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More than a small adult brain: Lessons from chemotherapy-induced cognitive impairment for modelling paediatric brain disorders

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ABSTRACT

Childhood is recognised as a period of immense physical and emotional development, and this, in part, is driven by underlying neurophysiological transformations. These neurodevelopmental processes are unique to the paediatric brain and are facilitated by augmented rates of neuroplasticity and expanded neural stem cell populations within neurogenic niches. However, given the immaturity of the developing central nervous system, innate protective mechanisms such as neuroimmune and antioxidant responses are functionally naïve which results in periods of heightened sensitivity to neurotoxic insult. This is highly relevant in the context of paediatric cancer, and in particular, the neurocognitive symptoms associated with treatment, such as surgery, radio- and chemotherapy. The vulnerability of the developing brain may increase susceptibility to damage and persistent symptomology, aligning with reports of more severe neurocognitive dysfunction in children compared to adults. It is therefore surprising, given this intensified neurocognitive burden, that most of the pre-clinical, mechanistic research focuses exclusively on adult populations and extrapolates findings to paediatric cohorts. Given this dearth of age-specific research, throughout this review we will draw comparisons with neurodevelopmental disorders which share comparable pathways to cancer treatment related side-effects. Furthermore, we will examine the unique nuances of the paediatric brain along with the somatic systems which influence neurological function. In doing so, we will highlight the importance of developing *in vitro* and *in vivo* paediatric disease models to produce age-specific discovery and clinically translatable research.

1. Introduction

Conceptions of childhood have undergone continuous and historical evolution, and as a result, children are no longer regarded as "small adults". However, when it comes to understanding and treating diseases that occur in both adults and children, this sentiment is variably acknowledged, with approaches established in adults often extrapolated to paediatric cohorts. The term childhood is used relatively generically; the field of paediatric oncology treats patients up to the age of 17 (with 18 years and above considered adulthood), while the area of adolescent and young adult oncology relates to 15–39 year-olds (Coccia et al., 2012; Rose, 2020). However, there is no clear consensus and formal definition of the term 'childhood' across neurodevelopment. For the purpose of this review, we use childhood to refer to the years between birth and adolescence (14-years-old) – excluding neurodevelopment changes during and post-adolescence. Overall, neurodevelopment is undoubtedly a continuum without clear cut categories and common variation between individuals.

The central nervous system (CNS) undertakes various developmental milestones during childhood and adolescence. Neurological functions emerge in a "bottom-up" order with peak development of autonomic (e.g., heart rate and blood pressure regulation) processes occurring first (prenatal development), followed by integration of sensory-motor cognition (developing between 0 and 6 years old), language formation

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and social behaviours such as communication (<12 years) and finally higher-order processes such as decision making (<20–25 years) (Leisman et al., 2015). In parallel to the emergence of these functions, macroscopic changes occur within the corresponding cortical and subcortical regions. MRI studies demonstrate expansion of white and grey matter, followed by reduction of cortical plates (Jernigan et al., 2011; Shaw et al., 2008; Tsujimoto, 2008). Peak cortical expansion generally occurs by the age of 10-years, producing an augmented metabolism of glucose within the cortical tissue – 2-fold higher than seen during adulthood (Leisman et al., 2015). The subsequent reduction of grey matter density during adolescence is attributed to the refinement of neural pathways via synaptic pruning (Peter R, 1979; Webb et al., 2001). In regard to white matter expansion, myelination of neuronal axons has been proposed to occur in distinct stages: early childhood, childhood, adolescence, adult myelination and myelin reduction with age (de Faria et al., 2021).

It is important to acknowledge that achievement of these neurological hallmarks is heavily influenced by an individual's experiences and environment, due to the human brain's extensive capacity for 'self-organisation' (Leisman et al., 2015). In fact, environmental enrichment or diminution during neurological development can induce biochemical and neurophysiological changes, which can dictate the capacity for learning and memory (Greenough et al., 1978; Le Grand et al., 2001). As the majority of synaptic reorganisation occurs during childhood and adolescence (Blakemore, 2012), environmental influences (specifically extreme or long-lasting) have the capability to change neural systems and cognitive processes during this time. In the context of cancer survivorship, extensive literature indicates that the extreme and often long-lasting influence of cancer treatments induces significantly greater neurological dysfunction in the developing brain (Castellino et al., 2014; Jim et al., 2012; Vardy et al., 2007). Once this synaptic reorganisation is complete, the brain's plasticity decreases and, with age, the susceptibility to influence neurological function also declines (Leisman et al., 2015).

Microscopic cellular changes unique to the paediatric CNS orchestrate development and provide a means for environmental influences to alter brain function. Expansive progenitor pools allow for the high rates of neurogenesis necessary to populate higher cortical networks and drives the dramatic neuroplasticity which defines early life (Lui et al., 2011; Wang et al., 2022). CNS protective structures in the developing brain, such as a potentially permeable blood–brain barrier (Blondel et al., 2022; Coelho-Santos and Shih, 2020), may allow peripherally circulating signalling molecules greater access to parenchymal tissues. In addition, pro-inflammatory phenotypes in the infant cerebrum produce hyper-reactive responses from neuroimmune cells (increased proliferation and release of inflammatory cytokines) to these invading signals (Christensen et al., 2014; Janeczko, 1994; Santambrogio et al., 2001). Further, immature redox mechanisms are saturated by the high metabolic demands of neurodevelopment and thus can be overwhelmed by oxidative DNA damage resulting from augmented neurogenesis (Khan and Black, 2003). Cumulatively, this demonstrates a vulnerable period where foundational functions for brain maturation are executed. Further to this, systemic mediators of neurocognitive function are also influenced by age, and the gut microbiota – the collection of micro-organisms which reside in the gut – is capable of exerting influence over the CNS (Morais et al., 2021; Quigley, 2017). These micro-organisms dynamically transform from birth to death, changing in abundance, compositional structure, and functionality (Boehme et al., 2021). Intriguingly, the developmental windows of the gut microbiota parallel critical periods of neurodevelopment with unique and specific microbial profiles seen in neonates, infants, early and mid-childhood, adolescence, and adulthood (Agans et al., 2011; Davis et al., 2020). These unique profiles have functional and therapeutic consequences as seen in age-dependent responses to microbial interventions such as probiotics.

These inherent differences in children and adults highlight the need to appropriately consider the nuances of childhood physiology and biochemistry in our collective approach to understanding and modelling neurological diseases which affect children. As such, this review provides an overview of the key variables known to impact neurobiology between children and adults, as well as how systemic and metabolic variables which influence neurocognition, differ with age. We summarise areas where these differences have been adequately acknowledged and incorporated into preclinical modelling of paediatric disease and use these approaches to inform emerging areas which require age-specific fundamental and translational research. This review will specifically focus on the increasingly recognised, yet poorly understood, neurological symptoms documented in childhood cancer survivors.

2. Current understanding of the neurocognitive side-effects of cancer therapy in children

The neurocognitive deficits which result from cancer therapy have become more relevant during the 21st century. Due to advances in the detection and treatment of cancers, we have seen profound improvements in childhood cancer survival (84%, all cancers) (AIHW, 2020), and this can be largely attributed to the use of aggressive, multi-modal cancer treatments. However, these treatments come with the cost of increased prevalence and severity of long-term side-effects, with 94% of survivors of childhood cancer reporting a chronic condition by the age of 35, compared to 40% of the general population (AIHW, 2019; Cheung et al., 2018). Almost half (48%) of all childhood cancer diagnosis occur before the age of 4-years-old, with twice the incidence rate for 0–4 than 5–9 years of age (AIHW, 2022; Kaatsch, 2010). Similarly, peak incidence of acute lymphoblastic leukaemia (most prevent childhood cancer worldwide) is in children less than 5 years of age (Harshman et al., 2012; Ward et al., 2014). This indicates that the majority of paediatric anti-cancer treatment occurs in the first few years of postnatal development.

Neurologically, 1 in 3 childhood cancer survivors demonstrate a degree of cognitive impairment which persists into adulthood, with deficits exacerbated with younger age-at-treatment (Cheung et al., 2018; Vardy et al., 2007; Williams et al., 2021). This impairment includes reduced IQ, deficits in attention and processing speeds, poor short- and long-term memory and executive dysfunction (i.e., poor self-regulation) (Blakemore, 2012; Wengenroth et al., 2015). In fact, utilisation of special education services occurs in 23% of survivors of childhood cancer in comparison to 8% of sibling controls, with this number increasing in subsets of children exposed to intrathecal methotrexate chemotherapy or CNS irradiation (Mitby et al., 2003). Further to this, exacerbated attention deficits are observed in children with leukaemia (50% prevalence) and CNS malignancies (80%) compared with other malignant diseases (Zeltzer et al., 2009). This highlights that specific subsets of survivors present with variations in severity and specific cognitive faculties. These cognitive deficits impact the ability of childhood cancer survivors to reach some developmental milestones, as illustrated by reduced likelihood of completing secondary education, obtaining and retaining employment and earning equal to, or above national income averages (Amonoo et al., 2019; Zeltzer et al., 2009). In addition to these considerable cognitive impairments, cancer therapies also inflict a range of psychosocial burdens upon survivors of childhood cancer, with mental ill-health in common domains of depression (prevalence of 1 in 3), anxiety and post-traumatic stress disorder (Loberiza Jr et al., 2002; Prieto et al., 2005). In fact, clinically diagnosed psychological distress is 80% more prevalent in childhood cancer survivors than their siblings, with largest effect sizes observed following CNS tumour or osteosarcoma (Zeltzer et al., 2009). Survivors of paediatric brain tumours are also at greater risk of developing a psychotic disorder, with a 25-fold increase in schizophrenia diagnosis compared to general population statistics (Shah et al., 2015). Dose-response associations have been identified between chemotherapy and mental ill-health, with increased depression reported with higher dosage and exposure to alkylating chemotherapeutics (Zeltzer et al., 2009). Fatigue

is also burdensome in survivors of childhood cancers, with 50% higher prevalence than survivors of adult cancer, and exacerbated burden following cranial irradiation (Bower et al., 2006; Cella et al., 2001; Christen et al., 2020; Zeltzer et al., 2009). Similarly to cognitive dysfunction, psychosocial burdens are associated with reduced ascertainment of milestones including employment status (Amonoo et al., 2019; Ness et al., 2008).

