketogenic and Mediterranean diets and Omega-3 supplementation. On the other side, gut dysbiosis includes poor microbiota diversity with an imbalance in the bacteria community composition promoting the establishment of pathogenic bacteria. This environment diminishes SCFAs and neurotransmitter production and increases LPS. The mucin layer production is affected as well as the intestinal barrier, leading to an impairment in gut integrity and functionality. This imbalance results in altered intestinal permeability and gut inflammation with an increase in circulating LPS and cytokines. Imbalance in the aforementioned processes will be associated with impairment in gut integrity and functionality, ultimately resulting in altered intestinal permeability and gut inflammation and establishing an aberrant gut environment. This gut dysbiosis has been associated with a wide range of neurodegenerative diseases and cognitive disorders. Environmental factors such as stress, Western and high-fat diets and strenuous (stressful) exercise can promote those features. SCFAs (short-chain fatty acids), LPS (lipopolysaccharide).

diversity of microbiota and the balance between beneficial and pathogenic bacterial communities (Allen et al., 2015; Evans et al., 2013). A recent systematic review identified *Firmicutes* and *Actinobacteria* as the main phyla that respond to exercise (Dalton et al., 2019), corroborating the findings of Mitchell and collaborators (Mitchell et al., 2018), who were able to conclude that exercise indeed produced a positive effect on microbiota, in general, increasing butyrate-producing bacteria, such as *Roseburia hominis*, *Faecalibacterium pausnitzii* and *Ruminococcaceae*. This is also reflected by an exercise-induced increase in butyrate concentration, both in rodents and humans (Allen et al., 2018a,b; Batacan et al., 2017; Campbell et al., 2016; Matsumoto et al., 2008; Queipo-Ortuño et al., 2013).

Additionally, exercise is also able to reduce transient stool time in the gastrointestinal tract, which reduces the contact of pathogens with the gastrointestinal mucus layer and consequently with the circulatory system, decreasing the action of this undesired population even when they are present. Recently, a causal role of exercise in modulating the gut microbiome for health benefits was demonstrated by the colonization of germ-free mice with the microbiota from exercised mice compared to the colonization from sedentary controls, resulting in an improved gut morphology, inflammatory profile and response to induced colitis (Allen et al., 2018a). In addition, one study recently reported a specific close link between *Veillonella atypica* and exercise performance, since inoculation of this strain to mice was able to increase their performance in treadmill running, via its metabolic conversion of exercise-induced lactate into propionate, suggesting a performance-enhancer microbe (Scheiman et al., 2019).

The potential mechanisms by which exercise modulates gut microbiota have been explored, and besides the modulation of gut microbiome composition, the close relationship with the immunological system has been implicated as a critical pathway of mediation (Bermon et al., 2015; Cerdá et al., 2016). Preclinical studies have shown that exercise increases key antioxidant enzymes (catalase and glutathione peroxidase), anti-inflammatory cytokines (including IL-10) and anti-apoptotic proteins (including Bcl-2) in intestinal lymphocytes, while it decreases proinflammatory cytokines (TNF-α and IL-17) and pro-apoptotic proteins (caspase 3 and 7), leading to an overall reduction in gut inflammation (Hoffman-Goetz et al., 2010; Hoffman-Goetz and Quadrilatero, 2003; Packer and Hoffman-Goetz, 2012). Unfortunately, human clinical research in this area is limited, and the knowledge behind the mechanisms underlying the effects of exercise on gut microbiota is still based mainly on animal models. In fact, the first study that has longitudinally examined the effects of exercise in human gut was recently published, demonstrating a compositional and functional modulation of endurance-based training on gut microbiota and fecal SCFAs, specifically in lean volunteers, showing a decrease in *Bacteroides* and an increase in *Faecalibacterium* and *Lachnospira* followed by an increase in fecal SCFAs (Allen et al., 2018b). In contrast, these investigators found a decrease in *Faecalibacterium* and an increase in *Bacteroides* and *Collinsella* populations in obese volunteers (Allen et al., 2018b).

Mitchell and collaborators have identified some inconsistencies between studies after a systematic review, which not only made the intra-systematic analysis difficult, but also limited the possibilities of translatability to humans (Mitchell et al., 2018). This finding flagged the need to standardize protocols when studying physical exercise, considering mainly the heterogeneity of study design: protocol intensity, training duration, anatomical gastrointestinal region examined (Denou et al., 2016), age (Mika and Fleshner, 2016), control for dietary factors (Batacan et al., 2017) and also for the consistency of reporting (e.g. index used for diversity assessment).

Some exercise protocol details, including the intensity, have to be thoroughly considered, especially since this feature has the power to differentiate healthy physical exercise from a stress model (reviewed by (Clark and Mach, 2016)). Most of the studies mentioned above referred to voluntary or regular to moderate physical activity, which maintains the intestinal blood flow during the period of activity, positively modulating the gastrointestinal motility (Oettlé, 1991), and are well-accepted protocols for reducing inflammation (Lambert et al., 2008; Walsh et al., 2011). On the other hand, strenuous exercise (≥60–70% VO2max) has been shown to produce a classical stress response, with higher concentration of stress-related molecules such as cortisol and epinephrine (Clark and Mach, 2016; Qamar and Read, 1987), combined with a reduction in blood supply to the intestinal epithelium which leads to subsequent reperfusion that ultimately is able to damage the gut barrier, increasing the permeability and promoting inflammation/gastrointestinal distress (Lambert et al., 2008; Lamprecht and Frauwallner, 2012; van Wijck et al., 2012).

The positive effects of exercise on gut health contribute to the understanding of the general promotion of well-being and quality of life that exercise physiologically promotes (recently reviewed by (Cerdá et al., 2016)), as well as, to the known primary prevention and improvement of several pathologies, including neurodegenerative diseases.

2.3. Is the gut microbiome the missing link between exercise and neurodegenerative diseases?

Considering the already discussed dysbiosis present in various neurodegenerative diseases, as well as the effects of exercise on both the gut microbiome and neurodegeneration, it makes sense to triangulate the three, and investigate whether exercise can, at least partly, modulate neurodegeneration via gut microbiota. The gut microbiome has been suggested as a driver of variation in cognitive function, with a positive feedback loop between microbiome diversity and cognition. As mentioned above, there have been only a few studies that have looked to the effects of exercise in humans and its influence on the gut microbiota, and unfortunately, cognition was not one of the scientific questions covered by those works (Allen et al., 2018b). Fortunately, a few animal studies have already addressed this question, showing promising outcomes (Table 1).

