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Protocol for a systematic review on the role of the gut microbiome in paediatric neurological disorders

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Abstract

Introduction: The gut–brain axis refers to the bidirectional communication that occurs between the intestinal tract and central nervous system (CNS). Through a series of neural, immune, endocrine, and metabolic signalling pathways, commensal microbiota are able to influence CNS development and neurological function. Alterations in gut microbiota have been implicated in various neuropathologies. The purpose of this review is to evaluate and summarise existing literature assessing the role of specific bacterial taxa on the development of neurodevelopmental, neuropsychiatric, and neurodegenerative pathologies of childhood. We will also discuss microbiota-based therapies dietary interventions and their efficacy. *Methods and analysis:* We will search PubMed, Cochrane Library, and OVID electronic databases for articles published between January 1980 and February 2021. A search method involving two rounds of reviewing the literature using a three-step method in each round will be performed. Two researchers will be selected, and screen titles and abstracts independently. The full text of selected articles will be assessed against inclusion criteria. Data will be extracted and evaluated using the appropriate Critical Appraisal Skills Programme (CASP) checklist. *Ethics and dissemination:* Findings from this study will be shared across relevant paediatric neurology and gastroenterology societies and submitted for peer review. This study did not require institutional ethics approval.

Significant outcomes

We anticipate that this systematic review will identify and describe the following:

- The role of the intestinal microbiome in paediatric neurological disorders.
- The relationship between early life alterations of the gut microbiome and the development of later life neurological disorders.
- Specific bacterial taxa of the intestinal microbiome that have been implicated in the pathogenesis or treatment of paediatric neurological disorders.
- Microbiota-derived metabolites and their effect on neurotransmitter balance and neuroglia modulation in neurodevelopmental, neuropsychiatric, and neurodegenerative disorders.
- The role of the gut microbiome in autoimmunity, immunomodulation, and neuroinflammation associated with paediatric neurodevelopmental, neuropsychiatric, and neurodegenerative disorders.
- An exploration of host–microbiome interactions between intestinal microbiota and the intestinal mucosa and their potential effect on paediatric neurodevelopmental, neuropsychiatric, and neurodegenerative disorders.

This will also be the first review to explore microbiota-based interventions that have been assessed for their role in improving symptoms of paediatric neurological disorders, including FMT, probiotics, and prebiotic-based therapies and dietary interventions.

Protocol

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Limitations

- This is the first study to evaluate the strength of available evidence on the association between paediatric neuropathologies and the intestinal microbiome, as well as evidence for the efficacy of microbiota-based therapeutics in managing these conditions.
- A systematic review of the prospective, retrospective, cohort, and case–control studies will be performed as per PRISMA-P guidelines using the CASP checklist.
- Available paediatric-based literature on this topic may be limited, particularly as we will be eliminating case series, case studies, and expert opinions to maintain data integrity and high-quality level of evidence.

Introduction

The gut–brain axis refers to the bidirectional communication that occurs between the gastrointestinal tract and the central nervous system (CNS) (Mayer *et al.*, 2015). This network of highly integrated communication is facilitated by neural, hormonal, immune, endocrine, and metabolic pathways and is essential for the maintenance of homeostasis (Westfall *et al.*, 2017). The importance of the gut–brain axis in health and disease is highlighted by associations between chronic intestinal inflammation, dysregulation of the immune system, and alterations in gut microbiota and its respective metabolites. Changes in immune activation, neuronal apoptosis, and neurotransmitter concentrations have all been associated with changes in the CNS (Forsythe *et al.*, 2014; Stilling *et al.*, 2014; Evrensel & Ceylan, 2015; Dinan & Cryan, 2017). The clinical manifestations of disruptions in this axis have been extensively studied in mood disorders (Foster & McVey Neufeld, 2013; Liu & Zhu, 2018), and are becoming increasingly recognised as aggravators in the development of adult-onset neurodegenerative diseases such as Alzheimer's (Hu *et al.*, 2016; Kowalski & Mulak, 2019) and Parkinson's disease (Houser & Tansey, 2017; Caputi & Giron, 2018). Limited research has investigated the role of the intestinal microbiome in paediatric neuropathologies.

