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The microbiota-gut-brain axis: An emerging therapeutic target in chemotherapy-induced cognitive impairment

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ABSTRACT

Chemotherapy-induced cognitive impairment (CICI) is an ill-defined complication of chemotherapy treatment that places a significant psychosocial burden on survivors of cancer and has a considerable impact on the activities of daily living. CICI pathophysiology has not been clearly defined, with candidate mechanisms relating to both the direct cytotoxicity of chemotherapy drugs on the central nervous system (CNS) and more global, indirect mechanisms such as neuroinflammation and blood brain barrier (BBB) damage. A growing body of research demonstrates that changes to the composition of the gastrointestinal microbiota is an initiating factor in numerous neurocognitive conditions, profoundly influencing both CNS immunity and BBB integrity. Importantly, chemotherapy causes significant disruption to the gastrointestinal microbiota. While microbial disruption is a well-established factor in the development of chemotherapy-induced gastrointestinal toxicities (largely diarrhoea), its role in CICI remains unknown, limiting microbial-based therapeutics or risk prediction strategies. Therefore, this review aims to synthesise and critically evaluate the evidence addressing the microbiota-gut-brain axis as a critical factor influencing the development of CICI.

1. Introduction

Chemotherapy is an integral part of cancer care for a variety of solid and non-solid tumours. It is routinely used in the neoadjuvant and adjuvant settings, with both curative and palliative intent (Wigmore, 2013). Despite improvements in clinical efficacy, its use is limited by non-selective cytotoxicity and associated adverse effects impacting nearly all body systems (Nurgali et al., 2018). Cognitive impairment is a particularly burdensome complication of chemotherapy, with neurocognitive symptoms affecting quality of life both during treatment and long after its cessation (Holmes, 2013). Cognitive symptoms are most commonly reported to affect processing speeds, memory, executive function, learning and concentration (Ahles et al., 2010; Apple et al., 2017, 2018; Kesler et al., 2011).

Critically, both the existence and impact of chemotherapy-induced cognitive impairment (CICI) has been underestimated by healthcare professionals in the past and has led survivors of cancer to question the existence of their symptoms, creating a significant psychosocial burden (Selamat et al., 2014). Standard neuropsychological testing often fails to capture the full breadth of symptoms and their impact on cancer survivorship. As such CICI remains an under-reported and enigmatic complication of chemotherapy with limited understanding among clinicians and researchers (Selamat et al., 2014).

Despite considerable research interest over the past decade, the fundamental mechanisms underlying CICI are yet to be fully elucidated. Historically, research has focused on the direct cytotoxic properties of anti-cancer agents (Ren et al., 2019), although these have failed to form the basis for an effective CICI intervention. More recently, advances in our understanding of neurocognitive disease has supported neuroinflammatory-based mechanisms. Importantly the immunomodulatory properties of the gastrointestinal microbiota, and its ability to control neuroinflammation, has gained increasing popularity as a factor thought to initiate the underlying pathology of various neurocognitive conditions (Luczynski et al., 2016).

In the setting of CICI, the extensive connections between the microbiota, the gastrointestinal system and the brain, known as the

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microbiota-gut-brain axis, presents as a novel mechanistic hypothesis, given that the microbiota is significantly disrupted during chemotherapy (Secombe et al., 2019). Furthermore, epidemiological data demonstrate overlap in gastrointestinal and neurological side effects in patients receiving chemotherapy, suggesting a common molecular basis (Aprile et al., 2008). Despite significant advances in our understanding of the microbiota-gut-brain axis in other neurocognitive diseases (Dinan and Cryan, 2017), the same level of appreciation has not been achieved for CICI, highlighting an area in need of enhanced understanding.

Given the chronicity of the symptoms and the increasing focus on optimising cancer survivorship and minimising late treatment effects, developing translational research techniques that identify methods of personalised risk prediction and targetable mechanisms to alleviate symptom burden for this complication is warranted. Therefore, the current review aims to synthesise and critically evaluate preclinical and clinical evidence addressing dysregulated microbiota-gut-brain communication in the context of CICI highlighting areas with translational potential in the provision of personalised cancer care.

2. The clinical relevance of CICI: prevalence and risk factors

While CICI is experienced by almost all subsets of patients with cancer treated with chemotherapy, it has been most extensively characterised in individuals with breast cancer due to the high survival rates and unique characteristics of the chemotherapy agents typically used throughout treatment. A perceived cognitive decline, as determined by the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) tool, was reported in 45 % of individuals with breast cancer (Janelsins et al., 2017). Although CICI is transient for most patients, with symptoms typically resolving 6–12 months following treatment cessation, there is evidence of these symptoms persisting up to 20 years post-chemotherapy in some individuals (Koppelmans et al., 2012; Lange and Joly, 2017).

Due to under-reporting, the subtle nature of cognitive symptoms and limitations of neurocognitive testing, risk factors for the development of CICI are poorly defined. Of the limited data available, increasing age, low baseline cognitive reserve, depression and anxiety prior to chemotherapy treatment are associated with elevated CICI risk (Ahles et al., 2010; Janelsins et al., 2017). Single nucleotide polymorphisms of the catechol-O-methyltransferase (COMT) and apolipoprotein E (APOE) genes, which have known roles in cognitive function, have also been associated with CICI in survivors of breast cancer (Ren et al., 2019; Lengacher et al., 2015). However, this neuronal genetic predisposition and the aforementioned CICI risk factors fail to adequately account for the number of people developing CICI in survivors of breast cancer and other cancers.