Kang et al. (2014) performed a forced exercise paradigm using running wheels for 16 weeks in adult mice, demonstrating memory

Table 1
Exercise, diet and stress effects on microbiota and cognition

Model	Protocol	Details of protocol	Behavioural tests	Cognitive outcomes	Gut/microbiome outcomes	Other outcomes	Main conclusion	Reference
Exercise								
Male C57BL/6 mice	Running wheels (for 16 w)	Training: 2 weeks, speed gradually increased 3–7 m/min, duration 6–60 min/day. Followed by 1 hour at 7 m/min, 5 days/week Controls: placed in running wheels (~1 m/min)	Contextual fear conditioning	↑ contextual memory Trend ↑ cued memory	↑ abundance of *Firmicutes* ↓ abundance of *Bacteriodetes* and *Tenericutes*	Association between *Ruminococcaceae* and *Lachnospiraceae* with % of freezing context	Exercise was able to enhance cognition and modify the gut-microbial profile	Kang et al., 2014
LCR – animal model of metabolic syndrome and HCR male rats	Treadmill running (for 6 w prior to surgery)	One week of habituation Training: 5 days a week (31.5 min at a speed of 20 m/min). Controls: placed on a non-moving treadmill Additional intervention: open tibial fracture to mimics postoperative cognitive decline	Trace Fear Conditioning and Morris Water Maze (3 days and 3 months after surgery, respectively)	Improved postoperative freezing time and the decrement in recall (dwelling time) in LCR rats	Improved α and β diversity in LCR rats ↑ abundance of *Firmicutes* ↓ abundance of *Bacteriodetes*	Attenuated the postoperative inflammatory state in LCR rats (expression of IL-6, HMGB-1, MCP-1, Netrin-1)	Prevented postoperative neuroinflammation, acute and persistent cognitive impairment and improved the dysbiosis in LCR rat	Feng et al., 2017
Male APP/PS1 transgenic mice (AD animal model)	Treadmill running (for 20 w)	Two weeks of habituation Training: ten cycles of four minutes at high intensity (20 m/min) and two minutes at low intensity (10 m/min). Controls: placed on a non-moving treadmill	Morris water maze and Y-maze	↑ spatial memory Alone it was not able to prevent the decreased spontaneous alteration in the AD mice but combined with a probiotic treatment had a positive effect	↑ abundance of *Eubacteria*, *Roseburia* and *Clostridia* in AD mice ↓ abundance of *Prevotella*, *Bacterioides*, *Bacterioides fragilis* and *L. johnsonii* in AD mice	↓ AD histological changes (mean number of plaques in hippocampus and mean % of the areas covered by plaques) The *B. thetaiotaomicron* levels correlated with poorer results in The Morris Maze Test and the *L. johnsonii* levels positively correlated with beta amyloid content and area	Exercise improved cognitive functions and decreases the levels of microorganisms involved in disease exacerbation and increase the abundance of beneficial SCAFs producing bacteria	Abraham et al., 2019

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Table 1 (*continued*)

Model	Protocol	Details of protocol	Behavioural tests	Cognitive outcomes	Gut/microbiome outcomes	Other outcomes	Main conclusion	Reference
Diet								
Male C57BL/6 mice	High-fat, high sucrose, or normal chow diet (6 w)	Mice were individually housed and randomly assigned high-fat (42% fat, 43% carbohydrate), high sucrose (12% fat, 70% sucrose) or normal chow (13% fat, 62% carbohydrate)	Step-down latency Novel object/ location recognition (2 w prior and 2 w after treatment) Water maze testing for long and short-term memory and cognitive flexibility (5 and 6 w post-diet change)	↓ performance in long-term, short-term spatial memory, and reversal training in high-sucrose diet group No effect on step-down, exploration or novel recognition High sucrose diet group was significantly impaired in early development of spatial bias for long- & short-term memory and reversal training when compared to normal diet group	↑ *Clostridiales* in high fat and high sucrose diet ↑ abundance of *Erysipelotrichales* only in high-fat diet group ↑ abundance of *Lactobacillales* (specifically *Enterococcus*, *Lactococcus*, *Lactobacillus*) only in high-sucrose diet group ↓ abundance of *Bacteroidales* in both high-fat and high-sucrose diet, greater effect in high-sucrose diet	Higher percentages of *Clostridiales* and lower expression of *Bacteroidales* in high-energy diets were related to poorer cognitive flexibility in reversal trials	High sucrose diet impaired spatial memory and cognitive flexibility High sucrose diet altered more gut bacterial orders and genera than high fat	Magnusson et al., 2015
Adult male C57BL/6 mice	HFD (16w)	Mice were assigned either ND (10% calories from fat) or HFD (60% calories from fat)	Open field testing Three chamber social interaction test Light/dark box Contextual fear conditioning	HFD did not impact open field activity and sociability (3 chamber) between ND and HFD HFD mice spent less time in open arm and travelled less in light/dark box No difference in contextual memory between HFD and ND	HFD ↑ prevelance of *Firmicutes* phylum, *Streptococcaceae*, *Lachnospiraceae*, *Clostridiaceae* family, and *Steptococcus* genus ↓ abundance of *Bacteroidetes* and *Tenericutes*, *Porphyromonadaceae*, *Erysipelotrichaceae* family.	Higher levels of 3 OTUs from *Lachnospiraceae* family correlated with less anxiety OTUs from *Lactococcus* genus, *Ruminococcaceae* family, *Lachnospiraceae* family and *Butyricicoccus* genus negatively correlated with anxiety	HFD impacts the microbiome and has an anxiogenic effect on mice	Kang et al., 2014
Male C57Bl/6 mice	Cecal transplantation from mice assigned either HFD (60% fat calories) or normal chow (13% fat calories) (10 w)	Recipient mice received antibiotic cocktail for 14 days and were recolonized via oral gavage from donor microbiota. Behavioural tests were performed on donor mice approx. 2 w after transplantation. Fecal samples were collected during final week of behavioural testing	Elevated plus maze Open field assay Contextual fear conditioning Marble burying behaviour	HFD-recipient spent less time exploring open arm in EPM HFD-recipient spent less time in inner zone of open field HFD-recipient increased marble burying behaviour HFD-recipient had ↑ freezing to tone	Microbiota shift similar between cecal and fecal samples: HFD-recipient had ↑ abundance of *Lachnospiraceae* and *Ruminococcaceae* ↓ abundance of *Akkermansia municiphila* ↑ abundance of *Bilophila sp.*	↑ intestinal inflammation and permeability (assessed by circulating endotoxin and inflammatory markers) in HFD-recipient ↑ expression of microglial marker, calcium-binding adapter molecule 1, toll-like receptor 4 in HFD-recipient ↓ tight junction proteins and ↑ matrix metallo-proteinase 9 in HFD-recipient No effect of BDNF levels in medial prefrontal cortex	Microbiota from HFD alone is able to negatively impact the behaviour, brain and intestinal inflammation	Bruce-Keller et al., 2015
Male and female C57Bl/6 mice	Social isolation and then assigned either normal diet, or normal diet with DHA supplementation	Mice initially were individually housed for 28 days followed by random assignment to either normal diet, normal diet +0.1% weight DHA supplementation or normal diet +1% weight DHA supplementation. Fecal pellets were collected at 28th day of social isolation, 24 hours and 7 days post diet switch for microbiome analysis. Behavioural tests performed 7 days post diet switch.	Open field test Elevated plus maze Sucrose preference test	DHA supplementation did not impact general locomotion in OFT but sex did. Male mice consuming control diet have significantly fewer entries into open arms of EPM DHA supplementation positively affected anhedonia-like behaviour (SPT) in male mice but not females	↑ abundance of *Allobaculum*, *RF39*, *Lactobacillus* and *Rikenellaceae* family in male mice ↑ abundance of *Clostridium*, *Ruminococcous*, *Coprococcus* and *Anaerotruncus* in female mice ↑ methane metabolism and C5 dibasic acid metabolism in male mice whereas ↑ bacterial chemotaxis and fatty acid metabolism in female mice (predicted by PICRUSt) In male mice, DHA supplementation ↓ abundance in *Lactococcus* and *Leuconostoc*, ↑ abundance of *Streptococcus* and *Helicobacter* In female mice, no significant effect of DHA supplementation on the gut microbiome	Abundance of Ruminococcus and Allobaculum have negative and positive correlation, respectively, on open arm entries and sucrose intake in male mice	Male mice exhibit significantly more anxiety and depressive-like behaviour following social isolation stress and dietary supplementation of DHA ameliorates this effect Sexual dimorphic effect of social isolation on the gut microbiota	Davis et al., 2017