While the pathogenesis of (non-surgical) cancer-treatment related neurocognitive side-effects have not been fully elucidated, extensive research in pre-clinical models and survivorship cohorts have identified several key pathways and pathologies. Cancer therapies (particularly chemotherapy) can induce neuronal apoptosis, neuroinflammation, mitochondrial dysfunction, oxidative stress, DNA damage and neuroendocrine imbalance whilst disrupting cortical white matter, blood–brain barrier integrity and hippocampal neurogenesis (Janelsins et al., 2014; Mounier et al., 2020; Ren et al., 2019a; Ren et al., 2019b). Intriguingly, many of these pathways are also heavily implicated in other paediatric neurocognitive diseases, namely neurodevelopmental disorders (Fiorentino et al., 2016; Kochunov and Hong, 2014; Markkanen et al., 2016; Panisi et al., 2021; Parenti et al., 2020; Srikantha and Mohajeri, 2019; Theoharides and Zhang, 2011; Valenti et al., 2014; Zamanpoor, 2020). However, in contrast to the rigorous and age-appropriate investigation of diseases such as autism spectrum disorder (ASD) and schizophrenia, cancer survivorship research is often translated from adult cohorts to childhood cancer survivors. Furthermore, cancer treatment-induced neurotoxicity is not an endogenously sourced disease with minimal genomic contribution, although catechol-O-methyltransferase (COMT) and apolipoprotein (APO)-E (Alzheimer's disease risk factor allele) have been associated with greater neurocognitive burden following chemotherapy (Cheng et al., 2016; Fernandez et al., 2020).

As neurocognitive dysfunction due to cancer therapy is age indifferent, i.e., occurring in children and adults, researchers have tended to extrapolate molecular and clinical findings and novel therapies from the adult setting to paediatric survivorship. However, childhood survivors are more likely to experience these side-effects and at greater severity, and importantly possess unique neurobiology that undoubtedly impacts the aetiology and presentation of these symptoms. In addition, the transition of acute chemobrain (during active treatment) to chronic cognitive impairment after treatment cessation clearly has unique impact during early life, with persistent symptoms likely related to psychosocial factors such as parental stress and time away from their education (Gurney et al., 2009; Harper et al., 2019; Jones and Pattwell, 2019). Given their age and inherently different social, academic, and physical capabilities, it is also likely that children require specific neurocognitive symptom management approaches which differ to those used in adults. Collectively, these factors underscore the need to approach neurocognitive dysfunction with an appreciation for the unique nuances of the paediatric setting, recognising the age-dependent differences in neurobiology.

3. A child brain is not a small adult brain

Critical periods of neuroplasticity that occur during childhood and adolescence, along with the concurrent weakness of innate defence systems, result in a developing CNS with unique nuances compared with the fully developed adult brain. These have an undeniable impact on neurocognitive function and, thus by extension, dysfunction leading to disease. Different CNS pathways and structures mature at different stages during development, and extensive work has been undertaken to

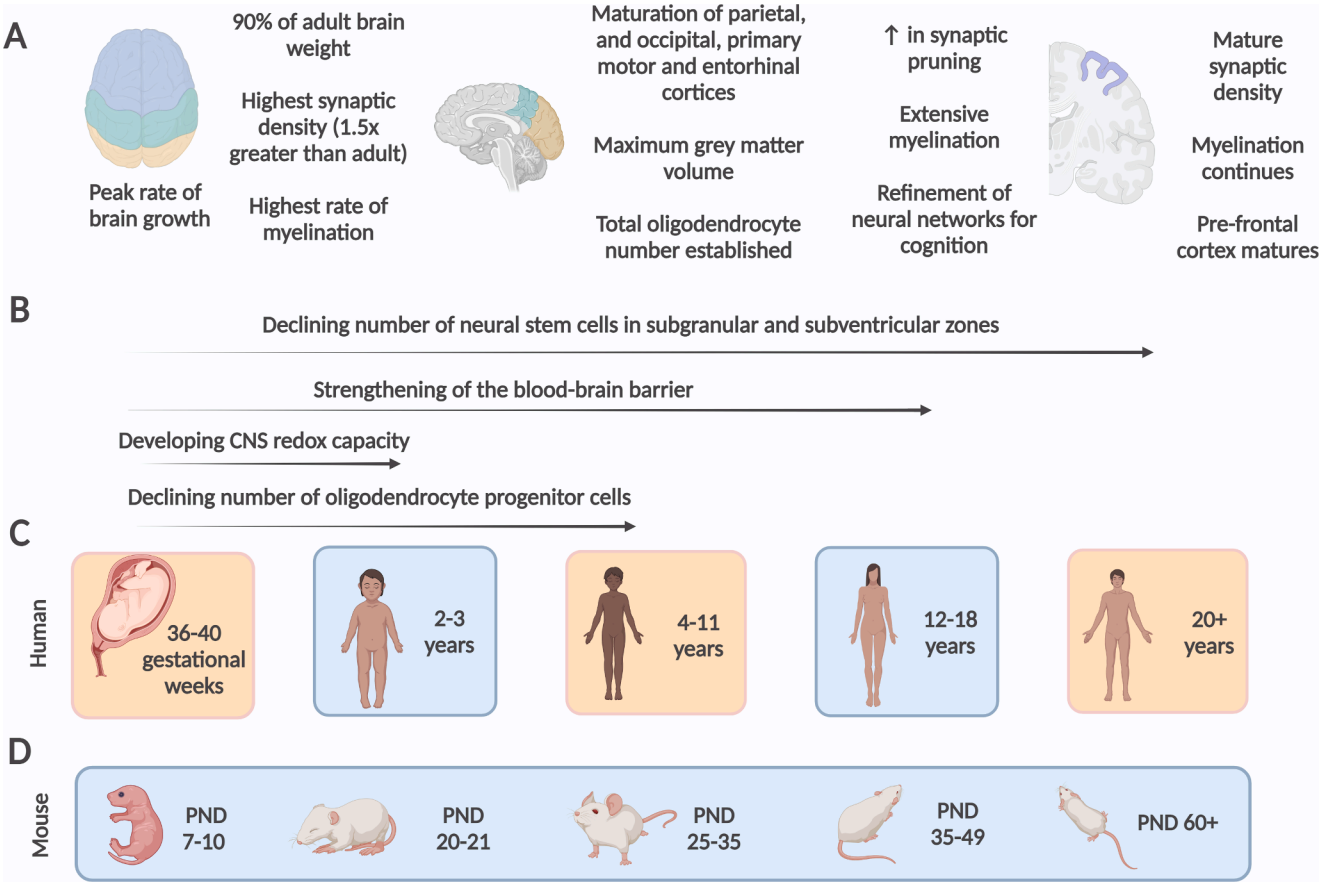

Fig. 1. Neurodevelopmental milestones of the human brain (A) and periods of maturation of neurophysiology (B) in relation to age of humans (C) and mice (D; postnatal day, PND) (Gogtay et al., 2004; Semple et al., 2013). Figure created with Biorender.com.

match neurodevelopmental stages of animal models to human milestones. Fortunately, milestones of neurodevelopment and maturation of somatic organs which exert significant influence upon the brain, have been extensively conserved between mammals (Fig. 1) (Gogtay et al., 2004; Semple et al., 2013). In the following sections, we have selected to discuss the predominant mechanisms implicated in chemotherapy-induced cognitive impairment and highlight the key differences between the paediatric and adult brain in relation to these mechanisms. We focus on how these differences may result in a paediatric-specific aetiology of the neurocognitive dysfunction caused by cancer therapy.

3.1. Heightened neurogenesis characterises the paediatric brain

Neurodevelopment relies upon the differentiation and migration of neural stem cells to produce new neurons in a process called neurogenesis (Lui et al., 2011). Neurogenesis, in turn, is reliant on the availability of multipotent neural stem cells (NSCs) and their progeny, neural progenitor cells (NPCs), which contain diminished potency (Homem et al., 2015). During embryonic brain development, neurogenesis occurs in all regions of the neural tube but over age neurogenesis only persists in two regions of the postnatal CNS: the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampus (Kalamakis et al., 2019; Sorrells et al., 2021). While the existence of neurogenesis within the mature human brain has been extensively disputed in the past, the current consensus is that new neurons continue to be generated in these two loci in the human adult brain (Alonso et al., 2012; Bardy and Pallotto, 2010; Gonçalves et al., 2016; Kempermann et al., 2018; Nissant et al., 2009). In fact, many cognitive processes, such as learning and memory, are now thought to be dependent upon neurogenesis, particularly based on extensive evidence implicating dysfunctional neurogenesis in a number of neurological diseases (Boldrini et al., 2018; Wang et al., 2022). Given the temporal importance of the production of new neurons for neurodevelopment, the rate of neurogenesis is greatest in early life, in both the SVZ and SGZ, with rapid decline during childhood, plateauing at approximately 10 years of age (Dennis et al., 2016).

Although, neurogenesis does continue within these neurogenic niches in the adult brain, adult neurogenesis occurs at a reduced rate due to a diminution of the NSC pool within the SVZ and SGZ as the CNS matures (Coletti et al., 2018). A decline in the expression of a number of NSC markers (SRY-box 2, paired box-6, doublecortin/DCX, Bromodeoxyuridine/BrdU, and Ethylnyl-2′-deoxyuridine) within the postnatal human and primate SGZ (post-mortem) has been identified from the age of 4 to 10 years of age, with no further decline recorded by the age of 23 (Boldrini et al., 2018; Sorrells et al., 2021; Wang et al., 2022). Within the SVZ, a similar decline in NSC markers, Ki67 + and DCX+, occur between 0 and 10 years, with no DCX + cells observed in post-mortem tissue from individuals older than 4 years of age (Dennis et al., 2016). Kalamakis et al. (2019) applied mathematical models to suggest a rationale for this decline, determining a higher probability for NSCs to differentiate into a terminal fate, than to renew the progenitor pool, resulting in progenitor depletion with time. Once a differentiated neural precursor is generated, it migrates from the neurogenic niche along the migratory streams to integrate into circuitry within cortical layers and promote healthy brain development. Importantly, migrating DCX + cells have not been observed in post-mortem tissue from individuals older than 2-years, suggesting that neurotoxic insult during early years may have unique consequences for cortical connectivity (Paredes et al., 2016). This pathway has now been linked to the pathogenesis of schizophrenia, emphasising that disrupted neuronal migration results in adverse development and brain function (Goo et al., 2023; Greenberg et al., 2015; Muraki and Tanigaki, 2015).