The need for clinicians to evaluate cognitive ability post-treatment and refer those with signs of CICI for cognitive assessment, rehabilitation and group training has been recognised by expert committees in published guidelines relating to the management of CICI (Runowicz et al., 2016). While these guidelines are pivotal in improving the recognition of CICI as an important aspect of supportive cancer care, they fail to provide universal recommendations for the longitudinal monitoring of neurocognitive side effects or comprehensive management protocols for CICI, reflecting substantial inadequacies in our current understanding of CICI.

3. Pathobiology of CICI: current understanding and emerging candidates

3.1. Anatomical observations

Imaging studies using standard and functional magnetic resonance imaging (MRI) have identified structural and metabolic changes in in[illegible]ted breast cancer when compared to [illegible]crease in overall left hippocampal volume, hyporesponsiveness of the dorsolateral prefrontal cortex during a task involving planning skills and significant alterations in cerebral blood flow to specific regions of the frontal cortex during a short term memory task (Kesler et al., 2011; de Ruiter et al., 2011; Silverman et al., 2007). Such changes were associated with decreases in executive function, specifically planning skills, and deficits in verbal memory respectively (Kesler et al., 2011; de Ruiter et al., 2011). Demyelination and decreased fibre density of frontal and temporal white matter tracks have also been detected using diffusion tensor imaging in individuals with chemotherapy-treated breast cancer, which may explain decreases in processing speeds (Ahles et al., 2010; Deprez et al., 2011; Li et al., 2018). Cancer itself is also known to cause cognitive impairment, although, the use of non-chemotherapy treated cancer patients as controls in these studies separates cancer-related cognitive impairment from CICI, suggesting that the structural and metabolic changes observed in the hippocampus, pre-frontal cortex and white matter tracks are likely attributable to chemotherapy-related cytotoxicity.

3.2. Molecular candidates

While imaging studies have provided critical insight into the central manifestations of CICI, the molecular mechanisms underpinning these changes are less clearly defined with other factors such as depression, anxiety, concurrent treatments (including radiation, hormone or immunotherapy), confounding our ability to pinpoint a distinct cause (Holmes, 2013; Lange and Joly, 2017; McGinnis et al., 2017). CICI molecular candidates may relate directly to the mechanism of action of traditional chemotherapy drugs. Such agents may result in DNA damage and associated deficits in DNA repair mechanisms, as well as telomere shortening of both neurons and supportive cells (Ren et al., 2019; El-Agamy et al., 2019). The mechanism of action and neurocognitive side effects of common chemotherapy classes is displayed in Table 1. However, due to the use of combination chemotherapy for the treatment of solid and non-solid tumors, our ability to attribute neurocognitive side effects, observed in clinical studies, to specific classes of drugs is limited. The cognitive domains impaired following treatment with common chemotherapy regimens has been comprehensively described in a recent systematic review by *Huehnchen* et al. (Huehnchen et al., 2020). Seeing as these are a direct result of chemotherapy agent mechanism of action, and thus efficacy, attention has now shifted to identifying other mechanisms of CICI that are potentially targetable.

3.3. Emerging neuroinflammatory mechanisms

It is well documented that direct cytotoxic damage initiates secondary pathological mechanisms which serve to exacerbate off-target tissue injury, typically mediated by reactive oxygen species (ROS). In the context of CICI, indirect inflammatory based mechanisms have recently been proposed to contribute to symptomology, with particular focus on blood brain barrier (BBB) disruption and neuroinflammation (Wardill et al., 2016a).

Chemotherapeutic agents have long been considered unable to cross the BBB due to their molecular mass, a hypothesis based on their poor efficacy in treating CNS malignancies. However, evidence of systemically administered chemotherapeutic agents in the CNS contests this (Gangloff et al., 2005; Miura et al., 2018). Importantly, like other tight junction mediated barriers, the BBB is highly malleable with alterations in its permeability mediated by numerous physiological and pathological factors. Indeed chemotherapy agents, such as oxaliplatin and irinotecan, are able to alter BBB permeability (Branca et al., 2018; Wardill et al., 2016b). Similarly, numerous proinflammatory mediators which are known to be released in high levels during chemotherapy, such as tumour necrosis factor alpha (TNFα) (Logan et al., 2008a, 2007), are also able to disrupt BBB integrity (Varatharaj and Galea, 2017; Rochfort et al., 2014). Consequently, chemotherapy appears to be

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eurocognitive side effects of common chemotherapy classes, as determined by clinical and preclinical studies. Abbreviations: WAIS: Wechsler adult intelligence scale; MWM: Morris water maze; NLR: novel location ition; NOR: novel object recognition; SRTT: simple reaction time task; 5CSRTT: 5-choice serial reaction time task. *Clinical data is only presented when cognitive impairment could be attributed to a defined class of otherapy agents.

