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Review article

Mining microbes for mental health: Determining the role of microbial metabolic pathways in human brain health and disease

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ABSTRACT

There is increasing knowledge regarding the role of the microbiome in modulating the brain and behaviour. Indeed, the actions of microbial metabolites are key for appropriate gut-brain communication in humans. Among these metabolites, short-chain fatty acids, tryptophan, and bile acid metabolites/pathways show strong pre-clinical evidence for involvement in various aspects of brain function and behaviour. With the identification of neuroactive gut-brain modules, new predictive tools can be applied to existing datasets.

We identified 278 studies relating to the human microbiota-gut-brain axis which included sequencing data. This spanned across psychiatric and neurological disorders with a small number also focused on normal behavioural development. With a consistent bioinformatics pipeline, thirty-five of these datasets were reanalysed from publicly available raw sequencing files and the remainder summarised and collated. Among the reanalysed studies, we uncovered evidence of disease-related alterations in microbial metabolic pathways in Alzheimer's Disease, schizophrenia, anxiety and depression. Amongst studies that could not be reanalysed, many sequencing and technical limitations hindered the discovery of specific biomarkers of microbes or metabolites conserved across studies. Future studies are warranted to confirm our findings. We also propose guidelines for future human microbiome analysis to increase reproducibility and consistency within the field.

1. Introduction

1.1. Role of metabolites in the microbiota-gut-brain axis

Since the serendipitous discovery of the antibacterial properties of penicillin in 1928, microbial metabolites have been harnessed for their various antimicrobial properties and are emerging as mediators of mammalian health and behaviour (Fleming, 1946b, a; O'Mahony et al., 2015; Blacher et al., 2017; Levy et al., 2017; McCarville et al., 2020). The mammalian gastrointestinal tract is colonised at birth by a diverse collection of microorganisms, collectively called the microbiota (Codagnone et al., 2019; Theis et al., 2019). One of the core functions of the gut microbiota is the modification of host, xenobiotic and dietary-derived molecules into bioactive metabolites that can impact host health and disease (Clarke et al., 2019; Sharon et al., 2014; Spanogiannopoulos et al., 2016; Morris et al., 2017; Sun et al., 2017). The ecological community coexisting within a shared space is defined as the microbiome (Lederberg and McCray, 2001). One of the most surprising findings over the past decades is the cornucopia of genes within the microbiome that enable the production and modification of neuroactive metabolites which may modify gut-brain axis function (Zimmermann et al., 2019; Strandwitz et al., 2019; Lyte, 2014; Clarke et al., 2014; Tennoune et al., 2014; Lee et al., 2015). Most studies in this field characterise the predominant bacterial and archaeal components of the gut microbiota.

Microbial metabolites communicate through dynamic bi-directional pathways within the microbiota-gut-brain axis to mediate host brain immunity and physiology (Spichak et al., 2019; Erny et al., 2017; Pott and Hornef, 2012; Blacher et al., 2017; Levy et al., 2017; McCarville et al., 2020). They exert effects directly after being transported across the blood-brain barrier or indirectly through immune, neuroendocrine or vagal mechanisms (Alenghat, 2015; McCarville et al., 2020; Roager

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and Licht, 2018; Stilling et al., 2016; Fulling et al., 2019). Advances in sequencing technologies over the past decade enable the relatively rapid and comprehensive illumination of the gut microbiome composition (Song et al., 2018; Bailey et al., 2019; Shakya et al., 2019). For the most part, sequencing of faecal samples is used as a surrogate of the gut microbiota composition of individuals. However, since most studies differ in methods, developing a consensus from this data is difficult (Pollock et al., 2018). Nonetheless, these studies are invaluable for assessing the role of the bacterial metabolites within the human host's central nervous system (CNS).

Three of the most-studied metabolic pathways within the gut microbiota are the short-chain fatty acids (SCFAs), tryptophan metabolism and bile acid metabolism and will form the focus of our paper.

1.2. Aims and scope

Knowledge on the role of the main microbial metabolic pathways influencing the brain and behaviour is emerging. It is important to collate all the currently available datasets in order to identify gaps and point to novel areas of discovery. Thus, the aim of this paper is to assess metabolic signatures of different human brain health and disease states. All publicly available datasets will be reanalysed and all existing data from the remaining studies will be collated. This study focuses on SCFAs, tryptophan pathway metabolites and bile acids. To the best of our knowledge, this is the first extensive analysis of the microbiota-gut brain axis involving all publicly available data to determine whether any clear microbial composition and metabolic signatures emerge for psychological and psychiatric diseases. Briefly this will involve the following steps:

1 An extensive literature review (PubMed) on all studies involving sequencing the faecal microbiota in humans to compare with a functional or clinical brain measure, or disease status. Significant findings at the genera level related to the metabolites involved in the scope of this study will be recorded, along with significance and effect size, if available. Differentially abundant microbes known to be involved in metabolic pathways (tryptophan, SCFA and bile acid) will be identified from the existing literature (Molinero et al., 2019; Roager and Licht, 2018; Valles-Colomer et al., 2019; O'Mahony et al., 2015).
2 A reanalysis of all publicly available datasets with a common, updated pipeline to identify differentially abundant microbes and gut-brain modules (GBMs). Recently the concept of GBMs has emerged, providing an additional predictive index for bacterial 16S rRNA gene sequencing studies (Valles-Colomer et al., 2019). Briefly, the authors performed an extensive literature review to inform the assembly of pathways with neuroactive potential in bacteria. Existing databases don't curate all these pathways or predict their ability to bypass the blood-brain barrier (Valles-Colomer et al., 2019). After construction and validation from genomes of human-associated microbes, GBMs were validated on a large cohort of human 16S rRNA gene sequencing data (Valles-Colomer et al., 2019). This revealed novel insight into the gut metabolic signatures of depression (Valles-Colomer et al., 2019). To fulfil a GBM, the microbe must possess each enzyme within the pathway (Valles-Colomer et al., 2019). Though this method does not directly measure the abundance of these metabolites, it provides stringent associations validated on large independent cohorts. In addition to changes in microbial composition and GBMs, effect sizes and 95 % confidence intervals will also be reported.
3 Assess if common disease signatures exist across studies. If there is a specific host-microbe-metabolite interaction within a disease, we would expect a common unique signature of differentially-abundant taxa and GBMs across all studies of that disease.

2. Methods

2.1. Study selection

PubMed database searches were conducted by searching for disease or health-related terms along with 'microbiome'. These terms were: obesity brain, anorexia, ADHD, ASD, PANDAS, schizophrenia, Alzheimer's Disease, amyotrophic lateral sclerosis, neurovascular, ischemia, temperament, personality trait, multiple sclerosis, IBS anxiety depression, fibromyalgia, migraine, stress AND human, post-traumatic, anxiety OR depression human faecal, alcohol-dependence, bipolar disorder, epilepsy, opioid use, smoking human faecal, human drug addiction faecal, sleep human faecal, human 'psychological stress', Rett syndrome. An example of one search would be: microbiome AND obesity brain. This search yielded a total of 3552 results on June 10th, 2020. The abstracts were manually searched and any studies not involving humans, the colonic microbiota or any brain or behaviour-related measures were excluded leaving 249 studies. 35 of these datasets were reanalysed. 39 more studies published after June 10th 2020 were also included.

In the studies where the raw microbiome data was not reanalysed the sequencing strategy, relevant results relating to differential abundance of microbes involved in neuroactive pathways and limitations were summarised.

2.2. Downloading datasets

Raw sequencing files (.fastq or. fastq.gz format) were downloaded from the European Nucletotide Archive or the Sequence Research Archive by generating a bash script to download the dataset (https://sra-explorer.info). For data deposited on the China National GeneBank Database Sequence Archive or Qiita sequencing files were downloaded by writing bash scripts to download each individual dataset (Gonzalez et al., 2018). Some data was also downloaded from the Metagenomic Rapid Annotations using Subsystems Technology (MG-RAST) using scripts from https://github.com/MG-RAST/MG-RAST-Tools (Meyer et al., 2008; Wilke et al., 2015). Two studies were excluded from reanalysis because one could not be demultiplexed and another was sequenced using the SOLiD platform and could not be processed through the same pipeline.

2.3. Generating counts tables for 16S rRNA gene sequencing platforms

Raw sequencing files for each dataset were processed through the DADA2 pipeline (Callahan et al., 2016). Briefly, files were first filtered and trimmed to 200 base pairs (where possible with the following settings: 'trimLeft = 37, truncLen = 237, maxEE = 2, truncQ = 2, maxN = 0, rm.phix = TRUE') (Callahan et al., 2016). Next, sequence quality reports were generated using FastQC, using a threshold score of 28 (Andrews, 2010). If necessary, samples were filtered again and trimmed. Forward and reverse error rates (settings: nbases = 1e8) were generated for each dataset, followed by merging of individual files into a sequence table and the removal of *de novo* bimeras (Callahan et al., 2016). The SILVA v132 training set was input into the RDP classifier in DADA2 to assign taxonomy to the sequence table (Glockner et al., 2017; Pruesse et al., 2019; Quast et al., 2013; Yilmaz et al., 2013, Wang et al., 2007).

Scripts used for bioinformatics analysis are found here: https://github.com/simon-sp/Mining-Metabolites.

2.4. Bioinformatics analysis: differentially abundant microbes

R version 3.6.3 was used in R Studio v1.2.5 for Ubuntu 18.04. Any amplicon-sequence variants (ASVs) with fewer than 2 raw counts were filtered out, and data was transformed using the centred-log-ratio (CLR) in ALDEx2 with 1000 Monte-Carlo sampling permutations (Fernandes

Table 1
Microbiome-brain studies of healthy human cohorts.

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
Infant Temperament and Stress	WGS (no)	N = 63 Infants	**Negative Emotionality (High vs Low Scoring Group)** ↑ *Bifidobacterium pseudocatenulatum* (LFC: 4.085) ↓ *Streptococcus vestibularis* (LFC – 3.12) **Regulation/Orienting (High vs Low Scoring Group)** ↑ *Bifidobacterium pseudocatenulatum* (LFC: 4.085) ↑ *Bifidobacterium catenulatum* (LFC: 4.177) **Functional Connectivity: Left Default Network (High vs Low Scoring Group)** ↓ *Clostridium perfingens* (LFC: 3.559) **Functional Connectivity: Left Fronto-Parietal Network (High vs Low Scoring Group)** ↑ *Enterococcus fragilis* (LFC: 3.765) ↑ *Collinsella* (LFC: 3.665) ↑ *Clostridium disporicum* (LFC: 3.415) ↑ *Prevotella copri*(LFC: 3.415) ↑ *Clostridium perfingens* (LFC: 3.415) ↑ *Clostridium tertium* (LFC: 3.367) ↑ *Clostridium* (LFC: 3.167) ↑ *Bacteroides caccae* (LFC: 3.164) ↓ *Streptococcus salivarius* (LFC : 3.397) ↓ *Enterococcus* (LFC = 3.042) **Functional Connectivity: Homologous Interhemispheric Network** ↑ *Escherica coli (*LFC: 4.357) ↓ *Bifidobacteirum dentae (*LFC: 4.012)	**Negative Emotionality (High vs Low Scoring Group)** ↑ *Bifidobacterium pseudocatenulatum* (LFC: 4.085) **Regulation/Orienting (High vs Low Scoring Group)** ↑ *Bifidobacterium pseudocatenulatum* (LFC: 4.085) ↑ *Bifidobacterium catenulatum* (LFC: 4.177) **Functional Connectivity: Left Default Network (High vs Low Scoring Group)** ↓ *Clostridium perfingens* (LFC: 3.559) **Functional Connectivity: Left Fronto-Parietal Network (High vs Low Scoring Group)** ↑ *Clostridium disporicum* (LFC: 3.415) ↑ *Clostridium perfingens* (LFC: 3.415) ↑ *Clostridium tertium* (LFC: 3.367) ↑ *Clostridium* (LFC: 3.167) ↑ *Bacteroides caccae* (LFC: 3.164) **Functional Connectivity: Homologous Interhemispheric Network** ↓ *Bifidobacteirum dentae (*LFC: 4.012)	None		(Kelsey et al., 2021)
	16S (no)	N = 34 Infants	None	None	None		(Rosin et al., 2020)
	16S (no)	N = 89 Infants	None	None	None	Genera level findings not reported; clustered microbiomes and associated these clusters with infant cognition	(Carlson et al., 2018)
	16S (no)	N = 201 Infants	↓ *Prevotella**** associated with a decrease in behavioural problems	None	None	Potential bias in parent reported measures; DeSeq2 is inappropriate for microbiome analysis	(Loughman et al., 2020)
	16S (no)	N = 51 Infants (42 taking probiotics)	*Bifidobacterium*** associated with soothability				(Wang et al., 2020b)
	16S (no)	N = 301 Infants	↑ *Bifidobacterium* and *Streptococcus* associated with postive emotional regulation	↑ *Bifidobacterium* with positive emotional regulation		Greengenes, QIIME 1.9	(Aatsinki et al., 2019)
	16S (no)	N = 39	*None*	None	None	No genus-level associations with functional connectivity	(Gao et al., 2019)
		N = 77 Infants	None	None	None		(Christian et al., 2015)

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Table 1 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
Adult Emotion and Personality	16S via 454 Pyrosequencing (no)						
	16S (no)	N = 91 Healthy ♀ Focus on psychiatric measures	None	None	None		(Kleiman et al., 2017)
	16S (no)	N = 15 Probiotics N = 15 Placebo	**Probiotics vs Placebo** ↑ *Bacteroides* sp.; associated with response accuracy neutral stimuli scores*, general depression scale* **Probiotics vs Placebo** ↑ *Bacteroides* sp.; associated with response accuracy neutral stimuli scores*, general depression scale*		None	Rarefaction	(Bagga et al., 2018)
	16S (no)	N = 135 Healthy Individuals	**When accounting for fibre intake** In males, DASS-42 anxiety scores negatively correlated with *Blautia* abundance	None	None	Greengenes, rarefaction	(Taylor et al., 2019)
	16S (no)	N = 672	↑ *Roseburia*** in high Conscientiousness group	None	Valine, leucine, isoleucine degradation pathways enriched in high neuroticism group***	Greengenes	(Kim et al., 2018)
	16S (no)	N = 655	**Sociability (combination of extraversion, social skill and communication) as microbiome a predictor** + *Oscillospira****	None	None	Sample collection in buffer to stabilise at room temperature	(Johnson, 2020)
	16S via 454 Pyrosequencing (no)	N = 40 Healthy Women (N = 33 in *Prevotella* cluster, N = 7 in *Bacteroides* cluster)	High *Prevotella* abundance associated with negative affect after negative valence picture block	None	None	Rarefaction	(Tillisch et al., 2017)
	16S gene array (no)	N = 60	No genus-level associations reported	None	None		(Kim and Park, 2017)
	FISH (no)	N = 40 Focus on self-judgment and empathy measures	**Negative Associations:** *Lactobacillus*: cognitive depression* affective empathy** **Positive Associations:** *Lactobacillus:* self-judgment*** over identification*		None		(Heym et al., 2019)
Sleep	16S (yes)	N = 10 Insomnia N = 10 Control	**None**	**None**	**Insomnia vs Control** ↓ *Alloprevotella* (effect = -1.16 [-14.97; 0.17]) *		(Liu et al., 2019a)
	16S (no)	N = 113 Focus on sleep	Disruptions in sleep across stages in *Prevotella* enterotype	None	None		(Ko et al., 2019)
	16S (no)	N = 22	None	None	None		(Liu et al., 2020c)
	16S (no)	N = 8 Control N = 7 Obstructive Sleep Apnoea	**Apnea-Hypopnea Index Correlations** *Eubacterium** (rho = 0.785) **Wake After Sleep Onset** *Escherichia*** (rho = 0.915) *Klebsiella** (rho = 0.768) **Arousals Index**	None	None		(Valentini et al., 2020)

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Table 1 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			*Clostridium** (rho = 0.852) *Ruminococcus** (rho = 0.738) *Oscillospira** (rho = 0.842)				
	16S (no)	N = 20 Acute Insomnia Disorder (AID) N = 38 Chronic Insomnia Disorder (CID) N = 38 Control	**AID vs Control** ↑ *Bacteroides** ↓ *Lachnospira** **CID vs Control** ↑ *Blautia**** ↓ *Faecalibacterium**** ↓ *Prevotella*** ↓ *Roseburia***	**CID vs Control** ↑ *Bacteroides**			(Li et al., 2020b)
	16S (no)	N = 37	None	None	None	Genus-level changes not reported	(Anderson et al., 2017)
	16S (no)	N = 35 Narcolepsy Type 1 (NT1) N = 41 Control	**NT1 vs Control** ↓ *Bacteroides**** ↑ *Flavonifactor***	**NT1 vs Control** ↓ *Bacteroides****			(Lecomte et al., 2020)
	16S (no)	N = 24	**Negative Associations** Sleep efficiency and total sleep time: *Blautia* Number of awakenings: *Holdemania, Corynebacterium,* **Positive Associations** Number of awakenings: *Coprococcus, Neisseria*	None	None	Faecal swab; no post-hoc testing for correlation coefficients	(Smith et al., 2019)
	16S (no)	N = 11 MCI with Risk of AD N = 6 Aged-Control Randomised double-crossover intervention Ketogenic Mediterranean diet vs American heart association diet	**MCI vs Control at Baseline** ↑ *Phascolarctobacterium* ↓ *Dialister* ↑ *Bifidobacterium* after Mediterranean Ketogenic Diet in MCI but not in Controls	↑ *Bifidobacterium* after Mediterranean Ketogenic Diet in MCI but not in Controls		QIIME 1.9.1, Greengenes, rarefaction, Unbalanced groups	(Nagpal et al., 2019)
Healthy Aging and Cognition	16S (no)	N = 26 PBO N = 27 Probiotic 12 weeks *Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI (1 × 109 CFU/d) 2 week washout	**Probiotic vs PBO** ↓ *Eubacterium* **In probiotic group** *Eubacterium* negatively correlated with serum BDNF	None	None		(Kim et al., 2020)
	16S via 454 Pyrosequencing (no)	N = 37 Aged N = 39 Aged with Cirrhosis	**Amnesia vs No Unimpaired** ↑ *Paraprevotella* ↓ *Faecalibacterium* ↓ *Coprobacillus*	None	None		(Bajaj et al., 2016)
	T-RFLP (no)	N = 34 Dementia N = 94 Control	**Dementia vs Control** ↓ *Bacteroides*		None		(Saji et al., 2019)

Legend: LFC: log-2 fold change; LC: log change; RA: relative abundance; DASS-42: Depression Anxiety Stress Scales; ADHD: Attention-Deficit Hyperactivity Disorder; HE: hepatic encephalopathy; FOS: Fructo-oligosaccharide; HADS-A: Hamilton Anxiety and Depression Scales – Anxiety Subscale; HADS-A: Hamilton Anxiety and Depression Scales – Depression Subscale; *: $p_{adj} < 0.1$; **: $p_{adj} < 0.01$; ***: $p_{adj} < 0.001$; Reanalysed studies are highlighted; 95 % CI reported between square brackets [lower 95 % CI; upper 95 % CI].

et al., 2014, Quinn et al., 2018). Three studies were excluded where the majority of ASVs were filtered out, leaving a counts table with only 2–10 microbial taxa.

An overall PCA was generated by principal component analysis for visualisation and quality check purposes using the ggplot2 package (Wickham, 2016).

A list of differentially abundant microbes was generated with the Tjazi pairwise_DA_wrapper by incorporating the Wilcoxon Rank-Sum test for comparing the abundance of each individual microbe across groups, followed by a Benjamini-Hochberg post-hoc test (Bastiaanssen, 2019; Pounds and Cheng, 2004). Microbes were reported if they had a $P_{adj} < 0.1$ and an effect size > 0.65 to increase the robustness of these findings. The 95 % confidence intervals are also reported.

2.5. Bioinformatics analysis: differentially abundant gut brain modules

Raw sequencing data was transformed to be input into Piphillin for predicted functional analysis of the sequencing data (Iwai et al., 2016). The output of Piphillin produced a counts table of the Kyoto Encyclopdia of Genes and Genomes (KEGG) orthologs, which could then be used to assess the abundance of GBMs via omixerRpm, using the *GBM_v1.0* dataset (Kanehisa et al., 2019; Kanehisa and Goto, 2000; Kanehisa, 2019; Valles-Colomer et al., 2019). Differential abundance of GBMs was determined using the Tjazi pairwise_DA-wrapper. GBMs were reported if they had a $P_{adj} < 0.1$ and an effect size > 0.4 to increase the robustness of these findings. The 95 % confidence intervals are also reported.

2.6. Generating counts tables for WGS shotgun analysis

First, adapter sequences were trimmed using bbduk (ktrim = r, mink = 6, hdist = 1, qtrim = rl, trimq = 20, minlength = 70, tpe, tbo, rcomp = T) followed by decontamination using bbmap (-Xmx16 g, minid = 0.95, qtrim = rl, trimq = 10, untrim) against the masked human genome (Hg38) and merging using bbmerge (bbmerge-auto.sh, -Xmx24 g, rem, k = 62, extend2 = 50, ecct) (Bushnell, 2020; Bushnell et al., 2017). The fastq.gz files were then processed through 'biobakery_workflows wmgx' run within a separate Miniconda environment (Python v2.7) with the following parameters: '–bypass-strain-profiling –bypass-quality-control' using the UniRef default databases for MetaPhlAn2 and HUMAnN2 (Truong et al., 2015; McIver et al., 2018; Franzosa et al., 2018). The rest of bioinformatics analysis of the count tables for genes and gene pathways is described in Section 2.3 with two differences. Piphillin is not used because HUMAnN2 provides counts tables of gene pathways/proteins as outputs and thus do not need to be inferred. Counts tables for bacterial genes as well as gene pathways/proteins were first run through the guess_counts function within the Tjazi R library, before CLR transformation (Bastiaanssen, 2019). Two whole genome shotgun (WGS) studies were excluded from re-analysis because the publicly available dataset did not contain all sequenced samples or the fastq.gz files were not labelled.

3. Results

3.1. Healthy humans

3.1.1. Infant temperament and behaviour

3.1.1.1. Studies where raw microbiome data was not reanalysed.. The only WGS study found multiple associations between *Bifidobacterium, Clostridium* and *Bacteroides* species associated with brain connectivity and temperament. However, four 16S sequencing studies did not find any genus-level associations between infant temperament and microbiota composition (Carlson et al., 2018; Gao et al., 2019; Christian et al., 2015; Rosin et al., 2020). Two studies showed positive associations of increased *Bifidobacterium* abundance in infants with positive behaviours (soothability and emotional regulation) (Wang et al., 2020b; Aatsinki et al., 2019). Though Loughman et al. (2020) did not find associations with *Bifidobacterium, Prevotella* abundance was associated with behavioural problems. See Table 1 for more detail.

3.1.2. Adult personality and behaviour

3.1.2.1. Studies where raw microbiome data was not reanalysed.. Many descriptive studies have associated individual genera of bacteria with personality traits. In healthy participants, Taylor et al. (2019) found a negative correlation of *Blautia* abundance with anxiety. Tillisch et al. (2017) did not assess anxiety but found a negative correlation of *Prevotella* abundance with negative affect. Interestingly, Kim et al. (2018) found associations between increased *Roseburia* abundance and conscientiousness while Johnson (2020) instead found *Oscillispira* associated positively with sociability.

3.1.3. Sleep characteristics and quality

3.1.3.1. Studies where raw microbiome data was reanalysed.. Liu et al. (2019a) collected faecal samples from ten individuals who reported insomnia and another ten who served as healthy controls. Though no GBMs were differentially abundant, *Alloprevotella* abundance was significantly reduced in individuals with insomnia ($p_{adj} < 0.1$, effect = -1.16; 95 % CI: [-14.97; 0.17]). No other microbes or GBMs relating to SCFA, tryptophan or bile acid pathways were differentially abundant within this dataset.

3.1.3.2. Studies where raw microbiome data was not reanalysed.. Few studies focused on associating sleep-quality and microbiota composition (see Table 1). Among these, two showed no genera-level associations between microbes and sleep (Liu et al., 2020c; Anderson et al., 2017). One 16S sequencing study found disruptions across different sleep stages in individuals with a *Prevotella* enterotype (Ko et al., 2019). Smith et al. (2019) collected extensive metadata, correlating specific microbes to sleep parameters. While *Holdemania* and *Corynebacterium* abundance negatively associated with number of awakenings, *Coprococcus* and *Neisseria* associated with increased awakenings (Smith et al., 2019). *Blautia* also negatively associated with sleep efficiency and total sleep time (Smith et al., 2019). Though these findings are interesting, participants used faecal swabs to collect microbiota samples (Smith et al., 2019).

An additional three studies compared the gut microbiome of individuals with sleep disorders such as insomnia and narcolepsy type 1 to controls (Lecomte et al., 2020; Li et al., 2020b; Valentini et al., 2020).

3.1.4. Ageing and cognition

3.1.4.1. Studies where raw microbiome data was not reanalysed.. No common genus-level differences associated with healthy cognitive ageing across existing studies (see Table 1). However, these studies all compared different subsets of unhealthy cognitive aging. One study compared healthy ageing to mild-cognitive impairment, another with Cirrhotic individuals, another with dementia and finally one was a 12 week crossover-double blind trial (Nagpal et al., 2019; Kim et al., 2020; Bajaj et al., 2016; Saji et al., 2019).

3.2. Neurodevelopmental disorders

3.2.1. Attention-deficit hyperactivity disorder

3.2.1.1. Studies where raw microbiome data was reanalysed.. One 16S sequencing study was reanalysed, involving 19 individuals with Attention-Deficit Hyperactivity Disorder (ADHD) and 77 control participants, including a wide age-range for their participants (Aarts et al.,

Table 2
Microbiome-brain studies involving neurodevelopmental disorders.