Neural progenitor cells demonstrate a heightened vulnerability to neurotoxic exposure than the terminally differentiated neurons (Chan et al., 2013; Pierozan et al., 2020; Pierozan and Karlsson, 2021). In the context of chemotherapy-induced neurocognitive impairment, the highly proliferative and migrational nature of these neural precursors positions them as key targets of chemotherapeutic agents, given that these agents inherently target rapidly dividing and migrating cell populations (Blagosklonny, 2006; Zhao, 2016). Importantly, this contrasts the relatively quiescent mature neuron populations which appear to be less susceptible to direct chemotoxicity (Blagosklonny, 2006; Zhao, 2016). Of note, cultured NSCs demonstrate greater vulnerability to temozolomide (chemotherapy used to treat brain tumours) than mature neurons and even glioma cell lines (Gong et al., 2011; Lomeli et al., 2020). A dose of 200 μM temozolomide reduced NSC viability by 50% but was ineffective on low and high-grade glioma-like stem cells and this was independent of temozolomide-resistance enzyme (O6-methylguanine-DNA methyl transferase, MGMT) expression; in comparison mature neuron viability was only reduced by 26% after a 500 μM dose (Gong et al., 2011; Lomeli et al., 2020). A similar affinity for NSCs, over glioma cells, was observed after treatment with cisplatin, a chemotherapy used to treat a wide variety of cancers (Gong et al., 2011). As there is a greater population of NSCs within the child brain (particularly during early childhood), this indicates a larger pool of cells with a heightened susceptibility to the mechanism of action of chemotherapy. This period of heightened susceptibility to neurotoxic damage from chemotherapy parallels clinical observations of increased severity of side-effects with decreased age-at-treatment (Castellino et al., 2014; Duffner, 2010; Packer et al., 1989). Additionally, the NSCs within the neurogenic niches of the postnatal brain become progressively more quiescent with age, taking significantly longer to complete the cell cycle (Kalamakis et al., 2019). This implies a reduced susceptibility of mature and aging vs. young NSCs to the chemotherapy mechanism of action. Further to this, the increasingly quiescent nature of NSCs has been linked to an age-related pro-inflammatory microenvironment within the SVZ and SGZ, evidenced by a 30% increase in the proportion of interleukin (IL)–23 + NSCs from 2-month to 22-month-old healthy rats (Kalamakis et al., 2019). Given the chronic neuroinflammation produced by chemotherapy, this finding interestingly suggests these agents may indirectly drive NSCs towards premature quiescence in the developing brain and hence impair neurogenesis.

Suppressed hippocampal neurogenesis is an extensively documented component of chemotherapy-induced neurocognitive impairment in adult rodent models, an observation highly conserved between different chemotherapeutic agents (Christie et al., 2012; Seigers et al., 2009; Sritawan et al., 2020; Winocur et al., 2014; Winocur et al., 2015). This diminution of postnatal SGZ neurogenesis can be extensive with a reported 90% reduction in BrdU + cells in the (2-month-old) rodent hippocampus after a combination treatment of cyclophosphamide and doxorubicin (Christie et al., 2012). Given the unique and essential importance of neurogenesis during neurodevelopmental periods in childhood, exposure to toxic agents (i.e., chemotherapeutics) during these periods is likely to have uniquely damaging consequences. For instance, chemotherapy can induce DNA damage to healthy cells and when this occurs to progenitor cells these disruptions to the genome are generally present in the progeny (Lomeli et al., 2020; Qing et al., 2022; Sánchez-Suárez et al., 2008). Unrepaired genomic corruptions during neurodevelopment have substantial consequences for overall function of the CNS, and as such, DNA damage is a common denominator in neurodevelopmental and neurodegenerative disorders (Madabhushi et al., 2014; McKinnon, 2013; Qing et al., 2022). Specifically, pathogenesis of both ASD and schizophrenia share a deficient DNA repair system, with unrepaired damage to the genome during critical periods of brain maturation related to cognitive and behavioural symptoms (Cabungcal et al., 2014; Kern and Jones, 2006; Kim et al., 2014; Markkanen et al., 2016; Melnyk et al., 2012). DNA damage induced by doxorubicin is sufficiently neurotoxic to induce neuronal apoptosis, suggesting that chemotherapy exposure during childhood may instigate a premature loss of neural progenitors within the developing brain (Lee et al., 2006). Given the longevity of mature neurons, DNA damage accumulates and drives cognitive deterioration (Qing et al., 2022); the diminution of repair processes with normal aging has been linked with reduced

expression of genes coding for synaptic plasticity and hence impacting learning capabilities (Madabhushi et al., 2014). As such, pathological DNA damage has been causally related to neurodegenerative disorders such as amyotrophic lateral sclerosis, and Parkinson's and Alzheimer's diseases (Kok et al., 2021; Martin, 2008). With this knowledge, it is apparent that rigorous investigation into long-term functional and pathological consequences of suppressed neurogenesis (compromised proliferation, migration, and function) and DNA damage, caused by cancer therapy or other neurotoxic compounds, needs to be collected in paediatric cohorts and relevant animal models.

3.2. *The paediatric neuroimmune system is pro-inflammatory*

Neuroinflammation is recognised to play a role in many neurological diseases, in addition to direct effects upon neurogenesis, or the induction of neurodegeneration. Mirroring the activity of the peripheral immune system, the neuroimmune system exerts both important protective effects coupled with potentially damaging consequences. Physiologically, neuroinflammation serves to protect the brain from pathogenic insult and promote the repair and recovery of neuronal tissues (Linnerbauer and Rothhammer, 2020); however, when dysregulated or persisting chronically, excessive neuroinflammation damages the brain parenchyma, impacting learning and memory (Lyman et al., 2014). As a result, neuroinflammation is a commonly shared mechanism or observation in several neurodevelopmental disorders including ASD, schizophrenia, cerebral palsy, and chemotherapy-induced neurotoxicity (Hagberg et al., 2012; Kim et al., 2022; Konsman et al., 2022; Mounier et al., 2020; Rummel et al., 2021). However, just like neurogenesis, the neuroimmune system evolves with age, and is in fact pro-inflammatory in early life, which is hypothesised to compensate for the developing peripheral immune system during critical periods of neurodevelopment (Fig. 2) (Christensen et al., 2014). In fact, stimulating neonatal rats with the endotoxin lipopolysaccharide (LPS) produced elevated levels of IL-1α, IL-1β, IL-2, tumour necrosis factor (TNF) and chemokine ligand (CCL)-2, CCL3 and CXCL9 (Christensen et al., 2014). This pro-inflammatory response has been theorised to contribute to the clinical severity of CNS infection in children compared to those experienced in adults, as well as their propensity to cause long-term neurological dysfunction (Christensen et al., 2014; Kim et al., 2022). Significantly, it has also been considered that this neurological damage is not solely driven by the invading pathogenic agent, but also by the innate immune reactivity and consequent pro-inflammatory response within the brain (Kim et al., 2022). In a similar manner, systemic LPS is elevated after chemotherapy and drives neuroinflammation via the innate immune system through toll-like receptor 4 (TLR4)-dependent mechanisms (Ciernikova et al., 2021; Subramaniam et al., 2020). The associated neuropsychological symptom of fatigue, is also driven by aberrant immune signalling mediated through the TLR4 accessory protein, MYD88 (myeloid differentiation 88) (Wolff et al., 2021), although this has not been studied in the paediatric setting. As such, considering the unique neuroimmune capacity of the paediatric brain is critical in understanding neurocognitive dysfunction in children with cancer.

Immune pathways of the brain are largely mediated by glial cell populations, namely microglia and astrocytes (Fig. 2), that survey the CNS microenvironment for pathogens, toxins, and other noxious compounds. Microglia are the resident immunocompetent cells of the CNS and are most recognised for their ability to shift phenotypically from surveilling, ramified cells to activated, ameboid cells which can phagocytose cellular waste, apoptotic cells, and invading microbes (Bar and Barak, 2019; Sominsky et al., 2018). This phagocytic function also allows microglia to play their critical role in the maturation of neuronal circuits, via engulfing the axonal terminals and dendritic spines which compose synapses, and as such pruning unnecessary neuronal connections (Bennett et al., 2021; Sominsky et al., 2018; Thion et al., 2018). Microglia are fundamental mediators of chronic neuroinflammation observed in ASD, with increased microglial and myeloid markers

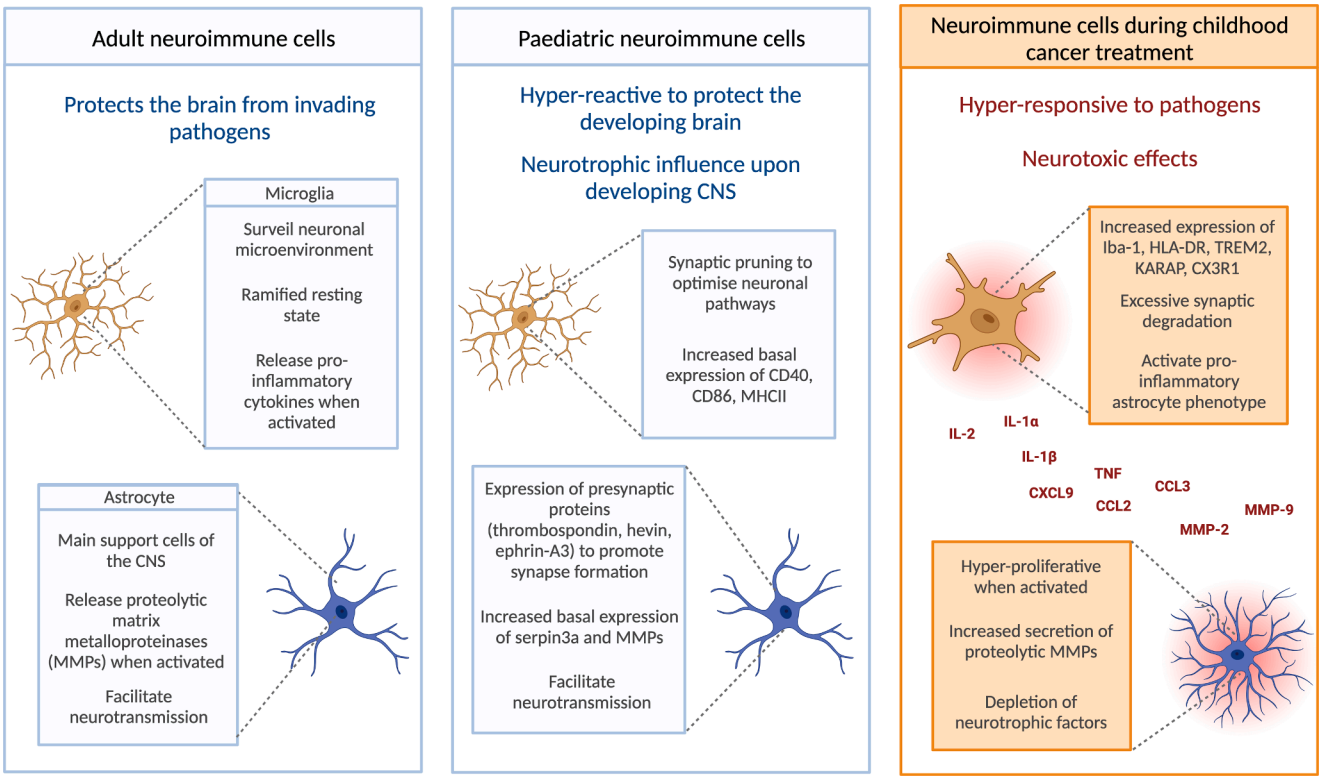

Fig. 2. The uniquely hyper-responsive neuroimmune system which characterises paediatric neurodevelopment has implications for children treated with chemotherapy (and other cancer therapies) during this period of heightened vulnerability (Christensen et al., 2014; Clarke et al., 2018; Edmonson et al., 2014; Kim et al., 2022; Matta et al., 2019; Ranasinghe et al., 2009; Vargas et al., 2005). Figure created with BioRender.com.