er Treatment Class	Mechanism of Action	Preclinical data		Clinical data	
		Cognitive domains effected	Cognitive tests used & references	Cognitive effects	Cognitive tests used
racyclines (doxorubicin, epirubicin, daunarubicin)	● DNA intercalation ● Inhibition of the topoisomerase II enzyme, disrupting DNA synthesis ● Induction of oxidative stress (Martins-Teixeira and Carvalho, 2020)	1 Spatial working memory (short & long term) 2 Recognition memory (short & long term) 3 Contextual memory (long term)	1 Barnes maze (Seigers et al., 2015) & MWM (Lim et al., 2016) 2 NLR (Christie et al., 2012) & NOR (Barry et al., 2018) 3 Contextual fear test (Christie et al., 2012)	Anthracyclines-based chemotherapy is associated with lower verbal memory performance when compared to non-anthracyclines based chemotherapy (Kesler and Blayney, 2016).	Hopkins verbal learning test – revised
Taxanes (paclitaxel, docetaxel)	● Prevent microtubules from disassociating thereby disrupting cellular division (Abal et al., 2003)	1 Recognition memory (short term) 2 Inhibitory control	1 NLR (Callaghan and O'Mara, 2015) & NOR (Fardell et al., 2014) 2 SRTT(Seigers et al., 2015)	Taxane-based chemotherapy was associated with the development of symptoms affecting: Processing speed Auditive attention Learning where non-taxane based chemotherapy was not (Cerulla et al., 2017).	WAIS – digit speed WAIS digit span CLVT verbal learning
Platinums (carboplatin, cisplatin, oxaliplatin)	● Interact with nuclear DNA to form inter-strand cross links to distort DNA double helix structure (Johnstone et al., 2014)	1 Spatial working memory (short & long term) 2 Recognition memory (short & long term) 3 Contextual memory (long term) 4 Attention 5 Behavioral flexibility	1 MWM [113] & Y-maze [114] 2 Social recognition [115], NOR [116] & NLR [117] 3 Contextual fear test [118] 4 5CSRTT [119] 5 Iowa gambling task (Mu et al., 2015)	Platinum-based chemotherapy was associated with lower learning and memory when compared to non-chemotherapy treated patients (Amidi et al., 2017).	Rey auditory verbal learning test
Alkylating agents (cylcophos-phamide)	● Covalently bind alkyl groups to DNA nucleotides enabling inter- or intra-strand cross link formation & mispairing of nucleotides (Hall and Tilby, 1992)	1 Spatial working memory (short term) 2 Recognition memory (short & long term) 3 Contextual memory (long term) 4 Inhibitory control	1 Delayed spatial alternation task (Janelsins et al., 2016) 2 NLR, temporal order task (Acharya et al., 2015) & NOR (Yang et al., 2010) 3 Contextual fear test (Christie et al., 2012) 4 SRTT (Seigers et al., 2015)	Neurocognitive side effects evident with combination chemotherapy*	–
Vinca alkaloids (vinblastine, vincristine)	● Prevents polymerisation of tubulin into microtubules (Florian and Mitchison, 2016)	1 Spatial working memory (short & long term)	1 MWM (Shabani et al., 2012b)	Neurocognitive side effects evident with combination chemotherapy*	–
Antimetabolites (5-flourouracil, capecitabine, methotraxate)	● Act as substitutes for essential metabolites, thereby preventing the use of that metabolite in cell growth and function (Peters, 2014)	1 Spatial working memory (short & long term) 2 Recognition memory (short & long term) 3 Contextual memory (long term) 4 Discrimination learning 5 Inhibitory control 6 Behavioral flexibility	1 Barnes maze (Seigers et al., 2015) & MWM (Seigers et al., 2009) 2 NLR (Lyons et al., 2011) & NOR (Yang et al., 2011) 3 Contextual fear test (ElBeltagy et al., 2010) 4 Autoshaping (Bisen-Hersh et al., 2013) 5 Go/no go task (Fardell et al., 2010) 6 MWM (Dubois et al., 2014)	Neurocognitive side effects evident with combination chemotherapy*	–
Topoisomerase inhibitors (irinotecan, etoposide)	● Inhibit the topoisomerase I & II enzymes disrupting DNA synthesis (Liang et al., 2019)	1 Spatial working memory (short term) 2 Inhibitory control	1 Barnes maze (Seigers et al., 2015) 2 SRTT (Seigers et al., 2015)	Neurocognitive side effects evident with combination chemotherapy*	–