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
ADHD	16S (yes)	N = 19 ADHD N = 77 Control	None	None	None	Wide age range	(Aarts et al., 2017)
	WGS (no)	N = 17 ADHD N = 17 HC	**ADHD vs Control** ↓ *Faecalibacterium** ↓ *Ruminococcus gnavus** ↑ *Bacteroides caccae** ↑ *Odoribacter** ↑ *Enterococcus**	**ADHD vs Control** ↑ *Bacteroides caccae**	**ADHD vs Control:** ↓ in KO terms for dopamine pathways**		(Wan et al., 2020)
	16S (no)	N = 10 ADHD + Nutrient Intervention N = 7 ADHD (Placebo)	**ADHD Associations with Symptomology** ↑ *Bifidobacterium* associated with lower ADHD-IV-RS score (t = −2.3, df = 15, $p = 0.04$); possibly due to 3 outliers		None	Pilot study on intervention so no comparisons with controls	(Stevens et al., 2019)
	16S (no)	N = 14 ADHD N = 17 Control	**ADHD vs Control** ↓ *Prevotella* ↓ *Parabacteroides* ↑ *Neisseria*	None	None	Incomplete methods section, males only	(Prehn-Kristensen et al., 2018)
	16S (no)	N = 42 ADHD N = 15 Subthreshold ADHD N = 50 HC	**ADHD vs Control** ↑ *Ruminoclostridium 9**, *Ruminococcus 2** **ADHD Medicated vs ADHD Unmedicated** *Ruminococcus 2* (B = 1.525, P = 0.001) associated with inattention score	None	None		(Szopinska-Tokov et al., 2020)
	16S (no)	N = 30 ADHD N = 30 Control	**ADHD vs Control (Genus-level)** ↓ *Lactobacillus* ↑ *Fusobacterium* **ADHD vs Control (Species-Level)** ↑ *Bacteroides uniformis* ↑ *Bacteroides ovatus* ↑ *Sutterella stercoricanis* ↓ *Bacteroides coprocola*	**ADHD vs Control (Genus-level)** ↓ *Lactobacillus* **ADHD vs Control (Species-Level)** ↑ *Bacteroides uniformis* ↑ *Bacteroides ovatus* ↓ *Bacteroides coprocola*	None	Rarefaction	(Wang et al., 2020a)
	16S via 454 Pyrosequencing (no)	N = 51 ADHD N = 32 Control	**ADHD vs Control** ↓ *Faecalibacterium* ↓ *Dialister* ↓ *Faecalibacterium*; associated with total CPRS Score (Pearson Correlation: $p < 0.001$, $R^2 = -0.564$) and hyperactivity index score (Pearson Correlation: $p < 0.037$, $R^2 = -0.294$)	None		Rarefaction	(Jiang et al., 2018b)
	qPCR (no)	N = 35 Placebo N = 40 Probiotic	↓ *Bifidobacterium spp.* at 6 weeks of life in children that developed ASD/ADHD		None		(Pärtty et al., 2015)
ASD	WGS (yes, from species counts table)	N = 36 ASD N = 21 Control	None	None	None		(Averina et al., 2020)
	16S (yes)	N = 51 ASD N = 40 Control	None	None	None		(Son et al., 2015)
	16S (yes)	N = 20 ASD N = 20 Control	**ASD vs Control** ↑ *Roseburia*** (effect = 0.9 [-1.9; 10.38]	None	None		(Pulikkan et al., 2018)
	16S (yes)	N = 20 ASD N = 19 Control	None	None	None		(Kang et al., 2019)
	16S (yes)	N = 20 ASD N = 19 Control	**ASD with ATEC score below median (62) vs ASD with score above median** ↓ *Ruminoclostridium 9** (effect = −0.78 [-7.28, 1.80])	None	None		(Kong et al., 2019)
	16S (yes)	N = 20 ASD Faecal samples taken before and after Vitamin A supplementation	None	None	None		(Liu et al., 2017)
	16S via 454 Pyrosequencing	N = 40 ASD N = 40 Control	None	None	None		(Strati et al., 2017)

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Table 2 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
	(yes – unable to identify bacterial sequences)						
	WGS (no)	N = 43 ASD (19 with GI symptoms, 24 without) N = 31 Control	None	None	None	Focus on immune epitopes	(Wang et al., 2019b)
	WGS (no)	N = 39 ASD N = 40 Control	**ASD vs Control** ↑ *Veillonella parvula* ↑ *Butyrivibrio* unclassified ↑ *Streptococcus pasteurianus* ↑ *Lactobacillus rhamnosus* ↑ *Megasphera micronuciformis* ↑ *Lachnospiraceae bacterium 6163FAA* ↑ *Haemophilus haemolyticus* ↓ *Bifidobacterium longum* ↓ *Prevotella copri* ↓ *Bacteroides stercoris* ↓ *Dorea* unclassified ↓ *Lachnospiraceae bacterium 1456FAA* ↓ Eubacterium limosum	**ASD vs Control** ↑ *Lactobacillus rhamnosus* ↓ *Bifidobacterium longum* ↓ *Bacteroides stercoris*	None		(Zhang et al., 2020b)
	WGS (no)	N = 30 ASD N = 14 Control	None	None	None		(Carissimi et al., 2019)
	WGS (no)	N = 166 Infants aged 6 weeks N = 158 Infants aged 1 year N = 129 Infants aged 2 years N = 140 Infants aged 3 years Assessing ASD-related social behaviors with Social Responsiveness Scale (SRS-2) T-scores	**At One Year** *Blautia producta* + association with SRS-2 **At Two Years** *Coprococcus* + association with SRS-2 *Ruminococcus gnavus* + association with SRS-2 *Bifidobacterium* + association with SRS-2 *Sutterella* + association with SRS-2 **At Three Years** *Bytyricoccus pulliacaerum* – association with SRS-2	**At Two Years** *Bifidobacterium* + association with SRS-2	None		(Laue et al., 2020)
	WGS (no – ASD and controls not specified in metadata)	N = 92 ASD N = 42 Control	**ASD vs Control** ↑ *Eggerthella lenta** ↑ *Eggerthella lenta* DSM2243* ↑ *Clostridium botulinum* A3 and Ba4* ↓*Bacteroides vulgaris***	**ASD vs Control** ↓*Bacteroides vulgaris***	**ASD vs Control** ↓ Glutamate/ Glutamine metabolism		(Wang et al., 2019a)
	16S and WGS (no)	N = 143 ASD N = 143 Control WGS: N = 30 ASD with Constipation (C-ASD) N = 30 Non-Constipated ASD (NC-ASD) N = 30 Control	**ASD vs Control** ↑ *Dialister* ↑ *Escherichia-Shigella* ↑ *Bifidobacterium* ↓ *Prevotella 9* ↓ *Megamonas* ↓ *Ruminococcus 2* **C-ASD vs NC-ASD** ↑ *Alistipes*** ↑ *Anaerotruncus*** ↑ *Ruminoclostridium 6*** ↑ *Ruminococcus 2*** ↑ *Subdolingranlum** ↑ *Coprococcus 1** ↑ *Blautia** ↑ *Roseburia** ↑ *Butyricoccus** ↑ *Ruminococcus 1** ↑ *Coprobacter** ↓ *Veillonella*** ↓ *Collinsella*** ↓ *Megasphera*** ↓ *Bacteroides***	**ASD vs Control** ↑ *Bifidobacterium* **C-ASD vs NC-ASD** ↓ *Bacteroides***	None	QIIME 1.9, No post-hoc correction, rarefaction	(Dan et al., 2020)
	16S (no)	N = 77 ASD N = 50 Control	**ASD vs Control** ↓ *Bacteroides** ↓ *Faecalibacterium** Negative association	**ASD vs Control** ↓ *Bacteroides**	None		(Ding et al., 2020)

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Table 2 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			between *Faecalibacterium* and ASD severity Multiple other genera associated with ASD severity				
	16S (no)	N = 60 ASD + Sleep disorder (ASD-S) N = 60 ASD without Sleep disorder	**ASD-S vs ASD** ↓ *Faecalibacterium* (also correlated to 3-hydroxybutyric acid abundance in feces)	None	None	Rarefaction	(Hua et al., 2020)
	16S (no)	N = 78 ASD N = 58 Control	**ASD vs Controls** ↑ *Bacillus*** ↑ *Bacteroides*** ↑ *Bilophila*** ↑ *Parabacteroides*** ↑ *Sutterella***	**ASD vs Controls** ↑ *Bacteroides***	None	Qiime v1.9.1 (outdated since Jan 1, 2018)	(Zhai et al., 2019b)
	16S (no)	N = 30 ASD N = 20 Control	**ASD vs Controls** ↑ *Megamonas* ↓ *Eubacterium* ↑ Faecal valerate ↓ Faecal butyrate	**ASD vs Controls** ↓ *Eubacterium*	None		(Liu et al., 2019b)
	16S (no)	N = 21 ASD N = 23 Control	**ASD vs Control** ↓ *Faecalibacterium**** ↓ *Heamophilus****	None	None		(Kang et al., 2018)
	16S (no)	N = 9 ASD N = 6 Control	None	None	None	Greengenes	(Sun et al., 2019)
	16S (no)	N = 37 ASD + Probiotic (4 weeks) N = 77 ASD (no Probiotic) N = 40 Control Faecal samples not analysed after intervention	**ASD vs Controls (Baseline)** ↓ *Bacteroides**** ↓ *Bifidobacterium**** ↓ *Ruminococcus*** ↓ *Lachnospira**** ↓ *Roseburia**** ↓ *Blautia****	**ASD vs Controls (Baseline)** ↓ *Bacteroides**** ↓ *Bifidobacterium****	None		(Niu et al., 2019)
	16S (no)	N = 25 ASD N = 35 Control	**ASD vs Controls** ↓ *Lactobacillus* ↓ *Ruminococcus* ↑ *Bacteroides* ↑ *Akkermansia* ↑ *Coproccous* ↑ *Ruminococcus* (different OTU assigned to the same genera)	**ASD vs Controls** ↓ *Lactobacillus* ↑ *Bacteroides*	None	Greengenes	(Zurita et al., 2019)
	16S (no)	N = 24 ASD N = 24 Control FOS + Probiotics Interverntion	**ASD vs Controls at Baseline** ↓ *Bifidobacterium* ↓ *Veillonella* ↓ *Acidaminococcus* ↓ *Enterococcus* ↑ *Odoribacter* ↑ *Oscillispira* ↑ *Ruminococcus* **Day 80 vs Baseline ASD** ↓ Acetate, butyrate, propionate; increases over 80 days of intervention ↑ *B. longum* to control levels ↓ *Clostridium* Most short term measures were not sustained after the end of the study	**ASD vs Controls at Baseline** ↓ *Bifidobacterium* **Day 80 vs Baseline ASD** ↑ *Bifidobacteriun longum* to control levels	↑ L-histidine and L-histamine over course of intervention	Rarefaction	(Wang et al., 2020c)
	16S (no)	N = 63 ASD N = 27 Control	**ASD vs Control** ↑ *Aenerococcus* ↑ *Burkholderia,* ↑ *Desulfovibrio* ↑ *Oxalobacter* ↓ *Bilophila*			Lack of clarity in methods section, no post-hoc	(Tomova et al., 2019)
	16S (no)	N = 46 ASD N = 16 Control	None	None	None	Lack of clarity in methods section, no post-hoc	(Tomova et al., 2020)
	16S (no)	N = 76 ASD N = 47 Control	**ASD vs Control** Focus on co-abundance groups finding correlations	None	None		(Chen et al., 2020b)

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Table 2 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			with co-abundant *Bacteroides* ASVs and various ASD behaviours				
	16S (no)	N = 14 Unrestricted Diet ASD (split into PBO and B-GOS) N = 12 Exclusion Diet (split into PBO and B-GOS)	None	None	None	Rarefaction, reporting on genus-level differences within groups is unclear	(Grimaldi et al., 2018)
	16S (no)	N = 48 ASD 30 with no mental regression (ANMR) 18 with mental regression (AMR) N = 57 Control	**ASD vs Controls** ↑ *Bacillus* ↑ *Bifidobacterium* ↑ *Butyrivibrio* ↑ *Enterococcus* ↑ *Prevotella* ↑ *Clostridium boltae* ↑ *Clostridium difficile* **AMR vs ANMR** ↑ *Enterococcus*	**ASD vs Controls** ↑ *Bifidobacterium*	None		(Plaza-Diaz et al., 2019)
	16S (no – unable to demultiplex)	N = 59 ASD N = 30 Control	**ASD vs Control** ↑ *Clostridium* ↑ *Pseudomonas* ↑ *Streptococcus* ↓ *Prevotella*	None	**None**	Greengenes, Qiime v1.9.1 (outdated since Jan 1, 2018), rarefaction	(Li et al., 2019d)
	16S (no)	N = 11 ASD N = 14 Control	**ASD vs Control** ↑ Faecal butyrate ↓ *Streptococcus*** ↓ *Coprocccus*** ↓ *Blautia*** ↓ *Eggerthella*** ↓ *Corynebacteirum*** ↑*Parabacteroides** ↑ *Bacteroides*** ↑ *Faecalibacterium prausnitzii*** ↑ *Roseburia*** ↑ *Ruminococcus***	**ASD vs Control** ↑ *Bacteroides***		Greengenes, QIIME 1.9, rarefaction	(Coretti et al., 2018)
	16S (no)	N = 45 ASD N = 45 Control	**ASD vs Control** ↓ *Flavonifractor***	None	None		(Ma et al., 2019a)
	16S (no)	N = 26 ASD N = 32 Control	Faecal butyrate associated with diet quality within ASD No butyrate producing bacteria reported to correlate with butyrate	None	None	Greengenes	(Berding and Donovan, 2019, 2018)
	16S (no)	N = 26 ASD N = 32 Control	**ASD + Temporally Unstable Microbiome vs ASD + Temporally Stable Microbiome** ↓ *Turcibacter** ↓ *Dorea** ↓ *Phascolarctobacterium**	None	None	Greengenes	(Berding and Donovan, 2019)
	16S (no)	N = 6 ASD N = 6 Control	**ASD vs Control** ↓ *Blautia* ↓ *Faecalibacterium*	None	None		(Inoue et al., 2016)
	16S (no)	N = 6 ASD Probiotic then PBO N = 4 ASD PBO then Probiotic VISBIOME crossover pilot trial	None	None	None		(Arnold et al., 2019)
	16S (no)	N = 35 ASD N = 6 Control	**ASD vs Control** ↓ *Streptococcus** ↓ *Vaillonella** ↓ *Escherichia**	None	None		(Zhang et al., 2018a)
	16S (no)	N = 21 ASD + GI problems (ASD^{GI}) N = 29 ASD^{noGI} N = 34	None	None	None		(Luna et al., 2017)

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Table 2 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
		Control^{noGI} N = 7 Control^{GI}					
	16S via 454 Pyrosequencing (no)	N = 10 ASD N = 10 Other Neurodevelopmental Disorder (OND) N = 10 Control	Bacteria assessed at species-level; impossible to do reliably with 16S	None	None	Rarefaction, no post-hoc testing	(De Angelis et al., 2013)
	16S via 454 Pyrosequencing (no)	N = 23 ASD without GI dysfunction N = 28 ASD with GI dysfunction N = 53 neurotypical siblings	No significant microbiome differences found	None	None		(Gondalia et al., 2012)
	qPCR (no)	N = 41 ASD N = 45 Non-ASD Siblings N = 45 Control	**ASD vs Control** ↑ *Bacteroides** ↑ *Ruminococcus*** ↓ *Prevotella** **Non-ASD Siblings vs Control** ↑ *Bacteroides*** ↑ *Ruminococcus***	**ASD vs Control** ↑ *Bacteroides** **Non-ASD Siblings vs Control** ↑ *Bacteroides***			(Ahmed et al., 2020)
	qPCR (no)	N = 30 ASD Received probiotics (*L. acidophilus, L. rhamnosus, B. longum*)	**After 3 Mo. Probiotics vs Baseline** ↑ *Lactobacillus**** ↑ *Bifidobacterium****	None	None	No control/PBO	(Shaaban et al., 2018)
	qPCR (no)	N = 30 ASD N = 30 Control	**ASD vs Control** ↑ *Clostridium difficile**** ↑ *C. paraputrificum** ↑ *C. clostridioforme**** ↑ *C. bolteae**** ↑ *C. clostridioforme****	None	None		(Kandeel et al., 2020)
	qPCR (no)	N = 23 ASD N = 22 Non-ASD Siblings N = 9 Control	**ASD vs Control** ↑ *Sutterella spp.** **Non-ASD Siblings vs Control** ↑ *Sutterella spp.**	None	None		(Wang et al., 2013)
	qPCR (no)	N = 10 ASD N = 10 Control Siblings N = 9 Unrelated Controls	*Desulfvibrio* correlated to autism intensity with ADI RRB **ASD vs Unrelated Control Baseline** ↑ *Lactobacillus spp.**** (no difference with siblings) **ASD After Probiotic vs Before Probiotic** ↓ *Bifidobacterium spp.**** ↓ *Desulfvibrio spp.****	**ASD vs Unrelated Control Baseline** ↑ *Lactobacillus spp.**** (no difference with siblings) **ASD After Probiotic vs Before Probiotic** ↓ *Bifidobacterium spp.****	None		(Tomova et al., 2015)
Schizophrenia	16S (yes)	N = 64 SZ N = 53 Control	**SZ vs Control** ↑ *Fusicatenibacter**** (effect = 0.67[-1.48; 7.56]) **SZ vs Control** ↓ *Lactobacillus**** (effect = -1.28 [-12.85; 0.11]) ↑*Fusicatenibacter**** (effect = 1.06 [-1.05; 7.60])	None	None		(Shen et al., 2018)
	16S (yes)	N = 40 SZ N = 40 Control	↑ *Ruminococcus 1**** (effect = 0.80 [-2.23; 7.33] Butyrate Synthesis II*** (effect = 0.61 [-1.83; 5.41]) ↑ Kynurenine synthesis*** (effect = 0.68 [-2.10; 6.12]), Inositol Degradation*** (effect = 0.83 [-1.58; 6.96]),	**SZ vs Control** ↓ *Lactobacillus**** (effect = -1.28 [-12.85; 0.11])	**SZ vs Control:** ↓ Histamine Synthesis* (effect = -0.48 [-5.41; 1.89])		(Xu et al., 2019)
	16S (yes)	N = 21 taking atypical antipsychotics N = 16 taking Lithium or Lamotragine	None	None	None		(Flowers et al., 2019)
	16S (yes)	N = 25 SZ N = 25 Control	None	None	None	Faecal swabs used	(Nguyen et al., 2019)

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Table 2 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
	WGS (no)	N = 84 SZ N = 84 Control	**SZ vs Control:** ↑ *Bifidobacterium adolescentis**** ↑ *Clostridium perfringens**** ↑ *Lactobacillus gasseri****	**SZ vs Control:** ↑ *Bifidobacterium adolescentis**** ↑ *Lactobacillus gasseri****	None		(Xu et al., 2019)
	WGS (no)	N = 90 Drug-Naïve SZ N = 81 Control	**SZ vs Control** ↑ *Eubacterium siraeum** ↑*Bacteroides plebius** ↑ *Bifidobacterium adolescentis** ↑ *Bifidobacteriun bifidum** ↑ *Bifidobacteriun dentium** ↑ *Bifidobacteriun longum** ↑ *Clostridium bolteae** ↑ *Clostridium ramosum** ↑ *Clostridium symbiosum** ↑ *Enterococcus faecium** ↑ *Lactobacillus crispatus**, ↑ *Limosilactobacillus fermentum** ↓ *Clostridium perfogens** ↓ *Bacteroides intestinales** ↓ *Bacteroides finegoldii** ↓ *Lactococcus lactis** ↓ *Lactobacillus acidophilus** ↓ *Lactobacillus johnsonii**	**SZ vs Control** ↑ *Eubacterium siraeum** ↑*Bacteroides plebius** ↑ *Bifidobacterium adolescentis** ↑ *Bifidobacteriun bifidum** ↑ *Bifidobacterium dentium** ↑ *Bifidobacteriun longum** ↑ *Enterococcus faecium** ↑ *Lactobacillus crispatus**, ↑ *Limosilactobacillus fermentum** ↓ *Bacteroides intestinales** ↓ *Bacteroides finegoldii** ↓ *Lactobacillus acidophilus** ↓ *Lactobacillus johnsonii*	None	Metadata is unlabelled	(Zhu et al., 2020)
	WGS (no)	N = 28 First Episode Psychosis (FEP) N = 16 Matched Control	**FEP vs Controls** ↑ *Lactobacillus*	**FEP vs Controls** ↑ *Lactobacillus*	None		(Schwarz et al., 2018)
	16S (no)	N = 40 Drug Naive SZ (DSZ) N = 85 Treated SZ (TSZ) N = 69 Control	**TSZ vs DSZ** ↑ *Escherichia* (LFC = 1.65)*** ↑ *Fusobacterium* (LFC = 2.43)** ↑ *Megasphaera* (LFC = 5.76)*** ↑ *Enterococcus* (LFC = 3.69)*** ↑ *Lactobacillus* (LFC = 5.02)*** ↑ *Streptococcus* (LFC = 2.67)*** ↑ *Shigellia* (LFC = 1.18)** ↑ *Veillonella* (LFC = 2.81)*** ↑ *Clostridium* (LFC = 1.26)** ↑ *Enterobacter* (LFC = 1.93)** ↑ *Ruminococcus* (LFC = 0.95)*** ↑ *Sutterella* (LFC = 1.06) **DSZ vs Control** ↑ *Escherichia* (LFC = 1.86)*** ↓ *Fusobacterium* (LFC = -2.99)*** ↓ *Megasphaera* (LFC = -4.60)*** **TSZ vs Control** ↓ *Bacteroides* (LFC = -0.73)** ↑ *Enterococcus* (LFC = 2.82)*** ↑ *Lactobacillus* (LFC = 3,74)*** ↑ *Parabacteroides* (LFC =	**TSZ vs Control** ↑ *Enterococcus* (LFC = 3.69)*** ↑ *Lactobacillus* (LFC = 5.02)***5.02)*** **TSZ vs Control** ↓ *Bacteroides* (LFC = -0.73)** ↑ *Enterococcus* (LFC = 2.82)*** ↑ *Lactobacillus* (LFC = 3,74)***74)***	None	Greengenes, rarefaction	(Ma et al., 2020)

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Table 2 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			-0.76)** ↑ *Shigella* (LFC = 1.66)*** ↑ *Streptococcus* (LFC = 1.29) ↓ *Turcibacter* (LFC = -2.04)*** ↑ *Veilonella* (LFC = 2.31)*** ↑ *Clostridium* (LFC = 1.67)**				
	16S (no)	N = 82 SZ N = 80 Control	**SZ vs Control** ↑ *Collinsella* ↑ *Prevotella* ↑ *Lactobacillus* ↑ *Eubacterium* ↑ *Corynebacterium* (negatively assocaited with negative SZ symptoms) ↑ *Succinovibrio*(correlated to severity of SZ symptoms) ↓ *Anaerostipes* ↓ *Faecalibacterium* ↓ *Aldercreutzia* ↓ *Butyricimonas*	**SZ vs Control** ↑ *Lactobacillus*	None		(Li et al., 2020a)
	16S (no)	N = 48 SZ N = 48 Control	**SZ vs Control** No genera-level differences identified	None	None		(Nguyen et al., 2021)
	16S (no)	N = 26 SZ with no history of violence N = 16 SZ with violent behaviours (SZV)	**SZV vs SZ** ↓ *Delftia* ↓ *Allobaculum*	None	None		(Chen et al., 2021)
	16S (no)	N = 29 SZ in remission N = 29 SZ in disease onset Used controls from Human Microbiome project	**Remission vs Acute SZ** ↑ *Clostridium sensu stricto*	None	None		(Pan et al., 2020)
	16S (no)	N = 81 High Risk of Psychosis N = 69 Control N = 19 Ultra High Risk of Psychosis	**Ultra High Risk vs High Risk** ↑ *Lactobacillus* ↑ *Prevotella*	None	None	Rarefaction	(He et al., 2018)
	16S (no)	N = 30 patients *B. breve A1* probiotic given daily for 4 weeks, washout for 4 weeks $1*10^{11}$ CFU daily	**Responders vs Non-Responders (4 weeks vs Baseline)** ↑ *Parabacteroides** Improved HADS and PANSS	None	None	Used QIIME 1.8, Greengenes, Pilot study	(Okubo et al., 2019)
	16S (no)	N = 20 Sampled before olanzapine and after 7 day washout 6 weeks later	None	None	None	Greengenes, Did not report differences between 6 weeks and baseline; generated heirarchical cluster for stratification	(Pelka-Wysiecka et al., 2019)
	16S (no)	N = 16 Control N = 10 First Episode Drug Naive Schizophrenia	**Schizophrenia vs Control** ↓ *Faecalibacterium* ↓ *Fusicatenobacter* ↓ *Coprococcus 1* ↓ *Coprococcus 2* ↓ *Butyricoccus* ↑ *Actinomyces* ↑ *Eggerthella* ↑ *Anaerotruncus* ↑ *Flavonifactor* ↑ *Holdemania* ↑ *Eisenbergiella* ↑ *Prevotella* ↑ *Ruminoccocus gnavus* ↑ *Ruminoclostridium 5*	None	None		(Zhang et al., 2019b)

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Table 2 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			↑ *Dorea* ↑ *Hungatella* ↑ *Bilophila* ↑ *Oscillibacter* ↑ *Prevotella* ↑ *Blautia*				
	16S (no)	N = 63 Schizophrenia N = 69 Control	None	None	None	Genus-level differences not reporter	(Zheng et al., 2019)
	T-RFLP (no)	N = 16 Schizophrenia Inpatients Sampled before and after intervention (6 months) Prebiotic: 3 g/day 4G-β-D-galactosylsucrose	**Post- vs Pre- Prebiotic Intake** ↑ *Bifidobacteirum*** ↓ *Clostridium XIVa**	**Post- vs Pre-Prebiotic Intake** ↑ *Bifidobacteirum***			(Nagamine et al., 2018)
	qPCR (no)	N = 41 SZ N = 41 Control	**SZ vs Control** ↑ *Clostridium coccoides**** ↓ *Bifidobacterium spp.**** ↓ *Escherichia coli**** ↓ *Lactobacillus spp.**** Ameliorated after 24 weeks of risperidone	**SZ vs Control** ↓ *Bifidobacterium spp.**** ↓ *Lactobacillus spp.****	None	No control/PBO	(Yuan et al., 2018)
PANS/ PANDAS	16S (yes)	N = 30 with PANS/ PANDAS N = 70 Control	None	None	None		(Quagliariello et al., 2018)
	16S (yes)	N = 8 RTT N = 10 Control	**RTT vs Control** ↑ Faecal iso-butyrate** ↑ Faecal iso-valerate**	None	None		(Borghi et al., 2017)
Rett's Syndrome	16S via 454 Pyrosequencing (yes)	N = 50 RTT N = 29 Control	**RTT vs Control** ↑ Faecal propionate* ↑ Faecal iso-butyrate*** ↑ Faecal iso-valerate** No differences even when accounting for constipation and severity	None	None		(Strati et al., 2016)

Legend: LFC: log-2 fold change; LC: log change; RA: relative abundance; DASS-42: Depression Anxiety Stress Scales; ADHD: Attention-Deficit Hyperactivity Disorder; HE: hepatic encephalopathy; FOS: Fructo-oligosaccharide; HADS-A: Hamilton Anxiety and Depression Scales – Anxiety Subscale; HADS-A: Hamilton Anxiety and Depression Scales – Depression Subscale; RTT: Rett's Syndrome; *: $p_{adj} < 0.1$; **: $p_{adj} < 0.01$; ***: $p_{adj} < 0.001$; Reanalysed studies are highlighted; 95 % CI reported between square brackets [lower 95 % CI; upper 95 % CI].

2017). Upon reanalysis, no significant differences within the microbial composition or GBM abundance were found (Aarts et al., 2017) (see Table 2).

The study is notable because 28 of these participants underwent a further fMRI analysis and found associations between microbial compositions with responses to reward anticipation (Aarts et al., 2017). Since fMRI data was not provided, this aspect of the study was not reanalyzed.

3.2.1.2. Studies where raw microbiome data was not reanalysed.. Wan et al. (2020) used a WGS strategy to identify a reduction in KEGG Orthologs for dopaminergic pathways in individuals with ADHD. Consistent with Jiang et al. (2018b), ADHD individuals had a lower abundance of *Faecalibacterium* (Wan et al., 2020). In fact, *Faecalibacterium* abundance negatively associated with the total Conners Parent Rating Scales score, which assesses children's behavioural difficulties, as well as the hyperactivity index (Jiang et al., 2018b). No other common differences in microbial genera between ADHD and controls were reported across a set of five other studies (Stevens et al., 2019; Prehn-Kristensen et al., 2018; Szopinska-Tokov et al., 2020; Pärtty et al., 2015; Wang et al., 2020a). However, one of these studies used a compositional approach for their data analysis (Szopinska-Tokov et al., 2020). They found an increased relative abundance of *Ruminoclostridium 9* and *Ruminococcus 2* in ADHD individuals, and correlated *Ruminococcus 2* with inattention scores (B = 1.525, p = 0.001) (Szopinska-Tokov et al., 2020).

3.2.2. Autism spectrum disorder (ASD)

3.2.2.1. Studies where raw microbiome data was reanalysed.. Across seven reanalysed studies (see Table 2), only two showed a robust effect of Autism Spectrum Disorder (ASD) on microbiota composition (Averina et al., 2020; Son et al., 2015; Pulikkan et al., 2018; Kang et al., 2019; Kong et al., 2019; Liu et al., 2019b; Strati et al., 2017). In the data collected by (Pulikkan et al., 2018), *Roseburia* abundance was increased in ASD ($p_{adj} < 0.001$, effect = 0.9; 95 % CI: [-1.9, 10.38]). When stratifying individuals with ASD by the median Autism Treatment Evaluation Checklist score, those below the median of 62 showed a reduction in *Ruminoclostridium 9* ($p_{adj} < 0.1$, effect = -0.78; 95 % CI: [-7.28, 1.80]) (Kong et al., 2019). However, none of these studies found any differentially abundant GBM pathways. Interestingly, in the dataset collected by Son et al. (2015), twins discordant for ASD showed no overall differences in microbiota composition.

3.2.2.2. Studies where raw microbiome data was not reanalysed.. Over 30 other studies assessed differences between the ASD microbiota and controls, or differences within ASD subgroups (see Table 2). Across the WGS studies, only one found changes in GBM abundance (Wang et al.,

2019a). They reported decreased gut glutamate/glutamine metabolism in ASD individuals (Wang et al., 2019a).

Bacteroides abundance was increased in ASD groups amongst four datasets (Zhai et al., 2019b; Zurita et al., 2019; Coretti et al., 2018; Ahmed et al., 2020) and reduced in four (Dan et al., 2020; Niu et al., 2019; Ding et al., 2020; Zhang et al., 2020b). Similarly, the relative abundance of *Bifidobacterium* in ASD was increased in two datasets (Dan et al., 2020; Plaza-Diaz et al., 2019), and decreased in three others (Niu et al., 2019; Wang et al., 2020a; Zhang et al., 2020b). Another compelling argument from the use of ASVs over OTUs is identifying whether a specific genus is increased or decreased. For example, in Zurita et al. (2019), one *Ruminoccocus* OTU is increased in ASD while another is reduced. Until recently, the important *Lactobacillus* genera encompassed many distinct strains; with updated nomenclature it might be possible to differentiate amongst the genera and find other potential signatures (Zheng et al., 2020a). Overall, there is great heterogeneity in the methods, reporting and results.