(human leukocyte antigen (HLA)-DR, ionised calcium binding molecule (Iba)-1, chemokine receptor 3 (CX3R)-1, triggering receptor expressed on myeloid cells (TREM)-2, killer cell activating receptor-associated protein, KARAP) observed in the pre-frontal cortex in comparison to neurotypical controls (Edmonson et al., 2014; Matta et al., 2019; Vargas et al., 2005). In children with ASD, these phagocytic cells perform aberrant synaptic pruning which likely contributes to dysconnectivity in this neurodevelopmental condition (Morgan et al., 2010; Zhan et al., 2014; Zhang et al., 2023b).

Aligning with a pro-inflammatory state for the paediatric neuroimmune system, microglia in neonates have greater basal expression of immune markers, including cluster of differentiation (CD)86, CD40, and major histocompatibility complex (MHC)-II (Santambrogio et al., 2001). Additionally, neonatal microglia also demonstrate a greater functional pro-inflammatory response *in vitro*. Treatment of primary neonatal rat microglia cultures with adenosine 5′-triphosphate (ATP) elicited greater secretion of nitric oxide and TNFα and higher glutamate uptake than primary adult (2–8 months) or aged (9–15 months) rat microglia (Lai et al., 2013). Other data indicate that primary microglia from 18 to 25 month old rodents have a higher basal expression of immune marker CD11b, but that expression levels were more sensitive to transient ischemia in male neonates than aged (Ngwa et al., 2021). *In vivo* research also found that neonatal microglia were more proliferative following hypoxic-ischemia, with 2-3x greater cell number than in 4-week-old mice (Ferrazzano et al., 2013). There are some publications which suggest that microglial reactivity is not only more rapid in neonates but also more prolonged following transient ischemia (Cikla et al., 2016; Derugin et al., 2000; Liu and McCullough, 2013).

While the temporal kinetics of this age-related microglial reactivity are not well understood beyond the neonate, this heightened reactivity is likely due to the increased requirements of synaptic pruning during early-life. However, this could contribute to heightened severity of immune-dependent neuropathology in children. Additionally, it is important to acknowledge that other cells of myeloid lineage can access the brain in the context of inflammation or disease conditions. Bone marrow-derived myeloid cells, in particular, invade brain tumours, induced by factors relating to both the tumour and treatment (i.e., irradiation), which can result in a neurodegenerative cascade impacting microglia and neuron physiology (Hohsfield et al., 2020; Pinton et al., 2019). While the effect of invading monocytes on an immature brain have not been fully elucidated, evidence suggests this potentiates an inflammatory phenotype and may predispose to neurodevelopmental disorders (Onore et al., 2014; Tanabe and Yamashita, 2018).

In line with microglia dynamics throughout neurodevelopment, astrocytes are equally dynamic showing transient increases in reactivity during early development. Upregulation of inflammatory astrocytic gene serpina3n and signalling protein matrix metalloproteinase 2 (MMP-2) have been identified during infancy and early development (Clarke et al., 2018; Ranasinghe et al., 2009). Additionally, neonatal rodents (postnatal day, PND 6–14) exposed to mechanical brain injury exhibit elevated astrocyte proliferation than at PND 30 (Janeczko, 1994). Astrocytes are also intimately involved in neuroinflammation, with secretion of IL-1α and TNF by reactive microglia which instigate a pro-inflammatory astrocyte phenotype. Like microglia, astrocytes hold a dual role in facilitating neurotransmission and secreting neurotoxic cytokines when reactive. Resting-state astrocytes express presynaptic proteins (e.g., thrombospondins, hevin, ephrin-A3) which regulate excitatory synapse formation and dendritic spine longevity (Christopherson et al., 2005; Kim et al., 2022; Kim et al., 2021; Kucukdereli et al., 2011; Murai et al., 2003). The astrocyte phenotype shift results in downregulation of these trophic factors in exchange for pro-inflammatory mediators: TNF, IL-1β, IL-6 and MMPs (Bianco et al., 2005; Choi et al., 2014; Hart and Karimi-Abdolrezaee, 2021; Nagy et al., 2006). MMPs as proteolytic enzymes are particularly neurotoxic, by breaking down the extracellular matrix which form the protective perineuronal nets around neurons and resultingly are strong instigators of neuronal apoptosis. Unsurprisingly, increasing MMP activity is related to the neurotoxicity underlying both ASD and schizophrenia (Abdallah and Michel, 2013; Chopra et al., 2015; Lepeta and Kaczmarek, 2015).

Astrocyte reactivity has also been linked to both neurodevelopmental disorders and chemotherapy-induced neurological impairment with elevated glial fibrillary acidic protein (GFAP) in the prefrontal cortex of people with ASD and cancer survivors (Laurence and Fatemi, 2005; Shi et al., 2019). A further concern of prolonged astrocyte reactivity during development is the consequent deficiency of astrocyte-derived neurotrophic factors required for appropriate neurodevelopment. Postnatal (PND 7–21) astrocyte ablation models in rodents lead to a reduction in the number of synaptic connections between neurons and overall network instability, indicating the role astrocytes play to synchronise neuronal and synaptic survival (Schober et al., 2022). The wingless/integrated (Wnt) and β-catenin pathway, orchestrated via astrocyte signalling, exerts paracrine effects to activate downstream neurotrophic factors such as brain-derived neurotrophic factor (BDNF) which is essential for learning and memory (Zhou et al., 2020). Predictably, decreased Wnt/β-catenin signalling is implicated in abnormal neurodevelopment, most readily in ASD, with concurrent changes in astrocyte morphology (reduced branching number and length) indicative of a pro-inflammatory phenotype (Sloan and Barres, 2014). Given this dual role of astrocytes, it is important to consider the effects of chronic pro-inflammatory signalling upon neurodevelopment but also the consequences of chronic deficiencies in astrocyte-derived trophic factors.

Collectively, these data underscore that not only is the developing brain of a child more vulnerable to the direct cytotoxic properties of anti-cancer therapies, but also that the relative hypersensitivity of the paediatric neuroimmune system is more likely to perpetuate secondary neuroinflammation and its effects on long-term cognition. Contrastingly, critical periods of neuronal maturation are concluded by adulthood and as such, the results of glial reactivity and cytokine dysregulation are less detrimental and long-lived in older patients. These underscore the knowledge that the childhood brain is inherently different to that of an adult, and as such, both discovery and translational research must acknowledge these differences in experimental design and methodology.

3.3. *The paediatric blood–brain barrier is leaky*

When considering neuropathological changes in response to exogenous triggers – including infection, or, in the context of childhood cancer, chemotherapy – the ability of peripherally circulating factors to access the CNS is critical. CNS access is largely mediated by the blood–brain barrier, a monolayer of brain microvascular endothelial cells (BMECs) (Abbott et al., 2010; Obermeier et al., 2013). BMECs are highly specialised for this role with upregulation of tight and adherence junction proteins to restrict paracellular permeability as well as low expression of receptors and transporters for active transport, meaning most molecules must be transcellularly trafficked across BMECs through caveolae (Sweeney et al., 2018; Zhao et al., 2015). BMECs also highly express efflux transporters to further limit access of toxins to the CNS (Kadry et al., 2020).

'Barrier-genesis' commences during embryonic development, concurrently with angiogenesis, and continues to mature postnatally (Coelho-Santos and Shih, 2020). The development of the blood–brain barrier is a sequential process, and the ongoing angiogenic processes and microvasculature modification which occur during childhood are paralleled by changes in expression of structural barrier components which are vastly different to the stable vascular networks seen during adulthood (Fig. 3) (Blondel et al., 2022; Coelho-Santos and Shih, 2020). The perinatal capillary system is sporadic and immature, and concurrent angiogenesis and integration of neurovascular support cells (astrocytes, pericytes, neurons and microglia) with endothelial cells gradually leads to a functional blood–brain barrier. This process has been reported to

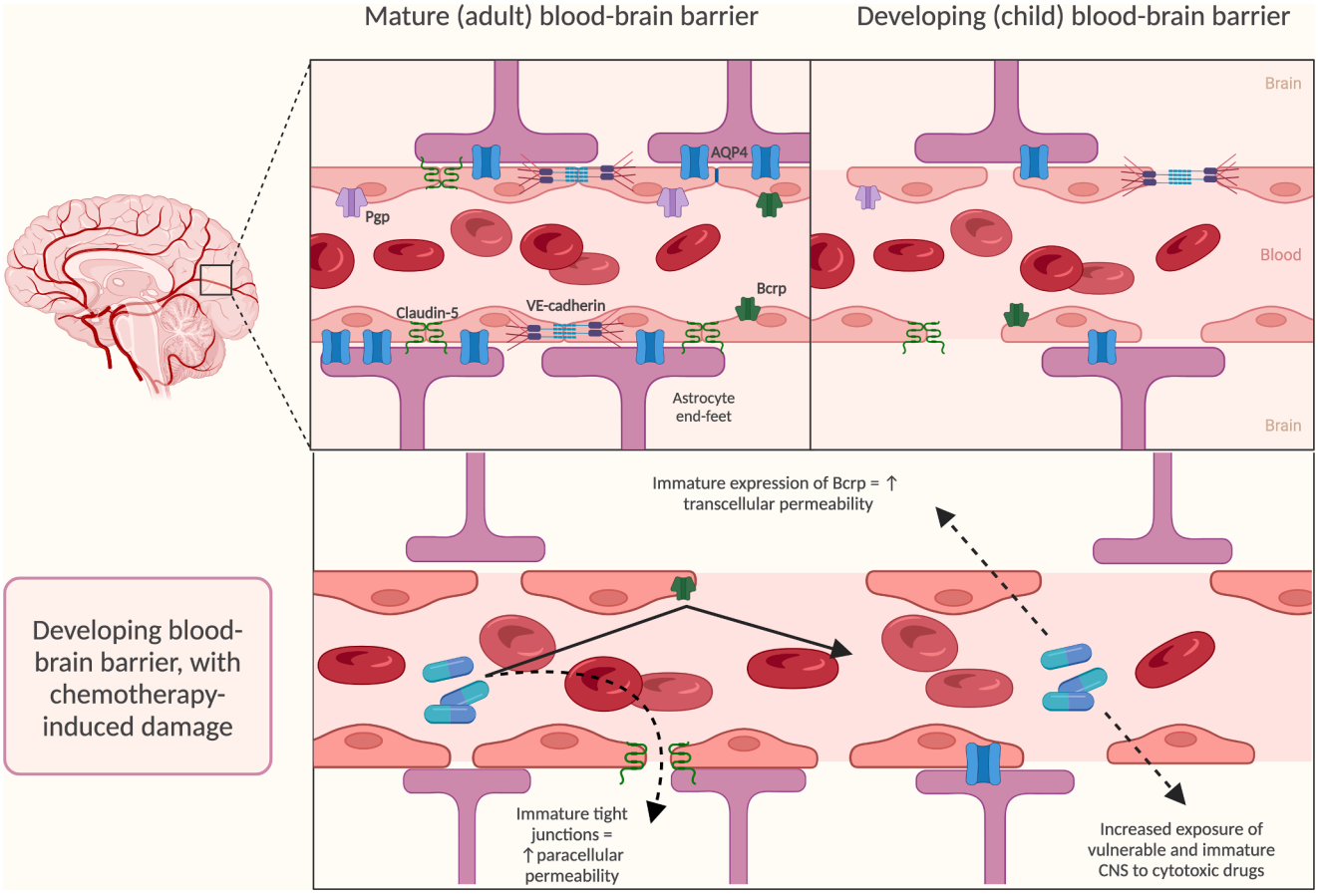

Fig. 3. Comparison of the mature signature of the adult to the developing blood–brain barrier, with consideration of the consequences for chemotherapy entry to the vulnerable brain parenchyma (Amawi et al., 2019; Coelho-Santos and Shih, 2020; Ito et al., 2011; Omori et al., 2020). Figure created with BioRender.com.

occur up to two weeks postnatally in mice, which equates to an estimated 12-months of age in humans (Coelho-Santos and Shih, 2020; Dutta and Sengupta, 2016; Lam et al., 2015). While published evidence of Trypan blue testing in rodent and pig embryos found no penetration of dye into the prenatal, newborn, nor adult CNS (Goldman, 1913; Grazer and Clemente, 1957), indicating no functional difference, the age of these findings does raise concerns regarding its validity. In fact, analysis of human tissues from the first year of life shows immature levels of key BMEC proteins (Coelho-Santos and Shih, 2020; Dutta and Sengupta, 2016; Lam et al., 2015).