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Table 1 (*continued*)

Model	Protocol	Details of protocol	Behavioural tests	Cognitive outcomes	Gut/microbiome outcomes	Other outcomes	Main conclusion	Reference
Stress								
Male C57BL/6 mice	Psychosocial Stress (6 w)	Chronic unpredictable social stress Additional intervention: Prebiotic administration: FOS and GOS	Novel object recognition test	↓ long-term memory in discrimination index	↓ abundance of *Bifidubacterium* ↓ Actinobacteria: Proteobacteria ratio ↑ abundance of *Alloprevotella, Peptococcus, Anaerotruncus* ↓ abundance of *Allobaculum, Prevotella* and *Enterorhabdus*	Prebiotic administration could prevent not only stress-related behaviours as well as the microbiota effect	Stress induced impairment in cognition and significantly microbiota modification which were prevented by prebiotic administration	Burokas et al., 2017
Male C57BL/6 mice	Psychosocial Stress (6–12 w)	Chronic unpredictable restraint stress Restrain in 50 mL conical tubes for 2 hours/day (5 days/week) in unpredictable times Additional intervention: Rotenone-induced PD pathology	-	-	↑ intestinal permeability (demonstrated by increased urinary excretion of sucralose/ lactulose) ↑ endotoxemia (high levels of LPS) ↑ Intestinal barrier dysfunction (abnormal tight junction proteins ZO-1, 6occluding, and claudin-1 expression) ↓ butyrate in feces,↑ Inflammation in colon and neuroinflammation in combination with rotenone ↓ abundance of *Lactobacillus* (after 6w of RS) ↑ abundance of *Akkermansia*	Inverse correlation between relative abundance of *Akkermansia* with muscle strength performance on the hanging grip test and a positive correlation between fecal butyrate levels and striatal dopamine levels	Stress exacerbate the PD phenotype, associated with a dysfunctional gut-brain axis	Dodiya et al., 2018
Male Sprague–-Dawley rats	Prenatal stress and acute restraint stress (offspring) (1 w during the last week of pregnancy)	Pregnant dams were placed 3 times (45 min daily) into transparent plastic restraints. Control dams were left undisturbed in their home cages	Novel object recognition test	↓ discrimination between novel and familiar objects	↑ abundance of *Oscillibacter*, *Anaerotruncus* and *Peptococcus* (from *Clostridiales* order) ↓ abundance of *Streptococcaceae*	↓ distal colon innervation with enhanced colonic secretory response to norepinephrine	Prenatal stress leads to long-term effects, as exacerbated HPA response to acute stress, cognitive impairment and a dysfunctional gastrointestinal development and function associated with changes in intestinal microbiota composition	Golubeva et al., 2015
Female C57BL/6 mice	Prenatal restraint stress (from embryonic days 10–16)	Pregnant dams were placed into 50 mL conical tube (for 2 h). Control dams were left undisturbed in their cages home	Novel Object Recognition Test	↓ preference for a novel object	↓ *Bacteriodetes* and *Firmicutes* ↑ *Proteobacteria* ↓ *Bifidobacteriaceae*, *Rikenellaceae* and *S24–7*	Prenatal stress produced inflammatory changes *in utero,* BDNF levels impairment in placenta and altered the microbiome during pregnancy	Prenatal stress was able to produce long-term modifications in cognition and microbiome composition as well as intrauterine dysfunction, indicating the microbiota as a link between the acute and chronic effects of stress	Gur et al., 2016