3.2.3. Schizophrenia

3.2.3.1. Studies where raw microbiome data was reanalysed.. Four studies were reanalysed (see Table 2), but we found differentially abundant genera in only two of these studies (Xu et al., 2020; Shen et al., 2018; Flowers et al., 2019; Nguyen et al., 2019). In these two studies, individuals with schizophrenia had higher abundances of the acetate-producing *Fusicatenibacter* (padj < 0.001, effect: 0.67; 95 % CI: [-1.48; 7.56]; padj < 0.001 and effect $= 1.06$; 95 % CI: [-1.05; 7.60]) (Shen et al., 2018; Xu et al., 2020). In the samples collected by Xu et al., 2020, individuals with schizophrenia also showed an increase in the following GBMs: Butyrate synthesis II (padj < 0.001, effect: 0.61; 95 % CI:[-1.83; 5.41]), Kynurenine synthesis (padj < 0.001, effect: 0.68; 95 % CI:[-2.10; 6.12]), and Inositol degradation (padj < 0.001, effect: 0.83; 95 % CI:[-1.58; 6.96]). In addition, *Lactobacillus* abundance was reduced (padj < 0.001, effect: - 1.28; 95 % CI:[-12.85; 0.11]) (Xu et al., 2020).

3.2.3.2. Studies where raw microbiome data was not reanalysed.. Across three WGS studies, various *Lactobacillus* OTUs are increased in schizophrenia compared to controls (Zhu et al., 2020; Xu et al., 2020; Schwarz et al., 2018), however some OTUs were also reduced in one of the studies (Zhu et al., 2020). In two studies, *Bifidobacterium adolescentis* was increased in patients, while *Clostridium perfingens* was increased in one dataset (Xu et al., 2020) but reduced in the other (Zhu et al., 2020). Interestingly, this contrasts with the reduction found when reanalyzing the 16S dataset from (Xu et al., 2020). This discrepancy is resultant from the different sequencing and bioinformatics pipelines used. The majority of 16S sequencing studies assessed different subpopulations of schizophrenia and thus are difficult to compare with each other. Combined with reanalysed results, there is evidence supporting *Lactobacillus* and *Bifidobacterium* dysregulation in schizophrenia, as well as potential changes in tryptophan and SCFA-related GBMs (see Table 2).

3.2.4. Pediatric acute-onset neuropsychiatric syndrome and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection

3.2.4.1. Studies where raw microbiome data was reanalysed.. One 16S sequencing study was reanalysed but no relevant bacterial genera or differences in GBMs were found (Quagliariello et al., 2018).

3.2.5. Rett's syndrome

3.2.5.1. Studies where raw microbiome data was reanalysed.. A small descriptive study was reanalysed (Borghi and Vignoli, 2019) but no genus-level differences were found between Rett's Syndrome and age-matched controls. However, both faecal isobutyrate and isovalerate were increased in Rett's syndrome (see Table 2).

3.2.5.2. Studies where raw microbiome data was not reanalyzed.. Strati et al. (2016) found an increased abundance in faecal isobutyrate, isovalerate and propionate (see Table 2). However, after controlling for constipation and disease severity, no bacteria were differentially abundant within the disease group.

3.3. Epilepsy

3.3.1. Studies where raw microbiome data was reanalysed

In the dataset from Lindefeldt et al. (2019), twelve children with epilepsy provided two faecal samples, one before commencing the ketogenic diet and three months afterwards (see Table 3). While no age-matched controls were included within the study, the children's parents were used as controls instead (Lindefeldt et al., 2019). The dataset was reanalysed through the WGS pipeline described in Section 2.6. We found that the ketogenic diet increased abundance in L-tryptophan biosynthesis pathways (padj < 0.1, effect $= 0.9$; 95 % CI: [-1.07; 10.67]) and S-adenosyl methionine biosynthesis (padj < 0.1, effect $= 0.63$; 95 % CI: [-1.89; 8.86]) (Lindefeldt et al., 2019). Though the study's authors found a reduction in relative abundance of *Bifidobacterium* their data was not treated compositionally (see 3.4.3 for limitations of non-compositional data approaches) (Lindefeldt et al., 2019).

Another reanalysed study looked at individuals co-morbid with cerebral palsy and epilepsy (Huang et al., 2019a). While over 20 differentially abundant bacteria had an absolute effect size >0.65, there were no differences across GBM abundance (Huang et al., 2019a).

3.3.2. Studies where raw microbiome data was not reanalysed

Four 16S studies used different types of cohorts and comparisons (see Table 3). (Xie et al., 2017) assessed microbiome differences between epileptic infants and healthy controls. Two studies compared individuals with drug-responsive epilepsy, to drug-resistant epilepsy and controls from the same family (Peng et al., 2018; Zhang et al., 2018b). Peng et al. (2018) looked at the efficacy of dietary intervention while Şafak et al. (2020) focused on idiopathic focal epilepsy. Another study compared same-family controls to epileptic individuals finding many genera-level differences (Liu et al., 2020a).

3.4. Neurodegenerative disease

3.4.1. Alzheimer's disease

3.4.1.1. Studies where raw microbiome data was reanalysed.. Most of the raw sequences from one 16S study could not be aligned to ASVs (Liu et al., 2019b). In the other 16S sequencing study (Li et al., 2019a), a reduction was detected in the SCFA-producing *Ruminoclostridium 5* (padj< 0.01, effect $=$ -0.67; 95 % CI: [-8.52, 1.59] while the following SCFA-specific GBMs were upregulated when comparing Alzheimer's Disease (AD) to healthy controls: isovaleric acid synthesis II (padj < 0.1, effect $= 0.42$; 95 % CI: [-2.11; 5.62]), butyrate synthesis I (padj < 0.1, effect $= 0.44$; 95 % CI: [-2.33; 6.25]), butyrate synthesis II (padj < 0.1, effect $= 0.52$; 95 % CI: [-3.60; 4.79]), and acetate synthesis III (padj $<$ 0.1, effect $= 0.50$; 95 % CI: [-2.04; 5.92]) (Li et al., 2019a).

Though no differentially abundant microbes were identified when comparing individuals with mild cognitive impairment (MCI) to healthy controls, several SCFA and tryptophan related GBMs were increased: isovaleric acid synthesis II (padj < 0.01, effect $= 0.43$; 95 % CI: [-2.48; 5.98]), butyrate synthesis I (padj < 0.1, effect $= 0.44$; 95 % CI: [-2.33; 6.25]), acetate synthesis I (padj < 0.01, effect $= 0.58$; 95 % CI: [-1.93; 5.86]), acetate synthesis II (padj < 0.1, effect $= 0.47$; 95 % CI: [-1.81; 5.33]), acetate synthesis III (padj < 0.01, effect $= 0.64$; 95 % CI: [-1.52; 6.26]), tryptophan synthesis (padj < 0.1, effect $= 0.48$; 95 % CI: [-1.94; 6.71]), quinolinic acid synthesis (padj < 0.01, effect $= 0.49$; 95 % CI:

Table 3
Microbiome-brain studies involving epilepsy.

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
Epilepsy	WGS	N = 12 Patients with epilepsy – before and after ketogenic diet	**After diet vs Before** ↑ L-tryptophan biosynthesis* (effect = 0.9 [-1.07; 10.67])	None	**After diet vs Before** ↑ SAM Biosynthesis* (effect = 0.63 [-1.89, 8.86] ↓ L-tyrosine biosynthesis* (effect = -0.60 [-12.29; 0.96]	Low sample size, no age-matched control	(Lindefeldt et al., 2019)
	16S (yes)	N = 25 Cerebral Palsy with Epilepsy (CPE) N = 21 Control	**CPE vs Control** ↓ *Acidaminococcus* (effect = -1.14 [-9.60; 1.17])*** ↓ *Akkermansia* (effect = -1.52 [-11.32; 0.40])*** ↓ *Alistipes* (effect = -1.33 [-10.13; 0.48]) ↓ *Bacteroides* (effect = -0.72 [-7.75; 2.23])*** ↓ *Bifidobacterium* (effect = -2.97 [-24.09; 0.35]) *** ↓ *Blautia* (effect = -1.83 [-14.30; 0.41]) ↓ *Catenibacterium* (effect = -1.67 [-11.67; 0.60]) *** ↓ *Clostridium sensu stricto 1* (effect = -0.96 [-11.22, 0.81]) *** ↓ *Collinsella* (effect = -1.88 [-12.63; 0.41]) *** ↓ *Desulfovibrio* (effect = -1.40 [-11.91; 0.53]) *** ↓ *Enterococcus* (effect = -1.56 [-13.23; 0.46]) *** ↓ *Escherichia/Shigella* (effect = -1.73 [-14.91; 0.43]) *** ↓ *Eubacterium* (effect = 1−.09 [-10.91; 0.61]) *** ↓ *Faecalibacterium* (effect = -1.70 [-12.12; 0.37])*** ↓ *Flavonifractor* (effect = -0.98 [-9.93; 1.26])*** ↓ *Gemella* (effect = -0.97 [-9.03; 1.85])*** ↓ *Haemophilus* (effect = -0.95 [-8.94; 1.39])*** ↓ *Klebsiella* (effect = -1.27 (-10.67; 0.93])*** ↓ *Lactobacillus* (effect = -0.70 [-8.59; 2.31])** ↓ *Methanobrevibacter* (effect = -0.89 [-8.59; 0.78])*** ↓ *Neisseria* (effect = -0.70 [-8.07; 2.44])** ↓ *Oscillibacter* (effect = -1.10 [-10.04; 1.18])*** ↓ *Parabacteroides* (effect = -1.95 [-13.85; 0.39])*** ↓ *Prevotella_2* (effect = -0.67 [-8.09; 2.23])** ↓ *Prevotella_9* (effect = -1.08 [-9.34; 0.90])*** ↓ *Ruminiclostridium_5* (effect = -1.06 [-9.16; 1.20])*** ↓ *Ruminiclostridium_9* (effect = -0.79 [-9.80; 1.25])*** ↓ *Streptococcus* (effect = -2.20 [-19.31; 0.38])*** ↓ *Sutterella* (effect = -0.79 [-12.31; 0.56])*** ↓ *Veillonella* (effect = -1.32 [-10.60; 0.45])***	**CPE vs Control** ↓ *Bacteroides* (effect = -0.72 [-7.75; 2.23]) *** ↓ *Bifidobacterium* (effect = -2.97 [-24.09; 0.35]) *** ↓ *Eubacterium* (effect = 1−.09 [-10.91; 0.61]) *** ↓ *Lactobacillus* (effect = -0.70 [-8.59; 2.31]) **	None		(Huang et al., 2019a)

(*continued on next page*)

Table 3 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
	16S (no)	N = 30 Idiopathic Focal Epilepsy N = 10 Control	None	None	**None**		(Şafak et al., 2020)
	16S (no)	N = 55 Epilepsy N = 46 Control For validation cohort: N = 13 Epilepsy N = 10 Control	**Epilepsy vs Control** ↓ *Stutterella* ↓ *Klebsiella* ↓ *Lachnospiraceae* NK4A613 ↓ *Escherichia shigella* ↓ *Lachnoclostridium* ↑ *Prevotella* ↑ *Blautia* ↑ *Bifidobacterium* ↑ *Ruminococcaceae* UCG 014 ↑ *Ruminococcus gnavus* ↑ *Megamonas* ↑ *Akkermansia* ↑ *Eubacteirum hallili* **Drug-Resistant vs Responsive Epilepsy** ↑ *Blautia* ↑ *Bifidobacteirum* ↑ *Dialister* ↑ *Anaerostipes* ↑ *Subdoligranulum*	**Epilepsy vs Control** ↑ *Bifidobacterium* ↑ *Eubacteirum hallili* **Drug-Resistant vs Responsive Epilepsy** ↑ *Bifidobacterium*			(Gong et al., 2020)
	16S (no)	N = 20 Samples collected from children with refractory epilepsy before and 6 mo. after diet	**After Diet vs Before** ↓ *Faecalibacterium* ↓ *Leucabacter* ↓ *Actinobacter* ↓ *Coprobacter* ↓ *Lachnospiracea incertae sedis* ↑ *Bacteroides* **Non-Responders vs Responders** ↑ *Alistipes* ↑ *Clostridium i* ↑ *Oscillibacter* ↑ *Gordonibacter* ↑ *Lachnospiracea incertae sedis* ↑ *Helicobacter* ↑ *Blautia* ↑ *Dorea* ↑ *Ruminococcus2* ↑ *Fusicatenibacter* ↑ *Eggerthella* ↑ *Anaerotruncus* ↑ *Streptococcus*	**After Diet vs Before** ↑ *Bacteroides*	None	Unclear if comparisons were done in a paired manner; no age-matched controls	(Zhang et al., 2018b)
	16S (no)	N = 42 Drug-Responsive N = 49 Drug-Resistant N = 65 Control (from same families as patients)	**Drug-Resistant vs Responsive** ↑ *Bacteroides* ↑ *Barnesiell* ↓ Roseburia ↓ *Phoscolarctobacterium* *a*↓ Methanobrevibacter ↓ *Fusobacterium* ↓ *Coprococcus* ↓ *Neisseria* ↓ *Akkermansia* ↓ *Gemmiger* ↓ *Ruminococcus2* ↓ *Paraprevotella* ↓ *Coprobacillus* ↓ *Delftia* ↓ *Saccharibacteria incertae sedis* ↓ *Dorea* ↓ *Holdemania* ↓ *Atopobium* ↓ *Clostridium* XVIII	**Drug-Resistant vs Responsive** ↑ *Bacteroides*	None	No comparisons reported for controls; statistical methods unclear	(Peng et al., 2018)
	16S (no)	N = 30 Healthy Infants N = 14 Epileptic Infants	Difficult to interpret	None		Greengenes, No pair-wise group comparisons	(Xie et al., 2017)

Legend: LFC: log-2 fold change; LC: log change; RA: relative abundance; DASS-42: Depression Anxiety Stress Scales; ADHD: Attention-Deficit Hyperactivity Disorder; HE: hepatic encephalopathy; FOS: Fructo-oligosaccharide; HADS-A: Hamilton Anxiety and Depression Scales – Anxiety Subscale; HADS-A: Hamilton Anxiety and Depression Scales – Depression Subscale; RTT: Rett's Syndrome; *: $p_{adj} < 0.1$; **: $p_{adj} < 0.01$; ***: $p_{adj} < 0.001$; Reanalysed studies are highlighted; 95 % CI reported between square brackets [lower 95 % CI; upper 95 % CI].

[-1.93; 6.43]), quinolinic acid degradation (padj < 0.01, effect = 0.56; 95 % CI: [-1.93; 6.43]) (Li et al., 2019a).

Additionally, several other GBMs were differentially abundant in the MCI and AD groups compared to the controls, indicating an increase in overall pathways promoting excitatory neuronal signalling (Li et al., 2019a) (see Table 4).

3.4.1.2. Studies where raw microbiome data was not reanalysed.. *Bacteroides* is differentially abundant across the two 16S and one WGS study comparing AD to controls. However, it is increased in two of these studies – one of which involves WGS (Haran et al., 2019; Vogt et al., 2017), and decreased in the third study (Zhuang et al., 2018). Additionally, *Alistipes* abundance was increased in the AD individuals in two of these studies (Haran et al., 2019; Vogt et al., 2017).

3.4.2. Multiple systems atrophy

3.4.2.1. Studies where raw microbiome data was not reanalysed. Three studies analyzing the gut microbial composition of individuals with Multiple Systems Atrophy (MSA) have been conducted (see Table 4), with two of these studies finding genus-level differences in bacterial abundance (Du et al., 2019; Engen et al., 2017; Tan et al., 2018). However, none of the genera are found differentially abundant across these two studies (Tan et al., 2018; Du et al., 2019). Interestingly, Tan et al. (2018) also found a reduction in faecal acetate, propionate and butyrate in their disease cohort.

3.4.3. Amyotrophic lateral sclerosis (ALS)

3.4.3.1. Studies where raw microbiome data was not reanalysed.. There were no consistent findings across three studies (Zhai et al., 2019a; Brenner et al., 2018; Mazzini et al., 2018; Zeng et al., 2020; Nicholson et al., 2020; Ngo et al., 2020) (see Table 4). (Blacher et al., 2019) did not find any significant microbes using a WGS approach but found an overall reduction in tryptophan metabolism-related genes in ALS compared with controls. Two other WGS studies did however find differentially abundant microbes, involved in SCFA and tryptophan metabolism (Nicholson et al., 2020; Zeng et al., 2020). Indeed, alterations in serum tryptophan and nicotinamide metabolites suggest the serum metabolome may be altered by the gut microbiota (Blacher et al., 2019).

3.4.4. Parkinson's disease

3.4.4.1. Studies where raw microbiome data was reanalysed. Surprisingly, across six studies (one WGS, five 16S) only 1 ASV was found differentially abundant (Bedarf et al., 2017; Heintz-Buschart et al., 2018; Aho et al., 2019; Pietrucci et al., 2019; Qian et al., 2018; Weis et al., 2019) (see Table 4). When stratifying 16S sequencing data from Weis et al. (2019) by gastrointestinal symptoms and L-DOPA dosage, there was one differentially abundant genus. Individuals with Parkinson's disease (PD) taking a L-DOPA dose of <300 mg/day had a lower abundance of *Lactobacillus* than controls (effect = 0.83; 95 % CI: [-2.10, 8.07]) (Weis et al., 2019). No GBMs related to SCFAs, tryptophan or bile-acid modifying bacteria were identified.

3.4.4.2. Studies where raw microbiome data was not reanalysed.. Hill--Burns et al. (2017) found significant differences in bacterial abundance between PD and controls after controlling for covariates. They reported an increased abundance of *Bifidobacterium*, *Lactobacillus*, *Akkermansia* and *Roseburia* (Hill-Burns et al., 2017). Ren et al. (2020) used a generalised linear model to control for sex, age, body mass index and education and did not find any changes in these four genera. Instead, they reported a reduction in *Ruminococcus* and *Blautia* in their PD group which had not experienced MCI (Ren et al., 2020). However, three other studies reported an increased abundance of *Lactobacillus* in PD (Petrov et al., 2017; Barichella et al., 2019; Cirstea et al., 2020). Additionally, three 16S studies reported a reduction in *Roseburia* compared to their control cohorts (Barichella et al., 2019; Keshavarzian et al., 2015; Cristea et al., 2020). Four other 16S studies also found an increased abundance of *Akkermansia* (Keshavarzian et al., 2015; Vidal-Martinez et al., 2020; Li et al., 2019b; Zhang et al., 2020a) and *Bifidobacterium* (Petrov et al., 2017; Cirstea et al., 2020; Barichella et al., 2019; Tan et al., 2020). Interestingly, Lin et al. (2019) found *Akkermansia* was increased in the tremor PD subtype when accounting for age, sex and diet. Finally, Unger et al. (2016) reported reductions in faecal acetate, butyrate and propionate.

3.5. Addiction and substance use

3.5.1. Alcohol

3.5.1.1. Studies where raw microbiome data was reanalysed.. Stadlbauer et al. (2019) collected faecal samples from participants before an acute 2 mL alcohol binge, and one day afterwards in 15 healthy participants. We did not find any significant effects on the microbiota composition or GBMs in this dataset (Stadlbauer et al., 2019). The alcohol binge was likely too mild to exert any robust effects.

Another dataset focused on the long-term effects of alcohol-dependence on the gut microbiota (Bjorkhaug et al., 2019). Bacteria involved in SCFA and tryptophan metabolism were altered in the alcohol-dependent cohort (Bjorkhaug et al., 2019). Specifically, *Ruminococcus 2* abundance was increased ($p_{adj} < 0.1$, effect = 0.72, 95 % CI: [-2.91; 6.75]) and a reduction in *Ruminoclostridium 9* ($p_{adj} < 0.001$, effect = - 0.99, 95 % CI: [-7.99; 1.00]) (Bjorkhaug et al., 2019). Though SCFA-related GBMs were not altered, the tryptophan degradation module was reduced in alcohol-dependent subjects ($p_{adj} < 0.1$, effect = -0.46, 95 % CI: [-5.78; 2.47]) (Bjorkhaug et al., 2019). In addition, other GBMs suggested increased GABA synthesis as well as a reduction in g-hydroxybutyrate and dopamine degradation (Bjorkhaug et al., 2019).

3.5.1.2. Studies where raw microbiome data was not reanalysed.. Due to differences in cohorts, it is challenging to draw conclusions from other alcohol-related studies (see Table 5). Briefly, a WGS investigation using the SOLiD sequencing platform compared the microbiota of individuals with alcoholic dependence syndrome, alcoholic liver cirrhosis and control (Dubinkina et al., 2017). Dubinkina et al. (2017) reported an increased abundance of *Lactobacillus salivarius* in alcohol-dependent subjects. These results are not easily reconciled, with findings from Leclercq et al., 2014, where a three-week detoxification increased *Lactobacillus spp.* in alcohol-dependent subjects. Two other studies involving alcohol-dependence and alcohol overconsumption did not report changes in *Lactobacillus* abundance (Tsuruya et al., 2016; Bjorkhaug et al., 2020). Meanwhile, a study of the microbiota and drinking habits of 212 twin pairs only found a reduction in *Roseburia* abundance associated with alcohol consumption, after correcting for heritability (Seo et al., 2020). Interestingly, one study associated *Haemophilia* abundance with drinking only (Lin et al., 2020) while other genera

associated with both drinking and smoking (*Bacteroides, Phascolarctobacteirum, Ruminococcus UCG-002, Ruminococcus UCG-003, Ruminoclostridium-9)*. Many of these genera are associated with SCFA/tryptophan metabolism.

3.5.2. Smoking and tobacco use

3.5.2.1. Studies where raw microbiome data was reanalysed.. Stewart et al. (2018) collected faecal samples from tobacco smokers, electronic cigarette users and controls (see Table 5). Though we did not uncover genus-level differences in microbial abundance, we found an increase in the tryptophan degradation module ($p_{adj} < 0.1$, effect = 0.84, 95 % CI: [-0.97; 8.52]) and the propionate synthesis III module ($p_{adj} < 0.1$, effect = - 0.80, 95 % CI: [-9.86; 1.45])(Stewart et al., 2018).

3.5.2.2. Studies where raw microbiome data was not reanalysed.. Among other studies assessing the microbiota composition of smokers, only a qPCR study identified microbial changes (Ishaq et al., 2017).

3.5.3. Addiction and recreational drug use

3.5.3.1. Studies where raw microbiome data was reanalysed.. There were no differentially abundant microbial or GBM-related associations within the (Barengolts et al., 2018) dataset of men characterised with a high-disease burden and opioid use.

3.5.3.2. Studies where raw microbiome data was not reanalysed.. While Fulcher et al. (2018) reported specific changes in microbial abundance with many recreational drugs, Xu et al. (2017) did not find any differences between users and non-users when controlling for age and sex (see Table 5). Panee et al. (2018) recently found that *Prevotella* abundance in marijuana users positively associated with cognitive functions.

3.6. Multiple sclerosis and demyelinating diseases

3.6.1. Studies where raw microbiome data was reanalysed

Across two 16S sequencing datasets, no differences in microbial abundance or GBMs related to SCFA, tryptophan or bile acid metabolism were identified (Miyake et al., 2015; Jangi et al., 2016) (see Table 6). When comparing individuals with neuromyelitis optica spectrum disorder (NMOSD) to control samples in the (Gong et al., 2019) dataset, *Streptococcus* abundance was reduced in diseased individuals ($p_{adj} <$ 0.001, effect = - 0.74, 95 % CI: [- 6.40; 1.53]). The researchers also reported an overall reduction of faecal SCFAs and associations between acetate, butyrate and disease severity (Gong et al., 2019).

3.6.2. Studies where raw microbiome data was not reanalysed

There were no consistent effects across Multiple Sclerosis (MS) studies. Using WGS, Ventura et al. (2019) found *Clostridium* increased across individuals with MS with Caucasian, Hispanic and African American ethnicities. Interestingly, (Berer et al., 2017) compared faecal samples from 34 discordant twin pairs and did not find-any genus-level compositional changes when accounting for heritability. Other recent studies found a few dysregulated genera but did not take ethnicity into account (Ling et al., 2020b; Kishikawa et al., 2020).

A recent investigation by Reynders et al. (2020) found associations between multiple bacterial genera and clinical subtypes of MS. Another study also found differences in SCFA-producing genera between different subtypes of multiple sclerosis and controls (Saresella et al., 2020). Zeng et al. (2019) compared microbial and faecal SCFA abundance between MS, NMOSD and controls finding a reduction in acetate, butyrate and propionate when comparing either MS or NMOSD to controls. Interestingly, they also reported that faecal acetate and propionate are reduced in NMOSD individuals compared to those with MS (Zeng et al., 2019).

3.7. Pain-related disorders

3.7.1. Fibromyalgia

3.7.1.1. Studies where raw microbiome data was reanalysed.. In the 16S dataset collected by Minerbi et al. (2019), only one bacterial genus was associated with the disease state (see Table 7). The abundance of *Sutterella* was increased in fibromylagia compared to controls living at the same address as the patient (p_{adj} <0.1, effect = 0.66; 95 % CI: [-0.43; 0.92]) (Minerbi et al., 2019). However, no differences were found when comparing to overall controls in both this 16S dataset as well as in the samples from (Clos-Garcia et al., 2019).

3.7.1.2. Studies where raw microbiome data was not reanalysed.. One study found several SCFA-associated bacteria were differentially abundant between individuals with fibromyalgia and unrelated controls, corresponding to changes in serum SCFA concentrations (Minerbi et al., 2019). Compared to the 16S data produced from this cohort (discussed in **3.7.1.1**), WGS provides species level resolution and identifies many more differentially abundant microbes (Minerbi et al., 2019).

3.7.2. Irritable-bowel syndrome (IBS)

3.7.2.1. Studies where raw microbiome data was not reanalysed.. Ten 16S sequencing studies to date, investigated the associations between psychological well-being, IBS and the microbiota (see Table 7). While one study found *Bacteroides* abundance positively associated with perceived stress (Peter et al., 2018b), while Jeffery et al. (2012) reported that it was reduced in IBS individuals compared with controls. Since no controls were included in the study by (Peter et al., 2018b), these results are not necessarily contradictory. As many of these studies involved different probiotic, prebiotic and faecal microbiota transplant interventions and a lack of controls, the results of these studies could not be compared. Several studies report changes in SCFA and tryptophan-associated bacteria, with Labus et al. (2019) finding that *Clostridium* XIVa and *Coprococcus* associated with differences in brain connectivity between IBS and controls.

3.7.3. Other pain-related disorders

3.7.3.1. Studies where raw microbiome data was not reanalysed.. A recent WGS study (see Table 7) reported the increased abundance of the kynurenine synthesis GBM and a reduction in quinolinic acid degradation in elderly women with migraines compared to healthy age-matched control (Chen et al., 2020c). In addition, *Faecalibacterium prausnitzii* and *Bifidobacterium adolescentis* were reduced in the women who experienced migraines (Chen et al., 2020c). However, this was the only microbiota study assessing migraines to date. Another conducted on a cohort with myalgic encephalomyelitis/chronic fatigue syndrome found negative correlations between *Faecalibacterium* and total sleep awakening (Kitami et al., 2020). Meanwhile, a study of chronic widespread pain patients found a decrease in *Coprococcus comes* abundance (Freidin et al., 2020)

3.8. Eating disorders

3.8.1. Obesity

3.8.1.1. Studies where raw microbiome data was not reanalysed.. Across studies of obesity where psychological or other brain measures were recorded, no genus-level associations were reported (see Table 8). However, one study used a commercially available dysbiosis test (GA-Map Dysbiosis) to compare the morbidly obese microbiomes to controls (Farup and Valeur, 2018). *Bacteroides*, *Prevotella* and faecal SCFAs were negatively associated with the WHO-5 Wellbeing Index Score within the

Table 4
Microbiome-brain studies involving neurodegenerative disorders.