Furthermore, investigation of temporal dynamics of expression levels of these proteins in rodents indicates mature levels are still not reached by postnatal week two (Omori et al., 2020). Efflux transporter P-glycoprotein (Pgp, ATP-binding cassette transporter ABCB1) expression is 80% less than adult levels (PND 24–84) at PND 7 and still 60% less at PND 14 (Omori et al., 2020).

Pgp was first identified as multi-drug resistant protein 1 (Mrp1) due to its role in anticancer drug resistance by expelling chemotherapeutics from tumour loci (Amawi et al., 2019). However, in this context, depleted Pgp during childhood suggests the blood–brain barrier defence systems are insufficient to prevent small molecule chemotherapies from entering the brain parenchyma. In effect, Pgp substrates have shown increased blood–brain barrier penetration in juvenile vs adult rats, concurrent with 10-fold upregulation of the efflux transporter with maturation (Kupferberg and Way, 1963; Matsuoka et al., 1999; Morimoto et al., 2012). Similarly, another efflux transporter, breast-cancer resistant protein (Bcrp, ABCG2) demonstrates continuously increased expression during development from PND 1 to 2 and 3 weeks old in rats and from birth to adulthood in rhesus monkeys (Ito et al., 2011; Omori et al., 2020). Bcrp substrates include commonly administered chemotherapies methotrexate, topotecan and irinotecan (Robertson et al., 2012; Suzuki et al., 2003) and as such, the early life deficit in blood–brain barrier expression of this transporter leaves the CNS more vulnerable to drug permeability and consequent neurotoxicity than during adulthood (Fig. 3). While Daneman et al. (2010) found no upregulation of pathways relating to cellular transport from PND 2–8 animals to PND 60–70 animals, more recently several transporters have shown increased expression through postnatal neurodevelopment. These include GLUT1 (glucose transporter), MCT1 (monocarboxylate transport) and Cav1 (transcellular transport via caveolae) from PND 1 to 14, 21 and 56 (Omori et al., 2020). Cumulatively, this may suggest an immature signature of the developing blood–brain barrier with consequences for CNS protection and energy transport.

Paracellular permeability is the alternate route by which solutes may penetrate the blood–brain barrier; however, this too is highly regulated via the localised expression of tight and adherens junction proteins. In fact, intraperitoneal injection of (3 kDa) biotinylated dextran amines to embryonic and adult rodents did not result in paracellular leakage at either age (Liddelow et al., 2013). This may suggest that any early-life increase in molecular penetration of the CNS is via transcellular pathways to meet increased metabolic demands. Conversely, tight junction proteins, enriched within BMECs (Daneman et al., 2010), claudin-5 and claudin-3 demonstrate an age-dependent increase in blood–brain barrier expression at PND 1, 14, 21 and 56 and from PND 15–70, respectively, in rodents (Omori et al., 2020; Solarz et al., 2021). An adherens junction protein, VE-cadherin (CD144), displays a similar progressive increase in the rhesus monkey (Ito et al., 2011).

The blood–brain barrier is further reinforced by astrocyte paracrine communication with astrocytic end-feet in direct contact with BMECs. These end-feet were identified in fluorescent imaging via positive

staining for aquaporin-4 (AQP4, water transporter). Of note, AQP4 is lowly expressed at PND 7 and shows further age-dependent increases in expression from PND 15–70, suggesting deficient microenvironmental support for adequate barrier function in early life (Coelho-Santos and Shih, 2020). In line with age-dependent upregulation of critical blood–brain barrier components, there is an inverse correlation between postnatal age and plasma S100-β levels (Solarz et al., 2021) – an astrocytic product too large to exit the CNS via an intact barrier. Hence, decreased S100-β levels from PND 15–70 indicates increased blood–-brain barrier leakiness (Solarz et al., 2021). Collectively, this suggests the paediatric brain has a less robust blood–brain barrier, and thus is more vulnerable to insult from noxious substances in circulation (Solarz et al., 2021). This may also contribute to the pro-inflammatory profile of the paediatric neuroimmune system, as the first line of defence is weakened. Ultimately, this impaired physical defence in combination with heightened drug transport, makes the paediatric brain more readily accessible by intravenously administered anti-cancer agents.

3.4. Impaired redox capacity imparts a heightened sensitivity to oxidative stress in the paediatric brain

The CNS is exposed to high levels of oxidative stress under basal physiological conditions as the brain consumes more oxygen than any other organ – 20% of the body's total oxygen intake (Franco et al., 2019; Omori et al., 2020). While the brain has innate antioxidant defences to offset this high oxygen usage, physiological nuances of neural tissue further increase the susceptibility of the CNS to oxidative damage. These include, enrichment of unsaturated lipids, glutamate pathway enrichment (thus risk of mitochondrial calcium overload), redox active transition metals, high mitochondrial demand, and auto-oxidation of neurotransmitters (Cobley et al., 2018; Franco et al., 2019). In fact, the metabolic demand of the CNS is so high that a single cortical neuron can use 4.7 billion ATP molecules per second, which results in high production of reactive oxygen species (ROS) (Zhu et al., 2012). The subsequently dysfunctional or apoptotic neurons can lead to a variety of neurodevelopmental and neurodegenerative diseases (Annunziato et al., 2003; Méndez-Armenta et al., 2014).

The developing environment of the paediatric brain is recognised to have immature antioxidant enzymes, resulting in a lower redox capacity. For example, glutathione (GSH) levels – inversely associated with Alzheimer's disease (Liguori et al., 2018; Saharan and Mandal, 2014) and schizophrenia symptoms (Matsuzawa and Hashimoto, 2010) – are significantly lower in PND 14 rat brain sections than the levels reached at PND 21 (Khan and Black, 2003). Similarly, glutathione peroxidase, responsible for the redox of lipids and hydrogen peroxides, increases in activity in the brain from PND 1–45 in rodents (Khan and Black, 2003). In line with these findings, superoxide dismutase and catalase (responsible for ROS mitigation) are lowly expressed in the brain up to and including PND 14 in rodents, representing underdeveloped mechanisms to defend against hydrogen peroxide toxicity and consequently DNA damage within the CNS (Khan and Black, 2003). These findings have direct implications for neurotoxicity and neurocognitive impairment caused by anti-cancer (cytotoxic) drugs, especially chemotherapy. Notably, nearly 50% of approved chemotherapy agents of different drug classes/types (e.g., cyclophosphamide, doxorubicin, methotrexate, carmustine, carboplatin) are known to produce extensive oxidative stress in the brain as well as depleting innate antioxidant activities (Joshi et al., 2010; Rummel et al., 2021).

NPCs are inherently more sensitive to oxidative stress, a sensitivity shared by the myelinating cells of the CNS – oligodendrocytes. Oligodendrocytes are responsible for myelinating neuronal axons and thus, maintaining white matter connectivity within the brain. Interestingly, oligodendrocytes are especially vulnerable to damage induced by oxidation as these cells promote high ROS production through elevated metabolic activity and iron content (Roth and Núñez, 2016; Thorburne and Juurlink, 1996). Additionally, oligodendrocytes are innately deficient in GSH compared to other glia, indicating poor redox defences (Roth and Núñez, 2016). Further depletion of antioxidant mechanisms, such as following chemotherapy, is associated with loss of white matter integrity, such as, within the cingulum which connects the frontal, temporal and parietal lobes (Monin et al., 2015). As the brain matures throughout childhood, oligodendrocytes become less vulnerable as GSH levels increase and these myelinating cells exchange oxidative for glycolytic metabolism (Back et al., 1998; Roth and Núñez, 2016). In schizophrenia, oxidative damage to oligodendrocytes is a leading pathogenic hypothesis, indicating the relevance of white matter integrity to appropriate neurodevelopment (Cuenod et al., 2022; Maas et al., 2017).

The vulnerability of oligodendrocytes is heightened further at the progenitor stage (OPC), displaying differentiation dependent survival when exposed to free radicals (Back et al., 1998). Total brain OPC number is greatest during the first prenatal years with gradual declines until 5 years old, at which age stability is reached. Similarly, the total number of oligodendrocytes is established within the first decade of life (turnover rate of 1/300 oligodendrocytes per year) with 86% of final white matter volume established within the first 5 years (Yeung et al., 2014). OPC proliferation and differentiation is inhibited, and apoptosis induced by depleting GSH, and consequently inducing redox imbalance (Back et al., 1998). This indicates an opportunity for mechanisms of chemotherapy-induced neurotoxicity to deplete progenitor niches and subsequently disrupt the precise pathways of brain connectivity during critical periods of neurodevelopment occurring uniquely during childhood, with the potential for long-lasting consequences for cognition.

4. Systemic influences of neurocognitive function

It is increasingly recognised that despite its relative isolation from the periphery, the CNS is influenced by systemic events, particularly those involving the immune system. Events occurring in the periphery, e.g., immune activation or inflammation, have the capacity to impact CNS physiology and induce neuropathology. This is well documented in the case of vaccines or infection, whereby peripheral immune activation is associated with hallmark traits of cognitive impairment, brainfog and fatigue (Thomson et al., 2014). For instance, people with the autoimmune disorder rheumatoid arthritis are often diagnosed with co-morbid neurocognitive symptoms (e.g., depression and cognitive impairment) with associated increases in pro-inflammatory cytokines within the cerebrospinal fluid (Covic et al., 2012; Fuggle et al., 2014; Shin et al., 2012; Won et al., 2022). More recently, brainfog as a result of COVID-19-mediated astrocyte, microglia and brain lymphocyte activation, has emerged with deficits in memory, executive functioning and attention and concurrent functional changes in neuroimaging studies of the hippocampus and prefrontal cortex (Becker et al., 2021; Bertuccelli et al., 2022; Najt et al., 2021).