LCR - Low Capacity Runner; HCR - High Capacity Runner; HMGB-1 - High Mobility Group Box 1; IL-6 – Interleukin-6; MCP1 - Monocyte chemotactic protein-1; AD – Alzheimer Disease; SCAFs – Short-chain fatty acids; ND – Normal diet; HFD - High-fat diet; OTUs – Operational taxonomic unit; DHA – Docosahexaenoic acid, OFT – Open field test; EPM – Elevated plus maze; SPT – sucrose preference test; FOS - fructo-oligosaccharides; GOS - galacto-oligosaccharides; PD – Parkinson's disease; ZO-1 - zonula occludens-1; RS – Restraint stress; HPA – Hypothalamic–pituitary–adrenal; BDNF – Brain-derived neurotrophic factor.

improvement and a significant alteration in the gut microbial community. Specifically, the exercise was able to increase the abundance of *Firmicutes* and decrease the abundance of *Bacteriodetes* and *Tenericutes*. Lastly, they found an association between *Ruminococcaceae* and *Lachnospiraceae* with some fear-conditioning relevant measures. The authors suggest that the associations demonstrated between the microbial abundance and the contextual memory could be used as potential microbiota biomarkers of the exercise effects on cognition, although further investigation is clearly required (Kang et al., 2014).

The postoperative cognitive decline is considered a devastating complication of surgeries, mainly for elderly people (Avidan and Evers, 2016). Interestingly, preoperative exercise, performed 6 weeks before open tibial fracture in a rat model of metabolic syndrome, was able to prevent the expected postoperative acute cognitive decline together with an improvement in α and β diversity in the gut microbiome and increasing abundance of *Firmicutes* and to decrease the abundance of *Bacteriodetes*, indicating an enhancement of dysbiosis induced by the operation. Furthermore, attenuation in the postoperative neuroinflammatory state was observed, and a persistent cognitive improvement induced by the exercise after three months of the surgery. Since a less diverse microbiome is associated with a hyperinflammatory state (Buford et al., 2018), this study supports the hypothesis that the gut microbiota may have contributed to the inflammatory modulation and suggests a possible pathway of mediation for exercise in cognitive-related disorders (Feng et al., 2017). This further suggests that exercise is a therapeutic intervention to prevent postoperative cognitive decline, neuroinflammation and to enhance the diversity and stability of the gut microbiome.

It has recently been demonstrated that exercise could improve cognitive functions and histological markers of AD, while decreasing the levels of microorganisms involved in disease exacerbation and increasing the abundance of beneficial SCAFs-producing bacteria (Abraham et al., 2019). This is the first study addressing the intestinal microbiome mediation of exercise in an AD model. Specifically, APP/PS1 transgenic mice were exposed to 20 weeks of a protocol of treadmill running, inducing an increase in spatial memory, the abundance of *Eubacteria*, *Roseburia*, and *Clostridia* in AD mice and to decrease the abundance of *Prevotella*, *Bacterioides*, *Bacterioides fragilis* and *L. johnsonii* in AD mice. Another interesting finding was the correlation between *B. thetaiotaomicron* levels and poorer results in the Morris water maze test (assessing spatial hippocampal memory) and the positive correlation between *L. johnsonii* levels and β-amyloid content and localisation. Altogether these data suggest that the beneficial effects of exercise could be partly mediated by alteration of the microbiome in AD. Furthermore, these findings suggest potential pathways linking gut microbiota with neurodegenerative diseases and open exciting new therapeutic possibilities. More studies should address this relationship to establish the link between gut dysbiosis and AD pathogenesis, as well as expand to other neurodegenerative diseases which might share common gut-related mechanisms.

3. Diet

3.1. Diet as an intervention for neurodegenerative diseases

There are extensive studies documenting a close relationship between dietary patterns and risk factors for neurodegenerative diseases (reviewed by Erro et al., 2018; Luchsinger et al., 2007; Solfrizzi et al., 2011). For example there is evidence that high consumption of saturated fat exacerbated neurodegeneration in AD and PD (Bousquet et al., 2012; Petrov et al., 2015) by enhancing oxidative stress and lipid peroxidation (Morris et al., 2010; Studzinski et al., 2009). Epidemiological studies in HD have associated higher diary consumption and higher caloric intake with earlier onset of the disease (Marder et al., 2013). However, a preclinical study reported no effects of high fat diet on the progression of HD in a preclinical model (van der Burg et al., 2008). Other studies have shown that increased consumption of saturated fat induces an inflammatory response whereby peripheral immune cells are recruited to the central nervous system (Buckman et al., 2014), which may explain the exacerbation of symptoms in diseases mentioned previously.

Dietary manipulation has been sought after as a therapy for modifying the symptoms of the aforementioned diseases. An underlying theme of such diet-based intervention is that nutrients and metabolic substrates can exert beneficial effects on neuroinflammation and neuronal function as well as improving the dysfunctional metabolic homeostasis commonly reported in these diseases.

The ketogenic diet (KD) was initially introduced as an intervention for epilepsy treatment and its therapeutic potential has been studied in various neurological disorders including AD, PD, HD, multiple sclerosis and autism spectrum disorder (Newell et al., 2016; Ruskin et al., 2013; Swidsinski et al., 2017; Van der Auwera et al., 2005). This diet is characterized by a high-fat, adequate-protein and low-carbohydrate intake and aims to restrict glycolysis and increase fatty acid oxidation to ketone bodies, resulting in a state of ketosis whereby ketone bodies replace glucose as primary energy source for the brain. There has been some success in utilizing KD to improve symptoms of preclinical models of AD, PD and HD (Beckett et al., 2013; Brownlow et al., 2013; Ruskin et al., 2011; Van der Auwera et al., 2005) as well as clinical trials for PD and AD patients (Henderson et al., 2009; VanItallie et al., 2005).

Several studies have elucidated the therapeutic effects and mechanisms of KD, which has been extensively reviewed elsewhere (Gasior et al., 2006). For example, KD can protect against oxidative stress and normalize neuronal bioenergetics by stimulating mitochondrial biogenesis and stabilizing synaptic function, as well as stimulating BDNF production (Genzer et al., 2016). Thus, the effects of KD in attenuating the symptoms of various neurological diseases could be mediated by therapeutic effects on mitochondrial impairment, a well-documented deficit in AD, PD and HD. Notably, the neuroprotective effects of KD may be, in part, mediated by ketone bodies. AD risk scores were reported to improve when β-hydroxybutyrate, a ketone body released during KD, was administered to AD patients (Henderson et al., 2009). Infusion of β-hydroxybutyric acid protects mice from dopaminergic neurodegeneration and motor deficits induced by MPTP (Tieu et al., 2003). Furthermore, β-hydroxybutyrate could inhibit the degradation of an important neurotransmitter, γ-aminobutyric acid (GABA), and therefore increase the availability of GABA in the brain, as enhancement of GABA levels were shown in clinical models (Dahlin et al. 2005, Wang et al. 2003, Suzuki et al. 2009).