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
	16S (yes – extreme proportion of unmapped reads)	N = 33 AD N = 32 Mild Cognitive Impairment (MCI), N = 32 Control	None	None	None	Too many unmapped reads	(Liu et al., 2019b)
AD and MCI	16S (yes)	N = 30 AD N = 30 MCI N = 30 Control	**AD vs Control** ↓ *Ruminoclostridium 5*** (effect = -0.67[-8.52; 1.59]) ↑ Isovaleric-Acid Synthesis II* (effect = 0.42 [-2.11, 5.62]) ↑ Acetate Synthesis III* (effect = 0.50 [-2.04, 5.92]) ↑ Butyrate Synthesis I* (effect = 0.44 [-2.33, 6.25]) ↑ Butyrate Synthesis II* (effect = 0.52 [-3.60, 4.79]) **MCI vs Control** ↑ Isovaleric-Acid Synthesis II** (effect = 0.43 [-2.48; 5.98]) ↑ Acetate Synthesis I** (effect = 0.58 [-1.93; 5.86]) ↑ Acetate Synthesis II* (effect = 0.47 [-1.81; 5.33]) ↑ Acetate Synthesis III** (effect = 0.64 [-1.52; 6.26]) ↑ Tryptophan synthesis* (effect = 0.48 [-1.94, 6.71] ↑Quinolinic Acid Synthesis** (effect = 0.49 [-2.02; 6.43]) ↑Quinolinic Acid Degradation ** (effect = 0.56 [-1.93; 6.43])	None	**MCI vs Control** ↑ Glutamate synthesis I** (effect = 0.50 [-1.94; 5.90]) ↑ Glutamate synthesis II** (effect = 0.71 [-1.4; 6.25]) ↑ Histamine degradation* (effect = 0.46 [-2.36, 5.46]) ↑ p-Cresol Synthesis** effect = 0.64 [-1.61; 7.26]) ↑ClpB** (effect = 0.55 [-1.99; 6.30]) ↑17-Beta-Estradiol Degradation** (effect = 0.65 [-1.46; 6.58]) ↑ SAM Synthesis* (effect = 0.58 [-2.01; 5.92]) ↓ Glutamate Degradation II** (effect = -0.50 [-7.02, 2.42]) ↓ Vitamin K2 Pathway Synthesis II** (effect = -0.42 [-1.52; 6.3]) **AD vs Control** ↑ Glutamate Synthesis II* (effect = 0.45 [-2.03; 5.63]) ↑ Histamine Degradation* (effect = 0.46 [-2.51; 5.64]) ↑ p-Cresol Synthesis* (effect = 0.54 [-2.26, 5.82]) ↓ Vitamin K2 Pathway Synthesis II* (effect = -0.44 [-5.73, 2.83]) ↓ Glutamate Degradation II* (effect = -0.50 [-7.02, 2.42]) ↓ GABA Synthesis III* (effect = -0.48 [-5.90, 1.57]) ↓ Vitamin K2 Pathway Synthesis I (effect = -0.46 [-5.79, 2.03])		(Li et al., 2019a)
	WGS (no)	N = 24 AD N = 33 Other Dementia N = 51 Control	**AD vs Control** ↑ *Bacteroides** ↑ *Alistipes**** ↑ *Odoribacter**** **AD vs Other Dementia**	**AD vs Control** ↑ *Bacteroides**	None		(Haran et al., 2019)

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Table 4 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			↑ *Odoribacter** ↓ *Eubacterium**** ↓ *Roseburia**				
	16S (no)	N = 43 AD N = 43 Age and Gender-Matched Control	**AD vs Control** ↑ *Subdoligranulum*** ↓ *Bacteroides***	**AD vs Control** ↓ *Bacteroides***	None		(Zhuang et al., 2018)
	16S (no)	N = 25 AD N = 25 Control	**AD vs Control** ↑ *Blautia** ↑ *Bacteroides**** ↑ *Alistipes** ↑ *Phascolarctobacterium** ↓ *Bifidobacterium** ↓ *Dialister**** ↓ *Clostridium** ↓ *Turcibacter****	**AD vs Control** ↑ *Bacteroides**** ↓ *Bifidobacterium**	None	Greengenes	(Vogt et al., 2017)
	qPCR (no)	N = 40 Cognitively Impaired with Amyloidosis (AMY+) N = Cognitively Impaired No Amyloidosis (AMY-) N = 10 Control (Age and sex-matched)	**AMY + vs AMY-** ↑ *Escherichia/Shigella**** ↓ *Eubacterium rectale**** **AMY + vs Control** ↑ *Escherichia/Shigella**** ↓ *Bacteroides fragilis** ↓ *Eubacterium rectale**** **AMY- vs Control** ↑ *Escherichia/Shigella*** ↓ *Eubacterium rectale***	**AMY + vs AMY-** ↓ *Eubacterium rectale**** **AMY + vs Control** ↓ *Bacteroides fragilis** ↓ *Eubacterium rectale**** **AMY- vs Control** ↓ *Eubacterium rectale***	None		(Cattaneo et al., 2017)
	qPCR (no)	N = 20 AD Outpatients Prospective trial of probiotic treatment (28 days)	**AD after Probiotic vs Baseline** ↑ *Faecalibacterium prausnitzii****	None	None	Faeces stored at -18C	(Leblhuber et al., 2018)
	16S (no)	N = 40 MSA N = 40 Control (spouses)	**MSA vs Control** ↑ Lactobacillus ↑ Gordonibacter ↑ Phascolarctobacterium ↓ *Haemophilus*	**MSA vs Control** ↑ Lactobacillus	None	Rarefaction	(Du et al., 2019)
MSA	16S (no)	N = 6 MSA N = 11 Control	None	None	None		(Engen et al., 2017)
	16S (no)	N = 17 MSA N = 17 Control	**MSA vs Control** ↑ *Bacteroides*** ↓ *Prevotella clara** ↓ *Paraprevotella**** ↓ Faecal acetate, propionate and butyrate	**MSA vs Control** ↑ *Bacteroides***	None		(Tan et al., 2018)
	WGS (no)	N = 37 ALS N = 29 Age and BMI-Matched Control 16S	**ALS vs Control** ↓ Tryptophan metabolism genes				(Blacher et al., 2019)
	WGS and 16S (no)	N = 20 ALS N = 20 Control WGS N = 10 ALS N = 10 Control	**ALS vs Control** ↑ *Enterococcus columbae*	None	None		(Zeng et al., 2020)
ALS			**ALS vs Control** ↑ *Prevotella copri* ↑ *Phascolarctobacterium succinatutens* ↑ *Bacteroides clarus* ↑ *Dorea* ↑ *Escherichia* ↓ *Aldercreutzia equolifaciens* ↓ *Lachnospiraceae bacterium* 5 1 63FAA ↓ *Coprobacter fastidiosus* ↓ *Ruminococcus lactaris* ↓ *Eubacterium eligens* ↓ *Ruminococcus* sp 5 1 39BFAA ↓ *Bifidobacterium longum* ↓ *Roseburia intestinalis* ↓ *Eubacterium rectale* Decrease in butyrate producers **ALS vs ND**				
	WGS & 16S (no)	N = 66 ALS N = 12 Neurodegenerative Control (ND) N = 61 Healthy Control		**ALS vs Control** ↑ *Bacteroides clarus* ↓ *Bifidobacterium longum*	None		(Nicholson et al., 2020)

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Table 4 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			↑ *Ruminoccous gnavus* ↑ *Veillonella parvula* ↓ *Lachnospiraceae* bacterium 3 1 57FAA CT1 ↓ *Lachnospiraceae* bacterium 1 1 57FAA ↓ *Lachnospiraceae* bacterium 5 1 63FAA ↓ *Parasutterella excrementihominis* ↓ *Roseburia hominis* ↓ *Burkholderiales* bacterium 1 1 47 ↓ *Oscillibacter*				
	16S (no)	N = 8 ALS N = 8 Control	None	None	None	No differential abundance testing	(Zhai et al., 2019a)
	16S (no)	N = 49 Motor Neuron Disease N = 51 Control	None	None	None		(Ngo et al., 2020)
	16S via 454 Pyrosequencing (no)	N = 25 ALS N = 32 Control	No differences in known microbes	None	None		(Brenner et al., 2018)
	qPCR (no)	N = 50 ALS N = 50 Control	**ALS vs Control** ↑ *Enterobacter* ↑ *Escherichia coli* ↓ *Clostridium*	None	None		(Mazzini et al., 2018)
	WGS (yes)	N = 31 PD N = 28 Control N = 76 PD	None	None	None		(Bedarf et al., 2017)
	16S (yes – extreme proportion of unmapped reads)	N = 21 idiopathic rapid eye movement sleep behaviour disorder N = 78 Control	None	None	None	Extreme proportion of unmapped reads	(Heintz-Buschart et al., 2018)
	16S (yes)	N = 64 PD N = 64 Control	None	None	**PD vs Control at Follow-up** ↑ p-Cresol **synthesis (effect = 0.45 [-2.03; 5.18])		(Aho et al., 2019)
	16S (yes)	N = 80 PD N = 72 Control	None	None	None		(Pietrucci et al., 2019)
	16S (yes)	N = 34 PD N = 25 Control	**PD with Low L-DOPA (<300 mg/day) dose vs Control** ↓ *Lactobacillus* (effect = 0.83 [-2.10; 8.07]		None		(Weis et al., 2019)
	16S (yes, large proportion of sequences could not be classified)	N = 45 PD N = 45 Control (spouses)	None	None	None		(Qian et al., 2018)
Parkinson's Disease	WGS (no)	N = 40 PD N = 40 Control (spouses)	**PD vs Control** ↑ *Alistipes* ↑ *Holdemania* ↑ *Streptococcus* ↑ *Gordonibacter* ↑ *Lactobacillus* ↑ *Enterobacter* *Streptococcus salivarius* negatively correlated to L-DOPA dose equivalency *Enterobacter cloacae* positively correlated with unified Parkinson's Disease rating scale	**PD vs Control** ↑ *Lactobacillus*	None		(Qian et al., 2020)
	16S (no)	N = 197 PD N = 130 Control	**PD vs Control (significant via Kruskal-Wallis and ANCOM after adjusting for covariates and COMT/AC)** ↑ *Bifidobacterium**** (Abundance: 0.0089 vs 0.0076) ↑ *Lactobacillus**** (Abundance: 0.0017 vs 0.0004)	**PD vs Control (significant via Kruskal-Wallis and ANCOM after adjusting for covariates and COMT/AC)** ↑ *Bifidobacterium**** (Abundance: 0.0089 vs 0.0076) ↑ *Lactobacillus****	None	Greengenes, Rarefaction, No direct comparison between individuals taking COMT/AC to those that aren't	(Hill-Burns et al., 2017)

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Table 4 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			↑ *Akkermansia*** (Abundance: 0.0476 vs 0.0185) ↓ *Roseburia* (OTU1)* (Abundance: 0.0073 vs 0.0125)	(Abundance: 0.0017 vs 0.0004)			
	16S (no)	N = 13 PD-MCI N = 13 PD with no MCI (PD-NC) N = 13 Control Spouses	GLMs incorporated sex, age, bMI, education **PD-MCI vs Control** ↓ *Alistipes**** ↓ Odoribacter*** ↓ *Barnesiella**** ↓ *Butyricomonasi**** **PD-MCI vs PD-NC** ↓ *Alistipes**** ↓ Odoribacter*** ↓ *Barnesiella**** ↓ *Butyricomonasi**** ↑ *Ruminococcus**** ↑ *Blautia**** **PD-NC vs Control** ↓ *Ruminococcus**** ↓ *Blautia****				(Ren et al., 2020)
	16S (no)	N = 666 Aged individuals	Motor deficits indicating subthreshold parkinsonism associated with ↓ *Odoribacter*			Associative study looking to identify prodromal markers for Parkinsonism	(Heinzel et al., 2020)
	16S (no)	N = 80 PD N = 77 Control	**PD vs Control after accounting for age, sex, diet** ↑ *Parabcteroides* ↓ *Prevotella* (reduced by 46.6%) **PD Tremor-Subtype vs PD Non-Tremor Subtype accounting for age, sex, diet** ↑ *Clostridium* ↑ *Akkermansia* ↓ *Propionibacterium* ↓ *Sutterella* ↓ *Desulfvibrioo* **Positive Correlations:** *Bacteroides* abundance and TNFα			Greengenes	(Lin et al., 2019)
	16S (no)	N = 89 PD N = 66 Control	**PD vs Control** ↑ *Lactobacillus**** ↑ *Bifidobacterium** ↓ *Faecalibacterium** ↓ *Prevotella** ↓ *Dorea****	**PD vs Control** ↑ *Lactobacillus**** ↑ *Bifidobacterium**			(Petrov et al., 2017)
	16S (no)	N = 29 PD N = 29 Control	None	None	None	No genus information reported	(Hopfner et al., 2017)
	16S (no)	N = 104 PD N = 96 Control	**PD vs Control** ↑ *Bacteroides fragilis* ↑ *Lactobacillus acidophilus* ↑ *Megasphaera* ↑ *Veillonella* ↑ *Coriobacteria* ↑ *Akkermansia muciniphilia* ↑ *Bifidobacterium bifidum BGN4* ↑ *Bacteroides fragilis NCTC 9343* ↑ *Clostridium saccharolyticum WM1* Reduction in all fecal acetate, butyrate and propionate in low cognitive scoring patients	**PD vs Control** ↑ *Bacteroides fragilis* ↑ *Lactobacillus acidophilus* ↑ *Bifidobacterium bifidum BGN4* ↑ *Bacteroides fragilis NCTC 9343* ↓ Bile acid degradation pathways			(Tan et al., 2020)

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Table 4 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
	16S (no)	N = 25 PD Sequenced at baseline, 1 year, 2 year and 3 year follow-up	↓ *Roseburia* linked to development of non-motor, severity of mnesic-attention disorders ↓ *Roseburia* and *Faecalibacterium* at baseline linked to faster cognitive decline ↑ *Oscillospira* at baseline linked to faster cognitive decline Results not significant after post-hoc correction			Greengenes, collection at -20C	(Cilia et al., 2020)
	16S (no)	N = 63 PD N = 63 Healthy spouses (HS) N = 74 Control	**PD vs Control** ↑ *Oscillospira**** ↑ *Akkermansia**** ↓ *Fusobacterium*** **PD vs HS** ↑ *Oscillospira**** ↑ *Akkermansia**** ↓ *Fusobacterium*** **Genera positively associated with disease stage and duration:** *Parabacteroides, Akkermansia, Coprococcus, Bilophila, Collinsella, Methanobrevibacter, Eggerthella, Adlercreutzia*	None	None		(Zhang et al., 2020a)
	16S (no)	N = 64 PD N = 51 Control	**PD vs Control** ↑ *Veillonella**** (mean difference = 1.556) ↓ *Blautia** (mean difference = -0.596) ↓ *Butyrivibrio*** (mean difference = -0.951) ↓ *Coprococcus** (mean difference = -0.873)	None	None	Greengenes	(Vascellari et al., 2020)
	16S (no)	N = 24 PD N = 14 Control	**PD vs Controls** ↑ *Enterococcus*** ↑ *Escherichia-Shigella** ↑ *Streptococcus*** ↑ *Proteus** ↓ *Blautia** ↓ *Faecalibacterium** ↓ *Ruminococcus**	**PD vs Controls** ↑ *Escherichia-Shigella***, ↑ *Enterococcus***	None	Rarefaction, 80 % confidence level for SILVA alignment	(Li et al., 2017)
	16S (no)	N = 75 PD N = 45 Control	None	None	None	Greengenes, rarefaction	(Lin et al., 2018)
	16S (no)	N = 10 PD N = 10 Control	**PD vs Controls** ↑ *Akkermansia,** ↑ *Parasutterella* * ↑ *Subdoligranulum** ↑ *Butyricimonas** ↓ *Clostridium** ↓ *Collinsella** ↓ *Bacteroides**	**PD vs Controls** ↓ *Bacteroides**	None	QIIME v1.8 (outdated since Jan 1, 2018), Greengenes	(Li et al., 2019b)
	16S (no)	N = 193 PD (de novo – 39, early – 57, mid-stage – 53, advanced – 44) N = 113 Control	**PD vs Control** ↑ *Bifidobacterium** ↓ *Roseburia** ↓ *Ruminococcus*** **Mid-Stage and Advanced PD vs Control** ↑ *Lactobacillus****	**PD vs Control** ↑ *Bifidobacterium** **Mid-Stage and Advanced PD vs Control** ↑ *Lactobacillus****	**PD vs Control** ↑ *Bifidobacterium**: GABA pathway **Mid-Stage and Advanced PD vs Control** ↑ *Lactobacillus****: GABA pathway	Greengenes	(Barichella et al., 2019)
	16S (no)	N = 197 PD N = 103 Control	**PD vs Control** ↑ *Bifidobacterium**** *(4.02 fold change)* ↓ *Roseburia**** *(0.71 fold change)* ↓ *Faecalibacterium prasunitzii**** *(0.75 fold change)*	**PD vs Control** ↑ *Bifidobacterium**** *(4.02 fold change)*	**PD vs Control** ↑ p-Cresol synthesis	Greengenes	(Cirstea et al., 2020)
	16S (no)	N = 9 PD N = 13 Control	**PD vs Control** ↑ *Akkermansia**	None	None	Qiime 1.8	(Vidal-Martinez et al., 2020)

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Table 4 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
	16S (no)	N = 34 PD N = 31 Control	**PD vs Control** ↑ *Bacteroides** ↑ *Oscillospira** ↑ *Akkermansia** ↓ *Blautia** ↓ *Coprococcus** ↓ *Dorea** ↓ *Roseburia**	**PD vs Control** ↑ *Bacteroides**	None	Rarefaction, compared raw # of sequences compared raw # of sequences	(Keshavarzian et al., 2015)
	16S (no)	N = 54 PD N = 34 Control Enema and Nutrition Intervention	None	None	None	No genus information reported	(Hegelmaier et al., 2020)
	16S via 454 Pyrosequencing (no)	N = 74 PD N = 75 Control	**PD (IBS+) vs PD (IBS-)** ↓ *Bacteroides* (LFC = -4.929) * ↓ *Prevotella* (LFC = -5.675) ***	**PD (IBS+) vs PD (IBS-)** ↓ *Bacteroides* (LFC = -4.929) *	None		(Mertsalmi et al., 2017)
	16S via 454 Pyrosequencing (no)	N = 72 PD N = 72 Control	None	None	None	No genus information reported	(Scheperjans et al., 2015)
	qPCR (no)	N = 45 PD N = 35 Control	**PD vs Control** ↑ *Lactobacillus* ↓ *Clostridium coccoides*** ↓ *Clostridium leptum** ↓ *Bacteroides fragilis**	**PD vs Control** ↑ *Lactobacillus* ↓ *Bacteroides fragilis**	None		(Hasegawa et al., 2015)
	qPCR (no)	N = 28 PD N = 17 Stable N = 11 Deteriorated	**Follow-up vs Baseline (All PD)** ↓ *Bifidobacterium* ↓ *Clostridium leptum* subgroup ↓ *Bacteroides fragilis* group ↓ *Atopobium* cluster ↓ *Enterococcus* ↓ *L. gasseri* subgroup ↓ *Lactobacillus reuteri* subgroup ↓ *Prevotella* **Follow-up vs Baseline (Stable)** ↓ *Bifidobacterium* ↓ *Clostridium leptum* subgroup ↓ *Bacteroides fragilis* group ↓ *Atopobium* cluster ↓ *Enterococcus* ↓ *Lactobacillus. gasseri* subgroup ↓ *Lactobacillus reuteri* subgroup **Follow-up vs Baseline (Deteriorated)** ↓ *Lactobacillus gasseri* subgroup	**Follow-up vs Baseline (All PD)** ↓ *Bifidobacterium* ↓ *Bacteroides fragilis* group ↓ *Lactobacillus gasseri* subgroup ↓ *Lactobacillus reuteri* subgroup **Follow-up vs Baseline (Stable)** ↓ *Bifidobacterium* ↓ *Bacteroides fragilis* group ↓ *Lactobacillus gasseri* subgroup ↓ *Lactobacillus reuteri* subgroup **Follow-up vs Baseline (Deteriorated)** ↓ *Lactobacillus gasseri* subgroup	None		(Minato et al., 2017)
	qPCR (no)	N = 19 PD with COMT inhibitor N = 14 PD without COMT inhibitor	**COMT inhibitor (Entacapone) vs No COMT Inhibitor** ↓ *Faecalibacterium prausnitzii* **COMT inhibitor (Entacapone) vs Other COMT Inhibitors** ↓ *Faecalibacterium prausnitzii*	None	None		(Grun et al., 2020)
	16S qPCR (no)	N = 34 PD N = 34 Control	**PD vs Age-Matched Control** ↑ *Bifidobacterium**** ↓ *Faecalibacterium prausnitzii* ↓ *Lactobacilli/ Enterococci**** ↓ Acetate** ↓ Butyrate** ↓ Propionate**	**PD vs Age-Matched Control** ↑ *Bifidobacterium**** ↓ *Lactobacilli/ Enterococci****	None		(Unger et al., 2016)

Legend: LFC: log-2 fold change; LC: log change; RA: relative abundance; DASS-42: Depression Anxiety Stress Scales; ADHD: Attention-Deficit Hyperactivity Disorder; HE: hepatic encephalopathy; FOS: Fructo-oligosaccharide; HADS-A: Hamilton Anxiety and Depression Scales – Anxiety Subscale; HADS-A: Hamilton Anxiety and

Depression Scales – Depression Subscale; RTT: Rett's Syndrome; AD: Alzheimer's Disease, PD: Parkinson's Disease; MCI: mild-cognitive impairment; MSA: multiple-systems atrophy; ALS: amyotrophic lateral sclerosis*: $p_{adj} < 0.1$; **: $p_{adj} < 0.01$; ***: $p_{adj} < 0.001$; Reanalysed studies are highlighted; 95 % CI reported between square brackets [lower 95 % CI; upper 95 % CI].

obese group (Farup and Valeur, 2018). In addition, other SCFA and tryptophan modulating microbes, *Faecalibacterium prausnitzii* and *Dorea* were positively associated with this measure (Farup and Valeur, 2018). Recent studies associate microbiome, brain connectivity and structure as well as food craving (Dong et al., 2020b, a). Another study finds alterations in aromatic amino acid metabolism in obesity impairing short-term memory (Arnoriaga-Rodríguez et al., 2020).

3.8.2. Anorexia nervosa

3.8.2.1. Studies where raw microbiome data was reanalysed.. Using the raw dataset from (Borgo et al., 2017), we were unable to find any significant differences in microbial abundance or GBMs between anorexic individuals and controls. Another dataset (see Table 8) with a higher sample size however, found increased abundance in isovaleric acid synthesis I ($p_{adj} < 0.1$; effect = 0.44, 95 % CI: [-2.80, 5.07]), quinolinic acid synthesis ($p_{adj} < 0.1$; effect = 0.48, 95 % CI: [-2.13, 5.35]), and quinolinic acid degradation ($p_{adj} < 0.01$; effect = 0.42, 95 % CI: [-2.33, 4.80]) (Mack et al., 2016). After gaining weight and subsequent release from the hospital, individuals with anorexia had a reduction in butyrate synthesis II compared to controls ($p_{adj} < 0.01$; effect = -0.43, 95 % CI: [-4.88, 2.55]) (Mack et al., 2016). Importantly, ClpB was also elevated at baseline admission, compared to controls ($p_{adj} < 0.1$; effect = 0.43, 95 % CI: [-2.30, 4.98]) (Mack et al., 2016).

3.8.2.2. Studies where raw microbiome data was not reanalysed.. There were no consistent findings across microbial genera in six other studies (Morkl et al., 2017; Morita et al., 2015; Kleiman et al., 2015; Armougom et al., 2009; Schulz et al., 2020; Monteleone et al., 2020) (see Table 8).

3.9. Neurovascular disease

3.9.1. Studies where raw microbiome data was not reanalysed

Many preclinical studies identified butyrate as a potential neuroprotective agent for ischemia (Akhoundzadeh et al., 2018; Lee et al., 2020; Sadler et al., 2020; Singh et al., 2018; Sun et al., 2016a). There are fewer studies assessing changes in the gut microbial composition responses to stroke in humans. One study compared the gut microbiota of infants who received hypothermia treatment for hypoxic ischemic encephalopathy (Watkins et al., 2017). Indeed compared to control infants, those undergoing treatment for ischemia showed a reduction of *Bacteroides* abundance (Watkins et al., 2017). Wang et al. (2018) assessed gut microbial composition in individuals after cerebral infarction but did not find any genus-level abundance changes compared to controls. The butyrate and tryptophan metabolism associated bacterial genera *Bacteroides, Parabacteroides, Akkermansia, Prevotella* and *Faecalibacterium* were reduced after cerebral infarction when compared to controls (Ji et al., 2017).

Studies where participants were stratified by type of stroke and stroke severity uncovered more compositional differences that may impact SCFA, bile acid and tryptophan metabolism. Liu et al. (2020a) found many such genera which were altered when comparing participants who suffered post-stroke cognitive impairment with controls. Another study compared individuals post-stroke with no cognitive impairment along with those co-morbid with depression and cognitive impairment, finding few differences (Ling et al., 2020a). Another study stratified individuals with ischemic stroke by severity and found *Enterobacter* was reduced in severe ischemic stroke compared to mild stroke. Across two different studies comparing ischemic stroke to controls, *Akkermansia* was differentially abundant (Ji et al., 2017; Li et al., 2019c). However, in one study it was more abundant in the ischemic stroke (Li et al., 2019c) while it was reduced in the other study, though it only two individuals in the ischemic stroke cohort (Ji et al., 2017).

Polster at al. (2020) found robust differences and correlations within a large sample (N = 122) of individuals with cavernous angioma using a combination of 16S and WGS techniques. Compared with controls from the human microbiome project, individuals in the disease group showed an increased abundance of *Bacteroides thetaomicron* and *Odoribacter sphlancus* along with a reduction in *Bifidobacterium adolescentis* and *Faecalibacterium prausnitzii* (Polster et al., 2020). They found evidence that these changes in abundance promoted gut inflammation and increased lipopolysaccharide (LPS) synthesis pathways (Polster, 2020). Indeed, this robust methodology even identified differentially abundant species by cavernous angioma subtype and severity (Polster et al., 2020). See Table 9 for more detail.

3.10. Stress and psychiatric disorders

3.10.1. Stress

3.10.1.1. Studies where raw microbiome data was not reanalysed.. The effect of stress on the human microbiota is difficult to study, often involving associating lifetime stress metrics with microbiota composition (see Table 10). One 16S sequencing study identified that pregnant women that experienced more than 2 adverse childhood events had an increased abundance of *Prevotella* (Hantsoo et al., 2019). Another study of 75 women with pregnancy-related anxiety was unable to find genus-level associations between maternal anxiety and the infant meconium (Hu et al., 2019a). Interestingly, Naude et al. (2020) found infants born to mothers exposed to intimate partner violence had an increased abundance of *Citrobacter* and *Weisella*. (Carson et al., 2018) showed that *Fusobacterium* abundance increased with stress in participants that identified as Black but not amongst other demographics, indicating host-mediated contributions to the microbiome stress responses.

Another strategy focused on providing probiotic interventions, later comparing microbiome and stress metrics between individuals receiving controls or a placebo. Of three such randomised control trials, two found genus-level associations with psychological stress measures (Nishida et al., 2017, 2019; Soldi et al., 2019). One study administered *Lactobacillus gasseri* CP2305 which reduced the magnitude of *Bifidobacterial* reduction after the stressor and increased faecal valerate concentrations (Nishida et al., 2019). Another study using the same probiotic intervention found different magnitudes of changes in the abundances of *Corynebacterium* in addition to improved sleep quality and a reduction in stress symptoms in female participants (Nishida et al., 2017).

3.10.2. Pos-ttraumatic stress disorder

3.10.2.1. Studies where raw microbiome data was not reanalysed.. Two studies assessed the impact of post-traumatic stress disorder on the gut microbiota. Hemmings et al. (2017) did not find any differentially abundant genera when using a trauma-exposed comparison group (does not meet threshold for post-traumatic stress disorder). Bajaj et al. (2019) used a conventional control cohort, finding differences even after accounting for hepatic encephalopathy. In individuals without hepatic encephalopthay, the post-traumatic stress disorder individuals showed

an increased abundance of *Streptococcus* and a reduction in *Acidaminococcus*, *Ruminococcus, Roseburia, Anaerostipes, Clostridium XIVA*a and *Pseudoflavonicbacter* compared to controls (Bajaj et al., 2019). In the subset of individuals with hepatic encephalopathy, post-traumatic stress disorder individuals only showed a reduction in *Subdoligranulum* (Bajaj et al., 2019).

3.10.3. Bipolar disorder

3.10.3.1. Studies where raw microbiome data was not reanalysed.. There were no consistent microbial changes observed across eleven 16S and WGS studies of bipolar disorder (see Table 10). In the two WGS studies, the SCFAs and tryptophan associated genera *Streptococcus, Clostridium, Oscillibacter* and *Bifidobacterum* were increased in bipolar individuals compared with controls (Rong et al., 2019; Lai et al., 2021). Due to differences in methodology and data analysis, other studies did not see these same differences in abundance. Evans et al. (2017) only reported reductions in *Facealibacterium* in bipolar individuals but did associate its abundance with sleep and depressive symptoms. Contrary to these findings, Painold et al. (2019) reported increased *Faecalibacterium* abundance in bipolar disorder. Two other studies noted increased abundance of *Bacteroides* in bipolar disorder but their other findings differed (Hu et al., 2019b; Zheng et al., 2020b). Interestingly, some of the studies did not find any genus-level differences in microbial composition (Coello et al., 2019; Vinberg et al., 2019; McIntyre et al., 2019). Coello et al. (2019) found that all the differences in abundance that they observed were explained by sex effects, heritability and smoking.