Systemic inflammation including that associated with inflammatory bowel disease, is now known to be associated with characteristic neuroinflammatory changes in the brain (Sun et al., 2022), prompting extensive investigation of how the gut, the largest immunological system in the body, influences CNS physiology and behaviour. Numerous CNS diseases are now recognised to incorporate concurrent changes in the gastrointestinal environment, including intestinal leakiness, altered mucous production and changes in the resident micro-organisms (the gut microbiota). The vagus nerve, responsible for communicating metabolic signals from the gastro-intestinal tract to the CNS, influences higher-order cognitive functions, such as memory and motivation, and plays a role in neurocognitive disease (Décarie-Spain et al., 2023; Makdissi et al., 2023). In fact, deposition of α-synuclein has been observed in the vagal nerve before the clinical presentation of Parkinson's disease (Makdissi et al., 2023). This is only one example of the many neurodegenerative diseases which are now thought to originate in the gut with gastrointestinal symptoms observed (sometimes years) prior to the onset of neurological symptoms (Haikal et al., 2019;

Makdissi et al., 2023; Sampson et al., 2016).

Alterations in the gastrointestinal microenvironment, in particular intestinal barrier dysfunction, permit unrestricted communication between luminal microbes and the mucosal immune system; a mechanism in which the pattern recognition receptor, TLR4, plays a mediatory role. When activated, TLR4 initiates a rapid and profound systemic inflammatory response, weakening the blood–brain barrier to drive neuroinflammation and associated pathology (Gao et al., 2015; Kuzmich et al., 2017; Zhang et al., 2015). Similarly, a disrupted gut microbiota, which is metabolically deficient, will result in poor production of fibre fermentation by-products – short chain fatty acids (SCFAs). Under healthy circumstances, SCFAs are readily absorbed and can transverse the blood–brain barrier where they exert numerous neuroprotective effects. The most commonly referenced SCFAs in relation to neurocognition are acetate, propionate and butyrate, which are known to promote neuronal function via inhibiting histone deacetylases (HDACs) and eliciting changes to chromatin and gene transcription (Dalile et al., 2019). HDACs are implicated in cognitive impairment as evidenced by their role in schizophrenia and Alzheimer's disease, and opposingly, HDAC inhibitors have been shown to promote cognition in preclinical studies (Dalile et al., 2019; Volmar and Wahlestedt, 2015). For example, 4-week regimen of butyrate administration can alleviate depressive phenotypes, increase BDNF production and promote restoration of learning and memory in mice with neuronal atrophy (Fischer et al., 2007; Schroeder et al., 2007). Emerging evidence suggests that the microbiota-gut-brain axis is implicated in a number of neurological diseases, and that age plays an important role. This was exhibited with the ability of a transplant of the faecal microbiota from 3 to 4 month old mice to ameliorate the effects of aging on both systemic and CNS immune activity and the hippocampal transcriptome (Boehme et al., 2021). This clearly points to the dynamic changes in both the gut microbiota, intestinal barrier and immune system that occur throughout development.

It is well documented that in early-life innate immunity is suppressed (Clapp, 2006), a concept which has been comprehensively documented in neonates, with monocytes from cord-blood exhibiting blunted TNFα production (up to 1000-fold less than adult monocytes) following LPS activation (Clapp, 2006). This reduced inflammatory response reportedly extends to IL-12p70 from LPS and interferon (IFN)-α and IFNγ following stimulation with TLR9 agonist CpG oligonucleotide (Nguyen et al., 2010). However, other cytokines in cord-blood show an assumed transient upregulation vs adult samples including IL-1β, IL-6, IL-23 and IL-10, levels which are reported to be depleted by 2-months of age (Yerkovich et al., 2007). While the kinetics of innate immune development outside the neonate period are poorly defined, the available data suggests that there is a slow increase in cytokine expression and monocyte number from the infant through to adulthood. At 4-years, TLR4 activation by LPS still induces significantly lower levels of IL-6, IL-10 and TNFα and this result was maintained up to 13-years for IL-18 and IFN-γ (Yerkovich et al., 2007). Interestingly, comparison of monocyte TLR4 expression identified no variation in basal levels in 1-year-olds and adults (Levy et al., 2006; Yerkovich et al., 2007); however, translocation to the cytoplasm was far more rapid in infants potentially explaining the suppressed cytokine response in this cohort (Yerkovich et al., 2007). While young rhesus macaques <4 years of age are TLR4 and TLR5 deficient in comparison to adult animals, they also lowly express the negative regulator of TLRs (sterile alpha and TIF-motif containing protein, SARM1) (Asquith et al., 2012). The absence of this reduced negative regulator may allow for sufficient innate immunity despite lower pattern recognition receptor expression.

Certainly, the deficiencies in the paediatric immune system are linked with their relatively immature gut microbiota. During the first few years of life, the immature gut microbiota develops in complexity; however, this is still vastly different than the abundance and richness which characterises the adult gut microbiota (Ringel-Kulka et al., 2013). Studies of 7–12 year-olds shows that the paediatric gut microbiota is enriched in *Bifidobacterium spp.*, *Faecalibacterium spp.*, and *Lachnospiraceae* in comparison to the adult microbiome which is more abundant in *Bacteroides spp* (Hollister et al., 2015; Ihekweazu and Versalovic, 2018). Use of metagenomics to understand the functional consequences of this difference indicates prioritisation of genes pertaining to developmental processes (e.g., vitamin and folate synthesis, metabolism of amino acids) in comparison to aging processes (e.g., inflammation, adiposity) in adults (Hollister et al., 2015). Even during adolescence (11–18 years) variation in relative abundance can be observed with distinctive characteristics of the adult microbiota, such as increased stability, only appearing once pubescent transitions are complete (Agans et al., 2011). Maturation of the gut microbiota is also demonstrated in changes in levels of gut-derived metabolites. In neonates, acetate is the sole SCFA present (in faecal matter) with enrichment of acetate producing *Bifidobacteriaceae*, levels of which increase steadily throughout the first 6-months of life before stabilising (Tsukuda et al., 2021). As such, acetate levels in toddlers (approximately 2-years old) are significantly greater than in adults and in exchange, production of propionate and butyrate are lower (Fournier et al., 2022). The production of SCFAs with the progressive addition of carbon atoms is related not just to increased diversity with addition of *Lachnospiraceae* and *Clostridiaceae* to the gut microbiota, but also dietary changes with the exchange of breast milk for solid foods (Davis et al., 2020; Fournier et al., 2022; Sandin et al., 2009). This is evidenced by a more adult-like microbiota and higher SCFA concentrations present in formula-fed compared to breast-fed infants, with the absence of human milk oligosaccharides in formula pre-emptively maturing the microbiota (Bridgman et al., 2017). Further to this, dietary fibre is the predominant substrate for SCFA production and an estimated 1.5x increase in daily fibre intake is seen from ages of 2–3 years to 14–16 years, and hence a greater ability to produce SCFAs is seen from childhood to adolescence (Edwards et al., 2015).

These critical windows of active microbial development have significant implications for neurodevelopment, influencing the formation of synapses and myelination of neurons in brain regions responsible for cognitive function. As such, perturbations to the microbiota during these windows can have long-term consequences for neurological functioning. Experimentation using germ-free (GF) mice demonstrate that the absence of commensal colonisation produces aberrant neuroanatomy with abnormal neuronal morphology and dendritic spine structure in the hippocampus and amygdala (Luczynski et al., 2016). Similarly, GF mice demonstrate reduced synaptic functionality with downregulation of synaptic proteins, namely synaptophysin and postsynaptic density (PSD)-95, as well as increased blood–brain barrier permeability (with an associated reduction in expression of tight junction proteins) (Braniste et al., 2014; Diaz Heijtz et al., 2011). A lack of microbial regulation also impacts glial cells with a lack of maturation in microglia of GF mice, as seen by the absence of requisite cell surface molecules and appropriate morphology (Abdel-Haq et al., 2019; Erny et al., 2015). This effect was temporally replicated via microbial depletion through administration of broad-spectrum antibiotics and was alleviated through the provision of SCFAs (Erny et al., 2015). Further to this, GF oligodendrocytes demonstrate over-expression of myelinating genes and hypermyelination in the pre-frontal cortex, and significantly, commensal colonisation successfully downregulated aberrant transcription activity but not the hypermyelination (Hoban et al., 2016). These molecular and anatomical changes correspond with neurocognitive disease states, with an increased risk of developing depression (Lima-Ojeda et al., 2017), schizophrenia (Hoffman et al., 2020; Klein-Petersen et al., 2021; Köhler-Forsberg et al., 2019), and neurodevelopmental disorders ADHD and ASD (Aversa et al., 2021; Neufeld et al., 2011; Slykerman et al., 2019) seen with early life microbial disruption (such as antibiotic treatment). Given the pervasive gastrointestinal dysfunction observed in ASD (23–70%) with high correlation to neurological symptoms, in addition to altered microbiota composition, taxonomic richness, and metabolite levels, an aetiological role of the microbiota-gut-brain axis is highly implicated in this neurodevelopmental disease (Hoban et al., 2016; Kang

et al., 2018). Likewise, chemotherapy-induced neurocognitive complications are linked to a disrupted gut microbiota characterised by production of immunomodulatory metabolites (Bilenduke et al., 2022; Ciernikova et al., 2021; Song and Bai, 2021; Subramaniam et al., 2020). In fact, gut microbiota disruption and anti-cancer treatment-induced gut toxicity allows these metabolites to translocate into the bloodstream (Subramaniam et al., 2020). The consequent invasion of these gut-derived immunomodulators into the CNS may explain the manner by which systemically administered chemotherapies can induce neurotoxicities (Subramaniam et al., 2020).

Consequently, we must consider the impact of these differences in the microbiota-gut-brain axis in children compared to adults when developing microbial-based therapies for neuropathology, as they are known to impact therapeutic response. In fact, neurological benefits of probiotic interventions are numerous in adult populations, but children <3-years are predominately non-responsive (Chou et al., 2010). Interestingly, while children with ASD between 7 and 12 years are reported to respond well to probiotics, adolescences (13–15 years) have less therapeutic benefit (Liu et al., 2019). This highlights the complexity of the microbiota-gut-brain axis and the dynamic changes that occur throughout development. Importantly, these may also be influenced by dietary habits, which are also known to change with age, and as such, ensuring evidence is generated in appropriately designed models to reflect the paediatric setting, rather than repurposing approaches developed in adults, is critical for therapeutic success.