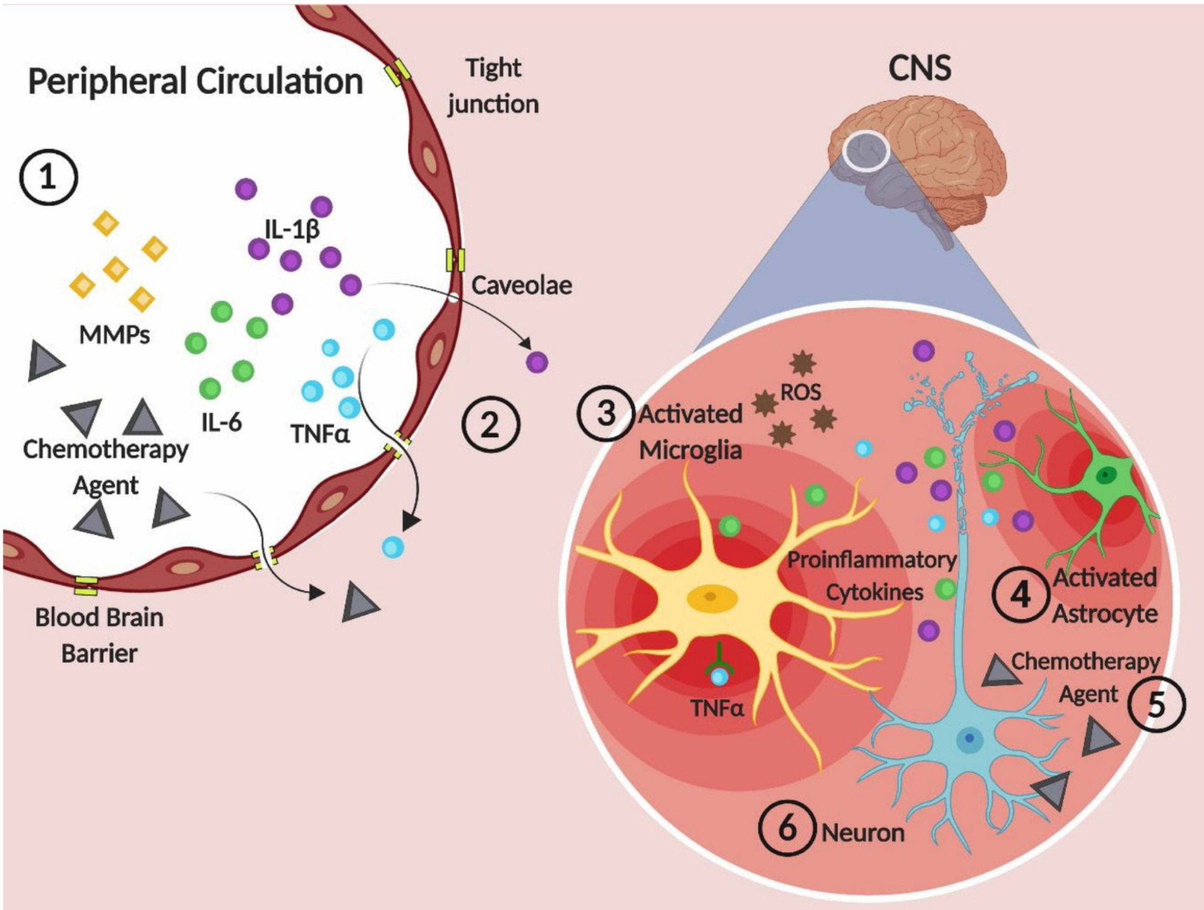

Fig. 1. The BBB and neuroinflammation in CICI: (1) peripheral inflammatory mediators and the chemotherapy agent present in systemic circulation increase BBB permeability through tight junction disruption and increased caveolae-mediated transcytosis. (2) The mediators and chemotherapy agent cross the BBB and enter the CNS. (3) Proinflammatory cytokine TNFα and the chemotherapy agent activate resident microglia which initiate a neuroinflammatory response. (4) Activated microglia cause activation of astrocytes and together, microglia and astrocytes release proinflammatory cytokines and ROS which contribute to neuroinflammation and further BBB damage. (5) The chemotherapy agent, once present in the CNS, contributes to neuroinflammation and causes direct toxicity to neurons. (6) As a result of neuroinflammation and cytotoxicity neurons are damaged, and apoptosis may occur. Abbreviations: MMPs; matrix metalloproteinases; IL-1β: interleukin-1 beta; IL-6: interleukin-6; TNFα: tumour necrosis factor alpha; CNS: central nervous system; ROS: reactive oxygen species.

able to disrupt the BBB via direct and indirect mechanisms.

BBB damage, and a resulting increase in permeability, is a critical event in facilitating peripheral and central communication (Varatharaj and Galea, 2017), with peripherally derived factors, such as proinflammatory cytokines or the chemotherapeutic agent itself, allowed access to the CNS, where they can initiate a neuroinflammatory response (see Fig. 1) (Lively and Schlichter, 2018; Gibson et al., 2019; Banjara and Ghosh, 2017; Dheen et al., 2007; Kirkley et al., 2017). Accordingly, breakdown or disruption of the BBB is an important event in facilitating microbiome-gut-brain axis communication, with microbial derived products able to gain direct access to the CNS. While the importance of the microbiome-gut-brain axis is accepted in various neurocognitive conditions (Luczynski et al., 2016), it is only recently emerging as a potential contributor to the underlying pathology of CICI (Jordan et al., 2018) and thus a potential target in the provision of supportive cancer care and treatment of CICI.