Initial development of the infant microbiome through *in utero* exposure is controversial as the placenta contains no microbiota, but may contain potential pathogens (Charbonneau *et al.*, 2016; Stinson *et al.*, 2019). Instead, the majority of bacterial colonisation begins with parturition (Jašarević *et al.*, 2016; Warner, 2019) as the neonate is exposed to microbes during vaginal delivery and close contact with maternal feces (Jost *et al.*, 2014; Obata & Pachnis, 2016). Mode of feeding also plays an important role in early life bacterial colonisation (Belkaid & Hand, 2014; Jost *et al.*, 2014). The infant microbiome undergoes further expansion and diversification through early childhood, stabilising by approximately 2 years of age (Braniste *et al.*, 2014; Jašarević *et al.*, 2016). Subsequent alterations to the gut microbiota profile have been observed through adolescence with final stabilisation in adulthood (Heijtz *et al.*, 2011). Upon the colonisation of the GI tract at birth, gut microbes establish a symbiotic relationship with the intestinal epithelium, where they play a crucial role in training the innate and adaptive immune systems to select and calibrate responses against pathogens while maintaining tolerance towards host- and commensal-derived molecular profiles (Belkaid & Hand, 2014). This intimate crosstalk between the microbiota and the immune system preserves the intestinal mucosal integrity and barrier function. Perturbations of gut microbiota composition in early life have been shown to affect intestinal barrier permeability, with consequent inappropriate translocation of bacterial-derived products and antigens that can reach and cross the blood–brain barrier, which is still immature at this stage, leading to microglia hyperactivation in the CNS and neuroinflammation (Fiorentino *et al.*, 2016). On the other hand, disturbances of the microbiota–immune system axis in early life could favour potential infections from pathogens that share molecular mimicry with host antigens, causing immunological cross-reactions and autoimmunity, all conditions associated with the pathogenesis of some neurodevelopmental (Hughes *et al.*, 2018) and neuroinflammatory disorders (Haase *et al.*, 2018).

Disruptions in intestinal bacterial colonisation during the critical windows of development in early life have been attributed to various exogenous insults: intrapartum maternal antibiotic use, mode of infant delivery, perinatal feeding practice, and early life exposures to antibiotics (Carabotti *et al.*, 2015; Dinan & Cryan, 2017). Animal models have helped elucidate the role of gut microbiota in modulating enteric neural maturation and establishment of neural circuits (Heijtz *et al.*, 2011; Vasquez, 2017), priming the immune system to discriminate self from non-self-antigens (Houser & Tansey, 2017; Vuong & Hsiao, 2017), and metabolising short-chain fatty acids essential for gut (Dinan & Cryan, 2017) and brain health (Carabotti *et al.*, 2015). Germ-free (GF) mice have been used to show alterations in multiple neurotransmitters and signalling pathways including the hippocampus and amygdala, in contrast to conventionalised animals (Bercik *et al.*, 2011; Braniste *et al.*, 2014). While animal models have shown clear impacts of intestinal microbiota on brain development and neuropathologies, translation of this work to human hosts has been complicated by genetic, epigenetic, and environmental factors (Putignani *et al.*, 2014). While directly assessing the effects of specific microbial species on brain development is generally not feasible for human study, early life alterations in the gut microbiome have been associated with various paediatric neuropathologies including: neurodevelopmental disorders such as autism spectrum disorder (ASD) (Vasquez, 2017; Vuong & Hsiao, 2017), attention deficit hyperactivity disorder (ADHD) (Cenit *et al.*, 2017), and Rett syndrome (Borghi *et al.*, 2017); and neuropsychiatric disorders, such as schizophrenia, mood disorders, and dementia (Stuchlik & Sumiyoshi, 2014) Due to the impact of intestinal dysbiosis on the onset and expression of these pathologies, there is increasing interest in investigating the role of microbiota-based treatment approaches. Probiotics, prebiotics, and fecal microbiota transplantation (FMT) (Dinan & Cryan, 2017; Westfall *et al.*, 2017) have received considerable attention for their potential roles in manipulating the intestinal microbiome to a 'healthier' milieu, in an effort to offer symptomatic improvement for these neurological disorders.