It is not only important to consider the age-dependent changes in treatment response but also to develop treatments to ensure microbial disturbances do not impede the critical windows of neurodevelopment. An example of this which is relevant to the context of cancer-treatment induced neurotoxicities is malnourishment induced cognitive deficits. Prevalence of malnourishment in children living with and beyond cancer ranges between 5 and 48% (Brinksma et al., 2012; Murphy et al., 2015; Tripodi et al., 2022). Further to this, as a result of chemotherapy-induced gut toxicity in children, renourishment is necessary after >70% of chemotherapy courses indicating the frequency of malnourishment during active treatment (Kuiken et l., 2017). Notably, malnourishment is associated with pervasive neurodevelopmental delays and cognitive impairment in a microbial dependent manner (Blanton et al., 2016). As the gut microbiota is reliant upon the host's food intake, malnourishment depletes these gut micro-organisms and pre-clinical stabilisation of appropriate neurodevelopment is only seen with microbial-targeted refeeding and not with standard renourishment diet (Gehrig et al., 2019). As such, the necessity of promoting microbial function during cancer treatments has an urgency in childhood which is not present in adulthood with the associated closure of critical windows.

5. Considerations for modelling paediatric neuropathology

Here, we have provided clear evidence of how the childhood brain differs to that of an adult, and how these differences are uniquely positioned to influence the development of paediatric neuropathology. Indeed, in some recent work, these nuances have been appreciated and applied to investigating chemobrain in a paediatric setting. Gibson et al. (2019) treated PND 21 mice with methotrexate and identified oligodendrocyte precursor cell depletion and white matter loss with localised microglial activation and impairment on cognitive behavioural tests (lasting up to 6 months). Intriguingly, this demyelination and impaired cognition was effectively alleviated through small molecule inhibition of colony-stimulating factor receptor 1, an essential factor for microglial survival, without any reported adverse effects (Gibson et al., 2019). Further investigation into the effects of methotrexate upon myelination in the developing brain (PND 21 mice) indicated a role for microglial-dependent reduction in BDNF and OPCs (Geraghty et al., 2019). Application of a TrkB (BDNF receptor) agonist prevented this depletion and restored adaptive myelination and cognitive function in the chemotherapy-treated mice (Geraghty et al., 2019). Both studies identified a novel role of OPCs in the sequalae of CNS side-effects of methotrexate, and established efficacy of pharmacological interventions to reverse neuropathologies and cognitive side-effects. Given that these treatments were performed in juvenile, age-matched animals, the results suggest these interventions do not have adverse effects upon neurodevelopment and therefore have greater clinical relevance than data obtained in adult populations. What remains unclear is their effect on chemotherapy efficacy and if they can be used in combination with standard treatment to prevent chemobrain.

More recent studies have further improved the approach to pre-clinical modelling of paediatric chemobrain with the addition of tumour bearing models (Konsman et al., 2022; Laaker et al., 2023). A dosing regimen of methotrexate, vincristine and leucovorin to PND 21 mice, in addition to injection with leukaemia tumour cells (PND 19), identified upregulation of pro-inflammatory (and microglial associated) genes within the prefrontal cortex with concurrent cognitive impairment behavioural phenotypes (Laaker et al., 2023). Further to this, downregulation of claudin-1 (blood–brain barrier tight junction protein) and myosin-light chain kinase (role in endothelial junction integrity) genes were identified following chemotherapy in female and both female and male mice, respectively (Laaker et al., 2023). Not only does this data suggest the first evidence of reduced blood–brain barrier function in a paediatric pre-clinical model of chemobrain, but also indicates a sex-dependent effect. It is likely that sex is a significant factor determining the impact of cancer therapies upon the brain (and surely the developing one); however, this topic is beyond the scope of this article and has been discussed previously by other authors (Armstrong et al., 2007; de Guzman et al., 2015; Haller et al., 2023; Ossorio-Salazar and D'Hooge, 2023; Panwala et al., 2019; Philpot et al., 2016; Sekeres et al., 2021; Shabani et al., 2012a; Shabani et al., 2012b; Tonning Olsson et al., 2014).

This same chemotherapy regimen (methotrexate, vincristine and leucovorin) in combination with leukemic cells was also used to identify the first age-matched preclinical evidence for a role of the gut-brain-axis in consequent neuropathologies (Konsman et al., 2022). Specifically, chemotherapy acutely increased expression of pro-inflammatory TNFα within the small intestine, which correlated with expression of CCL2 in the pre-frontal cortex and deficits in executive function (Konsman et al., 2022). This fundamental research suggests that gut-targeted management strategies for chemotherapy CNS toxicities previously considered for adults (Ciernikova et al., 2021; Deleemans et al., 2019; Subramaniam et al., 2020), may also be effective for lessening cognitive symptom burden in a paediatric setting. Alexander et al. (2018) developed the first pre-clinical model of intrathecal methotrexate and cytarabine treatment to young mice (PND 21), as this method of drug administration is prevalent in the treatment for acute lymphoblastic leukaemia (26.8% of global childhood cancer diagnoses) (Ward et al., 2014). This model allowed the authors to characterise the effects of direct exposure of the developing CNS to chemotherapy upon dendrite formation. Identified impacts were upon the density of mushroom (mature) dendritic spines in the CA1 and CA3 of the hippocampus and also the dorsal ganglion, with functional consequences for performance in cognitive tests (Alexander et al., 2018). As such, this novel and age-appropriate model indicates that intrathecal chemotherapy for acute lymphoblastic leukaemia impacts synaptogenesis by reduced formation of mature dendrites in the paediatric brain.

These recent examples demonstrate successful utilisation of age-appropriate animal models for temporally relevant findings. Moving forward it is important to consider not only the unique attributes of the developing childhood brain, but also its interaction with other organ systems and networks (outside of the brain), especially the gut microbiota and unique confounding factors (e.g., diet). As such, it is critical to consider how to accurately replicate these attributes and interactions to improve discovery and translational research in paediatric disease. In the context of animal studies, ensuring preclinical models are developed and executed in appropriately aged animals is critical. In this section we

describe important considerations and inherent strengths and limitations of current approaches to modelling paediatric neurophysiology (Fig. 4).

5.1. Considerations for developing in vivo paediatric models

When considering developing models of paediatric disease, their unique metabolic capacity cannot be ignored, especially in the context of drug-induced neuropathology. There is a stark lack of research regarding the pharmacokinetics of drugs, including chemotherapies, in young children. What is known is that paediatric body composition in regard to total body water, adipose tissue and concentrations of plasma proteins alters body-wide drug distribution (Filler et al., 2008). For example, the high lipid content within the brain, compared to other body tissues in children, makes the developing CNS a highly attractive location for hydrophobic drug deposition (Filler et al., 2008). Variation in plasma proteins has consequences for drug exposure, as evidenced by investigation of prednisolone (chemotherapeutic for acute lymphatic leukaemia) availability. Sassen et al. (2021) found that prednisolone binding to plasma proteins decreased with age and hence, exposure to the active unbound drug was correlated with age. As such, children often require higher body size adjusted doses than adults (Sassen et al., 2021). Additionally, the expression of metabolic enzymes (Phase 1: cytochrome P450, Phase 2: UDP glycosyltransferases) which are unique to the stage of maturation, varies the rate of drug clearance from the bloodstream (Job et al., 2019). Pharmacokinetic studies have found that when children receive the equivalent dose of chemotherapy to adults, there can be a 20-fold difference in drug exposure (Norris and Adamson, 2012). Moreover, administration of efavirenz to treat HIV/AIDS results in markedly lower bio-availability in children less than 12-years compared to adults which is related to 1.5x greater efavirenz plasma clearance in paediatrics (Fletcher et al., 2008; ter Heine et al., 2008). Similar findings were observed with the anti-coagulant warfarin (Takahashi et al., 2000). These findings suggest that paediatric pharmacokinetic interactions require more rigorous investigation as children are exposed to variable and inconsistent doses in contrast to adults, and as such, is an important variable to consider when studying paediatric disease in a laboratory setting.

When developing an animal model of a paediatric neurological disease we recommend considering the many age-dependent and inter-species variabilities which may impact the relevance of subsequent findings. Cognitive and behavioural testing is widely used to define functional consequences of neuropathologies. However, these tests have been developed in adult mice and as such, they do not necessarily account for the functional immaturity and developmental stages of young mice. The Morris Water Maze is a robust and reliable cognitive test developed to examine the spatial memory and learning capacity of adult mice; however, healthy paediatric mice lack the capacity to recall the location of the submerged platform before PND 35 (Schenk, 1985). As such, this could produce a type II error, and confound potential neurocognitive deficits in paediatric models. In fact, in animal models of ASD, young, adolescent, and adult rodents demonstrated diverse responses in several tests investigating standard behavioural parameters (social interaction, repetitive behaviours, spatial memory and learning, and anxiety) (Paudel and Singh, 2021). As social behaviours are a learned trait which take time to develop, social behavioural tests developed in adults likely require age-appropriate adjustments for younger rodents (such as pre-weanling) (Semple et al., 2016).

Weaning occurs on PND 21 in rodents, exhibiting an accelerated transition from milk to solid foods than the time-course followed by human infants (Moser et al., 2005). In order to study drug toxicity in early development, pre-weanling animal models are required; however,