4. The microbiota-gut-brain axis

The gastrointestinal microbiota, a collection of bacteria, viruses, archaea and other microorganisms present within the gastrointestinal tract, is made up of almost one hundred trillion microorganisms (Ley

olved with humans and as such, a

ween a host and their indigenous

microbes offering bidirectional benefits. The intimate connection which exists between the CNS and the gastrointestinal microbiota, termed the *microbiota-gut-brain axis* (Rhee et al., 2009), is an extensive bidirectional communication system by which the microbiota can exert profound influence over the CNS, effecting behavioral, emotional and cognitive domains. Experimental evidence has revealed many potential pathways of communication between the microbiota and the brain, encompassing microbial-derived metabolites (Long-Smith et al., 2019) and their impact on the neural, hormonal and immune-related signalling routes previously recognised as the gut-brain axis (Mayer, 2011)

4.1. Microbiota-brain communication

Microbial metabolites: Gastrointestinal microbes are able to produce a variety of bioactive molecules, including neurotransmitters, facilitating neurochemical communication between microbes and the host's CNS (Cryan et al., 2019). Short-chain fatty acids (SCFAs) can enter systemic circulation and may interact with the brain via this route (Sarkar et al., 2016) whereas transformed secondary bile acids and branched chain amino acids may influence brain function through regulating gastrointestinal barrier permeability and immune status (Cryan et al., 2019; Sarathy et al., 2017).

SCFAs appear to be of particular relevance to cognitive function as these microbial-derived metabolites, produced through bacterial fermentation of dietary fibre (Dalile et al., 2019), are capable of modulating CNS maturation, innate immunity and BBB permeability. In germ-free mice, maturation of microglia, the resident macrophages of the CNS, is significantly altered with markedly different gene expression profiles and abnormal morphology (Erny et al., 2015). These microglia also show an inability to activate in response to viral or bacterial exposure, indicating that the presence of a functional microbiome is necessary for an appropriate CNS innate immune response to be mounted. Interestingly, the administration of the SCFAs (sodium propionate, sodium butyrate and sodium acetate) fully restored microglial maturity and function (Erny et al., 2015). Similarly, the development and function of the BBB is severely altered in germ-free mice, with increased permeability due to reduced expression of occludin and claudin-5; two key junctional proteins that maintain a selective and semi-permeable barrier. Critically, recolonisation with conventional GI microbiota restored normal BBB permeability and tight junction protein expression (Braniste et al., 2014). Similarly, the SCFA sodium propionate prevented lipopolysaccharide-induced tight junction disruption *in vitro* (Hoyles et al., 2018). Therefore, it is possible that SCFAs are important in mediating the influence of the microbiome over CNS innate immunity and BBB permeability, both of which are likely to be important in explaining CICI development, as discussed above.

Neural pathways: The vagus nerve provides extensive innervation to the gastrointestinal tract and thus acts as a direct route for communication within the microbiota-gut-brain axis (Fulling et al., 2019). Microbes within the lumen of the small and large intestine are able to signal to vagal afferents directly or via a functional synapse with the intrinsic primary afferent neurons of the enteric nervous system (Perez-Burgos et al., 2014; McVey Neufeld et al., 2015). In experimental models where the composition of the microbiota has been altered, by direct small intestine infusion of *Lactobacillus rhamnosus* (now referred to as *Lacticaseibacillus rhamnosus* based on an updated taxonomic classification (Zheng et al., 2020)) or in germ-free animals, both intrinsic primary afferent neurons and vagal afferents show altered firing patterns (McVey Neufeld et al., 2015, 2013). In the context of CICI, vagal afferent signalling has been proposed to influence memory through a neural connection between the medial nucleus tractus solitarius and hippocampal neurons (Suarez et al., 2018). As such, it is possible that chronic changes to Vagal afferent signalling seen in response to microbial disruption, may impact memory, and thus cognitive function via this neural circuit. For a more comprehensive review, Breit et al. (Breit et al., 2018) elegantly outline the role of the vagus nerve as a modulator of the gut-brain axis in both psychiatric and inflammatory disorders.

Hormonal communication: The hypothalamic-pituitary-adrenal (HPA) axis, which is primarily recognised for its role in coordinating the neuroendocrine response to stress, has also been implicated in microbiota-gut-brain communication (Cryan et al., 2019). A link between the HPA axis and the gastrointestinal microbiota was first established in germ-free mice, which exhibited hyperactivity of the HPA axis when subjected to restraint stress (Sudo et al., 2004). It has long been recognised that stress and HPA activity are related to cognitive performance (de Souza-Talarico et al., 2011), with higher levels of activity, and associated cortisol levels, being linked to both lower cognitive performance (Keller et al., 2017) and a higher risk of developing diseases characterised by cognitive impairment, such as Alzheimer's disease (Ouanes and Popp, 2019). Accordingly, it is possible that the gastrointestinal microbiota, and changes to microbial homeostasis, may influence cognitive function by disrupting the HPA axis and altering stress circuitry.

While the mechanisms by which the gastrointestinal microbiota influence cognition require further clarification, there is mounting evidence of a link between microbiota composition and various neurological functions, including mood and cognition (Goh et al., 2020; Liu et al., 2019). For example, there is a wealth of data supporting the symptoms in individuals with major 2020). A significantly altered

microbiota composition has also been seen in individuals with Alzheimer's disease, linking certain microbial profiles with impaired cognitive function (Liu et al., 2019). Whilst this interaction has not been well studied in the setting of supportive cancer care, emerging evidence suggests that the microbiota may in fact be a critical mediator of CICI.