In addition to the KD, consumption of a Mediterranean diet (MD) has been reported to be protective against the occurrence of several different health outcomes. MD is not a specific diet but rather a collection of eating habits traditionally adhered to by people in the countries bordering the Mediterranean Sea. The diet is characterized by a high dietary intake of fruit, vegetables, legumes, complex carbohydrates, with moderate consumption of fish and olive oil as the main source of fats and a low-to-moderate amount of red wine during meals. A meta-analysis on the consumption of MD revealed better cognitive scores (Psaltopoulou et al., 2013; Sofi et al., 2010) and hence, was thought to have potential as a therapeutic treatment for various neurological disease. Indeed, multiple preclinical and clinical studies provided evidence for a favourable relationship of MD with reduced risk of AD (Mosconi et al., 2014; Scarmeas et al., 2006, 2009) and later onset of PD (Alcalay et al., 2012), although there are no clear benefits of MD on HD (Marder et al., 2013). The Mediterranean diet is high in monounsaturated and polyunsaturated fats, both of which have been linked to overall reduced risks for AD and PD (Calon and Cole, 2007; de Lau et al., 2005; Kamel et al., 2014). In addition, docosahexaenoic acid (DHA), an omega-3 fatty acid enriched in the brain and enriched in the MD from high fish intake, is known to have anti-depressive effects and is capable of improving cognitive performance including learning and memory (Gamoh et al., 1999, 2001; Gharekhani et al., 2014; Hashimoto

et al., 2002). Interestingly, KD also results in enhanced levels of DHA and other fatty acids, including eicosapentaenoic acid (EPA) and linoleic acid (LA) in children (Dahlin et al., 2007).

Given that DHA is known to promote neuronal growth and learning, as well as neuroimmunomodulation (Salem Jr et al., 2001), it is not surprising that DHA supplementation has been beneficial in improving the symptoms of neurodegenerative diseases (Bousquet et al., 2009; Cansev et al., 2008; Hacioglu et al., 2012; Ozsoy et al., 2011). Several epidemiological studies revealed that high dietary intake of DHA and other PUFAs, was associated with reduced risk of AD, PD, HD and ALS as well as improving depressive symptoms in PD (Barberger-Gateau et al., 2002; da Silva et al., 2008; Fitzgerald et al., 2014; Morris et al., 2003; Quinn et al., 2010; Vaddadi et al., 2002). Notably, the DHA levels in AD and PD subjects were extremely reduced (Fabelo et al., 2011; Tully et al., 2003) and oral supplementation with DHA could normalize its deficiency. Preclinical studies have also elucidated the disease-modifying mechanisms of DHA which decreased neuro-inflammation and amyloid-beta load in AD brain, as well as attenuating dopaminergic neuronal death in PD through activation of Akt/p-Akt and Bcl-2 pathways (Calon et al., 2004; Hacioglu et al., 2012; Lim et al., 2005; Oksman et al., 2006; Salem Jr et al., 2001).

Moreover, the Mediterranean diet is rich in polyphenols, vitamins C, E, B12, folate and carotenoids, and may counteract the detrimental effects of oxidative stress and lipid peroxidation, so as to be protective against not just cardiovascular disease, but also beneficial for brain health. This diet is rich in dietary antioxidants and limited in amount of saturated fat which may contribute to the lower risk for specific neurodegenerative diseases, such as PD (Gao et al., 2007).

Although there are some inconsistencies between preclinical and clinical studies, the neuroprotective effects of these dietary manipulations observed in preclinical models warrant further investigation of the mechanisms, as well as more clinical research to explore their therapeutic potentials for other neurodegenerative diseases beyond AD and PD. The beneficial effects of these dietary patterns may be partly due to the direct action of the supplementation of specific compounds on the host cells (Rabot et al., 2016). However, given the important role of diet in shaping the bacterial communities in the gut, it is also likely that some of the neuroprotective effects may be mediated by the gut microbiota.

3.2. Modulation of gut microbiota through diet

Diet is a key contributor in sculpting the microbial communities in the gut, and changes in dietary pattern can directly influence the composition and functionality of the gut microbiota, through the availability of macro- and micronutrients in the gut. Extensive studies have been performed, both preclinically and clinically, to examine the effect of dietary patterns on gut bacterial composition. Long-term high dietary intake of saturated fat and simple sugars, characteristic of a 'Western diet', has been linked to *Bacteroidetes*, especially the bile-tolerant microorganisms including *Alistipes* spp. and *Bacteroides* spp., with decreased levels of *Firmicutes* in humans as well as preclinical models (Turnbaugh et al., 2009). A short-term dietary change can alter gut microbial populations within 24 hours, although the main enterotypes remain largely similar (Turnbaugh et al., 2009). Individuals consuming plant-based diets have a more complex microbiome compared to those with animal-based diets, more specifically, they have enhanced levels of fiber-fermenting bacteria which leads to augmented levels of fermentation end products including the SCFA in the local gut environment as well as the circulatory system (Wu et al., 2011).

It is not surprising that the aforementioned dietary interventions would have some effect on the gut microbial population. There are some studies on the effect of KD on the gut microbiota, albeit with some contradictory evidence. Ma et al. reported a reduction in the relative abundance of *Desulfovibrio* and *Turicibacter* and an enrichment in *A.muciniphila* and *Lactobacillus* (Ma et al., 2017), one of which is a known SCFA producer and both are commensal bacterium (Dao et al., 2016; Derrien et al., 2004; Lukovac et al., 2014). Many independent studies reported that KD decreased overall microbial diversity based on the Shannon index and observed taxa (Ma et al., 2018; Newell et al., 2016; Olson et al., 2018). However, there is evidence that the effects of KD are biphasic, whereby the bacterial diversity is reduced in the beginning of a KD intervention, which subsequently normalizes and then exceeds the baseline (Swidsinski et al., 2017). Notably, the microbiota composition shaped by intermittent fasting is not similar to those in KD (Beli et al., 2018).