3.10.4. Depression and anxiety

3.10.4.1. Studies where raw microbiome data was not reanalysed.. Multiple studies have investigated the explanatory power of the gut microbiota in anxiety and depression (see Table 10). Only three 16S or WGS sequencing studies did not find any significant differences in major depressive disorder (MDD) compared to controls at the genus-level (Paulsen et al., 2017; Bharwani et al., 2020; Naseribafrouei et al., 2014). (Jiang et al., 2020) compared the gut microbiota of individuals currently undergoing a depressive episode to controls, finding increased abundance of *Akkermansia, Veillonella, Ruminococcus gnavus* and reductions in *Fusicatenibacter, Sutterella, Dialister*. A previous study (Jiang et al., 2015), reported a reduction in *Dialister* during active MDD. Other studies did not find any similarities with Jiang et al. (2020), thus it is unclear if the gut microbiota changes throughout depression or if these differences are a result of different methodologies.

Few other similarities in gut microbial signatures were reported across other studies. Two studies did report an increased abundance of the SCFA and tryptophan metabolism-associated microbe *Collinsella* in their respective depressed cohorts (Stevens et al., 2018; Zheng et al., 2016). Three studies also reported an increased abundance of *Blautia* in MDD (Huang et al., 2018; Jiang et al., 2015; Yang et al., 2020). When predicting clinical outcomes from baseline microbiome data, researchers did not find that the microbiota in MDD predicted clinical response (Liśkiewicz et al., 2021). Nonetheless, they did find *Paraprevotella* strongly correlated with the Hamilton Depression Rating Scale-24 Item metric (Liśkiewicz et al., 2021)

Madan et al. (2020) compared rates of remission in psychiatric inpatients and aimed to identify microbial genera that predicted readmission or remission from severe depression or anxiety. *Coprococcus catus* was associated with moderate anxiety at admission and was reduced in individuals that had lower rates of remission from anxiety or depression (Madan et al., 2020). Interestingly, the *Coprococcus* genera was found increased in the depressed cohort by Huang et al. (2018). Other studies did report however, a reduction in *Coprococcus* abundance in depression (Valles-Colomer et al., 2019; Liu et al., 2016).

Valles-Colomer et al. (2019) used compositional data methods as well as large cohorts in their study, where they found *Coprococcus* as well as *Faecalibacterium* associated with a higher quality of life and that *Dialister* and *Coprococcus* were depleted in depression. Interestingly, the *Dialister* finding is consistent with other studies (Jiang et al., 2015, 2020). Indeed, other studies also found negative correlations between *Facalibacterium* and anxiety or depression A recent systematic-review also found a reduction in SCFA-producing bacteria such as *Faecalibacterium* across studies of anxiety and depression (Simpson et al., 2020).

4. Discussion

4.1. Short-chain fatty acids (SCFAs) in brain health and disease

4.1.1. Biochemistry and function

SCFAs are molecules consisting of a 1–6 carbon chain with a carboxylic acid group (Dalile et al., 2019). Colonic bacterial fermentation of non-digestible, non-absorbable fibres (inulin, cellulose, wheat bran and resistant starches) produces SCFAs as a by-product (Cummings, 1981). The following genera commonly found in the gut are known to produce SCFAs: *Akkermansia, Bifidobacterium, Lactobacillus, Lactocaseibacillus, Ligilactobacillus, Ruminococcus, Ruminoclustridium, Blautia, Bacteroides, Roseburia, Prevotella, Eubacterium, Fusicatenibacter, Faecalibacterium, Enterococcus, Clostridium* and *Coprococcus* (Takada et al., 2013; Dalile et al., 2019; Joseph et al., 2017; Valles-Colomer et al., 2019; Basson et al., 2016; Zheng et al., 2020a). It is unclear how these genera impact the absorption of SCFAs in the colon (Ruppin et al., 1980) nor how GI absorption may differ between individuals independent of these microbes (Dalile et al., 2019). Other factors that may impact differences in SCFA circulating concentrations include host genetics, dietary intake and colonic absorption of SCFAs (Dalile et al., 2019).

SCFA production involves overlap with pyruvate metabolism and other molecules involved in the Krebs Cycle (see Fig. 1). The most abundant SCFAs in humans are acetate, butyrate and propionate (Dalile et al., 2019). They differ in their aliphatic tail length and the position of their carboxylic acid group (Dalile et al., 2019). These minor differences affect affinity and specificity to G-protein coupled receptors (GPCRs; (FFAR1, FFAR2, FFAR3, GPR109A, GPR164 and OR51E2)) (Dalile et al., 2019). SCFAs also act as histone deacetylase inhibitors in enteric neurons, enterochromaffin cells, and microglial cells (Stilling et al., 2016; Erny et al., 2015; Dalile et al., 2019; Woo and Alenghat, 2017; Yang et al., 2019). Through these mechanisms, SCFAs impact host physiology by driving the expansion of $FOXP3^{+}$ T_{reg} cells (Woo and Alenghat, 2017), or mediating the release of IL-6, IL-10 and IL-12, dendritic cells and macrophages, in turn driving T cell maturation (Woo and Alenghat, 2017).

Many SCFA-sensing GPCRs are located on enteric immune and neuronal cells (Nohr et al., 2013; De Vadder et al., 2014). In the millimolar concentration range butyrate depolarises enteric neurons (Neunlist et al., 1999), and reduces monocyte activation and mast cell degranulation (Digby et al., 2012; Diakos et al., 2006). Though a growing body of preclinical evidence suggests SCFAs are neuroactive metabolites influencing the brain and behaviour (Liu et al., 2020b; Sadler et al., 2020; van de Wouw et al., 2018; Lee et al., 2020), few clinical studies thus far have reported on these effects in humans. Some promising evidence shows that SCFA production correlates with health outcomes in humans. For example, increasing dietary-fibre intake from an average of 12.12 g daily to 37.10 g over the course of 84 days modulated clinically-relevant host outcomes in Type 2 Diabetes, including reducing the levels of haemoglobin A1C (Zhao et al., 2018).

4.1.2. Potential of SCFAs to cross the blood-brain barrier

To reach the brain, SCFAs must cross the intestinal epithelium through passive diffusion or via monocarboxylate transporters (MCT1, SMCT1) (Bergersen, 2015; Chiry et al., 2006), before passing through

Table 5
Microbiome-brain studies involving alcohol, nicotine and recreational drug use/addiction.

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
Alcohol Use and Dependence	16S (yes)	N = 15 Healthy participants, compared before and after acute binge	None	None	None	Binge is only 2 mL of vodka	(Stadlbauer et al., 2019)
	16S (yes)	N = 15 Alcohol-Dependent N = 15 Control	**Alcohol-Dependent vs Control** ↑ *Ruminoccocus 2** (effect = 0.72 [-2.91; 6.75]) ↓ *Ruminoclostridium 9**** (effect = -0.99 [-7.99; 1.00]) ↓ Tryptophan degradation* (effect = -0.46 [-5.78; 2.47])	None	**Alcohol-Dependent vs Control** ↑ GABA synthesis III* (effect = 0.52 [-1.99; 5.66]) ↓ g-Hydroxybutyric acid (GHB) degradation** (effect = -0.77 [-6.99; 1.27]) ↓ Dopamine degradation* (effect = -0.56 [-7.71; 1.95])		(Bjorkhaug et al., 2019)
	Shotgun (no - SOLiD platform)	N = 72 Alcohol dependence syndrome (ADS) N = 27 Alcoholic liver cirrhosis (ALC) N = 60 Control	**ADS vs Control** ↑ Lactococcus ↑ Lactobacillus salivarius ↑ Lactococcus lactis subsp. Cremoris ↓ *Prevotella* **ALC vs Control** ↑ Bifidobacterium (B. longum, dentium, and breve) ↑ Streptococcus (S. thermophilus and mutans) ↑ Lactobacillus species (L. salivarius, antri, and crispatus) ↓ Coprococcus	**ADS vs Control** ↑ *Lactobacillus salivarius* **ALC vs Control** ↑ *Bifidobacterium* (B. longum, dentium, and breve) ↑ *Lactobacillus* species (L. salivarius, antri, and crispatus)	None		(Dubinkina et al., 2017)
	16S (no)	N = 14 Non-Smoking, Non-Drinking N = 31 Smoking only N = 28 Drinking only N = 43 Smoking and Drinking	**Associations with Smoking and Drinking** *Bacteroides*** *Phascolarctobacterium** *Ruminococcus UCG-002*** *Ruminococcus UCG-003*** *Ruminoclostridium 9**** **Associations with Drinking Only** *Haemophilus**	**Associations with Smoking and Drinking** *Bacteroides***	None		(Lin et al., 2020)
	16S (no)	N = 212 twins pairs	**AUDIT score III (high alcohol consumption) vs Medium and Low Alcohol Consumption Groups** ↑ *Prevotella copri** ↑ *Megamonas**** (4 OTUS) ↓ *Blautia obeum** ↓ *Roseburia** *Roseburia* survived correction for heritability	None	None	Greengenes	(Seo et al., 2020)
	16S via 454 Pyrosequencing & qPCR (no)	N = 13 Alcohol Dependent (6 with high intestinal permeability (IP), 7 without) N = 15 Control	**High IP vs Low IP** ↓ *Ruminococcus* ↓ *Faecalibacterium* ↓ *Clostridium* ↓ *Bifidobacterium* spp. *Bifidobacterium* spp. and *Blautia* negatively correlated to IP **After 3 Weeks of Detoxification** ↑ *Bifidobacteria* spp., ↑ *Lactobacillus* spp.	**High IP vs Low IP** ↓ *Bifidobacterium* **After 3 Weeks of Detoxification** ↑ *Bifidobacteria* spp. ↑ *Lactobacillus* spp	None None		(Leclercq et al., 2014)

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Table 5 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			Alcoholic vs Control ↑ *Streptococcus* ↓ *Bacteroides* ↓ *Eubacterium* ↓ *Anaerostipes* **Alcoholic + Smoker vs Control Non-Smoker** ↑ *Streptococcus* ↓ *Bacteroides* ↓ *Eubacterium* ↓ *Anaerostipes* ↓ *Ruminococcus* **Alcohol + Non-Smoker vs Non-Smoker Control** ↓ *Bifidobacterium* ↓ *Anaerostipes* **Control Smoker vs Control Non-Smoker** ↓ *Faecalibacterium*	**Alcoholic vs Control** ↓ *Bacteroides* ↓ *Eubacterium* **Alcoholic + Smoker vs Control Non-Smoker** ↓ *Bacteroides* ↓ *Eubacterium* **Alcohol + Non-Smoker vs Non-Smoker Control** ↓ *Bifidobacterium*			
	16S via 454 Pyrosequencings (no)	N = 16 Alcohol Dependent N = 48 Control					(Tsuruya et al., 2016)
	16S rRNA for *Proteobacteria* and *Faecalibacterium* (no)	N = 28 Alcohol Overconsumption N = 25 Control	None	None	None	No associations found	(Bjorkhaug et al., 2020)
Opioids	16S (yes)	N = 99 High-disease burden/ opioid use men	None	None	None		(Barengolts et al., 2018)
	16S (yes)	N = 10 Electronic Cigarette N = 10 Tobacco N = 10 Control	**Tobbacco Smoker vs Non-Smoker** ↑ Tryptophan Degradation* (effect = 0.84 [-0.97; 8.52]) ↑ Propionate Synthesis III* (effect = 0.94 [-0.90; 7.52]) ↓ Propionate Synthesis II* (effect = - 0.80 [9.86; 1.45])	None	**Tobbacco Smoker vs Non-Smoker** ↓17-beta-Estradiol degradation* (effect = - 0.74 [9.90; 1.19])		(Stewart et al., 2018)
Nictoine/ Tobacco/ Smoking	WGS (no)	N = 21 Smokers with Crohn's Disease N = 21 Smokers without Crohn's Disease	None	None	None	No non-smoking controls	(Opstelten et al., 2016)
	454 Pyrosequencing (no)	N = 5 Continuing Smokers N = 5 Non-Smokers N = 10 Undergoing smoking cessation	None	None	None	Lack of genus-level resolution	(Biedermann et al., 2013)
	qPCR (no)	N = 14 Smokers N = 6 Non-Smokers	**Smokers vs Non-Smokers** ↓ *Bifidobacterium**				(Ishaq et al., 2017)
	Fluorescence in-situ hybridization (no)	N = 101 with Crohn's (29 smokers) N = 58 Control (8 smokers)	None	None	None	Lack of genera level resolution	(Benjamin et al., 2011)
Recreational Drug Use	16S (no)	N = 37 at two timepoints (HIV + cohort)	↓ *Ruminococcus2* with methamphetamines, prescription drug use ↑ *Ruminoccus2* with synthetic drugs, 'poppers' use	None	None	Rarefaction	(Fulcher et al., 2018)
	16S (no)	N = 48 Users N = 45 Control	No significance after controlling for sex and age				(Xu et al., 2017)
	16S (no)	N = 20 Marijuana users N = 19 Control	*Prevotella* abundance associated positively with cognitive function in users				(Panee et al., 2018)

Legend: LFC: log-2 fold change; LC: log change; RA: relative abundance; DASS-42: Depression Anxiety Stress Scales; ADHD: Attention-Deficit Hyperactivity Disorder; HE: hepatic encephalopathy; FOS: Fructo-oligosaccharide; HADS-A: Hamilton Anxiety and Depression Scales – Anxiety Subscale; HADS-A: Hamilton Anxiety and Depression Scales – Depression Subscale; RTT: Rett's Syndrome; AD: Alzheimer's Disease, PD: Parkinson's Disease; MCI: mild-cognitive impairment; MSA: multiple-systems atrophy; ALS: amyotrophic lateral sclerosis*: $p_{adj} < 0.1$; **: $p_{adj} < 0.01$; ***: $p_{adj} < 0.001$; Reanalysed studies are highlighted; 95 % CI reported between square brackets [lower 95 % CI; upper 95 % CI].

Table 6
Microbiome-brain studies involving demyelinating disease.

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
Multiple Sclerosis and Other Demyelinating Conditions	16S (yes)	N = 60 MS N = 43 Control	None	None	None		(Jangi et al., 2016)
	16S (yes)	N = 84 NMOSD N = 54 Control	**NMOSD vs Control** ↑ *Streptococcus* (effect = -0.74 [-6.40; 1.63])*** ↓ Faecal SCFAs Acetate and butyrate negatively associated with severity				(Gong et al., 2019)
	16S via 454 Pyrosecuencing (yes)	N = 40 Controls N = 40 MS	None	None	**MS vs Control** ↓ GABA Degradation* (effect = -0.61 [-2.24, 8.46]) ↑ p-Cresol Synthesis* (effect = -0.54 [-2.07, 8.10])		(Miyake et al., 2015)
	WGS (no)	N = 26 MS N = 77 Control	**MS vs Control** ↑ *Sutterella* sp.** (effect = 2.73) ↓ *Gemella morbillorum*** (effect = −0.95)	None	None		(Kishikawa et al., 2020)
	WGS and 16S (no)	N = 34 Discordant twin pairs	None	None	None		(Berer et al., 2017)
	WGS and 16S (no)	Caucasion N = 15 MS N = 15 Control Hispanic N = 16 MS N = 15 Control African American N = 14 MS N = 14 Control	**Caucasian: MS vs Control** ↑ *Akkermansia* ↑ *Clostridium* **Hispanic: MS vs Control** ↑ *Blautia* ↑ *Clostridium* ↑ *Dorea* ↑ *Holdemania* ↓ *Dialister* ↓ *Prevotella* **African American: MS vs Control** ↑ *Clostridium*				(Ventura et al., 2019)
	16S (no)	N = 22 MS N = 33 Control	**MS vs Control** ↑ *Blautia* ↑ *Flavonifractor* ↓ *Faecalibacterium* ↓ *Roseburia* ↓ *Haemophilus* ↓ *Bilophila* ↓ *Dorea* ↓ *Butyricicoccus* ↓ *Gemella* ↓ *Clostridium* XIVb			Greengenes	(Ling et al., 2020b)
	16S (no)	N = 26 Relapse-Remitting MS (RRMS) N = 12 Secondary Progressive MS (SPMS) N = 38 Control	**MS vs Control** ↑ *Akkermansia* ↑ *Collinsella* ↑ *Eubacterium* ↓ *Parabacteroides* ↓ *Roseburia* ↓ *Coprococcus* ↓ *Blautia* **SPMS vs Control** ↑ *Akkermansia* ↑ *Collinsella* ↓ *Roseburia* ↓ *Coprococcus* ↓ *Blautia* ↓ *Dorea* **RRMS vs Control** ↑ *Streptococcus* ↓ *Roseburia* ↓ *Coprococcus* ↓ *Blautia* ↓ *Lachnospira*	**MS vs Control** Increased serum intestinal-fatty acid binding protein correlated with *Parabacteroides*			(Saresella et al., 2020)

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Table 6 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			↓ *Ruminococcus* ↓ *Parabacteroides*				
	16S (no)	N = 98 MS N = 120 Control	**MS vs Control** ↓ *Alistipes* (Effect = -0.18)* ↓ *Anaerotruncus* (Effect = -0.16)* ↓ *Butyricoccus* (Effect = -0.24)** ↓ *Clostridium* cluster IV (Effect = -0.35)*** ↓ *Gemmiger* (Effect = -0.30)*** ↓ *Lactobacillus* cluster IV (Effect = -0.18)* ↓ *Methanobrevibacter* (Effect = -0.20)* ↓ *Olsonella* (Effect = -0.19)* ↓ *Parabacteroides* (Effect = -0.15)* ↓ *Roseburia* (Effect = -0.17)* ↓ *Ruminococcus* (Effect = -0.17)* ↓ *Sporobacter* (Effect = -0.39)*** Many differences within clinical subtypes : *Butyricoccus, Clostridium* cluster IV and XCIII, *Gemmiger, Methanobrevibacter, Parabacteroides, Sporobacter*	**MS vs Control** ↓ *Lactobacillus* cluster IV (Effect = -0.18)*			(Reynders et al., 2020)
	16S (no)	N = 17 Pediatric MS	None	None	None	Greengenes, no genus-level associations reported	(Tremlett et al., 2016a)
	16S (no)	N = 18 Pediatric MS N = 17 Control	**MS vs Control** ↑ *Bilophila*** (FC = 3 [2.9; 3.2]) ↑ *Bifidobacterium*** (FC = 4.2 [3.9; 4.5]) ↑ *Desulfovibrio*** (FC = 5.1 [4.7; 5.7]) ↑ *Prevotella copri*** (FC = 5 [4.4; 5.6])	None	None		(Tremlett et al., 2016c)
	16S (no)	N = 15 Pediatric Relapse-Remitting MS N = 9 Control	None	None	None	No genus-level changes reported	(Tremlett et al., 2016b)
	16S (no)	N = 15 Primary Progressive MS N = 15 Control	**MS vs Control** ↑ *Gemmiger*	None	None		(Kozhieva et al., 2019)
	16S (no)	N = 17 Pediatric MS	None	None	None	No genus-level differences reported	(Nourbakhsh et al., 2018)
	16S (no)	N = 9 Relapsing-Remitting MS N = 13 Control Given VSL-3 probioticcs	VSL3 Administration associated with ↑ *Lactobacillus, Streptococcus, Bifidobacterium*			Greengenes	(Tankou et al., 2018)
	16S (no)	N = 8 MS No Fasting N = 8 MS With Fasting Intermittent fasting (IF) pilot	None	None	None		(Cignarella et al., 2018)
	16S (no)	N = 34 relapsing-remitting MS N = 33 Neuromyelitis optica spectrumdisorder (NMOSD) N = 34 Control	**MS vs Control** ↑ *Streptococcus* ↓ *Faecalibacterium* ↓ *Prevotella 9* ↓ Faecal acetate*** ↓ Faecal butyrate* ↓ Faecal propionate***	None	None		(Zeng et al., 2019)

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Table 6 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			NMOSD vs MS ↑ *Prevotella 9* ↓ Faecal acetate*** ↓ Faecal butyrate*** **NMOSD vs Control** ↓ Faecal acetate*** ↓ Faecal propionate*** ↓ Faecal butyrate***				
	16S (no)	N = 27 MS treated with dimethyl fumarate N = 9 MS treated with other therapy 12 week treatment	None	None	None	No genus-level differences reported	(Storm-Larsen et al., 2019)
	16S (no)	N = 10 MS on high-vegetable/low protein diet (HV/LP) N = 10 MS on Western Diet (WD) Faecal samples collected at baseline and after 12 months	None	None	None	Greengenes, genus-level differences not reporter	(Saresella et al., 2017)
	16S via Pyrosequencing (no)	N = 13 MS N = 13 Neuro-Behçet Disease (NBD) N = 14 Control	**MS vs Control** ↑ *Coproccocus*** (LFC = 9.3) ↑ *Ruminococcus 2*** (LFC = 11.79) ↑ *Butyricoccus*** (LFC = 8.41) ↑ *Clostridium* XVIII** (LFC = 12.07) ↑ *Dorea** (LFC = 3.60) ↑ *Escherichia/Shigella** (LFC = 5.85) ↑ *Parabacteroides** (LFC = 7.05) ↑ *Gemmiger** (LFC = 4.43) ↓ *Succinivibrio** (LFC = 0.03) ↓ *Prevotella** (LFC = 0.12) **NBD vs HC** ↑ *Parabacteroides*** (LFC = 11.4) ↓ *Vampirovibrio** (LFC = 0.03) **NBD vs MS** ↑ *Butyricomonasi*** (LFC = 32.29) ↓ *Erysipelotichaceae incertae sedis** (LFC = 0.09)	None	None		(Oezguen et al., 2019)
	Phylochip (no)	N = 8 Controls N = 7 MS (2 untreated) Measured change in RA after Vitamin D supplementation	**MS Untreated vs Control** ↑ *Akkermansia* ↑ *Faecalibacterium* ↑ *Coproccus*	None	None	Exploratory study	(Cantarel et al., 2015)
	Phylochip (no)	N = 16 NMOSD N = 16 MS N = 16 Control	**NMOSD vs Control** ↑ *Clostridium perfingensr**** ↑ *Coprococcus**** ↑ *Corynebacterium**** ↑ *Ruminoococcus**** ↑ *Trepenomaoe**** ↑ *Bacteroides**** ↑ *Blautia producta**** ↓ *Prevotella****	**NMOSD vs Control** ↑ *Bacteroides****	None		(Cree et al., 2016)
	FISH (no)	N = 25 MS (10 on ketogenic diet for 6 months) N = 14 Control	None	None	None		(Swidsinski et al., 2017)

Legend: LFC: log-2 fold change; LC: log change; RA: relative abundance; DASS-42: Depression Anxiety Stress Scales; ADHD: Attention-Deficit Hyperactivity Disorder; HE: hepatic encephalopathy; FOS: Fructo-oligosaccharide; HADS-A: Hamilton Anxiety and Depression Scales – Anxiety Subscale; HADS-A: Hamilton Anxiety and Depression Scales – Depression Subscale; RTT: Rett's Syndrome; AD: Alzheimer's Disease, PD: Parkinson's Disease; MCI: mild-cognitive impairment; MSA: multiple-

systems atrophy; ALS: amyotrophic lateral sclerosis; NMOSD: neuromyelitis optica spectrum disorder*: $p_{adj} < 0.1$; **: $p_{adj} < 0.01$; ***: $p_{adj} < 0.001$; Reanalysed studies are highlighted; 95 % CI reported between square brackets [lower 95 % CI; upper 95 % CI].

the hepatic circulation without being completely depleted by hepatic enzymes (Stilling et al., 2016). In recently-deceased or fasting individuals, researchers found SCFAs in peripheral circulation were depleted to around 20 % after passing through hepatic circulation (Stilling et al., 2016; Cummings and Macfarlane, 1997; Peters et al., 1992; Hamer et al., 2008).

SCFAs are transported across the blood-brain barrier by MCT1 or SMCT1, but it is unclear if they reach a relevant physiological concentration in the brain (Bergersen, 2015; Chiry et al., 2006). One human study used PET in vivo imaging to microbially-produced acetate from the colon reached the hypothalamus to regulate satiety signalling (Frost et al., 2014). In addition, butyrate is involved in mediating the integrity and permeability of the blood-brain barrier by increasing occludin expression in preclinical models (Braniste et al., 2014; Li et al., 2016; Sun et al., 2016a, b). Meanwhile, in vitro studies show that propionate can act on GPCR receptors at 1μM to promote neuroprotective pathways (Hoyles et al., 2018). The human metabolomic database assessed concentrations of SCFAs in the cerebrospinal fluid, finding ranges of 0–171 μM for acetate, 0–6 μM for propionate and 0–2.8 μM for butyrate (Wishart et al., 2018). An older study performed gas chromatography on human brains, finding higher SCFA concentrations than the metabolomics study found in the cerebrospinal fluid (Bachmann et al., 1979). These studies are not conclusive but suggest that SCFAs do enter the brain. It is unknown if these SCFA levels induce effects on circumventricular organs such as the hypothalamus.

4.2. Tryptophan pathway metabolites

4.2.1. Biochemistry and function of bacterially-produced indoles

The gut microbiota can generate and modify neurotransmitters as well as their precursors, including serotonin and tryptophan (see Gheorghe et al. (2019), (Lee et al., 2015) for review). The potential for gastrointestinal microbes to metabolise tryptophan and its various metabolites was first characterised in the 1970s (Allison et al., 1974; Whitt and Demoss, 1975). In the decades since, metabolites exclusively produced by microbial enzymes communicate with the host, called indoles were functionally characterised (Lee et al., 2015; O'Mahony et al., 2015). While indoles are commonly produced by pathogenic strains of bacteria to improve their survival, they are also present in a symbiotic ecosystem (Lee et al., 2015). While the neurotransmitter serotonin is produced from the dietary-derived essential amino acid tryptophan (Reigstad et al., 2015), indoles are produced by the breakdown of tryptophan using the bacterial enzyme tryptophanase (Lee et al., 2015).

Many of the bacterial strains capable of expressing tryptophanase are also involved in the other tryptophan metabolic pathways described below. These genera include *Bacteroides, Butyrivibrio, Clostridium, Enterococcus, Escherichia, Eubacterium, Haemophilus, Fusobacterium, Peptostreptococcus, Bifidobacterium, Parabacteroides, Megamonas, Anaerostipes, Ruminococcus* (Roager and Licht, 2018; Valles-Colomer et al., 2019; O'Mahony et al., 2015).

Indoles are present in the high nanomolar to low millimolar range in the colon (Bansal et al., 2010; Karlin et al., 1985). These metabolites, produced by the enzyme tryptophanase, signal with human intestinal epithelial cells in the millimolar concentration range, increasing tight junction resistance and mucin production (Bansal et al., 2010; Karlin et al., 1985). Indole metabolites also regulate enteric neuronal signalling and motility in the myenteric plexus through the aryl-hydrocarbon receptor (Obata et al., 2020). In the brain, indoles act on this same receptor in the CNS astrocytes to regulate inflammation and immunity (Rothhammer et al., 2016, 2018).

4.2.2. Biochemistry and function of serotonin

Microbial tryptophan metabolism regulates bioavailability of precursors required for host serotonin (5-HT) production (Kennedy et al., 2017; Yano et al., 2015). To produce 5-HT, tryptophan hydroxylase converts tryptophan into 5-hydroxytryptophan, which then requires an enzymatic decarboxylation reaction to form 5-HT (Gheorghe et al., 2019; Kennedy et al., 2017). 5-HT is important for gastrointestinal motility, absorption and secretion tract (Kennedy et al., 2017). Around 95 % of 5-HT is produced by the enterochromaffin cells in the gut and secreted into the lumen in response to different stimuli (Kuo et al., 2002; Gershon and Tack, 2007). The enterochromaffin cells can uptake tryptophan or 5-hydroxytryptophan and generate serotonin via tryptophan hydroxylase (Kuo et al., 2002; Gershon and Tack, 2007). In disorders such as ulcerative colitis or IBS, tryptophan hydroxylase 1 mRNA, serotonin transporter mRNA and serotonin transporter expression were markedly reduced (Coates et al., 2004). There is also cross-talk with SCFAs which modulate the expression of serotonin production within enterochromaffin cells by promoting tryptophan hydroxylase 1 gene expression (Reigstad et al., 2015).

The serotonergic system within the brain is involved in regulating cognition, mood and behaviour, and is dysfunctional in depression, anxiety and other neuropsychiatric disorders (Jacobs and Azmitia, 1992; Gheorghe et al., 2019).