5. Symptom clusters: the link between CNS and gastrointestinal side effects

Perhaps the most convincing evidence suggesting the microbiota's contributory role in CICI development, is the mechanistic link proposed to exist between CICI and chemotherapy-induced gastrointestinal toxicity (Wardill et al., 2016a; Bajic et al., 2017, 2018). Gastrointestinal toxicity is an umbrella term used to describe the constellation of gastrointestinal symptoms caused by chemotherapy agents that includes diarrhoea, constipation, gastrointestinal bleeding and pain, which largely result from cytotoxic injury to intestinal epithelial cells (clinically referred to as mucositis) (Logan et al., 2008b). The hypothesised link between CICI and gastrointestinal mucositis was built upon clinical observations of both neurological (memory, executive function and learning impairments) and gastrointestinal (diarrhoea, abdominal bleeding and pain) symptom clusters; a phenomenon whereby patients simultaneously present with both clusters of symptoms suggestive of common causes (Aprile et al., 2008).

Experimentally, neurological and gastrointestinal symptom clusters have been observed with a study demonstrating the development of central neurotoxicity in a model of gastrointestinal mucositis (Wardill et al., 2016b). Importantly, a more recent pre-clinical study has demonstrated a strong relationship in paclitaxel treated mice, between structural differences in colonic tissue, such as increased crypt depth, and microglial activation in the dentate gyrus and prefrontal cortex; two regions of the brain intrinsically linked with the symptoms of CICI (Loman et al., 2019). Importantly, microbiota composition during chemotherapy treatment, and its interactions with the host's innate immune system, have been heavily implicated in the development of gastrointestinal mucositis (Secombe et al., 2019; Brandi et al., 2006; Pedroso et al., 2015).

6. Chemotherapy-microbiota interactions

Recently, the direct relationship between non-antibiotic drugs and the microbiota has received significant attention, with evidence of changes to microbiota composition following the intake of drugs (Maier et al., 2018), and suggestions that the microbiota can influence the action of drugs, impacting metabolism and efficacy (Clarke et al., 2019). Importantly, gastrointestinal mucositis is characterised by significant microbial disruption (Secombe et al., 2019; Brandi et al., 2006; Pedroso et al., 2015) and aberrant immune signalling; both of which are compounded by other aspects of cancer therapy including prophylactic and empirical antibiotic use, altered food/nutrition status (either cachexia or need for total parental nutrition) and the tumour microenvironment. While the exact microbial changes caused by chemotherapy vary in different patient cohorts, these changes are all largely underpinned by decreased diversity/richness and a shift towards a gram-negative dominated enterotype with deficiencies in the commensal taxa (such as *Lactobacillus*, *Bifidobacterium* and *Clostridium cluster XIV*) and expansion of pathobionts (including *Escherichia coli* (E. coli) *Staphylococcus* and *Bacteriodetes*) (Lin et al., 2012; Montassier et al., 2015; Stringer et al., 2013, 2009a; Stringer et al., 2007, 2009b; Stringer et al., 2008; Zwielehner et al., 2011). *Secombe* et al. (Secombe et al., 2019) provide a comprehensive review of the changes to microbial composition and its communication with the innate immune system during chemotherapy treatment.

While the specific changes vary, chemotherapy-induced microbial disruption impairs the protective, immunomodulatory effects that a diverse microbiota would normally provide to its host and increases the abundance of damaging products produced by pathogenic microbes. Of particular relevance to supportive cancer care and CICI is the increase in lipopolysaccharide, a key driver of intestinal inflammation via its interaction with toll-like receptor 4 (Secombe et al., 2019). Importantly, lipopolysaccharide is well recognised for its ability to degrade tight junction proteins, resulting in an increase in intestinal permeability enabling systemic translocation of lipopolysaccharide to peripheral circulation (Chelakkot et al., 2018), where it is able to modulate BBB permeability, activate glia and induce neuroinflammation (Varatharaj and Galea, 2017). This mechanistic interaction between the gastrointestinal system and the brain has prompted investigation of the microbiome as a therapeutic target for CNS dysfunction, and subsequently the term 'psychobiotic' has been formed.

7. Psychobiotics and their relevance to CICI

Whilst psychobiotics are strictly defined as a microbial intervention with psychological benefits to the host, probiotic interventions have also been shown to induce cognitive benefits and therefore may have relevance to the treatment of CICI. The impact of orally administered microbial strains on cognition has been elegantly demonstrated by numerous preclinical studies. *Savignac*et al. (Savignac et al. (2015)), showed that treatment with the gram-positive *Bifidobacterium longum* improved memory and learning in mice with anxiety. Furthermore, age-related deficits in hippocampal long term potentiation, a model of neuronal plasticity which may underlie memory consolidation, were attenuated in rats receiving the probiotic VSL#3, which contains 8 gram-positive bacterial strains (Distrutti et al., 2014). In contrast, the gram-negative, enteric pathogen *Citrobacter rodentium* has been shown to induce memory and learning deficits in mice (Gareau et al., 2011).

Currently, comprehensive clinical trials are lacking but small pilot studies have revealed promise for probiotic intervention as a potential treatment of cognitive impairment in various disease states. For example, multi-strain probiotic supplementation has been shown to improve cognitive function in a small number of individuals with Alzheimer's disease, hepatic encephalopathy and those who are HIV positive (Akbari et al., 2016; Roman et al., 2019; Ceccarelli et al., 2017). Furthermore, a three month daily regime of probiotic treatment in individuals with bipolar disorder improved executive function, attention and processing speeds (Reininghaus et al., 2020). While the results require validation, they highlight the influence that certain microbial strains can have on the CNS, reiterate the importance of microbial stability on neurocognitive function and thus warrant further investigation in the setting of CICI.