Adherence to the Mediterranean diet has been shown to be beneficial to cognitive health and was associated with higher abundance of Bacteroidetes and *Prevotellaceae* and *Prevotella* and lower concentration of *Firmicutes* and *Lachnospiraceae* (De Filippis et al., 2016). Higher levels of fecal propionate and butyrate were detected in subjects with higher adherence to MD (Gutiérrez-Díaz et al., 2016), which were associated with increased diversity when compared to those consuming a Western diet.

Increased consumption of omega-3 fatty acids, found in fatty fish, led to increased circulating DHA levels which correlated with high levels of *Lachnospiraceae* and *Ruminococcacae* family, taxonomic groups of the human gut involved in the fermentation of dietary fibers to produce SCFA (Biddle et al., 2013). Some of these dietary associations with gut bacteria appear to be mediated by the abundance of fecal metabolite N-carbamylglutamate (Menni et al., 2017). In addition, the dietary intake of polyphenols, vitamins and other micronutrients also have the capacity to shape the gut microbiome (reviewed by Serra et al., 2018).

The gut microbiome composition is malleable and quick to respond to changes in dietary patterns. Hence, it entirely plausible that dietary manipulations could exert at least some of their effects on general physical as well as cognitive well-being through gut microbiota.

3.3. Gut microbiota as mediators of dietary effects on neurodegenerative disease

The gut microbiota appears to play pivotal roles in regulating host metabolism, endocrinology and physiology. A seminal study demonstrated that gut microbiota are not merely reflective of dietary intake but they can be key mediators of metabolic state (Turnbaugh et al., 2006). Subsequent studies have highlighted the link between the regulatory effect of diet on cognition and behaviour to the compositional changes in the gut microbial population (Table 1).

The high-fat diet is known to play a key role in the aetiology of various metabolic diseases, or 'metabolopathies', and has been associated with increased risk for various neurodegenerative diseases including AD and PD. The cognitive impairments and the increased neuroinflammation induced by high-fat diets appear to be mediated, at least partly, by gut microbiota (Bruce-Keller et al., 2015). Furthermore, high-fat diets increase anxiety-like behaviours, and this association also appears to be mediated by the gut microbiota (Kang et al., 2014), possibly through the HPA axis (Sivanathan et al., 2015). Since the HPA axis establishes a crucial communication between the gut and the brain, it has been suggested that HPA dysfunction may lead to modification in intestinal permeability, motility and mucus production (Fung et al., 2017), effects which may be attenuated by the supplementation of polyphenols and other dietary interventions (Li et al., 2018).

There are additional studies highlighting the role of the gut microbiota in mediating the effects of the aforementioned dietary patterns. A diet high in fiber would result in an enrichment of fiber fermentation and SCFA producers, leading to an overall increase in microbial by-products, which has been shown to benefit cognitive performance in both humans and animal models (Hanstock et al., 2004, 2010).

Moreover, dietary intake of DHA has been shown to be associated with reduced risk of AD and PD. The antidepressant-like effects of

dietary consumption of DHA may be, in part, mediated by the gut microbiome in addition to directly regulating gene expression and neurotransmission (Müller et al., 2015). Recent evidence demonstrated that omega-3 PUFAs differentially shaped the murine gut microbiota (Davis et al., 2017). The authors reported that *Allobaculum* and *Ruminococcus* significantly correlated with behavioural changes observed in the male mice. Supplementation of EPA and DHA changed gut microbiome composition and attenuated corticosterone response from early-life stress (Pusceddu et al., 2015). Moreover, transplantation of microbiota from mice fed with fish oil, to mice fed with lard, resulted in the alleviation of inflammation and adiposity caused by high saturated fat intake (Caesar et al., 2015). This study highlighted the role of *A. muciniphila* in mediating the anti-inflammatory effects of fish-oil supplementation and, yet again, demonstrated the key role of microbiota in mediating protective effects of dietary manipulation.

KD has been shown to elicit its neuroprotective effects via several pathways (reviewed in Masino and Rho, 2012), including the gut-microbiota. The anti-seizure effects of KD were negated in germ-free mice as well as antibiotic-treated mice and restored once the gut was recolonized with SPF gut microbiota (Olson et al., 2018). The gut microbiota may confer its beneficial effects via modulating selective metabolism of gamma-glutamylation and other ketogenic amino acids which were reflected in the serum and resulted in an increase in brain GABA levels (Olson et al., 2018). Another study revealed that mice fed with KD had enhanced cerebral blood flow, as well as elevated relative abundance of beneficial microbes which inhibited mechanistic target of rapamycin (mTOR) signaling by activating endothelial nitric oxide synthase (eNOS), resulting in improved neurovascularisation (Ma et al., 2018). Furthermore, (D)-3-hydroxybutyrate ketone body production, which is altered by HD interventions, is regulated by the gut microbiota and has the capacity to interact with the peripheral tissues as well as the brain via GPCR signaling, in addition to epigenetically regulated genes, to protect against oxidative stress (Ma et al., 2018).

Diet has thus been used as a therapeutic agent to modify the severity of various neurological diseases with some degree of success and there is evidence that at least some of the observed effects may be mediated by gut microbiota.

4. Stress

4.1. Stress as a risk factor for neurodegenerative diseases

Stress can be classified as environmental (e.g. climatic extremes, noise, toxicants/pollutants), physical (e.g. sleep deprivation, undernutrition, strenuous exercise) and psychological (e.g. chronic anxiety, fear, excessive cognitive demands) (reviewed by (Karl et al., 2018)) and it is present ubiquitously, to varying extents, in daily life. Different biological effects, including the core stress response system, the hypothalamic–pituitary–adrenal (HPA) axis, promoted by severe, chronic or uncontrolled exposure to those stressors, have been studied and the maladaptive changes in brain structure and function leading to negative physical and mental consequences are well described (Lupien et al., 2009; McEwen, 1998; Nutt and Malizia, 2004). The ability of stress to mediate pathological changes increasing the vulnerability or even predisposing susceptibility to diseases has been widely explored, including for cardiovascular diseases, gastrointestinal and psychiatric disorders (Caruso et al., 2018; Ross et al., 2018). Similarly, there is substantial evidence that stress can modulate the pathogenesis of various neurodegenerative diseases.