4.2.3. Biochemistry and function of other tryptophan catabolites

Tryptophan is degraded in the colon and throughout the rest of the body by the ubiquitously expressed indoleamine-2,3-dioxygenase (IDO1) or tryptophan-2,3-dioxygenase in the liver (TDO2) (Seifert, 1993; Ruddick et al., 2006). The expression of these enzymes is increased past homeostatic levels by stress-released cytokines and elevated levels of glucocorticoids, toll-like-receptor activation or aryl hydrocarbon receptor activation (Morris et al., 2017; Maes et al., 2011; Schrocksnadel et al., 2006; Kennedy et al., 2017). This increases the presence of downstream catabolites including quinolinic acid and kynurenic acid, which act within the CNS or the enteric nervous system (ENS) (Morris et al., 2017; Maes et al., 2011; Schrocksnadel et al., 2006; Kennedy et al., 2017).

Kynurenic acid is a GPR35 agonist in the gastrointestinal tract and in mononuclear immune cells in the ENS (Wang et al., 2006) and provides neuroprotection in the CNS as an antagonist of the N-methyl-D-aspartate (NMDA) receptor and the α-7-nicotinic receptor (Foster et al., 1984; Hilmas et al., 2001). Quinolinic acid on the other hand exerts agonistic excitotoxic activity in the CNS through activation of the NMDA receptor (Foster et al., 1984).

Interestingly, in a recent a double-blind randomised placebo-controlled trial in humans it was found that probiotic supplementation with *L. plantarum* 299v altered kynurenine metabolites and improved cognition measures in individuals with major depressive disorder. However, the microbiota compositional changes were not characterised in this trial (Rudzki et al., 2019). It could be hypothesised that the changes introduced into the gut microbial ecosystem sufficiently altered the expression of hepatic TDO2, indirectly influencing peripheral tryptophan metabolism.

4.2.4. Transport into the brain

Tryptophan is absorbed in the small intestine and transported into peripheral circulation and can be catabolised by IDO1 throughout the body or TDO2 in the liver (Seifert, 1993; Kennedy et al., 2017). Remaining tryptophan is transported across the blood-brain barrier via the large neutral amino acid transporter, where it can be converted to 5-HT or kynurenine catabolites (Ruddick et al., 2006). Kynurenic acid

and quinolinic acid cannot cross the blood-brain barrier but other catabolites such as indoles and kynurenine have been detected in the brain (Morris et al., 2017; Maes et al., 2011; Schrocksnadel et al., 2006; Kennedy et al., 2017; Gheorghe et al., 2019). Serotonin transporters in the brain can mediate the reuptake of excess 5-HT at the synaptic cleft, and is a common target of pharmaceutical interventions for depression and anxiety (Schwarcz et al., 2012).

4.2.5. Bile acids and the brain

Bile acids are molecules synthesised from cholesterol in the liver, characterised by amphipathic steroidal functional groups (Mertens et al., 2017; Kiriyama and Nochi, 2019). They play crucial roles facilitating the digestion and absorption of dietary lipids and fat-soluble vitamins (Mertens et al., 2017; Kiriyama and Nochi, 2019; Enright et al., 2018). Most bile acids are generated through the hydroxylation reaction by CYP7A1, while the rest are synthesised via the alternative pathway involving the liver enzymes CYP271 and CYPB1 (Enright et al., 2018). In the mouse, the expression of these three enzymes is mediated by the host microbiota (Sayin et al., 2013). Shortly after they are generated in the liver, the bile acids are conjugated with taurine or glycine before being transported for storage in the gall bladder (Dawson and Karpen, 2015; Long et al., 2017). Once released to aid in the digestion and absorption of lipids, they travel through the gastrointestinal tract and can be deconjugated and bio transformed by gut microbes where they can be absorbed into peripheral circulation (Enright et al., 2017). These bile acids are also involved in cellular signalling, particularly as ligands for nuclear receptors and various transmembrane surface receptors (Mertens et al., 2017; Kiriyama and Nochi, 2019).

Bile salt hydrolases, enzymes produced by members of the mammalian gut microbiota, deconjugate bile acids (Long et al., 2017) (Fig. 1). Currently, these genera are known to produce this enzyme: *Bacteroides, Clostridium* cluster VIA, *Lactobacillus, Bifidobacterium, Eubacterium* (Molinero et al., 2019). In the gut, the primary bile acid deoxycholic acid, can inhibit colonic motility through the GpBAR1 (TGR5) receptor on enteric neurons (Sun et al., 2004a, b; Poole et al., 2010). Disruptions and alterations in the gut microbiota contribute to bile acid dysregulation in the BTBR mouse model of autism-like behaviour (Golubeva et al., 2017). It is unclear how these gut microbial and bile acid changes relate to the behaviour in this model.

Conjugated and unconjugated bile acids, as well as taurine or glycine alone are potential neuroactive ligands in humans (Mertens et al., 2017; MahmoudianDehkordi et al., 2019). Taurine is thought to be neuroprotective as it functions as an agonist of glycine, $GABA_A$ and $GABA_B$ receptors in the brain (Albrecht and Schousboe, 2005; Boldyrev et al., 1999; Choe et al., 2012; Hilgier et al., 2005; El Idrissi and Trenkner, 1999; Beetsch and Olson, 1998). It is unknown how much taurine is transported into the brain and if it is sufficient for signalling (Albrecht and Schousboe, 2005). Recently (Sharon et al., 2019a) showed that offspring of mice colonised with a human autism faecal microbiota produced less taurine than offspring of controls colonised with a neurotypical faecal microbiota. These mice were impaired in their social behaviours, suggesting a gut-brain connection is involved in these behaviours (Sharon et al., 2019a). Indeed, when they supplemented BTBR mice with taurine, characterised as socially-impaired, researchers could rescue these deficits (Sharon et al., 2019b)

Recently, a large multicentre metabolomics study of 1464 total participants found that the bacterially produced deoxycholic acid, as well as its glycine and taurine conjugated forms were increased in the serum metabolome of individuals with AD (MahmoudianDehkordi et al., 2019), suggesting increased 7α-dehydroxylation of cholic acid by the gut microbiota, as these metabolites cannot be produced by the host. Importantly, deoxycholic acid was also associated with cognitive decline, providing human evidence of a link between microbial bile acid metabolism and mental health (MahmoudianDehkordi et al., 2019).

4.3. Sequencing and software

4.3.1. Sample preparation and sequencing technology

There is great heterogeneity in sequencing preparation, sequencing strategy and downstream bioinformatics analysis despite multiple studies identifying a clear need and multiple efforts for standardisation of these protocols (Fouhy et al., 2016; Clooney et al., 2016; Pollock et al., 2018; Aigrain et al., 2016; McLaren et al., 2019; Hogue et al., 2019; Santiago et al., 2014; Cardona et al., 2012).

Even before a sample is sequenced many factors influence the microbial community within it. Many studies reported a bias in different DNA extraction protocols biasing towards gram-positive or gram-negative bacteria (Watson et al., 2019), delivery-conditions and speed of the faecal sample and library preparation (Yeoh et al., 2019), fractional subsampling of faecal material (Yeoh et al., 2019), and storage (Panek et al., 2018; Chen et al., 2020a; Neuberger-Castillo et al., 2020; Carruthers et al., 2019).

Early microbiome studies used real time quantitative PCR (RT-qPCR) based techniques to amplify bacterial specific sequences from stool samples for species and genera-level identification. Other techniques hybridised fluorescent primers to these sequences for quantification or used terminal-restriction fragment length polymorphism analysis. These preliminary methods did not produce high-throughput, high coverage outputs and only describe the abundance of a few specific genera. There are indeed considerations in terms of bacterial load that could not have been addressed in these studies, making it difficult to draw robust conclusions about overall abundance without a clear picture of the entire microbiome (Vandeputte et al., 2017). With the decline in cost of sequencing, most high-throughput microarray-based technologies were replaced with next-generation sequencing (NGS), also known as high-throughput sequencing. NGS emerged as a method that provided untargeted information about the community as well as more reads and coverage (Bonk et al., 2018).

One method of sequencing the faecal microbiota involves the amplification of the hypervariable regions of bacterial 16S rRNA gene, found within the DNA of all bacteria. However, there is no universal consensus for selecting a hypervariable region to amplify despite substantial evidence showing its impact on the abundances of different detected taxa within a sample (Clooney et al., 2016; Kumar et al., 2011). The metagenomic GC content also biases the amplification process resulting in a decreased abundance of microbial taxa with higher GC content (Laursen et al., 2017). In addition, there is no consensus for determining when single-end sequencing preparation is adequate and when paired-end sequencing methods must be used. While single-end reads often provide more coverage, paired-end reads provide more phylogenetic resolution (Werner et al., 2012; Chen et al., 2018).

When using a 16S rRNA gene based sequencing platform, there is great variation between different technological platforms such as 454 Roche Pyrosequencing, Illumina HiSeq and Illumina MiSeq (Clooney et al., 2016; Fouhy et al., 2016; Degnan and Ochman, 2012). Newer Illumina-based platforms improve coverage while reducing costs, predominantly replacing the use of 454 Roche Pyrosequencing (Degnan and Ochman, 2012). While 16S rRNA gene-base sequencing methods can accurately-identify taxa with genus-level resolution, WGS is required for quality species, strain and substrain identification in faecal samples. In addition, they identify previously uncultured bacteria and their genes. Since WGS amplifies all metagenomic information within a sample, it provides a more accurate view of the community composition and diversity while also providing functional information; however, preferably amplified fragments lead to overestimation in abundance of certain microbes (Clooney et al., 2016; Ranjan et al., 2016; Tessler et al., 2017). The currently most commonly-used platforms involve the use of Illumina sequencers; however, studies have not compared different WGS methods with each other.

Table 7
Microbiome-brain studies involving pain-related disorders.

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
Fibromyalgia	16S (yes)	N = 77 Fibromyalgia N = 79 Total Controls N = 11 First-Degree Relatives (Control) N = 20 Household Members of Patients (controls) N = 48 Unrelated control	**Fibromyalgia vs Same Household Address as Patient** ↑*Sutterella* (effect = 0.66 [-0.43; 0.92])* **Fibromyalgia vs Unrelated Control** ↑ Serum butyrate ↓ Serum propionate ↓ Serum isobutyrate				(Minerbi et al., 2019)
	16S (yes)	N = 105 Fibromyalgia N = 54 Control	None	None	None		(Clos-Garcia et al., 2019)
	WGS (no)	N = 77 Fibromyalgia N = 79 Total Control N = 11 First-Degree Relatives (Control) N = 20 Household Members of Patients (controls) N = 48 Unrelated Control	**Fibromyalgia vs Unrelated Control** ↑ *Parabacteroides merdae* ↑ *Clostridium scindens* ↑ *Blautia hydrogentrophica* ↑ *Eisenbergella massiliensis* ↑ *Hungatella hathewayi* ↑ *Alistipes oderdonkii* ↑ *Blautia massilensis* ↑ *Butyricoccus desmolans* ↑ *Flavonifractor plautii* ↓ *Faecalibacterium prausnitzii* ↓ *Blautia faecis* ↓ *Haemophilus parainfluenzae* ↓ *Prevotella copri* ↓ *Bacteroides uniformis* ↑ Serum butyrate ↓ Serum propionate ↓ Serum isobutyrate				(Minerbi et al., 2019)
Irritable Bowel Syndrome (IBS)	16S (no)	N = 48 with IBS	↑ *Bacteroides* with higher perceived stress None		None	No control group, rarefaction	(Peter et al., 2018a)
	16S (no)	N = 38 IBS; Samples taken before and after gut-directed hypnotherapy	None	None	None	No hypnotherapy control, rarefaction	(Peter et al., 2018b)
	16S (no)	N = 11 Abdominal pain after flood disaster; received *B. infantis* M-63 N = 20 Control	**Probiotic vs Control** Improved anxiety score, mental component of QoL			Greengenes; genus-level differences not reported	(Ma et al., 2019b)
	16S (no)	N = 211 Flood Survivors (80 with abdominal pain, 131 without) Subset of 72 consented to faecal samples	**Abdominal Pain vs No Pain** ↑ *Staphylococcus* ↑ *Megamonas* ↑ *Fusobacterium* **IBS vs No IBS** ↑ *Paraprevotella* No genus-level differences for anxiety found				(Yusof et al., 2017)
	16S (no)	N = 10 IBS, sampled at 0, 4, 12 weeks after FMT	**Donor for Responder vs Non-Responder** ↑ *Bifidobacterium* No community change detected in responders or non-responders Reduction in HAM-A anxiety after 12 weeks in responders			Prospective trial	(Mizuno et al., 2017)
	16S (no)	N = 37 IBS N = 20 Age and Sex-Matched Control	**IBS vs Control** ↑ *Bifidobacterium adolescentis**** ↑ *Dialister**** ↑ *Papilibacter**** ↑ *Dorea**** ↑ *Blautia**** ↑ *Sporobacter**** ↑ *Escherichia**** ↓ *Odoribacter**** ↓ *Alistipes**** ↓ *Bacteroides**** No genera level	**IBS vs Control** ↑ *Bifidobacterium adolescentis**** ↓ *Bacteroides****			(Jeffery et al., 2012)

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Table 7 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			associations with anxiety or depression				
	16S (no)	N = 17 IBS, sampled at 0, 1, 2, 4 weeks after FMT	**Baseline: HAM-D > = 8 vs HAM-D <8** ↓ *Eubacterium* **Week 4 vs Baseline HAM-D > = 8** ↑ *Eubacterium* **HAM-D Responders vs Non-Responders :** ↑ *Streptococcus*	**Baseline: HAM-D > = 8 vs HAM-D <8** ↓ *Eubacterium* **Week 4 vs Baseline HAM-D > = 8** ↑ *Eubacterium*	None	Prospective pilot	(Kurokawa et al., 2018)
	16S (no)	N = 44 IBS with moderate anxiety and/ or depression N = 22 PBO N = 22 *B. longum NCC3001*	Improvement in HAD-D subscale for *B. longum* group	None	None		(Pinto-Sanchez et al., 2017)
	16S (no)	N = 30 with refractory IBS; sequenced stool before FMT and 1 mo. after	**1 Month vs Baseline in Responders** ↑ *Methanobrevibacter* ↑ *Akkermansia*		↑ Quality of life 1 mo. and 3 mo. after FMT but not after 6 mo.	Prospective pilot	(Huang et al., 2019b)
	16S via 454 Pyrosequencing (no)	N = 65 IBS N = 21 Control	*Clostridium* XIVa, *Coprococcus* associated with differences in connectivity of cortical and subcortical networks between IBS and Control	None	None		(Labus et al., 2019)
	16S array (no)	N = 13 Post-Infectious IBS N = 19 General IBS N = 16 Control	No genus-level information	None	None		(Sundin et al., 2015)
	Fluorescence In-Situ Hybridization (no)	N = 44 IBS Receiving trans-GOS suppplementation or PBO (0 g, 3.5 g, 7 g daily)	**PBO vs trans-GOS 3.5 g** ↑ *Bifidobacterium spp.** ↑ *E. rectale/C. coccoides**** **PBO vs trans-GOS 7 g** ↑ *Bifidobacterium spp.**** ↓ *Clostridium perfingensr** ↓ *Bacteroides/ Prevotella**** ↓ HADS-A Score* ↑ QOL Score*	**PBO vs trans-GOS 3.5 g** ↑ *Bifidobacterium spp.** ↑ *E. rectale/C. coccoides**** **PBO vs trans-GOS 7 g** ↑ *Bifidobacterium spp.**** ↓ *Bacteroides/ Prevotella****	None		(Silk et al., 2009)
	Primers from GA-map Dysbiosis Test (no)	N = 16 IBS, Sampled at 0, 1, 3, 12, 20/28 weeks after FMT	**Responders vs Non-Responders** ↑ *Bacteroides**** before FMT ↑ *Megasphera/Dialister** at week 1, 12, 20/28	None	No strong association with HADS-A or HADS-D (only significant at Week 3 vs baseline but becomes insignificant by week 20/28)	Prospective pilot	(Mazzawi et al., 2018)
	qPCR (no)	N = 40 IBS receiving short-chain FOS (scFOS) N = 37 PBO 4 week trial	**scFOS vs PBO** ↓ HAD-D score **scFOS at D28 vs Baseline** ↑ *Bifidobacterium** **PBO at D28 vs Baseline** ↑ *Roseburia/Eubacterium rectale*				(Azpiroz et al., 2017)
	Shotgun (no)	N = 54 Older Women with Migraines N = 54 Control	**Migraine vs Control** ↓ *Faecalibacterium prausnitzii*** ↓ *Bifidobacteirum adolescentis** ↑ Kynurenine synthesis* GBMs ↓ Quinolinic Acid Degradation*	**Migraine vs Control** ↓ *B. adolescentis**	**Migraine vs Control** ↑ GABA Synthesis III* ↓ SAM Synthesis* ↓ Glutamate Degradation*		(Chen et al., 2020c)
Other Pain Disorders	16S (no)	N = 48 Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) N = 48 Control	**ME-CFS vs Control** ↑ *Blautia** ↑ *Coprobacillus*** ↑ *Eggerthella*** ↓ *Faecalibacteirum** ↓ *Lachnospira* ↓ *Collinsella* Negative correlation between *Faecalinacterium*	None	None		(Kitami et al., 2020)

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Table 7 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			and total sleep awakenings				
	16S (no)	N = 113 Chronic Widespread Pain (CWP) N = 1623 Control	**CWP vs Control** ↓ *Coprococcus comes* ***	None	None		(Freidin et al., 2020)

Legend: LFC: log-2 fold change; LC: log change; RA: relative abundance; DASS-42: Depression Anxiety Stress Scales; ADHD: Attention-Deficit Hyperactivity Disorder; HE: hepatic encephalopathy; FOS: Fructo-oligosaccharide; HADS-A: Hamilton Anxiety and Depression Scales – Anxiety Subscale; HADS-A: Hamilton Anxiety and Depression Scales – Depression Subscale; RTT: Rett's Syndrome; AD: Alzheimer's Disease, PD: Parkinson's Disease; MCI: mild-cognitive impairment; MSA: multiple-systems atrophy; ALS: amyotrophic lateral sclerosis; NMOSD: neuromyelitis optica spectrum disorder*: $p_{adj} < 0.1$; **: $p_{adj} < 0.01$; ***: $p_{adj} < 0.001$; Reanalysed studies are highlighted; 95 % CI reported between square brackets [lower 95 % CI; upper 95 % CI].

4.3.2. Taxonomic databases and classifiers

Differences in taxonomic classification databases and taxonomic assignment likely contributed to inconsistent classification of microbial sequences across studies. In addition, researchers that conducted studies >3 years ago did not have access to more extensive taxonomic databases (Glockner et al., 2017; Pruesse et al., 2019; Quast et al., 2013; Yilmaz et al., 2013). Many existing studies have used the Greengenes database for assigning microbial taxonomy, but this database is problematic because it has not been curated/updated since 2013 and thus cannot identify novel sequences (DeSantis et al., 2006). Greengenes has a significant overrepresentation of certain taxa; for example, at the species level around 15 % of all sequences are assigned to *Faecalibacterium prausnitzii* (Allard et al., 2015). This is in contrast to other databases such as SILVA, which do not have a single species level assignment allocated to even 5 % of all sequences within the database (Allard et al., 2015). This means that studies which used Greengenes to assign taxonomy were also a lot more likely to find an enrichment in *Faecalibacterium prausnitzii* and an underrepresentation of other taxa. In studies using untransformed relative abundance metrics, a non-specific assignment of *Faecalibacteirum prausnitzii* would affect the relative abundance of other identified genera.

One reason that different databases would assign a different classification to the same sequence is the size of the database (Balvociute and Huson, 2017). Having a larger taxonomic database can improve the specificity of these classifications since there will be more sequences with similarity to the read (Balvociute and Huson, 2017). Since taxonomic classes above the genus-level are very diverse, these differences were not reported in this analysis because they do not provide adequate resolution to infer the production of bacterial metabolites. Even bacterial members within the same family can differ in their enzymatic and metabolic capabilities.

In addition, the use of ASVs rather than operational taxonomic units (OTUs) provide more replicable and meaningful identification of taxa across studies (Callahan et al., 2017). However, many past studies have used, and many still use OTUs, hindering comparison across datasets. Often, studies may even identify some OTUs belonging to one microbial genus increased in one group while also finding other OTUs belonging to the same genus reduced in that same group. This confounds interpretation and replicability.

The gut microbiota functions as an ecological community with keystone species and genera necessary for its function. Identifying individual ASVs that are altered in a disease could help identify these keystone members. Thus, if an important keystone genus is disrupted, the metabolic output of the community is altered which may impact host health (Chng et al., 2020; Banerjee et al., 2018; Berg et al., 2020; Fisher and Mehta, 2014).

4.3.3. Compositional data analysis

Widely used relative abundance and general logarithmic transformations are inappropriate for microbiome data. Microbiome data is, by definition, compositional and thus using relative abundance, or rarefaction during processing is inappropriate and would skew study results (Gloor et al., 2017). In addition, issues within correlational analysis of compositional data have long been noted and are another challenge when analysing microbiome data (Gloor et al., 2017; Lovell et al., 2015; Friedman and Alm, 2012; Kurtz et al., 2015; Pearson, 1897). There is a known bias for spurious and negative correlations within microbiome datasets (Gloor et al., 2017). Additionally, we found many studies where rarefaction is used when processing reads. This involves subsampling of each sample's read counts to a common sequencing depth but results in a loss of information and precision (McMurdie and Holmes, 2014). Finally, it is also possible to mathematically model the bias within metagenomic experiments (McLaren et al., 2019). This would allow for reference calibration to correct these biases, but only if the data has already been compositionally transformed (McLaren et al., 2019).

4.3.4. Use of outdated tools and software

Additionally, we also found that bioinformatics tools are often used after they are deprecated; a few studies described in Table 1 used Quantitative Insights into Microbial Ecology (QIIME) Version 1 past the date that it was still supported by its developers, while many studies did not specify the version used.

4.4. Healthy humans

4.4.1. Infant temperament and behaviour

Many of the studies assessing infant temperament relied on correlational analysis but since the microbiota is compositional by nature, these datasets are prone towards spurious correlations (see 4.4.3) (Gloor et al., 2017). Though *Bifidobacterium* and *Prevotella* participate in tryptophan and SCFA metabolic pathways (Valles-Colomer et al., 2019), it is still unclear whether these specific pathways are implicated in these behaviours.

4.4.2. Adult personality and behaviour

There were no consistent findings at the genus-level within these studies, resultant from limitations described in Table 1. Without additional metadata and strain level resolution, it is difficult to associate personality traits with microbial genera. While many studies identified associations with bacteria involved in SCFA and tryptophan metabolic pathways, the current state of the evidence for robust microbial associations with personality traits is weak.

4.4.3. Sleep characteristics and quality

Many of the studies carried out thus far are small but compelling, pointing to possible associations of different microbial genera and healthy sleep. While the interactions between circadian rhythm, sleep and the microbiome are compelling and gaining more traction (Godinho-Silva et al., 2019; Govindarajan et al., 2016; Li and Cui, 2018;

Table 8
Microbiome-brain studies involving eating-related disorders.

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
Obesity	WGS (no)	N = 14 Obese N = 13 Non-obese	None	None	None		(Blasco et al., 2017)
	WGS (no)	N = 35 Obese N = 35 Non-obese	No genus-level differences or associations identified	None	None		(Palomo-Buitrago et al., 2019)
	WGS (no)	N = 65 Obese N = 51 Control	Bacterial genera positively associated with memory: *Bacteroides, Citrobacter, Enterobacter, Salmonella, Klebsiella* Specifically associated with verbal learning: *Ruminococcus* CAG353, *Roseburia* CAG357, *Veillonella magna* Negatively associated with memory scores: *Eubacterium, Clostridium,* Proteobacteria *Roseburia* and *Bacteroidetes* associated with volume in left hippocampus Altered tryptophan metabolism in obesity associated with reductions in short term and working memory, as well as volume of frontal interior orbital right gyrus and left hippocampus	Bacterial genera positively associated with memory: *Bacteroides*			(Arnoriaga-Rodríguez et al., 2020)
	16S (no)	N = 86 Women Without Food Addiction (FA) N = 19 Women With FA	OTUs enriched in FA: *Megamonas* OTUs depleted in FA: *Bacteroides, Akkermansia, Eubacterium biforme.* Reduction is associated with decreased plasma indolepropionate in the brain reward system	OTUs depleted in FA: *Bacteroides*			(Dong et al., 2020b)
	16S (no)	N = 8 Obese With Bariatric Surgery	None	None	None	Greengenes	(Sanmiguel et al., 2017)
	16S (no)	N = 18 Obese With Bariatric Surgery	Precueneus-Putamen connectivity and food addiction symptoms negatively associated with *Bacteroides, Ruminococcus, Holdemanella*	Precueneus-Putamen connectivity and food addiction symptoms negatively associated with *Bacteroides*	None		(Dong et al., 2020a)
	16S (no)	N = 57 Obese N = 54 Control	None	None	None		(Kreutzer et al., 2017)
	16S via 454 Pyrosequencing (no)	N = 20 Obese N = 19 Non-obese	None	None	None	No genera level differences reported	(Fernandez-Real et al., 2015)
	GA-Map Dysbiosis Test	N = 102 Morbid Obesity N = 15 Control	**Associations in Obese Group: WHO-5 Wellbeing Index** Negatively associated with *Bacteroides spp.* and *Prevotella* Negatively associated with faecal acetate, butyrate and propionate Positively associated with *Faecalibacterium prausnitzii*, *Dorea* spp. **Associations in Obese Group: Hopkin Symptom Checklist 10** Negatively associated with *Faecalibacterium prausnitzii* Positively associated with *Bacteroides stercoris*	None	None		(Farup and Valeur, 2018)
Anorexia	16S (yes)		None	None	None	None	(Borgo et al., 2017)

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Table 8 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
		N = 15 Anorexia N = 15 Control					
	16S (yes)	N = 55 Anorexia Baseline (AN-1) N = 44 Anorexia After Weight Gain (AN-2) N = 55 Control	**AN-1 vs Control** ↑ Isovaleric acid synthesis I (effect = 0.44 [-2.80, 5.07])* ↑ Quinolinic acid synthesis (effect = 0.48[-2.13; 5.35])* ↑ Quinolinic acid degradation (effect = 0.42 [-2.33; 4.80])** **AN-2 vs Control** ↓ Butyrate Synthesis II (effect = -0.43 [-4.88; 2.55])**	None	**AN-1 vs Control** ↑ p-Cresol synthesis (effect = 0.49 [-2.37; 5.20])** ↑ S-Adenosylmethionine (SAM) synthesis (effect = 0.40 [-2.12; 5.05])* ↑ Glutamate synthesis II (effect = 0.46 [-2.32; 5.03])** ↑ ClpB (ATP-dependent chaperone protein) (effect = 0.43 [-2.30; 4.98])* **AN-2 vs Control** ↓ Inositol degradation (effect = -0.43 [-5.09; 2.32]) *		(Mack et al., 2016)
	16S (no)	N = 18 Anorexia N = 20 Athletes N = 26 Normal Weight N = 22 Overweight N = 20 Obese All women	None	None	None	Storage at -20C	(Morkl et al., 2017)
	16S (no)	N = 21 Anorexia at Enrollment N = 16 Anorexia at Discharge N = 29 Healthy Women	**Anorexia at Admission vs Control** ↑ *Weissella** ↑ *Coprococcus** ↓ *Parabacteroides** **Anorexia at Discharge vs Control** ↑ *Collinsella** ↑ *Actinobacteria** ↑ *Parabacteroides**	None	None		(Monteleone et al., 2020)
	16S (no)	N = 19 Anorexia N = 20 Healthy Control	**Anorexia at Admission vs Control** ↑ *Anaerostipes** **Anorexia at Discharge vs Control** ↑ *Unclassified Lachnospiraceae*** ↑ *Fusicatenibacter** **Anorexia at Admission vs Discharge** ↓ *Bacteroides** ↑ *Unclassified Ruminococcaceae** ↑ *Unclassified Lachnospiraceae*** ↑ *Faecalibacterium** ↑ *Fusicatenibacter**	None	None		(Schulz et al., 2020)
	16S via 454 Pyrosequencing (no)	N = 16 at Timepoint 1 (Admission to Hospital) N = 10 at Timepoint 2 (Discharge after Nourishment)	↑ *Ruminococcus** after nourishment	None	None	Greengenes	(Kleiman et al., 2015)
	qPCR (no)	N = 25 Anorexia (11 Binge Eating, 14 Restrictive) N = 21 Control	**Anorexia vs Control** ↓ Total bacteria*** ↓ *Clostridium coccoides**** ↓ *Clostridium leptum**** ↓ *Bacteroides fragilis**** ↓ *Streptococcus****	**Anorexia vs Control** ↓ *Bacteroides fragilis****	None		(Morita et al., 2015)
	qPCR (no)	N = 20 Obese N = 9 Anorexia N = 20 Control	**Obese vs Control** ↑ *Lactobacillus** **Obese vs Anorexia** ↑ *Lactobacillus** **Anorexia vs Control** ↑ *Methanobrevibacter smithii**	**Obese vs Control** ↑ *Lactobacillus** **Obese vs Anorexia** ↑ *Lactobacillus**	None		(Armougom et al., 2009)

Legend: LFC: log-2 fold change; LC: log change; RA: relative abundance; DASS-42: Depression Anxiety Stress Scales; ADHD: Attention-Deficit Hyperactivity Disorder; HE: hepatic encephalopathy; FOS: Fructo-oligosaccharide; HADS-A: Hamilton Anxiety and Depression Scales – Anxiety Subscale; HADS-A: Hamilton Anxiety and Depression Scales – Depression Subscale; RTT: Rett's Syndrome; AD: Alzheimer's Disease, PD: Parkinson's Disease; MCI: mild-cognitive impairment; MSA: multiple-systems atrophy; ALS: amyotrophic lateral sclerosis; NMOSD: neuromyelitis optica spectrum disorder*: $p_{adj} < 0.1$; **: $p_{adj} < 0.01$; ***: $p_{adj} < 0.001$; Reanalyzed studies are highlighted; 95 % CI reported between square brackets [lower 95 % CI; upper 95 % CI].