To date, knowledge about the role of the gut microbiome in paediatric brain development remains limited. This will be the first rigorous systematic review attempting to document the role of the gut microbiome in paediatric neurological disorders. There is a clear need to investigate the relationship between early life alterations to the gut microbiome and the development of later life neurological disorders, particularly as early onset disease may be most amenable to intervention. The review will attempt to identify specific bacterial taxa of the intestinal microbiome that have been implicated in the pathogenesis or treatment of paediatric neurodevelopmental, neuropsychiatric, and neurodegenerative disorders. We will discuss hormonal regulation as well as inflammatory and other biochemical pathways associated with these relevant

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disorders. Further, we will explore microbiota-based interventions that have been examined for their role in improving symptoms associated with paediatric neuropathologies, including FMT, probiotics, and prebiotic-based therapies.

Objectives

To conduct a systematic review on the role of the gut microbiome in paediatric neurological disorders.

Methods and analysis

Study design

As is outlined by Grant and Booth (Grant & Booth, 2009), we will be conducting a systematic review of the relevant literature. In this context, we will be systematically searching, appraising, and synthesising evidence surrounding the gut microbiome in paediatric neurological disorders, including neurodevelopmental, neuropsychiatric, and neurodegenerative diseases. We aim to draw upon a wider range of study designs that incorporate quantitative, qualitative, and mixed-method studies.

This review will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocols checklist (Liberati *et al.*, 2009). The systematic review protocol was prospectively registered on PROSPERO (ID: CRD42020158734) (National Institute for Health Research, 2020).

Data management

The search results will be imported into the Mendeley reference management software (https://www.mendeley.com). Once the two rounds of study identification have been completed, we will be using Covidence (https://www.covidence.org), a review management software program that is in partnership with Cochrane collaboration. Covidence is a core component of Cochrane's review production toolkit and will be used to assess the risk of bias within the identified studies as well as assist with data extraction.

Data sources and search strategy

Relevant studies will be identified using PubMed, Cochrane Library, and OVID electronic databases. Articles published between January 1980 and February 2021 will be considered. The following search terms will be used to identify potential articles: *(FMT OR fecal microbiota OR microbiome) AND (neurodevelopmental) AND (paediatric OR children), (FMT OR fecal microbiota OR microbiome) AND (neurodegenerative) AND (paediatric OR children), (FMT OR fecal microbiota OR microbiome) AND (neuropsychiatric disorder) AND (paediatric OR children).* Further, we will explore the relationship between the gut microbiome and subsequent immunomodulation, nutritional modulation, molecular mimicry, and microglial responses involved in paediatric neurological disorders. Our review will also investigate key concepts including epitopes, lymphocytic responses, molecular mimicry, antigenic cross-reactions, autoimmunity, and glial activation. To achieve this, the following search terms will be used to identify potential articles: *(microbiome OR microbiota OR gut microbiome) AND (immunomodulation OR autoimmunity OR inflammation) AND (neurodevelopmental) AND (paediatric OR children), (microbiome OR microbiota OR gut microbiome) AND (immunomodulation OR autoimmunity OR inflammation) AND (neurodegenerative) AND (paediatric OR children), (microbiome OR microbiota OR gut microbiome) AND (immunomodulation OR autoimmunity OR inflammation) AND (neuropsychiatric disorder) AND (paediatric OR children).*

Table 1. Inclusion and exclusion criteria

Inclusion criteria	
1	Original data
2	Studies conducted in humans
3	Studies conducted in paediatric patients (0–18 years)
4	Investigating neuropsychiatric, neurodegenerative, or neurodevelopmental disorders
5	Assessing the intestinal microbiome
6	Prospective, retrospective, case–control, and cross-sectional study designs
Exclusion criteria	
1	Studies conducted in adults (>18 years)
2	Commentaries, book chapters, letters, editorials, conference proceedings, case reports, conference, abstracts, or non-peer-reviewed articles
3	Studies conducted in animals

We will implement a rigorous search strategy that involves two rounds of literature review, using a three-step method in each round. The first round will involve a review of articles from the search results of the databases; the second round will involve a review of works cited by those articles identified in the first round (Table 1). Titles, abstracts, and full texts will be independently screened by at least two authors (L.H., J.P., M.F., V.C., E.H., M.M., N.P.). Articles will be excluded if they are unrelated or meet the exclusion criteria outlined in Table 1.