Preclinical and clinical studies have shown that stress can accelerate onset of AD and exacerbate pathology (reviewed by (Futch et al., 2017; Machado et al., 2014)). Stressful events can trigger cellular, molecular and behavioural hallmarks of AD, accelerating the appearance of the disease (reviewed by (Caruso et al., 2018)). Furthermore, increased cortisol levels are consistently observed in patients affected by AD (Curto et al., 2017; Greenwald et al., 1986; Hoogendijk et al., 2006; Peskind et al., 2001), and this is not surprising considering the burden of the diagnosis and the devastating nature of the disease, which in itself can be considered a stressful condition. Some mechanisms of mediation between stress and AD have been proposed, such as altered expression and function of amyloid β (Aβ) and tau proteins, as well as neuroinflammation (Carroll et al., 2011; Chong et al., 2005; Ricci et al., 2012). In addition, glucocorticoids and/or corticotropin-releasing hormone (CRH) could act as mediators, and centrally contribute to the pathology, since transgenic mice overexpressing CRH show increased levels of phosphorylated tau in the hippocampus (Carroll et al., 2011). Similarly, antagonism of CRH demonstrated positive effects on both Aβ amyloid and tau pathology, supporting the idea of a potential new therapeutic target for AD based on the stress response (reviewed by (Futch et al., 2017)). Moreover, a role for stress as a link between psychiatric disorders and AD, focusing on neuronal resilience and allostatic load, has been suggested (reviewed by (Ross et al., 2018)).

Similarly, the potential role of stress in the pathogenesis of PD has been explored (Djamshidian and Lees, 2014). Extreme psychological stress exposure, including that associated with holocaust and war, was found to be clinically associated with the development and incidence of PD (Gibberd and Simmonds, 1980; Salganik and Korczyn, 1990). Furthermore, the burden of diagnosis together with the uncertainty of PD progression is itself a psychological stressor, and has been shown to worsen symptoms and the functional capacity leading to an overall impairment in the quality of life (Austin et al., 2016). Indeed, patients with PD demonstrate increased levels of stress, indicated by increased cortisol levels when compared to healthy controls (Charlett et al., 1998; Soares et al., 2019). Regarding mechanisms, it has been suggested that stress could contribute directly to dopaminergic loss, culminating in nigrostriatal degeneration in susceptible individuals (Smith et al., 2002, 2008). Furthermore, stress as a link between psychiatric disorders and neurodegenerative diseases is also relevant for PD; specifically stress as a contributor to the development of depression, which is a common non-motor symptom that precedes the motor symptoms in PD patients (Dallé and Mabandla, 2018). Besides the shared role for stress in the aetiology of both depression and PD, it has been suggested that depression may contribute to worsening the motor symptoms, possibly injuring the nigrostriatal system, although more studies are needed to clarify this relationship (Hemmerle et al., 2012).

Similarly, for HD, stress is also able to modulate the pathogenesis of the disease (reviewed by (Mo et al., 2015)). Preclinical studies have suggested an increased susceptibility to stress in R6/1 HD transgenic mice together with relevant changes in the HPA axis and hippocampus (Du et al., 2012; Mo et al., 2013, 2015). Clinical studies have revealed a similarly dysfunctional HPA axis in HD patients, including the balance between mineralocorticoid and glucocorticoid receptor signaling (Aziz et al., 2009), correlating with HPA-axis changes in the R6/2 transgenic mouse model of HD (Björkqvist et al., 2006) (reviewed by (Rodrigues et al., 2018)). Collectively, these data suggest that stress should be considered as a potential risk factor for neurodegenerative diseases and that it is necessary to uncover the mechanisms of modulation interconnecting stress with these diseases.

4.2. Stress modulates microbiota

Recent evidence has linked stress to gut dysbiosis suggesting that the intestinal microbiota could serve as mediators of chronic stress responses (Karl et al., 2018; Mackos et al., 2016; Sudo et al., 2004). Indeed, one study in germ-free mice demonstrated that a mild restraint stress induced an exacerbated release of corticosterone and adrenocorticotropic hormone (ACTH) when compared with controls, indicating a critical role of microbiota in the development of the HPA axis and the stress response (Sudo et al., 2004). In fact, gut microbes have been shown to contribute to several physiological and behavioural consequences of stress exposure, such as the above-cited HPA axis dysregulation (Gareau et al., 2007; Sudo et al., 2004), increased

inflammation (Bailey et al., 2011; Maslanik et al., 2012), impaired cognition (Gareau et al., 2011), altered social behaviour (Bailey and Coe, 1999) and impaired intestinal barrier function (Bailey and Coe, 1999; Gareau et al., 2007; Mackos et al., 2016; Söderholm and Perdue, 2001; Zheng et al., 2013, 2017) leading to intestinal permeability and ultimately establishing a 'leaky gut' (Ait-Belgnaoui et al., 2012; Eutamene et al., 2007; Zareie et al., 2006). Nevertheless, stressor exposure is able to directly affect the composition of the gut microbiota, damaging the ecology of the intestinal microbial community, and is thus considered a dysbiosis promoter (Karl et al., 2018; Mackos et al., 2016; Mika and Fleshner, 2016; Tannock and Savage, 1974).

Animal and clinical studies have shown that stressors negatively impact the gut microbiota (reviewed by (Bailey et al., 2011; Bailey and Coe, 1999; De Palma et al., 2014; Karl et al., 2018; Tannock and Savage, 1974)) identifying new avenues by which stress disrupts health. Regarding animal models of stress, different models were able to alter the gut microbiota composition, such as maternal separation, restraint conditions, heat stress, noise and crowding (Bailey et al., 2011; Bailey and Coe, 1999; O'Mahony et al., 2009; Tannock and Savage, 1974). Specifically, one robust finding has been the lower levels of *Lactobacillus* observed after maternal separation (Bailey and Coe, 1999) and chronic restraint stress (Zheng et al., 2013). Interestingly, the reduced abundance correlated with stress and did not correlate with cortisol levels, indicating an independent pathway of modulation (Bailey and Coe, 1999). In accordance with these findings, when oral *Lactobacillus* was administered in a rodent model of stress, the behaviour, cognition and biochemical parameters were improved (Liang et al., 2015), whereas the corticosterone levels were decreased (Gareau et al., 2011) and the barrier leakiness prevented (Ait-Belgnaoui et al., 2012). Also, an increase in the family *Clostridiales* has been observed after different chronic stress paradigms, as well as a decrease in abundance of *Bacteriodes* due to stress, both correlating with the altered levels of proinflammatory cytokines (Bailey et al., 2011; Galley and Bailey, 2014; O'Mahony et al., 2009). Collectively, these data support the importance of the gut-brain axis in modulating the stress response (Cryan and Dinan, 2012).