Weger et al., 2018; Teichman et al., 2020), more human studies are necessary to investigate this interaction.

4.4.4. Ageing and cognition

While compelling large-cohort studies associated microbial populations with frailty and diet in aging (Ghosh et al., 2020; Meehan et al., 2015; O'Toole and Jeffery, 2018; Ticinesi et al., 2017; Verdi et al., 2018) they do not overtly focus on the cognitive aspects of ageing *per se*. More research is warranted.

4.5. Neurodevelopmental disorders

4.5.1. Attention-deficit hyperactivity disorder

There is weak evidence for specific SCFA or tryptophan associated microbial pathway alterations in ADHD (see Table 2). This is in part due to the lack of studies with similar findings or compositional data approaches.

4.5.2. Autism-spectrum disorder

In our reanalysis, we saw few robust associations between bacterial genera and ASD. Through our reanalysis, we found that most differences were explained by host genetics and diet. Nonetheless, there may be differences in SCFA metabolism not reflected through microbiome sequencing.

Though they did not find correlations between ASD symptoms and faecal SCFAs, Berding and Donovan (2019) found that the SCFAs correlated strongly with diet. A separate study reported increased valerate and decreased butyrate in ASD faecal samples (Liu et al., 2019b).

As many as 90 % of individuals with ASD display picky and repetitive eating behaviours, which can further impact their nutrient intake and microbiota (Kral et al., 2013). It's unclear whether SCFA dysregulation is a result of the microbial production or dysregulation in gut absorption. Along with host genetics, this is an important consideration for future studies.

4.5.3. Schizophrenia

Across both Chinese cohorts, *Fusicatenibacter* was differentially abundant in people with schizophrenia. This was not seen in the North American cohorts, perhaps attributable to dietary and environmental differences. This genera participates in aspects of SCFA metabolism. However across other datasets, differences in *Lactobacillus* and *Bifidobacterium* were more prominent.

The majority of 16S sequencing studies assessed different subpopulations of schizophrenia and thus are difficult to compare with each other. Combined with reanalysed results, there is evidence supporting *Lactobacillus* and *Bifidobacterium* dysregulation in schizophrenia, as well as potential changes in tryptophan and SCFA-related GBMs (see Table 2).

4.5.4. Pediatric acute-onset neuropsychiatric syndrome and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection

From one study, we do not find any compelling evidence of differences in bacterial genera or GBMs.

4.5.5. Rett's syndrome

There may be host-genotype microbiota associations involved in influencing SCFA production or absorption in Rett's Syndrome. More research is warranted.

4.6. Epilepsy

Since many studies assessed different cohorts of epilepsy, more research is warranted. Perhaps there are differences between subtypes of epilepsy in the microbiome as well. We cannot make any definitive conclusions about GBM-related bacteria or signatures within epilepsy and epilepsy-responses to dietary or pharmacologic treatment. Interactions between diet, epilepsy, epileptic medication and the microbiome remain unclear.

4.7. Neurodegenerative disease

4.7.1. Alzheimer's disease

Though findings from one reanalysed dataset are strong (Li et al., 2019a), additional measures of metadata are needed to disentangle GBM differences in AD or mild-cognitive impairment from sex, diet and age. Nonetheless, there is some evidence for SCFA dysregulation in AD and MCI.

4.7.2. Multiple systems atrophy

Early studies suggest that MSA may alter the production or absorption of SCFAs, though it is unclear if individual microbial genera are involved.

4.7.3. Amyotrophic lateral sclerosis

Early studies suggest that differences in the gut microbiome may alter the serum metabolome in people with ALS (Blacher et al., 2019). Specifically, tryptophan metabolism may be involved. More research is warranted to connect specific genera to different aspects of the disease and its symptoms.

4.7.4. Parkinson's disease

While many studies reported microbiome differences, we did not find any upon the reanalysis. Many of these studies used Greengenes, rarefaction and relative abundance. It is nonetheless fascinating that differences in microbial abundance at the genus-level were found in almost every PD study, especially those comparing different subtypes. It is unclear if the effect sizes in these studies are robust when data is analysed in a compositional manner (see Table 4). If effect sizes are small, there is a higher probability that the effect sizes will not replicate in other studies. This may either obscure real differences in the PD microbiota or provide false positives.

4.8. Addiction and substance use

4.8.1. Alcohol

Long-term alcohol use likely alters the gut microbiome. However, a lack of metadata make it difficult to understand which specific genera associate with alcohol, as opposed to other confounding variables. Future studies must account for factors such as diet, heritability and drinking frequency to demystify the effects of alcohol on gut microbiota composition and metabolism.

4.8.2. Smoking and tobacco use

Though evidence is limited, it does suggest that smoking/tobacco

Table 9
Microbiome-brain studies involving neurovascular disease.

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
Neurovascular Disease	16S and WGS (no)	N = 122 Neruovascular Cavernous Angioma (CA) Controls from Human Microbiome Project	CA vs Control ↑ *Bacteroides thetaomicron**** ↑ *Odoribacter sphlancus**** ↓ *Bifidobacterium adolescentis**** ↓ *Faecalibacterium prausntzii**** Aggressive vs Non-Aggressive CA ↑ *Bifidobacterium adolescentis**** ↓ *Bacteroides eggerthii** CA with Symptomatic Hemmorhage vs CA No Hemmorhage ↑ *Faecalibacterium prausnitzii* ↑ *Oscillobacter*	CA vs Control ↑ *Bacteroides thetaomicron**** ↓ *Bifidobacterium adolescentis**** Aggressive vs Non-Aggressive CA ↑ *B. adolescentis**** ↓ *Bacteroides eggerthii**	None		(Polster et al., 2020)
	16S (no)	N = 8 Cerebral Infarction (CI) N = 2 Ischemic Stroke (IS) N = 10 Control	**CI vs Control** ↓ *Bacteroides* ↓ *Parabacteroides* ↓ *Akkermansia* ↓ *Prevotella* ↓ *Faecalibacterium* **IS vs Control** ↑ *Escherichia* ↑ *Dialister* ↑ *Bifidobacterium* ↓ *Bacteroides* ↓ *Megamonas* ↓ *Parabacteroides* ↓ *Akkermansia* ↓ *Prevotella* ↓ *Faecalibacterium* ↓ *Ruminococcus* **CI vs IS** ↑ *Escherichia* ↑ *Bacteroides* ↑ *Megamonas* ↑ *Prevotella* ↑ *Ruminococcus* ↓ *Parabacteroides* ↓ *Akkermansia* ↓ *Faecalibacterium* ↓ *Dialister* ↓ *Bifidobacterium*	**CI vs Control** ↓ *Bacteroides* **IS vs Control** ↓ *Bacteroides* **CI vs IS** ↑ *Bacteroides* ↓ *Bifidobacterium*	None	N = 2 for Ischemic Stroke	(Ji et al., 2017)
	16S (no)	N = 30 Ischemic Stroke N = 30 Control	**Ischemic Stroke vs Control** ↑ *Odoribacter* ↑ *Akkermansia* ↑ *Victivallis* ↓ *Anaerostipes* ↓ *Ruminoclostridium 5* **Severe vs Mild Stroke** ↓ *Enterobacter*	None	None	Rarefaction	(Li et al., 2019c)
	16S (no)	N = 30 Post-Stroke Cognitive Impairment (PSCI) N = 35 non-PSCI	**PSCI vs non-PSCI** ↑ *Fusobacterium* ↑ *Bacteroides* ↑ *Colstridium* XIVa ↑ *Gemella* ↑ *Flavonifractor* ↓ *Prevotella* ↓ *Gemminger* ↓ *Alistipes* ↓ *Ruminococcus* ↓ *Akkermansia* ↓ *Coprococcus* ↓ *Barnesiella* ↓ *Clostridium* IV ↓ *Odoribacter* ↓ *Methanobrevibacter* ↓ *Oxolobacter* ↓ *Hydrogenanaerobacterium*	**PSCI vs non-PSCI** ↑ *Bacteroides*	None		(Liu et al., 2020a)

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Table 9 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
	16S (no)	N = 41 Post-Stroke Cognitive Impairment (PSCI) and Depression N = 25 non-PSCI	**PSCI vs non PSCI** ↓ *Fusicatenibacter* ↑ *Veilonella*	None	None		(Ling et al., 2020a)
	16S (no)	N = 10 Cerebral Infarction N = 10 Control	None	None	None	Not properly filtered, chloroplasts included in results	(Wang et al., 2018)
	16S (no)	N = 10 Infants with Hypoxic Ischemic Encephalopathy Treated with Hypothermia N = 9 Control	**Hypoxic Ischemic Encephalopathy vs Control** ↓ *Bacteroides*** None		None		(Watkins et al., 2017)

Legend: LFC: log-2 fold change; LC: log change; RA: relative abundance; DASS-42: Depression Anxiety Stress Scales; ADHD: Attention-Deficit Hyperactivity Disorder; HE: hepatic encephalopathy; FOS: Fructo-oligosaccharide; HADS-A: Hamilton Anxiety and Depression Scales – Anxiety Subscale; HADS-A: Hamilton Anxiety and Depression Scales – Depression Subscale; RTT: Rett's Syndrome; AD: Alzheimer's Disease, PD: Parkinson's Disease; MCI: mild-cognitive impairment; MSA: multiple-systems atrophy; ALS: amyotrophic lateral sclerosis; NMOSD: neuromyelitis optica spectrum disorder*: $p_{adj} < 0.1$; **: $p_{adj} < 0.01$; ***: $p_{adj} < 0.001$; Reanalysed studies are highlighted; 95 % CI reported between square brackets [lower 95 % CI; upper 95 % CI].

may alter the overall metabolism of the gut microbiota as well as its composition.

4.8.3. Addiction and recreational drug use

More studies investigating recreational drug use, controlling for age, sex and type of drug, must be conducted to deconvolute any potential changes.

4.9. Multiple sclerosis and demyelinating diseases

Findings accumulated from previous studies and our reanalysis suggest SCFA metabolism is affected in multiple sclerosis and demyelinating diseases. Measurements of faecal SCFAs and stratification by clinical subtype are crucial for uncovering any potential robust changes in bacterial abundance or GBMs.

4.10. Pain-related disorders

4.10.1. Fibromyalgia

More studies are warranted to determine if the microbiome is altered in people with fibromyalgia.

4.10.2. Irritable-bowel syndrome (IBS)

While the overall changes in microbiota composition are unclear, there is some evidence that manipulating its composition may improve various psychological symptoms in IBS. However more changes and randomised trials are needed to confirm this.

4.10.3. Other pain-related disorders

Preliminary evidence suggests that the microbiome is altered in people with migraines, encephalomyelitis and widespread pain.

4.11. Eating disorders

4.11.1. Obesity

There is insufficient evidence to conclude microbial-derived metabolites associate with psychological measures in obesity. More research is warranted.

4.11.2. Anorexia nervosa

There is strong evidence that ClpB is elevated in people with anorexia nervosa. This *Escherichia coli* produced protein is an alpha-melanocortinin stimulating hormone mimetic, known to reduce appetite in mice (Tennoune et al., 2014). It's unclear if the microbes involved in ClpB production also impact SCFA, tryptophan and bile-acid metabolism directly or indirectly

4.12. Neurovascular disease

Exciting findings from (Polster et al., 2020) warrant more investigation into gut-brain communication after other neurovascular insults such as stroke. In other types of stroke, *Akkermansia* and *Faecalibacterium* may be altered.

4.13. Stress and psychiatric disorders

4.13.1. Stress

While many different types of cohorts were assessed across studies, there is evidence that stress may lead to persistent changes in the microbiome and immunity. Even though there are clear links between stress and the microbiome (see for reviews (Cussotto et al., 2018a; Dinan and Cryan, 2012; Foster and McVey Neufeld, 2013; Liu, 2017) for extensive reviews of the subject), these studies indicate how much metadata is needed to properly stratify participants and identify some of these changes.

4.13.2. Post-traumatic stress disorder

More studies are warranted to determine the specific gut-microbial changes associated with post-traumatic stress disorder. Thus far, few studies have been conducted on cohorts with post-traumatic stress disorder.

4.13.3. Bipolar disorder

Many studies showed changes in the gut microbiome. However, Coello et al. (2019) found that all the differences were attributed to sex effects, heritability and smoking. These variables are not accounted for in other studies.

4.13.4. Depression and anxiety

Across many studies of depression and anxiety, *Dialister* is depleted in depression. *Faecalibacterium* is reduced across many depressed or anxious cohorts.

4.14. Limitations of existing studies

There are many challenges that prevent researchers from drawing causal conclusions from their datasets beyond the technical and bioinformatics limitations discussed in Section 3.4, especially in

Table 10
Microbiome-brain studies involving stress-related and psychiatric disorders.

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
Stress	16S (no)	N = 50 Healthy subject in double-blind PBO RCT	None	None	None		(Soldi et al., 2019)
	16S (no)	N = 47 Black ♀ N = 33 white ♀	↑ *Fusobacterium** with stress in Black participants, but not in white participants	None	None	Greengenes	(Carson et al., 2018)
	16S (no)	N = 25 Low Adverse Childhood Events (ACE) (<2) N = 23 High ACE (> = 2) All participants pregnant at time of study	**High ACE vs Low ACE Score** ↑ *Prevotella****	None	None		(Hantsoo et al., 2019)
	16S (no)	N = 75 Pregnancy-related anxiety associated to meconium of newborn	None	None	None	QIIME 1.9, Greengenes, No genus-level associations of identified microbes reported	(Hu et al., 2019a)
	16S (no)	N = 84 Mothers (psychological stress collected) Infant faecal samples collected at birth, 4–12 weeks and 20–28 weeks	**Mothers with Exposure to Intimate Partner Violence vs Control** ↑ *Weisella**** at 4–12 weeks ↑ *Citrobacter*** at all timepoints	None	None	QIIME 1.7	(Naude et al., 2020)
	16S (no)	N = 31 Probiotic (*Lactobacillus gasseri* CP2305) N = 29 PBO	**Probiotic vs Placebo after stressor** Smaller decrease in *Bifidobacteria* after stressor Increased faecal Valeric acid with probiotic	None	None		(Nishida et al., 2019)
	16S via 454 Pyrosequencing (no)	N = 16 PBO N = 16 Probiotic *L. gasseri* CP2305 Probiotic Administration	**Probiotic vs PBO after Stressor** Differences in *Corynebacterium* Improved sleep quality Reduced stress symptoms in females	None	None	No post-hoc Identification of species-level differences with 16S	(Nishida et al., 2017)
	HITChip (no)	N = 28 High Prenatal Stress N = 28 Low Prenatal Stress Measured composition at 5 points in first 110 days	None	None	None	Results difficult to interpret; table of p-values or statistics not provided; unclear if post-hoc used	(Zijlmans et al., 2015)
Post-Traumatic Stress Disorder (PTSD)	16S (no)	N = 29 PTSD N = 64 Control	**PTSD without Hepatic Encephalopathy (HE) vs Control (no HE)** ↑ *Streptococcus* ↑ *Acidaminococcus* ↓ *Ruminococcus* ↓ *Roseburia* ↓ *Anaerostipes* ↓ *Colstridium* XIVAa ↓ *Pseudoflavonibacter* **PTSD with HE vs Control with HE** ↓ *Subdoligranulum*	None	None		(Bajaj et al., 2019)
	16S (no)	N = 18 PTSD N = 12 Trauma-Exposed Control	None	None	None	Greengenes	(Hemmings et al., 2017)
Bipolar Disorder (BD)	WGS (no)	N = 31 BD N = 31 MDD N = 31 Control	**BD vs Control** ↑ *Streptococcus* ↑ *Clostridium* ↑ *Oscillibacter*	**BD vs Control** ↑ *Bifidobacterium* ↑ *Bacteroides* **MDD vs Control**			(Rong et al., 2019)

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Table 10 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			↑ *Bifidobacterium* ↑ *Bacteroides* **MDD vs Control** ↑ *Streptococcus* ↑ *Clostridium* ↑ *Oscillibacter* ↑ *Bifidobacterium* Various *Prevotella* and *Bifidobacterium* species and strains differed between BD and Control	↑ *Bifidobacterium* *Bifidobacterium* species and strains differed between BD and Control			
	WGS (no)	N = 25 BD N = 28 Control	**BD vs Control** ↑ *Escherichia* ↑ *Bifidobacterium* ↑ *Lachnoclostridium* ↑ *Megasphera* ↑ *Clostridium* ↑ *Oscillibacter* ↑ *Acidaminococcus* ↑ *Streptococcus* ↓ *Bacteroides* Dysregulation in tryptophan metabolism pathway in BD	**BD vs Control** ↑ *Bifidobacterium* ↓ *Bacteroides*			(Lai et al., 2021)
	16S (no)	N = 115 BD N = 64 Control	**BD vs Control** ↓ *Faecalibacterium* **Associations** *Faecalibacterium* associated with higher PCS, lower PSQI and PHQ9 *Anaerostipes* associated with increased PCS	None	None		(Evans et al., 2017)
	16S (no)	N = 23 BD N = 23 Control	None	None	None	Greengenes	(McIntyre et al., 2019)
	16S (no)	N = 217 BD N = 165 MDD N = 217 Control	**BD vs Control (From top 5 LDA)** ↑ *Ruminococcus gnavus* (2 OTUs) ↑ *Clostridium sensu stricto* ↑ *Bacteroides* ↑ *Pseudomonas* (2 OTUs) ↓ *Prevotella 9* (2 OTUs) ↓ *Bacteroides* ↓ *Ruminococcus 2* ↓ *Klebsiella* **MDD vs Control (From top 5 LDA)** ↑ *Citrobacter* ↑ *Fusobacterium* ↑ *Ruminococcus gnavus* ↑ *Bacteroides* ↑ *Ruminococcus 2* ↓ *Bacteroides* (5 OTUs) **BD vs MDD (From top 5 LDA)** ↑ *Blautia* ↑ *Bacteroides*	**BD vs Control (From top 5 LDA)** ↑ *Bacteroides* (OTU) ↓ *Bacteroides* (OTU) **MDD vs Control (From top 5 LDA)** ↑ *Bacteroides* ↓ *Bacteroides* (5 OTUs) **BD vs MDD (From top 5 LDA)** ↑ *Bacteroides* ↓ *Eubacterium rectale* ↓ *Eubacterium hallii* ↓ *Bacteroides*	None		(Zheng et al., 2020b)

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Table 10 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			↑ *Lachnoclostridium* ↑ *Dialister* ↓ *Eubacterium rectale* ↓ *Eubacterium hallii* ↓ *Eggerthella* ↓ *Blautia* ↓ *Bacteroides*				
	16S (no)	N = 32 BD	None	None	None		(Bengesser et al., 2019)
	16S (no)	N = 113 BD N = 113 Control (37 unaffected relatives)	None	None	None	*Note all differences were explained by sex, family and smoking	(Coello et al., 2019)
	16S (no)	N = 52 BD (N = 12 BD-1 N = 38 BD-II) N = 20 After Treatment with Quetiapine N = 45 Control	**BD vs Controls** ↑ *Parabacteroides* ↑ *Bacteroides* ↓ *Roseburia* ↓ *Faecalibacterium* ↓ *Coprococcus* **BD-I (Baseline) vs BD-II (Baseline)** ↑ *Streptococcus* ↑ *Bacillus* ↑ *Veillonella* ↓ *Ruminococcus* **BD (treated) vs BD (untreated)** ↑ *Klebsiella* ↑ *Lactobacillus* ↑ *Collinsella* ↑ *Paraprevotella* ↑ *Veillonella* ↓ *Alistipes*	**BD vs Controls** ↑ *Bacteroides* **BD (treated) vs BD (untreated)** ↑ *Lactobacillus*			(Hu et al., 2019b)
	16S (no)	N = 32 Bipolar disorder (BD) N = 10 Control	**BD vs Controls** ↑ *Faecalabacterium** **Within BD** ↑ *Lactobacillus*** associated with high IL-6 ↑ *Prevotella** with low LDL cholesterol ↑ *Roseburia*** with less depressive symptoms ↑ *Lactobacillus*** associated with high serum tryptophan ↑ *Prevotella** with low LDL cholesterol ↑ *Roseburia*** with less depressive symptoms	None	None	Greengenes	(Painold et al., 2019)
	16S (no)	N = 117 BD 49 Treated with Atypical Antipsychotics (AAP) 68 non-AAP	**AAP vs Non-AAP** ↓ *Akkermansia* ↓ *Sutterella*	None	None		(Flowers et al., 2017)
	16S (no)	N = 128 Monozygotic Twins Discordant for BD	None	None	None		(Vinberg et al., 2019)
	qPCR (no)	N = 36 BD (Before Treatment) N = 27 Control	**BD vs Control** ↑ *Faecalibacterium prausnitzii**	**BD vs Control** ↓ *Bifidobacteria**	None		(Lu et al., 2019)

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Table 10 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
			↑ *Atopobium**** ↑ *Enterobacter**** ↑ *Clostridium* cluster IV*** ↓ *Bifidobacteria**				
	qPCR (no)	N = 13 BD I N = 26 BD II N = 58 Control	None	None	None		(Aizawa et al., 2019)
	16S and WGS (no)	N = 111 Psychiatric Inpatients	*Coprococcus catus* and *Clostridium symbiosum* associated with moderate anxiety at admission ↓ *Coprococcus catus* associated with lower remission from anxiety and depression	None	None		(Madan et al., 2020)
	16S and WGS (no)	N = 1054	*Faecalibacterium, Coprococcus* associated with higher quality of life indicators *Dialister*, *Coprococcus* spp. depleted in depression	None	Synthesis of dopamine metabolite 3,4-dihydroxyphenylacetic acid positively correlated with quality of life		(Valles-Colomer et al., 2019)
	WGS (no)	N = 156 MDD N = 155 Control	**MDD vs Control** ↑ Multiple *Bacteroides* ASVs ↓ Multiple *Blautia* ASVs Many upregulated and downregulated ASVs assigned to *Eubacterium*	**MDD vs Control** ↑ Multiple *Bacteroides* ASVs	None		(Yang et al., 2020)
	16S (no)	N = 37 MDD N = 18 Control	None	None	None		(Naseribafrouei et al., 2014)
Depression and Anxiety	16S (no)	N = 15 MDD, 11 Responders and 4 Non-Responders	None	None	None	Methods not clearly described	(Bharwani et al., 2020)
	16S (no)	N = 22 Depression/Anxiety N = 28 Control	**Depression/Anxiety vs Control** ↑ *Eubacterium* ↑ *Enterococcus* ↑ *Collinsella* ↓ *Faecalibacterium*	**Depression/Anxiety vs Control** ↑ *Eubacterium*	None		(Stevens et al., 2018)
	16S (no)	N = 23 MDD	Functional connectivity in lDLPFC inversely correlated with relative abundance of *Bacteroides*		None	Controls not in the scope of the study; focused on GABA	(Strandwitz et al., 2019)
	16S (no)	N = 24 Current depressive episode (CDE) N = 16 Control	**CDE vs Control** ↑ *Akkermansia* ↑ *Veillonella* ↑ *Ruminococcus gnavus* ↓ *Fusicatenibacter* ↓ *Sutterella* ↓ *Dialister*	None	None		(Jiang et al., 2020)
	16S (no)	N = 12 breast cancer survivors sampled at baseline and after 3mo Focus on psychosocial metrics	No significant microbiota differences after FDR adjustment	None	None		(Paulsen et al., 2017)
	16S (no)	N = 27 Control N = 27 MDD	**MDD vs Control** ↑ *Coprococcus** ↑ *Pseudomonas** ↑ *Blautia**			Greengenes	(Huang et al., 2018)

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Table 10 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
	16S (no)	N = 34 Depressed + Probiotic N = 37 + PBO N = 20 Non-Depressed	No differences between groups *Ruminococcus gnavus* associated with DASS depression score* (Correlation = 0.37)	None	None	QIIME 1.9.1, Greengenes, rarefaction	(Chahwan et al., 2019)
	16S (no)	N = 17 MDD inpatients Samples collected at baseline and after 6wks treatment with Escitalopram	None	None	None	No genus level differences reported, no control arm	(Liskiewicz et al., 2019)
	16S (no)	N = 16 Inpatients at admission and 6 weeks later	*Paraprevotella* positively associated with Hamilton Depression Scale-24 Item score* (r = 0.8)	None	None	Greengenes, rarefaction	(Liśkiewicz et al., 2021)
	16S (no)	N = 40 MDD taking psychotropics at three different timepoints	No genera-level associations with specific psychotropic medication within the cohort	None	None	Greengenes	(Tomizawa et al., 2020)
	16S (no)	N = 10 MDD N = 10 Control	**MDD vs Control** ↑ *Prevotella** (D1, D10 and D29) ↑ *Streptococcus** (D1, D10) ↑ *Clostridium XI** (D29)	None	None		(Lin et al., 2017)
	16S via 454 Pyrosequencing (no)	N = 58 MDD N = 63 Control	**MDD vs Control** ↑ *Collinsella* (RA = 4.2% vs 1.7%)* ↑ *Olsenella* (RA = 0.003% vs 0%)* ↑ *Blautia* (2 OTUs)** ↑ *Anaerostipes* (RA = 1.491% vs 0.303%)*** ↓ *Alistipes* (RA = 0.249% vs 0.761%)*	None	None		(Zheng et al., 2016)
	16S via 454 Pyrosequencing (no)	N = 38 Co-Morbid Anxiety and Depression N = 8 Anxiety N = 14 Depression N = 10 Control	↑ *Bacteroides* in anhedonia	None	None		(Mason et al., 2020)
	16S via 454 Pyrosequencing (no)	N = 29 MDD Responded N = 17 MDD Active N = 30 Control	**Active MDD vs Control** ↑ *Blautia* ↑ *Oscillibacter* ↑ *Roseburia* ↓ *Bacteroides* ↓ *Dialister* ↓ *Faecalibacterium* ↓ *Prevotella* ↓ *Ruminococcus* **Responded MDD vs Control** ↑ *Bacteroides* ↑ *Roseburia* ↓ *Oscillibacter* ↓ *Prevotella* ↓ *Ruminococcus* ↓ *Faecalibacterium* Negative correlation between *Faecalibacterium* and depressive symptoms	**Active MDD vs Control** ↓ *Bacteroides* **Responded MDD vs Control** ↑ *Bacteroides*	**Responded MDD vs Control** ↓ Escherichia/Shigella (ClpB)		(Jiang et al., 2015)

(*continued on next page*)

Table 10 (*continued*)

Cohort Details	Sequencing (reanalysed)	Groups and Sample Size	SCFA/Tryptophan-Modifying Bacteria	BA-Modifying Bacteria	Other Metabolites/ GBMs	Specific Limitations	Ref
	16S via 454 Pyrosequencing (no)	N = 40 Generalised Anxiety Disorder (GAD) N = 36 Control: N = 12 Anti-Depressant Naïve Patients N = 22 Control	**GAD vs Control** ↓ *Faecalibacterium** ↓ *Eubacterium rectale** ↓ *Sutterella** ↓ *Butyricoccus* ↑ *Bacteroides** ↑ *Ruminococcus gnavus** ↑ *Fusobacterium** **Treatment Naïve vs Control** ↑ *Lactobacillus** ↑ *Ruminococcus gnavus** ↑ *Fusobacterium** ↑ *Escherichia-Shigella** ↑ *Bacteroides** ↓ *Faecalibacterium** ↓ *Eubacteirum recetale* ↓ *Roseburia* ↓ *Subdoligranulum*	**GAD vs Control** ↑ *Bacteroides** **Treatment Naïve vs Control** ↑ *Lactobacillus** ↑ *Bacteroides** ↓ *Eubacteirum recetale*			(Jiang et al., 2018a)
	16S via 454 Pyrosequencing (no)	N = 40 with Diarrhea-Predominant IBS (IBS-D): N = 15 with Depression, N = 25 with Comorbid Patients (CM) N = 20 Control	**All Depression vs Control** ↑ *Bacteroides**** ↑ *Prevotella**** ↓ *Coprococcus****	**All Depression vs Control** ↑ *Bacteroides****	None		(Liu et al., 2016)
	16S via 454 Pyrosequencing (no)	N = 15 (co-morbid depression and diarrhoea predominant IBS) Treatments: Bifico Probiotic (n = 8), Duloxetine (n = 6)	**Post vs Pre Bifico** ↓ *Bifidobacterium* **Post vs Pre Duloxetine** ↑ *Faecalibacterium*	**Post vs Pre Bifico** ↓ *Bifidobacterium*	**Post vs Pre Bifico** ↓ *Bifidobacterium* **Post vs Pre Duloxetine** ↑ *Escherichia/Shigella* (ClpB)		(Zhang et al., 2019a)
	16S (qPCR)	N = 43 MDD N = 57 Control	**MDD vs Control** ↓ *Bifidobacterium* ↓ *Lactobacillus*		None		(Aizawa et al., 2016)
	RFLP (no)	N = 56 OI N = 9 Control	**OI vs Control** ↑ *Clostridium* subcluster XIVa* **OI Depressed vs OI Non-Depressed** ↓ *Bifidobacterium*	**OI Depressed vs OI Non-Depressed** ↓ *Bifidobacterium*	None		(Ishii et al., 2019)

Legend: LFC: log-2 fold change; LC: log change; RA: relative abundance; DASS-42: Depression Anxiety Stress Scales; ADHD: Attention-Deficit Hyperactivity Disorder; HE: hepatic encephalopathy; FOS: Fructo-oligosaccharide; HADS-A: Hamilton Anxiety and Depression Scales – Anxiety Subscale; HADS-A: Hamilton Anxiety and Depression Scales – Depression Subscale; RTT: Rett's Syndrome; AD: Alzheimer's Disease, PD: Parkinson's Disease; MCI: mild-cognitive impairment; MSA: multiple-systems atrophy; ALS: amyotrophic lateral sclerosis; NMOSD: neuromyelitis optica spectrum disorder*: $p_{adj} < 0.1$; **: $p_{adj} < 0.01$; ***: $p_{adj} < 0.001$; Reanalysed studies are highlighted; 95 % CI reported between square brackets [lower 95 % CI; upper 95 % CI].