Study selection

Titles and abstracts of the studies will be screened for eligibility by two independent reviewers (MF and LH) using criteria outlined in Table 1. Conflicts will be resolved by discussion between the two reviewers, and if needed, by adjudication of a third independent reviewer (J.P., E.H., M.M., N.P.). The full text of all studies selected during screening will be reviewed independently by two reviewers (M.F. and L.H.) with disagreement resolved as earlier described. A PRISMA flow chart will be used to show the details of the selection process (Fig. 1).

Data extraction

Data extraction will be completed by two reviewers (M.F. and L.H.) using a pre-piloted Microsoft Excel data extraction form. Data extraction will be checked for accuracy and completeness of the data by other members of the research team (N.P., J.P., E.H., M.M., and V.C.). Collected data will include the year of publication, country, setting, population, specific type of neuropathology, and microbiome-related data. The draft data extraction tool will be modified and revised during the process of extracting data from each included study. Any modifications will be detailed in the final systematic review report. Any disagreements that arise between the reviewers will be resolved through discussion. If consensus cannot be reached, the senior scientist (N.P.) will be consulted to offer a final decision.

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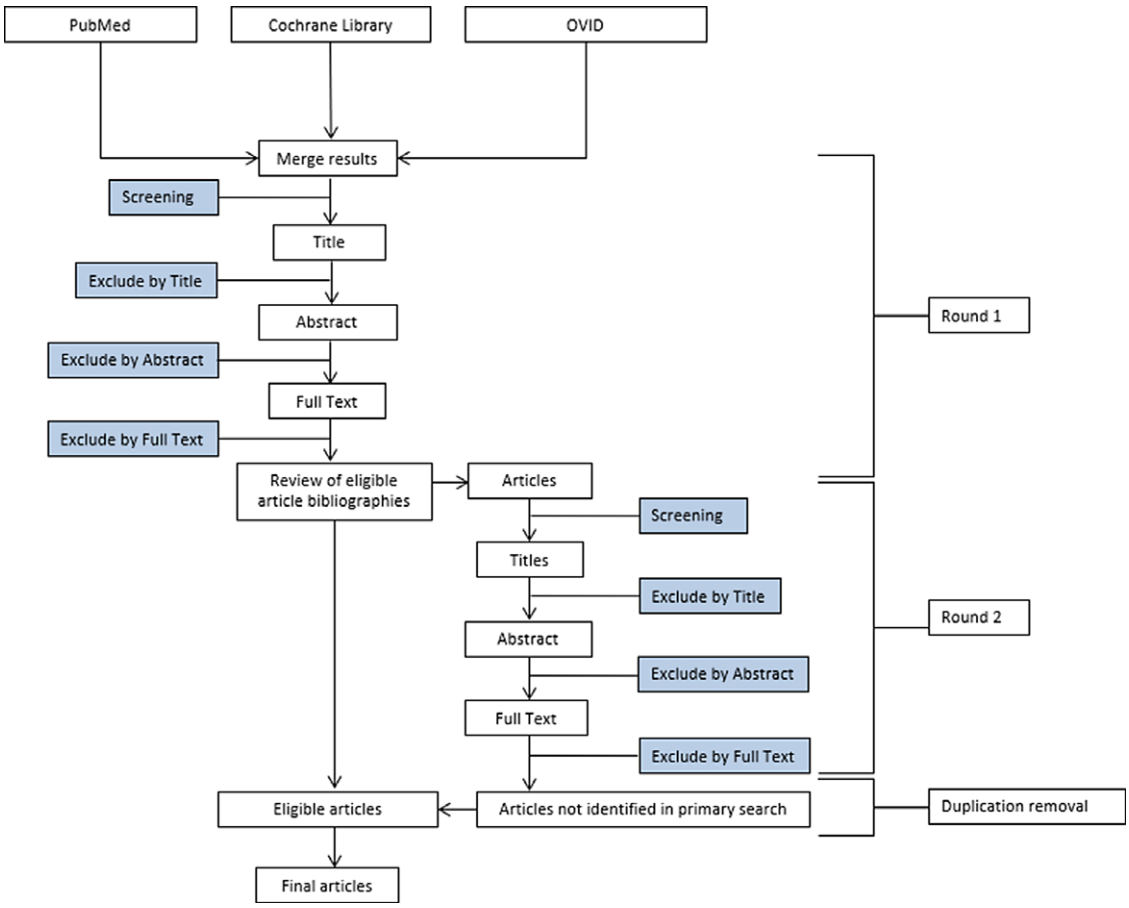

Fig. 1. Systematic review protocol flow diagram.