4.3. Are gut microbiota targets for stressors in neurodegenerative diseases?

The involvement of the gut-brain axis in various central nervous system disorders related to stress has been the focus of several reviews (Bravo et al., 2012; Collins et al., 2012; Cryan and Dinan, 2012; Foster and McVey Neufeld, 2013; Scott et al., 2013). However, the particular relationship between stress, gut microbiota, and neurodegenerative diseases, as well as cognition and behaviour, remain underexplored. Few studies have addressed this relationship, as shown in Table 1. Burokas and colleagues (Burokas et al., 2017) evaluated the effect of chronic psychosocial stress in mice focused on the microbiota effect and how the nurturing of the community with the use of prebiotics (fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) and a combination of both) could modulate this effect (Burokas et al., 2017). This study indicates an impairment of cognition induced by the stress model together with a change in the microbiome profile, with an essential decrease in the *Bifidobacterium* abundance and a decrease in the *Actinobacteria:Proteobacteria* ratio, which interestingly is the profile described in patients with major depressive disorder (Jiang et al., 2015; Kelly et al., 2016). All these effects were ultimately prevented by the prebiotic treatment.

Prenatal stress has also been shown to be able to modulate cognition and microbiota composition. In fact, restraint stress during the last week of pregnancy in rats can induce long-term exacerbation in the HPA response to acute stress, cognitive impairment and dysfunctional gastrointestinal development and function, associated with changes in intestinal microbiota composition (Golubeva et al., 2015). Specifically, male offspring from dams exposed to prenatal stress demonstrate an increase in the abundance of *Oscillibacter*, *Anaerotruncus*, and *Peptococcus* (from *Clostridiales* order) and a decrease in the abundance of *Streptococcaceae,* as well as an impairment in distal colon innervation with enhanced colonic secretory response to norepinephrine. Those findings suggest that prenatal stress has long-term effects that pass through the central nervous system but also affect the gastrointestinal tract, with impacts on gut neurodevelopment and gut microbiota. Likewise, prenatal stress was able to produce long-term modifications in cognition and microbiome composition in female offspring as well as intrauterine dysfunction, implicating the microbiota as a link between the acute and chronic effects of stress (Gur et al., 2017). Specifically, prenatal stress decreased the abundance of *Bacteriodetes* and *Firmicutes* as well as *Bifidobacteriaceae*, *Rikenellaceae* and *S24-7* and increased the abundance of *Proteobacteria*. In addition, prenatal stress produced inflammatory changes *in utero*, BDNF dysregulation and altered the microbiome during pregnancy. Overall, these studies indicate that exposure to stress during gestation can induce intestinal cognitive impairment together with dysbiosis into offspring adulthood, suggesting a new approach of modulation to prevent those negative outcomes.

More recently, a study showed that psychosocial stress could exacerbate the PD phenotype, associated with the establishment of a dysfunctional gut-brain axis in mice (Dodiya et al., 2018). Six weeks of restraint stress was able to increase stress markers as well as to increase intestinal permeability when compared to control mice. In addition, stress exacerbated pathological features including neuroinflammation, cell death in substantia nigra and reduced striatal dopamine and metabolite levels. The rotenone animal model of PD exhibited dysfunction in the intestinal barrier, as well as gut and central inflammation, which was exacerbated by the stress model. Regarding microbiome composition, it was demonstrated that the stress model can decrease the abundance of *Lactobacillus* when compared with control mice, which is considered a bad outcome since this genus is considered to promote anti-inflammatory function. Furthermore, the PD rotenone model can increase the abundance of *Akkermansia*, mucin-degrading bacteria, and stress was also able to potentiate this effect. Altogether, these data provide evidence that stress leads to a dysfunctional gut-brain axis, establishing a dysbiosis environment including gut permeability and inflammation which is capable of potentiating the PD pathology and phenotype. More studies are needed to further test this hypothesis, clarifying whether this dysbiosis is a key component of PD pathogenesis or whether it is another consequence of the disease. If indeed the gut microbiome can modulate pathogenesis this could provide a new therapeutic target for the prevention and treatment of PD.

5. Concluding remarks

A higher diversity in the gut microbial community and a positive balance between commensal/pathogenic bacteria, together with general gut health including integrity and functionality, have been remarkably associated in recent years with various aspects of brain function, affect and cognition. Furthermore, gut dysbiosis has been associated with a wide range of neurodegenerative diseases. The concept that human gut microbiota constitutes a dynamic ecosystem constantly challenged by many variables, including environmental factors, provides hope for new potential therapeutic targets for dysbiosis-related diseases. In fact, negative effects of stress on gut dysbiosis, associated with exacerbation of pathogenesis and of neurological impairments, suggest that the gut microbiota could be a stressor target in neurodegenerative diseases. Furthermore, positive effects of exercise and diet on gut microbiota and cognition, have been shown for non-strenuous exercise and ketogenic diet, Mediterranean diet and Omega-3 supplementation, with impressive cognitive outcomes. In contrast, opposite effects have been observed for strenuous (stressful) exercise, as well as Western and high fat diets (schematized in Fig. 1). Nevertheless, a causal relationship between gut microbiota and the pathogenesis and progression of neurodegenerative diseases is yet to be comprehensively

demonstrated, either preclinically or clinically. Understanding the mechanisms by which key environmental factors (e.g. exercise, diet and stress) can modulate neurodegeneration, via interactions between the periphery and the nervous system, including intermediates such as gut microbiota, will have major therapeutic implications. More research is needed to address the many remaining questions in this field and systematically investigate the gut, and its microbiota, as potential therapeutic targets for neurogenerative diseases, and other dysbiosis-associated disorders.

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