Despite the lack of interventional clinical trials, controlled studies have investigated changes to microbial composition and performance in various cognitive battery tools (Table 2). Within each study, distinct associations between microbial strains and good or poor cognitive performance were highlighted. However, these were not frequently replicated between studies, even when similar population groups were investigated (Liu et al., 2019; Zhuang et al., 2018). This could be related to the heterogeneity in what defines 'good' or 'poor' performance, the cognitive tests used and the cross-sectional design of these trials. Consequently, longitudinal studies would be beneficial in identifying microbial profiles associated with cognitive function over the course of different diseases. This could allow the development of probiotic treatments, in the same mold as psychobiotics, tailored specifically to cognitive deficits, and may be of use in treating CICI.

8. The microbiota-gut-brain axis in supportive cancer care: shortcomings and avenues for personalised care

While the influence of microbiota composition over both cognition and the development of gastrointestinal mucositis is compelling, a role [illegible] previously been reported. However, [illegible] d psychoneurological symptoms (a constellation of symptoms including depression, anxiety, fatigue and pain) in cancer have been identified and may provide insight into the microbiota's role in CICI. Recent findings have provided the first evidence for an association between post-treatment gastrointestinal microbiota and fear of cancer recurrence, a significant yet unmet psychological need of survivors of cancer (Okubo et al., 2019). Fear of cancer recurrence encompasses depression, anxiety and post-traumatic stress related symptoms and while not necessarily impacting cognition, similar brain regions, such as the hippocampus, are involved in both fear of cancer recurrence and CICI. In survivors of breast cancer, severe fear of cancer recurrence was associated with lower microbial diversity, increased *Bacteroidetes* (gram-negative) and decreased *Firmicutes* (gram-positive) at phylum level (Okubo et al., 2019). Whilst only correlative with high order microbial taxa, these findings support the proposed role of chemotherapy-induced microbial disruption in CICI and highlights the need to understand the dynamics of the microbiota-gut-brain axis and its contribution to acute and chronic neurocognitive, cancer-related side effects.

The concept that an individual's unique microbiome composition determines their risk of disease and/or response to treatment/intervention is an increasingly popular hypothesis under investigation in a variety of clinical scenarios, including supportive cancer care (Wardill and Tissing, 2017). For example, an individual's microbiome composition has been shown to predict their response to diet interventions, and therefore can be used to tailor dietary advice to the individual (Hughes et al., 2019a; Hughes et al., 2019b). This concept reflects the high degree of individualisation in the microbiome, reflecting the cumulative impact of host genetics and an increasingly long list of environmental factors known to profoundly shape the composition of the microbiome. In the setting of supportive cancer care, an individual's baseline microbiome has been directly correlated with outcomes of treatment, including radiation-induced gastrointestinal toxicity, immunotherapy colitis and blood stream infection (Kumagai et al., 2018; Li et al., 2019; Montassier et al., 2016), with authors suggesting that an individual's microbial enterotype determines their baseline immune tone and sensitivity to inflammatory triggers.

Exploiting the microbiome as a potential risk predictor of chemotherapy-induced toxicities, including CICI, holds great clinical potential. A major obstacle in cancer therapy is the heterogeneity in treatment response, particularly in terms of treatment toxicity (Secombe et al., 2019). Despite intensive research efforts to uncover genetic reasons for this phenomenon, it remains largely unclear why some individuals with cancer are highly susceptible to toxicity and others are not. Based on current evidence and emerging mechanistic detail, the microbiome holds great promise in identifying patients at risk of toxicities, including CICI, enabling targeted and proactive supportive care interventions and tailored treatment regimens for high risk individuals (Wardill and Tissing, 2017). This could involve identification of patients with cancer at risk of developing severe CICI based on their pre-treatment microbial profile, thus allowing for the management of this risk early in their treatment plan. Remodelling of their microbial profile to reduce risk could be achieved through the use of microbiota-targeted therapeutics, such as probiotics, prebiotics, postbiotics and faecal microbiota transplantation (FMT).

As discussed above, probiotic interventions, which deliver live exogenous microbes, have been shown to induce cognitive benefits in preclinical models (Savignac et al., 2015; Distrutti et al., 2014) and thus may have relevance in the treatment of CICI. Similarly, prebiotics and postbiotics, which deliver compounds promoting the beneficial activity of host microbes and microbiota-derived metabolites, respectively (Wong and Levy, 2019), may also have the potential to counteract the negative effects of chemotherapy treatment on microbiota composition. However, with heterogeneity in treatment response, achieving predictable outcomes on both the microbial community and host health using these therapies remains a significant challenge in need of further refinement (Wong and Levy, 2019).

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ary of human studies investigating microbial profiles associated with cognitive performance. Abbreviations; hepatic encephalopathy (HE), post-traumatic stress disorder (PTSD), Alzheimer's disease (AD), amnestic cognitive impairment (aMCI), healthy controls (HC), Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Cambridge Neuropsychological Test Automated Battery (CANTAB-PAL), tive abundance (RA), proton pump inhibitors (PPI).