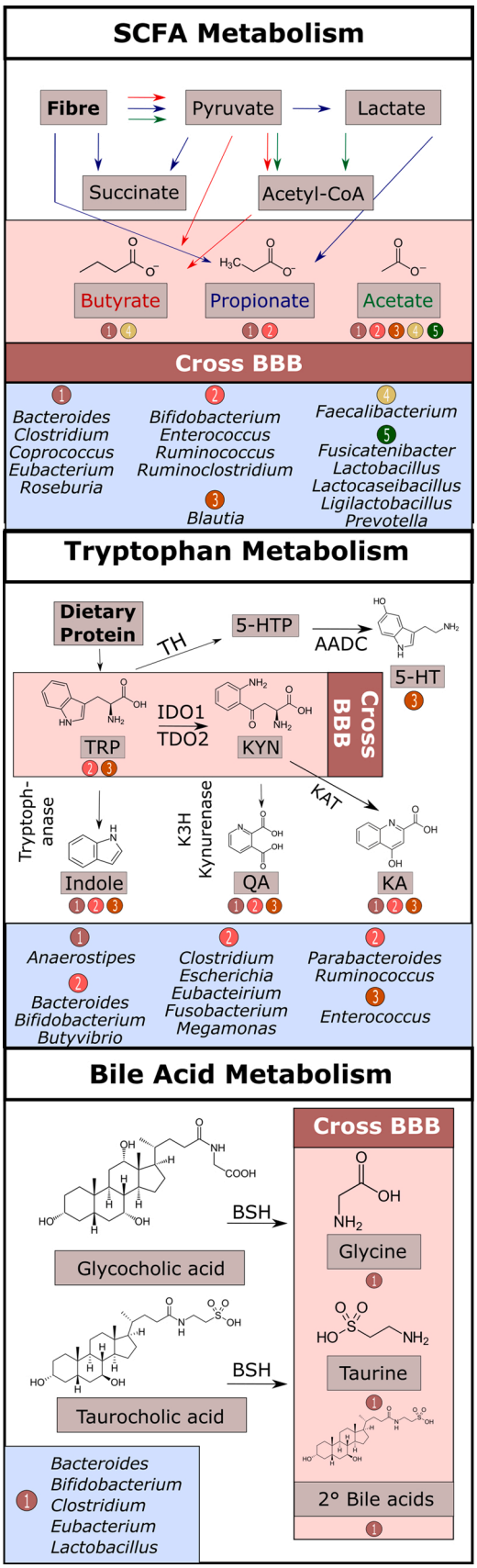

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Fig. 1. Microbial metabolic pathways. A summary of pathways used by different microbes to generate SCFA, tryptophan-kynurenine or bile acid related metabolites. Due to the amount of different microbial genera known to generate these metabolites, only a subset of these microbes is referred to in this figure. Many different genera use multiple metabolic pathways; it is yet unclear if all human enzymes in the kynurenine/tryptophan pathway are found in the microbiome. *5-HTP: 5-hydroxytryptophan; 5-HT: serotonin; AADC: aromatic amino acid decarboxylase; IDO1: indoleamine-2,3-dioxygenase; TDO1: tryptophan-2,3-dioxygenase; TH: tryptophan hydroxylase; K3H: kynurenine-3-hydroxylase; KAT: kynurenine amino-transferase; BSH: bile salt hydroxylase.*

observational human studies (Ma et al., 2019c; Lynch et al., 2020; Koh and Bäckhed, 2020; Walter et al., 2020; Ma, 2020). See Table 11 for a description of these common limitations and available tools to address them. In addition to those limitations, even functional analysis of WGS data does not provide direct information about the proteomics or metabolomics within the gut community.

4.14.1. *Sources of inter-individual variance*

One of the greatest challenges with human microbiota studies is making inferences about the composition of the colonic microbiota from faeces. There are known differences between the faecal and caecal microbiota composition in humans along with spatial variation across the gastrointestinal tract (Gevers et al., 2014; Lavelle et al., 2015). Finding healthy volunteers willing to provide one or multiple biopsies for a microbiota study is challenging. In addition, it's difficult to determine whether certain microbes are overrepresented in the faeces compared to others. The overall microbial load, though seldom measured, is an important determinant of microbiota composition (Vandeputte et al., 2017). It is also recognised that microbiota composition changes day-to-day in response to diet, circadian rhythms and sex hormones among other confounds (Jaggar et al., 2020; Johnson et al., 2019; Nobs et al., 2019; Markle et al., 2013).

In addition to long-term dietary patterns (Wu et al., 2011), food alters the microbiota on a smaller timescale as well. (Johnson et al., 2019) assessed day-to-day variations within microbiota composition by collecting detailed daily food diaries and daily faecal samples for seventeen days. While the microbiota composition was correlated with food preferences, it was not associated with individual nutrients (Johnson et al., 2019). Subjects had different responses to the same types of foods, which could affect the microbiome for up to two days after consumption (Johnson et al., 2019). Meanwhile (Berry et al., 2020) reported that even twins had different metabolic responses. Interestingly, the microbial composition of individuals explained more variation in postprandial lipemia than meal macronutrients (Berry et al., 2020). Metabolic disease and obesity is common amongst sufferers of anxiety and depression (Rajan and Menon, 2017) while food pickiness is common in ASD (Kral et al., 2013). In addition, microbiota correlates with both the diet and other peripheral health measures in elderly individuals (Claesson et al., 2012). Many neuropsychiatric disorders involve alterations in food preference (Greenwood et al., 2005; Yau and Potenza, 2013; Folley and Park, 2010). To detangle interindividual differences in dietary responses from microbial-brain-disease associations, multi-timepoint sampling and dietary records must be incorporated. Other considerations when collecting dietary-related data or integrating dietary interventions include study design, control selection, measuring subject compliance, diet-measurement error, participant bias and method of collecting dietary information (Swann et al., 2020; Willett, 2012).

Another large confound in many of these studies is the medication that individuals may take for their disease or disorder, as well as recreational alcohol and drug use (Maier et al., 2018; Fulcher et al., 2018; Cussotto et al., 2018b; Vich Vila et al., 2020; Forslund et al., 2015; Vieira-Silva et al., 2020; Barengolts et al., 2018; Peterfreund et al., 2012; Zhernakova et al., 2016; Falony et al., 2016; Panee et al., 2018; Bjorkhaug et al., 2019; Dubinkina et al., 2017; Seo et al., 2020; Tsuruya et al., 2016; Coello et al., 2019; Ishaq et al., 2017; Stewart et al., 2018).

Table 11
Common limitations of human microbiome brain studies.

Challenge	Standard approach	Recommended approach
Metadata collection	Often confounding variables are not measured or included in studies. There are several confounds that must be accounted for during analysis.	Participant data: • Consider whether the sample size is sufficient to answer your question • Food diary • Alcohol-use • Smoking status • Prescription and recreational drug-use • Exercise frequency and intensity • Symptom frequency and severity • Note time of day that samples are collected
Updating tools for data analysis	Occasionally, studies use databases or tools that are no longer updated, outdated or obsolete i.e. QIIME version 1 or Greengenes database from 2013	Make sure installed packages are up-to-date.
Assigning taxonomy to sequences	Many studies use operational taxonomic units which are less precise and more prone to error.	ASVs are a more precise alternative which can be implemented through DADA2 (Callahan et al., 2017).
Non-compositional data analysis	Counts data must be properly transformed to account for its relational data structure • Normalization with rarefaction or DESeq2 • Measuring distance between groups using Bray-Curtis, UniFrac, Jenson-Shannon; often used with Principal Co-ordinate Analysis • Pearson or Spearman Correlations (compositional data is prone to spurious correlation) • Differential abundance with LEfSe, DESeq, metagenomSeq	• Log-ratio transformation (i.e. CLR, IQLR, ALR) (Gloor et al., 2017) • Measure distance between groups with the Aitchison metric in conjunction with Principal Component Analysis • SparCC, SpiecEasi, Φ for Correlations • Differential abundance with ALDEx2 (Quinn et al., 2018, Fernandes et al., 2014)
Functional microbiome analysis	Since they are relatively new, GBMs are not currently in widespread use.	Use gut-brain module analysis to provide more insight into your data.
Reporting Statistical Analysis	While adjusted p-values are often reported, studies seldom mention effect sizes or confidence intervals.	Report effect sizes and 95 % confidence intervals. Sparse microbiome datasets are prone to uncertainty. If the confidence interval does not overlap with 0, then there is more certainty in the direction of the effect.
Methods, Code and Data	Often, the methods and code are not provided within microbiome publications.	Deposit the data and code publicly if possible in one of the following locations: - Sequence Read Archives - MG-RAST - GitHub

In addition to diet, and drugs, sex hormones play an important component in many of these neuropsychiatric disorders, the microbiota is also able to participate in 17-β-estradiol degradation (Valles-Colomer et al., 2019), and potentially other pathways (Fuhrman et al., 2014; Shin et al., 2019). (Shin et al., 2019) reported that the faecal abundance of multiple bacterial genera was associated with serum levels of testosterone and oestrogen in humans.

There are also limitations in diagnosing and subtyping different types of diseases and disorders. There are a wide spectrum of symptoms and conditions associated with the disorders mentioned within the study. The heterogenous nature of many disorders and conditions such as ASD, anxiety, depression and stress serve as large confounders (Feczko et al., 2019). Much of the metadata does not detail specific symptoms or subtypes of a diagnosis or a disorder. Having this information would allow for a higher resolution analysis of gut-brain interactions.

Even when accounting for host-genotype effects with larger cohorts, accounting for sex, body mass index and genotype, it is difficult to interpret microbiome-host associations without identifying the driving influence in such an interaction (Hughes et al., 2020). A preprint by (Rothschild et al., 2020) suggests that large cohort studies may require thousands of participants on order to reach 20 % explanatory power for a certain host-trait with specific microbiota-associated metrics (Shannon diversity, relative microbial abundance). The collection of metadata is important to allow for a better comparison between studies and to identify differentially abundant microbes arising from confounding variables.

4.14.2. Reporting of effect sizes and confidence intervals

The magnitude of the effect size is also important to consider, as the microbiome is a dynamic system, and effect size measurements prove more informative than p-values alone though they are seldom reported (Sullivan and Feinn, 2012). In addition, tools involving linear discriminant analysis for identifying differentially expressed microbes and their effect sizes do not consider the compositional nature of microbiome data. Unfortunately, most studies did not report effect sizes.

5. Conclusion

Though the evidence for the involvement of individual microbial genera or GBMs related to SCFA, tryptophan or bile acid metabolism within humans is weak, we found several salient findings and features within these datasets. GBMs allow us to search metagenomic data for specific neuroactive metabolic pathways leading to mechanistic insights. Within a very short time after their release, several human (Butler et al., 2020; Chen et al., 2020c; Tomizawa et al., 2020; Zhu et al., 2020) and preclinical studies have taken advantage of their descriptive properties (O'Connor et al., 2020; Van De Wouw et al., 2020).

Many studies involving healthy humans are currently investigating associations between temperament, cognition and personality across the lifespan. While these studies may continue to find various associations, without proper compositional data analysis these associations are likely spurious and biased towards negative correlations (Gloor et al., 2017). Even with compositional data methods, finding explanatory genera or ASVs may require thousands of participants to power the study (Hughes et al., 2020).

Neurodevelopmental disorders accounted for many of the human-microbiome-brain studies. While a WGS study suggests reductions in the KO abundance of dopamine pathways in ADHD (Wang et al., 2020a), it is hindered by a lack of compositional analysis. Other studies suggested correlations between *Faecalibacterium*, *Ruminococcus* and *Ruminoclostridium 9* with symptoms of ADHD (Jiang et al., 2018b; Szopinska-Tokov et al., 2020). These microbial genera may alter SCFA or tryptophan related pathways but must be further validated through metabolomic methods. Across dozens of ASD studies, very few consistencies were found across these studies. When reanalyzing raw microbiome data, very few differentially regulated microbes or GBMs reached the significance and effect size thresholds. In the dataset from Son et al. (2015), there were no differences in microbial composition within a sample of twins discordant for ASD. However, some of these studies suggested the important interplay between diet and faecal SCFAs within ASD (Berding and Donovan, 2019; Liu et al., 2019b; Wang et al., 2020c). Meanwhile there is moderate level of evidence that *Lactobacillus* and *Bifidobacteria* are dysregulated amongst multiple schizophrenia studies, as well as dysregulation within SCFA and tryptophan-related GBMs (Zhu et al., 2020; Xu et al., 2020; Schwarz et al., 2018; Shen et al., 2018).

While there are difficulties in determining strong associations because of the diversity and new nomenclature of *Lactobacillus* genera (Zheng et al., 2020a), we found evidence of broad dysregulation across most existing schizophrenia studies.

In one longitudinal study assessing the impact of ketogenic diet on the microbiota of young epileptic children, we found increased abundance of the Tryptophan biosynthesis and S-Adenosyl Methionine biosynthesis GBMs (Lindefeldt et al., 2019). This would imply different mechanisms for the efficacy ketogenic diet on epilepsy than seen in mice (Olson et al., 2018). In studies assessing the overall microbial differences found in epilepsy, we found that most studies assessed different cohorts making them difficult to compare with each other.

These results are not consistent with the findings in mice by Olson et al. (2018). In mice, the gut microbiota is required for mediating the anti-epileptic effects of the ketogenic diet; specifically, *Akkermansia* and *Parabacteroides* were implicated as mediators (Olson et al., 2018). In healthy adult humans, there is evidence that the ketogenic diet alters the gut microbiota and intestinal immunity, but more studies are needed to determine the mechanisms of anti-epileptic effects in humans (Ang et al., 2020).

Across neurodegenerative disorders, there is evidence of changes in SCFA and tryptophan-related GBM abundance in AD and MCI (Li et al., 2019a). However, most of this evidence is emergent from one reanalysed study. Though the microbiota is an intriguing target for amytotrophic lateral sclerosis and MSA, we did not find enough studies investigating this link to warrant a consensus. Preclinical evidence suggests PD pathogenesis can be initiated through α-Synuclein overexpression in the myenteric plexus, reaching the brain through the vagus nerve (O'donovan et al., 2019; Holmqvist et al., 2014; Ulusoy et al., 2013; Uemura et al., 2018; Manfredsson et al., 2018). However, when reanalyzing raw data and accounting for recorded metadata we did not find evidence of consistent gut microbiota alterations. While PD is progressive and features many different subtypes, it may be necessary to stratify participants by medication and subtype. Nonetheless, this was a somewhat surprising finding.

A lack of dietary metadata may have hindered cross-comparison across alcohol-dependence studies. Though various genera involved in SCFA and tryptophan metabolism were identified across many of these datasets (Bjorkhaug et al., 2019; Seo et al., 2020; Dubinkina et al., 2017; Leclercq et al., 2014). Even with a small sample size consisting of 10 tobacco smokers and 10 controls, we found an increased abundance of the tryptophan degradation module and a reduction of propionate synthesis III (Stewart et al., 2018). In addition, studies investigating the impact of recreational drug-use also reported differences in tryptophan and SCFA-associated genera (Fulcher et al., 2018; Panee et al., 2018). This must be taken into consideration when collecting metadata, as some of the strong microbiota-related changes between two groups may be explained by alcohol and drug use.

Reductions in faecal SCFA concentrations were reported in two studies investigating demyelinating diseases (Gong et al., 2019; Zeng et al., 2019). It is unclear if this is a result of subtle microbiota changes or gastrointestinal physiology within the disease group.

There are too few fibromyalgia and migraine microbiome-related studies to make definitive conclusions. However, one fibromyalgia study found altered microbial species associated with SCFA and tryptophan metabolism, as well as changes in serum levels of SCFAs (Minerbi et al., 2019). Similarly the sole migraine-microbiota study reported an increased abundance of the kynurenine synthesis GBM (Chen et al., 2020c). While few taxa were consistently associated with psychological metrics within IBS, interventions involving faecal matter transplantation of material high in *Bifidobacterium* (Mizuno et al., 2017) or probiotic *Bifidobacterium* strains (Ma et al., 2019b; Pinto-Sanchez et al., 2017) may improve the psychological dimensions of this disease.

Across studies of obesity involving 16S and WGS methods, we did not find differentially abundant microbes and microbial metabolic pathways consistently associated with psychological aspects of obesity. When

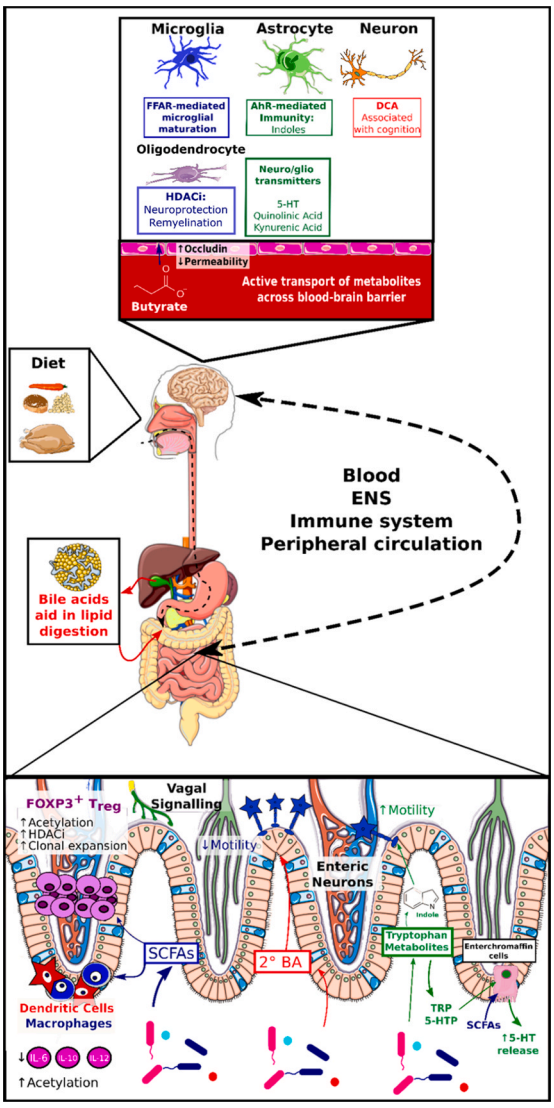

Fig. 2. Potential pathways for microbiota-gut-brain axis communication. While it's is unclear exactly how microbial-derived metabolites impact the brain, there are several potential pathways. Non-digestible fibres are broken down into SCFAs which act as histone deacetylase inhibitors on FOXP3$^+$ T_{Reg} cells in the gut, leading to clonal expansion. SCFAs many also influence the enteric dendritic and marcrophage cell population by increasing acetylation at specific gene targets. This leads to a decreased release of interleukin-6, interleukin-10 and interleukin-12. SCFAs may also affect enterochromaffin cells in the gut, stimulating the release of serotonin into the lumen. Travelling through the blood, the SCFA butyrate may increase occludin expression at the blood-brain barrier as well as decrease its permeability to different molecules. If present in a sufficient concentration, SCFAs may impact microglial maturation through free-fatty acid receptor-mediated mechanisms. Bile acids used to aid in lipid digestion are deconjugated and biotransformed into secondary bile acids. These act on myenteric neurons to inhibit gut motility. In the brain, there is evidence that the secondary bile acid, deoxycholic acid (DCA) is associated with cognition. Tryptophan derived from dietary protein sources impacts both the enteric and central nervous system environments. Briefly, bacteria may generate indole molecules which can act on myenteric neurons to increase gut motility. Tryptophan (TRP) or 5-Hydroxytryptophan (5-HTP) are also generated from dietary protein sources. TRP and 5-HTP can be converted into 5-HT in enterochromaffin cells. In the brain, indoles impact immunity through activation of the Aryl-Hydrocarbon receptor in astrocytes. Alternatively, TRP or 5-HTP can be transported across the blood-brain barrier and converted into the neurotransmitters 5-HT, quinolinic acid or kynurenic acid. It is unclear what role the vagal nerve pathway plays in mediating microbial-derived metabolite signalling. In oligodendrocytes, SCFAs may contribute to neuroprotection and remyelination through HDACi pathways.

Box 1
Guidelines for metadata and bioinformatics analysis of human-microbiome-brain studies.

1 If at all possible, ensure that extensive metadata is collected, including dietary intake, medication, supplement use, etc.
2 Make sure all software is up-to-date.
3 Use SILVA or other curated taxonomy databases instead of Greengenes.
4 Use compositional data method to transform the counts tables (ex. CLR).
5 Use compositional analysis methods to check for significance and employ a strict effect size cut-off.
6 Use compositional alternatives to standard correlational statistics.
7 Report effect sizes and confidence intervals along with p-values and p-adjusted values.
8 When possible, provide open access to datasets, scripts and pipelines to reproduce the results.

Box 2
Questions crucial for understanding the interactions between microbial metabolic pathways and the brain.

1 How ubiquitous is the expression of any specific GBM across the same genera/species?
2 How explanatory are GBMs compared to metabolomic and proteomic faecal analysis?
3 Can we accurately develop a GBM framework for bile-acid metabolism?
4 How do we address causality when many microbes possess enzymes for multiple GBMs?
5 How do we design studies to avoid the pitfalls of interindividual variation within the microbiome, metabolism and disease subtype/severity?

Box 3
Methods to improve cross-study replicability and provide more accurate microbial quantification.

1 **Decomposition of Variance Using Replicate Sampling:** A combination of using technical replicates and spike-in controls to estimate absolute abundance.
2 **Spike-In:** Adding a known amount of synthetic 16S rRNA sequences to samples for estimation of absolute abundance.
3 **Reference Materials and Biobank:** Collecting and storing faecal samples from different cohorts of healthy individuals. This material would provide controls for multiple studies. It would allow for accurate quantification of variability between populations, labs and pipelines.

reanalyzing studies of anorexia, we found an increased abundance in isovaleric acid synthesis I, quinolinic acid synthesis, quinolinic acid degradation when comparing anorexia to control individuals (Mack et al., 2016). While the ClpB GBM, produced by *Escherichia coli* (Tennoune et al., 2014), was elevated at admission compared to controls, after weight gain it was ameliorated (Mack et al., 2016). It is unclear whether microbial-host pathways involving ClpB and hunger also interact with SCFA and tryptophan metabolism.

Due to the heterogeneity of stroke and vascular disease conditions, it is difficult to make substantial comparisons between studies. However, (Polster et al., 2020) report convincing evidence for the involvement of specific microbial genera/species and a neurovascular condition in humans. However, rather these taxa were linked to LPS biosynthesis rather than SCFA production (Polster et al., 2020).

Several studies suggest lasting microbial changes in response to prenatal or postnatal stress (Naude et al., 2019; Hantsoo et al., 2019; Carlson et al., 2018) though these do not provide evidence for the involvement of SCFA, tryptophan or bile-acid modifying bacteria. Similar to stress, there are very few studies assessing the impact of post-traumatic stress disorder on the microbiota. Though multiple studies have assessed the microbiota composition in bipolar disorder, there were no consistent signatures across studies. In fact, one study found sex effect, heritability and smoking explained all observed changes in the gut microbiota between bipolar disorder and controls (Coello et al., 2019). Meanwhile, across studies of anxiety and depression there is moderate evidence for *Dialister* and *Faecalibacterium* reductions in depression and anxiety (Valles-Colomer et al., 2019; Jiang et al., 2015, 2020; Jiang et al., 2018a; Stevens et al., 2018). It is unclear if the metabolic pathways that these microbes contribute to, mainly SCFA and tryptophan-related pathways, impact the host phenotype.

6. Future directions

In part due to the many limitations of existing 16S and WGS studies as well as their collected metadata, we did not find many consistent changes in the gut microbiota or their associated metabolic pathways. Despite the limitations outlined in Section 3.**15**, there is still potential for rigorous, well-designed human studies to uncover the potential roles of these metabolites. Fig. 2 briefly outlines the potential pathways and known interactions of SCFAs, tryptophan metabolism and deconjugated bile acids in brain function and health. Although none of these pathways have been directly linked to changes in the gut microbiota, we are hopeful that consensus guidelines for sequencing and downstream analysis of the human microbiota will contribute to uncover these changes. It is also difficult to compare studies within a human disease without the multiple publicly available datasets, detailed dietary information and medical information, effect sizes, confidence intervals or detailed bioinformatics procedures. The widespread use of relative abundance as opposed to methods incorporating the compositional nature of the microbiota (i.e. using the CLR transformation) is problematic within the microbiome field (Gloor et al., 2017, 2016; Fernandes et al., 2014, 2013). Reporting effect sizes along with 95 % confidence intervals when finding differentially abundant microbes or metabolites would increase the interpretability of these results. For example, if a

differentially abundant microbe is increased in one group, but its effect size has a very small lower bound (i.e. a large negative value), this is indicative of a spurious finding.

We provide some guidelines for scientists analyzing their microbiome data when building their pipeline and selecting their methodology (see Box 1).

In conjunction with metabolomic and proteomic studies, consistent well-designed bioinformatics pipeline can identify the involvement of microbially-associated SCFA, tryptophan and bile acid metabolites. There are still important questions that must be addressed or considered when designing these studies (see Box 2).

While we may standardise protocols and adapt to new sequencing platforms in the future, some researchers suggest the development of microbiome standards to better quantify microbial abundance within a sample (Ji et al., 2019; Venkataraman et al., 2018; Tourlousse et al., 2018; Vandeputte et al., 2017; Stämmler et al., 2016; Tkacz et al., 2018). In addition, a biobank of standardised references could be shared as controls across multiple studies (see Box 3).

This analysis provides a novel approach for understanding the mechanisms behind metabolite-mediated communication within the microbiota-gut brain axis and reiterates many technical and bioinformatics considerations that must be acknowledged when interpreting results. Despite that, we found novel links between gut microbial metabolic pathways in schizophrenia, AD, and anxiety/depression.

Declaration of Competing Interest

J.F.C, GC and T.G.D have research support from Cremo, Pharmavite, Dupont and Nutricia. These authors have spoken at meetings sponsored by food and pharmaceutical companies. All other authors report no potential conflicts of interest.

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