Inclusion and exclusion criteria

The inclusion and exclusion criteria are summarised in Table 1.

Definition of neuropsychiatric disorders

Neuropsychiatric disorders are characterised by their influence on an individual's brain activity, and subsequently their emotional state of mind (Taber *et al.*, 2010). Although their symptoms vary by pathophysiology, all neuropsychiatric disorders interrupt day-to-day lifestyle, impacting the individual, their social network, and society as a whole (Hyman, 2008). According to the World Health Organization, neuropsychiatric disorders account for 20% of health-related disabilities (Kessler *et al.*, 2005). These disorders are characterised by high prevalence, early onset, and contribute as primary risk factors for suicide (Kessler *et al.*, 2005; Hyman, 2008; Insel, 2009).

Quality assessment

We will assess the quality of the included studies using the appropriate Critical Appraisal Skills Programme (CASP) checklist (https://casp-UKnet/) based on study methodology. Although CASP does not provide a numeric score, it will enable a systematic assessment of the trustworthiness, relevance, and results of published papers.

Level of evidence assessment

Level of evidence will be assessed using established methods (Obremskey *et al.*, 2005). Accordingly, the articles will be assessed in compliance with a hierarchy of evidence. Randomised controlled trials and high-quality studies will be included. The highest quality studies are prospective cohort studies and are considered to be level I; lower quality (smaller sample sizes and weaker methodology prospective studies and retrospective studies) are considered to be level II; cross-sectional and case–control studies are considered to be level III; case series studies are level IV; and finally, expert opinions are considered to be level V.

Patient and public involvement

There will be no patients or members of the public involved in this systematic review.

Data analysis and synthesis

The extracted data and results will be presented as a table to help summarise and map the existing literature. Descriptive data will be tabulated (publication, country, setting, population, specific type of pathology, and microbiome-related data) within evidence tables. If sufficient evidence exists, we will explore the possibility of conducting further meta-analyses. Data relating to specific neuropsychiatric disorders and gut microbiome factors will be grouped to

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derive common themes, and their relationships will be explored. These themes will be organised to provide tabular and narrative summaries of key characteristics.

The strength of evidence will be assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Andrews *et al.*, 2013). The GRADE approach uses four quality levels such as high, moderate, low, and very low. The strength of evidence will be downgraded by one level according to the following criteria: (1) limitations in the design and implementation of available studies suggesting risk of bias; (2) indirectness of evidence; (3) unexplained heterogeneity or inconsistency; (4) imprecision of results; and (5) high probability of publication bias. Three criteria for upgrading the certainty of evidence include large magnitude of effect, dose–response, and residual confounding opposing the observed effect. The certainty of evidence will be reported as high, moderate, low, or very low. High certainty means that further research is very unlikely to change our confidence in the estimate of effect; moderate certainty means that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low certainty means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low certainty means that we are very uncertain about the estimate. Assessment will be reported in the GRADE summary of findings tables.

Ethics and dissemination

Our study is a systematic review of previously published literature and as such, ethical approval is not necessary according to the Hamilton Integrated Research Ethics Board. In addition to the prospective publication of our current protocol, we will be disseminating our results through local and international conferences to encourage broader uptake. The final manuscript will be submitted for peer-reviewed publication.

Author contributions. All authors (LH, JP, MF, VC, EH, MM, and NP) contributed to the study conceptualisation and study design. Authors LH, JP, and MF contributed to the writing of the first draft of the manuscript. Authors VC, EH, MM, and NP contributed to the review and revision of the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest. The authors have no conflicts of interest to declare.

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