Study Participants	Cognitive battery tools	Specific microbial findings relating to cognitive performance			Reference
		Microbial diversity and cognitive domains involved	Good cognitive performance	Poor cognitive performance	
93 Veterans with liver cirrhosis with/without HE, 29 of whom were diagnosed with PTSD	- Inhibitory control test - Block design test	GI microbiota composition is associated with executive function and intelligence.	↑ Faecalibacterium RA	↑ Escherichia/Shigella RA ↑ Enterococcus RA	(Bajaj et al., 2019)
35 subjects – 19 obese and 16 non-obese, with similar age and sex.	- Trail making test A & B	GI microbiota composition is associated with mental flexibility and processing speeds.	↑ Burkholderiaceae RA ↑ Corynebacteriaceae RA	↑ Streptococaceae RA	(Palomo-Buitrago et al., 2019)
97 subjects – 33 AD, 32 aMCI and 32 HC.	- MMSE - MoCA - Clinical dementia rating	AD subjects had lower overall microbial diversity.	↑ Bacteroidetes RA ↑ Ruminococcaceae RA	↑ Enterobacteriaceae RA ↑ Veillonellaceae RA	(Liu et al., 2019)
1551 subjects – largely female (90%) and over 40 years of age.	- Verbal Fluency Test - Deary-Liewald - Reaction time test - MMSE - CANTAB-PAL	Poorer reaction times were associated with lower overall microbial diversity.	↑ Burkholderiales RA (In subgroup excluding subjects taking PPIs and antibiotics and dietary index was included as a covariate)	–	(Verdi et al., 2018)
86 subjects – 43 AD and 43 age and gender matched HC.	- MMSE - Activities daily living test	Microbial diversity was altered in AD subjects compared to HC.	–	↑ Ruminococcaceae RA ↓ Lachnospiraceae RA	(Zhuang et al., 2018)
37 healthy subjects 50 – 85 years of age	- Stroop Colour-Word Test	Microbiota composition is associated with cognitive flexibility.	↑ Verrucomicrobia RA (when controlling for carbohydrate intake and hypertension) ↑ Lentisphaerae RA (independent of carbohydrate intake)	–	(Anderson et al., 2017)
43 healthy subjects 50 – 85 years of age	- MMSE - Frontal assessment battery - The Hopkins verbal learning test revised - Verbal fluency test	GI microbiota composition is associated with attention, executive function and learning.	↑ Firmicutes RA ↑ Verrucomicrobia RA	↑ Bacteroidetes RA ↑ Proteobacteria RA	(Manderino et al., 2017)
39 subjects – 20 obese and 19 nonobese all between the ages of 30 – 65	- Trail making test	Actinobacteria RA is associated with attention and cognitive flexibility.	↑ Actinobacteria RA	–	(Fernandez-Real et al., 2015)

FMT, which involves transfer of a faecal suspension into the gastrointestinal tract to manipulate microbiota composition, has proven to be more successful as a microbiota-based therapeutic (Wong and Levy, 2019; Wardill et al., 2019) and is now routinely used for the treatment of recurrent or refractory *Clostridium difficile* infection (Cammarota et al., 2017; Trubiano et al., 2016; Quraishi et al., 2017). In the setting of clinical oncology, the use of FMT in the management of both treatment-related toxicities such as gastrointestinal mucositis and immunotherapy colitis, as well as secondary complications of therapy, specifically graft versus host disease and blood stream infection, has been proposed. However, this has been met with caution due to the immunocompromised status of individuals undergoing cancer therapy and the perceived risk of bacterial translocation and sepsis (Wardill et al., 2019). As such, the safety of FMT as an adjunctive supportive care intervention for individuals undergoing cancer therapy would need to be established in this population prior to it presenting as a viable treatment for CICI. Nevertheless, characterisation of the microbiota-gut-brain axis' role in CICI and identification of pre-treatment microbial profiles associated with CICI development, is necessary to fully appreciate how the microbiota could be targeted to prevent CICI in patients with cancer.

9. Summary

Given the superior outcomes being achieved by cancer treatment, clinical focus has increasingly shifted to cancer survivorship and CICI is a significant complication of chemotherapy that requires wider acknowledgment. Further appropriate research efforts are warranted to better understand its pathobiology which, to date, remains unclear. A chronic state of increased BBB permeability and neuroinflammation is an attractive, and increasingly convincing, hypothesis for the development of CICI. However, further investigation and comprehensive characterisation of the putative molecular mediators discussed is still required. Finally, although the microbiota-gut-brain axis has not been well studied in the setting of CICI, evidence linking the microbiome to cancer related outcomes, such as gastrointestinal mucositis, and other neurodegenerative conditions suggests that the microbiota may in fact be a critical mediator of CICI which warrants further attention.

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CRediT authorship contribution statement

Courtney B. Subramaniam: Writing - original draft. **Joanne M. Bowen:** Supervision, Writing - review & editing. **Marc A. Gladman:** Supervision, Writing - review & editing. **Maryam B. Lustberg:** Writing - review & editing. **Samantha J. Mayo:** Writing - review & editing. **Hannah R. Wardill:** Conceptualisation, Supervision, Writing - review & editing.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.07.002.

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