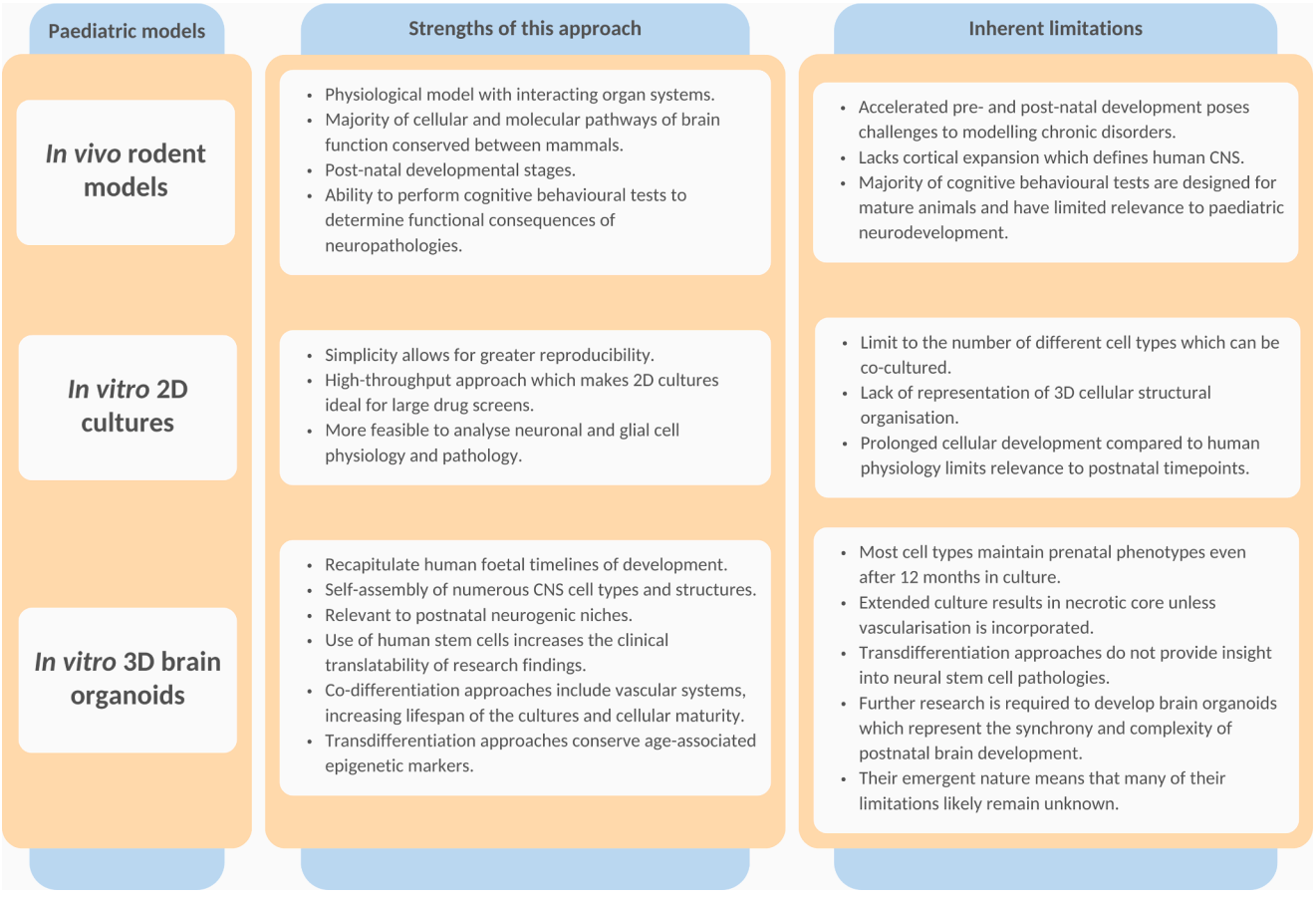

Fig. 4. Summary of the current and predominant approaches to modelling the paediatric brain and neurological disorders.

this introduces unique methodological considerations relating to drug delivery. Oral gavage is a common route for direct administration (vs. indirect where dam is dosed, and pup exposed through milk) in pre-weanling rodents. It is important to consider when designing these experiments that the oral dose must be significantly less than the pup's daily milk intake (1 – 2.5 g/day) (Maeda et al., 2000) to avoid overloading the pup with liquids and hence, lessening the pup's motivation to engage in nursing behaviour (Moser et al., 2005). Nursing is essential to foster maternal-offspring interactions, which is critical factor in the pups ability for healthy neurodevelopment (Moser et al., 2005). In relation to anatomical development, for intravenous drug delivery via the tail vein (standard route for adult mice), success is dependent on the researchers' ability to observe the vein, and this is challenging in young rodents (<PND 21) (Moser et al., 2005; Prabhakar et al., 2021). For PND 1–3 the facial vein is easily observed, providing more consistent results; however, as the skin pigments and thickens with age, visualisation declines (Gombash Lampe et al., 2014; Prabhakar et al., 2021). An alternative is *retro*-orbital injection which is available for rodents of all ages and initial results display reduced stress to the animal with *retro*-orbital vs. tail vein injections (Nanni et al., 2007; Prabhakar et al., 2021; Steel et al., 2008). However, as with any procedure or handling of pre-weanling rodents, if the dam observes unfamiliar scents or injuries, it can cause maternal rejection (Moser et al., 2005; Prabhakar et al., 2021). With the significant consequence of a failure to thrive, care must be taken to avoid any distinguishing characteristics on treated pups.

5.2. Considerations for developing in vitro paediatric models

Perhaps the most fundamental interspecies difference is the disparity in developmental time course. Prenatal development for a human foetus encompasses 40 gestational weeks for a full-term infant, in comparison the gestational period for a mouse (predominant model organism) which is only 20 days (Mariani et al., 2015). This is related to the cortical expansion characteristic of the human CNS in comparison to other mammals and allows for the higher-order cognitive functioning observed in humans (Sidhaye and Knoblich, 2021). Postnatal development is also protracted in humans, with mice achieving CNS maturation within 4–5 weeks. This creates some logistical challenges when attempting to model the consequences of chronic environmental exposures or chronic disease due to the accelerated lifespan (and thus experimental opportunities) in rodents.

An emerging solution to interspecies developmental timeline disparities are brain organoids. Derived from human pluripotent stem cells, these multi-cellular self-assembling 3D systems recapitulate human foetal timelines in addition to structure and cellular populations. To date, brain organoids have been developed for neurodevelopmental disorders (ASD, Down's syndrome), neuropsychiatric disorders (schizophrenia), neurodegenerative disorders (Alzheimer's disease, Parkinson's disease) and epilepsy, predominantly through reprogramming patient-derived fibroblasts (Sidhaye and Knoblich, 2021). Promisingly, these *in vitro* models successfully developed the pathological hallmarks of these diseases. By mimicking the temporal dynamics of human brain development, the ASD model, as an example, was able to distinguish variation in cell cycle dynamics with ASD progenitors completing the cycle more rapidly, and this resulted in over-production of neurons (Mariani et al., 2015). As these models align with foetal neurodevelopment they also provide an opportunity to characterise disruption of neurogenic niches, a highly conserved pathway between paediatric disease states (pre- and postnatal). However, further work is required to develop brain organoids during the later (postnatal) stages of neurodevelopment; use of single-cell RNA-seq to compare the organoid transcriptome at 9- and 12-months identifies that only 15% of neurons and astrocytes match profiles of post-mortem infant brain tissues (Herring et al., 2022).

The goal of age-matching *in vitro* is a challenging one, particularly so in the past, with immortalised cell lines innately 'ageless' due to immortalisation negating the use of telomere length and epigenetics to estimate biological age (Xu et al., 2012). Further to this, immortalised cells from paediatric sources are unable to mature and this phenotypical stagnation presents them as poor tools to study neurodevelopment (Xu et al., 2012; Xu et al., 2015). Unfortunately, the reprogramming of induced pluripotent stem cells (iPSCs), the predominant foundation of brain organoid research, removes evidence of age with the return to pluripotency (Mertens et al., 2018). Additionally, embryonic stem cells, the other pluripotent cell source for brain organoids, are clearly prenatally derived and as such have limited potential for postnatal age-matching. A potential workaround to iPSC reprogramming is the use of direct conversion or transdifferentiation protocols, involving transcription factors or micro (mi)RNAs to direct terminally differentiated somatic cells towards another phenotype (i.e., neuronal) (Mertens et al., 2018). For example, induced neurons which are derived from mature astrocytes and maintain age-associated epigenetic markers. These methods were developed in the field of aging diseases (such as Alzheimer's, amyotrophic lateral sclerosis) by converting aged fibroblasts to neurons; however, cells from any stage of life could be used.

A further challenge of studying human (protracted) neurodevelopment in a dish, are the technical risks and financial costs of long-term culture. This is particularly relevant to the use of brain organoids, which are prone to developing a necrotic core. This necrosis is attributed to the lack of vascularisation of the organoid (endothelial cells resulting from mesoderm, not ectoderm like neuronal tissues) and as such, insufficient nutrients and oxygen delivered to cells located centrally. Again, various methods are being investigated to address this limitation. Some take the approach of transplanting human brain organoids (around 50 days in culture) into the mouse parenchyma. This has shown preliminary success with extended lifetime of organoids (233 days) as well as neurons more comparable to postnatal functionality as determined by calcium imaging (Mansour et al., 2018). Similar results were produced when *in vitro* vascularisation was achieved through co-differentiation of neural and endothelial cell types, with not only increased lifespan of the organoids but also a more rapid maturation of the neurons (Cakir et al., 2019; Ham et al., 2020; Karzbrun and Reiner, 2019). Additionally, whilst brain organoids do not innately develop microglia (derived from myeloid progenitors within the embryonic yolk-sac), integration of these CNS myeloid cells has recently been achieved to increase the physiological recapitulation achieved by 3D cultures (Adams et al., 2019; Zhang et al., 2023a). While these are significant leaps in the field of tissue culture methods for studying neurodevelopment, further work is required to establish reproducible brain organoids of postnatal stages of neurodevelopment. It is also important to note, that monolayer 2D models of the CNS, i.e., monoculture of iPSC-derived/induced neurons or co-culture of iPSC-derived neurons and astrocytes, do not have the same limitations relating to nutrient delivery (Bardy et al., 2015). The relative simplicity of these models allows greater reproducibility and ease for analysing cell physiology and, as a result, 2D cultures are an ideal option for drug screening experiments (Logan et al., 2019; Zabolocki et al., 2020). New methods which allow long-term functional aging of human neurons *in vitro* will facilitate studies of human specific drug mechanisms at various stages of neuronal maturation (Milky et al., 2022). Additionally, a monolayer of iPSC-derived NPCs can provide insight into the effects of compounds upon neurogenic pools within the brain, which as we have described throughout this review, has consequences for appropriate neurodevelopment. The simplicity of 2D cultures is also clearly a constraint, with an inherent limit upon number of cell types involved, structural recapitulation, and growth and development which are provided by more complex *in vitro* models (Mertens et al., 2016). As such, complementary two- and three-dimensional *in vitro* and *in vivo* preclinical models are necessary to account for the limitations of each approach.

6. Conclusion

Given the numerous unique characteristics of the developing CNS outlined in this review, it is remarkable that research regarding cancer treatment-related neurocognitive disease is consistently extrapolated from adult to paediatric cohorts. Given the expansive neurogenic niches with inherent sensitivity to neurotoxicity which define the developing brain, there is potential for toxic insult during critical windows to drive long-term neurological deficits. This is exacerbated by an immature blood–brain barrier and naïve redox mechanisms which lead to greater CNS infiltration and DNA damage. Furthermore, the hyper-reactive neuroimmune responses in early life permit pathologies of greater severity to exogenous insult than what is seen in the mature brain. This pro-inflammatory CNS is likely linked to the deficiency of the innate peripheral immune system during early post-natal development. In turn, this immune naivety is related to an immature gut microbiota, a system which exerts profound influence over the brain. Further to this, we certainly have not discussed every aspect in which the paediatric brain is unique, such as synaptic refinement or the influence of thyroid hormones on brain development, as there is currently only limited evidence implicating these processes in the pathogenesis of chemobrain. However, development of paediatric models may provide the tools to interrogate the roles of these functions in the symptom sequalae, and even identify novel targets for intervention.

This importance of developing age-specific pre-clinical models is evident in studies which successfully incorporate paediatric neurobiology. These research findings highlight that chemotherapy promotes an inflammatory microenvironment within the developing brain with consequences for myelination and lasting cognitive function. The tendency to translate research from adult cohorts to children is likely related to the challenges of developing *in vivo* or *in vitro* models of early human (postnatal) development. Fortunately, greater attention is being placed upon improving our approaches to these models which means that researchers now have the responsibility to ensure that experimental design reflects the developmental stage relevant to the research's target population. This will ensure that children are no longer considered biological 'small adults', an inaccuracy which can have consequences for healthy development and their quality of life.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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